ANDERSON JUNIOR COLLEGE
Preliminary Examination 2016

Higher 3 **Pharmaceutical Chemistry** **9812**

19 Sep 2016 **Monday** **2h 30 min**

READ THESE INSTRUCTIONS FIRST

1. Answer any **five** questions.
2. Begin each question on a fresh sheet of paper.
3. At the end of the exam, attach the cover page in front of your answers.
4. Write your name and PDG on the cover page, circle the question numbers you have attempted.
5. Write your name and PDG on all the writing papers submitted.

Name:_____ **PDG:**_____

Question						Total
1						
2						
3						
4						
5						
6						

This question paper consists of 16 printed pages including 1 cover page and 1 blank page.

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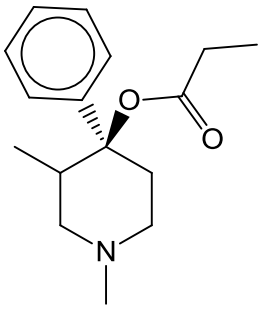
1 (a) Prodine is an analgesic and exists in two isomeric forms, alphaprodine and betaprodine.



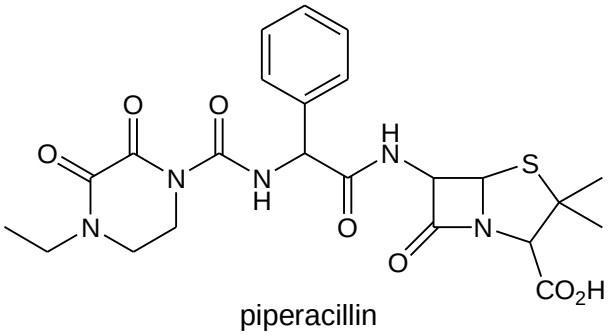
prodine

Both alphaprodine and betaprodine contain a six-membered ring which exists in a chair conformation. The bulky benzene ring is found in the axial position for both alphaprodine and betaprodine. The conformation of alphaprodine is less stable than that of betaprodine.

Draw and label the chair conformations of both alphaprodine and betaprodine. Hence, discuss the stereochemistry and the relationship of alphaprodine and betaprodine.

Explain why alphaprodine is less stable. [6]

(b) Piperacillin, $C_{23}H_{27}N_5O_7S$ (M_r = 517), is a broad-spectrum penicillin used to treat some serious bacterial infections.



piperacillin

(i) Piperacillin is a *semi-synthetic* penicillin. What is meant by *semi-synthetic* penicillin? [1]

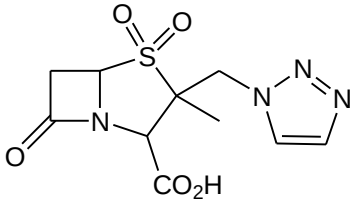
(ii) Explain how piperacillin work against bacteria. [2]

(iii) What are the products formed when piperacillin is subjected to complete acid hydrolysis.

[3]

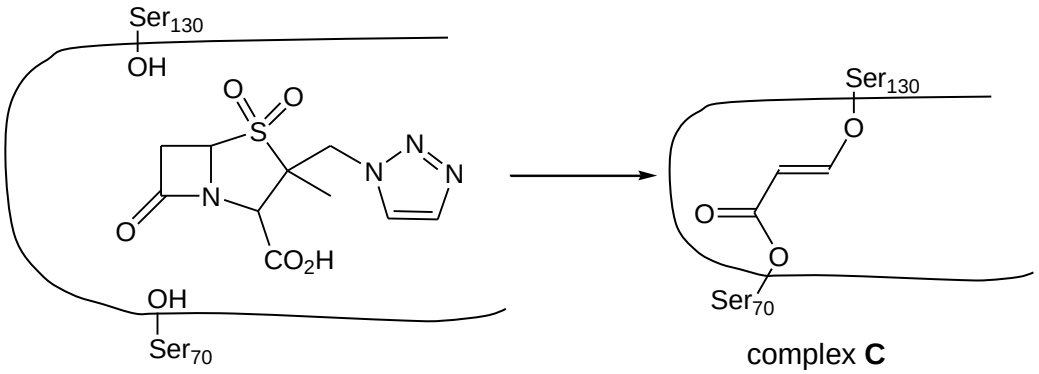
(iv) Compound **D** is a metabolite of piperacillin excreted from the body. Closely related in structure to piperacillin, the mass spectrum of **D** shows a molecular ion peak at m/e 489. Suggest the structure of **D**. [1]

(c) Piperacillin is ineffective against β–lactamase-producing bacteria, so it is usually administered together with tazobactam, a β–lactamase inhibitor.



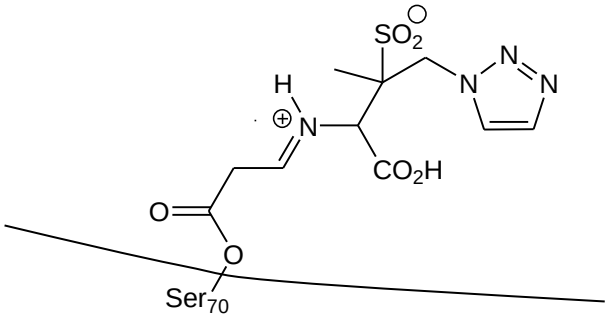
tazobactam

(i) Tazobactam fits into the active site of β–lactamase and both rings are opened by serine residues on the enzyme, resulting in the formation of stable complex **C** below.



complex **C**

Suggest a mechanism for the reaction of tazobactam with the enzyme to give complex **C**, given that the following protonated imine is an intermediate.



[3]

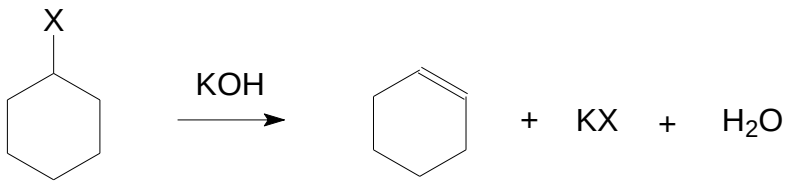
(ii) Explain why the ester linkage in complex **C** is stable towards hydrolysis. [1]

(iii) What type of inhibitor is tazobactam. Explain your answer. [2]

(iv) Explain why, even if the ester linkage in **C** was hydrolysed, tazobactam functions as an effective inhibitor of the enzyme.
[1]

[Total: 20m]

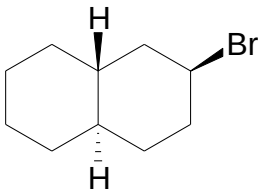
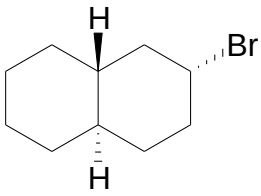
2 **(a)** Alkyl halides, RX, undergo elimination reaction with strong bases to form alkenes. The following equation is an example of such a reaction.



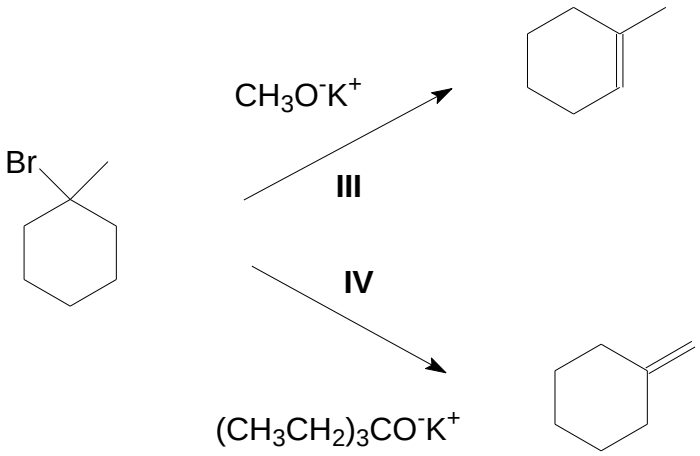
The rate of elimination is dependent on the reagents and conditions used.

(i) Account clearly for the observations for both Experiment A and Experiment B.

Experiment A

No.	*Structure of RX*	*Relative rate of elimination reaction (in hot ethanolic NaOH)*
I		200
II		1

Experiment B

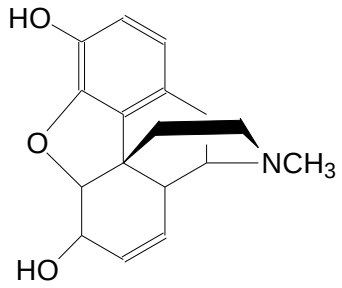


[5]

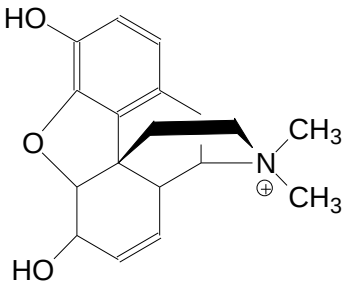
(ii) Referring to **(a)(i)**, suggest how the rate of **reaction I** in **Experiment A** will vary with concentration of NaOH. [1]

(b) Morphine is a narcotic analgesic obtained from opium and used clinically to relieve pain. Itself and many of its analogues act as agonists on a variety of receptors in the brain. In order to be effective, they have to pass through the blood brain barrier to dock on their receptors.

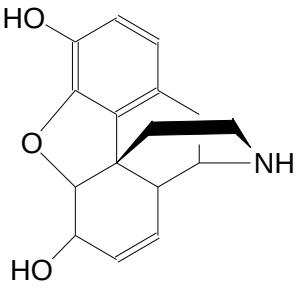
The structures and the relative analgesic activity of morphine and some of its analogues when administered intravenously are shown below.



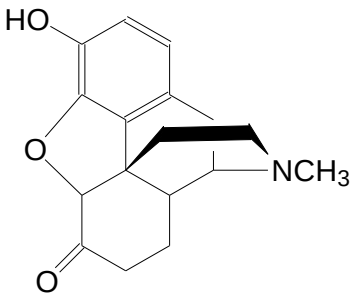
Morphine
100%



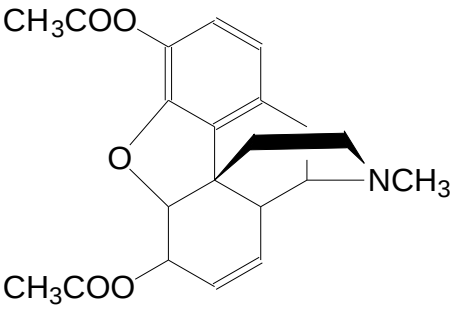
A
0%



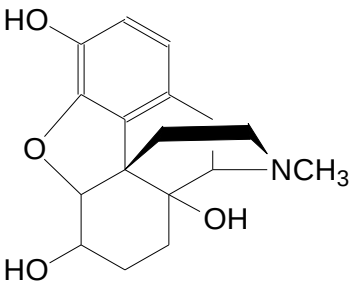
B
25%



C
850%



D
200%



E

You may need to refer to the structures to answer the following question.

(i) Explain the terms *narcotic analgesic* and *agonist*. [2]

(ii) Suggest three important groups on the morphine molecule that is necessary for its potency. In each case, state the type of interaction that would be involved. [3]

(iii) Analgesic activities of **A**, **B**, **C** and **D** compared with that of morphine in vitro had been studied.
Explain the differences.

I **A**, **B** and **C** shows comparable analgesic activities compared to morphine when studied in vitro. However, when administered intravenously, the analgesic activities of them vary significantly. Explain the differences. [2]

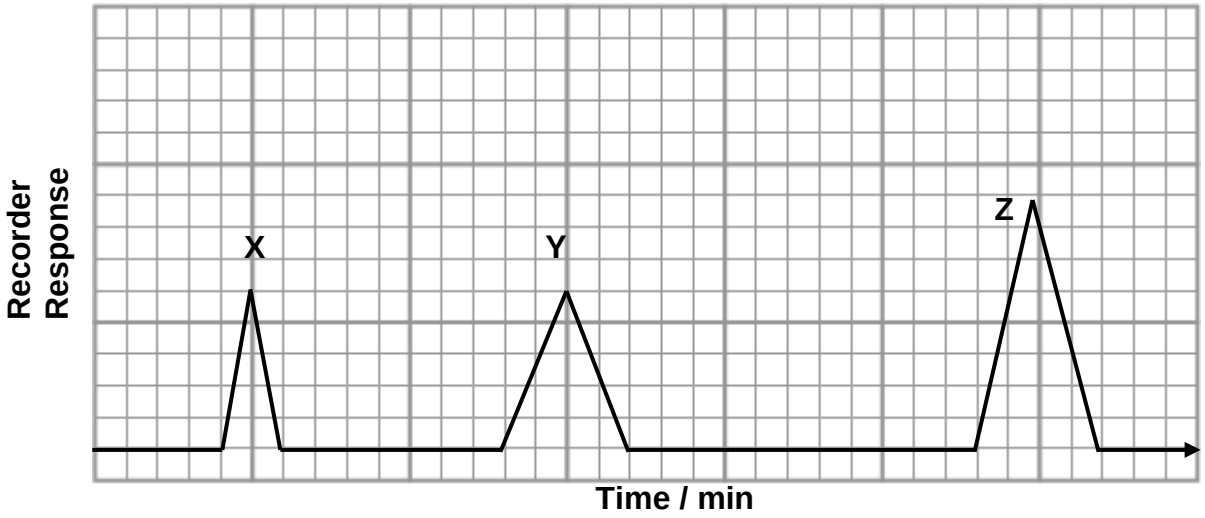
II **D** shows analgesic activity when administered intravenously, but no activity when studied in vitro. [1]

(iv) The pK_b of morphine is 5.79. What is the relative concentration of molecular morphine compared to the ionized morphine in an aqueous solution of physiology pH 7.4. [2]

(c) Narcotics analgesic can be separated and analysed using a chromatographic method.

(i) Suggest whether Gas-Liquid Chromatography (GLC) or High Performance Liquid Chromatography (HPLC) should be used for this analysis. Explain your answer. [1]

When morphine, **C** and **E** were subjected to the chromatographic analysis with the mobile phase was buffered at physiological pH, the following chromatogram was obtained.



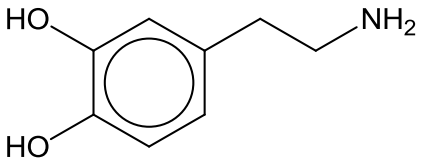
(ii) The compound corresponding to peak **X** was isolated and further analysed. Reaction of compound **X** with PCl_5 gives white fumes. Suggest the drug which corresponds to peak **X**. Explain your answer. [1]

(iii) Hence suggest the nature of the mobile phase and stationary phase as well as the identity of compounds corresponding to peaks **Y** and **Z**. Explain your answer. [2]

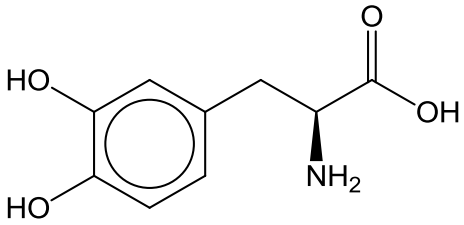
[Total: 20m]

[Turn over

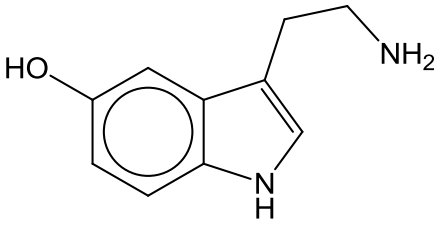
3 **(a)** Dopamine and seratonin are neurotransmitters. L-dopa is the physiological precursor to dopamine. Bufotenin is an alkaloid that is structurally related to seratonin.



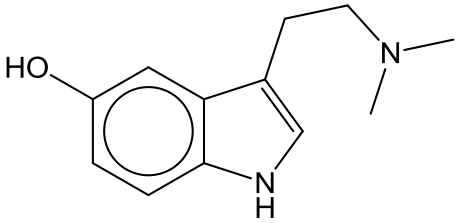
dopamine



L-dopa



serotonin



bufotenin

(i) State which of the four compounds above can be easily distinguished from the other three using infrared spectroscopy.
Describe the characterstic feature of its spectrum. [2]

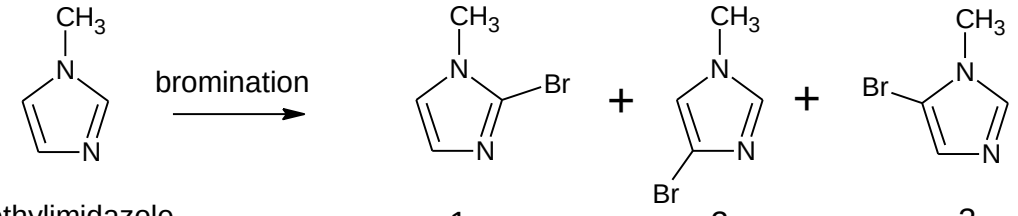
(ii) Suggest a synthesis of bufotenine from seratonin. [1]

(iii) The mass spectra of both bufotenine and seratonin show a base peak at m/e = 146. Identify the structure responsible for the base peak, and suggest a reason for its high relative abundance. [2]

L-dopa is administered in the treatment of Parkinson's disease. The compound shows an absorption peak at 278 nm in its UV spectrum, with a molar extinction coefficient of 24 500. A clinical solution of L-dopa shows an absorbance of 0.78 at a wavelength of 278 nm in a cell of path length 1.0 cm.

(iv) Use Beer's Law to calculate the concentration of L-dopa in the solution. [1]

(b) Caffeine contains the 1–methylimidazole ring as shown below. Under suitable conditions, 1–methylimidazole can undergo electrophilic substitution reaction to give three different products.



1-methylimidazole 1 2 3

(i) Draw the resonance structures of all the three intermediates and hence state the major product formed in this reaction. [4]

(ii) Write a balanced equation for the reaction between 1–methylimidazole and hydrochloric acid. [1]

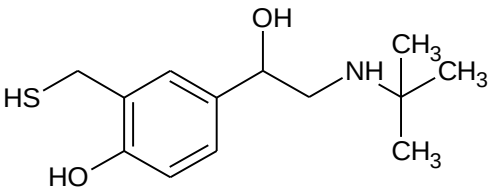
(iii) Compare the aromaticity of 1–methylimidazole and benzene. Suggest a reason for any difference.
[2]

(c) Caffeine, nicotine and amphetamine are stimulants that mimic the effect of natural neurotransmitter noradrenaline and hormone adrenaline.

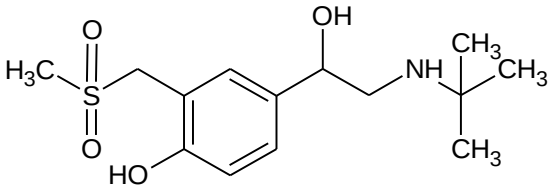
(i) Outline two similarities and two differences in the physiological effects of caffeine and nicotine.

[2]

T and **U** are sulfur–containing compounds that are derivatives of amphetamine.

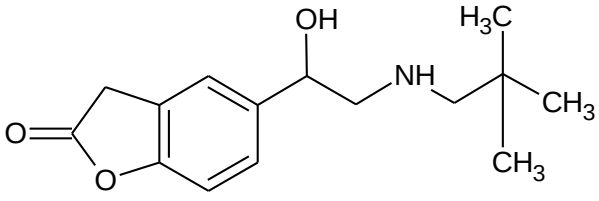


T



U

(ii) Suggest a reaction sequence for the synthesis of **T** from the following lactone.



[3]

(iii) Suggest a reaction sequence for the conversion of **T** to **U**. [2]

[Total: 20m]

4 (a) Phenobarbital is a depressant that is commonly used in developing countries to treat children suffering from epilepsy. It is a neutral compound containing C, H, N and O only. Most synthetic routes to phenobarbital involves a condensation reaction with urea $CO(NH_2)_2$.

Phenobarbital has M_r = 232. In its mass spectrum, the ratio of intensities of the M^+ and $(M+1)^+$ peaks is 7.51:1. The base peak occurs at m/e = 204.

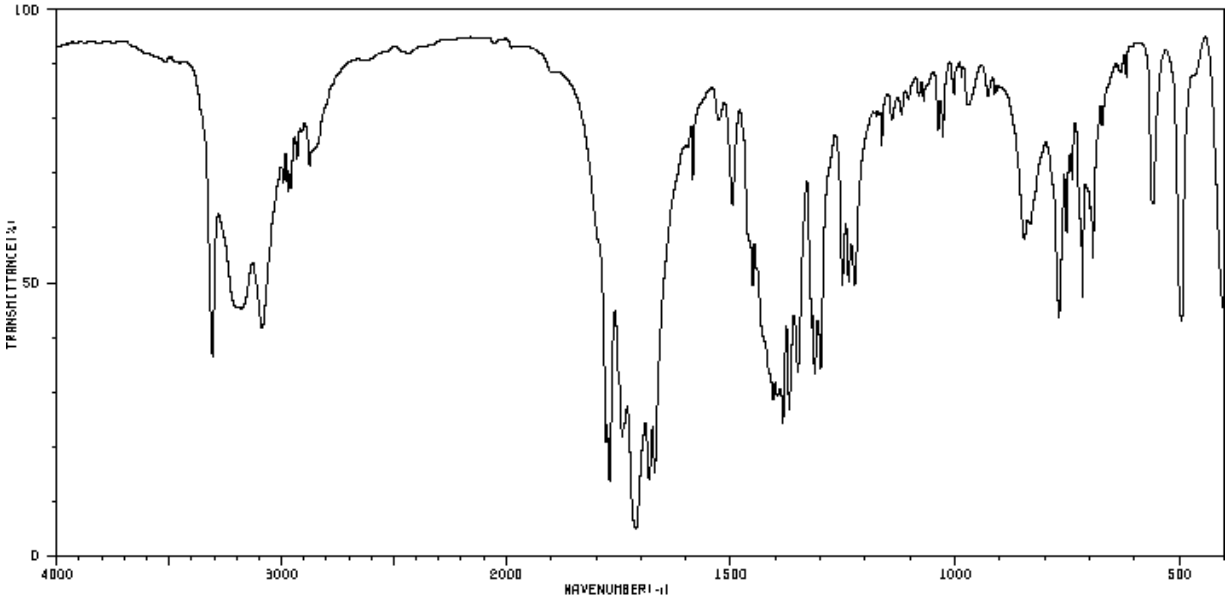
The NMR spectrum of phenobarbital shows resonances as follows.

δ / ppm	splitting	Number of protons
0.99	t	3
2.49	q	2
7.36	m	5
8.79	s	2

The signal at δ 8.79 disappears upon addition of D_2O.

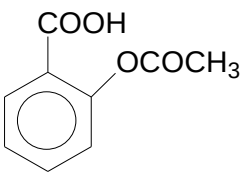
The compound has neither E/Z nor R/S isomers.

The IR spectrum of phenobarbital is shown below.

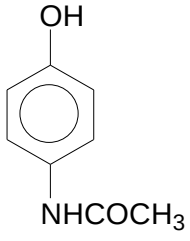


Use the given data to deduce the structure of phenobarbital. Explain your answer fully. [8]

(b) Aspirin and paracetamol are non-narcotics analgesic.



aspirin



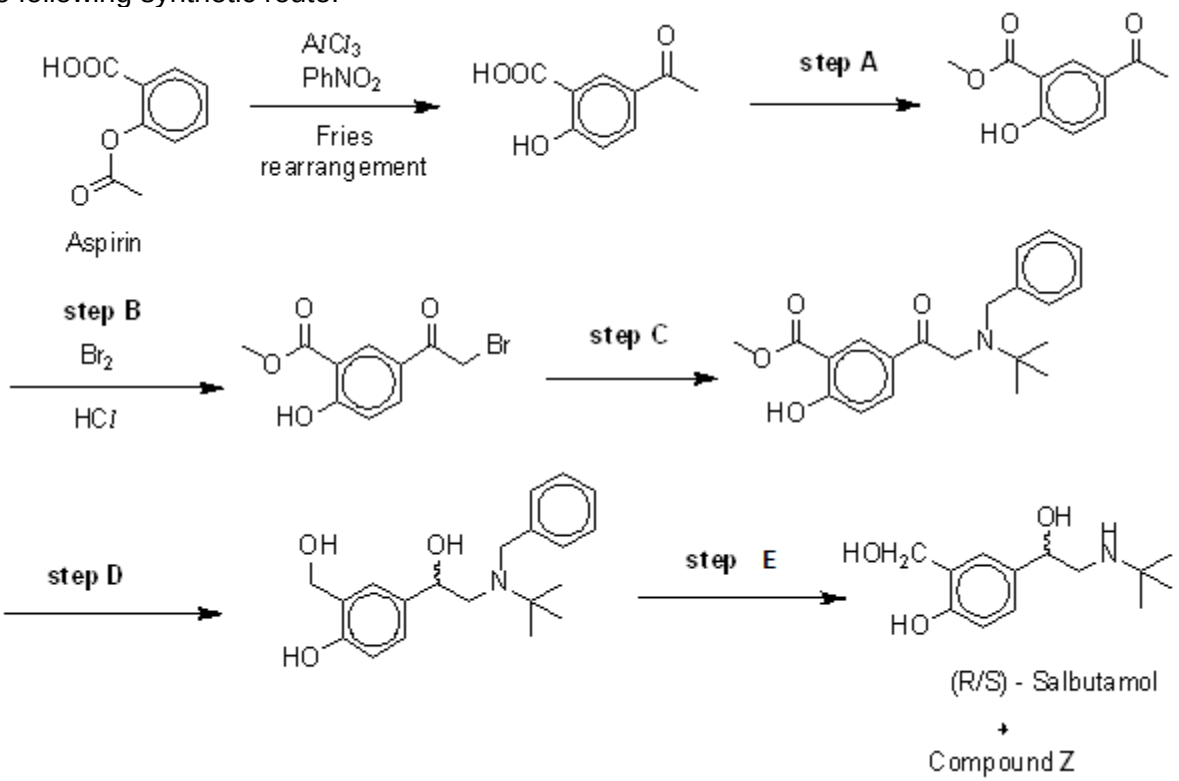
paracetamol

In a sample of a mixture of aspirin and paracetamol, the two analgesics can be separated through the following steps.

- Addition and subsequent shaking the mixture with equal volumes of aqueous $NaHCO_3$ and ethyl ethanoate
- Separation of aqueous and organic layers
- Dry the organic layer, filter and evaporate to collect the residue
- Addition of hydrochloric acid to the aqueous layer
- Filter and collect the residue

Explain the chemistry which allows the separation of the two analgesics in the mixture. [3]

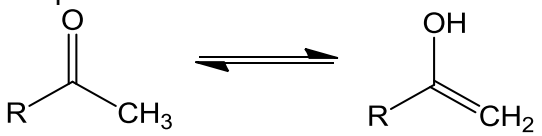
(c) Salbutamol is an important anti-asthmatic drug. It can be synthesized from aspirin according to the following synthetic route.



(i) Suggest the reagents and conditions for steps **A** and **C**. [2]

(ii) Suggest the structure of compound **Z** formed in step **E**. [1]

Carbonyl compounds exist in equilibrium between the keto and enol tautomers.



keto enol

Under normal conditions, equilibrium constant, K_c, is of the order of 10^{-5}.

(iii) Suggest a reason to explain the position of the keto-enol equilibrium. [1]

(iv) Propose a mechanism for step **B**, given that the react ion proceeds via an enol intermediate. [2]

(d) The (R)-enantiomer is responsible for the pharmacological activity of salbutamol.

(i) Draw the structure of (R)-salbultamol. [1]

(ii) Salbultamol is commercially sold as a racemic mixture. Explain why this is uncommon.[2]

[Turn over

5 **(a)** Hydrogen cyanide, HCN, can be studied using infra-red (IR) spectroscopy.

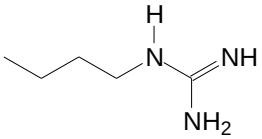
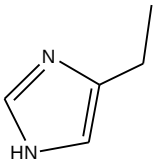
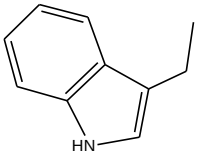
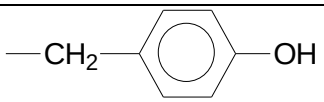
(i) Identify the molecular vibrations which give rise to absorption bands in an IR spectrum of HCN. [2]

(ii) One of the absorption bands occurs at 712 cm^{-1}. Indicate which of the vibrational mode is responsible for this absorption. [1]

(b) Electrophoresis is the routine method employed to separate the amino acid residues. Discuss the principle of gel electrophoresis in separating amino acids. [3]

(c) A small peptide chain undergoes complete hydrolysis and breaks into individual amino acids. A sample was subjected to electrophoresis for analysis. The amino acids in the sample are arginine, histidine, tryptophan, tyrosine and cysteine.

Some information of these amino acids is indicated in the table.

Amino acid (Abbreviation)	pI value	Structure of R group
Arginine (Arg)	10.76	
Histidine (His)	7.59	
Tryptophan (Trp)	5.89	
Tyrosine (Tyr)	5.66	
Cysteine (Cys)	5.07	$-CH_2SH$

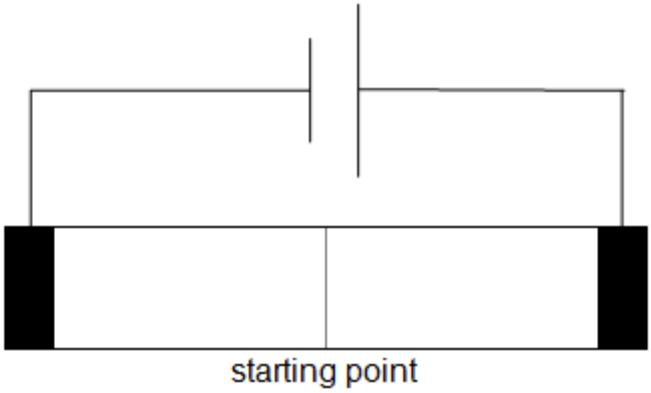
(i) Naturally occurring 19 amino acids, 18 have the S configuration at the α carbon. Cysteine is the only amino acid that have an R configuration. Explain this.

Hence, using Fischer projections, draw the zwitterions of Arg and Cys. [3]

(ii) Copy the setup below on your writing paper and indicate the relative positions of the five amino acids on the gel when the electrophoresis buffer is set at

- pH = 5.89
- pH = 7.59

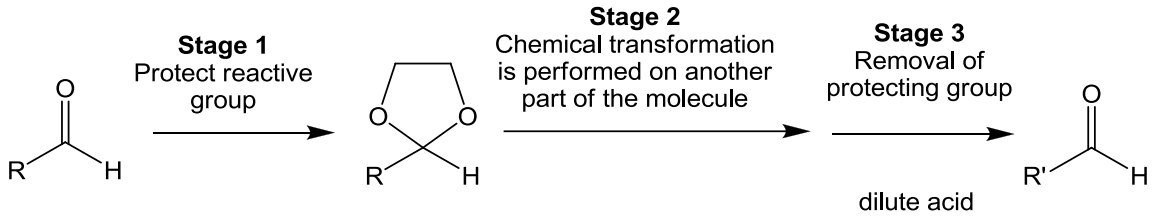
Use the abbreviations to represent the amino acids. For example, 'tyrosine' is to be represented by 'Tyr'.



[4]

(iii) Suggest a chemical use to identify the spots on the gel. [1]

(d) Acetals are frequently used to prevent unwanted side-reactions on carbonyl groups. The general strategy is described in the diagram below:



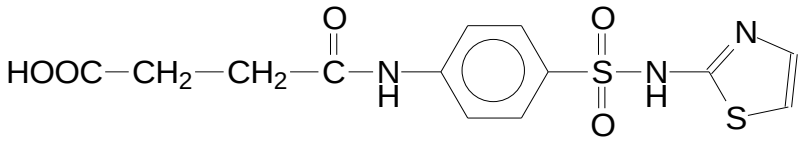
(i) State the type of reaction in stage 1. [1]

(ii) Suggest a mechanism for the reaction between propanone and ethane-1,2-diol, which proceeds with protonation of the carbonyl oxygen atom. [3]

(iii) Using the general acetal protecting group strategy, suggest a synthesis of $CH_3COCH_2CH_2CH_2OH$ from ethyl 4-oxopentanoate, $CH_3COCH_2CH_2COOCH_2CH_3$. [2]

[Total: 20m]

6 **(a)** Succinyl sulfathiazole is a prodrug of sulfathiazole, mainly used for treating intestinal infections. It is not readily absorbed by the gastrointestinal tract and hence it is classified as ultra-long acting drug.



succinyl sulfathiazole

Sulfathiazole mimics *p*-aminobenzoic acid which is a natural substrate of dihydropteroate synthetase and act as competitive enzyme inhibitors.

(i) Explain what you understand by the term *competitive* enzyme inhibitors. [1]

(ii) Suggest a reason why succinyl sulfathiazole is not readily absorbed by the gut wall. [1]

(iii) In the gastrointestinal tract, succinyl sulfathiazole undergoes enzymatic hydrolysis to release the active drug, sulfathiazole.

Sketch a diagram to show clearly how the structure of sulfathiazole interacts at the active site of dihydropteroate synthetase. [3]

(b) The effect of an inhibitor on the rate of reaction catalyzed by an enzyme can be studied.
In a typical series of experiments, the rate of the enzyme-catalyzed reaction is measured with respect to different substrate concentrations in the absence of the inhibitor studied, then and again with the presence of the inhibitor.

The kinetics of an enzyme catalysed reaction can be described by the Michaelis-Menten equation:

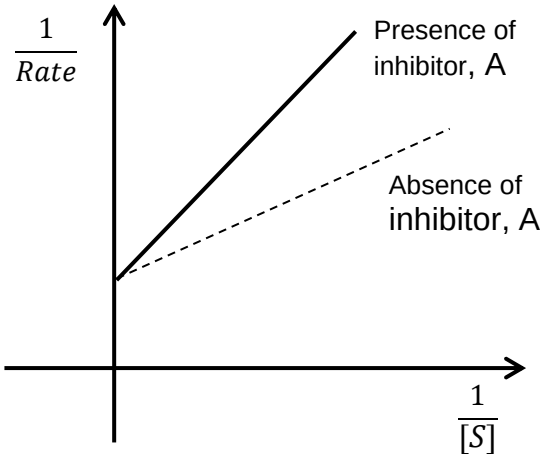
$$Rate = Rate_{max}\left(\frac{[S]}{[S] + K_M}\right)$$

$Rate_{max}$ is the maximum rate of reaction
[S] is the substrate concentration
K_M is a constant.

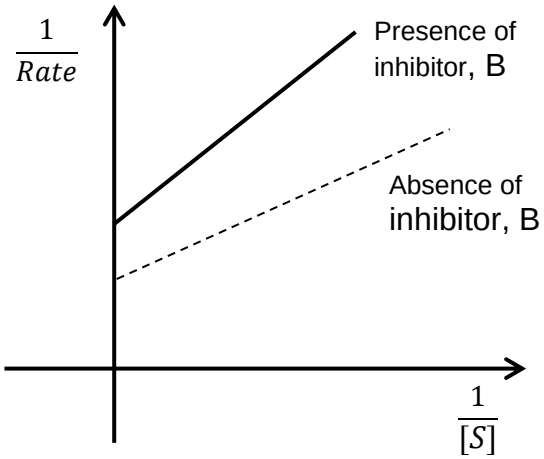
(i) Show that K_M represents the concentration of substrate at which the rate of the reaction is half its maximum. [2]

(ii) Express the Michaelis-Menten equation in a linear form relating $\frac{1}{Rate}$ to $\frac{1}{[S]}$. [1]

(iii) The following shows 2 graphs obtained from such experiments.



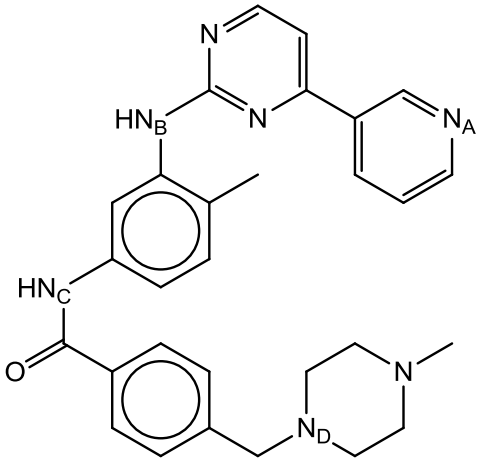
Graph A



Graph B

Identify which graph corresponds to the study of the kinetics of a competitive inhibitor. Explain your answer. [2]

(c) Imatinib is another benzene-containing drug that is used to treat certain cancers.



Imatinib

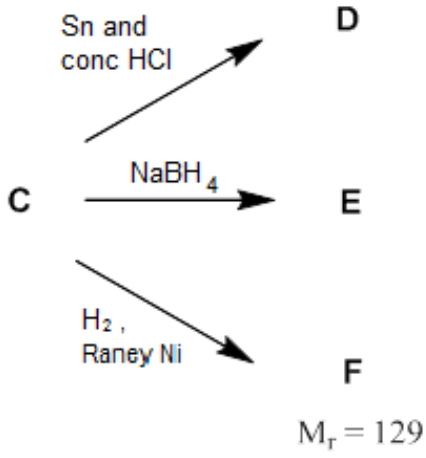
Arrange the basicity of the four nitrogen atoms labeled from N_A to N_D, in order of increasing basicity, and briefly explain your reasoning. [4]

(d) A neutral compound **C** contains the elements C, H, N and O only. The proton NMR spectrum of **C** is given below.

δ / ppm	Relative intensity
8.1	2
8.4	2
10.2	1

Addition of D_2O has no effect on the spectrum.

C reacts with different reducing agents as shown below.



$M_r = 129$

Both **D** and **F** dissolve in dilute acid.
Both **E** and **F** react with Na, but neither reacts with NaOH.
Both **C** and **D** react with Tollen's reagent to give a silver mirror.

Deduce the structures of **C** - **F**, showing your reasoning. [6]

[Total: 20m]