ChemFactsheet

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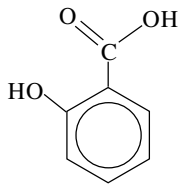
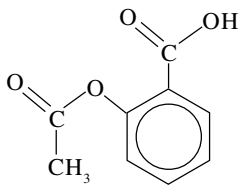
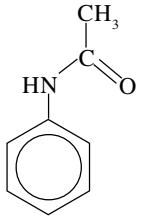
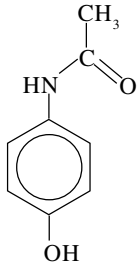
The Syntheses of Aspirin & Paracetamol

To succeed in this topic you need to:-

- Be familiar with basic organic nomenclature
- Have some knowledge of the nucleophilic addition-elimination mechanism (AQA only)
- Know the names of common laboratory apparatus

After working through this Factsheet you will:-

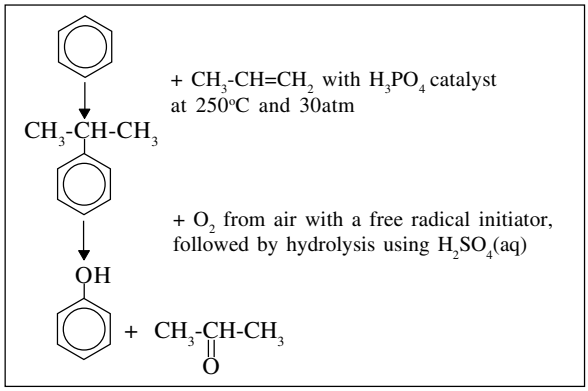
- Know the basic history of the development of aspirin and paracetamol as drugs
- Know the reactions used to produce aspirin and paracetamol
- Be familiar with the laboratory procedures involved in the preparation of aspirin and paracetamol
- Be able to compare and contrast the reactions and processes involved in the syntheses of aspirin and paracetamol
- Be able to transfer your knowledge to other situations.

Aspirin	Paracetamol
It was first noticed in the eighteenth century that an extract of willow bark reduced fever and, by 1838, the active ingredient had been isolated; salicylic acid or 2-hydroxybenzoic acid. The painful side-effects, due mainly to its being a strong enough acid to irritate the stomach, led to attempts to synthesise a less-corrosive but still effective alternative. In 1898 Felix Hoffmann produced aspirin, 2-acetoxybenzoic acid. **Question 1: Why is aspirin less acidic than salicylic acid?**	It is thought that the painkilling properties of paracetamol were discovered by accident when a similar molecule (acetanilide, *N*-phenylethanamide or *N*-phenylacetamide) was added to a patient's prescription about 100 years ago. But, since acetanilide is very bitter and caused nausea and vomiting in moderate doses, chemists modified its structure to try and find a compound that was less harmful but which still retained the analgesic properties. One of these compounds is *N-(4-hydroxyphenyl)acetamide*, which is also known as acetaminophen in the US and paracetamol (from ***para-acet***yl-**am**ino-phen**ol**) in the UK.
 2-hydroxybenzoic acid (Salicylic Acid)  2-acetoxybenzoic acid (Aspirin)	 N-phenylacetamide (Acetanilide)  N-(4-hydroxypheny)acetamide (Paracetamol) **Notes** : "para" is the old method for indicating the C4 position. Also, "N" indicates the hydroxyphenol group is bonded to the nitrogen of the amide group
Paracetamol and aspirin have some structural similarities and, because of this, they are recognised by the same group of enzymes (COX - cyclooxygenases). These enzymes are responsible for the biosynthesis of prostaglandins, which are involved in the dilation of blood vessels that causes the pain experienced in a headache. Reduction of the amount of prostaglandin helps prevent headaches and other pain.	

Preparation

The starting point for the preparation of both aspirin and paracetamol is phenol, originally using phenol that was readily available as a by-product of the destructive distillation of coal to produce gas for lighting. Phenol was in wide use as an antiseptic at this time.

These days, as shown opposite, most phenol is produced from benzene, which is obtained by processing fractions from crude oil, using the Cumene process where benzene is alkylated (substitution by a C_nH_{2n+1} group) by propene, followed by oxidation to form phenol, along with equally useful propanone.

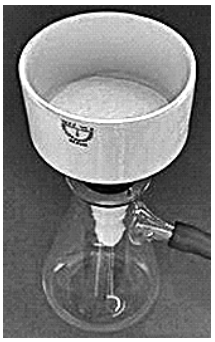


Aspirin	Paracetamol
The first stage in the synthesis of aspirin from phenol is the preparation of 2-hydroxybenzoic acid by the Kolbe Process, which involves reacting phenol with alkali (to form sodium phenoxide which is more susceptible than phenol to electrophilic attack) and the electrophile, carbon dioxide, followed by acidification C_6H_5OH (phenol) $\xrightarrow[2.\ H_2SO_4]{1.\ NaOH/CO_2}$ HOC_6H_4COOH (2-hydoxybenzoic acid) This is then acylated with ethanoic anhydride to produce aspirin $HOC_6H_4COOH + (CH_3CO)_2O \rightarrow H_3CCOOC_6H_4COOH + CH_3COOH$ (Aspirin) ***Question 2: Draw displayed formulas for all the structures in the equations above***	The first stage in the synthesis of paracetamol from phenol is nitration. This is achieved by reacting the phenol with dilute (20%) nitric acid at room temperature (20-25ºC). Using the 'normal' nitrating conditions of a mixture of conc. HNO_3/H_2SO_4 would oxidise the ring so is not suitable in this case. $C_6H_5OH \xrightarrow{HNO_3} HOC_6H_4NO_2$ (mixture of 2- and 4- nitrophenol) The two isomers have different boiling points and so they can be separated using steam distillation. The 4-nitrophenol is then reduced to 4-aminophenol using alkaline sodium tetrahydridoborate, $NaBH_4$, in the presence of a palladium catalyst. $C_6H_5NO_2 + 6[H] \rightarrow HOC_6H_4NH_2 + 2H_2O$ Finally the 4-aminophenol is acylated with ethanoic anhydride $HOC_6H_4NH_2 + (CH_3CO)_2O \rightarrow HOC_6H_4NHOCCH_3 + CH_3COOH$
In a school laboratory, this synthesis is often used for practical assessment purposes and also to introduce some techniques such as recrystallisation and the use of Buchner filtration. A typical set of instructions is given below, with a commentary on each stage in the process. 1. Place 10 g of 2-hydroxybenzoic acid (salicylic acid) and 15g (an excess ; 14 cm^3) of ethanoic anhydride in a large conical flask. Add 5 drops of concentrated sulphuric acid (CARE) and swirl the flask to ensure thorough mixing. ***Question3: Although the AQA syllabus includes the requirement that you recognise the mechanism of nucleophilic addition-elimination you do NOT need to be able to reproduce it for an acid anhydride. Give a mechanism for the reaction of ethanoyl chloride with phenol as an example of this mechanism*** 2. Warm the flask on a water bath to about 50ºC; stir with a thermometer for 15 minutes. *The warming provides the activation energy for the reaction but without over-heating, so avoiding too many unwanted by-products* 3. Allow the mixture to cool to room temperature and stir occasionally. *The addition of cold water in the next stage will cause a very exothermic reaction with any remaining sulphuric acid so cooling to room temperature first is a sensible safety precaution. It also hydrolyses the excess anhydride to ethanoic acid.*	The laboratory synthesis provides a useful illustration of some familiar transformations and procedures including nitration, steam distillation, reduction and acylation. Any of these might also be used for assessment purposes. 1. Place a round-bottomed flask in an ice-bath with a thermometer in one of the necks. Add 15 g of $NaNO_3$, 40 cm^3 of water and stir. 2. Carefully add concentrated H_2SO_4 (13.6 cm^3, 25.0 g), a little at a time. *The $NaNO_3$ and H_2SO_4 react together in situ to produce HNO_3* 3. Slowly add 9.4 g of phenol – making sure that the temperature does not rise above 20°C. This will mean adding the phenol about half a spatula at a time over about 20 minutes. *Careful addition is needed as the reaction is exothermic and, if the temperature rises too much, the risk of multiple substitution increases.* 4. Stir, preferably with a magnetic stirrer, for 2 hours *Keeping the temperature low also keeps the rate low so time is needed for the reaction to complete* 5. Remove the thermometer and decant off the liquid then add 25-30 cm^3 of water to the residue in the flask. 6. Set up the flask for distillation, with a dropping funnel of water in the second neck of the flask so that water can be constantly dripped in.

Laboratory preparation continued...

Aspirin

4. Add 150 cm^3 of distilled water, stir well, keep in suspension and filter using a Buchner apparatus.



A Buchner funnel allows solid to be separated from liquid using suction filtration, which makes the filtration much quicker than by conventional, gravity methods and also, by drawing air through the solid collected, allows initial drying of the solid.

The filter paper is placed onto a perforated plate in the funnel. *The low solubility of the aspirin means that, on addition of water, it will remain as a solid suspension while many of the impurities present, such as CH_3COOH and H_2SO_4, will dissolve readily in the water, so aiding subsequent separation and purification.*

5. The crude Aspirin is dried and then recrystallised (see below) from a mixture of ethanol and water.

6. Allow the solution to cool slowly to room temperature and collect the recrystallised product by suction filtration, washing with 5 cm^3 of ice-cold ethano l/ water.

Question 4: In step one, the reaction mixture is acidified with sulphuric acid, but in steps 15 and 16 for paracetamol the mixture is not acidified. Explain this difference.

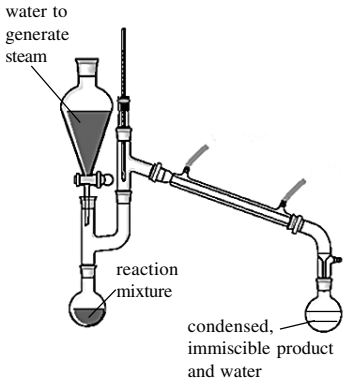
The reagents and conditions used here are the classic combination needed for an esterification reaction. Ethanoic anhydride is used as the acylating agent in both preparations. This is in preference to ethanoyl chloride to avoid the production of highly corrosive HCl as a by-product and because it is cheaper and less easily hydrolysed on contact with water. The reaction proceeds by a nucleophilic addition-elimination mechanism and, overall, results in the replacement of the H of the phenolic -OH group or the H of the $-NH_2$ group with an ethanoyl group, CH_3CO.

Recrystallisation is used to separate a solid product from other solid impurities. The solvent is chosen so that the required product is only sparingly soluble in the cold solvent but will readily dissolve in the hot solvent; impurities need to be very soluble in the cold solvent. The chosen solvent is heated (usually on a water bath) and then added a little at a time to the solid so that the minimum possible amount of solvent is used to form a solution. On cooling, as much product as possible will then crystallise, leaving the impurities in solution. The product is then washed with ice-cold solvent during Buchner filtration.

Paracetamol

7. Heat the flask and distil off the 2-nitrophenol with the steam (i.e. steam distillation).

Steam distillation is used, as the addition of water to the organic material reduces the boiling point so that the product can be distilled off at a lower temperature than by simple distillation, so reducing the risk of any decomposition of temperature-sensitive materials.



8. Filter the residue in the flask to collect the 4-nitrophenol – this can be recrystallised from 0.5M hydrochloric acid.

9. Place 10 cm^3 of 1 mol dm^{-3} sodium hydroxide in a conical flask.

10. Add 0.56 g of sodium tetrahydridoborate(III), followed by 50 mg of palladium on charcoal (5% or 10%). Cool in ice to ~13 °C.

11. Add 1.0 g of 4-nitrophenol in very small amounts over 30 minutes. Keeping the temperature between 13–17°C.

12. After the addition is complete the mixture should be stirred for a further 15 min and acidified with 2 mol dm^{-3} hydrochloric acid (about 17 cm^3).
Acidification is needed to reform the phenolic group from the phenoxide that will have been formed in the presence of the alkali and to protonate the amino group ($-NH_2 \rightarrow -NH_3^+$) so that the product remains in solution.

13. Filter the mixture and adjust the filtrate to pH 7–8 by carefully adding solid sodium hydrogencarbonate a little at a time.

14. Filter off the precipitate and wash with a little cold water. *Making the solution very slightly alkaline will ensure that the $-NH_3^+$ group loses a proton to reform $-NH_2$ without the –OH group also donating a proton. The uncharged species will therefore precipitate out of solution so that it can be separated by filtration.*

15. Place 1.0 g of 4-aminophenol and 9 cm^3 of distilled water in a 50 cm^3 conical flask and stir briskly at room temperature.

16. In a fume cupboard, add 1.1 cm^3 (1.17 g) of ethanoic anhydride and gently shake to mix. The solid will dissolve after about 30 seconds. Continue shaking and a precipitate will form after 2 minutes.

17. Filter off the solid under suction using a Buchner apparatus (see opposite), wash with a little cold water and dry.

18. The product may be purified by recrystallisation (see opposite) from distilled water.

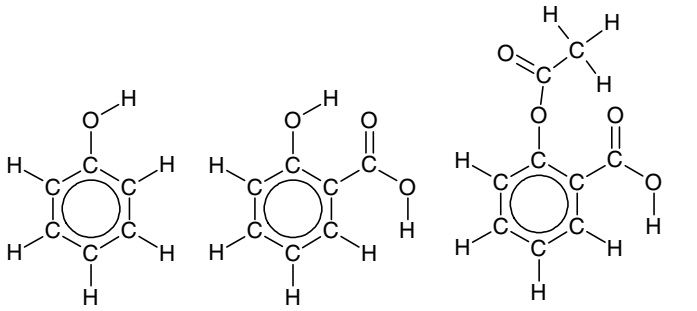
19. Allow the solution to cool slowly to room temperature and collect the recrystallised product by suction filtration, washing with 5 cm^3 of ice-cold distilled water

Answers to Questions in the Text

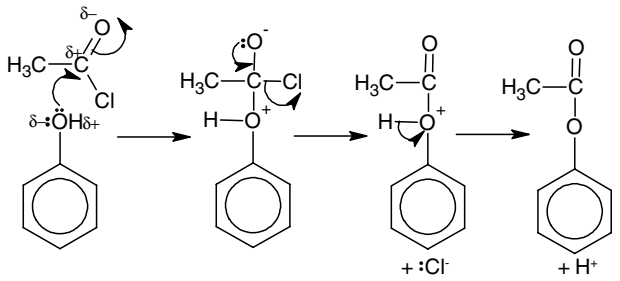
Question 1:

In-In salicylic acid both the carboxylic acid group, COOH, and the phenolic group, OH, are acidic and both will dissociate in aqueous solution to contribute to the acidity of the compound. However, in aspirin, the phenolic group has been acylated and the resulting ester group is not acidic so the acidity in this compound is now only due to the dissociation of the COOH group.

Question 2



Question 3



Question 4

In acidic conditions the phenolic –OH group involved in the aspirin preparation is protonated and can act as a nucleophile through the lone pair on the delta negative oxygen. However, if acidic conditions were used in the preparation of paracetamol then the $–NH_2$ group would be protonated to give $–NH_3^+$ and there would then be no lone pair to allow nucleophilic attack.

Acknowledgements: *This Factsheet was researched and written by Tony Tooth.*
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