Storyline: answers to assignments

1 Students should be able to identify absorptions by
C=O (carboxylic acid) at about 1700 cm^{-1}
OH (free or more likely internally hydrogen bonded) at about 3600 cm^{-1}.
OH (hydrogen-bonded) at about 3250 cm^{-1}.
C–H (arene) at about 3100 cm^{-1}
These correspond to what chemical tests have revealed about the structure of salicylic acid, ie a phenolic OH group, a COOH group, and an aromatic ring system with some C–H groups.

2 **a** Both H atoms are in OH groups, but OH group 1 is attached to C=O whereas OH group 2 is bonded directly to the benzene ring.
b Both H atoms are part of benzene ring CH groups, but H atom 3 is closer to COOH whereas H atom 4 is closer to the phenolic OH.

3 The atoms of CO_2 need to be added. In the Kolbe reaction, a solution of phenol in sodium hydroxide is heated to about 125 °C under a moderate pressure of CO_2. The temperature is important – if it is too high the 4-hydroxy isomer is formed in preference.

Activities: notes and answers to questions

WM1 The origins and development of the modern pharmaceutical industry

This is a group activity. Students divide into three groups to consider and report on

Part 1 Folklore in medicine
Part 2 Medicine discovery and the nation's health
Part 3 The British pharmaceutical industry

They are encouraged to search the Internet to research their topic. The **Salters Advanced Chemistry Web Site** is a good starting point.

1 Folklore in medicine

The information on the web should make students aware that folk medicines are certainly worth investigating, provided they can be separated from the superstitions and mysteries which surround them. Discussion could spread into areas such as 'alternative' medicine – homeopathic cures and acupuncture, for example, which seem to work, but which science cannot explain.

2 Medicine discovery and the nation's health

An OHP transparency based on Table 1 may be useful.

Some points related to the questions are

- drugs and immunisation have reduced deaths from the first 10 diseases in the table
- social factors, eg increased hygiene, diet and exercise, also contribute to longevity
- the main killers today are cancer and cardiovascular disease
- the average age of death is probably a better indicator of the nation's health than the death rate.

3 The British pharmaceutical industry

Data handling skills are important here – there is much information to process. The group should be encouraged to use OHP transparencies in their presentation.

Some points about the questions posed are

- the pharmaceutical industry makes a large contribution to the visible trade surplus
- the industry has grown considerably since 1960
- the UK pharmaceutical industry is of major international importance.

The message which should come across is of an expanding highly capitalised industry with a good surplus of exports over imports.

WM2 Extraction of salicylic acid

Safety note Information about hazardous chemicals is given on the activity sheet. Means for safe disposal of solvent residues are necessary.

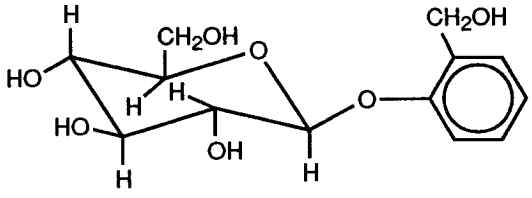
Salicylic acid is fairly soluble in hot water. Care must be taken to cool the mixture following the hydrolysis of the oil of wintergreen and subsequent acidification.

The t.l.c. plates need heating in an oven before use, and should contain a fluorescent dye if ultraviolet light is to be used for detection.

a Reflux condenser allows volatile organic compounds to be heated without loss. Vapour is condensed and returned to the flask.
b Reaction is slow.
c Salicylic acid is present. One of the products from the alkaline hydrolysis of the oil is the sodium salt of salicylic acid.
d Prior to acidification of the solution by hydrochloric acid and following the hydrolysis of the oil (step **4**), the mixture could be fractionally distilled. One of the volatile products is methanol.
e Salicylic acid is slightly soluble in water. It is less soluble in cold water and thus more solid acid will have been formed and filtered off (step **5**).

Note In a previous version of this activity, students attempted to extract salicylic acid from willow bark.

The substance in willow bark is *salicin*, a glucoside of 2-hydroxybenzyl alcohol.



This is hydrolysed and oxidised in the body to produce 2-hydroxybenzoic acid (salicylic acid). We have found it very difficult to reproduce this process consistently in the laboratory.

WM3 Investigating the chemistry of the –OH group in various environments

Advance preparation

The melting point of 2-methylpropan-2-ol (*t*-butyl alcohol) is 25.5 °C. If kept in a cold store, it will take some time to melt.

Part 1: Comparing ethanol, phenol, ethanoic acid and 2-hydroxybenzoic acid

Safety note Information about hazardous chemicals is given on the activity sheet. Phenol can cause sores and blisters if spilt on the skin. Glycerol, propane-1, 2, 3-triol, can be applied to counteract phenol burns. Glacial ethanoic acid is corrosive and has an unpleasant smell. The bottle should be used in a fume cupboard if possible.

The expected results are:

Test	A Ethanol	B Phenol	C Ethanoic acid	D 2-Hydroxy-benzoic acid
pH value	7	5–6	3	3–4
Sodium carbonate test	No reaction	Solid dissolves	Gas evolved lime water test positive	Gas evolved lime water test positive
Iron(III) chloride test	No colour change	Violet coloration	No colour change	Deep purple coloration
Potassium dichromate(VI) test	Turns green	Turns dark brown	No colour change	Turns dark brown
Methanol and conc. sulphuric acid test	Smell of ethanol/ methanol remains	Smell of phenol remains	Vinegar smell sweetened	Sweetish smell of oil of wintergreen

a D has acidic properties similar to ethanoic acid, and resembles phenol in its reactions with iron(III) chloride and potassium dichromate(VI).

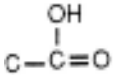
b There is a –COOH group and an –OH group attached directly to a benzene ring.

Part 2: Comparing different alcohols

Safety note Information about hazardous chemicals is given on the activity sheet.

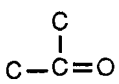
c Primary and secondary alcohols react readily with the acidified potassium dichromate(VI); tertiary alcohols do not react under the conditions used in this experiment. Secondary alcohols are oxidised to the corresponding carbonyl compound (a ketone); primary alcohols can be oxidised further to the carboxylic acid.

d Students should see that primary alcohols, in which the carbon atom attached to the –OH group is bound to only one other carbon atom (and two hydrogens) can form a



group in a carboxylic acid.

Two of the bonds on a secondary carbon atom are



attached to other C atoms. Therefore, the three bonds of the carboxyl group cannot be formed without breaking the carbon chain in the molecule. Mild oxidation of secondary alcohols therefore leads only to

Tertiary alcohols cannot be oxidised without breaking a C–C bond in the carbon chain.

WM4 Interpretation of the mass spectrum of salicylic acid

1 and **2** $M_r \approx 138$

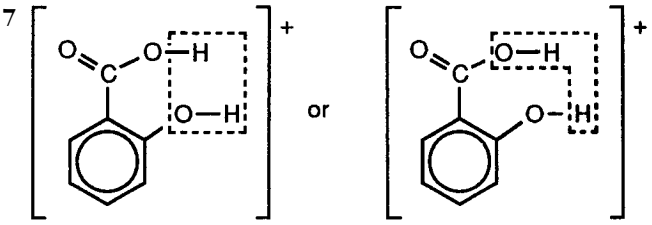
3 The ^{13}C peak suggests that salicylic acid contains 7 carbon atoms. Therefore $C_7H_6O_3$ is the likely molecular formula.

4 Salicylic acid is 2-hydroxybenzoic acid.

5 Peaks not shared are 64, 92 and 120.

6 H_2O

7



8 Elimination of H_2O occurs between groups of atoms which are in close proximity in 2-hydroxybenzoic acid. In the 3- and 4-hydroxy isomers, the groups are too far apart for elimination to take place.

WM5.1 A preparation of aspirin

Safety note Information about hazardous chemicals is given on the information sheet. Means for safe disposal of solvents are necessary.

Students may need quite a lot of help before starting this practical. In particular, they may need to go through the principles of esterification and realise that ethanoic anhydride is an ethanoylating agent.

b M_r (salicylic acid) = 138
M_r (aspirin) = 180
138 g salicylic acid would be expected to produce 180 g aspirin.
So, 2.0 g salicylic acid would be expected to produce 2.6 g aspirin
% Yield = $\frac{1.7}{2.6} \times 100 = 65\%$

c Impurities are left behind in solution.

d A pure sample should give a single spot (and no residue at the origin).

Activity 5.2 Using spectroscopy

a **Figure 1** refers to **B** (2-hydroxybenzoic acid): characteristic i.r. absorptions at 1720 cm^{-1} (carbonyl in carboxylic acids) and 3600 cm^{-1} (phenolic OH). (It has been sharpened as there is internal hydrogen bonding between the phenolic OH and the carbonyl CO in the acid group.)
The mass spectrum contains the molecular ion (at 138). The ion at 120 indicates a loss of 18, ie H_2O. This is unusual. It is due to the proximity of the two functional groups. There is a further loss of 28, presumably CO, giving the fragment at 92.

Figure 2 refers to **C** (aspirin) with i.r. absorption at 1700–1750 cm^{-1} (carbonyl in acids and esters) and the broad peak at

2500–3000 cm^{-1} (carboxylic acids). The mass spectrum contains the molecular ion (at 180). The fragment at 163, a loss of 17, indicates loss of OH. It also contains the fragments at 138 and 120, similar to those obtained from **B**. Note also the fragment at 43, probably CH_3CO^+.

Figure 3 refers to **A** (phenol) with i.r. absorption at 1600 cm^{-1} and 3600 cm^{-1} (phenolic OH).

The mass spectrum contains the molecular ion (at 94). (Although the phenyl ring is usually stable, phenols do exhibit fragmentation as seen by the peaks at 66 and 65 which must contain either 4 or 5 carbon atoms. They are probably $C_5H_6^+$ and $C_5H_5^+$.)

b **B** $C_7H_6O_3$
C $C_9H_8O_4$
A C_6H_6O

These calculations illustrate how important it is to have accurate numbers for the percentage composition by mass.

WM6 An aspirin assay

Safety note Information about hazardous chemicals is given on the activity sheet.

This activity is a good starting point for further discussion of what is meant by the percentage of aspirin in a tablet. A tablet labelled as '300 mg' may actually weigh 327 mg. What is the extra mass?

WM8 Which product should a pharmaceutical company develop?

This activity consists of a general information sheet, an evaluation sheet, and information on each of two potential drugs (AP1011 and H2202).

Every student will need a copy of the general information sheet and the Evaluation Report Form. Half the group will need the sheets relating to the Initial Technological and Economic Appraisal, and half will need the sheets relating to the Second Technological and Economic Appraisal.

It is suggested that the group should be divided into smaller groups of 2–4 students. Some of these smaller groups will work on the Initial Appraisal, the others on the Second Appraisal. Each small group should prepare a summary of the points for and against each drug and recommend which is better to adopt for further development.

The conclusions reached from the Initial Appraisal can be discussed first. The small groups who have worked on this should reach an overall recommendation about which drug to develop. The other groups can question them on their reasons as the discussion develops.

The small groups who worked on the Second Appraisal can then report. Thus those who worked on the first stage can see how their decision has worked out at the next stage. Finally, the whole group should agree on which drug should be marketed. At this stage it can be revealed that **compound AP1011 is aspirin and compound H2202 is thalidomide.** Students could be provided with information about the 'thalidomide disaster' and the reasons why the drug was withdrawn.

Discussion should lead to a consideration of how such tragedies can be made less likely in future and may cover questions such as the following.

- How easy is it to foresee such disasters?
- How culpable are the drug companies?
- Who should be responsible if a product is licensed in accordance with agreed safety procedures and then turns out to be harmful?
- Must the patient always accept some risk with any medication?

Note that, although this exercise makes some important points, it is contrived in the sense that it applies modern screening procedures to medicines that were developed some time ago.

1 Because of its early discovery and development, aspirin never actually went through the kind of evaluation described in the exercise.

2 Thalidomide is a more recent discovery, but even so it did not go through the full evaluation procedure described. Indeed, the modern painstaking screening procedure for medicines was largely introduced as a response to the thalidomide tragedy. The effect of thalidomide in crossing the placenta was only discovered after it was marketed: modern screening procedures would have detected this effect in pregnant animals.

3 At the time of the introduction of thalidomide, the main sedatives in use were in fact barbiturates, which are far more addictive than the benzodiazepines like Mogadon and Valium which are used today. There was therefore more incentive to introduce a non-addictive sedative/hypnotic like thalidomide.