RAFFLES INSTITUTION
2017 YEAR 6 PRELIMINARY EXAMINATION

Higher 3

PHARMACEUTICAL CHEMISTRY 9812/01

Paper 1

21 September 2017
2 hours 30 minutes

Additional Materials: Answer Paper
Data Booklet

READ THESE INSTRUCTIONS FIRST

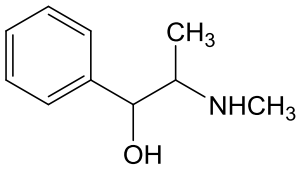
Write your name, class and index number on the Cover Page and writing paper.
Write in dark blue or black pen on both sides of the writing paper.
You may use a soft pencil for any diagrams or graphs.
Do not use staples, paper clips, highlighters, glue or correction fluid.

Answer any **five** questions.
Begin each question on a fresh sheet of paper.
At the end of the examination, fasten all your work securely together, with the cover page on top.

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 document consists of **20** printed pages.

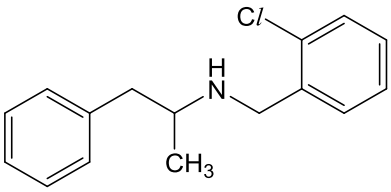
1 (a) Pseudoephedrine, a common decongestant, is a stimulant belonging to the amphetamine class of drugs.



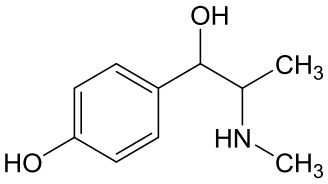
pseudoephedrine

(i) Describe one mechanism by which amphetamines act as stimulants. [2]

(ii) Clobenzorex and oxilofrine are two other compounds which belong to the amphetamine class.



clobenzorex



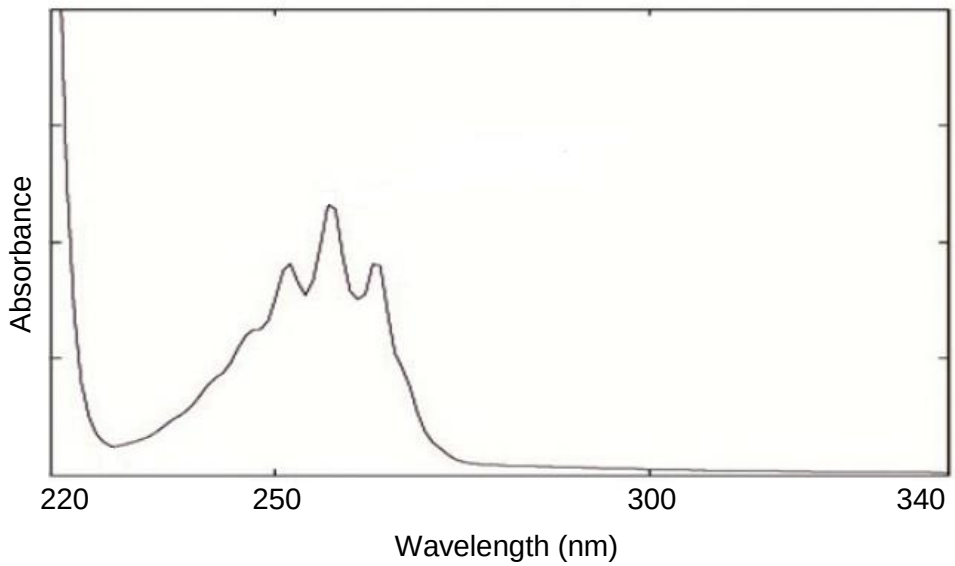
oxilofrine

Identify the most likely part(s) of the amphetamine class of drugs which is responsible for their stimulant effects. [1]

(iii) Nicotine is another stimulant drug which is highly addictive.

Explain why withdrawal symptoms such as anxiety and tension occur if nicotine is suddenly withdrawn from a regular user. [2]

(b) The UV absorption spectrum of pseudoephedrine is shown below.



(i) Explain why pseudoephedrine shows more than one absorption peak in the UV region. [1]

(ii) Actifed®, a combination medication used to relieve cold and allergy symptoms, contains pseudoephedrine and triprolidine as its active ingredients.

One Actifed® tablet was dissolved and the sample solution gave absorbance values of 0.146 and 0.143 at 245 nm and 251 nm respectively.

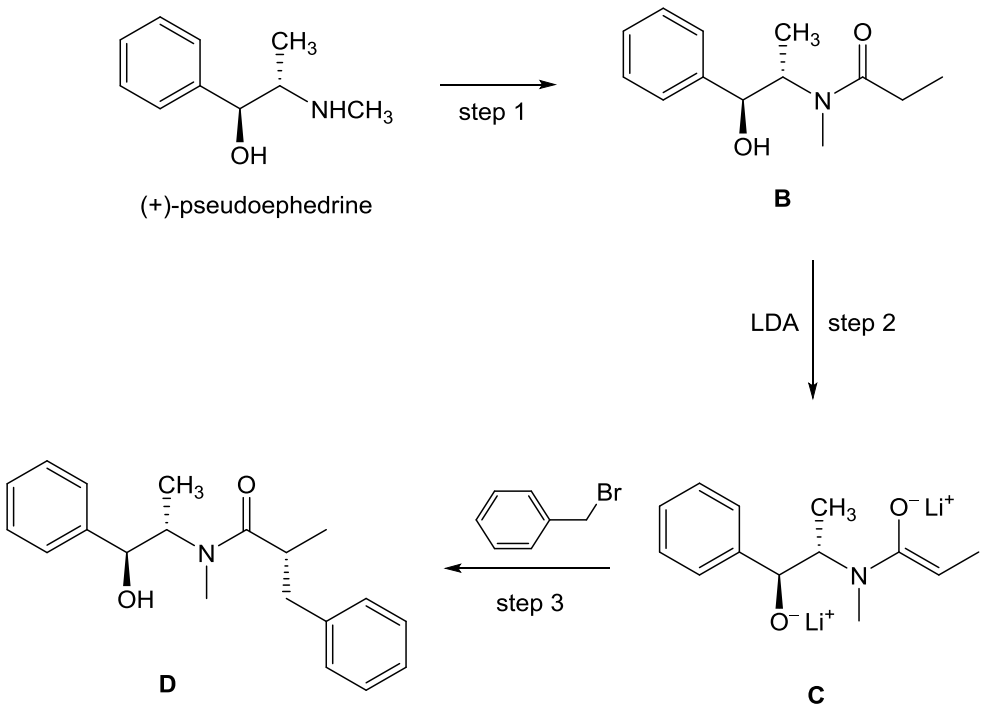
The molar extinction coefficient (ε) values at 245 nm and 251 nm for pseudoephedrine and triprolidine in a 1.0 cm cell are given below. Calculate the concentration of pseudoephedrine in the sample solution.

compound	**wavelength / nm**	**ε / dm^3 mol^{-1} cm^{-1}**
pseudoephedrine	245	129
	251	185
triprolidine	245	13600
	251	11100

[2]

(c) Due to its low cost, pseudoephedrine is often used as a starting material in asymmetric chemical synthesis.

In the reaction scheme below, (+)-pseudoephedrine acts as a chiral auxiliary, in a reaction which incorporates an alkyl group stereoselectively.



(+)-pseudoephedrine

B

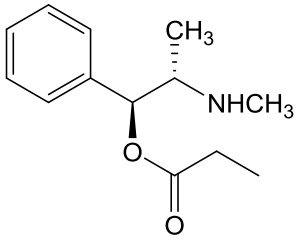
D

C

(i) Copy the structure of (+)-pseudoephedrine onto your writing paper, and assign the R/S configuration to all the chiral centres present. [1]

(ii) Suggest a suitable anhydride reagent to be used in step 1. [1]

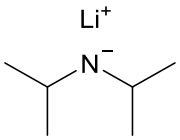
(iii) Compound **A** is a minor product of step 1.



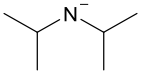
A

In the presence of a neutral or basic medium, compound **A** undergoes an intramolecular acyl substitution to form **B**. Describe the mechanism for the reaction. [2]

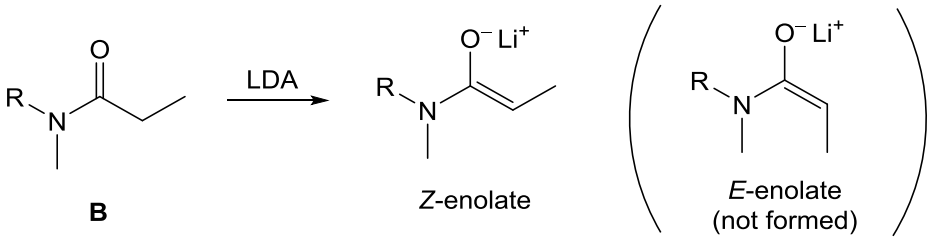
(iv) Lithium diisopropylamide (LDA) is a non-nucleophilic strong base. It has the structure below.



LDA

Using $\mathbf{B:}^{\ominus}$ to represent the base,  , propose a mechanism for the conversion of compound **B** to **D** via steps 2 and 3. You may ignore the stereochemistry of the product formed. [2]

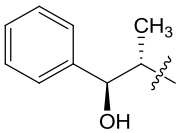
(v) Step 2 occurs via a 6-membered chair conformation transition state involving a 1:1 adduct between amide **B** and LDA. This forms compound **C** which contains an enolate functional group. Although the enolate can exhibit geometric isomerism, it is found that only the *Z*-enolate was formed.



B

Z-enolate

E-enolate
(not formed)

where R– represents 

Draw the 6-membered chair conformation transition state between amide **B** and LDA which leads to the formation of the *E*-enolate, and explain why the *E*-enolate is not formed. [2]

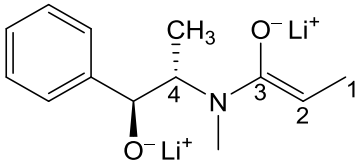
(vi) In step 3, compound **C** attacks the benzyl bromide molecule preferentially on one face of the enolate, to give **D** with 94% diastereomeric excess.

Calculate the value of the ratio

$$\frac{\text{[major diastereomeric product]}}{\text{[minor diastereomeric product]}}$$

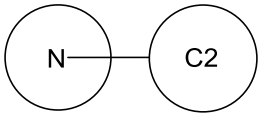
[1]

(vii) Draw a Newman projection of compound **C** when viewed through the C2=C3 and N–C4 bonds.



C

A part of the Newman projection from C2 to N is given below. Copy the diagram and complete the Newman projection of compound **C**.

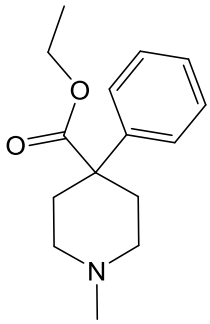


Considering that step 3 of the reaction is stereoselective, show the most stable comformation of compound **C** expected. Briefly justify your answer.

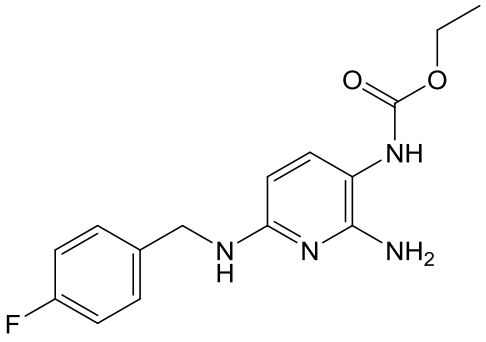
[3]

[Total: 20]

2 Meperidine is a narcotic analgesic of the phenylpiperidine class. Flupirtine is a non-narcotic and non-steroidal analgesic of the aminopyridine class.

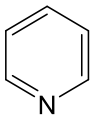


meperidine

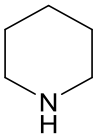


flupirtine

(a) The two drugs contain each of the following ring systems.



pyridine



piperidine

Explain why pyridine is basic but much less basic than piperidine. [2]

(b) **(i)** Describe how meperidine differ from non-narcotic analgesics in the way they function as analgesics. [2]

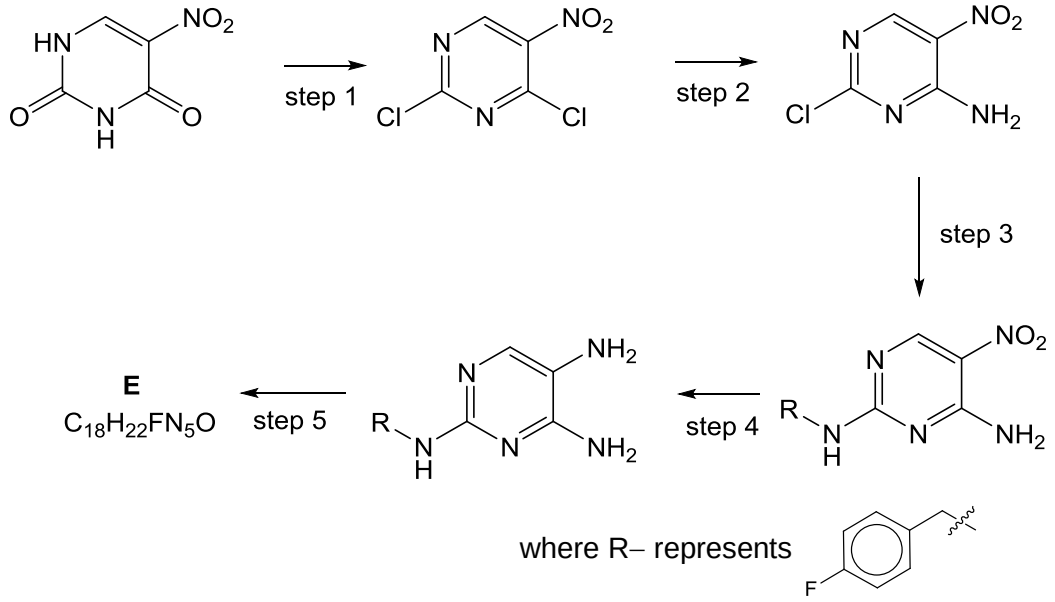
(ii) State **one** advantage and **one** disadvantage of narcotic and non-narcotic analgesics. [2]

(c) Flupirtine functions as a potassium ion channel opener of the $GABA_A$ receptor. Its unique mode of action opens new possibilities in designing a different class of analgesics.

(i) Explain the meaning of the term *receptor agonist* in terms of how flupirtine functions as an ion channel opener. [2]

(ii) Consider the structure of flupirtine and suggest one type of binding site at the $GABA_A$ receptors. [1]

(d) Flupirtine analogues using pyrimidine derivatives were synthesised and tested for pharmaceutical activity. One of the analogues, compound **E**, was synthesised in the following reaction scheme.



The IR spectrum of **E** shows a sharp absorption band at 1684 cm^{-1}.

The ^1H NMR spectrum of **E** is shown in the table below. The solvent used was deuterated dimethyl sulfoxide, $(CD_3)_2SO$, containing a small amount of TMS.

δ (in ppm)	splitting	number of protons
1.10	t	4
1.55	m	4
2.15	m	1
2.40	d	2
4.53	d	2
7.12 – 7.48	m	4
8.09	s	1
8.45	s	2
8.53	t	1
12.40	s	1

s: singlet; d: doublet; t: triplet; m: multiplet

(i) Suggest reagents for steps 3 and 4. [2]

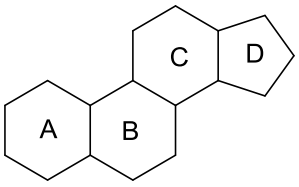
(ii) Explain the use of the deuterated solvent and TMS in ^1H NMR spectroscopy. [2]

(iii) Using the spectral data and the information provided in the reaction scheme, deduce the structure of **E**. Explain your reasoning fully. [6]

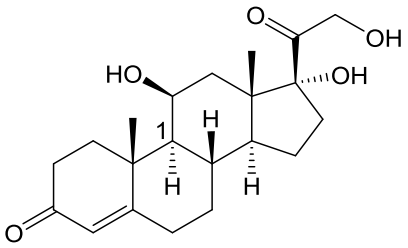
(iv) Use your structure of **E** in **(d)(iii)** to suggest the reagent used in step 5. [1]

[Total: 20]

3 Glucocorticoids are a class of steroid hormones produced in the adrenal cortex of vertebrates. Synthetic and semi-synthetic glucocorticoid drugs are widely used in medicine as anti-inflammatory agents. Cortisol is one example of a glucocorticoid.



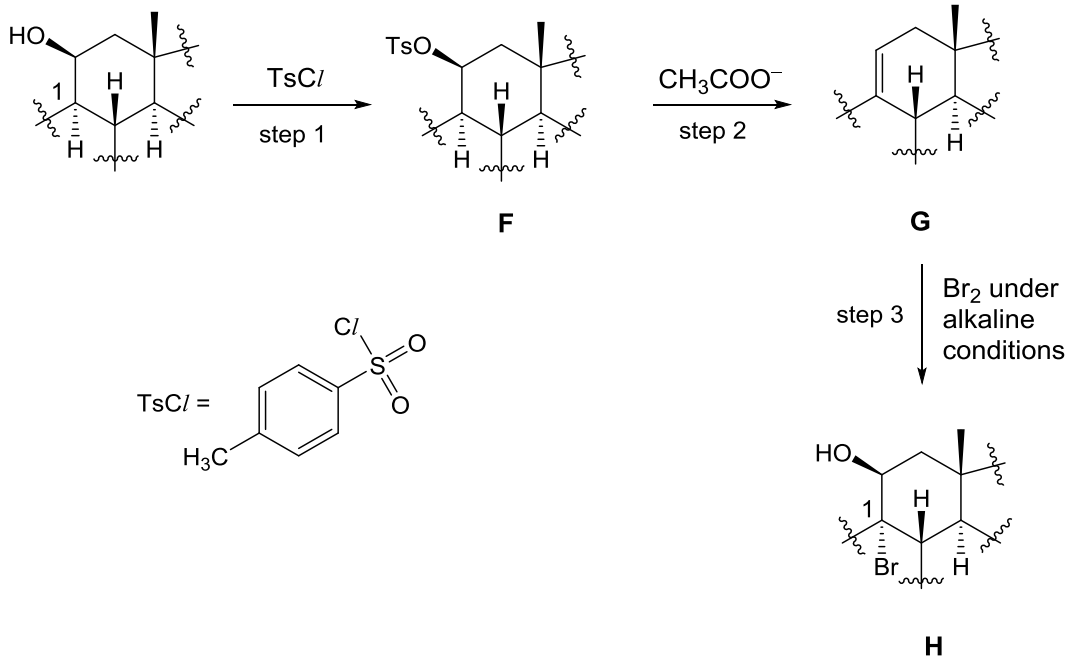
steroidal ring system



cortisol

(a) Extensive synthetic effort has been made to optimise anti-inflammatory activity while minimising undesirable side effects. One successful modification made to cortisol was to introduce a halogen atom at C-1 as indicated. Halogenation was achieved via the following reaction.

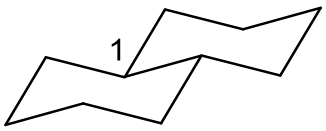
Note: only ring **C** of the steroidal ring system is shown.



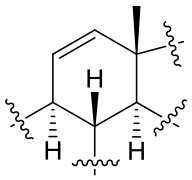
(i) What is the purpose of adding *p*-toluenesulfonyl chloride (TsC*l*) in step 1? [1]

(ii) Outline the E2 elimination mechanism in step 2 to form compound **G** by using the chair conformations for rings **B** and **C** of cortisol's steroidal ring system.

Copy the diagram below and complete the chair conformations for compound **F**, showing clearly the stereochemistry of all the chiral centres in the structure. [3]



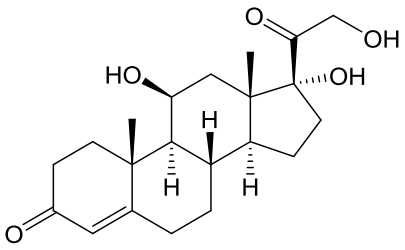
(iii) Suggest a reason why **G** is the major product in step 2 instead of **G′**. [1]



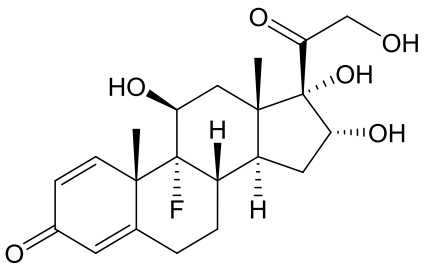
G′

(iv) By considering the entire steroidal ring system of **G**, explain why **H** was formed as the only product in step 3. Hence, outline the mechanism in step 3, showing clearly the stereochemistry involved. [3]

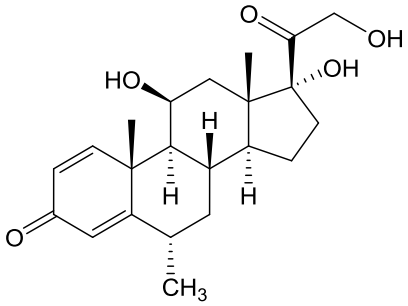
(b) Triamcinolone and methylprednisolone are synthetic analogues of cortisol.



cortisol



triamcinolone



methylprednisolone

Reversed-phase HPLC was used to separate and analyse the presence of glucocorticoid drugs in blood plasma. The UV absorption of the eluate was measured at 254 nm. Under a certain set of conditions, the retention times for the three glucocorticoid drugs above are 2.7, 3.9 and 4.5 minutes.

(i) Describe the principles of reversed-phase HPLC. [2]

(ii) Cortisol was found to have the highest concentration in the blood plasma sample.

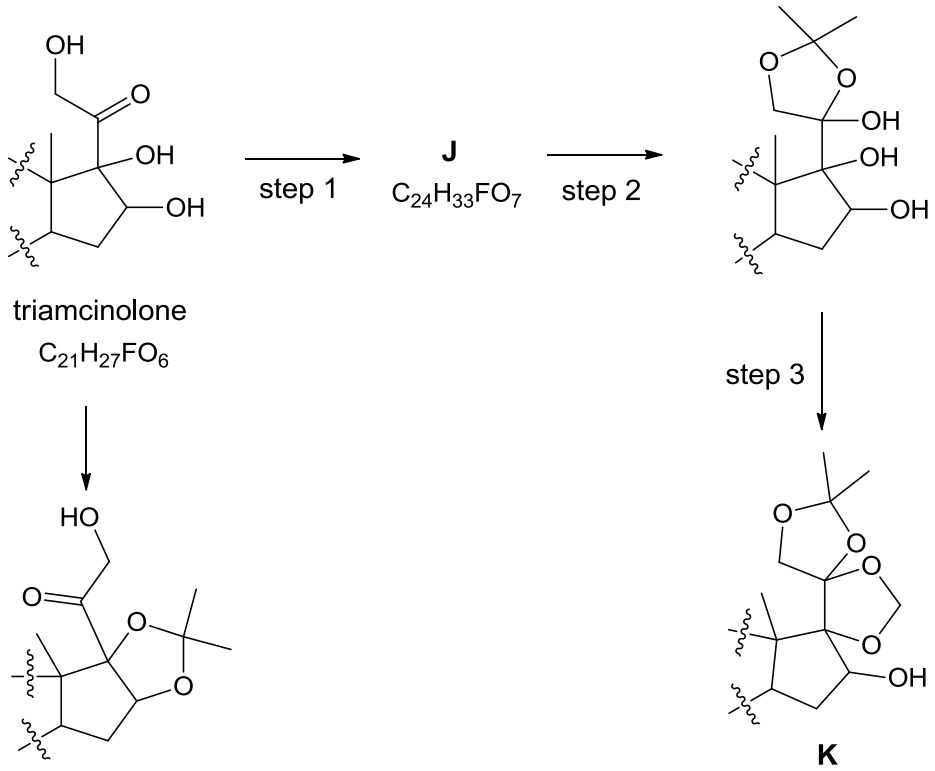
Draw a labelled sketch of the chromatogram of the blood plasma sample. Assume that all three compounds have similar ε values at 254 nm.

Briefly explain the order of elution of the three glucocorticoid drugs. [4]

(c) Triamcinolone acetonide is often applied directly onto the skin to treat inflammation. It exhibits a higher physiological response compared to triamcinolone.

Triamcinolone acetonide and compound **K** can be synthesised from triamcinolone.

Note: only ring **D** of the steroidal ring system is shown.



triamcinolone acetonide

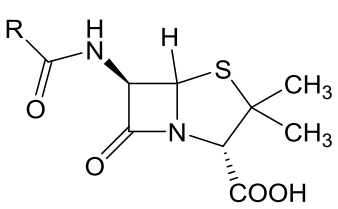
(i) Suggest the structure of **J**. [1]

(ii) Suggest the reagents for step 3. Hence outline the mechanism. [4]

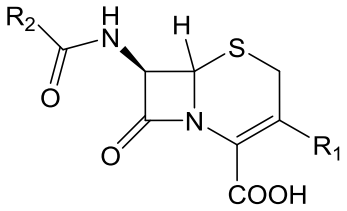
(iii) By considering the structure of triamcinolone acetonide, suggest why it exhibits a higher physiological response compared to triamcinolone. [1]

[Total: 20]

4 Penicillins and cephalosporins are classified as β-lactam antibiotics. They disrupt the synthesis of cell walls in some bacteria by binding to transpeptidases involved in the synthesis.



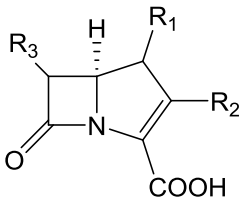
penicillin



cephalosporin

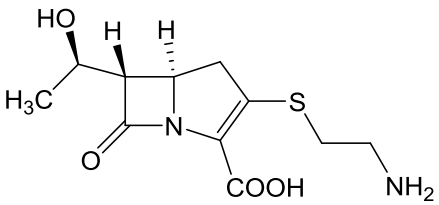
(a) State two other ways in which antibiotics work. [1]

A third group of β-lactam antibiotics, carbapenems, possesses the broadest spectrum of activity against bacteria and are often used as "antibiotics of last resort" when patients with infections are suspected of harbouring resistant bacteria.

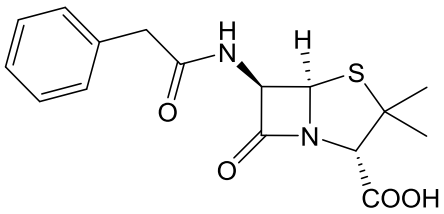


carbapenem

(b) The first carbapenem, thienamycin, was discovered in the search for antibiotics with increased activity against bacteria.



thienamycin



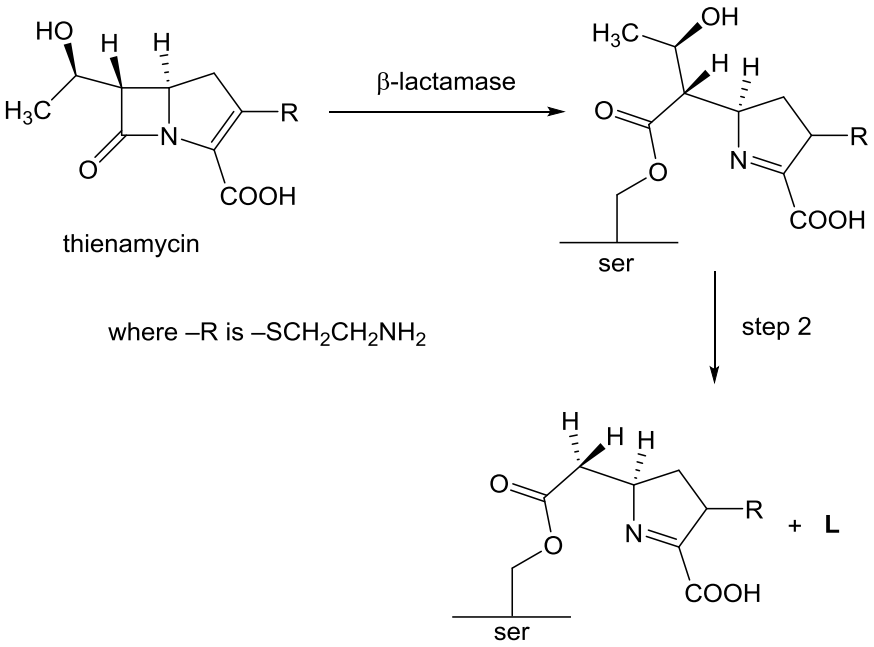
penicillin G

(i) Suggest two reasons why the β-lactam in thienamycin undergoes acid hydrolysis more readily than a tertiary amide such as *N*,*N*-dimethylethanamide, $CH_3CON(CH_3)_2$. [2]

(ii) Identify the stereochemistry of the C=C double bond in thienamycin as *E* or *Z*.[1]

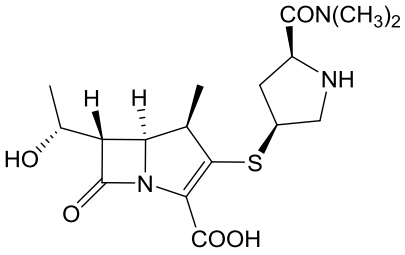
(iii) Suggest two features of the structure of thienamycin, compared to penicillin G, which could explain its improvement as an antibiotic. [2]

(iv) When thienamycin reacts with a serine residue at the active site of β-lactamase, the following transformation occurs. An organic by-product, **L**, is also produced.



Outline the mechanism for step 2 and hence, identify **L**. [3]

(c) Unfortunately, thienamycin was found to be unstable in aqueous solution, sensitive to mild base hydrolysis and highly reactive to nucleophiles. Meropenem is a more stable carbapenem that is currently in use.



meropenem

(i) Meropenem is provided as a sterile powder to be prepared in solution for intravenous infusion. Suggest one reason why meropenem is poorly absorbed through the gut wall. [1]

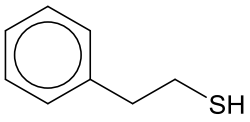
(ii) Based on your answer to **(c)(i)**, suggest two ways in which the meropenem molecule could be modified to enhance its bioavailability.

In your answer, you should:

- state the ways in which you would modify the structure
- explain how each modification would help its bioavailability
- state the reactions used to modify the structure of meropenem
- suggest how meropenem would be re-formed from the modified structure once inside the target cells.

[4]

(d) A key reagent in the synthesis of new carbapenems are thiols such as 2-phenylethanethiol.



2-phenylethanethiol

(i) Outline the synthesis of 2-phenylethanethiol from (2-bromoethyl)benzene. [1]

(ii) Describe how 2-phenylethanethiol may be converted to ethyl phenylethyl sulfide. [2]

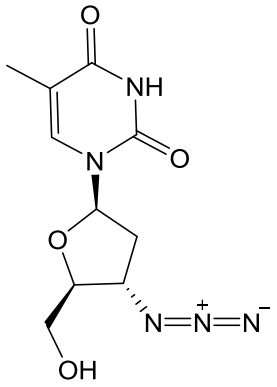
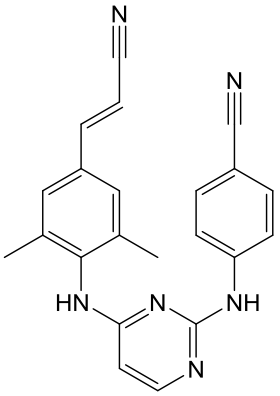
(iii) Suggest why thiolate ions are better nucleophiles than alkoxide ions, by considering the relative polarisability of the relevant lone pairs. [1]

(iv) Suggest a suitable reagent for the oxidation of ethyl phenylethyl sulfide, and draw the structures of the two products that you would expect. [2]

[Total: 20]

5 When HIV infects a cell, reverse transcriptase (RT) copies the viral single stranded RNA genome into a double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which then allows host cellular processes, such as transcription and translation, to reproduce the virus.

Azidothymidine, more commonly known as AZT, and rilpivirine are both RT inhibitors but they have different modes of action.

 AZT	 rilpivirine
AZT is similar in structure to the DNA nucleoside thymidine, which could be mistakenly incorporated by RT into viral DNA, stopping the replication process.	Rilpivirine binds at the non-nucleoside inhibitor-binding pocket (NNIBP) of RT, causing the RT active site to change its conformation.

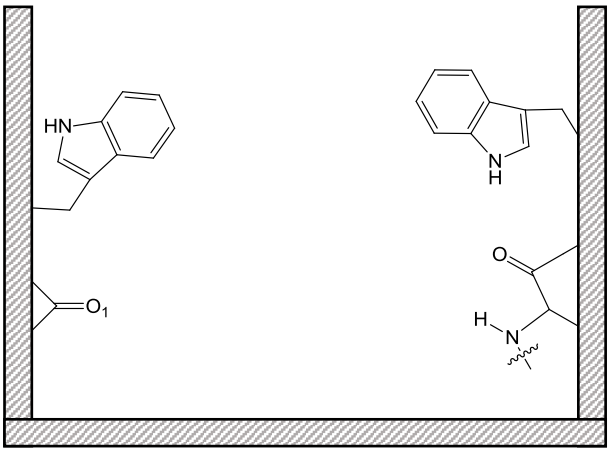
(a) **(i)** Which drug is an allosteric inhibitor? Explain your answer. [1]

(ii) Explain how the two drugs differ in their effects on the rate of reaction at different substrate concentrations. [1]

(iii) The diagram on the next page represents the NNIBP of RT. When rilpivirine binds to it, a complex is formed. Some information about the complex is given below.

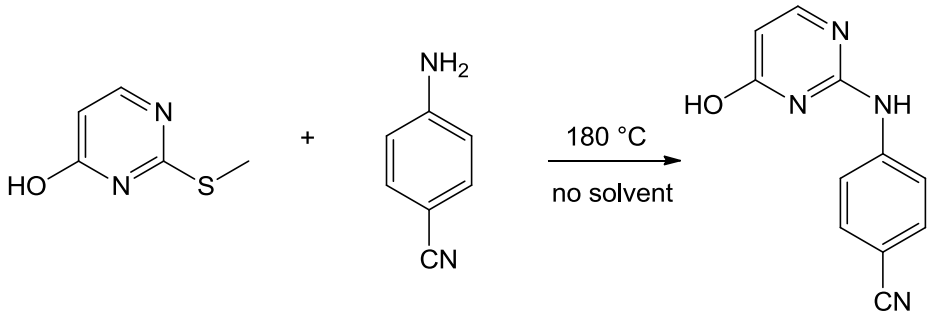
- The oxygen atom labelled O_1 in NNIBP forms a hydrogen bond to a water molecule. This water molecule is also hydrogen-bonded to rilpivirine.
- The right-side wall of NNIBP forms two hydrogen bonds with different groups on rilpivirine.
- One other type of interaction is formed between NNIBP and rilpivirine.

Copy the following diagram onto your writing paper and draw the rilpivirine-NNIBP complex. Label all relevant interactions in your diagram clearly. [3]



NNIBP of RT

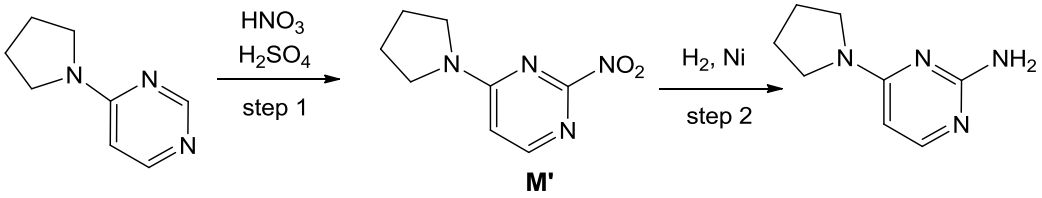
(b) The first step of one synthetic route for rilpivirine is shown below.



(i) Suggest a mechanism for this reaction. [2]

(ii) Suggest two reasons why the –OH group is not substituted in the above reaction. [2]

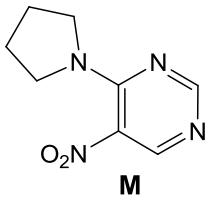
(c) To lower the cost of production, another synthetic route for rilpivirine was proposed. Its first two steps are shown below.



(i) State the types of reactions in steps 1 and 2. [1]

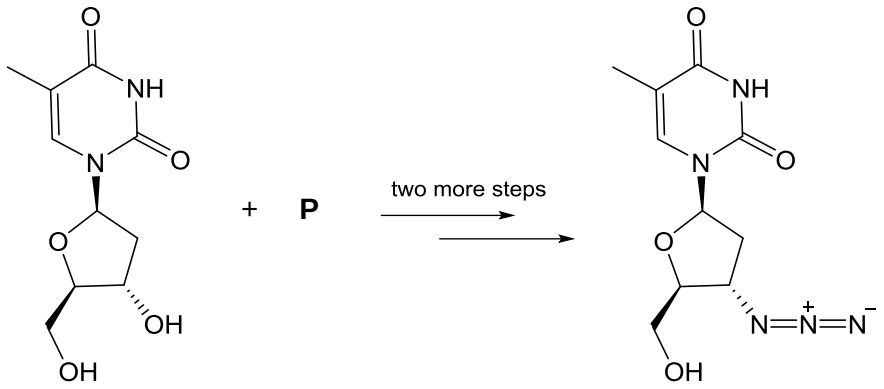
(ii) The proposed synthetic route was unsuccessful as **M′** is produced with very low yields. Using resonance structures of the intermediate formed in step 1, explain why **M′** is the minor product. [2]

(iii) Suggest a mechanism for step 1 to form the major product, **M**. [2]



M

(d) AZT can be synthesised from thymidine in three steps. In the first step, thymidine reacts with compound **P**.



thymidine AZT

(i) With the aid of suitable resonance structures, explain whether the nitrogen-containing ring in thymidine is aromatic. [2]

(ii) An elemental analysis of compound **P** found that it contains only C, H and two other elements.

The ^{1}H NMR spectrum of **P** shows the following signals: δ 3.9 ppm (3H, singlet), δ 7.0 ppm (2H, doublet), δ 8.1 ppm (2H, doublet).

The mass spectrum of **P** shows the following peaks in the region of its molecular ion peak at *m/e* 170.

m/e	relative abundance (%)
170	2.000
171	0.176
172	0.652

Interpret the data as fully as you can and suggest a structure for **P**.

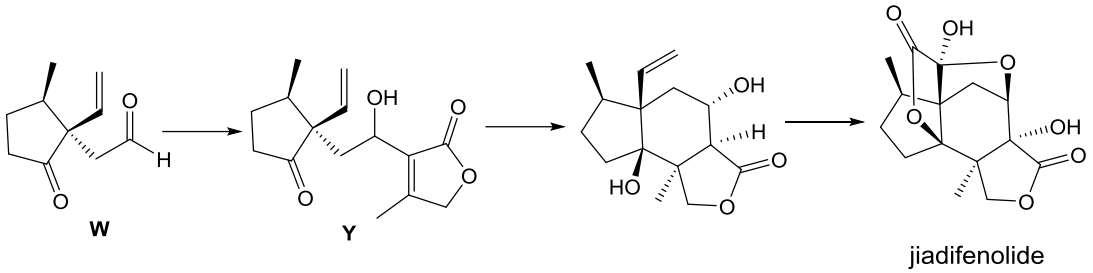
[4]

[Total: 20]

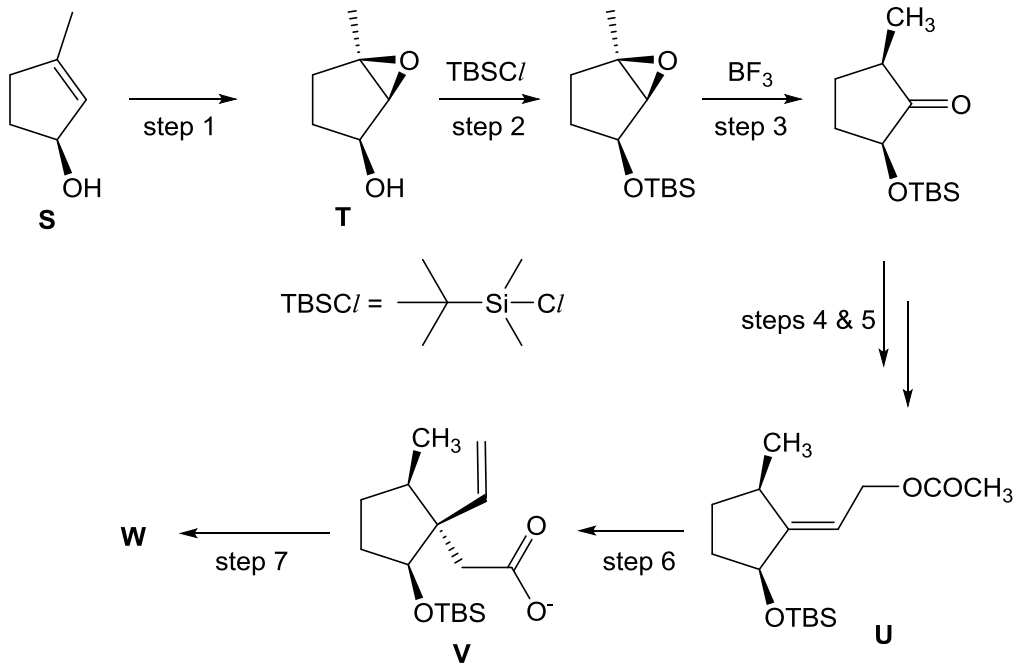
Turn over for question 6.

6 (a) Jiadifenolide is a complex sesquiterpenoid extracted in small quantities from the plant *Illicium jiadifengpi*, a species of star anise. It has powerful neurotrophic properties and is thus a valuable lead for the potential therapeutic treatment of neurodegenerative diseases such as Alzheimer's disease.

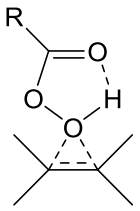
A total synthesis approach to jiadifenolide follows the scheme below:



The precursor compound **W** is synthesised via the following synthesis route:



(i) In step 1 of the synthesis, a peroxyacid with the formula R(CO)OOH was used as the reagent. The reaction proceeds via a concerted mechanism through a transition state with a structure similar to the following:

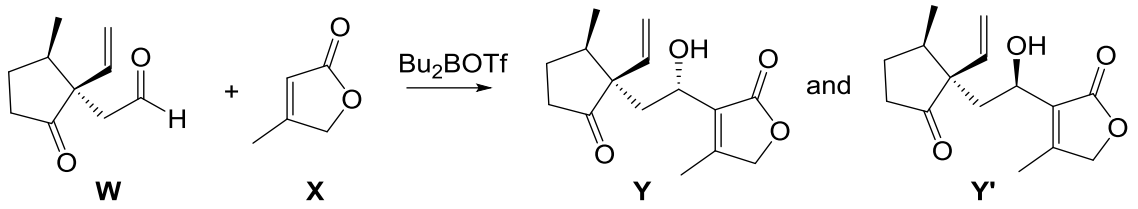


Taking into consideration the relative stereochemistry of the epoxide and hydroxy groups in **T**, propose the mechanism for step 1. [3]

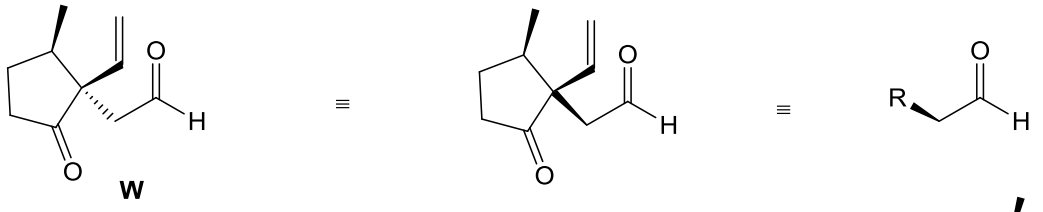
(ii) In step 3, BF_3 functions as a Lewis acid, allowing a rearrangement reaction to take place. Identify the intermediate formed and propose the mechanism for this reaction, accounting for the stereochemical outcome. [3]

(iii) Step 6 of the reaction is carried out under basic conditions. Given that the α-hydrogen of a C=O group is acidic, propose the mechanism for rearrangement in step 6, accounting for the stereochemical outcome. [3]

Compound **W** is used to prepare compound **Y** using the Bu_2BOTf reagent.



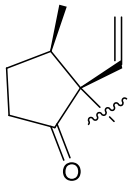
To visualise the stereochemistry around the aldehyde group in **W**, its structure can be represented in the following manner:



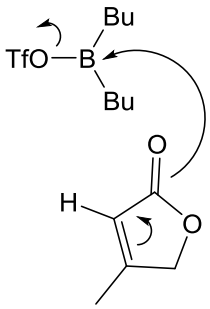
When the cyclopentane group is "on the plane", the aldehyde is "behind" the plane.

When the aldehyde group is "on the plane", the cyclopentane group is "in front" of the plane.

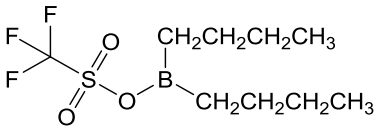
where R =



The mechanism for the reaction is initiated by Bu_2BOTf as shown below. The –OTf group gives a stable OTf^- anion, making it a good leaving group. The Bu_2B moiety is then readily coordinated by O atoms.



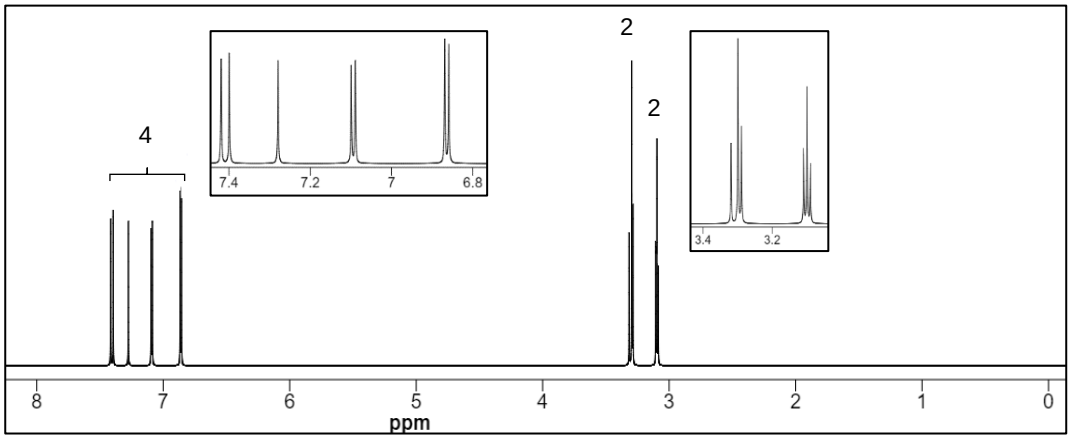
where Bu_2BOTf is



(iv) Using the above information and the suggested representation of **W**, outline the mechanism for the reaction between **W** and **X** and hence explain why isomer **Y** is the major product. [4]

(b) Compound **Z** is an isomer of serotonin, a neurotransmitter. **Z** contains the elements C, H, N, and O. **Z** reacts with aqueous bromine to give a mixture of different substitution products, but no addition product.

The ^{1}H NMR spectrum of **Z** in D_2O is shown below.

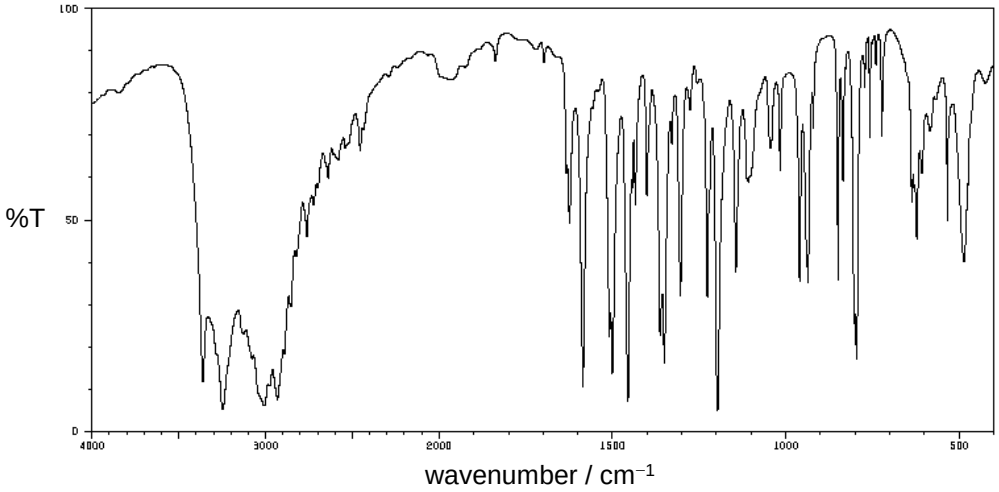


(peaks at δ 3.1–3.3 ppm and δ 6.8–7.4 ppm are magnified in inset)

Without D_2O, the following peaks can be observed:

- at δ ~6.0 ppm very broad with an integration of 3
- at δ ~8.0 ppm doublet with an integration of 1.

The IR spectrum of **Z** is shown below.



The mass spectrum of **Z** gave the following peaks with significant relative intensity.

m/z	Rel. intensity (%)
132	30
146	100
176	20
177	2.2

Using the information given, deduce the molecular formula and structure of **Z**. Show your reasoning fully. [7]

[Total: 20]

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