

# Chemistry in your cupboard: Nurofen

## Introduction

Ibuprofen is one of four active ingredients found in UK over-the-counter painkillers and is marketed under the brand name Nurofen™. It acts on a group of compounds known as prostaglandins to reduce pain, inflammation and fever. As prostaglandins have a wide range of actions not all the effects of ibuprofen are beneficial - by taking the recommended dose of ibuprofen you will ensure the benefits will outweigh any adverse effects.

## Links to the curriculum

This section contains information relevant to the following areas of your chemistry curriculum:

- Bonding and solubility
- Isomerisation
- Reactions of organic functional groups

## NUROFEN

Nurofen is the brand name under which Reckitt Benckiser sells ibuprofen. Ibuprofen is an over-the-counter remedy for mild to moderate pain which also reduces inflammation and fever.

Nurofen is available in a number of formulations, see Figure 1. These include tablets and caplets to be taken by mouth, gels to be applied to the skin and soluble oral powders which can be drunk. Also available is Nurofen Express in which ibuprofen, the active ingredient, has been chemically modified to make it more soluble. This means that it is absorbed more quickly by the body and therefore acts faster.

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Figure 1: Some of the Nurofen product range.

In the UK, analgesic medicines are formulated from active ingredients such as: aspirin, paracetamol, codeine and ibuprofen, see Figures 2 and 3. These may be sold separately under their own names, as a branded product (Aspro™, Panadol™, Nurofen™, Nuromol™ etc), or as combined preparations containing two or more of these ingredients (Veganin™ contains aspirin, codeine and paracetamol, for example).

Ibuprofen was patented by the Boots Company in the 1960s and became available without prescription in the UK in the mid-1980s.

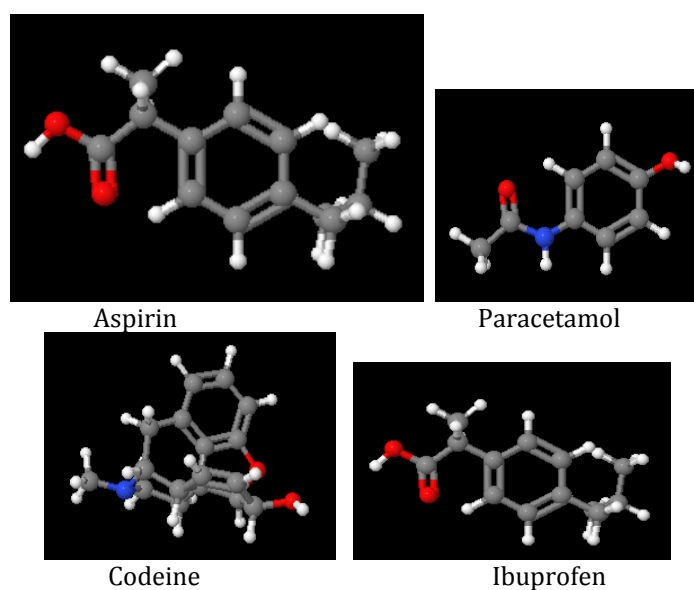


Figure 2: 3D representation of active ingredients in over-the-counter painkillers.

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Make sure that you can relate the two representations of the active ingredients in over-the-counter painkillers to one another. In the 3D representation, carbon atoms are coloured grey, hydrogen white, oxygen red and nitrogen blue. You may find it helpful to make a model of the active ingredients using a ball and stick modelling kit such as Molymod™.

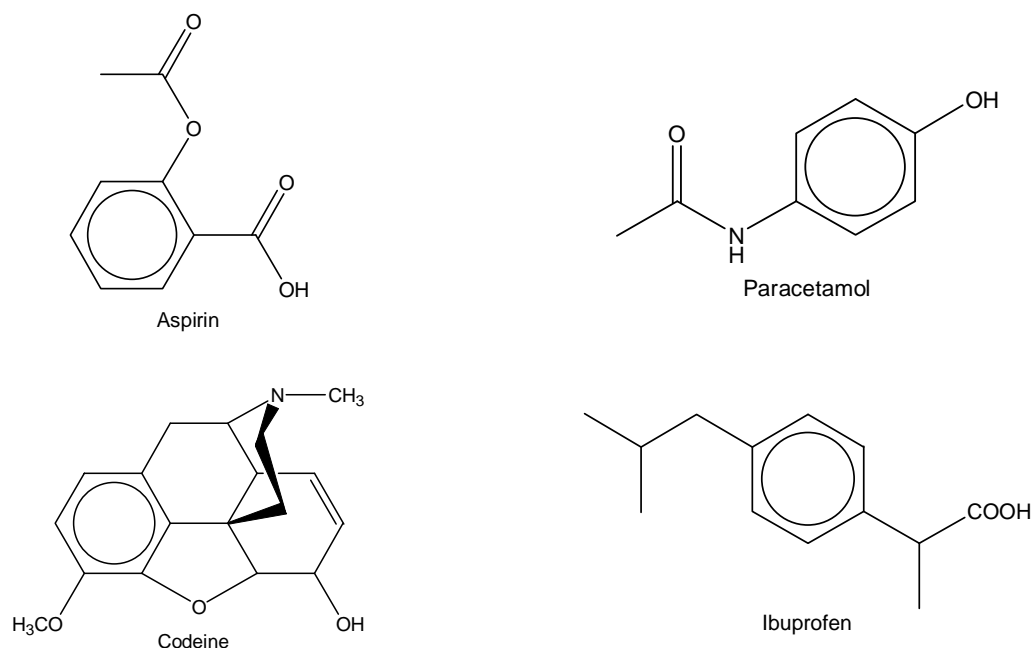


Figure 3: Structures of the active ingredients in over-the-counter painkillers.

### Question 1

Draw the displayed structural formula of ibuprofen, ie the structure should show every atom and every bond.

### How does ibuprofen work?

Ibuprofen is classed as a non-steroidal anti-inflammatory drug or NSAID. It works by acting on a group of compounds called **prostaglandins**.

Prostaglandins are sometimes called local hormones because they act close to where they are produced rather than all over the body. They have a remarkably wide range of effects. One of their actions is to cause inflammation.

### Inflammation

When a part of the body is injured, protective mechanisms go into action. White blood cells accumulate at the site of the injury, and this causes swelling, heat, redness, loss of function, fever and pain - together called inflammation.

All these effects are potentially beneficial. Swelling can help to immobilise injured joints, heat and increased blood flow promote healing, and pain alerts the injured person that

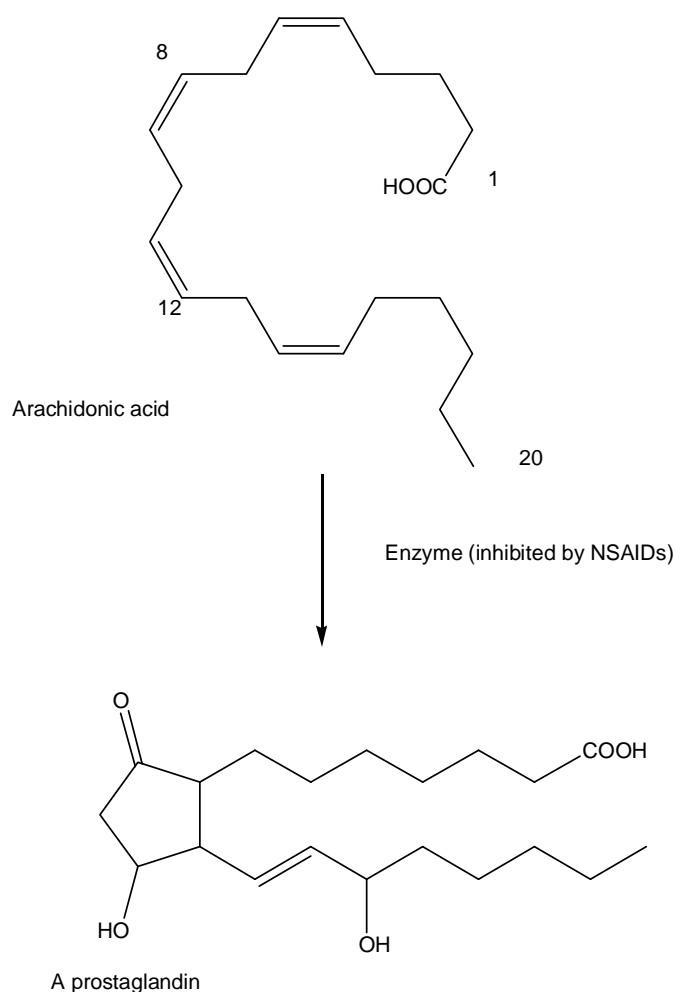
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there is a problem (so that he or she will quickly remove their hand from a hot stove, for example, to prevent further injury). However, they can often be too much of a good thing - once we know we are injured, the pain no longer has a function and we wish to be rid of it; often the inflammatory response is too powerful and can do more harm than good.

Prostaglandins are involved in bringing about the inflammatory response. Ibuprofen's action as a painkiller and antipyretic (fever-reducing) compound is due to its ability to inhibit the synthesis of prostaglandins. It does this by interfering with the action of an enzyme called **cyclo-oxygenase** which catalyses the conversion of a compound called arachidonic acid into prostaglandins, (see Figure 4). Aspirin and other NSAIDs work in a similar way.



**Figure 4: Prostaglandin synthesis.**

At first sight you may think that the structures of arachidonic acid and prostaglandins are very different but imagine a bond forming between carbon 8 and carbon 12 in arachidonic acid to form the five-membered ring of the prostaglandin and you should

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see the similarity. (The carbon atoms have been numbered from the  $-\text{COOH}$  end of the molecule.)

### Side effects of NSAIDs

In common with other NSAIDs ibuprofen has some unwanted effects (side effects). This is because prostaglandins have many other roles in the body as well as their control of inflammation. Inhibiting prostaglandin synthesis inevitably affects these too. Two of these roles are that they help protect the lining of the gut and that they are important for blood clotting to work properly. So taking NSAIDs can cause irritation of the gut and reduced blood clotting, which makes bleeding more likely. However, taking the correct dose ensures that the positive effects (a reduction in pain, swelling and inflammation) outweigh the undesirable ones (possible bleeding in the gut). Ibuprofen causes less stomach irritation than aspirin.

The difference in dose between the start of the beneficial effect and the onset of side effects is called the therapeutic (curative) window.

### The structure of ibuprofen

The skeletal formula of ibuprofen is shown in Figure 5.

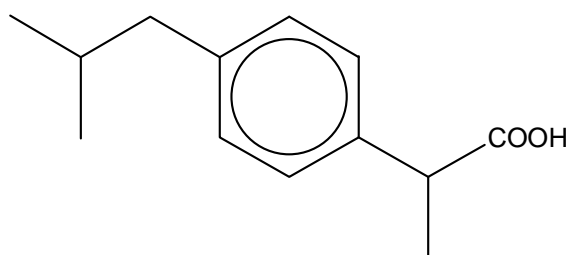


Figure 5: Structure of ibuprofen.

#### Question 2

What functional groups does ibuprofen have?

#### Question 3

Look at the displayed formula of ibuprofen and identify the carbon atom that has four different groups bonded to it.

### Optical activity of ibuprofen

Ibuprofen has a particularly interesting property - it can exist as a pair of optical isomers that are mirror images of each other. These mirror images are non-superimposable, ie they are like a pair of shoes - left and right shoes are mirror images but not identical. This mirror image property occurs in molecules that have a carbon atom to which four different groups are bonded. The two optical isomers of ibuprofen are identified by the prefixes R- and S+ (see Figure 6).

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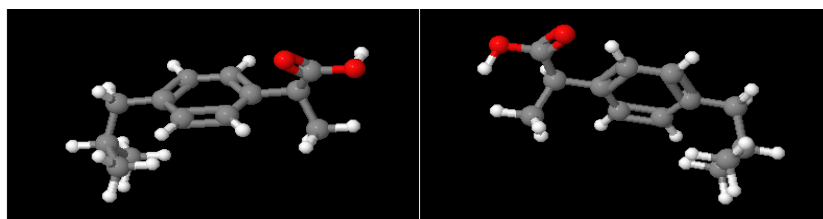
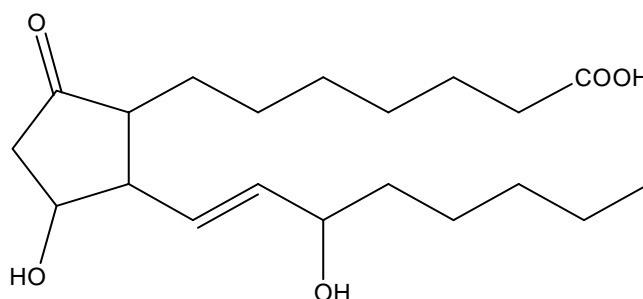


Figure 6: 3D appearances of S+ibuprofen (left) and R-ibuprofen (right) showing their mirror image relationship

Mirror image isomers are identical in many properties such as solubility, melting point and boiling point. They can be distinguished by the fact that they rotate the plane of polarisation of polarised light in different directions: the + isomer clockwise as the observer looks at the light, and the – anticlockwise. The symbols R and S refer to the 3D arrangement of the atoms in space. The two isomers do, however, behave differently when they interact with other 'handed' molecules such as the prostaglandins. A full explanation of the R and S nomenclature is beyond the scope of this article but if you are interested see <http://www.cem.msu.edu/~reusch/VirtualText/sterism3.htm>.

#### Question 4

Identify any asymmetric carbon atoms in the following prostaglandin molecule:



Of the two optical isomers of ibuprofen it is the S+ form which is the pharmacologically active component that inhibits prostaglandin synthesis while the R- form has no anti-inflammatory effect.

However, it has been found that there is an enzyme in the body that converts the R- form into the S+. In fact 60% of the R- form is converted into S+. This means that in a typical dose of ibuprofen of 400 mg, 200 mg is S+ and 200 mg R-. Of the 200 mg of R-, 60% (ie 120 mg) is converted into the active R+ form, giving a total of active form of 320 mg. Therefore there is little point in going to the trouble of synthesising the S+ form only, and ibuprofen is sold as a racemic mixture (one initially containing equal amounts of both optical isomers). However a stereospecific synthesis is possible.

#### Question 5

What do you expect the effect of ibuprofen on plane polarised light to be?

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## The synthesis of ibuprofen (1 of 3)

Boots' method of making ibuprofen described in their patent starts from the compound 2-methylpropylbenzene, (Figure 7).

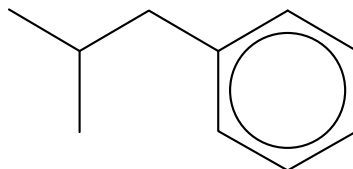


Figure 7: Structure of 2-methylpropylbenzene

2-methylpropylbenzene can be made from compounds separated from crude oil and has a similar carbon skeleton to that of ibuprofen.

### Question 6

- What is the only functional group of 2-methylpropylbenzene?
- What type of reactions does this functional group usually undergo?

### Question 7

- What extra functional group does ibuprofen have compared with 2-methylpropylbenzene?
- What sorts of reactions can be used to prepare this functional group?

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971,700



## PATENT SPECIFICATION

NO DRAWINGS

971,700

Inventors: JOHN STUART NICHOLSON  
and STEWART SANDERS ADAMS

Date of filing Complete Specification: Jan. 12, 1962.

Application Date: Feb. 2, 1961.

No. 3999/61.

Complete Specification Published: Sept. 30, 1964.

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Index at acceptance:—C2 C(2A2, 2A14, 2R15, 2T16, 3A8A2, 3A8B2, 3A8C3, 3A8K, 3A10A4E, 3A10A4F, 3A10A5A1, 3A10A5A2, 3A10A5E, 3A10A5F, 3A10A5G2, 3A10A5K, 3A10B2C, 3A10B5E, 3A10E3C1, 3A10E4A3, 3A10E6D, 3A10E5E, 3A10E5F1A, 3A10E5F1E, 3A10E5F2A, 3A10E5F3A, 3A10E5F3D, 3A13A3A2, 3A13A3A3, 3A13A3B1, 3A13A3F3); A5 B(1S, 2S)

International Classification:—C 07 e (A 61 k)

## COMPLETE SPECIFICATION

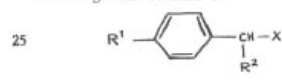
## Anti-Inflammatory Agents

We, BOOTS PURE DRUG COMPANY LIMITED, a British Company, of Station Street, Nottingham, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to phenylalkane derivatives. More particularly it relates to novel pharmaceutical and veterinary compositions which comprise as the active ingredient one or more members of a specified group of derivatives of toluene. The invention also relates to the provision of novel members of this specified group of compounds.

It is an object of the invention to provide therapeutic compositions for the relief of pain, fever and inflammation in man and animals which do not suffer from the disadvantages of similar therapeutic compositions based on aspirin, phenylbutazone or adrenocorticosteroids.

We have now discovered that compounds of the general formula I



wherein R<sup>1</sup> represents ethyl, propyl, butyl, alkenyl (C<sub>2</sub>—C<sub>6</sub>), pentyl (except n-pentyl), alkoxy (C<sub>1</sub>—C<sub>6</sub>), allyloxy, phenoxy, phenylthio or cycloalkyl (C<sub>3</sub>—C<sub>6</sub>) optionally substituted by methyl or ethyl in the 1-position, R<sup>2</sup> represents hydrogen or methyl and X represents the radical COOH, COOR<sup>3</sup> wherein R<sup>3</sup> represents alkyl (C<sub>1</sub>—C<sub>6</sub>) or optionally N-alkylated aminoalkyl (C<sub>2</sub>—C<sub>6</sub>), COOM wherein M represents the ammonium ion or a single

[Price 4s. 6d.]

equivalent of a non-toxic metallic cation, COOH.B wherein B represents a non-toxic organic base, CONH<sub>2</sub>, CH<sub>3</sub>NH<sub>2</sub> or the group CH<sub>3</sub>OR<sup>4</sup> where R<sup>4</sup> represents hydrogen or lower alkanoyl (C<sub>1</sub>—C<sub>6</sub>) have valuable anti-inflammatory, analgesic and antipyretic properties.

Furthermore in general the compounds exhibit low toxicity and low irritancy to the gastric mucosa, they do not have other undesirable pharmacological activities which might give rise to unwanted side effects and they are stable in the presence of water.

According to the present invention there are provided therapeutic compositions comprising as active ingredient one or more compounds of the general formula I in association with a pharmaceutically acceptable diluent or carrier.

The following compounds are typical of the active compounds of the general formula I, but do not limit the invention in any way:—

4-*n*-Propylphenylacetic acid  
4-Ethoxyphenylacetic acid  
4-Isopropylphenylacetic acid  
4-propoxyphenylacetic acid  
4-Isopropoxyphenylacetic acid  
4-*n*-Butylphenylacetic acid  
4-Allyloxyphenylacetic acid  
4-*l*-Butylphenylacetic acid  
4-Cyclopentylphenylacetic acid  
4-*isobutyl*phenylacetic acid  
4-Cycloheptylphenylacetic acid  
4-Cyclohexylphenylacetic acid  
4-(1-Ethylpropyl)phenylacetic acid  
4-Phenoxyphenylacetic acid  
4-(1,2-dimethylpropyl)phenylacetic acid  
4-Phenylthiophenylacetic acid  
*o*-(4-Cyclohexylphenyl)propionic acid

Figure 1.8: The Patent Specification for the UK Patent No. 971,700 covering the therapeutic compositions of phenylalkanoic acid derivatives, including ibuprofen, for the relief of pain, fever and inflammation that were developed by Dr John Nicholson and Dr Stewart Adams. The filing of the complete specification was on 12 January 1962.

Figure 8: The first page of the original patent for ibuprofen. (Courtesy of the International Ibuprofen Foundation)

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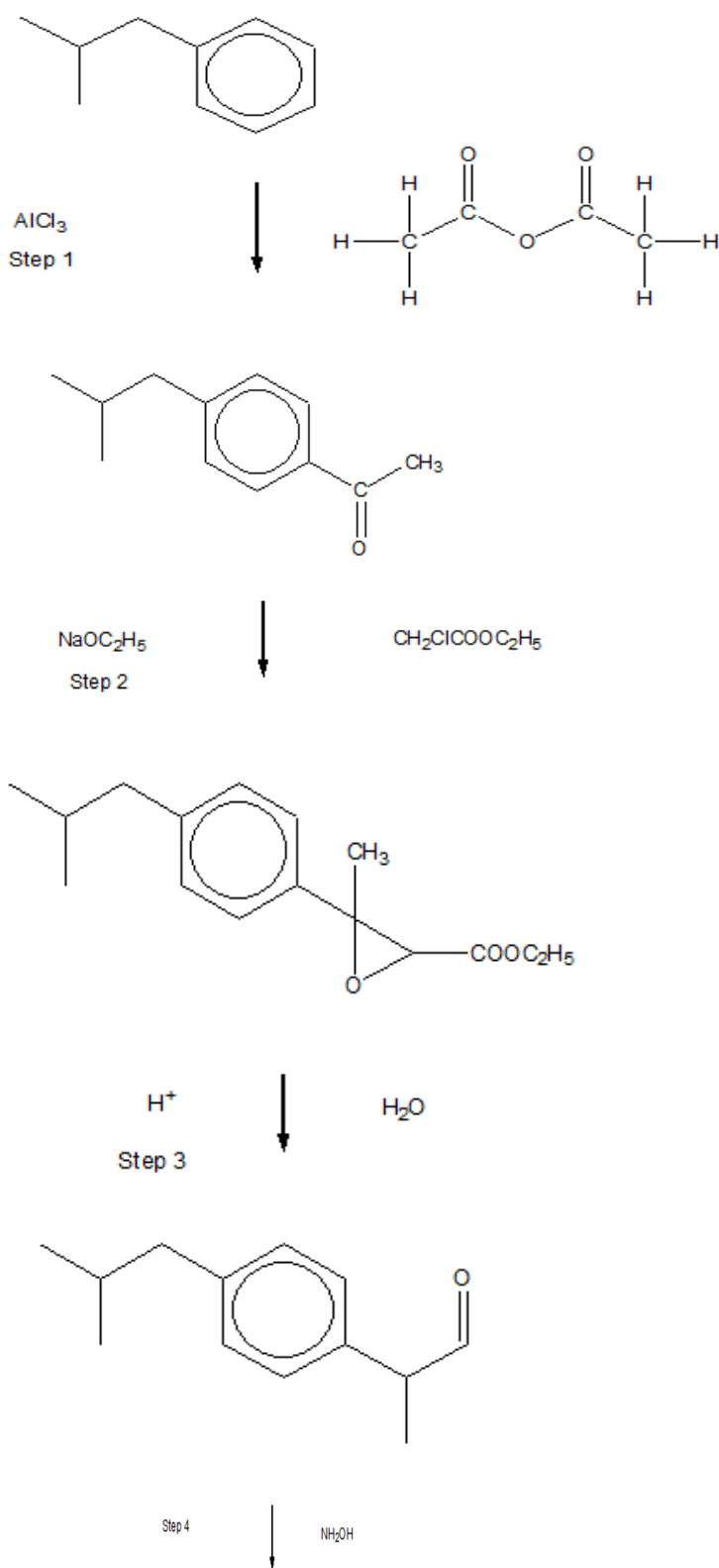
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## The synthesis of ibuprofen (2 of 3)

The Boots' synthesis requires six steps:



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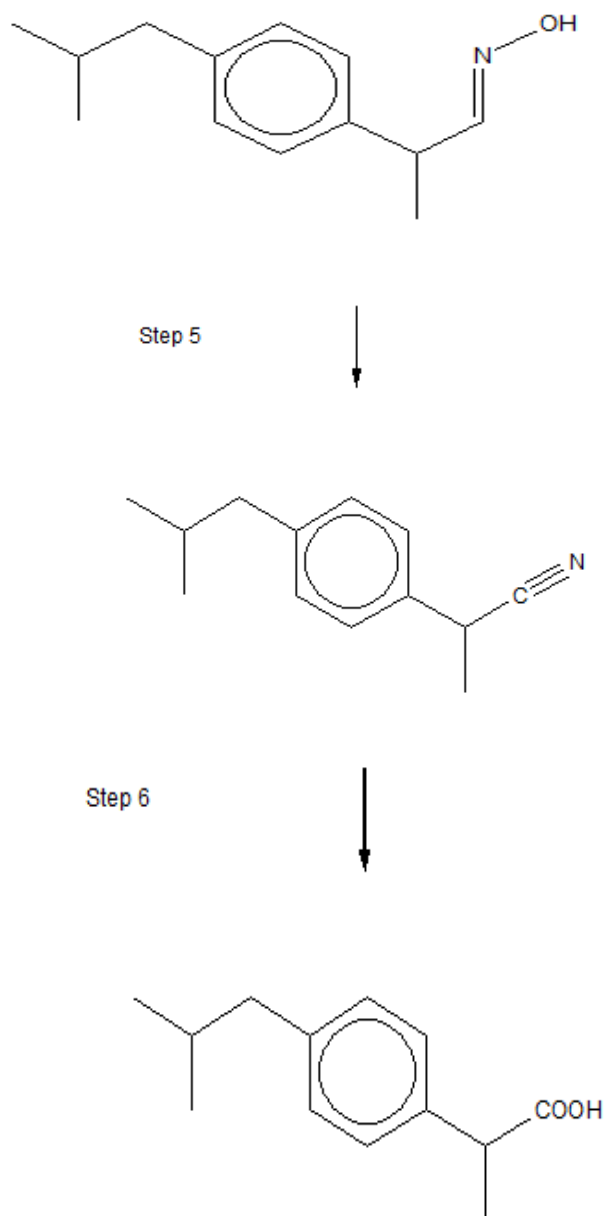


Figure 9: Boots' synthesis of ibuprofen.

### Question 8

- What type of reaction is step 1?
- What is the role of the aluminium chloride?

### Question 9

Suggest the approximate size of the bond angles in the three-membered ring which forms part of the molecule produced after step 3. Why does this make the molecule unstable?

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**Question 10**

- a) What small molecule is removed in step 5?  
 b) Suggest a reagent that might be used for this step.

**Question 11**

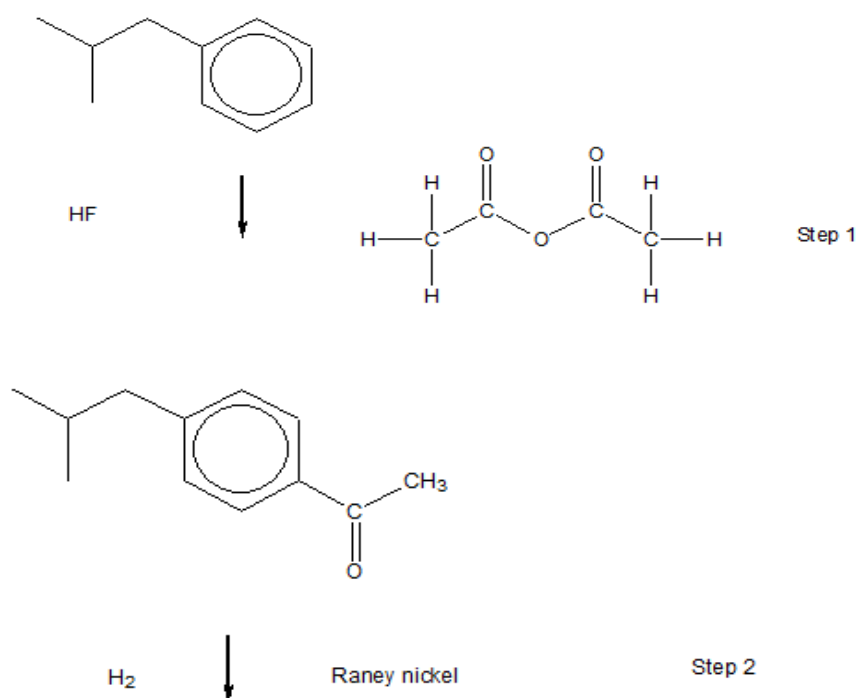
- a) What is the name of the functional group  $-C\equiv N$ ?  
 b) What reagent could be used to convert it into  $-COOH$  in the final step?

**Question 12**

One problem with a synthesis that takes several steps (a multi-step synthesis in the jargon) is that it produces a low overall yield. Imagine each step has a yield of 90%. A 1-step process would have a 90% yield, a 2-step process one of  $90\% \times 90\% = 81\%$ . What would be the yield of a 6-step process?

**The synthesis of ibuprofen (3 of 3)**

The Boots' synthesis has been replaced by the new, more efficient synthesis shown in Figure 10. It starts with the same compound but has fewer steps – it has been described as the 'green' synthesis.



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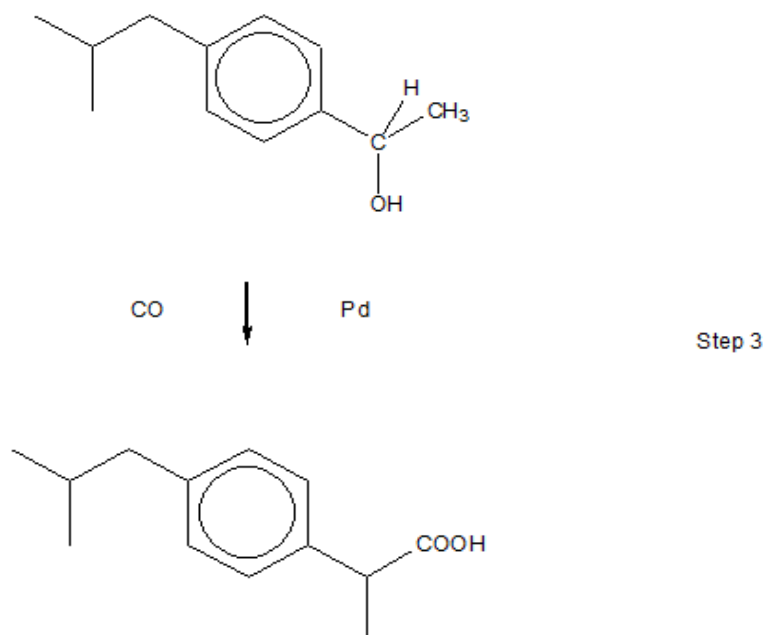


Figure 10: The 'green' synthesis of ibuprofen.

### Question 13

Suggest one reason why this synthesis is more efficient than the Boots' synthesis. Explain your answer.

### Question 14

Select from the following list two terms that describe step 2; reduction, oxidation, acid/base, addition, elimination, condensation.

### Question 15

Suggest the functions of the HF in step 1 and the palladium (Pd) in step 3. Explain your answer.

### The discovery of ibuprofen

Ibuprofen was developed and discovered as a drug by the Boots Company. The leaders of the team were Dr Stewart Adams and his colleagues John Nicholson and Colin Burrows (Figure 11) but hundreds of people were involved.

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**Figure 11: Stewart Adams, John Nicholson and Colin Burrows, the discoverers of ibuprofen.**  
(Courtesy of the International Ibuprofen Foundation)

Work started in the 1950s to find a drug to treat rheumatoid arthritis (inflamed joints) that had fewer side effects than aspirin. However ibuprofen was not launched until 1969. This timescale is not unusual for development and testing of a drug. The timeline was as follows:

**1955** The discovery is made that anti-inflammatory drugs reduce inflammation of the skin caused by ultra-violet light. This gives a simple screening test for new chemical compounds (called new chemical entities or NCEs in the jargon) that the research chemists produced.

**1958** After some 600 compounds had been made and screened for activity, a promising compound code named BTS 8402 is given a clinical trial (ie a trial on patients). It is found to be no better than aspirin.

**1961** A patent (see Figure 7) is filed for the compound 2-(4-isobutylphenyl) propanoic acid - later called ibuprofen.

**1964** Ibuprofen is selected for further development.

**1966** Clinical trials of ibuprofen take place at the Northern General Hospital in Edinburgh and show its anti-inflammatory effect in patients.

**1969** Ibuprofen is launched in the UK on prescription only.

**1983** Because of its safety record, ibuprofen is made available without prescription.

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**Nurofen Express**

Anyone who takes a painkiller wants it to act fast. Before it can act, ibuprofen must be absorbed into the bloodstream through the gut wall. The more soluble it is in water, the faster this will occur. Ibuprofen itself is not very soluble in water.

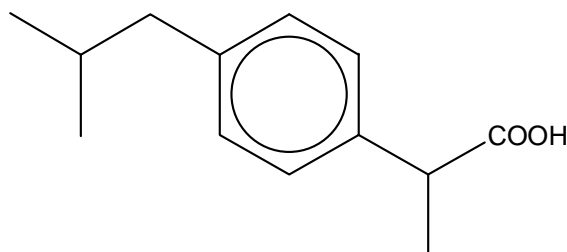


Figure 12: Structure of ibuprofen.

**Question 16**

Look at the structure of ibuprofen in Figure 12 and explain why ibuprofen is not very soluble in water.

The problem of making ibuprofen soluble in water has been solved by a neat bit of chemistry - by reacting it with a second, water soluble compound. The one chosen was the amino acid lysine.

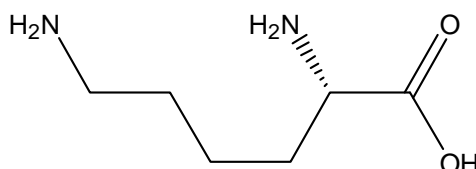


Figure 13: Structure of lysine.

**Question 17**

Look at the structure of lysine in Figure 13 and explain why lysine is soluble in water.

Ibuprofen and lysine react together to form a salt, ibuprofen lysinate. In the bloodstream, the above reaction can reverse, releasing the active ibuprofen and lysine, which is non-toxic.

**Question 18**

Suggest how the salt ibuprofen lysinate forms.

**Question 19**

Why might this salt be expected to be more soluble than ibuprofen itself.

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**Question 20****Why can we be confident that lysine is non-toxic?****Formulation of Nurofen products**

A tablet or caplet of Nurofen contains much more than just ibuprofen, the active ingredient.

The dose of ibuprofen contained in a standard strength tablet is 200 mg (0.2 g), Figure 14.



Figure 14: Standard strength Nurofen tablets.

This is a very small amount and would be difficult to handle and pick up conveniently. So for this reason a tablet needs extra ingredients to bulk it out to make it easy to take. Other ingredients help the tablet to break up, or disintegrate, after being taken. They do this by absorbing water and swelling. Further ingredients help to hold the tablet together and yet others help the tablet to slide easily through the machines that make them.

Ibuprofen tablets consist of a core and a coat. The coat contains sugar for taste and a pigment to give the tablet an acceptable colour. A whole tablet weighs approximately 1000 mg (1 g).

The science of blending these ingredients is called formulation. Table 1 gives some idea of the variety of ingredients, their function and their location in the tablet.

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Table 1: Ingredients of Nurofen 200 mg tablets.

Component	Function	Location
Ibuprofen	Active ingredient	Core
Croscarmellose sodium	Disintegrant	Core
Sodium laurylsulfate	Lubricant	Core
Sodium citrate	Buffering agent	Core
Stearic acid	Lubricant	Core
Colloidal anhydrous silica	Anticaking agent	Core
Carmellose sodium	Coating agent	Coat
Calcium sulfate dihydrate	Diluent	Coat
Acacia spray dried	Binding agent	Coat
Sucrose	Binding agent	Coat
Titanium dioxide	Pigment	Coat
Carnauba wax powder	Coating ageny	Coat
Purified water	Diluent	Coat

### Nurofen Gel – a topical formulation

When taken by mouth (as tablets or caplets, for example) Nurofen works by being absorbed into the bloodstream and is carried to all parts of the body, not just the site of the pain. This of course is inefficient - the drug is only required at the site of the pain. It is also a potential source of side effects. As we have seen all NSAIDs may cause bleeding in the gut but, if you have a bad back, there is no need for any medicine in the gut, only the at site of the pain.

Topical application medicines are applied to the skin as creams or gels. Nurofen is available as a gel that can be rubbed into painful parts of the body. This is advantageous in that the active ingredient is applied directly to the site of the pain rather than being spread over the whole body. It also helps to reduce side effects because the drug does not reach the parts of the body, such as the gut, where side effects may occur.

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Figure 15: Nurofen Gel.

The problem in formulating a topical application is getting the active ingredient through the skin. The outer layer of the skin consists of non-polar molecules and the inner layer of polar ones. Ibuprofen is, as we have seen, relatively non-polar and will therefore have difficulty penetrating the inner layer. This is because non-polar molecules tend to mix with other non-polar ones rather than polar ones. This is an example of the 'like dissolves like' rule.

So ibuprofen gel is formulated with propan-2-ol (isopropanol in the list of ingredients on the pack, Figure 16). This is of medium polarity. It is sufficiently polar to carry the ibuprofen through the inner layer of the skin but not so polar that it will not dissolve ibuprofen. Other ingredients such as hydroxymethylcellulose (a substance similar to starch) are used to make the product into a gel which will stay on the skin rather than running off.

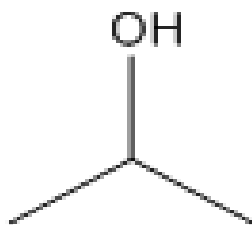


Figure 16: Structure of propan-2-ol (isopropanol).

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**Further information**

Nurofen is sold in the UK by Reckitt Benckiser ([www.nurofen.co.uk](http://www.nurofen.co.uk)). There are other products that contain the active ingredient ibuprofen.

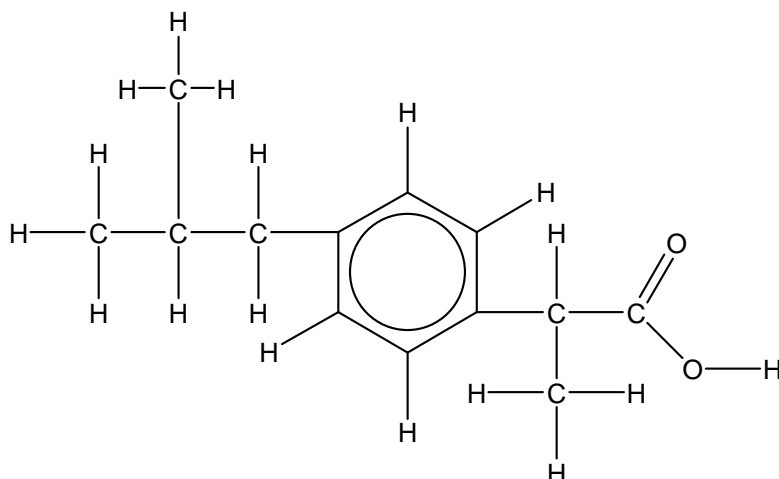
**Acknowledgements**

The Royal Society of Chemistry wishes to thank Reckitt Benckiser for their help in preparing this material.

The Royal Society of Chemistry gratefully acknowledges that this project was initially supported by Reckitt Benckiser in 2007. Reckitt Benckiser conducted a final review in 2013 so please note that certain information may be out of date.

**QUESTIONS AND ANSWERS****Question 1**

Draw the displayed structural formula of ibuprofen ie the structure should show every atom and every bond.

**Question 2**

What functional groups does ibuprofen have?

A carboxylic acid and an aromatic ring.

**Question 3**

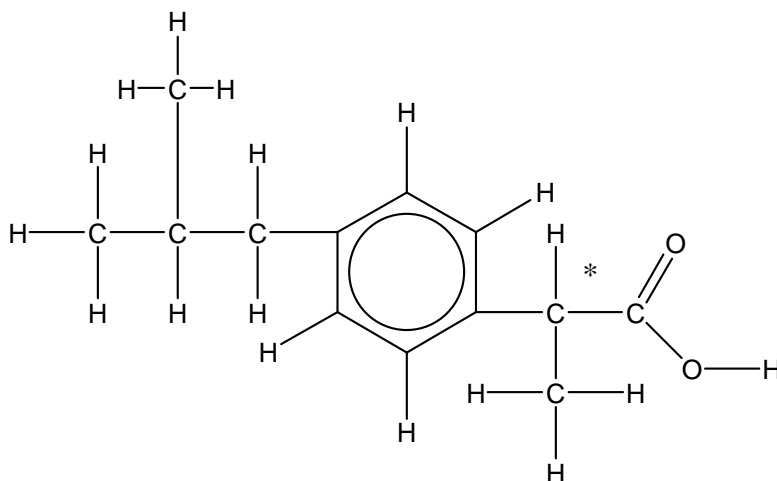
Look at the displayed formula of ibuprofen and identify the carbon atom that has four different groups bonded to it.

The carbon atom marked with a star \*

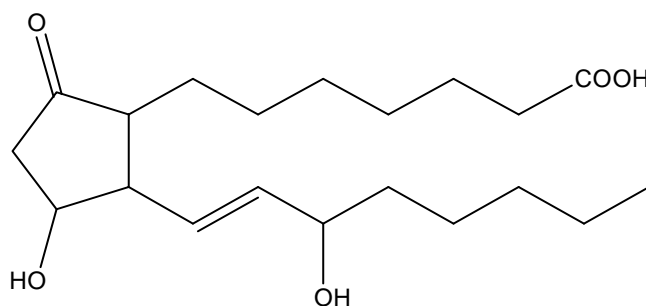
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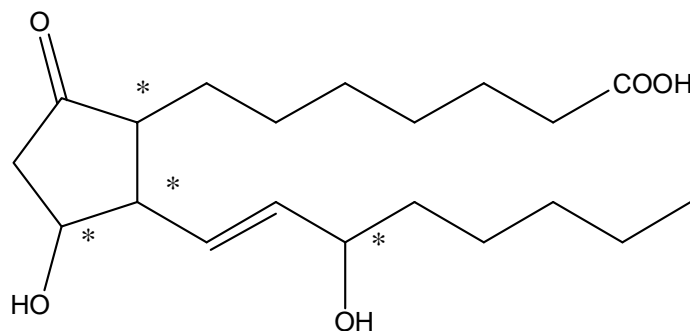
**Question 4**

Identify any asymmetric carbon atoms in the following prostaglandin molecule:



The atoms marked with a star below are asymmetric (they have four different groups bonded to them. (It may help you to see this if you draw in all the hydrogen atoms on the skeletal formula.)

NB: you must consider the whole group bonded to an asymmetric carbon, not just the first atom(s).

**Question 5**

What do you expect the effect of ibuprofen on plane polarised light to be?

No effect. The opposite rotations of the + and - forms will cancel out.

**Question 6**

a) What is the only functional group of 2-methylpropylbenzene?

A benzene ring.

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**b) What type of reactions does this functional group usually undergo?**

Electrophilic substitutions.

#### Question 7

**a) What extra functional group does ibuprofen have compared with 2-methylpropylbenzene?**

A carboxylic acid.

**b) What sorts of reactions can be used to prepare this functional group?**

Oxidation of primary alcohols and aldehydes, hydrolysis of nitriles, hydrolysis of acid derivatives such as acid chlorides, esters, and amides.

#### Question 8

**a) What type of reaction is step 1?**

A Friedel-Crafts acylation.

**b) What is the role of the aluminium chloride?**

The aluminium chloride is a catalyst.

#### Question 9

**a) Suggest the approximate size of the bond angles in the three-membered ring which forms part of the molecule produced after step 3.**

Approximately  $60^\circ$ . The usual angle would be approximately  $109^\circ$ .

#### Question 10

**a) What small molecule is removed in step 5?**

Water.

**b) Suggest a reagent that might be used for this step.**

Phosphorus pentoxide (or other dehydrating agent).

#### Question 11

**a) What is the name of the functional group  $-C\equiv N$ ?**

Nitrile group.

**b) What reagent could be used to convert it into  $-COOH$  in the final step?**

A dilute acid.

#### Question 12

**One problem with a synthesis that takes several steps (a multi-step synthesis in the jargon) is that it produces a low overall yield. Imagine each step has a yield of 90%. A 1-step process would have a 90% yield, a 2-step process one of  $90\% \times 90\% = 81\%$ . What would be the yield of a 6-step process?**

$(90\%)^6 = 53.1\%$

#### Question 13

**Suggest one reason why this synthesis is more efficient than the Boots' synthesis. Explain your answer.**

It has fewer steps so the overall yield is likely to be greater.

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**Question 14**

Select from the following list two terms that describe step 2; reduction, oxidation, acid/base, addition, elimination, condensation.

Reduction and addition.

**Question 15**

Suggest the functions of the HF in step 1 and the palladium (Pd) in step 3. Explain your answer.

Catalysts, as neither F nor Pd appears in the respective products.

**Question 16**

Look at the structure of ibuprofen in Figure 12 and explain why ibuprofen is not very soluble in water.

It consists mostly of hydrocarbon groups which are non-polar and will not hydrogen bond with water. Only the  $\text{-COOH}$  group contains electronegative atoms, that make it polar. This group is also partially ionised losing its H atom as a proton ( $\text{H}^+$  ion) and leaving a negative ion.

**Question 17**

Look at the structure of lysine in Figure 13 and explain why lysine is soluble in water.

Lysine has a  $\text{-COOH}$  group and two  $\text{-NH}_2$  groups which are polar and will form hydrogen bonds with water. Also, a proton may transfer from the  $\text{-COOH}$  group to one of the  $\text{-NH}_2$  groups to form a zwitterion with a  $\text{-COO}^-$  group and a  $\text{-NH}_3^+$ .

**Question 18**

Suggest how the salt ibuprofen lysinate forms.

By the transfer of a proton (a  $\text{H}^+$  ion) from the  $\text{-COOH}$  group of ibuprofen to one of the  $\text{-NH}_2$  groups of lysine.

**Question 19**

Why might this salt be expected to be more soluble than ibuprofen itself.

It is ionic and has  $\text{-NH}_2$  and  $\text{-COOH}$  groups, which contain electronegative atoms (nitrogen and oxygen). This makes it polar and therefore able to hydrogen bond with water.

**Question 20**

Why can we be confident that lysine is non-toxic?

It is one of the 20 or so naturally-occurring amino acids and is therefore found naturally in the body.

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