RAFFLES INSTITUTION
2011 YEAR 6 PRELIMINARY EXAMINATION

Higher 3

PHARMACEUTICAL CHEMISTRY 9812/01

Paper 1 **20 September**

2 hours 30 minutes

Additional Materials: Answer Paper
Data Booklet

READ THESE INSTRUCTIONS FIRST

Write your index number, civics tutorial group and name on the Cover Page.
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.

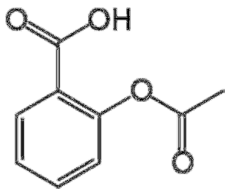
The number of marks is given in brackets [ ] at the end of each question or part question.
You may use a calculator.
You are reminded of the need for clear presentation in your answers.

1 Analgesics are a group of drugs which are capable of relieving pain. Analgesic drugs act in various ways on the peripheral and central nervous systems. They are distinct from anaesthetics, which reversibly eliminate sensation. One class of analgesic drugs are the non-steroidal anti-inflammatory drugs (NSAIDs). As analgesics, NSAIDs are unusual in that they are *non-narcotic*. These drugs display analgesic and antipyretic (fever-reducing) effects and, in higher doses, have anti-inflammatory effects. The most prominent members of this group of drugs are aspirin and ibuprofen.

(a) Outline the differences in the ways in which narcotic and non-narcotic analgesics work in preventing pain.

[2]

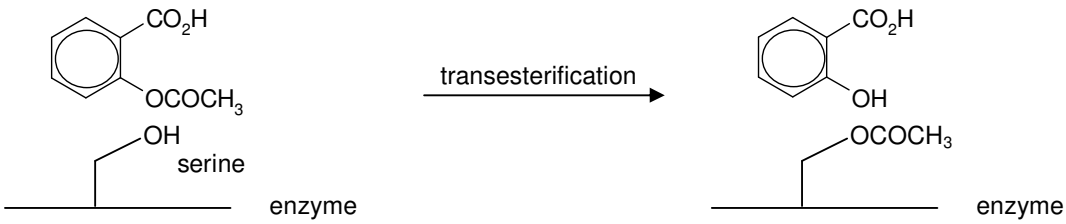
Aspirin has analgesic property and is capable of anti-inflammatory and anti-coagulant activities.



(b) Briefly explain how aspirin acts as an anti-inflammatory.

[2]

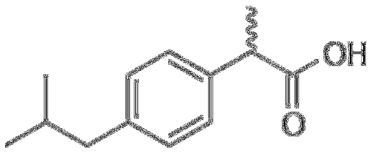
Aspirin acts as an acylating agent to bring about covalent bond (ester) formation at the serine binding site in the enzyme receptor, as shown below.



(c) Show the mechanism of the transesterification reaction.

[3]

Ibuprofen, another NSAID, is also analgesic and has anti-inflammatory properties.



ibuprofen

2-(4-(2-methylpropyl)phenyl)propanoic acid

Ibuprofen is produced industrially as a racemate. The compound contains a chiral centre in the α-position of the propionate moiety. As such, there are two possible enantiomers of ibuprofen, (*S*)- and (*R*)-ibuprofen, each with the potential for different biological effects and metabolism from the other. When a racemic mixture of ibuprofen is esterified with butan-2-ol, four possible diastereomers can be obtained.

(d) Draw the structures of (*S*)-ibuprofen and the diastereomer, (*R*)-1-methylpropyl (*S*)-2-(4-(2-methylpropyl)phenyl)propanoate. **[2]**

(e) A proton-NMR analysis of an ibuprofen enantiomer in D_2O was done.

(i) Explain the term *chemical shift*.

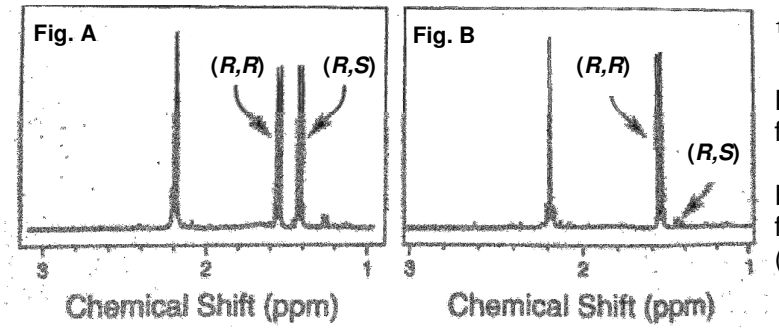
(ii) The table below shows some ^1H NMR data of the ibuprofen enantiomer. Copy the table on your answer sheet, and complete the table.

δ/ ppm	Multiplicity of signal	Ratio of number of protons
0.9		
1.5		
1.9		
2.5		
3.7		
7.1 – 7.3	multiplet	4
12.0	singlet	1

[3]

An enzyme, isomerase (alpha-methylacyl-CoA racemase), is capable of converting one form of the ibuprofen enantiomers totally to another. In a study to investigate such a conversion, (*R*)-butan-2-ol is used to form esters with a racemic mixture of ibuprofen. ^1H NMR analysis is conducted on the disastereomers formed.

The ^1H NMR spectrum shows that the benzylic methyl groups from the two diastereomers have different chemical shifts. The figures below show an expansion of the 1–3 ppm regions of the ^1H NMR spectra. The two forms can be distinguished by the ^1H NMR signals of the methyl doublets near 1.5 ppm. The doublet at 1.54 ppm is attributed to the (*R,R*) diastereomer, whereas the doublet at 1.41 ppm comes from the (*R,S*)-diastereomer.



^1H NMR spectra:

Fig. **A**, 50:50 mixture of diastereomers formed from ibuprofen and (*R*)-butan-2-ol.

Fig. **B**, mixture of diastereomers derived from reaction between (*R*)-ibuprofen and (*R*)-butan-2-ol.

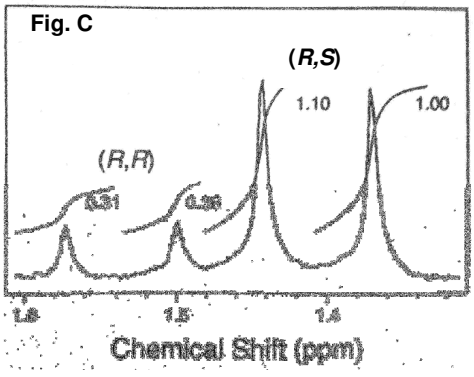


Figure **C** shows a higher resolution ^1H NMR spectrum of the diastereomers formed by the addition of isomerase to ibuprofen, followed by reaction with (*R*)-butan-2-ol.

(f) Using evidence from the ^1H NMR spectra from Figures **A**, **B** and **C**, what conclusion can you make about the activity of the enzyme isomerase? **[2]**

Acetaminophen and phenacetin are also non-narcotic analgesic and antipyretic agents. Acetaminophen has been reported to be a selective inhibitor of COX-3, which is found in the brain. Although phenacetin is a prodrug of acetaminophen, it is no longer used clinically because of the hepatotoxicity of its metabolites.

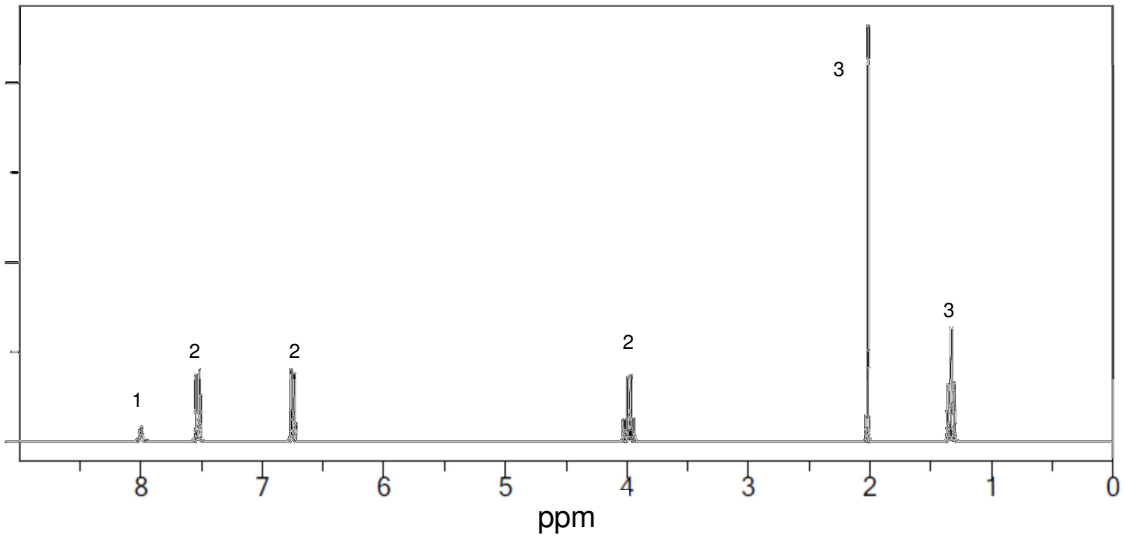
(g) What is a *prodrug*?

[1]

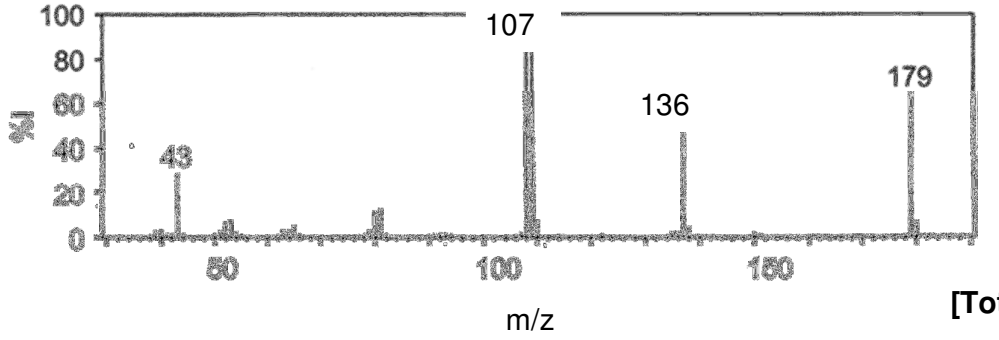
(h) The molecular formula of phenacetin is $C_{10}H_{13}NO_2$. The ^1H NMR and mass spectra of phenacetin are shown below. Analyse the data and suggest the structure of phenacetin, explaining how you arrive at your conclusion.

[5]

^1H NMR spectrum of phenacetin

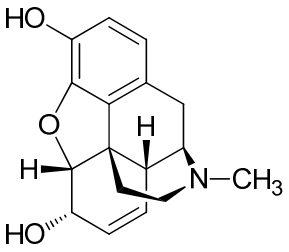


Mass spectrum of phenacetin

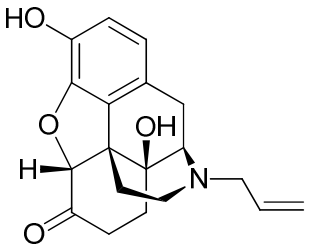


[Total: 20]

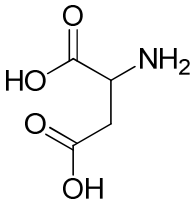
2 Morphine, an opium alkaloid first isolated in 1804 by a German pharmacist, is a potent narcotic analgesic. It is known to have very high affinity for the μ-opioid receptors located mostly in the posterior horn of the spinal cord. These receptors are integral membrane proteins which are made up of different α-amino acid residues.



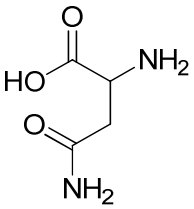
morphine



naloxone



aspartic acid



asparagine

(a) In a research study, it was discovered that binding to morphine was significantly reduced when the aspartic acid residue in the μ-opioid receptor was replaced with asparagine. With the aid of a diagram, suggest why this might be the case.

[2]

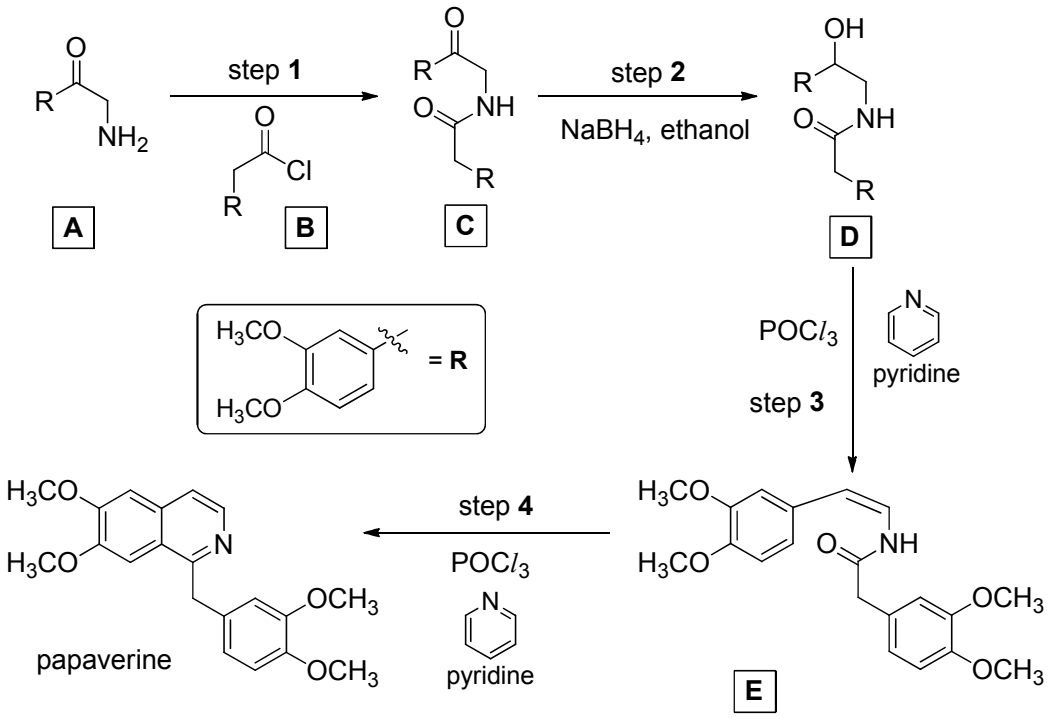
(b) Naloxone is a competitive antagonist of the μ-opioid receptor and is used in emergency treatments for morphine overdose.

(i) From the structure of naloxone, describe another feature that is necessary for binding to the μ-opioid receptor and suggest the type of binding interaction involved.

(ii) With reference to the term *competitive antagonist*, explain how naloxone counters the effects of morphine overdose.

[3]

Papaverine is another opium alkaloid used primarily in the treatment of visceral spasm. While it is also found in the opium poppy, it differs largely in structure and pharmacological action from the other opium alkaloids such as morphine. The synthesis of papaverine from compounds **A** and **B** is shown in the reaction scheme below.



(You can use **R** to represent the aryl functional group in your answers where necessary.)

(c) Compounds **A** and **B** have similar structures. However, they can be differentiated from their infra red (IR) spectra.

(i) Suggest one prominent IR absorption peak that could be used to distinguish **A** from **B**.

(ii) How would you expect the C=O absorption peak of compound **A** to differ from that of propanone? Explain your answer.

[2]

(d) The reaction progress of step **1** is followed using reverse phase HPLC by monitoring the amounts of **A** and **C** in the reaction mixture. Which compound, **A** or **C**, would be eluted first? Explain your answer.

[2]

(e) The synthesis of papaverine proceeds via four steps as shown above.

(i) Name the types of reaction in steps **1** and **2**.

(ii) Suggest whether the preparation of **D** in step **2** produces an optically pure product.

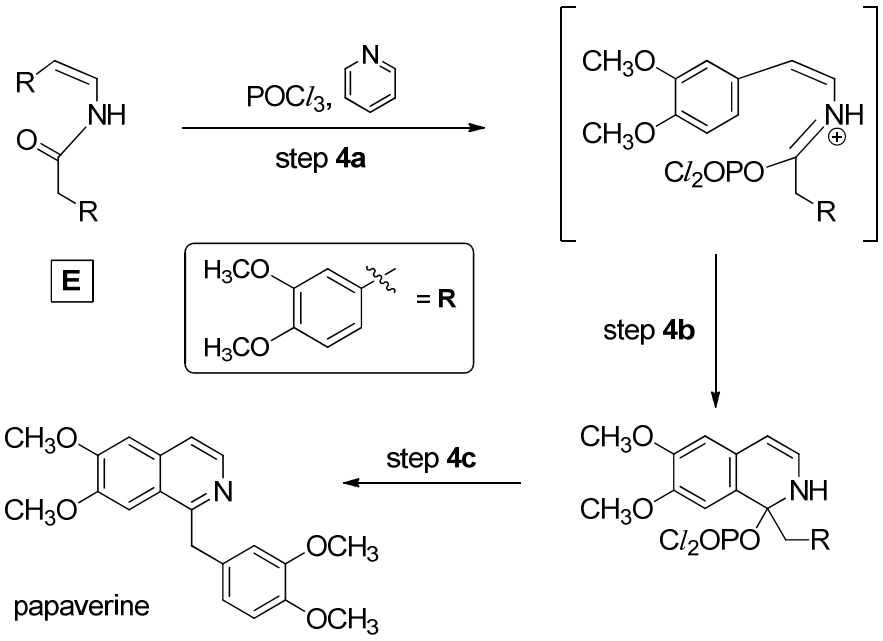
(iii) Suggest and explain whether step **2** can be carried out before step **1**.

[4]

(f) State the role of $POCl_3$ in Step **3** and outline the mechanism for the formation of **E** from **D**. (Hint: –$OPOCl_2$ is a better leaving group than –OH.)

[3]

(g) Step **4** is a key step in the synthesis of papaverine and it involves the use of the Bischler-Naperialski reaction to form the required isoquinoline structure in papaverine. The reaction first proceeds via the formation of the iminium intermediate as shown below.



(i) Outline the mechanism for the formation of the intermediate in step **4a**.

(ii) Name the type of reaction in step **4b**, and propose a suitable mechanism for the reaction.

(iii) Outline the mechanism for step **4c**.

[4]

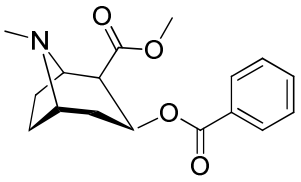
[Total: 20]

3 Stimulants are drugs that act on nerve synapses of the central nervous system. Effects vary depending on the drug ingested.

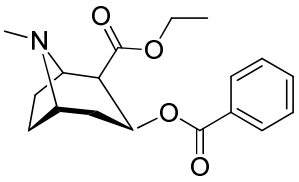
Cocaine is a central nervous system stimulant that also functions as a topical anaesthetic. It is a dopamine reuptake inhibitor. As a stimulant, it is more effective than amphetamines, which operate to inhibit reuptake of dopamine via a different mode. The metabolism of cocaine produces inactive metabolites via hydrolysis with water.

However, concomitant use of cocaine and alcohol will result in the formation of cocaethylene. It is precisely because of the formation of this active metabolite that many cocaine users will consume it together with alcohol – cocaethylene produces far greater euphoric effects than cocaine.

Cocaine and cocaethylene have the following structures:



cocaine



cocaethylene

(a) Discuss the ways in which a drug can reduce the transmission of a nerve signal at a synapse. **[4]**

(b) **(i)** What do you understand by the term *reuptake inhibitor*?

(ii) Describe how cocaine's role as a reuptake inhibitor can produce a feeling of euphoria in the user. **[5]**

(c) With reference to the stereochemistry at the chiral centres of cocaine, explain briefly why synthetic cocaine is rarely produced although this would have been highly lucrative to the illegal drug industry. **[3]**

(d) Cocaine can be ingested via various methods. It can be snorted, i.e. inhaled through the nose, injected, smoked and used as a suppository. While cocaine is medically supplied as the hydrochloride salt, inhalation of cocaine is done using the freebase.

Suggest a reason why inhalation of the freebase is preferred to inhalation of the salt. **[2]**

(e) Cocaine is converted to cocaethylene via a transesterification mechanism. Both cocaine and cocaethylene are psychoactive.

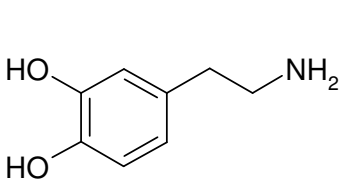
(i) What is a psychoactive drug?

(ii) With reference to the structures of cocaine and cocaethylene, explain why cocaine is less psychoactive than cocaethylene.

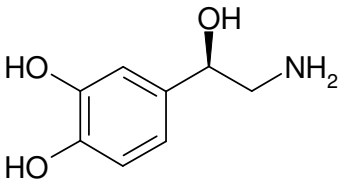
(iii) Suggest why cocaethylene is formed more readily than other non-active metabolites. **[6]**

[Total: 20]

4 Dopamine and noradrenaline are two naturally occurring neurotransmitters. After crossing the synaptic gap and binding to the adrenergic receptors, they are rapidly metabolised by monoamine oxidase.

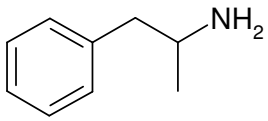


dopamine



noradrenaline

Amphetamine is a stimulant drug which was first synthesised by Edeleanu in 1887 and is reported to be used as a performance enhancer by athletes and high school students in the United States of America.



amphetamine

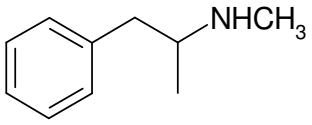
(a) By comparing the structure of amphetamine with that of noradrenaline, explain whether amphetamine is an agonist of the adrenergic receptor.

[2]

(b) Describe one way in which amphetamine affects the concentration of neurotransmitters in the synaptic gap, and hence, explain why amphetamine is used as a performance enhancer.

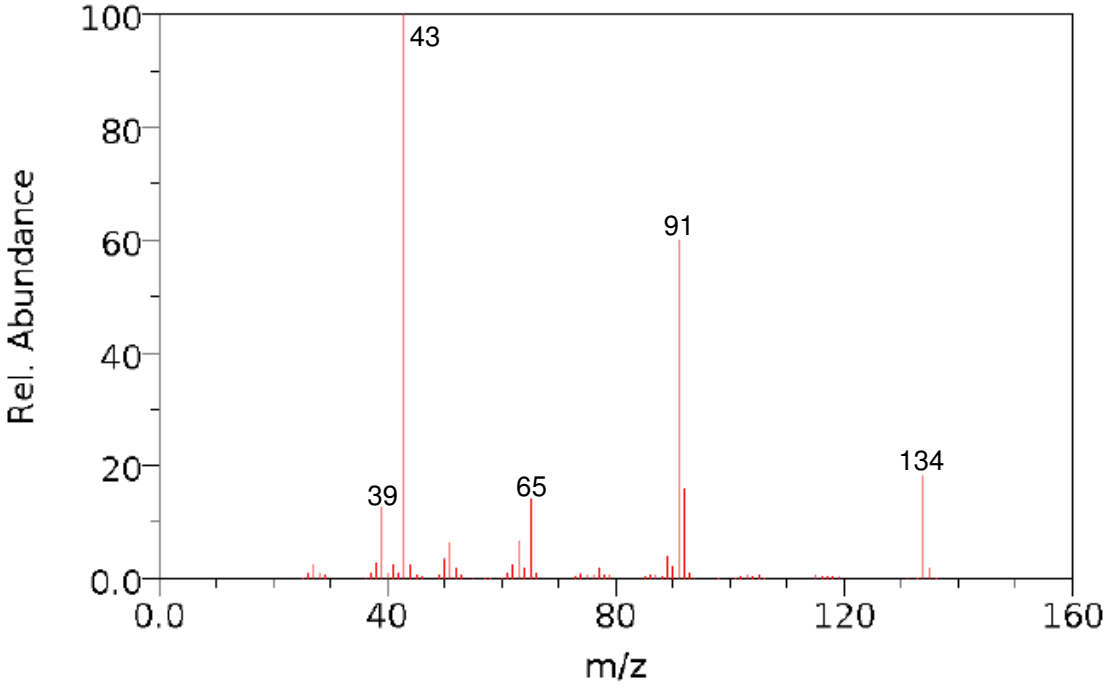
[2]

Methamphetamine, an analogue of amphetamine, is often sold illegally in Asian countries as “Ice” or “Yaba”. According to a report released in 2010 by the Central Narcotics Bureau, methamphetamine is one of the two most abused drugs in Singapore.



methamphetamine

(c) In humans, methamphetamine is metabolised in the liver and excreted in urine. The mass spectrum of a metabolite of methamphetamine is given below.



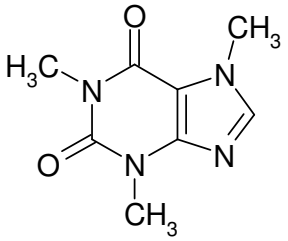
(Source: NIST Chemistry WebBook)

(i) By identifying the structures which give the two most abundant peaks, deduce the full structural formula of the metabolite.

(ii) Explain why the metabolite is more soluble in water than methamphetamine.

[3]

(d) Drugs sold illegally on the streets often contain adulterants such as caffeine. To test for the presence of amphetamine, methamphetamine and caffeine in such drugs, thin layer chromatography may be used.



caffeine

A sample solution of an approximate concentration of 10 mg cm^{-3} was prepared. Two chromatographic plates were spotted with the same sample solution. Each plate was placed in a different solvent system for separation to be carried out.

Solvent system **A** is a mixture of methanol and concentrated ammonia in the volume ratio 100:1.

Solvent system **B** is a mixture of cyclohexane, methylbenzene and diethylamine in the volume ratio 75:15:10.

The following R_f values were obtained.

Compound	**Solvent A**	**Solvent B**
amphetamine	0.46	0.34
methamphetamine	0.28	0.42
caffeine	0.68	0.06

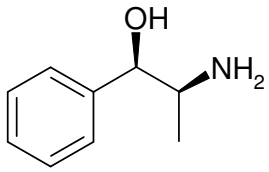
(i) Suggest why ammonia is included in solvent system **A**.

(ii) Explain why the difference between the two R_f values of caffeine is so large.

(iii) The chromatographic plates were dried and viewed under ultraviolet light. Describe and explain the observations made when the plates were placed under ultraviolet light.

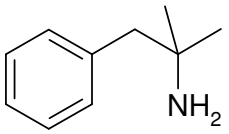
[3]

Phenylpropanolamine, or PPA, is a stimulant that is commonly used in over-the-counter cough and cold preparations. Since 2011, human use of PPA is banned in India.

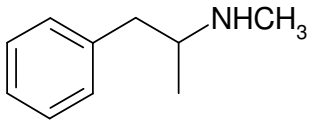


phenylpropanolamine

Phentermine is an appetite suppressant and is prescribed to help obese patients lose weight.



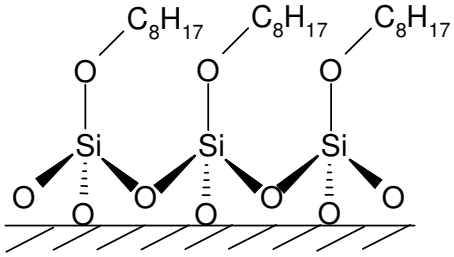
phentermine



methamphetamine

(e) The police found a packet of powder on a person who was suspected of selling "Ice" illegally on the streets. In a forensics laboratory, a small amount of the powder was dissolved in a solution that was buffered at pH 3. The sample was analysed using reverse phase high performance liquid chromatography and found to contain methamphetamine, phentermine and phenylpropanolamine.

(i) The diagram shows the surface of the silica gel in the C8 column that was used in the analysis.



column packing (silica)

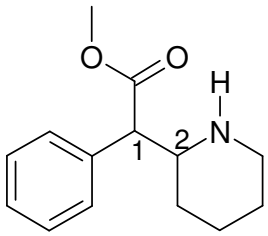
Suggest how phenylpropanolamine might be adsorbed on the silica. You should draw a diagram to illustrate two points of interactions.

(ii) The mobile phase was a mixture containing 85% phosphate buffer (pH 3) and 15% acetonitrile (CH_3CN).

Arrange the three compounds in increasing order of elution time and explain how you arrived at that conclusion.
(Hint: consider the dominant species of the compounds in the mobile phase)

[3]

Methylphenidate, which is also a stimulant drug, is approved for treating attention-deficit hyperactivity disorder by the Food and Drug Administration in the United States of America.

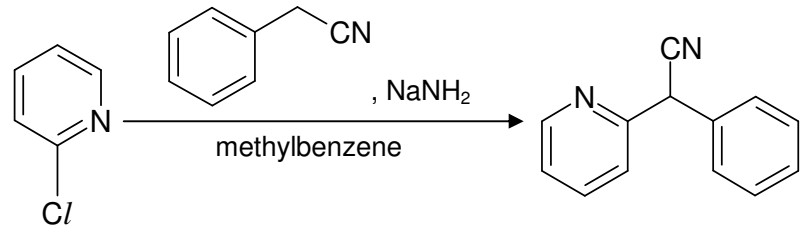


methylphenidate

(f) Methylphenidate has two chiral centres at carbon atoms 1 and 2. Draw the Newman projections along the C1-C2 axis of a diastereomer of the (1*R*,2*R*)-isomer in its most stable conformation and use the *R*, *S* convention to assign the stereochemical configurations at carbon atoms 1 and 2 in your structure.

[2]

(g) Methylphenidate was first synthesised in 1944 by Panizzon. One of the steps in the synthesis involves the conversion of 2-chloropyridine into compound **X**. Methylbenzene is used as a solvent in this reaction.

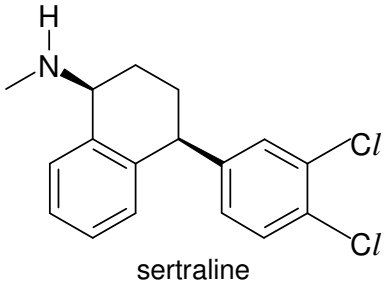


2-chloropyridine compound **X**

Suggest a mechanism for the reaction.

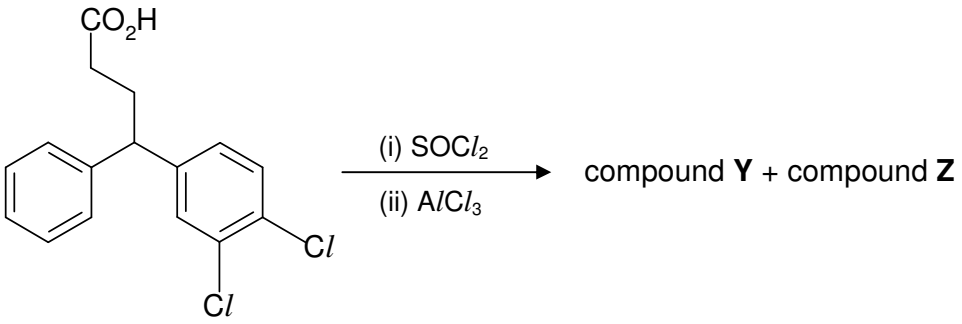
[3]

Sertraline is an anti-depressant that is used to treat obsessive compulsive disorder.



sertraline

A particular step in the synthesis of sertraline is given below.



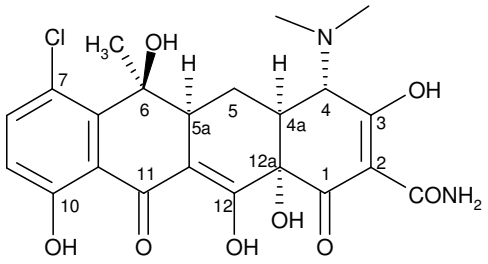
(h) Compound **Y** is the major product of the reaction. Give the structures of compounds **Y** and **Z**, and explain why the formation of compound **Y** is more favourable.

[2]

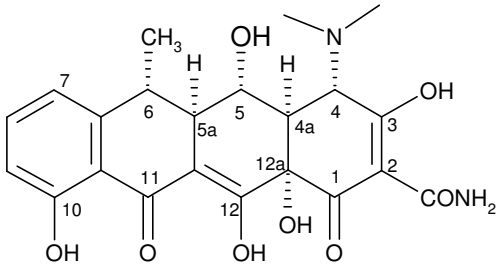
[Total: 20]

5 **(a)** The tetracyclines have been an important class of antibiotics notable for their broad spectrum, bacteriostatic action. The primary mechanism of action generally depends on binding to the A site of bacterial 30*S* ribosome subunit in the mRNA translation complex, thus inhibiting the binding of aminoacyl-tRNA to the translation complex. Essentially, protein synthesis is inhibited.

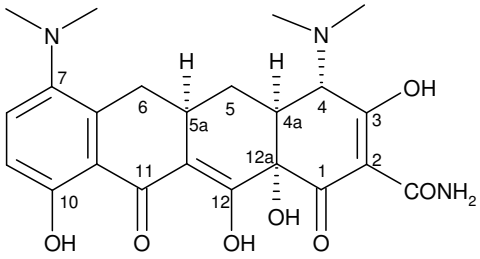
The structures of some typical tetracyclines are shown below.



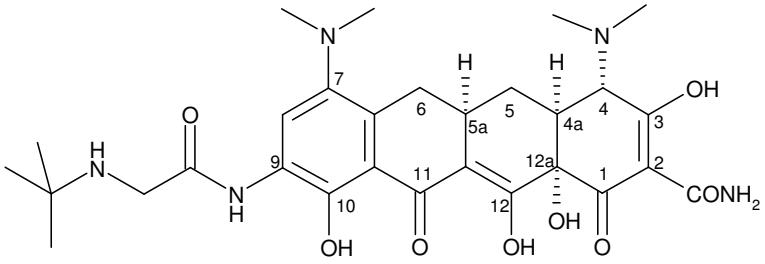
1
7-chlortetracycline (naturally occurring)
First tetracycline discovered.



2
doxycycline (semi-synthetic)
Effective against bubonic plague and anthrax.



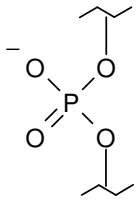
3
minocycline (semi-synthetic)
Used for treating central nervous system infections.



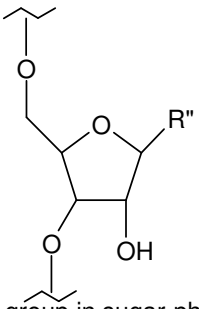
4
tigecycline
The latest derivative; considered a new class of drug (glycylcycline).

(i) By considering the structures of the tetracyclines **1** to **4**, propose the structure of the minimum pharmacophore that can exert the desired antibacterial effect.

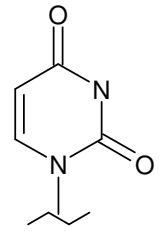
(ii) Some examples of structures found in ribosome RNA are shown below.



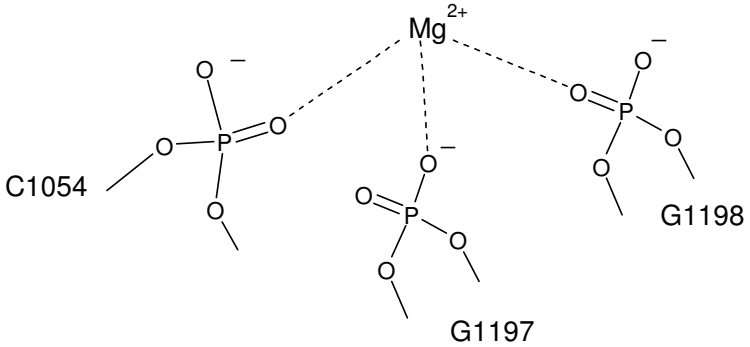
phosphodiester group in sugar-phosphate backbone of RNA



ribose group in sugar-phosphate backbone of RNA, where R" is a nitrogenous base



uracil, an example of a nitrogenous base in RNA



magnesium complex involving phosphodiester groups from cytidine 1054, guanidine 1197 and guanidine 1198 in ribosome

Propose how the tetracyclines bond to the binding pocket on the A site of the 30*S* ribosome subunit, using diagram(s) to illustrate your answer.
(Hint: There are 4 different types of interactions.)

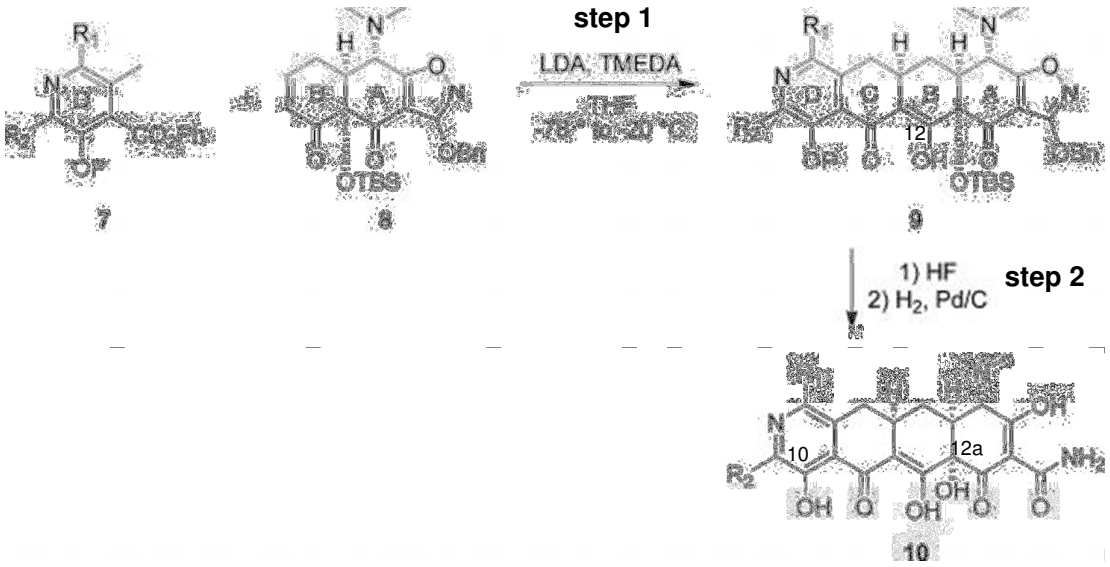
(iii) Why is minocycline **3** more effective in reaching the central nervous system compared to 7-chlortetracycline **1** and doxycycline **2**?

[5]

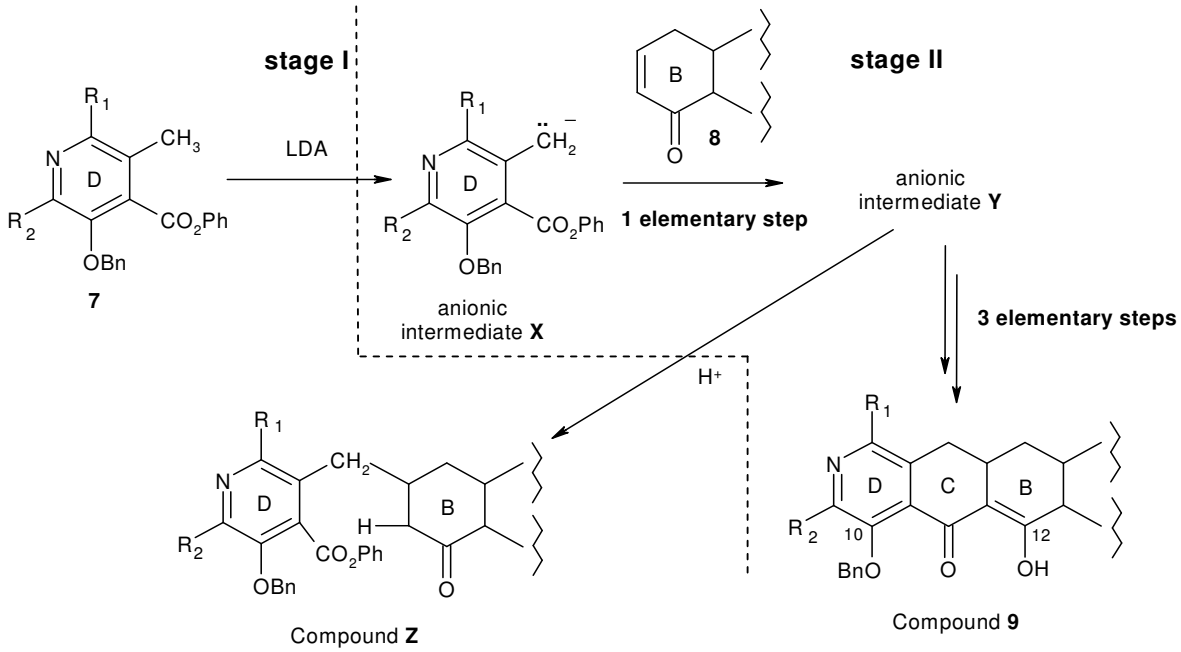
Tigecycline **4** is an example of a novel antibiotic discovered and approved for medical use in recent years. While most tetracyclines have fallen out of use due to widespread resistance developed in clinically relevant pathogens, tigecycline is able to exert antibiotic effect and overcome resistance.

In the past, semi-synthetic antibiotics are usually derived from chemical modification of natural products. However, new reactions discovered have enabled the synthesis of antibiotics from other precursors and afforded greater flexibility in structural modification.

An example is the synthesis of 8-azatetracyclines, shown below:



(b) In step 1, LDA functions as a strong base, and the C ring is formed when compounds **7** and **8** reacts to give **9**. Step 1 proceeds through the anionic intermediate **X** in the following scheme:



(i) Explain why **X** is stable and can be formed from **7**.

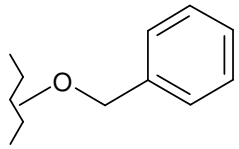
(ii) The likely structure of **Y** can be deduced from **Z**. Hence or otherwise, propose the mechanism of stage **II** of the reaction, where **X** and **8** react to form **9**. You may omit the A ring in your structures.
(Hint: Pay attention to the enol at C12 on ring B in compound **9**.)

[6]

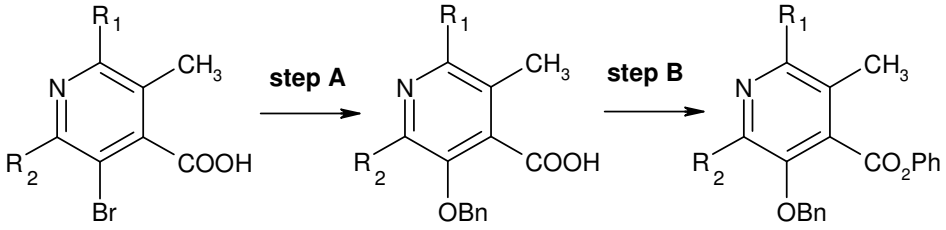
(c) In step 2 above, the –OH groups at C10 and C12a are generated to give compound **10**. Explain why the –OH groups should not be present in the starting materials **7** and **8**. Hence, state the function of the –OBn group in compound **7**.

[2]

(d) The –OBn group is a benzyl ether group and has the structure:



A synthesis of compound **7** using compound **5** is shown below:



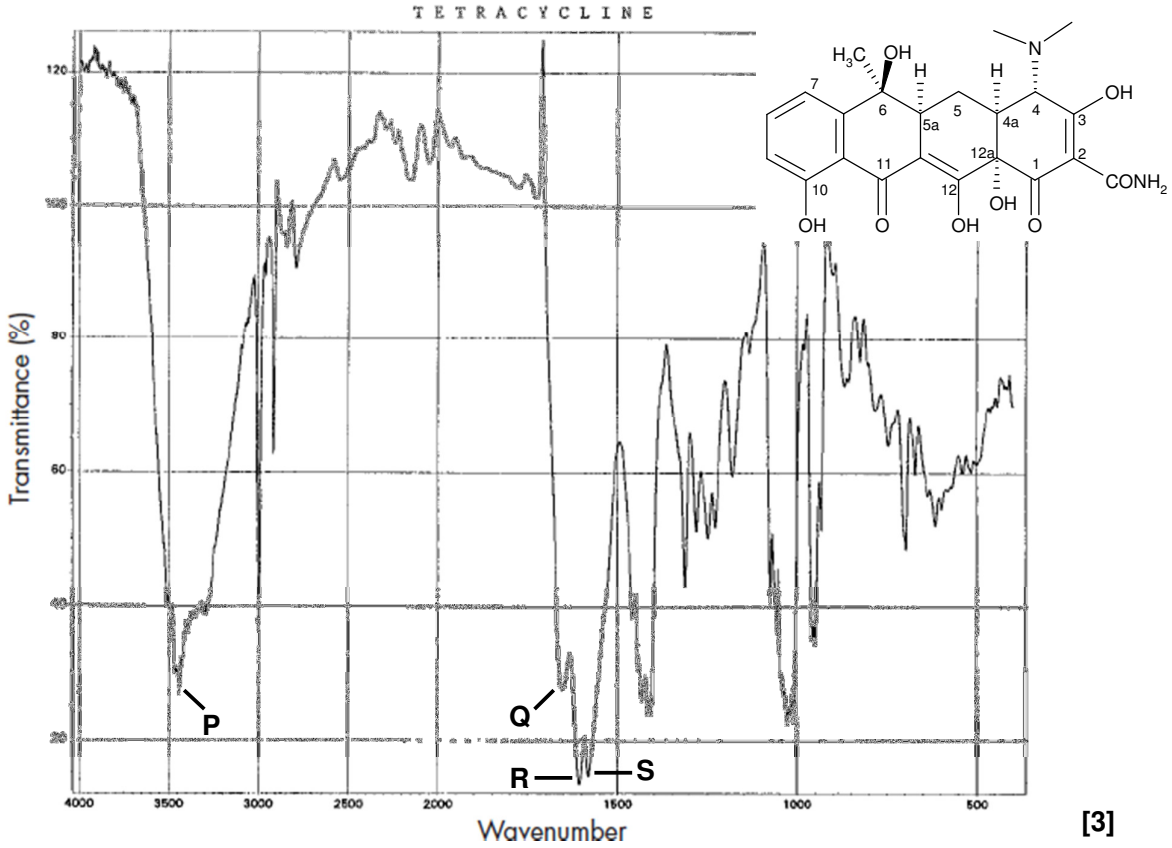
5 **6** **7**

(i) Suggest reagents and conditions for steps **A** and **B**.

(ii) State the type of reaction in step **A** and explain why it takes place even though **5** is aromatic.

[4]

(e) The enol groups in the tetracycline ring are stabilized by hydrogen bonding to the neighbouring C=O groups. Hence, assign the IR signals, **P**, **Q**, **R** and **S**, indicated in the IR spectrum below, to the relevant functional groups, explaining your answer.

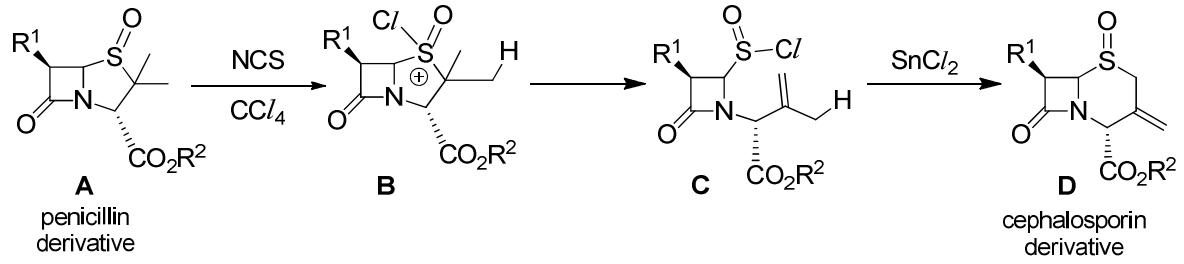


[3]

Source: "Synthesis and analysis of ethylated tetracycline, an antibiotic derivative that inhibits the growth of tetracycline-resistant XL1-Blue bacteria" Bartzatt *et al*, Biotechnol. Appl. Biochem. (2001) **33**, 65–69

[Total: 20]

6 **(a)** Penicillin derivatives and cephalosporins are a class of β-lactam antibiotics. The conversion of penicillin to cephalosporin can be carried out in the laboratory and follows a general route as shown below.

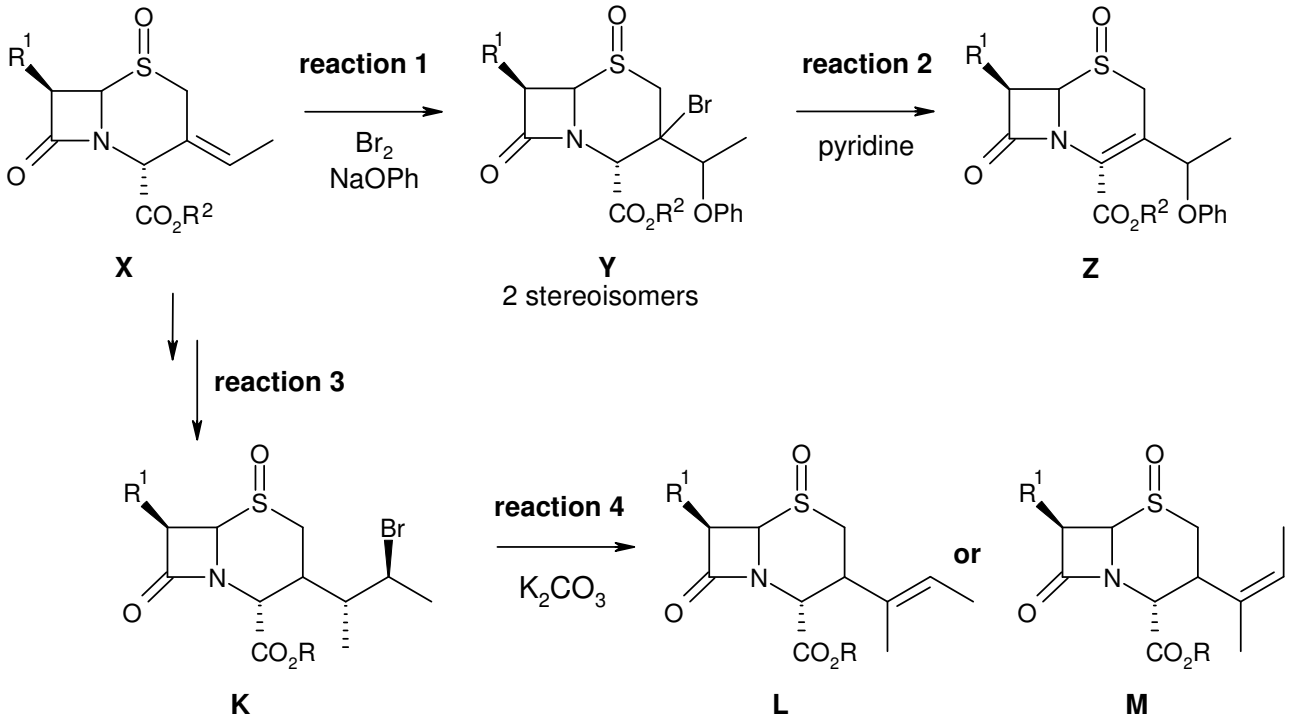


(i) What is the purpose of the first step in the above synthesis?

(ii) Propose a mechanism for the formation of **D** from **B**.

[4]

(b) In order to synthesize further derivatives of cephalosporin, the following scheme was considered.



(i) Propose the mechanism of the reaction for the formation of **Y** from **X,** accounting for the formation of 2 optical isomers. Show clearly the structures of the 2 stereoisomers of **Y**, and assign the *R*/*S* stereochemistry of the new chiral centres using CIP rules.

(ii) Determine if **L** or **M** is the only product of **reaction 4**. Justify your answer by outlining the mechanism.

[4]

(c) **L** and **M** are expected to have different physical properties.

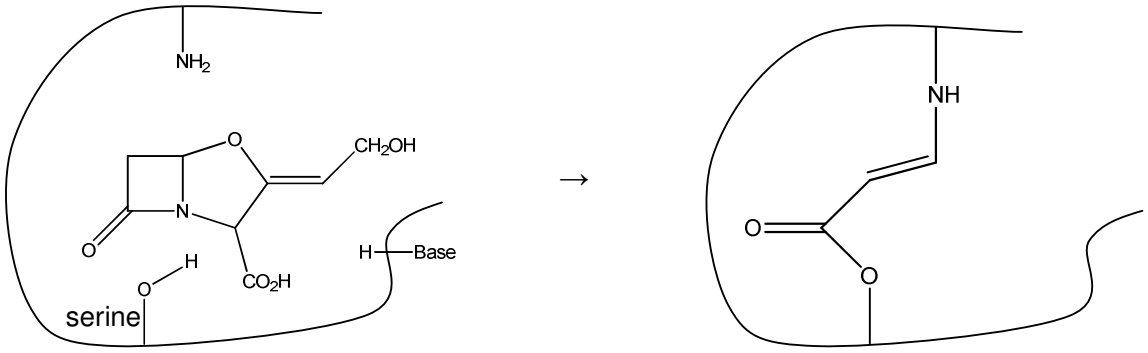
(i) Outline the principles of gas chromatography.

(ii) Explain why gas chromatography may not be suitable for the analysis of a mixture of compounds **L** and **M.**

[4]

(d) Many β-lactam antibiotics face the problem of drug resistance. To overcome this problem, many of such antibiotics are combined with clavulanic acid or its potassium salt. By itself, clavulanic acid has almost no antibiotic activity but it is a very effective irreversible inhibitor of β-lactamases, which are produced by the bacteria to inactivate the actual antibiotic.

Clavulanic acid fits into the active site of β-lactamases and inhibits it permanently. In the process, the β-lactam ring of clavulanic acid is first opened by a serine residue and protons are lost and gained at various stages, resulting in the blocked enzyme as shown below.



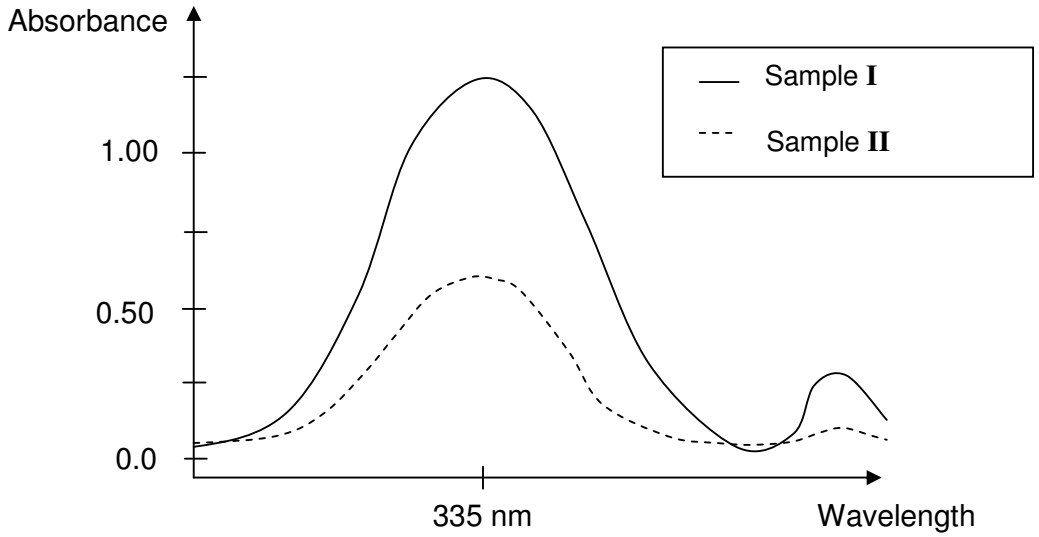
β-lactamase binding pocket irreversibly blocked

Provide a mechanism for this. Show clearly the structure of the molecule eliminated in the process. **[4]**

(e) Amoxicillin, is an analogue of penicillin and a broad spectrum antibacterial used in the treatment of various infections. Like all antibiotics, amoxicillin is subjected to degradation.

Ultraviolet spectroscopy can be employed to assay amoxicillin. A newly developed green bi-enzymatic UV-spectrophotometric method for the determination of amoxicillin in pharmaceutical preparations has been based on two enzymatic reactions in which the side chain of amoxicillin was selectively cleaved off by penicillin acylase, and subsequently, reacted with 2-oxoglutarate, by the catalysis of an enzyme, aminotransferase, to yield a compound **P** with a chromophore of high UV absorption at 335 nm. Thus the amount of amoxicillin can be determined by analyzing the amount of compound **P** produced using UV absorption at 335 nm.

Two samples containing amoxicillin were obtained. Sample **I** was from a recently manufactured batch of pills, while sample **II** was from leftover stock which have been kept for a period of time. The two samples were analysed using the above method. The measurements were made in 1.00 cm cells with the molar extinction coefficient **(ε)** of 13200 $dm^3\ mol^{-1}\ cm^{-1}$ for the chromophore at 335 nm. The following UV absorption spectra were thus obtained:

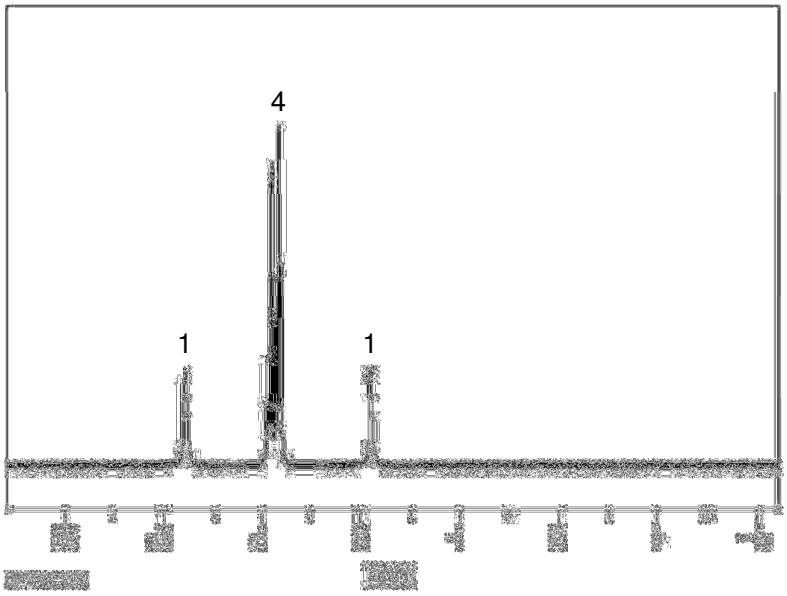


(i) Calculate the concentration of compound **P** obtained from sample **I**. **[1]**

(ii) Calculate the change in transmittance of compound **P** due to the degradation of amoxicillin with time in the stock used to prepare sample **II**. **[1]**

(iii) The molecular formula of compound **P** is $C_8H_6O_4$, and its M_r is 166.
The ^{1}H-NMR spectrum of **P** is given below. Peaks at 5.8 ppm and 9.6 ppm disappear in D_2O solvent.

Analyze the spectrum and propose a possible structure of compound **P**, giving your reasons. **[2]**



[Total: 20]

COVER PAGE

Name:	Index Number:	CT Group:

RAFFLES INSTITUTION
2011 YEAR 6 PRELIMINARY EXAMINATION

Higher 3

PHARMACEUTICAL CHEMISTRY **9812/01**

Attach this Cover Page on top of your answer script.

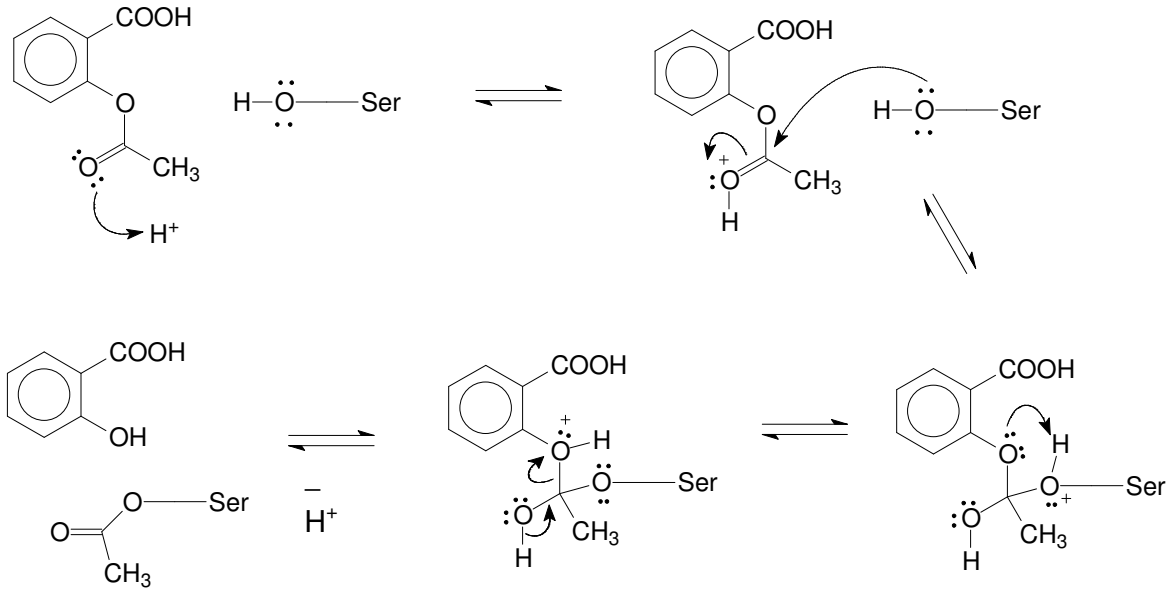
Question Number (Please **circle** the questions you have attempted.)	**Marks**
1	**/ 20**
2	**/ 20**
3	**/ 20**
4	**/ 20**
5	**/ 20**
6	**/ 20**
Total	**/ 100**

Suggested solutions to RI 2011 H3 prelim exams

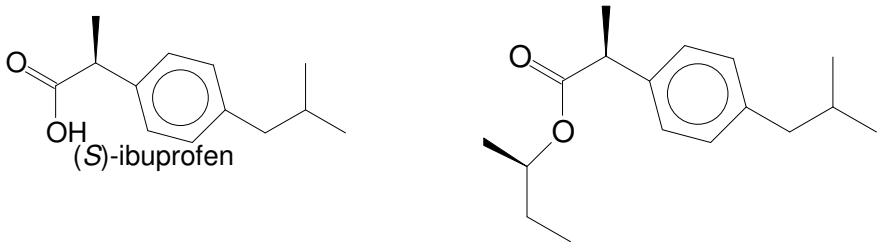
1(a) Non-narcotics work on the pain receptors themselves, preventing them from responding normally to pain stimuli, as opposed to narcotics, which have an effect in depressing the central nervous system, hence affecting the capacity of the brain to appreciate pain.

1(b) Its anti-inflammatory effect is due to the **irreversible inhibition** of the cyclooxygenase (**COX-2**) enzymes. The COX-2 catalyses the synthesis of chemical mediators (**prostaglandin**) of the inflammatory and allergic response, thus inhibition of COX-2 reduces inflammatory and allergic response.

1(c) Acid-catalysed transesterification mechanism



1(d)



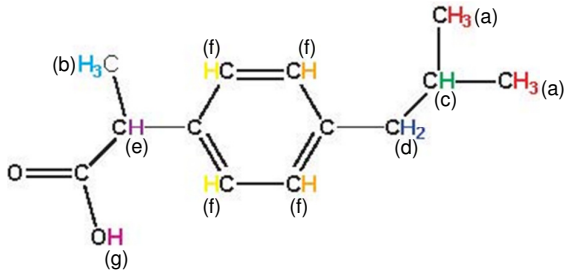
(*S*)-ibuprofen

(*R*)-1-methylpropyl (*S*)-2-(4-(2-ethylpropyl)phenyl)propanoate

1(e)(i) Chemical shift is the position of NMR absorption along the NMR spectrum, at which resonance occurs for the nucleus, arising from electronic shielding or deshielding in a specific chemical environment.

1(e)(ii)

δ/ ppm	Multiplicity of signal	Ratio of number of protons
0.9	doublet	6
1.5	doublet	3
1.9	multiplet	1
2.5	doublet	2
3.7	quartet	1
7.1 – 7.3	multiplet	4
12.0	singlet	1

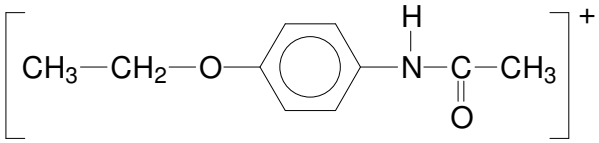
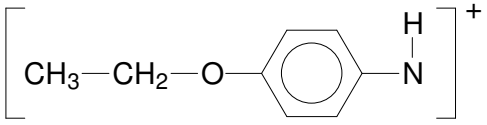
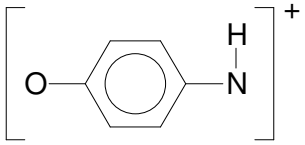
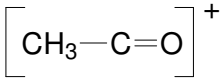


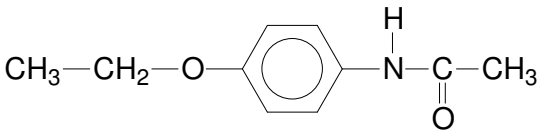
1(f) The ^{1}H NMR spectrum shows that the majority of the diastereomers are of the (*R,S*) type. This indicates a preference of the isomerase for the (R)-enantiomer of ibuprofen. The isomerase converted (*R*)-ibuprofen to the active (*S*)-enantiomer.

1(g) A prodrug is a molecule that is inactive in itself, but which is converted to the active drug in the body, normally by an enzymatic reaction.

1(h)

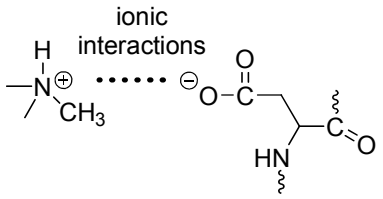
δ / ppm	**Relative area**	**Multiplicity of signal**	**Protons responsible for the signal**
1.4	3	triplet	C**H$_3$**–CH$_2$–O–
2.0	3	singlet	C**H$_3$**–CO–
4.0	2	quartet	Me–C**H$_2$**–O–
6.7	2	doublet	Aromatic proton
7.5	2	doublet	Aromatic proton
8.0	1	singlet	Amide proton

m/z values	**ion**
179	Molecular ion 
136	
107	
43	

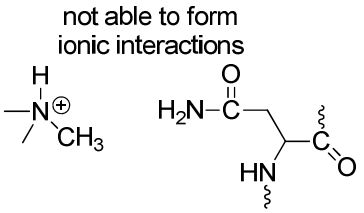


Phenacetin

2 **(a)** Binding between morphine and the μ-opioid receptor involves ionic interactions between the carboxylate side-chain of aspartic acid and the protonated amine group in morphine. When the aspartic acid residue was replaced with asparagine, ionic interactions are disrupted as the -$CONH_2$ group cannot form ionic interactions, hence the binding is reduced.



aspartic acid residue



asparagine residue

(b) **(i)** The phenol group is also necessary for binding to the μ-opioid receptor via hydrogen bonding. (OR benzene and van der Waals forces)

(ii) Naloxone, as a competitive antagonist, binds to the <u>active site</u> of the μ-opioid receptors and prevents morphine from binding to them. Being an antagonist, it <u>does not cause any change in the shape of the receptor</u> and there is <u>no resulting physiological effect</u>, hence the effects of morphine overdose can be countered.

(c) **(i)** N-H absorption at 3350–3500 cm^{-1} present in **A** but not **B**

(ii) C=O absorption peak of **A** will be at a lower wavenumber. The C=O bond in **A** is weaker due to resonance with the benzene ring.

(d) Compound **A** will be eluted first. This is because **A** would <u>interact better</u> with the polar mobile phase due to the presence of the more polar NH_2 group. (or **C** will interact better with the non-polar stationary phase due to the presence of more hydrophobic benzene rings.)

(e) **(i)** Step **1**: condensation/nucleophilic acyl substitution Step **2**: reduction

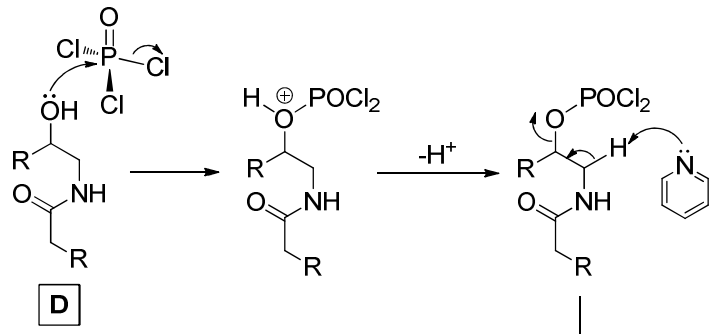
(ii) Step **2** does not produce an optically pure product. The reduction occurs via a nucleophilic addition reaction. The nucleophile (H^-) can attack from the top or bottom of the plane of the carbonyl functional group, giving rise to both enantiomers.

(iii) If Step **2** were to be carried out first, a molecule containing –OH and $–NH_2$ will be obtained.

Besides the $–NH_2$ group, the –OH group in the molecule will also react with acid chloride **B** (to give an ester) , hence resulting in a mixture of products and low yield of **D**.

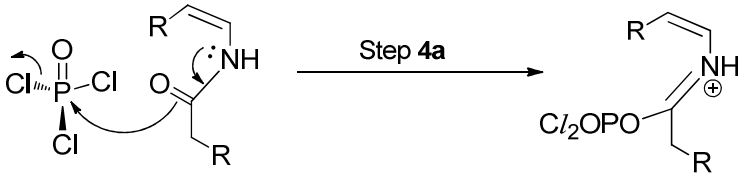
(f) $POCl_3$ is a dehydrating agent.

E2 mechanism (E1 mechanism will also be accepted)

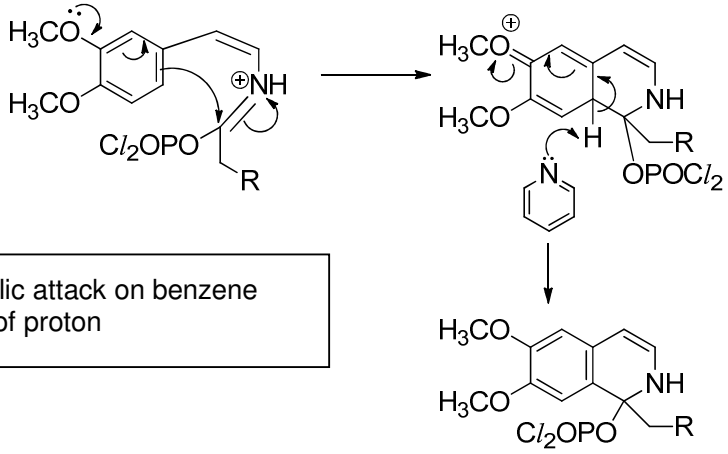


Formation of –OPOCl_2 leaving group
Deprotonation
Formation of C=C bond

(g) **(i)** Appropriate arrow-pushing (3 arrows in one step)

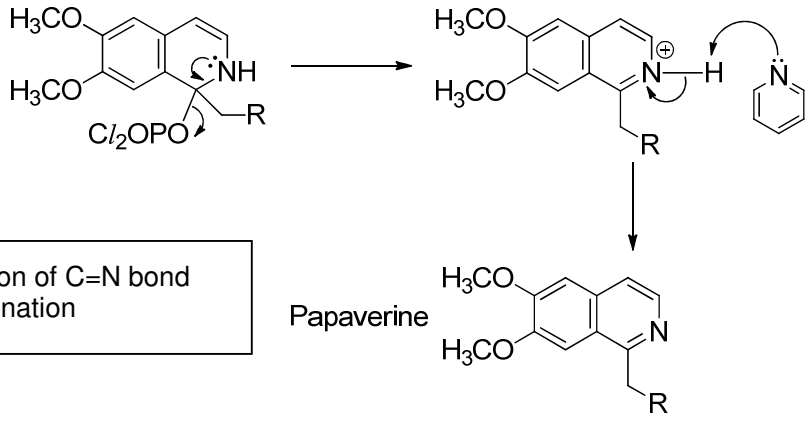


(ii) Type of reaction: Electrophilic Aromatic Substitution



Electrophilic attack on benzene
Removal of proton

(iii)



3 **(a)** A drug can

- inhibit the synthesis of the neurotransmitter in the pre-synaptic nerve
- inhibit the release of the neurotransmitter from the vesicles into the synaptic cleft
- act as antagonists at the receptor protein.

(b) **(i)** A reuptake inhibitor is a drug that prevents the reuptake of the neurotransmitter at pre-synaptic nerve resulting in an increased extracellular concentrations of the neurotransmitter.

(ii) Cocaine binds tightly to the dopamine transporter and prevents the reuptake of dopamine into the pre-synaptic nerve, resulting in an accumulation of dopamine at the synaptic cleft. This results in prolonged signalling at the dopamine receptors of the post synaptic nerve, hence producing euphoria.

(c) Cocaine possesses four chiral carbons, having a possible total of 16 different stereoisomers. This makes asymmetric synthesis of the psychoactive isomer of cocaine especially difficult.

(d) Inhaling the hydrochloride salt of cocaine will result in a dilute solution of HCl forming on the mucous membranes, resulting in the destruction of the membranes over time.

(e) **(i)** A psychoactive drug is one which crosses the blood-brain barrier and affects the central nervous system to produce various changes in mood, behaviour, etc.

(ii) With reference to the structure, cocaine is less non-polar than cocaethylene and hence does not cross the blood-brain barrier as easily as cocaethylene .

(iii) The electron-releasing ethyl side chain makes ethanol a more powerful nucleophile, hence favouring its attack at the acyl carbon of cocaine.

4 **(a)** Unlike noradrenaline, amphetamine does not have two hydroxyl groups on the benzene ring (or catechol) and a hydroxyl group on the benzyl carbon.

Without these hydroxyl groups, amphetamine is unlikely to dock well at and bind strongly to the adrenergic receptor site to bring about the desired physiological effect. Hence, amphetamine is not an agonist of the adrenergic receptor.

(b) Any **<u>one</u>** of the following:

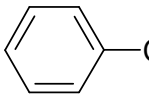
Amphetamine, which is structurally similar to noradrenaline, is transported into the nerve cells by the carrier proteins of noradrenaline. Because amphetamine competes with noradrenaline for carrier proteins, noradrenaline is more slowly reabsorbed into the nerve cells.

Amphetamine inhibits monoamine oxidase, one of the important enzymes involved in the metabolism of monoamines such as noradrenaline. This, in turn, leads to a build-up of noradrenaline and dopamine levels in the synaptic gap.

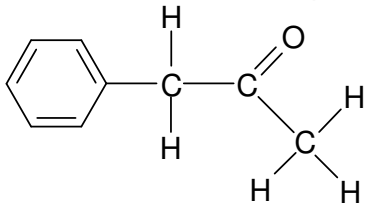
Amphetamine opens up the protein carrier molecule channels in the surface of the pre-synaptic nerve and allows stored noradrenaline and dopamine molecules to leak out from the nerve into the synapse. In addition, amphetamine is also able to release stores of another neurotransmitter, serotonin, from the pre-synaptic vesicles.

<u>AND</u>

Increasing the synaptic concentrations of the neurotransmitters leads to stronger nerve impulses and keeps the person alert over a longer period of time. **(OWTTE)** Being able to focus for a longer time is likely to improve performance. **[1]**

(c) **(i)** m/z = 91: $[C_6H_5CH_2]^{\bullet+}$ or [ $CH_2]^{\bullet+}$ **and** m/z = 43: $[CH_3CO]^{\bullet+}$

full structural formula of 1-phenylpropanone



Note: 3-phenylpropanal gives major peaks at m/z = 77 and m/z = 105.

(c) **(ii)** Compared to the secondary amine of methamphetamine, the ketone is able to form stronger intermolecular hydrogen bonds with water molecules.
Note: "O---H–O" hydrogen bond is stronger than "N---H–O" hydrogen bond.

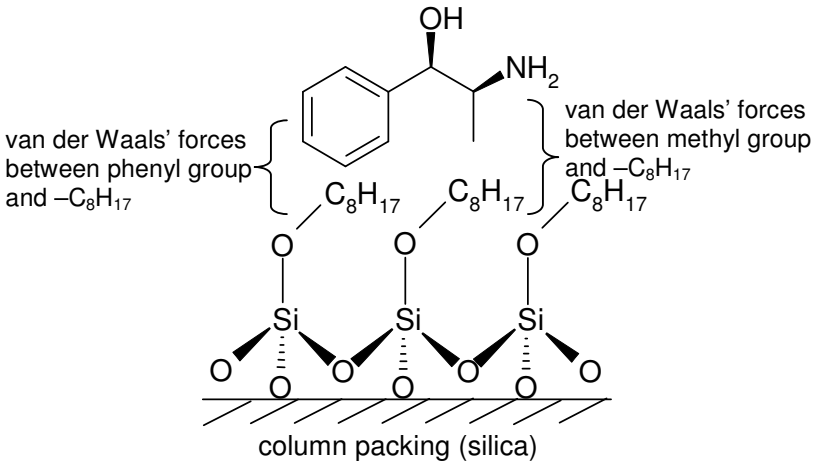
(d) **(i)** Ammonia converts protonated amines back into their free base forms so as to prevent tailing, which is caused by the strong ion-dipole interactions between the protonated amine and the silanol groups on the silica gel plate.

(ii) Caffeine is highly polar because it has many ketone and amine functional groups. Solvent system **A** is much more polar than solvent system **B**. When system **A** is used, caffeine is relatively more soluble in the mobile phase and is therefore less strongly adsorbed on the stationary phase. Hence, caffeine is able to move further along the chromatographic plate and result in a larger R_f value.

(iii) The silica gel on the plate contains a chromophore which fluoresces when exposed to ultraviolet radiation. The parts that are masked by the sample

spots will appear darker because the molecules of the samples, in which there is delocalisation of π electrons (or a conjugated π system), absorb ultraviolet radiation. This allows the spots, which would otherwise be invisible, to be seen.

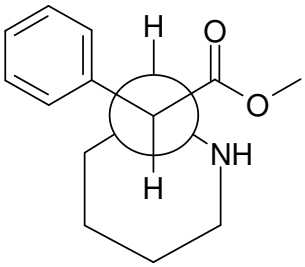
(e) **(i)**



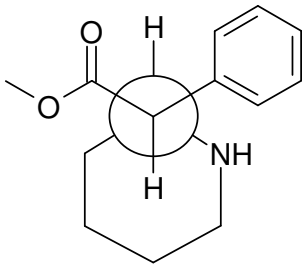
(ii) increasing order of elution time:
phenylpropanolamine < methamphetamine < phentermine

At pH 3, the amino groups are protonated. The more polar the compound is, the more soluble it is in the mobile phase, and the shorter the elution time becomes. Due to the hydroxyl and protonated amino groups, phenylpropanolamine will be the most polar and is eluted first. As the secondary amine of methamphetamine is a stronger base than the primary amine of phentermine, more methamphetamine molecules than phentermine molecules will be protonated at pH 3. Therefore, methamphetamine is more likely to be eluted after phenylpropanolamine.

(f)



or

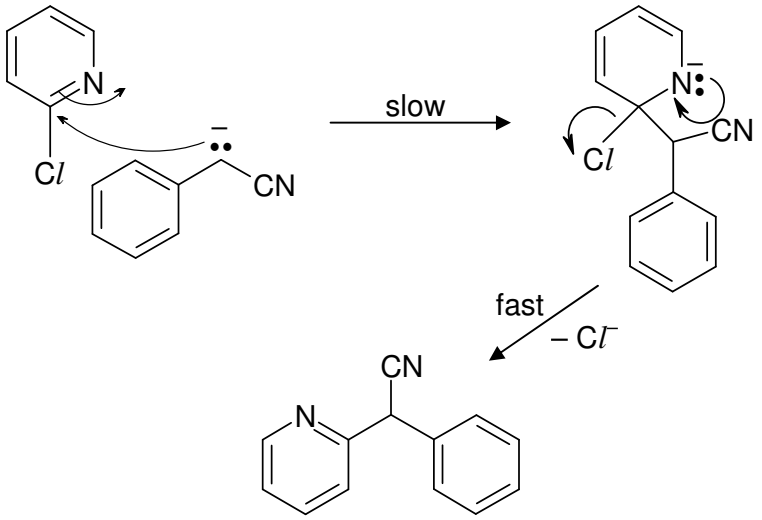


1*S*,2*R* **1*R*,2*S***

(For both structures, C1 is in front.)

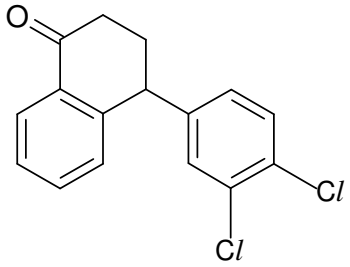
(g) nucleophilic aromatic substitution

$C_6H_5CH_2CN + NaNH_2 \longrightarrow [C_6H_5\bar{C}HCN] + Na^+ + NH_3$

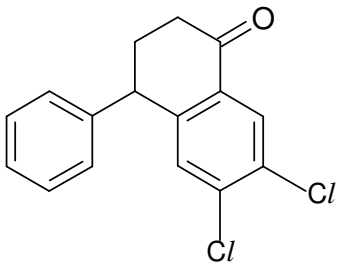


each step (including arrows, lone pairs, charges, intermediate, etc.)

(h)



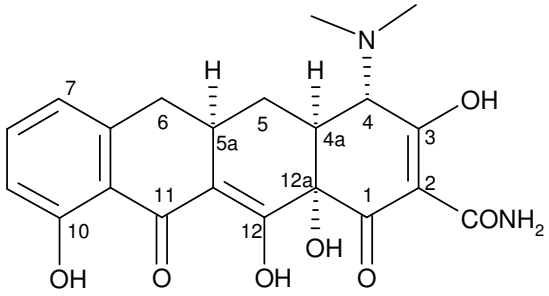
compound **Y**



compound **Z**

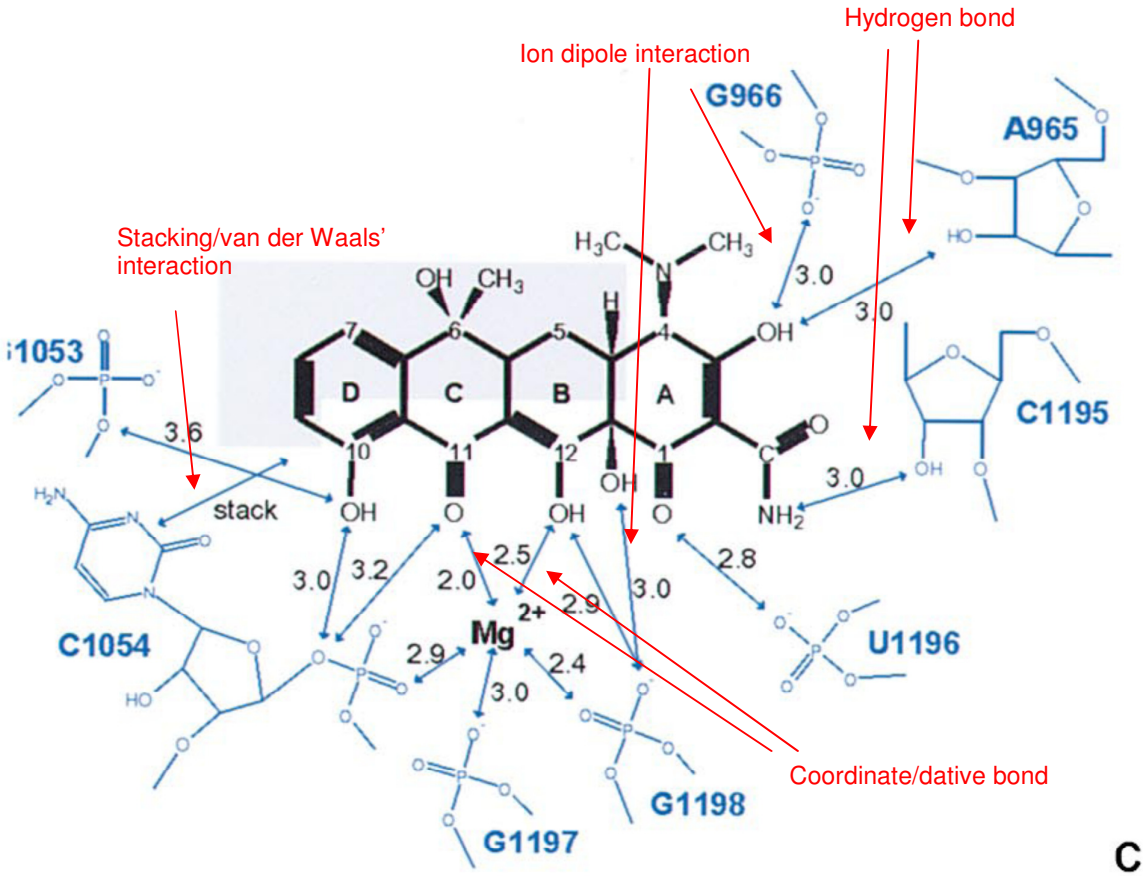
Compounds **Y** and **Z** are products of an intramolecular electrophilic aromatic substitution reaction. Since the benzene ring without the chloro groups has greater π electron density than the benzene ring bonded to two electron-withdrawing chloro groups, the former attacks the electrophile more readily and leads to the formation of a larger amount of compound **Y**.

5(a)(i)



Minimum pharmacophore, based on common structural features of all the tetracycline derivatives

5(a)(ii)

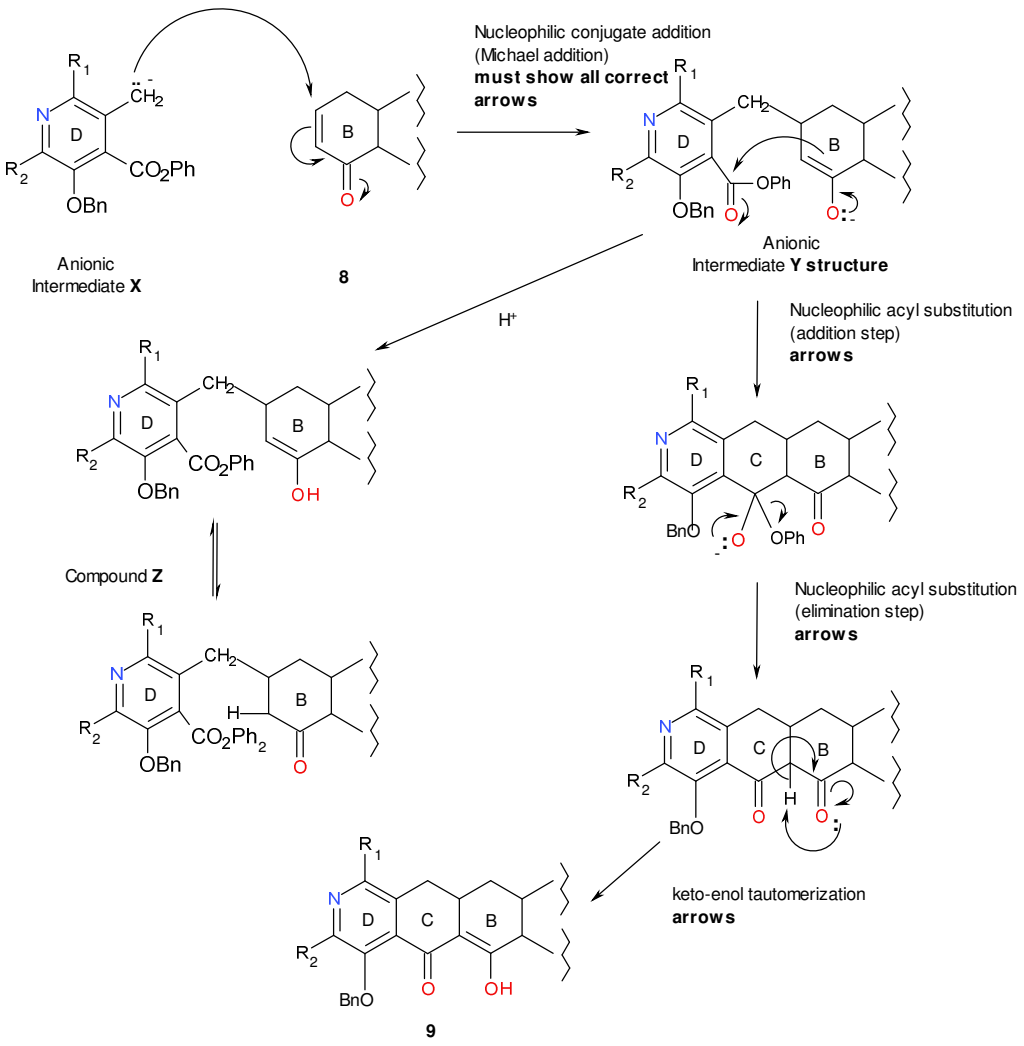


Taken from:
"The Structural Basis for the Action of the Antibiotics Tetracycline, Pactamycin, and Hygromycin B on the 30S Ribosomal Subunit"
Ramakrishnan *et al*, **Cell, Vol. 103, 1143–1154, December 22, 2000**

5 (a)(iii) Minocycline has an –OH group removed at C6. It is less hydrophilic and more lipophilic. Thus it can cross the blood-brain barrier more effectively.

5 (b)(i) The –ve charge on the CH_2 side chain in **X** can be dispersed via delocalisation with the pyridine π electron cloud. Thus the anion **X** is stabilized**.**

5(b)(ii)



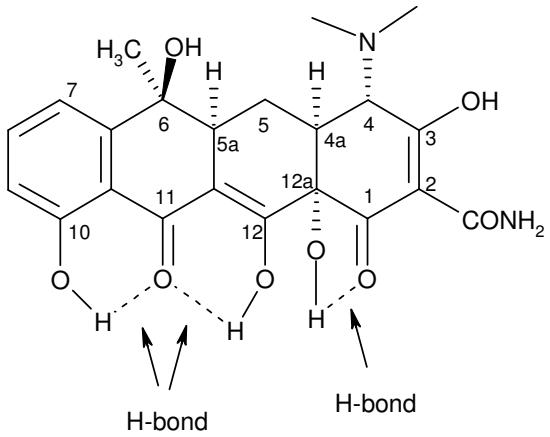
5(b)(iii) The OH groups have a labile H^+ which will react with the strong base LDA, as well as protonate the anionic intermediates **X** and **Y**.
OR, the OH groups can be deprotonated to give -O:$^-$ groups, which can act as nucleophiles to attack the C=O and C(O)OPh groups.

Thus the –OBn group acts as a protecting group **OWTTE**

5(c)(i) Step A: $BnO^-\ Na^+$, warm Step B: $SOCl_2$, followed by PhO^-Na^+

5(c)(ii) Nucleophilic aromatic substitution (accomplishing the Williamson's ether synthesis)
This is possible because the N atom is electron withdrawing, and reduces the electron density in the pyridine ring, hence making nucleophilic attack possible/the N atom acts as electron sink during nucleophilic attack.

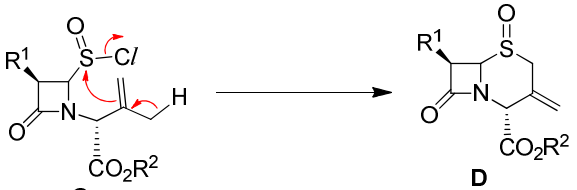
5(d) **P** – O-H group,
Q – C=O of $CONH_2$ group**,** 1656 cm^{-1}, lower frequency due to delocalisation of C=O π and N: lone pair electrons
R – C=O of C1**.** The C=O bond electron density is reduced partially by hydrogen bonding of the O atom to the neighbouring H-O group.
S – C=O of C11**,** The C=O bond electron density is reduced to a larger extent by hydrogen bonding of the O atom to **two** neighbouring H-O groups.



6(a)(i) To make the sulfur a better leaving group (for elimination)

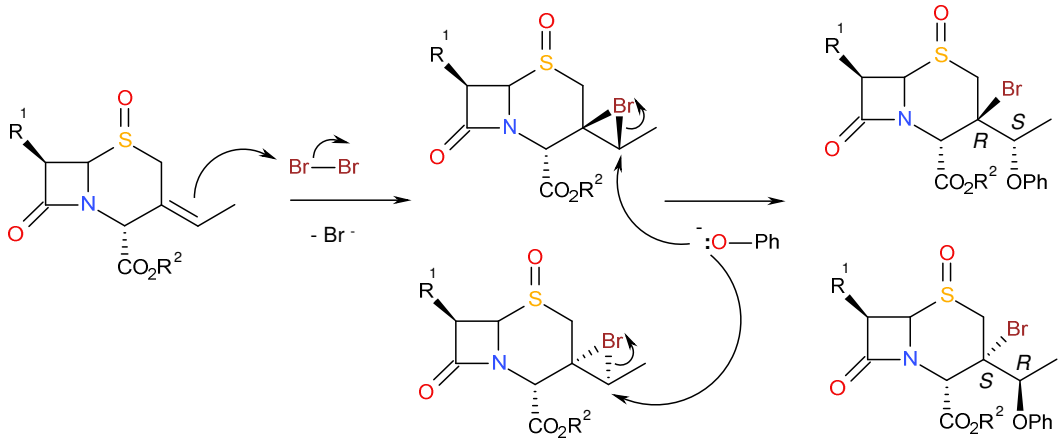
(ii) Mechanism

B C

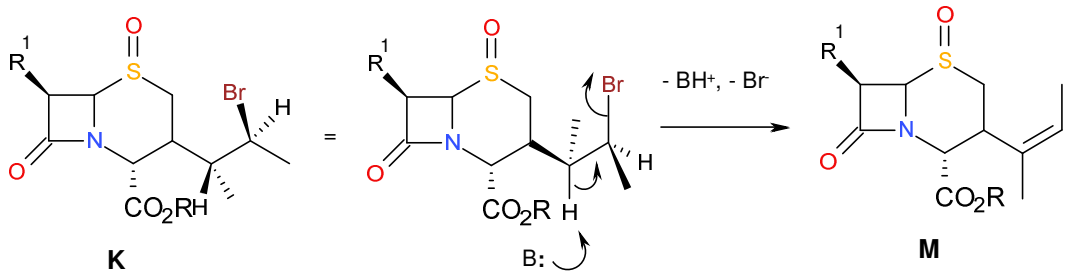


C D

6(b)(i)



(b)(ii)



K **M**

must be anti-periplanar
note methyl group and ring are "up"

methyl group and ring should be cis

6(c) **(i)** In order to use gas chromatography for analysis, the analytes must be volatile.

The mobile gas phase (e.g. helium, nitrogen) carries the vaporised analytes through a heated column that contains the stationary phase, which is usually a non-volatile liquid impregnated on a solid support.

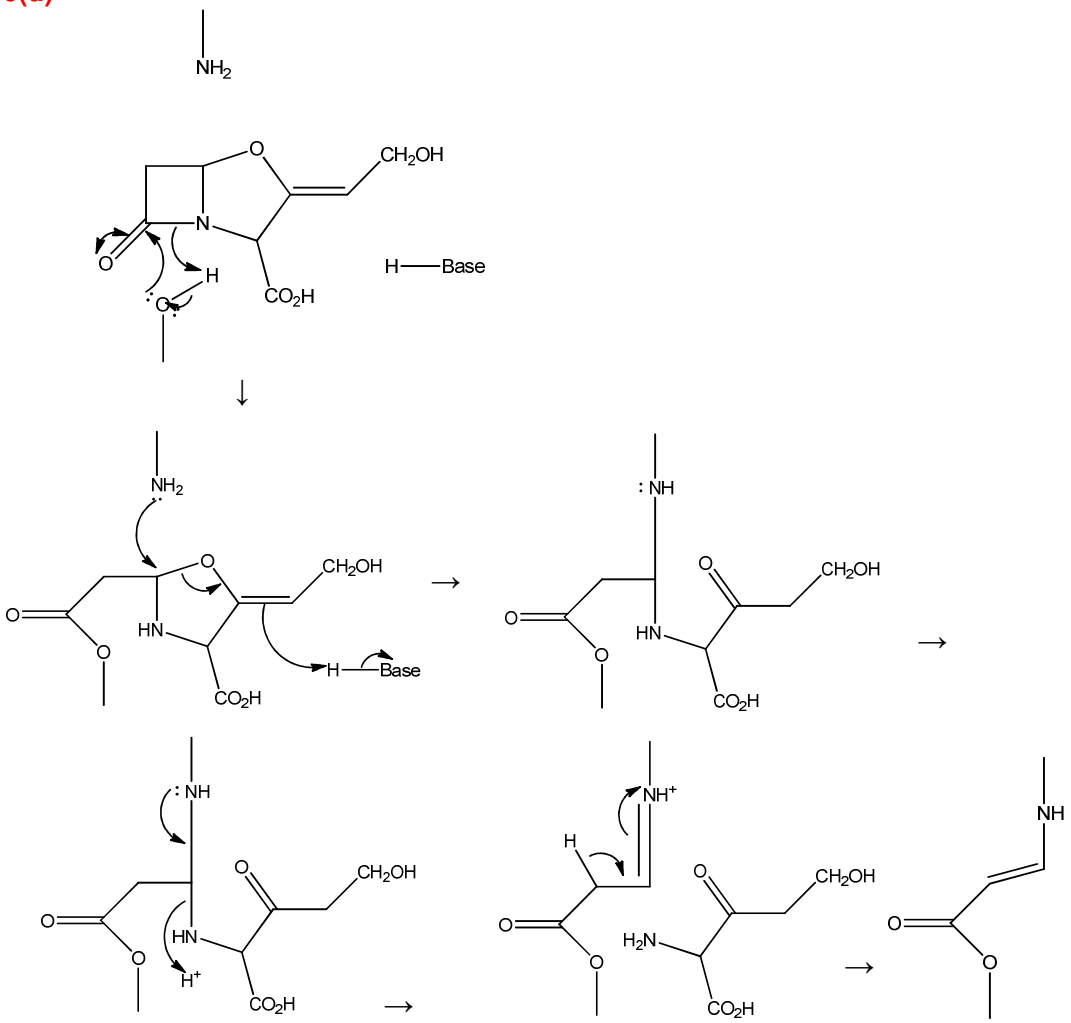
As each analyte has a different solubility in the stationary phase, the analytes move through the column at different speeds and are separated.

The analyte that is least soluble in the stationary phase is eluted and detected first while the one that is most soluble is eluted and detected last.

(ii) **L** and **M** have large relative molecular masses and may not be volatile.

In addition, their almost identical structures will likely cause them to be equally soluble in the stationary phase and move equally fast in the mobile gas phase.

6(d)



6(e)

(i) A = εcl, hence c = 1.250/(13200 x 1) = **9.47×10^{-5} mol dm^{-3}**

(ii) T = (I/I_o) x 100% , hence

Before degradation, A = 1.250

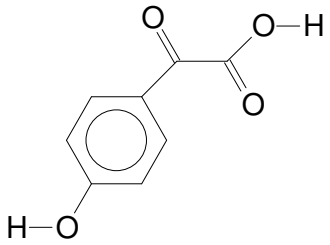
since A = log (I_o/I), I/I_o = 0.0562, therefore T = 5.62%

After degradation, A = 0.625

since A = log (I_o/I), I/I_o = 0.237, therefore T = 23.71%

Hence, the change in transmittance = 23.71 – 5.62 = **<u>18.09%</u>**

(iii) Compound **P** is



Mr of **P** = 166
Molecular formula is $C_8H_6O_4$

The peaks for O-H and –COO–H will disappear under D_2O solvent due to proton exchange.
The multiplet at near 8 ppm corresponds to the 4 aromatic protons.
OH at 5.8 ppm, COOH at 10ppm

Compound **P** is 4-hydroxybenzoyl formate, or 2-oxo-2-(4-hydroxyphenyl) ethanoic acid, with M_r = 166 and molecular formula $C_8H_6O_4$.