NATIONAL JUNIOR COLLEGE
SH2 PRELIMINARY EXAMINATION
Higher 3

CANDIDATE NAME			
SUBJECT CLASS		REGISTRATION NUMBER	

PHARMACEUTICAL CHEMISTRY 9812/01

Paper 1

Friday 15 September 2017
2 hours 30 minutes

Additional Materials: Answer Paper
Data Booklet

READ THE INSTRUCTIONS FIRST

Write your subject class, registration number and name on all the work you hand in.
Write in dark blue or black pen.
You may use an HB pencil for any diagrams or graphs.
Do not use staples, paper clips, highlighters, glue or correction fluid.

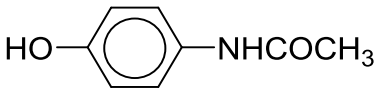
Answer any **five** questions.
At the end of the examination, fasten all your work securely together.

The number of marks is given in brackets [ ] at the end of each question or part question.
The use of an approved scientific calculator is expected, where appropriate.
You are reminded of the need for clear presentation in your answers.

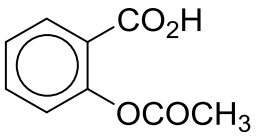
This document consists of **17** printed pages and **1** blank page.

1 **(a)** Analgesic can be classified according to narcotic and non-narcotics analgesics.

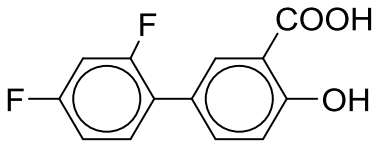
The following are 4 examples of commonly used analgesics in healthcare.



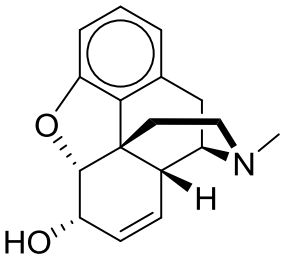
paracetamol



aspirin



diflunisal



codeine

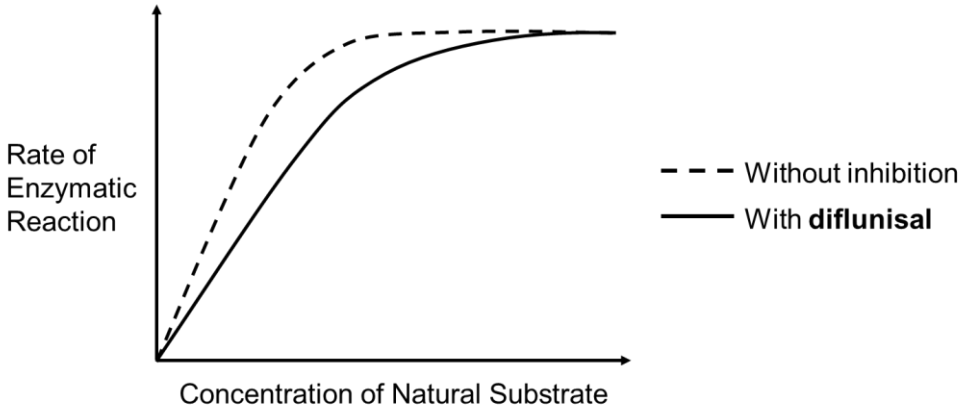
(i) Classify these 4 analgesics as narcotic or non–narcotic analgesics. [2]

(ii) Outline the different ways narcotic and non–narcotic analgesics act as pain-killer. [2]

(iii) One side effect of prolonged consumption of aspirin is stomach bleeding and ulcers. Describe how aspirin causes stomach bleeding and ulcers. [2]

(iv) Paracetamol is an analgesic which is capable of pain relief yet not causing stomach bleeding and ulcers as in the case of aspirin.
Suggest two other advantages of using paracetamol over the use of aspirin. [2]

Both diflunisal and aspirin inhibit the same enzyme in its mechanism of action to reduce pain. The inhibition effect of these drugs on the target enzymes can be studied using a Michaelis–Menten graph. The higher the rate of enzymatic reactions, the greater the pain level. The inhibition effect of diflunisal against the natural substrate of the target enzyme is as shown below.



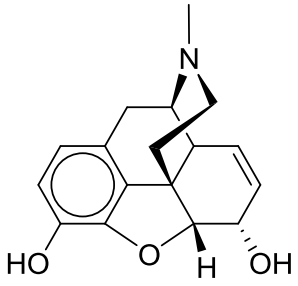
(v) Suggest the type of inhibition exhibited by diflunisal. Explain your answer. [2]

(vi) Copy the graph shown above on your writing paper and draw a graph illustrating the expected inhibition effect of aspirin as compared to that of diflunisal. Explain your answer. [3]

(b) **(i)** Morphine is one of the most effective painkillers that can be extracted from dried juice obtained from unripe seed pods of opium poppy. In order to be effective as an analgesic, the morphine molecule has to pass through the blood brain barrier to dock onto receptors in the brain.

Esterases, enzymes that are able to hydrolyse ester linkages but not ether linkages, are found in the brain.

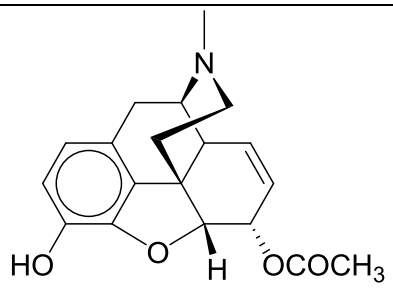
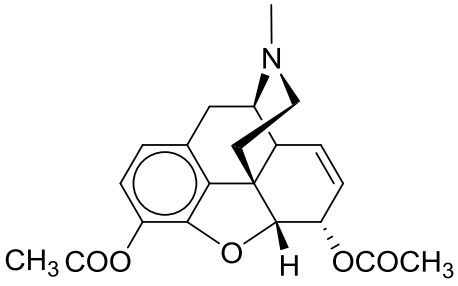
Morphine has several functional groups, and a study of structure-activity relationships (SAR) is important in identifying groups that are important for its activity.



morphine

Identify the functional groups in morphine that are important for analgesic activity. Suggest the interactions they have at the binding site. [3]

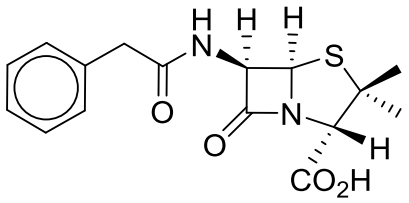
(ii) The activities of 6-acetylmorphine and diamorphine (heroin) compared to morphine are shown in the table below.

Drug	Structure	Analgesia with respect to morphine
6-acetylmorphine		4 x
diamorphine		2 x

Account as fully as you can the difference in the analgesic activity of diamorphine, 6-acetylmorphine and morphine. [4]

[Total: 20]

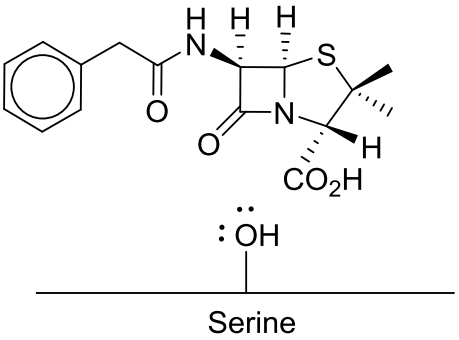
2 **(a)** Penicillin G is the naturally occurring penicillin that shows pharmaceutical value. It can be obtained from the mould *Penicillium notatum* cultured from yeast extract.



penicillin G

Penicillin G inhibits the transpeptidase enzyme irreversibly through formation of a covalent bond with a serine amino acid residue at the active site. The reaction involves the hydrolysis of the β lactam ring of penicillin G.

(i) Suggest the mechanism for the hydrolysis reaction.



Serine

[3]

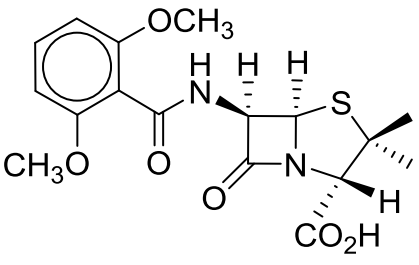
(ii) Explain how the inhibition described in **(a)(i)** leads to the death of bacteria. [2]

(iii) Suggest why the subsequent hydrolysis by water on the ester group linking the penicillin to the active site does not take place. [1]

(iv) Penicillin G can only be administered via injection and not oral means such as pills. Explain why oral administration of penicillin G is ineffective.

[2]

(b) Methicillin was synthesized in the 1960s to counter the threat of penicillin-resistant strains of *Staphylococcus aureus*.

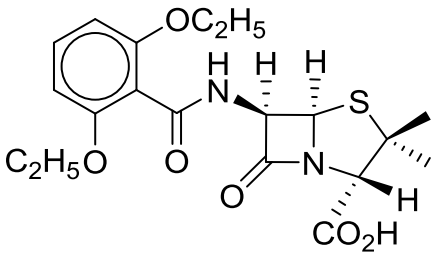


methicillin

(i) Explain the feature of the methicillin molecule which allows it to overcome the

problem of penicillin resistance. [2]

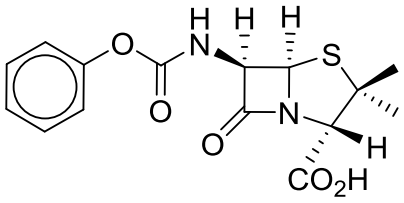
(ii) The following structure is an analogue of methicillin.



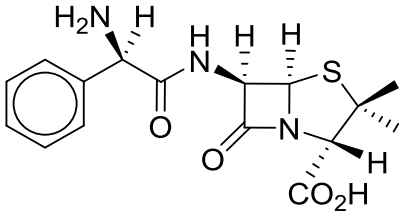
Analogue of methicillin

Suggest, with explanation, how you would expect the antibacterial activity of this analogue to compare with that of methicillin. [2]

(c) The structures of two other antibiotics, penicillin V and ampicillin, are shown below. These two antibiotics can be administered orally, but not penicillin G and methicillin.



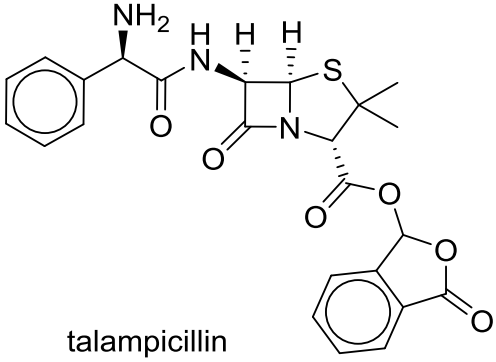
penicillin V



ampicillin

Comment on this difference. Using the structures of the penicillin shown, explain your answer. [3]

(d) Ampicillin can cause diarrhoea due to poor absorption through the gut wall. This problem can be overcome by using prodrugs. Talampicillin is an example of such a prodrug.



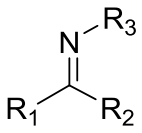
talampicillin

Explain why ampicillin is poorly absorbed and how the prodrug improves the absorption of ampicillin. [2]

(e) Outline, with examples, two other ways in which drugs act against bacteria, other than by inhibiting cell wall biosynthesis. [3]

[Total: 20]

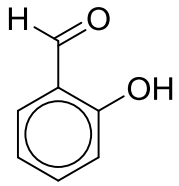
3 Schiff base is a compound that contains C=N functional group, in which the nitrogen atom is bonded to an alkyl or aryl group. It has the general structure as shown below. The C=N functional group is an analogue of the carbonyl functional group.



R_3 = alkyl or aryl group
R_1, R_2 = alkyl, aryl or H group

Schiff base is a common enzymatic intermediate when the enzyme reacts reversibly with a cofactor such as pyridoxal 5'-phosphate and retinal. It has also been explored for its interesting optoelectronic and gas storage properties.

(a) An unknown amino acid, with R group expected to be either $–CH_3$, $–CH(CH_3)_2$ or $–CH_2CH(CH_3)_2$, underwent a condensation reaction with salicylaldehyde to form an amino acid schiff base **A**, with the expulsion of a water molecule.



salicylaldehyde

The following data are obtained from the ^{1}H NMR spectrum of Schiff base **A**.

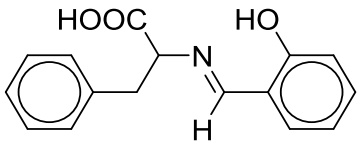
Chemical shift / ppm	Splitting Pattern	Integral value
1.01	doublet	6
2.20	multiplet	1
3.99	doublet	1
5.00	singlet	1
6.76 – 7.45	multiplet	4
8.13	singlet	1
11.00	singlet	1

(i) Using the ^{1}H NMR data provided, deduce the structure of the unknown amino acid used to make Schiff base **A**. [4]

(ii) Suggest the structure of Schiff base **A**. [1]

(iii) Suggest the changes to the ^{1}H NMR spectrum if a few drops of deuterated water are added to a sample of Schiff base **A**. [2]

(b) Schiff base **B** is an analogue of **A** and has the following structure.



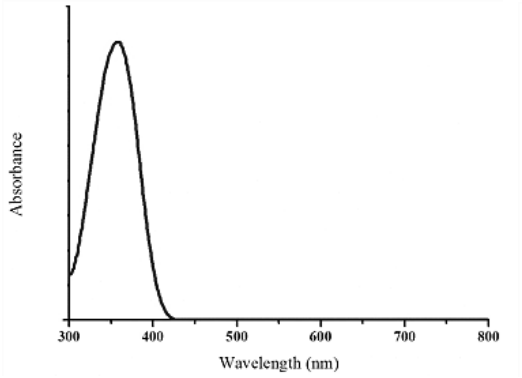
Schiff Base **B**

Schiff base **B** is observed to display three major peaks at m/e = 120, 252 and 269 in the mass spectrum.

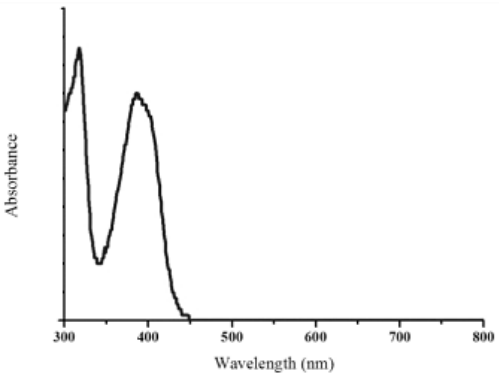
(i) Identify the ions responsible for each of the three peaks. [3]

(ii) Describe the fragmentation pathway that lead to the formation of the fragment with m/e = 252. You should include curly arrows showing the movement of electrons and any relevant charges. [2]

(c) Compound **C** and **D** are two analogues of **A**, derived from the achiral amino acid, glycine, were analysed in a UV-visible spectrometer. The UV spectra of both compounds **C** and **D** are shown below.



UV spectrum of **C**



UV spectrum of **D**

(i) Explain the underlying principles of UV spectroscopy of organic molecules. Details of instrumentation are not required. [2]

(ii) Suggest a possible reason for the presence of an additional peak in the UV spectrum of **D**. Explain your answer. [2]

(iii) Compounds **C** and **D** have the following molar extinction coeffients at absorption wavelength of 358 nm and 394 nm respectively.

Compound	Absorption wavelength/ nm	molar extinction coefficient, ε / mol^{-1} dm^3 cm^{-1}
C	358	17200
D	394	19300

When separate samples of **C** and **D** were analysed under 358 nm and 394 nm, the following absorption data is obtained.

Compound	Absorption Wavelength /nm	Absorbance
C	358	0.53
	394	0.18
D	358	0.24
	394	0.68

A solution, containing a mixture of **C**, **D** and other drugs, has measured absorbance of 0.78 at 358 nm and 0.92 at 394 nm.

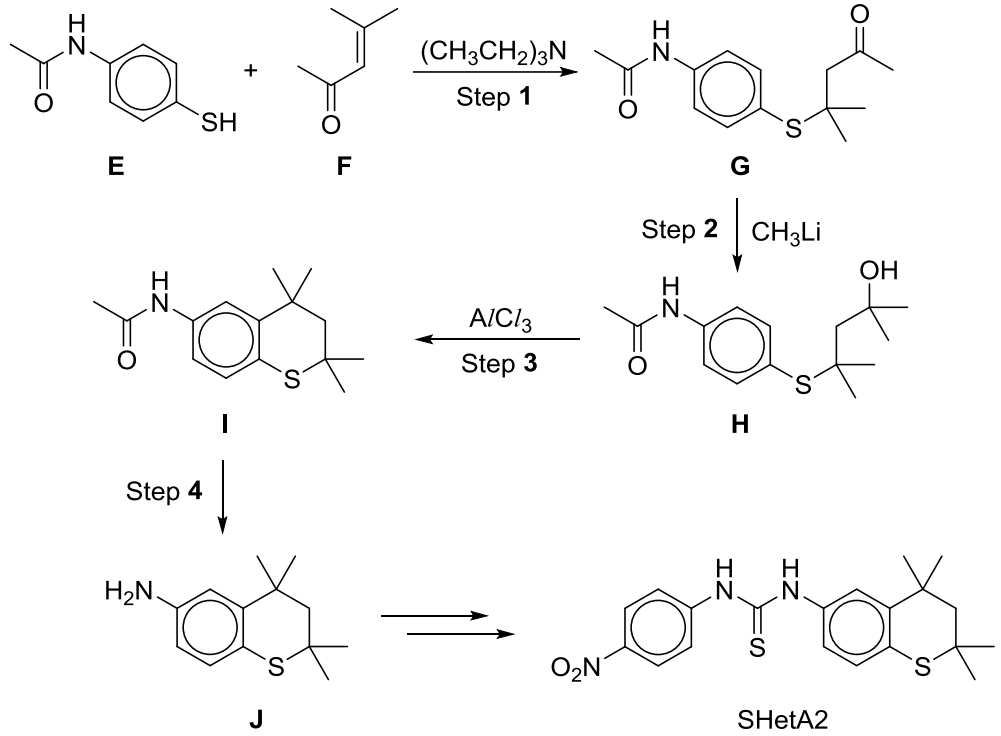
Using the abve information, determine the concentrations of **C** and **D** in the solution. [3]

(iv) State one key assumption made in the calculation of the concentrations of **C** and **D** in **(c)(iii)**. [1]

[Total: 20]

4 SHetA2 is a potential anticancer drug candidate. It has shown great level of efficacy, potency and selectivity in the inhibition of various cancer cell lines (such as head and neck cell carcinoma), while retaining low or no activity in normal cells.

SHetA2 can be synthesized from compound **E** and **F** via the synthetic scheme as shown below.



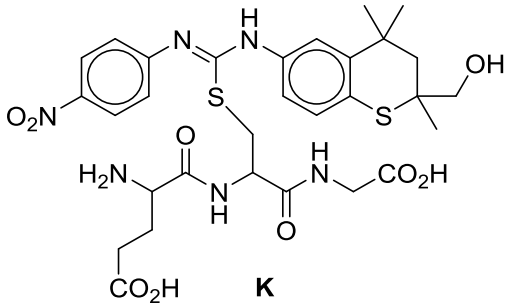
(a) **(i)** Given that the key step in the mechanism for step **1** is a *1,4–Michael addition* which is similar to nucleophilic addition, suggest the mechanism for step **1**. [3]

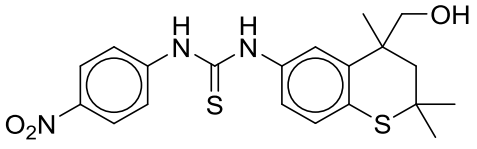
(ii) Based on the synthetic scheme provided above, suggest the purpose of the amide group in compound **E**. [1]

(iii) State the reagents and conditions for step **4**. [1]

(iv) Describe the mechanism for step **4**. [3]

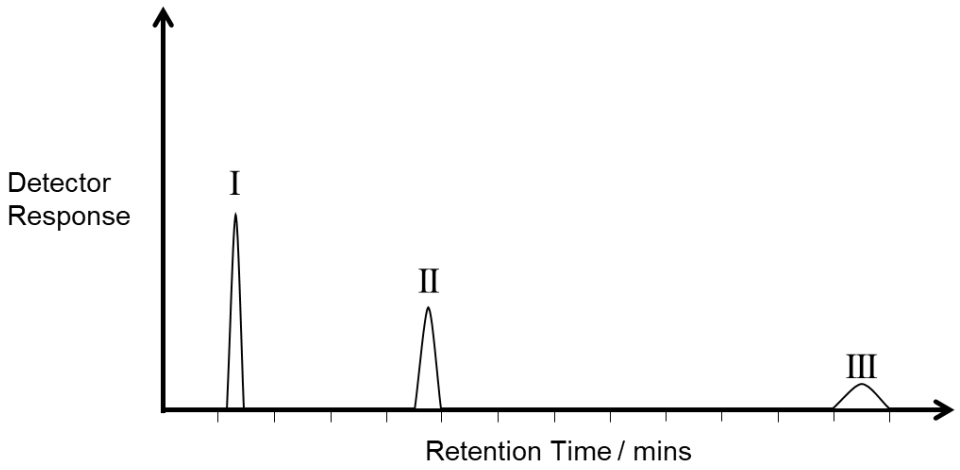
(b) It was found from an in vivo testing that SHetA2 was first metabolised to increase the hydrophilicity before transporting to the cancer cell. Compound **K** and **L** are 2 of the many metabolites that were isolated from the investigation.


K


L

Suggest a reason why the drug is being metabolized before being transporting to the cancer cell. [1]

(c) A sample, containing only SHetA2, compound **K** and **L**, is separated using normal phased high-performance liquid chromatography (HPLC). The HPLC profile is as shown below.



Peak	Peak Area	Detector response
I	34.1	0.54
II	19.2	0.37
III	5.8	0.23

(i) Outline the underlying principle behind normal phase HPLC which allows this separation to occur. [3]

(ii) Suggest a suitable detection method for obtaining the above HPLC profile. Explain your answer. [1]

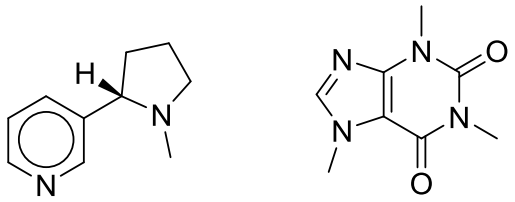
(iii) Suggest the compound which is responsible for each of the peaks shown in the HPLC profile. [3]

(iv) Calculate the percentage composition of SHetA2 in the solution. [2]

(v) Comment on the suitability of normal phased HPLC for this separation. Suggest a better separation technique for the isolation of the metabolites. [2]

[Total: 20]

5 Nicotine and caffeine are potent stimulants which are used medically.



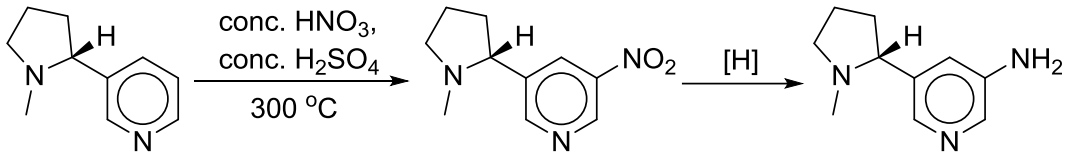
nicotine caffeine

(a) **(i)** Outline the mechanism of action with allows nicotine to produce its stimulating effects. [2]

(ii) Explain how nicotine addiction occurs. [2]

(iii) Use the *R, S* convention to identify the stereochemistry of nicotine. Explain your answer. [1]

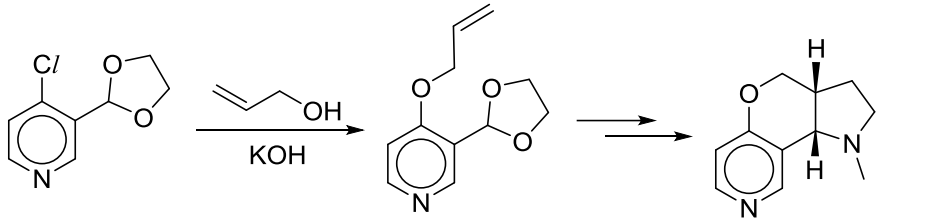
One method of introducing an amine group, $–NH_2$, on the pyridine of nicotine is through the following reaction scheme. Substitution occurs predominantly on the 3–position of the pyridine.



(iv) Explain why the condition for nitration is harsher than that for benzene. [1]

(v) Using suitable canonical structures, explain the position of the substitution. [2]

An analogue of nicotine was synthesized via the following synthetic scheme for testing of its potential stimulant properties.



M **N** **analogue of nicotine**

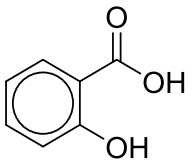
(vi) State the type of reaction that occurred in the conversion of compound **M** to **N**. [1]

(vii) Suggest the mechanism for the conversion of compound **M** to **N**. [3]

(b) Caffeine can be isolated from tea by first extracting brewed tea with dichloromethane, followed by purification by sublimation.

The purity of the caffeine can be determined by checking the melting point of caffeine or a caffeine salt. The caffeine salt gives a sharp melting point which is ideal for determining purity.

One such caffeine salt is caffeine salicylate, which can be made by adding salicylic acid into caffeine dissolved in dichloromethane, followed by precipitation upon addition of ether.

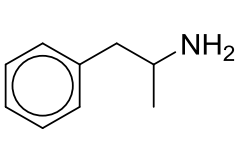


salicylic acid

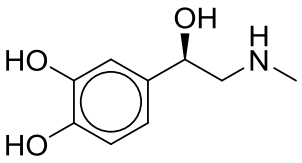
(i) State the type of reaction that occurred between caffeine and salicylic acid. [1]

(ii) Suggest the structure of the caffeine salicylate, given that the phenolic –OH group of salicylic acid is inert in this reaction. [1]

(c) Amphetamine is another class of stimulants which mimics the action of adrenaline.



amphetamine

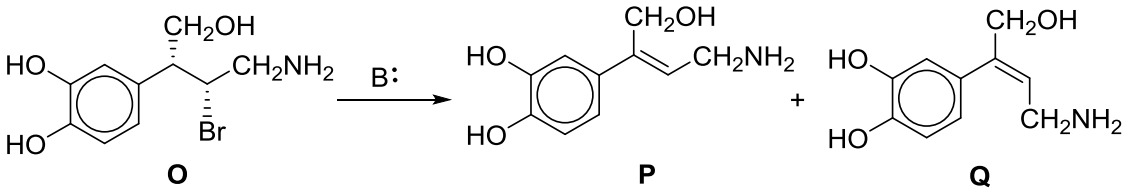


adrenaline

(i) Outline the difference in physiological effects between amphetamine and adrenaline. [3]

Compound **O** is structurally similar to adrenaline and is being used to synthesize other analogues of amphetamine.

When compound **O** undergoes elimination in the presence of a base (B**:**), compounds **P** and **Q** are formed in significant quantity. This elimination process is also found to be a second order reaction.



O **P** **Q**

(ii) Suggest whether compound **P** or **Q** is a major product. Using suitable diagram(s), explain your answer. [3]

[Total: 20]

6 **(a)** For millennia, the extract from the roots of *atropa belladonna*, the deadly nightshade plant, has been used as a poison, most prominently by the Romans in their court intrigue. The active ingredient, atropine, has found a use in medicine. It is used to relax the smooth muscles in the intestinal tract and the pupils of the eyes.

In order to separate and identify the active compound, four hexane solutions were prepared.

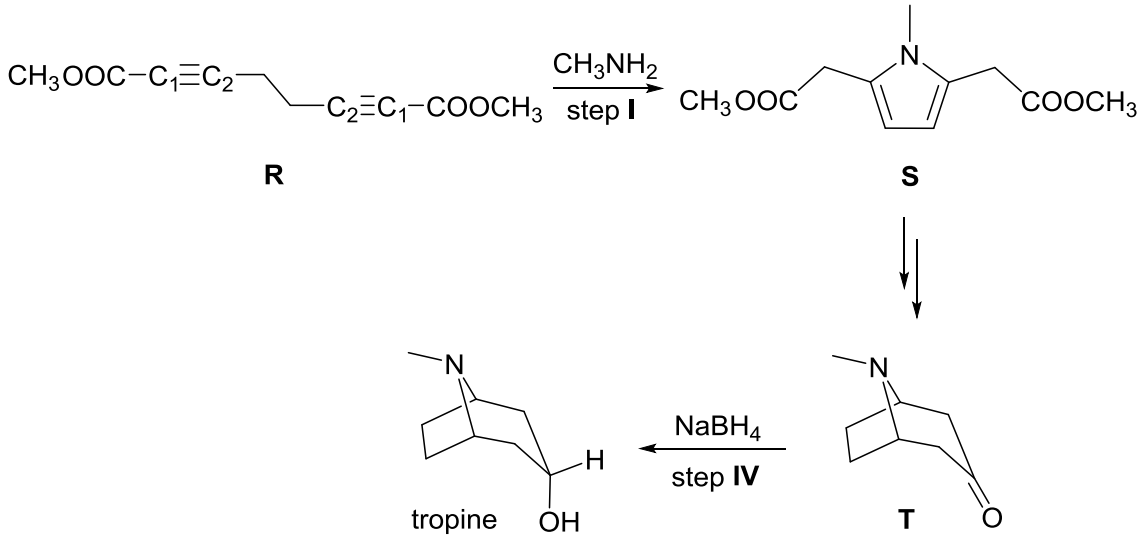
	1st step	**2nd step**	**3rd step**	**4th step**
1	Grind roots with water	Filter	Extract with hexane	
2	Grind roots with hexane	Filter		
3	Grind roots with NaOH (aq)	Filter	Add excess HC*l* (aq) to filtrate	Extract with hexane
4	Grind roots with HC*l* (aq)	Filter	Add excess NaOH (aq) to filtrate	Extract with hexane

The pharmacological activity of atropine in each hexane solution was investigated, with the following results:

- solution **1** – very low activity
- solution **2** – high activity
- solution **3** – zero activity
- solution **4** – very high activity

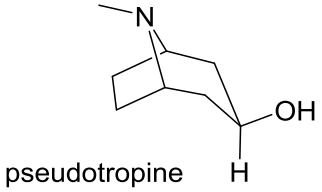
Use the information above to deduce the solubility and acid/base property of atropine. Explain your answer clearly. [4]

(b) Tropine is a precursor to many nitrogen–containing natural drug compounds. It can be synthesized according to the following scheme.



(i) Suggest two reasons why the $\mathbf{C_2}$ atoms in compound **R**, are attacked by methylamine in step **I**, rather than the $\mathbf{C_1}$ atoms. [2]

Pseudotropine and tropine are *epimers*, stereoisomers which differ in the three-dimensional orientation of the substituent groups at only one atom.

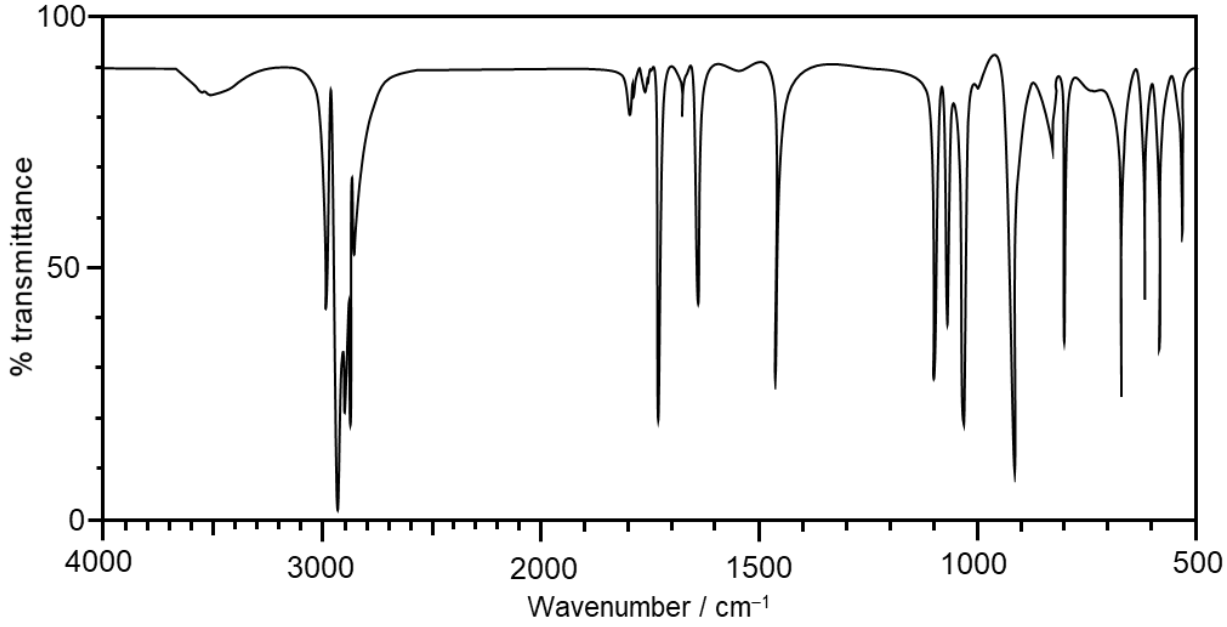


(ii) Explain why pseudotropine is energetically more stable than tropine. [1]

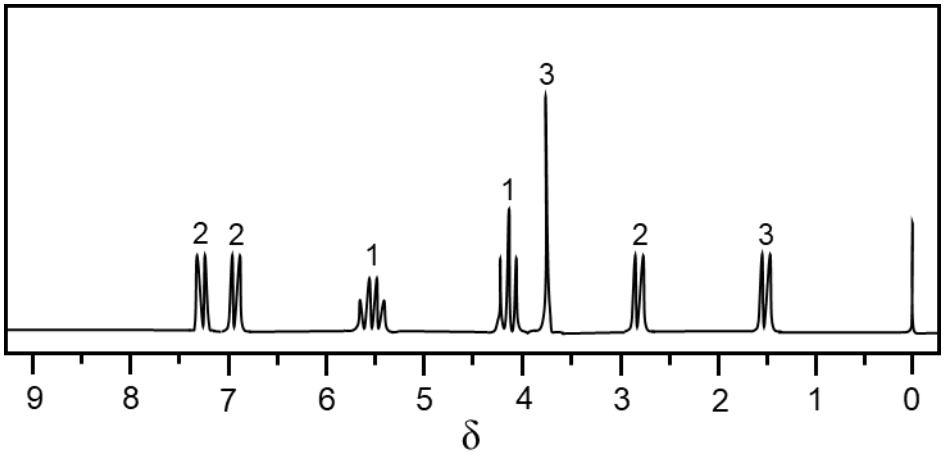
(iii) Explain why then, in step **IV**, tropine is formed instead of pseudotropine. [1]

(c) An unknown compound **U** was isolated from a mixture which was shown to have medicinal property and analysed for its structure. Compound **U** has a molecular ion at m/e value of 218, with relative abundance of 67.1%, and a peak at m/e value of 219 with a relative abundance of 9.5%. It is found that **U** is made of 22% oxygen by mass.

The IR spectrum of compound **U** is as shown.



The ^{1}H NMR spectrum of a sample of **U** dissolved in CDCl_3 is shown below.



Upon heating compound **U** under reflux with dilute H_2SO_4, compound **V** was obtained as the only organic product. When aqueous sodium carbonate is added to separate samples of compounds **U** and **V**, effervescence is observed only for compound **V**.

Heating **U** with aqueous HI, a compound **W** is produced. A violet colouration is observed when aqueous neutral FeCl_3 is added to a sample of **W** but not with compounds **U** and **V**.

All compounds **U**, **V** and **W** decolourise orange aqueous bromine.

(i) Identify the reagent which gives the peak at 0.00 ppm. [1]

(ii) Explain the role of the reagent you have identified in **(c)(i)** in ^{1}H NMR spectroscopy. [1]

(iii) Use the spectroscopic data and other information provided above, deduce the structure of compound **U**. Explain your answer fully. [10]

[Total: 20]

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