HWA CHONG INSTITUTION

C2 PRELIMINARY EXAMINATION
CHEMISTRY
9812
HIGHER 3: PHARMACEUTICAL CHEMISTRY

24 September 2009 **2 h 30 min**

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

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.
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.

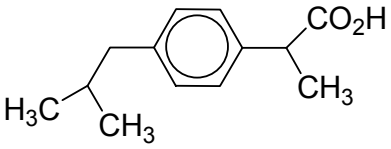
You are reminded of the need for good English and clear presentation in your answers.

1 Analgesic drugs are a diverse group of compounds that are capable of relieving pain. They can be classified into two categories, the narcotic and non-narcotic analgesics.

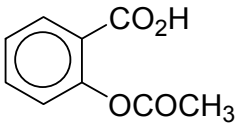
(a) Narcotic and non-narcotic analgesics act differently to prevent pain. Briefly describe the differences in their modes of action. **[2]**

(b) State **two** sources for which potential drug candidates may be identified. **[2]**

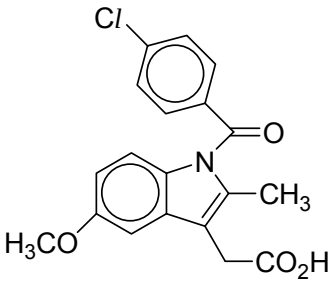
(c) Non-steroidal anti-inflammatory drugs (NSAIDs) belong to the class of non-narcotic analgesics. They include the following molecules:



ibuprofen

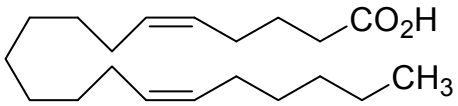


aspirin



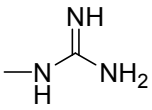
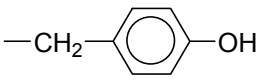
indomethacin

NSAIDs work by preventing arachidonic acid from binding to the active site of cyclooxygenase.



arachidonic acid

The active site of cyclooxygenase consists of the following amino acid residues:

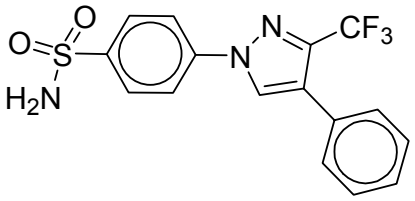
amino acid	serine	arginine	tyrosine
R-group	$-CH_2OH$		

The different modes of action for NSAIDs involves:

(1) covalent modification of the serine residue in cyclooxygenase
(2) reversible inhibition at the substrate-binding site
(3) competitive inhibition of cyclooxygenase via interactions with arginine and tyrosine

(i) Assign the NSAIDs modes of action (1) – (3) to ibuprofen, aspirin and indomethacin and justify your answer. Each NSAID should only be used once. **[4]**

(ii) SC−558 is also a type of NSAIDs. Copy the molecule onto your answer sheet and indicate on the diagram **two** different types of molecular interactions it can have with the amino acids at the cyclooxygenase active site.



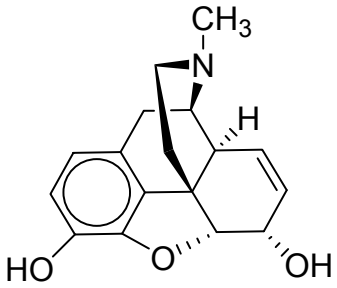
SC–558 **[2]**

(d) The ether group in indomethacin can be formed via a nucleophilic substitution reaction.

(i) Draw the precursor and state the reagents and conditions required for the reaction to take place. **[2]**

(ii) Suggest whether this reaction takes place via a S_N1 or S_N2 reaction. Justify your answer. **[2]**

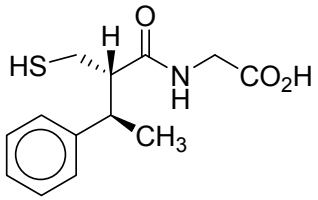
(e) Morphine belongs to the class of narcotic analgesics.



morphine

Copy the structure of morphine onto your paper and assign the R,S configuration about all the chiral carbon centres in morphine as well as the E,Z configuration about the double bond. **[3]**

(f) In the search for an alternative analgesics drug, a dipeptide was chosen as a lead compound and modified to give compound **A**.



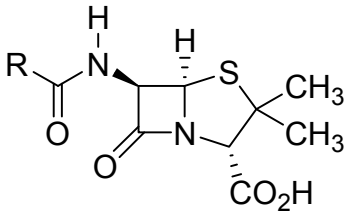
A

Draw the Fisher projections for all the possible stereoisomers and indicate their stereochemical relationships.

[3]

[Total: 20m]

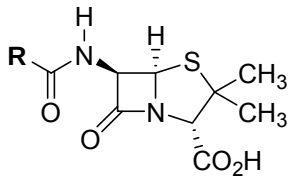
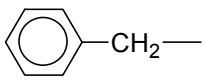
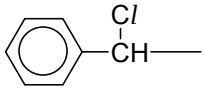
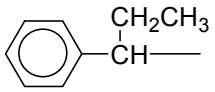
2 **(a)** One problem faced with penicillin-G, a useful antibacterial drug, was that it tends to break down in acid due to the hydrolysis of the β-lactam ring. The general structure of penicillin is shown below.



penicillin

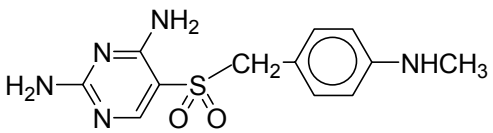
Pharmaceutical chemists have modified the R group side chain in semi-synthetic penicillins to make them more resistant to acid-catalysed hydrolysis.

(i) The rates of hydrolysis of the β-lactam ring in penicillin-G, and two other analogues **A** and **B** were measured and recorded. The R group of penicillin-G, **A** and **B** are shown below.

	R in 
penicillin-G	**R** = 
A	**R** = 
B	**R** = 

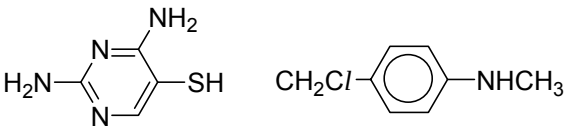
By considering the mechanism of the β-lactam ring-opening process, arrange these 3 compounds in order of increasing rate of hydrolysis. Explain your answer clearly. **[3]**

(ii) Sulfones, a class of antibacterial drugs, are also used in the treatment of leprosy. A structure-activity relationship study was done to test the efficacy of sulfones against leprosy. One of the molecules studied was sulfone **C**.



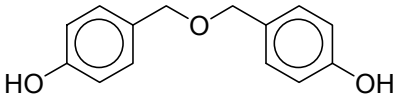
C

Propose a 3-step synthesis of **C** using the following molecules.



State any other reagents and conditions you would use for each step. **[3]**

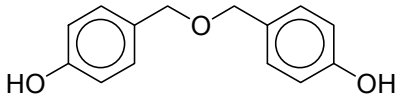
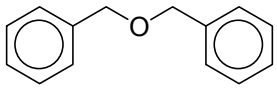
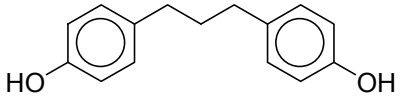
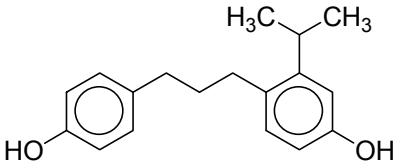
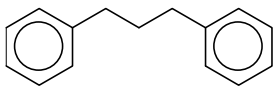
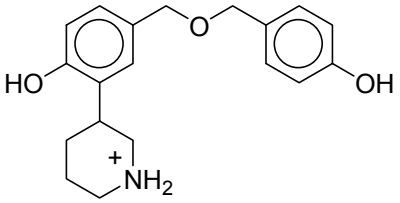
(b) In a hypothetical case study, pharmacologists discovered a receptor involved in mediating cellular growth in the brain. The endogenous agonist of this receptor in normal cells was found to be compound **I**. Tumour cells also contain this endogenous agonist, but they were found to have an extremely high level of **I**. They bind to the receptors causing harmful physiological effects.



I

A series of five different analogues of **I** was synthesized and tested in an *in vitro* cell line assay. The size of the tumour growth was graded on a 10 point scale (1 being small and harmless; 10 being huge and invasive). All tumours used in the experiment started with a scale of 5. After the compounds were added and incubated for 2 weeks, the size of the individual tumours was graded.

The table shows the result of the test with **I** and its analogues:

compound	scale	compound	scale
 **I**	**7**	 **II**	**5**
 **III**	**7**	 **IV**	**9**
 **V**	**5**	 **VI**	**2**

(i) Explain clearly how agonists and antagonists differ in their interactions with receptors. **[2]**

(ii) Using the data given, deduce which compounds are acting as agonists and justify your answer. **[1]**

(iii) Based on the data given, suggest the functional groups in **I** and the types of intermolecular forces involved in binding **I** to the receptor. **[2]**

(c) Analogues **II** and **III** can be differentiated using IR spectroscopy.

Suggest how infrared spectroscopy could be used to distinguish these two compounds. **[1]**

(d) Compound **III** was also analyzed using ^{1}H NMR spectroscopy.

(i) Explain why TMS is suitable as a reference in ^{1}H NMR spectroscopy. **[1]**

(ii) *The use of Data Booklet is relevant to this question.*

Sketch the NMR spectrum of **III** in the presence of $CDCl_3$, indicating clearly the following:

- number of signals in the spectrum
- integral of each signal
- splitting pattern of each signal

[4]

(iii) Account for the chemical shifts of the **two** most deshielded NMR signals in your sketch in **(d)(ii)**. **[2]**

(iv) Describe and explain how the NMR spectrum will differ from your sketch in **(d)(ii)** when the solvent is replaced with deuterated water. **[1]**

[Total: 20 m]

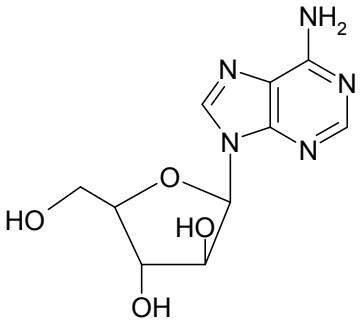
3 **(a)** Viruses are a type of pathogen which account for about 60% of illnesses.

(i) Give a reason why it is particularly difficult to design effective antiviral drugs. **[1]**

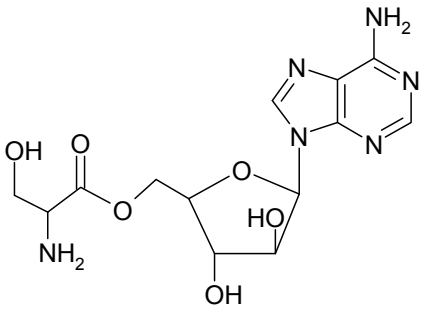
(ii) Some antiviral drugs may be described as *monoclonal antibodies*. What do you understand by the terms in italics? **[2]**

(iii) Vidarabine, an analogue of the nucleoside adenosine, is an intravenously administered antiviral drug active against herpes viruses. Some of its drawbacks include:

- limited solubility at physiological pH
- susceptibility to deamination by the enzyme adenosine deaminase in the body which converts the amino group to a ketone group, with loss of much antiviral effect.



vidarabine



J

J, a derivative of vidarabine, was synthesized and its properties compared with vidarabine.
(**I**) **J** shows improved solubility.
(**II**) **J** shows less evidence of deamination.

Briefly suggest an explanation for each observation (**I**) and (**II**). **[2]**

(b) The antioxidant glutathione was once thought to be a dipeptide of glutamic acid and cysteine. In 1927, George Hunter suggested that glutathione contained a third amino acid residue, probably serine. Hunter also described a method to hydrolyse glutathione, obtaining the separate amino acids in a solid hydrolysate. It is now confirmed that glutathione is a tripeptide, with glycine as the third amino acid.

An electrophoresis experiment was carried out to prove that Hunter's suggestion of a serine residue in gluthathione was incorrect. A sample of Hunter's hydrolysate was dissolved in a buffer of pH 5.8.

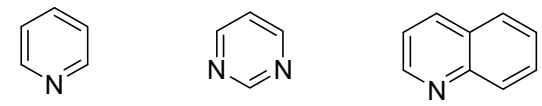
(i) Sketch the setup for the electrophoresis experiment described above. You should include a clearly labeled diagram of the experimental set-up and the expected electrophoretogram. The following data may be useful:

amino acid	R-group	isoelectric pH
glutamic acid	$-CH_2CH_2CO_2H$	3.2
cysteine	$-CH_2SH$	5.0
serine	$-CH_2OH$	5.7
glycine	$-H$	6.0

[2]

(ii) Account for the results of your electrophoretogram in **(b)(ii)**. **[2]**

(c) Benzene, pyridine, pyrimidine and quinoline are all aromatic compounds.

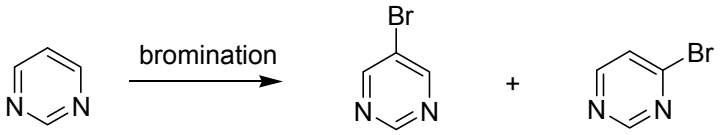


pyridine pyrimidine quinoline

(i) Explain why they can all be classed as *aromatic* in terms of their electronic structure. **[2]**

(ii) Give a reason why pyridine is more resistant to electrophilic substitution than benzene. **[1]**

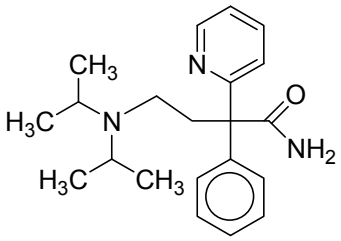
(iii) Under suitable conditions, pyrimidine may also undergo electrophilic substitution reactions.



5-bromopyrimidine more than 95% 4-bromopyrimidine less than 5%

With the aid of the resonance structures of the intermediate, explain why 5-bromopyrimidine, not 4-bromopyrimidine, is the major product formed in the bromination of pyrimidine. **[3]**

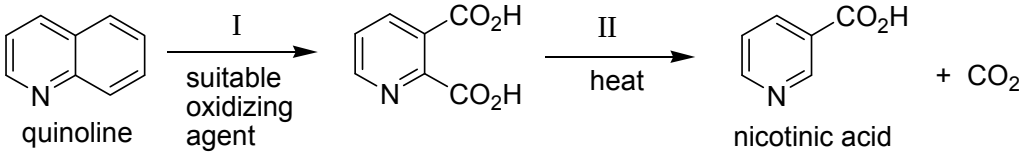
(iv) Disopyramide is a drug used to suppress fast heart rhythms. Copy out the structure of disopyramide below and suggest the order of basicity of the three nitrogen atoms, indicating the **least** basic as $\mathbf{N_A}$ and the **most** basic as $\mathbf{N_C}$. Briefly give reasons for your choice.



disopyramide

[3]

(v) Nicotinic acid is a pyridine derivative commonly known as Vitamin B_3. It can be made via the following reaction scheme, starting from quinoline.



quinoline nicotinic acid

Suggest a mechanism for step **II**. **[2]**

[Total: 20m]

4 Caffeine is a stimulant found commonly in coffee and tea. It has the effect of temporarily warding off drowsiness and restoring alertness. This drug effect has potential application in the military, where soldiers are required to maintain operational effectiveness for 24 hours a day continuously for several days. Inevitably, both cognitive and physical performance will deteriorate because of sleep loss.

In 2002, the military carried out a study to examine the effect of caffeine on the physical performance of the soldiers. The study provided information on the following points:

- the time to exhaustion (*t*) when the soldiers are working at 80 percent of their maximal physical work capacity
- the effect of caffeine on regular user and non-user of caffeine
- how long the stimulating effect of a single dose of caffeine can last (after 1, 3 and 6 hour of ingestion)

The soldiers are divided into four sample groups:

group	history of caffeine use	drug given (5mg/ kg)
A	non-user of caffeine	caffeine
B	non-user of caffeine	placebo
C	regular user of caffeine	caffeine
D	regular user of caffeine	placebo

The results are summarized in Figure 1:

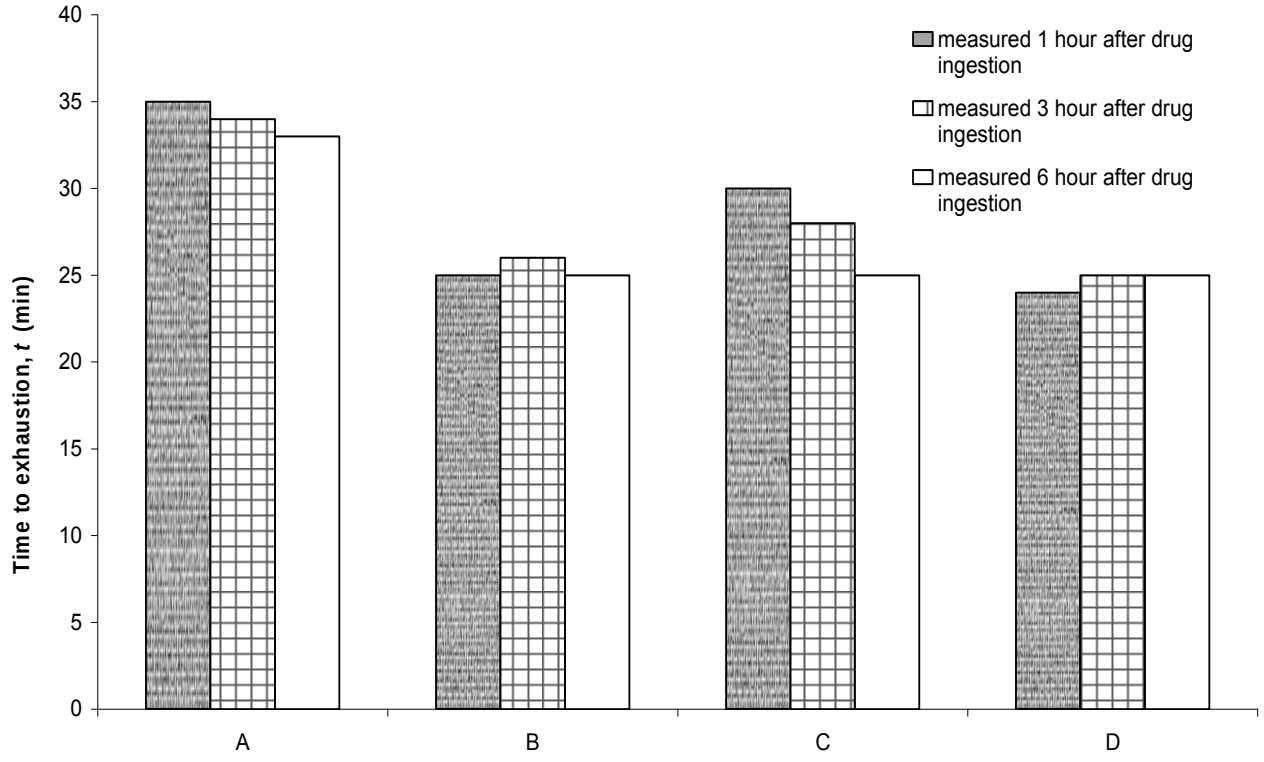


Fig. 1 Time to exhaustion, t, at 80% maximal physical work capacity in caffeine regular user and non-users after 1, 3 and 6 hours of caffeine ingestion.

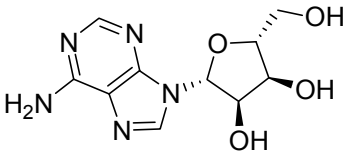
(a) (i) Define the term *placebo*. **[1]**

(ii) From the graph, state **two** differences in the effect of caffeine on regular users and non-users of caffeine. **[2]**

(iii) The time to exhaustion for a control group of non-users (no drug administered) after 1 hour is 20 min.

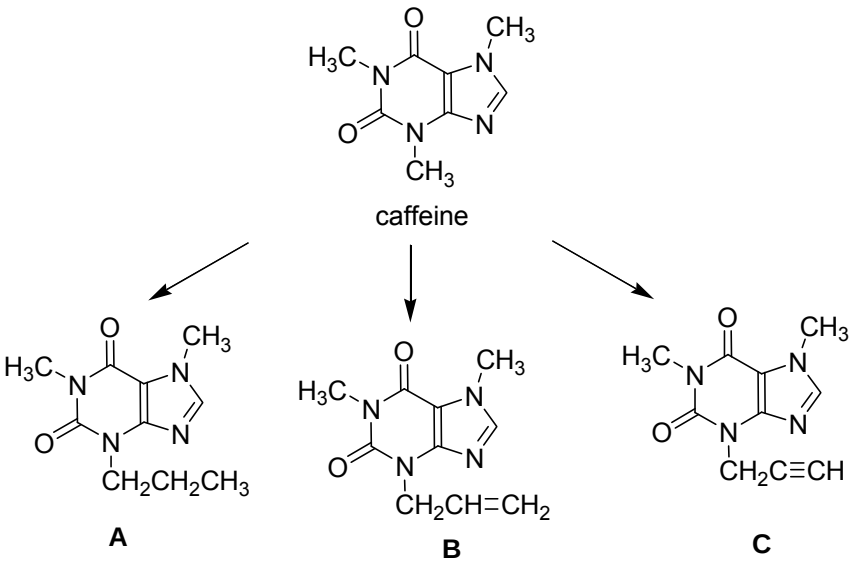
Calculate the percentage increase in time to exhaustion, *t*, for the non-users that received the placebo in group A as compared those that received the caffeine in group B after 1 hour of ingestion. **[1]**

Caffeine acts as a competitive antagonist to adenosine receptors on the surface of the cells in the central nervous system.



adenosine

A structure-activity relationship studies was carried out to design a more effective stimulant than caffeine.



caffeine

A **B** **C**

Compounds **A**, **B** and **C** are analogues of caffeine. They are 7 – 10 times more effective than caffeine as a stimulant.

(iv) Suggest what structural features caffeine have in common with adenosine to enable it to act as its competitive inhibitor. **[1]**

(v) Explain in terms of drug solubility and drug-receptor interactions involved, why analogues **A**, **B** and **C** exhibit different physiological effects from caffeine. **[2]**

(vi) One of the potential problems of providing the soldiers with caffeine and its derivatives is that it can lead to drug dependence. Describe the chemical basis of drug dependence (addiction) as in the case of caffeine. **[3]**

(b) The UV spectra of caffeine in various solvents were analyzed and the results tabulated.

solvent	water	0.1 mol dm^{-3} HC*l*
λ_{max}**/ nm**	273	270
ε	10000	9610

(i) State Beer's Law, indicating clearly the units of each term. **[2]**

(ii) In an acidic medium, the λ_{max} is observed to decrease. Explain the observation. **[2]**

A new beverage drink Zap, containing artificial flavourings and colourings, was sent to a laboratory for analysis before it could be licensed for sale. The ingredient label indicates that there is 25 mg of caffeine in 100 cm^3 of Zap.

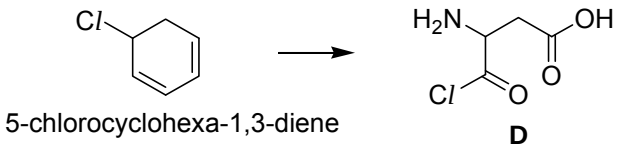
A laboratory technician was tasked to verify the caffeine (Mr = 194) concentration in Zap. He added 50 cm^3 of Zap to a standard volumetric flask and topped up its volume to 1 dm^3 with water. The concentration of caffeine in the diluted sample of Zap was analysed using UV spectroscopy at 273 nm.

(iii) Calculate the theoretical A_{273} value for the caffeine concentration in the diluted sample of Zap. **[2]**

(iv) The A_{273} for the diluted sample of Zap was found to be 0.72. Suggest a reason for the discrepancy. **[1]**

Aspartame, an artificial sweetener, was also present in Zap. A chemist attempts to synthesize aspartame from 5-chlorocyclohexa-1,3-diene.

Part of the synthesis pathway involves converting 5-chlorocyclohexa-1,3-diene to compound **D** in not more than four steps.



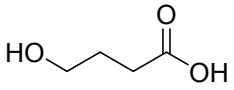
5-chlorocyclohexa-1,3-diene **D**

(v) Propose a synthesis of **D** from 5-chlorocyclohexa-1,3-diene, in not more than 4 steps, stating clearly the reagents and conditions required for each step. **[3]**

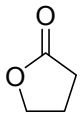
[Total: 20m]

5 Hypnotic drugs are a class of psychoactives whose primary function is to induce sleep and are used in the treatment of insomnia and in surgical anesthesia.

(a) Gamma-hydroxybutyric acid, GHB, is an example of a hypnotic drug that has been used in sleeping pills. However, some drug abuse issues were identified with this substance and its sale was restricted in 2003.



GHB



GBL

Gamma-butyrolactone, GBL, is a prodrug of GHB and is rapidly converted into GHB by enzymes found in the body.

(i) Propose a mechanism for the conversion of GBL into GHB. **[3]**

(ii) On reaction of GBL with $LiAlH_4$, a molecule that has the same effect on the body as GHB, called GHB alcohol, is formed.

Draw the structure of GHB alcohol. **[1]**

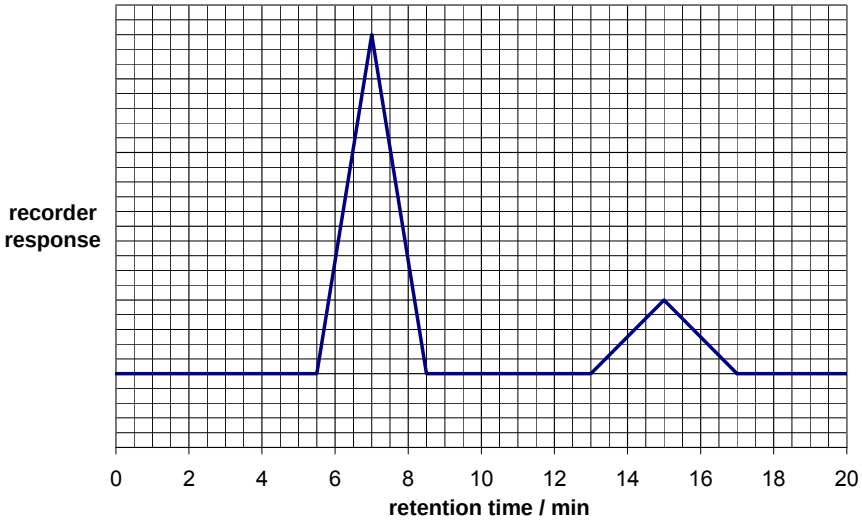
(iii) GBL can be easily synthesized from GHB in the laboratory using an acid catalyst.

$$GHB = GBL + H_2O$$

The conversion is an equilibrium reaction and the extent of reaction can be investigated using gas-liquid chromatography (GLC).

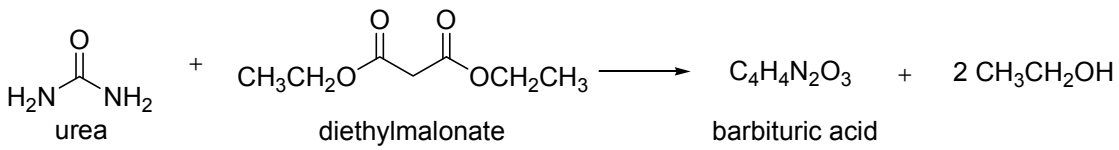
I Outline the principle of GLC. **[3]**

II An equilibrium mixture containing GHB and GBL was analyzed using a polar stationary phase. The chromatogram obtained is shown below.



Calculate the equilibrium constant, K_c, for the conversion of GHB into GBL. Assume that $[H_2O]$ is constant at 55.0 mol dm^{-3}. **[2]**

(b) Barbituric acid, a precursor of some hypnotic drugs, contains a six-membered ring and can be formed from the condensation reaction between urea and diethylmalonate.



(i) Draw the structure of barbituric acid. **[1]**

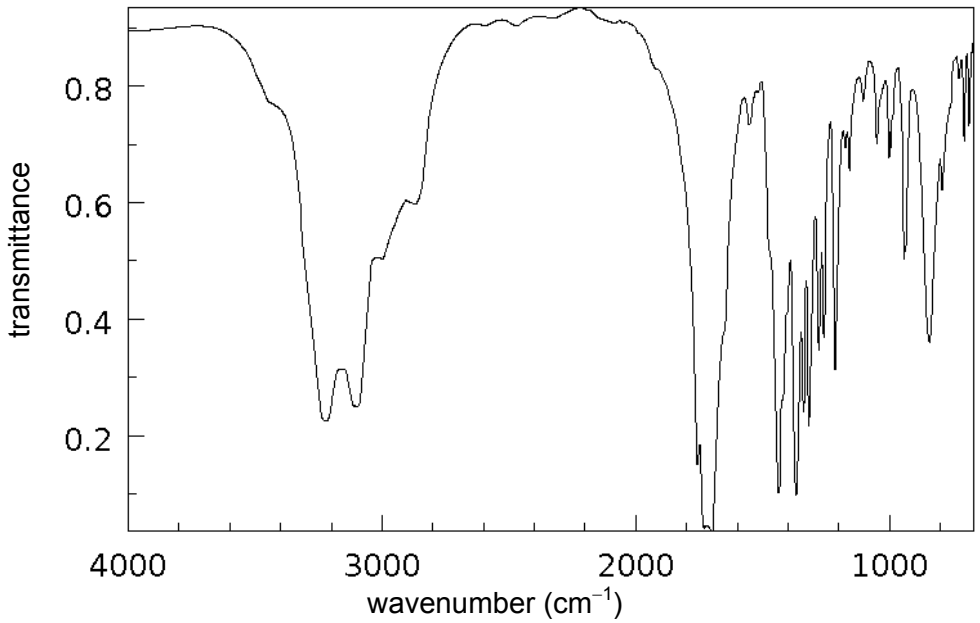
Aprobarbital, a barbituric acid derivative, was used primarily for the treatment of insomnia.

The mass spectrum of aprobarbital shows the following peaks and the molecular ion peak at m/z = 210.

m/z value	relative abundance
41	40
167	100
210	2.7
211	0.3

The ^{1}H NMR spectral data and IR spectrum of aprobarbital are given below.

chemical shift / ppm	integration	multiplicity
1.0	6	doublet
2.3	1	multiplet
2.4	2	doublet
5.0	2	multiplet
5.7	1	multiplet
10.0	2	singlet



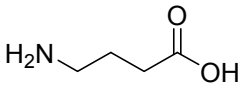
(ii) Using the mass spectrum data, deduce the number of carbon atoms in aprobarbital. **[1]**

(iii) Use your answer in **(b)(i)** – **(ii)** and the spectral information given to deduce the structure of aprobarbital, explaining clearly how you arrived at your conclusion. **[9]**

[Total: 20m]

6 Flunitrazepam, a benzodiazepine derivative, is marketed as a hypnotic drug and has sedative properties. The prescription of flunitrazepam as a hynoptic is generally intended to be for short-term treatment of chronic or severe insomnias that are not responsive to other hypnotics. It is, however, a controversial sedative which has been misused to 'spike' people's drinks.

Flunitrazepam binds to the gamma-aminobutyric acid-A ($GABA_A$) receptors in the central nervous system. $GABA_A$ is a ligand-gated chloride ion channel and it is responsive to the binding of GABA, a major inhibitory neurotransmitter in the brain. When GABA binds to $GABA_A$, the conformation of the receptor changes, causing the chloride ion channel to open and leading to inhibition of neuron-firing. When flunitrazepam binds to the $GABA_A$ receptor site, a conformational change also occurs in the receptor that enhances the binding of GABA.

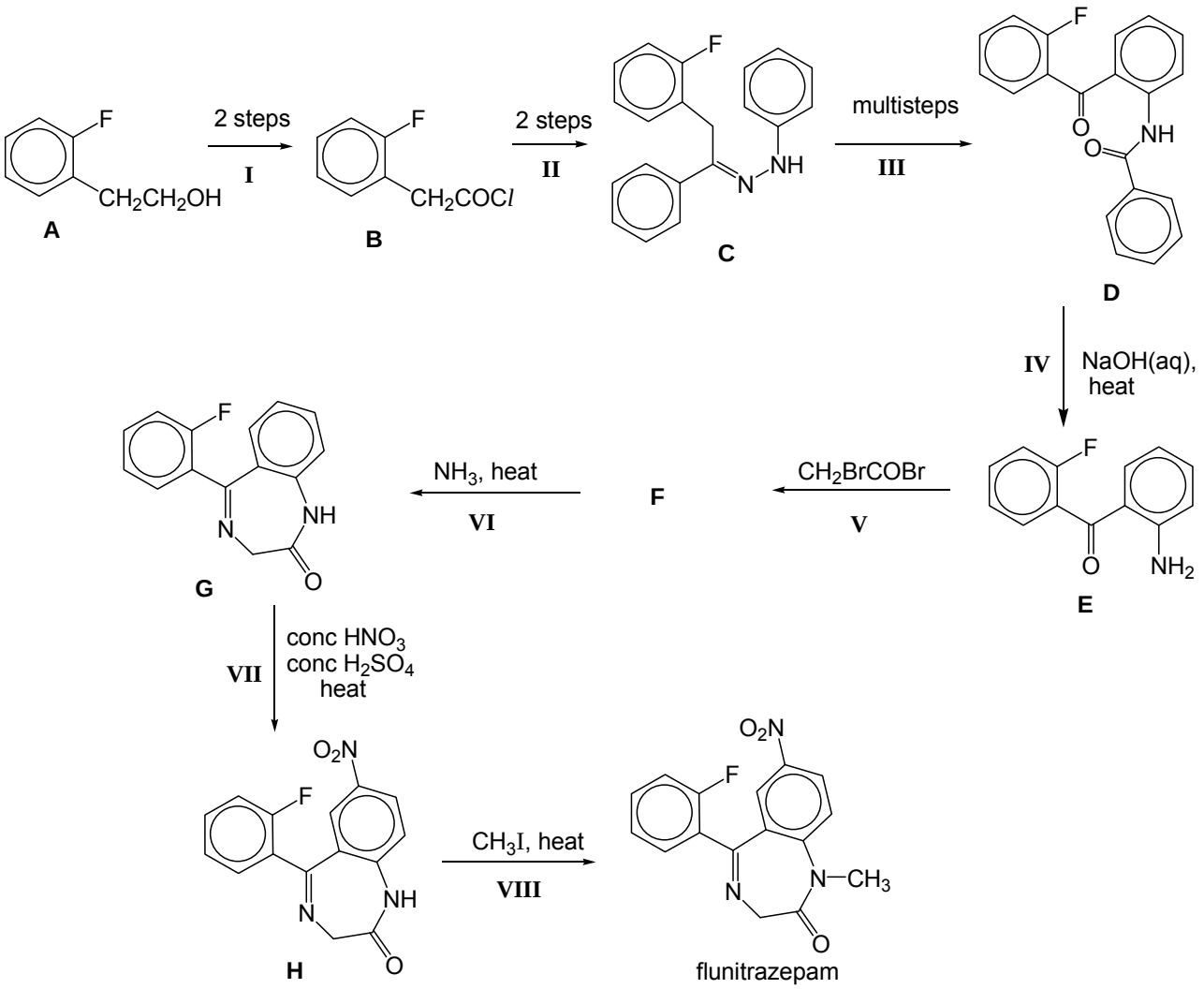


GABA

(a) **(i)** Draw Newman projections (along the C2–C3 bond) to show the 3 gauche and 3 eclipsed conformations of GABA and sketch a potential energy diagram to illustrate the relative stability of these conformers. **[4]**

(ii) Suggest whether flunitrazepam is an agonist or antagonist at the $GABA_A$ receptor site. **[1]**

Flunitrazepam can be synthesized from **A** as outlined below:



(b) **(i)** Flunitrazepam can be classified as a *hallucinogen*. Explain what is meant by the term in italics. **[1]**

(ii) Provide the reagents and conditions for the conversion in steps **I** and **II**. Include the structures of all organic intermediates obtained during these multistep conversions. **[4]**

(iii) State the type of stereoisomerism exhibited in **C**, illustrating your answer with relevant diagrams. **[2]**

(iv) Draw the structure of **F**. **[1]**

(v) Propose a mechanism for the following reactions:

(I) **E** to **F**; **[2]**

(II) **F** to **G**. **[3]**

(vi) State the types of reactions involved in the conversion of **G** to **H** and **H** to flunitrazepam.

(I) **G** to **H**;

(II) **H** to flunitrazepam. **[2]**

[Total: 20m]

- End of Paper -