Name:		Index Number:		Class:	

DUNMAN HIGH SCHOOL
Preliminary Examination 2011
Year 6

H3 CHEMISTRY 9812/01

Paper 1

23 September 2011
2 hours 30 minutes

Additional Materials: Data Booklet
Writing papers

INSTRUCTIONS TO CANDIDATES

1 Write your **name**, **index number** and **class** on this cover page.
2 Answer any **five** questions.
3 Start each question on a fresh sheet of paper.
4 Write in dark blue or black pen on both sides of the paper.
5 You may use a soft pencil for any diagrams, graphs or rough working.
6 Do not use staples, paper clips, highlighters, glue or correction fluid.
7 You are reminded of the need for good English and clear presentation in your answers.
8 The number of marks is given in brackets [ ] at the end of each question or part question.
9 At the end of the examination:
- Fasten all work securely together with the Cover Sheet on top.
- Hand in the question paper separately.

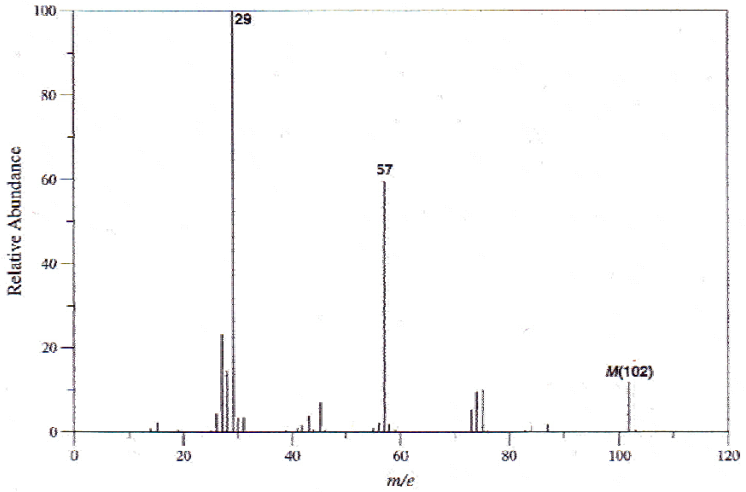
10 The total marks for this paper is 100 marks.

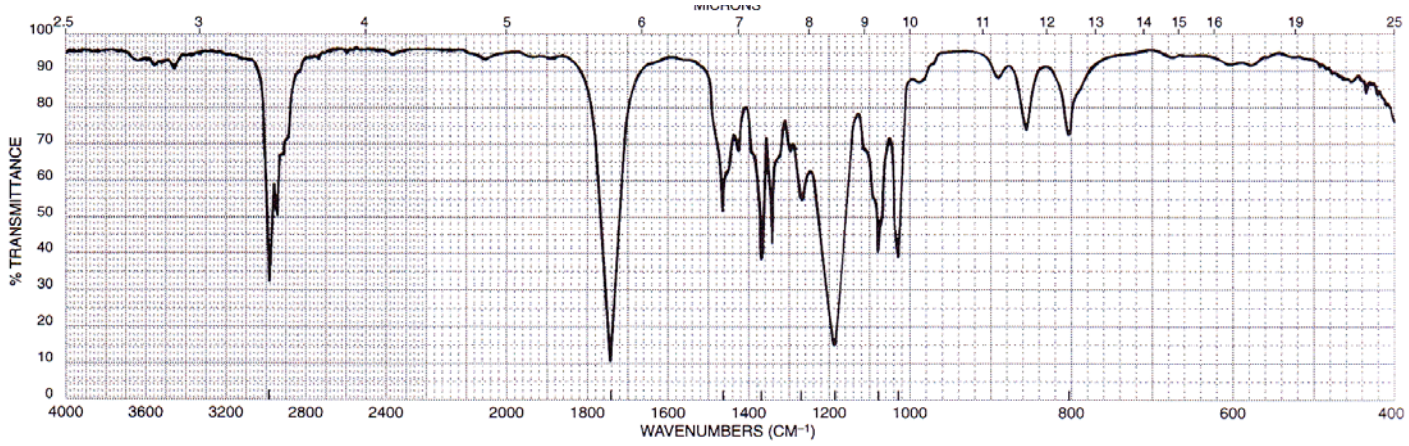
1 **(a)** ^{1}H NMR is a common analytical technique used to determine the molecular structures of various compounds.

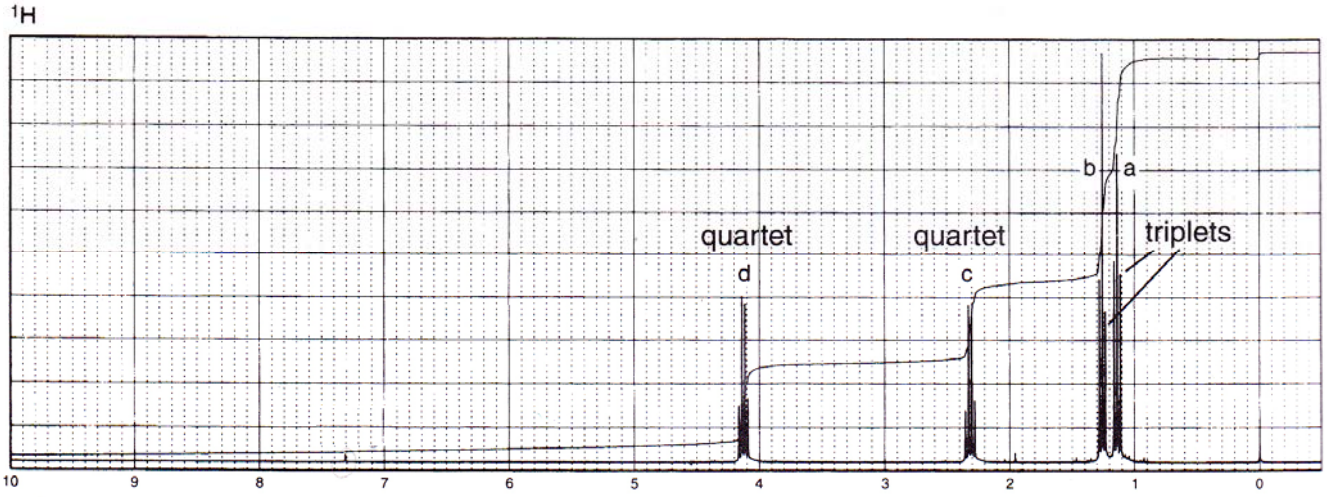
(i) Outline the basic working principles of NMR. [2]

An unknown compound **A**, $C_5H_{10}O_2$, was synthesised in the laboratory. It is used to manufacture various propionates which are used as anti–bacterial agents. Its MS, IR and ^{1}H NMR spectra data given below.

(ii) Deduce the structure of compound **A**, giving your reasoning. [8]



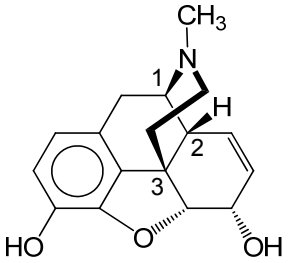




(b) Opium is the air–dried milky exudate, or latex, obtained by incising the unripe capsules of the opium poppy *Papaver somniferu.*

It contains up to 12% morphine, an alkaloid, which is frequently processed chemically to produce heroin for the illegal drug trade.

Morphine is also used as a *narcotic analgesic* and for the treatment of dry cough and diahorrea.



morphine

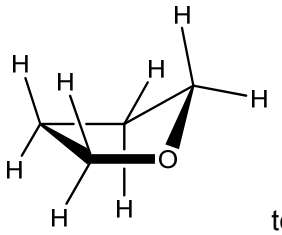
(i) Explain the term *narcotic analgesic*, using morphine as an example. [1]

(ii) Narcotic and non–narcotic analgesics act differently to prevent pain. Briefly outline the modes of action of non–narcotic analgesics. [1]

(iii) Assign the stereochemical configuration at C1, C2 and C3.

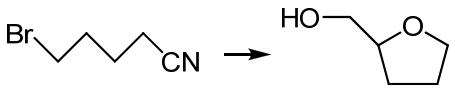
[2]

(c) Many drugs, like morphine, contain cyclic ether in their structures. Shown below is the puckered conformation of a cyclic ether, tetrahydrofuran.



tetrahydrofuran

(i) Suggest a simple synthetic pathway for the formation of the cyclic ether, **C**, from compound **B**. State clearly all reagents and conditions required for the proposed steps of the synthesis. [4]

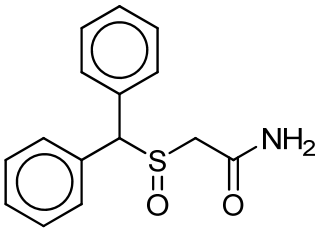


B **C**

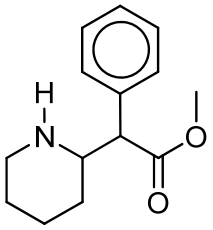
(ii) Draw two different conformers of cyclic ether, **C**, showing the positioning of the substituent on the ring. State which of the two conformers is more stable, giving your reasoning. [2]

[Total: 20]

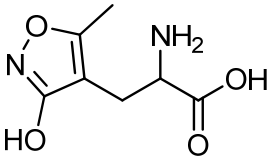
2 **(a)** Stimulants are psychoactive drugs which induce temporary improvements in either mental or physical function or both. Modafinil, methylphenidate and ampakine are stimulant drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of various disorders. The structures of all three compounds are shown below.



modafinil



methylphenidate



ampakine

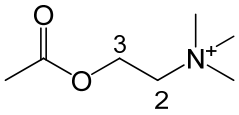
A mixture of these compounds can be analysed by reversed phase column HPLC. The compounds are detected as they emerge from the column using UV spectroscopy.

(i) Predict the order at which the compounds will be eluted and explain the difference in their retention times.

(ii) Explain why the three compounds may be detected using UV, and state what happens in their molecules when UV radiation is absorbed.

[5]

Some stimulants exert their effects by mimicking the action of the neurotransmitter acetylcholine.

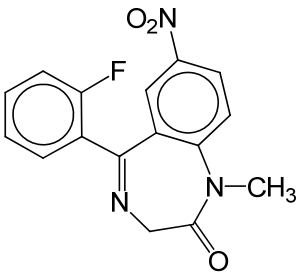


acetylcholine

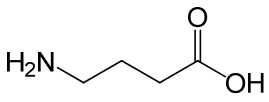
(iii) Draw and label the Newman projections (along the C2–C3 bond) to show the six conformations of acetylcholine. Sketch a potential energy profile diagram to illustrate the relative stability of these conformers.

[4]

(b) Rohypnol, a benzodiazepine derivative, is marketed as a highly potent hypnotic drug with sedative properties. It binds to the gamma–aminobutyric acid–A ($GABA_A$) receptors in the central nervous system and prevents the neurotransmitter, gamma–aminobutyric acid (GABA), from binding to the receptors thereby inhibiting neurotransmission.



rohypnol



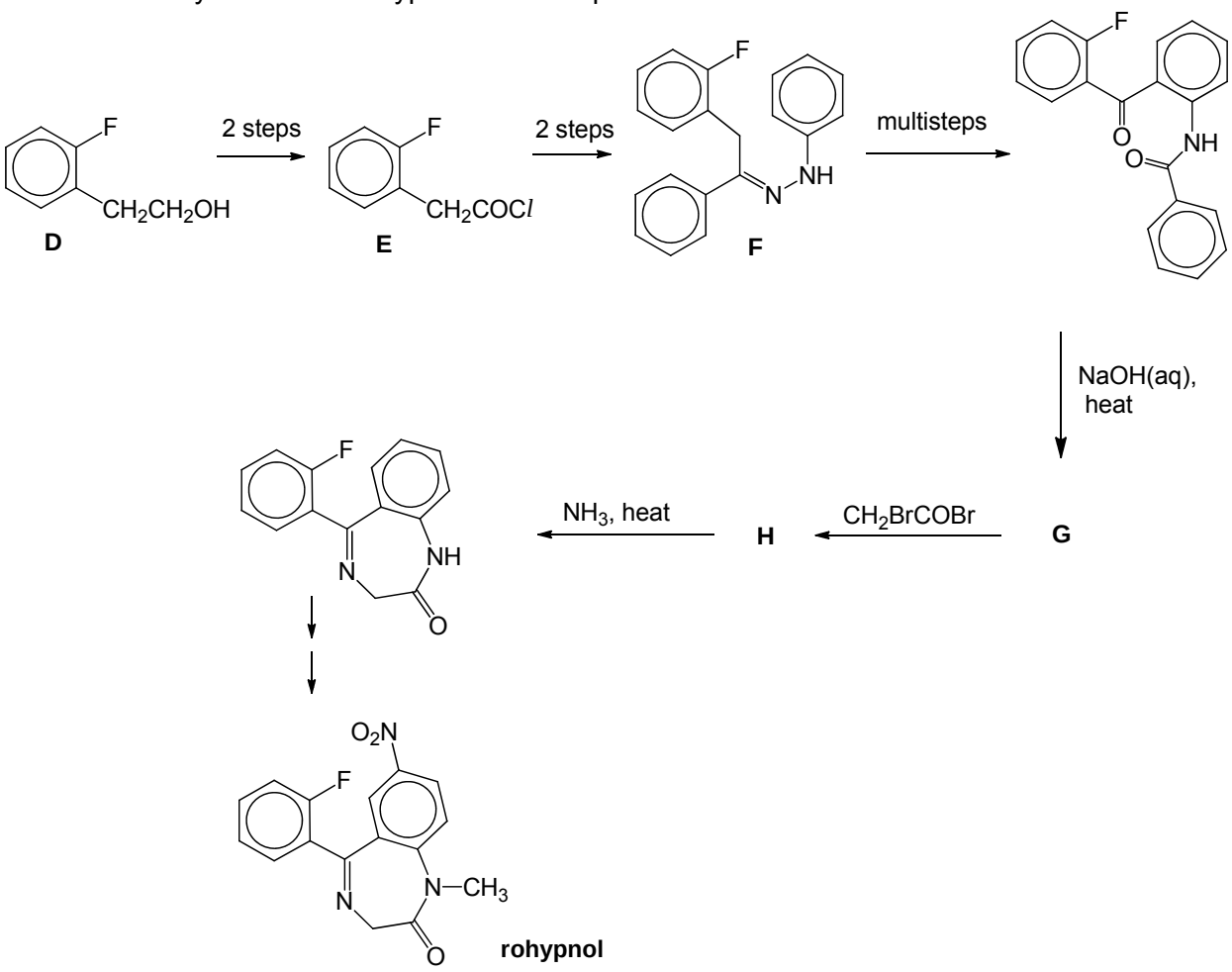
GABA

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

(ii) Suggest with reason if rohypnol is more likely to be an agonist or antagonist.

[1]

The synthesis of Rohypnol from compound **D** is as outlined below.



(iii) Suggest reagents and conditions for the conversion of **D** to **E** and subsequently to **F**. Include in your answers, the structures of all organic intermediates obtained during these multistep conversions.

[4]

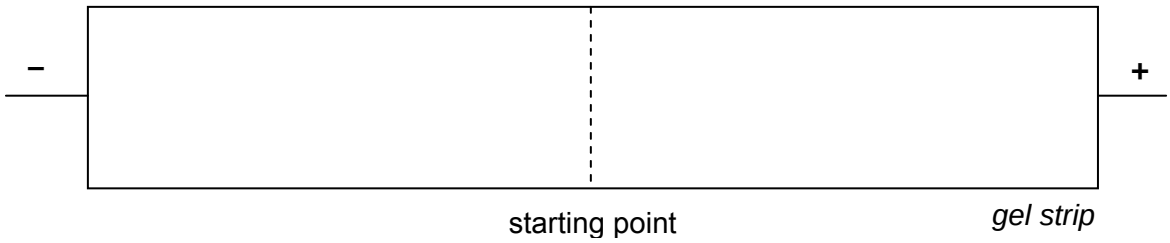
(iv) Give the structures of compounds **G** and **H**.

[2]

(c) Gel electrophoresis is often employed to separate and analyse mixtures of biological molecules like amino acids.

In this experiment, electrophoresis is used to separate GABA (pKa_1: 4.23, pKa_2: 10.43) and alanine, $H_2NCH(CH_3)COOH$ (pKa_1: 2.35, pI: 6.11, pKa_2: 9.87) in a solution of pH 3.6.

The diagram below shows the gel strip obtained after electrophoresis. Indicate the positions of GABA and alanine by drawing their structures on the diagram printed behind the cover sheet. [2]



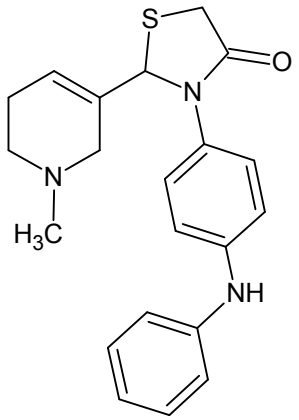
[Total: 20]

3 Alzheimer's disease (AD) is the most common form of dementia. It is hypothesised that AD is caused by the reduced synthesis of nerve cells in the forebrain, which are in turn mainly affected by two receptors M1 and M2. Receptor M1 provides linkages towards important nerve cell functions while receptor M2 causes a deficit in nerve cell transmission.

(a) (i) State **one** type of drug–receptor interaction. [1]

(ii) Using your knowledge on agonists and antagonists, suggest types of drugs that should be used to target each receptor M1 and M2, in the treatment of AD. [2]

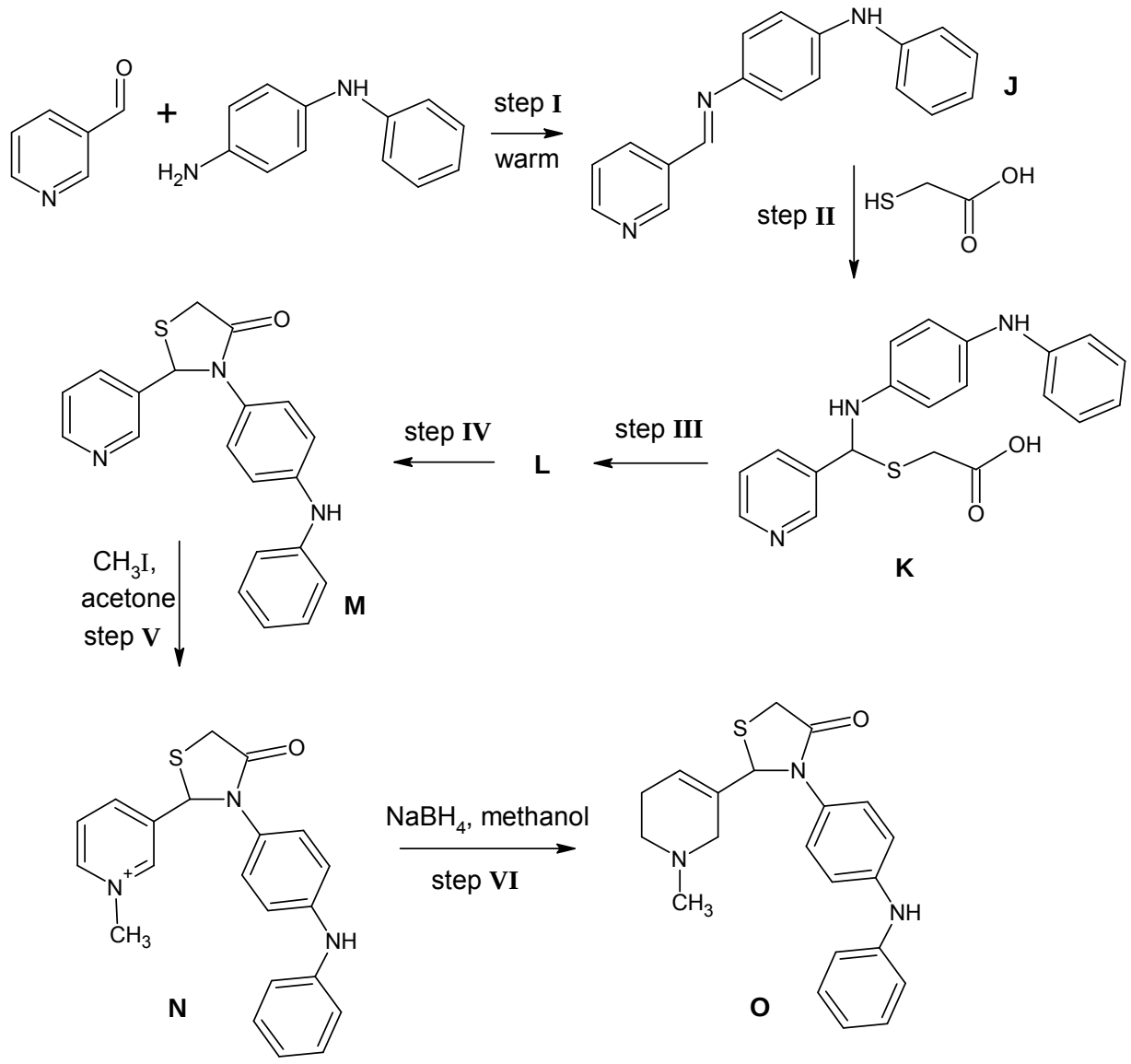
(b) Compound **O** has been identified as a potential drug to treat AD.



O

State the features of the molecule that allows it to be developed as an oral drug which can pass through the blood brain barrier. [2]

(c) The following reaction scheme shows the synthesis of **O** in the laboratory.



(i) Draw the mechanism for the formation of **J**, given that it is formed via addition–elimination. [2]

(ii) Suggest the structure of **L** and the reagent required for step **III**.

[2]

(d) **(i)** State and explain the type of reaction that the aromatic heterocycle in **M** is most likely to undergo. [2]

(ii) Explain why the aromatic heterocycle in **N** can be so easily reduced in step **VI.**

[3]

(e) The ^{1}H NMR spectrum of compound **O** shows the following 8 signals.

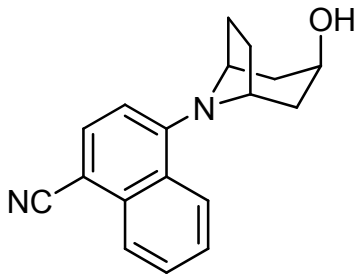
δ/ppm	
2.01	(m, 2H)
2.27	(s, 3H)
2.47	(t, 2H)
2.85	(s, 2H)
3.50	(s, 2H)
5.38	(s, 1H)
5.66	(t, 1H)
6.5–7.3	(m, 9H)

(i) Assign five of the signals to particular protons found in **O**. [5]

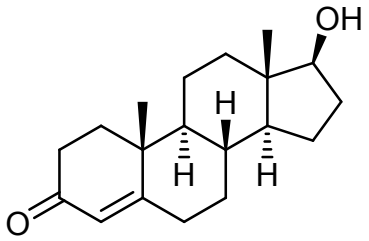
(ii) Given that a deuterated solvent was used in the ^{1}H NMR analysis, suggest the identity of the missing peak. [1]

[Total: 20]

4 Many pharmaceutical companies are developing non–steroidal drugs to treat various hormone related diseases and conditions. Some of these drugs bind competitively with the natural hormone molecules at the hormone receptors. For example, compound **G** is found to mimic the molecule testosterone in binding towards the androgen receptor.



P



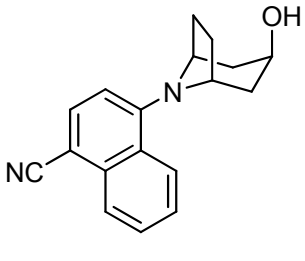
testosterone

(a) State two similar structural features between compound **P** and testosterone. [2]

(b) State and explain if the six–membered ring in compound **P** would undergo a ring flip. [2]

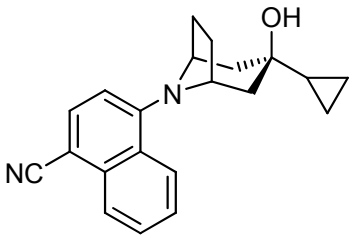
(c) State and explain if compound **P** contains an aromatic moiety. [2]

Analogues of compound **P** have been synthesised and tested using the bioassay procedure. The scheme below outlines main steps in the synthesis of compounds **Q**, **R** and **S** from compound **P**.

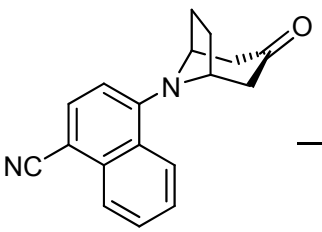


P

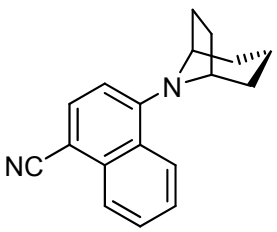
Swern oxidation



Q



R



S

(d) (i) State the type of reaction occurred in the synthesis of **S** from **R**. [1]

(ii) State the number of chiral carbons in compound **Q**. [1]

(e) Compound **Q** is synthesised from **R** using a Grignard reagent, cyclopropyl magnesium chloride. During the synthesis, a small amount of its isomer is also formed in the ratio 9:1.

(i) Draw the structure of the isomer of compound **Q** formed. [1]

(ii) Suggest why **Q** is formed in preference when **R** was reacted. [2]

(f) The mass spectrum of compound **Q** clearly shows a peak at 319, corresponding to the $[M+H]^+$ ion. Predict three other possible peaks in the mass spectrum of compound **Q**, and draw their respective fragments. [3]

(g) Predict two absorbances in the IR spectrum of compound **R**. [2]

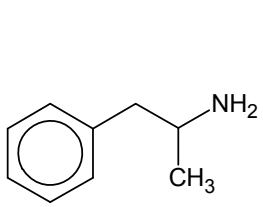
(h) The pure compound **Q** is separated from the crude mixture using reverse–phase HPLC.

(i) Outline the differences between reverse and normal phase HPLC. [3]

(ii) Explain why reverse–phase HPLC was chosen over normal phase HPLC. [1]

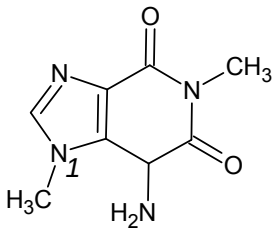
[Total: 20]

5 Stimulants are drugs that are commonly used in the modern society. Amphetamine and caffeine are both stimulants but amphetamine is an illicit drug under the laws of Singapore whereas caffeine is commonly available. All compounds shown below show absorption peaks in their UV spectra.



amphetamine

pK_b = 4.1



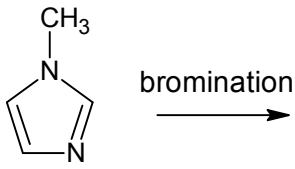
caffeine

(a) (i) What is meant by the term *stimulant*? Describe briefly the pharmacological effect of amphetamine and caffeine. [4]

(ii) Identify the chromophore in amphetamine. [1]

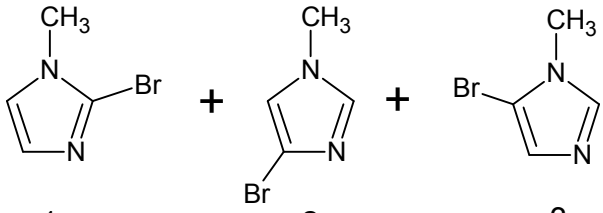
(iii) Predict, with a reason, the approximate pK_b of N_1 of caffeine. [2]

Caffeine contains the 1–methylimidazole ring as shown below. Under suitable conditions, 1–methylimidazole can undergo electrophilic substitution reaction to give three different products.



1-methylimidazole

bromination



1 2 3

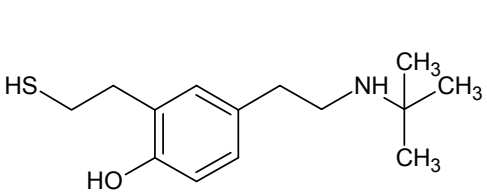
(b) (i) Draw the resonance structures of all the three intermediates and hence state the **major product** formed in this reaction. [4]

(ii) Write a balanced equation when 1–methylimidazole is reacted with hydrochloric acid. [1]

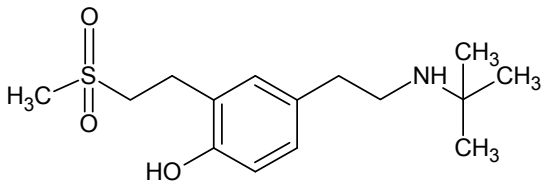
(iii) Compare the aromaticity between 1–methylimidazole and benzene. Suggest a reason for the difference. [2]

(iv) Predict the relative proton shift of benzene with respect to the proton shift of the protons of 1–methylimidazole. [1]

(c) **T** and **U** are sulfur–containing compounds that are derivatives of amphetamine.

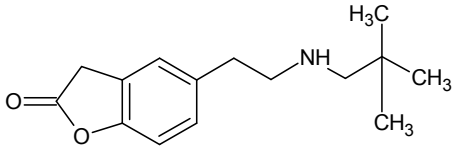


T



U

(i) Suggest how **T** may be prepared from the following lactone.



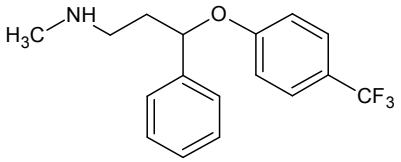
[3]

(ii) Suggest how **T** may be converted into **U**.

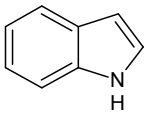
[2]

[Total: 20]

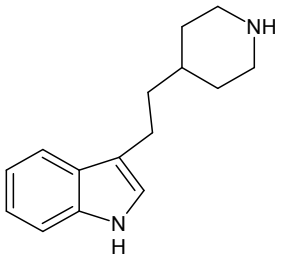
6 Indole is an aromatic heterocyclic organic compound with a bicyclic structure. Substituted indole represents as an interesting molecular architecture that exists in nature as well as synthetic drugs. Serotonin is a naturally occurring neurotransmitter that is responsible for the "feel good" effect. It is the research into this molecule that lead to the discovery of the first Selective Serotonin Reuptake Inhibitor (SSRI) – indalpine. Today fluoxetine which is a chiral drug is the most widely prescribed SSRI for treating depression and obsessive compulsive disorder. Unlike most sedating benzodiazepines, there has been no report of fluoxetine causing tolerance and dependency when used under medical supervision. Fluoxetine is a competitive inhibitor of serotonin uptake.



fluoxetine



indole



indalpine

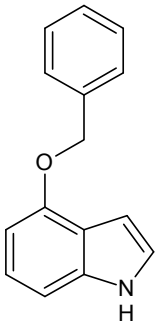
(a) (i) What is meant by the term *tolerance* and *dependency*? [4]

(ii) Briefly describe how a competitive inhibitor works. [2]

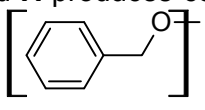
(iii) Suggest why the asymmetric synthesis of fluoxetine is important and how the enantiomers can be separated.

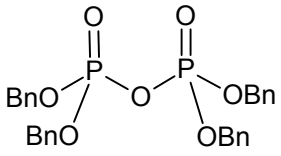
[2]

A halloucinogen undergoing trials for the treatment of obsessive compulsive disorder is psilocybin $C_{12}H_{17}N_2O_4P$. Like indalpine, psilocybin is an indole–based drug. The synthesis of psilocybin by David E Nicols *et al*. in 1999 is described below. The starting material is compound **V**, $C_{15}H_{13}NO$.



V

Compound **V** undergoes electrophilic substitution with $(COCl)_2$ at the 3 position of the indole ring to form compound **W**, $C_{17}H_{12}NClO_3$. On heating compound **W** with dimethylamine, compound **X**, $C_{19}H_{18}N_2O_3$ is obtained. When reacted with $LiAlH_4$ in dry ether, compound **X** produces compound **Y**, $C_{19}H_{22}N_2O$. Catalytic hydrogenolysis of the *O*–benzyl group  in **Y** produces a hydroxyl group in **Z**, $C_{12}H_{16}N_2O$. Upon reacting with *n*–BuLi, a nucleophile is produced which is further reacted with the phosphorylation agent TBPP. Further debenzylation produces psilocybin which is a phosphoester (ester form of phosphoric acid).



TBPP

Where OBn = *O*-benzyl group

(b) (i) Suggest structures for **W**, **X**, **Y**, **Z** and psilocybin. [6]

(ii) What is the role of *n*–BuLi? [1]

(iii) Suggest a mechanism for the S_N2 reaction between the nucleophile and TBPP showing clearly the stereochemistry at each stage. You may represent the nucleophile as Nu^-. [3]

(iv) The *O*–benzyl group serves as a protecting group which is removed at the later stage of the synthesis. Why is it not removed at the second step of the synthesis? [1]

(v) Suggest, with a reason, the major difference between the UV spectra of indalpine and compound **V**. [1]

[Total: 20]

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