



**Lab:1**

**Salicylic Acid**

**Historically**, salicylates\* were among the 1st of the NSAIDs to achieve recognition as analgesics. The parent cpd. Salicylic acid has been known since 1839 and is found in the free state as salts & esters.

**Many derivatives of salicylic acid have been introduced into medicine for a variety of purposes such as:**

1- Preservative for food and pharmaceuticals.

They have strong antiseptic and germicidal properties.

2- Local treatment of warts, corns and athlete's feet.

They have good escharotic and keratolytic properties.

3- Internally, (although seldom taken in the free state).

They show good anti-inflammatory, antipyretic and analgesic activities characteristics of their many commonly used salts and derivatives.

**Derivatives of S.A. were introduced in an attempt to:**

1- Prevent the gastric symptoms (gastric disturbances, hemorrhage, irritation,..).

2- Prevent the undesirable taste inherent in the common salts of SA.

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\* Salicylates, are salt, ester or amide derivatives of salicylic acid.



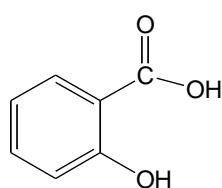
## Types of S.A. derivatives:

### **Type I:**

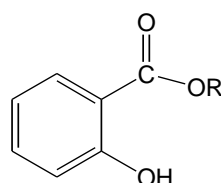
Represents those that are formed by modifying the carboxyl group of S.A. ( e.g. salts, esters or amides).

### **Type II:**

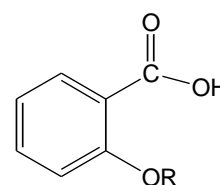
Represents those that are derived by substitution on hydroxyl group of S.A.



Salicylic acid

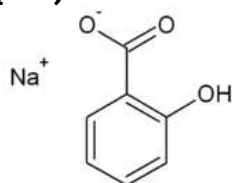


Type I  
derivative

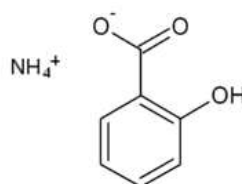


Type II  
derivative

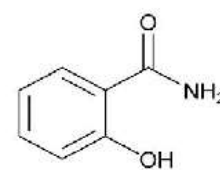
### **Examples (Type I):**



Sodium Salicylate



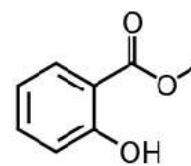
Ammonium Salicylate



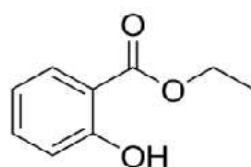
Salicylamide



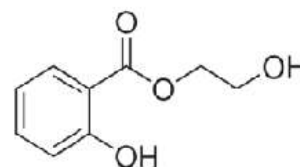
Strontium salicylate



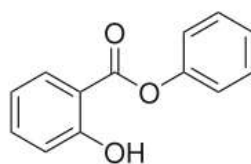
Methylsalicylate



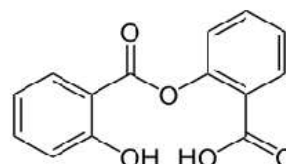
Ethylsalicylate



Hydroxyethylsalicylate  
( Spirosal )



Phenylsalicylate  
( Salol )



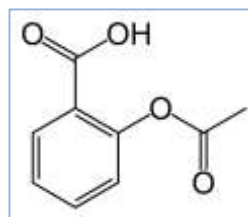
Salicylsalicylic acid  
( Salsalate )



**Example ( Type II ):**

Aspirin,  $C_9H_8O_4$ , Acetyl salicylic acid,

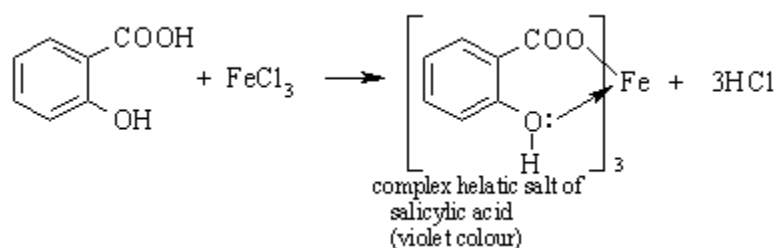
*m.p.* 135°C, *m.wt.* 180.



**Salicylic acid:**

S.A. has the formula  $C_7H_6O_3$ , or  $C_6H_4(OH)COOH$ , the OH group is *ortho* to the carboxyl group. It is also known as *2-hydroxybenzoic acid*.

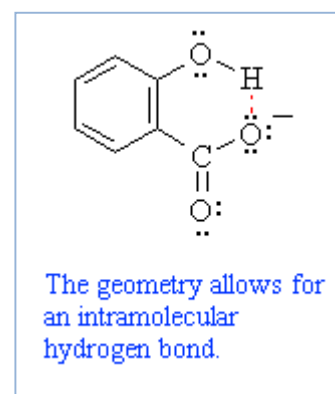
*m.wt.* = 138 , *m.p.* = 159 °C, with  $FeCl_3$  it gives violet color.



***1 g of S.A. is soluble in 460 ml of water***

**While *1 g of aspirin is soluble in 300 ml of water***

This low solubility of salicylic acid in water compared to that of Aspirin is attributed to the intramolecular hydrogen bonding in S.A. molecule, so that more molecules of solvent (water) is required to surround and solvate each S.A. molecule.





## Preparation of S.A.:

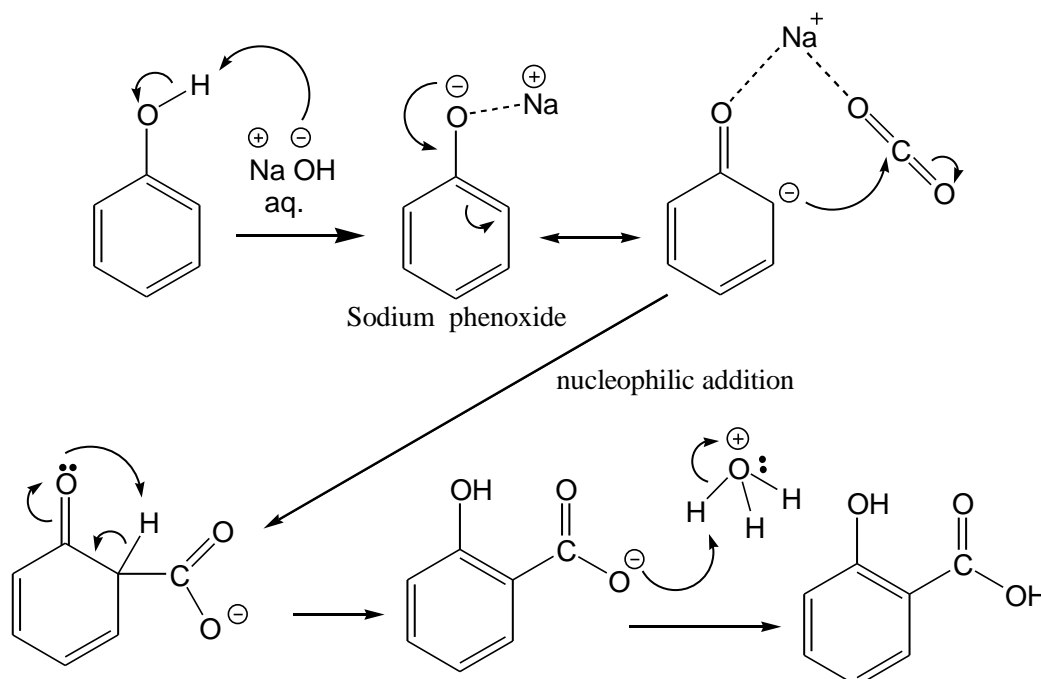
- 1- Kolbe reaction ( industrial method ).
- 2- Oxidation of salicylaldehyde.
- 3- Alkaline hydrolysis of ester.

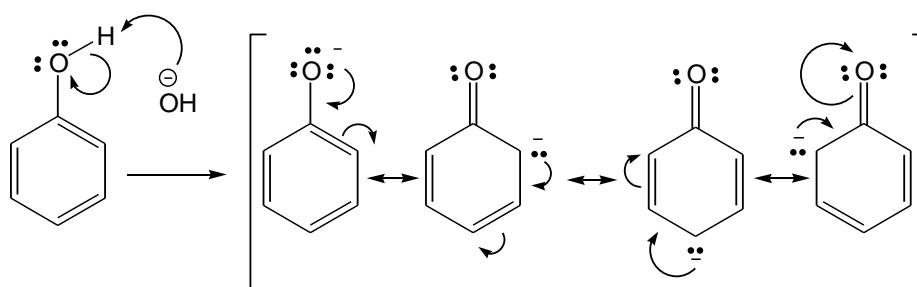
### 1-Kolbe reaction :

Is a carboxylation chemical reaction that proceeds by heating sodium phenolate (the sodium salt of phenol) with carbon dioxide under pressure (100 atm, 125 °C), then treating the product with sulfuric acid. The final product is an aromatic hydroxy acid which is also known as salicylic acid (the precursor to aspirin).

#### THE MECHANISM OF THE REACTION:

The Kolbe – Schmitt reaction proceeds via the nucleophile addition of a phenolate to carbon dioxide to give the salicylate. The final step is reaction of the salicylate with acid to form the desired salicylic acid.





( Phenoxide anion )

Some *p*-hydroxybenzoic acid is formed ( in small quantities ) as well, the separation of the two isomers can be carried out by steam distillation, the ortho isomer being more volatile. (*Why?*)

Structural formula		
Compound name	<i>o</i> -hydroxybenzoic acid (S.A.)	<i>p</i> -hydroxybenzoic acid
Molecular formula	C <sub>7</sub> H <sub>6</sub> O <sub>3</sub>	C <sub>7</sub> H <sub>6</sub> O <sub>3</sub>
Molecular weight	138.121 g/mol	138.121 g/mol
Appearance	colorless to white crystals	white crystalline
Melting point	159 °C	214.5 °C

**H.W.** Principal of steam distillation.

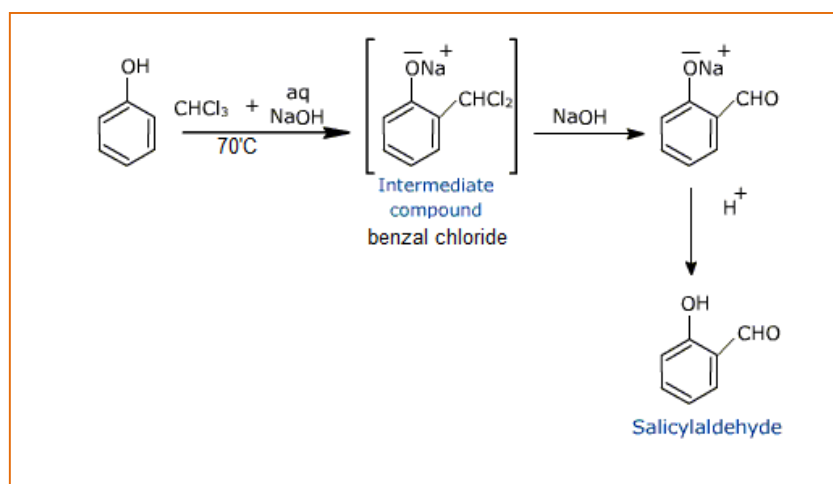
Reference: Vogel, Arthur, *Textbook of Organic Chemistry*, 4<sup>th</sup> edition. Page 143-146.

## 2- Oxidation of salicylaldehyde:

On treating phenol with chloroform in presence of sodium hydroxide an aldehyde group, a -CHO group, is introduced at ortho position of benzene ring. This reaction is known as **Reimer - Tiemann reaction**. This results in the formation of *O* - hydroxybenzaldehyde (salicylaldehyde) and *p* -hydroxybenzaldehyde, the ortho isomer being the major product.

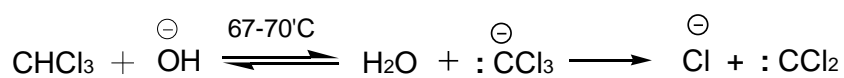


*Overall reaction:*



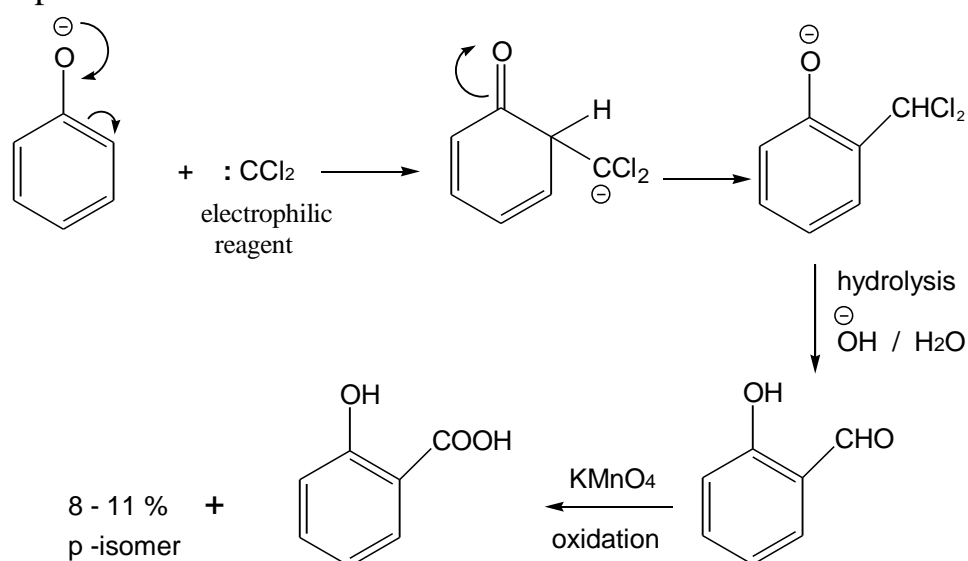
### MECHANISM OF THE REACTION:

Reimer Thiemann reaction is an electrophilic substitution reaction. The first step is the generation of electrophile.



**Dichlorocarbene**  
(reactive intermediate)  
Electrophile

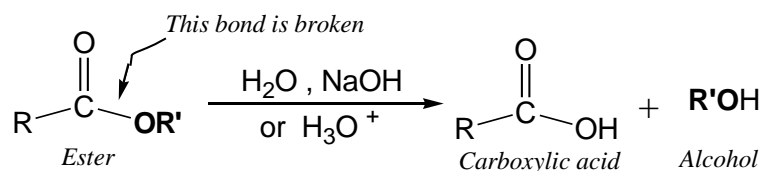
Dichlorocarbene contains a sextet of electrons and thus is a strong electrophile.





### **3- Alkaline hydrolysis of ester:**

An ester is hydrolyzed either by aqueous base or by aqueous acid, to yield a carboxylic acid plus an alcohol.



Ester hydrolysis in basic solution is called **Saponification** .

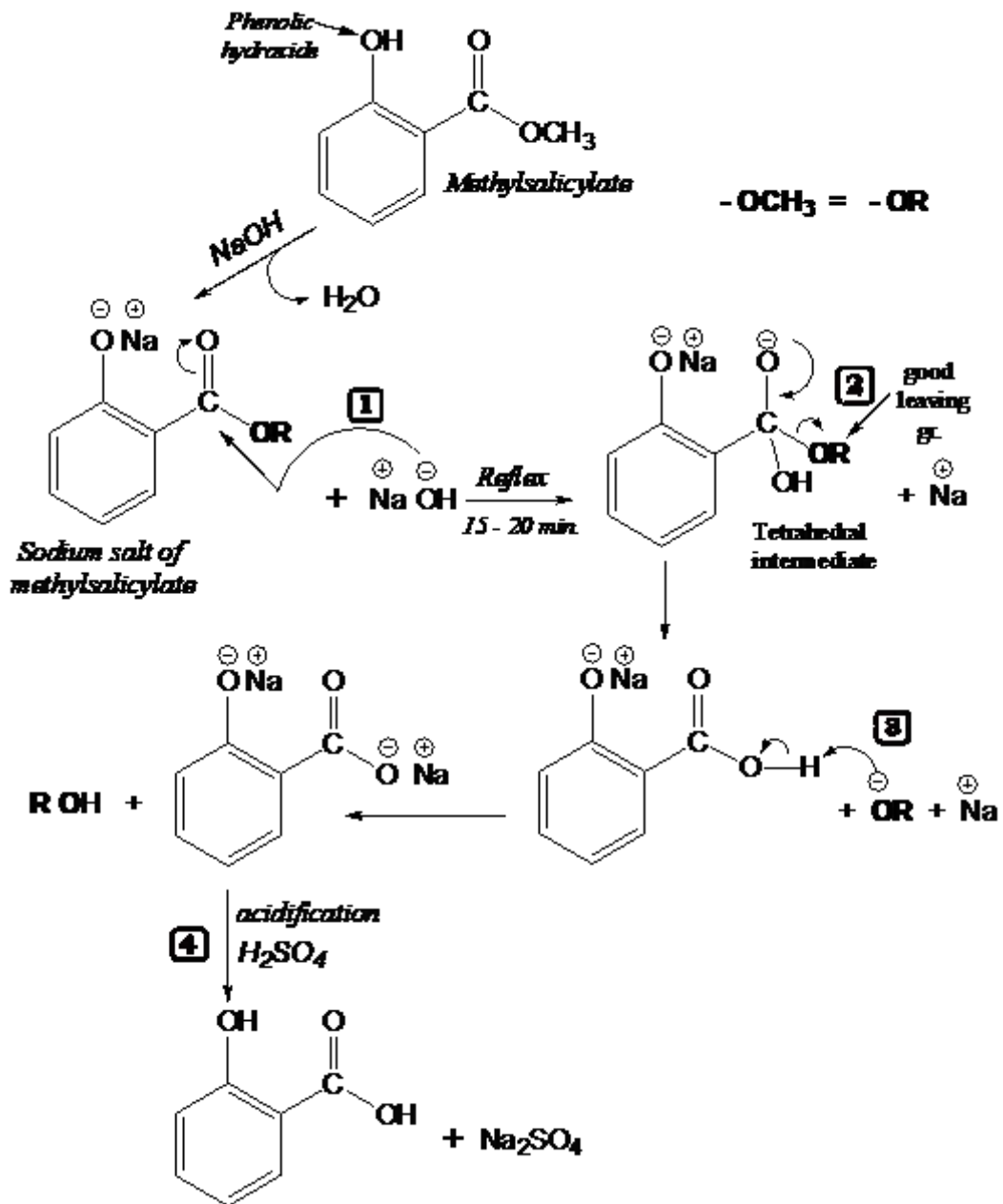
#### **MECHANISM OF SAPONIFICATION:**

- 1** Nucleophilic addition of hydroxide ion to the ester carbonyl group gives the usual tetrahedral alkoxide intermediate.
- 2** Elimination of alkoxide ion, ( $\text{OR}'$ ), then generate the carboxylic acid.
- 3** Alkoxide ion abstracts the acidic proton from the carboxylic acid and yields a carboxylate ion.
- 4** Protonation of the carboxylate ion by addition of aq. mineral acid in a separate step then gives the free carboxylic acid.

★ In our lab we will use the alkaline hydrolysis of Methylsalicylate \* method for preparation of S.A.

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\* *Methylsalicylate* is an ester of S.A. easily recognized by its odor and is known as oil of wintergreen because of its natural source.



H.W. Mechanism of acid-catalyzed ester hydrolysis.



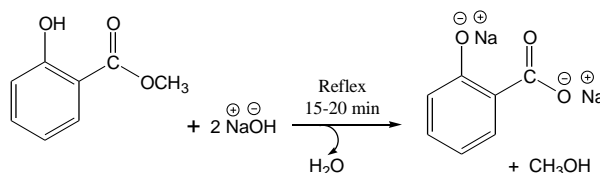


Name of Experiment: **Alkaline Hydrolysis of Ester.**

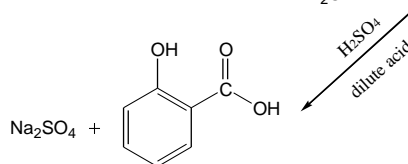
Aim of experiment: **Preparation of Salicylic Acid by Alkaline**

**Hydrolysis of Methylsalicylate.**

Principal:



Procedure:



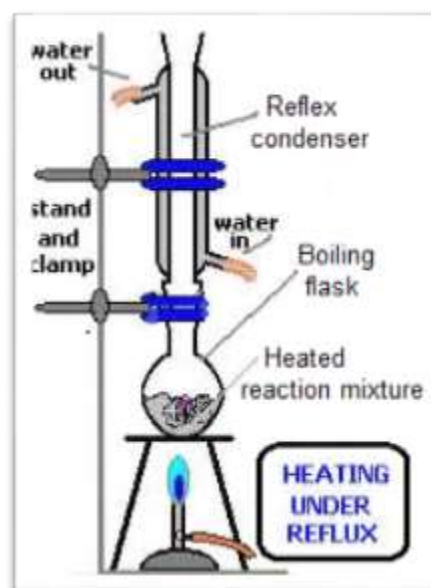
1- Put 2.1 ml of methylsalicylate in 250 ml boiling flask with few boiling chips.

2- Add 25 ml of 20% aq. NaOH sol. & mix ;  
at this point a white ppt. appears which  
will redissolve again by heating . \*

3- Reflex for 15 – 20 min.

4- Stop reflex, cool & transfer the mixture  
to a beaker.

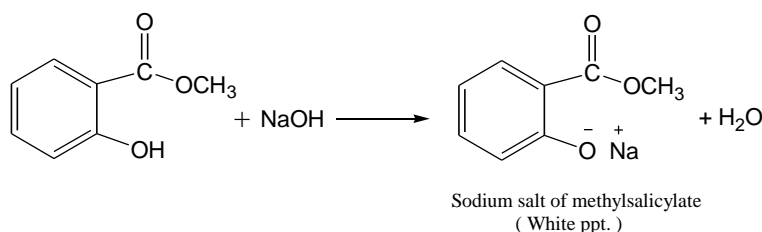
5- Add 35 ml of dil. H<sub>2</sub>SO<sub>4</sub> to get the acid  
( S.A. ppt. ).



6- Further cooling is required then filter & collect the ppt.

7- Recrystalize S.A. from the minimum amount of hot water.

\* The white solid that is formed immediately ( before reflex ) when methylsalicylate was introduced to the aqueous solution of sodium hydroxide is the sodium salt of methylsalicylate that will disappear by boiling ( re-dissolve ).





### **Post lab exercises:**

- 1- The carboxyl group is more acidic than the hydroxyl group in salicylic acid molecule, explain why?
- 2- Rank the following compounds in order of increasing acidity:  
Phenol,  $\text{CH}_3\text{COOH}$ , Salicylic acid,  $\text{CH}_3\text{OH}$ ,  $\text{H}_2\text{SO}_4$ .
- 3- Draw the stepwise mechanism for the alkaline and acidic hydrolysis of ester. Mention which one of them is preferred for hydrolysis of an ester? Why?
- 4- What is the *salol* principal?
- 5- Explain the reason for the addition of aqueous NaOH solution in S.A. synthesis?
- 6- Why is it necessary to add the acid at the end of alkaline hydrolysis of methylsalicylate?

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### References:

# *Practical Medical Chemistry, 4<sup>th</sup> year students, Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad, 2009-2010.*

# *Vogel, Arthur, Textbook of Organic Chemistry, 4<sup>th</sup> edition.*

# *Morrison and Boyd, Organic Chemistry, 6<sup>th</sup> edition.*

# *John E. McMurry, Organic Chemistry, 8<sup>th</sup> edition, 2012.*

# *Michael B. Smith and Jerry March, March's Advanced Organic Chemistry, 6<sup>th</sup> edition, 2007.*

## **Recrystallisation of Salicylic acid**

### **Theoretical aspects:**

Solid organic compounds when isolated from organic reaction are usually impure; they are contaminated with small amounts of other compounds that are produced along with the desired product.

The purification of impure crystalline compound is usually done by recrystallisation from a suitable solvent or a mixture of solvents.

Purification of solids by recrystallization is based up on differences in their solubility in a given solvent or a mixture of solvents.

### ***The most desirable characteristics of a solvent for recrystallisation is as follows:***

- 1- It should be chemically inert toward the solute,( the solvent does not react chemically with the substance to be purified).
- 2- It should dissolve the solute to be purified readily at or near it's boiling point, but sparingly at the laboratory temp. or below ( 0 – 25 °C ).
- 3- It should dissolve the impurities readily or not at all.
- 4- It should be capable of easy removal from the crystals of the purified cpd. , ( i. e. ) possess a relatively low boiling point.
- 5- It should yield well-formed crystals of the purified cpd.
- 6- If two or more solvents appear to be equally suitable for crystallisation the final selection will depend up on such factors as ease of manipulation, toxicity, flammability, and cost.

### ***Types of impurities in the sample:***

- 1- Impurities that are insoluble in the solvent used for recrystallisation.
- 2- Impurities that are soluble in the solvent used for recrystallisation.
- 3- Coloured cpd.s.

***In it's simplest form, recrystallisation process consist of :***

- 1- Dissolving the impure substance in some suitable solvent at or near the boiling point.
- 2- Filtering the hot solution from the particles of insoluble material and dust.
- 3- Allowing the hot solution to cool thus causing the dissolved substance to crystallize out.
- 4- Separating the crystals from the supernatant solution.

The resulting solid after drying is tested for purity (usually by melting point determination), but also by spectroscopic method or by TLC and if it's found impure is again recrystallised from fresh solvent.

**Practically**, to choose a good solvent take about 0.1 g of the cpd. to be purified ( a pure sample) and try to dissolve it in 1 ml of solvent,

If it dissolves in the cold solvent then the solvent is not suitable.

If it dissolves in the solvent with heating then the solvent will be used for recrystallisation.

If it doesn't dissolve in the solvent even at elevated temp. then the solvent will not be used for recrystallisation.

**Example:**

Results of solubility tests for compound ( A ) are shown in the following table (g/mL). Which solvent will you choose for recrystallisation?

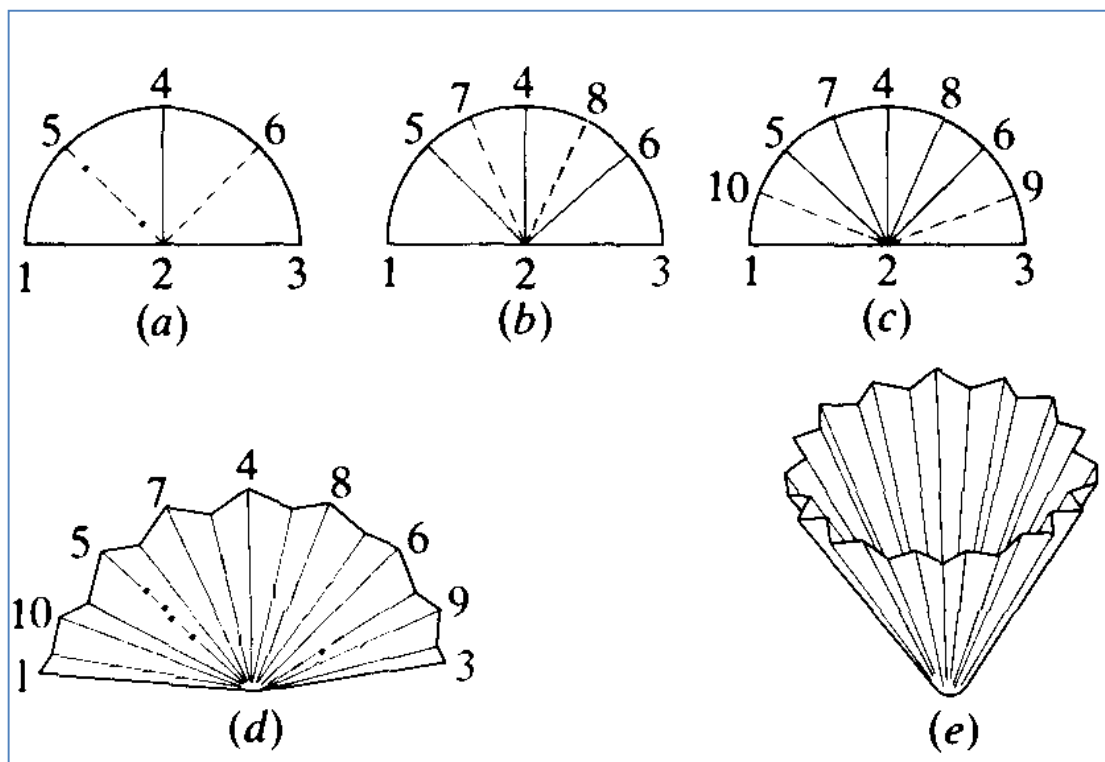
Solvent	Water	Ethanol	Diethyl ether
Cold	20	3	5
Hot	30	25	5

***Common solvents used For recrystallisation:***

Solvent	b.p. (°C)	
Water (distilled)	100	To be used whenever suitable
Methanol*	64.5	Flammable; toxic
Ethanol	78	Flammable
Industrial spirit	77-82	Flammable
Rectified spirit	78	Flammable
Acetone	56	Flammable
Ethyl acetate	78	Flammable
Acetic acid (glacial)	118	Not very flammable, pungent vapours
Dichloromethane (methylene chloride)*	41	Non-flammable; toxic
Chloroform*	61	Non-flammable; vapour toxic
Diethyl ether	35	Flammable, avoid whenever possible
Benzene*†	80	Flammable, vapour highly toxic
Dioxane*	101	Flammable, vapour toxic
Carbon tetrachloride*	77	Non-flammable, vapour toxic
Light petroleum	40-60	Flammable‡
Cyclohexane	81	Flammable

***Filtration of hot solution***

The boiling and the hot solution must be rapidly filtered before undue cooling using fluted filter paper.



***Use of decolourising charcoal:***

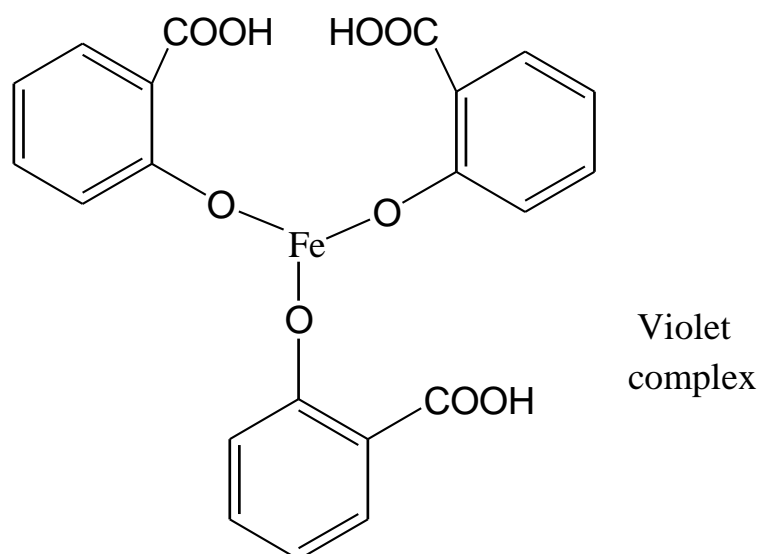
Samples to be purified may contain soluble colored impurities that may cause the solution and the crystals to be colored. Upon recrystallisation these impurities dissolve in the boiling solvent and adsorb on the crystals produced upon cooling yielding a colored product.

These impurities can be removed by treating the colored samples with decolorizing (activated) charcoal that is composed of fine carbon particles with a large active surface area on which the colored impurities will be adsorbed.

Charcoal is added to the hot solution before boiling and the solution is kept hot at or near the boiling point for about 3 – 5 min. with shaking to wet the charcoal, the solution is then filtered through a fluted filter paper.

*Notes about using activated charcoal:*

- An excessive quantity of decolorizing charcoal should be avoided since it may adsorb some of the cpd. which is being purified.
- Charcoal should not be added to a superheated solution or at the boiling point of the solvent because its particles function as thousands of boiling chips causing the solution to boil over and foam.
- Charcoal is not used for recrystallisation of phenolic cpd. because it contains ferric ions that upon heating the solution for some time it can react with the phenolic hydroxyl forming red coloured complexes thus impairing the purification process.



*Recrystallisation using mixed solvents:*

This is applied when our cpd. is readily soluble in a solvent at room temp. and at the same time is insoluble in the other solvent. The two solvents must be miscible with each other such as alcohol & water, ether & pentane and glacial acetic acid & water.

*Procedure:*

- 1- The cpd. is dissolved in the solvent that is soluble in it.
- 2- Charcoal is used if required.
- 3- The solution is filtered to get rid of the insoluble impurities.
- 4- The other solvent ( in which the cpd. is insoluble), is added to the filtrate gradually until turbidity appears.
- 5- The mixture is then left a side to facilitate crystallization.

*Notes:*

● If recrystallisation fails to occur then you should:

- 1- Scratch the sides or the bottom of the container below the surface of the solution with a glass rod.
- 2- Add small crystals of the pure cpd.
- 3- Or you can evaporate some of the solvent to induce crystallisation process.

● Funnel, Filter paper, & the container of the solution should be kept hot throughout the filtration process to prevent the deposition of the crystals on the filter paper or on the neck of funnel therefore it's recommended to wash the filter paper after completing the filtration process with small amount of hot solvent.

● Minimum volume of solvent is used to prevent the loss of cpd., large volumes of solvent will keep most of the cpd. dissolved in it.

● Drying of the purified substance can be achieved by air dryer, oven, freeze drying or by using desiccator containing a drying agent such as anhydrous calcium chloride or silica gel.

***Procedure for recrystallisation of Salicylic acid:***

- 1- Put 1 g of S.A. (impure sample) in a beaker.
- 2- Try to dissolve it in a minimum amount of hot water with heating.
- 3- Filter the solution while it's hot ( all equipments should be kept hot during the 1<sup>st</sup> filtration), (*hot filtration*).
- 4- Cool the filtrate, S.A. will crystallize.
- 5- Filter again (*cold filtration*).
- 6- Collect the crystals of S.A. on the filter paper.
- 7- Dry them by oven.

**Post Lab. Questions:**

1. What is the purpose of recrystallisation?
2. How might the melting point of a material differ before and after recrystallization?
3. For what purpose is charcoal used in recrystallisation?
- 4- Compound A has the following solubility properties:

solubility at 25°C	solubility at 100°C
0.01 g/mL	0.1 g/mL

You have a sample of 0.1 g of compound A which is contaminated with a compound B. To crystallize A, you would dissolve the 0.1 g in 1 mL of hot solvent and allow it to cool. When cool, 0.09 g of A would crystallize and 0.01 g would remain in solution.



a) If compound B is completely insoluble in water and 2 mg of compound B is present, how could you purify Compound A?

Since B is completely insoluble in water, it will be a solid when 0.1 g of compound A is dissolved in 1 mL of water. It could be removed from the solution by hot filtration.

b) If compound B has the same solubility behavior as A and 2 mg of this compound is present, how could you purify compound A? Would one recrystallization produce absolutely pure A?

If only 2 mg (or 0.002 g) of compound B is present, it would be totally soluble in the 1 mL of cool solvent. Therefore, one crystallization would produce absolutely pure A.

c) If 25 mg (or 0.25 g) of B is in the 1 mL of cool solution, 0.01 g of this will precipitate out and contaminate the 0.09 g of compound A, so one crystallization would not produce pure A. Therefore, you would now need to crystallize again, starting with the mixture of 0.09 g of A and 0.01 g of B.

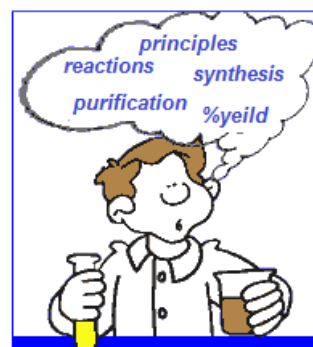
Dissolve it in 0.9 mL of hot solvent. When cooled, 0.009 g of A would remain in solution, and 0.081 g would crystallize. For B, 0.01 g would remain in solution, and therefore the crystals of A would not contain any B. Two crystallizations would be required and 0.081 g of compound A would be isolated.

## ***Preparation of acetylsalicylic acid***

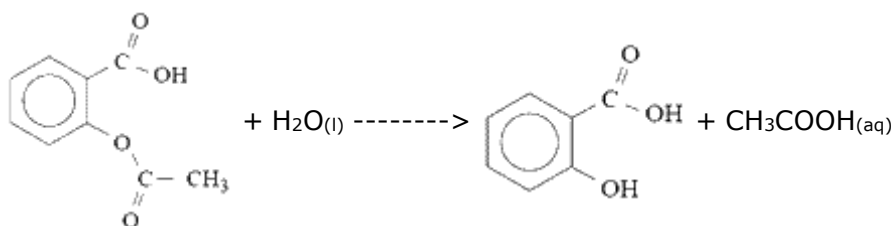
### **Acetylsalicylic acid, Aspirin,**

$C_9H_8O_4$ , m.wt. = 180 , m.p. = 135 °C.

### **Properties of acetylsalicylic acid:**

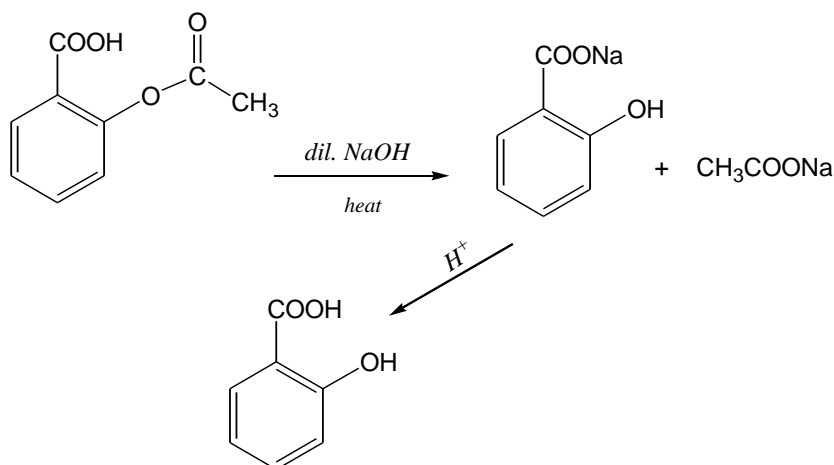


- 1- Aspirin occurs as white crystals or as a white crystalline powder.
- 2- It's slightly soluble in water, ( 1 : 300 ), soluble in alcohol ( 1 : 5 ), chloroform ( 1 : 17 ) and ether ( 1 : 15 ). It dissolves easily in glycerin.
- 3- It's stable in dry air, but in the presence of moisture, it slowly hydrolyzes into acetic acid and salicylic acid.



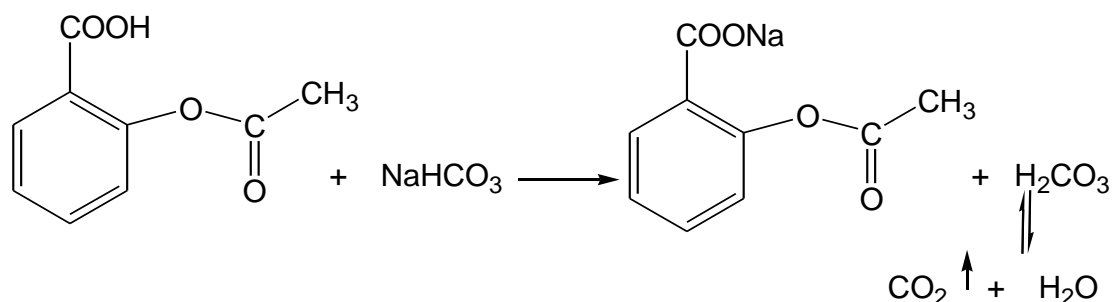
So old aspirin tablets may have a smell like vinegar as a result of the hydrolysis reaction that produces acetic acid (ethanoic acid).

- 4- Salicylic acid will crystallize out when an aqueous solution of aspirin and NaOH is boiled and then acidified.



So it decomposes in the presence of alkaline hydroxides & carbonates.

5- Aspirin itself is acidic enough to produce effervescence with carbonates.



6- Practically all salts of aspirin (soluble in aqueous media), except those of aluminum and calcium (insoluble in aqueous media), are unstable for pharmaceutical use.

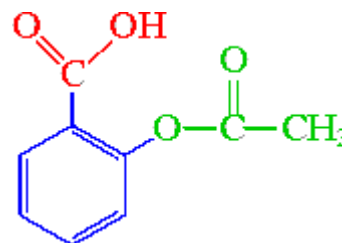
7- Aspirin gives no color with FeCl<sub>3</sub> solution.

8- It's used as antipyretic, analgesic and ant rheumatic in tablets, suppositories, vials, ...etc. dosage form.

### Acetylsalicylic acid:

Aspirin (acetylsalicylic acid) contains three groups:

- carboxylic acid functional group (R-COOH)
- ester functional group (R-O-CO-R')
- aromatic group (benzene ring)



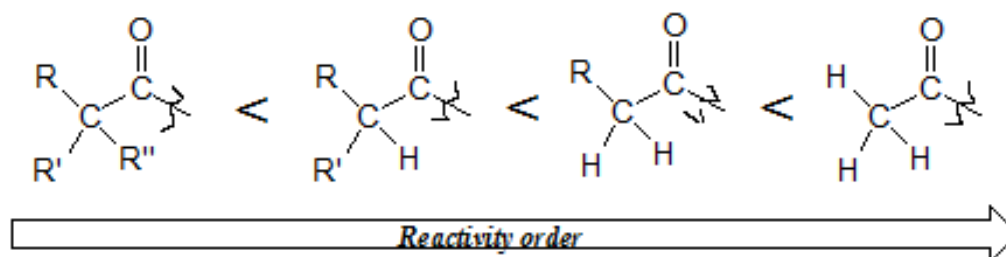
### Carboxylic acid derivatives:

- 1- Acid chloride, RCOCl .
- 2- Acid anhydrides, RCO<sub>2</sub>COR' .
- 3- Esters, RCO<sub>2</sub>R' .
- 4- Amides, RCONH<sub>2</sub> .
- 5- Thioesters, RCO<sub>2</sub>S' .
- 6- Acyl Phosphates, RCO<sub>2</sub>PO<sub>3</sub><sup>2-</sup> and RCO<sub>2</sub>PO<sub>3</sub>R' .

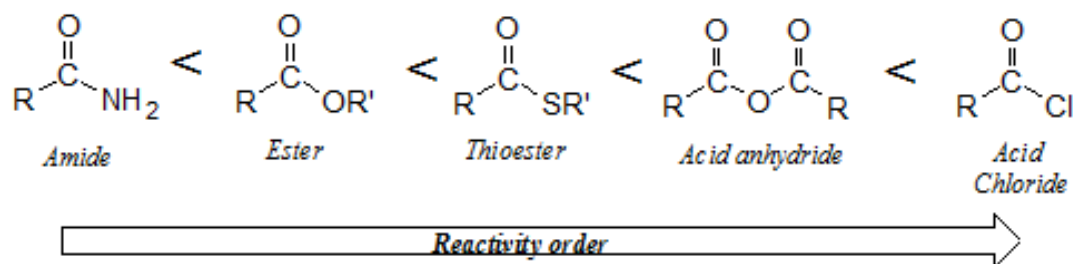
### Relative reactivity of carboxylic acid derivatives:

Steric and electronic factors are both important in determining reactivity.

**Sterically**, within a series of similar acid derivatives that unhindered, accessible carbonyl groups react with nucleophiles more readily than do sterically hindered groups. The reactivity order is



**Electronically**, strongly polarized acyl compounds react more readily than less polar ones. Thus, acid chlorides are the most reactive because the electronegative chlorine atom withdraws electrons from the carbonyl carbon, whereas amides are the least reactive.



### Preparation of ester:

#### **1- Direct esterification procedure:**

The interaction between a carboxylic acid and an alcohol is

- (a) Reversible.      (b) Proceeds very slowly.

#### **2- Esterification using acid chlorides:**

Acid chlorides reacts readily with primary and secondary alcohols to give esters in very good yields.

### ***3- Esterification using acid anhydrides:***

Esterification can also be carried out with acid anhydrides in the presence of a suitable catalyst either an acidic catalyst such as sulphuric acid, or a basic catalyst.

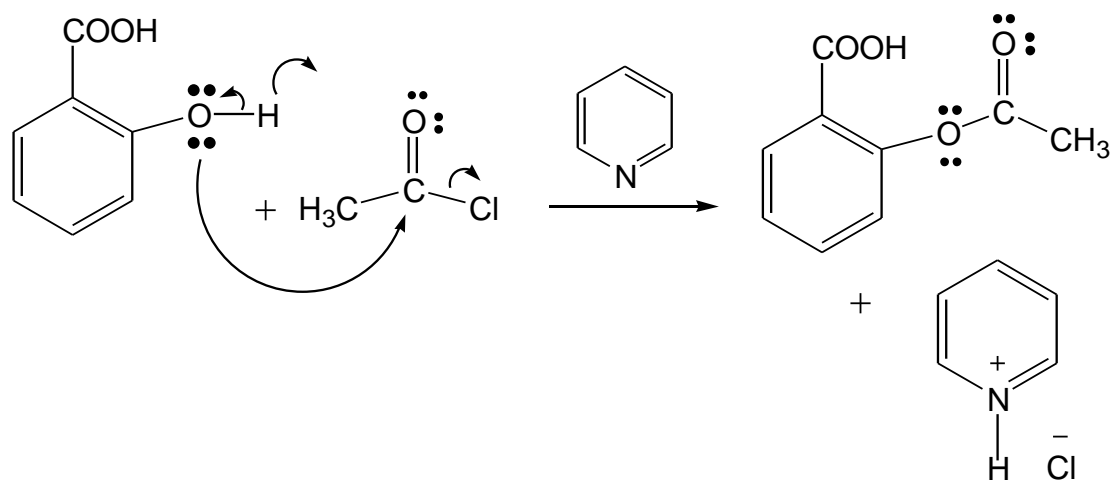
### **Preparation of acetyl salicylic acid (Aspirin):**

#### **Method I:**

#### ***Preparation of aspirin by using acetyl chloride with salicylic acid:***

Acetyl chloride is an acyl chloride, is very reactive it reacts vigorously with Salicylic acid to form aspirin the reaction is fast but it's not safe and it produces HCl gas so pyridine should be used as a base to pick up a (H<sup>+</sup>) proton and gives pyridinium chloride.

Pyridine is teratogenic and air pollutant.



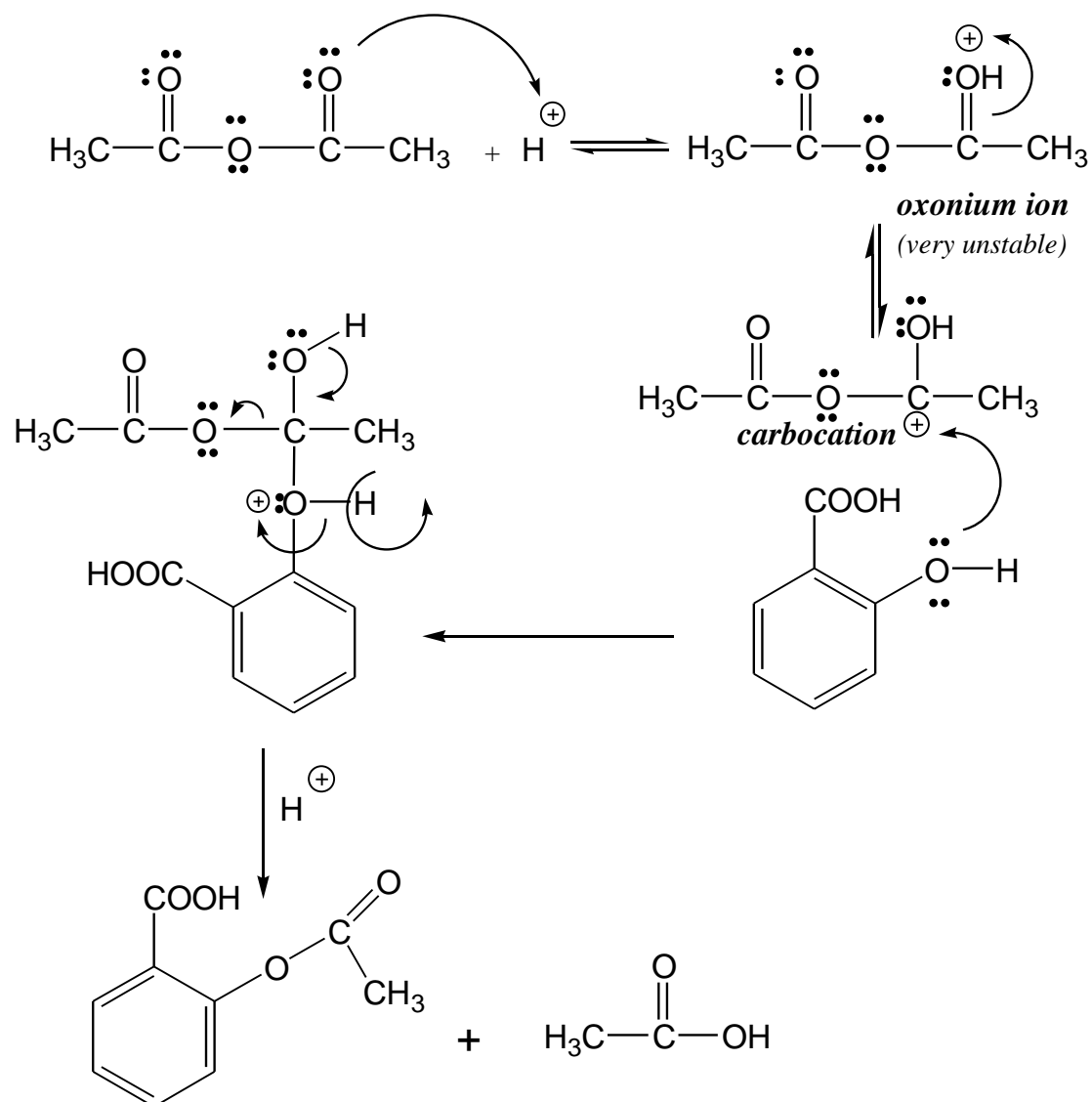
#### **Method II:**

#### **Preparation of aspirin by the reaction of S.A. and acetic anhydride**

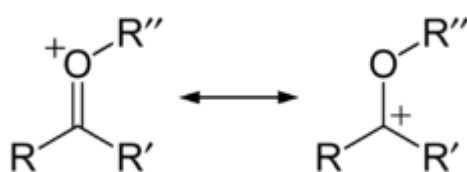
Acetic anhydride, Ac<sub>2</sub>O, is an acid anhydride which is used chiefly to make esters that cannot be made by direct esterification with acetic acid, it's cheap, readily available, easily handled and not forming corrosive HCl gas, with moderate reactivity, the acetylating reaction is moderate but safer than that of acid chloride.

There are two proposed mechanisms:

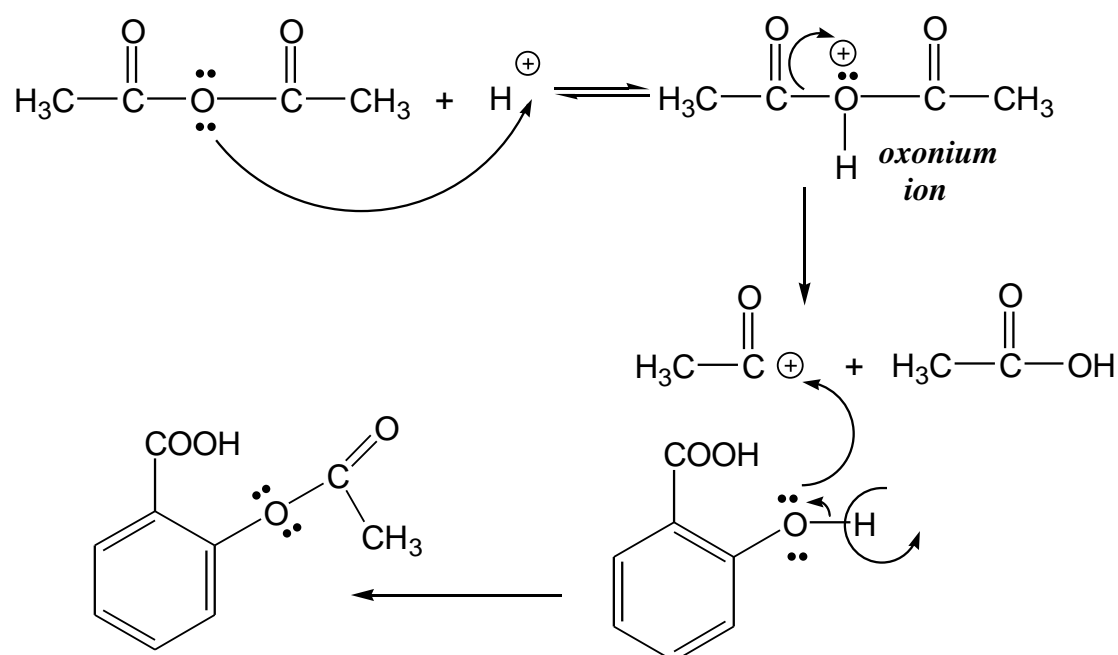
**Mechanism I:**



- Oxonium ion:** is any oxygen cation with three bonds. The simplest oxonium ion is the hydronium ion  $\text{H}_3\text{O}^+$ . Another oxonium ion frequently encountered in organic chemistry is obtained by protonation or alkylation of a carbonyl group which forms a resonance structure with the fully fledged carbocation.



**Mechanism II:**

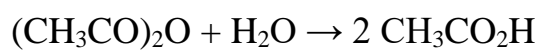


**Notes:**

- The order of acetylating power:

Acetyl chloride > Acetic anhydride > Acetic acid.

- Acetic anhydride dissolves in water to approximately 2.6% by weight. Aqueous solutions of acetic anhydride have limited stability because, like most acid anhydrides, it hydrolyses to give carboxylic acids. In this case, acetic acid is formed.



***Procedure:***

- 1) Put 2.5 gm of S.A in a dry conical flask\*.
- 2) Add 5 ml of acetic anhydride\*\*.
- 3) Shake well.
- 4) Add 3-5 drops conc. H<sub>2</sub>SO<sub>4</sub>\*\*\*.
- 5) Warm on water bath to (50-60) °C for (10-15) min\*\*\*\*.
- 6) Stirring, cooling (ppt. of aspirin ) then add 75 ml D.W.\*\*\*\*\* .
- 7) Filtration, wash the ppt. with cold D.W. and collect the product (aspirin).

**Notes:**

\* The conical flask should be dried well since the presence of moisture could hydrolyze acetic anhydride.

\*\* The first step in this esterification is to create a suspension of salicylic acid (a solid at room temperature) in an excess of acetic anhydride, Ac<sub>2</sub>O, (a liquid at room temperature). Acetic anhydride serves as both a reactant and a solvent.

\*\*\* A catalyst is required for this reaction. Conc.H<sub>2</sub>SO<sub>4</sub>, donates a proton which binds to the reaction complex. As a catalyst, H<sup>+</sup> is regenerated, not consumed by the end of the reaction.

\*\*\*\* As the reaction proceeds, the solid salicylic acid disappears and the acetylsalicylic acid product remains dissolved in the hot solution. Once all solid has disappeared (all the SA has been consumed) the reaction is complete.

Avoid very high temperature or prolonged heating period since aspirin may decompose.

\*\*\*\*\* At this point the excess unreacted acetic anhydride must be hydrolyzed (split apart by the addition of water) to acetic acid. Acetic anhydride is *very* reactive toward water, so the hydrolysis must be done slowly – water should be added drop-wise. More water is then added and



the flask is placed in an ice bath to lower the solubility and precipitate the prepared aspirin. The crude product (ASA) is then collected by filtration and recrystallized to further purify the product.

● **The product's purity is analyzed by 3 ways:**

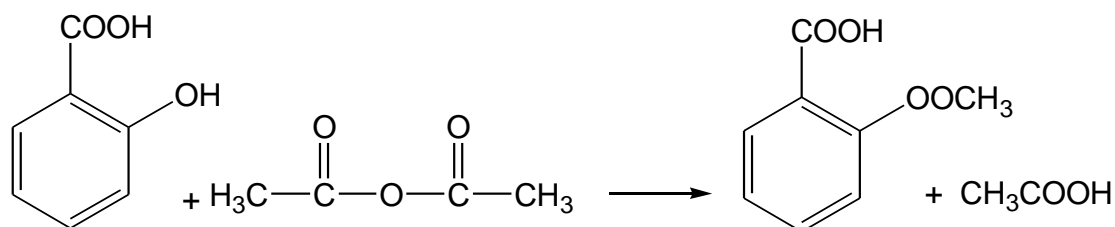
☐ Melting point is a physical property inherent to a substance's identity. The purer the substance, the smaller the melting range. The broader range of an impure sample (a mixture) results from the creation of a solution upon melting.

☐ Samples with unreacted salicylic acid complex with  $\text{FeCl}_3$  to create a purple to violet complex in aqueous solution. Pure ASA samples will remain colorless.

☐ The number of impurities in different samples will be determined by thin layer chromatography.

**The percent yield of the reaction:**

☺ Write a balanced equation for the reaction:



**1 Mole S.A.**

**1 Mole Acetic anhydride**

**1 Mole Aspirin**

☺ Calculations:

Weigh the aspirin (ASA) and calculate the theoretical (maximum) yield.

**Note:** The acetic anhydride is in excess and the salicylic acid is the limiting reagent. Use the salicylic acid to calculate the theoretical yield.

1 mole of S.A = 1 mole of ASA

Wt /m.wt S.A = wt/m.wt ASA

\* No. of moles = wt. (g) / m.wt.

*In our experiment today we used 2.5 g of SA.*

$$2.5\text{gm} / 138 = \text{wt} / 180$$

Wt = 3.25 g ASA theoretically.

$$\% \text{ yield} = (\text{wt of ASA practically} / \text{wt of ASA theoretically}) * 100$$

$$\% \text{ yield} = (2.7 \text{ g "for example"} / 3.25) * 100$$

$$\% \text{ yield} = 83 \%$$

### **Post Lab exercises:**

**Q1-** A student's theoretical yield was 12.0g of aspirin, but he only obtained 7.5g. What was his percent yield?

**Q2-** What would happen to your percent yield if the aspirin you prepared was not dried completely?

**Q3-** Calculate the theoretical yield of aspirin to be obtained when 2.0 g of salicylic acid and 5.0 ml of acetic anhydride (density = 1.08 g/ml) are mixed together. (*Molar masses: acetic anhydride = 102.1 g/mol; salicylic acid = 138 g/mol; aspirin = 180 g/mol*)?

**Q4-** Write the structure of the products that you would expect from the following reactions. Please write a complete reaction for each.

a) *Salicylic acid + Ethanol*

b) *Phenol + Acetic anhydride*

**Q5-** In preparation of aspirin by acid anhydride method, we should use a dry conical flask, why?

**Q6-** In our experiment, temp. should be between 55-60 °C ?

**Q7-** Explain the reason for the addition of 75 ml H<sub>2</sub>O ?

**Q8-** If 0.150 moles of salicylic acid and excess acetic anhydride are used during a synthesis of aspirin, how many grams of aspirin will be obtained if the reaction gives a 38% yield?

*Back Titration*

**Aspirin Tablets**  
***Quantitative Assay***

# QUANTITATIVE ASSAY:

Volumetric method

Gravimetric analysis

Spectrophotometric Analysis

# *Requirements For Titrimetric Assay:*

The reaction should be complete & irreversible

The reaction should be fast.

The end point should be easily detected.

The reaction can be represented by a chemical equation.

# **Titration:**

---

- 1- Forward titration (*direct titration*).
- 2- Back titration (*indirect titration*).

## **Back titration:**

*It includes the addition of an excess of a std. solution to a weight amount of a sample & then the excess unreacted std. solution is determined by titration with another std. solution.*

# Back Titration Is Used For:

1-

- *Volatile substances e.g. :  $\text{NH}_3$*

2-

- *Insoluble or slightly soluble substances e.g. :  $\text{CaCO}_3$*

3-

- *Slow reaction or the reaction is rapid in the presence of excess reagent e.g. : Lactic acid , ASA.*

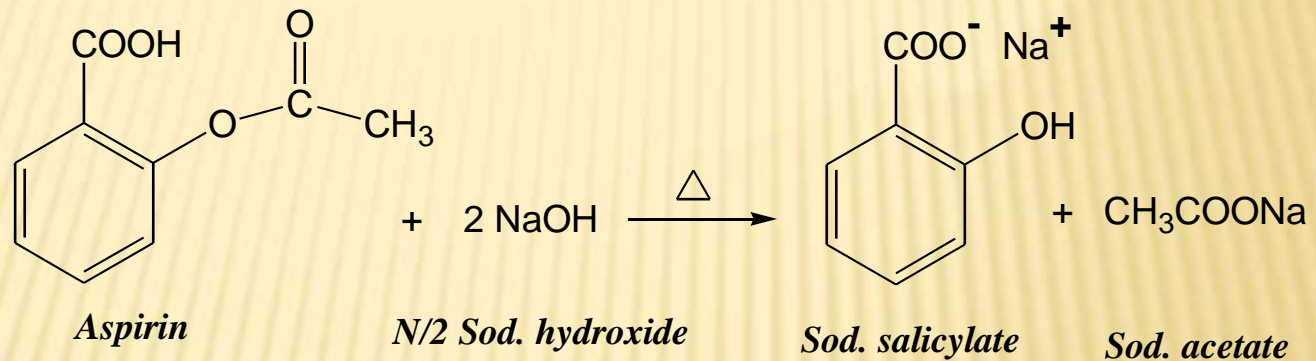
4-

- *For substances which decomposes on heating. e.g. : Formaldehyde.*



# Assay Of Aspirin:

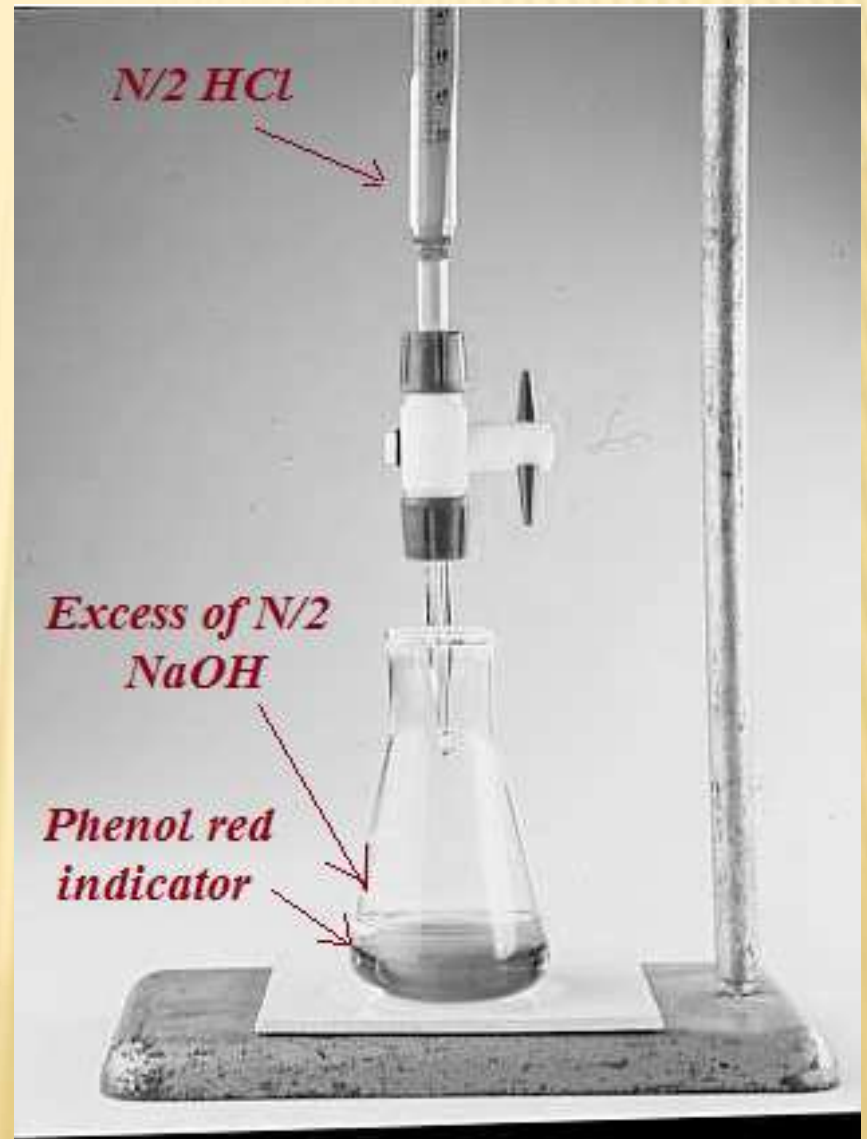
Determination of aspirin is done by hydrolysis & back titration.



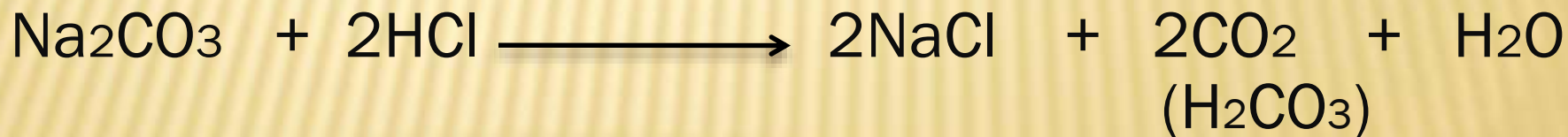
Aspirin readily dissolved in dilute NaOH solution & hydrolysed completely by heating for 10 min. with an excess of a base.



Titration of the excess unreacted alkali with  $N/2$  HCl using phenol red indicator



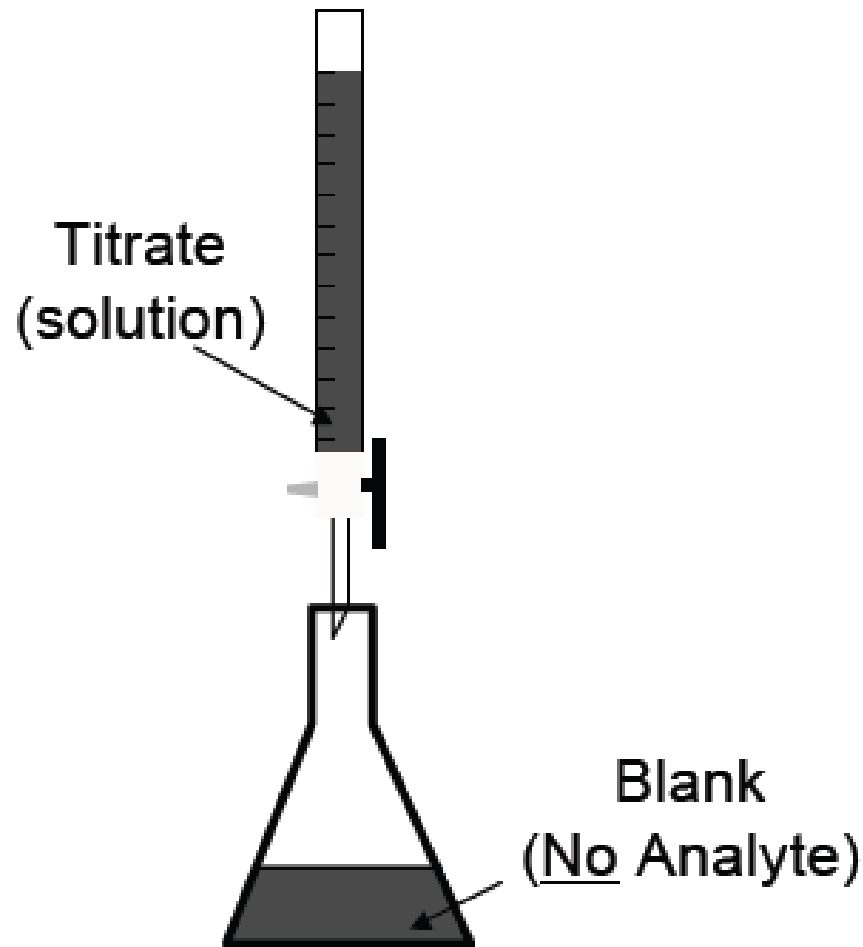
- It is necessary to carry out a blank experiment without aspirin in order to minimize any error
- Error( change in the strength of alkali media ) this may be due to
  - interaction of the reagent (NaOH) with glass
  - absorption of atmospheric CO<sub>2</sub> to form sodium carbonate , in the back titration with acid , the liberated CO<sub>2</sub> cause color change of the indicator before the actual end point



## Blank Titration:

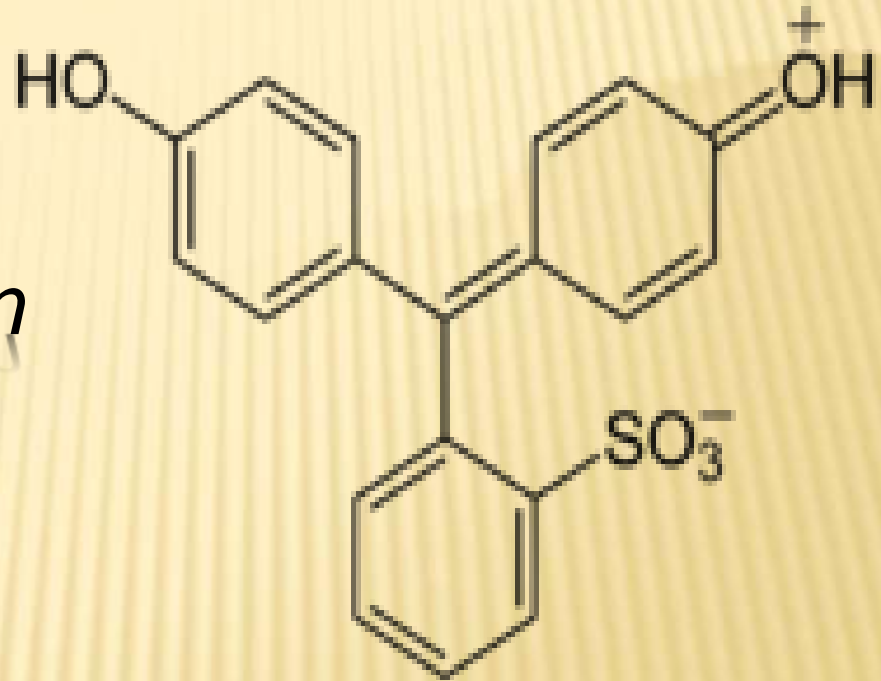
*1- To minimize any error due to small unavoidable losses.*

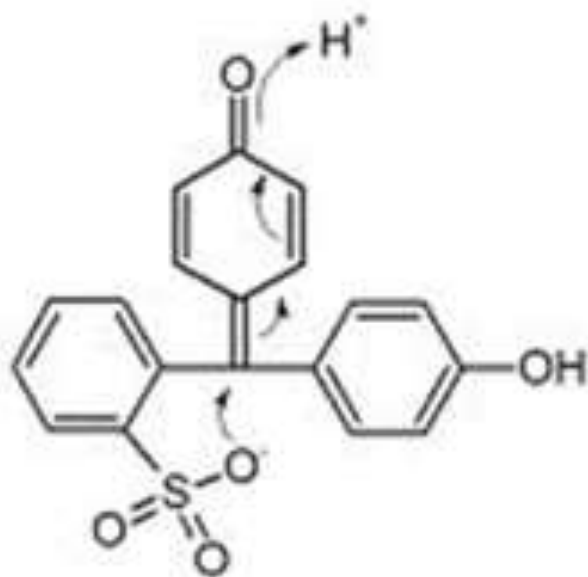
*2- Heating & cooling an alkaline liquid results in an apparent change in the strength if certain indicators are used.*



# Phenol Red Indicator:

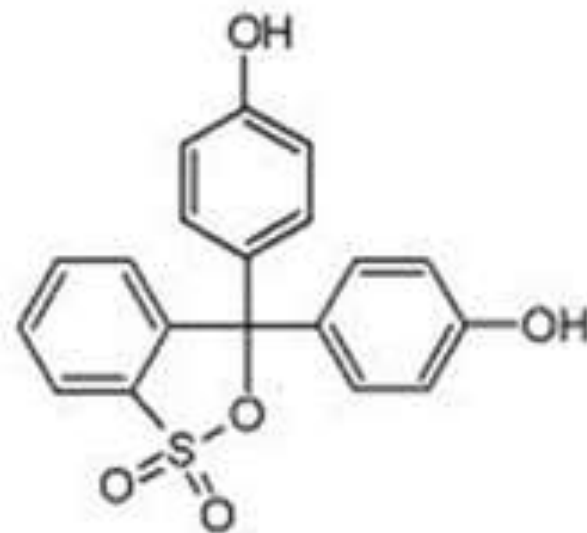
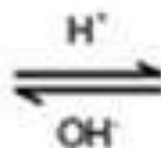
Also known as  
phenolsulfonphthalein  
(PSP) is a pH  
indicator





8.2

*Basic media*  
*Pink to red*



6.4

*Acidic media*  
*Yellow*



# *Chemical Factor:*

1 mole of aspirin  $\equiv$  2 moles of NaOH

1 M.wt. of aspirin  $\equiv$  2 Eq.wt. NaOH

180/2 of aspirin  $\equiv$  1000 ml of 1N NaOH

90/2 of aspirin  $\equiv$  1000 ml of N/2 NaOH

0.045 g of aspirin  $\equiv$  1ml of N/2 NaOH

Volumes should be corrected to 0.5 N since procedure require that.

## **Example:**

---

If you have tablets of 0.3 g aspirin/tab., Then to do analysis take at least 20 tablets, and powder them.

$20 \times 0.3 = 6$  g of pure aspirin.

Weigh the powder if it's for e.g. 6.65 g then set a proportion

$$6.65 / 6 = x / 0.3$$

X = ---- g of powder should be assayed

Do titration and correct the normality.

# PROCEDURE

- ✗ Dissolve the unk. In 5 ml ethanol 95% then add 25 ml 0.5 N of NaOH solution (use stopper conical flask ); stand 30 minute then titrate with 0.5 N HCl using ph.ph. Indicator
- ✗ blank titration without aspirin
- ✗ Calculation :  $V_1$  blank -  $V_2$  excess =  $V_3$  volume of NaOH react with aspirin

$V_3 * \text{chemical factor}(0.045) = x$  gm of aspirin in the unk.

$$\begin{array}{l} \text{## } V_2 \text{ excess} \quad N \cdot V = N \cdot V \\ \quad \quad \quad 0.5 \cdot x = \text{known} \cdot \text{From burette} \end{array}$$



# Home Work:

---

Define the followings: ✕

1-Titration. ✕

2- End point. ✕

3- Equivalent point. ✕

4- Indicator. ✕

5- Standard solution ✕

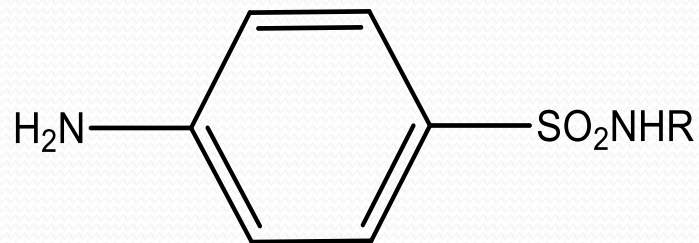
6- Molarity. ✕

7- Normality. ✕

# Sulfonamides

Sulfonamides: they are mostly antibacterial agents, act as bacteriostatic that stops the growth of bacteria by competition with PABA needed by bacteria to synthesize its folic acid, so sulfa drug is metabolite antagonist.

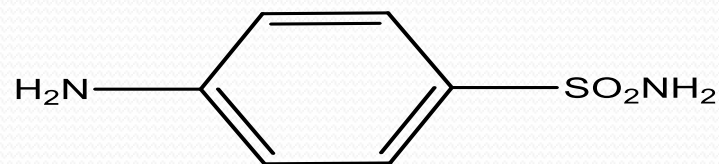
Sulfonamides are derivatives of para amino benzene sulfonamide.



## Classification of sulfonamides :

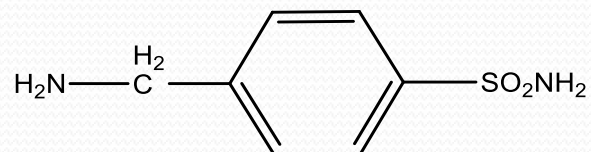
### A-antibacterial derivatives

1- aniline substituted sulfonamides: e.g sulfanilamide



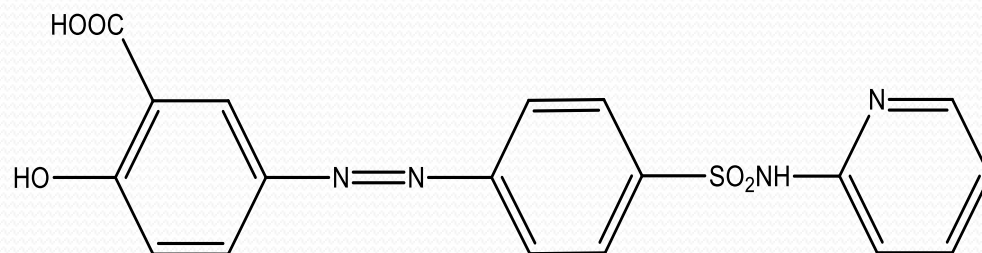
sulfanilamide

2- non-aniline substituted sulfonamides e.g.mafenide



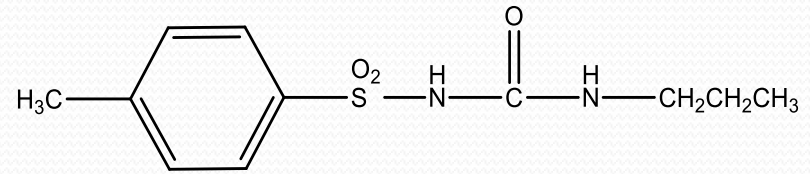
mefenide

3-prodrug that produce sulfonamide e.g. sulfasalazine



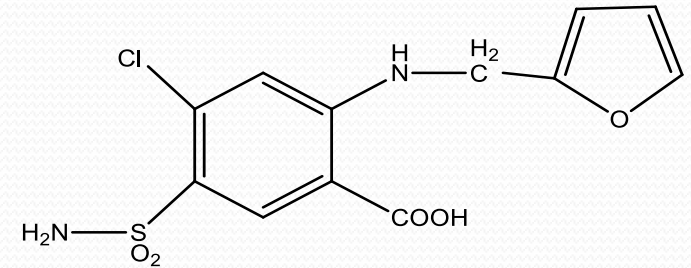
# B-non -antibacterial sulfonamides :

1-oral diabetic drugs e.g. tolbutamide  
(sulfonyl urea derivatives)



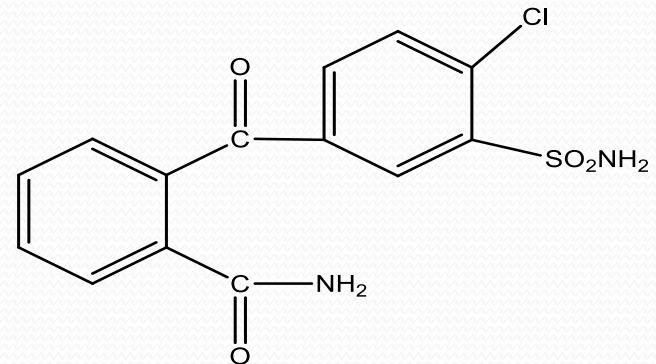
tolbutamide

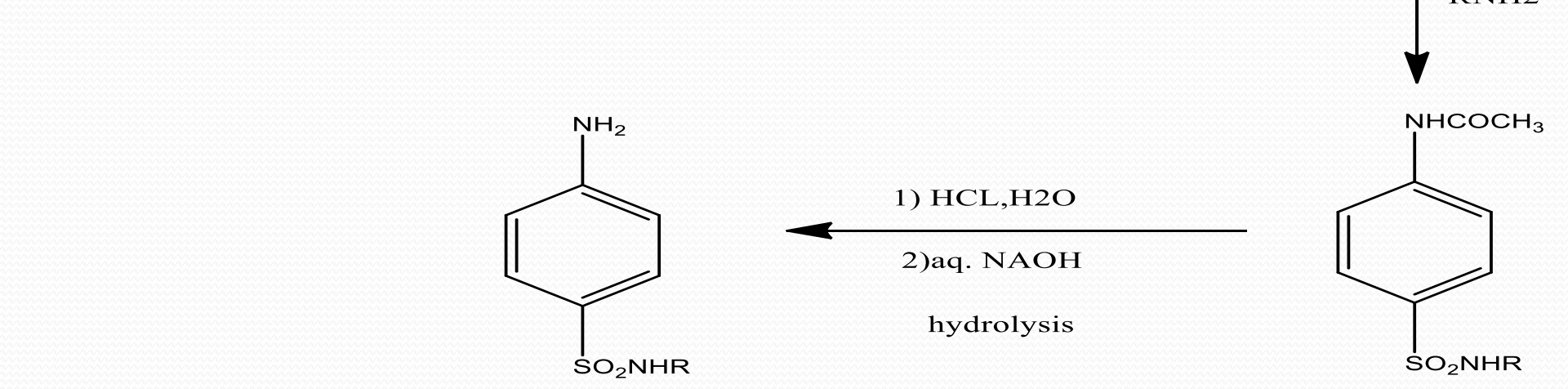
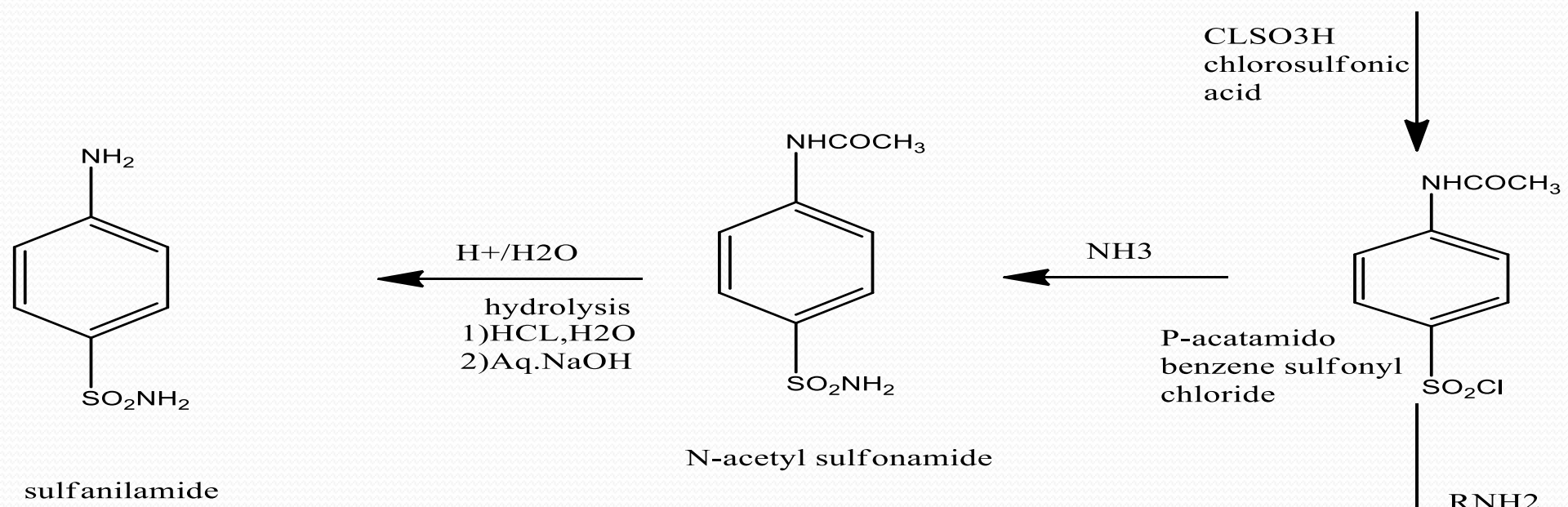
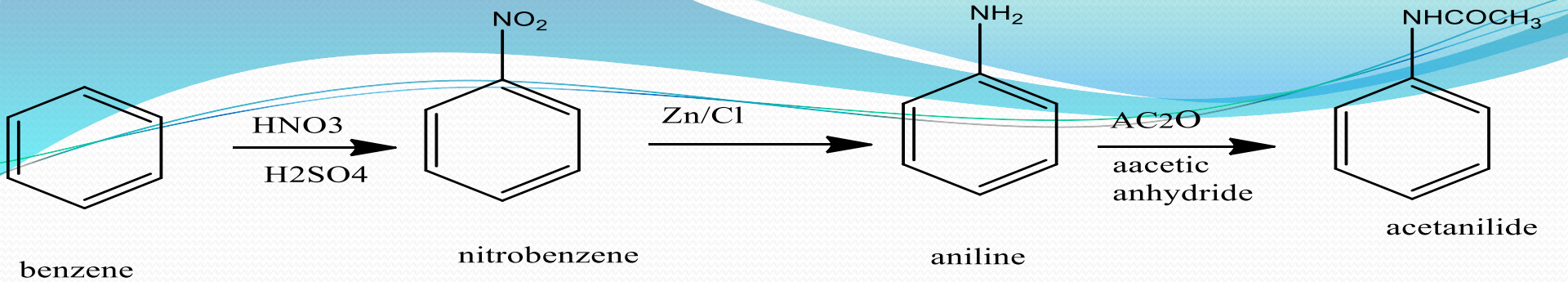
2-potent diuretics e.g. furasemide



furasemide

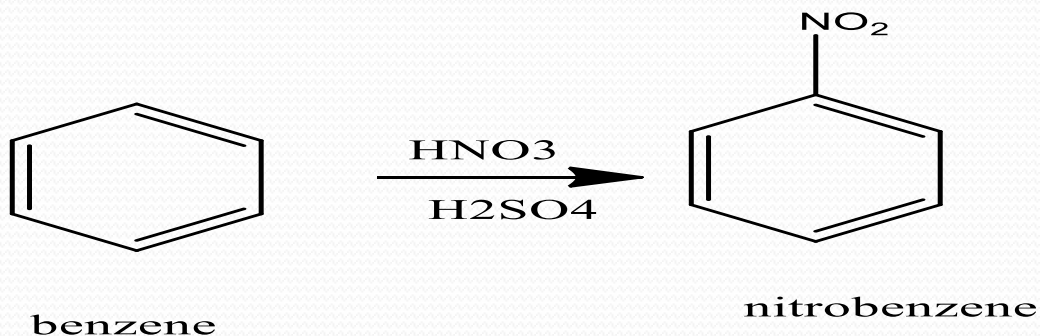
Another example :chlorthalidone (sulfonyl benzoic acid derivatives)



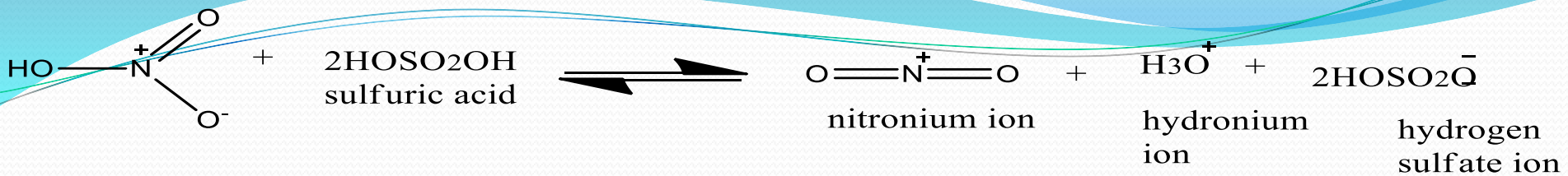


## Nitration of benzene:

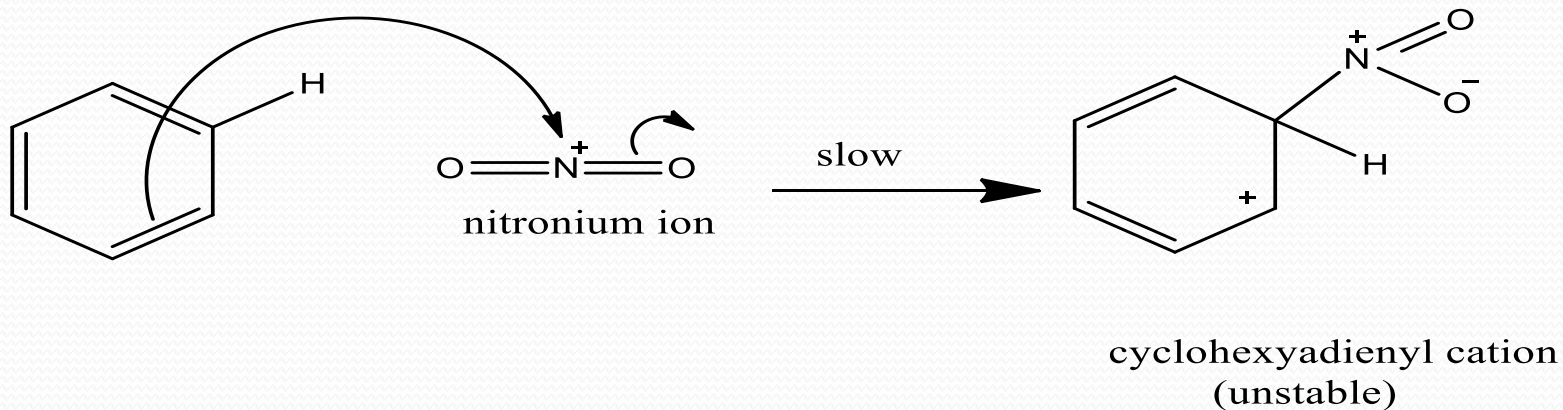
Aromatic nitration of benzene is a direct nitration using conc.  $\text{HNO}_3$  in the presence of conc.  $\text{H}_2\text{SO}_4$ .



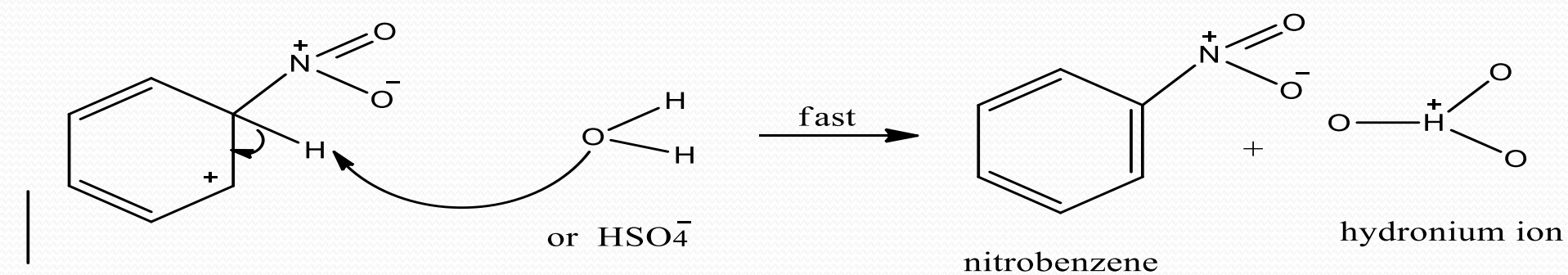
mechanism of the reaction:



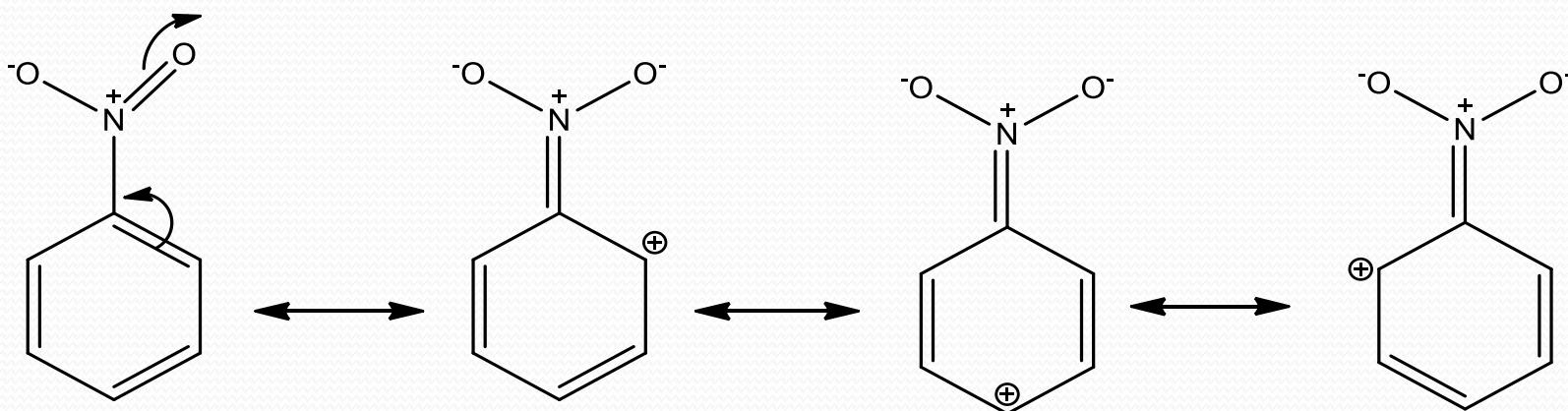
step 1:



step 2:



# Resonance of nitrobenzene



## Properties of nitrobenzene :

1-heavy oily liq. (pale yellow).

2-has high B.Pt 210 c (if its pure)

3-has a characteristic odor like almond.

4-it is insoluble in water and soluble in org. solvent to be extracted like ether.

5-it is volatile with steam.



## Procedure:

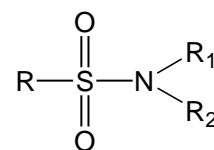
- 1-put 5ml of D.W in a conical flask.
- 2-add carefully 12.5ml of conc.  $\text{H}_2\text{SO}_4$ ,cool.
- 3- add carefully 7.5ml of conc.  $\text{HNO}_3$ ,cool.
- 4-add carefully 9ml of benzene ,cool.
- 5-insert thermometer (temp.should be between 55-60 c) and shake vigorously to induce reaction ,if the temp. more than 60c ,cool in ice bath and if the temp. below 55c ,heat on water bath ,this process continue for 10 minutes .
- 6-cool and add 15ml D.W.
- 7-transfer to sep. funnel , add 10 ml ether and shake.
- 8-take the upper layer (ethereal layer ) which contain nitrobenzene ,collect in a beaker ,dry it with drying agent.

## Note :

Optimum temp. of the reaction is necessary between 55-60 c because high temp. should be avoided since dinitration ,polynitration is more likely to occur also oxidative breakdown of the aromatic ring may occur.

## Sulfonamides

The sulfonamide antimicrobial drugs were the 1<sup>st</sup> effective chemotherapeutic agents that could be used for the cure of bacterial infection in human.

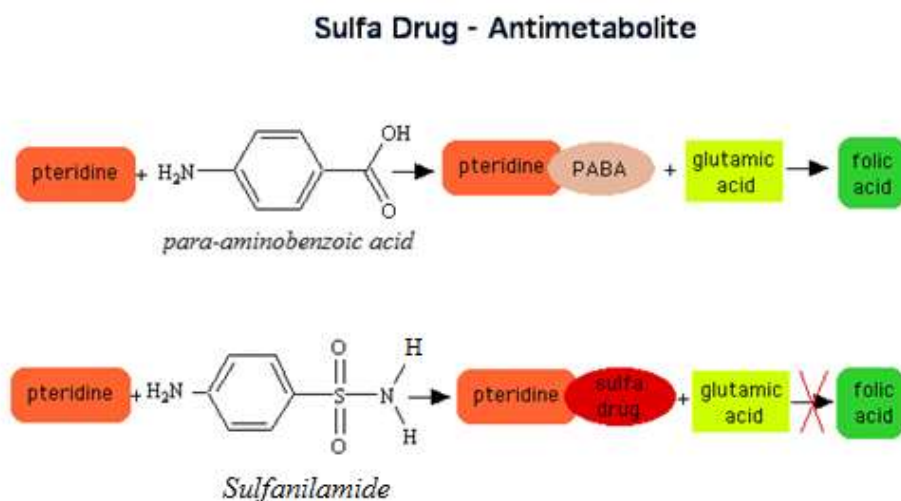


General Sulfonamide Structure

### **Mechanism of action:**

They are structural analogs of PABA that competitively inhibit the action of dihydropteroate synthase, preventing the addition of PABA to pteridine diphosphate and blocking the net biosynthesis of folate coenzymes. This action arrest bacterial growth and cell division so they are bacteriostatic.

Folate coenzymes are biosynthesized from dietary folic acid in humans and other organisms. Bacteria and protozoa must biosynthesize them from PABA and pteridine diphosphate.



**On the basis of their use Sulfonamides can be grouped in to :**

- a- Oral absorbable agents such as sulfamethoxazole.
- b- Oral nonabsorbable agents such as sulfasalazine.
- c- Topical agents such as sodium sulfacetamide ophthalmic drops.

## ***Nomenclature of the sulfonamide:***

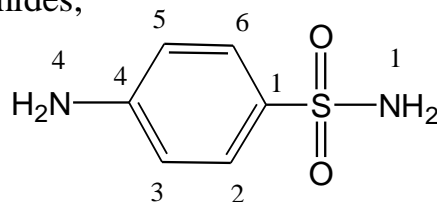
### ***A- The Antibacterial Sulfonamides:***

1- Aniline substituted sulfonamides,

( *the Sulfanilamides* ).

e.g. : Sulfanilamide,

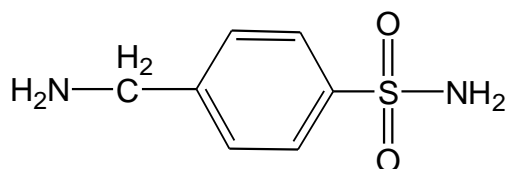
*4-aminobenzenesulfonamide.*



2- Nonaniline substituted sulfonamides.

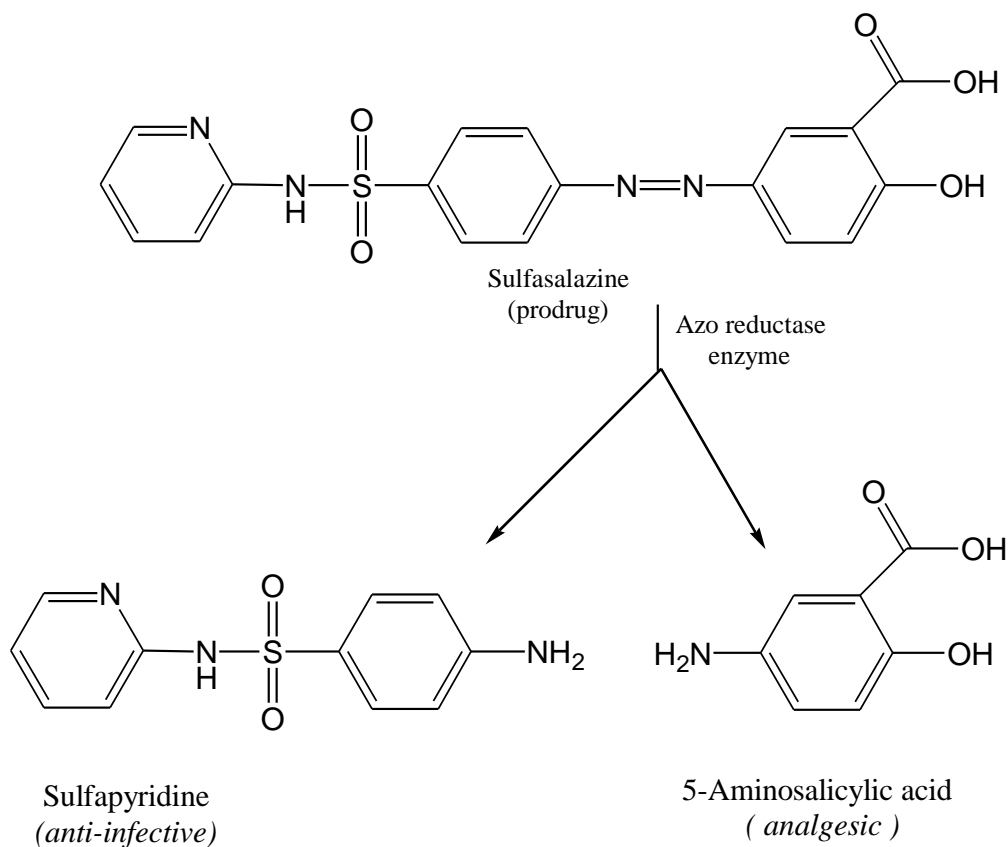
e.g. : Mafenide, 4-(aminomethyl)

*benzenesulfonamide.*



3- Prodrugs that reacts to generate active sulfanilamides.

e.g. Sulfasalazine , 5-[*p*-(2-pyridylsulfamoyl)phenylazo] salicylic acid.

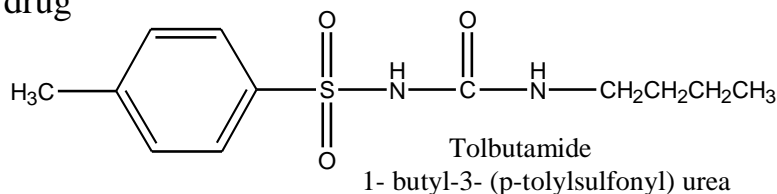


### ***B- The Non-Antibacterial Sulfonamides:***

There are other commonly used drugs that are sulfonamides or sulfanilamides. Among these are:

1- The oral hypoglycemic drug

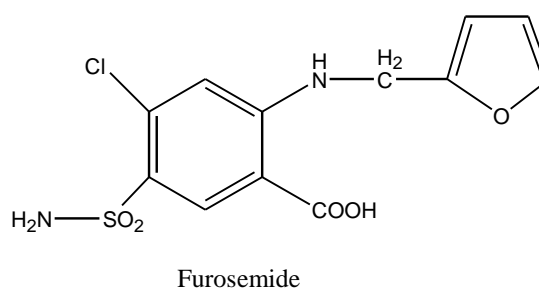
e.g. :Tolbutamide.



2- The diuretic Furosemide,

*4-chloro-2-(furan-2-ylmethylamino)*

*- 5-sulfamoylbenzoic acid.*

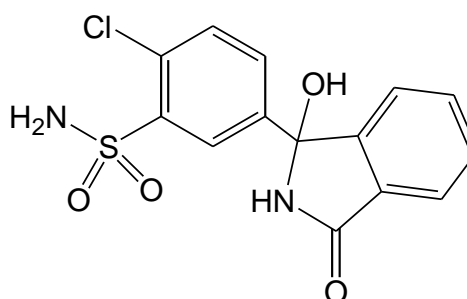


3- Other diuretic Chlorthalidone,

*2-chloro-5-(1-hydroxy-3-oxo-*

*2,3-dihydro-1H-isoindol-1-yl)*

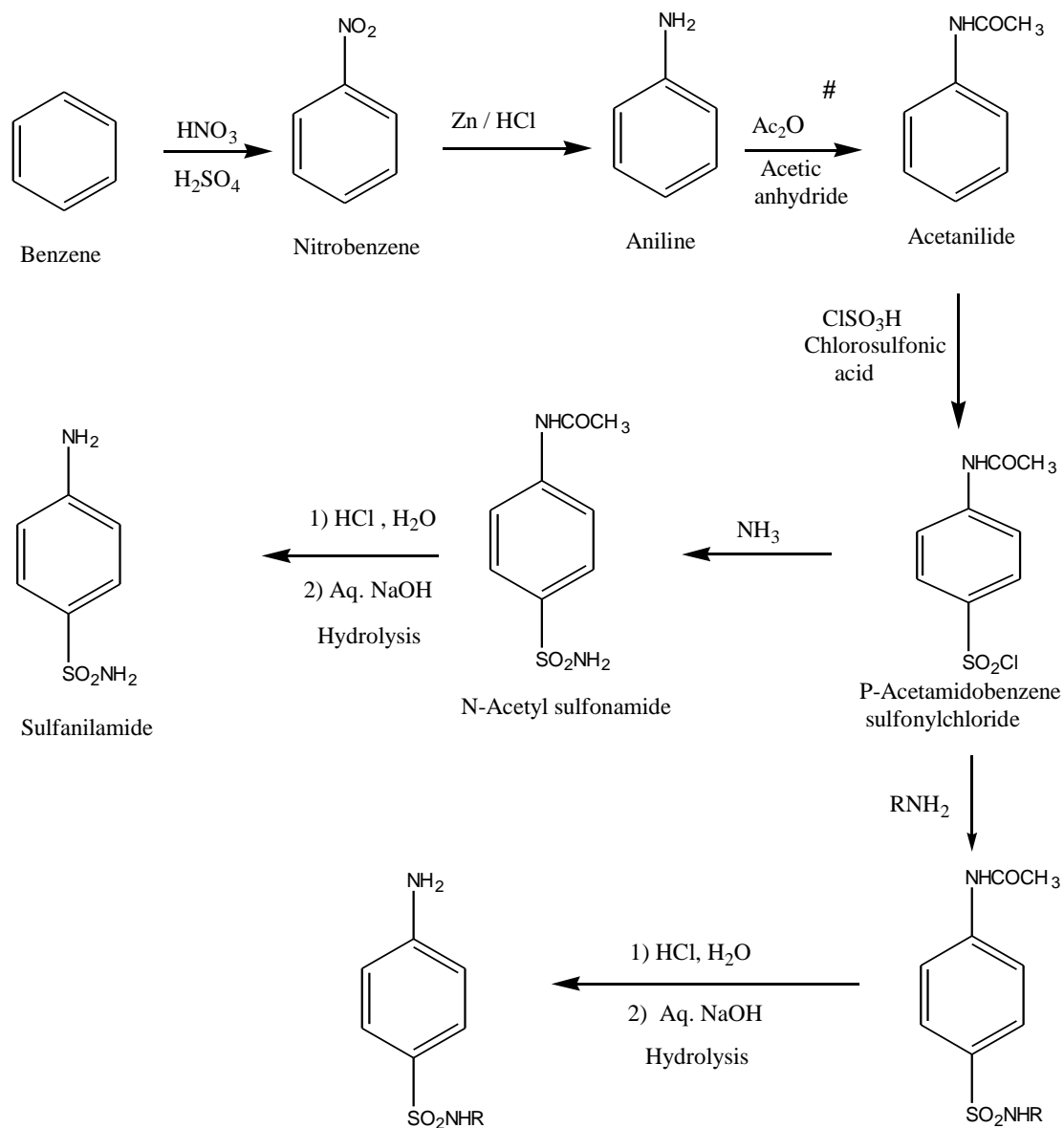
*benzene-1-sulfonamide*



### ***Preparation of sulfa drugs:***

The preparation of sulfonamides is very similar until the last step. The procedure is simple and one can start with benzene or a host of other intermediates. The Chlorosulfonation of acetanilide is considered to be the method of choice.

*The sequence of reactions is as follows:*



---

# Acetylation of aniline using acetic anhydride is done for protection of the amine group of aniline.

## ***Nitration of Benzene:***

The nitration of benzene is conducted with a mixture of conc. nitric and conc. sulfuric acid ( *Nitrating mixture* ) diluted with a small amount of water.

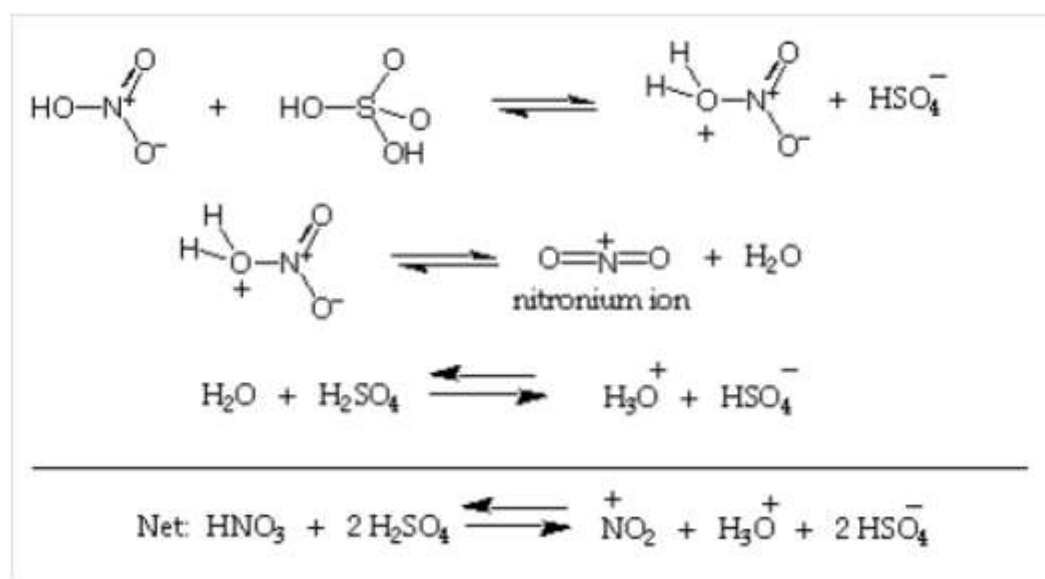
*Generally*, in its typical reactions the benzene ring serves as a source of electrons, i.e. as a base\*, thus the compounds with which it reacts are deficient in electrons, i.e. electrophilic reagents or acids. So the typical reactions of the benzene ring are **Electrophilic Aromatic Substitution** reactions ( **EAS** )\*\*.

### ***Mechanism of Nitration:***

The commonly accepted mechanism for nitration with a mixture of Nitric acid and Sulfuric acid involves the following sequence of reactions:

#### ***Step I:***

The generation of the electrophile.



Step I generates the nitronium ion  $\text{NO}_2^+$  (the electrophilic reagent). Sulfuric acid serves as the acid and the much weaker nitric acid serves as a base. The very strong acid  $\text{H}_2\text{SO}_4$  causes  $\text{HNO}_3$  to ionize in the sense  $\text{HO}^- \dots \text{NO}_2^+$ , rather than in the usual way,  $\text{H}^+ \dots \text{ONO}_2^-$ . Needing electrons nitronium ion finds them in the  $\pi$  cloud of benzene ring.

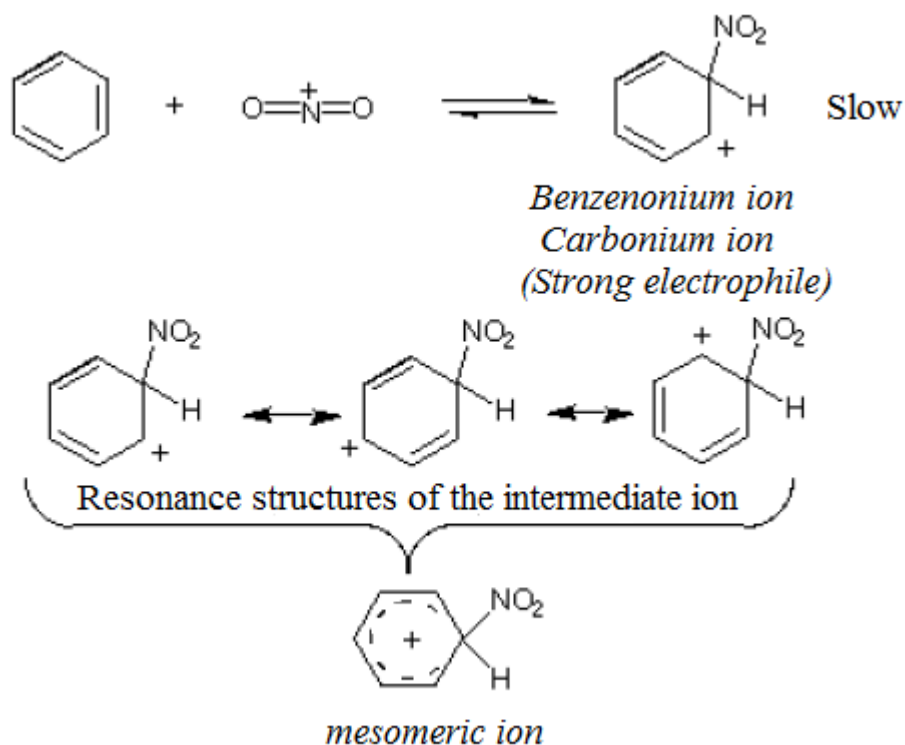
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\* *Lewis base is an electron – pair donor.*

*Lewis acid is an electron –pair acceptor.*

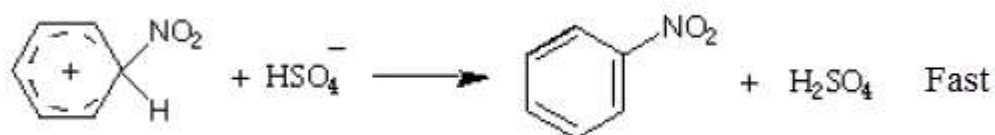
**Step JJ:**

Electrophilic attack on aromatic  $\pi$  system forms the carbocation.



**Step JJJ:**

Attachment of the nitronium ion to the aromatic ring destroys the aromatic character of the ring.  $\text{HSO}_4^-$  abstracts a proton to yield the substitution product (Nitrobenzene) which retains the resonance-stabilized ring.



---

\*\* Mesomeric effect: is the re-distribution of electrons which takes place in unsaturated and especially in conjugated systems via their  $\pi$ -orbitals.



### ***Properties of Nitrobenzene :***

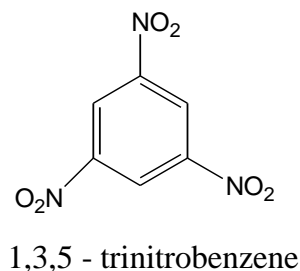
- 1- Heavy oily liq. (pale yellow).
- 2- Has high B.p 210 °C, (if its pure)
- 3- Has a characteristic odor like almond.
- 4- It is insoluble in water and soluble in organic solvents to be extracted like ether.
- 5- It is volatile with steam.

### ***Procedure:***

- 1- Put 5 ml of *D.W* in a conical flask.
- 2- Add 12.5ml of conc. *H<sub>2</sub>SO<sub>4</sub>* carefully and cool.
- 3- Add 7.5 ml of conc. *HNO<sub>3</sub>* carefully and cool.
- 4- Add 9 ml of *Benzene* carefully and cool.
- 5- Insert a thermometer ( the temp. should be between **55-60** °C ), shake vigorously to induce reaction , if the temp. raised above **60** °C cool in an ice bath and if the fall below **55** °C then heat on a water bath , this process will continue for 10 minutes .
- 6- Cool and add 15ml *D.W*.
- 7- Transfer the solution to a separatory funnel, add 10 ml *Ether* and shake.
- 8- Take the upper layer (ethereal layer ) which contain the prepared *Nitrobenzene* , collect the product in a beaker and dry it with a drying agent.

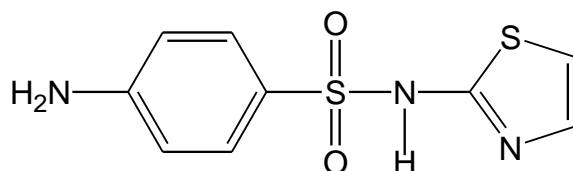
### **Notes:**

- 1- Care should be taken when working with ether ( flammable ), keep away all flames.
- 2- Do not distill to dryness, if traces of m- dinitrobenzene is present in the mixture they may decompose explosively.
- 3- Optimum temperature of the reaction is necessary  
Between 55-60 °C , high temp. should be avoided since dinitration and polynitration are more likely to occur also oxidative breakdown of the aromatic ring may occur.

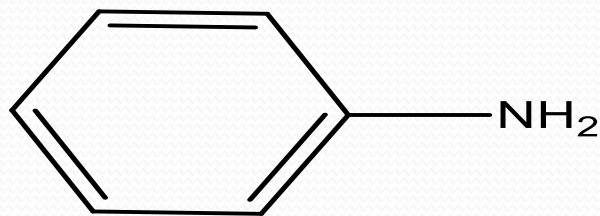


### **Post lab exercises:**

- 1- What is the structure of benzenonium ion?
- 2- What is the electrophile produced from the reaction of sulfuric acid and nitric acid?
- 3- Why is it important to maintain the temperature low during the addition of nitric acid to sulfuric acid?
- 4- Propose a synthetic scheme for the synthesis of the drug sulfathiazole from benzene and any necessary amine?



# Preparation of aniline

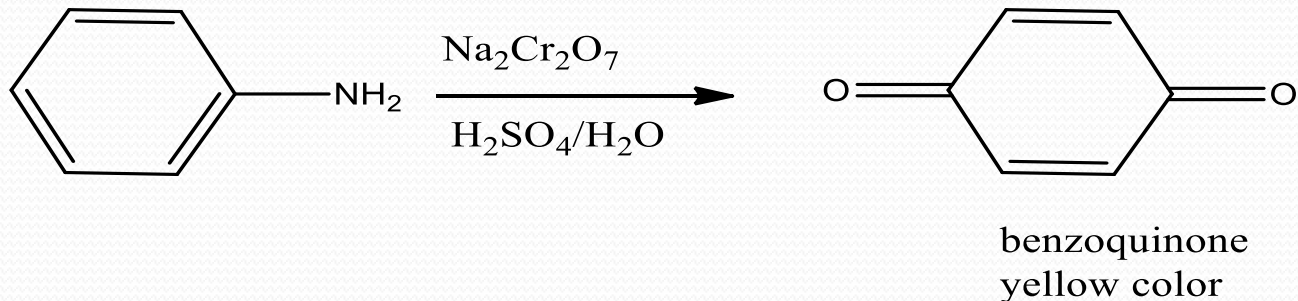


aniline

\*Aniline is the simplest aromatic amine

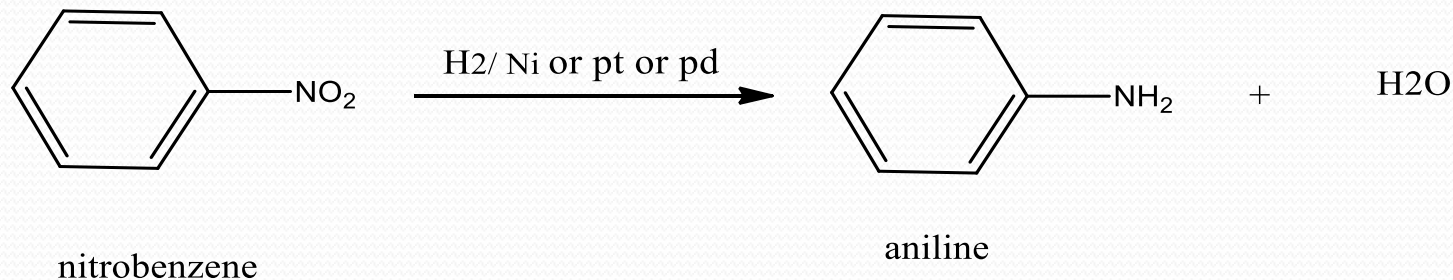
## Physical properties

- Has B.P = 184c and it has bitter taste.
- Solubility:
- It is colorless liq. When freshly prepared but on exposure to air and light it develops a deep brown color .
- It is used for manufacture of dyes, drugs, perfumes.....
- When aniline react with dichromates ion, its oxidized and giving p-benzoquinone

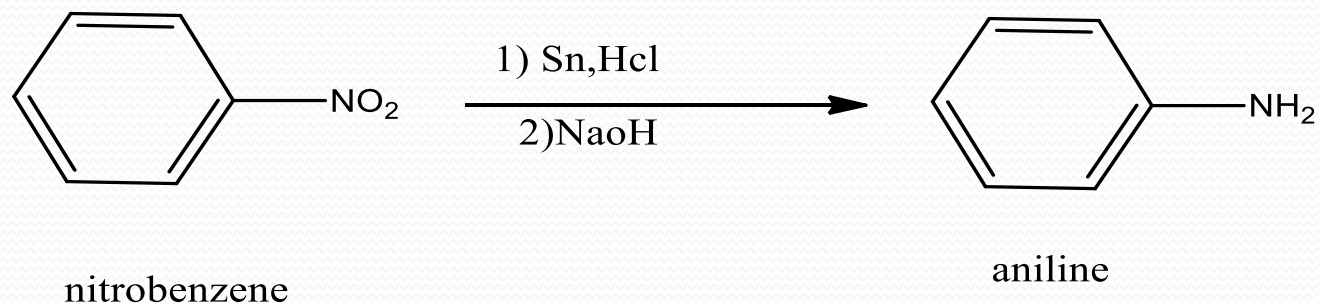


# Preparation of aniline

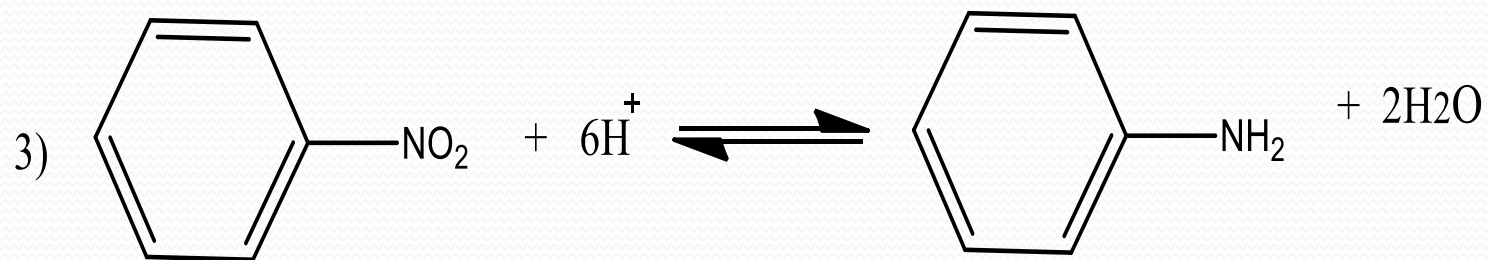
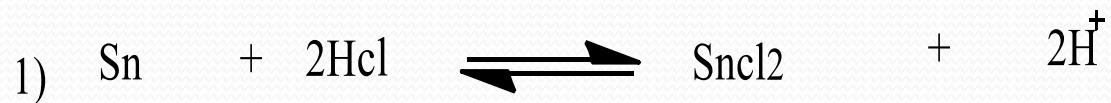
1-catalytic hydrogenation over platinum, palladium or nickel is often used.



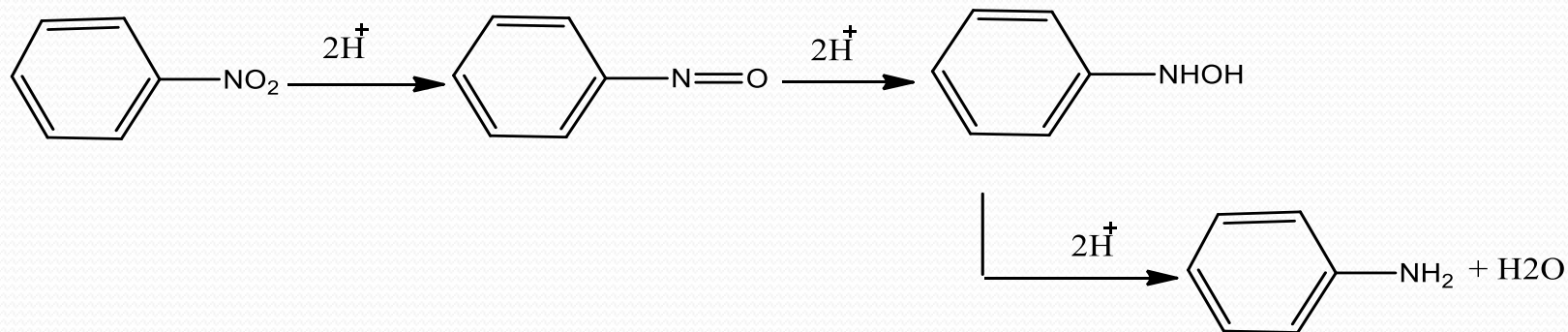
2-chemical reduction by using typical reducing agents including tin(sn), iron(Fe) or zinc (zn) in hydrochloric acid.



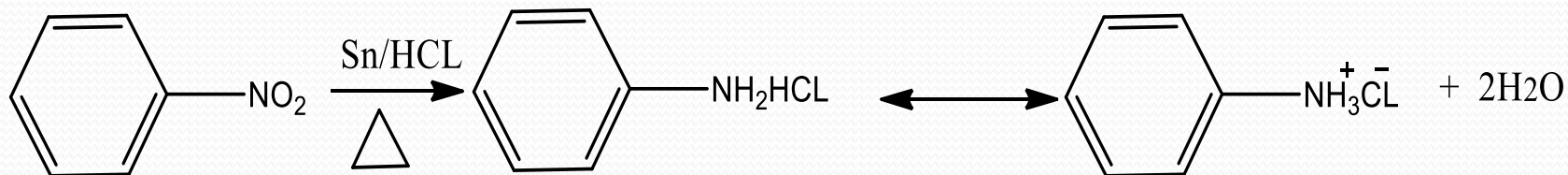
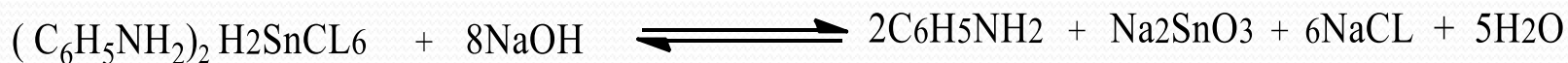
When a mixture of nitrobenzene and tin is treated with HCL :



So each NO<sub>2</sub> group need 6H<sup>+</sup> to be reduced to NH<sub>2</sub> group

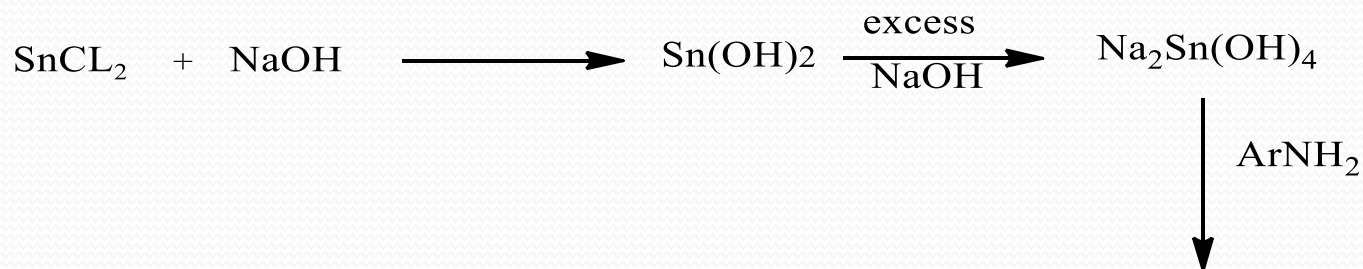


The PH adjustment with sodium hydroxide in the last step :



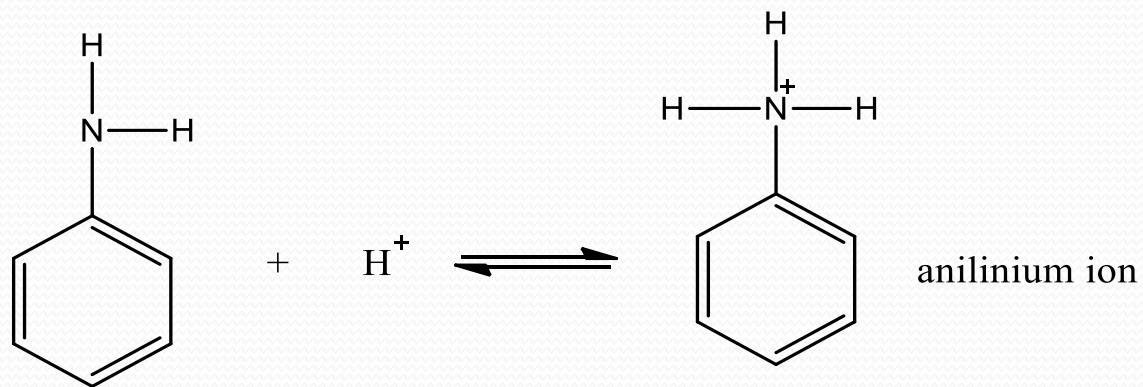
anilinium chloride salt  
or anilinium hydrochloride salt

\* Reduction of aniline is done in acidic medium not in alkaline because in alkaline medium the following reaction take place:

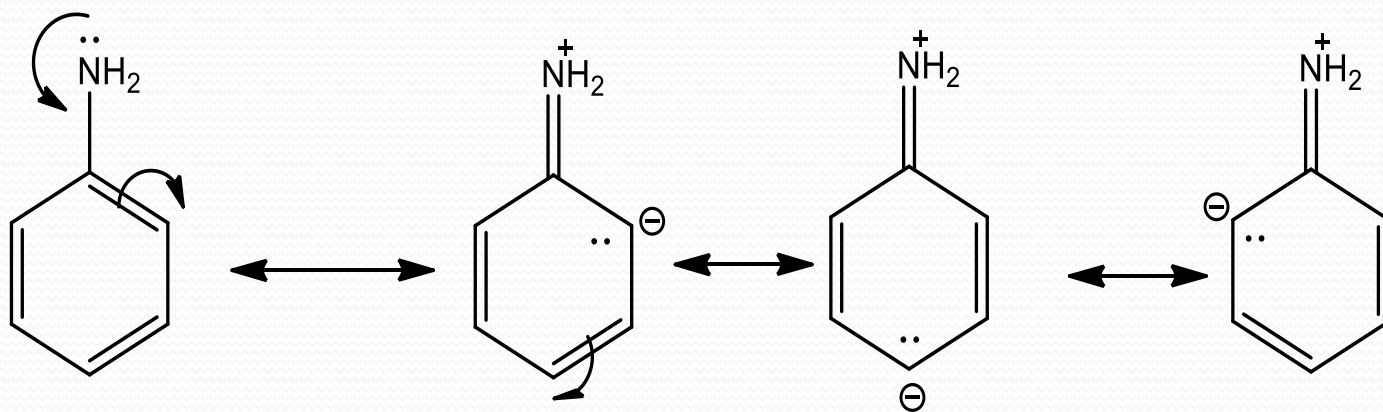


many side products  
i.e  $\text{C}_6\text{H}_5\text{NO}=\text{NC}_6\text{H}_5$   
 $\text{C}_6\text{H}_5\text{N}=\text{NC}_6\text{H}_5$   
azo compounds

## Basicity of aniline :



## Resonance of aniline:



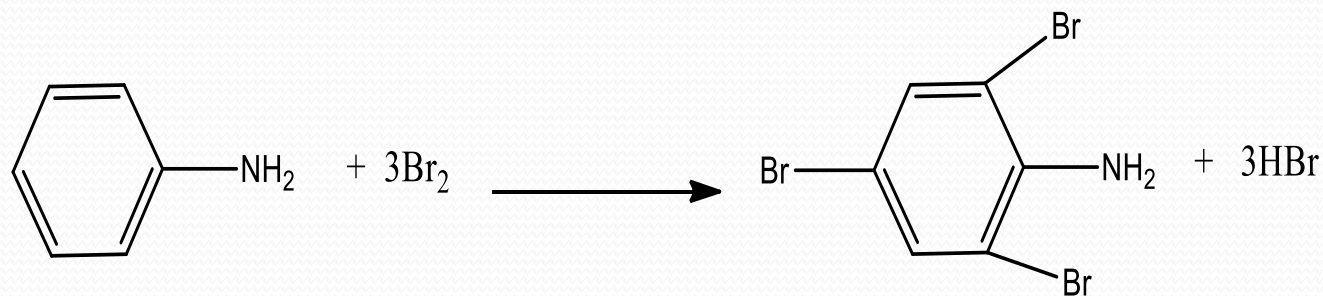


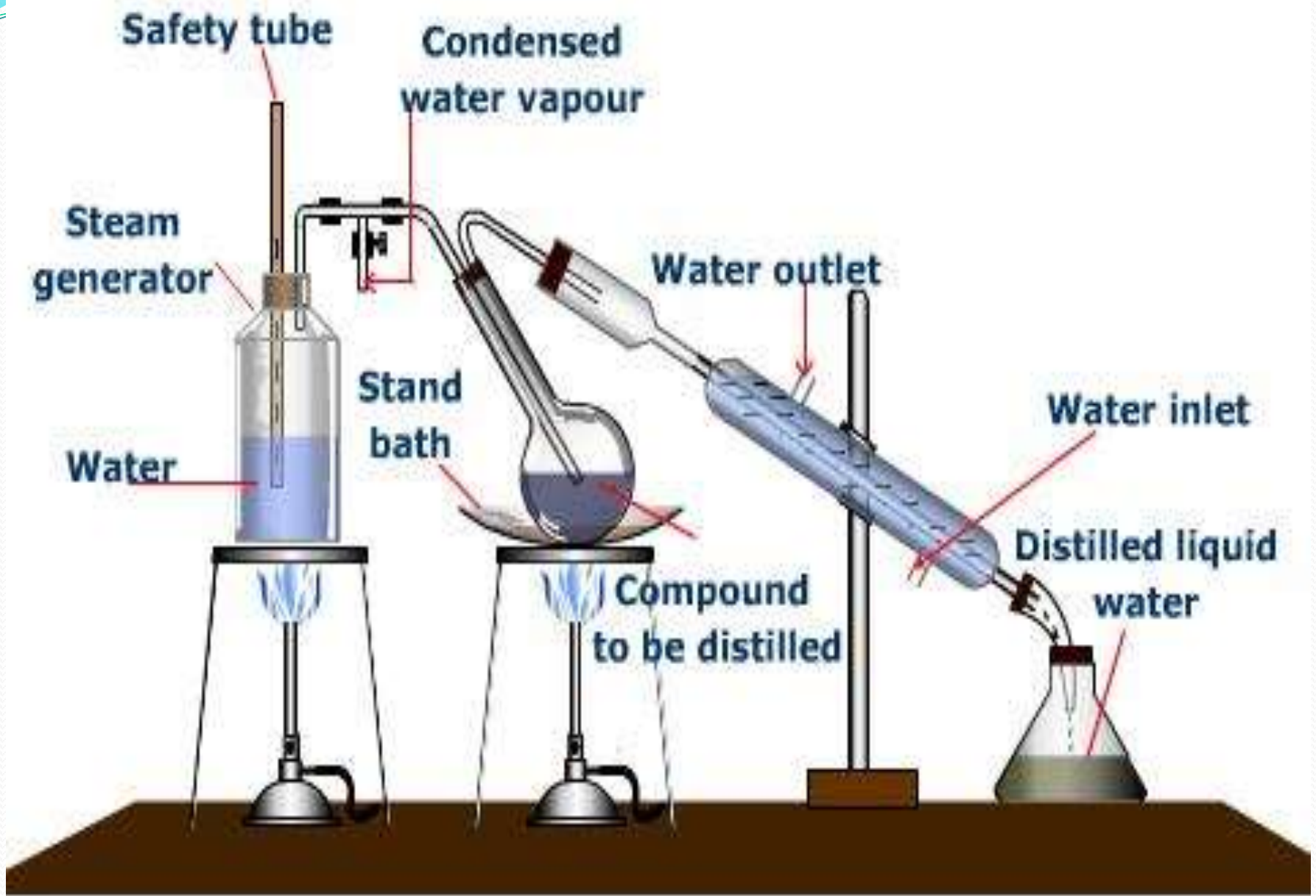
## Notes:

- sulfonamides derived from primary amines have an acidic hydrogen and dissolve in alkali but precipitate out when the mixture is acidified.

Sulfonamides derived from secondary amines are insoluble in alkali and appear as precipitate which persist upon acidification of the mixture.

- When aniline is shaken with bromine water, 2,4,6-tribromoaniline is yielded as a white ppt.





# Steam distillation :

- It is used for purification and separation of liq. And solids (two immisible sub.s)
- For separation of slightly vol. water insoluble sub.s from non volatile material by means of steam.
- It is convenient for purification of high B.pt substances because :...
- Steam dist. Offers the advantage of selectivity ,since.....
- It is useful for recovery of anon steam –volatile solid from its solution on high boiling solvent such as nitrobenzene (B..Pt. 210 c) all traces of the solvent can be eliminated and the temp. can be kept low.
- For the separation of such compounds from mix. Containing non volatile org. compounds from natural sources(plants) .
- for separation of such compounds from mixture containing non – volatile impurites .