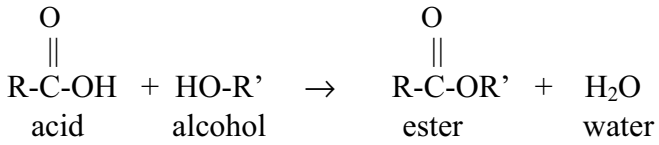
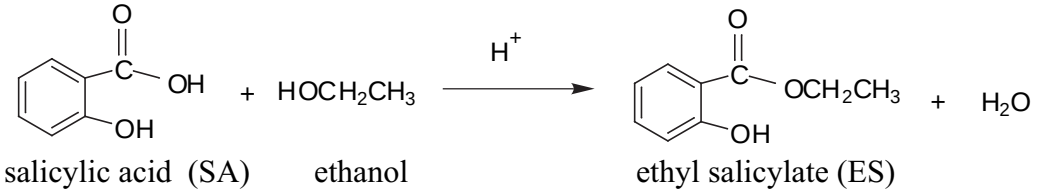
#15 Synthesis of Ethyl Salicylate from Salicylic Acid

Purpose: Salicylic acid is converted to the liquid ethyl salicylate by addition of ethanol. Yields of salicylic acid (week 1) and ethyl salicylate will be found, as well as the overall yield of the 2-step conversion of acetyl salicylic acid to ethyl salicylate.

Introduction:
Esters are formed from the reaction of acids and alcohols:



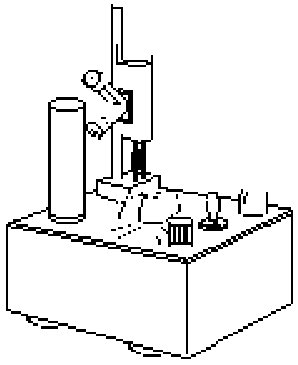
The pleasant smelling oil of ethyl salicylate is made by reacting salicylic acid (week 1) with excess ethanol. An acid catalyst is also needed.



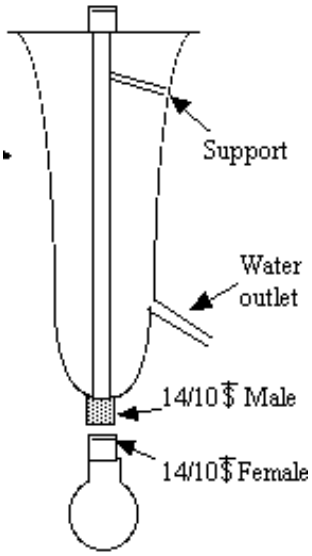
The overall yield is determined from multiplying yields of the two reactions:

1. ASA + HCl(aq) →SA and 2. SA + ethanol → ES + water

Apparatus
The reaction takes place by refluxing (gentle boiling) in a 100-mL round bottom flask. This time the ice-cooled condenser is essential, otherwise the ethanol reactant (b.p.79˚C) would evaporate before the reaction was over.


MelTemp

Melting points of acetyl salicylic acid and salicylic acid (dried from week 1) are taken with MelTemp devices. If you have never used one your instructor will demonstrate.



Procedure

Part A: Esterification of Salicylic Acid with Ethanol

1. Before starting remove a spatulaful (that will be < 0.1 g) of SA (salicylic acid) and place in a labeled plastic vial to use for melting points.

2. In a 100 mL round bottom flask, mix at least 5 g dry salicylic acid (0.043 mol) with 20 mL 100% ethanol. The salicylic acid should be weighed out to two decimal places and recorded on the data sheet. The alcohol is in excess. It can be poured from a graduated cylinder, and should not be scaled down.
Note: Use more salicylic acid if you have more from the first week. You should have between 7 and 8 g. Adjust amount of ethanol accordingly, say to 30 mL.

3. Add approximately 1/2 gram of boric acid catalyst that we use as a substitute for concentrated sulfuric acid in this particular esterification.

4. Place entire assembly on a hot plate and heat until the alcohol is boiling. A setting of around 3 on the hot plate can be tried and then adjusted up or down as needed. You may need to add more ice.
Note: While the refluxing is taking place, you can work on Part B, in which the materials you have already made are characterized by taking their melting points.

5. Reflux for a minimum of 1 hour and 30 minutes or longer as time allows. Cool until the flask is no longer hot, then in an ice bath, until the mixture is at room temperature. Transfer to a clean separatory funnel.

6. Add 10 mL 2M NaOH(aq) .The mixture turns milky as approximately 2-3 mL of ester appears at once as an insoluble bottom layer. Ethyl salicylate is an oily liquid with a density of 1.1 g/mL. Wait a few minutes until the cloudy emulsion begins to clear up. You can estimate the yield by marking the funnel and measuring an equal volume of water. Record this. You will probably get about 1/2 mL for every 1 gram of salicylic acid.

7. You should be able to recover about 1.5 mL of the ester oil by separating the layers using a separatory funnel. Allow the bottom layer to pour into a vial. This layer contains mostly ethyl salicylate and should have a very pleasant odor, something like wintergreen. It will also include a little NaOH solution and thus will not be clear and sparkling. If you have enough liquid you can attempt the next step.

8. Dry by mixing with a small amount of anhydrous magnesium sulfate. See your instructor to get help with this. Pour off the clear ethyl salicylate.

Part B: Melting Points

1. Measure melting points of the dry acetyl salicylic acid and the salicylic acid using the small samples reserved for this purpose. Record on data sheet and compare with literature values.

Part C: Yields

1. The 50 aspirin tablets contained 16.25 g ASA. To estimate yields in your next 2 reactions, assume the wet ASA you used contained 12 g ASA. Then from the mass of dry salicylic acid obtained find the yield of salicylic acid.

2. Convert the volume of ethyl salycilate to grams using the density, 1.1 g/mL. Record. Estimate yield of ethyl salicylate from salicylic acid and record, retaining just 2 significant figures.

3. Find the overall yield of the two-step process:

Step 1: Acetyl salicylic acid (ASA) to salicylic acid (SA)

Step 2: Salicylic acid (SA) to ethyl salicylate (ES)

Data and Results (yield of ethyl salicylate)

Name(s) _____

Part B: Melting Points

Compound	Measured Melting Point (˚C)	Literature Value (˚C)
Acetyl Salicylic Acid		134 - 135
Salicylic Acid		158 - 160

Yields:
Assuming ASA (from extraction of 50 aspirin tablets) = 12 g

SA (from hydrolysis of ASA) _____ *g*

Reactant SA esterified: _____ (usually most of the amount above)

Approximate volume of ethyl salicylate: _____ mL (density ES = 1.1 g/mL)

Mass ethyl salicylate _____g

Maximum g SA:

Maximum g ES:

Enter amounts where indicated in the table below and find the yields.

Reaction Reactant → Product	Mass Reactant (g)	Mass Product (g) Maximum	Mass Product (g) Actual	Yield % (2 sig. figures)
ASA → SA	12 g ASA*	g SA	g SA	
SA → ES	g SA	g ES	g ES	

*Assuming 75% extraction yeild.
Overall Yield for 2 steps (product of 2 yields above) :

Questions:
1. Recalculate the overall yield for a three-step process including the 75% extraction.
2. The synthesis of a new drug may require as many as 30 steps, some of which produce much less than 90% yields. Comment on this (without doing any calculations).

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Ethyl Salicylate

Part B: Melting Points

Compound	Measured Melting Point (˚C)	Literature Value (˚C)
Acetyl Salicylic Acid	134	134 - 135
Salicylic Acid	159	158 - 160

Yields:
Assuming ASA (from extraction of 50 aspirin tablets) = 12 g

SA (from hydrolysis of ASA) *7.3 g*

Reactant SA esterified: 7.0 g (usually most of the amount above)

Approximate volume of ethyl salicylate: *3.0* mL (density ES = 1.1 g/mL)

Mass ethyl salicylate *3.3* g

Maximum g SA: $\frac{10\text{ g ASA} \times 1\text{ mol ASA} \times 1\text{ mol SA} \times 138\text{ g SA}}{180\text{ g ASA} \quad 1\text{ mol ASA} \quad 1\text{ mol SA}} = 9.2\text{ g SA}$

Maximum g ES: $\frac{7.0\text{ g SA} \times 1\text{ mol SA} \times 1\text{ mol ES} \times 166\text{ g ES}}{138\text{ g SA} \quad 1\text{ mol SA} \quad 1\text{ mol ES}} = 8.4\text{ g ES}$

Enter amounts where indicated in the table below and find the yields.

Reaction Reactant → Product	Mass Reactant (g)	Mass Product (g) Maximum	Mass Product (g) Actual	Yield % (2 sig. figures)
ASA → SA	12 g ASA*	*9.2* g SA	*7.3* g SA	*79%*
SA → ES	*7.0* g SA	*8.4* g ES	*3.3* g ES	*39%*

*Assuming 75% extraction yeild.

Overall Yield for 2 steps (product of 2 yields above): *0.79 x 0.39 x 100 = 31%*

Questions:
1. Recalculate the overall yield for a three-step process including the 75% extraction.
2. The synthesis of a new drug may require as many as 30 steps, some of which produce much less than 90% yields. Comment on this (without doing any calculations).

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1. *Overall yield = 0.75 x 0.79 x 0.39 x 100 =* 23%
2. *The yield would be very very small, making this an expensive process.*

Instructor's Guide
Ethyl Salicylate(cont'd)

Time: maximum

Equipment and Materials: per group

Items	**Number**	**Comment**
stir/hot plates	1	
stir bars	1	
100-mL round bottom flasks	1	
Weighing papers	1 pack per class	
Ice		
50-mL graduates	1	
Top loading balance	2 per class	With power supply
MelTemps	2 per class	
thermometer	2 per class	For Meltemp
m.p. tubes (closed)	50 per class	
250-mL beakers	1	for water heating bath
Microscale glass clamp	1	(yellow)
ice-cooled condensers	1	
Ring stand	1	
Ring stand clamp	1	
separatory funnels	1	
boric acid	5 g per class	antifungal agent
spoon spatulas	1	
100% ethanol	1 L per class	
2 M NaOH	50 mL	
magnesium sulfate	10 g per class	Epsom salts
Safety glasses	1 per student	
Rubber gloves	1 box per class	

Ideas/ Information

We make ethyl rather than methyl salicylate, because methanol is toxic.
Under Part A. 3. *Note*: This experiment was designed to be done using household chemicals. Although Science in Motion can provide concentrated sulfuric acid, we have decided that it is too dangerous to handle.
Under Part C. 1. *Note*: Repeated extractions were done in our lab. They all gave about 75% yields and about 12 g dry ASA.

2M NaOH solution could be prepared by adding solid NaOH to a volumetric flask and then diluting with distilled water to the mark on the flask.

Molarity mol/L	g NaOH for 1 L solution	g NaOH 500 mL solution
2	80	40