HWA CHONG INSTITUTION

C2 PRELIMINARY EXAMINATION
CHEMISTRY
9812
Higher 3: Pharmaceutical Chemistry

18 September 2008 **2 h 30 min**

Do not open this booklet until you are told to do so.

INSTRUCTIONS TO CANDIDATES

1) This paper consists of **12** 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 all the work you hand in.
3) Begin each question on a **FRESH** sheet of writing paper. A **nil return** is necessary for any unattempted question.
4) At the end of the examination, fasten your cover page securely together with your answer scripts.

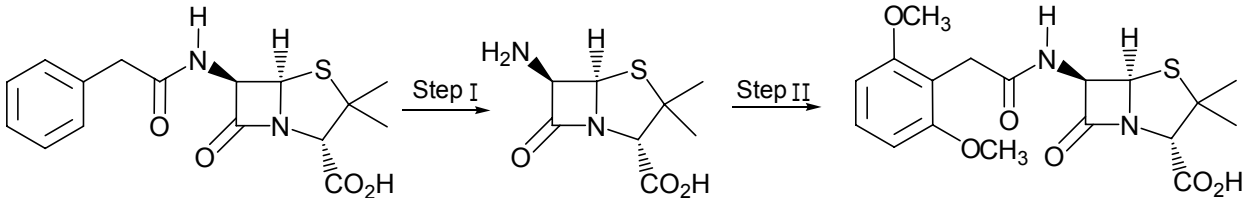
INFORMATION FOR CANDIDATES

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 Antibacterials are aimed at either killing bacteria (bacteriocidal) or inhibiting them from multiplying (bacteriostatic). One type of antibacterial drugs is the penicillins, which have revolutionized the history of modern medicine by their effectiveness against several pathogenic bacterial species that cause various forms of infections.

Penicillin G, the parent of all these antibiotics, was first isolated from a fungal species, *Penicillium notatum*. Since the discovery of this antibiotic, several modifications have been introduced to the parent structure. The discovery of 6-amino penicillamic acid (6-APA) in fermentation products constituted a major breakthrough in semisynthetic penicillin synthesis.

The reaction scheme for the formation of methicillin is shown below:



penicillin G 6-APA methicillin

(a) **(i)** Describe the mode of action of penicillins. [2]

(ii) Assign the R/S configuration for the asymmetric carbons found in penicillin G. [2]

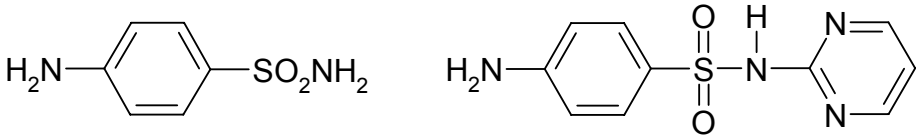
(iii) Suggest why chemical hydrolysis in step I to form 6-APA is not appropriate. [1]

(iv) Give the reagent in step II and outline the mechanism for the formation of methicillin. [2]

(v) Many bacteria have developed resistance to drugs by producing enzymes (β-lactamases) capable of hydrolyzing the β-lactam ring. Describe the β-lactamase mediated β-lactam ring hydrolysis, starting with penicillin G. You may assume that the reactive species in a β-lactamase enzyme is the hydroxyl group of a serine residue in the protein. [3]

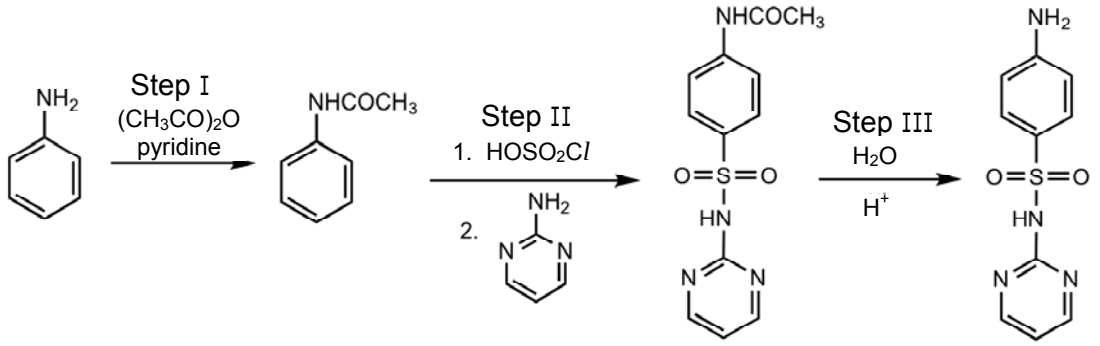
(vi) Suggest why methicillin shows improved resistance to β-lactamase mediated β-lactam ring hydrolysis. [1]

Another class of antibacterial drugs are the sulphadrugs, e.g. sulphanilamide. N-heterocyclic derivatives of sulphanilamides such as sulphadiazine have a broad-spectrum antimicrobial activity.



sulphanilamide sulphadiazine

The multistep synthesis of sulphadiazine, starting from phenylamine is summarized below:



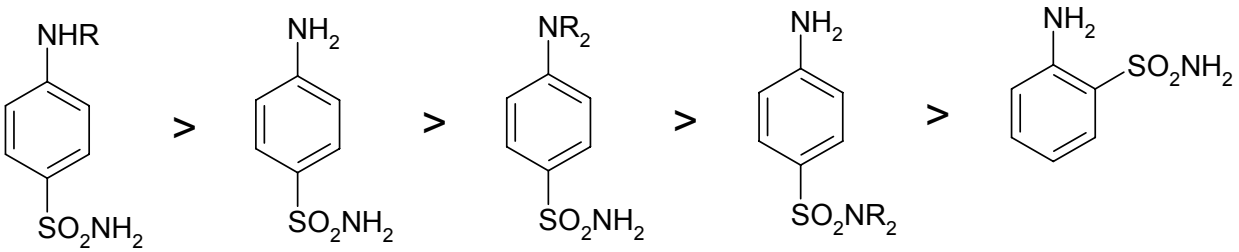
sulphadiazine

(b) (i) Describe the mode of action of sulphadrugs. [2]

(ii) Suggest why reaction of *N*-acetylaminobenzene with chlorosulphonic acid ($HOSO_2Cl$) results in chlorosulphonation, rather than sulphonation. [1]

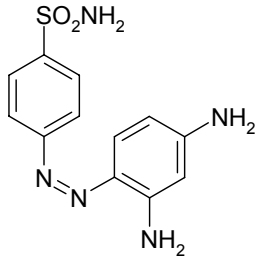
(iii) Outline the reaction mechanism for Step II in the conversion of phenylamine into sulphadiazine. [3]

To date, over 10000 structural analogues of sulphanilamide, the parent of all sulphadrugs have been synthesized and used in structure-activity relationship (SAR) studies. From numerous studies, it has been established that the antibacterial activity of the sulphadrugs decreases in the following order:



(c) (i) Give two deductions that could be obtained from the SAR studies. [2]

(ii) The structure of Prontosil is quite similar to the structure of sulphanilamide, with the $-NH_2$ group modified. It does not have any *in vitro* antibacterial activity but displays antibacterial activity *in vivo*. Suggest a reason for this behaviour.



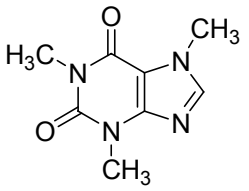
prontosil

[1]

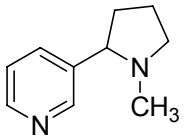
[Total: 20]

2 In the preparation of major examinations, a large number of students depend on coffee or tea to keep them awake through the long nights of self-revision. This is due to the effects of caffeine found in these beverages.

Nicotine is another drug which belongs to the same class of drugs as caffeine. Both drugs have similar effects as adrenaline and may cause problems of addiction.



caffeine



nicotine

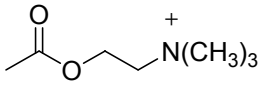
(a) Name the class of drugs that both caffeine and nicotine belong to. [1]

(b) Even though the overall physiological effects of caffeine and nicotine are very similar, the modes of the action of these stimulants are somewhat different. Contrast the modes of action of these two drugs. [3]

(c) **(i)** Explain, in terms of structures, why you would expect both caffeine and nicotine to absorb UV radiation. [2]

(ii) Deduce which of these two drugs will absorb at a longer wavelength. [2]

(d) Nicotine works as an acetylcholine agonist at nicotinic receptor, which are acetylcholine receptor on skeletal muscles and nerve synapses. The structure of acetylcholine is shown below:



acetylcholine

(i) When there is a lack of acetylcholine acting at a certain part of the body, acetylcholine is not administered into the body even though it is easy to synthesize in the laboratory. This is due to the ease of hydrolysis of acetylcholine in the stomach.

Describe the mechanism of the hydrolysis of acetylcholine in the stomach. [3]

(ii) Suggest why acetylchloline is more prone to hydrolysis than other esters. [2]

(iii) Suggest a possible structure of an analogue of acetylcholine that is less prone to hydrolysis. [1]

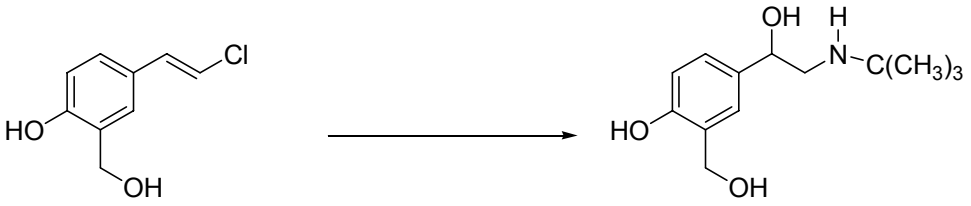
(e) With reference to the structure of nicotine, determine whether an aqueous solution of nicotine would be acidic, basic or neutral. [1]

(f) Suggest the form of nicotine that is active pharmacologically and explain your answer. [2]

(g) Explain how nicotine may cause addiction to smokers. [3]

[Total: 20]

3 Salbutamol is used in the treatment of asthma. It can be synthesized from compound **A**.



A salbutamol

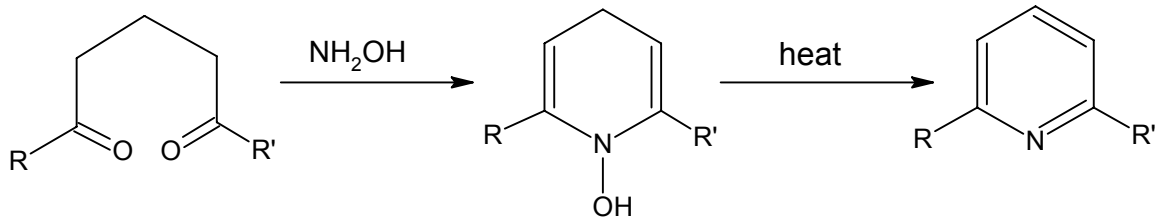
(a) Propose a two step synthesis to obtain salbutamol from **A**, showing the intermediate formed. [2]

(b) When salbutamol is synthesized from **A**, a mixture of compounds is formed. Column chromatography can be used to separate the stereoisomers that are present.

(i) Briefly describe the principles of column chromatography [2]

(ii) State the conditions required to separate the stereoisomers present using column chromatography. [2]

Apart from the benzene ring, there are many other ring systems that are aromatic, one of which is the pyridine ring. The pyridine ring can be synthesized using hydroxylamine and a 1,5-diketone.



(c) Propose the mechanism for the reaction from the 1,5-diketone to the pyridine ring. [4]

(d) An unknown compound **B** was synthesized in the laboratory. Its ^{1}H NMR, IR and MS spectra data are given below. Deduce the structure of **B** giving your reasoning.

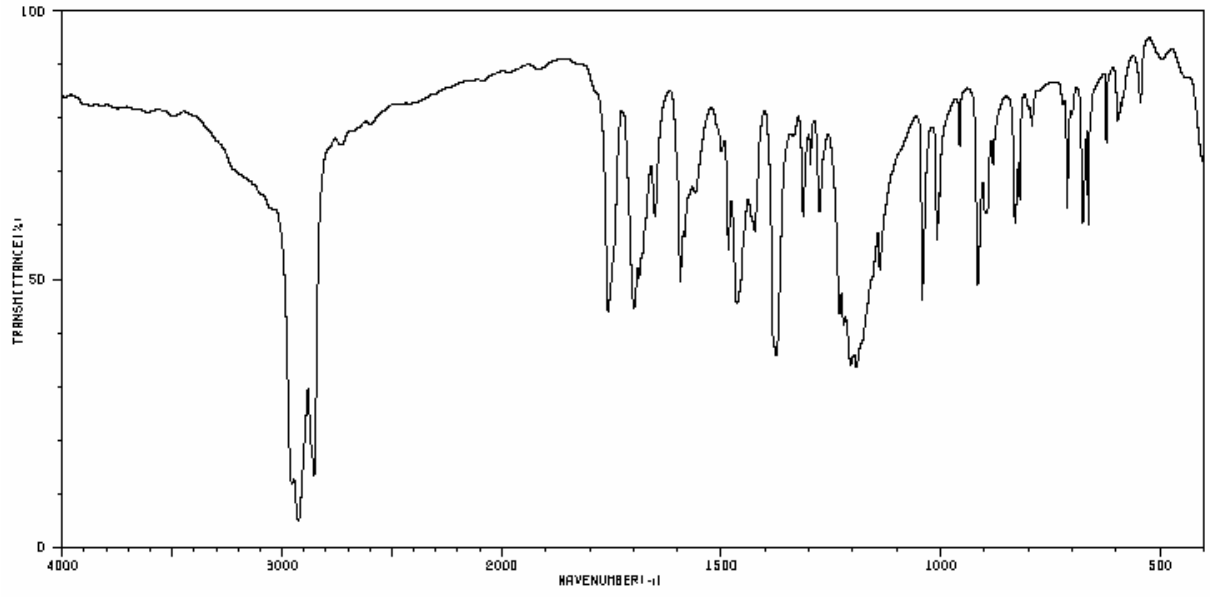
^{1}H NMR spectrum of **B**

δ/ ppm	**Integral**	**Multiplicity**
9.50	1	Singlet
7.50 – 7.70	3	Multiplet
2.30	3	Singlet

Major fragments in MS spectrum of **B**

m/z	**Intensity**
163	40
200	100
242	30
244	30

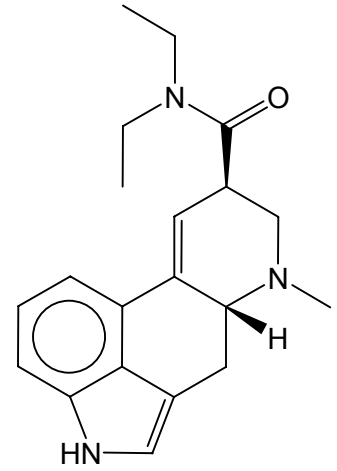
IR spectrum of **B**



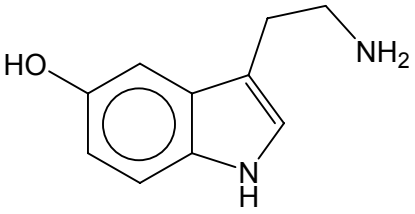
[10]

[Total: 20]

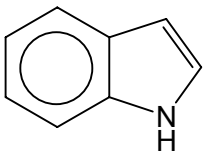
4 (a) Lysergic acid diethylamide is a hallucinogenic drug which contains an indole ring made up of a benzene ring and a pyrrole ring fused together.



Lysergic acid diethylamide
(LSD)



serotonin



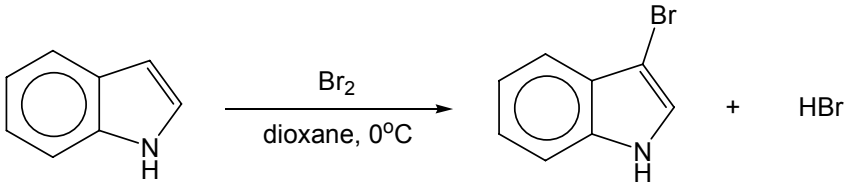
indole

(i) State and explain which nitrogen atom in LSD is the most basic. [2]

(ii) It has been found that LSD interacts with serotonin receptors. Suggest two groups that could be in the binding sites of the receptor and explain the types of intermolecular interactions involved. [2]

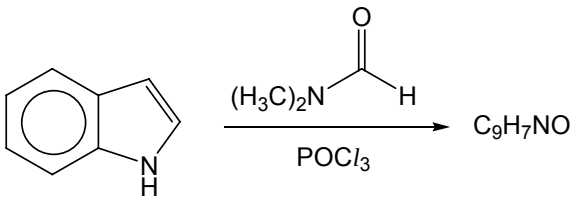
(iii) The chemistry of indole is in many ways similar to pyrrole. It also undergoes electrophilic substitution but unlike pyrrole, substitution is preferred at the 3-position with almost all reagents instead of the 2-position for pyrrole.

For example,



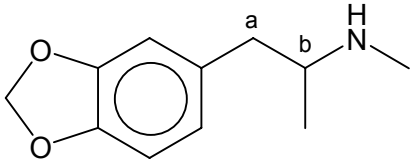
I By considering the stability of the intermediates involved, explain why electrophilic substitution of indole is preferred at the 3-position. [3]

II Reaction of indole with *N*,*N*-dimethylformamide, $(CH_3)_2NCHO$, and $POCl_3$ produces a product with formula C_9H_7NO. The IR spectrum of the product shows a peak at around 1650 - 1700 cm^{-1}.

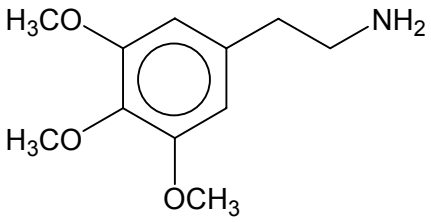


Deduce a structure for the product. [2]

(b) Another class of hallucinogenic drugs is based on phenethylamines. Some examples include methylenedioxy methylamphetamine and mescaline.



Methylenedioxy methylamphetamine
(MDMA, ecstacy)



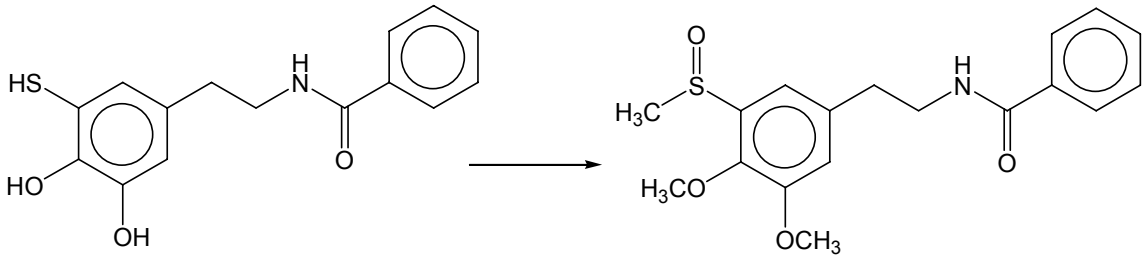
mescaline

(i) Outline how MDMA acts as a hallucinogenic drug. [2]

(ii) Draw Newman projections to show all the staggered and eclipsed conformations of MDMA about C_a–C_b. Illustrate the relative stability of these conformers by means of an energy profile diagram. [4]

(iii) Thiomescaline is an analogue of mescaline that has been found to have a higher potency than mescaline as a hallucinogenic drug.

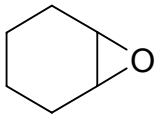
Suggest reagents and conditions for the conversion of the derivative of 3-thiomescaline into compound **X**, giving the structure of the intermediate formed.



derivative of 3-thiomescaline **X**

[2]

(c) Treatment of *trans*-2-chlorocyclohexanol with a strong base such as sodium methoxide, $NaOCH_3$, yields 1,2-epoxycyclohexane, but reaction of the *cis* isomer under the same conditions yields cyclohexanone. Propose mechanisms for both reactions.



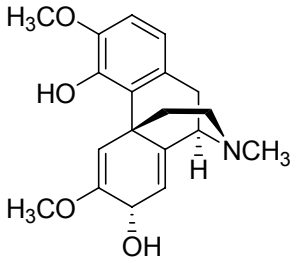
1,2-epoxycyclohexane

[3]

[Total: 20]

5 Opium is the air-dried milky exudate, or latex, obtained by incising the unripe capsules of the opium poppy *Papaver somniferum*. The entire plant tops are harvested and dried, then extracted and purified for their alkaloid content in the pharmaceutical industry. It has been used as an analgesic, narcotic and for the treatment of cough.

(a) Salutaridinol is found as a minor alkaloid constituent in the opium poppy *Papaver somniferum*.

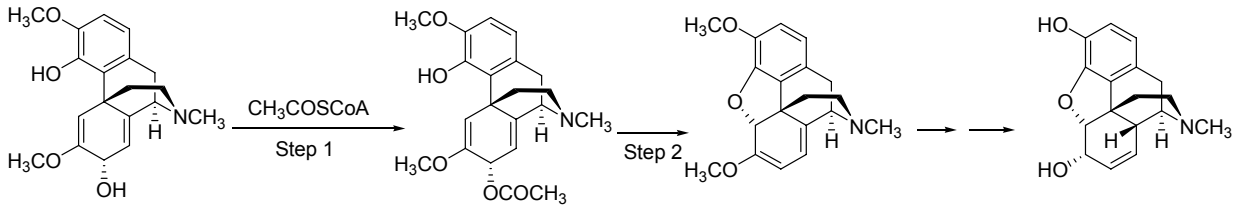


salutaridinol

(i) Copy the structure of salutaridinol onto your writing paper. Assign the stereochemical configuration about all the chiral carbon atoms. [2]

(ii) Suggest whether the nitrogen atom in salutaridinol is chiral, and explain your answer. [1]

(b) A chemist proposed the following reaction scheme for the synthesis of morphine from salutaridinol.



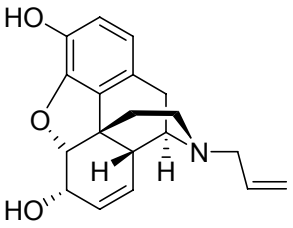
salutaridinol **A** thebaine morphine

(i) Draw a mechanism to account for the formation of **A** in step 1. [2]

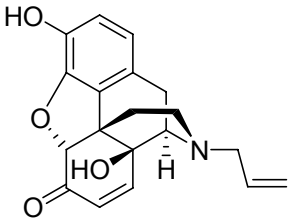
(ii) With the aid of a suitable mechanism, account for the stereospecific formation of the ether group in step 2. [2]

(iii) Suggest a reason why thebaine cannot be synthesized directly from salutaridinol and has to go through **A**. [1]

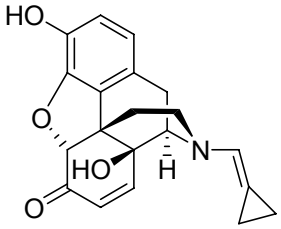
(c) Morphine is a powerful narcotic analgesic. Chemical modifications at the nitrogen atom produce analogues with different analgesic properties. A reaction mixture contains the following three morphine analogues: nalorphine, naloxone and naltrexone.



nalorphine



naloxone



naltrexone

(i) Explain the term *narcotic analgesic*, using morphine as an example. [2]

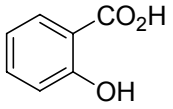
(ii) Identify suitable stationary and mobile phases for the separation of the reaction mixture. [2]

(iii) These three analogues act as competitive antagonists of morphine. They do not exhibit agonist effect and have different indications. Briefly explain how nalorphine functions as an antagonist. [2]

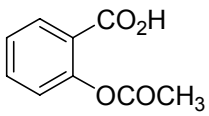
(iv) Suggest a clinical use for nalorphine. [1]

(v) Nitrogen oxidation of morphine greatly diminishes its analgesic potency. Explain. [1]

(d) Both aspirin and salicyclic acid are analgesic. Dewey suspected that aspirin was a prodrug which was metabolized to salicyclic acid *in vivo*.



salicyclic acid



aspirin

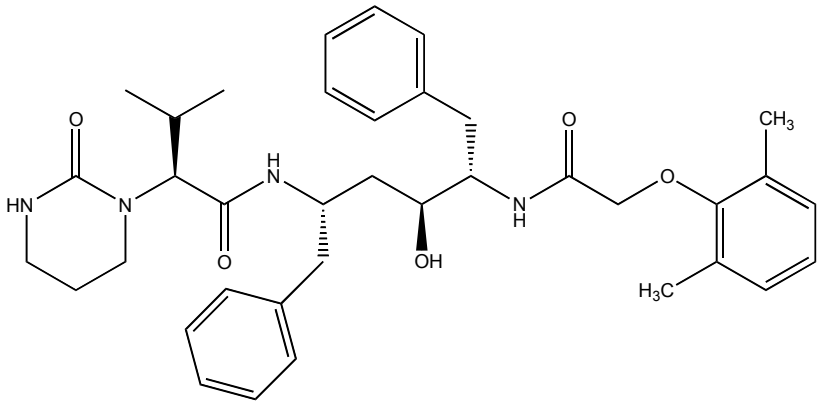
He decided to carry out an experiment to prove that his hypothesis was true. A urine sample, from a patient who had consumed aspirin, was collected, purified and analyzed using NMR spectroscopy.

(i) Suggest how NMR spectroscopy could be used to determine if the hypothesis is true or false? [2]

(ii) Explain why the protons in the $-CO_2H$ and $-OH$ functional groups have different chemical shifts. [2]

[Total: 20]

6 Viruses consist of genetic material and a capsular envelope made up of proteins (often with a coat of phospholipid bilayer with embedded proteins). They lack a metabolic system but depend on the infected cell for their growth and replication. Targeted therapeutic suppression of viral replication using antiviral drugs, to date, can only be achieved to a limited extent. An example of an antiviral agent is Lopinavir, which is a HIV antiviral protease inhibitor.



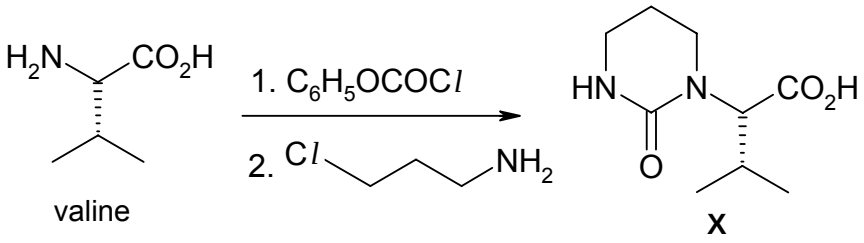
Lopinavir

(a) Outline the ways in which antivirals work, giving an example of each. [3]

(b) Assign the R/S configuration for the asymmetric carbons found in Lopinavir. [3]

(c) A terminal cyclic urea derivative of valine is present at one terminus in Lopinavir.

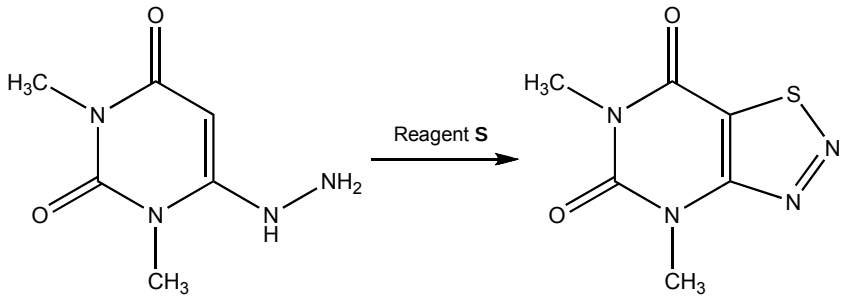
(i) Outline the mechanism for the multistep synthesis of this heterocyclic moiety **X** beginning with valine as the starting material.



valine **X** [4]

(ii) Draw the most stable conformation of the heterocyclic moiety **X**, showing clearly the stereochemistry about any asymmetric carbons. [2]

(d) The reaction scheme for a key reaction involved in the synthesis of another antiviral is shown below.



Y **Z**

(i) By considering their molecular structures, suggest why **Z** shows an absorption at a higher wavelength than **Y** in the UV-visible spectra of two separate equimolar solutions. [1]

(ii) The molar absorptivity, ε, for **Y** at 250 nm has a value of 11500. Given that the cell used has an optical path length of 1.0 cm, calculate the concentration of **Y** in mol dm^{-3} in the solution, given that the absorbance for Y at 250 nm is 0.85. [1]

(iii) Calculate the ε value for **Z** at 270 nm, given that the absorbance for **Z** at 270 nm is 0.65. [1]

(iv) Suggest a suitable reagent **S** used for the conversion of **Y** to **Z**. [1]

(e) Aside from relying on antivirals, another strategy makes use of monoclonal antibodies. Outine the use of monoclonal antibodies in drug therapy. [4]

[Total: 20]

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