

NATIONAL JUNIOR COLLEGE
SH2 PRELIMINARY EXAMINATION
Higher 3

CANDIDATE
NAME

SUBJECT
CLASS

REGISTRATION
NUMBER

PHARMACEUTICAL CHEMISTRY

Paper 1

Additional Materials:

Answer Paper
Data Booklet

9812/01

Fri 19 Sep 2014

2 hours 30 minutes

READ THESE INSTRUCTIONS FIRST

Write your name, subject class and registration number on all the work you hand in.

Write in dark blue or black pen on both sides of the paper.

You may use a soft pencil for any diagrams or graphs.

Do not use staples, paper clips, highlighters, glue or correction fluid.

Answer any **five** questions.

At the end of the examination, fasten all your work securely together.

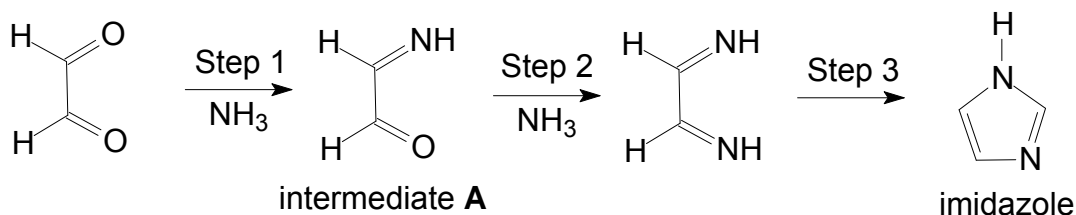
The number of marks is given in brackets [] at the end of each question or part question.

You may use a calculator.

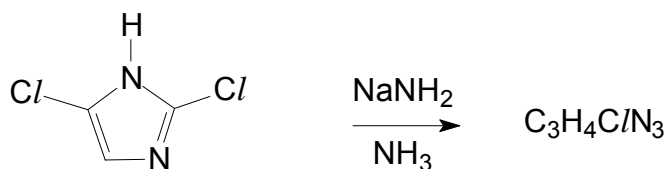
You are reminded of the need for clear presentation in your answers.

This paper consists of **15** printed pages.

- 1(a) The synthesis of imidazole was achieved in 1858 by Heinrich Debus through a series of condensation reactions.



- (i) Condensation reactions are also known as “addition–elimination” reactions. Describe the mechanism for **Step 1**. [3]
- (ii) Intermediate **A** exists as a pair of stereoisomers. Identify the type of isomerism it exhibits and illustrate this with suitable drawings. [2]
- (iii) Suggest a suitable reagent for the condensation reaction in **Step 3**. [1]
- (b) State the criteria for a compound to exhibit aromaticity and hence determine if imidazole is an aromatic compound. [3]
- (c) Imidazole is amphoteric, it has a pK_a value of 14.5 and pK_b value of 6.95.
- (i) By considering the structure of its conjugate base, explain why imidazole exhibits acidic properties. [2]
- (ii) Despite having 2 nitrogen atoms, explain why imidazole only has one pK_b value. [2]
- (d) 2,4–dichloroimidazole, $C_3H_2Cl_2N_2$, can undergo nucleophilic aromatic substitution as shown in the following reaction.



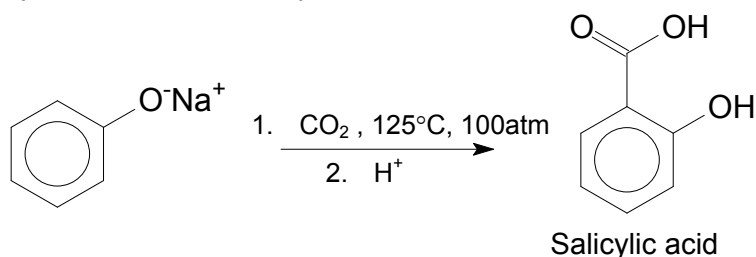
Describe the mechanism for this reaction. [2]

- (e) A derivative of imidazole, compound **B**, $C_5H_9N_3$, gives the following 1H NMR signals in D_2O solvent.

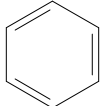
Chemical shift (ppm)	No. of protons	Splitting patterns
3.02	2	t
3.29	2	t
7.14	1	s
7.99	1	s

- (i) Explain the rationale of using D_2O . Your answer should include an equation. [2]
- (ii) Deduce the full structure of **B**. Explain the logic behind your deductions. [3]

- 2 Salicylic acid is known for its ability to ease aches and pains. It is commercially prepared by the Kolbe-Schmitt synthesis shown below:

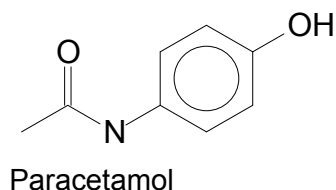
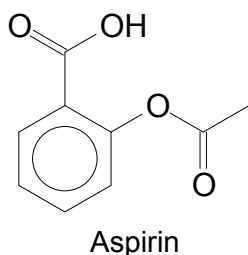


- (a) Describe the mechanism for the Kolbe-Schmitt synthesis. In your answer, you should include curly arrows showing the movement of electrons and any relevant charges.

You should use  to represent the benzene ring in your mechanism. [3]

- (b) Aspirin, also known as acetylsalicylic acid, acts as the pro-drug to salicylic acid. It is a member of the non-steroidal anti-inflammatory drug (NSAIDs).

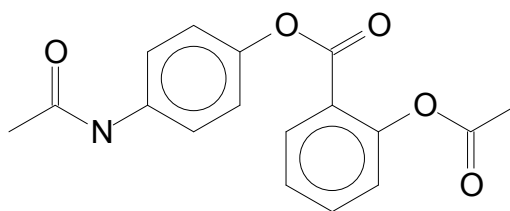
Paracetamol is another widely used analgesic which is found in painkillers such as Panadol.



- (i) What is a *pro-drug*? [1]
- (ii) Describe how aspirin acts as a pain killer. [2]
- (iii) Despite the widespread use of paracetamol, in some instances, aspirin is still used in preference.

Suggest one advantage of using aspirin over paracetamol. [1]

- (c) Benorylate, a codrug of aspirin and paracetamol, is a new anti-rheumatic drug.

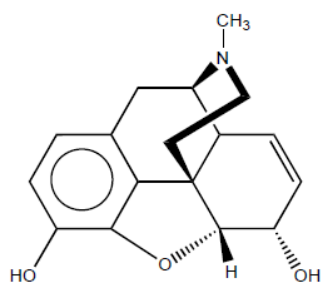


Benorylate

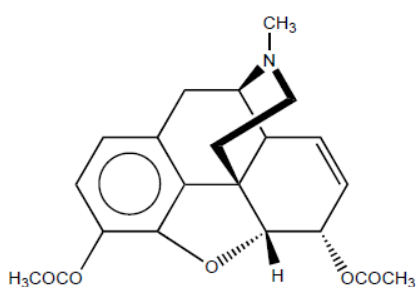
- (i) Suggest a suitable synthetic pathway for the production of benorylate from aspirin and paracetamol. [2]
- (ii) Studies on benorylate show that it has a lower activity in the treatment of fever as compared to paracetamol and aspirin taken separately.

Suggest, with reasoning, whether benorylate would be recommended as a treatment for fever in children. [1]

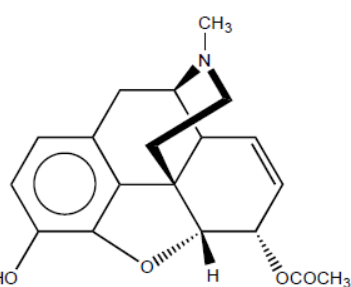
- (d) In contrast to aspirin and paracetamol, narcotic analgesics such as morphine are used to relieve intense pain. The structures of three narcotic analgesic molecules are given below.



Morphine



Heroin



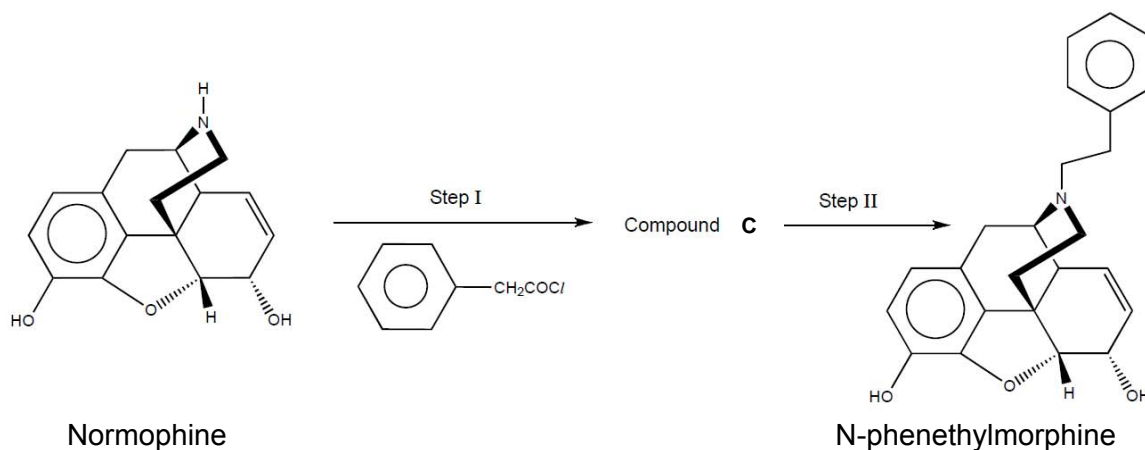
6-acetylmorphine

- (i) Describe how narcotic analgesics prevent pain and one disadvantage of using them. [2]

Morphine contains a phenol -OH and an alcohol -OH. Structure-activity studies done on morphine show that the phenol -OH is important and necessary for analgesic activity, but not the alcohol -OH.

- (ii) With reference to their structures, suggest an explanation why 6-acetylmorphine is 4 times more active than morphine. [2]
- (iii) Hence explain whether heroin is more or less active than morphine. [2]

- (e) N-phenethylmorphine can be synthesised in a two steps reaction from normorphine.

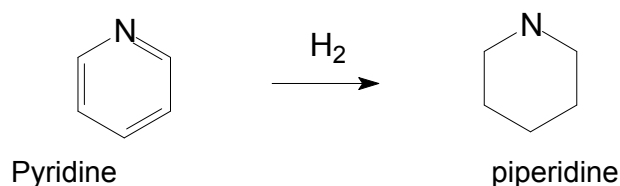


- (i) Draw the structure of **C** and state the reagents needed for step **II**. [2]
- (ii) When administered intracerebrally (directly into the brain), it was found that N-phenethylmorphine showed a 14-fold increase in activity compared to morphine.

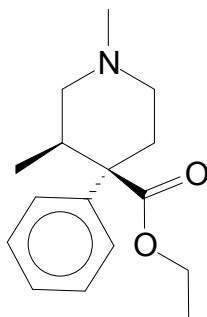
Suggest a plausible explanation for N-phenethylmorphine's much higher activity compared to morphine. [2]

- 3(a)** Pyridine is a basic heterocyclic organic compound. It is used as a precursor in pharmaceuticals and is also an important solvent and reagent.

Industrially, piperidine is produced by the hydrogenation of pyridine.



- (i) Explain why pyridine is less basic than piperidine. [2]
- (ii) Acetonitrile, CH_3CN , is another commonly used organic solvent. Suggest the basicity of acetonitrile as compared to pyridine. [2]
- (b)** One of the piperidine class analgesics is alphaprodine.



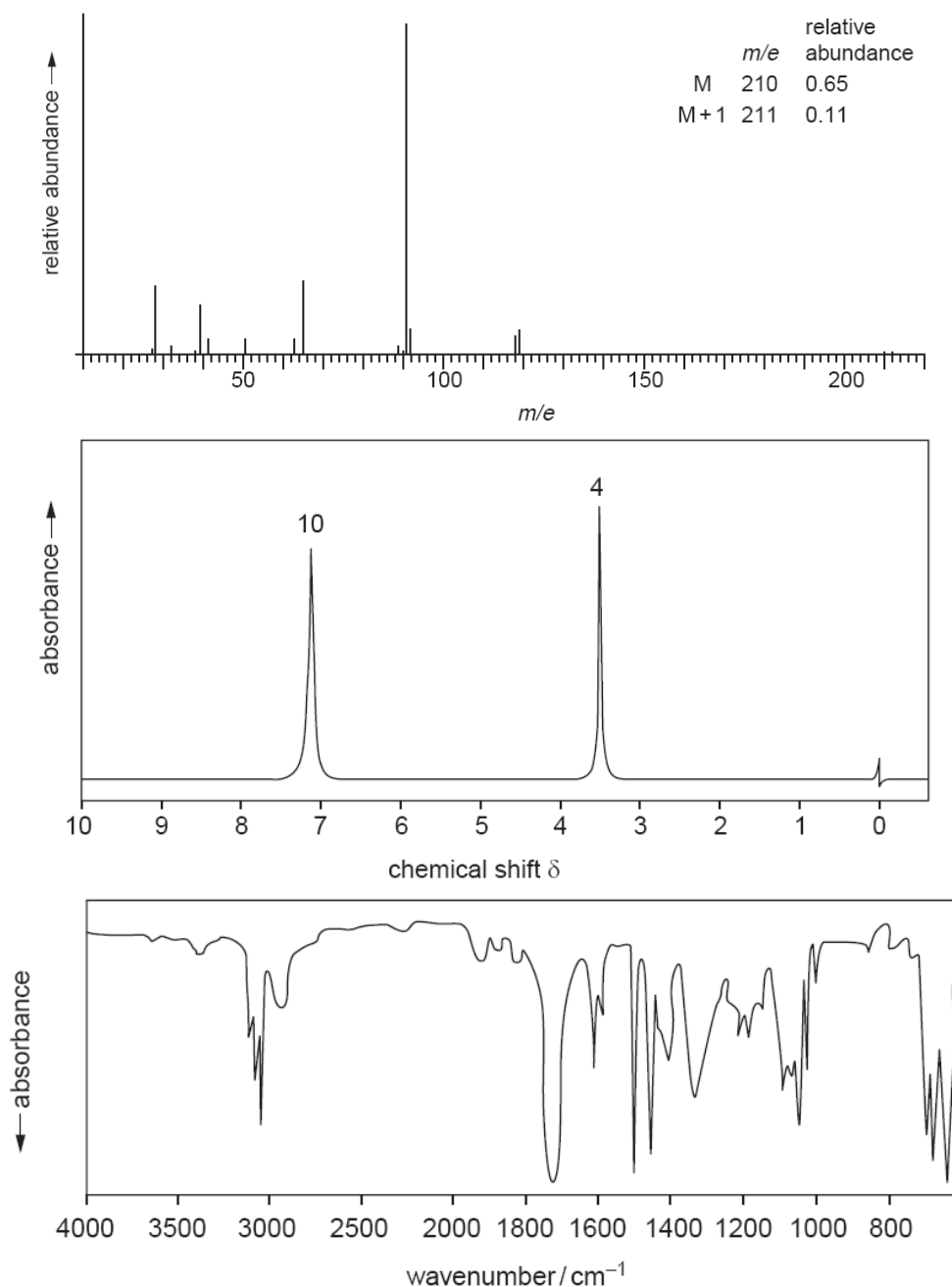
alphaprodine

- (i) Draw and label the boat and the two chair conformations for alphaprodine. [2]
- (ii) Arrange the conformers in increasing order of stability. Explain your answer. [2]
- (c)** Electrophoresis is the common method used in separating and detecting the amino acids from hydrolysis of proteins. Another method of separating the amino acids is two-way paper chromatography.

Outline the principles of two-way paper chromatography. You may include suitable illustrations in your answer. [3]

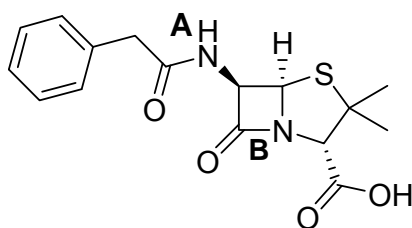
- (d) (i) By means of a labelled diagram, identify the basic features of a mass spectrometer. [2]

The spectra shown below were each obtained from compound **D**.



- (ii) Using the relative abundance of the M and M+1 peak, work out the number of carbon atoms in **D**. [1]
- (iii) Use the evidence from each spectra to suggest a structure for **D**. Explain how absorptions shown in each of the spectra lead to your suggested structure. [6]

- 4(a)** Penicillins are a group of antibiotics which inhibit the synthesis of cell walls in some bacteria. Penicillin G, the parent of these antibiotics, was first isolated from a fungal species, *Penicillium notatum*.



penicillin G

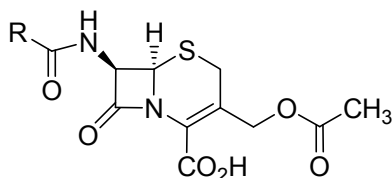
The presence of the β -lactam ring in penicillin is essential in the study of structure–activity relationship (SAR).

The bond lengths of the two C–N bonds **A** and **B** in Penicillin G are indicated below.

Bond length

Bond A	0.132 nm
Bond B	0.147 nm

- (i) Explain the difference in the bond length of **A** and **B**. [2]
- (ii) Compare and explain the rate of hydrolysis of the amide and lactam groups in Penicillin G. [2]
- (b)** Cephalosporin is the second major group of β -lactam antibiotics. The first cephalosporin (cephalosporin C) was derived from a fungus obtained in the 1940s from sewage water on the island of Sardinia.



Cephalosporin C

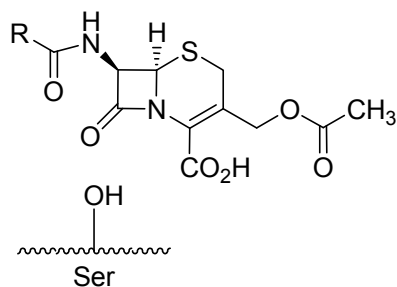
- (i) A study of the structure of cephalosporin reveals that it can be formed from two amino acids and two carboxylic acids.

Copy the structure of cephalosporin and circle the regions that originate from the two amino acids. [2]

- (ii) Cephalosporin in general is more resistant towards β -lactamase than penicillin.

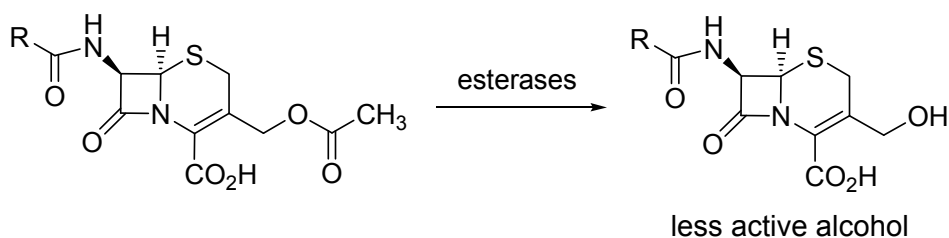
Comparing the structures of penicillin G and cephalosporin C, predict the bond length of C–N bond in the lactam ring of cephalosporin. Explain your reasoning. [2]

- (iii) The mode of action of cephalosporin involves the hydrolysis of β -lactam ring which results in the loss of CH_3COO^- .



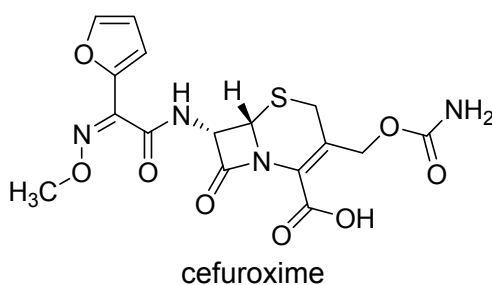
Copy the following diagram and suggest a possible mechanism for this reaction. [3]

- (iv) A disadvantage of cephalosporin is that the acetoxy group is readily hydrolysed by esterase enzymes to give the less active alcohol variant.



Assuming both compounds undergo similar hydrolysis mechanism, give an explanation for the difference in drug activity between cephalosporin and the alcohol variant. [1]

- (c) Cefuroxime is a second-generation cephalosporin antibiotic with 8% bioavailability, in which bioavailability is the fraction of the orally consumed drug that finally reaches blood circulation to exert its effect.

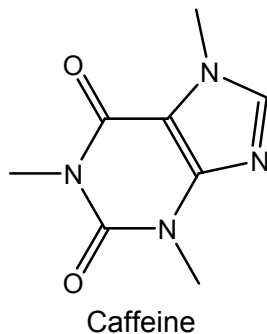


Therapeutic window is a well-defined range of a drug's serum concentration at which a desired effect occurs, below which there is little effect, and above which toxicity occurs. The therapeutic window for cefuroxime was determined to be between 2 and 8 mg dm^{-3} where the serum volume in an average human is 5 dm^3 .

Cefuroxime is taken by a patient twice a day (12-hour interval). Each dose consists of a single 500 mg tablet and the half-life of cefuroxime in the body is 1.5 hours.

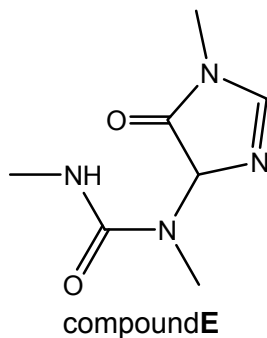
- (i) After the consumption of a single 500 mg tablet, calculate the concentration of cefuroxime in mg dm^{-3} that reaches the blood serum. [1]
- (ii) Calculate, to three decimal places, the equilibrium maximum and minimum concentration (in mg dm^{-3}) of cefuroxime reached in the body after 3 doses. [2]
- (iii) After a few days on the antibiotic, a patient realised that he had missed his 8.00 a.m. dose and decided to take a double dose at 8.00 p.m. on the same day to “compensate” for it.
- Calculate the maximum concentration (in mg dm^{-3}), to four significant figures, would be for the next 12 hours after taking the double dose.
- Explain why he should not have taken the double dose. [2]
- (iv) Suggest an alternative strategy to return the patient safely to the equilibrium levels calculated in (ii). [1]
- (v) The same non-compliant patient decided to stop his course of antibiotic as the symptoms of his infection have disappeared. Explain why he should have finished the entire course. [2]

- 5(a)** The compound caffeine is found in tea and coffee. It can be extracted from these sources by using organic solvents. The solid caffeine extracted may be recrystallised from hot water.



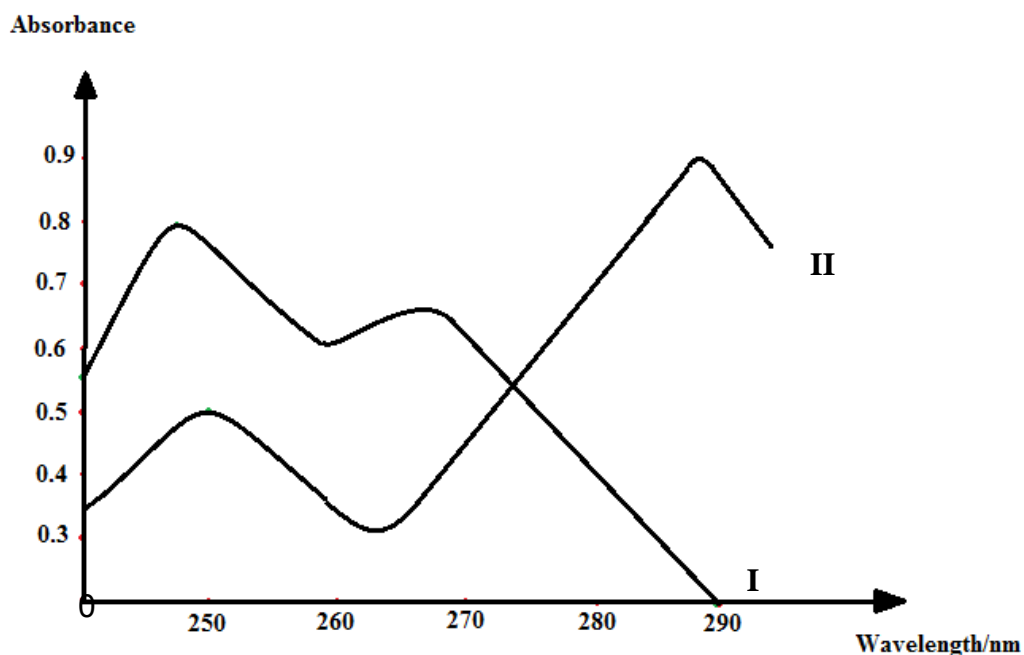
- (i)** State two effects of caffeine on the body. [2]

It is believed that caffeine reacts with alkaline aqueous potassium manganate(VII) to form compound **E**.



- (ii)** The NMR spectrum of compound **E** is different from that of caffeine. Suggest, with reasons, two ways in which it may differ. [2]

Both caffeine and compound **E** also absorb in the UV–vis region of the spectrum. Below shows the UV–vis spectra **I** and **II** of two solutions, one containing caffeine and the other containing compound **E**, each at an equal concentration of $3.30 \times 10^{-5} \text{ mol dm}^{-3}$.



(iii) Explain why these compounds absorb in the UV–vis region. [1]

(iv) Identify the two spectra, **I** and **II**, explaining your choice. [2]

A new sample containing a mixture of caffeine and compound **E** was collected and analysed with UV/VIS spectroscopy at 250 nm and 290 nm. The absorbance at each wavelength was recorded as shown.

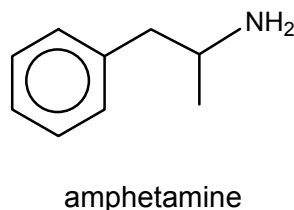
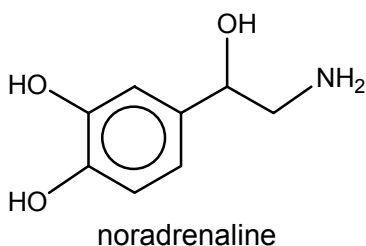
Wavelength/nm	Absorbance
250	0.87
290	0.40

(v) State Beer Lambert's law.

Hence, determine the concentrations of caffeine and compound **E** in this sample. [4]

- (b) Transmission of impulses in the nerves of smooth and cardiac muscles is carried out by the neurotransmitter noradrenaline. Noradrenaline molecules released into the synapse can trigger a response at the adrenergic receptor of the post-synaptic nerve. Eventually, the noradrenaline molecules bind with the carrier proteins and are re-absorbed into the pre-synaptic nerve.

The molecule of amphetamine is neither an agonist nor an antagonist at the adrenergic receptor, but it does compete with noradrenaline for the carrier protein.



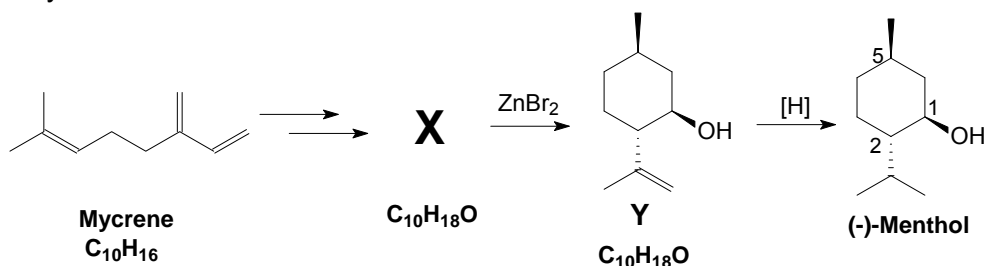
- (i) What is meant by the terms *agonist* and *antagonist*? [2]
- (ii) Explain why an agonist molecule is usually similar in structure to the natural ligand for a receptor, whereas antagonists are often larger molecules that can differ significantly in structure from the natural ligand. [2]
- (iii) Explain how the presence of amphetamine will affect nerve transmission. [1]
- (iv) Suggest a test (stating reagents and observations) that would enable to be distinguished amphetamine and noradrenaline from each other. [2]
- (c) Outline the short-term and long-term effects of nicotine consumption. [2]

- 6 Menthol is readily obtainable from plant sources such as cornmint, peppermint and other minty oils. It predominantly exists as one pure stereoisomer, (–)-menthol, in nature.

(–)-menthol is a local analgesic responsible for the cooling sensation when inhaled, eaten or applied to skin, due to the activation of the voltage-sensitive TRPM8 cold receptors in skin. It is also a weak agonist of κ -opioid receptors resulting in its analgesic properties and a counterirritant.

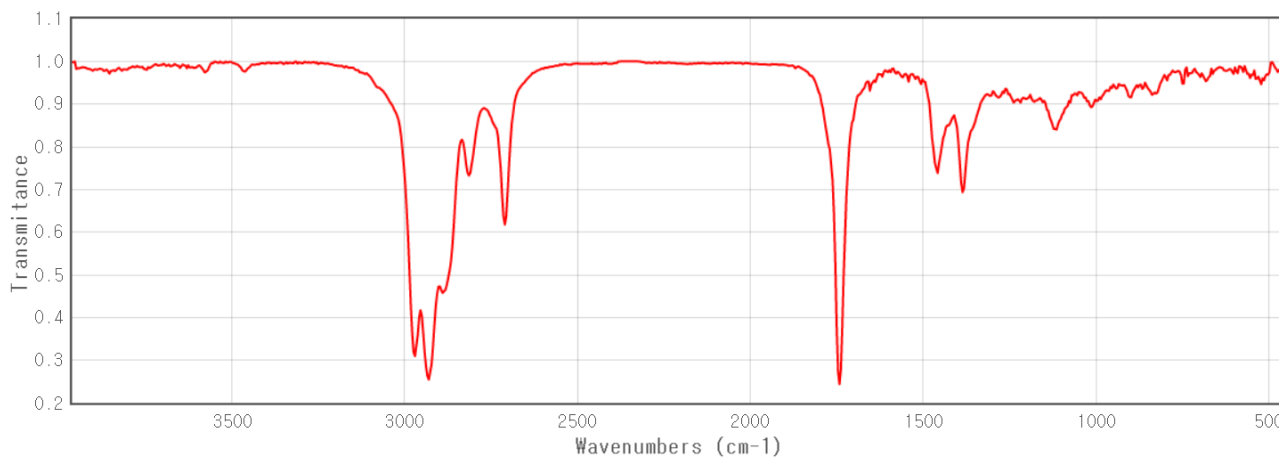
- (a) Explain the term “local analgesic”. [2]

Commercially, menthol was synthesised through a multiple steps synthesis from a terpene, myrcene, through an intermediate compound, **X**. **X** is a R-stereoisomer and is structurally similar to myrcene.



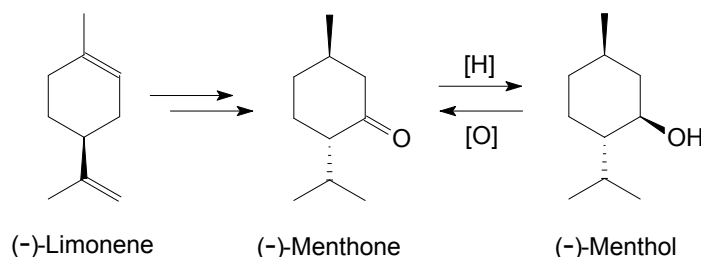
- (b) Using the R,S convention, assign the correct configurations to the three chiral centres at carbon atoms 1, 2 and 5 in (–)-menthol. Explain your assignment for **one** of the chiral carbons. [4]

- (c) The IR spectrum and 1H NMR signals of **X** are shown below.



Chemical shift (ppm)	Splitting Pattern	Integral values
0.96	d	3
1.54	q	2
1.70	s	3
1.82	s	3
1.88	m	1
1.96	q	2
2.48	m	2
5.20	t	1
9.72	t	1

- (c) (i) Using the data given, identify the proton environments responsible for the **key** chemical shifts. [4]
- (ii) Deduce the structure of **X**, indicating its stereochemistry. [1]
- (d) Conversion from **X** to (–)-menthol involves 2 steps: cyclisation to alicyclic compound **Y**, followed by reduction.
- (i) Explain the role of zinc bromide in this reaction. [1]
- (ii) Suggest a mechanism for the cyclisation process from **X** to **Y**. Include a diagram of the transition state to explain the stereochemistry observed in **Y**. Your answer should show clearly the stereochemistry present in the transition state and the final product. [4]
- (e) (–)-menthol is capable of being oxidised to (–)-menthone, a compound used in perfumery. (–)-menthol and (–)-menthone belong to a class of natural products known as terpenes. (–)-limonene is the precursor in the biosynthesis of menthone and menthol.



Reverse high performance liquid chromatography (HPLC) connected to a UV-vis spectrometer was proposed for analysing and separating the three compounds in a crude sample of peppermint oil.

- (i) State, with reasons, the order of elution of these three compounds. [3]
- (ii) Suggest and explain if the proposed detection method is suitable. [1]