

SYNTHESIS OF ANALGESICS: ASPIRIN & ACETAMINOPHEN

EXPERIMENTAL TECHNIQUES REQUIRED

[Recrystallisation](#) (T 2), [filtration](#) (T 3), [melting point determination](#) (T 4), [yield calculation](#) (T 14)

OTHER DOCUMENTS:

Experimental procedure : week 1 : [Synthesis of Acetaminophen](#) week 2 : [Synthesis of Aspirin](#)

Report templates: [Acetaminophen report](#) [Aspirin report](#)

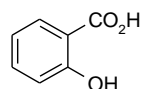
INTRODUCTION

In this experiment you will be synthesising and purifying two common analgesics (painkillers), week 1 : *acetaminophen* and week 2 : *aspirin* (*i.e.* practice the art of chemical synthesis) and to apply the previously learned techniques of recrystallisation, and melting point determination to confirm the synthesis and assess purity.

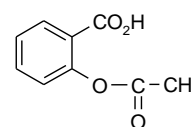
,Acetaminophen is prepared by the N-acylation (*i.e.* adding an acyl group to a nitrogen) of p-aminophenol. Similarly, aspirin is prepared by the O-acylation (*i.e.* adding an acyl group to an oxygen) of salicylic acid. Note the similarity between the two reactions. The crude samples will be purified by recrystallisation and the melting points of the products measured as a means of checking their identity and purity.

BACKGROUND ON ANALGESICS

Aspirin (acetyl salicylic acid or ASA) is one of the most commonly taken medications yet the mode of action is not yet completely understood. Aspirin is an analgesic (relieves pain), an antipyretic



salicylic acid



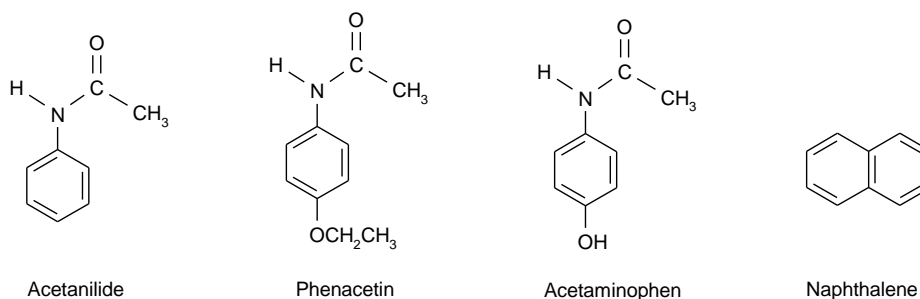
acetyl salicylic acid

(reduces fever) and an anti-inflammatory (reduces swelling). Studies also suggest that aspirin can also reduce the risk of heart attack. Aspirin was developed in order to avoid the irritation problems associated with salicylic acid, the active ingredient in willow bark, whose curative effects have been known since 1763.

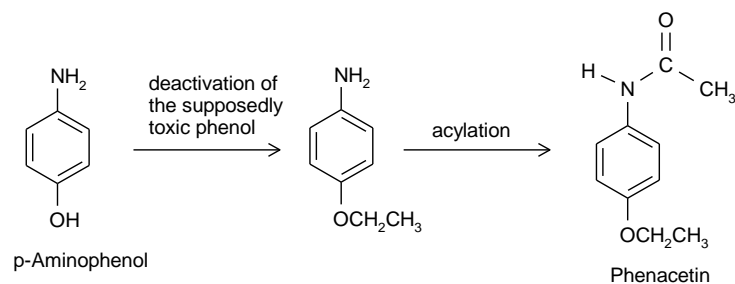
N-acylated aromatic amines (those having an acyl group, $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-$, substituted on nitrogen) are important in over-the-counter headache remedies. “Over-the-counter drugs” are those you can buy without a prescription. Acetanilide, phenacetin, and acetaminophen (see below for structures) are mild analgesics and antipyretics and are important, along with aspirin, in many nonprescription drug preparations (as you will see in a future experiment).

The discovery that acetanilide was an effective antipyretic came about by accident in 1886. Two doctors, Cahn and Hepp, had been testing naphthalene as a possible vermifuge (an agent that expels

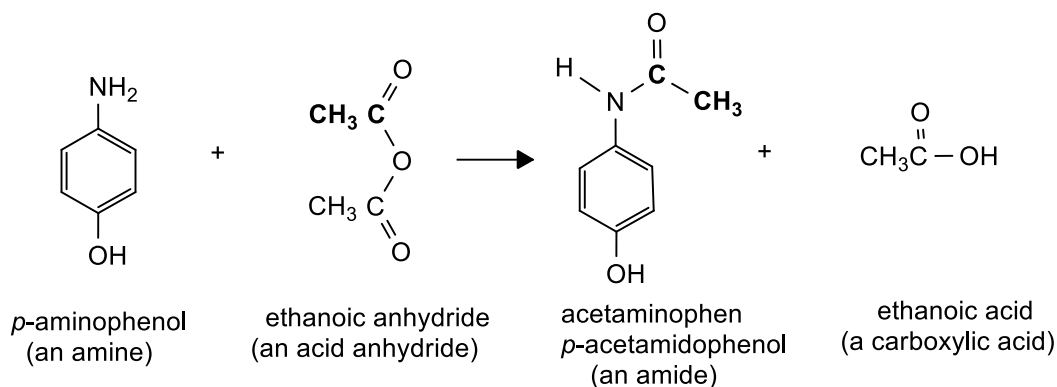
worms). By accident, they mixed up a bottle of acetanilide and the bottle of naphthalene. The patient's worms didn't disappear but his fever did - dramatically.



In another instance of serendipity, the publication of Cahn and Hepp describing their experiments with acetanilide, caught the attention of Carl Duisberg, director of research at the Bayer Company in Germany. Duisberg was confronted with the problem of profitably getting rid of nearly 50 tons of *p*-aminophenol, a by-product from the synthesis of one of Bayer's other commercial products. He immediately saw the possibility of converting *p*-aminophenol to a compound similar in structure to acetanilide, by putting an acyl group on the nitrogen. It was then believed, however, that all compounds having a hydroxyl group on a benzene ring (that is, phenols) were toxic. Duisberg devised a scheme of structural modification of *p*-aminophenol to get the compound phenacetin. The reaction scheme is shown here.



Phenacetin turned out to be a highly effective analgesic and antipyretic. A common form of combination pain reliever, called an APC tablet, was once available. An APC tablet contained **A**spirin, **P**henacetin, and **C**affeine (hence, **APC**). Phenacetin is no longer used in commercial pain-relief preparations. It was later found that not all aromatic hydroxyl groups lead to toxic compounds, and today the compound acetaminophen is very widely used as an analgesic in place of phenacetin. 'Acetaminophen' (4-acetamidophenol) is sold as the over-the-counter analgesic "Tylenol"®.

PREPARATION AND PURIFICATION OF ACETAMINOPHEN

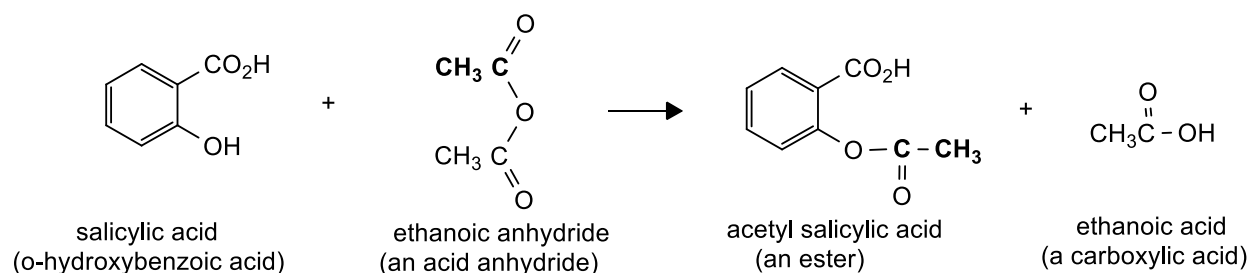
This synthesis will involve the reaction of two functional groups, an amine and an acid anhydride (an example of a carboxylic acid derivative) to form a product, an amide (an example of a carboxylic acid derivative). The amide product will be isolated, and purified by recrystallisation.

Reagents and Products

Compound	Name	M.W.	bp/mp	density
	<i>p</i> -aminophenol	109	m 188-190°	-
(CH ₃ CO) ₂ O	acetic anhydride	102	b 136°/760	1.08 g/mL
CH ₃ COOH	acetic acid	60	b 118°/760	1.05 g/mL
	acetaminophen	151	-	-

PREPARATION AND PURIFICATION OF ASPIRIN

This synthesis will involve the reaction of two functional groups, an alcohol (or more specifically a phenol) and an acid anhydride (an example of a carboxylic acid derivative), to form the product, an ester (also an example of a carboxylic acid derivative). The ester product will be isolated, and purified by recrystallisation. The efficiency of the recrystallisation will be monitored using a simple functional group test for phenols. Salicylic acid (also known as *o*-hydroxybenzoic acid) reacts with ethanoic anhydride (more commonly known as acetic anhydride) to form acetyl salicylic acid and ethanoic acid (more commonly known as acetic acid) according to the following equation:



The most likely impurities in the crude acetyl salicylic acid are unreacted salicylic acid and a polymeric ester by-product. The polymeric by-product is not soluble in sodium bicarbonate and can be removed by dissolving the crude product in sodium bicarbonate, filtering to remove the insoluble polymer then acidifying to recover the acetyl salicylic acid.

Reagents and Products

Compound	Name	M.W.	bp/mp	density
	salicylic acid	138	m 157-159°	-
$(\text{CH}_3\text{CO})_2\text{O}$	ethanoic anhydride	102	b 136°/760	1.08 g/mL
CH_3COOH	ethanoic acid	60	b 118°/760	1.05 g/mL
	aspirin	180	-	-

The phenol functional group reacts with ferric chloride to give a complex with a definite colour ranging from red to violet, depending on the particular phenol present. Unlike salicylic acid, pure acetyl salicylic acid has no phenolic -OH and therefore does not give a colour change. Therefore, the presence of contaminating salicylic acid in the crude product can be detected using ferric chloride and removed by recrystallization.

REFERENCES

- Organic Chemistry etext, <https://www.chem.ucalgary.ca/courses/351/Carey5th/Ch20/ch20-0.html>
<https://www.chem.ucalgary.ca/courses/351/Carey5th/Ch20/ch20-3-2.html>