RAFFLES JUNIOR COLLEGE
PRELIMINARY EXAMINATION 2008

HIGHER 3

PHARMACEUTICAL CHEMISTRY 9812/01

Paper 1 **28 August 2008**

2 hour 30 minutes

Candidates answer on separate paper.

Additional Materials: Answer Paper
Data Booklet

READ THESE INSTRUCTIONS FIRST

DO NOT open this question booklet until you are told to do so.

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

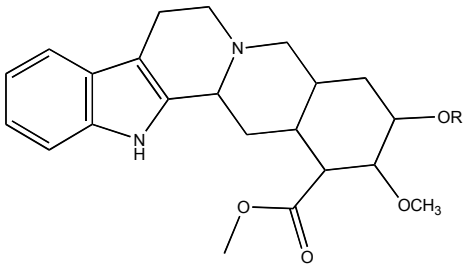
Answer any **five** questions.
Begin each question on a fresh sheet of paper.
A Data Booklet is provided. Do not write anything on it.
You are reminded of the need for good English and clear presentation in your answers.

The number of marks is given in brackets [ ] at the end of each question or part question.
At the end of the examination, fasten all your work securely together.

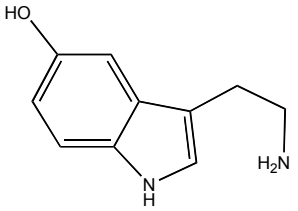
This question booklet consists of **12** printed pages.

 [Turn over

1(a) Reserpine is a natural occurring drug that has been used for centuries in ancient India to treat hypertension, cholera and snakebites. It competes with neurotransmitters such as serotonin and dopamine for the storage vesicles in the pre–synaptic nerve.



reserpine

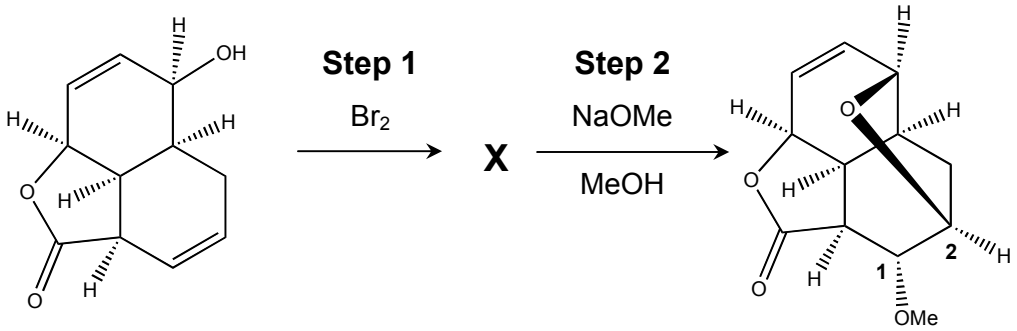


serotonin

(i) Based on the structure of serotonin as shown, copy out the structure of the reserpine molecule and circle the most likely part(s) of reserpine that is responsible for its action.

(ii) Suggest **two** physiological effects of the neurotransmitters mentioned above.

Two of the steps involved in the synthesis of reserpine are shown below.

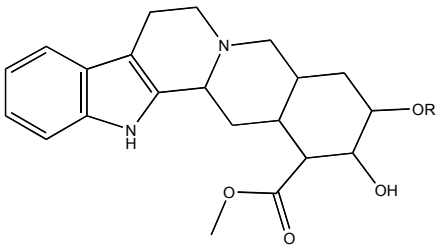


(iii) Predict the structure for **X**. Show the mechanism involved in **Step 1** and include the stereochemistry of the intermediate **X**. State also the configurations (*R* or *S*) of the two carbon centres (C–1 and C–2).

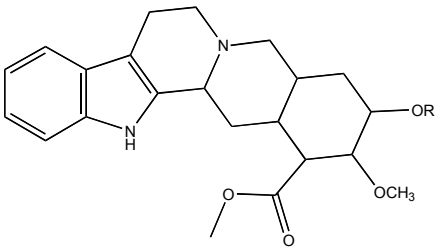
(iv) **Step 2** involves two reactions to give the desired product as shown above. What is / are the type of reaction(s) involved?

(v) Name the side reaction that might occur in **Step 2**. [10]

Pseudoreserpine is another natural product which is extracted from the roots of plants. Pseudoreserpine and reserpine are shown below, and both molecules contain a chromophore that absorbs UV radiation.



pseudoreserpine



reserpine

(vi) Explain the term *chromophore* and draw the chromophore that is responsible for the UV absorption.

(vii) Pseudoreserpine has λ_{max} = 282 nm and molar absorptivity, ε = 11.900 x 10^3 L cm^{-1} mol^{-1}. What is the concentration of pseudoreserpine in a solution whose absorbance, A = 0.065 with a sample path length, l = 1.00 cm?

(viii) State a solvent which is suitable for dissolving pseudoreserpine for UV analysis. [5]

1(b) Parkinson's disease is a result of the deficiency in dopamine transmission to certain parts of the brain. The prodrug Levodopa is supplied as a medication that acts on the sympathetic nervous system to increase dopamine levels in the body.

Although there are some adverse effects associated with Levodopa, it has fewer of these than other anti–Parkinson's drugs such as Parlodel.

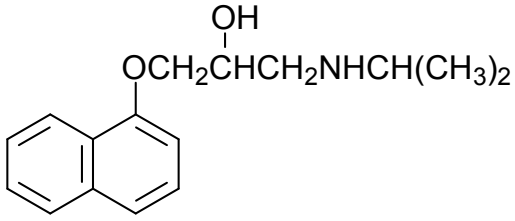
(i) Despite having these side effects, Levodopa has certain characteristics of an *ideal drug*.

Other than having no side effects, suggest **two** general characteristics that an ideal drug should have.

(ii) Parlodel is a dopamine *agonist*.

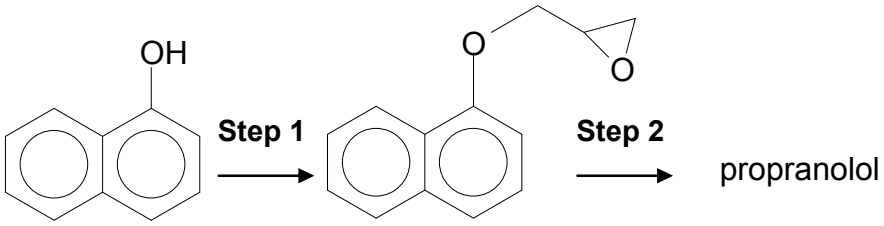
Explain how agonists and antagonists differ in their interactions with receptors. [5]

2 Propranolol was the first clinically successful "pioneer drug" that serves as the neurotransmitter– and endocrine–derived agonists for beta–adrenergic receptors associated with the mammalian sympathetic nervous system. However, propranolol is a nonselective beta–blocker and can cause cardiac depression.



propranolol

(a) The synthesis of propranolol is outlined below.

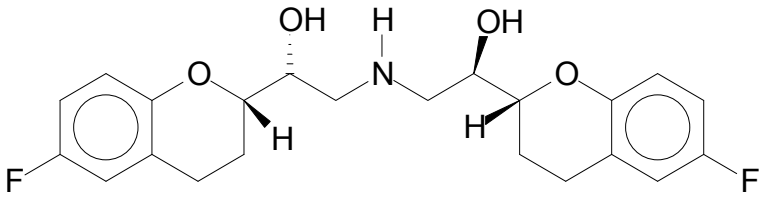


propranolol

(i) Suggest reagents for **Steps 1** and **2**.

(ii) Suggest a mechanism for both **Step 1** and **Step 2**. [6]

A new selective beta–blocking agent, nebivolol, was launched in the late 1990s.



nebivolol

(b) State the number of chiral carbon centres in nebivolol. Indicate the stereochemistry of these chiral carbon centres as *R* or *S*. [2]

(c) Draw the structure of the enantiomer of nebivolol. [1]

(d) Suggest what structural features propranolol and nebivolol have in common. [2]

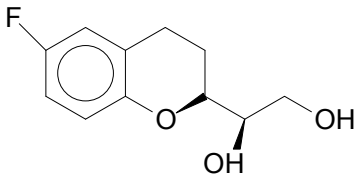
(e) Suggest why

(i) propranolol is a nonselective beta–blocker whereas nebivolol is a highly selective beta–blocking agent.

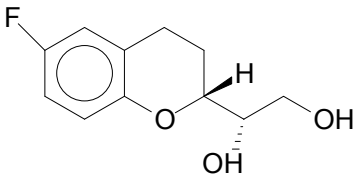
(ii) nebivolol exhibits nearly 200 times higher beta–adrenergic binding affinity than its enantiomer.

(iii) nebivolol is marketed as its racemic mixture. [4]

(f) Compound **W**, $C_{11}H_{13}FO_2$, is used in the synthesis of nebivolol. **W** reacts with sodium hydroxide to form two compounds **X** and **Y**.



X



Y

(i) What is the stereochemical relationship between **X** and **Y**?

(ii) Deduce the structure of compound **W** using the IR, NMR and mass spectra data given below:

The IR spectra showed the following absorptions:

3500, 3350, 3045, 2990, 1650, 1200, 650 cm^{-1}

The ^1H NMR spectra showed the following peaks:

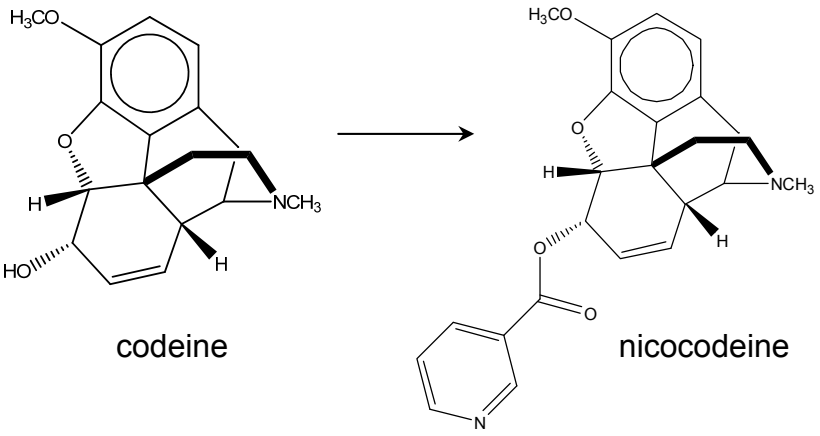
δ value	relative area	comment
2.25	2	multiplet
2.55	2	triplet
3.95	2	doublet
5.45 – 5.70	2	multiplet
4.5	1	disappears with D_2O
7.0	1	disappears with D_2O
6.72 – 6.50	3	multiplet

The mass spectra showed the mass numbers of major peaks observed:

m/z 195, 75, 41

[5]

3 Nicocodeine was first introduced in the late 1950s by Lannacher Heilmittel of Austria and it has been used as a cough suppressant and analgesic. Nicocodeine, a derivative of codeine, can be synthesized in the laboratory.



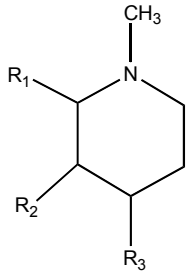
codeine nicocodeine

(a) Suggest the reagents and conditions required for the **one**–step synthesis. You are allowed to use additional organic molecule(s) if necessary. [1]

(b) Codeine is unstable under strong acid conditions. When heated with hydrogen iodide, it reacts to form compound **A** which is aromatic. Suggest the structure of **A**, showing any stereochemistry involved. [2]

(c) Codeine is a narcotic analgesic. Describe briefly how narcotic and non–narcotic analgesics act differently to prevent pain. [2]

(d) One of the N–containing rings in codeine can be represented as shown below.

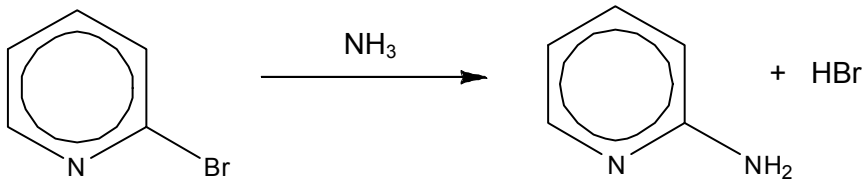


Draw the boat conformation and chair conformation showing the positioning of the substituents on the ring. State which of these two conformations is the more stable one. Give your reasons. [4]

Nicocodeine contains a pyridine ring. Like benzene, pyridine is an aromatic compound.

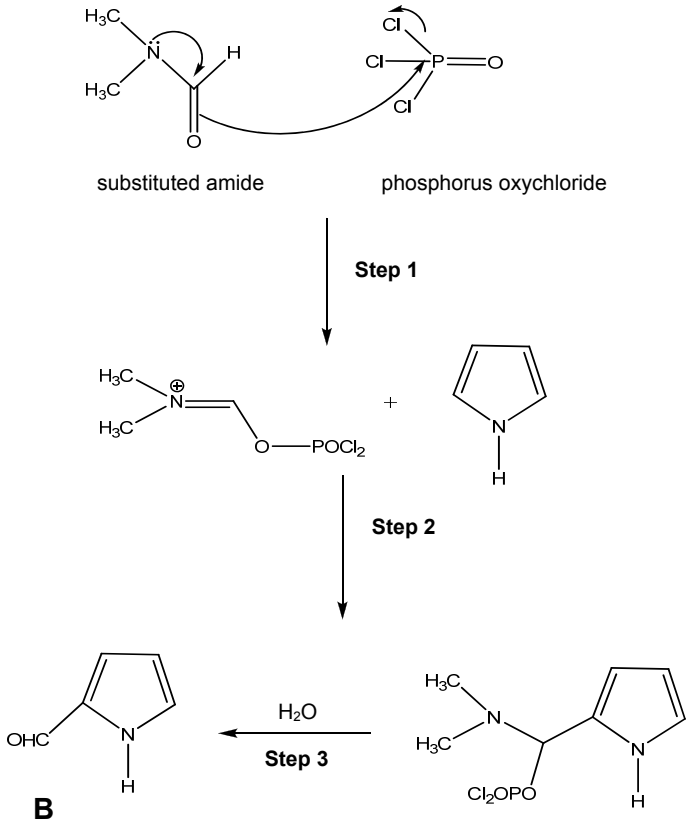
(e) Explain why the pyridine ring undergoes electrophilic substitution less readily than benzene. [1]

(f) Pyridine derivatives, such as 2–bromopyridine, undergo nucleophilic substitution readily. Describe the mechanism for the reaction shown below. [3]



Besides pyridine, pyrrole is another common nitrogen–containing aromatic heterocycle.

Pyrrole reacts readily in the Vilsmeier reaction to produce the aryl aldehyde, **B.** The reaction scheme of the Vilsmeier reaction is as shown below.

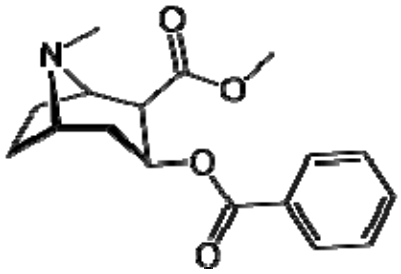


(The Vilsmeier reaction is the chemical reaction of a substituted amide with phosphorus oxychloride and an activated arene to produce an aryl aldehyde.)

(g) Describe the mechanism involved for **Step 2**. [4]

(h) In **Step 2**, explain, with the help of relevant mesomeric structures, why electrophilic substitution happens at position 2 instead of position 3 of the pyrrole ring. [3]

4 At least as far back as the 16th century, the Incas chewed the leaves of the coca bush, *Erythroxylon coca*, to combat fatigue. Chemical studies of *Erythroxylon coca* by Friedrich Wöhler in 1862 resulted in the discovery of cocaine as the active component.



cocaine

(a) Like caffeine and nicotine, cocaine belongs to the class of drugs known as stimulants. In the synapse, cocaine acts by binding tightly to the carrier protein whose function is to return dopamine, a neurotransmitter molecule, back to the pre–synaptic nerve. The carrier protein is thus subsequently unable to bind to dopamine.

(i) Identify two possible interactions between cocaine and the carrier protein, stating which groups on cocaine give rise to them.

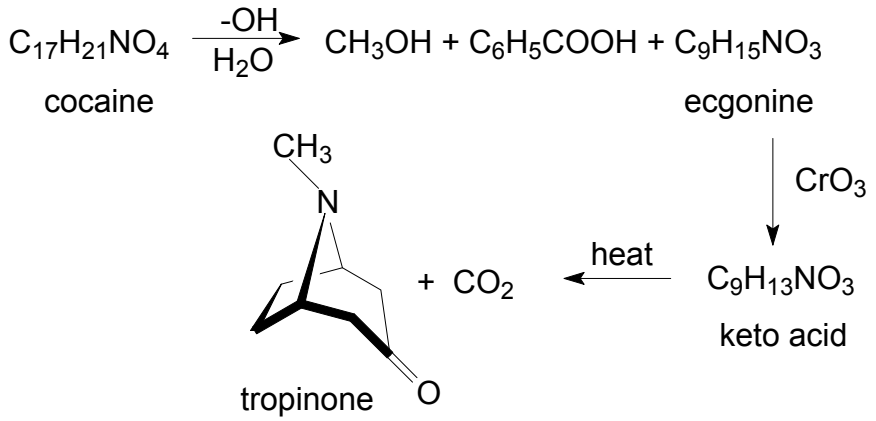
(ii) The principal routes of cocaine administration are oral, intranasal, intravenous, and inhalation. Suggest why cocaine is unlikely to be administered transdermally.

(iii) Cocaine is extensively metabolised in the liver. Suggest which functional group is most likely to undergo metabolism. Name the type of metabolism involved.

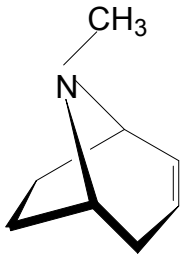
(iv) Briefly explain how a person's use of cocaine results in a stimulating effect.

(v) Based on your answer in **(iv)**, explain how the prolonged use of cocaine leads to addiction. [10]

It was found that basic hydrolysis of cocaine led to methanol, benzoic acid, and another compound called ecgonine. Chromium trioxide oxidation of ecgonine led to a keto acid that readily lost CO_2 on heating, giving tropinone.



(b) Tropinone can be synthesised in the laboratory from the compound tropidene.

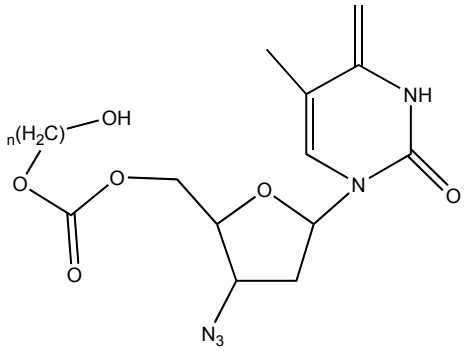


tropidene

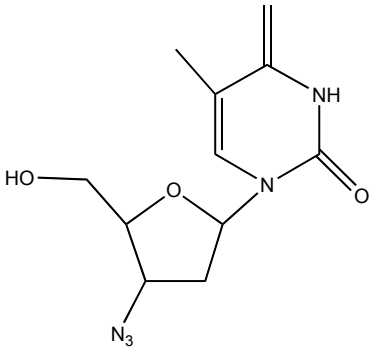
(i) Give a **three**–step synthetic pathway for the conversion of tropidene to tropinone. State the necessary reagents and conditions for each of the steps.

(ii) Sketch the ^1H NMR spectrum of tropinone. Show the relative position of the 4 signals (exact δ values are not required), the integration trace, and the appropriate splitting pattern. [10]

5(a) Prodrugs are chemicals that are converted to drugs within the body. The prodrug for zidovudine, an anti–HIV drug, is shown below.



prodrug for zidovudine



zidovudine

(i) State **two** important differences between viruses and bacteria that affect the design of antiviral drugs.

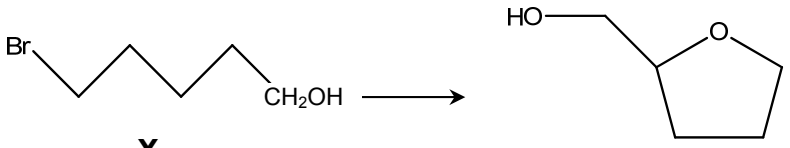
(ii) Outline **two** ways in which antiviral drugs work.

(iii) Describe a probable mechanism in which the prodrug is converted to zidovudine, given that the reaction is intramolecular.

(iv) Predict the value of **n** for which the reaction would happen most readily. Give a reason for your answer.

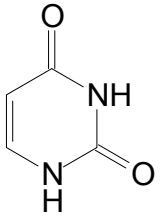
Many drugs, like zidovudine, contain the cyclic ether functional group.

(v) Suggest a simple synthetic pathway for the formation of the cyclic ether, **Y,** from compound **X**. State clearly all reagents and conditions required for the proposed steps of the synthesis. [12]

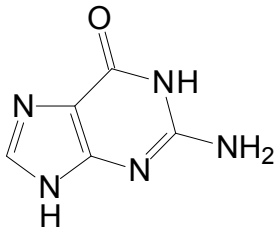


X **Y**

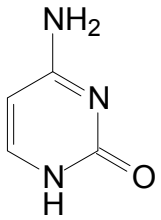
Like zidovudine, nucleosides are also cyclic amides. The hydrolysis of a DNA molecule produces three main nucleoside molecules, namely Uracil (U), Guanine (G) and Cytosine (C). Their structural formulae are shown below.



Uracil (U)

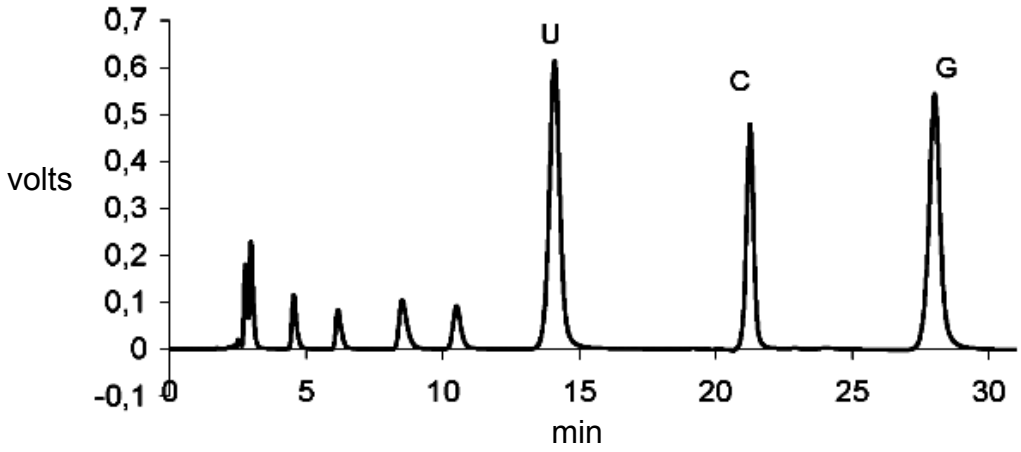


Guanine (G)



Cytosine (C)

The analysis and separation of the nucleosides is carried out using a conventional reversed phase column HPLC. The following diagram shows a portion of the chromatogram of the separation.



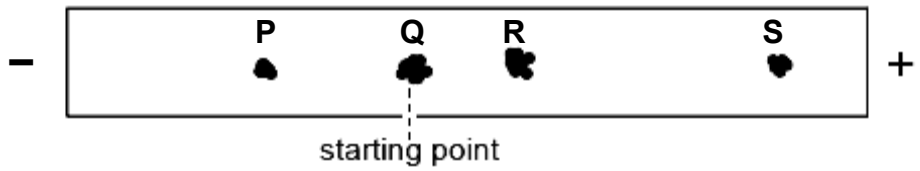
(vi) State what is "*reversed phase column"* HPLC.

(vii) Explain the difference in retention times of Uracil, Guanine and Cytosine, as shown in the chromatogram. [3]

5(b) Gel electrophoresis is often employed to analyze the mixtures of amino acids and small peptides obtained by the hydrolysis of proteins. In a particular experiment, glycine, H_2NCH_2COOH, is an amino acid obtained from the hydrolysis of a polypeptide protein molecule.

(i) Using the amino acid glycine (H_2NCH_2COOH, pI = 6.1) as an example, explain how the pH of the solution used for electrophoresis can influence the results.

The diagram below shows the result of carrying out electrophoresis on a sample of amino acids obtained from hydrolyzing a protein.



Assuming all the amino acids shown above are overall singly charged species at a particular operating pH,

(ii) which amino acid has the lowest relative molecular mass?

(iii) which amino acid has a positive charge? [5]

6 Mycomycin, a naturally occurring antibiotic isolated from the bacterium *Nocardia acidophilus*, is chiral and has $[\alpha]_D = -130^o$.

$$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2COOH$$

mycomycin

(a) State **four** ways how antibiotics can work against bacteria. [4]

(b) **(i)** When mycomycin is injected into a mass spectrometer, a signal is observed at the m/e ratio of 153. Give the displayed formula of the species at this value.

(ii) How would you use infrared spectroscopy to distinguish between mycomycin and compound **E**?

$$NC{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2CH_3$$

compound **E**

(iii) Why is the infrared absorption frequency for the –OH group in a carboxylic acid lower than that in an alcohol?

(iv) When the ultraviolet spectrum of mycomycin is measured in the presence of a small amount of sodium hydroxide, the λ_{max} increases to a larger value. Explain why there is an increase in λ_{max}. [9]

(c) Compound **F** is an analogue of Mycomycin.

$$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH_2{-}CH(Br){-}CH{=}CH{-}CH_2COOH$$

compound **F**

Using Newman projection formulae, give the mechanism of the **one**–step reaction which would recover Mycomycin from compound **F** in the presence of a strong base, e.g. OH^-. (The stereoconfiguration of C–5 on compound **F** is *R,* and the final product formed is an *E* conformer with respect to C–5 and C–6.) [4]

(d) Mycomycin can be converted into another synthetic antibiotic, compound **G**.

$$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2CONHC_6H_5$$

compound **G**

Give a **two**–step synthetic pathway for the conversion of mycomycin to **G**. State the reagents and conditions necessary for each of the steps. [3]

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Name ( )	CT Group

RAFFLES JUNIOR COLLEGE
PRELIMINARY EXAMINATION 2008

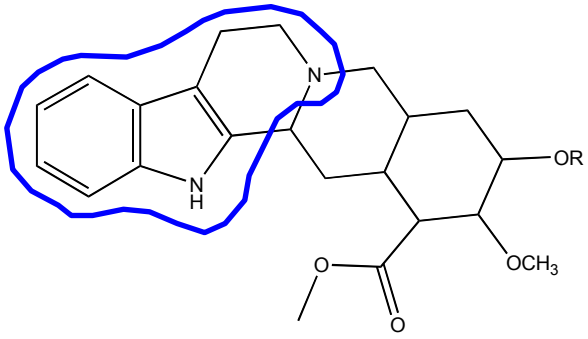
HIGHER 3
PHARMACEUTICAL CHEMISTRY 9812

Attach this Cover Page to the top of your answer scripts.

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

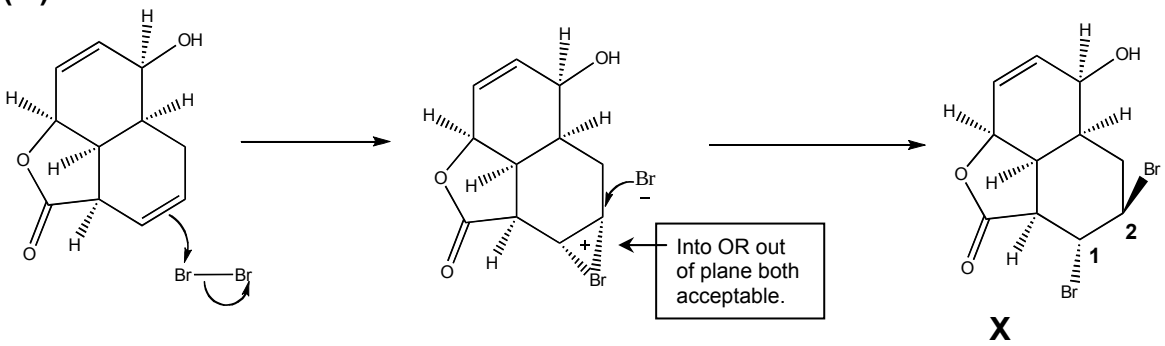
Raffles Junior College
2007/2008 H3 Pharmaceutical Chemistry
Preliminary Exams – Suggested Solutions

1(a)
(i)



(ii) Increased heart rate / respiration / blood pressure etc.

(iii)

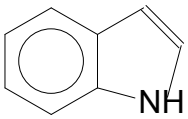


Configuration of C–1 is ***(R)***
Configuration of C–2 is ***(R)***

(iv) Substitution.

(v) Elimination.

(vi) A chromophore is a part of the molecule (usually an unsaturated group) that is responsible for the absorption of electromagnetic radiation by the molecule.



(vii) $A = \varepsilon c l$
max A = 0.065

$c_{max} = 0.065 / 11.900 \times 10^{3}$
$= 5.46 \times 10^{-6}$ mol dm^{-3}

(viii) Ethanol (i.e. any polar solvent which does not absorb at the wavelength that pseudoreserpine absorbs).

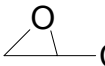
1(b)(i) Any **two** of the following:

- 100% effective in its action on the target receptor.
- Same effect on every member of the human population.
- Not poisonous and cannot be metabolized into something that is poisonous.
- Synthesized cheaply, quickly and in a high degree of purity.
- Capable of being modified in a straightforward manner.

(ii) Agonists **compete with the natural ligand** for the **receptor** site since they have **similar binding groups**, causing the necessary **change in shape** there.

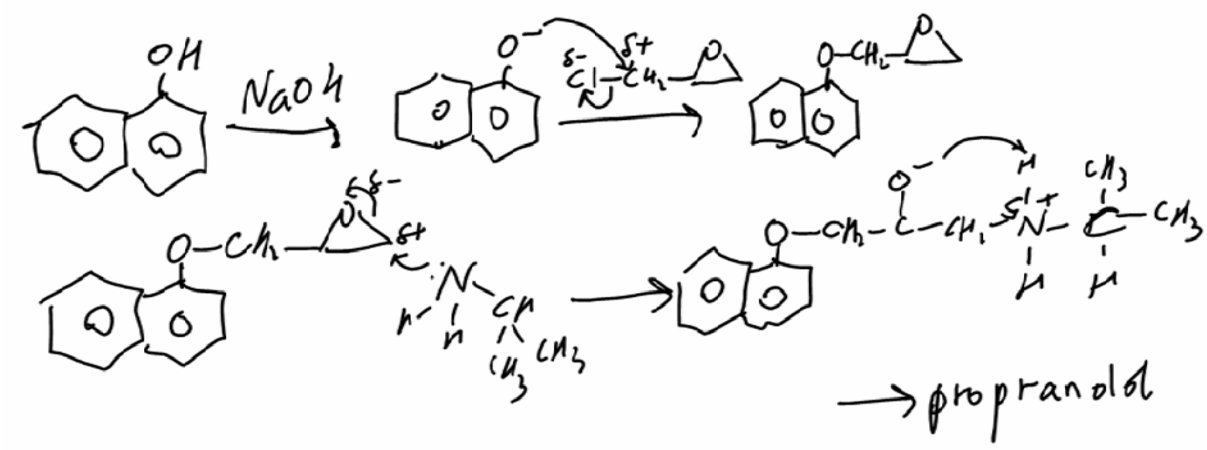
Antagonists **block the site without causing the necessary change in shape**, thus there is **no physiological effect**.

2

(a)(i) Step 1: NaOH,  (RX)

Step 2: $NH_2CH(CH_3)_2$

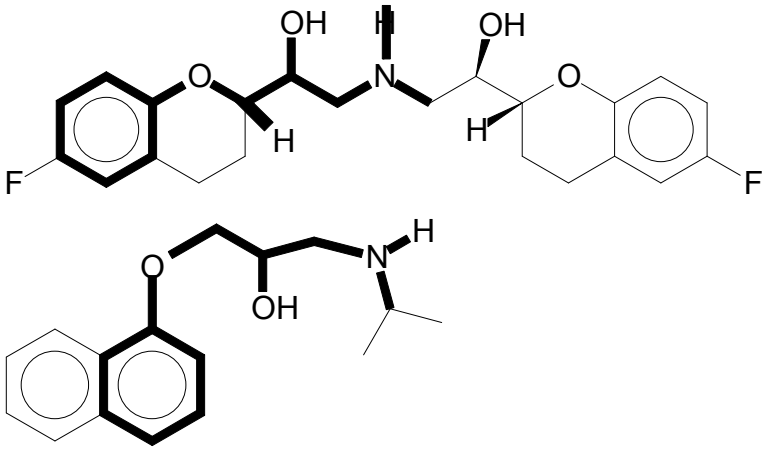
(ii)



(b) **4** (*S,R,R,R*)

(c) (*R,S,S,S*) enantiomer

(d)



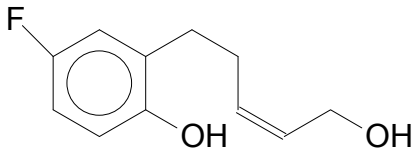
(e)(i) In nebivolol, C–O–C is part of cyclic ring, no free rotation and hence restricted the functional groups to bind with specific sites.
In propranolol, C–O–C can be freely rotated; functional groups could bind with more sites with varied sizes.

(ii) stereospecific, the different spatial arrangement may prevent the isomer from bonding effectively to the site.

(iii) (R,S,S,S) enantiomer - no harmful side effect

(f)(i) diastereomers

(ii)



IR spectra:
3500 (O–H), 3350 (O–H hydrogen bonded), 3045 (C–H), 2990 (C–H), 1650 (C=C), 1200 (C–O), 650 (C–F) cm^{-1}

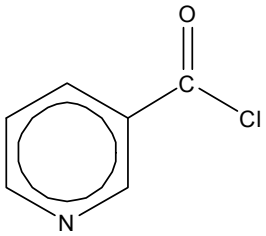
The ^1H NMR spectra showed the following peaks:

δ value	**relative area**	**comment**
2.25	2 (CH_2–CH=CH)	multiplet
2.55	2 (CH_2–C_6H_3)	triplet
3.95	2 (CH_2–OH)	doublet
5.45 – 5.70	2 (CH=CH)	multiplet
4.5	1 (R–OH)	disappears with D_2O
7.0	1 (Phenol)	disappears with D_2O
6.72 – 6.50	3 (C_6H_3–F)	multiplet

The mass spectra major peaks observed:
m/z 195, 75, 41

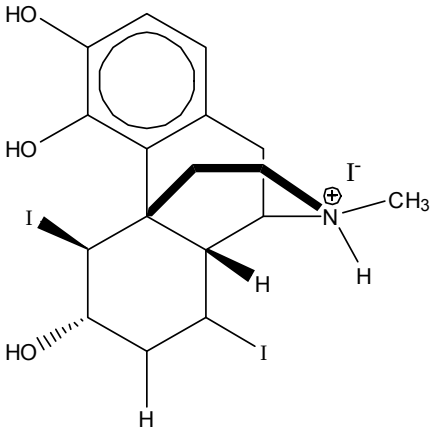
3

(a)

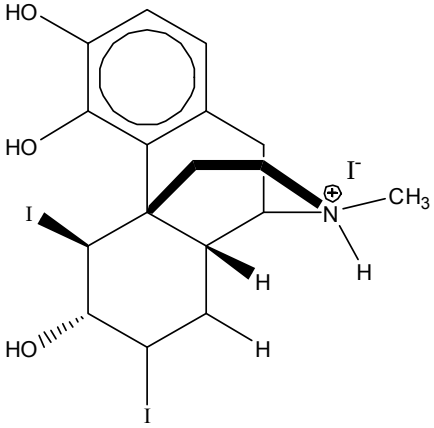


r.t.p.

(b) **A** is

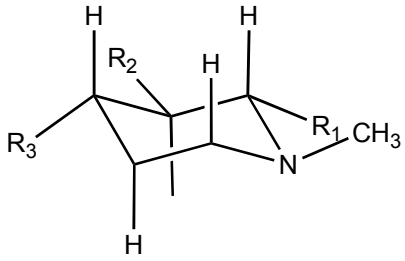


OR

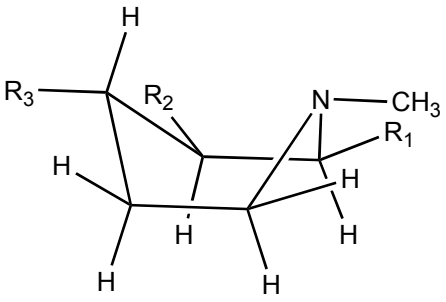


(c) Narcotics work by **depressing the CNS**, hence **affecting the capacity** of the **brain to appreciate pain** while non–narcotics work on the **pain receptors** themselves, preventing them from responding normally to pain stimuli.

(d)



chair conformer

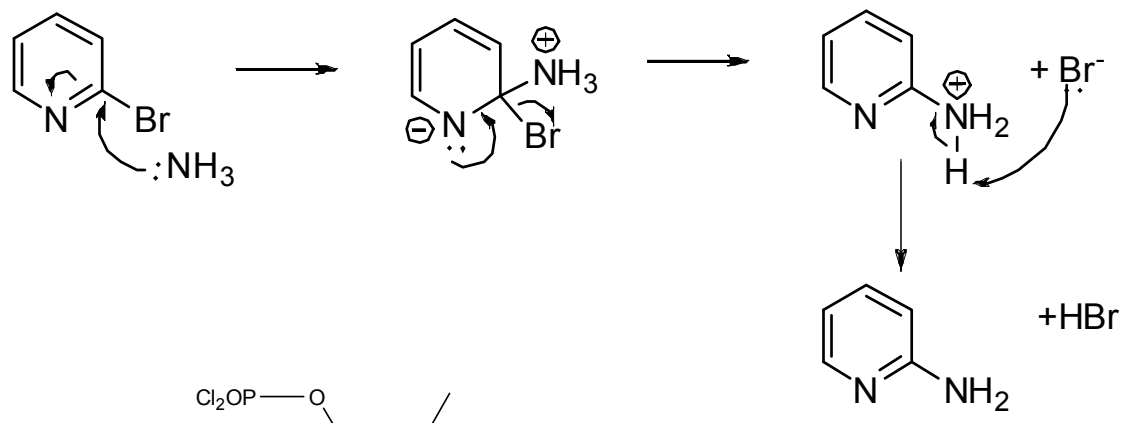


boat conformer

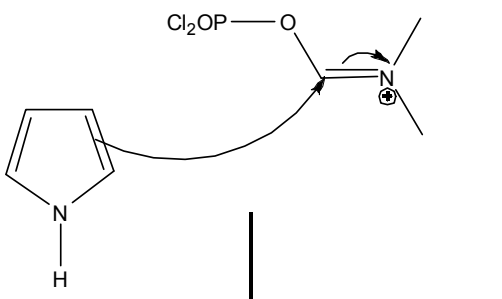
The chair conformer is more stable because the substituents are further away from each other, resulting in less repulsion between the electron clouds in the substituents.

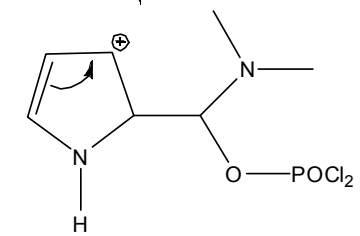
(e) The electron density of the ring is **decreased** (OR ring carbon atoms are positively polarized) due to the **electron–withdrawing effect** of the electronegative nitrogen atom. Hence pyridine undergoes electrophilic substitution less readily than benzene.

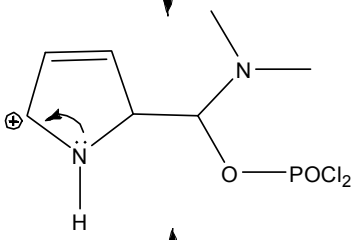
(f)

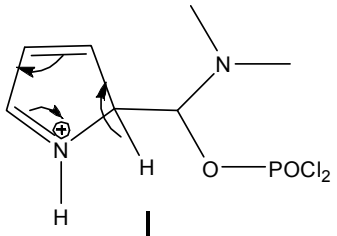

N
Br
:NH3
NH3
N
Br
+ Br-
N
NH2
H
+HBr
N
NH2

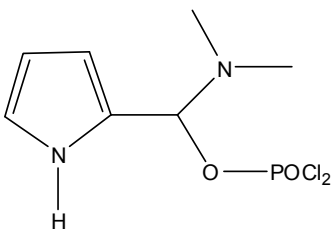
(g)


Cl2OP
O
N
N
H

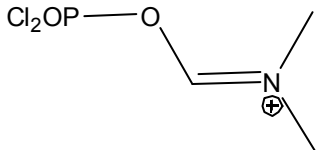

N
N
O
POCl2
H

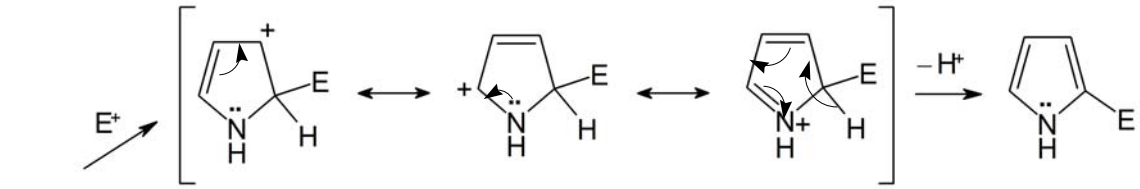

N
N
O
POCl2
H


N
N
H
O
POCl2
H

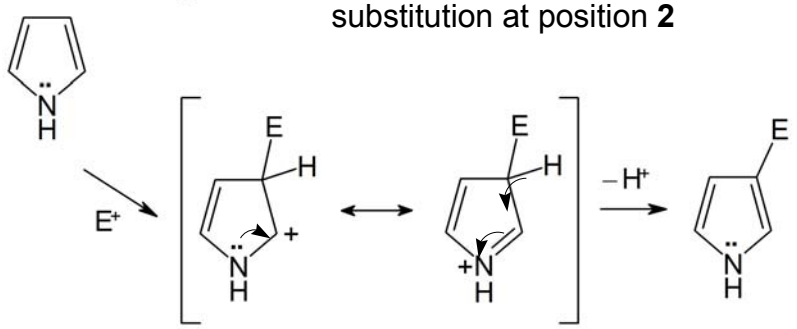

N
N
O
POCl2
H

(h)

Let E^+ be the electrophile 



substitution at position **2**



substitution at position **3**

- If we look at the possible mesomeric structures for the intermediates leading to 2– and 3– substitution,
- we can see that when substitution happens at position 2, **the positive charge can be spread over three atoms**.
- whereas when substitution happens at position 3, **the positive charge can only be spread over two atoms**.
- The larger number of atoms that share a charge, the more stable is the cation.

4(a)(i) Any **two:**
Electrostatic / ionic using the protonated amino group
Hydrogen bonding using the O on ester group
Van der Waals interactions using the hydrocarbon cyclic ring

(ii) It is **not lipophilic** enough.

(iii) Ester functional group; hydrolysis

(iv) As cocaine binds tightly to the carrier protein, the latter is unable to bind to dopamine.
This means that **dopamine** is not returned to the pre–synaptic nerve (OR cocaine inhibits the re–uptake of dopamine into the pre–synaptic nerve) but **accumulates in the synapse**.
This dopamine accumulation results in the **stimulation** of the receptors associated with the "reward" / pleasure centres of the brain for a **longer period of time**, thereby producing a stimulating effect.

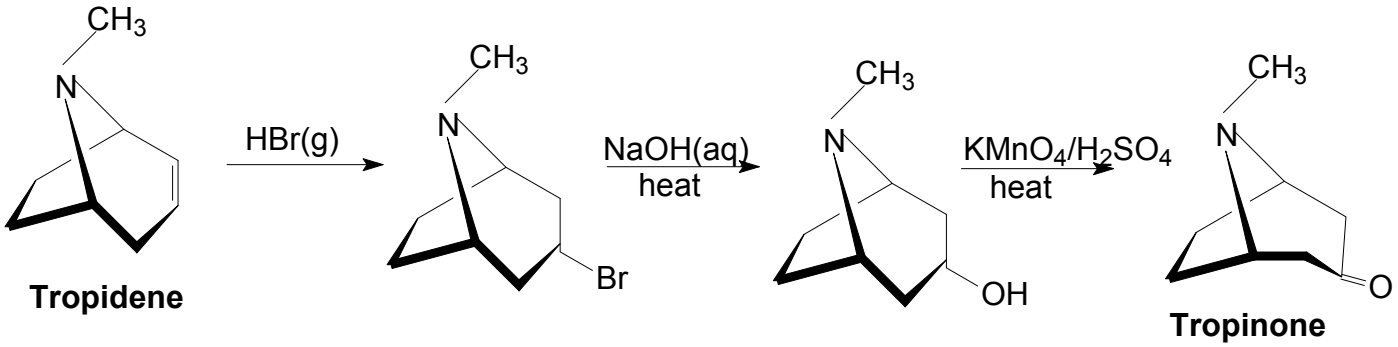
(v) The use of cocaine increases the dopamine level in the *nucleus accumbens*.

Because the body will attempt to keep the nerve transmission rate at a **steady level**, if there is a **continual stimulation** of the dopaminergic receptors (i.e. via prolonged use of cocaine), the number of those receptors on the post–synaptic nerves will gradually **decrease**, so as to reduce the stimulation.

This decrease in receptor numbers mean that the dosage of cocaine will need to be **increased** if the same effect is to be felt, and if it is withdrawn, **there will not be enough receptors to produce the same level of neurotransmission that the body requires** and so a general feeling of anxiety and tension ensues.

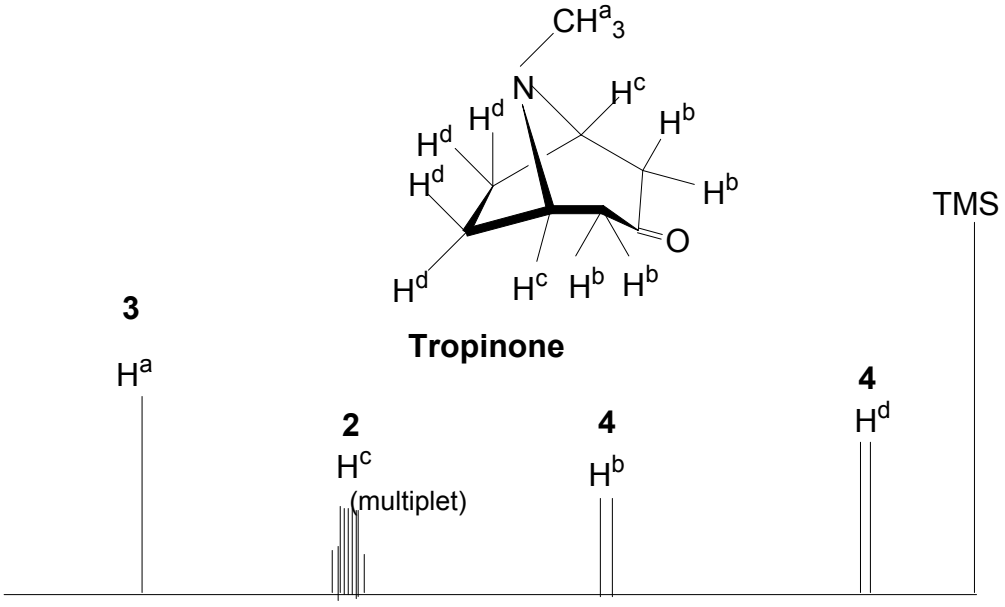
These strong withdrawal symptoms thus lead to or promote addiction.

4(b)(i)



Tropidene **Tropinone**

(ii)



Tropinone

5(a)

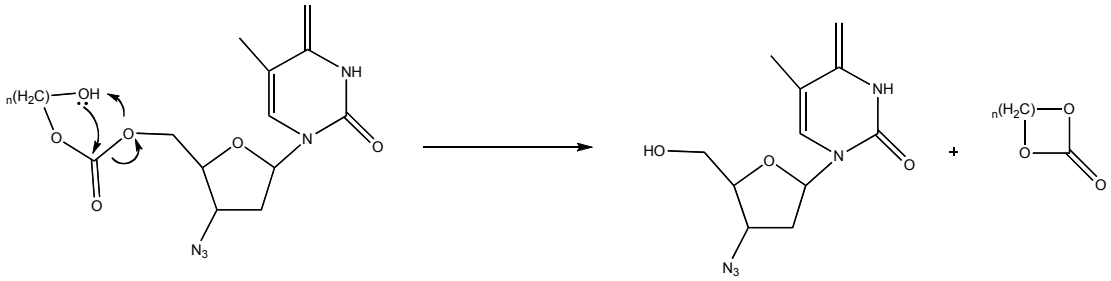
(i) Any **two** of the following:

- o bacteria use their own DNA and protein synthesis apparatus for reproduction, whereas viruses use the host cell's apparatus.
- o bacteria contain species–specific enzymes which can be individually targeted by drugs.
- o bacteria are surrounded by a specific cell wall (which can be targeted by antibacterial drugs) whereas viruses are not.
- o virus are more specific in the host cells they attack than are bacteria

(ii) Any **two** of the following:

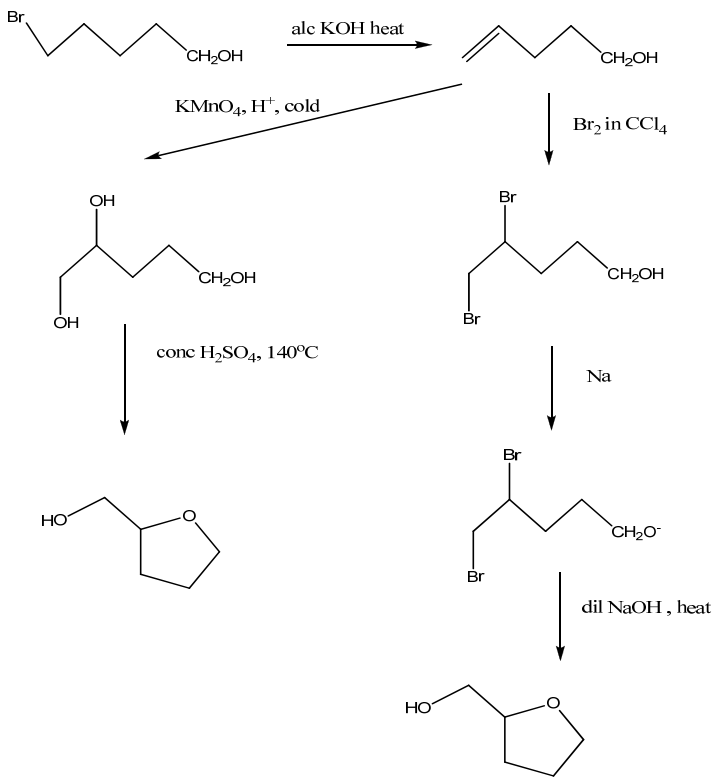
- o inhibition of nucleic acid synthesis
- o inhibition of host cell penetration
- o inhibition of viral protein synthesis.

(iii)



(iv) n = 2 or 3.
A five membered or six membered ring is most stable.

(v)



5(a)

(vi) This refers to the **stationary phase** in the HPLC column is *non–polar* (hydrophobic), and the **mobile phase** used is *polar* (hydrophilic).
[Note: the reverse of normal phase HPLC]

(vii) Uracil molecule is more polar (with more O atoms) than Cytosine molecule. Hence more effective hydrogen bonding can take place between the sample and the polar solvent mobile phase. Hence Uracil is eluted earlier than Cytosine. Guanine is eluted last due to its relatively larger non–polarity (or hydrophobicity) because of the presence of another aromatic (or cyclic) ring in the molecule.

5(b)

(i) When pH < 6.1, glycine molecules exist predominantly as positively charged species. Hence it is attracted and will migrate towards the negative electrode.

When pH > 6.1, glycine molecules exist predominantly as negatively charged species. Hence it is attracted and will migrate towards the positive electrode.

When pH = 6.1, glycine exists predominantly as a zwitterions and will be electrically neutral. It will migrate to neither of the electrodes.

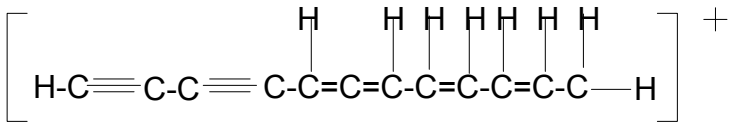
(ii) Amino acid **S**

(iii) Amino acid **P**

6(a) Any **four** of the following:

- o disruption of the synthesis of folic acid
- o disruption of protein synthesis
- o plasma membrane disruption
- o disruption of nucleic acid transcription
- o disruption of cell wall construction.

(b)(i)



Note: Displayed formula!!!

(ii) Infrared absorption for mycomycin:

O–H at 2500 to 3300 cm^{-1}
C=O at 1680 to 1750 cm^{-1}
C–O at 1000 to 1300 cm^{-1}
C≡C at 2070 to 2250 cm^{-1}

Infrared absorption for E:

N≡C at 2200 to 2280 cm^{-1}

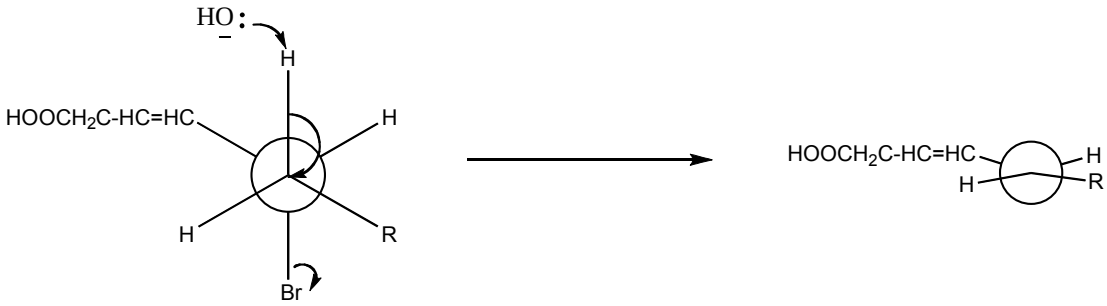
Note: Must quote the type of bond, not just the functional group.
Must state the range of wavenumber!

(iii) The **electron withdrawing** carbonyl group of the –COOH group draws electron density away from the –OH group, thus **weakening the –OH bond**.

(iv) The carboxylate anionic form exists in the solution when NaOH is added. The **carboxylate anionic group** is **less electron withdrawing** since it is more **electron rich than the –COOH group**, resulting in closer energy levels between the molecular orbitals of the pi-conjugation, hence smaller energy of absorption (longer wavelengths).

Note: The chromophore here is not the COOH or COO^- groups, but the pi-conjugation!

(c) **E2** mechanism**.**



(d) Let R be $HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2{-}$

$$RCOOH \xrightarrow{SOCl_2} RCOCl \xrightarrow{C_6H_5NH_2} RCONHC_6H_5$$