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.

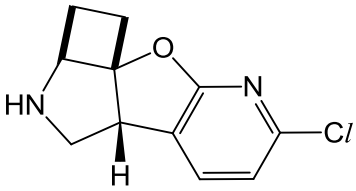
Answer any **five** questions.
At the end of the examination, fasten all your work securely together.

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.

ANSWERS

This document consists of **30** 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*.

Analgesic: A drug that reduces or eliminates pain
Agonist: A compound that mimics the natural ligand, bringing about a similar physiological response when bound to a receptor.

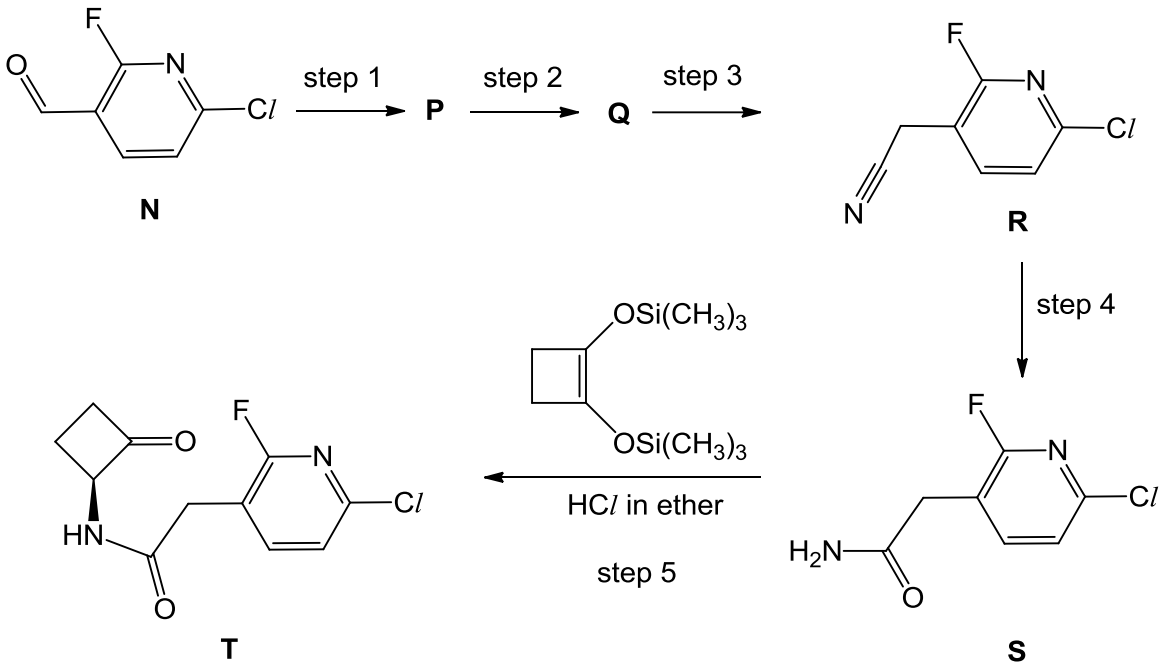
(ii) Outline the ways in which *narcotic* and *non-narcotic* analgesics work, and state one advantage and one disadvantage of each analgesic.

Narcotics are morphine like analgesics and work by depressing the CNS, hence affecting capacity of brain to appreciate pain. Non-narcotics work on pain receptors themselves, preventing them from responding normally to pain stimuli and this involves inhibition of COX enzymes or prostaglandin synthesis.

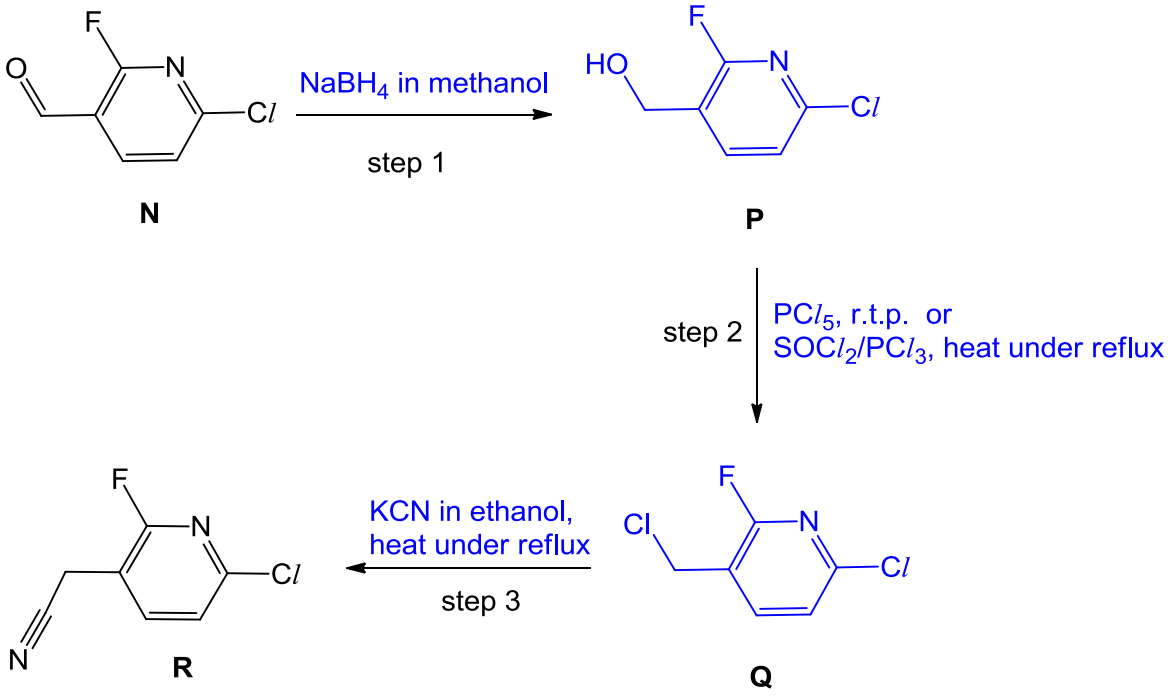
Narcotics are more powerful painkillers than non-narcotics. However, they lead to addiction or drug dependency issues, unlike non-narcotics. Non-narcotics on the other hand, are not habit-forming, and may have other uses such as being antipyretic or anti-inflammatory, but can result in problems such as liver damage or internal bleeding.

[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.



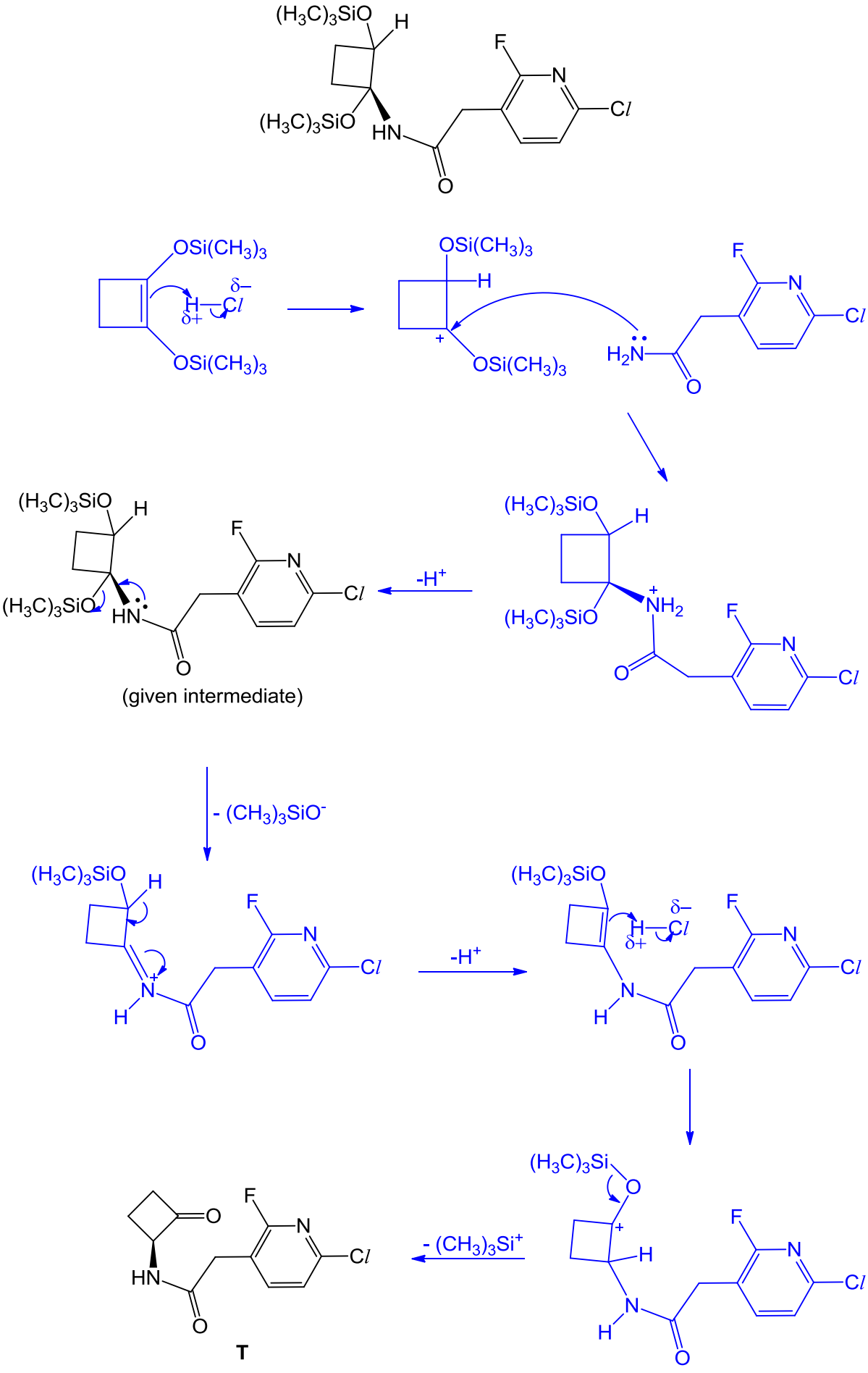
(b) **(i)** Suggest structures for the intermediates **P** and **Q**, and suggest reagents and conditions for the three steps 1–3.



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

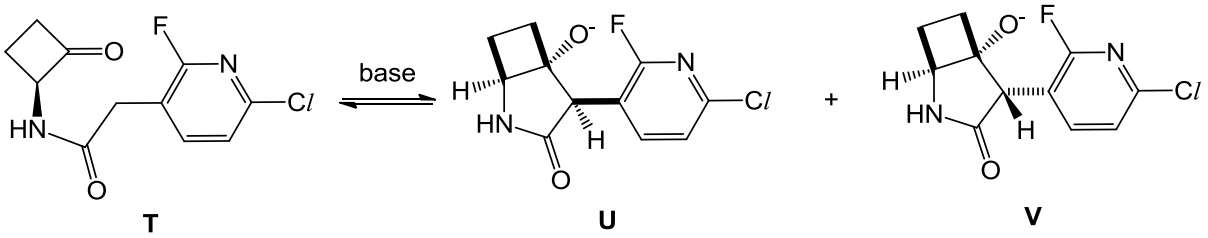
Hydrolysis

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

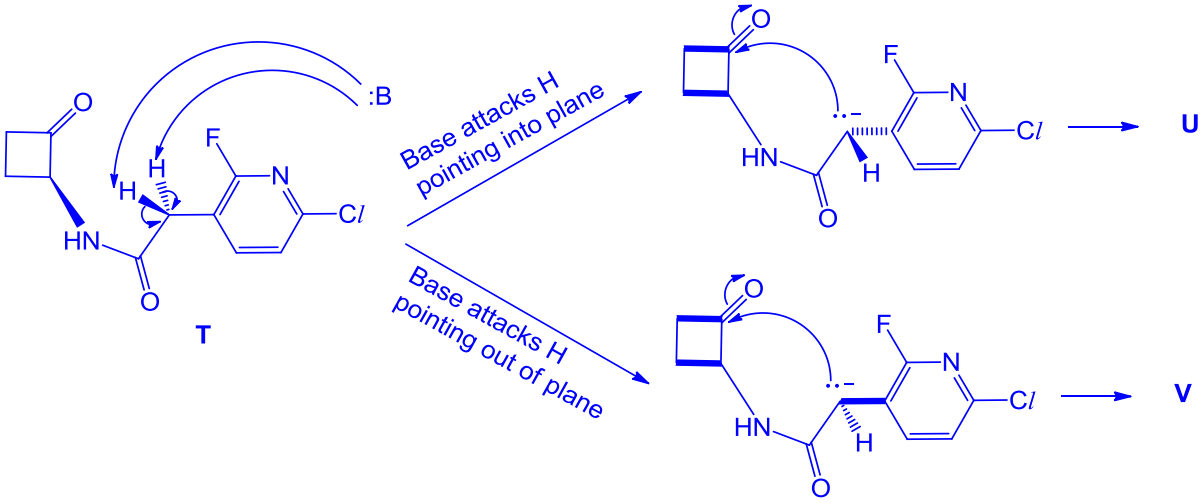

(given intermediate)
-H+
- (CH3)3SiO-
-H+
- (CH3)3Si+
T

[9]

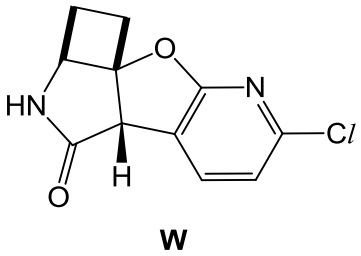
Upon treatment with base, compound **T** is deprotonated and cyclises to give two stereoisomers, **U** and **V**.



(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.

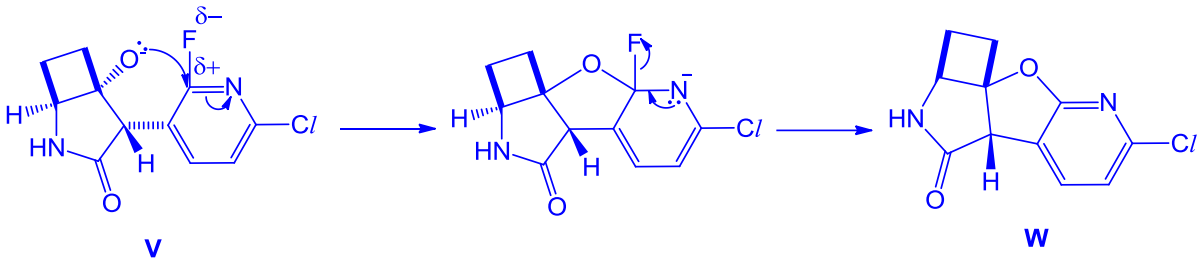


W

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

Both the pyridine ring and the alkoxide are pointing into the plane for V, but the pyridine ring points out of the plane for U. Thus only in V can the alkoxide approach the C-F carbon on the pyridine ring to form a furan ring.

(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.

OH^- present under alkaline conditions would act as a nucleophile, substituting F or Cl on the pyridine ring (or both).

[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.

Modes of action:

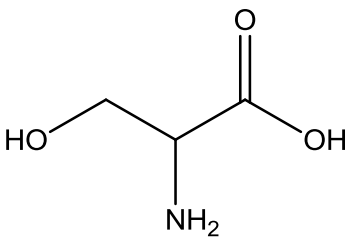
1. **disrupt the synthesis of folic acid by inhibiting the enzyme-catalysed conversion of 4-aminobenzoic acid.**
2. **disrupt/inhibit protein synthesis (translation of DNA or transcription of RNA)**
3. **disrupt/inhibit formation, polymerization or cross-linking of peptides in cell wall construction.**
4. **disrupt cell plasma membrane, allowing cations or other small molecules to enter the cell, disrupting the ionic balance**

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.

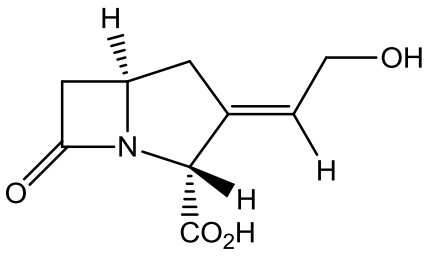
(ii) Explain why overprescription of penicillin antibiotics (e.g., in animal feedstocks) can increase the problem of bacterial resistance to penicillins.

Overprescription of penicillin antibiotics (e.g., in animal feedstocks) may result in the small numbers of naturally penicillin-resistant bacteria (arising from genetic variation or mutation) in a population surviving. These bacteria are left unchecked by penicillin and hence grow in numbers to make up a significant percentage of the population. They may also mutate and pass the resistant genes to each other. Thus further use of penicillin fails to significantly reduce the numbers of such bacteria, increasing bacterial resistance.

(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.

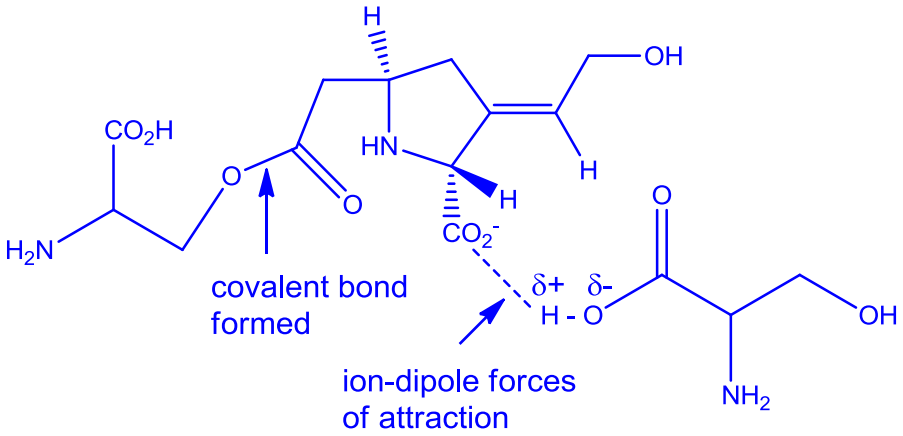


serine



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.

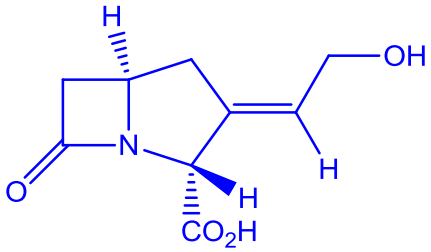


The covalent ester bond (and ion-dipole forces of attractions or another C-O bond) formed irreversibly inhibit β-lactamase, thus preventing it from hydrolysing the penicillins, so the penicillins will be able to reach the bacterial cells to to destroy the bacteria.

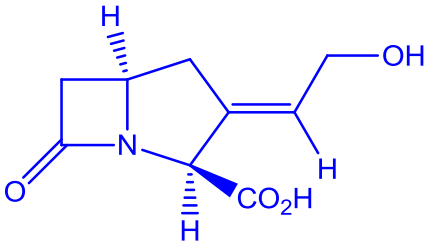
(iv) State the configuration of the C=C in clavulanic acid.

Z

(v) Draw a diastereomer of clavulanic acid.



clavulanic acid



diastereomer
(only 1 chiral centre's configuration reversed)

(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.

At the pH of the stomach (3.0), clavulanic acid exists in equilibrium with its salt RCOOH ⇌ $RCOO^-$ + H^+ in comparable proportions. The protonated form can diffuse into the hydrophobic stomach cell walls more readily than the salt, and the decrease in concentration outside the cell will cause the position of equilibrium to shift to the right, causing more of the salt outside the stomach cells to be protonated and hence to continue diffusing in.

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

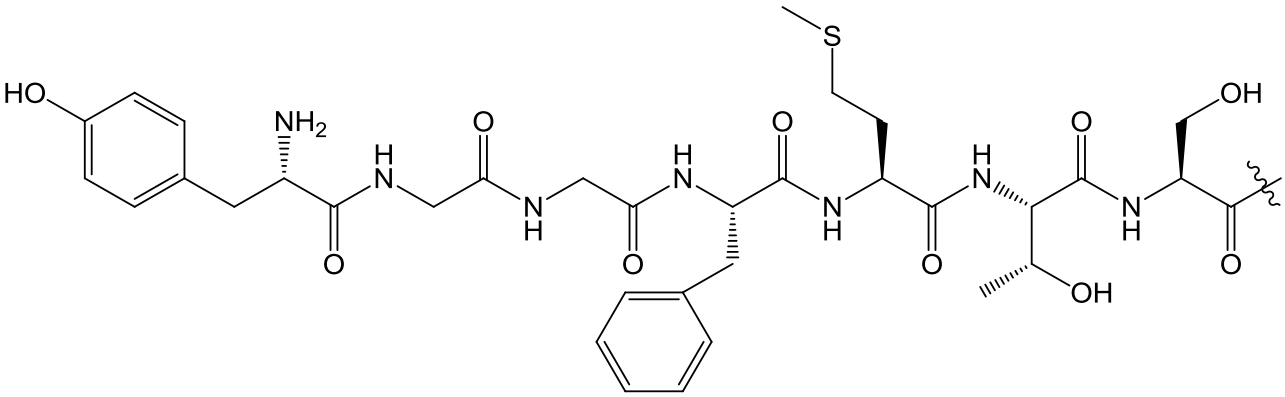
$$pH = pK_a + \lg\frac{[salt]}{[acid]}$$

$$3.0 = 3.32 + \lg\frac{[salt]}{[acid]}$$

$$\frac{[salt]}{[acid]} = \frac{[charged\ form]}{[uncharged\ form]} = 0.479$$

[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.



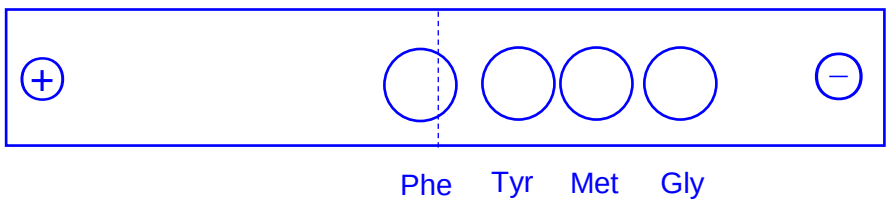
(i) State the number of **different** hydrolysis products of the peptide fragment shown above.

6 (2 glycines)

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.

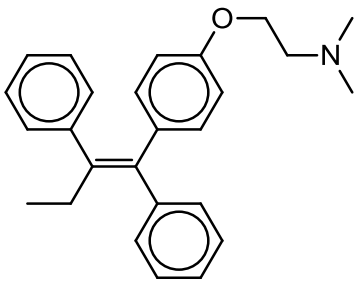
All four amino acids will be negatively charged, hence will migrate towards the positive electrode anode, with probable rates of Phe > Tyr > Met > Gly.

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

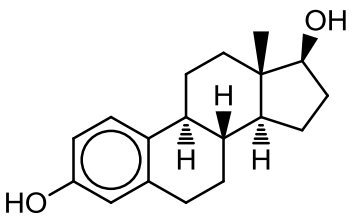
Separate/purify or analyse the components of a mixture of peptides and/or amino acids, measure the relative masses of macromolecules, prepare nucleic acids and polypeptides, etc.

[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*.

Competitive and non-competitive inhibitors prevent the substrates from binding to the active sites of the enzymes.

A competitive inhibitor usually has a similar structure to natural substrate for particular enzyme and hence can bind to active site. However, a non-competitive inhibitor, in a similar way to a competitive inhibitor, also can bind to the active site of particular enzyme, but the bond formed is of a covalent nature.

A competitive inhibitor inhibitor can be displaced by higher concentrations of substrate. The inhibitor-enzyme complex of a non-competitive inhibitor is so stable that increase in concentration cannot displace the inhibitor.

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

Competitive inhibitor. They have similar structure and can have similar interactions as estradiol such as van der waal' forces between the

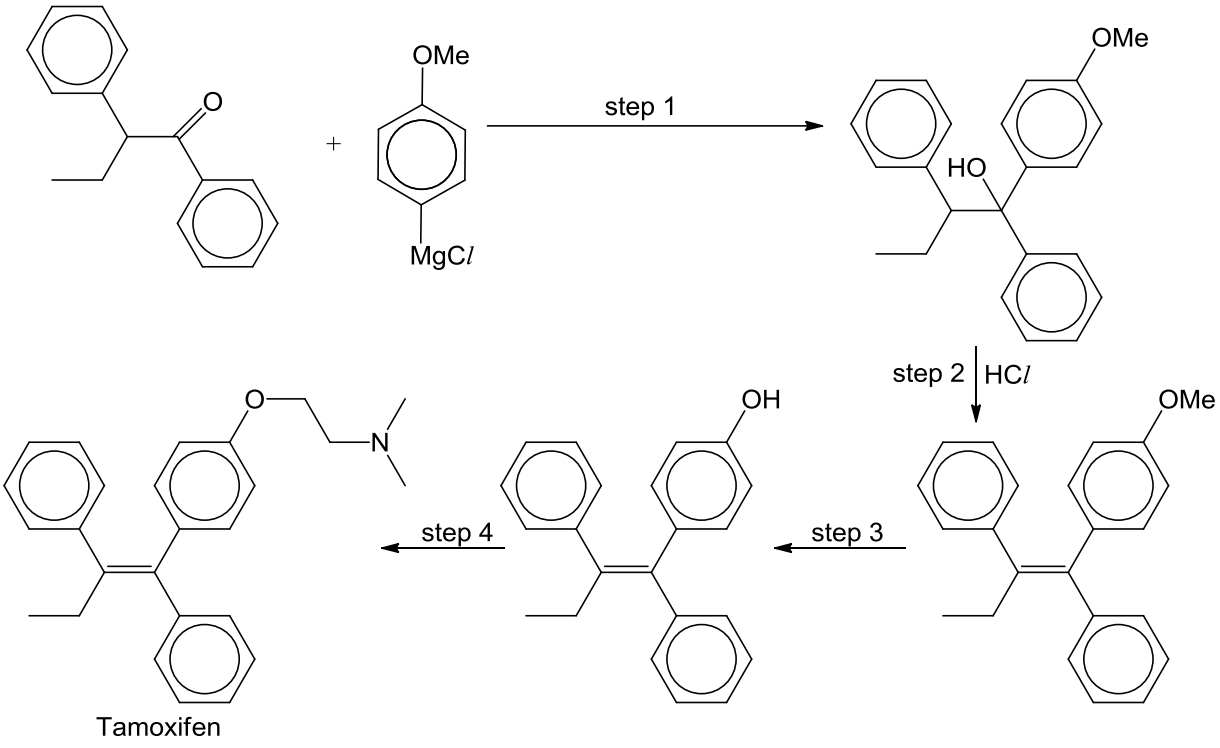
bulky benzene rings and hydrogen bonding between C-O group of ether and –NR groups of amines in tamoxifen (compared to –OH groups in estradiol).

(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.

- **Benzene ring: van der waals' forces with non-polar groups**
- **Nitrogen atom of amine group: hydrogen bonding with any –OH or $–NH_2$ groups.**
- **oxygen atom of ether group: hydrogen bonding with any –OH or $–NH_2$ groups.**

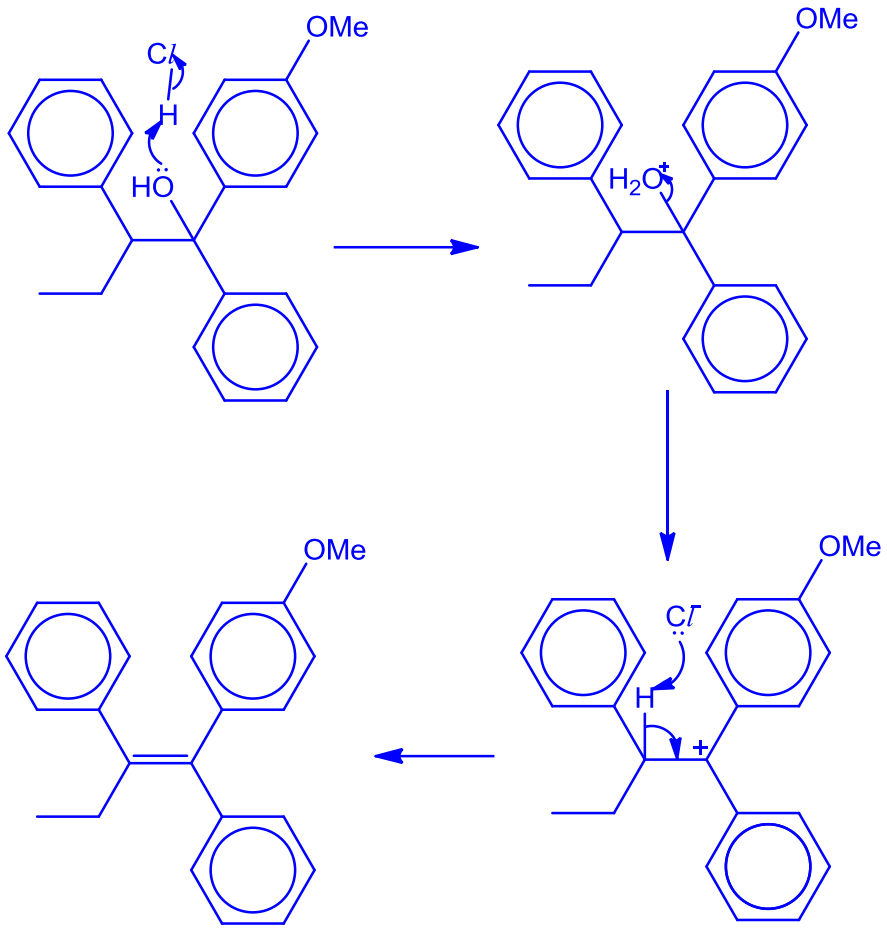
[5]

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



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

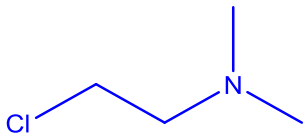
Elimination (E1).



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

The tertiary carbocation formed is stabilized due to the positive charge on the carbocation being dispersed by 1) delocalisation over two phenyl rings 2) 1 electron donating alkyl group.

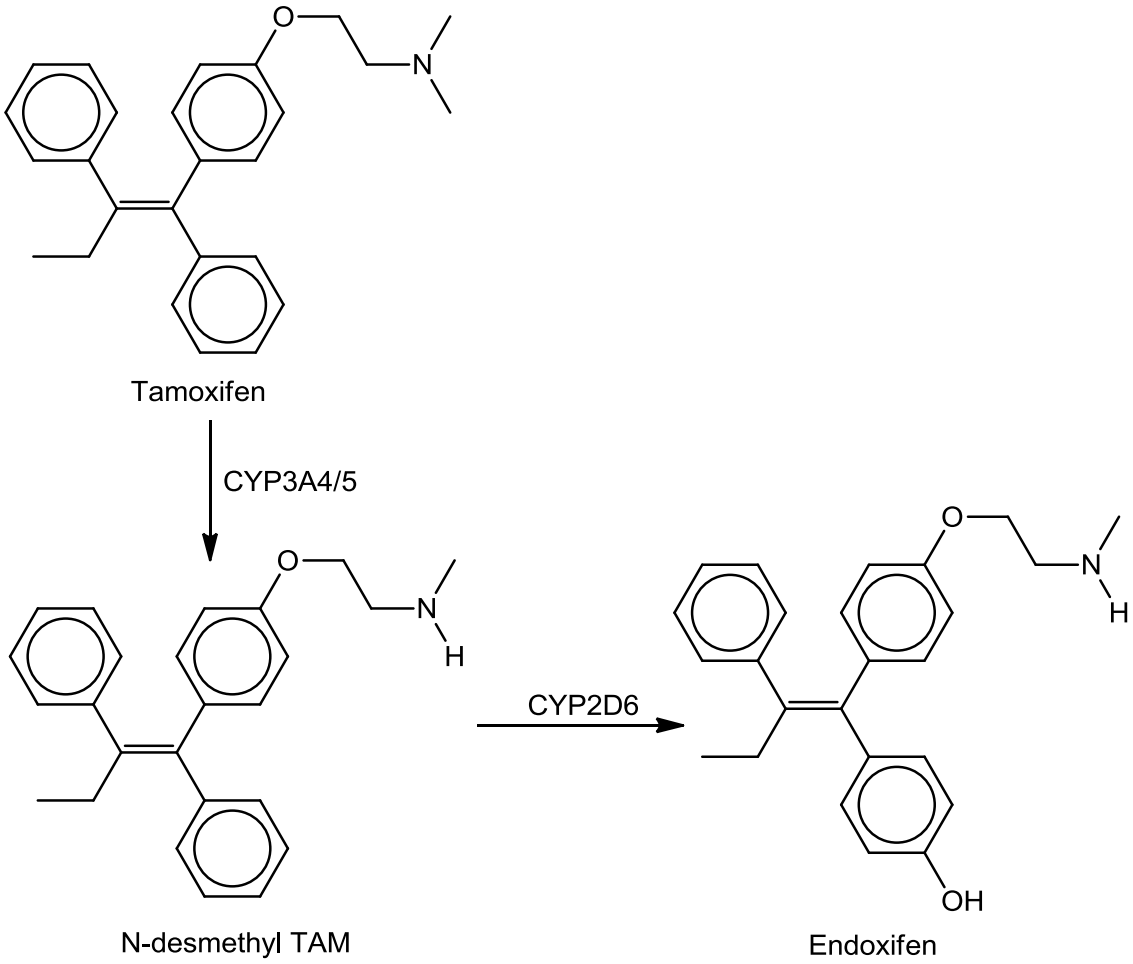
(iii) Suggest reagents and conditions for step 4.



1) Na 2)

[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.

The presence of delocalized system involving the benzene ring and presence of lone pair of electrons on N or O atoms in the molecules.

The electronic transitions n→π* (for lone pair of electrons on nitrogen atoms) and π→π* occur (for benzene ring).

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

Partition	**The compounds in the sample interact with the stationary phase by forming suitable interactions with it, thus partitioning itself between the mobile and stationary phase. Non-polar molecules will form stronger interactions (van der waals' forces) with the non-polar stationary phase. Thus, non-polar molecules will remain in the stationary phase for a longer time and thus be eluted later.**
Mobile phase/ stationary phase	**High purity solvent is used as mobile phase, solid uniform porous silica particles with large surface area as stationary phase. Such particles are packed into a narrow and short column.**
Type of analytes	**Sample for separation can be solids or liquids, and is especially useful for very polar compounds such as amines and amino acids. During separation, the sample partitions between the mobile and stationary phase depending on the affinity for each phase.**
Detector	**Detector at end of column measures amount of substance or fractions passing through usually by measuring the absorbance of peaks using UV spectroscopy.**

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

Endoxifen, N-desmethyl TAM, Tamoxifen

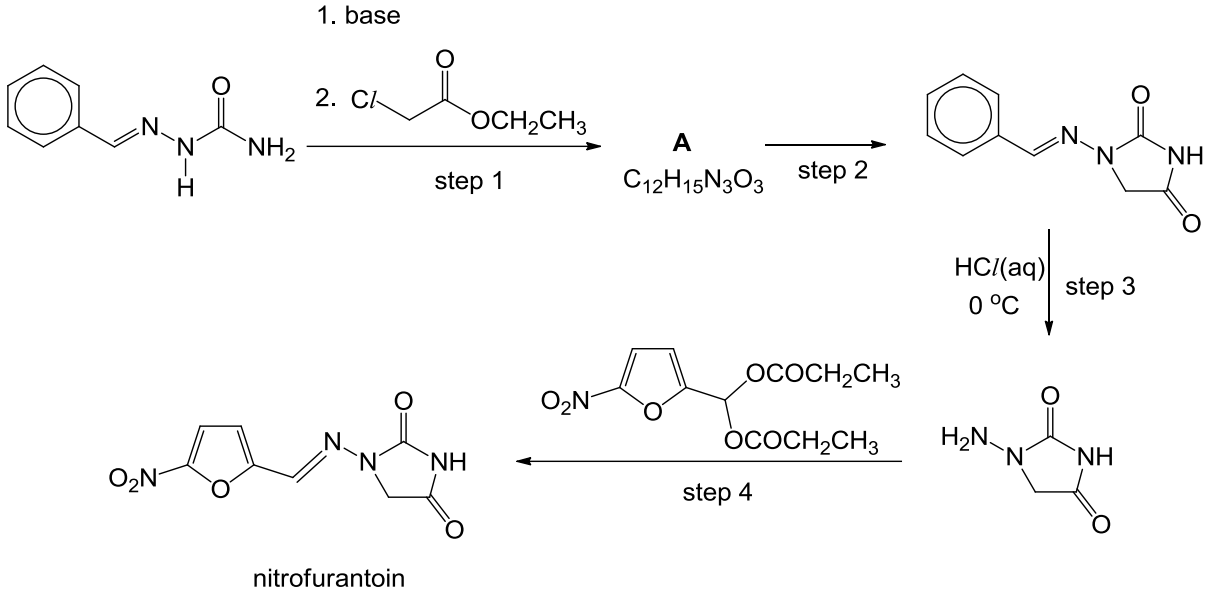
Endoxifen will be eluted out first since it is the most polar, having a –NH and –OH group. Tamoxifen will be eluted last since it has no polar groups such as –OH and –NH group. N-desmethyl TAM has only 1 –NH group and will be the second to be eluted out.

(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.

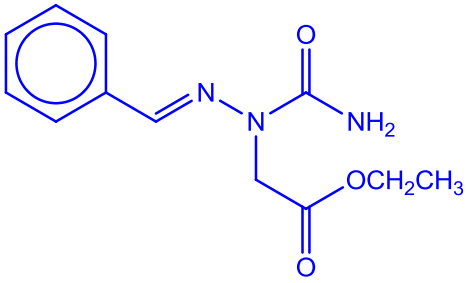
Add an internal standard of known concentration into the sample that is able to give a retention time that will not overlap with the peaks of the other three compounds. Determine the area under the peaks for each compound and internal standard. Calculate the relative amounts of each compounds by comparing the relative peak areas and using the known concentration of the internal standard.
Assumption: ε (molar extinction coefficient) for all compounds at 250nm are the same.

[10]
[Total: 20]

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

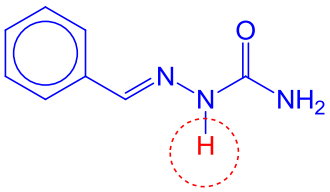


(i) Identify compound **A**.



(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.

The proton removed was attached to the nitrogen atom in the middle.



It is the most acidic as that nitrogen atom is directly attached to another nitrogen atom (which it is unable to draw electron density from, unlike a carbon atom), and a C=O group, which can draw electron density away and further polarise the N-H bond.

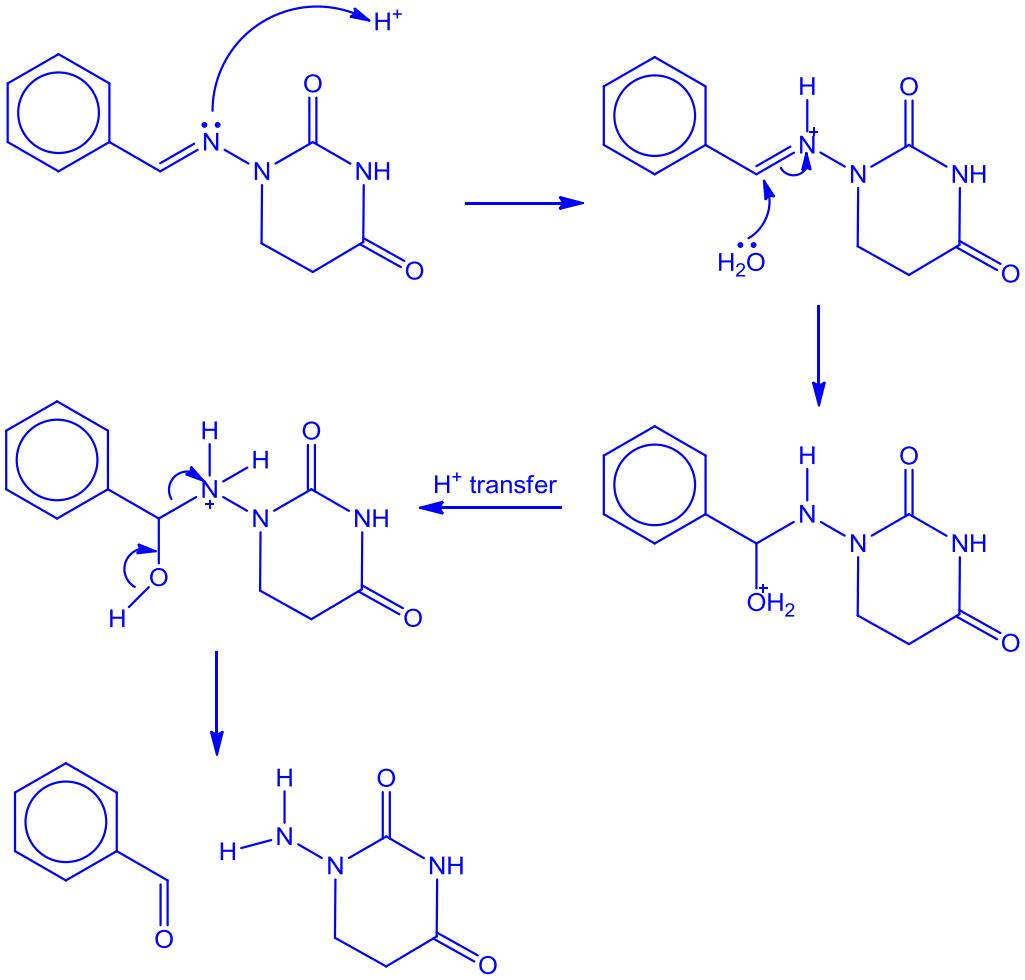
(iii) Hence, explain why compound **A** was the preferred product when ethyl chloroethanoate was added in step 1.

The nucleophile generated upon deprotonation is bulky and would experience steric hindrance if it were to attack the ester carbon instead of the more peripherally located chloro carbon.

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

The reaction is conducted at 0 °C. Heat is necessary for hydrolysis to occur appreciably.

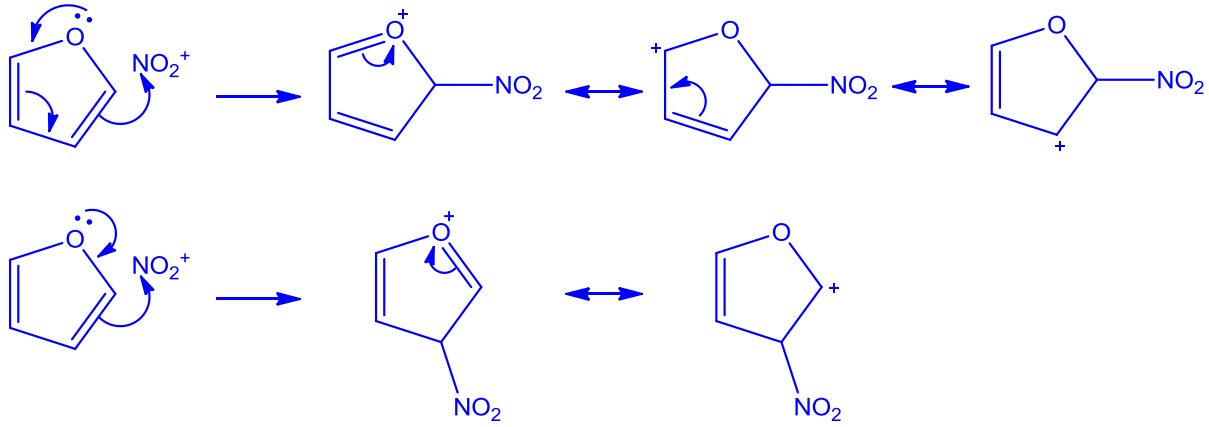
(v) Propose the mechanism for step 3.



(vi) State the type of reaction in step 4.
Addition-elimination / Nucleophilic substitution

[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.



There are fewer mesomeric structures for the intermediate when substitution occurs at the 3-position. Intermediate is more stable when substitution occurs at the 2-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:

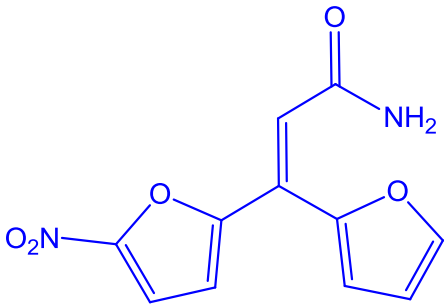
proton chemical shift value δ / ppm	splitting	number of protons
6.77	s	1
6.87	m	1
7.24	m	1
7.68	s	2
7.79	d	1
7.94	d	1
8.17	m	1

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

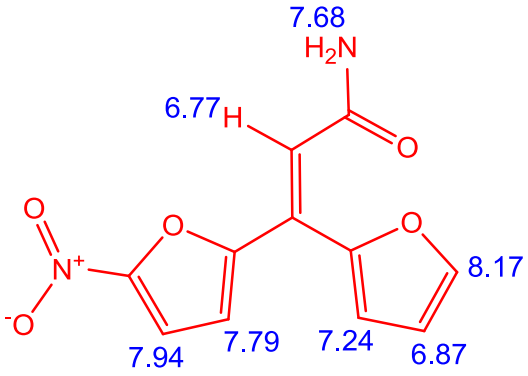
Use the above information to deduce the structure of compound **B**.

- **Two furan rings: 11 – 2(4) = 3 carbon atoms and 5 – 2(1) = 3 oxygen atoms that are not part of the furan rings (i.e., side chains).**
- **Similarity to nitrofurantoin: -NO_2 on furan ring may be present, this would account for 1 nitrogen atom and 2 oxygen atoms, leaving 1 nitrogen atom and 1 oxygen atom to be accounted for.**

- **No reaction with cold acid/alkali: No phenol, carboxylic acid or amine present. Possible ester, amide, alcohol.**
- **IR sharp strong peak at 1660 cm^{-1}: C=O stretch**
- **IR two medium strength peaks at 3500 cm^{-1}: 2 x N-H stretch**
- **IR spectrum hints at presence of $–CONH_2$**
- **NMR signal at δ 7.68 ppm (2H) disappears with D_2O: amide H, confirms $–CONH_2$**
- **NMR signal at δ 6.77 ppm due to alkene H. (No H across C=C bond, hence singlet)**
- **NMR signals at δ 7.79 and 7.94 ppm due to furan H, disubstituted furan ring**
- **NMR signals at δ 6.87, 7.24 and 8.17 ppm due to furan H, monosubstituted furan ring**



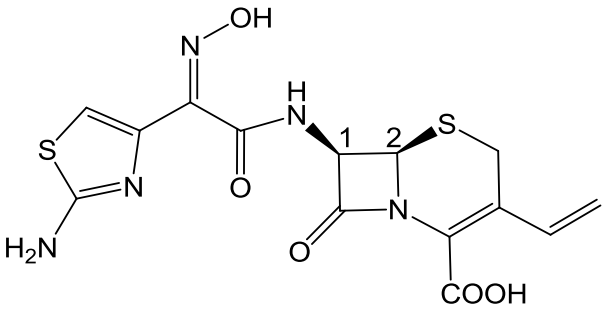
NMR assignments:



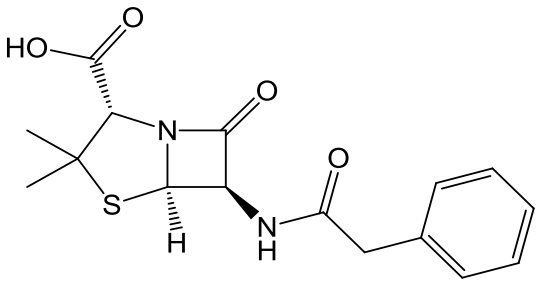
[9]

[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

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

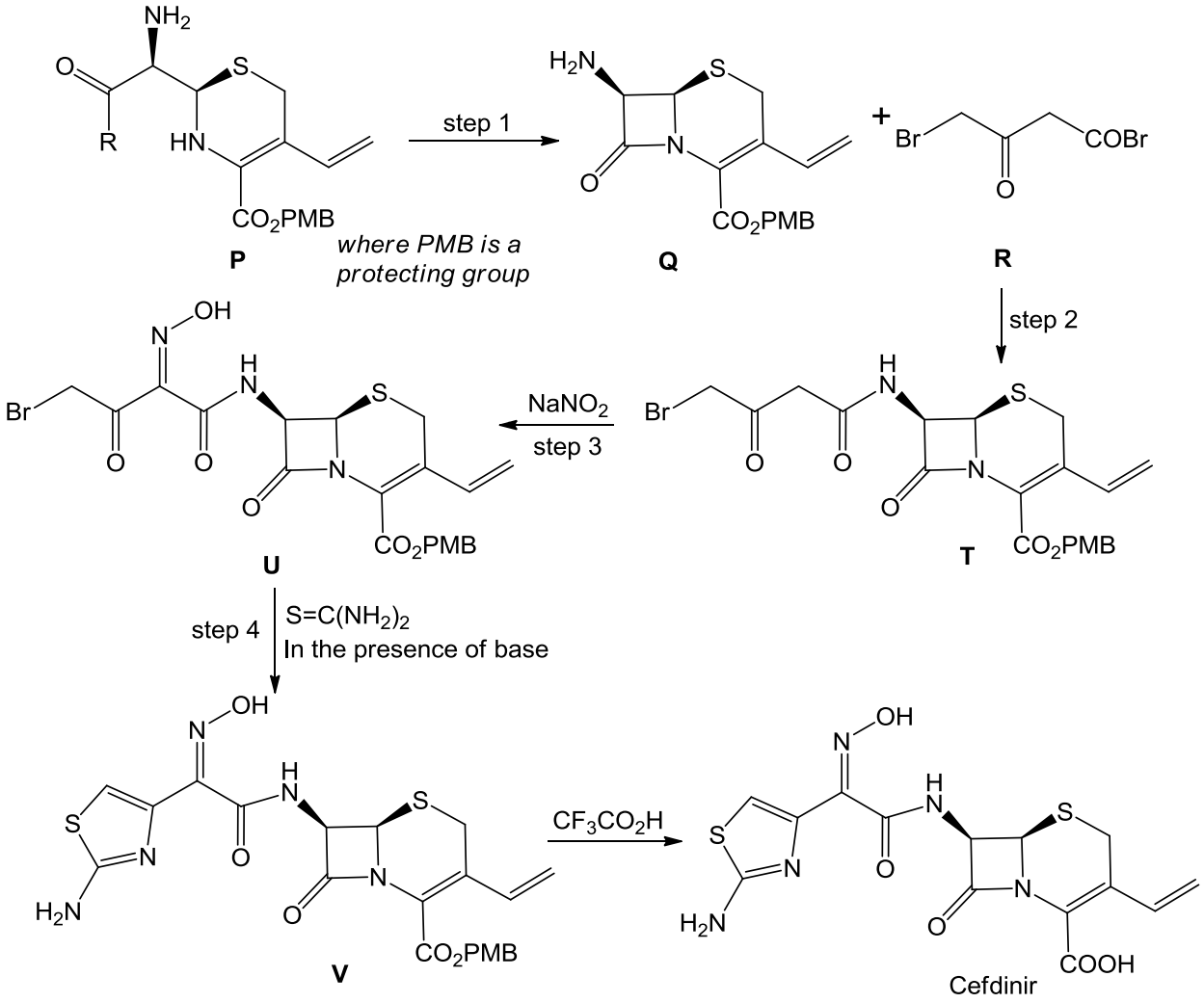
Penicillin G has a strained β-lactam ring and can undergo acid-catalysed hydrolysis readily in the stomach. However, Cefdinir has a NH_2 group which will get protonated first and hence it is resistant to acid-catalysed hydrolysis in the stomach.

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

C1: R C2: R

[3]

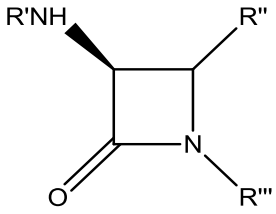
(b) The synthesis of Cefdinir from compound **P** is outlined below.



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

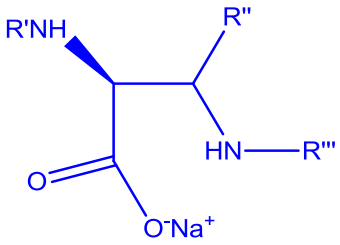
R can be –OCH_3 OR –C*l*.

(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:

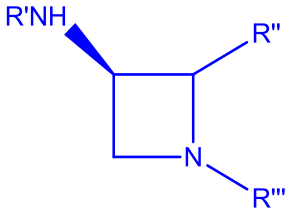


Cefdinir

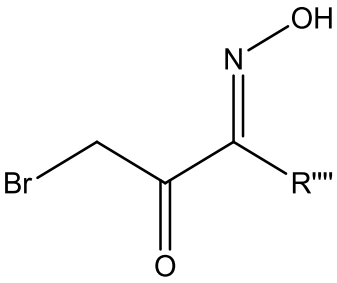
I NaOH(aq) and heat



II LiA*l*H_4 in dry ether

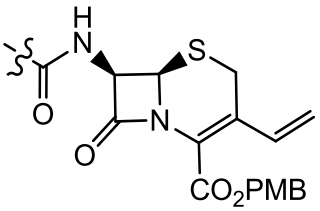


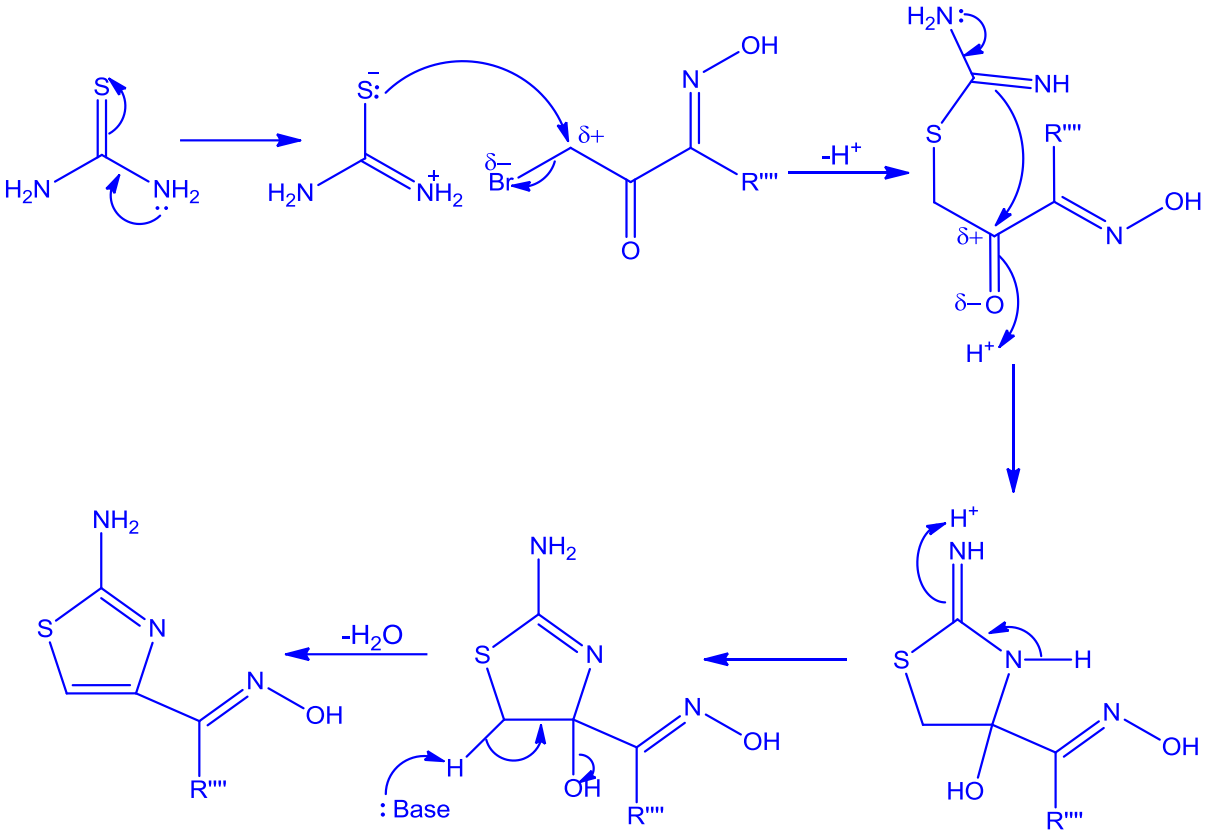
(iii) Suggest a mechanism for step 4, using the symbol **R’’’’** to represent part of the Compound **U**, as shown.



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 $C_{14}H_{13}N_5O_5S_2$.

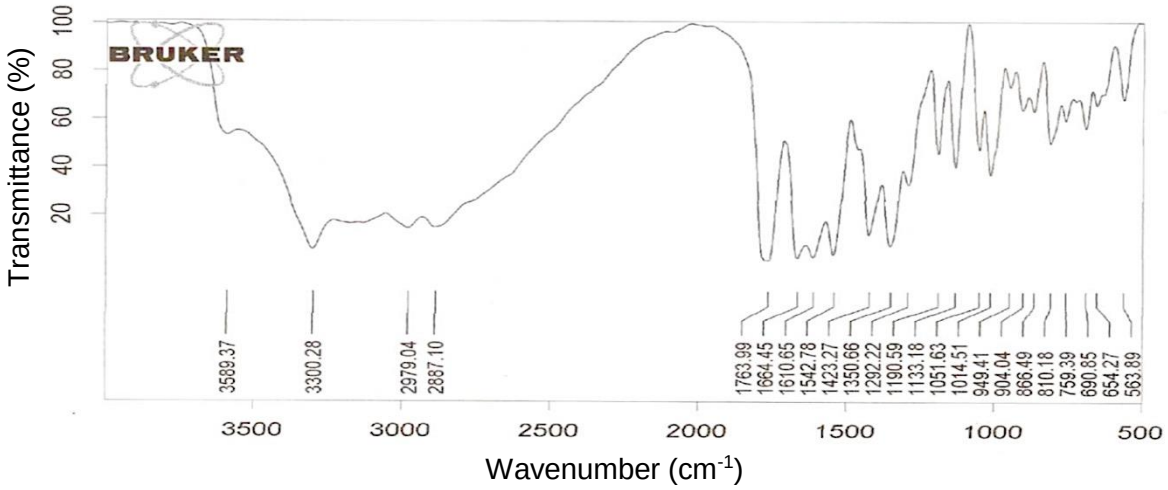
The ^1H NMR signals of Cefidinir after addition of D_2O are given below.

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.

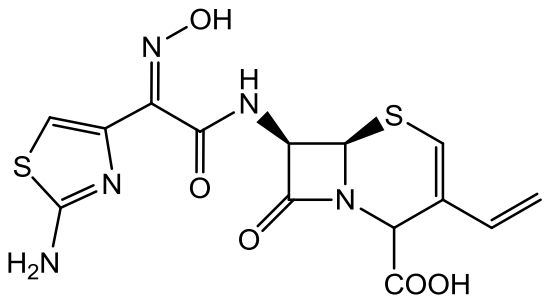
The two nuclei (-CH_2) of the vinyl group are not magnetically equivalent. OR The protons of –CH_2 are in different chemical environment. Thus, splitting the signals unevenly.

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

Type of stretching/ Functional Groups	Wavenumbers/ cm^{-1}
O-H (carboxylic acid or oxime)	3000
C-H (alkanes, alkenes)	2979, 2887
C=O (carboxylic acid, lactam)	1763
C=C (alkenes)	1664 or 1610

[3]

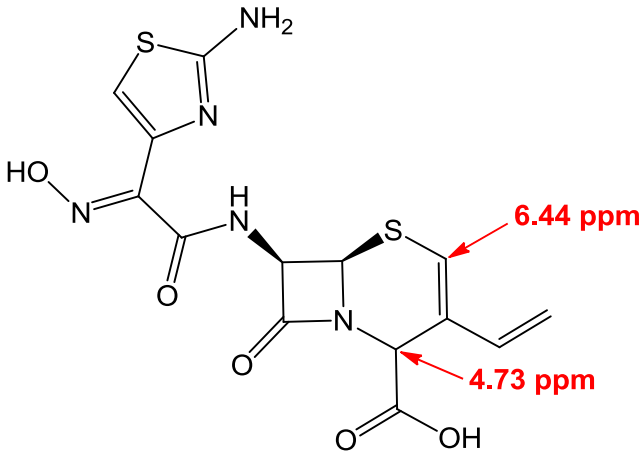
(d) Samples were taken from different batches of Cefdinir to be analysed and two impurities were found. One of the impurities obtained is as shown below.



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.

- **Signal at chemical shift 3.55ppm and 3.83ppm corresponding to $–SCH_2$ signal will not be present in the NMR of Impurity I.**
- **Signal at chemical shift at 4.73 ppm corresponding to –CH proton (–CHCOOH) will be present.**
- **Signal at chemical shift 6.44ppm corresponding to –CH proton (–CH(SR)=CH) will be present.**



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

Comparison of Mass Spectra of Cefdinir and impurity II:

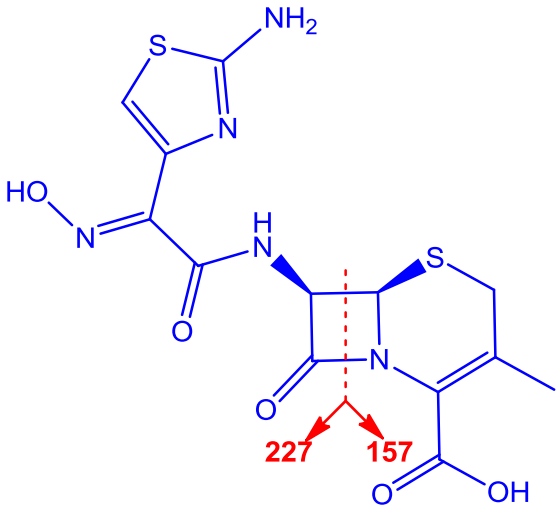
With reference to the molecular ion peak of impurity II and Cefdinir, it has a difference of m/e 12(395-383). This indicates there may be a loss of 1 carbon.

Both Cefidinir and impurity II gives m/e of 227. m/e of 227 corresponds to the left hand side of the Cefidinir. Need to indicate in molecule which fragment it corresponds to.

With reference to NMR spectra of Cefdinir and impurity II

Since signals at 5.31, 5.59 and 6.90ppm corresponds to vinyl protons (-CH=CH_2), this indicates Impurity II does not have the C=C bond to the ring.

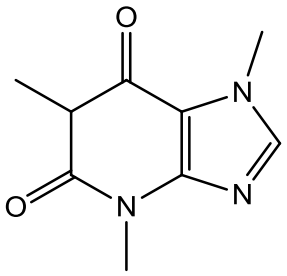
Since there is a new singlet at 2.00ppm that corresponds to 3 protons, this indicates the C=C bond has been replaced by a -CH_3



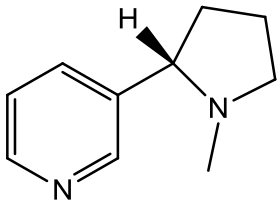
Impurity II

[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

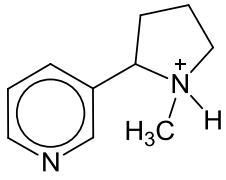
(a) **(i)** Outline the physiological effects of stimulants such as caffeine.
increase in respiration rate, heart rate, blood pressure, depression of appetite, increase in peristalsis, increase in urine flow, increase in alertness.

(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.

The nitrogen in tertiary amine is more basic than the pyridine nitrogen. The lone pair of electrons on the N atom in tertiary amine is in a sp^3 hybrid orbital (less s character), which is further away from nucleus, and hence more available for donation to acid, than the lone pair on pyridine nitrogen, which is in a sp^2 hybrid orbital.

Form at pH 7.4:



[tertiary amine: pK_b 6.1, pyridine: pK_b 11.0]

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

Nicotine can form ionic attractions from the protonated N with a negative receptor, and Van der Waals' forces of attraction from its heterocycles/non-polar hydrocarbon groups with non-polar eg. Alkyl groups on receptors.

Caffeine can form hydrogen bonding from the lone pairs on N and O with δ+ H on receptors, or Van der Waals' forces of attraction like nicotine.

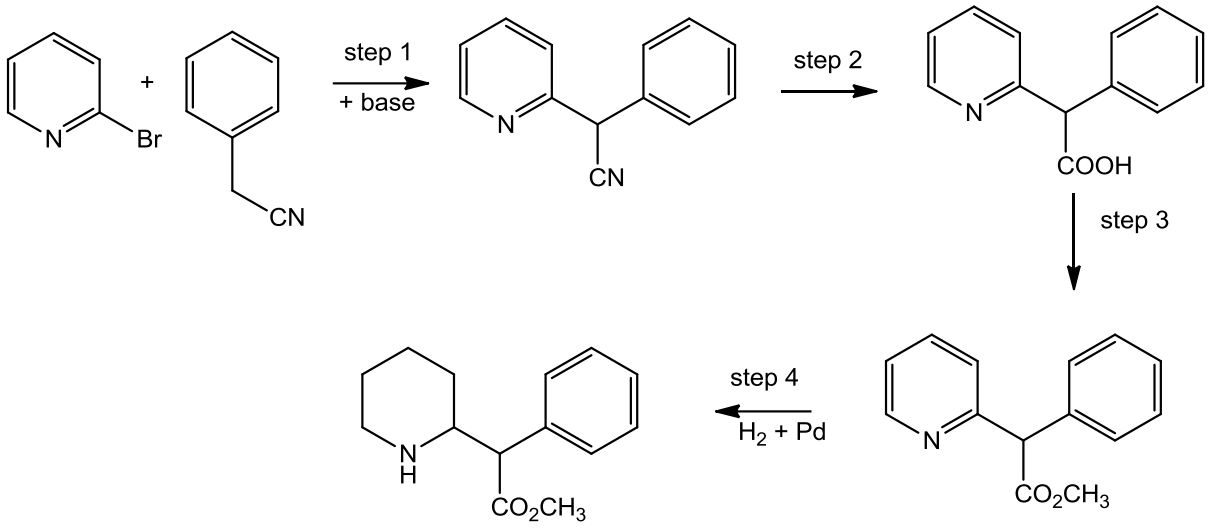
(iv) Nicotine acts as an agonist at acetylcholine receptors, stimulating nerve transmission. However, the human body prefers to keep the nerve transmission rate at a steady level. Explain how the body reduces nerve transmission, leading to addiction to nicotine and withdrawal symptoms if intake of nicotine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

The human body may decrease the number of acetylcholine receptors at post-synaptic nerves. This will require a higher dose of nicotine to produce the same stimulation of nerve transmission. If the nicotine is withdrawn, the natural ligands will also produce a lower effect than before due to the fewer receptors, hence the body will experience withdrawal symptoms which is described as an addiction or dependence on nicotine.

[10]

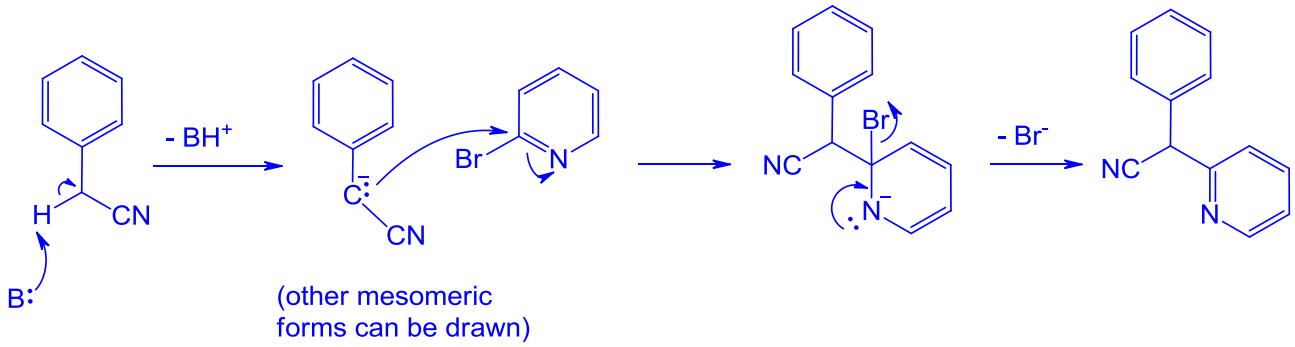
(b) Methyl phenidate is another stimulant used to treat attention deficit hyperactivity disorder, ADHD. It is available as a transdermal patch, called Daytrana, and delivers the drug through the skin.

A synthesis route for methyl phenidate is shown below.



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

It is to deprotonate the C-H as shown, which allows it to act as a nucleophile.

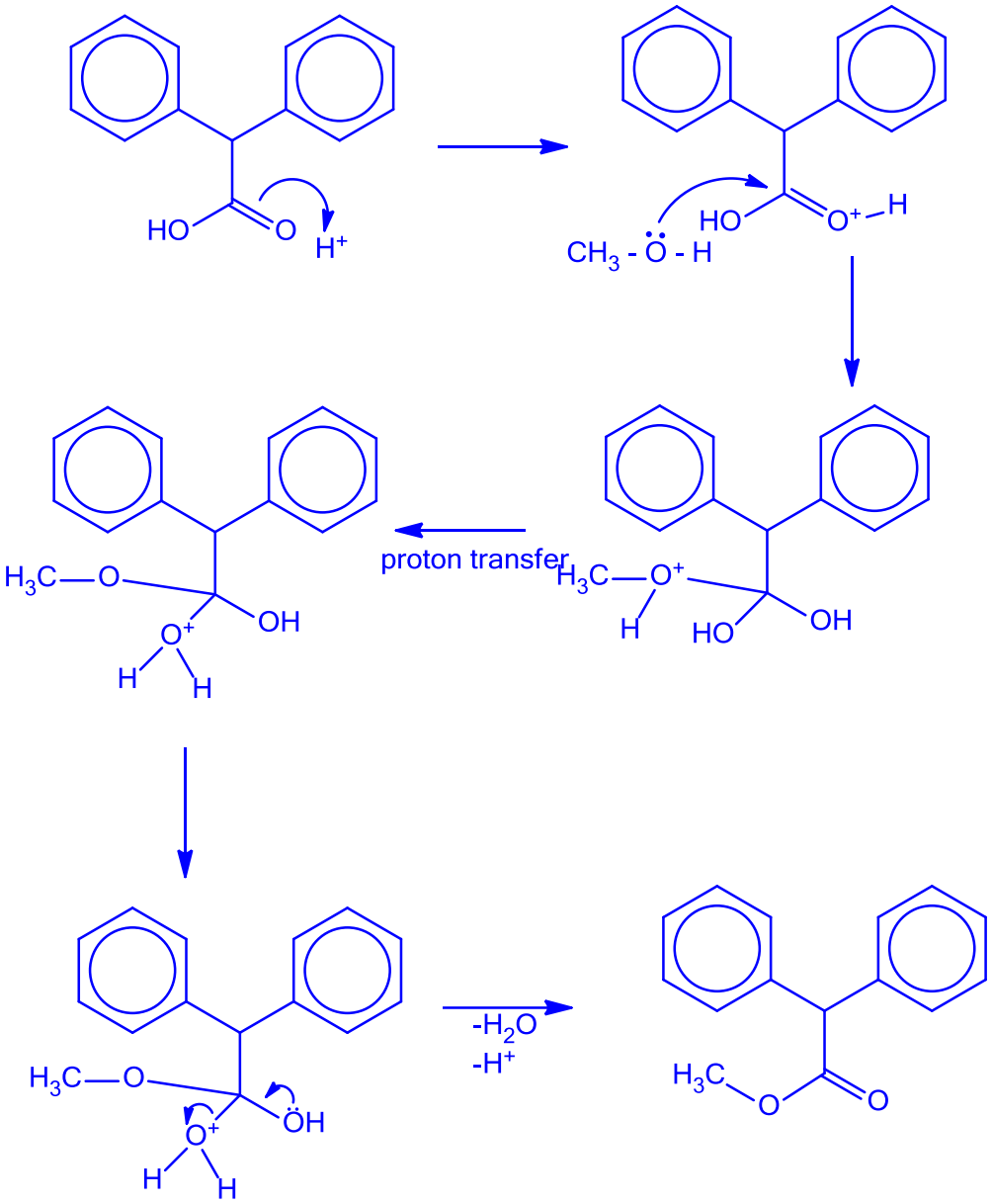


(ii) State reagents and conditions required for step 3.

CH_3OH, Conc. H_2SO_4, heat under reflux

OR **PCl_5 or other acylating agent, followed by CH_3OH**

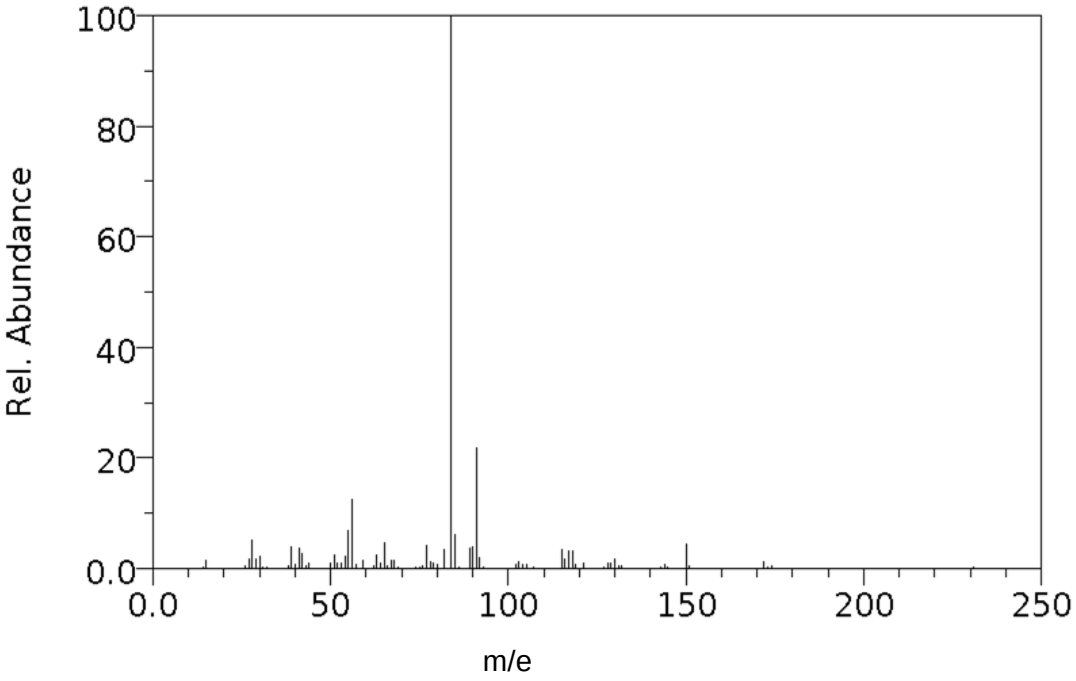
(iii) Suggest the mechanism for step 3.



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

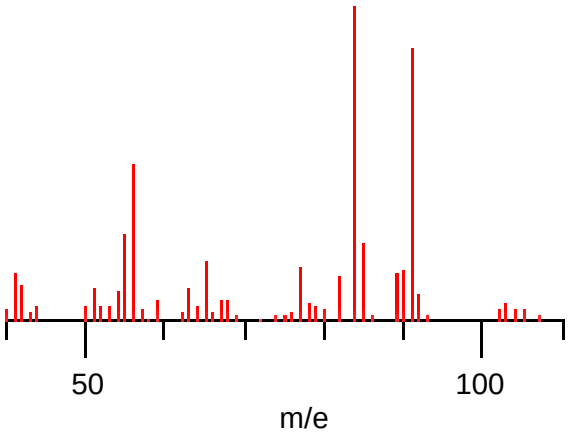
The reactant is a carboxylic acid while the product is an ester.
The IR spectrum of the product should not have any peak between 2500 to 3300 cm^{-1} (O-H in carboxylic acid).

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



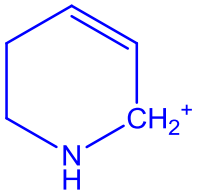
mass spectrum of methyl phenidate

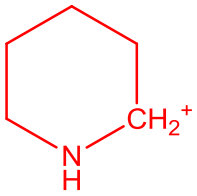
A close up of the region from m/e 50 to 100 is shown.



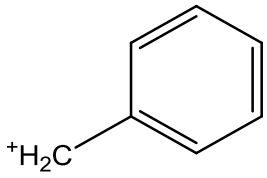
(v) Given that the base peak is due to an ion containing a nitrogen atom, suggest the structures of the fragment ions responsible for the 2 most abundant peaks in the spectrum, stating the m/e values.

m/e = 84 (base peak)



accept  (m/e = 86)

m/e = 91



(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.

A peak at m/e = 233 is expected, but may not be present as the molecular ion may be unstable hence have broken down to smaller fragments.

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

Advantage: Orally administered methyl phenidate may be metabolised (first-pass metabolism) before it is able to reach the target site, hence transdermal delivery may be able to deliver higher concentrations for the same amount of starting drug OR require less protection or modification.

Disadvantage: Transdermal drugs need to be lipophilic in order to pass through the hydrophobic skin cell walls OR drug delivery may take longer OR may cause other side effects eg. skin sensitivity.

[10]
[Total: 20]