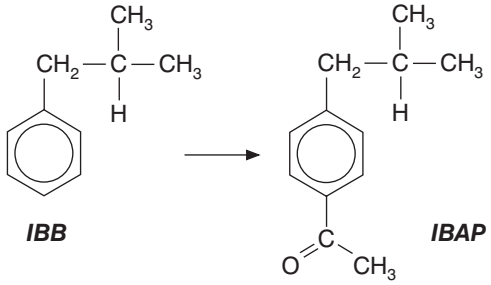
'MEDICINES BY DESIGN' TEST

60 marks (1 hour)

*A copy of the **MD Information Sheet** is required for this test, together with the spectroscopic data (i.r. and n.m.r.) from Tables 22 and 23 in the* **Data Sheets**.

1 Ibuprofen was developed by Boots Pharmaceuticals in the late 1960s, and was used to treat arthritis and similar problems. It has now become one of the biggest-selling analgesics along with paracetamol and aspirin.

a The first step in the manufacturing process is the conversion of 2-methyl-1-phenylpropane (known as **IBB**, short for its common name, isobutylbenzene) into the compound known as **IBAP**. The reaction is shown below.

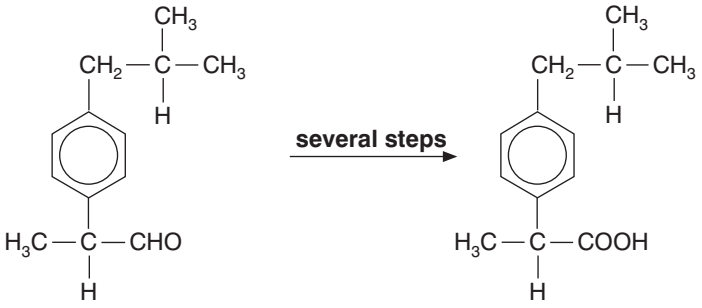


IBB *IBAP*

i Give the reagents and the conditions that you would use to carry out this reaction in the laboratory. *(3 marks)*

ii In a small-scale preparation of **IBAP**, starting with 5.00 g of **IBB**, the yield of pure **IBAP** was 6.24 g. Calculate the percentage yield of **IBAP**. (A_r: H, 1; C, 12; O, 16) *(3 marks)*

b In the second stage of the industrial synthesis of ibuprofen, **IBAP** is converted into compound **A**, whose structure is shown below. This then undergoes several further reactions to produce ibuprofen.



*Compound **A*** *Ibuprofen*

i Name the functional group that is present in compound **A** but not in **IBB** or **IBAP**. *(1 mark)*

ii Give the reagents and conditions for a one-step conversion of compound **A** to ibuprofen in the laboratory. *(3 marks)*

iii Suggest a reason why this method is not used in the manufacturing process. *(1 mark)*

c In their investigation of compound **A**, chemists reacted it with HCN (using a solution of potassium cyanide, KCN, in water).

This introduces a –CN group which can then be hydrolysed to –COOH.

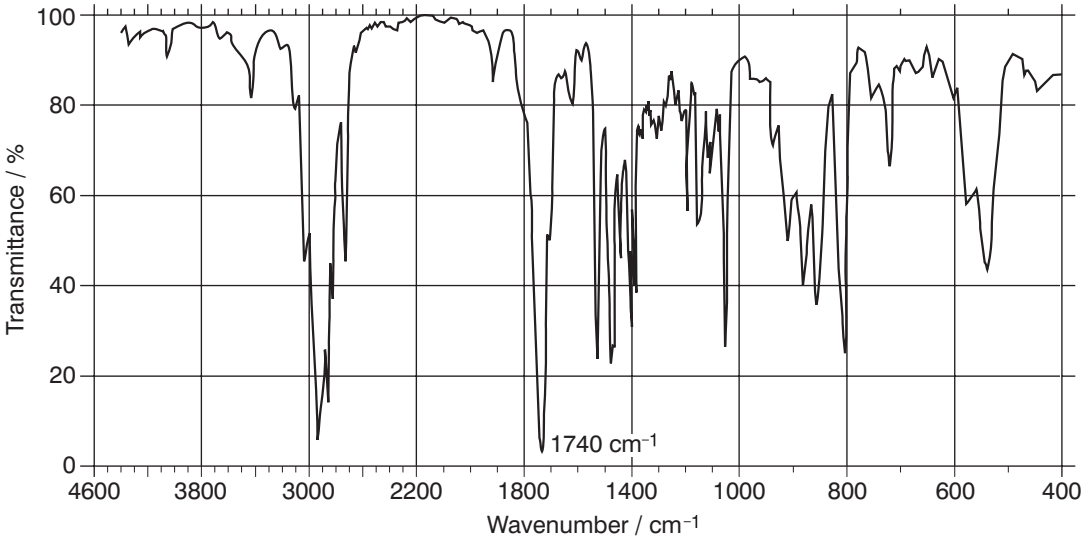
i Draw the structure of the product, after hydrolysis. *(2 marks)*

ii Classify the reaction of compound **A** with HCN by its reaction mechanism. *(2 marks)*

iii Draw a diagram to show the first part of this mechanism, the attack of CN^- ions on compound **A**. *(2 marks)*

d Research chemists attempting to discover a way of synthesising ibuprofen from compound **A** in one step isolated a substance **X** from one such attempt.

i The infrared spectrum of **X** is shown below.



The i.r. spectrum of X

Use this spectrum, together with the table of characteristic i.r. absorptions in organic molecules in the **Data Sheets** (Table 22), to determine whether the attempted synthesis of ibuprofen was successful or not. Briefly give the reasons for your answer. *(3 marks)*

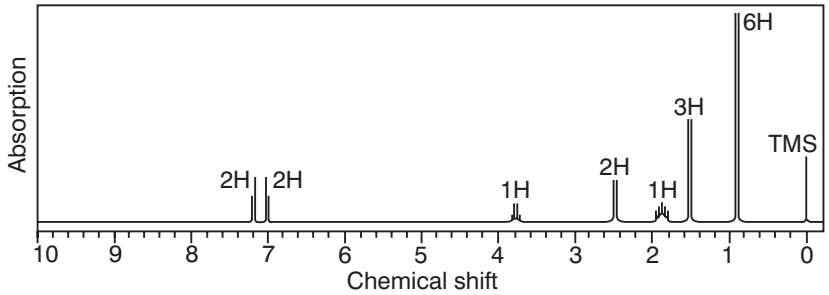
ii The chemists also took a mass spectrum of **X** to see whether it contained any ibuprofen. What key feature of the spectrum would suggest the presence of ibuprofen? *(1 mark)*

e This part of the question is about the purification of the final product. Impure ibuprofen is produced as a solution in hexane, a non-polar solvent.

i Explain why adding alkali enables ibuprofen to be removed from the hexane layer into the aqueous layer. *(2 marks)*

ii How could pure ibuprofen be removed from the alkaline solution? *(2 marks)*

iii The n.m.r. spectrum of ibuprofen is shown below.



The n.m.r. spectrum of ibuprofen (in solution)

Explain how this spectrum would differ if the ibuprofen sample were contaminated with compound **A**. *(2 marks)*

[TOTAL: 27 MARKS]

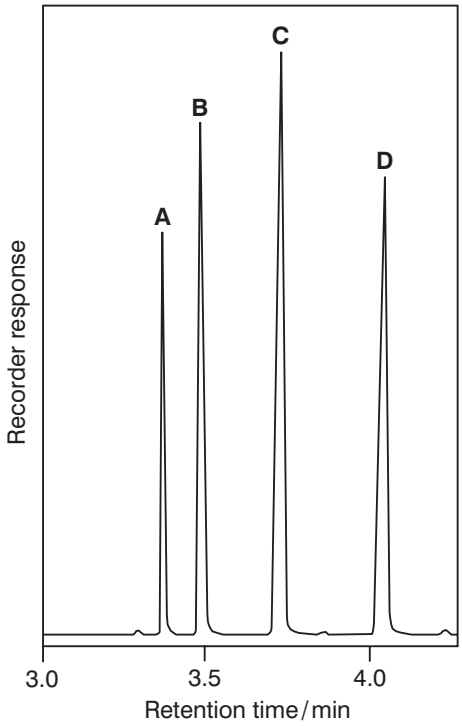
2 Various methods have been used to determine whether the driver of a motor vehicle has a blood alcohol concentration (BAC) in excess of the legal limit.

a The earliest method for detecting ethanol in breath was based on a reaction that produced a colour change: orange dichromate(VI) ions react with ethanol to produce green chromium(III) ions.

Give the structural formulae of **two** organic products which could be formed from ethanol by reaction with acidified dichromate(VI) ions. *(2 marks)*

b The method that has been in longest use for an accurate determination of BAC involves analysing a blood or urine sample by gas–liquid chromatography (g.l.c.).

Gas–liquid chromatography can be used to analyse a mixture of different alcohols. The following gas–liquid chromatogram was obtained from a mixture of isomeric alcohols with the molecular formula C_4H_9OH. The most volatile alcohol is retained on the column for the shortest time.



Data from the n.m.r. spectrum of the alcohol giving rise to the peak **C** are given in the table below.

Chemical shift centred at	Relative intensity of n.m.r. signal
0.9	6
1.7	1
3.7	2
4.5	1

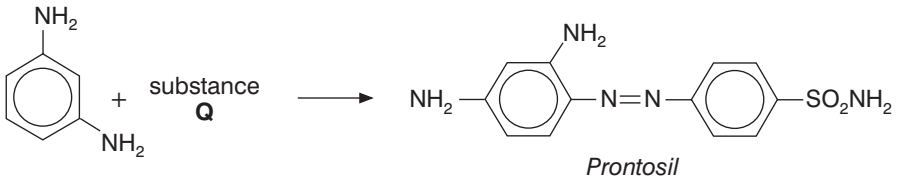
i Use the table of chemical shifts for some types of hydrogens in n.m.r. spectra in the **Data Sheets** (Table 23) to identify the alcohol giving rise to peak **C**. Write the structural formula of the alcohol and give your reasoning. *(4 marks)*

ii Write the structural formula of an isomer of your answer to **i** which gives rise to peak **A**. Give a reason for your answer. *(3 marks)*

[TOTAL: 9 MARKS]

3 The development of sulpha drugs started with studies by Paul Erlich on the staining of protozoal parasites (such as those which cause malaria and syphilis) on microscope slides using synthetic dyes. In 1934 Gerhard Domagk discovered that the red azo dye, Prontosil, cured mice of streptococcal bacterial infections.

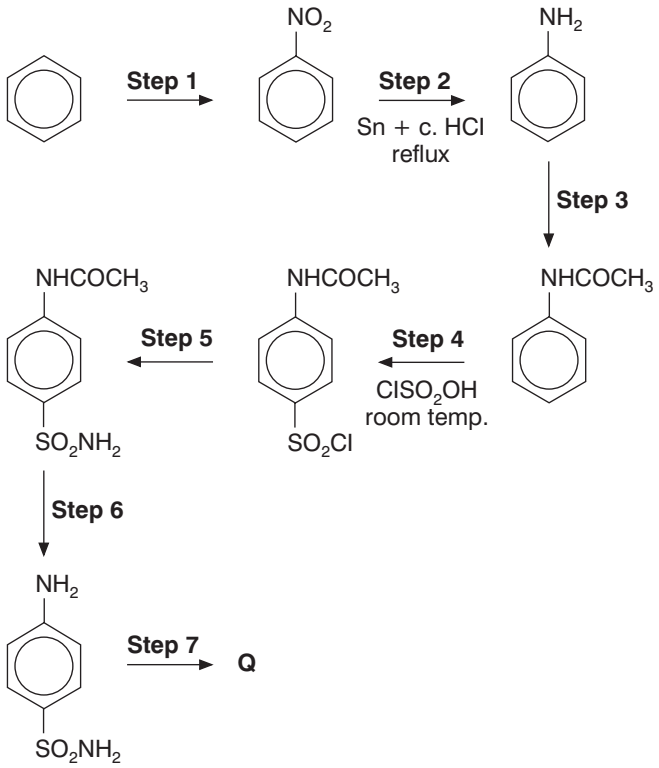
Prontosil can be synthesised by reacting 1,3-diaminobenzene with an aqueous solution of a substance **Q**.



Prontosil

a Give the structural formula of **Q**. *(2 marks)*

b **Q** can be synthesised from benzene in a series of steps, which are outlined below.



i Copy and complete the following table, giving the reagents and conditions for some of the steps in the reaction sequence. In the fourth column, classify each reaction as one of:

hydrolysis oxidation reduction condensation elimination substitution addition.
(9 marks)

Reaction step	Reagent(s)	Conditions	Classification
1			
3		room temperature	
5		room temperature	
6		reflux	

ii Of **all** the steps in the reaction sequence, which are examples of electrophilic substitution into a benzene ring? *(2 marks)*

[TOTAL: 13 MARKS]

4 **a** The discovery of the antibacterial properties of Prontosil was quickly followed by a wide search for other effective compounds with similar structural features. It became apparent that the azo group in the dye was not responsible for its biological activity. The important part of the Prontosil molecule was identified, and this led to the development of the *sulphonamides*.

i Explain why Prontosil may be regarded as the 'lead' compound in this search. *(1 mark)*

ii Suggest **two** reasons why chemists, having discovered Prontosil to be an effective drug, started to look for other effective drugs with similar structures. *(2 marks)*

iii Name the technique (which was not available in the 1930s and 1940s) available to modern chemists which enables them to study the shapes of molecules and the ways in which these fit together. *(1 mark)*

b Living things need a supply of an important chemical called folic acid. For us it is a *vitamin*, because our body chemistry is unable to make it. We need to take in ready-made folic acid in our diet. Most bacteria, however, are unable to absorb folic acid through their cell walls and have to make it themselves using simple starting molecules, such as 4-aminobenzoic acid, in a series of enzyme-catalysed reactions.

Sulphonamides interfere with one enzyme in the sequence shown below:

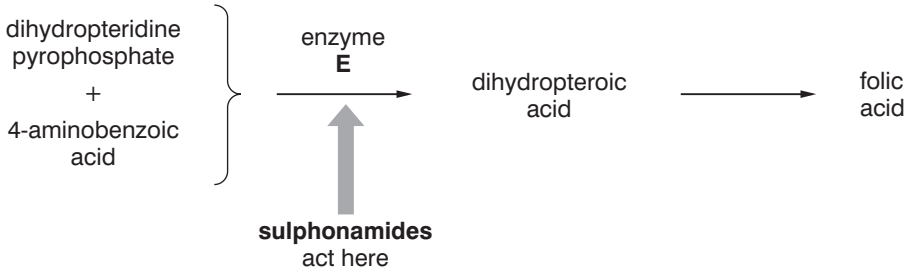


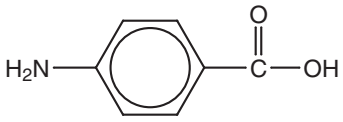
Table 1 on the **MD Information Sheet** lists the structural formulae of some sulphonamides, together with a simplified description of their activity against streptococcal bacteria.

i Using the information given on the **MD Information Sheet**, draw the part of the molecular structure that is essential if a sulphonamide is to have *any* antibacterial activity at all. *(1 mark)*

ii Copy and extend the diagram you have given in **i** to show the part of the structure that is essential if the sulphonamide is to have *high* antibacterial activity. *(1 mark)*

iii Which of your two answers, **i** or **ii**, would you regard as being the sulphonamide *pharmacophore*? Briefly explain your answer. *(2 marks)*

iv Compare the structures of the active sulphonamides to that of 4-aminobenzoic acid (given below), and then suggest, using the information in the sequence shown above, an explanation for their action in preventing the synthesis of folic acid. *(3 marks)*



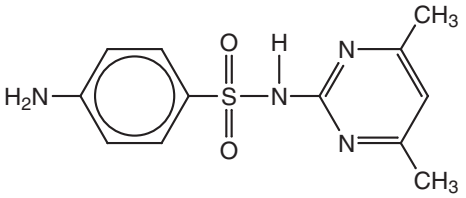
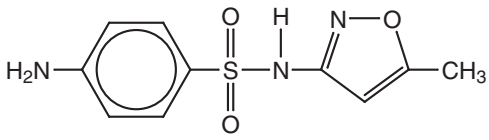
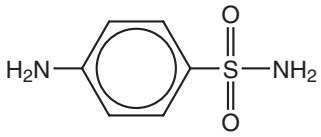
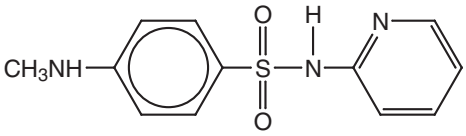
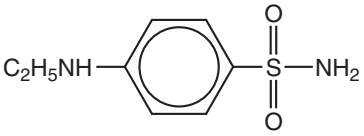
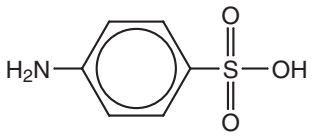
4-aminobenzoic acid

[TOTAL: 11 MARKS]

MD INFORMATION SHEET

You will also need access to the **Data Sheets** (Tables 22 and 23) for information about i.r. and n.m.r. spectra.

Table 1 The structural formulae and activity of some sulphonamides

Structural formula	Antibacterial activity
	high activity *used in cases of meningococcal meningitis*
	high activity *used in cases of urinary tract infections*
	moderate activity
	no activity
	no activity
	no activity