MDI.I

Aldehydes and ketones

This activity considers the formation and reactions of aldehydes and ketones.

Requirements

- potassium dichromate(VI) solution, 0.1 mol dm^{-3} (2 cm^3)
- protective gloves
- dilute sulphuric acid, 2 mol dm^{-3} (10 cm^3)
- propan-1-ol (3 drops)
- propan-2-ol (3 drops)
- 2-methylpropan-2-ol (3 drops)
- test-tubes and rack
- propanal (3 drops)
- propanone (3 drops)
- angled glass tubing and rubber bung
- Bunsen burner, tripod and gauze
- 400 cm^3 beaker (for hot water bath)
- Fehling's solution 1 (2 cm^3)
- Fehling's solution 2 (2 cm^3)

CARE Propanal, propanone and the alcohols are highly flammable liquids. Keep bottles stoppered when not in use and well away from naked flames. Avoid skin contact and do not breathe the vapours.

CARE Dichromates(VI) irritate the skin and are suspected carcinogens. Avoid all skin contact. Any spillage should be washed off at once. Wear protective gloves.

Fehling's solution 1
Fehling's solution 2

potassium dichromate(VI) solution

propan-1-ol
propan-2-ol
2-methylpropan-2-ol

propanal

propanone

sulphuric acid

CARE Eye protection and gloves must be worn.

What you do

1 Place about 1 cm depth of 0.1 mol dm^{-3} potassium dichromate(VI) solution (**CARE** Toxic. Avoid skin contact. Wear gloves) in a test-tube. Add 2 mol dm^{-3} sulphuric acid (**CARE** Corrosive) until the tube is half full. Then divide this mixture as equally as possible between five test-tubes.

You are going to investigate the effect of the oxidising mixture on various oxygen-containing compounds starting with propan-1-ol, propan-2-ol and 2-methylpropan-2-ol.

2 Add 3 drops of one of the alcohols to the oxidising mixture in one of the tubes. Be careful not to add too much alcohol. (**CARE** Alcohols are highly flammable. Keep the bottle well away from naked flames.)

Carefully **warm** the contents of the tube until they just begin to boil. (**CARE** Do not continue to boil the liquid in case alcohol vapour catches fire.)

3 Label the tube and leave it to stand. Repeat the procedure in step **2** with each of the other two alcohols.

4 Make a note of any changes of appearance of the mixtures in the tubes. Work out what has happened in each case, and present your results in the form of a table showing the structural formulae of the alcohols and any products which are formed.

5 Where reaction has occurred, distil out a few drops of liquid from each tube using the apparatus shown (Figure 1).

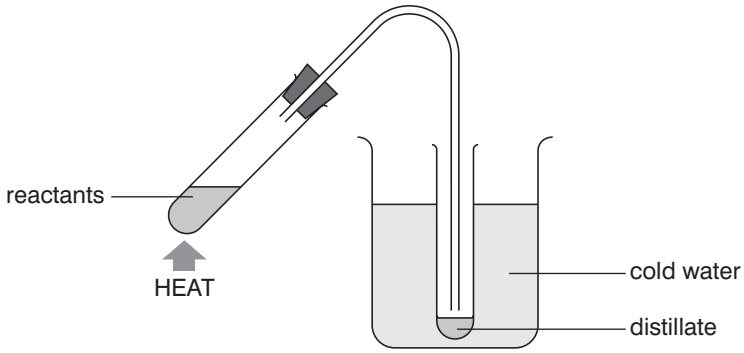


Figure 1 Distilling off the product of oxidation

6 The products which you have distilled over should be propanal and propanone (**CARE** Highly flammable liquids).

Use these liquids, or the liquids from stock bottles of propanal and propanone, and repeat steps **2** and **3** with the two liquids separately.

7 Prepare a hot water bath. A suitable arrangement is a 400 cm^3 beaker half full of water on a tripod and gauze over a Bunsen flame. Transfer about 1 cm^3 of one of the distillates (or reagents from the stock bottle) to a test-tube. Add about 1 cm^3 of Fehling's solution 1 followed by 1 cm^3 of Fehling's solution 2. (**CARE** Fehling's solution 2 contains sodium hydroxide and is corrosive.) Place the test-tube in the hot water bath and observe any colour changes.

Now repeat the experiment with the second liquid.

QUESTIONS

a Which of the alcohols, propan-1-ol, propan-2-ol and 2-methylpropan-2-ol reacted readily with potassium dichromate(VI) solution?

b Account for the change of colour of the mixtures, when one occurs, in the reactions above.

c Write down the full structural formulae of the organic products.

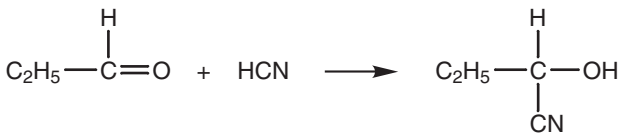
d One of the compounds formed from the reactions above reacts further with potassium dichromate(VI) solution. Write down the structural formulae of this compound and the organic product of this further reaction.

e The red precipitate formed on reaction with Fehling's solution is Cu_2O (the reagent contains $Cu^{2+}(aq)$ ions).

- **i** Suggest what has happened to the organic reagent in the tube when reactions have occurred.
- **ii** Compare this with the process that occurs with the organic reagent and potassium dichromate(VI) solution.

f Propanal and propanone can be reduced to alcohols using the reagent sodium tetrahydridoborate(III), $NaBH_4$. Give the names and structural formulae of the alcohols that will be produced.

g Propanal reacts with hydrogen cyanide, as shown in the equation below:



Write a corresponding equation for the reaction of propanone with hydrogen cyanide.

MDI.2

BAC determination using gas–liquid chromatography

By carrying out this activity you will learn more about the use of g.l.c. for measuring blood-alcohol concentrations. The technique can easily be adapted, and is used to analyse many other kinds of mixture. This activity illustrates ideas about g.l.c. which you learned in* Colour by Design*. You may need to refer to* Chemical Ideas 7.6 *before you begin.

Introduction

A sample which is a mixture of several similar compounds will produce a g.l.c. trace showing separate peaks for each compound. In general, for compounds of the same chemical type, more volatile compounds have shorter g.l.c. retention times.

What you do

Use the following information to investigate how g.l.c. can be used to estimate blood-alcohol concentration (BAC).

1 The chromatogram illustrated in Figure 1 was produced by a mixture of the first five straight-chain primary alcohols.

- **a** Measure the retention times for the five peaks. Record these in a table, together with the name and formula of the alcohol responsible for each peak.
- **b** Estimate a retention time for hexan-1-ol.

2 When blood is analysed for its alcohol content, an exactly measured sample is diluted with water and a standard amount of propan-1-ol is added. A measured sample of this mixture is then analysed by g.l.c.

The gas chromatogram consists of two peaks, corresponding to ethanol and propan-1-ol. The area of each peak is proportional to the amount of compound in the sample, but the instrument's sensitivity may vary from run to run. Using a propan-1-ol standard overcomes this error – the detector will give a high reading for all propan-1-ol peaks if its sensitivity is high, or a low reading for all peaks if the sensitivity is low. In either case, the *ratio* of the ethanol and propan-1-ol peak areas will be the same. It is this ratio which is used to calculate the BAC. For fairness, at least two determinations are made, and the equipment is calibrated periodically using an ethanol solution of known concentration.

Commercial instruments calculate peak areas electronically. However, it is possible to regard a peak as a triangle. The area is then the height of the triangle multiplied by half the length of the base.

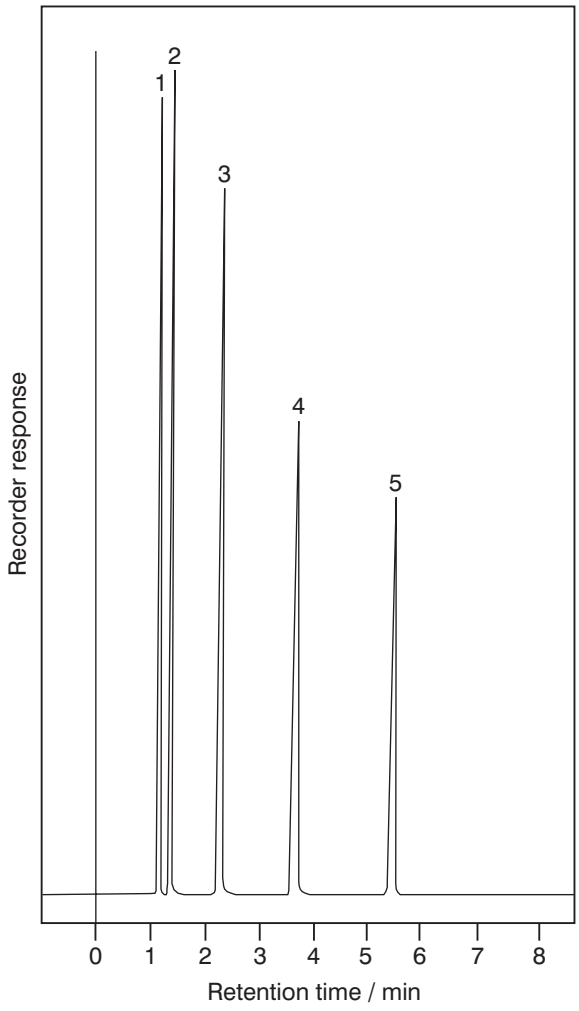


Figure 1 Chromatogram of a mixture of the first five straight-chain primary alcohols: 1, methanol; 2, ethanol; 3, propan-1-ol; 4, butan-1-ol; 5, pentan-1-ol.

Figure 2 shows g.l.c. traces for three blood samples. Trace I corresponds to a BAC of 80.

Note: In practice the peaks are much narrower, as in Figure 1, and the areas under the peaks are found using special computer programs built into the recorders attached to the gas chromatograph. Figure 2 is drawn to enable you to calculate the areas yourself.

Peak area is height times half-width of the triangle obtained by extrapolating the lines of the peak.

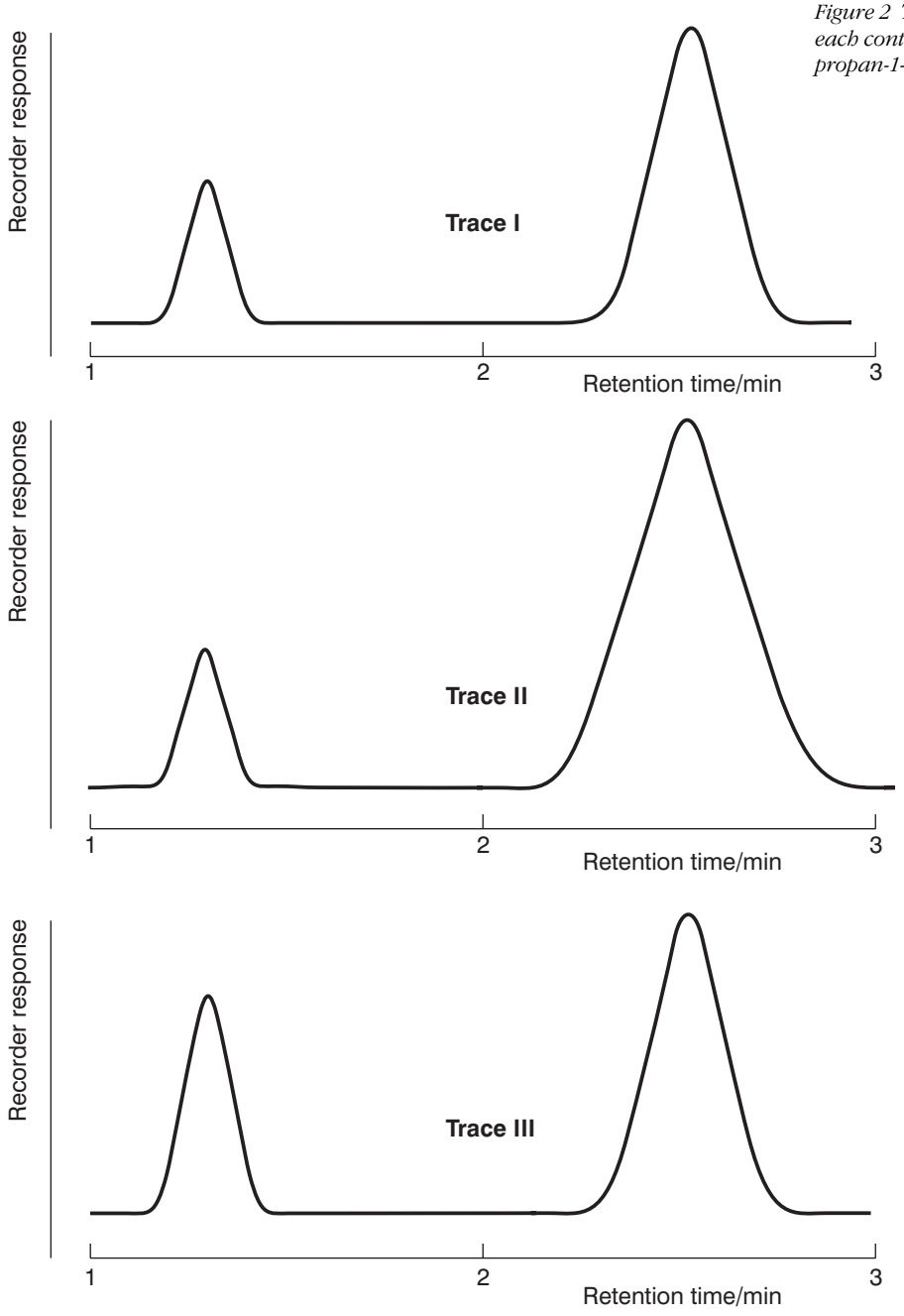


Figure 2 The g.l.c. traces of three blood samples each containing a standard amount of propan-1-ol

c Calculate the ratio of peak areas (ethanol peak : propan-1-ol peak) in trace I.

d Calculate the peak area ratios in traces II and III. Hence calculate BAC values for the other two blood samples. Was either over the limit?

e Suggest a reason why propan-1-ol is chosen for the standard rather than any of the other alcohols represented in Figure 1.

MD3.1

Making a toolkit of organic reactions

This activity will help you to revise and use some of the organic reactions you have met in the course.

What you do

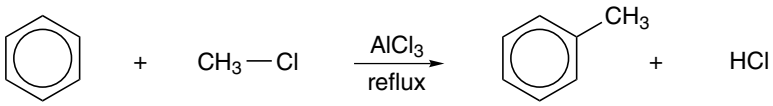
The idea is to organise some of the reactions you have met in the course, together with a few new ones, into a 'toolkit' of reactions which you can use to design organic syntheses.

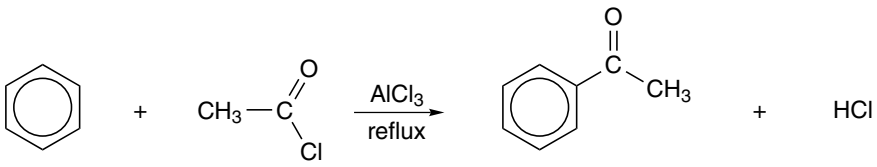
1. First make sure that you are familiar with the main reactions of the functional groups that you have met throughout the course. These are summarised in **Chemical Ideas 14.2.**
2. Read the **Reference section** below about useful synthetic reactions. This gives you some hints about making new C–C bonds as well as some extra reactions which are often useful in synthesis. *You are not expected to remember these extra reactions, but you should be able to use them correctly if you are given them.*
3. Then use the new reactions in the reference section, together with the more familiar ones you have met in earlier units, to complete the two flow sheets, **Chart A** and **Chart B**. These two flow sheets make up your 'toolkit'. To complete them, you should write the reaction conditions over each arrow and, where possible, the *reaction type* (substitution, oxidation, acylation, etc.) under the arrow.
4. Use the toolkit to answer the questions on page 315.

Reference section: Some useful synthetic reactions

When you design a synthesis, many of the reactions you will use will simply convert one functional group into another. But if you want to extend the carbon framework of the molecule and build up larger compounds, you need some way of making carbon–carbon bonds.

One way to do this is to use the Friedel-Crafts alkylation and acylation reactions:

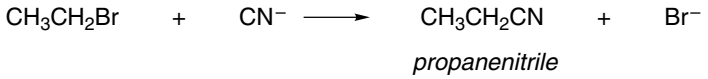




The C=O group can be modified further if necessary

These reactions are very useful because they provide a method of building side-chains onto a benzene ring.

A good way of *extending* a carbon chain is to use the reaction of cyanide ions, CN^-, with halogenoalkanes. The cyanide ion is a powerful nucleophile and will displace the halogen atom in much the same way as OH^-. For example:



propanenitrile

The reaction is carried out by refluxing the halogenoalkane with a solution of sodium cyanide in ethanol and water. The product is a *nitrile*.

Compare that reaction with this:

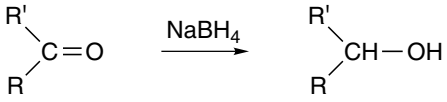
$$CH_3CH_2Br + OH^- \longrightarrow CH_3CH_2OH + Br^-$$

Nitriles themselves have few direct uses, but they are very important as synthetic intermediates. The important thing is that a new carbon–carbon bond has been made, and the nitrile group can then undergo further reactions. For example, when nitriles are hydrolysed with dilute acids, carboxylic acids are formed.

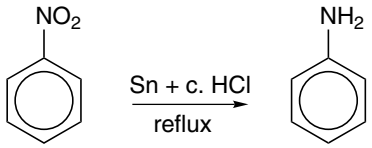
$$CH_3CH_2CN \xrightarrow[\text{reflux}]{H^+(aq)\ /\ H_2O} CH_3CH_2COOH$$

Sometimes it is necessary to reduce aldehydes and ketones back to alcohols. This does not take place readily and requires a powerful reducing agent. A complex metal hydride is used, called sodium tetrahydridoborate(III), $NaBH_4$:

$$RCHO \xrightarrow{NaBH_4} RCH_2OH$$



A different reducing agent, tin in the presence of concentrated hydrochloric acid, is used to convert nitro-groups into amino-groups:



One final reaction. You will find that *acyl chlorides* are very useful synthetic intermediates. These can be made from carboxylic acids by refluxing with a reactive liquid called sulphur dichloride oxide (SCl_2O). The reaction mixture must be completely dry.

$$CH_3COOH + SCl_2O \longrightarrow CH_3COCl + SO_2 + HCl$$

Note You should be familiar with Friedel-Crafts alkylation and acylation reactions (see **Chemical Ideas 12.4** and **14.2**) and the reduction of aldehydes and ketones (see **Chemical Ideas 13.7** and **14.2**). You are not expected to remember the rest of the reactions in this reference section, but you should be able to use them correctly if you are given them.

The toolkit: Chart A

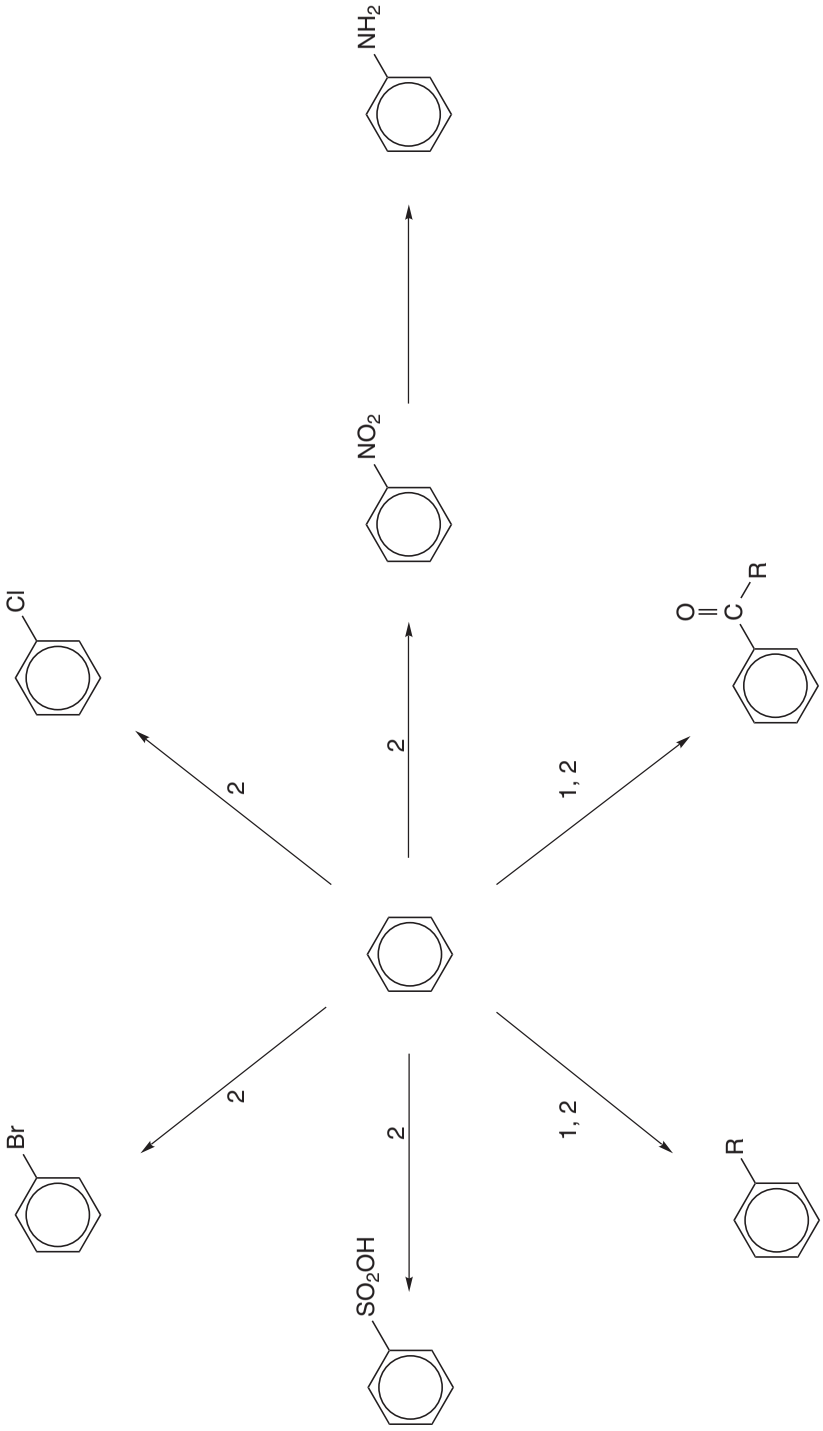
Notes

1 The formation of a nitrile from a halogenoalkane is a *carbon–carbon bond-forming reaction*.
The carboxylic acid formed from the nitrile has an extra carbon atom in the side-chain.
All other reactions are simple *functional group interconversion*.

2 The halogenoalkane shown will only be a minor product of the reaction from the alkene. The main product will be the isomer with the Br atom attached to the second carbon atom.

3 You may wish to add other reactions to this toolkit, for example, the formation of a secondary alcohol from an alkene, RCH = CHR', and a ketone from a secondary alcohol.

The toolkit: Chart B



Notes

1 The Friedel-Crafts reactions are *carbon–carbon bond-forming reactions.*

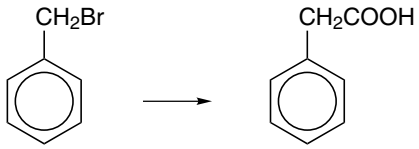
2 All the substitution reactions of arenes are *electrophilic.*

QUESTIONS

a Use the toolkit to design some simple two-step syntheses. In each case, write out the synthesis in the form of a flowchart and write the reagents and conditions on the arrows.

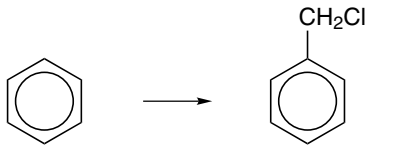
i $CH_3CH_2CH_2OH \longrightarrow CH_3CHBrCH_3$

ii



iii $CH_3CH_2COOH \longrightarrow CH_3CH_2CONH_2$

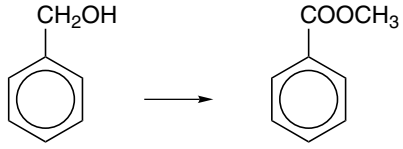
iv



v $CH_3CH_2OH \longrightarrow CH_3CH_2NH_2$

b Now, see whether you can work out routes for the following conversions. You should be able to carry out each conversion in no more than three steps. You have a supply of methanol in addition to the starting material, but no other organic compounds.

i

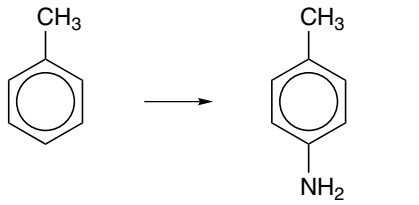


ii $CH_3CH{=}CHCH_3 \longrightarrow CH_3{-}\underset{\displaystyle COOH}{\underset{|}{CH}}{-}CH_2CH_3$

iii $CH_3CH_2CH_2Br \longrightarrow CH_3CH_2CH_2COOCH_3$

iv $CH_3CH_2OH \longrightarrow HOCH_2CH_2OH$

v



c Starting from ethene, work out a synthetic route for the preparation of the amide $CH_3CH_2CONHCH_2CH_3$ (six steps). You may not use any other organic compound.

MD3.2
Classifying reactions

This activity is based on the toolkits produced from Activity MD3.1 and will enable you to familiarise yourself with them.

What you do

Complete the table below by listing, for each type of reaction, one or more homologous series that undergo this reaction. Draw the functional group and give a balanced equation for an example of the reaction.

Type of reaction		Name of homologous series	Functional group	Example of reaction
Hydrolysis	**i** **ii** **iii**	Ester		$CH_3COOC_2H_5 + H_2O \xrightarrow{H^+} CH_3COOH + C_2H_5OH$
Esterification	**i**			
Elimination	**i**			
Acylation	**i** **ii** **iii** **iv**			
Addition electrophilic nucleophilic	 **i** **ii**			
Substitution radical electrophilic nucleophilic	 **i** **ii** **iii**			
Oxidation	**i** **ii**			
Reduction	**i** **ii**			

QUESTIONS

a Name each of the homologous series in your table that can act as an acid.

b Name a homologous series that can act as a base.

c What types of organic compound have hydrogen bonding as the main intermolecular force?

d Give two different reducing agents used in organic reactions and give examples of these reactions.

e Both sodium cyanide and hydrogen cyanide are extremely toxic. Why are they still used in organic synthesis?

MD3.3

Using the toolkit to synthesise medicines

In this activity you will use your knowledge of organic reactions to devise ways of synthesising some complex organic molecules.

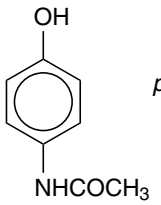
You will also see how spectroscopy can be used to monitor the chemical reactions under investigation.

What you do

In Parts 1 and 2, you will use the toolkit of organic reactions from **Activity MD3.1** to help you suggest synthetic routes for the preparation of two medicines, paracetamol and ibuprofen. In Part 3, you will use spectra to identify some of the organic molecules used in the synthesis of ibuprofen, and in Part 4, you will study the structure of some sex hormones.

Part 1: Making paracetamol from phenol

Paracetamol is widely used as a painkiller and to reduce fever. It is more expensive than salicylates like aspirin, but it is thought to have fewer side-effects in normal use. (Overdosing with paracetamol, however, can lead to irreversible liver damage.) You may remember looking at the n.m.r. spectrum of paracetamol in **Activity EP2.3**.



paracetamol

1 Use your toolkit to plan a synthesis of paracetamol from phenol. You should be able to do this in three steps. Write out your proposed scheme in the form of a flowchart. Write the reagents and conditions for each step above the arrows.

2 Indicate any stages where a reaction produces more than one isomer, such that the required product would have to be separated.

QUESTIONS

a Write out the *full* structural formula of the target molecule.

b For each step in your synthesis, choose a word from the list below to describe the *type of reaction* occurring:

substitution	oxidation	esterification
elimination	reduction	hydrolysis
addition	ethanoylation	polymerisation

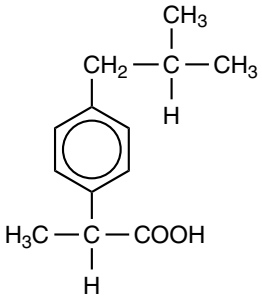
c Paracetamol is a white crystalline solid which melts at 169 °C. It is fairly soluble in hot water but insoluble in cold water. Explain how you could purify your product.

d Describe one way in which you could test whether your sample was pure paracetamol.

Part 2: Making ibuprofen from benzene

Over one million people in the UK are afflicted with rheumatoid arthritis, a disease in which their joints become painfully inflamed.

An early successful anti-inflammatory agent was a derivative of phenylpropanoic acid, called *ibuprofen*, which was introduced by Boots (now Knoll Pharmaceuticals) in the 1970s. It has also proved to be a safe and effective analgesic. Since 1983 it has been available from pharmacists as a non-prescription drug, sold under several tradenames. Its systematic name is 2-(4-(2-methylpropyl)phenyl) propanoic acid.



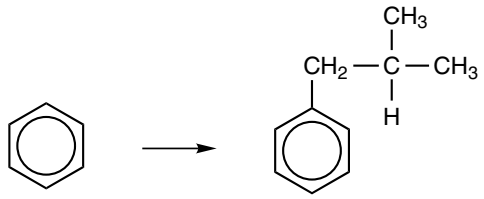
ibuprofen

3 Use your toolkit to devise a synthesis of the target molecule, ibuprofen, from benzene. You can use other simple organic molecules in your synthesis. It is quite complex (six steps) and, if you get stuck, you may find it helps to work through the following stages.

Help – if you need it

Start by comparing the structures of benzene and ibuprofen. Two **carbon–carbon bond-forming reactions** will be necessary to attach the two side-chains to the benzene ring. A Friedel-Crafts alkylation will enable the hydrocarbon side-chain to be attached directly, and if this is followed by Friedel-Crafts acylation at the 4-position in the benzene ring, the second side-chain can be added. This side-chain contains a reactive group which can be converted into the target molecule by a series of **functional group interconversions**.

Step 1: Attaching the alkyl side-chain

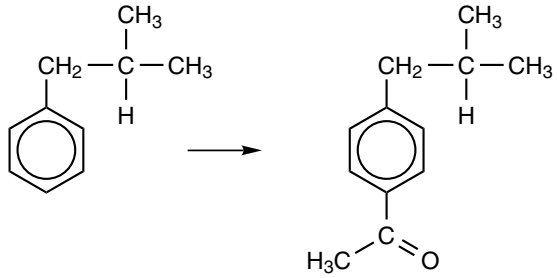


e Give the structure and name of the halogenoalkane needed for this Friedel-Crafts alkylation reaction.

f Classify this reaction by stating the type of reagent involved and the type of reaction.

g What catalyst is needed and how does it help the reaction?

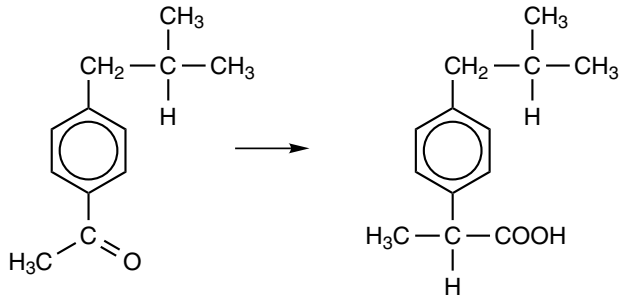
Step 2: Attaching an acyl side-chain



h What is the name and structure of the acyl chloride needed for this Friedel-Crafts acylation?

i What catalyst should be used?

Steps 3–6: Converting the acyl side-chain into a phenylpropanoic acid



j What *carbon–carbon bond-forming* reaction could be used to introduce a new functional group which could easily be changed to a carboxylic acid group?

k What key intermediate must be prepared from the ketone before this reaction can take place?

l What functional group must first be obtained from the ketone before the key intermediate can be prepared?

m Now write a total synthesis of the target molecule, giving the reaction conditions necessary for each step above the arrow linking the intermediates. Where possible, classify the reactions according to reagent and reaction type beneath the arrow.

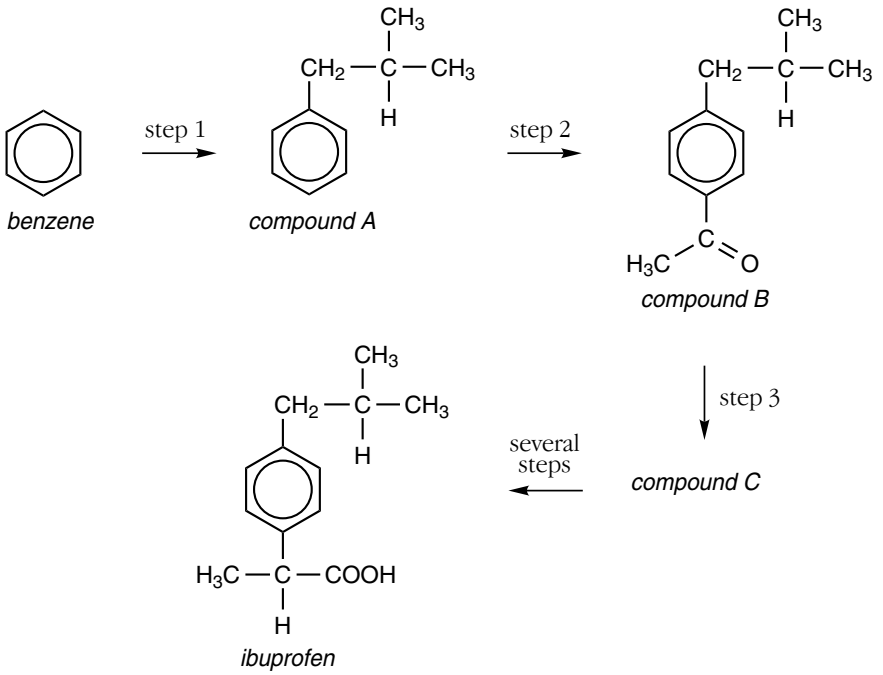
n The synthesis of a new medicine must be accompanied by the correct stereochemistry. This may be crucial to the medicine's action in the body. Place an asterisk (*) against any chiral carbon atom present in the target molecule.

Part 3: Analysing spectra

In this part of the activity you will analyse the infrared, nuclear magnetic resonance and mass spectra of some organic molecules used in the synthesis of the medicine ibuprofen.

You will need to refer to the charts of characteristic i.r. absorption frequencies and proton n.m.r. chemical shifts in the **Data Sheets**.

As you have seen in Part 2 of this activity, a possible synthesis of ibuprofen could involve the following route.



The i.r., n.m.r. and mass spectra of compounds A, B, C and ibuprofen are given in Figures 1, 2, 3 and 4, respectively. You will need to refer to these to answer the questions below.

QUESTIONS

o For compound A:

- **i** Why are there several peaks at around 3000 cm^{-1} in Figure 1(a)?
- **ii** Identify the hydrogen atoms responsible for each of the signals in Figure 1(b).
- **iii** Identify the ions responsible for the peaks at mass 134 and 91 in Figure 1(c). Why has the peak at mass 135 an abundance of about 10% of the peak at mass 134?

p Identify and explain the main changes that have occurred to the i.r., n.m.r. and mass spectra during step 2 of the synthesis, i.e. the conversion of compound A, in Figures 1(a), 1(b) and 1(c), to compound B, in Figures 2(a), 2(b) and 2(c).

q **i** By comparing the spectra for compound C, in Figures 3(a), 3(b) and 3(c), with those of compound B, deduce the structure of compound C.

- **ii** What type of reaction is involved in step 3, the conversion of B to C?

r The spectra for ibuprofen, in Figures 4(a), 4(b) and 4(c), are quite complex. Identify, with reasons, as many of the main features of these spectra as possible.

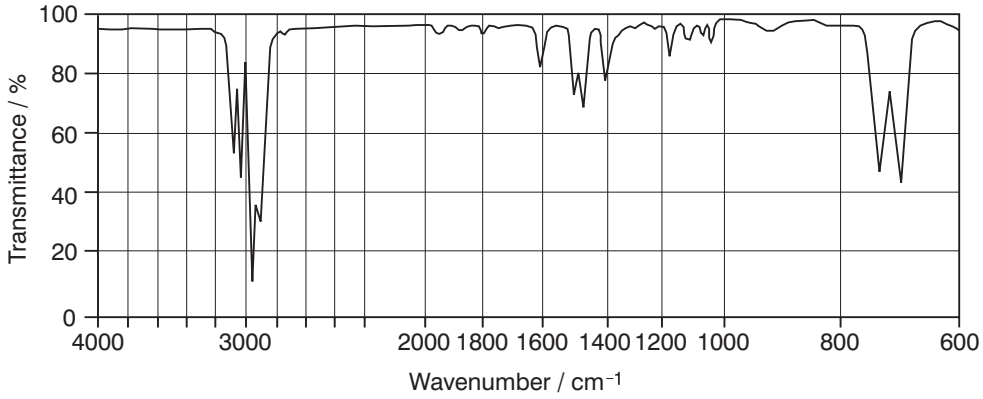


Figure 1(a) The i.r. spectrum of A (in the gas phase)

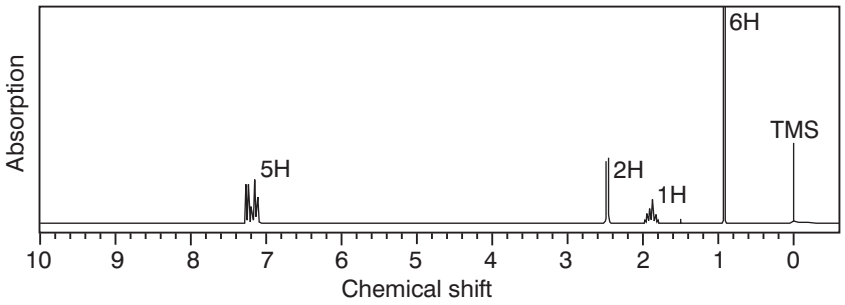


Figure 1(b) The n.m.r. spectrum of A

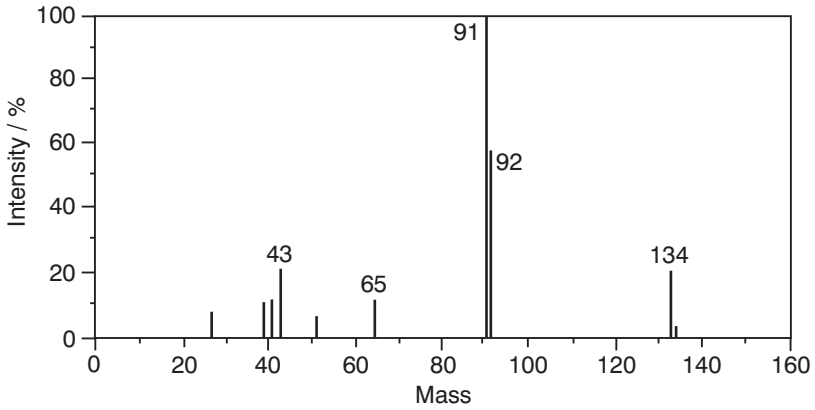


Figure 1(c) The mass spectrum of A

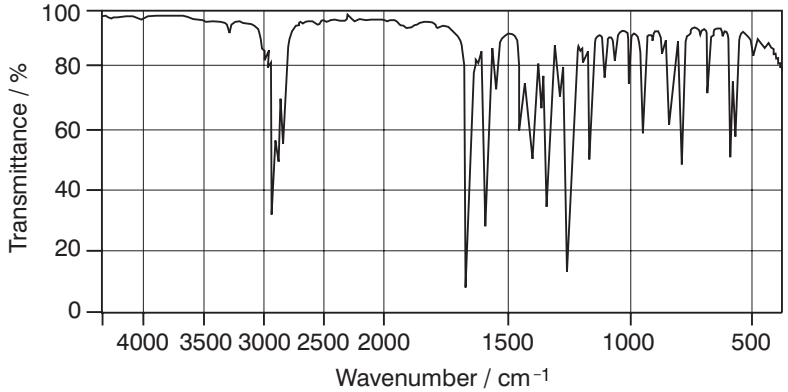


Figure 2(a) The i.r. spectrum of B (in solution)

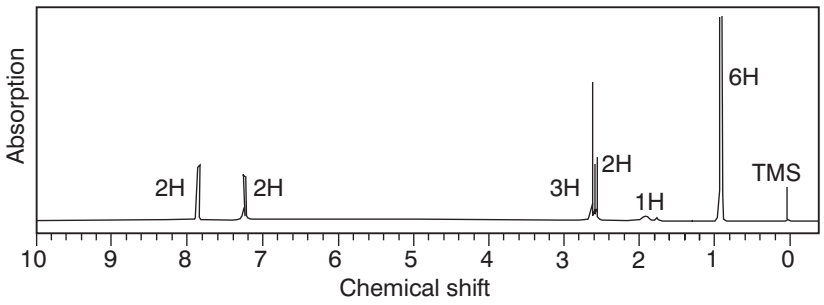


Figure 2(b) The n.m.r. spectrum of B

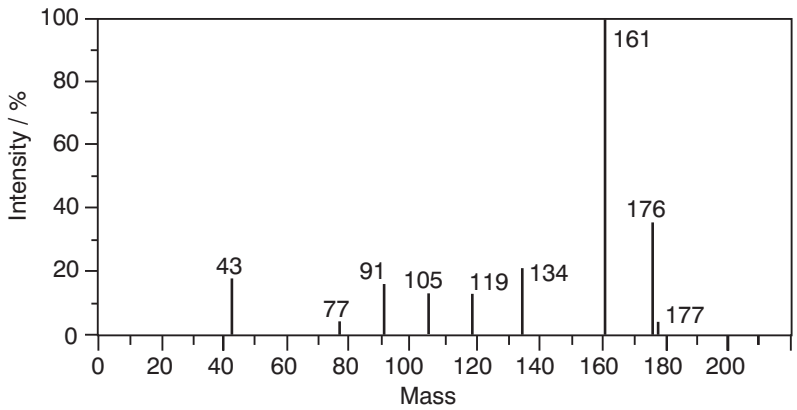


Figure 2(c) The mass spectrum of B

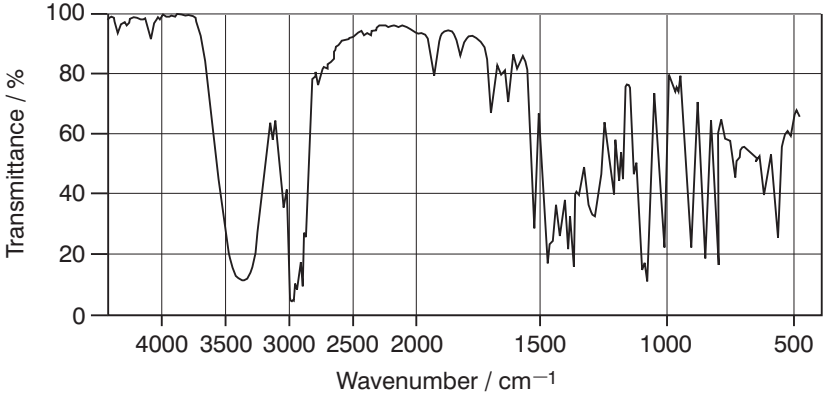


Figure 3(a) The i.r. spectrum of C (in solution)

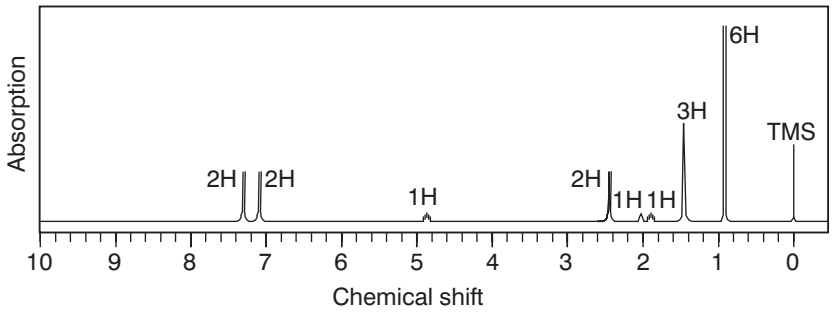


Figure 3(b) The n.m.r. spectrum of C

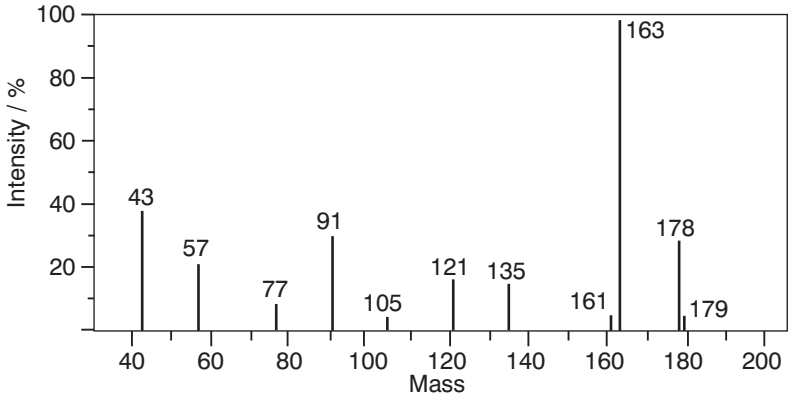


Figure 3(c) The mass spectrum of C

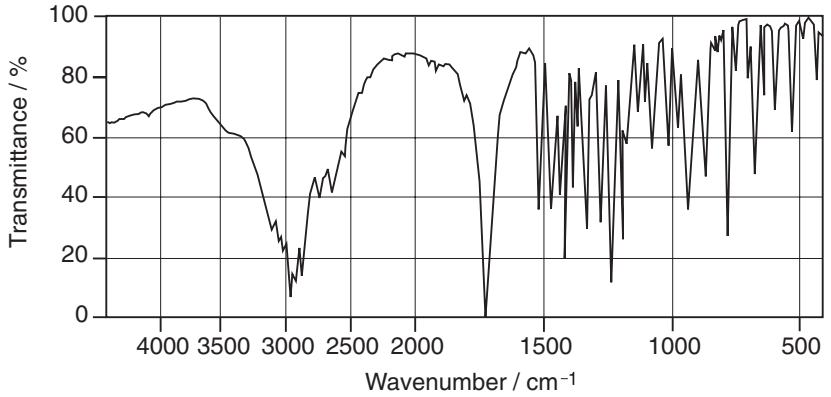


Figure 4(a) The i.r. spectrum of ibuprofen (in solution)

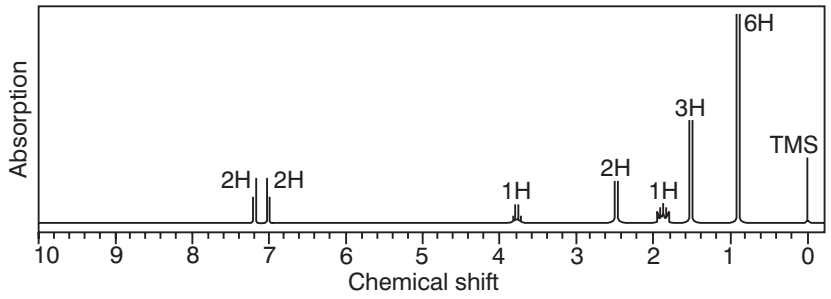


Figure 4(b) The n.m.r. spectrum of ibuprofen

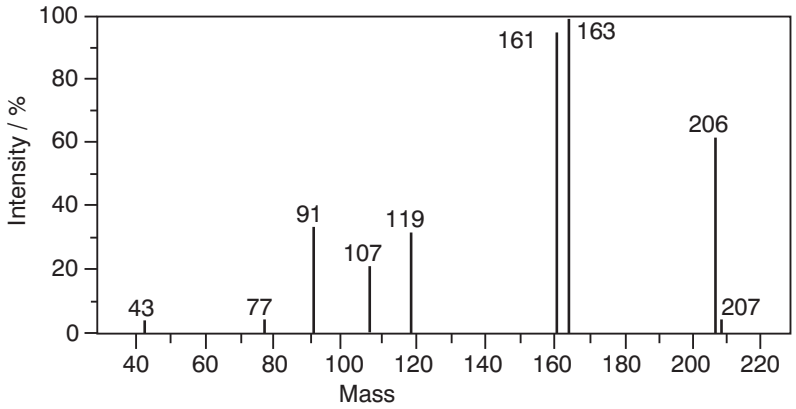
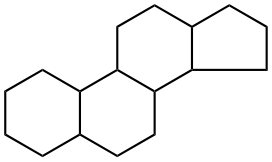


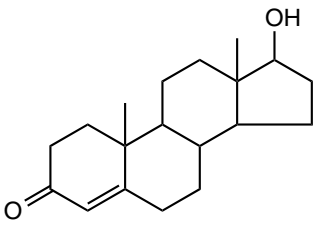
Figure 4(c) The mass spectrum of ibuprofen

Part 4: Investigating sex hormones

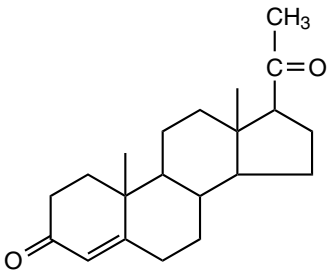
The *sex hormones* are steroids. They each contain the same carbon framework of four fused rings.



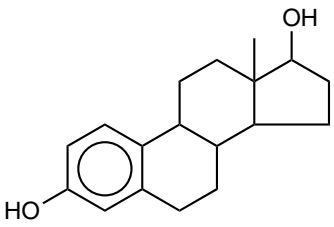
the steroid ring system



testosterone



progesterone



oestradiol

The male sex hormone, *testosterone*, is secreted in the testes and controls the development of secondary sexual characteristics at puberty and sexual activity in the adult.

Oestradiol is one of the principal female sex hormones controlling secondary sexual characteristics. It belongs to a group of female sex hormones called *oestrogens*. *Progesterone* is a second type of female steroid hormone. Its main function is to prepare the wall of the uterus for implantation of a fertilised ovum.

Contraceptive pills usually contain a combination of an oestrogen and progesterone. High levels of these two hormones suppress normal monthly ovulation; this is the natural mechanism used by the body to suppress ovulation during pregnancy.

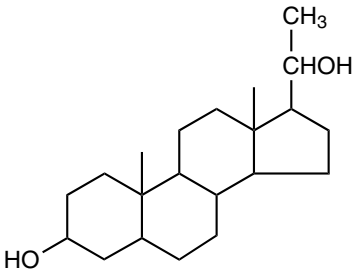
QUESTIONS

s Is the alcohol functional group in oestradiol primary, secondary or tertiary?

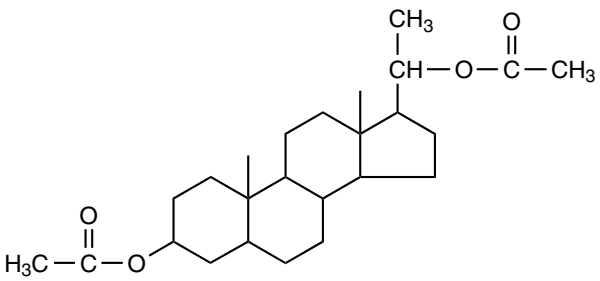
t Explain how a simple test-tube reaction using $FeCl_3$ solution could be used to distinguish between testosterone and oestradiol.

u As a synthetic chemist you wish to modify the progesterone structure in the hope of finding safer, more effective birth-control pills. Use your toolkit to show how you could make the following compounds from progesterone.

i

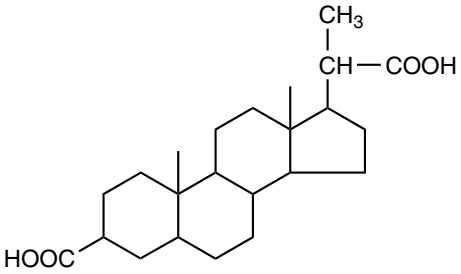


ii



Synthesise the molecule above from your product in **u i** in one step.

iii



Synthesise the molecule above from your product in **u i** in three steps.

v A steroid compound was known to be a female sex hormone. It was thought to be either progesterone or oestradiol.

The infrared spectrum of the steroid is shown in Figure 5. Use the chart of i.r. absorption frequencies in the **Data Sheets** to help you decide on the possible identity of the hormone. Give reasons for your decision.

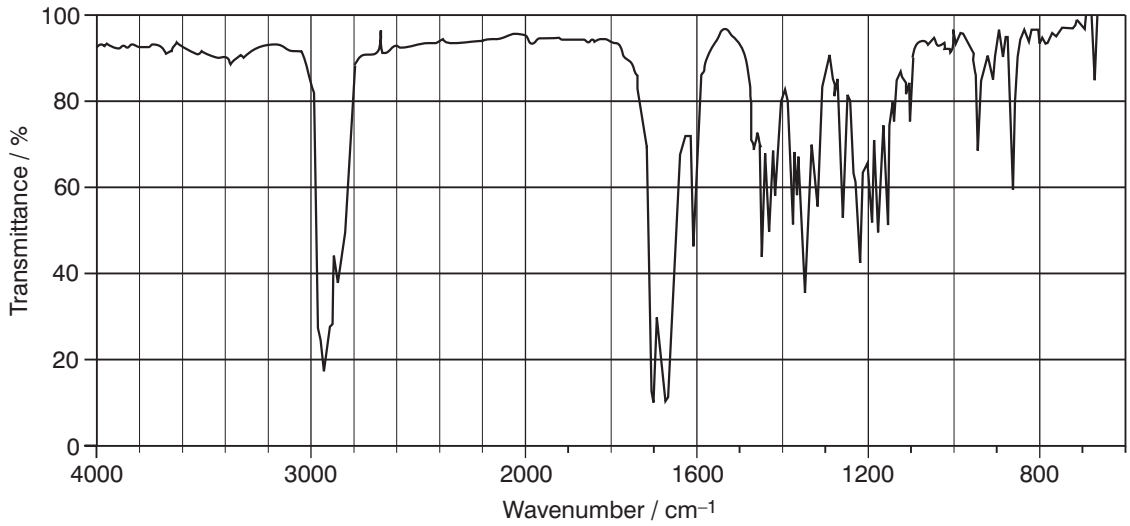


Figure 5 The i.r. absorption spectrum of the unknown steroid (in CCl_4 solution)

MD3.4

Manufacturing salbutamol (Optional extension)

***This activity looks in more detail at the reaction sequence which is used to make salbutamol, and at how much the chemicals used in its synthesis contribute to its cost. The infrared, nuclear magnetic resonance and mass spectra of these compounds are also analysed. There is more about salbutamol in* Chemical Storylines MD3.**

Part 1: Costing salbutamol

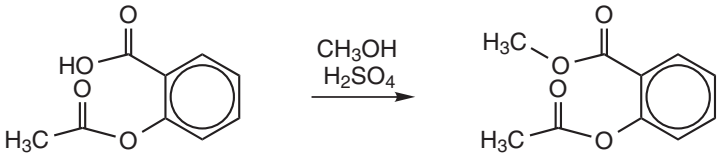
When designing a synthetic route for a new medicine, chemists in the pharmaceutical industry need to bear in mind the following points:

- The starting material should be cheap and readily available.
- The route should involve as few steps as possible, for speed and because every step involves some loss of material.
- Yields should be high for each step.
- Inexpensive and safe reagents and solvents should be used.
- Purification should be easy – medicines must not contain contaminants.

A possible synthesis of *salbutamol* begins with aspirin and involves five steps. The yields for these steps are high compared with many reactions in organic chemistry. Although the final step has a yield of 30% it should be remembered that 30% of the inactive isomer is also formed. The reaction sequence contains no unusual materials.

Reaction sequence

Step 1

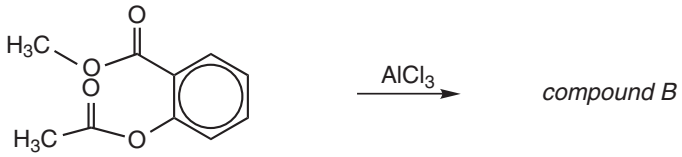


aspirin *compound A*

Solvent	Other reagent
methanol 10% w/v solution	sulphuric acid 10 g per kg aspirin

(w/v means weight (mass) of solute : volume of solvent. A solution containing 100 g of solute in 1 dm^3 of solvent would be a 10% w/v solution. In this case, the solute is aspirin and the solvent is methanol.)

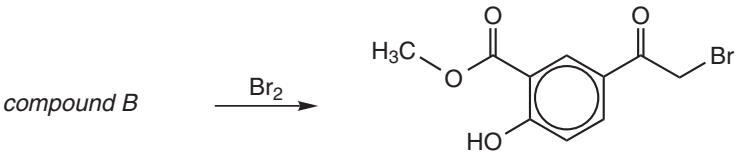
Step 2



compound A *compound B*

Solvent	Other reagent
nitrobenzene 10% w/v solution	aluminium chloride 1 mole per mole of A

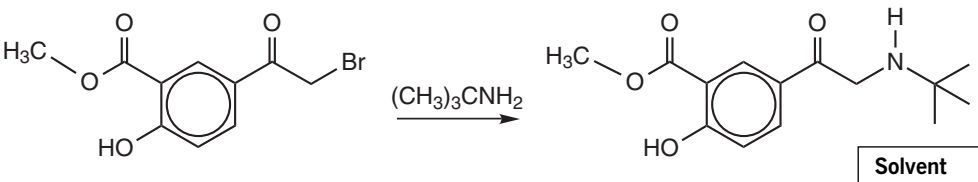
Step 3



compound C

Solvent	Other reagent
trichloromethane 10% w/v solution	bromine 1 mole Br_2 per mole of B

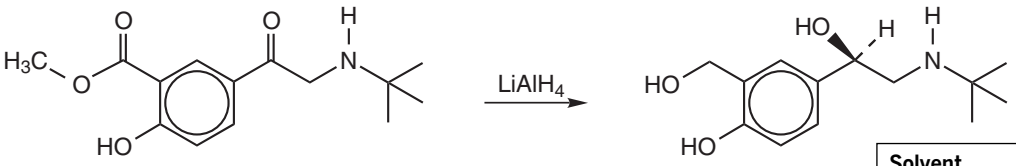
Step 4



compound C *compound D*

Solvent	Other reagent
trichloromethane 10% w/v solution	2-amino-2-methylpropane 2 moles per mole of C

Step 5



compound D

salbutamol (plus an equal amount of its optical isomer)

Solvent	Other reagent
ethoxyethane 2.5% w/v solution	lithium tetrahydridoaluminate 3 moles per mole of D

Costs

Solvents	Cost/£ dm^{-3}	Reagents	Cost/£ kg^{-1}
methanol	4.20	aspirin	12.80
nitrobenzene	9.30	sulphuric acid	2.17
trichloromethane	10.70	aluminium chloride	11.20
		bromine	13.20
ethoxyethane	6.00	2-amino-2-methylpropane	9.60
		lithium tetrahydridoaluminate	450.00

Economics of process

Table 1 gives the yields and relative molecular masses of the organic compounds in the reaction sequence.

1 Copy out Table 1 and complete the other entries to show the masses and amounts of these compounds which could be made *starting with 1 kg of aspirin*.

Compound	M_r	Yield/%	Mass produced/g	Amount produced/mol
aspirin	180	–	1000	5.56
A	194	85		
B	194	60		
C	273	75		
D	265	55		
salbutamol	239	30		

Table 1 Yields and quantities for salbutamol synthesis

2 Use information contained in the reaction sequence and in Table 1 to complete a copy of Table 2 to show the costs of the reagents and solvents used *to convert 1 kg of aspirin into salbutamol*.

Reagent/solvent	Quantity required	Cost/£
aspirin	1 kg	
methanol		
sulphuric acid		
nitrobenzene		
aluminium chloride		
trichloromethane		
bromine		
2-amino-2-methylpropane		
ethoxyethane		
lithium tetrahydridoaluminate		
	Total cost	

Table 2

3 You now know the cost of converting 1 kg of aspirin into salbutamol. What is the cost of synthesising 1 kg of salbutamol?

QUESTIONS

a What other costs will be involved in the production of salbutamol?

b What percentage of the cost of making salbutamol is from the use of solvents? Suggest how this cost may be reduced.

Part 2: Spectra of compounds involved in the synthesis of salbutamol

The product from each stage of the synthesis of salbutamol can be characterised by the use of infrared (i.r.) and nuclear magnetic resonance (n.m.r.) spectroscopy and mass spectrometry.

The i.r., n.m.r. and mass spectra of aspirin, compounds A, B and C (from the reaction sequence on pages 324–5), and salbutamol are given in Figures 1–5.

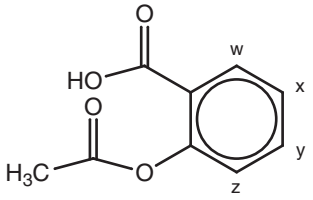
QUESTIONS

For some of the following questions, you will need to refer to the tables of characteristic i.r. absorption frequences and proton n.m.r. chemical shifts in the **Data Sheets**.

c For the starting material in this synthesis, aspirin (2-ethanoylhydroxybenzoic acid):

i identify the bonds responsible for the broad peak around 3000 cm^{-1}, and the sharp peaks at 1750 cm^{-1} and 1690 cm^{-1} in Figure 1(a).

ii identify the hydrogen atoms responsible for the signals at chemical shifts 2.2. and 13.1 in Figure 1(b). The hydrogen atoms responsible for the cluster of signals in the chemical shift range 7.5 ± 0.5 are indicated as w, x, y and z on the following structure of aspirin.



iii identify the ions responsible for the peaks at mass 180, 163, 120 and 43 in Figure 1(c).

d Compare Figures 1(a)–1(c) and Figures 2(a)–2(c). Identify and explain the main changes that have occurred to the i.r., n.m.r. and mass spectra during the conversion of aspirin into compound A in step 1.

e **i** Compound B and compound A both have molecular ion peaks of mass 194. How are compounds B and A related?

ii With the help of the relevant spectra, Figures 3(a)–3(c), deduce the structure of compound B.

f **i** Compare Figure 3(b) and Figure 4(b). Identify and explain the main change that has occurred to the n.m.r. spectrum in the conversion of compound B into compound C in step 3.

ii In the mass spectrum of compound C, Figure 4(c), there are *two* molecular ion peaks of equal intensity, at mass 272 and 274 respectively. Explain this observation.

g The n.m.r. spectrum of salbutamol is given in Figure 5. This also shows the integrated trace, which goes upward in steps. The height of each step in the trace is proportional to the number of hydrogen atoms absorbing at the chemical shift. Suggest which signals correspond to which hydrogen atoms in the salbutamol molecule and give reasons for your choice.

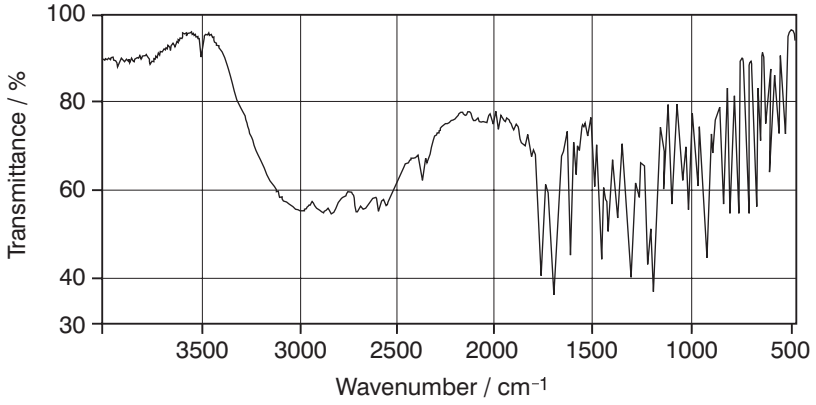


Figure 1(a) The i.r. spectrum of aspirin (in solution)

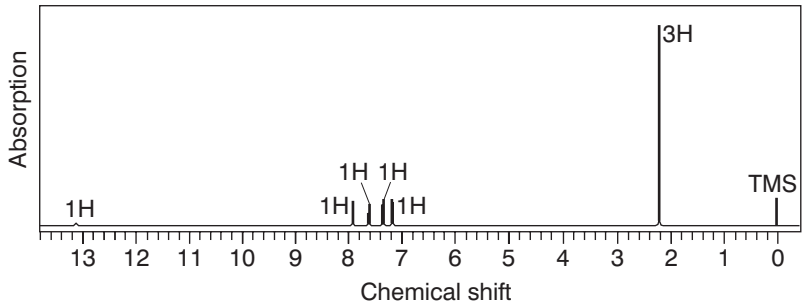


Figure 1(b) The n.m.r. spectrum of aspirin

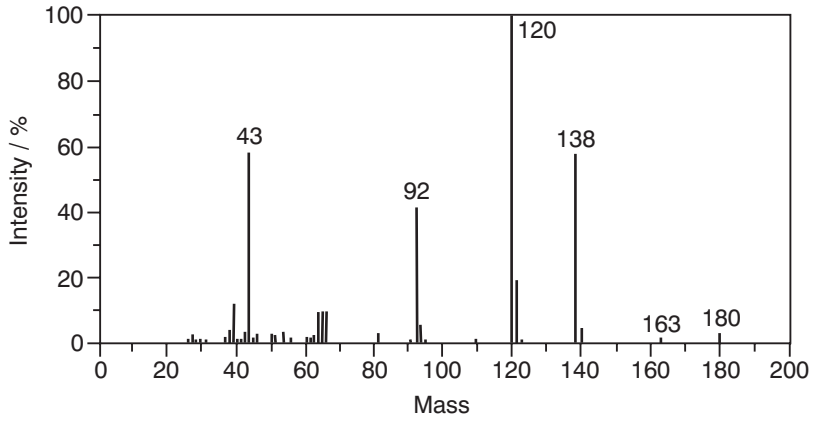


Figure 1(c) The mass spectrum of aspirin

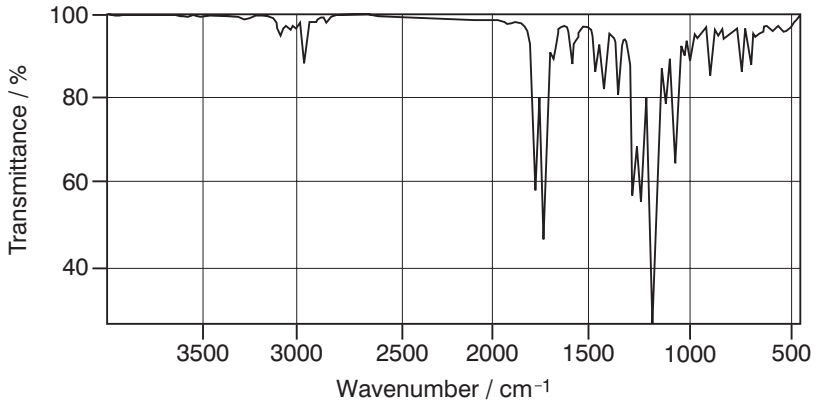


Figure 2(a) The i.r. spectrum of compound A (in the gas phase)

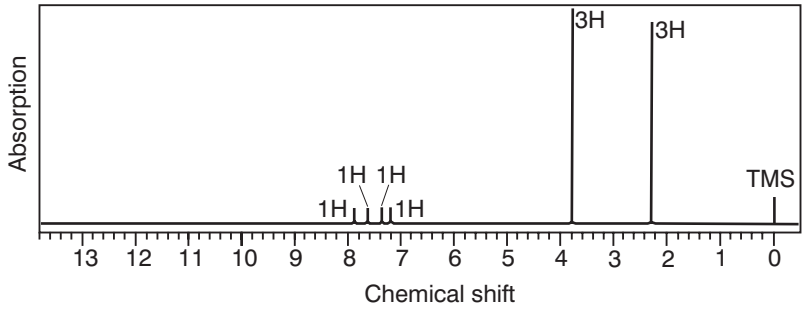


Figure 2(b) The n.m.r. spectrum of compound A

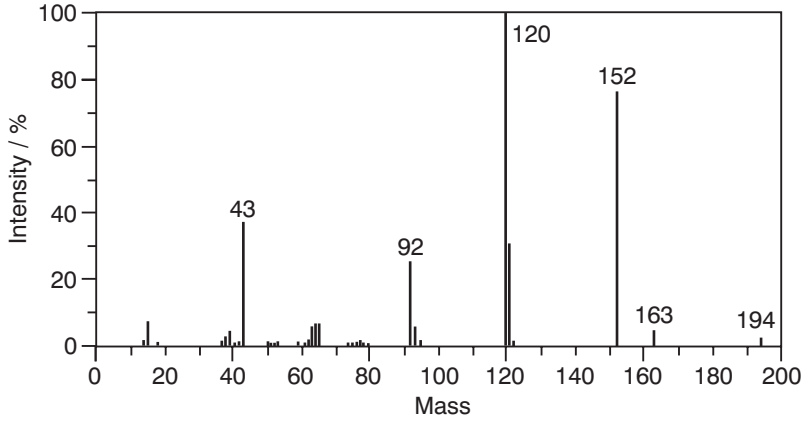


Figure 2(c) The mass spectrum of compound A

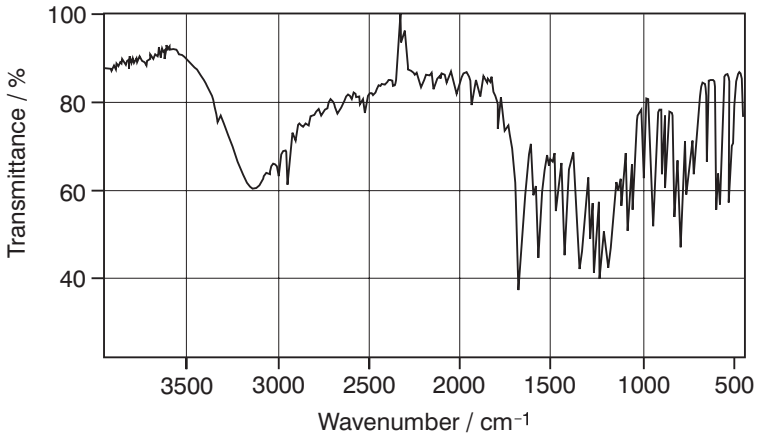


Figure 3(a) The i.r. spectrum of compound B (in solution)

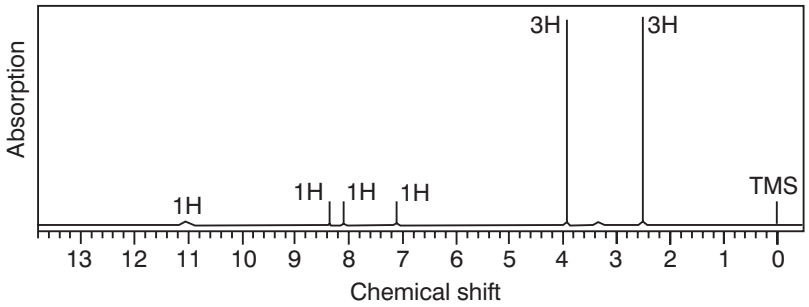


Figure 3(b) The n.m.r. spectrum of compound B (in solution)

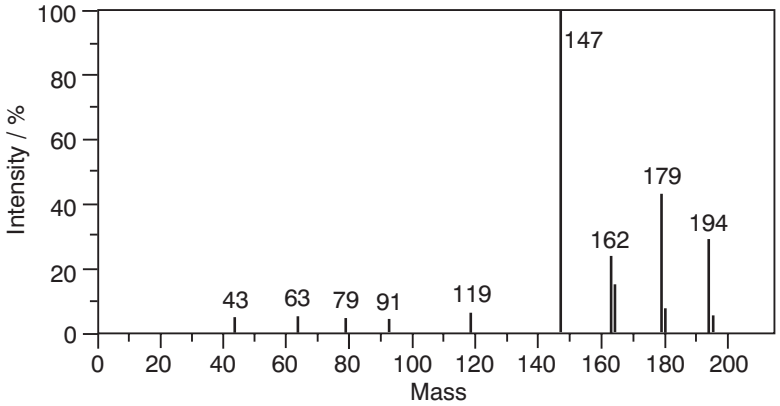


Figure 3(c) The mass spectrum of compound B (in solution)

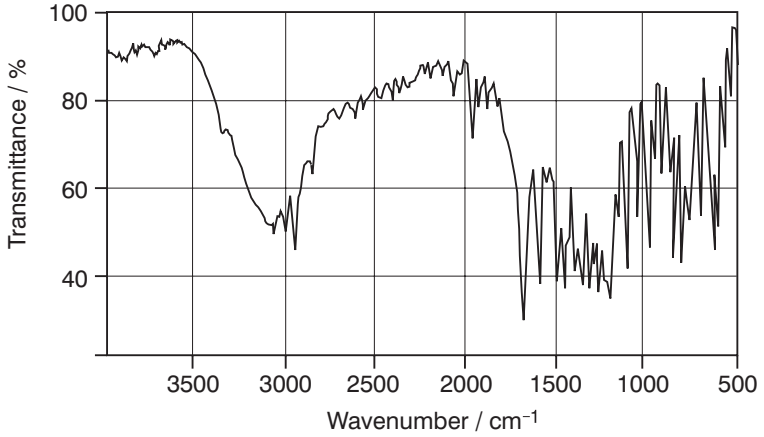


Figure 4(a) The i.r. spectrum of compound C (in solution)

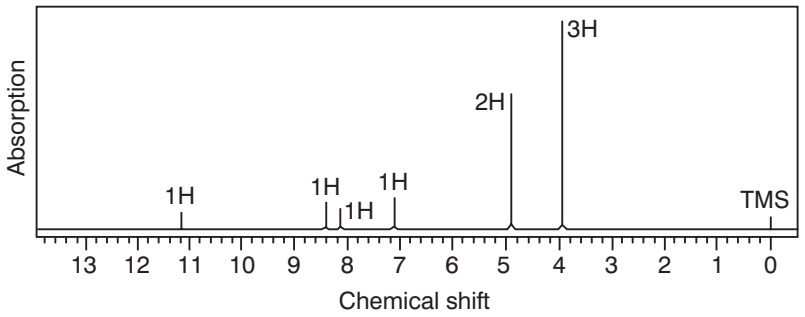


Figure 4(b) The n.m.r. spectrum of compound C

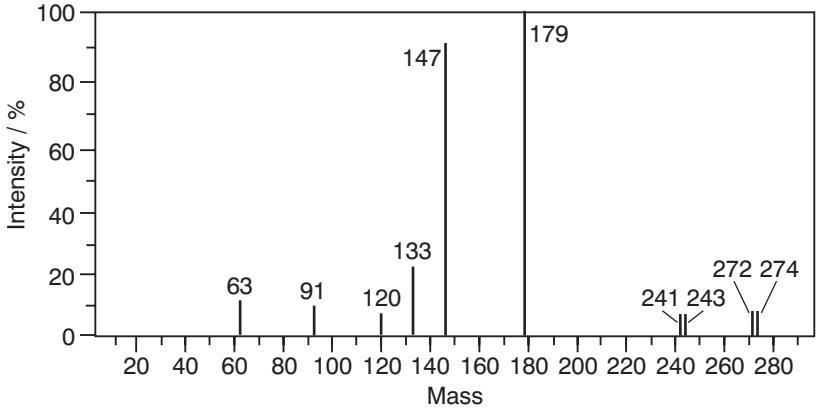


Figure 4(c) The mass spectrum of compound C

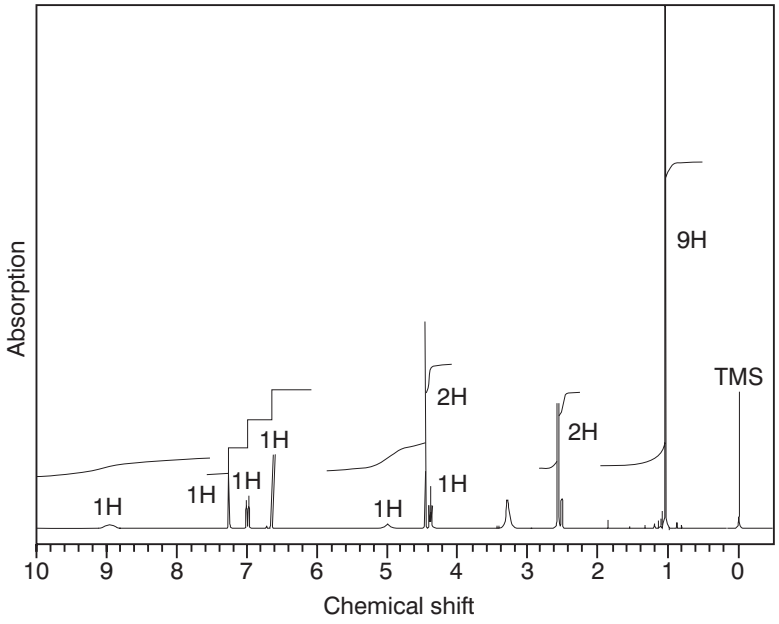


Figure 5 The n.m.r. spectrum of salbutamol

MD5.1

Making and testing a penicillin

In this activity you can use your skills in handling organic chemicals to prepare a semi-synthetic penicillin. You can then test your product for bacterial activity.

Requirements

- 100 cm^3 well-stoppered bottle (or conical flask)
- 6-aminopenicillanic acid (6-APA) (1.0 g)
- 25 cm^3 measuring cylinders (2)
- 10 cm^3 measuring cylinder
- sodium hydroxide solution, 1 mol dm^3 (5 cm^3)
- teat pipettes
- benzoyl chloride (0.5 cm^3)
- propanone (5 cm^3)
- test-tubes
- 100 cm^3 beakers (2)
- ethyl ethanoate (15 cm^3)
- glass rod (or magnetic stirrer)
- pH meter (or Universal Indicator paper)
- dilute hydrochloric acid, 1 mol dm^{-3} (10 cm^3)
- 50 cm^3 separating funnel
- saturated sodium hydrogencarbonate solution (25 cm^3)
- 4 agar plates impregnated with *Bacillus subtilis**
- cork borer (5–7 mm)
- ethanol (for sterilisation)
- beaker of disinfectant
- protective gloves
- adhesive tape
- small amounts of control solution for testing bacterial activity:
  - 6-APA solution (made by dissolving 0.13 g 6-APA in a solution of 0.15 g sodium hydrogencarbonate in 250 cm^3 water; take 10 cm^3 of this solution and dilute to 100 cm^3)
  - sodium benzoate solution (made by dissolving 0.13 g sodium benzoate in 250 cm^3 water; take 10 cm^3 of this solution and dilute to 100 cm^3 with water)

CARE Benzoyl chloride is corrosive and lachrymatory (it is a severe eye irritant) and must be used in a fume cupboard. It gives off fumes of hydrogen chloride gas in moist air. Wear gloves when measuring out, and use a pre-marked teat pipette.

CARE Propanone, ethyl ethanoate and ethanol are highly flammable liquids. Keep bottles stoppered when not in use, and well away from naked flames.

CARE Consult your teacher before handling the bacterial culture and follow the safety instructions carefully. Wear a lab coat and gloves all the time. Cover any skin cuts with effective waterproof dressings and wash your hands thoroughly at the end of the session. Report any spillages immediately. Any material which has come into contact with the bacterial culture must be sterilised before disposal, or before returning to stock cupboards. The sealed plates must be sterilised in a pressure cooker or autoclave before disposal.

benzoyl chloride


CORROSIVE


IRRITANT

ethanol


HIGHLY FLAMMABLE

ethyl ethanoate


HIGHLY FLAMMABLE

propanone


HIGHLY FLAMMABLE

sodium hydroxide solution


IRRITANT

CARE Eye protection must be worn.


WEAR EYE PROTECTION

CARE 6-APA can act as a sensitiser by inhalation or skin contact. Wear protective gloves and do not inhale the dust.


WEAR PROTECTIVE GLOVES

CARE If you are allergic to penicillins, you should not do this activity.

* See instructions for preparation in the Teacher's and Technician's Guide

The reaction scheme

You will be supplied with 6-aminopenicillanic acid (6-APA). This is obtained from penicillin G, which is made naturally. 6-APA can be reacted with different acyl chlorides to produce a variety of new penicillins with different properties and a wide range of antibacterial activity.

Your task is to convert 6-APA into phenylpenicillin. You will not be able to isolate your product in pure form, but you will be able to test its activity against bacteria.

The reaction scheme you will use is shown in Figure 1.

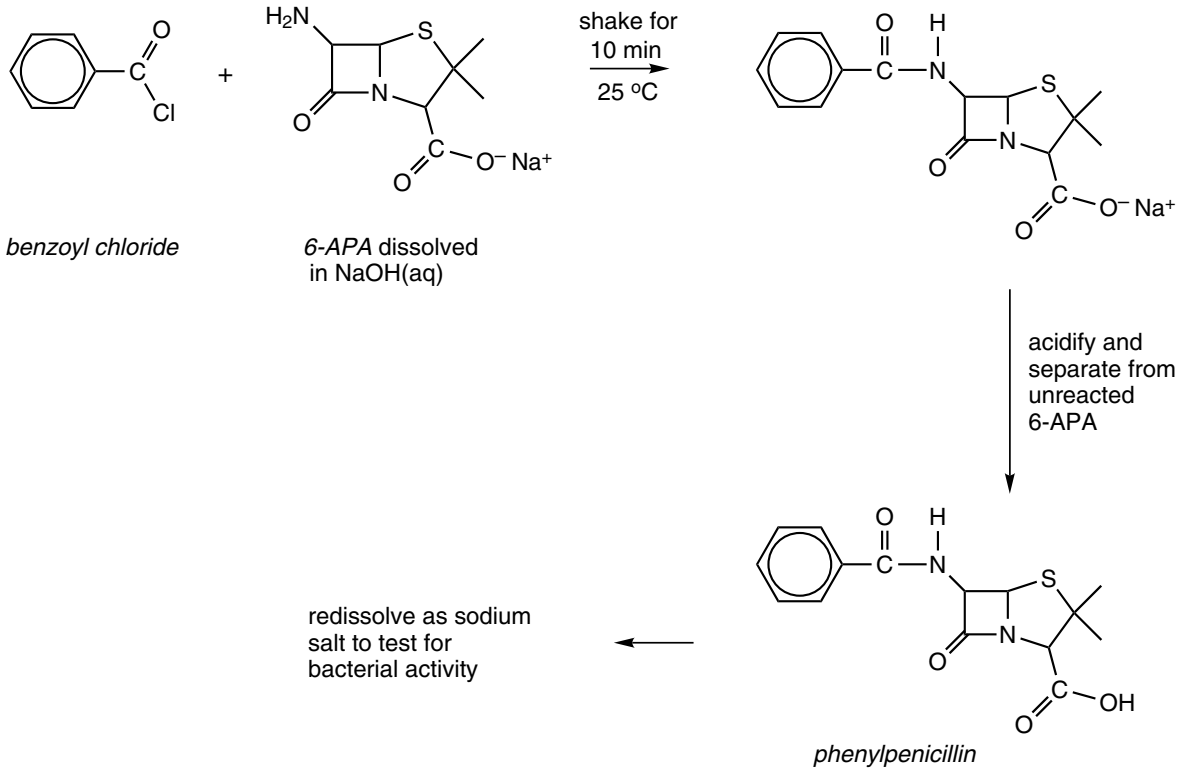


Figure 1 Reaction scheme for the synthesis of phenylpenicillin

Note that benzoyl chloride is a relatively unreactive acyl chloride and can be used in aqueous solution.

The 4-membered **lactam** ring is easily destroyed by strong acids and by alkalis. To reduce this hydrolysis reaction to a minimum, the pH of the solution is kept in the range pH 5–8 during the preparation. When you acidify the reaction mixture with hydrochloric acid during the purification procedure, the pH of the solution falls to pH 2, so you must work quickly at this stage.

As you go through the stages of the synthesis on page 332, use the column on the right-hand side to keep track of the changes taking place. Write the structure of the product where this has changed and a brief comment about what has happened at that stage. When you carry out the extraction with ethyl ethanoate to purify your product, make sure you know what is in each layer.

What you do

Part 1: Making and purifying the penicillin

Notes

1 Weigh out 1.0 g of 6-APA (**CARE** Wear protective gloves and do not inhale the dust) and mix it with 10 cm^3 of distilled water in a stoppered bottle (or conical flask).

2 Add 1 mol dm^{-3} of sodium hydroxide (**CARE** Irritant) drop by drop until a just-clear solution is obtained. This should take about 5 cm^3 of the sodium hydroxide solution.

3 In the fume cupboard, dissolve 0.5 cm^3 of the benzoyl chloride (**CARE** Corrosive and a severe eye irritant) in 5 cm^3 of propanone (**CARE** Highly flammable) in a clean, dry test-tube. Add this solution drop by drop, with swirling, to the dissolved 6-APA in the bottle. Stopper the bottle firmly and shake the mixture gently for about 10 minutes. (**CARE** You may need to release the pressure once or twice by easing off the stopper in a fume cupboard.)

4 Transfer the reaction mixture to a 100 cm^3 beaker and add 10 cm^3 of ethyl ethanoate (**CARE** Highly flammable). Using a pH meter (or pH paper) acidify the mixture with stirring, using 1 mol dm^{-3} hydrochloric acid. Add the acid until the pH of the solution falls to pH 2. (Any unreacted 6-APA forms a water-soluble hydrochloride. Phenylpenicillin is more soluble in organic solvents than water.)

5 Transfer both layers to a separating funnel and shake the mixture well. Separate into two 100 cm^3 beakers. Keep both layers. (The density of ethyl ethanoate is 0.90 g dm^{-3}. Make sure you know which layer is which.)

6 Return the aqueous layer to the funnel and add a further 5 cm^3 of ethyl ethanoate. Shake the mixture and separate it into the two beakers. You can now discard the aqueous layer down the fume-cupboard sink. (**CAUTION** Do not discard the wrong layer!)

7 Now add 10 cm^3 of water to the *organic* layer in the beaker. Adjust the pH to 6–7 by adding saturated sodium hydrogencarbonate solution. Transfer the mixture to the separating funnel and shake it well, taking care to release any build-up of pressure.

This time run the lower *aqueous* layer into a clean 25 cm^3 measuring cylinder. Add water to adjust the volume in the measuring cylinder to 25 cm^3 and stir well. This solution contains the phenylpenicillin you have made.

Part 2: Testing for antibacterial activity

Consult your teacher before handling the bacterial culture and **follow the safety instructions carefully**.

8 Take 1 cm^3 of your phenylpenicillin solution and dilute it to 10 cm^3 with distilled water. Stir well.

9 Dip the cork borer in ethanol in a beaker. **Hold the cork borer horizontally** so that flames do not pass up the centre and burn your hand. Pass the borer through a Bunsen flame to ignite the ethanol. Hold the borer to one side of the flame and allow the ethanol to burn off. This will heat the surface of the cork borer to about 60 °C so that it is sterilised. (**CARE** Make sure that the beaker containing the ethanol is not placed near the Bunsen flame. **Allow the cork borer to cool** before returning it to the ethanol beaker.)

10 Use the sterilised cork borer to make a well in the centre of an agar plate impregnated with *Bacillus subtilis,* by pressing the borer into the agar and then lifting out the cut plug of agar using a sterile spatula. (Flame the spatula in the same way as the cork borer.) Place the agar plug straight into a beaker of disinfectant. Re-flame the cork borer and spatula after use.

Almost fill the well in the agar with the diluted penicillin solution.

11 Cover the plate and seal using small pieces of adhesive tape, as shown in Figure 2. *Do not totally seal round the rim* as this may create anaerobic conditions and encourage the growth of harmful bacteria.

Label the plate with your initials, the name of the micro-organism and the date. Write something to indicate the treatment given to the plate. (**Do not lick the labels**.)

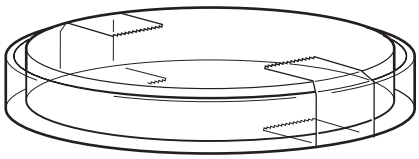


Figure 2

12 Now set up three control plates in the same way, to compare with your penicillin sample. Fill the well in the agar of the first plate with 6-APA solution, and the well in the second plate with sodium benzoate solution: you are provided with these two solutions. (Their concentrations have been adjusted to about $50\,\mu g\,cm^{-3}$, comparable to that of the penicillin solution). Leave the well in the third plate empty. Cover, seal and label the plates as before.

13 Take care not to tip the plates. Leave them on the bench at room temperature (20 °C) for 24–48 hours. Do not leave them where other people can interfere with them (a secure corner of the prep room is probably best).

14 Make sketches of the four plates at the end of this time. (**CARE** Do not open the plates once they have been sealed.) The agar will appear cloudy in the areas where bacteria are growing. (You will see this more clearly if you hold the plates up to the light.)

Using a ruler, measure the size of any inhibition of bacterial growth. Did your penicillin solution show any antibacterial activity?

CARE Any material which has come into contact with the bacterial culture must be sterilised before disposal, or before returning to stock cupboards. The sealed plates must be sterilised in a pressure cooker or an autoclave before disposal.

QUESTIONS

a Explain why the penicillin you made is called a *semi-synthetic* penicillin.

b Why was NaOH(aq) added to the 6-APA in step **2**, before treatment with benzoyl chloride?

c What product other than penicillin is formed when 6-APA reacts with benzoyl chloride? What *type* of bond is formed in this reaction?

d Explain how the penicillin you produced was purified.

e Why was it necessary to have the three control plates when testing for antibacterial activity?

MD5.2

A closer look at the structure of penicillins (*Optional extension*)

In this activity you will make a model of the 'penicillin nucleus', 6-APA, and investigate its stereochemistry. You will then investigate the effect of the structure of the side-chain on the antibacterial activity of different penicillins.

Requirements

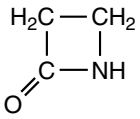
- set of molecular models
- molecular modelling software (optional)

What you do

Work in small groups to carry out this activity. This will speed up the model-building, and allow you to discuss the answers to the questions while you are looking at the models.

Part 1: Modelling penicillins

1 Start by making a model of a simple β-lactam ring:



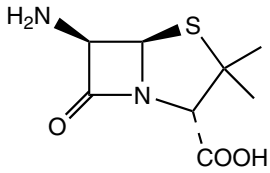
β-lactam ring

a What functional group is present in the β-lactam ring?

b Suggest why the β-lactam ring is so susceptible to attack by acids and alkalis, and reacts readily to form open-chain compounds.

2 Now convert your β-lactam model into a model of 6-amino penicillanic acid (6-APA). This is the 'pencillin nucleus' common to all penicillins.

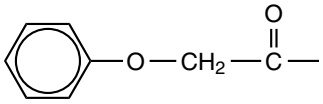
Before you do this, look at the formula of 6-APA very carefully. The molecule has a very precise stereochemistry:



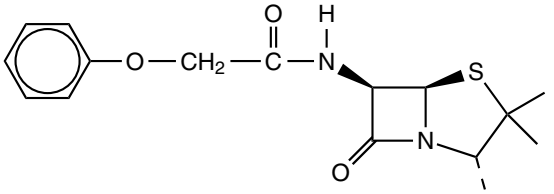
6-APA

c How many chiral carbon atoms are there in a molecule of 6-APA? Mark these on the diagram with an asterisk (*).

3 If your model kit is large enough, you could add an acyl group, and convert your model of 6-APA into a model of a penicillin. For example, substituting



for an H atom in the $-NH_2$ group converts 6-APA into penicillin V.



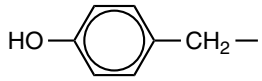
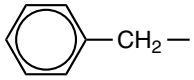
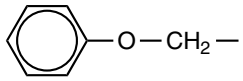
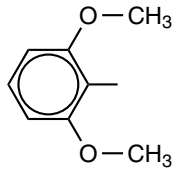
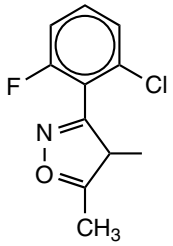
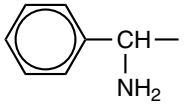
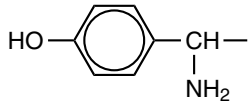
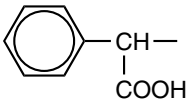
penicillin V

d The other optical isomers of penicillin V are much less active against bacteria. Explain why the correct stereochemistry is crucial.

e The structure of penicillin V was worked out in the 1940s, but it was not synthesised chemically until 15 years later. Why do you think totally synthetic penicillins have never been produced commercially on a large scale?

Part 2: Looking at the side-chain (R—CO—)

The table below shows the R groups in the side-chains of some natural penicillins and some semi-synthetic ones, together with some information about their main uses.

Name	R group in the side-chain	Natural/ semi-synthetic	Uses/properties
Penicillin F	$CH_3CH_2CH=CHCH_2-$	natural	not used commercially
Penicillin X		natural	not used commercially
Penicillin K	$CH_3(CH_2)_6-$	natural	not used commercially
Penicillin G		natural	general infections, gonorrhoea and syphilis
Penicillin V		natural and semi-synthetic	general infections, ear, nose and throat
Methicillin		semi-synthetic	controlling resistant *Staphylococcus*
Flucloxacillin		semi-synthetic	controlling resistant *Staphylococcus*
Ampicillin		semi-synthetic	lung and wound infections
Amoxycillin		semi-synthetic	lung and urinary tract infections
Carbenicillin		semi-synthetic	pneumonia, burns

f Explain the distinction between natural and semi-synthetic penicillins.

g **i** Look at the R group in the side-chains of methicillin and flucloxacillin. What structural feature of penicillins appears to be important in resisting attack by the β-lactamase enzyme?
(**Hint** Look at the groups attached to the first carbon in the side-chain. Remember that large groups affect the size and shape of a molecule.)

ii Suggest how penicillins such as methicillin and flucloxacillin are able to resist attack by the β-lactamase enzyme.

iii Penicillins act by inhibiting a bacterial enzyme that helps to make the bacterial cell wall. How might the active site of this enzyme differ from the active site of β-lactamase?

MD6

Check your notes on *Medicines by Design*

This activity helps you get your notes in order at the end of this unit.

Use this list as the basis of a summary of the unit by collecting together the related points and arranging them in groups. Check that your notes cover the points and are organised in appropriate ways.

Most of the points are covered in the **Chemical Ideas**, with supporting information in the **Storyline** or **Activities**. However, if the *main* source of information is the Storyline or an Activity, this is indicated.

- The chemical principles behind methods which can be used to detect ethanol in the body (g.l.c. and i.r. spectroscopy) (**Storyline MD1**; **Activity MD1.2**).
- The following reactions involving aldehydes and ketones: formation by oxidation of alcohols, oxidation to carboxylic acids, reduction to alcohols and reaction with hydrogen cyanide (**Activity MD1.1**).
- The mechanism of the nucleophilic addition reaction between an aldehyde or a ketone and hydrogen cyanide.
- The meaning of the terms: *drug, medicine, molecular recognition, pharmacological activity, pharmacophore, receptor site, agonist, antagonist, lead compound* (**Storyline** in general).
- The structure of a pharmacologically active material in terms of its functional components: pharmacophore and groups which modify the pharmacophore (**Storyline MD3**).
- The action of biologically active chemicals and how this relates to their interaction with receptor sites.
- The factors affecting the way that species interact in three dimensions: size, shape, bond formation and orientation (**Storyline MD4**).
- The role of chemists in designing and making new compounds for use as pharmaceuticals (**Storyline MD3**, **MD4** and **MD5**).
- The role of computer modelling techniques in the design of medicines (**Storyline MD4**).
- The identification of functional groups within a polyfunctional molecule, as a way of making predictions about its properties.
- How to devise synthetic routes for preparing organic compounds.
- The use of the following terms to classify organic reactions: *hydrolysis*, *oxidation*, *reduction*, *condensation* and *elimination*.
- The classification of organic reactions according to their reaction mechanisms: nucleophilic substitution, electrophilic addition, electrophilic substitution, nucleophilic addition and radical.
- The use of a combination of spectroscopic techniques (m.s., i.r., n.m.r. and u.v. and visible) to elucidate the structure of organic molecules.

Pulling together organic chemistry

1. Make sure you are familiar with the organic functional groups you have met throughout the course. It may help to draw up a table giving the name and formula of each functional group, and an example of a simple molecule containing the group.
2. Make sure you are familiar with the main reactions of each functional group. You should be able to write an equation and give essential conditions for each reaction.
3. Practise using the toolkit in **Activities MD3.1**, **MD3.2** and **MD3.3** as much as you can. You must be able to use the reactions you have learned in this course, together with any further ones you may be given, to devise synthetic routes for preparing organic compounds.