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# SALICYLATES


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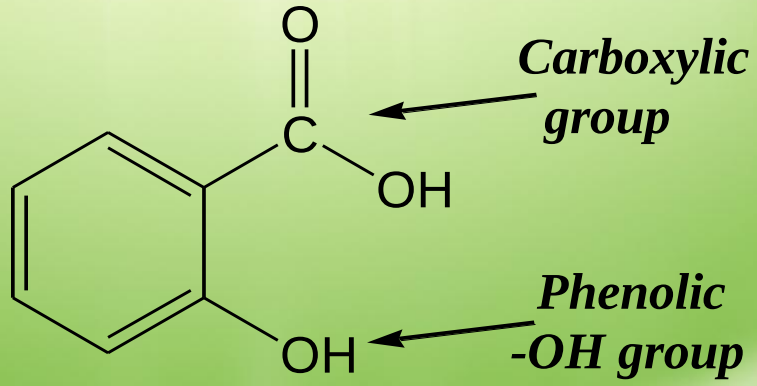
# Historically,

**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.

Salicylic acid ( from *Latin* *salix* , *willow tree*, from the bark of which the substance used to be obtained ) is a monohydroxybenzoic acid.




## Many derivatives of S.A. 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 Salicylic acid.

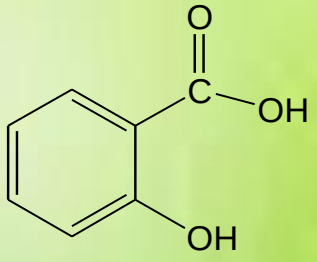
## Types of S.A. derivatives:

### TYPE I:

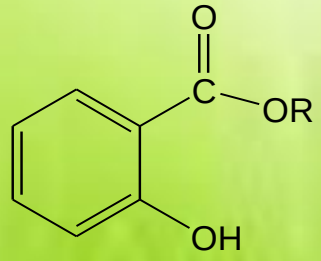
**Represents those that are formed by modifying the carboxyl group of S.A. , ( e.g. salts, esters or amides ) .**

### TYPE II:

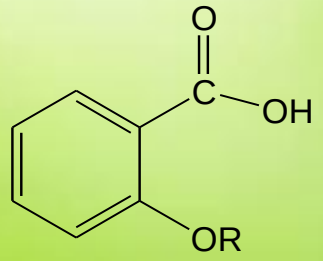
**Represents those that are derived by substitution on –OH group of S.A.**



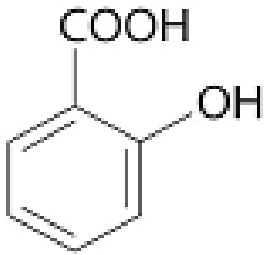
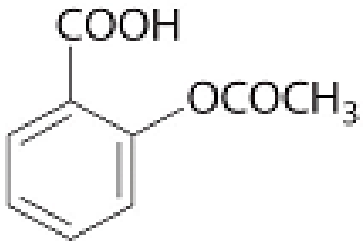

Salicylic acid




Type I derivative

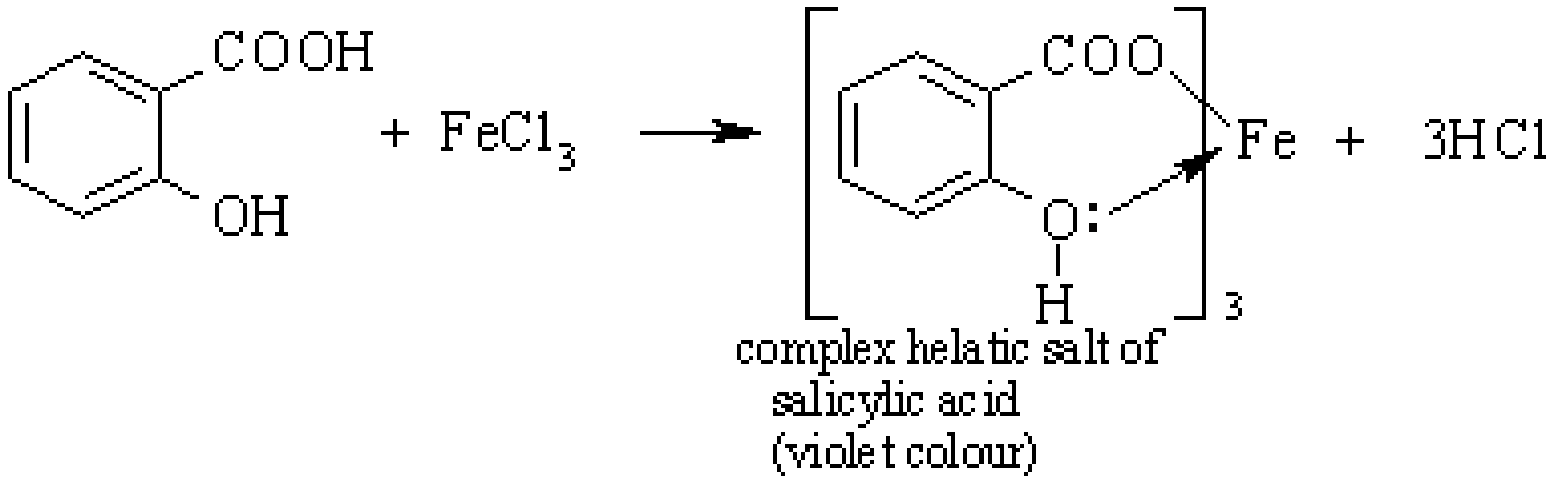



Type II derivative

| Properties | *Salicylic acid* | *Aspirin* |
|---|---|---|
| **Structure** |  Active substance |  *Type II* derivative of S.A. It's a prodrug |
| **Systematic (IUPAC) name** | 2-Hydroxybenzoic acid | 2-(acetoxy)benzoic acid |
| **Molecular formula** | $C_7H_6O_3$ | $C_9H_8O_4$ |
| **Molar mass** | 138.12 *g/mol* | 180.157 *g/mol* |
| **Melting point** | 158.6 °C | 135 °C |
| **Boiling point** | 200 °C | 140 °C |
| **Water solubility** | 1g of S.A. is soluble in 460 ml of water 2.48 g/L (25 °C | 1g of Aspirin is soluble in 300 ml of water 3 mg/mL (20 °C) ***Why?*** |

| **Route of administration** | Externally<br>Not given orally<br>*Why?* | Given orally |
|---|---|---|

**S.A. contains phenolic - OH group and it is *ortho* to the carboxyl group. It forms a violet colored complex when reacted with $FeCl_3$.**




**$FeCl_3$ is used to detect the presence of phenol compounds in organic synthesis e.g.: examining purity of the synthesized Aspirin.**

# Preparation of S.A.:

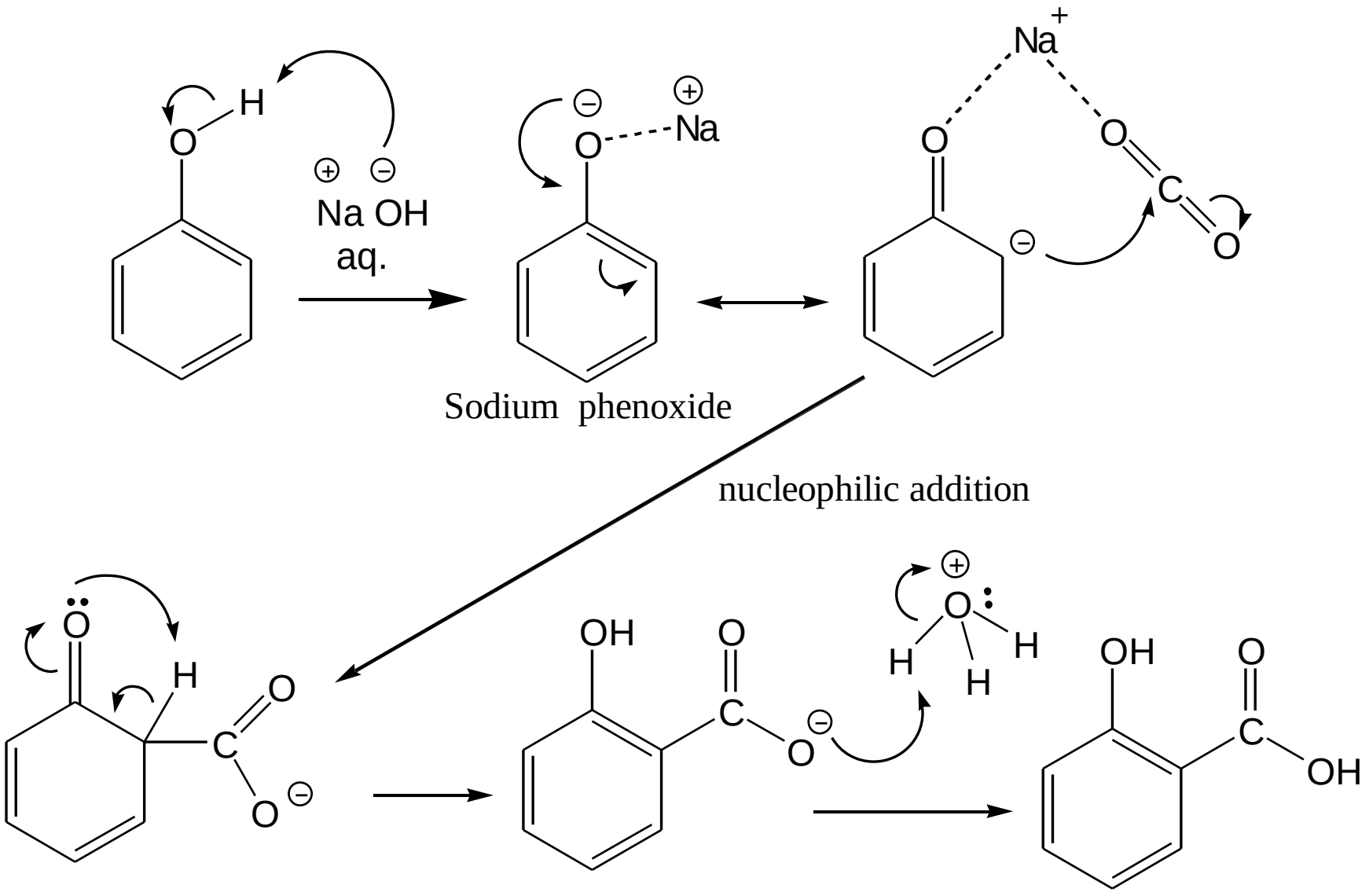
1- Kolbe reaction ( industrial method ).
2- Oxidation of salicylaldehyde.
3- Alkaline hydrolysis of ester.

## 1-Kolbe reaction :

It is a carboxylation chemical reaction that proceeds by heating sodium phenolate ( the sodium salt of phenol ) with $CO_2$ under pressure (100 atm , 125 °C), then treating the product with sulfuric acid .
The final product is an aromatic hydroxy acid which is 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 the reaction of the salicylate with acid to form the desired salicylic acid.


H
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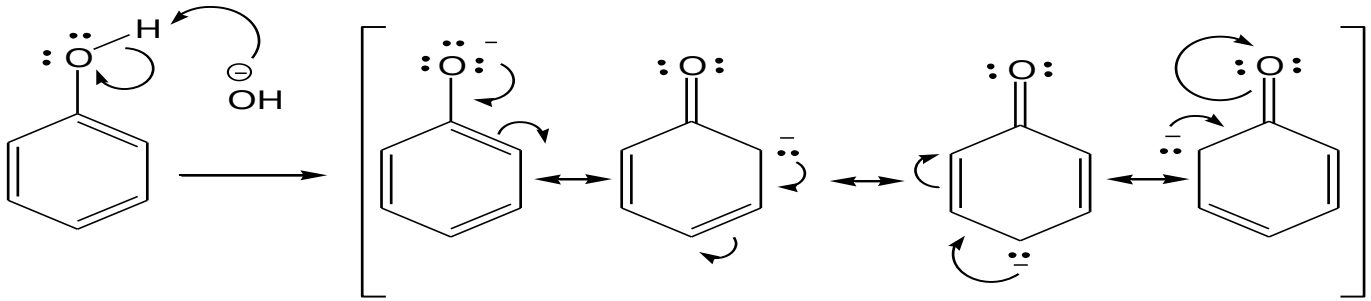
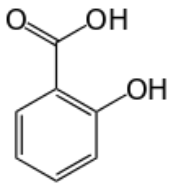
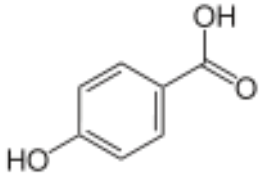


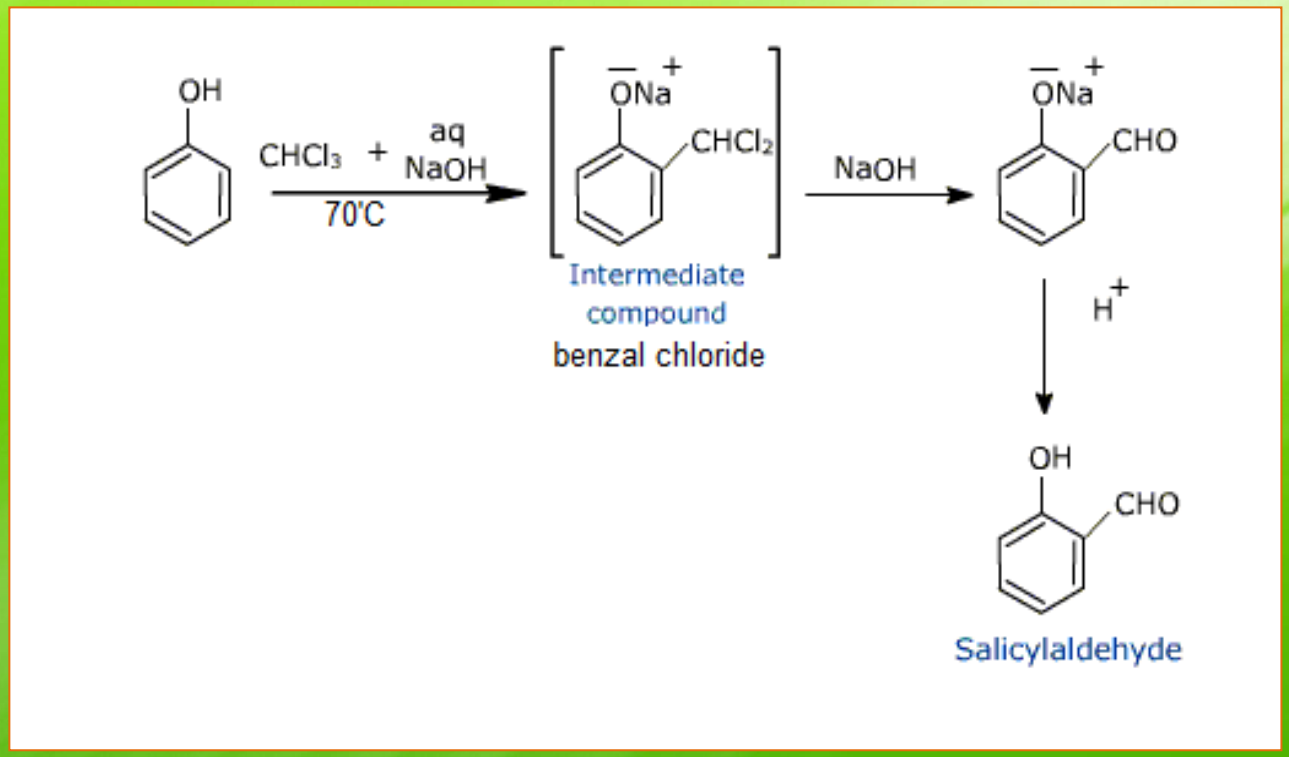
( Phenoxide anion )

**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?)***

| | | |
|---|---|---|
| ***Compound Structure*** |  |  |
| ***Compound name*** | *o*-hydroxybenzoic acid (S.A.) | *p*-hydroxybenzoic acid |
| ***Molecular formula*** | $C_7H_6O_3$ | $C_7H_6O_3$ |
| ***Molecular weight*** | 138.121 g/mol | 138.121 g/mol |
| ***Appearance*** | colorless to white crystals | white crystalline |
| ***Melting point*** | 159 °C | 214.5 °C |

# 2- Oxidation of salicylaldehyde:

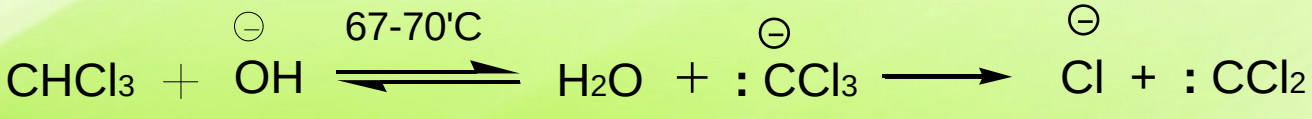
On treating phenol with chloroform in presence of sodium hydroxide an aldehyde group , a - CHO group, is introduced at ortho position of benzene ring . This reaction is known as ***Reimer – Tiemann reaction***. This results in the formation of *o* – hydroxybenzaldehyde (salicylaldehyde) and *p* – hydroxybenzaldehyde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



# MECHANISM OF THE REACTION:

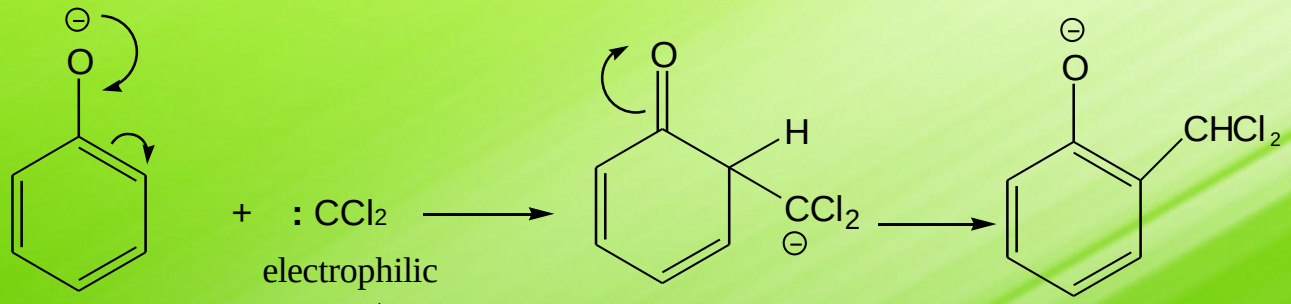
**Reimer Tiemann reaction is an electrophilic substitution reaction.**

**The first step is the generation of electrophile.**



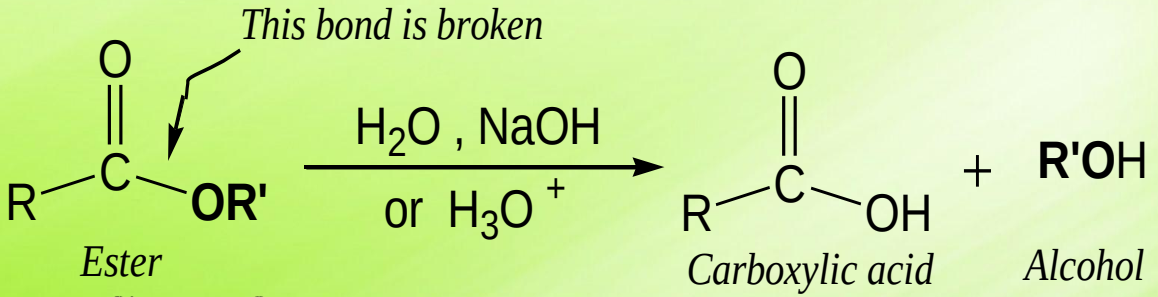

**Dichlorocarbene**
*(reactive intermediate)*
Electrophile

**Dichlorocarbene contains a sextet of electrons & thus is a strong electrophile.**



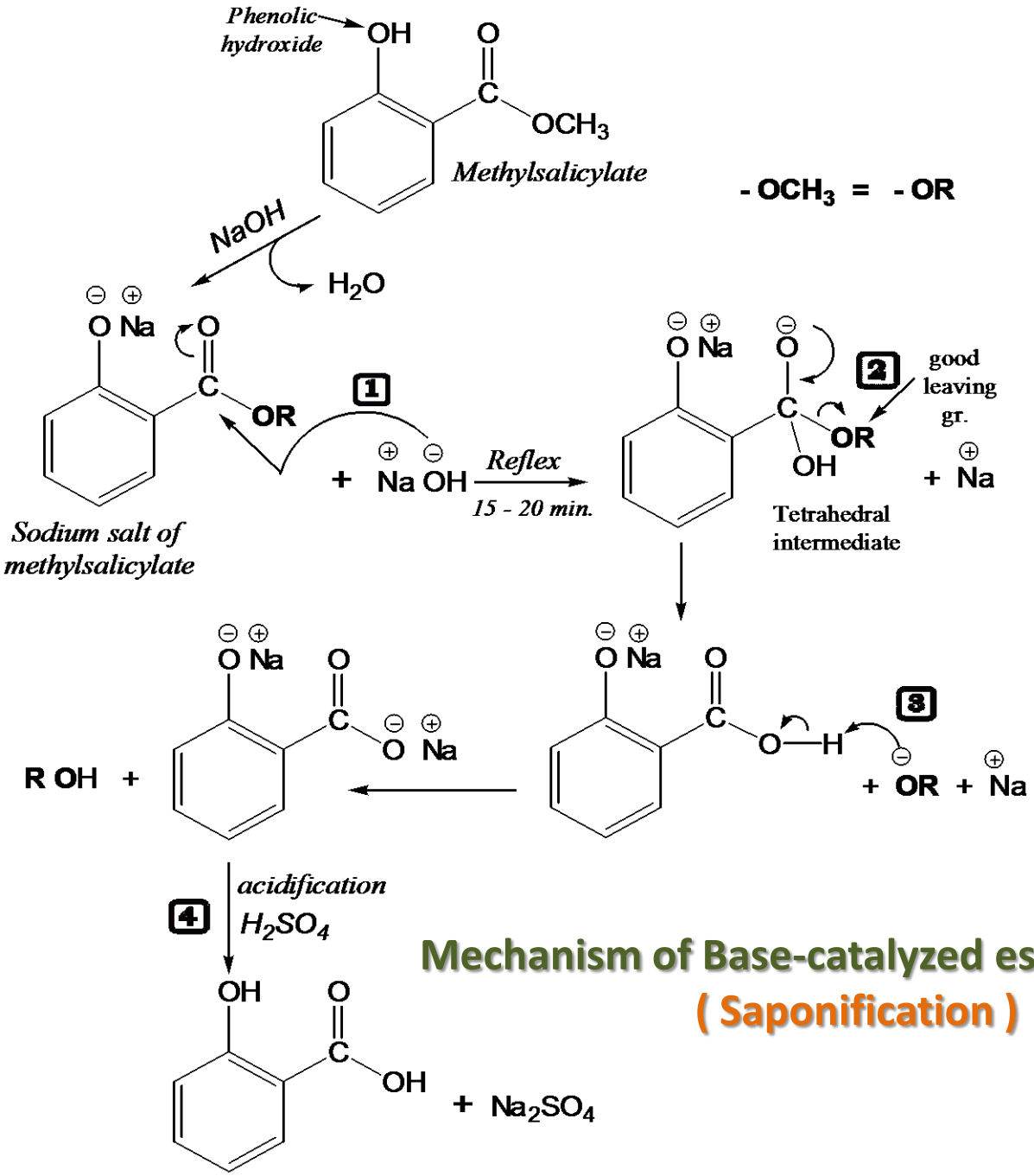
# 3- Alkaline hydrolysis of ester:

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




## MECHANISM OF SAPONIFICATION:

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

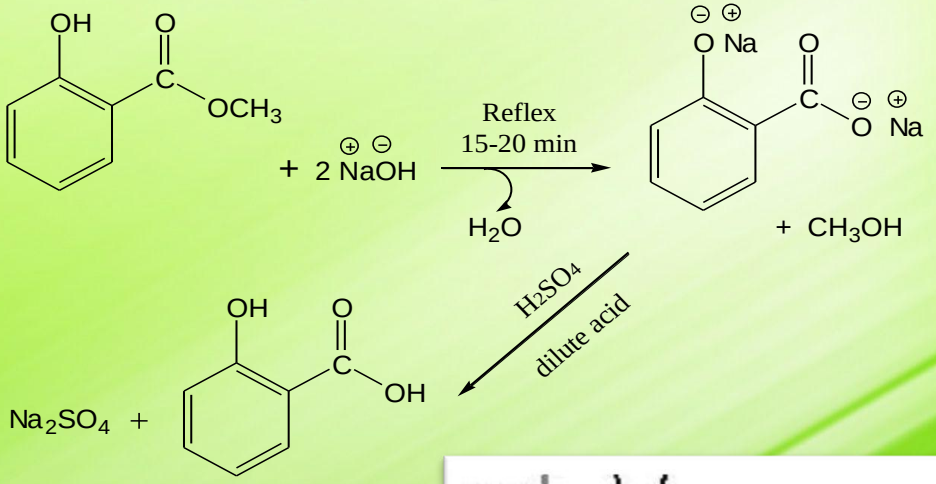



## Mechanism of Base-catalyzed ester hydrolysis

## ( Saponification )

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

**Aim of experiment:** Preparation of Salicylic Acid by Alkaline hydrolysis of Methylsalicylate.

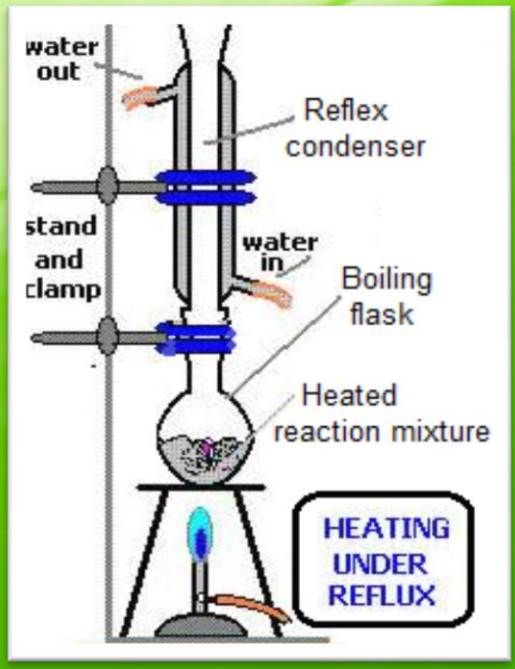



## Procedure:

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

***2- Add 25ml of 20% aq. NaOH solution & 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.***

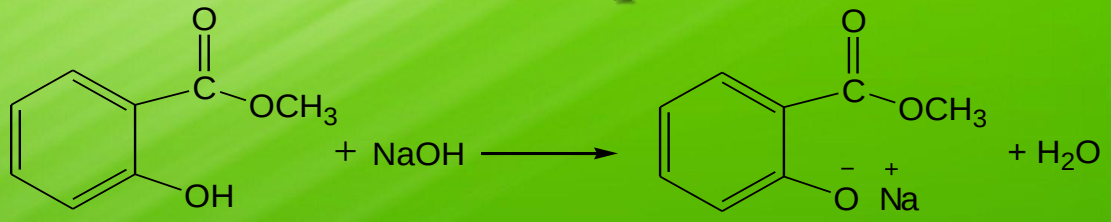
***5- Add 35 ml of dil. $H_2SO_4$ to get the acid ( S.A. ppt. ).***

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

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


Note

- **The WHITE SOLID that is formed immediately ( before reflex ) when ethylsalicylate was introduced to the aqueous solution of NaOH is the Na salt of methylsalicylate that will disappear by boiling ( redissolve ).**




Sodium salt of methylsalicylate
( White ppt. )

# Post lab exercises :

1- The carboxyl group is more acidic than the - OH group in S.A molecule, explain why?

2- Rank the following cpd.s inorder of increasing acidity: Phenol, $CH_3COOH$, S.A , $CH_3OH$, $H_2SO_4$.

3- Draw the stepwise mechanism for the alkaline & acidic hydrolysis of ester. Mention which one of them is preferred for hydrolysis of an ester ? And 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 ?**

References: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# *Vogel, Arthur, Textbook of Organic Chemistry, 4th edition.*
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