HWA CHONG INSTITUTION
JC2 Preliminary Examinations
Higher 3

CANDIDATE NAME		**CT GROUP**	**10S**
CENTRE NUMBER		**INDEX NUMBER**	

PHARMACEUTICAL CHEMISTRY

9812/01

Paper 1

21 September 2011

2 hours 30 minutes

INSTRUCTIONS TO CANDIDATES

1) This paper consists of **15** printed pages (including this page). You should have a *Data Booklet*, a cover page and a set of writing papers.
2) Answer any **five** questions.
3) Write your **name** and **CT** clearly on the cover page and on all the work you hand in.
4) Begin each question on a **FRESH** sheet of writing paper. A **nil return** is necessary for any unattempted question.
5) At the end of the examination, fasten your cover page securely together with your answer scripts.

INFORMATION FOR CANDIDATES

The number of marks is given in brackets [ ] at the end of each question or part question.

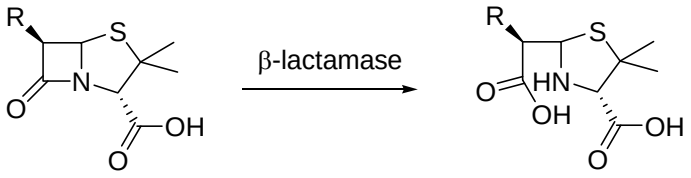
A *Data Booklet* is provided. You may use a calculator.

You are reminded of the need for good English and clear presentation in your answers.

1 **(a)** Penicillin belongs to a big family of β-lactam antibiotics which inhibits bacterial cell wall biosynthesis by inhibiting glycopeptides transpeptidase. The latter is an important enzyme in the synthesis of peptidoglycan.

(i) Describe two modes of actions of antibacterial drugs other than inhibitions of cell wall biosynthesis. [2]

(ii) Bacterial resistance to antibiotics is a problem in the pharmaceutical industry and one possible mode of action by β-lactamase can be represented as follow.



penicillin penicilloic acid

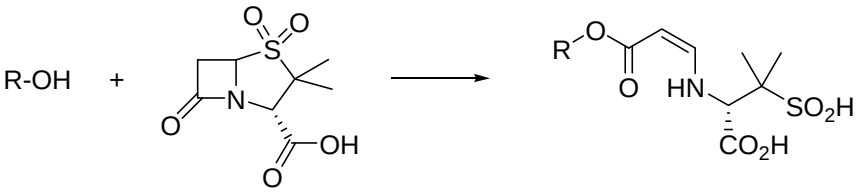
By representing β-lactamase as R-OH, suggest a mechanism to the above reaction. [3]

(iii) Penicillin works as an inhibitor because of the conformational similarity between the amide bond of the β-lactam ring and the D-Ala-D-Ala termini in glycopeptides transpeptidase.

Suggest why penicilloic acid is inactive in killing bacteria. [1]

(iv) One approach that was taken to fight β-lactamase was to develop potent inhibitors for β-lactamase. The β-lactamase inhibitor can be used in conjunction with penicillins to allow the antibiotic to destroy bacterial cell without being affected by the β-lactamase.

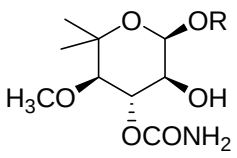
An example of a β-lactamase inhibitor is sulbactam and its reaction with β-lactamase is shown below.



sulbactam

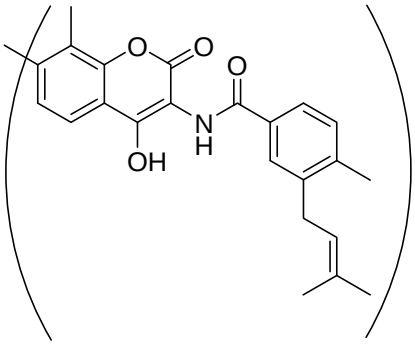
Is sulbactam a reversible or an irreversible inhibitor? Explain briefly. [2]

(b) Novobiocin is a coumarmycin-family antibiotics and it inhibits the function of DNA gyrase.



novobiocin

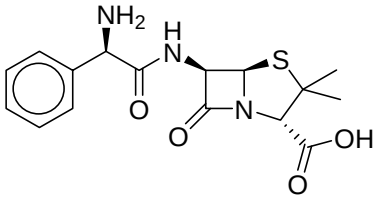
where R =



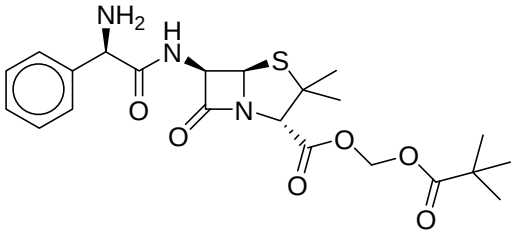
Draw two possible chair conformations of novobiocin, indicating the more stable conformation. Justify your answers. [4]

(c) Amoxicillin is a wide spectrum antibiotics. Although it is more acid resistant and shows more activity against certain Gram-negative bacteria than Penicillin G, it tends to cause diarrhoea due to its poor absorption through the gut wall. This is due to the presence of a free amino and a free carboxylic acid group.

A way to go around this problem is to use a prodrug where one of the polar groups is chemically modified which can then be removed metabolically once the prodrug has been absorbed. One such drug developed was pivampicillin.



ampicillin

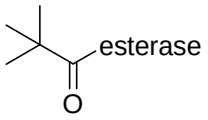


pivampicillin

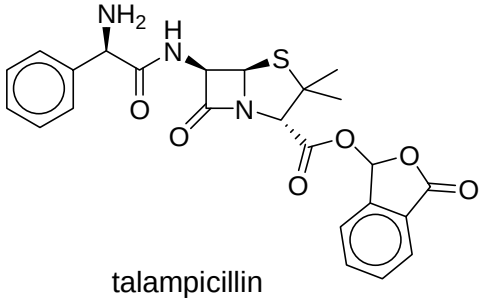
(i) Suggest why pivampicillin is less likely to cause diarrhoea in the patient. [1]

(ii) In the first stage of the metabolism of pivampicillin, the ester group further away from the penicillin nucleus was hydrolysed by esterase first. Suggest why this is so. [1]

(iii) In the metabolism of pivampicillin to ampicillin, the following two side products are obtained.

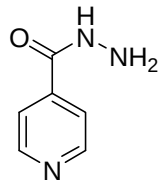


Suggest the side products from the metabolism of talampicillin, another prodrug of ampicillin. [1]

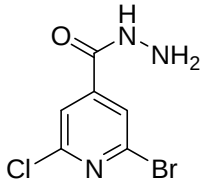


talampicillin

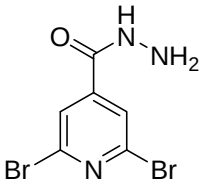
(d) Isoniazid is an antibacterial drug, commonly used against tuberculosis bacteria.



isoniazid



isoniazid-A

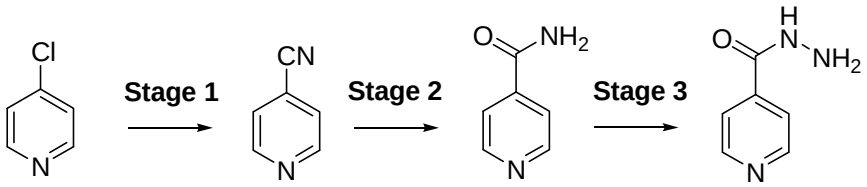


isoniazid-B

(i) A researcher synthesises isoniazid-A and isoniazid-B to see if they have improved activity against tuberculosis bacteria.

Sketch the mass spectra about the molecular ion peak for both compounds and state the ratio of the peaks. [2]

(ii) The synthesis of isoniazid is shown below.

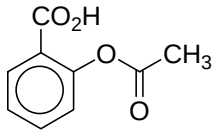


(I) Suggest the reagent for stage 1 and give the name of the mechanism.
(II) Given that stage 3 occurs via nucleophilic acyl substitution, suggest what reagent could be used. [3]

[Total : 20]

2 **(a)** A migraine headache can cause intense throbbing or pulsing in one area of the head and is commonly accompanied by nausea, vomiting, and extreme sensitivity to light and sound.

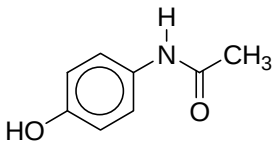
Excedrin is a drug that helps to ease migraine pain and contains aspirin as one of the active ingredients.



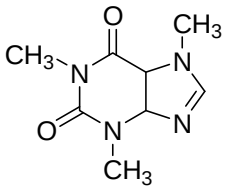
aspirin

(i) Explain how aspirin can reduce pain. [2]

Apart from aspirin, acetaminophen and caffeine are also found in Excedrin.

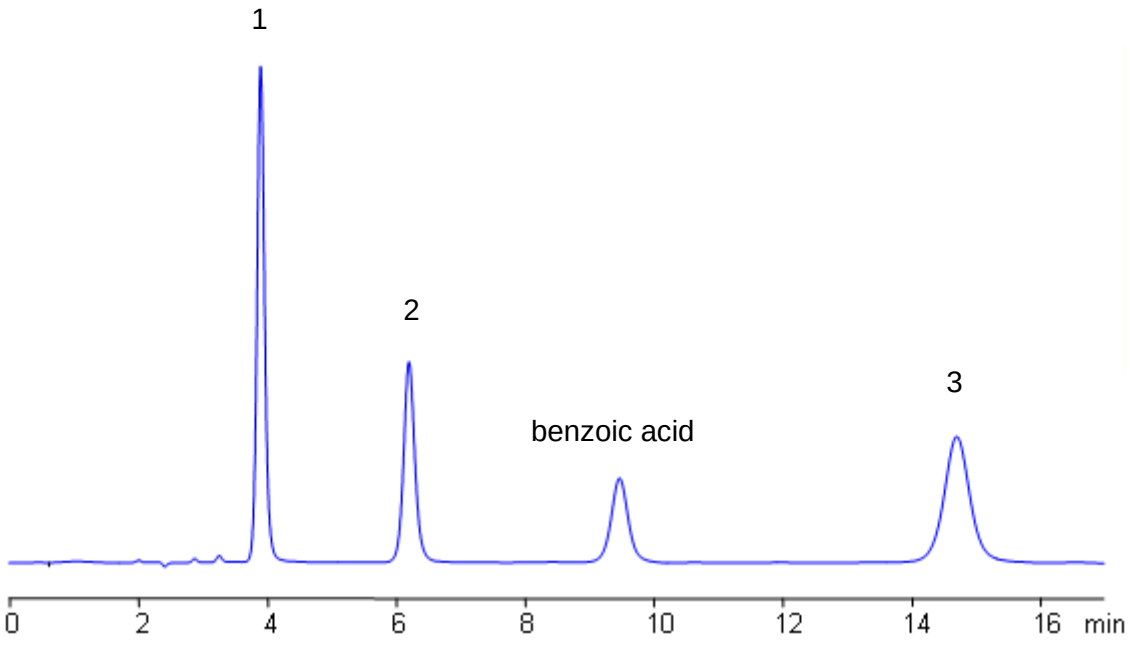


acetaminophen



caffeine

An analysis was carried on a sample of Excedrin using reversed-phase HPLC to which a known amount of benzoic acid has been added as an internal standard. The following spectrum was obtained.



(ii) Identify the peak due to aspirin, giving your reasoning. [1]

(iii) Determine the relative concentration of the three drugs in the given sample of Excedrin. [2]

[Note: Identification of peak due to acetaminophen and caffeine is not required]

(b) Compound **A** is used primarily as an anesthetic but studies have shown that it can help to relieve pain for certain headaches. It contains carbon, hydrogen, nitrogen and oxygen only.

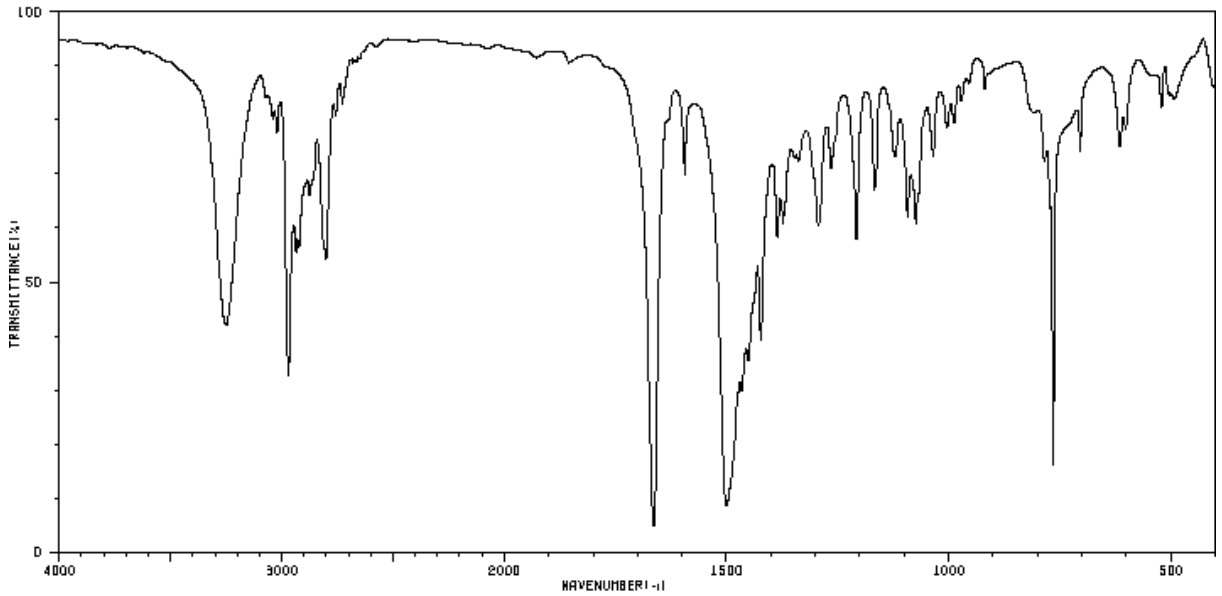
A has the following NMR spectrum. The resonance at δ 8.92 disappears in the presence of D_2O.

δ	1.13 (t 6H)
	2.23 (s 6H)
	2.29 (q 4H)
	3.22 (s 2H)
	7.09 (m 3H)
	8.92 (s 1H)

(s is singlet, t is triplet, q is quadruplet and m is multiplet)

The mass spectrum of **A** shows a molecular ion at m/e 234. The $(M+1)^+$ peak has an intensity 15.4 % of that of the molecular ion and the base peak occurs at m/e 86.

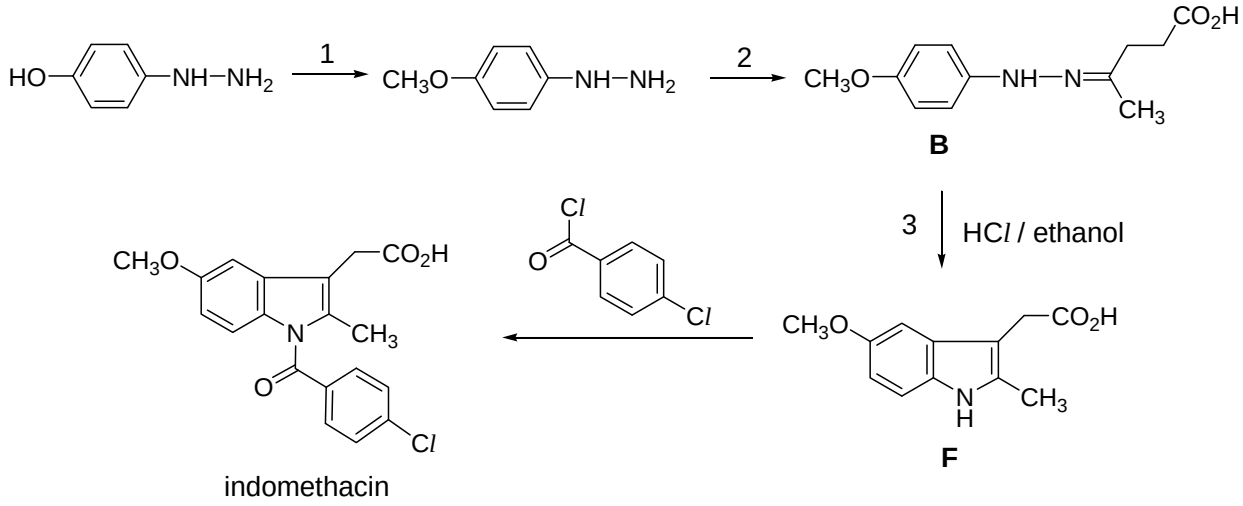
The IR spectrum of **A** is shown below.



Deduce the molecular formula of **A** and suggest a possible structural formula of compound. Show your reasoning. [10]

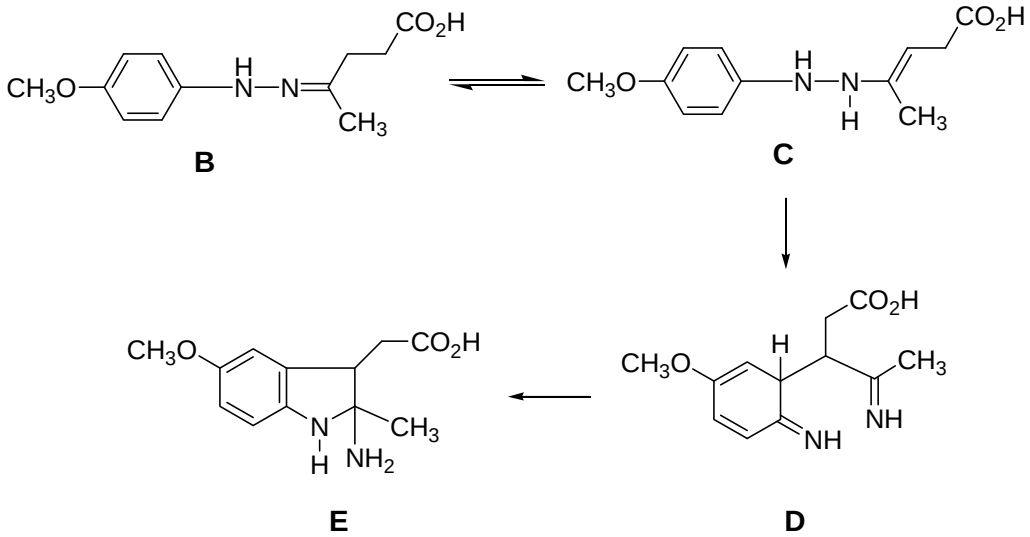
(c) Indomethacin is another analgesic that is used to treat inflammatory diseases such as rheumatoid arthritis.

The following scheme shows the synthesis of indomethacin.



(i) Suggest reagents and conditions for reactions 1 and 2. [2]

(ii) Reaction 3 involves tautomerisation of compound **B** to give **C** which undergoes a rearrangement to form **D**. **D** undergoes further reaction to form **E** which on losing an ammonia gives **F**.



Propose a mechanism for the formation of **E** from **C**. [3]

[Total : 20]

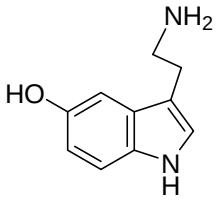
3 **(a)** The absorption of radiation in the IR region allows the identification of certain functional groups.

(i) Explain the origin of IR absorption of simple molecules. [2]

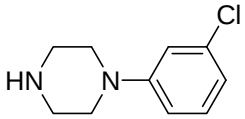
(ii) For each of the molecules $BeCl_2$ and Cl_2O, identify the molecular vibrations which give rise to the absorption bands in its IR spectrum. [2]

(b) Serotonin is an important neurotransmitter in the central nervous system, and abnormalities resulting in altered levels of serotonin are thought to be involved in a variety of disorders such as anxiety, depression and migraine.

Agents that can influence serotonin levels are useful in treating these disorders. For example, meta-chlorophenylpiperazine (mCPP) is an agonist which is able to treat depression.



serotonin

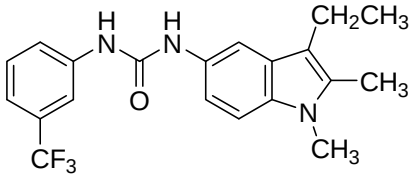


meta-chlorophenylpiperazine (mCPP)

(i) Describe two major differences in the IR spectra for serotonin and mCPP. [2]

(ii) Deduce the structural features of serotonin and mCPP that will bind on the same sites on the serotonin receptors. State the respective intermolecular interactions involved. [2]

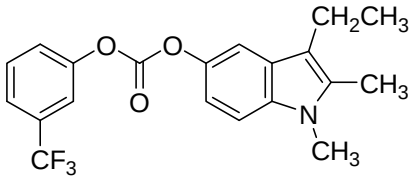
(c) There are several known serotonin antagonists which were used for treating schizophrenia, feeding disorders, depression and anxiety. Compound **G** is one such antagonist.



G

(i) Explain how compound **G** works as an antagonist. [2]

Compound **H** is an isostere for compound **G**.



H

(ii) Draw the structures of the products when compounds **G** and **H** are treated with lithium aluminium hydride. [3]

(iii) Explain whether compound **G** or **H** is more susceptible to hydrolysis. [1]

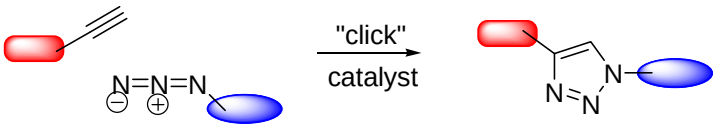
(iv) Compound **G** was one of the drugs produced to treat depression. However it faced several problems:

(1) Insolubility in water
(2) Flexibility of –NHCONH– (urea) functional group

Suggest two modifications that could be done to overcome the problems listed. [2]

(d) PTP1B, a protein tyrosine phosphatase enzyme, has been identified as the key enzyme which causes diabetes and obesity. Researchers have succeeded in synthesising a small library of PTP1B inhibitors using “click chemistry”.

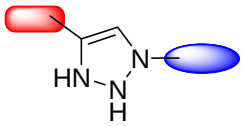
One such “click” reaction, which occurs in a single step, is shown as follow.



PTP1B inhibitor

(i) Propose the reaction mechanism to the above reaction and suggest its driving force. [2]

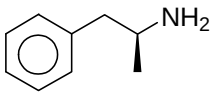
(ii) How would the UV spectrum of compound **J** shown below differ from that of a PTP1B inhibitor? [2]



J

[Total : 20]

4 **(a)** Amphetamine is a stimulant which exerts its physiological effects by modulating several key neurotransmitters in the brain.

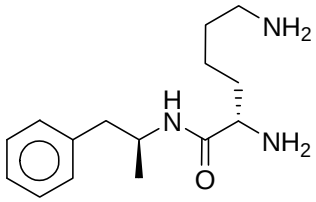


amphetamine

(i) What do you understand by the term *stimulant*? Describe briefly the physiological effects of stimulants like amphetamine. [3]

(ii) Suggest how amphetamine serves to increase the synaptic concentrations of neurotransmitters like noradrenaline and serotonin. [2]

Amphetamine may be used to treat conditions such as narcolepsy, a chronic sleep disorder. However, there is a great potential for abuse of the drug as indiscriminate users take amphetamine for an immediate sense of euphoria, known as a "euphoric rush". To address this concern, the prodrug Vyvanse was developed.



Vyvanse

(iii) Suggest why there is much less potential for abuse of Vyvanse. [2]

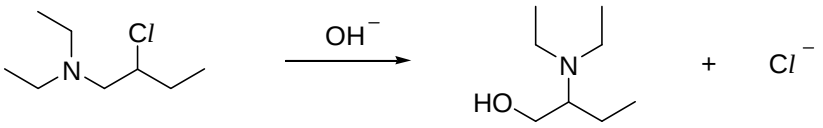
(iv) Abusers of stimulants like amphetamine often find over a period of time that they have to take ever-increasing doses to get the same stimulant effect. Explain. [2]

(v) Draw a Fischer projection of the Vyvanse molecule showing relevant stereogenic carbons and assign the R/S configurations at these carbons. [3]

(vi) Amphetamine is metabolised in the body, giving various metabolites including **K** and **L** as follows. **K**, $C_9H_{10}O$, gives a yellow precipitate with alkaline aqueous iodine while **L**, $C_9H_{13}NO$, turns hot acidified potassium dichromate (VI) from orange to green.

Suggest the structures of metabolites **K** and **L**. [2]

(b) When compound **M** is heated with sodium hydroxide, an unusual major substitution product is obtained.



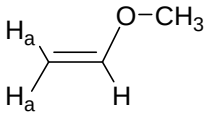
M

Propose an explanation for the above, with the aid of a mechanism. [3]

(c) Explain each of the observations below in relation to NMR spectroscopy.

(i) The chemical shift of the protons in methyl lithium, CH_3Li, is negative. [1]

(ii) The chemical shift of the protons marked H_a in methoxyethene has a smaller value than the protons in ethene. A diagram of relevant structures should be included in your answer.



[2]

[Total: 20]

5 (a) The sequencing of proteins usually involves eight basic steps, of which the last step involves locating the position of the disulfide cross-bridges formed between cysteine residues through the technique of diagonal electrophoresis.

The procedure of doing diagonal electrophoresis is as follows:

(1) A protein digest is streaked along the edge of a filter paper and subjected to electrophoresis. The filter paper is placed at the positive electrode and the peptides migrate towards the negative electrode.

(2) A strip, cut from the edge of the filter paper, is then exposed to performic acid fumes to oxidise any disulfide bridges.

(3) The paper strip is attached to a new filter paper at the positive electrode and a second electrophoresis is performed in a direction perpendicular to the first, using the same buffer solution.

Figure 1 is an example of the results obtained after the experiment is complete.

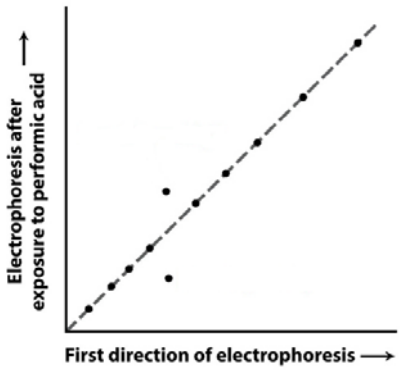


Figure 1

(i) Outline the principles of electrophoresis. [2]

(ii) Step (1) of the procedure for diagonal electrophoresis involves peptides migrating towards the negative electrode. Using the following data, suggest a suitable pH for the buffer solution to ensure it can be achieved. Explain your choice. [2]

	pK_a range
α-CO_2H groups	1.7 – 2.6
α-NH_3^+ groups	9.0 – 10.8

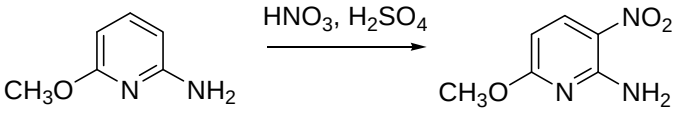
(iii) The spots off the diagonal in *Figure 1*, shows researchers the presence of the disulfide bridge. Suggest how the researchers are able to come to this conclusion. [2]

(iv) Suggest the structure of the compounds formed when the disulfide bridge is oxidised by performic acid. You may use $R–CH_2–S–S–CH_2–R$ to represent the structure of the disulfide bridge. [1]

(b) Simple pyridines are less likely to undergo electrophilic substitution as compared to other organic compounds.

(i) Give two reasons why pyridines are unlikely to undergo electrophilic substitution. [2]

Pyridine derivatives, such as compound **N**, are able to can undergo electrophilic substitution readily. An example occurs in the manufacture of the non narcotic analgesic, flupirtine.

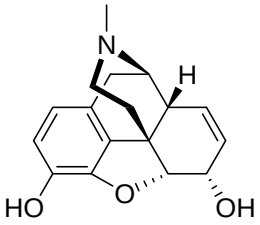


N

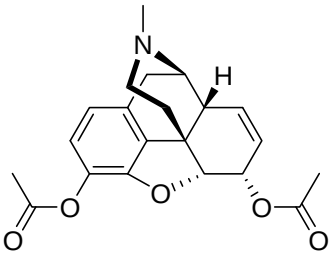
(ii) Explain how the substituent groups on compound **N** enable the pyridine ring to undergo electrophilic substitution. [2]

(iii) Draw a mechanism to illustrate the reaction, showing all the possible mesomeric forms of the intermediate obtained. [3]

(c) Morphine and heroin belongs to another class of analgesic drugs, known as the narcotic analgesic. Narcotic analgesics act on the opioid receptor to bring about pain relief.



morphine



heroin

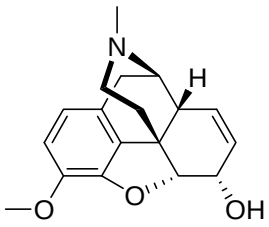
The important binding groups on morphine are the phenol, the aromatic ring and the ionised amine.

(i) Describe the factors and processes involved in morphine crossing the blood-brain barrier and attaching itself to a negatively charged receptor site in the brain. [3]

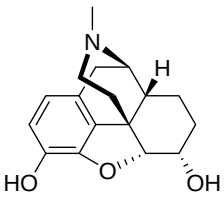
(ii) Suggest, with a reason, if morphine or heroin is better able to cross the blood-brain barrier. [1]

(iii) Predict, giving a reason if the following derivatives of morphine are more effective, of the same effectiveness or less effective, than morphine. [2]

(I)



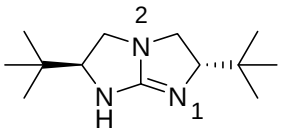
(II)



[Total: 20]

6 An organocatalyst is a small organic molecule that accelerates the rate of a chemical transformation when used in catalytic amount.

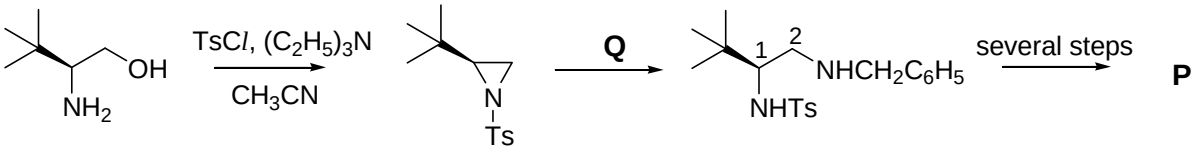
(a) An organocatalyst recently developed by researchers is a chiral bicyclic guanidine **P**.



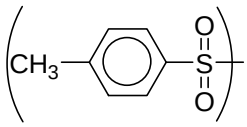
P

By drawing relevant structures of the conjugate acids, suggest why nitrogen 1 is more basic than nitrogen 2 in **P**. [4]

(b) The synthesis of chiral bicyclic guanidine **P** was optimised and part of it is illustrated in the reaction scheme below.



T **U**

where Ts = 

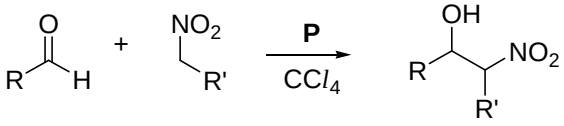
TsC*l* is needed in the first step of the synthesis so as to make the alcohol a good leaving group for the formation of the three-membered ring.

(i) Reagent **Q** in the second step is a nucleophile. Suggest what **Q** could be. [1]

(ii) Draw the Newman projection of **T** (along the 2 carbon atoms in the 3-membered ring) and indicate clearly on your diagram, how **Q** will approach **T** in the ring opening reaction leading to **U**. [2]

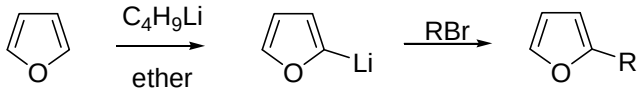
(iii) By drawing out the 3 staggered conformers of **U** (along C1-C2), indicate the most unstable conformation of **U**. Explain your choice. [3]

(c) Chiral bicyclic guanidine **P** can catalyse many reactions, one of which is known as the Henry reaction. An example of Henry reaction between an aldehyde and a nitroalkane is shown below.

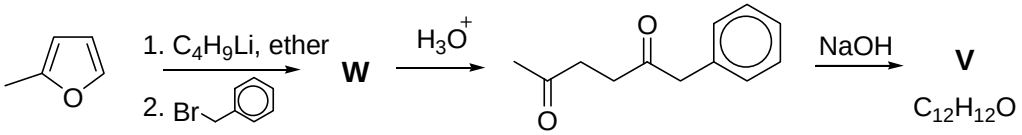


Illustrate the reaction mechanism of the Henry reaction using the above example. Your answers should clearly show how **P** acts as the catalyst and you may represent **P** using "R_3N". [3]

(d) Alkyl groups can be easily added to furan via lithiation using butyl lithium as illustrated below.



A precursor to a potential anti-cancer drug, **V** ($C_{12}H_{12}O$) is synthesized via the following reaction scheme.



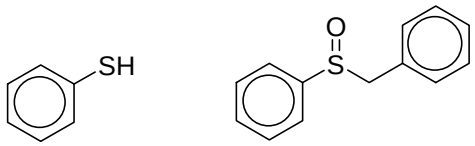
(i) Suggest a structure for intermediate **W** in the above reaction scheme. [1]

(ii) **V** was found to give a bright red precipitate with 2,4-dinitrophenylhydrazine and react with one equivalent of liquid bromine.

In addition, **V** was found to have the following peaks in the NMR spectrum (only the non-aromatic peaks are shown): δ 3.0 (t 2H), δ 2.0 (t 2H) and δ 1.7 (s 3H).

Base on the above information, deduce the structure of **V** and assign the peaks to the respective protons. [4]

(e) Suggest how **Y** could be made from **X** and bromomethylbenzene. [2]



X **Y**

[Total: 20]

- End of Paper -