NATIONAL JUNIOR COLLEGE

Preliminary Examinations 2008

H3 CHEMISTRY **9812**
12 Sep 2008 **TIME: 2 hour 30 mins**

Additional Materials: Data Booklet
Writing paper

READ THESE INSTRUCTIONS FIRST

Do not open this booklet until you are told to do so.
Write your name, class and registration number in the spaces provided on the answer cover sheet and on each piece of writing paper.
Write in dark blue or black pen.
You may use a pencil for any diagrams, graphs or rough working.
Do not use staples, paper clips, highlighters, glue or correction fluid.

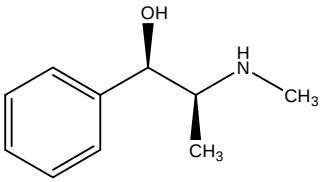
Answer any **5** questions on the writing paper provided.
Start each question on a fresh piece of paper.

A Data Booklet is provided.
You are reminded of the need for good English and clear presentation in your answers.
You may use a calculator.
At the end of the examination, fasten all your work securely together with the cover sheet placed on top.
The number of marks is given in brackets [ ] at the end of each question or part question.

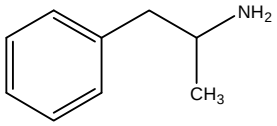
1) This question concerns the investigation of a sports supplement by the Health Science Authority (HSA) of Singapore.

HSA was called upon to investigate a new weight loss supplement, ***MusclePower***, launched in 2008, that targets bodybuilding beginners who wish to shed off extra fats.

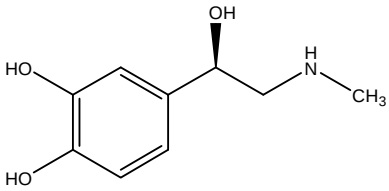
MusclePower claimed that their pills are 100% herbal in origin and contains no illegal proprietary drugs. The label on the ***MusclePower*** claims that it does not contain ***Ephedrine***, an amphetamine-like stimulant, which is banned in Singapore. The structure of Ephedrine is shown below.



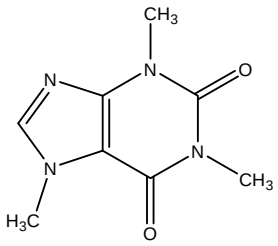
Ephedrine



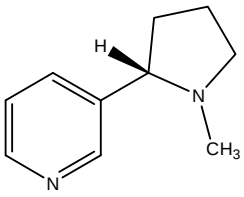
Amphetamine



Adrenaline



Caffeine



Nicotine

Ephedrine, together with caffeine, are common ingredient in many weight loss pills that speeds up metabolism and thus causes fats to burn faster. Before the former was banned in Singapore, body builders routinely consume them to increase performance.

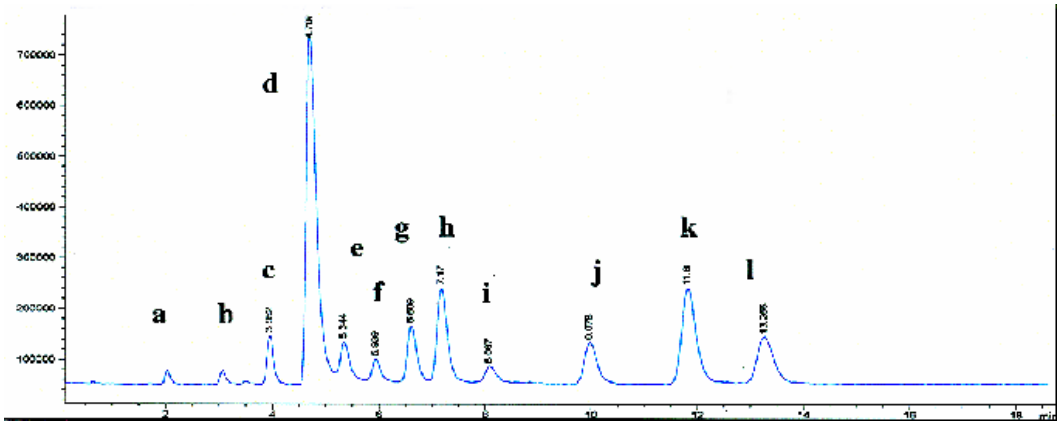
a) (i) Define what is meant by the term “stimulant”. [1]

(ii) Compare the structure of Ephedrine with amphetamine and adrenaline. Highlight what structural features Ephedrine has in common with amphetamine and adrenaline respectively. [2]

Many stimulants, such as the 5 listed above are basic compounds. One of the preliminary steps in the analysis of an herbal supplement is to isolate a subclass of compounds from the pills. ***MusclePower*** pills are of supposedly herbal origin and thus contain many natural organic compounds.

b) By means of simple glassware and common laboratory reagents, suggest how you can isolate <u>basic</u> organic compounds from grounded powder of ***MusclePower***. [2]

The process of isolating basic organic entities from a pill is an easy affair in contrast to the determination of the actual composition of the herbal pill. One of the common methods employed is the use of reverse phase HPLC followed by mass spectrometry to identify the organic composition of the pill.



The diagram above shows the reverse HPLC chromatogram of the crude extracts of ***MusclePower*** after the isolation step from b).

c) (i) Explain the working mechanism of reverse phase HPLC. What can you conclude from this chromatogram? [3]

(ii) Assuming you have a small sample of pure Ephedrine, what analytical tests can you perform to convince HSA whether any the fractions isolated from the reverse phase HPLC contains Ephedrine? Illustrate two methods to authenticate the identity. [2]

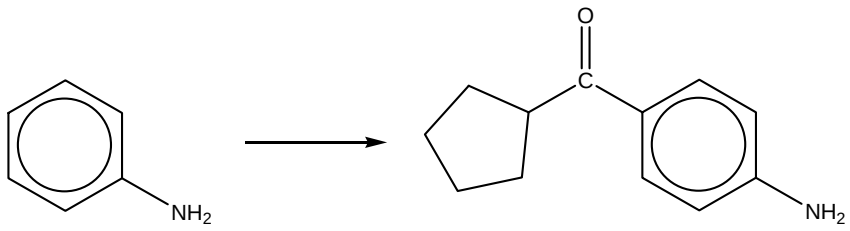
Nicotine is another stimulant that is highly regulated in Singapore and so routine checks were carried out to ensure that health supplements do not contain nicotine.

It was told that if ***MusclePower*** contains nicotine, it would also be isolated from part b) as a basic compound.

d) (i) Nicotine contains a basic pyridine functional group. Explain why pyridine is basic and whether the amine present in nicotine is relatively more or less basic than pyridine. [3]

(ii) With the aid of canonical structures, explain why electrophillic substitution of pyridine occurs mostly at the 3-position. [2]

(iii) Show, with balanced equations, how the following synthetic conversion can be obtained in good yield. [5]



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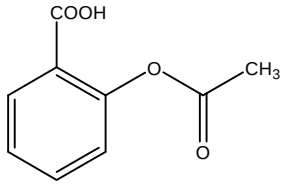
2)



Aspirin

Aspirin is a non-narcotic analgesic that is consumed is large quantities worldwide as a pain killer.

a) Explain how Aspirin works as a pain killer. [2]

b) Pharmacists advise people <u>not</u> to store aspirin in warm and damp places like in the bathroom, otherwise the air around will smell sour. Explain this phenomenon. [2]

c) Show how Aspirin is commercially synthesized from phenol. Indicate clearly the reagents and conditions used. [3]

d) With the aid of the data booklet,

(i) Construct a rough sketch of the infra-red spectrum of Aspirin. [3]

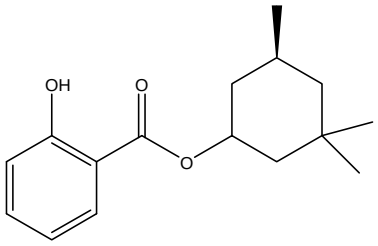
(ii) Predict how the 1H NMR spectrum of Aspirin would look like when it is dissolved in MeOD. Draw an annotated diagram of Aspirin structure, highlighting the characteristics of the peaks exhibited by each hydrogen atom. Give a detail description of the splitting pattern. [3]

e) Aspirin shows two major absorption peaks in the ultraviolet region, one peak at 210 nm due to the – $OCOCH_3$ group and another at 230 nm due to the – COOH group.

(i) A sample of aspirin was dissolved in hexane and analysed in a spectrophotometer at 210 nm with a 1 cm cuvette. It was found that the absorbance value was 0.80. Calculate the concentration of aspirin in the sample given that the molar absorptivity at 210 nm is 6200 mol^{-1} dm^3 cm^{-1} [2]

ii) Give two reasons why the sample was dissolved in hexane instead of propanone. [2]

f) As part of the continuous drug discovery efforts, pharmaceutical chemists developed a new salicylate – TMCS, with the structure shown below.



3,3,5-Trimethylcyclohexyl salicylate (TMCS)

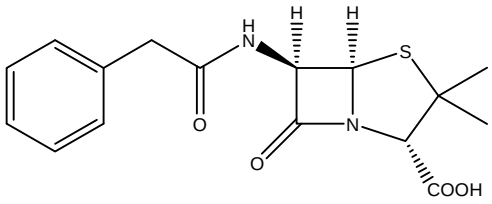
200 patients with frequent migraine were recruited in a clinical trial to evaluate if TMCS can be an effective analgesic for migraine. 100 patients were randomly assigned to take TMCS while the other 100 patients were given a placebo pill. 6 months later, a survey was conducted to see if the drug was effective. The patients were asked to rate the severity of the pain (10 being very pain, 0 being no pain) before and after trying the drug that was given to them. The table below summarizes the findings.

	Average pain ratings	
	Before	After
TMCS group	5.0	2.9
Placebo group	5.0	3.2

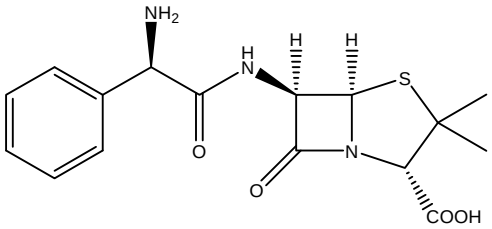
(i) Use the clinical trial data to explain what is meant by "placebo effect". Explain why a placebo test is necessary in a clinical trial. [3]

[Total: 20]

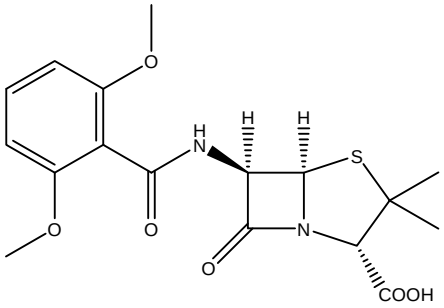
3) The structures of 4 penicillins are shown below.



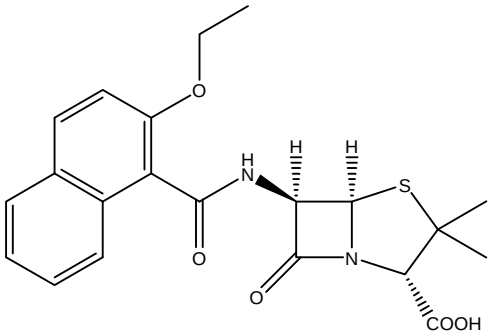
Penicillin G



Ampicillin



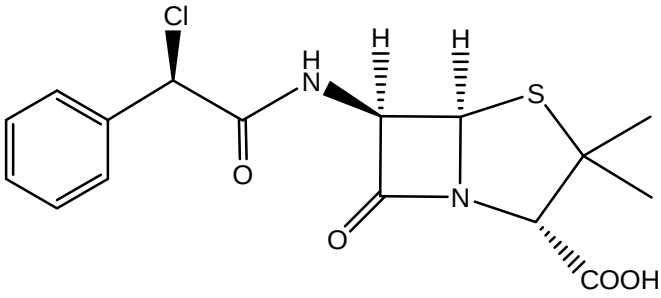
Methicillin



Nafcillin

a) The fused ring of Penicillin G is biosynthesized from two amino acids. Draw a diagram of penicillin G to demarcate which two amino acids it came from. [2]

b) When a student attempted to synthesize ampicillin from the following compound **A,** he obtained a racemic mixture of ampicillin and its optical isomer.



Compound **A**

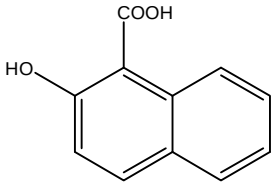
i) Describe the reaction for the synthesis of ampicillin from Compound **A** and explain why a racemic mixture is obtained. [4]

ii) Deduce the rate of formation of ampicillin if chlorine in Compound **A** is replaced by iodine. [2]

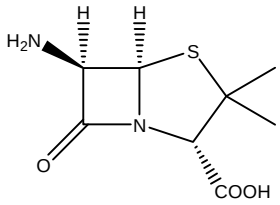
There are many problems faced by penicillin G as a suitable antibacterial agent. Ampicillin and Methicillin are two improvements of penicillin G that are more superior than penicillin G itself.

c) Describe the two problems faced by penicillin G which has been overcame by Ampicillin and Methicillin respectively. For each aspect, explain how the structural modifications of the newer drug manage to overcome these problems. [4]

d) Nafcillin is another penicillin member which works similar to methicillin. Derive an organic synthesis route to make Nafcillin using the following starting chemicals. You are not allowed to use any other organic reagent that has 3 carbons or more. State the reagents and conditions used and show the intermediates formed clearly. [4]

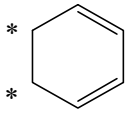


2-hydroxy-1-naphthoic acid



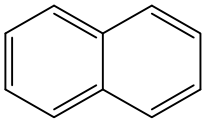
6-aminopenicillonic acid (6APA)

e) (i) Draw the Newman projection of the most stable conformer of cyclohexa-1,3-diene with respect to the carbons label with an asterix shown below. [2]



cyclohexa-1,3-diene

(ii) 2-Hydroxy-1-naphthoic acid contains a 10 carbon naphthalene ring as its parent structure.

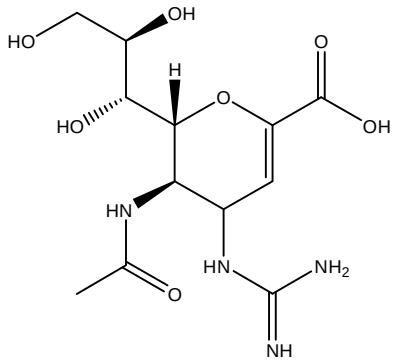


Naphthalene

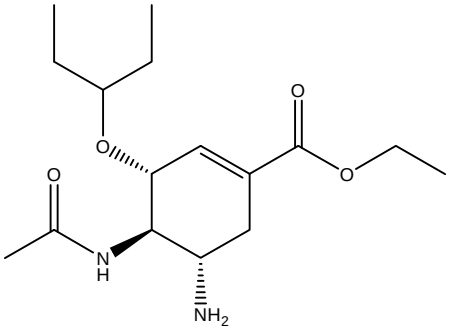
Suggest whether the ring on the right is planar like benzene or resembles the conformation of cyclohexa-1,3-diene in part (d)(i). Why is that so? [2]

[Total: 20]

4) Zanamivir and Oseltamivir are two antiviral drugs that are effective against influenza virus.



Zanamivir



Oseltamivir

a) Describe how zanamivir and oseltamivir function as anti-viral agents. [2]

Zanamivir was found to have excellent *in vitro* activity but failed to give efficacy when taken orally, hence it has to be given intravenously.

b) (i) What is meant by “intravenously”? [1]

(ii) Explain why Zanamivir failed to function when taken orally. In contrast, why is “intravenously” a better means to administer Zanamivir? [2]

c) Oseltamivir is an improved version of Zanamivir which can be taken orally. Compare the structures of Zanamivir and Oseltamivir. With the aide of a diagram, discuss what structural modifications have been employed, as well as the principles behind the drug design, which enables Oseltamivir to be taken orally. [4]

As a hypothetical situation, virologists discovered a new gene in the H5N1 influenza virus genome that codes for an enzyme, H5N1 protease, which is responsible for the construction of the viral protein coat. The active site of this enzyme was elucidated but no drug candidate was known. Drug development attempts were immediately embarked to target this new enzyme.

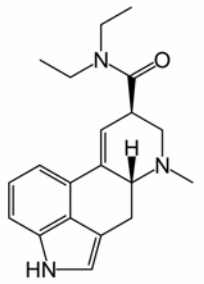
d) (i) Discuss 3 properties of an ideal drug. Explain why it is often not possible to design a drug that is perfect. [3]

(ii) Discuss in detail, the key stages of the drug discovery process that might be involved to develop such a new drug that targets H5N1 protease. [6]

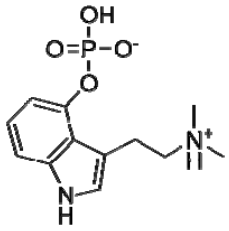
e) Body scanners use n.m.r. spectroscopy as a diagnostic tool. Explain why this form of spectroscopy can be used for this purpose, but infra-red spectroscopy cannot. [2]

[Total: 20]

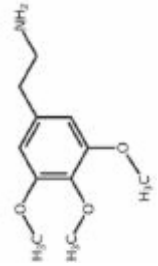
5)



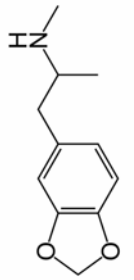
LSD



Psilocybin



Mescaline



MDMA

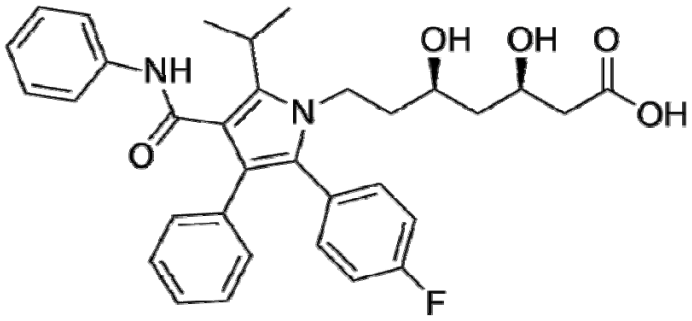
a) LSD, Psilocybin, Mescaline and MDMA are four commonly abused hallucinogens.

i) Give the full name for "LSD". [1]

ii) Compare and contrast the chemical structures and chemistry of these drugs. Illustrate what structural similarities these four compounds have. [4]

iii) Explain how LSD achieves its hallucinogenic effects. [2]

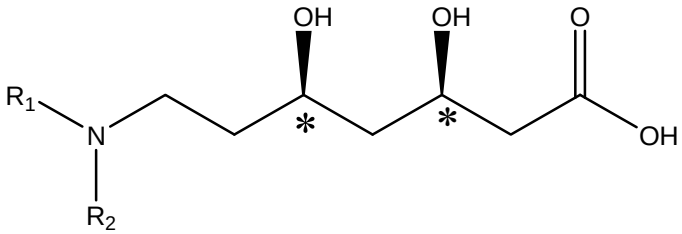
iv) Give two key effects of LSD consumption. [2]



Atorvastatin

b) Atorvastatin, also known as Lipitor, is a member of the drug class known as "statins", is used for lowering blood cholesterol.

i) The structure of Atorvastatin may be abbreviated as shown below.



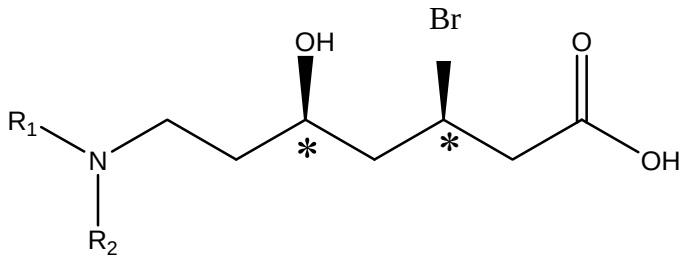
Atorvastatin can undergo “self-lactonization” reaction to give two different lactones.

ii) Draw the structures of these two lactones (stereochemistry of the chiral carbons are not required). Name the two lactones formed. [2]

iii) Explain which of the two lactones you have drawn are formed more readily. [2]

iv) Predict the difference in water solubility between the free Atorvastatin and lactonized Atorvastatin. How does the free and lactonized form differ in their ability to diffuse across the intestinal cells? [2]

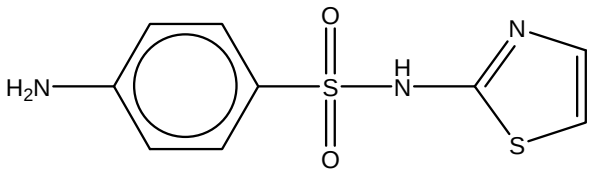
Another derivative of Atorvastatin, as shown below, reacts with ethanol in the presence of heat.



v) Predict the product of the following reaction, indicating stereochemistry where necessary. [2]

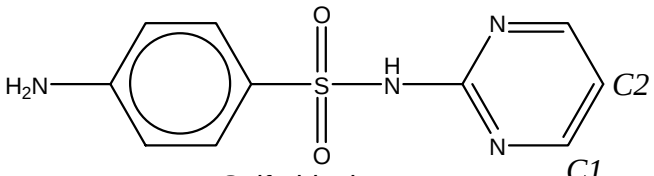
vi) Describe the mechanism. [3]

6) Sulfathiazole is a poorly soluble antibacterial drug which can prove fatal if it blocks the kidney tubules.



Sulfathiazole

It was discovered that the solubility problem could be overcome by replacing the thiazole ring in sulfathiazole with a pyrimidine ring to give sulfathiazine. The reason for the improved solubility lies in the acidity of the sulfonamide NH proton.

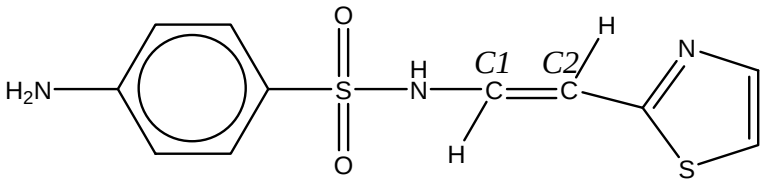


Sulfathiazine

a) i) Suggest why sulfathiazine is more soluble compared to sulfathiazole. [2]

ii) It was found that the presence of sulfathiazole inhibits the binding of p-aminobenzoic acid to the enzyme, dihydropterorate synthetase. Explain how sulfathiazole acts as an inhibitor. [2]

b) Another derivative of sulfonamide, as shown below, reacts with HBr in the presence of methanol to give a mixture of products.



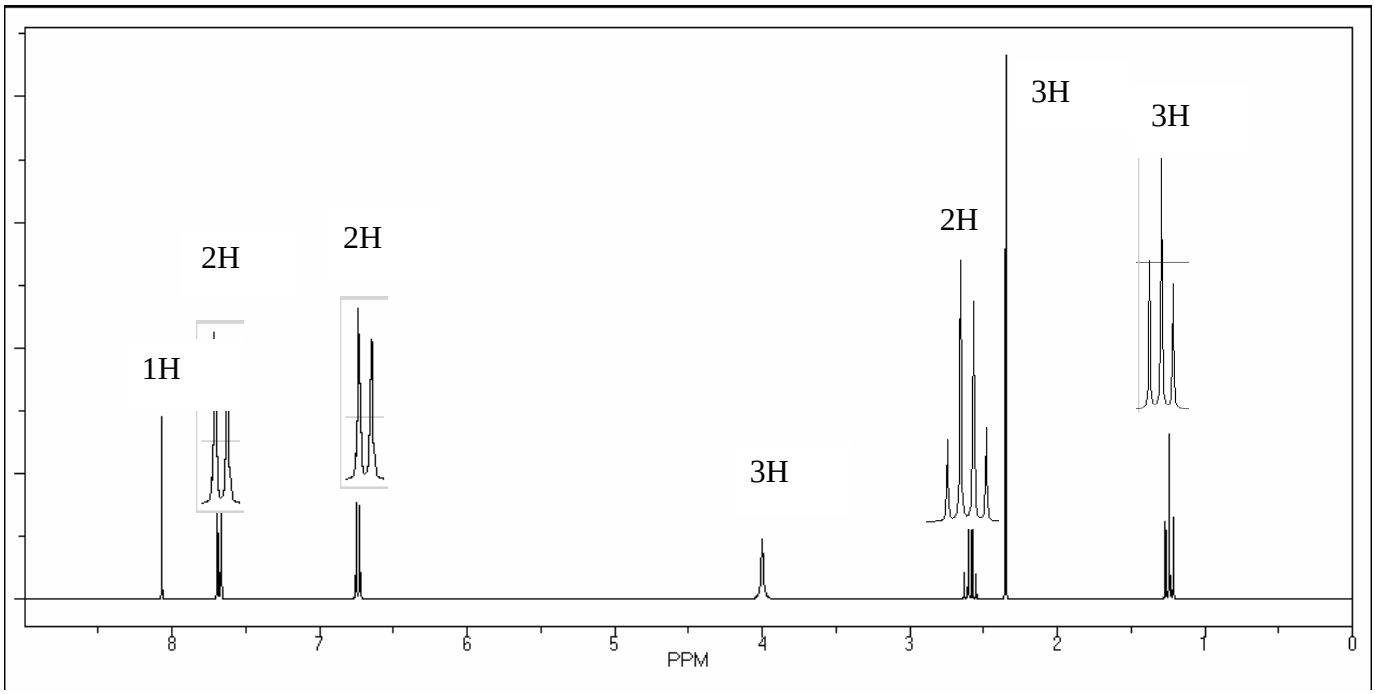
i) Give the possible products formed.

ii) Describe the mechanism of one of the products.

iii) Using one of your products, indicate the R, S configuration across carbon atom 1 and 2 (C1 and C2).

[7]

c) c) Sulfathiazine undergoes a certain reaction to give compound **B** of molecular formulae $C_{13}H_{16}N_4SO_2$. Compound A gives the following ^{1}H-NMR spectrum.



i) Based on the ^{1}H-NMR spectrum, deduce with reasonings, the structure of compound B. [6]

ii) Compound B was introduced into a mass spectrometer and few peaks were observed. The 2 major peaks appears at m/z = 278 and m/z = 156. Suggest the ions responsible at these two peaks. [3]

[Total: 20]