CATHOLIC JUNIOR COLLEGE
JC2 PRELIMINARY EXAMINATIONS
Higher 3

PHARMACEUTICAL CHEMISTRY

9812/01

Paper 1

Wednesday 31 August 2016
2 hours 30 minutes

Additional Materials: Answer Paper
Data Booklet

READ THESE INSTRUCTIONS FIRST

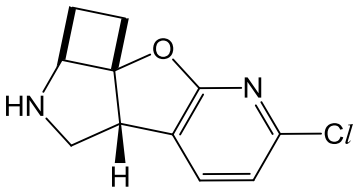
Write your name and class on all the work you hand in.
Write in dark blue or black pen on both sides of the paper.
You may use a soft pencil for any diagrams or graphs.
Do not use staples, paper clips, highlighters, glue or correction fluid.

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.
The use of an approved scientific calculator is expected, where appropriate.
You are reminded of the need for good English and clear presentation in your answers.

This document consists of **16** printed pages.

1 Phantasmidine is a compound isolated from the skin of the Ecuadorian phantasmal poison frog. It possesses a unique condensed tetracyclic structure incorporating pyridine, furan, pyrrolidine, and cyclobutane rings. It is a non-*narcotic analgesic* due to its interaction with acetylcholine nicotinic receptors as an *agonis*t.



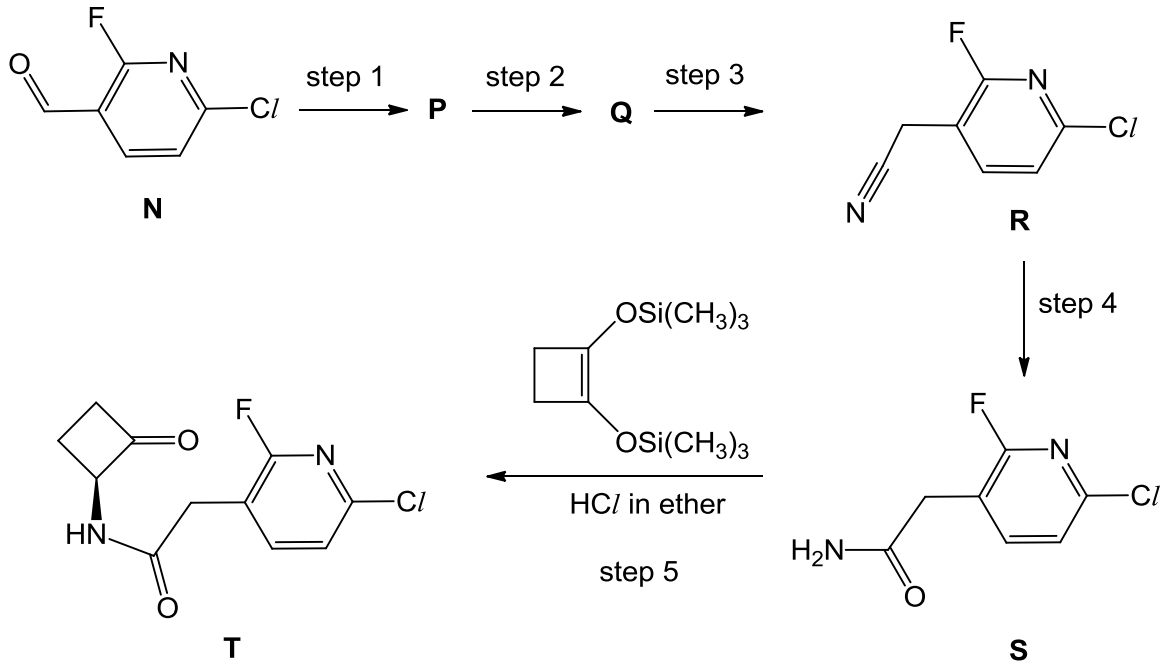
phantasmidine

(a) **(i)** Explain the meaning of the terms *analgesic* and *agonist*.

(ii) Outline the ways in which *narcotic* and *non-narcotic* analgesics work, and state one advantage and one disadvantage of each analgesic.

[5]

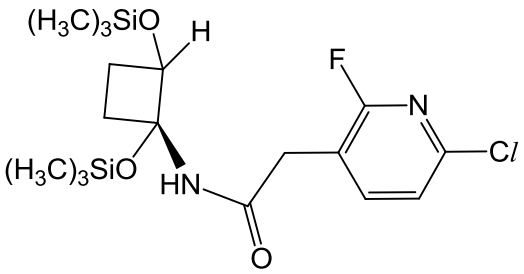
As phantasmidine has only been isolated in very small amounts so far, a method was developed to synthesize phantasmidine in the laboratory so that the compound can be made readily available for further biological studies. The first part of the synthesis to give intermediate compound **T** is shown below.



(b) **(i)** Suggest structures for the intermediates **P** and **Q**, and suggest reagents and conditions for the three steps 1–3.

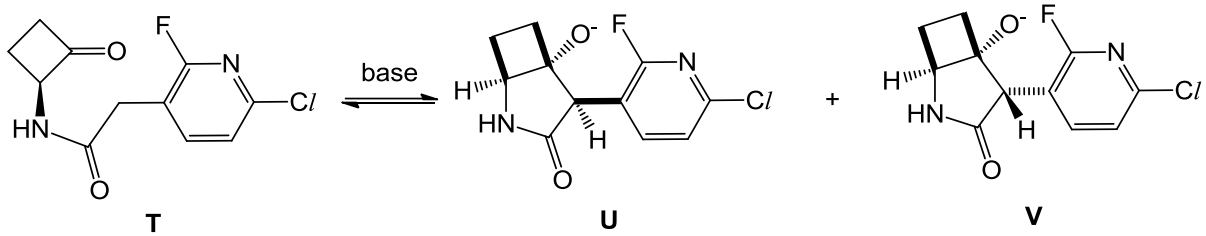
(ii) State the type of reaction in step 4.

(iii) Suggest a mechanism for step 5, given that it starts with the electrophilic attack of HC*l* on the alkene, followed by an addition-elimination mechanism involving the following intermediate:



[9]

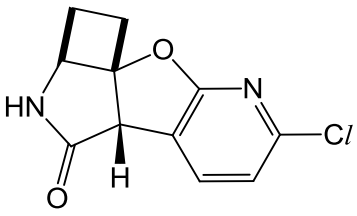
Upon treatment with base, compound **T** is deprotonated and cyclises to give two stereoisomers, **U** and **V**.



T **U** **V**

(c) **(i)** Suggest a mechanism for this reaction, showing the stereochemistry to explain how **U** and **V** are formed.

(ii) Of the two stereoisomers, only compound **V** can cyclise further to give compound **W**, which undergoes reduction to give phantasmidine.



W

Explain why only compound **V** is able to cyclise further.

(iii) Suggest a mechanism to show how **W** is formed from **V**.

(iv) In the synthesis process until the formation of **V**, the reaction conditions were either acidic or otherwise carefully controlled. Explain why this was necessary.

[6]

[Total: 20]

2 **(a)** The following are some processes occurring in a typical bacterial cell.

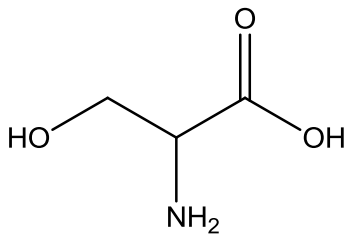
1. Enzyme-catalysed conversion of 4-aminobenzoic acid to folic acid
2. Transcription of DNA to nucleic acids (RNA)
3. Translation of RNA to proteins
4. Formation, polymerisation and cross-linking of peptides to construct cell wall

(i) With reference to the processes listed above or other features of a bacterial cell, outline 2 possible modes of action of anti-bacterials.

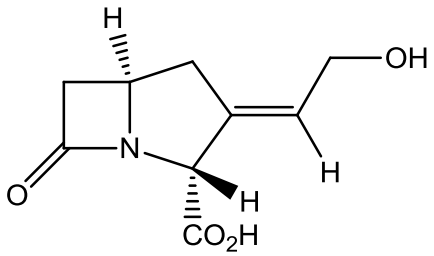
Some bacteria contain an enzyme, β-lactamase (or penicillinase), that they can secrete into the fluid around their cells. Hence, they are resistant to penicillin antibiotics.

(ii) Explain why overprescription of penicillin antibiotics (e.g., in animal feedstocks) can increase the problem of bacterial resistance to penicillins.

(iii) The active site of β-lactamase contains 2 serine side chains. Clavulanic acid, a very strong β-lactamase inhibitor, is sometimes administered together with a penicillin.



serine



clavulanic acid

Draw a labelled diagram to show interactions between clavulanic acid and β-lactamase, and explain how this can help to counter bacterial resistance to penicillins.

(iv) State the configuration of the C=C in clavulanic acid.

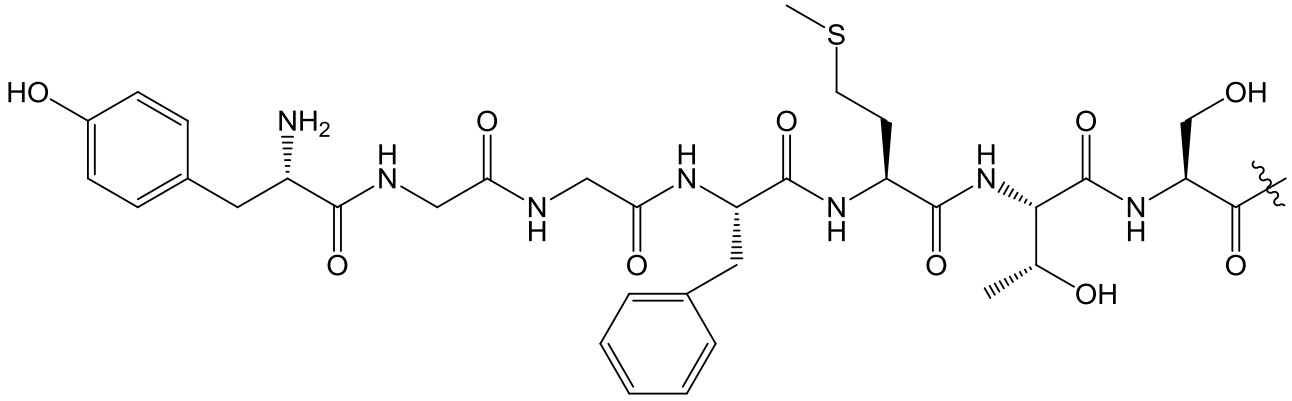
(v) Draw a diastereomer of clavulanic acid.

(vi) The pK_a value of clavulanic acid is 3.32. The pH of the stomach may be taken as 3.0. Explain the change in the equilibrium involved when clavulanic acid is absorbed in the stomach.

(vii) Calculate the relative proportions of the charged and uncharged forms of clavulanic acid present in the stomach.

[13]

(b) Enkephalins, or endorphins, are the natural ligands for opioid receptors in the brain. They are small peptides containing between 5 to 33 amino acid residues. α-endorphin contains 16 amino acid residues, and part of its structure is shown below.



(i) State the number of **different** hydrolysis products of the peptide fragment shown above.

The following table gives more information about some of the amino acids that make up α-endorphin.

compound name	abbreviation	R group	isoelectric point
glycine	Gly	-H	5.97
methionine	Met	$-CH_2CH_2SCH_3$	5.74
phenylalanine	Phe	$-CH_2C_6H_5$	5.48
tyrosine	Tyr	$-CH_2C_6H_4OH$	5.66

(ii) A mixture of the four amino acids in the table above was subjected to electrophoresis in a buffer at pH 5.50.

Draw a diagram of the electrophoretogram to show the direction and relative movement of each of the amino acids.

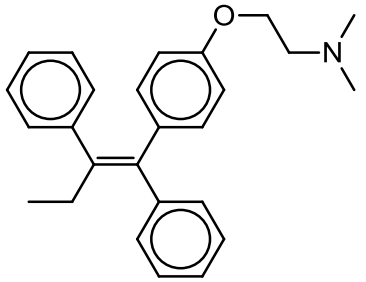
(iii) Explain how the appearance of the electrophoretogram would change if the electrolysis were carried out in a buffer at pH 10.

(iv) State two other uses of electrophoresis apart from separating amino acids.

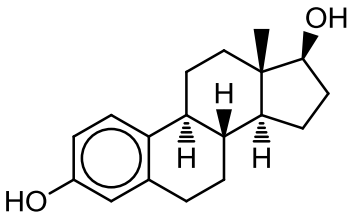
[7]

[Total: 20]

3 Tamoxifen is used for treating hormone-responsive breast cancer. It is the first chemopreventive agent for breast cancer in pre- and postmenopausal women. Tamoxifen acts as an inhibitor of estradiol binding to the estrogen receptor, and so prevent estrogen-stimulated growth of breast cancer cells.



Tamoxifen



Estradiol

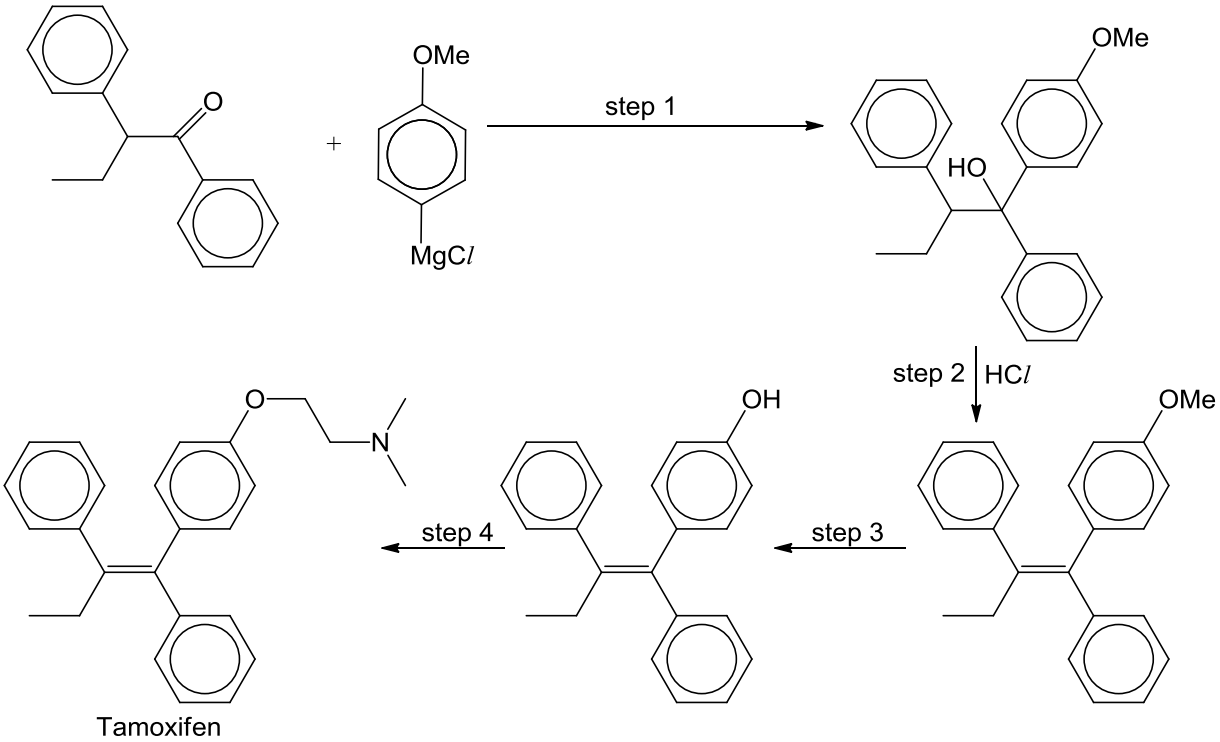
(a) **(i)** Compare and contrast the terms *competitive* and *non-competitive inhibitor*.

(ii) Based on its structure, explain whether tamoxifen is likely to be a competitive or non-competitive inhibitor of estrogen receptor.

(iii) Suggest two places on the tamoxifen molecule where it might bind to the estrogen receptor, stating in each case the type of interaction that would be involved.

[5]

(b) The following scheme outlines the synthesis of tamoxifen.



Tamoxifen

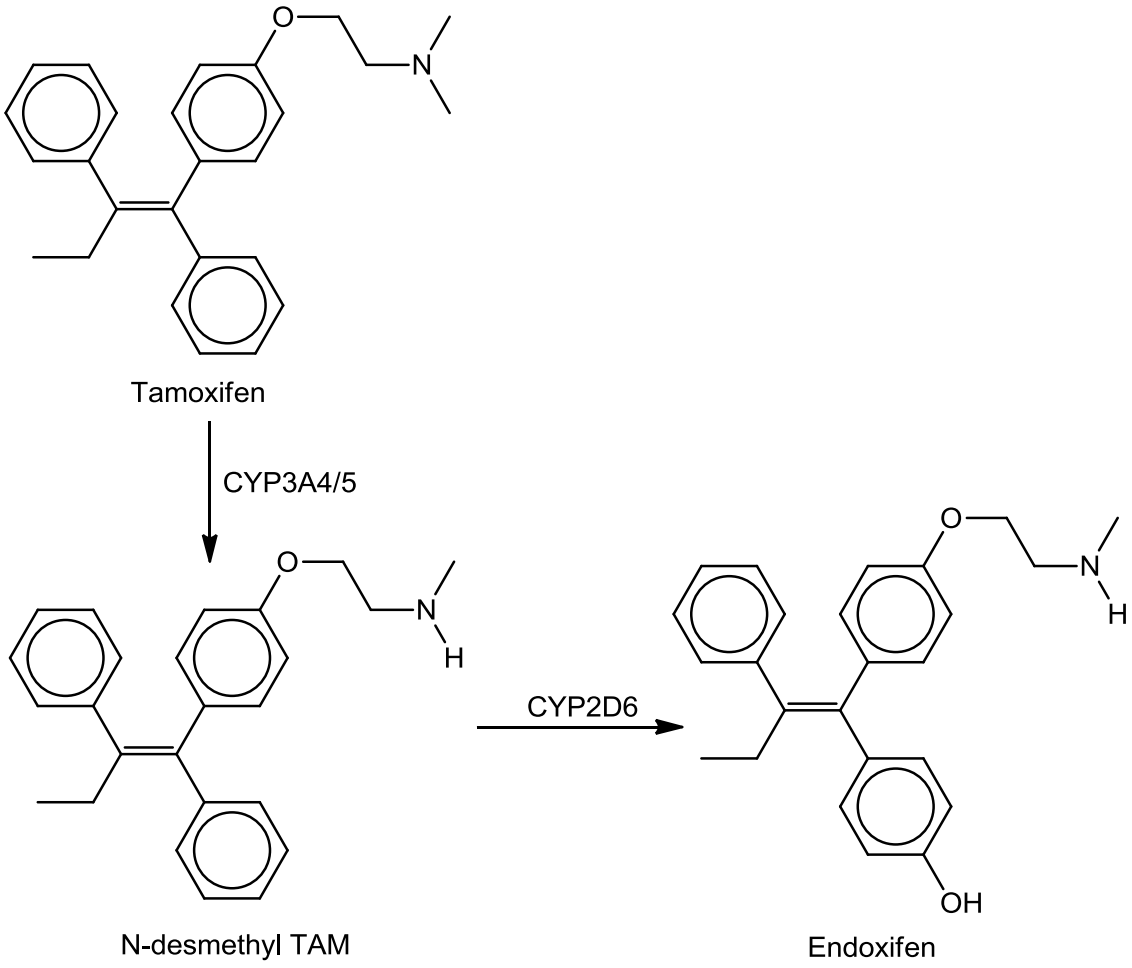
(i) What type of reaction is step 2? Suggest a mechanism for this reaction.

(ii) Give reasoning for your answer in **(b)(i)**.

(iii) Suggest reagents and conditions for step 4.

[5]

(c) Tamoxifen when taken by patients orally will be metabolized in the human liver by cytochrome enzymes via CYP3A4/5-mediated N-demethylation and CYP2D6-mediated hydroxylation to give metabolites such as N-desmethyl tamoxifen(TAM) and endoxifen as shown below.



Tamoxifen, N-desmethyl TAM and endoxifen are extracted from a human plasma sample. The sample was analysed by reverse-phase HPLC and the UV absorption of the eluate is measured at 250 nm.

(i) Explain why these compounds may all be detected using UV and state what happens in these molecules when UV radiation is absorbed.

(ii) Explain the principles underlying reverse-phase HPLC.

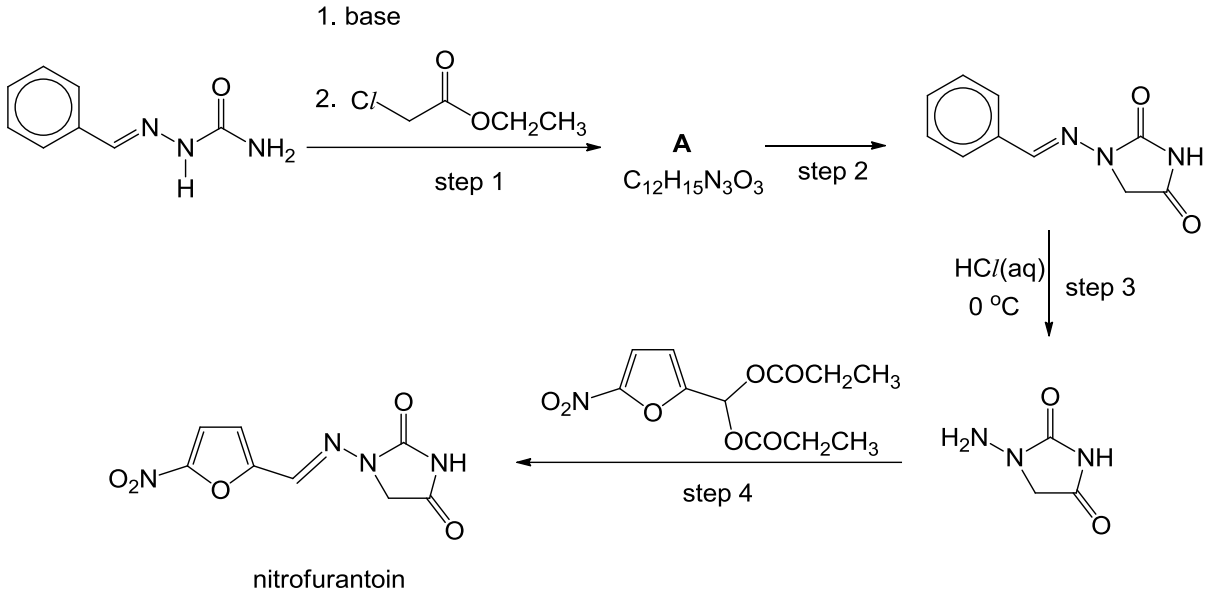
(iii) State the order of the elution of the peaks in the HPLC chromatogram. Explain your reasoning.

(iv) Suggest and explain how the relative amounts of each compounds in the human plasma sample can be accurately determined and state one assumption that is made.

[10]

[Total: 20]

4 **(a)** Nitrofurantoin is an antibiotic used for treating urinary tract infections. A synthesis of nitrofurantoin is presented below.



(i) Identify compound **A**.

(ii) The base in step 1 was used to deprotonate the starting compound. Identify the proton removed and explain briefly why this proton is the most acidic in this compound.

(iii) Hence, explain why compound **A** was the preferred product when ethyl chloroethanoate was added in step 1.

(iv) Explain why the lactam is not hydrolysed under the conditions used in step 3.

(v) Propose the mechanism for step 3.

(vi) State the type of reaction in step 4.

[9]

(b) In the synthesis of nitrofurantoin, the furan ring is substituted at the 2-position. With reference to the stability of the intermediate formed, explain why furan undergoes nitration at the 2-position and not the 3-position. [2]

(c) Compound **B**, $C_{11}H_8N_2O_5$, was previously used as a food preservative in Japan, but withdrawn from the market in 1974 when it was suspected to be carcinogenic. It bears some similarity in terms of structure to nitrofurantoin, although it has two furan rings which are substituted at the 2- and/or 5-position. Compound **B** also shows no reaction with cold NaOH(aq) or cold HC*l*(aq).

The IR spectrum of compound **B** has a sharp strong peak at 1660 cm^{-1}, and two medium-strength peaks in the region of 3500 cm^{-1}.

The ^1H NMR spectrum of **B** contains the following signals:

proton chemical shift value δ / ppm	**splitting**	**number of protons**
6.77	s	1
6.87	m	1
7.24	m	1
7.68	s	2
7.79	d	1
7.94	d	1
8.17	m	1

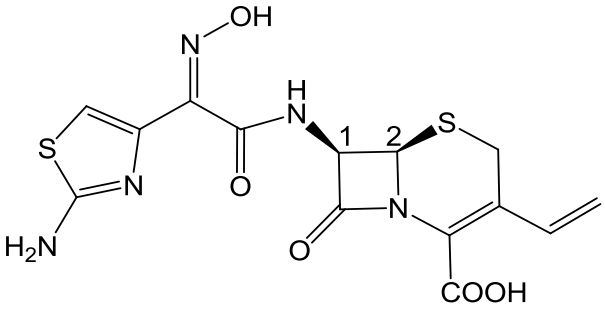
Only the signal at δ 7.68 ppm disappears on addition of D_2O.

Use the above information to deduce the structure of compound **B**.

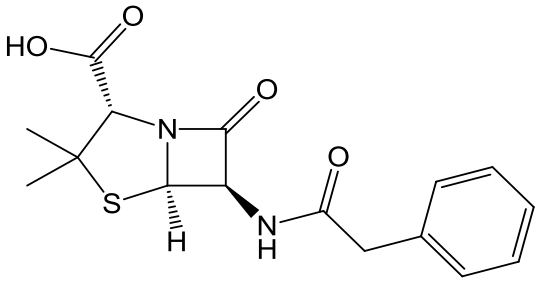
[9]

[Total: 20]

5 Cefdinir is a third generation β-lactam antibiotic for oral administration. It is used to reduce infection caused by Gram-positive and Gram-negative bacteria.



Cefdinir



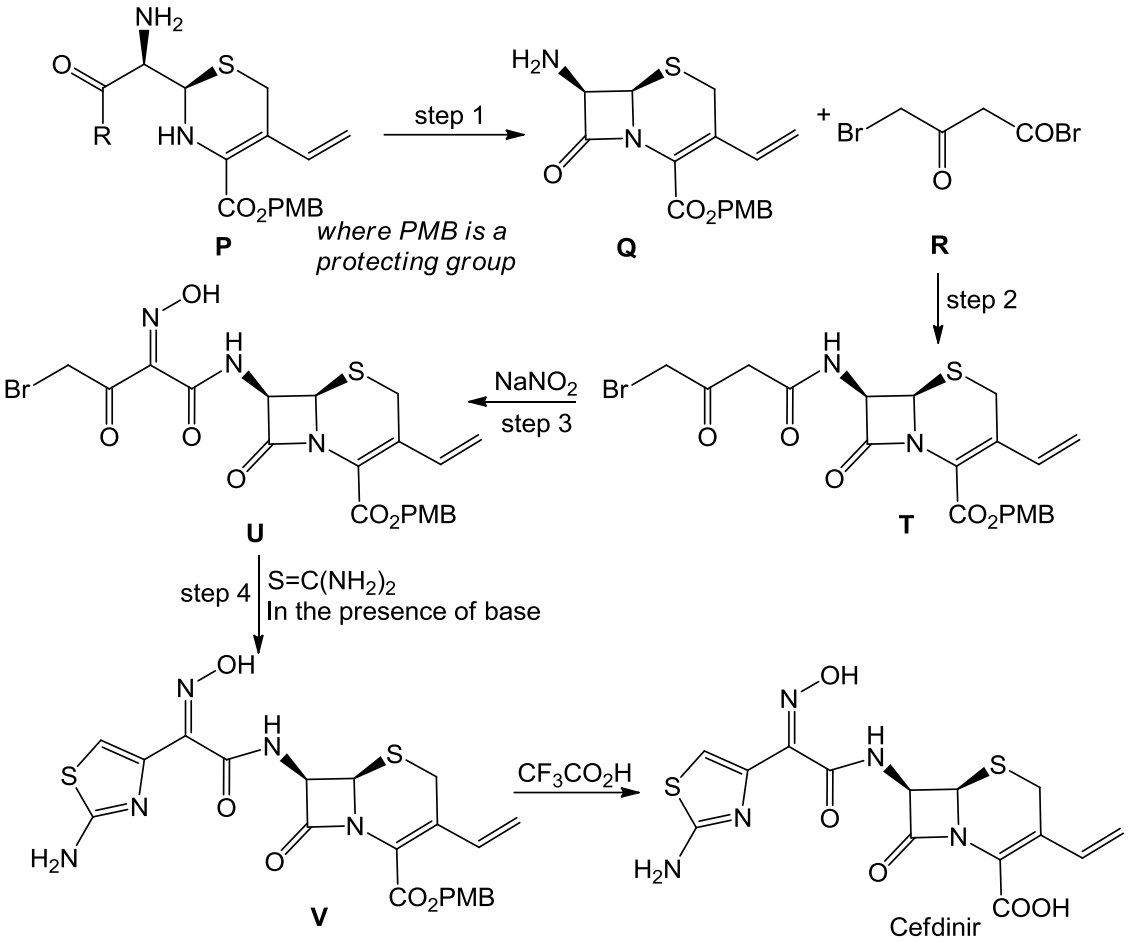
Pencillin G

(a) **(i)** Suggest why Cefdinir can be taken orally unlike penicillin G.

(ii) State the stereochemistry (R or S) at each of the carbon atoms 1 and 2 in Cefdinir.

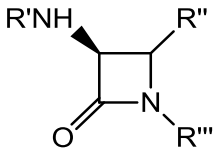
[3]

(b) The synthesis of Cefdinir from compound **P** is outlined below.



(i) Suggest the identity of the R group in compound **P**.

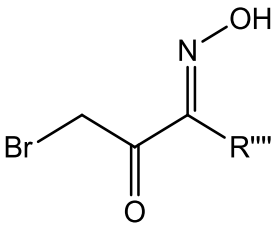
(ii) Suggest the products formed if Cefdinir is subjected to the following reagents and conditions, using the symbol **R'**, **R''** and **R'''** to represent part of the cefdinir molecule, as shown:



Cefdinir

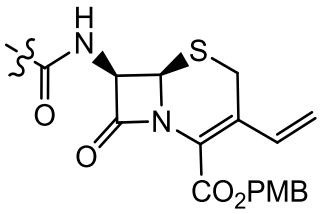
I NaOH(aq) and heat
II $LiAlH_4$ in dry ether

(iii) Suggest a mechanism for step 4, using the symbol **R''''** to represent part of compound **U**, as shown.



Compound **U**

where **R''''** =



[6]

(c) The characterisation of Cefidinir is done by analysis of its NMR, MS and IR spectra. The molecular formula of Cefidinir is $C_{14}H_{13}N_5O_5S_2$.

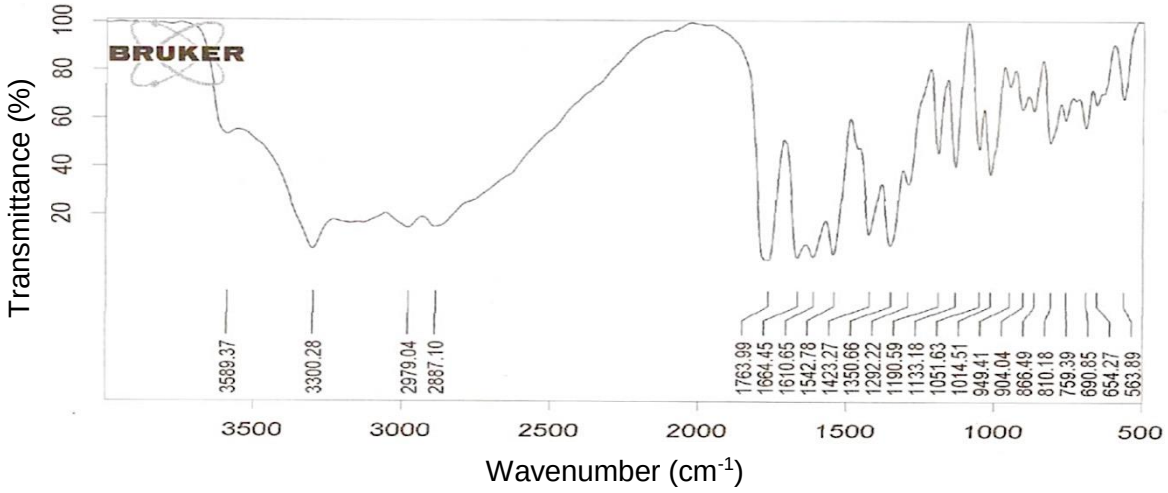
The ^1H NMR signals of Cefidinir after addition of D_2O are given below.

proton chemical shift value, δ/ ppm	splitting	number of protons
3.55, 3.83	m	2
5.19	d	1
5.79	m	1
5.31, 5.59	m	2
6.67	s	1
6.90	m	1

The peaks at 3.55 and 3.83 ppm correspond to one proton each, and so do the peaks at 5.31 and 5.59 ppm.

The mass spectrum of Cefidinir gives 4 major fragments of m/e of 128, 169, 227 and 395.

The IR spectrum of Cefdinir is as shown below.

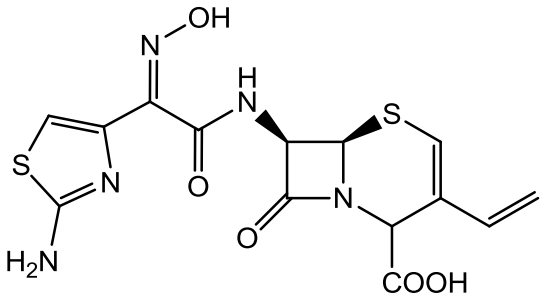


(i) Suggest why the NMR signals at 5.31 and 5.59 ppm that correspond to the vinyl (-CH=C$\underline{H_2}$ group) protons do not have a splitting pattern of triplet.

(ii) Account for any three signals in the IR spectrum of Cefdinir.

[3]

(d) Samples were taken from different batches of Cefdinir to be analysed and two impurities were found. One of the impurities obtained is as shown below.



Impurity I

(i) With reference to the NMR spectrum of Cefdinir given in **(b)**, state and explain the differences between the NMR spectra of Cefdinir and Impurity I.

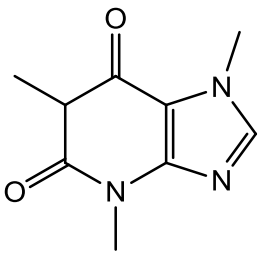
(ii) Deduce the structure of Impurity II given that:

- Mass spectrum has a protonated molecular ion peak of m/e 384.
- Mass spectrum shows major fragmentation of m/e of 227 and 157.
- One of the peaks present in the mass spectrum involved the breaking of 2 covalent bonds in the β–lactam ring.
- With comparison to the NMR spectra of Cefdinir
  1. signals at 5.31ppm, 5.59ppm and 6.90ppm are absent in the NMR of impurity II
  2. a new singlet at 2.00ppm corresponding to 3 protons has appeared

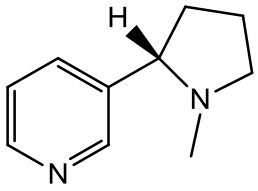
[8]

[Total: 20]

6 Caffeine and nicotine are stimulants with similar physiological effects, but different pharmaceutical mechanisms. The structures of caffeine and nicotine are shown below.



caffeine



nicotine

(a) **(i)** Outline the physiological effects of stimulants such as caffeine.

(ii) The pK_b values of nicotine are 6.1 and 11.0.

Explain why there is such a big difference between the 2 values, and hence suggest the structure of nicotine at physiological pH 7.4.

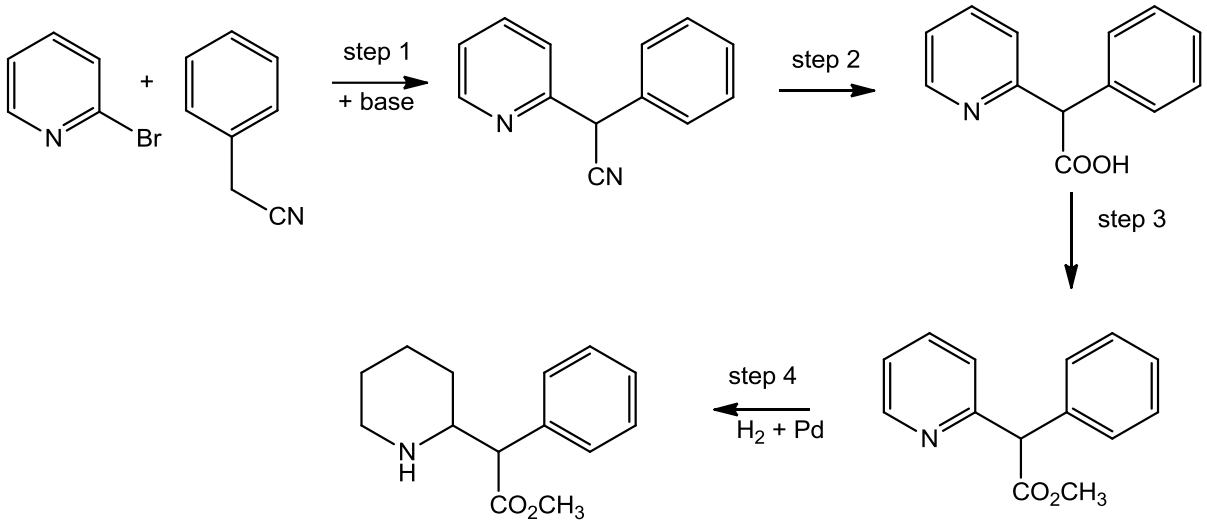
(iii) Briefly describe 2 types of interactions each that nicotine and caffeine are likely to form with their respective receptors at physiological pH.

(iv) Nicotine acts as an agonist at acetylcholine receptors, stimulating nerve transmission. However, the human body prefers to keep the nerve transmission rate at a steady level. Explain how the body reduces nerve transmission, leading to addiction to nicotine and withdrawal symptoms if intake of nicotine is stopped.

[10]

(b) Methyl phenidate is another stimulant used to treat attention deficit hyperactivity disorder, ADHD. It is available as a transdermal patch, called Daytrana, and delivers the drug through the skin.

A synthesis route for methyl phenidate is shown below.



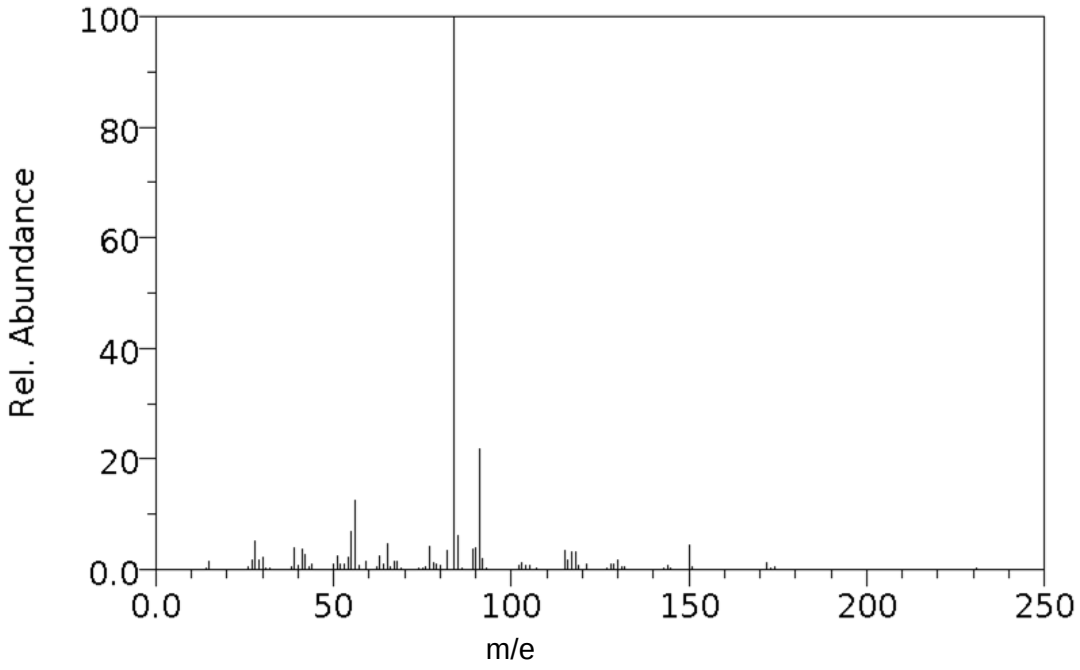
(i) Suggest the role of the base in step 1.

(ii) State reagents and conditions required for step 3.

(iii) Suggest the mechanism for step 3.

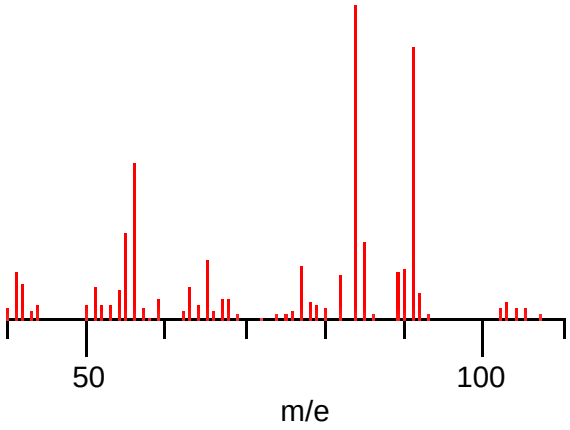
(iv) State the key difference(s) in the IR spectrum of the reactant and product involved in step 3.

At the end of step 4, the mass spectrum of methyl phenidate was obtained.



mass spectrum of methyl phenidate

A close up of the region from m/e 50 to 100 is shown.



(v) Given that the base peak is due to an ion containing a nitrogen atom, suggest the structures of the fragment ions responsible for the 2 most abundant peaks in the spectrum, stating the m/e values.

(vi) State the m/e value of another peak that might be predicted to be present in significant abundance, and suggest why it is not observed.

(vii) Suggest one advantage and one disadvantage of delivering a drug transdermally compared to other methods such as orally.

[10]

[Total: 20]