30 Organic synthesis and analysis

Many of the commercial applications of organic chemistry involve the synthesis of pharmaceutical compounds. This topic looks at how the reactions that have been introduced in the previous topics can be used to synthesise organic molecules of specific structures; how drug molecules are designed; and how the reactions covered can be used to identify the functional groups in an unknown molecule.

Learning outcomes

By the end of this topic you should be able to:

- **23.1a)** state that most chiral drugs extracted from natural sources often contain only a single optical isomer
- **23.1b)** state reasons why the synthetic preparation of drug molecules often requires the production of a single optical isomer, e.g. better therapeutic activity, fewer side effects
- **23.2a)** for an organic molecule containing several functional groups: identify organic functional groups using the reactions in the syllabus, and predict properties and reactions
- **23.2b)** devise multi-stage synthetic routes for preparing organic molecules using the reactions in the syllabus
- **23.2c)** analyse a given synthetic route in terms of type of reaction and reagents used for each step of it, and possible by-products.

30.1 The synthesis of organic compounds

Simple molecules

Many organic compounds have important uses as pharmaceuticals, pesticides, perfumes and dyes. These compounds often have quite complicated structures, and most of them are manufactured by organic chemists from much simpler starting materials. The science of organic synthesis is rather like building with molecular Lego™: a compound is constructed by combining a sequence of reactions – from two to perhaps 20 or so – which start from known, readily available chemicals and end up with the target molecule.

Figure 30.1 A laboratory where new organic compounds are synthesised

Organic synthesis requires much art and craft as well as science. If you have attempted an organic preparation in the laboratory you will know that the yield and purity of your product will often vary from those given in the 'recipe'. Skill and practice are needed to perfect practical techniques. The reagents and conditions

that give an excellent yield with one compound may not be as effective for another compound with an identical functional group.

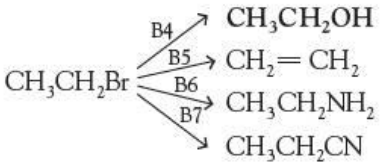
Nevertheless, it is possible to devise a multi-step method for synthesising a given organic compound by piecing together successive standard organic transformations. We shall illustrate this by making use of the reactions summarised in Charts A–G (see section 30.8), and Table 30.1, pages 535–536).

For example, suppose we needed to devise a synthesis of ethanoic acid, starting from bromoethane:

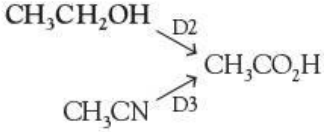
$$CH_3CH_2Br \longrightarrow CH_3CO_2H$$

The strategy is as follows:

1 Use Chart B (page 536) to work out the structures of all the compounds that can be made from bromoethane in one step.
2 Next we use Chart D (page 537) to work out the structures of all the compounds that could be used to make ethanoic acid.
3 Then we see whether there is a compound that is common between both charts.



from Chart B



from Chart D

The compound **ethanol** is common to both, so a viable synthetic route would have ethanol as an intermediate:

$$CH_3CH_2Br \longrightarrow CH_3CH_2OH \longrightarrow CH_3CO_2H$$

Finally, from Table 30.1, we find the reagents and conditions required to carry out these two transformations:

$$CH_3CH_2Br \xrightarrow{\text{heat with NaOH(aq)}} CH_3CH_2OH \xrightarrow{\text{heat with an excess of } Na_2Cr_2O_7+H_2SO_4(aq)} CH_3CO_2H$$

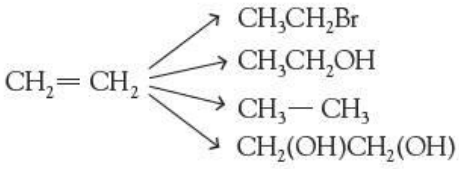
Steps 1 and 2 above using Charts A–G may need to be repeated if a common compound is not found.

Worked example

Devise a synthesis of propylamine, $CH_3CH_2CH_2NH_2$, from ethene, C_2H_4.

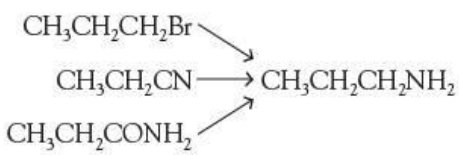
Answer

Chart A (page 536), shows that there are four reactions of ethene that may be useful:



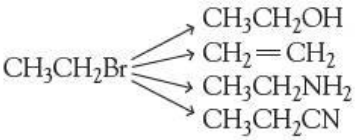
from Chart A

Next, considering the target molecule, we can see from Chart F (page 538) that there are three methods of making amines:

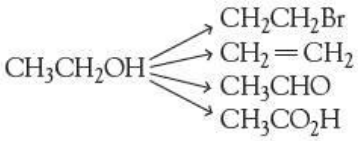


from Chart F

None of the three starting materials for making propylamine is the same as the four products from ethene, so the synthesis will need another step. Therefore we take each of the four products derived from ethene, and use the charts to carry out the same analysis on those products – what compounds can we make from each one in turn?



from Chart B



from Chart C

We stop immediately at Chart B, as we can see that there is a compound in common between Chart B (page 536) and Chart F (page 538): that is, propanenitrile, CH_3CH_2CN. The synthetic route therefore includes two intermediates:

$$CH_2=CH_2 \longrightarrow CH_3CH_2Br \longrightarrow CH_3CH_2CN \longrightarrow CH_3CH_2CH_2NH_2$$

Adding the reagents and conditions, the whole synthesis can be described as follows:

$$CH_2=CH_2 \xrightarrow{HBr(g)} CH_3CH_2Br \xrightarrow[\text{in ethanol}]{\text{heat with NaCN}} CH_3CH_2CN \xrightarrow{H_2 + Ni} CH_3CH_2CH_2NH_2$$

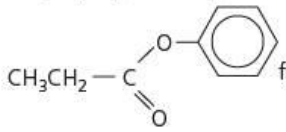
(Note that a 'shortcut' to the process here is given by the fact that the chain of the product contains one more carbon atom than the starting material: the synthesis must have had a step involving a nitrile.)

Now try this

Devise syntheses for the following compounds, starting with the specified compounds:

1 $CH_3CH(OH)CN$ from CH_3CH_2Br (three steps).

2 $CH_3CO_2CH_3$ from CH_3CN and CH_3OH (two steps).

3  from $CH_3CH_2CH_2OH$ and phenol (three steps).

4  from methylbenzene (two steps).

The synthesis of more complicated organic molecules

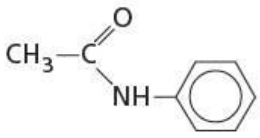


Figure 30.2 Phenylethanamide

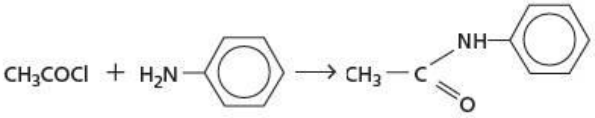
Many pharmaceutical compounds are made by joining together two or more organic parts, that are first synthesised separately. An example is the compound phenylethanamide that has been used as a pharmaceutical called *antifebrin* (Figure 30.2).

Worked example

Devise a synthesis of phenylethanamide, starting from ethene and benzene. (Both are readily available industrial chemicals that are derived from petroleum.)

Answer

As its name suggests, phenylethanamide is an amide. Amides are formed by reacting together amines and acyl chlorides. Phenylethanamide can be made as follows:



The synthesis is therefore in three parts, as shown in Figure 30.3.

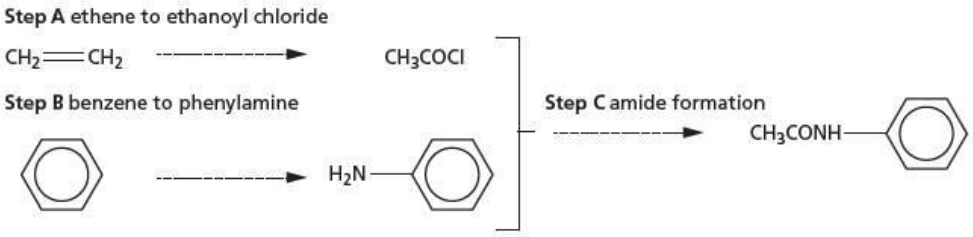


Figure 30.3 Synthesis of phenylethanamide from ethene and benzene

Step A Chart D (page 537) shows that acyl chlorides are made from carboxylic acids:

$$CH_3CO_2H \longrightarrow CH_3COCl$$

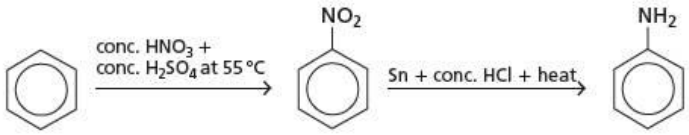
Carboxylic acids can be made from alcohols, which in turn can be made from alkenes:

$$CH_2{=}CH_2 \longrightarrow CH_3CH_2OH \longrightarrow CH_3CO_2H$$

So the overall synthesis of ethanoyl chloride from ethene is as follows:

$$CH_2{=}CH_2 \xrightarrow{H_2SO_4(aq)\text{ at R.T.}} CH_3CH_2OH \xrightarrow[\text{of } Na_2Cr_2O_7 + H^+]{\text{heat with an excess}} CH_3CO_2H \xrightarrow{PCl_5 + \text{heat}} CH_3COCl$$

Step B Chart G (page 538) shows a two-step synthesis of phenylamine from benzene:



Now try this

1. Suggest a synthesis of the ester prop-2-yl phenylethanoate, $C_6H_5CH_2CO_2CH(CH_3)_2$, from methylbenzene and propene (five steps in all).
2. Suggest a synthesis of ethyl 2-hydroxypropanoate, $CH_3CH(OH)CO_2CH_2CH_3$, from ethanol (four steps).
3. Devise a synthesis of N-phenylmethylbenzamide (Figure 30.4) with all its carbon atoms coming from methylbenzene, $C_6H_5CH_3$ (five steps in all).

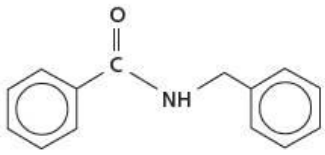


Figure 30.4 N-phenylmethylbenzamide

30.2 Design of drugs

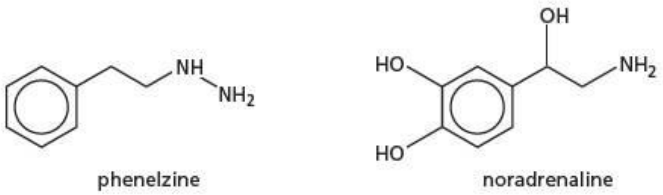
A drug is a chemical substance that interacts with the organs in the body to produce a physiological response. A drug may occur naturally or be synthetic. Naturally occurring drugs may be made within our own bodies by our own metabolism (e.g. hormones, nerve transmitters, endorphins), or may be extracted from some other organism, most often a plant or a fungus.

The effect of a particular drug on the body can be quite varied. In general, we can classify drugs as follows:

1 those aimed (usually lethally) at organisms that are foreign to our bodies, that is, bacteria, viruses and fungi
2 those aimed at cancer cells within our own bodies (again, hopefully, in a lethal manner)
3 those aimed at changing the physiology of our own cells, and hence our physical (and sometimes psychological) well-being.

Most commonly, drugs interact with enzyme and receptor proteins. **Enzymes** are responsible for catalysing most of the chemical reactions that occur within the cell. Little can be done to speed up an enzyme-catalysed reaction (apart from the usual chemical effects of increasing concentration and temperature), but they can be slowed down by using inhibitors. Some drugs have therefore been designed to act as such inhibitors, to treat illnesses that might be caused by an excess of the products of a particular enzyme-catalysed reaction, or to slow down the removal of an important compound from the body. For example, the drug phenelzine (Figure 30.5) inhibits the enzyme monoamine oxidase. This inhibition slows down the metabolism of the nerve transmitter noradrenaline, and thus the concentration of noradrenaline in the nerve synapses can increase. This drug is a successful treatment for depression caused by a deficiency of nerve transmitters.

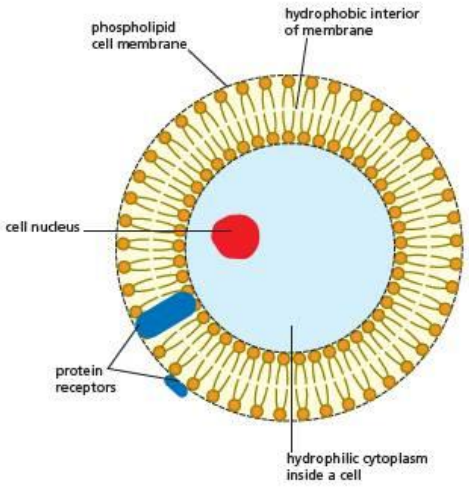
Figure 30.5 Phenelzine and noradrenaline



phenelzine noradrenaline

The other main role of proteins in cells is to act as **receptors**. Receptors are protein molecules that are often found within cell membranes. Much of their influence on the cell's physiology is due to the opposing physicochemical natures of the cell membrane and the cytoplasm. Cell membranes are hydrophobic because of the long alkyl chains in their phospholipid molecules, whereas the cytoplasm is aqueous and hence is hydrophilic (Figure 30.6).

Figure 30.6 Simple diagram of a cell, showing the hydrophobic lipid bilayer membrane, the hydrophilic cytoplasm, and a variety of receptors in the cell wall



Unlike enzymes, receptors do not catalyse chemical reactions, but when 'activated' they produce one of the following physiological responses:

- They stimulate a membrane-bound enzyme.
- They cause the release of secondary messengers within the cell's membrane. These migrate to other parts of the membrane, and either activate or inhibit further enzymes.
- They open ion channels through the membrane, allowing hydrophilic ions to pass through the hydrophobic membrane.

Receptors have active sites just like enzymes. When the natural substrate for a receptor binds with its active site, it changes the shape of the whole receptor molecule. It is this change of shape that causes the physiological response. Drugs have been designed to interact with receptors in either of the following two ways:

1 They can mimic the natural substrate – sometimes causing an even stronger physiological response through a larger change in shape. These drugs are called **agonists**.
2 They can bind with the active site – often more strongly than the natural substrate, and hence blocking the binding of the natural substrate - but they do not change the receptor's shape in the right way to cause a physiological response. These drugs are called **antagonists**. They are inhibiting the receptor's normal function.

Various methods are used to decide which molecules may be useful as drugs.

- The stereo-electronic shape of the active site of the enzyme or receptor can be determined by methods such as nuclear magnetic resonance (NMR) and X-ray crystallography. A compound is designed to fit into it.
- The natural substrate can be used to suggest compounds that could mimic its effect.
- If the molecular structure of a traditional remedy, such as the active ingredient of a plant extract, is known, that structure can be used as a basis for further development.

Figure 30.7 shows some examples of drug molecules whose structures have been developed in these ways.

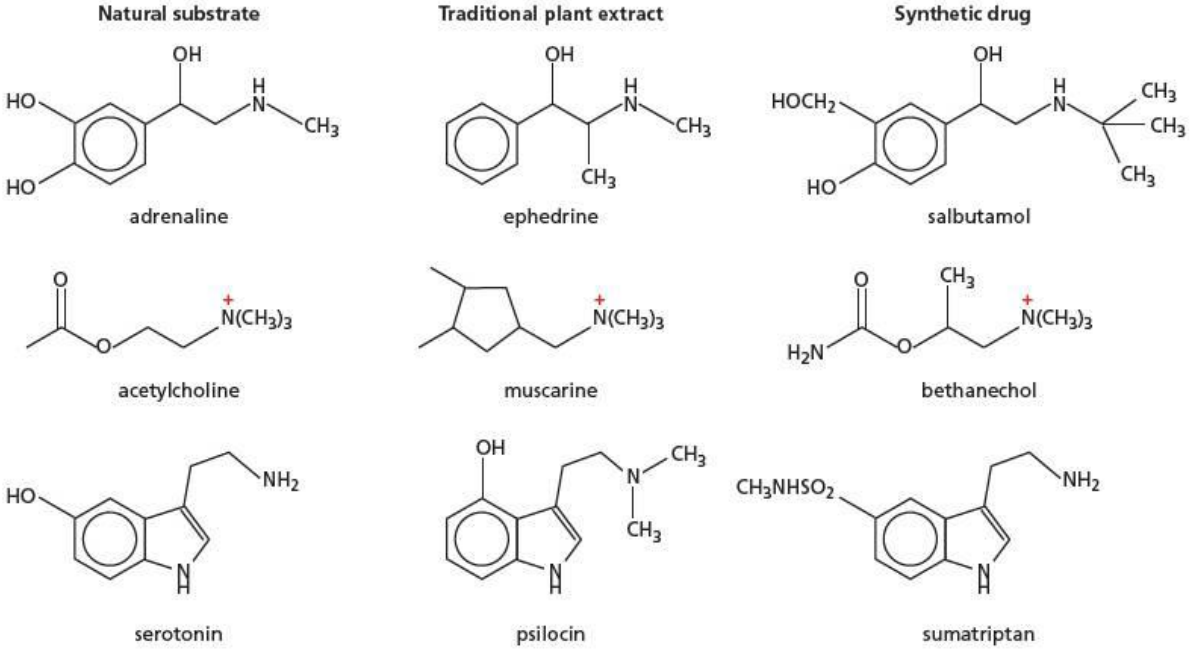


Figure 30.7 The relationship between the chemical structures of the natural substrates, traditional plant extracts and some synthetic drugs.

Now try this

Identify the key structural similarity between the molecules of:
a adrenaline, ephedrine and salbutamol
b acetylcholine, muscarine and bethanechol.

When a compound has been identified as having some of the therapeutic properties desired of the drug, pharmaceutical chemists begin to work on modifying its molecular structure to enhance its beneficial properties and minimise undesirable side effects. Many hundreds of compounds may be synthesised before one is found to have the right mix of characteristics to qualify it for further clinical trials.

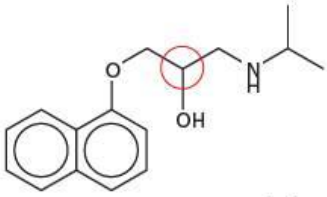
30.3 Synthesis of chiral molecules

Almost without exception, the active sites of enzymes and receptors are chiral; they are made up from naturally occurring amino acids, all of which (except glycine) are themselves chiral (see Topic 27). Consequently, if a drug molecule which contains a chiral centre interacts with an enzyme or receptor, it is almost certain that only one of its stereoisomers will interact. The other stereoisomer will probably not have the desired physiological effect, or could even have a detrimental effect on another receptor elsewhere in the body.

Apart from any possible harmful side effects the 'other' stereoisomer might have, the cost is another incentive for synthesising just one enantiomer of a chiral compound – if only 50% of the drug is going to be useful pharmacologically, it is wasteful to make twice as much as is needed.

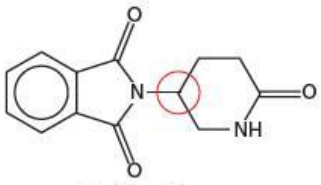
Some examples of pharmaceuticals whose enantiomers have different physiological effects are shown in Figure 30.8 (the chiral centres are circled in red). The modern convention for labelling the two different enantiomers is to use the prefixes **R** and **S**.

Figure 30.8 Different enantiomers can have different physiological effects.



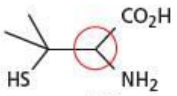
propranolol

R is a beta-blocker for the heart
S is a contraceptive



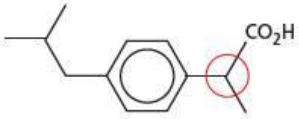
thalidomide

R is mutagenic
S is anti-emetic



penicillamine

R is anti-arthritic
S is highly toxic



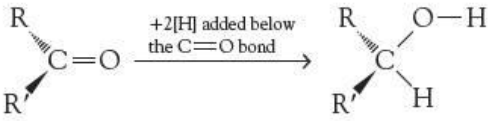
ibuprofen

R is anti-inflammatory
S is inactive

If we synthesise a chiral compound from non-chiral starting materials, we always obtain the **racemic mixture** of enantiomers (see page 224 in section 12.6). It is therefore important to ensure that our target compound, if chiral, is just the one enantiomer that we want. Pharmaceutical chemists have developed ways of preparing drug molecules in a stereoisomerically pure state. These methods can be divided into the following strategies.

1 Start with a chiral compound that is already enantiomerically pure. This will usually be a naturally occurring compound. The synthesis is carefully designed to make sure that the optical activity of the starting material is transferred to each intermediate and to the final target compound, by a process known as **asymmetric induction**.

2 A chiral reagent is used to induce chirality into a molecule at some step during the synthesis. A common method is to use a chiral reducing agent to reduce a symmetric carbonyl compound to just one enantiomer of a chiral alcohol:



symmetrical — chiral (one isomer)

3 A racemic mixture (either of the final product, or of an intermediate) is **resolved** into its two different enantiomers (see panel on page 527). This often means that the half of the mixture that is the unwanted isomer is wasted, so, economically, the earlier this is done during a long synthesis the better.

4 An enzyme is used to catalyse one of the reactions leading to the target compound. If the product of the enzyme-catalysed reaction is chiral, usually only one isomer will be produced since the enzyme itself is chiral.

5 In a similar (but more wasteful) manner, an enzyme is used to react with (e.g. break down) the unwanted isomer, leaving the desired isomer intact.

Resolving enantiomers

There are two main methods of resolving a mixture of enantiomers.

The first, now used increasingly, is to pass a solution of the racemic mixture through a column of a solid support which is itself chiral, a chiral stationary phase (CSP). Originally cellulose (a polymer of (+)D-glucose) was used, but now many semi-synthetic derivatives of cellulose (e.g. cellulose tribenzoate) or other optically active polymers and resins are used. The column preferentially absorbs one of the isomers, letting the other through at a quicker rate. They are thus separated, and a good yield of each isomer can be recovered.This called **enantioselective chromatography**.

The second method uses an optically active compound to form an adduct with the racemic mixture. The two adducts are no longer enantiomers, but diastereoisomers. They have different physical properties that can be used to separate them. **Diastereoisomers** are stereoisomers that are not mirror images of each other. They usually contain more than one chiral centre.

For example, if the racemic mixture is a carboxylic acid, forming a salt with an optically active natural base, such as strychnine, will produce the following:

$$\underset{\text{enantiomers}}{(+)\text{acid} + (-)\text{acid}} + 2\,(+)\text{base} \longrightarrow \underset{\text{pair of diastereoisomers}}{[(+)\text{acid-}(+)\text{base}] + [(-)\text{acid-}(+)\text{base}]}$$

The diastereoisomers will often have different solubilities, and so can be separated by fractional crystallisation. The free carboxylic acids can then be liberated from the salts by reaction with dilute HCl(aq).

Other adducts that have been used include carboxylic esters with an optically active alcohol such as menthol, or, if it is the alcohol that required resolution, with an optically active acid such as tartaric acid.

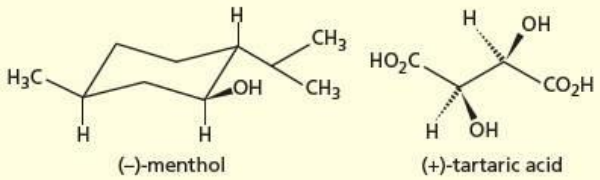


Figure 30.9 (–)-menthol and (+)-tartaric acid

30.4 The use of prodrugs

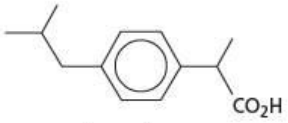
Even if a drug molecule has all the right properties to make it effective *in vitro* (in the test tube), it might still not be clinically useful. This is because there are so many obstacles between its point of entry into the body and its intended destination.

For example, if a drug is taken orally, it must be able to survive the strongly acidic conditions in the stomach and the multitude of hydrolytic enzymes in the intestines. To get into the bloodstream, it must be non-polar enough to diffuse through the hydrophobic cell walls of the intestines, but polar enough to dissolve in the blood. If its target is the brain, it must have an extremely non-polar form in order to pass through the blood–brain barrier. On the way it is likely to pass through the liver, where it will encounter many enzymes whose function is to rid the body of foreign molecules as soon as possible.

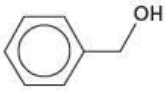
There are several ways the pharmaceutical chemist can overcome these problems. One is to create a compound, called a **prodrug**, that is inactive by itself but can be broken down into the active drug once inside the body. The prodrug is designed either to be stable to the extreme chemical conditions in the digestive tract, or to be lipophilic enough to pass through the intestinal cell walls, or both.

Worked example

An unwelcome side effect of the non-steroidal anti-inflammatory drug (NSAID) ibuprofen is irritation of the gastro-intestinal tract. This can be reduced by reacting it with phenylmethanol to form a prodrug.



ibuprofen



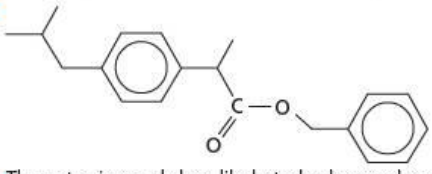
phenylmethanol

The resulting compound has the added advantage of being more easily transported through the intestinal cell walls into the bloodstream.

a What type of compound will the prodrug be?
b Suggest reagents and conditions for making the prodrug.
c Draw the structure of the resulting compound.
d Suggest why the prodrug is more readily absorbed through the cell walls than is ibuprofen.
e What type of reaction can occur within the target cell to re-form ibuprofen from the prodrug?

Answers

a The prodrug will be an ester.
b Heat ibuprofen and the alcohol in the presence of a small quantity of concentrated H_2SO_4.
c



d The ester is much less likely to hydrogen-bond with water than ibuprofen, which is a carboxylic acid. It is also more lipophilic, because the extra benzene ring allows it to form more van der Waals' attractions to the long alkyl chains within the phospholipid membrane of the cell wall.
e The ester can be **hydrolysed** back to ibuprofen, by an esterase enzyme.

Now try this

Compound **A** (Figure 30.10) has excellent *in vitro* activity as an antibacterial agent, but its *in vivo* (in the body) activity is poor because it is too polar to be absorbed through cell walls.

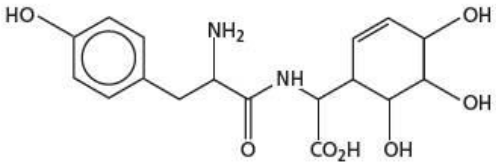


Figure 30.10 Compound **A**

a Name **four** polar functional groups in the molecule of **A**.
b Suggest reagents and conditions for masking each of these polar functional groups to make a prodrug. Draw the resulting structure of the prodrug you suggest.

30.5 Chemical tests for functional groups

Here we bring together the tests that have been described in the various topics of the organic sections of this book.

Alkanes (Topic 13)

These burn with a non-smoky flame, are immiscible with water, and less dense than water. They do **not** decolorise bromine water or dilute potassium manganate(VII).

Alkenes (Topic 14)

These burn with a slightly smoky flame, are immiscible with water, and less dense than water. They decolorise bromine water and dilute potassium manganate(VII) at room temperature.

Alcohols (Topic 16)

These are neutral to litmus solution and (if insoluble in water) do not dissolve in aqueous sodium hydroxide or sodium carbonate. They effervesce with sodium metal (giving off hydrogen) and with phosphorus(V) chloride (giving off hydrogen chloride). Primary, secondary and tertiary alcohols are most easily distinguished from each other by attempted oxidation with acidified dichromate(VI), followed by distillation and performance of tests on the products (see Figure 30.11).

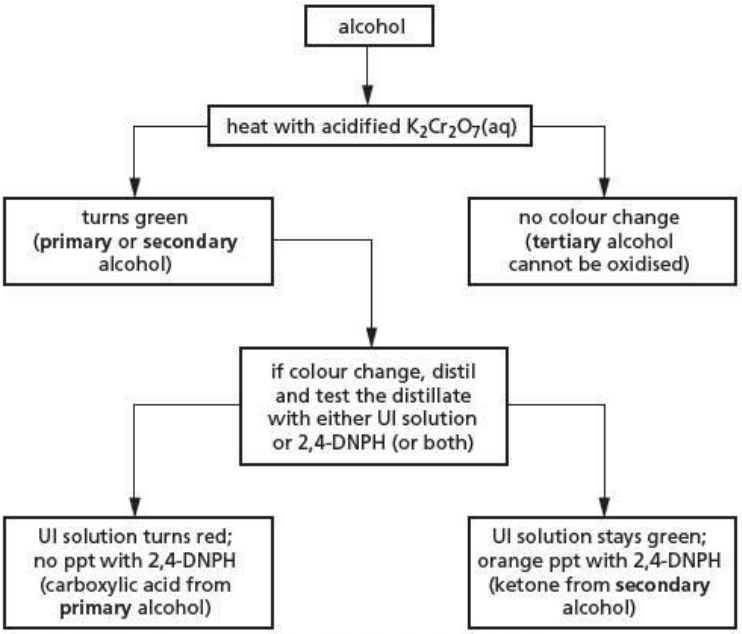


Figure 30.11 How to work out whether an alcohol is primary, secondary or tertiary. (UI, universal indicator)

Carbonyl compounds (Topic 17)

Both aldehydes and ketones produce orange precipitates with 2,4-dinitrophenylhydrazine (2,4-DNPH) (Figure 30.12). They may be distinguished from each other by warming with Tollens' reagent (ammoniacal silver nitrate solution) or Fehling's solution (alkaline copper(II) solution). Aldehydes reduce these reagents, to a silver mirror (Figure 30.13), or a red precipitate of copper(I) oxide, respectively, whereas ketones have no effect upon them.

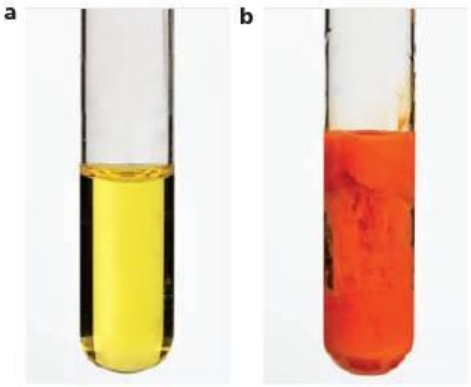


Figure 30.12 Aldehydes and ketones give a precipitate with 2,4-DNPH. **a** Ethanal reacting and, **b** forming an orange precipitate

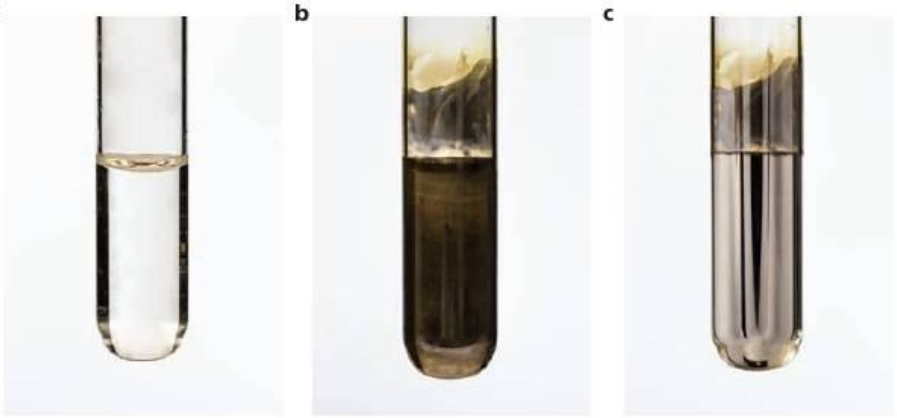


Figure 30.13 Aldehydes give a silver mirror with Tollens' reagent.

Carboxylic acids (Topic 18)

When a drop of a carboxylic acid is added to a solution of universal indicator, the solution turns red. (Note that some acid derivatives such as acyl chlorides and acid anhydrides will also turn universal indicator red because of their hydrolysis.) Carboxylic acids effervesce with sodium (giving off hydrogen) and with phosphorus(V) chloride (giving off hydrogen chloride). They also dissolve in aqueous sodium hydroxide and sodium carbonate (giving off carbon dioxide in the process).

Phenols (Topic 25)

These are usually insoluble in water, but will dissolve in aqueous sodium hydroxide. They do not dissolve in aqueous sodium carbonate. They effervesce with sodium (giving off hydrogen). When a phenol is added to a dilute neutral solution of iron(III) chloride, a violet coloration is produced. Phenols react with bromine water, decolorising it, and producing a white precipitate of the di- or tri-bromophenol.

Acyl chlorides (Topic 26)

These react with water to produce acidic solutions which turn universal indicator red, often giving off fumes of HCl(g) during the process. They may be distinguished from carboxylic acids by their **not** reacting with sodium metal or phosphorus(V) chloride.

Esters (Topic 18)

These are neutral, sweet-smelling liquids that are immiscible with water. They do not react with sodium metal or phosphorus(V) chloride, or with 2,4-DNPH. On heating with dilute acids or alkalis, however, they are hydrolysed to alcohols and carboxylic acids. These products can be tested for in the usual way.

Amides (Topic 27)

These are neutral, but will evolve the alkaline gas ammonia (test with moist red litmus paper) when boiled with NaOH(aq).

Amines (Topic 27)

These either dissolve in water to give alkaline solutions (if of low M_r), or if insoluble in water, they will dissolve in dilute HCl.

The triiodomethane reaction (Topics 16 and 17)

This is a useful test for the presence of the groups $CH_3CH(OH)$— or CH_3CO— in a molecule. When alkaline aqueous iodine is added to a compound containing one of these groups (ethanol, ethanal, methyl secondary alcohols or methyl ketones), a pale yellow precipitate of triiodomethane (iodoform) is formed.

30.6 The use of functional-group tests to deduce structures

If the molecular formula of a compound is known, its structure can often be deduced on the basis of the results of various functional-group tests. An example will make this clear.

Worked example 1

Three compounds, **J**, **K** and **L**, are isomers with the molecular formula $C_4H_8O_2$. Use the information below to identify the compounds **J–Q**, and write equations for all reactions that occur.

a Compound **J** is unaffected by hot dilute sulfuric acid, but reacts with sodium metal, Fehling's solution and alkaline aqueous iodine.

b Both **K** and **L** react with hot dilute sulfuric acid. Under these conditions compound **K** gives **M** (CH_2O_2) and **N** (C_3H_8O) and compound **L** gives **P** ($C_2H_4O_2$) and **Q** (C_2H_6O).

- Both **M** and **P** effervesce with sodium carbonate solution.
- **N** and **Q** both react with sodium metal, and are both oxidised by acidified potassium dichromate(VI).
- The oxidation product from **N** gives an orange precipitate with 2,4-dinitrophenylhydrazine, but does not produce a silver mirror when warmed with ammoniacal silver nitrate.
- The oxidation product from **Q** is identical to compound **P**.

Answer

a Compound **J** is not an ester (because it does not react with hot dilute sulfuric acid) but it could be an alcohol or a carboxylic acid (reaction with sodium). Reaction with Fehling's solution suggests an aldehyde, and reaction with alkaline aqueous iodine suggests the group $CH_3CH(OH)$— or CH_3CO—.

We now consider the second oxygen atom in the formula. Since at least one of the two oxygen atoms is taken up by the aldehyde group, **J** cannot be a carboxylic acid. It must therefore be an alcohol (reaction with sodium). So **J** contains the groups $CH_3CH(OH)$— and —CHO, and must therefore be **$CH_3CH(OH)CH_2CHO$**.
Equations:

$CH_3CH(OH)CH_2CHO + Na \rightarrow CH_3CH(ONa)CH_2CHO + H_2$

$CH_3CH(OH)CH_2CHO + [O] \rightarrow CH_3CH(OH)CH_2CO_2H$

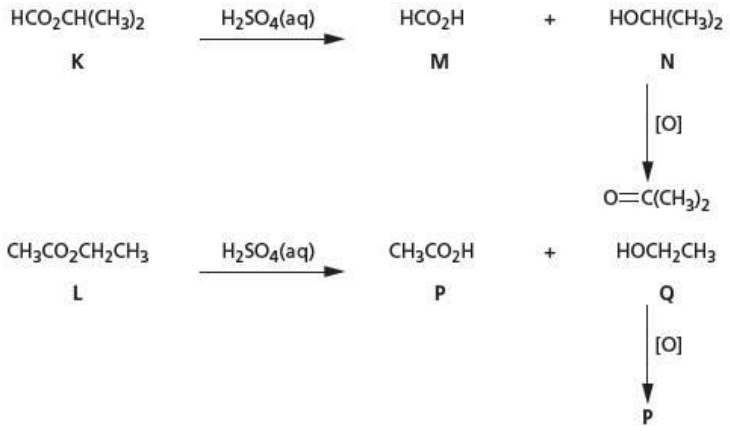
$CH_3CH(OH)CH_2CHO + 4I_2 + 6OH^- \rightarrow CHI_3 + {}^-O_2CCH_2CHO + 5I^- + 5H_2O$

b Both compounds **K** and **L** are esters (reaction with hot dilute sulfuric acid), being hydrolysed to acids (**M** and **P**) and alcohols (**N** and **Q**). **M** and **P** have unique structures for their molecular formulae. **M** is methanoic acid, HCO_2H, and **P** is ethanoic acid, CH_3CO_2H. Both acids will effervesce with aqueous sodium carbonate, giving off carbon dioxide.

The alcohols **N** and **Q** are both oxidised by acidified potassium dichromate(VI) solution, so neither is a tertiary alcohol. **N** produces a ketone on oxidation (orange precipitate with 2,4-DNPH, but no silver mirror with Tollens' reagent). So **N** is the secondary alcohol, propan-2-ol. **Q** must be ethanol, which is oxidised to ethanoic acid (**P**).

Putting all this together shows that **K** must be prop-2-yl methanoate, and **L** must be ethyl ethanoate (Figure 30.14)

Figure 30.14



Now try this

Deduce the structures of the following compounds, explaining your reasoning:

1 Compound **R** has the molecular formula C_8H_8O. It effervesces with sodium metal, but not with phosphorus(V) chloride. It decolorises bromine water, giving a white precipitate. It also decolorises dilute aqueous potassium manganate(VII) solution.

2 Compound **S** has the molecular formula $C_6H_{12}O_2$. It is unaffected by hot dilute sulfuric acid and also by hot acidified dichromate, but reacts with both sodium metal and alkaline aqueous iodine. It forms an orange precipitate with 2,4-dinitrophenylhydrazine, but does not react with Fehling's solution.

Functional-group tests are also useful for distinguishing between isomers. The following examples illustrate this.

Worked example 2

For each of the following pairs of isomers, suggest a test that will distinguish between the two compounds.

a $CH_3CH_2CH_2CHO$ and $CH_3CH_2COCH_3$

b $(CH_3)_3COH$ and $(CH_3)_2CHCH_2OH$

c $CH_2{=}CHCH_2OH$ and CH_3CH_2CHO

Answer

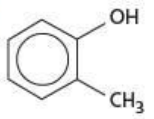
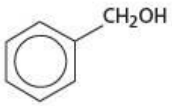
a One of the pair is an aldehyde, and the other is a methyl ketone. We could use either Fehling's solution (red precipitate with the aldehyde, no change with the ketone) or alkaline aqueous iodine (yellow precipitate with the methyl ketone, no change with the aldehyde). Note that 2,4-DNPH would not distinguish these: both will give orange precipitates.

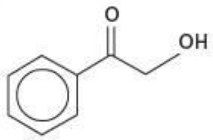
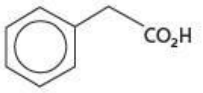
b Both compounds are alcohols, so sodium metal or phosphorus(V) chloride would not distinguish between them. One is a tertiary alcohol, so would not be affected by warming with acidified potassium dichromate(VI). The other is a primary alcohol, which would turn acidified dichromate(VI) from orange to green.

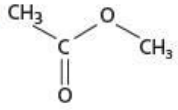
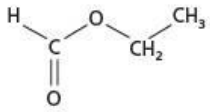
c Several tests could be used for this pair. The first compound is an alkene alcohol, so it would react with aqueous bromine, cold potassium manganate(VII) solution, sodium metal or phosphorus(V) chloride. None of these reagents would react with the second compound. Being an aldehyde, however, this second compound would react with 2,4-DNPH, Fehling's solution or Tollens' reagent. Note that both compounds would be oxidised by warm acidified dichromate(VI), so this reagent would not distinguish between them.

Now try this

Suggest tests that could be carried out on each of the following pairs of isomers that would distinguish between them.

1  and 

2  and 

3  and 

4 $CH_3—CH_2—COCl$ and $CH_3—CHCl—CHO$

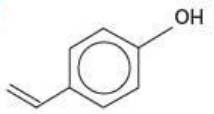
30.7 Predicting the reactions of multifunctional compounds

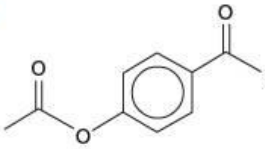
Just as we can deduce the functional groups in a compound from its reactions, so we can work out how a particular multifunctional compound reacts with a particular reagent. The reactions of many multifunctional compounds can be considered to be the sum of the reactions of each of the functional groups they contain, and so a particular compound may react with several different reagents, or a particular reagent may react with several groups in a molecule.

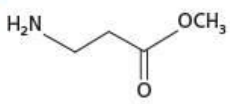
Here are some examples.

Worked example

Predict the product of the reactions between the following compounds and reagents.

a  + $Br_2(aq)$

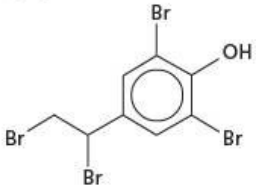
b  + hot NaOH(aq)

c  + hot HCl(aq)

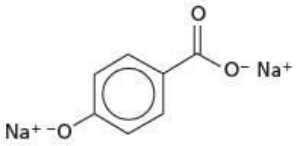
d  + Na(s)

Answer

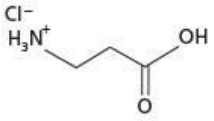
a The $Br_2(aq)$ will react with both the alkene and the phenol.



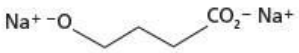
b Hot NaOH will hydrolyse both the ester and the amides, and produce the carboxylate and the phenoxide ions of the product.



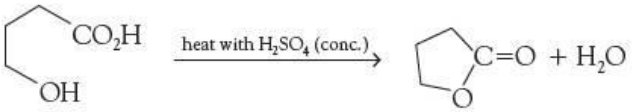
c The HCl(aq) will hydrolyse the ester, but will also form the salt from the amine.



d The sodium metal will react with both the carboxylic acid and the alcohol

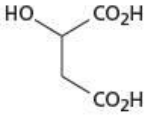


Some functional groups in multifunctional compounds might even react with each other under certain conditions. For example, reacting $HOCH_2CH_2CH_2CO_2H$ with concentrated H_2SO_4 causes the molecule to undergo an internal esterification to produce a cyclic ester (called a lactone).

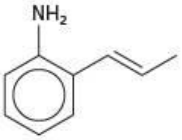


Now try this

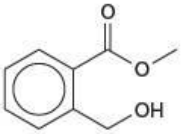
Predict the products **A** to **E** of the following reactions.

1 

$+ PCl_5 \longrightarrow$ **A**

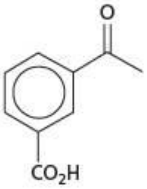
2 

$+ Br_2(aq) \longrightarrow$ **B**

3 

$\xrightarrow[\text{trace of } H_2SO_4(conc.)]{\text{heat with}}$ **C** ($C_8H_6O_2$)

4 $CH_3CH(OH)CO_2H \xrightarrow[\text{trace of } H_2SO_4(conc.)]{\text{heat with}}$ **D** ($C_6H_8O_4$)

5 

$\xrightarrow{LiAlH_4}$ **E**

30.8 Summary of organic transformations

Reagents for organic reactions

Reference (see key below)	Reagents and conditions	Reaction number on chart						
		Chart A Alkenes	Chart B Bromo-alkanes	Chart C Alcohols	Chart D Aldehydes and acids	Chart E Methyl ketones	Chart F Amines	Chart G Benzene
E1	$Cl_2(g) + AlCl_3$							G1
E2	$Br_2(l) + AlBr_3$							G2
E3	HBr(g) at R.T.	A3	B3					
E4	$H_2SO_4(aq)$ at R.T.	A4		C2		E1		
E5	conc. HNO_3 + conc. H_2SO_4 at < 55 °C							G5
E6	R'Cl + $AlCl_3$ + heat							G9
E7	R''COCl + $AlCl_3$ + heat							G10
F1	$X_2(g)$ + light (X═Cl or Br)		B2					G3
N1	NaOH(aq) + heat		B4	C1				
N2	NH_3 in ethanol + heat under pressure		B6			F1		
N3	NaCN in ethanol + heat		B7					
N4	HCN + NaCN in ethanol/ water				D5	E5		
N5	HBr(conc.) or NaBr + conc. H_2SO_4 + heat		B1	C4				
N6	$SOCl_2$ or PCl_5 + heat				D8			
N7	R'–OH at R.T.				D9			
N8	R'–OH + conc. H_2SO_4 + heat				D7			
N9	phenol + NaOH (aq) in the cold				D10			G8
N10	$H_2SO_4(aq)$ + heat				D3 D12			
N11	$R'NH_2$ at R.T.				D11			
O1	$Na_2Cr_2O_7(aq)$ + $H_2SO_4(aq)$ + heat			C6 C7	D1 D2 D6	E2		
O2	$KMnO_4(aq)$ at R.T.	A6						
O3	$KMnO_4$(conc.) + $H_2SO_4(aq)$ + heat	A7						
O4	$KMnO_4$(conc.) + $OH^-(aq)$ + heat							G4
R1	$H_2(g)$ + Ni catalyst at R.T.	A5		C3	D4	E3	F2	
R2	$NaBH_4$ in aqueous methanol + heat			C3	D4	E3		
R3	$LiAlH_4$ in dry ether			C3 C9	D4 D13	E3	F2 F3	
R4	Sn + conc. HCl(aq) + heat							G6
X1	NaOH in ethanol + heat	A1	B5					
X2	Al_2O_3 + heat	A2		C5				

Continued

Reference (see key below)	Reagents and conditions	Reaction number on chart						
		Chart A Alkenes	Chart B Bromo-alkanes	Chart C Alcohols	Chart D Aldehydes and acids	Chart E Methyl ketones	Chart F Amines	Chart G Benzene
X3	conc. H_2SO_4 + heat	A2		C5				
M1	$I_2(aq) + OH^-(aq)$ + warm					E4		
M2	HNO_2 (or $NaNO_2$ + HCl(aq)) at < 5 °C							G7
M3	R"COCl at R.T.			C8		F5		
M4	$R'CO_2H$ + conc. H_2SO_4 + heat			C8				
M5	R'Br + heat					F4		

Table 30.1 Reagents for organic reactions

E, electrophilic reagents; F, free-radical reagents; N, nucleophilic reagents; O, oxidising agents; R, reducing agents; X, elimination reagents; M, miscellaneous; R.T., room temperature

Charts for organic syntheses

Chart A: Synthetic routes involving alkenes

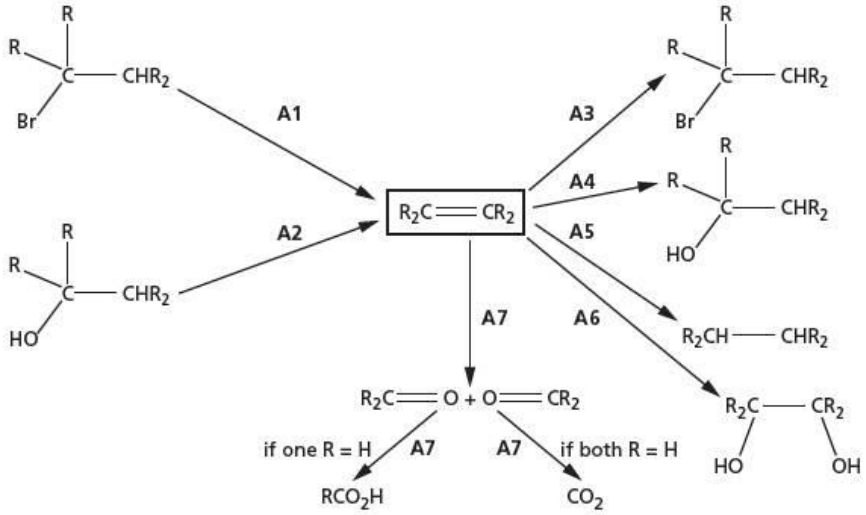


Chart B: Synthetic routes involving bromoalkanes (or chloroalkanes)

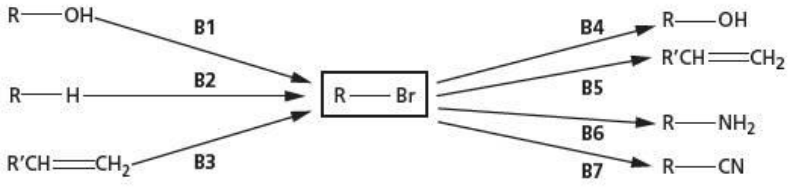


Chart C: Synthetic routes involving alcohols

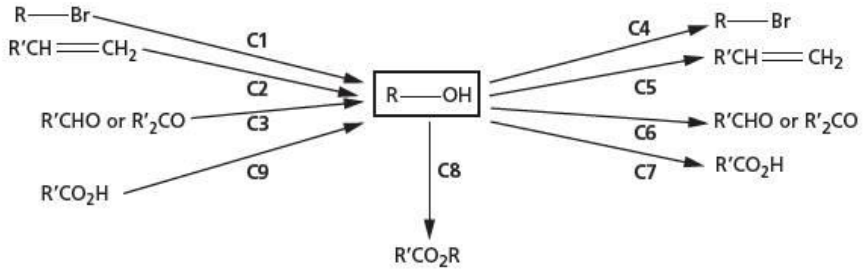


Chart D: Synthetic routes involving aldehydes and carboxylic acids

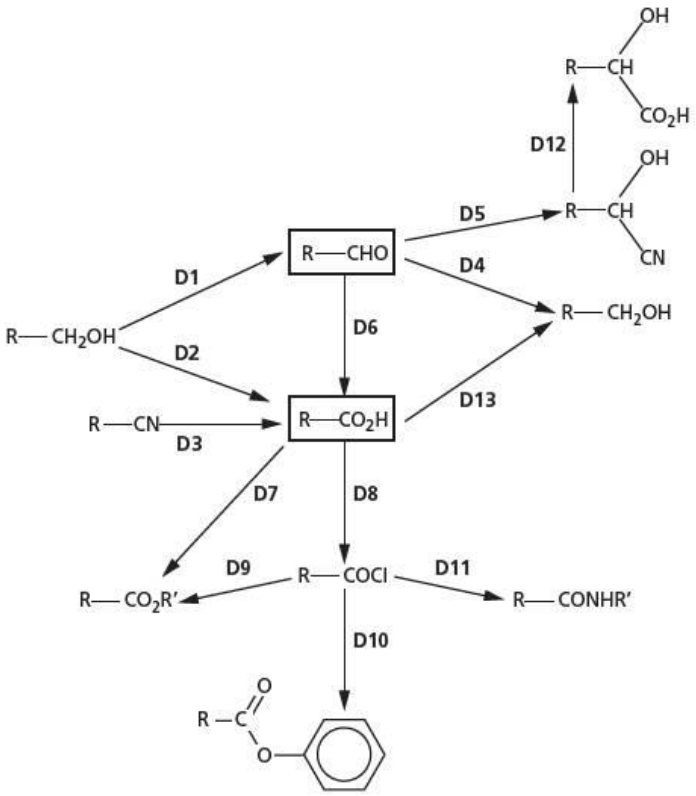


Chart E: Synthetic routes involving methyl ketones

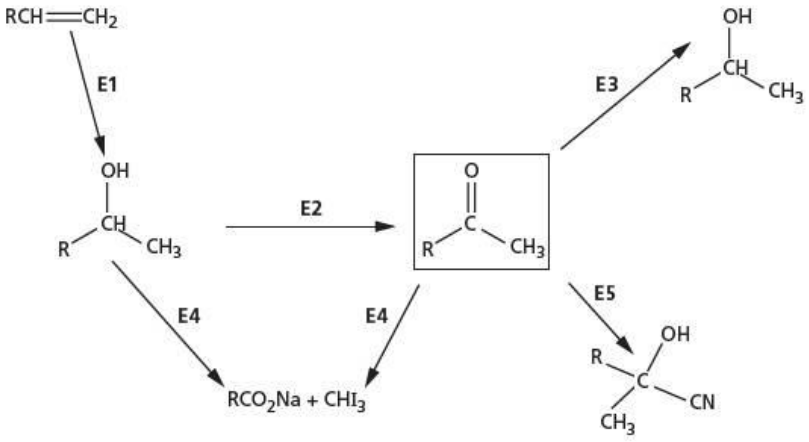


Chart F: Synthetic routes involving amines

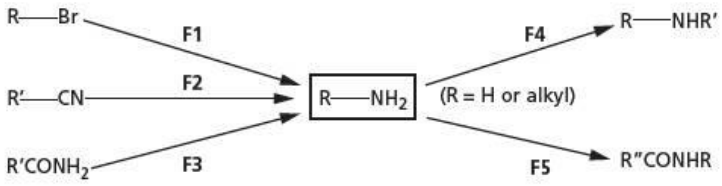
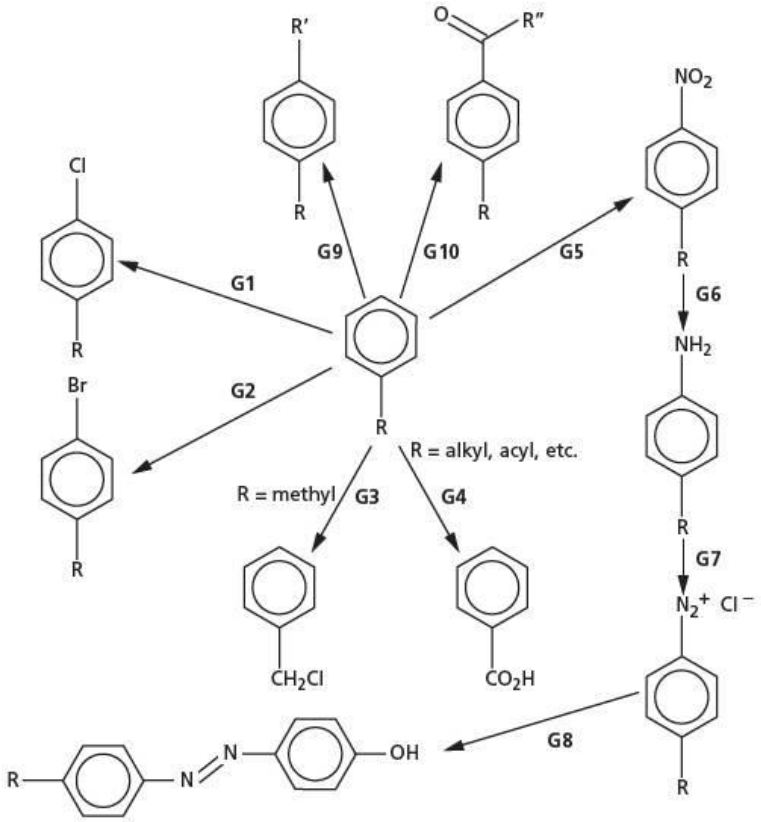


Chart G: Synthetic routes involving arenes



(R = hydrogen or methyl or other alkyl unless stated otherwise)

Summary

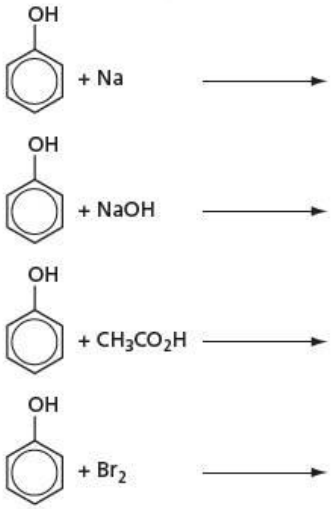
- General organic synthetic reactions can be used to make a large variety of organic compounds from simpler, easily available compounds.
- Pharmaceutical molecules can be designed to target specific enzymes and/or receptors, to treat a variety of diseases and illnesses.
- The use of **prodrugs** is a method of protecting drug molecules from degradation before they reach their site of action.
- Various methods are available for the synthesis of **optically pure** compounds for use as drugs.
- Knowledge of the reactions of organic functional groups allows the identities of organic compounds to be determined and isomers to be distinguished.

Examination practice questions

Please see the data section of the CD for any A_r values you may need.

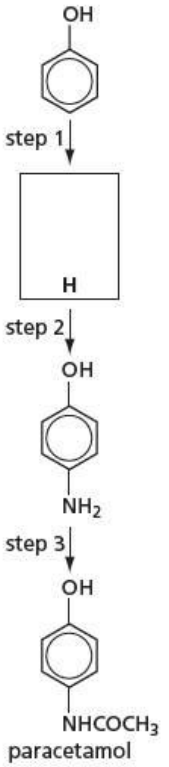
1 a Describe and explain how the acidities of ethanol and phenol compare to that of water. [4]

b Complete the following equations showing **all** the products of each of these reactions of phenol. Include reaction conditions where appropriate. If no reaction occurs write ***no reaction***.



[5]

c The analgesic drug paracetamol can be synthesised from phenol by the following route. Suggest reagents and conditions for the each of three steps, and suggest the structure of the intermediate **H**.



paracetamol [4]

[Cambridge International AS & A Level Chemistry 9701, Paper 42 Q5 June 2011]

2 Compound **C** has the molecular formula $C_7H_{14}O$. Treating **C** with hot concentrated acidified $KMnO_4(aq)$ produces two compounds, **D**, C_4H_8O, and **E**, $C_3H_4O_3$. The results of four tests carried out on these three compounds are shown in the following table.

test reagent	result of test with		
	compound C	compound D	compound E
$Br_2(aq)$	decolourises	no reaction	no reaction
Na(s)	fizzes	no reaction	fizzes
$I_2(aq) + OH^-(aq)$	no reaction	yellow precipitate	yellow precipitate
2,4-dinitrophenylhydrazine	no reaction	orange precipitate	orange precipitate

a State the functional groups which the above four reagents test for.

i $Br_2(aq)$

ii Na(s)

iii $I_2(aq) + OH^-(aq)$

iv 2,4-dinitrophenylhydrazine [4]

b Based upon the results of the above tests, suggest structures for compounds **D** and **E**. [2]

c Compound **C** exists as two stereoisomers. Draw the structural formula of **each** of the two isomers, and state the type of stereoisomerism involved. [3]

[Cambridge International AS & A Level Chemistry 9701, Paper 41 Q5 November 2011]