7.8 Organic Synthesis (A Level Only)

YOUR NOTES ⬇

CONTENTS

7.8.1 DRUGS FROM NATURAL RESOURCES

Chirality & Drug Production

- **Chiral molecules** are molecules that contain a carbon atom that is attached to four different atoms or groups of atoms
  - An example of a compound with a chiral centre is the $CH_3CHBrOH$ compound
- A molecule with a chiral centre has to **enantiomers** which are **non-superimposable mirror images** of each other

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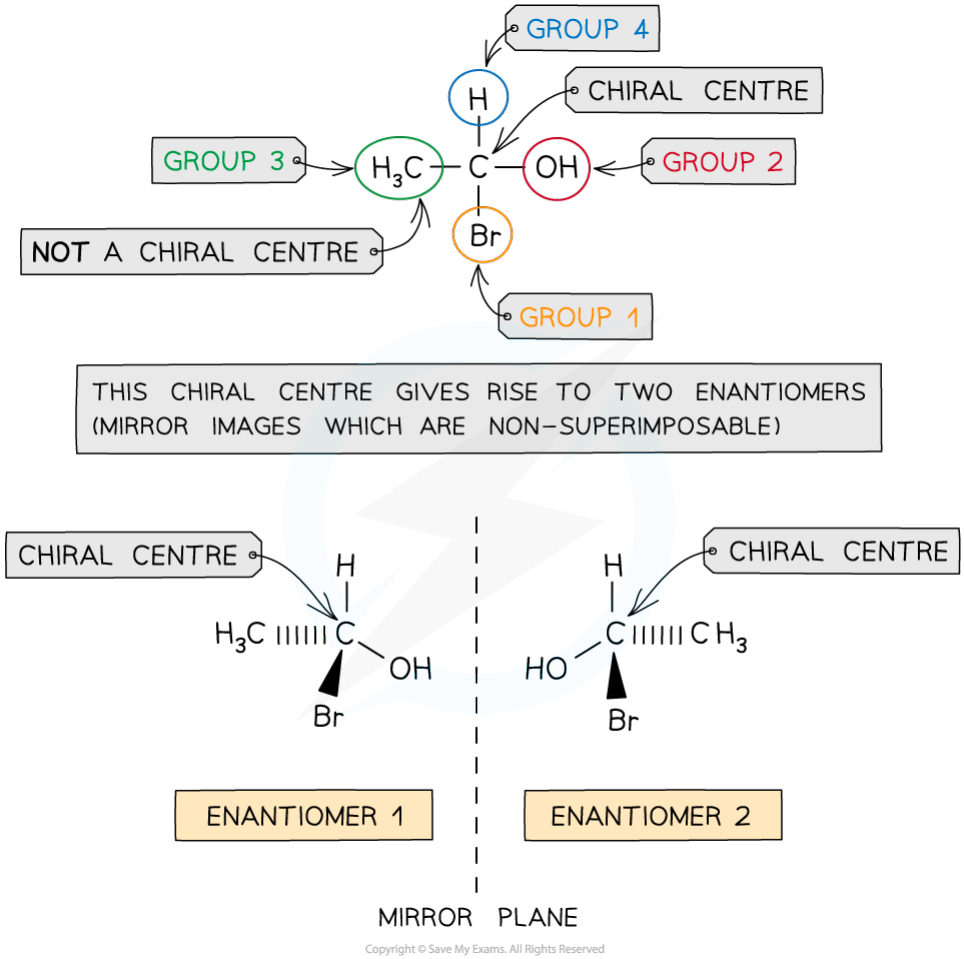

Examples of a molecule with a chiral centre

- These enantiomers have similar **chemical properties** but differ from each other in their ability to **rotate** the plane of plane polarised light

Chiral drugs

- Many drugs are derived from **natural sources** such as plants
- The chiral drugs extracted from these natural sources often contain a **single** optical isomer only
- An example of a drug derived from plants is the anti-cancer drug **Taxol**
- Taxol has many chiral centres so many optical isomers of this single compound could exist
- However, only one of these optical isomers is present in the bark of yew the tree which is extremely **beneficial**

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- In biological systems (such as cells), molecules are made and broken down by reactions involving biological catalysts called **enzymes**
- Enzymes only bind molecules (**substrates**) that fit the shape of the enzyme's active site by a **lock-and-key mechanism**
- If the substrate molecule doesn't have the correct shape, it will not bind to the enzyme
- Therefore, if there were many optical isomers (with each a different arrangement around the chiral centre) of the drug Taxol, they will no longer be able to fit the enzyme's active site for a reaction to occur
- Higher doses of the drugs would have to be administered for it to be effective
- This is why it is so useful that natural sources (such as the yew tree) produce only one optical isomer

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7.8.2 SYNTHESIS OF DRUGS

Chirality & Drug Production

- Most of the drugs that are used to treat diseases contain **one or more** chiral centres
- These drugs can therefore exist as **enantiomers** which differ from each other in their ability to rotate plane polarised light
- Another crucial difference between the enantiomers is in their potential **biological activity** and therefore their **effectiveness** as medicines
- Drug compounds should be prepared in such a way that only one of the optical isomer is produced, in order to increase the drugs' effectiveness
    - Some drug enantiomers can have very harmful side effects

Potential biological activity of enantiomers

- If **conventional organic reactions** are used to make the desired drug, a **racemic mixture** will be obtained
    - In a racemic mixture, there are equal amounts of the two enantiomers
- The **physical** and **chemical** properties of the enantiomers are the same, however, they may have opposite biological activities
- For example, the drug **naproxen** is used to treat pain in patients that suffer from arthritis
    - One of the enantiomers of naproxen eases the pain, whereas another enantiomer causes liver damage
- One enantiomer of a drug used to treat tuberculosis is effective whereas another enantiomer of this drug can cause blindness
- Thalidomide is another example of a drug that used to be used to treat morning sickness, where one of the enantiomers caused very harmful side effects for the unborn baby

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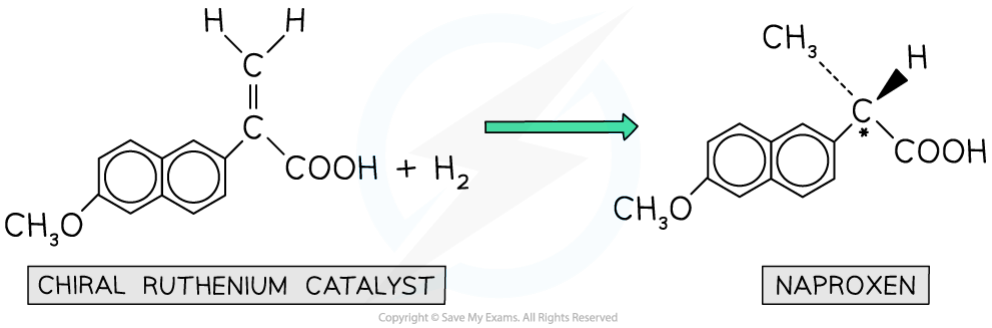
Separating racemic mixtures

- Due to the different biological activities of enantiomers, it is very important to **separate** a racemic mixture into **pure single enantiomers** which are put in the drug product
- This results in **reduced side-effects** in patients
  - As a result, it protects pharmaceutical companies from legal actions if the side effects are too serious
- It also **decreases** the patient's **dosage** by half as the pure enantiomer is more **potent** and therefore reduces production costs
  - A more potent drug has a better **therapeutic activity**

Chiral catalysts

- In order to produce single, pure optical isomers, **chiral catalysts** can be used
- The benefits of using chiral catalysts are that only **small amounts** of them are needed and they can be **reused**
  - For example, an organometallic ruthenium catalyst is used in the production of **naproxen** which is used in the treatment of arthritis



The organometallic ruthenium catalyst is a chiral catalyst which ensures that only one of the enantiomers is formed which can be used in treating arthritis

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- **Enzymes** are excellent biological chiral catalysts that promote **stereoselectivity** and produce single-enantiomer products only
    - **Stereoselectivity** refers to the preference of a reaction to form one enantiomer over the other
- Due to the **specific** binding site of enzymes, only one enantiomer is formed in the reaction
- The enzymes are fixed in place on **inert supports** so that the reactants can pass over them without having to later separate the product from the enzymes
- The **disadvantage** of using enzymes is that it can be **expensive** to isolate them from living organism
    - Therefore, more research has recently been carried out into designing **synthetic enzymes**
- Although using enzymes to produce pure enantiomers in drug synthesis takes longer than conventional synthetic routes, there are many advantages to it in the long run
    - For example, using enzymes to synthesise drugs is a **greener** process as fewer steps are involved compared to conventional synthetic routes

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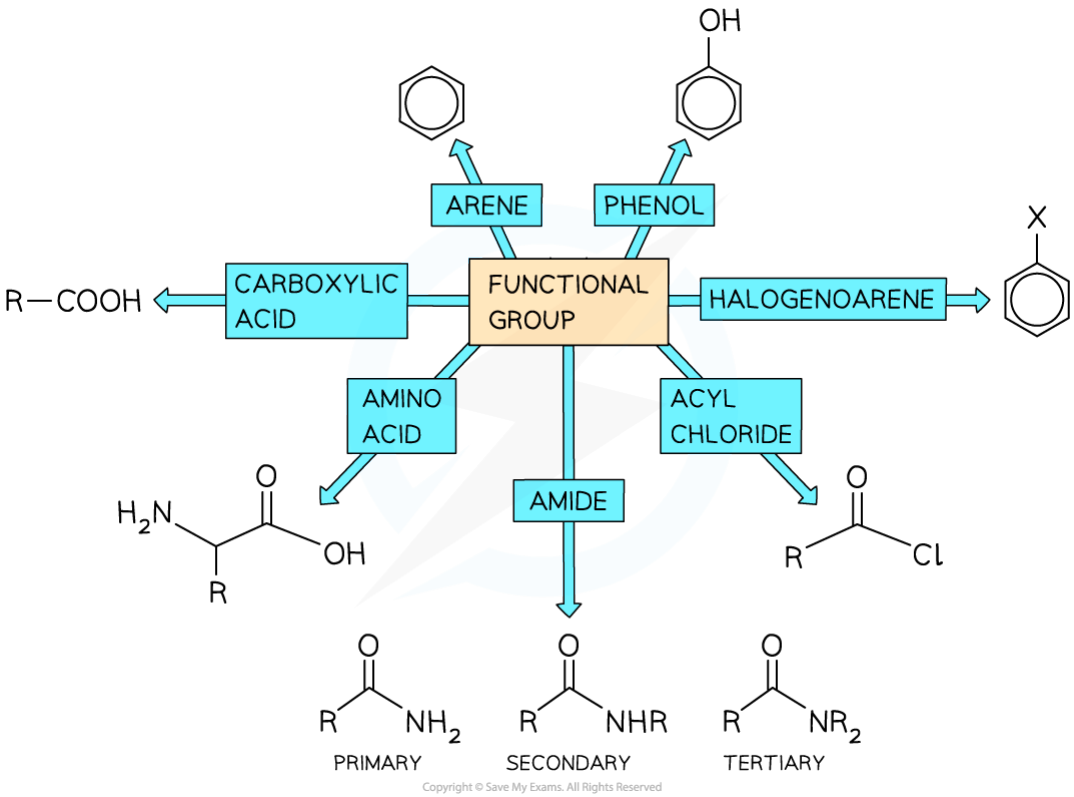
7.8.3 ELUCIDATING ORGANIC MOLECULES

Elucidating Organic Molecules

- Students should be able to identify organic functional groups and recall their properties and the reactions that they undergo

Properties of functional groups

- In addition to the functional groups mentioned in the AS course, students should also be familiar with additional functional groups and their properties including:
  - Arenes
  - Halogenoarenes
  - Carboxylic acids (and derivatives)
  - Phenols
  - Amides
  - Amino acids
  - Acyl chlorides



Overview of additional functional groups and their properties

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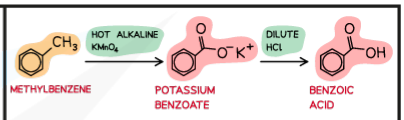
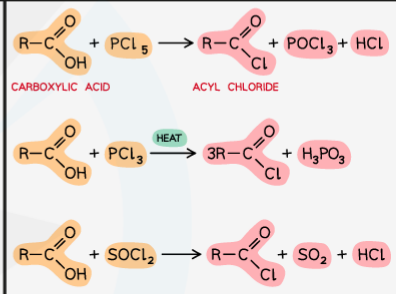
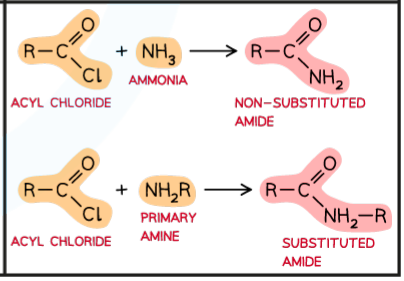
Reactions of functional groups

- Students should also be able to recall:
  - The reactions by which these functional groups can be produced
  - The reactions that these functional groups undergo

Benzoic acid	Oxidation	Heat under reflux with hot alkaline $KMnO_4$ dilute HCl	
Acyl chloride	Electrophilic Substitution	Solid PCl_5 liquid PCl_3 + heat liquid $SOCl_2$	
Amide	Condensation Reaction	Room temperature	

Reactions by which functional groups can be produced

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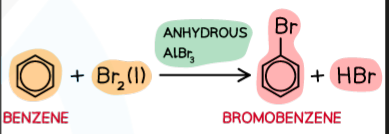
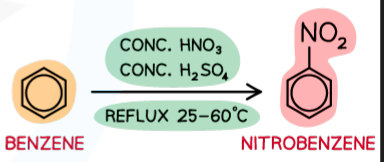
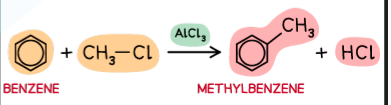
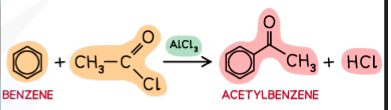
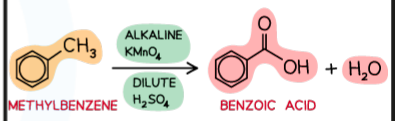
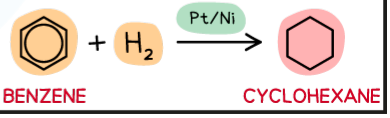
Functional group	Reaction	Product	Example
Arene	Halogenation	Halogenoarene	
	Nitration	Nitroarene	
	Friedel–Crafts Alkylation	Alkylbenzene	
	Friedel–Crafts Acylation	Acylbenzene	
	Complete Oxidation	Benzoic acid	
	Hydrogenation	Cyclohexane	

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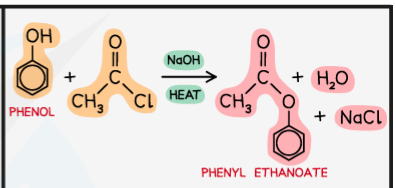
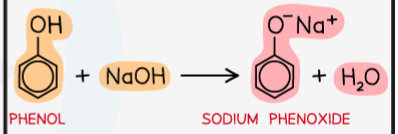
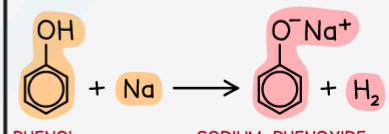
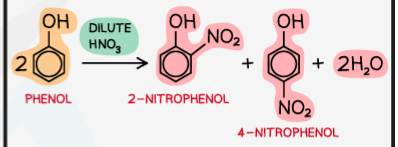
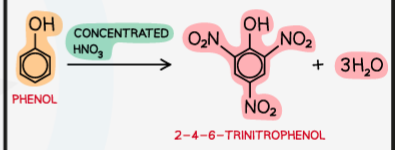
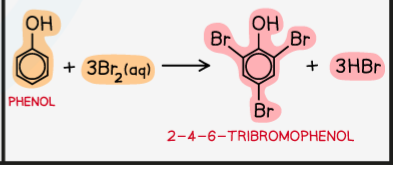
Phenol	Esterification	Ester	
	Acid/Base	Salt + water	
	Acid/Base	Salt + Hydrogen gas	
	Nitration	Nitrophenol	
			
	Bromination	Bromophenol	

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7.8.4 MULTI-STEP SYNTHETIC ROUTES

Multi-Step Synthetic Routes

- Many organic molecules are made in multi-step synthetic routes
- Students should be able to recall the different reactions each functional group undergoes and apply this knowledge when devising multi-step synthetic routes for preparing organic molecules
- These multi-step synthetic include reactions covered in the A level course in addition to those in the AS course

Analysis of Synthetic Routes

- Students should be able to apply their knowledge on functional groups and their reactions by critically analysing a given synthetic route in terms of:
  - The type of reaction
  - The reagents used for each step
  - Any possible by-products