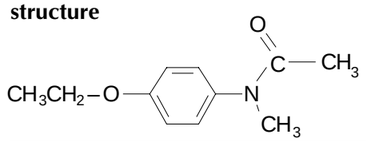
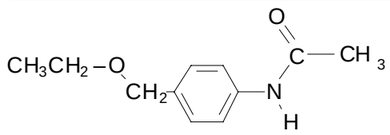
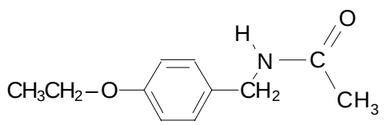
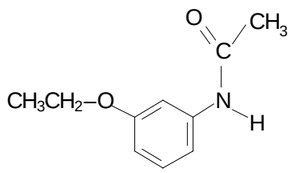
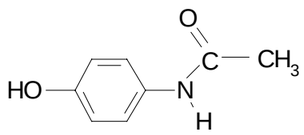
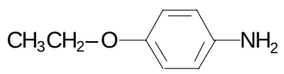
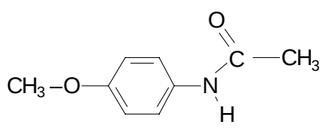
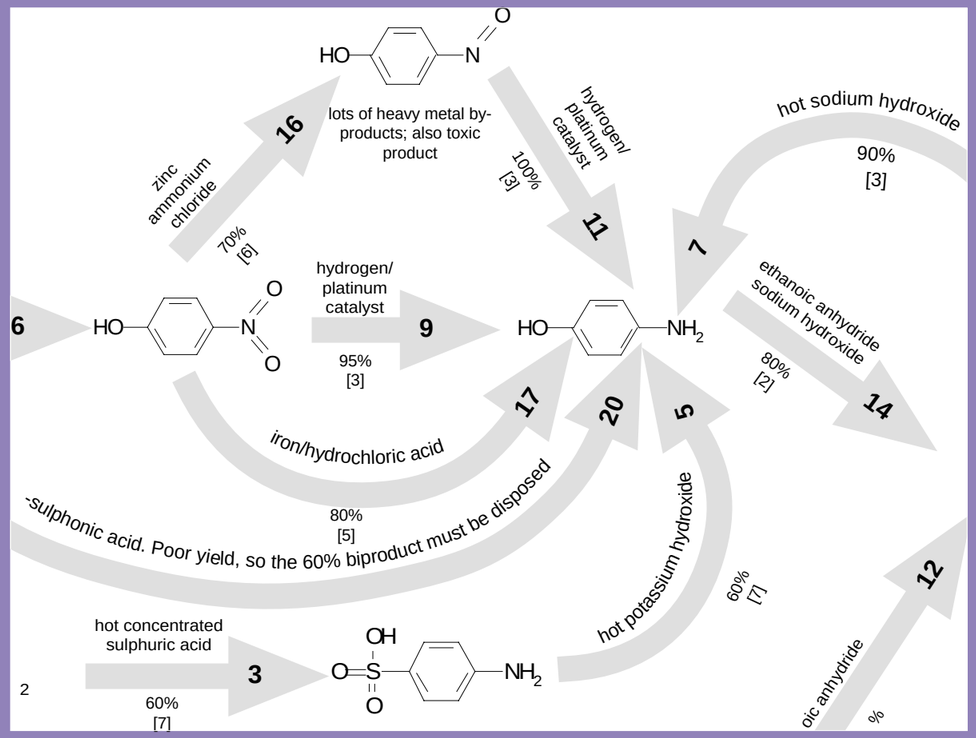
This book arose out of an exercise for students visiting the research laboratories of Glaxo Research and Development Ltd which has since then become Glaxo Wellcome plc. The students follow the decision making process by which new drugs are designed, synthesised and produced commercially. They choose a market area, look at existing products, select a new compound to synthesise, and finally work out the best synthetic route for commercial production, taking into account yield and environmental considerations.

Aimed at students on post-16 courses, the book is designed so that students move back and forth through the tasks depending on the decisions they make. It can be used for individual study or teamwork. A hypertext disk version of the book suitable for use with PCs running Windows is included, along with browsing software.

Possible structure	Reference	Action
	Compound A	**Go to page 27**
	Compound B	**Go to page 14**
	Compound C	**Go to page 31**
	Compound D	**Go to page 21**
	Compound E	**Go to page 24**
	Compound F	**Go to page 11**
	Compound G	**Go to page 7**

Which compound? Which route?

An exercise in chemical decision making



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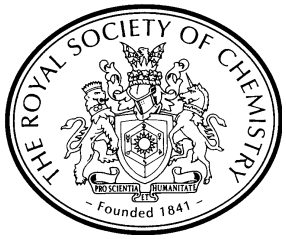
THE ROYAL
SOCIETY OF
CHEMISTRY

Introduction

This exercise was written for students who visited the research laboratories of Glaxo Wellcome in Ware, Hertfordshire. The contribution of Paul Harkin, Stephen Swanson and other Glaxo Wellcome staff to the development of this exercise is gratefully acknowledged. It is aimed at students on post-16 chemistry courses but will be of particular interest to students following vocationally orientated courses, especially the advanced General National Vocational Qualification (GNVQ).

The exercise leads students through the decision-making process when choosing which new drug substance to make and the best synthetic route to the target compound. Students can work through the book on their own or as part of a team.



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Which compound? Which route?

Written by Frank Ellis

Edited by Neville Reed and Karen Richardson

Designed by Imogen Bertin

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Which compound? Which route?

Written by Frank Ellis
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Which compound? Which route?

- As a team of Glaxo Wellcome group research chemists, you have to plan and execute the development of a new drug substance.
- You will be presented throughout this exercise with a number of issues, questions *etc*, which you must address collectively.
- You are advised to consider carefully all the information presented to you before making your decisions.

Please turn to page 2.

THE ROYAL SOCIETY OF CHEMISTRY

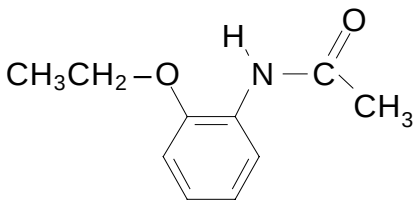
Choosing a target

Consider the three therapeutic areas described below. Choose the area that you believe is the most appropriate to pursue.

Therapeutic area	Action
Analgesics	
Analgesia Affects a large number of people annually. Well established class of compounds. Mode of action well understood.	**Go to page 9**
Bronchodilators	
Constriction of bronchioles Life-threatening disease. Large market world-wide. Plenty of information available on cause. Very distressing symptoms.	**Go to page 17**
Anti-halitosis agents	
Halitosis Affects a large number of people annually. Treatment considered quite easy. Socially embarrassing.	**Go to page 25**

THE ROYAL SOCIETY OF CHEMISTRY

Compound H



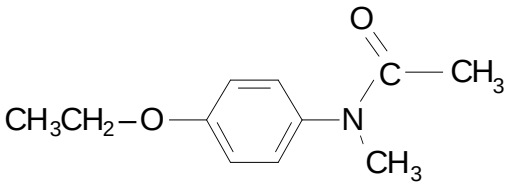
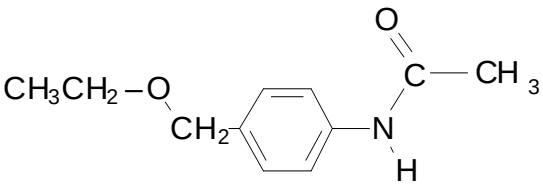
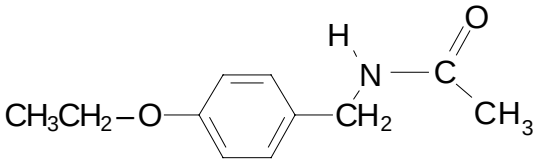
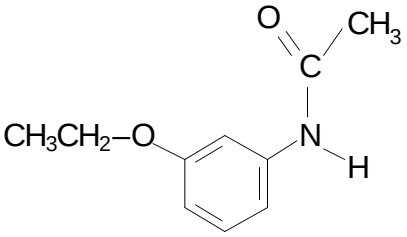
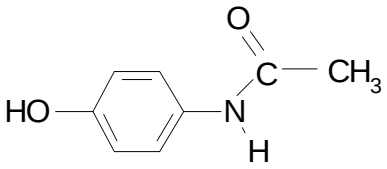
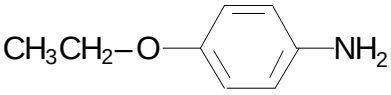
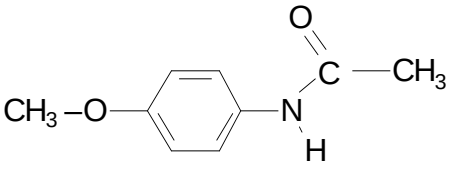
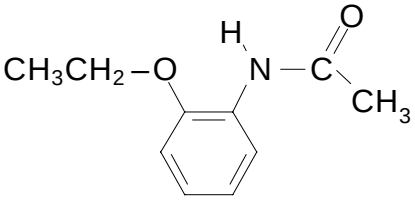
3

Not a very good choice. It is possible that the metabolic problem of replacing N–H by N–OH will be reduced because of the different substitution pattern on the benzene ring in compound H.

However, the two groups need to be opposite each other in the 1 and 4 position to have pain killing properties.

Please turn to the next page and choose another structure.

THE ROYAL SOCIETY OF CHEMISTRY

Possible structure	Reference	Action
	Compound A	**Go to page 27**
	Compound B	**Go to page 14**
	Compound C	**Go to page 31**
	Compound D	**Go to page 21**
	Compound E	**Go to page 24**
	Compound F	**Go to page 11**
	Compound G	**Go to page 7**
	Compound H	

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How can you improve on phenacetin?

First, it is useful to know what features of phenacetin result in it being a pain killer.

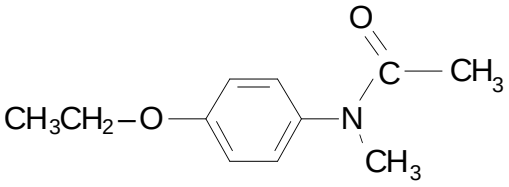
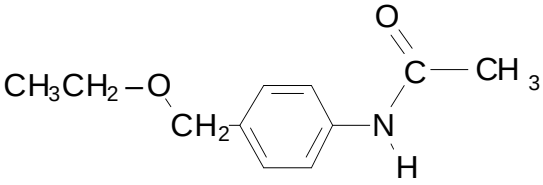
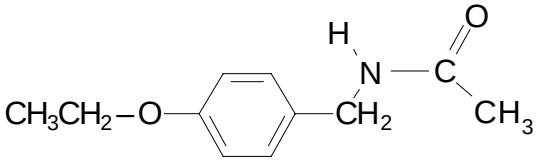
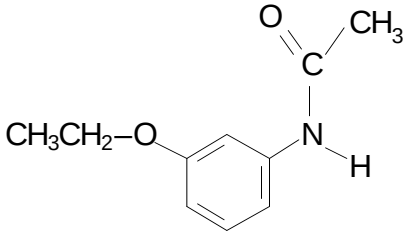
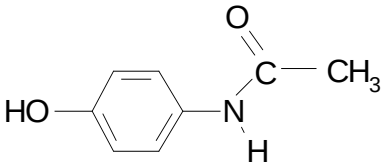
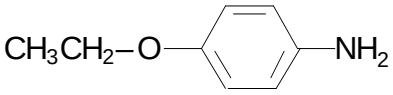
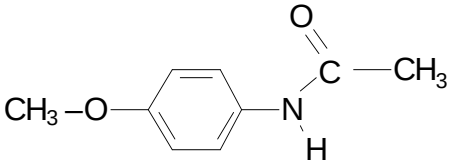
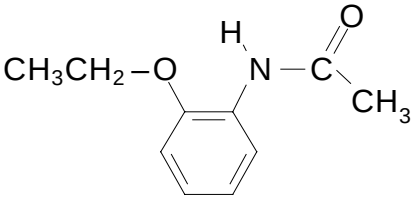
You can then think about blocking the troublesome metabolic step – the replacement of the hydrogen on nitrogen by hydroxyl – *eg* by changing the hydrogen to some other group that cannot be replaced.

Alternatively, you might be able to design a compound that is not metabolised at that position because the body's chemical reactions are diverted to another part of the compound.

5

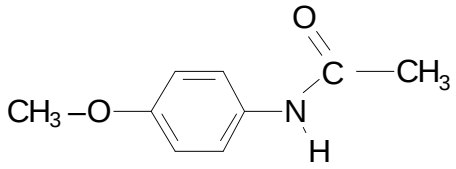
Which of the following compounds on page 6 are worth making?

THE ROYAL SOCIETY OF CHEMISTRY

Possible structure	Reference	Action
	Compound A	**Go to page 27**
	Compound B	**Go to page 14**
	Compound C	**Go to page 31**
	Compound D	**Go to page 21**
	Compound E	**Go to page 24**
	Compound F	**Go to page 11**
	Compound G	**Go to page 7**
	Compound H	**Go to page 3**

THE ROYAL SOCIETY OF CHEMISTRY

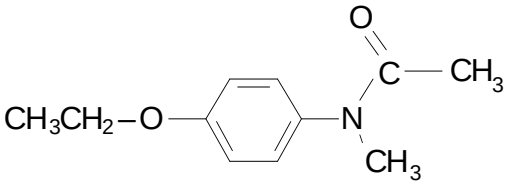
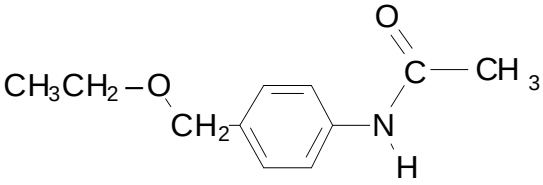
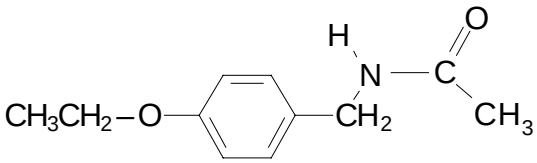
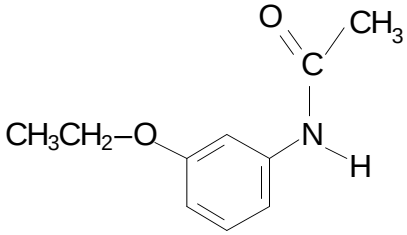
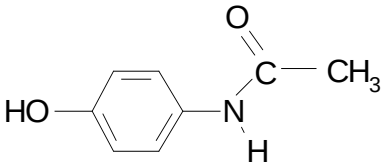
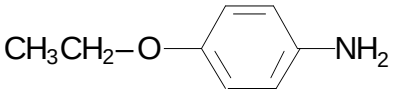
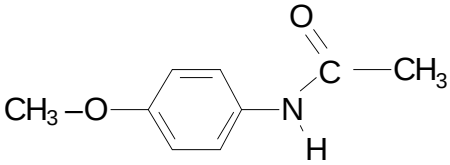
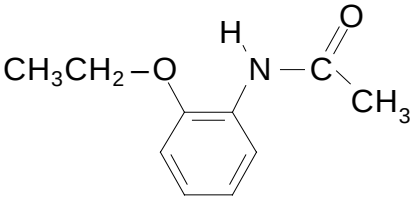
Compound G



A reasonable try. The trouble with compound G is that the only difference from phenacetin is a methyl substituent on the oxygen rather than an ethyl one. The pain killing properties of compound G would be the same and so would be the kidney damage. 7

Please turn to the next page and choose another structure.

THE ROYAL SOCIETY OF CHEMISTRY

Possible structure	Reference	Action
	Compound A	**Go to page 27**
	Compound B	**Go to page 14**
	Compound C	**Go to page 31**
	Compound D	**Go to page 21**
	Compound E	**Go to page 24**
	Compound F	**Go to page 11**
	Compound G	
	Compound H	**Go to page 3**

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THE ROYAL SOCIETY OF CHEMISTRY

Analgesics

Excellent choice! Analgesics are designed to relieve pain without loss of consciousness. Many of the top-selling medicines are analgesics. The projected market for a good drug candidate in this class is estimated to be about £8,000 million per annum. At present no compound has been patented that provides effective relief for all the most common symptoms. An analgesic compound called phenacetin used to be a market leader, but it was withdrawn after reports of serious side-effects associated with prolonged use.

News reports

Bloggs Pharmaceuticals takes a powder!

Following intense pressure from rival giant Bodge plc, Bloggs Pharmaceuticals announced today that the company has gone into receivership. The collapse of the former multi-national giant came after continuing losses in the sales of "Bloggeze". City analysts believe that the market in aspirin products has been completely saturated. Bodge plc's share price increased sharply with news of its investment in a programme of research into other types of analgesics.

The Money Times 29 September 1992

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Phenacetin - *can someone please flog this "dead horse"?*

Recent studies into analgesics by the country's leading scientist suggest that there remains a whole area of research not yet investigated. For a long time it was believed that all avenues of study into aspirin and related compounds had been fully exhausted. However, recent experiments have shown that one of the analogues, phenacetin, shows excellent results in clinical trial comparisons with existing generic aspirin formulations. Dr Alfred Boffen, senior research chemist at St Bartholomew's Teaching Hospital in Wargreen, predicted a "handsome bounty" for anyone who can overcome the known side-effects of phenacetin-type molecules.

Reed's Monthly Pharmacopoeia, September 1992, vol 345.

Please go to page 10.

THE ROYAL SOCIETY OF CHEMISTRY

Phenacetin

Phenacetin used to be sold widely as a pain killer, and it worked well. It filled a niche in the market and complemented the other mild pain killer, aspirin, by attacking pain by a different mechanism. However, it was no good for severe pain, which is treated by strong pain killers such as morphine, with the concomitant problem of addiction.

Phenacetin complemented aspirin, because aspirin can cause irritation and bleeding in the stomach in some patients, whereas phenacetin did not have this side effect.

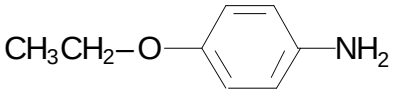
Unfortunately, phenacetin had to be withdrawn from the market because some patients experienced kidney problems, which led to death in some cases.

Therefore there is a gap in the market for a drug like phenacetin which has a similar action but does not damage the kidneys.

Please go to page 13.

THE ROYAL SOCIETY OF CHEMISTRY

Compound F

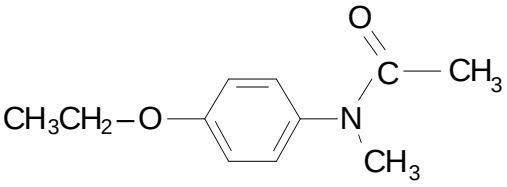
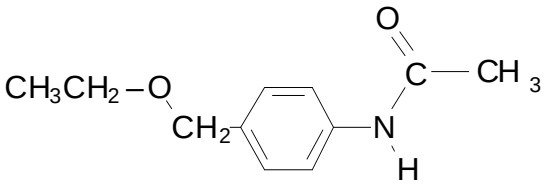
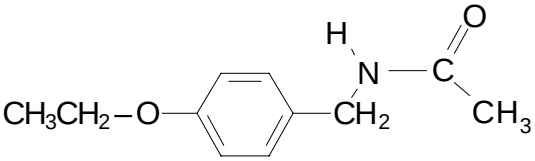
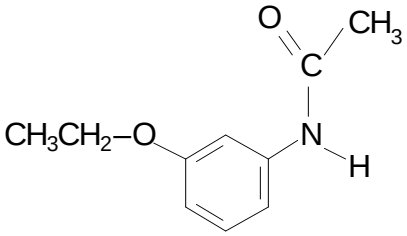
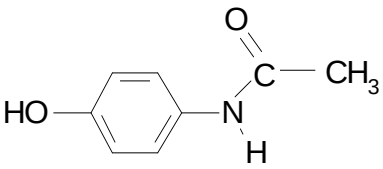
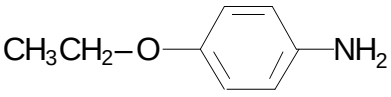
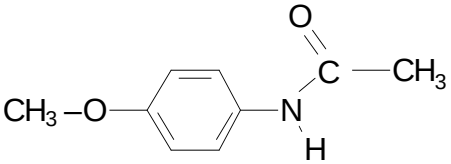
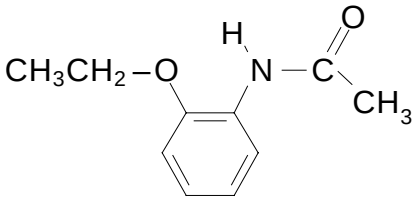


Compound F is a very good choice based on the information you have been given. The problem of the body replacing N–H by N–OH does not occur in compound F. Unfortunately other reactions of the NH_2 group make compound F a very poisonous compound.

Nice try. The patients would feel no pain – ever again!

Please turn to the next page and choose another structure.

THE ROYAL SOCIETY OF CHEMISTRY

Possible structure	Reference	Action
	Compound A	**Go to page 27**
	Compound B	**Go to page 14**
	Compound C	**Go to page 31**
	Compound D	**Go to page 21**
	Compound E	**Go to page 24**
	Compound F	
	Compound G	**Go to page 7**
	Compound H	**Go to page 3**

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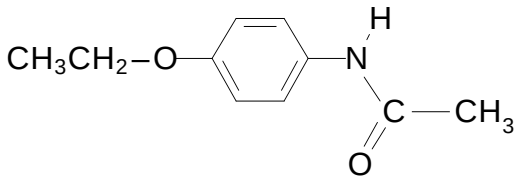
THE ROYAL SOCIETY OF CHEMISTRY

Phenacetin

Study the chemical structure of phenacetin and decide which of the following areas you need more information on to be able to design a new compound.



Information required	Action
Is the compound soluble in water? What colour is it?	Go to page 16
How much does phenacetin cost to make ? How does it compare with aspirin?	Go to page 19
How does phenacetin kill pain?	Go to page 20
Why is phenacetin toxic to the kidneys?	Go to page 23

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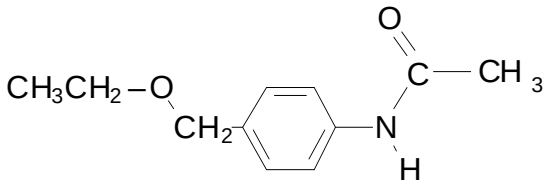
Once you have all the information you require, turn to page 5.

THE ROYAL SOCIETY OF CHEMISTRY

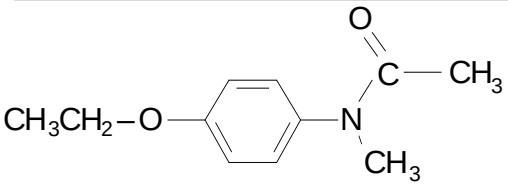
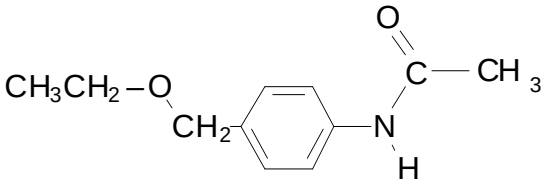
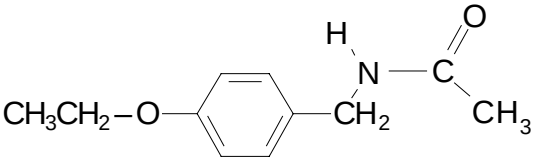
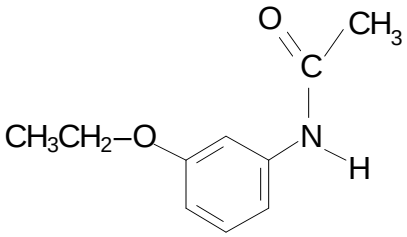
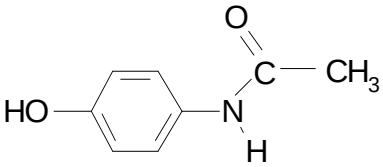
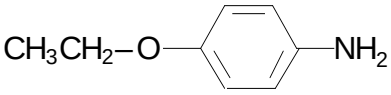
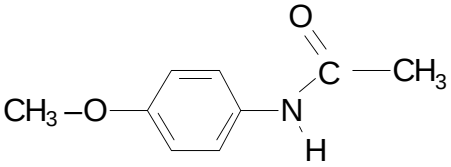
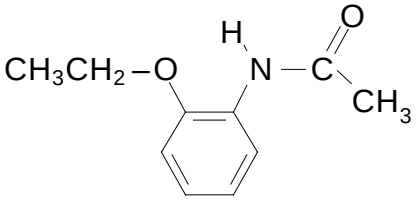
Compound B



Not a very good choice. The benzene ring in compound B is substituted by nitrogen and carbon, *not* nitrogen and oxygen as required for pain killing activity.

Please turn to the next page and choose another compound.

THE ROYAL SOCIETY OF CHEMISTRY

Possible structure	Reference	Action
	Compound A	**Go to page 27**
	Compound B	
	Compound C	**Go to page 31**
	Compound D	**Go to page 21**
	Compound E	**Go to page 24**
	Compound F	**Go to page 11**
	Compound G	**Go to page 7**
	Compound H	**Go to page 3**

THE ROYAL SOCIETY OF CHEMISTRY

Solubility

Phenacetin is only moderately soluble in water (1g in 1300 cm^3) but it has an advantage over aspirin in that the aqueous solution is stable. Aspirin is unstable in water.

When developing a drug, the absolute solubility is not a great influencing factor because the body has the ability to absorb all sorts of things.

Phenacetin, like aspirin, is a white crystalline solid. The colour of a drug is not that important, as even bright pink compounds can be hidden in white capsules.

Please return to page 13 and consider what other information might help you decide how to design a new compound.

THE ROYAL SOCIETY OF CHEMISTRY

Bronchodilators

Good choice. Asthma – constriction of the lung bronchioles – affects one in ten people. This results in a difficulty in breathing. The consequence to sufferers can at best be very distressing – at worst fatal. Glaxo has years of experience in researching ways of alleviating this constriction. So much so that one of the company's products, Ventolin, is market leader in this therapeutic area. Glaxo has planned a number of line-extensions and improvements in presenting the drug into the lung bronchioles. This will completely sew up the market leaving little demand or opportunity for a new drug substance.

Please turn to the next page and choose another therapeutic area to investigate.

THE ROYAL SOCIETY OF CHEMISTRY

Choosing a target

Consider the three therapeutic areas described below. Choose the area that you believe is the most appropriate to pursue.

Therapeutic area	Action
Analgesics *Analgesia* Affects a large number of people annually. Well established class of compounds. Mode of action well understood.	**Go to page 9**
B**ronchodilators** *Constriction of bronchioles* Life-threatening disease. Large market world-wide. Plenty of information available on cause. Very distressing symptoms.	**Market saturated! Try another therapeutic area**
Anti-halitosis agents *Halitosis* Affects a large number of people annually. Treatment considered quite easy. Socially embarrassing.	**Go to page 25**

THE ROYAL SOCIETY OF CHEMISTRY

Cost

Phenacetin is a very cheap drug to make and is similar in price to aspirin.

Price is a concern, but any new drug that works well, is non-toxic and fills a niche in the market can be set at a reasonable price to give a return on the absolute cost and also to cover the money spent on 10 years of research.

Anything related to phenacetin is likely to be in a similar price bracket.

Please return to page 13 and consider what other information might help you decide how to design a new compound.

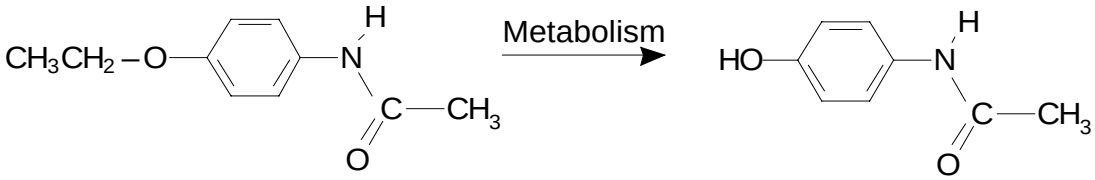
THE ROYAL SOCIETY OF CHEMISTRY

How does it work?

Phenacetin works by trapping the free radicals that ultimately lead to pain and inflammation. Free radicals are produced by infection and injury and they are very reactive substances.

For this mechanism to work, a compound like phenacetin must have a benzene ring substituted by an oxygen atom and a nitrogen atom in the 1 and 4 positions. The nitrogen must have at least one hydrogen on it.

There is evidence to suggest that phenacetin itself is not the active pain killer. The body chemically modifies it (metabolism) by removing the ethyl (CH_3CH_2) substituent from the oxygen atom. It is thought that compound X is the real radical trap and thus the pain killer.

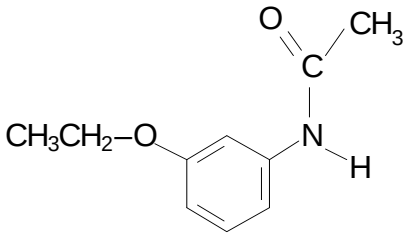


Phenacetin Compound X

Please return to page 13 to continue or to gather more information that you think you may need.

THE ROYAL SOCIETY OF CHEMISTRY

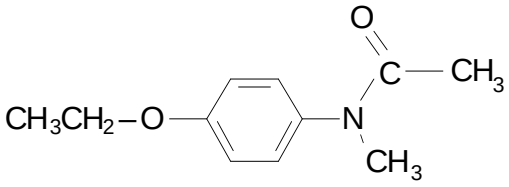
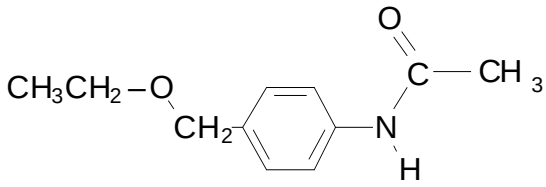
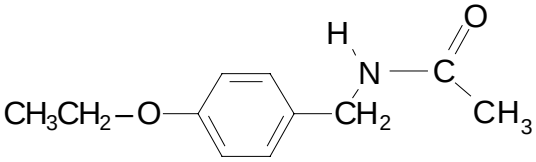
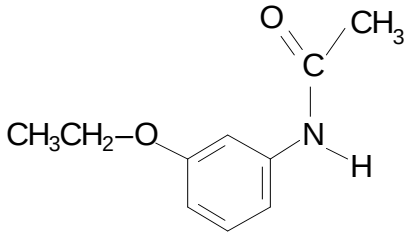
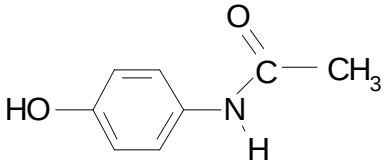
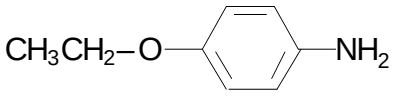
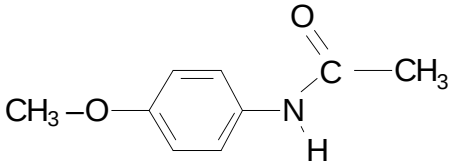
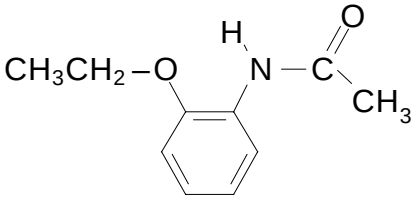
Compound D



Not a very good choice. It is possible that the metabolic problem of replacing N–H by N–OH will be reduced because of the different substitution pattern on the benzene ring in compound D. However, the two groups need to be opposite each other in the 1 and 4 positions to have pain killing properties.

Please turn to the next page and choose another structure.

THE ROYAL SOCIETY OF CHEMISTRY

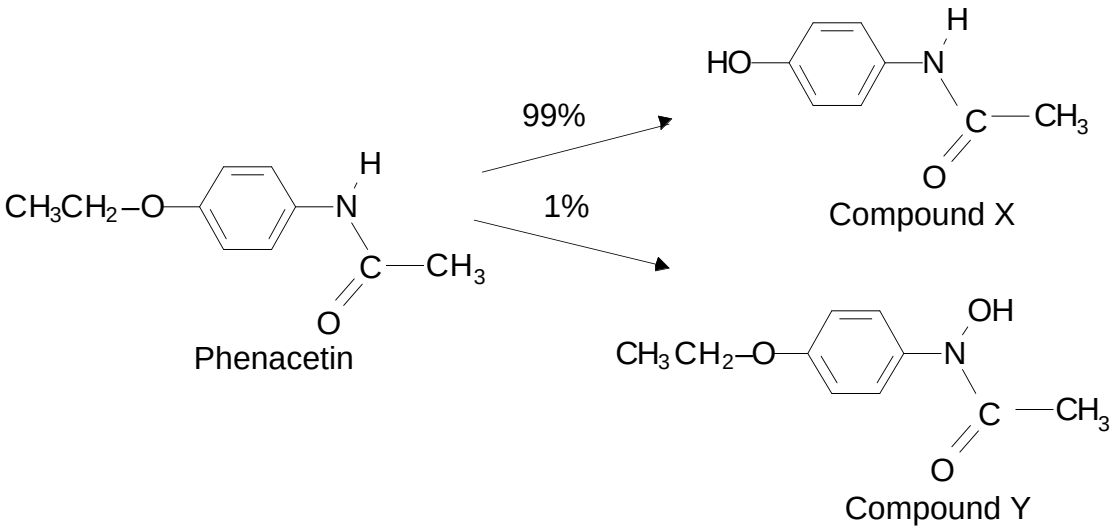
Possible structure	Reference	Action
	Compound A	**Go to page 27**
	Compound B	**Go to page 14**
	Compound C	**Go to page 31**
	Compound D	
	Compound E	**Go to page 24**
	Compound F	**Go to page 11**
	Compound G	**Go to page 7**
	Compound H	**Go to page 3**

THE ROYAL SOCIETY OF CHEMISTRY

Phenacetin toxicity

It is believed that phenacetin is toxic to the kidneys because the body chemically changes the structure of the drug. This process is called metabolism.

Phenacetin is metabolised to two compounds. One route involves removing the ethyl (CH_3CH_2) substituent from oxygen. The second involves replacing the hydrogen on the nitrogen with a hydroxyl (OH) group.



Compound X is the major metabolite and is fairly safe. It is not metabolised further to anything toxic. Compound Y is the problem – although it is only formed in small amounts, it is toxic enough to damage the kidneys.

If you can design a compound to stop this N-hydroxyl compound forming you may discover a new drug.

Please return to page 13 to continue or to gather more information that you think you might need.

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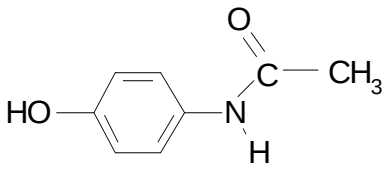
Compound E



A splendid choice. Compound E is not metabolised in the problematical way *ie* N–H going to N–OH, because the body's chemistry is directed towards the OH group on the ring. In fact, very little happens.

Furthermore, this compound is believed to be the active painkiller which is produced by the body from phenacetin. (It was called compound X on earlier pages).

The next step is, how do you make it?

To find out, please turn to page 29.

THE ROYAL
SOCIETY OF
CHEMISTRY

Anti-halitosis agents

Poor choice! Halitosis, or bad breath, is not a life-threatening illness. It does afflict a large percentage of the population, but can easily be treated by a wide range of currently available over-the-counter preparations. Attention to oral hygiene and considerations of diet can prevent most cases of halitosis.

Please turn to the next page and think of another therapeutic area to pursue.

THE ROYAL SOCIETY OF CHEMISTRY

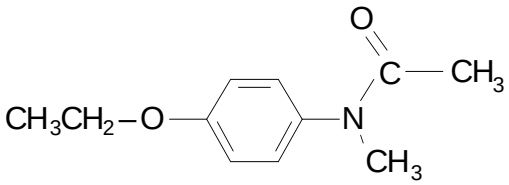
Choosing a target

Consider the three therapeutic areas described below. Choose the area that you believe is the most appropriate to pursue.

Therapeutic area	Action
Analgesics	
Analgesia Affects a large number of people annually. Well established class of compounds. Mode of action well understood.	**Go to page 9**
Bronchodilators	
Constriction of bronchioles Life-threatening disease. Large market world-wide. Plenty of information available on cause. Very distressing symptoms.	**Go to page 17**
Anti-halitosis agents	
Halitosis Affects a large number of people annually. Treatment considered quite easy. Socially embarrassing.	**Simple solution. Brush your teeth! Try another therapeutic area**

THE ROYAL SOCIETY OF CHEMISTRY

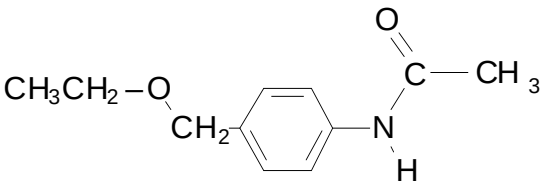
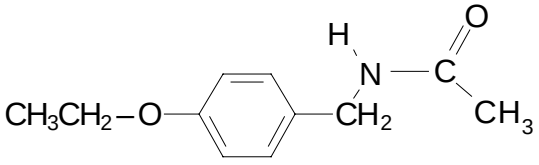
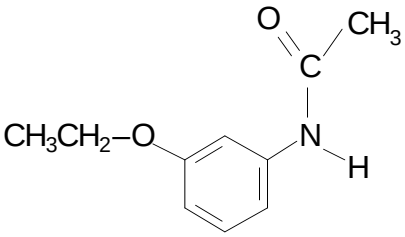
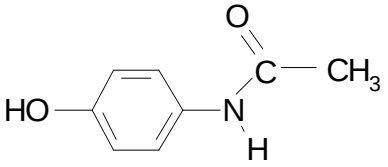
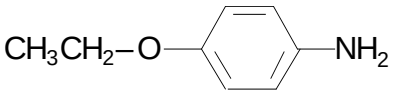
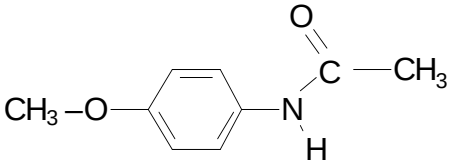
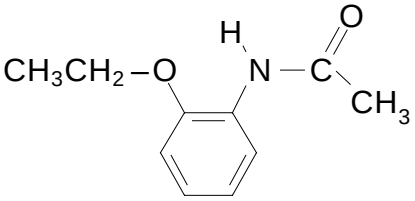
Compound A



An interesting choice because N-hydroxylation will not occur. However the compound A does not have an N–H group, which is important for killing pain.

Please turn to the next page and choose another structure.

THE ROYAL SOCIETY OF CHEMISTRY

Possible structure	Reference	Action
	Compound B	**Go to page 14**
	Compound C	**Go to page 31**
	Compound D	**Go to page 21**
	Compound E	**Go to page 24**
	Compound F	**Go to page 11**
	Compound G	**Go to page 7**
	Compound H	**Go to page 3**

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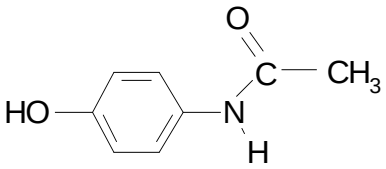
THE ROYAL SOCIETY OF CHEMISTRY

How do you make compound E?



Where do you start? What is the best route in terms of efficiency and safety?

▼ Please ask for the synthesis cards to help you plan out the best route.

Efficiency is measured by the yield of the reaction. If the yield of a reaction is 100%, then one mole of starting material gives one mole of product. If the yield is only 50%, then one mole of starting material gives half a mole of product. For a multi-step process the yields can be multiplied together to give the overall efficiency.

Safety is not measured in absolute terms, and much research goes into adapting procedures to make them safe. If it is absolutely necessary to carry out a dangerous procedure, then many safety precautions – often expensive – must be taken.

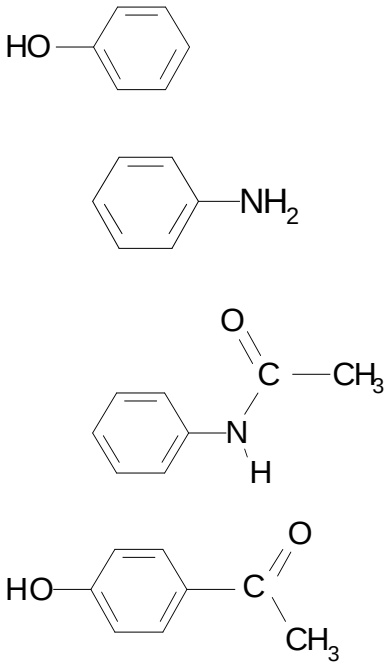
The synthesis cards give safety ratings for each individual reaction in the range [1] to [10]. [1] is a safe reaction, [10] is too dangerous a reaction to even consider. The overall safety and running costs of a multi-step process can be determined by adding up the separate safety ratings.

To assist you, a number of starting materials that you can use are shown on page 30.

THE ROYAL SOCIETY OF CHEMISTRY

Where to start?

The following starting materials are cheap and are available in bulk.



You may find two routes that turn out to be very similar in terms of yield (±5%) and safety (±2).

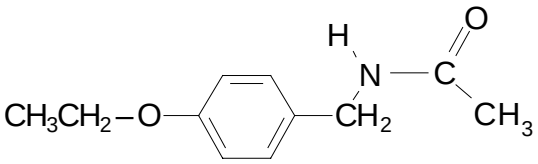
Use the information on the cards to decide which is the best route in terms of availability of starting material and environmental friendliness.

Once you are happy that you have the best possible route of synthesis contact a teacher to discuss your selection.

Congratulations, you have completed this exercise! But did you get the best route of synthesis?

THE ROYAL SOCIETY OF CHEMISTRY

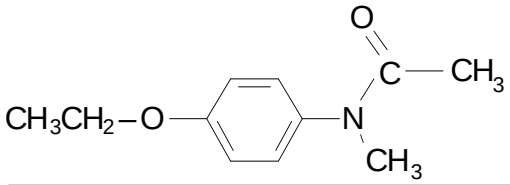
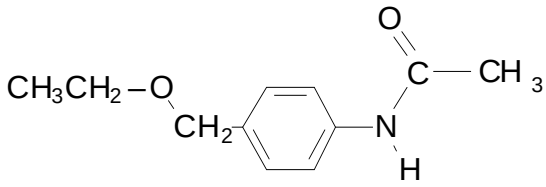
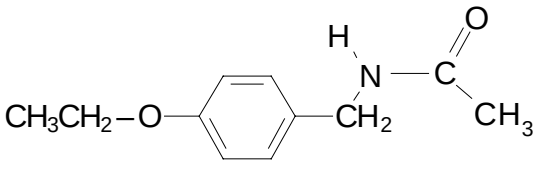
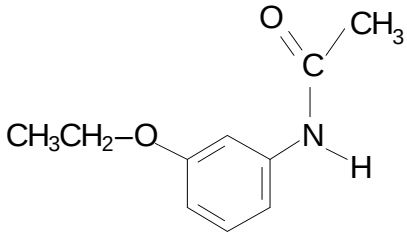
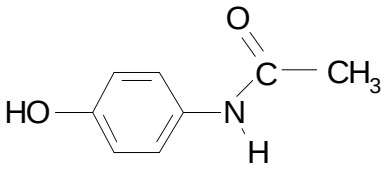
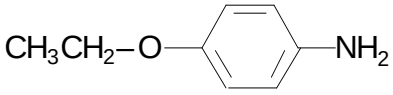
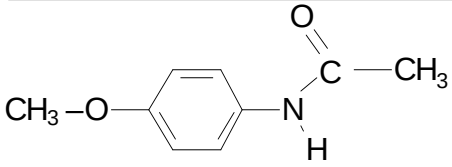
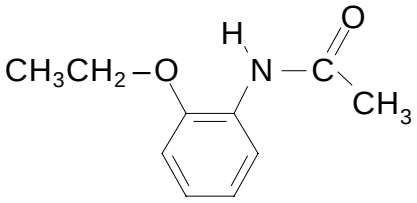
Compound C



Not a very good choice. The benzene ring in compound C is substituted by oxygen and carbon, *not* oxygen and nitrogen as required for pain killing activity.

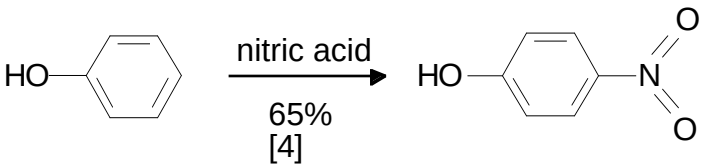
Please turn to the next page and choose another structure.

THE ROYAL SOCIETY OF CHEMISTRY

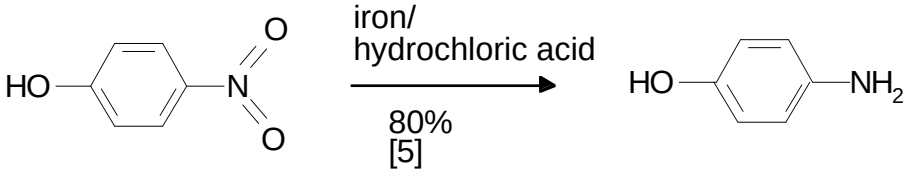
Possible structure	Reference	Action
	Compound A	**Go to page 27**
	Compound B	**Go to page 14**
	Compound C	
	Compound D	**Go to page 21**
	Compound E	**Go to page 24**
	Compound F	**Go to page 11**
	Compound G	**Go to page 7**
	Compound H	**Go to page 3**

GlaxoWellcome

CARD 6



CARD 17



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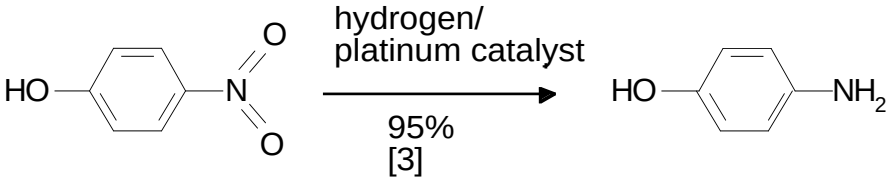

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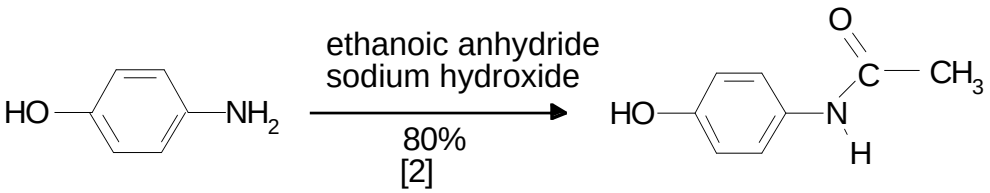

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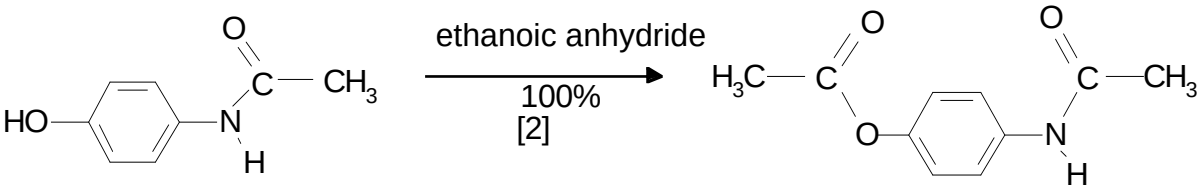

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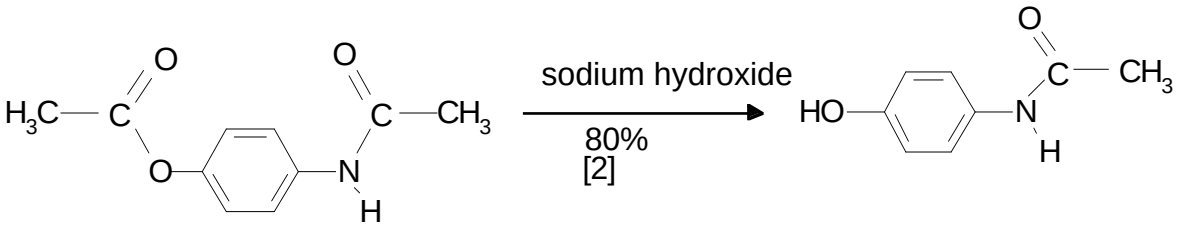

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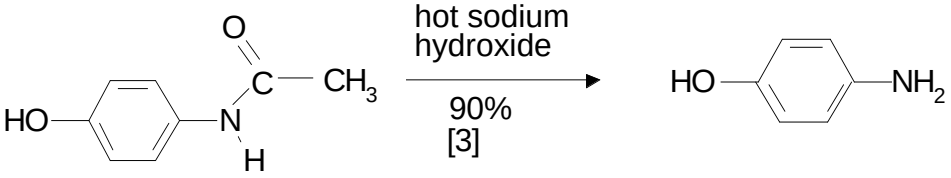

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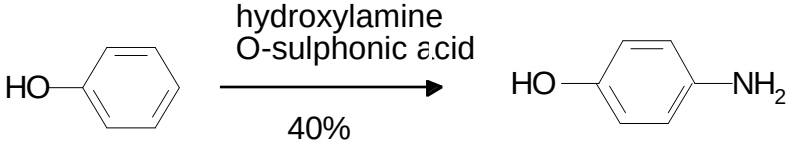
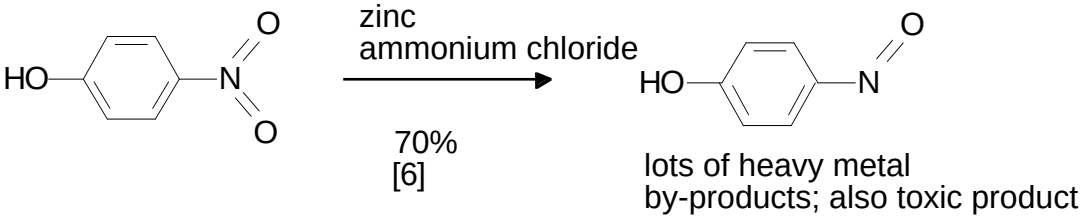


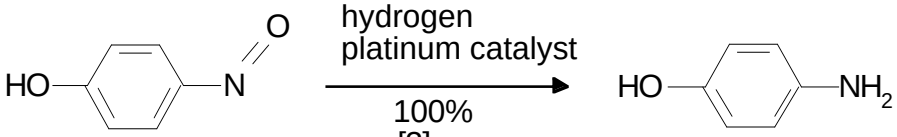
Poor yield; 60% by-products must be disposed of

CARD 16



lots of heavy metal
by-products; also toxic product

CARD 11



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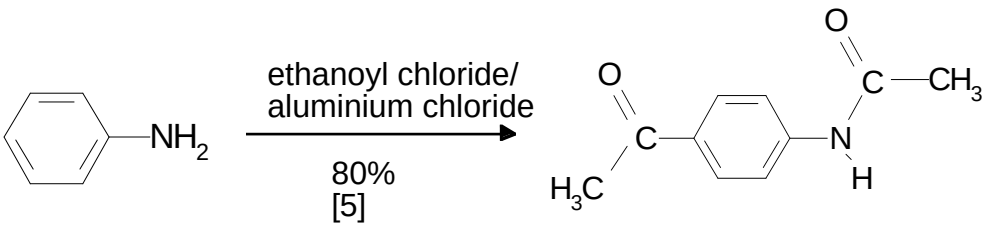

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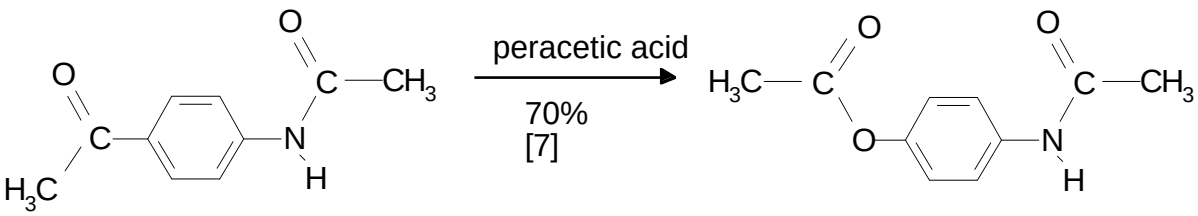

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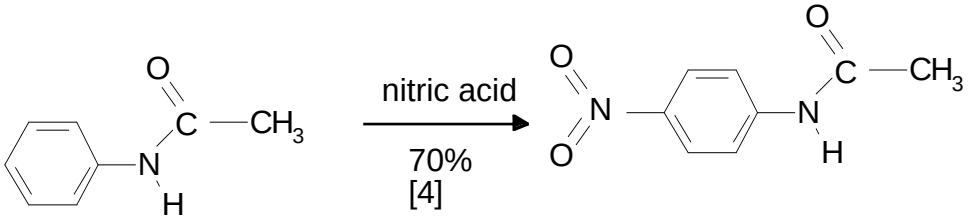

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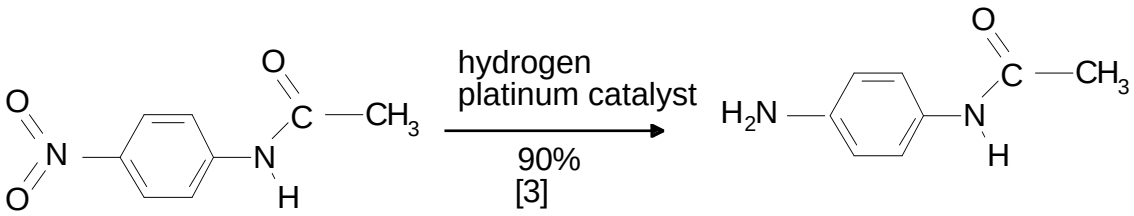
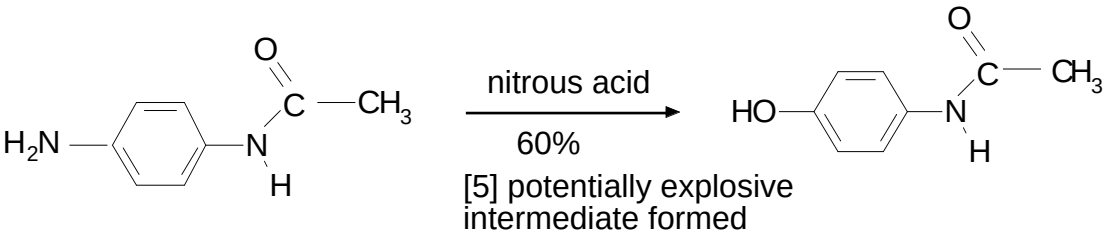


CARD 1



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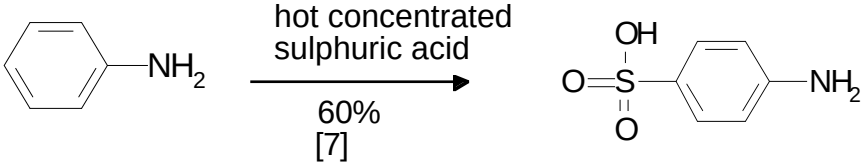

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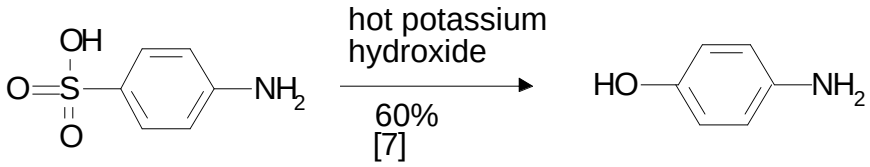
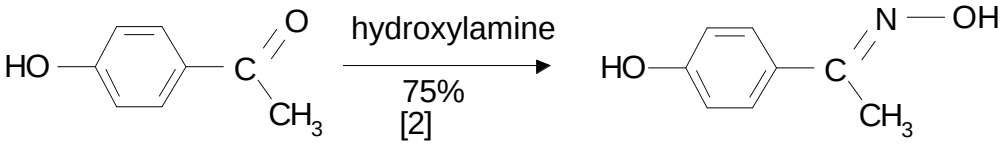
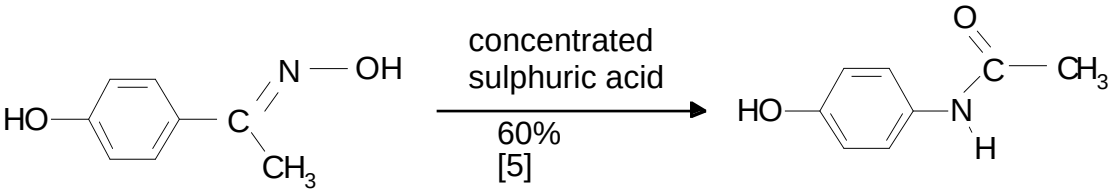


CARD 13



CARD 8



CARD 2