CATHOLIC JUNIOR COLLEGE
JC2 PRELIMINARY EXAMINATIONS
Higher 3

PHARMACEUTICAL CHEMISTRY

9812/01

Paper 1

Tuesday 29 August 2017
2 hours 30 minutes

Additional Materials: Answer Paper
Data Booklet

READ THESE INSTRUCTIONS FIRST

Write your name and class on all the work you hand in.
Write in dark blue or black pen on both sides of the paper.
You may use a soft pencil for any diagrams or graphs.
Do not use staples, paper clips, highlighters, glue or correction fluid.

Answer any **five** questions.
At the end of the examination, fasten all your work securely together.

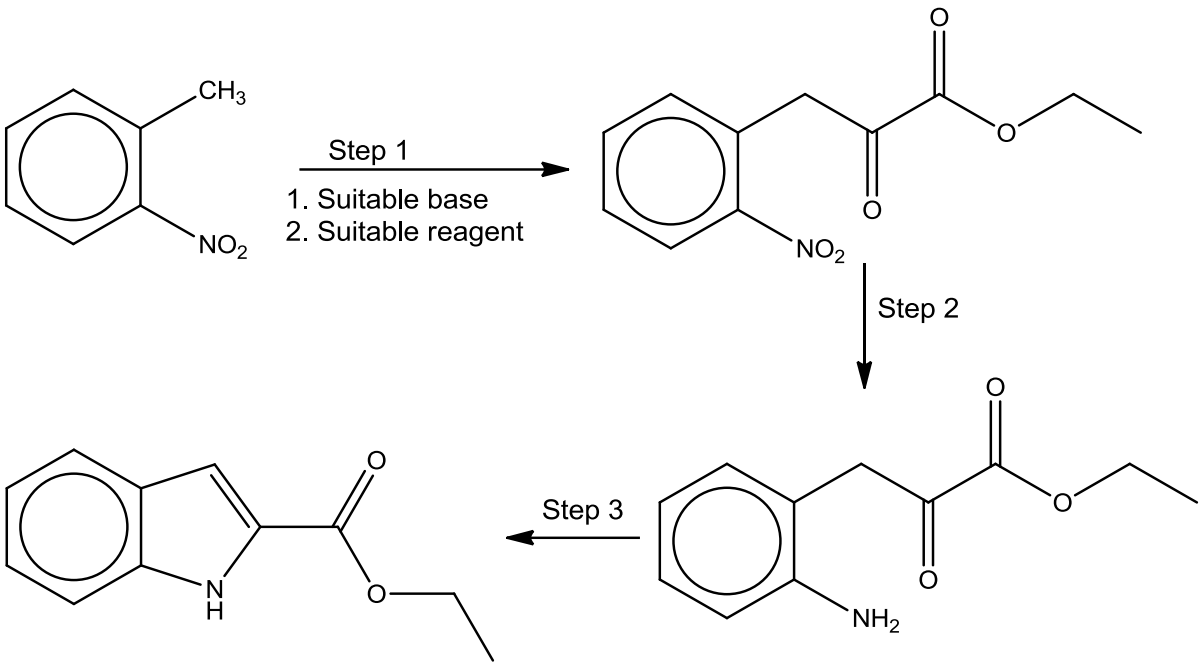
The number of marks is given in brackets [ ] at the end of each question or part question.
The use of an approved scientific calculator is expected, where appropriate.
You are reminded of the need for good English and clear presentation in your answers.

Mark Scheme

This document consists of **16** printed pages.

1 Indole derivatives are known for their medicinal properties in the pharmaceutical industry.

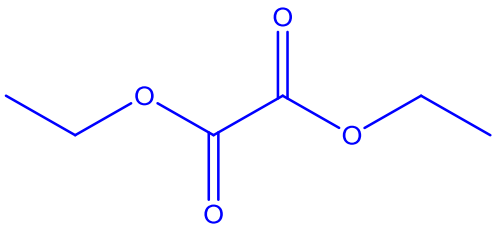
(a) The following diagram shows one route to synthesizing an indole derivative.



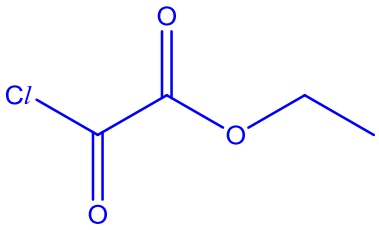
compound **A**

(i) A base is used in step 1 in order to deprotonate the methyl group attached to the benzene ring. Suggest the reagents and conditions required for step 1. [2]

1. $^{-}$OEt



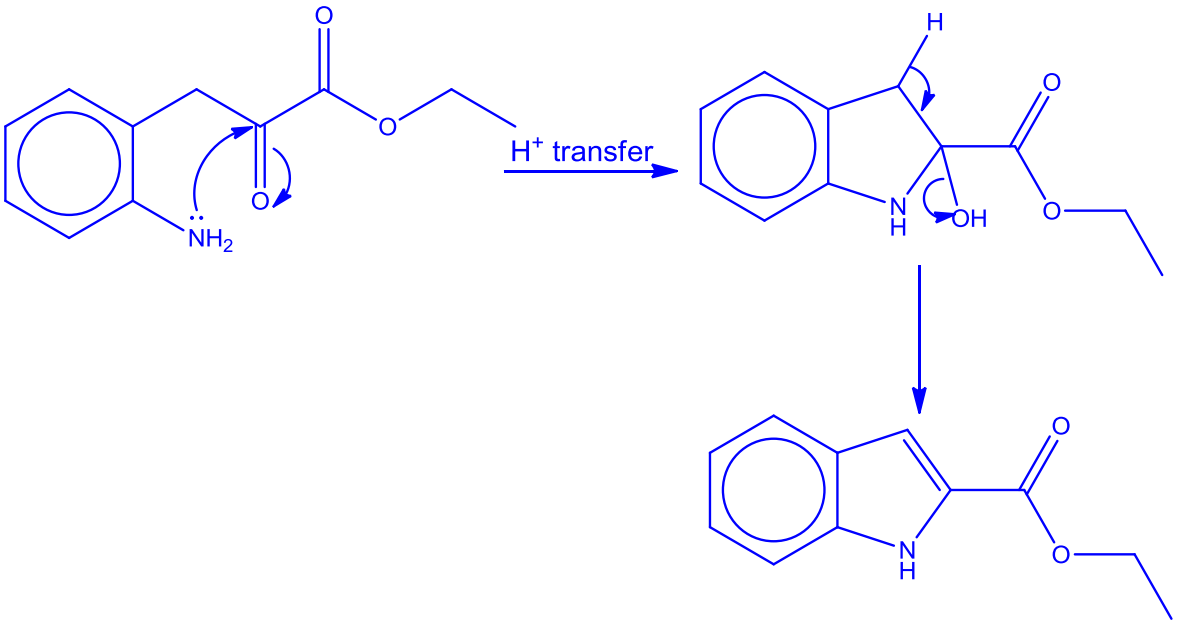
2. **OR**



(ii) Suggest the reagents and conditions required for step 2. [1]

1. Sn/conc HCl, heat
2. NaOH (aq)

(iii) Suggest a mechanism for step 3. [3]



(b) Outline in simple terms the principles of nuclear magnetic resonance. [4]

Hydrogen nuclei behave as tiny magnets as they are positively charged and possess a spin.
When placed in an external magnetic field, hydrogen nuclei either have their spin aligned with the external field or opposed to it, giving rise to two spin states. This gives rise to two different energy levels in presence of external magnetic field.
When nuclei at lower spin state absorb appropriate amount of energy from electromagnetic radiation, they get promoted to higher spin state.
The energy gap is proportional to the strength of the external magnetic field. Different hydrogen nuclei in different chemical environments have slightly different energy gaps.

(c) Explain the use of the δ scale with TMS as the reference. [2]

Protons in TMS are all equivalent and these would generate a sharp singlet. Low electronegativity of Si means that these protons are particularly well shielded, and hence resonate up-field of most organic compounds. Thus TMS is used as an internal reference and assigned a value of δ 0.0.

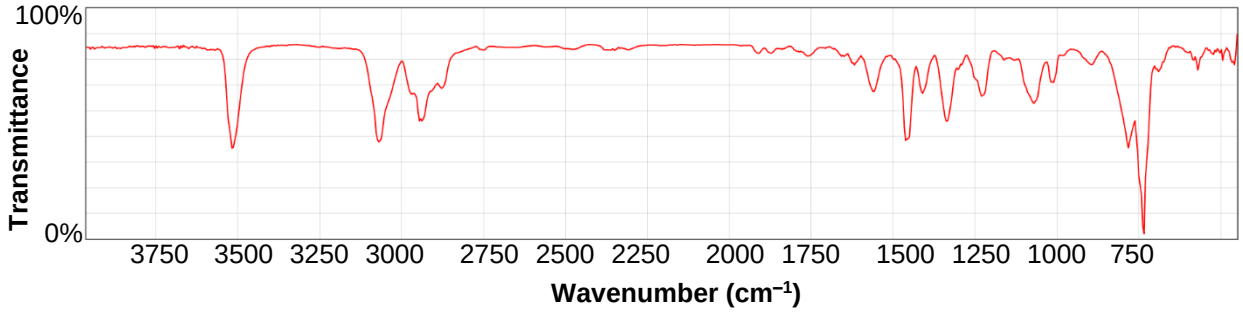
(d) Skatole, found in ice cream as a flavour enhancer, is structurally related to compound **A**. Skatole has the following NMR spectrum. The resonance at δ 6.99 disappears in the presence of D_2O.

δ 2.42 (d, 3H)
6.99 (s, 1H)
7.22 (m, 1H)
7.31-7.80 (m, 4H)

(s is singlet, d is doublet, m is multiplet)

The mass spectrum of skatole shows a molecular ion at m/e 131. The $(M+1)^+$ peak has an intensity 9.8% of that of the molecular ion.

The infra-red spectrum of skatole is as shown below.



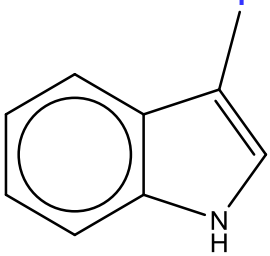
Use the above data to deduce the molecular formula and the chemical structure of skatole. [8]

NMR: δ 6.99 disappears in presence of D_2O indicates presence of labile proton suggests presence of –NH group.
MS: There are 9 carbon atoms per molecule

$$n = \frac{100}{1.1}\left(\frac{A_{M+1}}{A_M}\right)$$

= (100/1.1) x (9.8/100) = 9.8 = 9

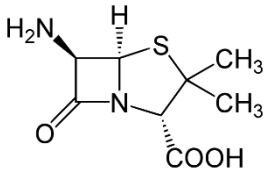
IR: lack of 1710-1750cm^{-1} strong stretching of C=O bond suggests that there is no ester functional group
NMR: δ 7.31-7.80 has 4H indicating benzene ring is substituted at 2 positions.
NMR: δ7.31-7.80. Presence of benzene ring since downfield chemical shift indicating indicates proton is very deshielded due to anisotropic effect.
NMR: δ7.22 indicating presence of presence of indole ring (chemical shift δ7.22 is very downfield suggest a double bond in 5 membered ring)
NMR: 3H at δ 2.42 suggests –CH_3 group bonded to indole ring since chemical shift is quite downfield as proton is very deshielded.



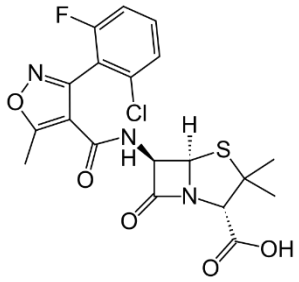
C_9H_9N

[Total: 20]

2 Penicillins such as 6-aminopenicillanic acid and flucloxacillin are a group of antibiotics that disrupt the bacterial cell wall construction by forming permanent covalent links with a transpeptidase involved in their synthesis.



6-aminopenicillanic acid

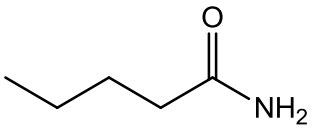


flucloxacillin

(a) Suggest two other ways in which antibiotics work. [2]

Disruption of synthesis of folic acid
Disruption of protein synthesis
Plasma membrane disruption
Disruption of nucleic acid transcription

(b) Suggest why β-lactam group in penicillins is more susceptible to hydrolysis than pentanamide.



pentanamide

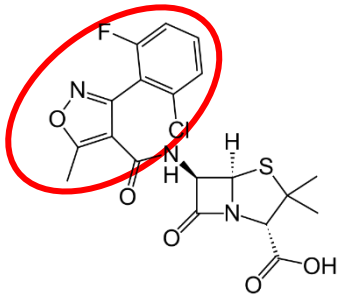
[2]

Due to presence of ring strain in the 4-membered ring, N in β-lactam prefers to be sp^3 hybridised to minimize ring strain. This thus prevents the formation of the formation of a partial double bond between C-N as the lone pair on N would not be able to delocalize with the π electron system of the C=O bond. The C-N bond in penicillin is thus easier to break than that in pentanamide which has a partial double bond character.

(c) Bacteria sometimes develop a resistance against penicillin, causing the organ to be re-infected. Research has been done to develop new penicillin to counteract this problem.

(i) Explain why the use of flucloxacillin can reduce the activity of penicillinases such as β-lactamase. [1]

Fluxocillin has a bulkier R-group (as circled below) that prevents it from binding effectively to penicillinases.



(ii) Explain why the use of flucloxacillin allow it to be more easily absorbed through membranes of the intestinal villi. [2]

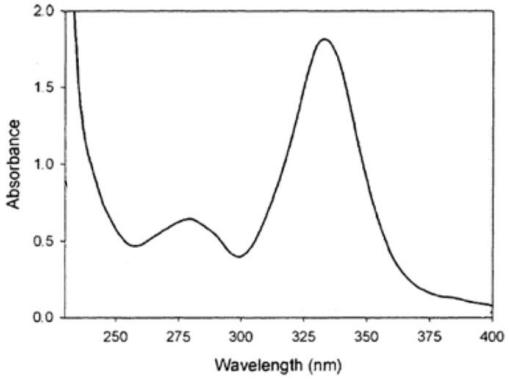
Fluxocillin has a chlorine atom attached which increases its potential for instantaneous-dipole induced-dipole interaction , making it more easily absorbed through the hydrophobic membranes of the intestinal villi.

(d) A spectrophotometric method using UV-visible spectrophotometer was used to determine the amount of flucloxacillin and 6-aminopenicillanic acid in a pharmaceutical formulation of a drug.

(i) Suggest why the flucloxacillin and 6-aminopenicillanic acid may be detected using UV and state what happens in these molecules when UV radiation is absorbed. [2]

The presence of delocalized system involving the benzene ring and presence of lone pair of electrons on N or O atoms in the molecules.
The electronic transitions n→π* (for lone pair of electrons on nitrogen atoms) and π→π* occur (for benzene ring).

(ii) Given the UV spectrum of 6-aminopenicillanic acid as shown below, suggest a suitable wavelength to measure concentration of 6-aminopenicillanic acid in the drug. [1]

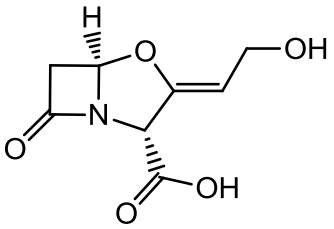


335nm

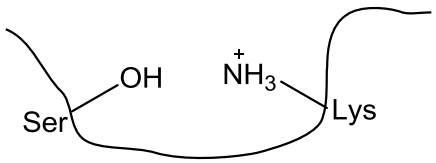
(iii) Using your answer in **(d)(ii)**, suggest a suitable wavelength to measure concentration of flucloxacillin in the drug sample and explain your answer.[2]

Accept any value larger than 335nm.
Flucloxacillin has more conjugation of π bonds due to N and Cl atoms containing a lone pair of electrons which lead to a longer wavelength.

(e) Another approach to overcome the problem of bacteria resistance is to administer a strong β-lactamase inhibitor such as clavulanic acid together with penicillin. Clavulanic acid will inhibit transpeptidase similarly as penicillin.

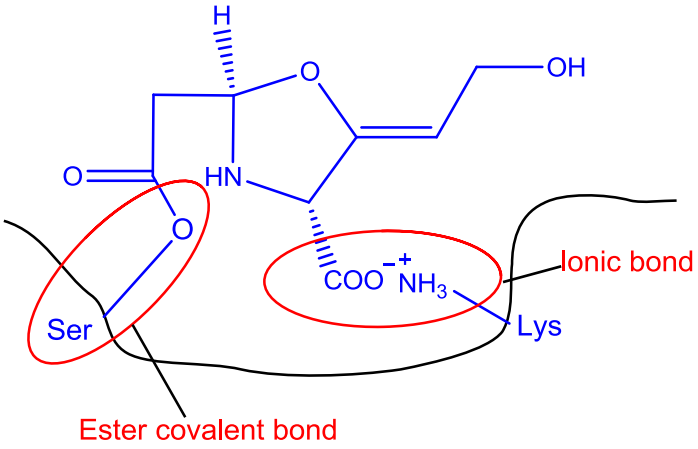


Clavulanic acid



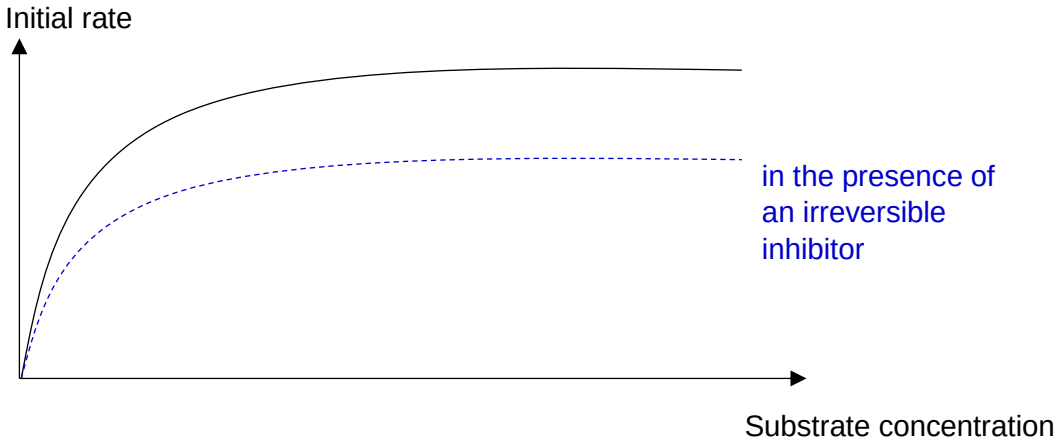
transpeptidase active site

(i) With the aid of a labelled diagram, show how clavulanic acid can act as a transpeptidase inhibitor. [2]



(ii) The graph below shows the initial rate of β-lactamase-catalysed reaction varies with substrate concentration. Re-draw the graph, and on the same

axes show how the initial rate would vary with substrate concentration in the presence of clavulanic acid. Explain your answer. [3]



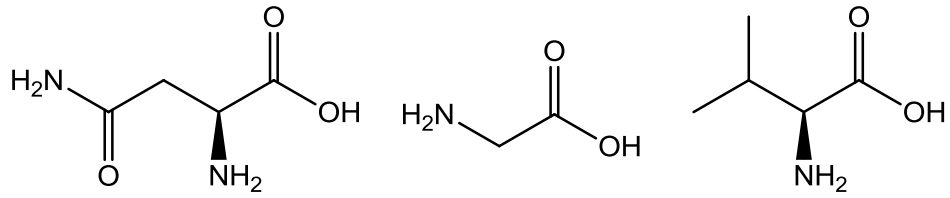
Clavulanic acid is a non-competitive inhibitor. The irreversible inhibitor permanently reduces the number of available active sites, hence the maximum rate decreases compared to before.

(f) Explain why failing to complete a prescribed course of penicillin antibiotics can increase the problem of bacterial resistance to penicillins. [3]

Although penicillin will be able to destroy most of the bacteria, there will be a small fraction who are already immune to the action of penicillin due to the long term use of penicillin.
Unless the body's immune system is utilised to deal with this resistant bacteria, otherwise they will start to multiply and pass its penicillin resistant genes on to other bacteria by means such as conjugation, thus re-infecting the organ with penicillin resistant bacteria.
Hence it is important to finish the whole course of treatment, which eases burden on body's immune system and to kill off penicillin resistant bacteria.

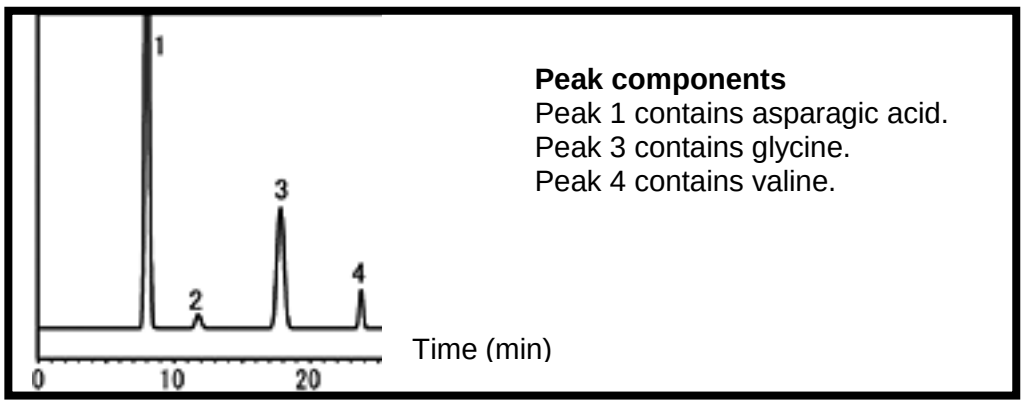
[Total: 20]

3 **(a)** Amino acids are essential for muscle building and storing nutrients. Athletes often take in drink supplement containing amino acids such as asparagic acid, glycine and valine to facilitate muscle repair.



asparagic acid glycine valine

The following shows a 1 cm^3 sample of a commercial amino acid drink supplement as analysed by HPLC. The peak components were identified as shown.



(i) By considering the polarities of the three molecules and the retention times of the three peaks, decide whether normal or reverse-phase HPLC was used to analyse the mixture. Explain your reasoning. [2]

Reverse-phase HPLC.
Asparagic acid, containing an additional $–NH_2$ group, is the most polar and is eluted first. Valine containing a bulky branched alkyl group is least polar and is eluted last.

(ii) Using standard solutions, peak areas of 1.00 cm^2 for glycine and valine in the chromatogram were found to correspond to concentrations of 50 mg dm^{-3} and 80 mg dm^{-3} respectively. Calculate the relative proportions by mass of each compound in the sample of amino acid beverage. [2]

Relative peak areas of glycine: valine
= ½ x 0.4 x 3.2 : ½ x 0.2 x 1.0 (see printout)
= 0.64 cm^2: 0.1 cm^2

Relative proportion by mass of glycine: valine
= (0.64 x 50): (0.1 x 80)
= 32 mg dm^{-3}: 8 mg dm^{-3}
= 4:1

(iii) Three amino acids, asparagic acid, glycine and valine from the amino acid beverage were isolated and subjected to electrophoresis.

(I) Briefly describe how the amino acids in the beverage can be separated by the process of electrophoresis. [3]

Separation of amino acids using a gel/paper support/medium which is buffered at a suitable pH in an electric field by applying a potential difference.
The basis of separation depends on the following:
(1) the charge of substance under separation. This depends on the form taken at that particular pH. Overall negatively charged would migrate to positively charged plate and positively charged to negatively charged plate. Neutral would remain stationary.
(2) size and shape of substance. In general, the smaller the substance (provided is charged overall) and without big bulky groups attached, would migrate towards plate at faster rate/travel longer distance from original spot.

(II) How can the individual amino acids be detected after electrophoresis? [1]

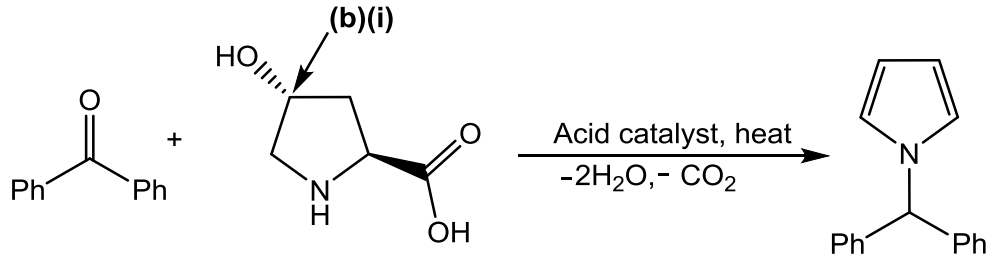
Ninhydrin (and heat)

(III) The isolectric point (pI) values of the three amino acids are given below.

compound name	abbreviation	isoelectric point
asparagic acid	Asp	2.77
glycine	Gly	5.97
valine	Val	5.96

Draw a diagram of the electrophoretogram and indicate the relative positions of the three amino acids when the electrophoresis buffer is set at pH = 5.00. [2]

(b) Pyrroles are building blocks in pharmaceutical chemistry. Thus, research has been ongoing to synthesize pyrroles in a single step from cheap and readily available materials. The diagram below shows the synthetic route of pyrroles from a modified amino acid, trans-4-hydroxyproline, in the presence of acid catalyst and heat.

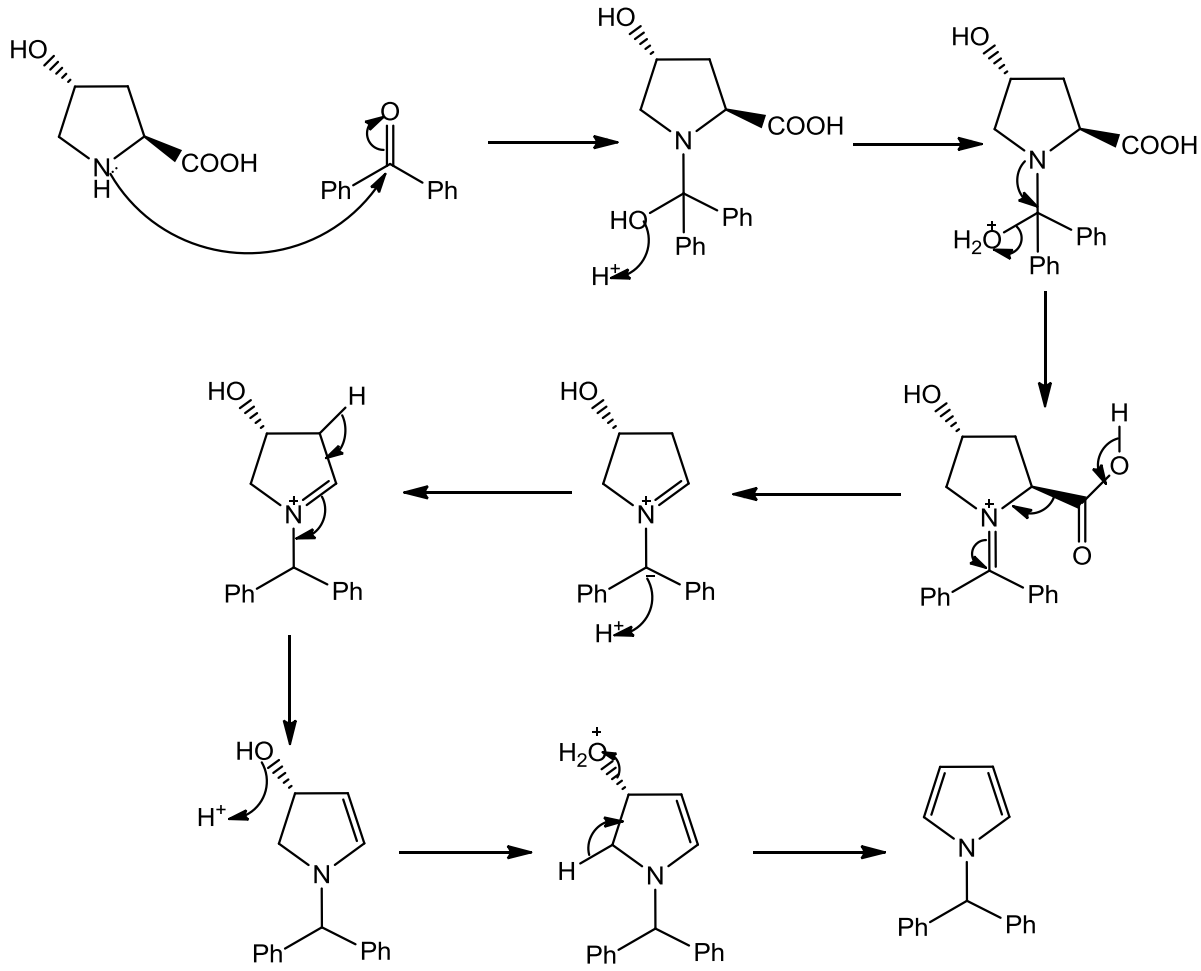


trans-4-hydroxyproline

(i) Determine the R/S configuration of the stereocentre labelled in the diagram above in trans-4-hydroxyproline. [1]

R

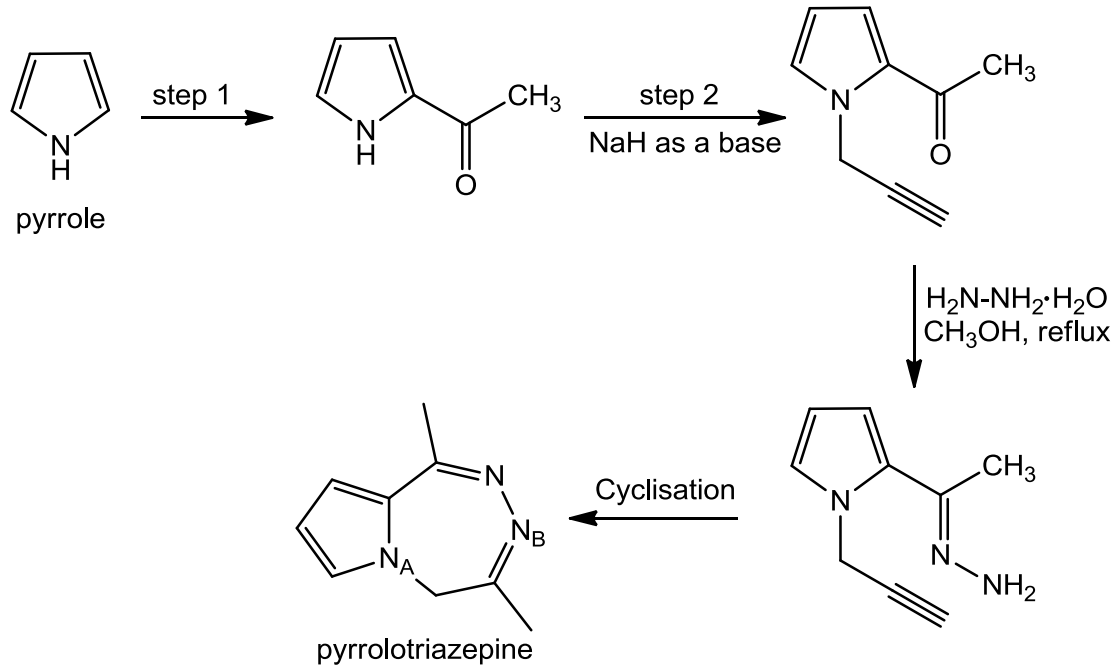
(ii) Suggest a possible mechanism for this reaction. [4]



(iii) A mixture of cis/trans isomers of 4-hydroxyproline was obtained. Suggest how the desired trans-4-hydroxyproline can be obtained. [1]

The two enantiomers may be separated by HPLC using a chiral stationary phase.

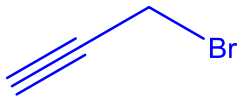
(c) Pyrroles can be used to synthesize pyrrolotriazepine derivatives which is being studied for its potential against diseases. The diagram below shows the synthetic route of a pyrrolotriazepine from pyrrole.



(i) State the reagents and conditions required for step 1. [1]

$(CH_3CO)_2O$

(ii) State the other reagent required for step 2. [1]



propargyl bromide

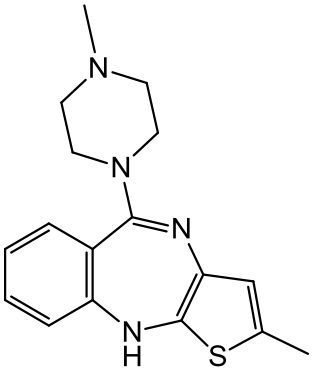
(iii) Suggest whether N_A or N_B in pyrrolotriazepine is less basic and explain why. [2]

N_A is less basic than N_B

Lone pair of electron on N_A is delocalised into the fused rings due to conjugation. Thus, the lone pair of electrons of Nitrogen atom is less available to accept a proton.
OR N_A has lack of an electron donating $-CH_3$ group (via inductive effect) on the ring. Thus, the lone pair of electrons of Nitrogen atom is less available to accept a proton.

[Total: 20]

4 (a) (i) Olanzapine is an antipsychotic medication used to treat schizophrenia and bipolar disorder. It acts as an antagonist at the D_2 dopamine receptor.



Olanzapine

Determine the aromaticity of olanzapine, explaining your decision. [2]

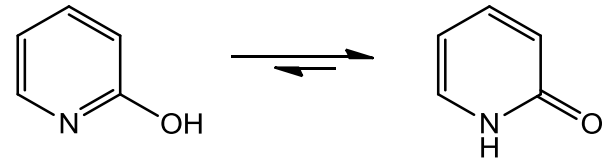
Olanzapine has 16 π electrons over the three fused rings.
16 = 4(4) which does not fulfil Huckel's Rule.
Hence olanzapine is anti-aromatic.

(iii) Hence, suggest how the binding pocket of the receptor is shaped, and two possible binding interactions that can take place between olanzapine and the binding pocket. [2]

To counter the instability which comes with having all three fused rings on the same plane (anti-aromatic), olanzapine is not planar, but instead bent about the central ring to give two separate aromatic systems (the benzene and the thiophene). Hence the binding pocket is likely to also be slightly curved.

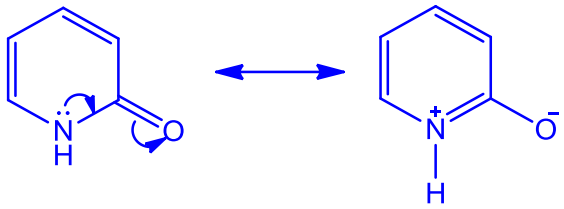
Instantaneous dipole-induced dipole attractions between the benzene ring of olanzapine and alkyl/aryl groups on the binding site.
Hydrogen bonding between the C=N nitrogen and –OH groups on the binding site.

(b) **(i)** 2-hydroxypyridine can tautomerize (undergo isomeric conversion) to 2-pyridone as shown below.



2-hydroxypyridine 2-pyridone

2-pyridone is a very weak base. Explain why this is so, and hence suggest why the position of the equilibrium shown above lies far to the right. [3]

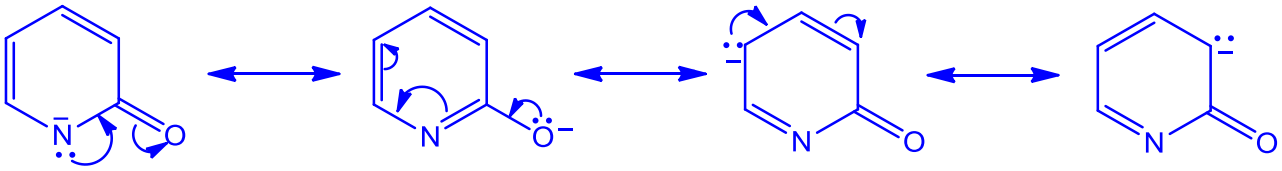


2-pyridone contains an amide group. The lone pair of electrons on nitrogen is delocalised into the C=O bond, hence making it unavailable for donation to act as a base.
This also makes 2-pyridone more stable as it is still aromatic and the resonance form has a positive charge on N and a negative charge on the more electronegative O.

(ii) Suggest why 3-hydroxypyridine does not tautomerize in a similar manner as 2-hydroxypyridine. [1]

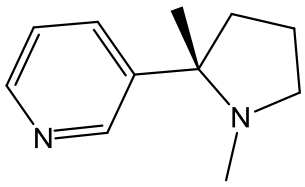
The structure of 3-pyridone cannot be drawn due to the position of the C=O (only the zwitterionic resonance form).
OR
There are no other resonance structures other than the zwitterionic form.
Any reasonable suggestion.

(iii) 2-pyridone is rather readily deprotonated. By considering the structure of the anion derived from the deprotonation of 2-pyridone, explain why this is the case. [2]



The conjugate base is well stabilized through its many resonance forms.

(c) Nicotine is a potent stimulant which can be found in cigarette smoke. It also contains a pyridine ring.



nicotine

(i) Outline four physiological effects of stimulants such as nicotine. [1]

Nicotine increases respiration rate, heart rate, blood pressure, reduces blood flow to peripheral regions, depresses appetite,

increases peristalsis of the bowels and causes diarrhoea, reduces urine flow, and increases adrenaline levels.

(ii) Use the concept of drug-receptor interactions to explain long-term dependence on nicotine, which acts as an agonist. [3]

Nicotine increases the level of dopamine. Because the body will attempt to keep the nerve transmission rate at a steady level, if there is continual stimulation of either the receptors, the number of those receptors on the post-synaptic nerves will gradually decrease, so as to reduce the stimulation.

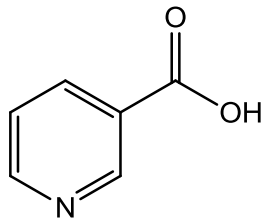
This decrease in receptor numbers results in:

(i) the dosage of the drug will need to be increased if the same effect is to be felt (i.e. more and more cigarettes smoked per day), and

(ii) if the drug is withdrawn, there will not be enough receptors to produce the same level of neurotransmission that the body requires, and so a general feeling of anxiety and tension will ensue, which intake of more nicotine will counteract.

These strong withdrawal symptoms last a long time because the nerves will take time to synthesise more receptor proteins – resulting in long-term dependence.

(d) Under suitable conditions, nicotine can be converted to nicotinic acid. Nicotinic acid is also known as niacin, and it is a component of vitamin B_3 complex.



nicotinic acid

Suggest the type of reaction undergone in this conversion, and suitable reagents and conditions to carry out this conversion. [1]

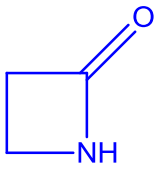
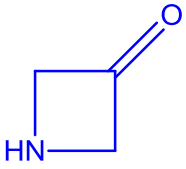
Oxidation; $KMnO_4/H_2SO_4$, heat

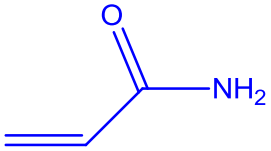
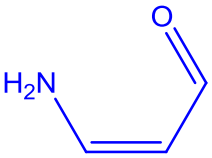
(e) Three compounds, each having the molecular formula C_3H_5NO, have the following features in their infra-red (IR) spectra:

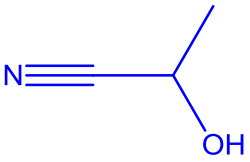
Compound	Wavenumber / cm^{-1}	Features
K	> 3000	1 weak band
	~ 1700	1 strong band
L	> 3000	2 weak bands
	1600-1700	2 bands
M	> 3000	1 strong, sharp band
	~2200	1 band

By assigning each of the absorbances to the likely bond(s) involved, suggest a possible structure each for compounds **K**, **L** and **M**. [5]

Compound	Wavenumber / cm^{-1}	Features	Assignment
K	> 3000	1 weak band	**N–H**
	~ 1700	1 strong band	**C=O**
L	> 3000	2 weak bands	**2 x N–H, possibly –NH_2**
	1600-1700	2 bands	**1 x C=C & 1 x C=O**
M	> 3000	1 strong, sharp band	**O–H**
	~2200	1 band	**C≡N**

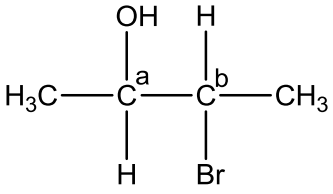
K:  or 

L:  or 

M:  or 

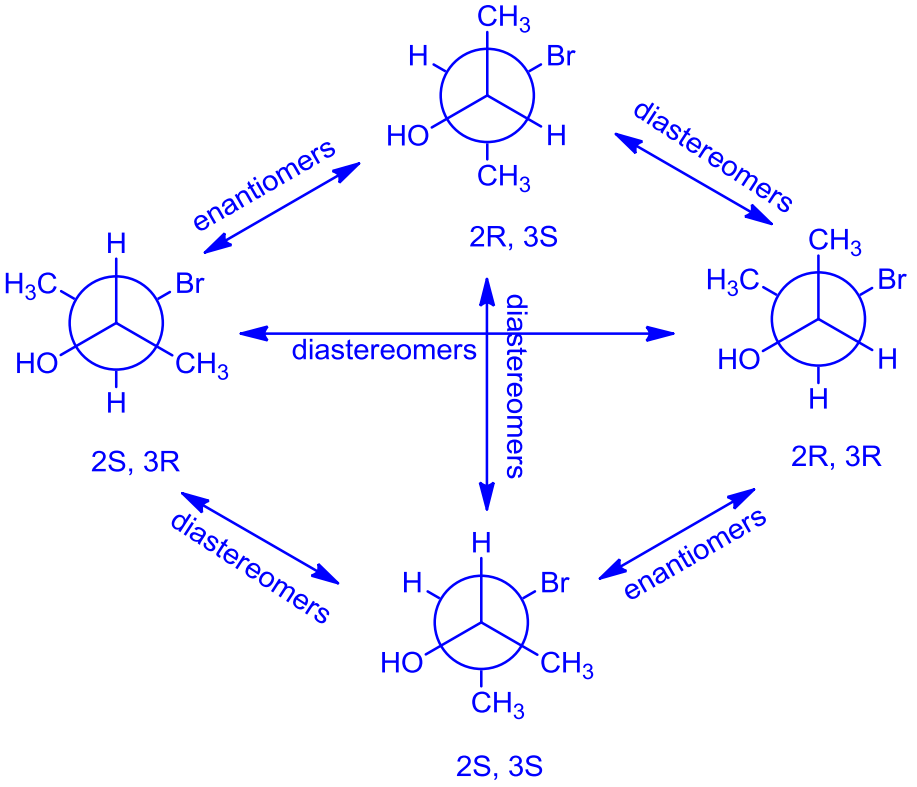
[Total: 20]

5 **(a)** The most stable conformation for 3-bromobutan-2-ol is when the Br and OH groups are anti to each other.



(i) Using Newman projections, sight along the C_a-C_b bond and draw all possible stereoisomers of 3-bromobutan-2-ol, in their most stable

conformation. Label the chiral carbons with the R, S configurations and indicate all stereoisomeric relationships. [3]



(ii) When the Br atom in 3-bromobutan-2-ol is replaced by C*l* to give 3-chlorobutan-2-ol, the most stable conformation is when the C*l* and OH groups are gauche to each other. Explain why this is so. [1]

The stability is due to the formation of intramolecular permanent dipole-permanent dipole/hydrogen bonding attractions between the $^{\delta+}$H on OH and $^{\delta-}$C*l* (possible since a 5-membered ring is formed).

(b) When an alcohol is reacted with HBr, a reaction occurs where HBr first protonates the oxygen atom, followed by attack at the alcohol carbon atom by Br^- and the loss of a water molecule.

$$ROH + HBr \rightarrow ROH_2^+ + Br^-$$
$$ROH_2^+ + Br^- \rightarrow RBr + H_2O$$

(i) State the type of reaction that has occurred. [1]

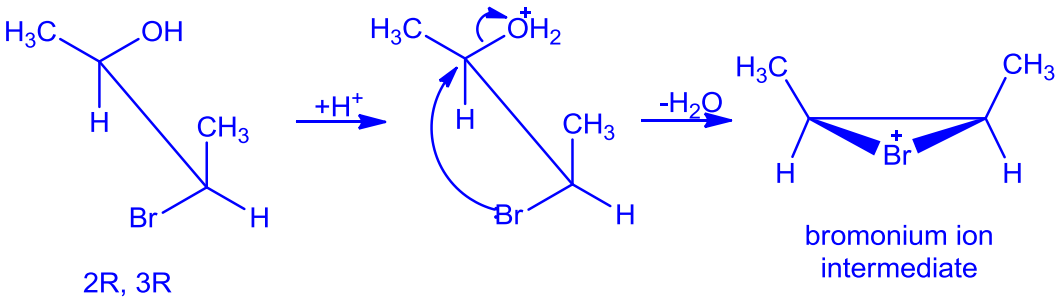
Nucleophilic substitution (S_N2)

(ii) When the various stereoisomers of 3-bromobutan-2-ol in **(a)(i)** are reacted with HBr, the abovementioned reaction takes place, with the following observations:

In one of the enantiomeric pairs of 3-bromobutan-2-ol, each enantiomer gives the same two products – one which exhibits retention of configuration, and another which exhibits inversion of configuration. The two products are themselves enantiomers.

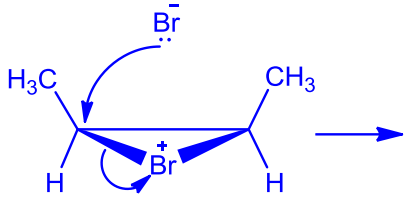
In the other enantiomeric pair of 3-bromobutan-2-ol, both enantiomers give the same product, and this product is optically inactive.

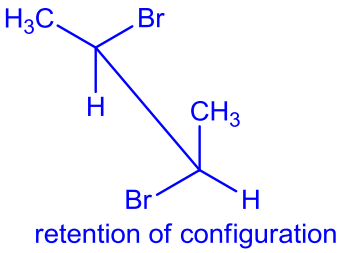
Suggest a possible mechanism for the reaction, and hence account for the above observations. You may make use of any suitable stereochemical representations in your answer. [4]



2R, 3R

Attack at C2:

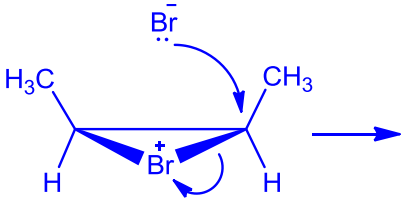


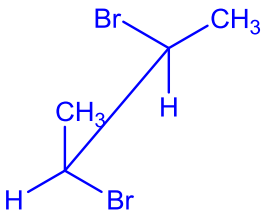


retention of configuration

enantiomers

Attack at C3:





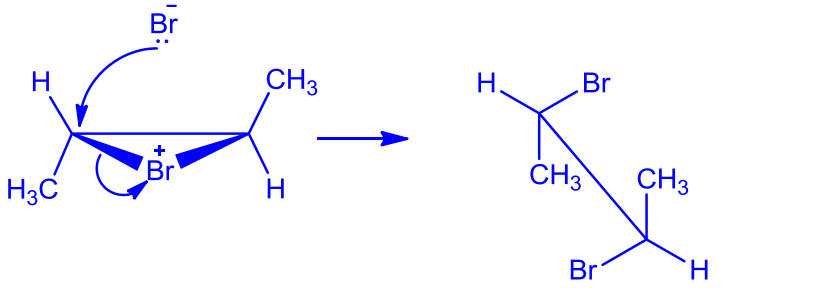
inversion of configuration

The same bromonium ion intermediate is obtained from (2S, 3S)-3-bromobutan-2-ol, to give the same two products.

The other pair of enantiomers (2R, 3S & 2S, 3R) give enantiomeric bromonium ion intermediates but they all give the same product.

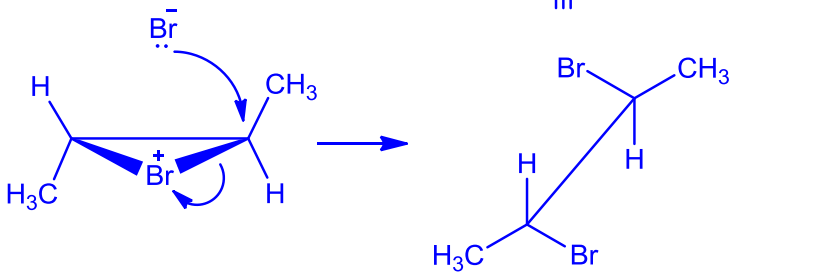
For (2S, 3R)-3-bromobutan-2-ol:

Attack at C2:

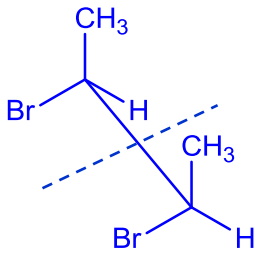


Attack at C3:

the same product!



The product is a meso compound (since it has an internal plane of symmetry), hence it is optically inactive.



(c) (i) Explain the origin of infra red (IR) absorptions of simple molecules. [2]

Infra red (IR) absorptions are associated with the vibrations of bonds or molecules. For the vibrational mode to be IR-active, there must be a change in dipole moment for absorption of radiation to take place.

(ii) For each of the molecules HF, CO_2 and OCS

- predict the number of absorption bands in its IR spectrum,
- identify the molecular vibrations which give rise to these absorptions.

[4]

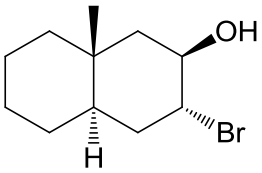
Molecule	No. of bands	Molecular vibrations
HF	1	H-F stretch
CO_2	2	O=C=O asymmetric stretch, O=C=O bending
OCS	3	O=C=S symmetric stretch, O=C=S asymmetric stretch, O=C=S bending

(iii) State and explain the difference between the IR spectra of ^{1}HF and ^{2}HF. [1]

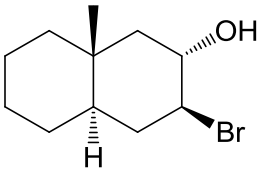
The absorption band of ^{2}HF is found at a lower wavenumber than that of ^{1}HF because the frequency of absorption decreases as the masses of the atoms joined by the bond increase.

(d) An epoxide is a cyclic ether with a three-membered ring.

(i) State and explain which of the compounds below will give an epoxide upon reaction with a base.



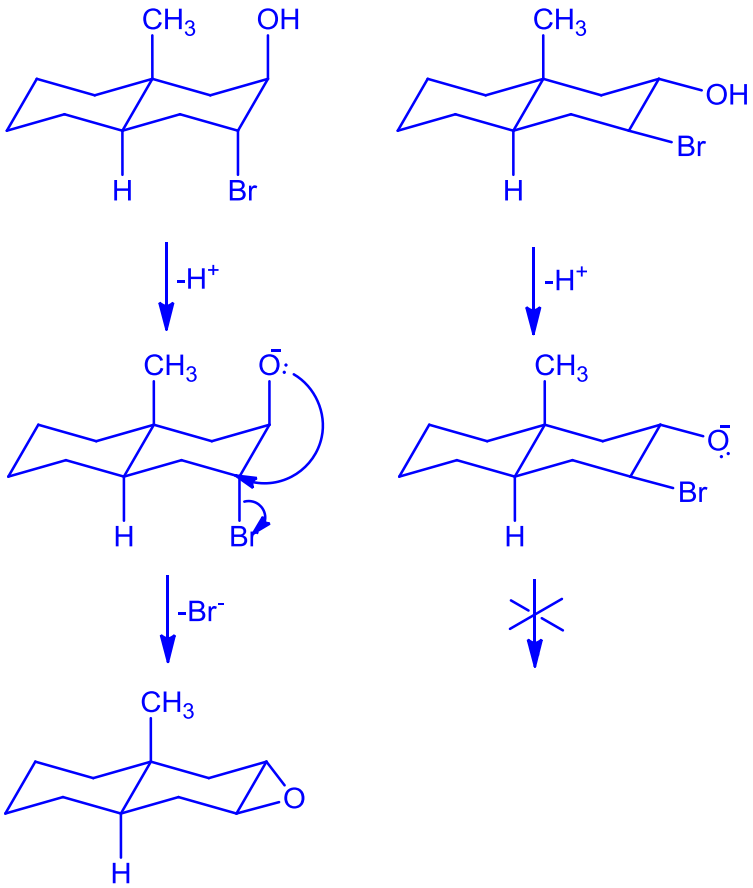
Compound X



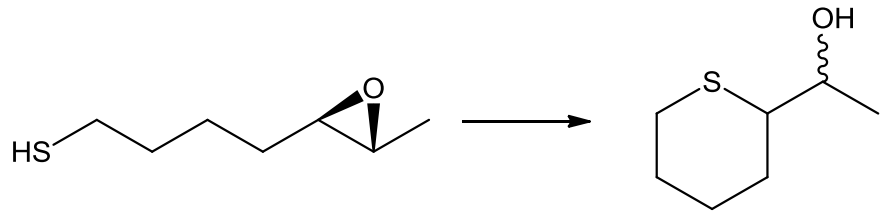
Compound Y

[2]

Compound X
Because S_N2 backside attack by the nucleophile (O^-) on the carbon with Br can only take place with compound X.

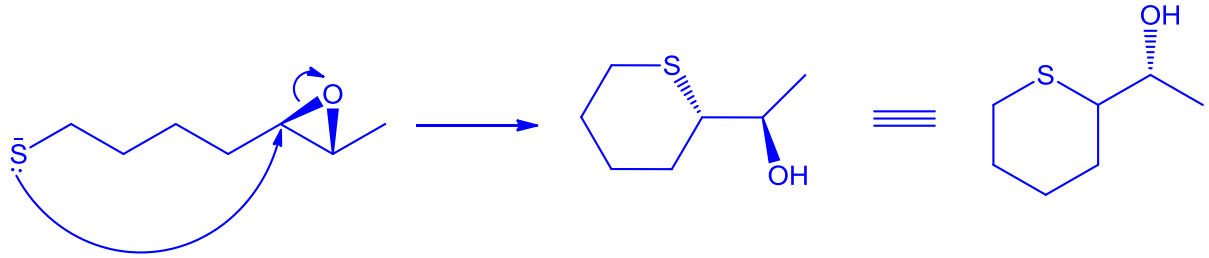


(ii) Suggest a suitable reagent for the following reaction and deduce the stereochemistry of the product.



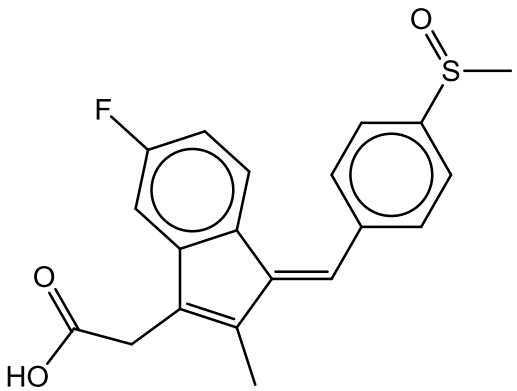
[2]

Na



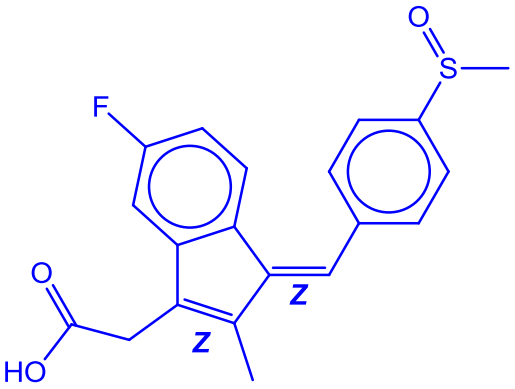
[Total: 20]

6 Sulindac is a non-steroidal anti-inflammatory drug (NSAID). It has an unusual property of reducing the growth of polyps and precancerous lesions in the colon, and may have other anti-cancer properties.

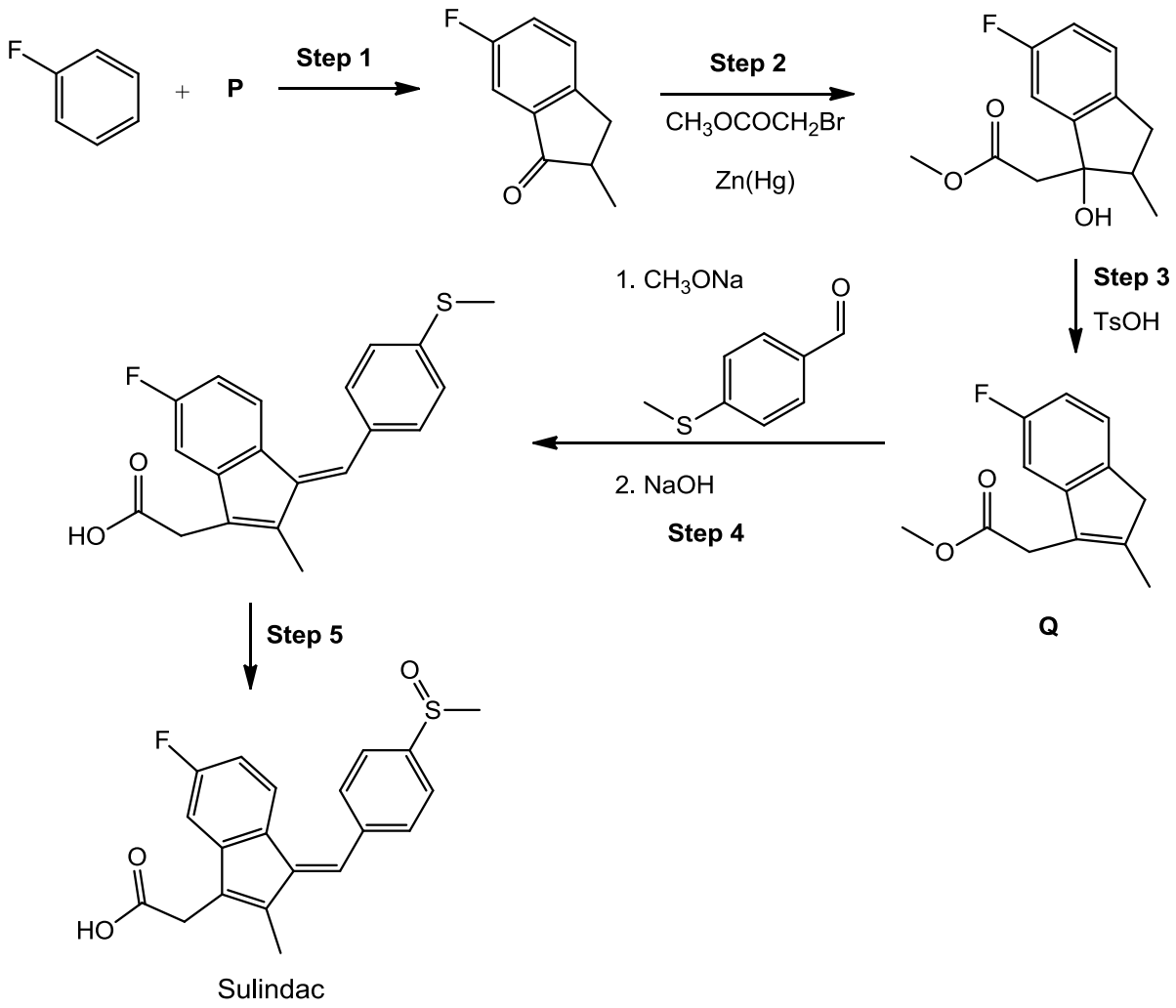


Sulindac

(a) Deduce the configuration of each C=C in sulindac. [2]



(b) Sulindac can be synthesized in the following manner:



Sulindac

(i) In Step 1, fluorobenzene reacts with compound **P** in the presence of a catalyst.

The mass spectrum of compound **P** contains peaks at m/e 228, 230 and 232 in a 1:2:1 ratio. The M^+ peak is at m/e 228. Additionally, there are two peaks of equal intensity at m/e 121 and 123.

Suggest structures corresponding to the peaks in the mass spectrum of compound **P**, and deduce the identity of the catalyst used. [4]

m/e 228: $[CH_2{}^{79}BrCH(CH_3)CO^{79}Br]^+$

m/e 230: $[CH_2{}^{79}BrCH(CH_3)CO^{81}Br]^+$ and $[CH_2{}^{81}BrCH(CH_3)CO^{79}Br]^+$

m/e 232: $[CH_2{}^{81}BrCH(CH_3)CO^{81}Br]^+$

m/e 121: $[CH_2CO^{79}Br]^+$ / $[CH_2{}^{79}BrCH(CH_3)]^+$

m/e 123: $[CH_2CO^{81}Br]^+$ / $[CH_2{}^{81}BrCH(CH_3)]^+$

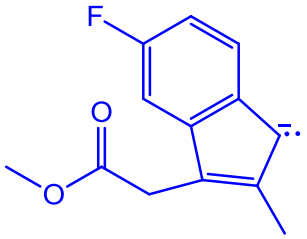
Catalyst used is $AlBr_3$ (or $AlCl_3$)

(ii) Name the types of reaction in Steps 2 and 3. [2]

Step 2: nucleophilic addition

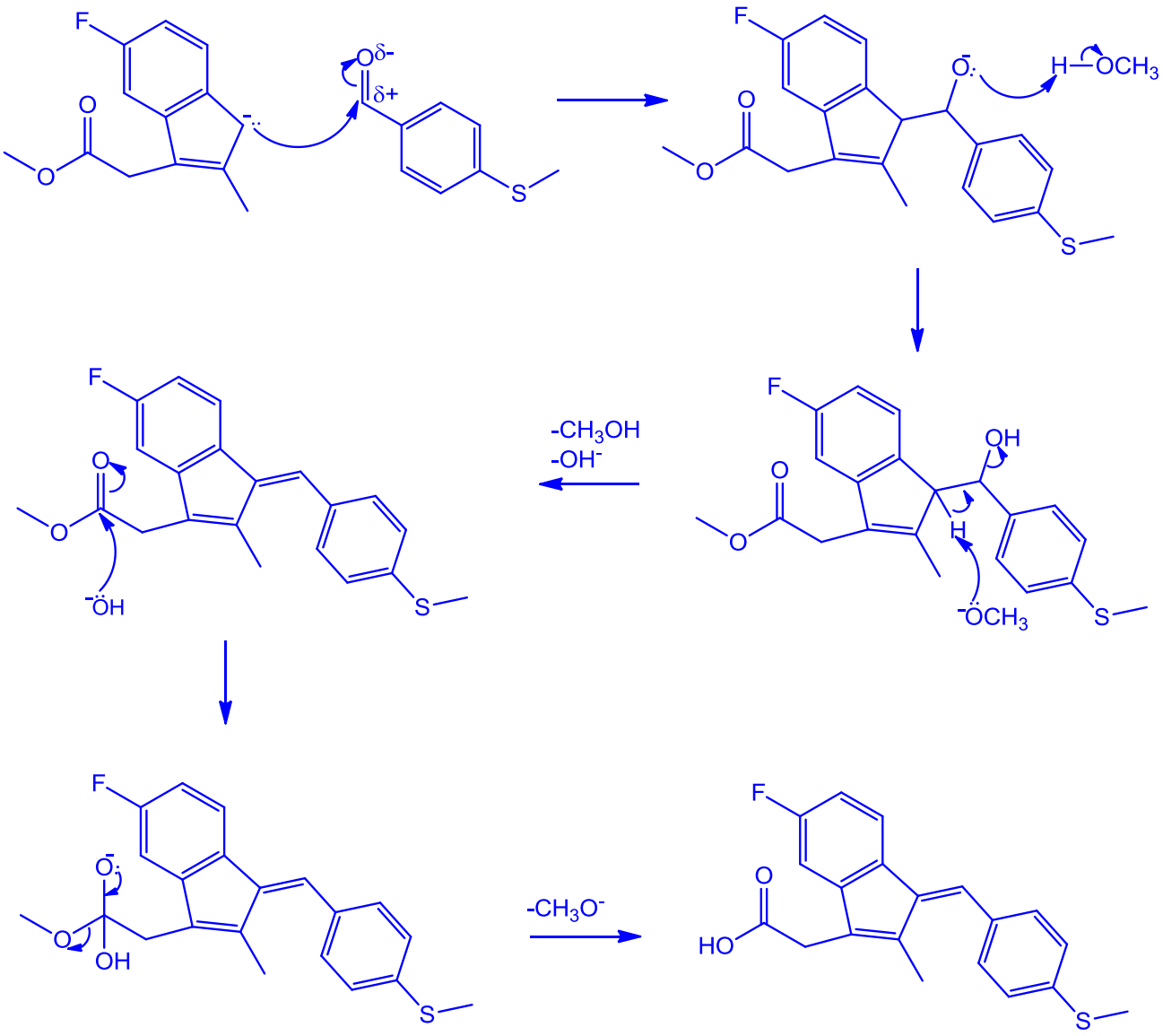
Step 3: dehydration/elimination

(iii) In Step 4, the reaction starts off with the deprotonation of compound **Q** by sodium methoxide. Draw the structure of the conjugate base of compound **Q** and use it to explain why that particular proton was lost. [2]



Deprotonation of the proton adjacent to the benzene ring is particularly favourable as it extends the conjugation of the ring over the fused 5-membered rings as well.

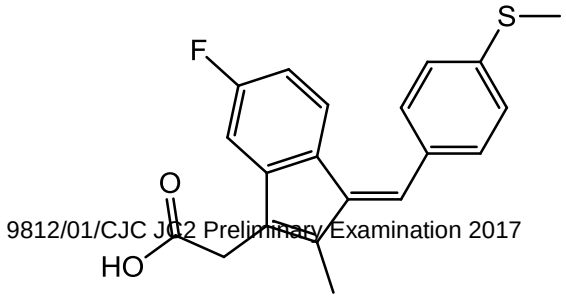
(iv) Suggest the mechanism of the reaction in Step 4. You may start from the conjugate base of compound **Q** which you have drawn in **(b)(iii)**. [3]



(v) State the reagent used in Step 5. [1]

$NaIO_4$ or 1 equivalent of H_2O_2

(c) Sulindac is metabolized in the body to give sulindac sulfide, which is the active drug. Suggest why sulindac is administered instead of its active metabolite sulindac sulfide.



[2]

The sulfoxide functional group of sulindac is more polar than the sulfide functional group of sulindac sulfide. This increases its solubility in aqueous media such as in the gastrointestinal tract, when the drug is ingested, and the bloodstream, where it can be transported to various parts of the body.

(d) The half-life of sulindac sulfide is 8 hours. During a course of treatment, a patient is given a dose of 100 mg of sulindac three times a day.

(i) Copy and complete the following table for as many lines as you need to determine the average steady state concentration of drug in the patient's body, in mg dm^{-3}.

Assume that the time taken for sulindac to be metabolized to sulindac sulfide is negligible, and that the blood volume of the patient is 5.0 dm^3.

time/h	amount of sulindac sulfide in body / mg	
	before dose	after dose
0	0	100
8		
16		
etc		

[3]

time/h	amount of sulindac sulfide in body / mg	
	before dose	after dose
0	0	100
8	50	150
16	75	175
24	87.5	187.5
32	93.8	193.8
40	96.9	196.9
48	98.4	198.4
56	99.2 ≈ 100	199.2 ≈ 200

Average steady state amount of sulindac = $\frac{100+200}{2}$ = 150 mg

Average steady state concentration of sulindac = $\frac{150}{5}$ = 30 mg dm^{-3}

(ii) Sulindac was developed as a less toxic alternative to another NSAID, indomethacin.

The ratio between the toxic dose and the lowest effective dose is called the *therapeutic index*, TI.

$$TI = \frac{maximum\ dose\ before\ toxic\ symptoms\ occur}{minimum\ effective\ dose}$$

The maximum concentration of sulindac in the blood before toxic symptoms occur is 52 mg dm^{-3}.

Using the average steady state concentration calculated in part **(i)** as the minimum effective dose, calculate the therapeutic index of sulindac. [1]

$\boldsymbol{TI = \frac{52}{30}}$ **= 1.73**

[Total: 20]