3. Synthesis of Aspirin

3.1. Introduction:

Derivatives of salicylic acid have been largely used in medicine for many years as:

- Pain relieving (analgesic).
- Fever reducing (anti pyretic).
- Joint pain reducing (anti rheumatic).
- Nerve ends inflammation (anti inflammatory).
- Aspirin is safe and well tolerated.

The side effects of aspirin were often worse than the original discomfort, Membranes lining the stomach and passages leading to it are irritated by the acid. The contents of the stomach are acidic, and most of the ingested aspirin passes through unchanged. Whereas, aspirin irritate the stomach wall due to it's relatively insolubility in neutral aqueous solution and acidity.
This effect can be partially over come under the alkaline conditions in the intestines aspirin forms sodium acetylsalicylate, which is absorbed through the intestinal wall (sodium salt is more soluble instead).
Few people suffer serious toxic effects from using aspirin, although some people are allergic to it.
People suffering from ulcers may find their condition made worse by the use of aspirin and pregnancy abortion. In addition, aspirin seems to interfere with the blood clotting process, limiting its use for the patients anticipating surgery.

3.2. Chemistry of reaction:

Esterfication means the reaction between hydroxyl groups of alcohol with the carboxylic group with the elimination of water:-

$$R\_OH + R'\_COOH \rightarrow R'\_COOR + H_2O \quad \ldots\ldots (1)$$

R= primary or secondary alcohols but no tertiary or aromatic.
R'=alkyl or aryl chain.

Esters of Phenols can be prepared from the reaction of Phenol and acid halide or acid anhydride in the presence of mineral acid as a catalyst as follows:-

$$PhOH + CH_3COCl \xrightarrow{H^{\oplus}} PhOCOCH_3 + HCl \quad \ldots\ldots (2)$$

$$PhOH + (CH_3CO)_2O \xrightarrow{H^{\oplus}} PhOCOCH_3 + CH_3CO_2H \quad \ldots\ldots (3)$$

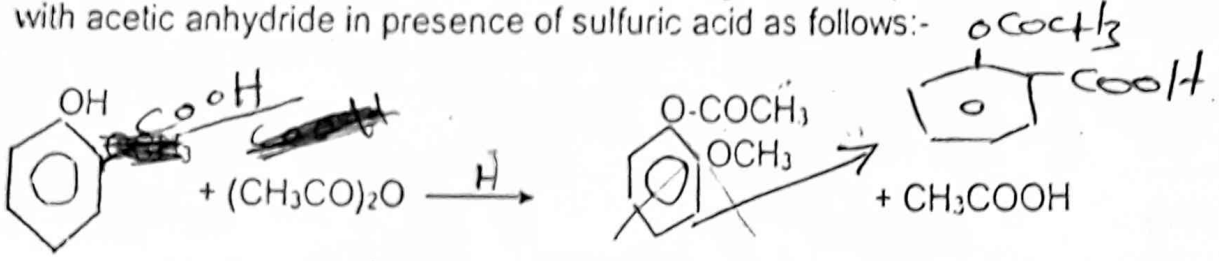
N.B.

1. Reactions 2 and 3 are used more than reaction 1, due to the equilibrium in reaction 1(i.e.; reversible reaction), while 2 and 3 are considered as irreversible reactions.

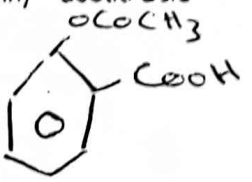
2. *all equipments must be dry before work, to prevent the hydrolysis of acetic anhydride and no reaction occurs as follows:-*

$$CH_3COOCOCH + H_2O \longrightarrow 2CH_3COOH$$
$$CH_3COOH + \text{salicylic acid} \longrightarrow \text{N.R.}$$

3. Aspirin is industrially prepared by acetylating of ortho-hydroxyl benzoic acid with acetic anhydride in presence of sulfuric acid as follows:-



Salicylic acid	acetic anhydride	acetyl Salicylic acid (aspirin)	acetic acid
M. P. 160°	B.P. 139°	M.P 135°-136°	
M.W 136 g/mol	M.W.102 g/mol	M.W.180 g/mol	
	Density 1.08 g/ml		



3.3. Procedure:

A: Preparation of Aspirin:

1. *Place in a 50-mL Erlenmeyer flask 1.4 g (0.01mole) of salicylic acid.*
2. *Add 3mL (3.1 g, 0.03 moles) of acetic anhydride in such a way as to wash down any material adhering to the walls of the flask.*
3. *Add 3 drops of concentrated sulfuric acid and mix the chemicals well by rotating the flask, (the mixture may become warm from the exothermic reaction).*
4. *Allow to stand for about ten minutes.*
5. *Heat the flask for 5 minutes in a 45-55° on a steam bath,*(less than range no complete the reaction, higher degree cause to decompose) *or in a beaker of water heated to 85-90°.*
6. *Allow the mixture to cool and stir occasionally.*
7. *Chill the mixture in an ice-water bath and scratch the bottom of the flask with a stirring rod until a semi-crystalline paste has formed.*
8. *Add 25 mL of cold water (to destroy unreacted molecules of an excess acetic anhydride after complete the reaction).*
9. *Stir the mixture to break up the pasty solid.*
10. *Filter the mixture then rinse the crystals that have collected with a few milliliters of cold water.*
11. *Press the product with large cork (to remove as mush water as possible).*
12. *Save a bit of it (0.1 g or less) for later analysis.*

B: Purification of Aspirin:

1. Dissolving the crystals in 10 mL of ethanol (not more) in a 50 mL beaker (if the crystals do not dissolve at room temperature, warm the mixture with a hot water bath, probably no filtration is necessary at this stag.
2. Pour the solution into 13mL of warm water (55-60°), (if a solid separate at this point, warm the mixture until solution is completely dissolved).
3. Cover the beaker with a watch glass (to retard evaporation).
4. Let the solution cool at room temperature for 10-15 minutes.
5. set in a beaker of ice (to accelerate the cooling process).
6. Beautiful needle-like crystals will separate, filter, and wash it with2-3 mL of cold water.
7. Allow the crystals to dry thoroughly at room temperature and then weigh your product (practical weight).
8. Calculate your percentage yield.
9. Measure it's melting point of your un recrystallized and recrystallized aspirin sample (the melting range of the aspirin that you synthesized is a good way to assess it's purity).

C: Reactions of aspirin:

1. Shake up with water in to clean test-tubes a few crystals:-

(a) Pure salicylic acid.

(b) recrystallized aspirin.

2. Add 1 drop of ferric chloride solution to gives with:

(a) Immediate purple coloration, due to the presence free hydroxyl group.

(b) No coloration, if the aspirin is pure.

N.B.

1. Could not use $_{conc}HCl$ instead $_{conc}H_2SO_4$, due to that $_{conc}HCl$ contains water.

2. the optimum period to complete the reaction is 15 minutes, since shorter period reduce yield percentage and longer period dose not increase yield percentage.

3. $Weigh_{(gm)} = volume_{(mL)} * density_{(gm/mL)}$

4. How to calculate the yield percentage:

1. Calculate theoretical weight:-

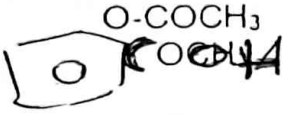
Salicylic acid

$C_7H_6O_3$

C; 7*12=84
H; 6*1= 6
O; 3*16 =48

M.W. =138

Weigh=1.4



Aspirin

$C_9H_8O_4$

C; 9*12=108
H; 8*1 = 8
O; 4*1 = 64

M.W. =180

Weigh=?

Weigh = (1.4*180) / 138

Theoretical weight = 1.826 g

2.Recovery percentage=

$$\frac{\text{practical weight}}{\text{theoretical weight}} * 100$$

$$\frac{\text{practical weight}}{1.826} * 100$$

= %