

2023 - 2024



# SALICYLATES

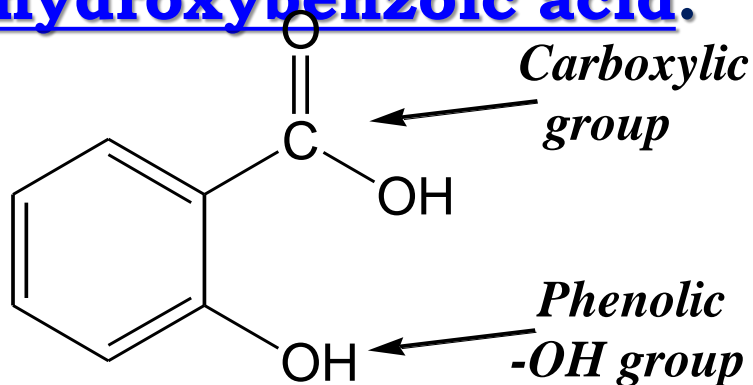


# Historically,

**salicylates** were among the 1st of the NSAIDs that are recognized as analgesics.

The parent cpd. **Salicylic acid** has been known since 1839 and it is found as free form, salts & esters.

Salicylic acid (from Latin salix, *willow tree*, from the bark of which the substance used to be obtained) is an **beta- or ortho-**  
hydroxybenzoic acid.



# Salicylates have been introduced 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 characteristic of their many commonly used salts and derivatives.

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

## 1- Minimize the gastric symptoms

Gastric disturbances, hemorrhage, irritation. (Pka=2.97).

## 2- Minimize the undesirable taste

## 3- Prepare suitable dosage forms

## 4- Improve the physicochemical properties

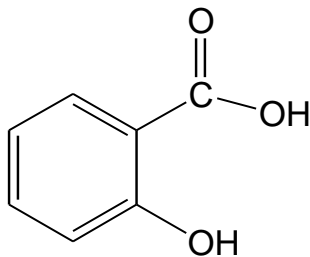
### **Types of S.A. derivatives:**

#### **TYPE I:**

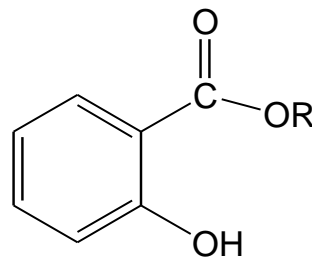
Represents those that are formed by modifying the carboxyl group of S.A., ( e.g. salts, esters or amides ).

#### **TYPE II:**

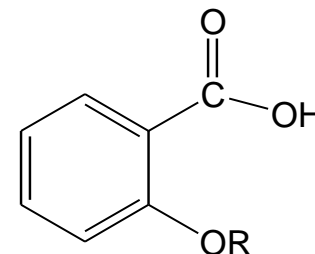
Represents those that are derived by substitution on –OH group of S.A.



Salicylic acid

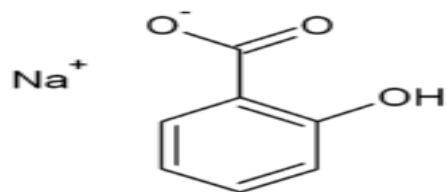


Type I  
derivative

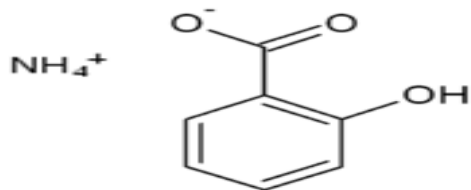


Type II  
derivative

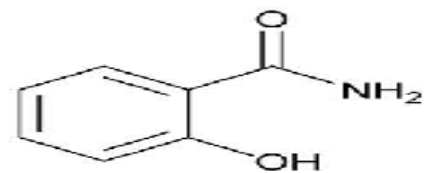
# Examples (Type I derivatives):



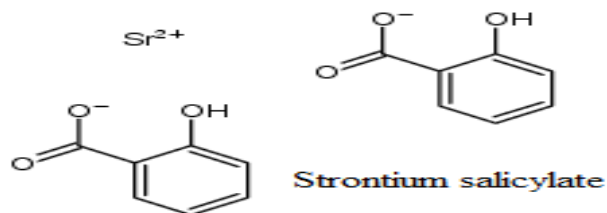
Sodium Salicylate



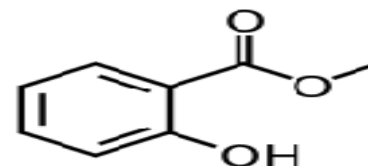
Ammonium Salicylate



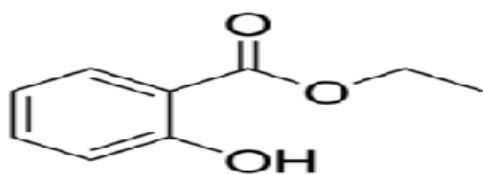
Salicylamide



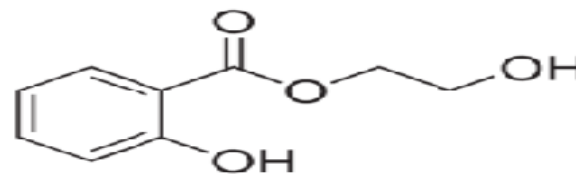
Strontium salicylate



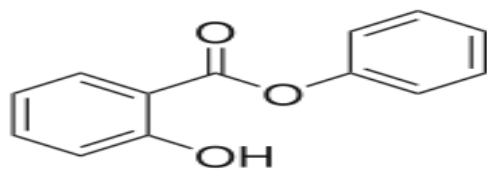
Methylsalicylate



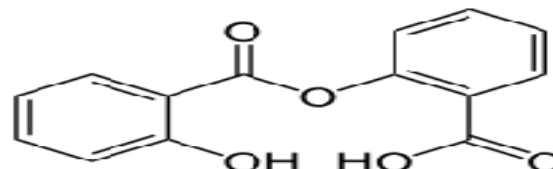
Ethylsalicylate



Hydroxyethylsalicylate  
( Spirosal )



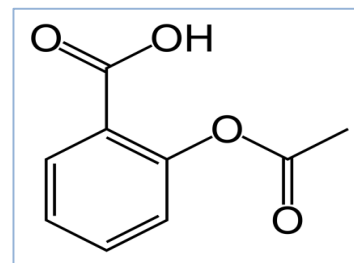
Phenylsalicylate  
( Salol )



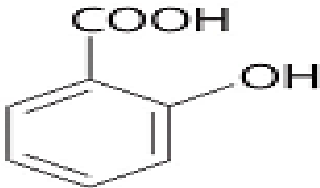

Salicylsalicylic acid  
( Salsalate )

## Example ( Type II derivative) :

Aspirin,  $C_9H_8O_4$ , Acetyl salicylic acid.

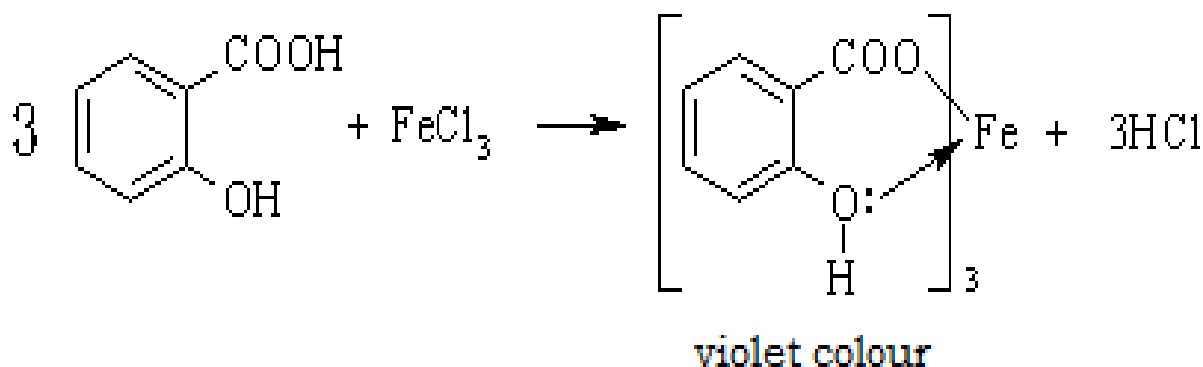


### Differences between S.A and aspirin :

Properties	Salicylic acid	Aspirin
Structure	 <p>Active substance</p>	 <p>Type II derivative of S.A It's a prodrug</p>
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) <i>Why?</i>

<p style="text-align: center;"><b>Route of administration</b></p>	<p style="text-align: center;">Externally Not given orally <i>Why?</i></p>	<p style="text-align: center;">Given orally</p>
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S.A. contains phenolic - OH group and it is ortho to the carboxyl group. It forms a violet colored complex when reacted with FeCl<sub>3</sub>.



FeCl<sub>3</sub> 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 :(electrophilic aromatic substit**

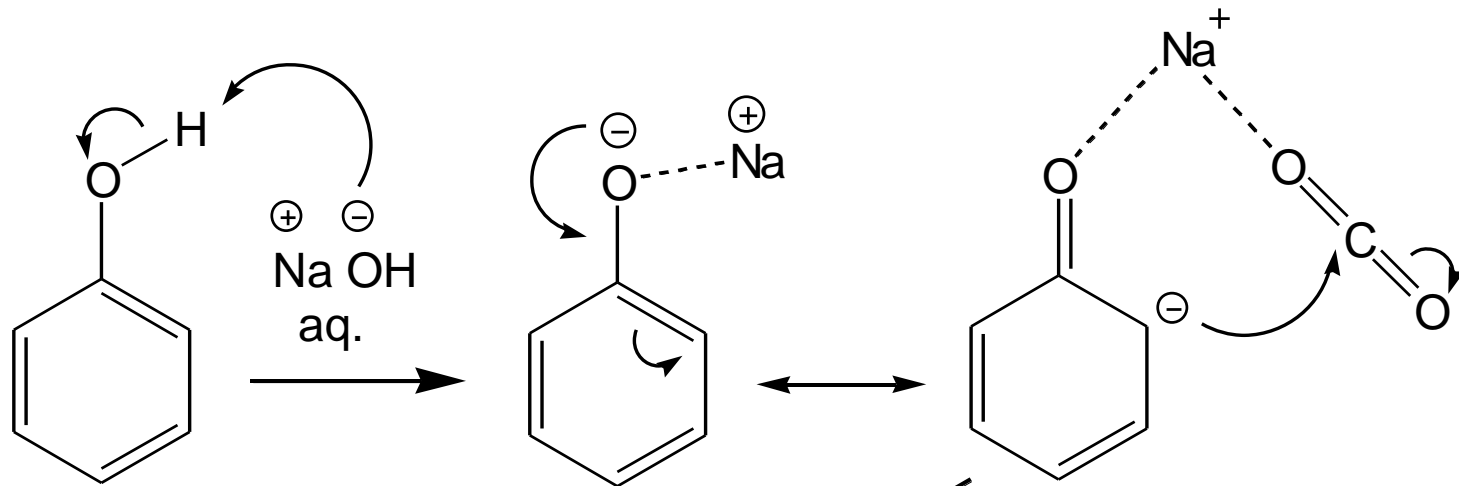
It is a **carboxylation chemical reaction** that proceeds by heating sodium phenolate ( the sodium salt of phenol ) with  $\text{CO}_2$  under pressure (100 atm , 125 °C), then treating the product with sulfuric acid .

The final product is an aromatic hydroxy acid which is known as **salicylic acid** (the precursor to **aspirin**).

### **THE MECHANISM OF THE REACTION:**

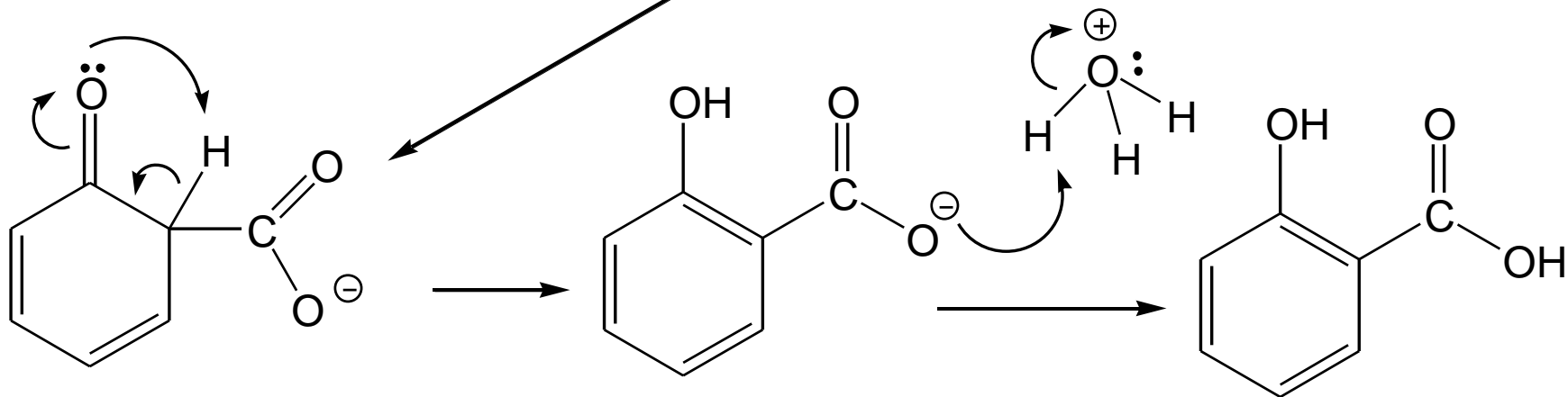
The Kolbe – Schmitt reaction proceeds via the nucleophile addition of a phenolate to carbon dioxide to give the salicylate.

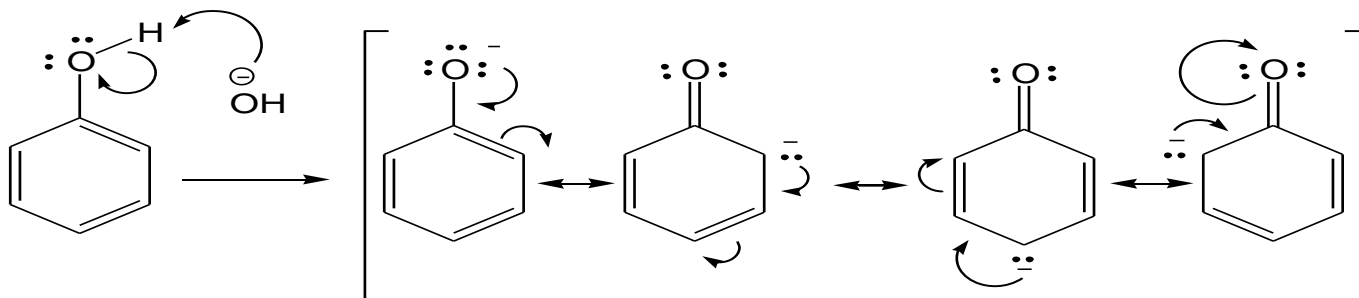
The final step is the reaction of the salicylate with acid to form the desired salicylic acid.



Sodium phenoxide

nucleophilic addition





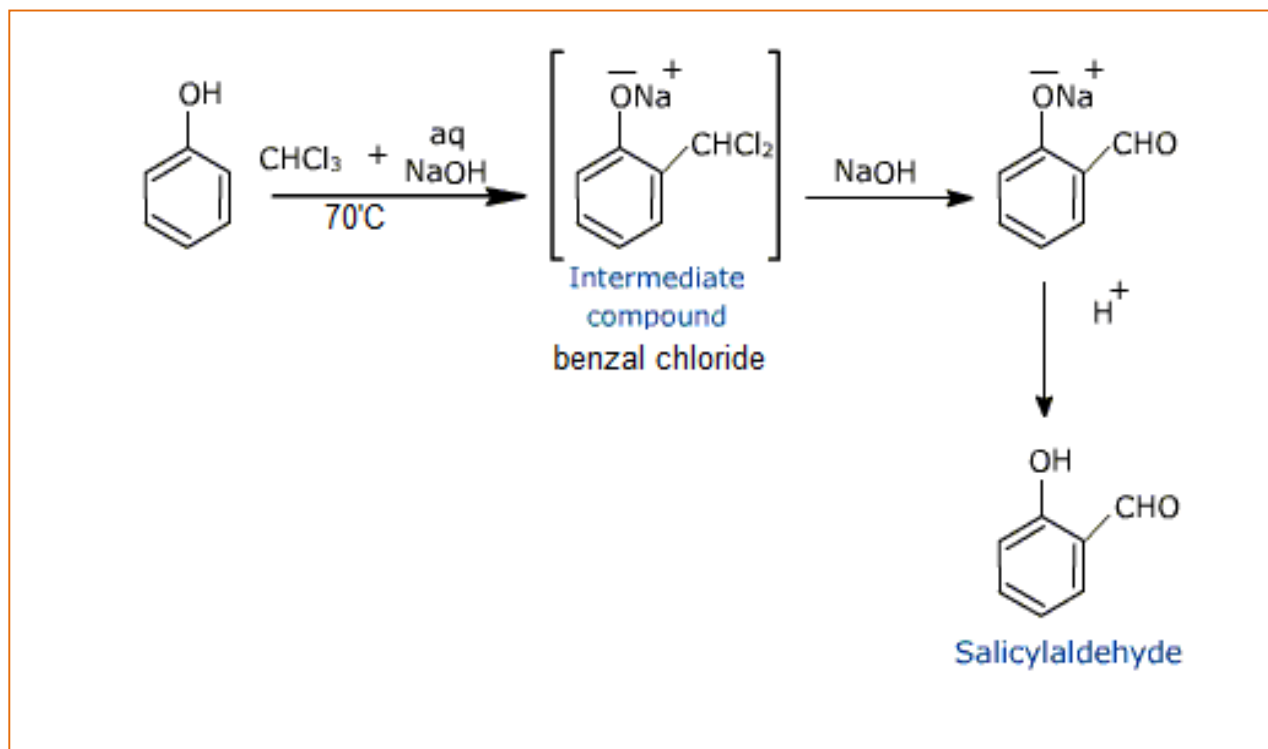
( Phenoxide anion )

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 (sublimes at 76). (Why?)

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

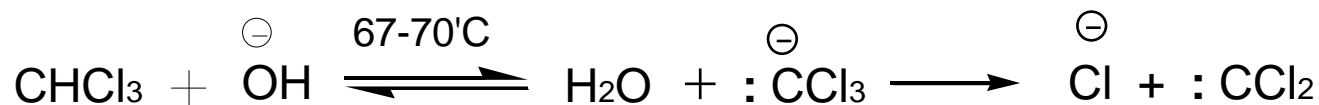
## 2- Oxidation of salicylaldehyde:

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.



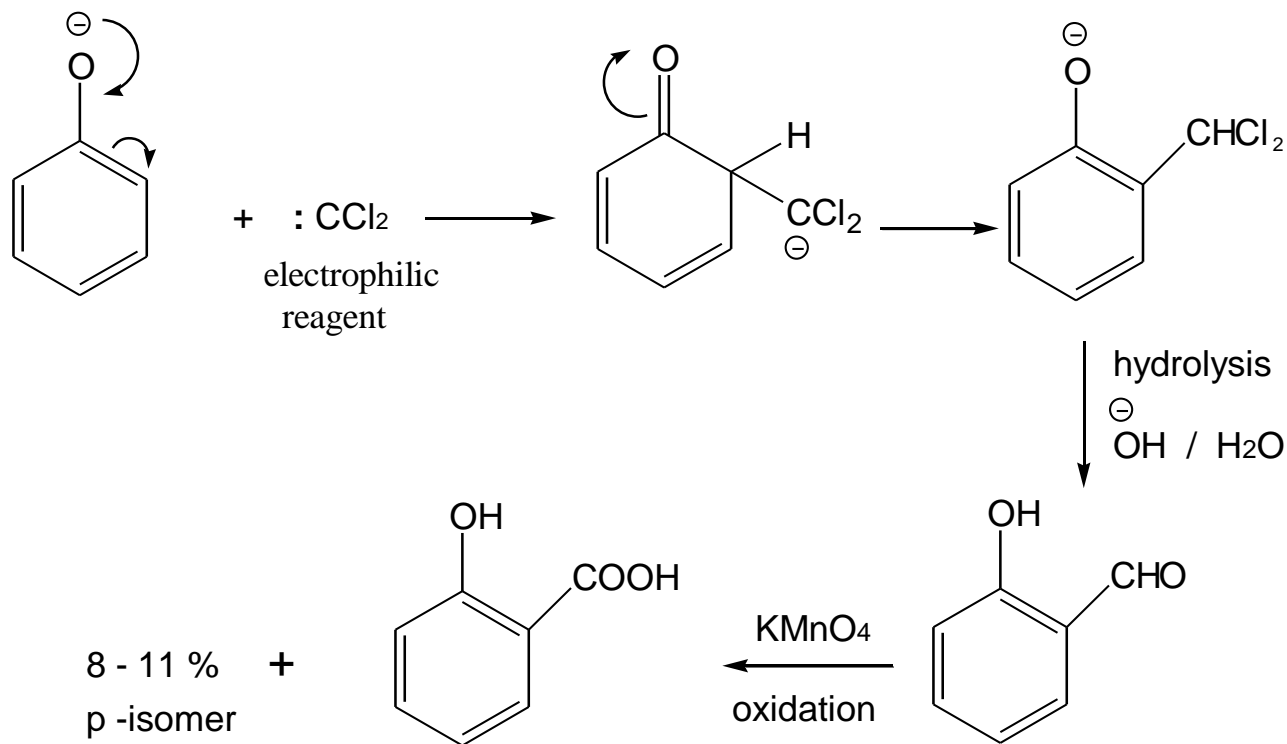
## MECHANISM OF THE REACTION:

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



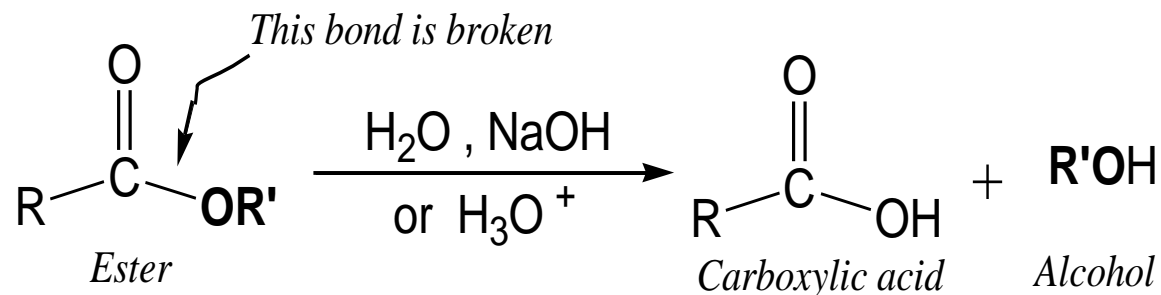
Dichlorocarbene contains a sextet of electrons & thus is a strong electrophile.

**Dichlorocarbene**  
(reactive intermediate)  
Electrophile



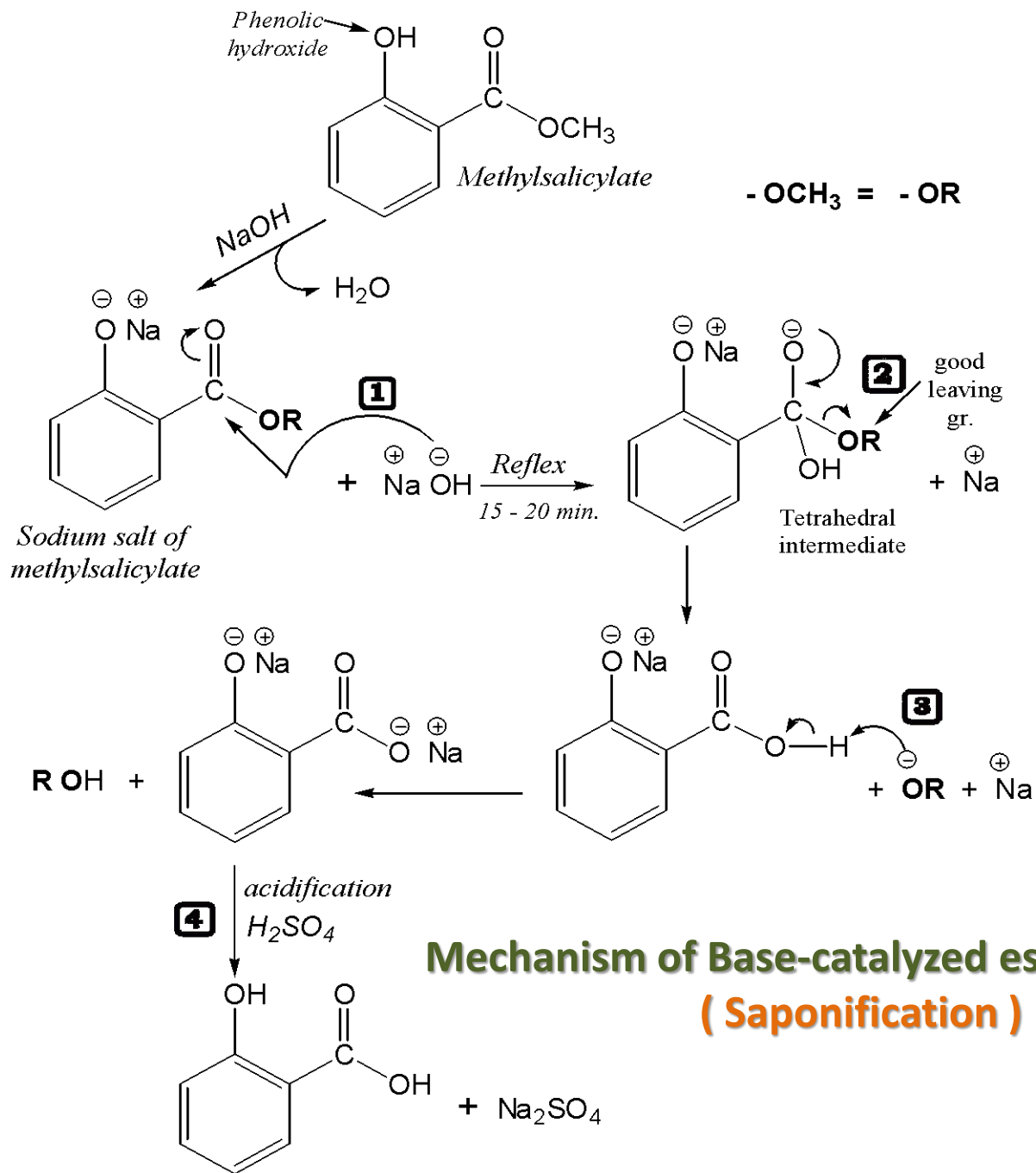
### 3- Alkaline hydrolysis of ester:

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  $\text{OH}^-$  ion to the ester carbonyl group gives the usual tetrahedral alkoxide intermediate.
- 2** Elimination of alkoxide ion, ( $\text{RO}^-$ ), 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.



Name of Experiment: Alkaline Hydrolysis of Ester.

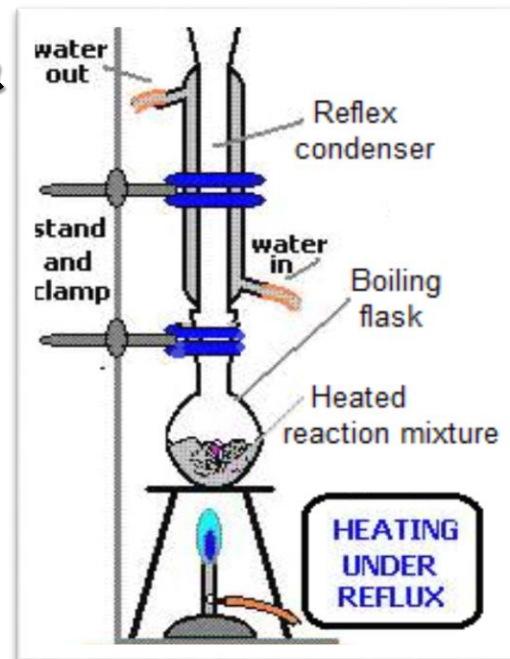
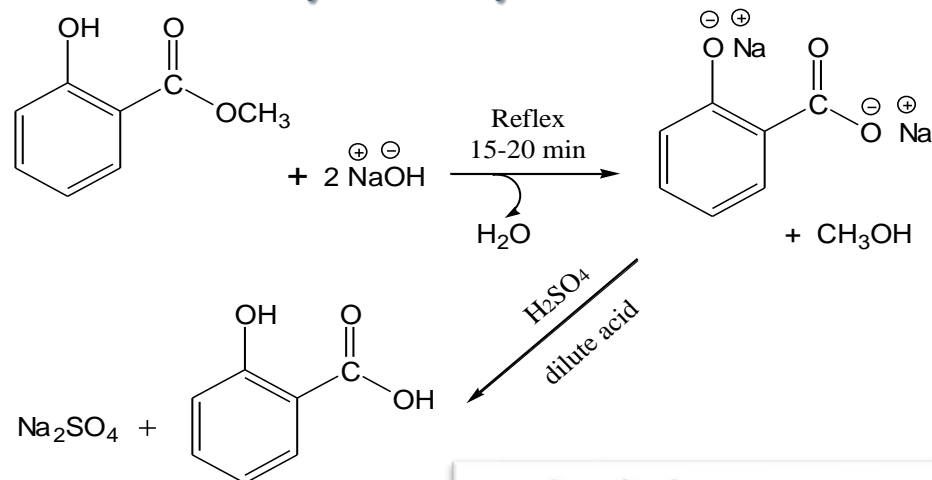
Aim of experiment: Preparation of Salicylic Acid by Alkaline hydrolysis of **Methylsalicylate**.

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 re-dissolve 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. ).**

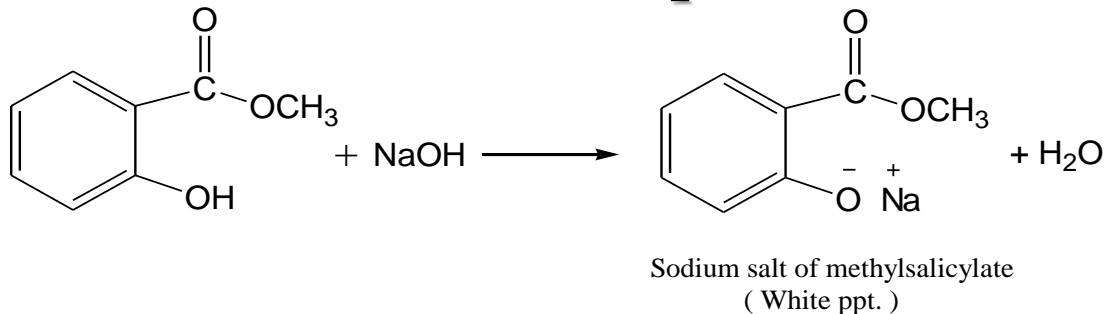
**6- Further cooling is required then filter & collect the ppt.**

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



**Note**

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



# Safety and Health Notifications

## Salicylic acid:

*Eye hazards(severe irritation), Skin hazards(mild irritation), danger, and it has been listed as experimental teratogen.*

*Salicylic acid upon heating converts to phenyl salicylate with further heating it gives xanthone.*

*At the boiling point =200-230, it slowly decomposes or degrades to phenol and CO<sub>2</sub>.*

*With log P= 2.25, using high concentration ointment of salicylic acid will lead to absorption to blood stream across the skin.*

# Safety and Health Notifications

## Methyl salicylate:

*Harmful, use with warning. It is potentially deadly especially for young children who may accidentally ingest preparations containing methyl salicylate. Also excessive application of topical muscle pain-relief products can be toxic and fatal due to accumulation of salicylate in blood plasma or serum.*

# Safety and Health Notifications

## NaOH:

*Caustic soda and danger. It can readily decompose proteins and lipids via amide and ester hydrolysis with consequently chemical burns and may induce blindness if contact with eyes. The alkali spills on skin is first aided with irrigation with large quantities of water continued for at least 10-15 min.*

