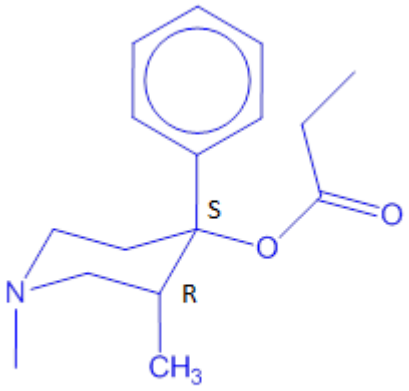
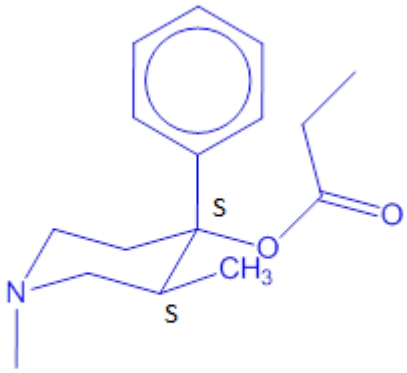
**H3 Pharmaceutical Chemistry 9812**
**AJC Solution to H3 Chemistry Preliminary Examination 2016**

**1 (a)**




alphaprodine




betaprodine

N at axial position
Alphaprodine – *S*,*R* Betaprodine – *S*,*S*
identify the S, R configuration
They are <u>diastereoisomers.</u>

Alphaprodine has a trans configuration whereas betaprodine has a cis configuration.

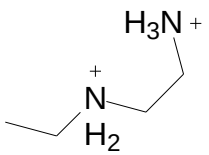
Alphaprodine is less stable due to the presence of <u>additional 1,3-diaxial interactions/steric repulsion</u> from the methyl group that is in the axial position.

**(b) (i)** In the laboratory synthesis of analogues of penicillin, the use of <u>natural</u> penicillin, <u>isolated from fermentation medium</u> is used as the starting material.

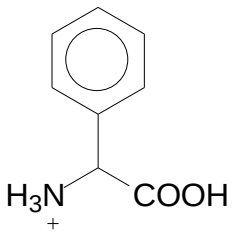
**(ii)** The <u>4 membered lactam</u> is highly strained and would undergoes hydrolysis readily at the <u>transpeptidase and inhibit the enzyme</u>.

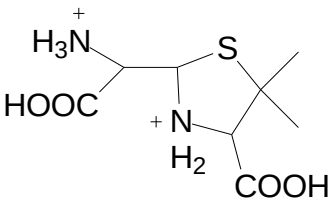
This will stop <u>the cross-linking of peptide chains during</u> step 7 of <u>cell wall synthesis in bacteri</u>a. Hence, the bacteria are killed due to lysis.

**(iii)**

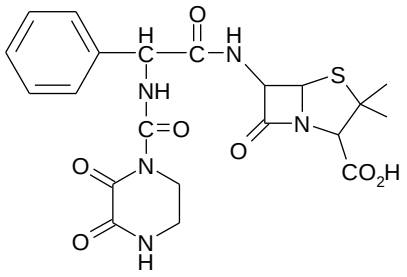



$CO_2$

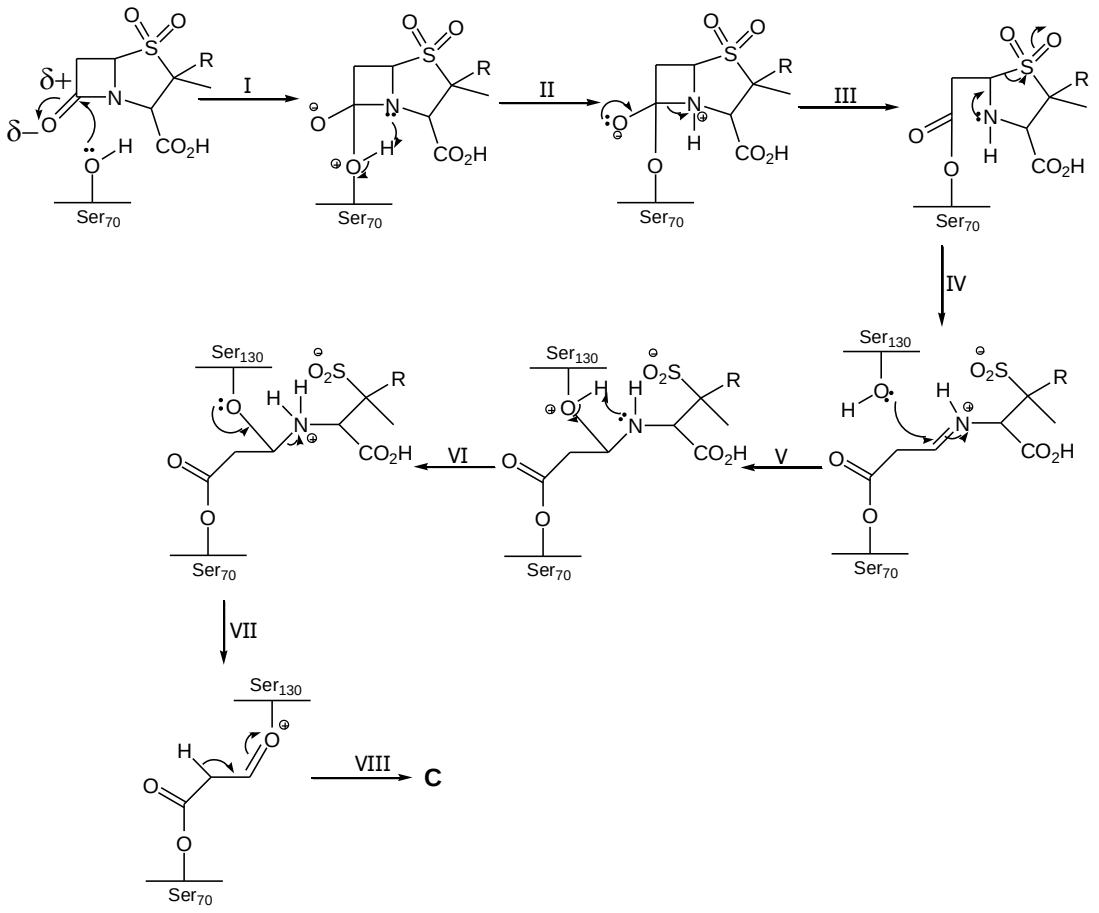


**1** **(iv)**



**(c)** **(i)**




**(ii)** There is <u>extended conjugation</u> up to and including the oxygen atom of $Ser_{130}$ which <u>increases electron density</u> at the ester carbon making it <u>less susceptible to nucleophilic attack</u> (by water).

**(iii)** It forms a strong covalent bond hence function as an <u>irreversible non-competitive inhibitor</u>.

It forms strong covalent bond with the active site that cannot be broken such that the enzyme is permanently disabled.

**(iv)** As the vinyl carboxylic acid is still covalently bonded to $Ser_{130}$, the active site of the enzyme remains blocked.

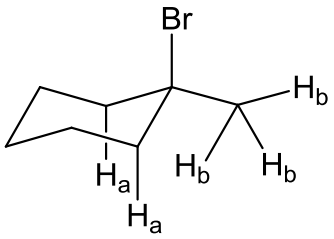
**2 (a) (i)** **Experiment A**

The reactions occur via the stereospecific E2 mechanism that always requires an anti-periplanar geometry.

In reaction **I**, C-H and C-Br bonds are locked in an anti-periplanar arrangement, making the RX molecule ideal for reaction. Hence, rate of reaction **II** is much faster than that of reaction **I**.

The trans-fused ring  is locked in this conformation
E2 is not possible as there are no C-H bonds anti-periplanar to the C-Br bond in II.

**Experiment B**




The less bulky base $CH_3O^-$ is able to approach $H_a$ easily, forming the thermodynamic product / more stable product / more substituted alkene.

$(CH_3CH_2)_3CO^-$ is bulky and will encounter steric hindrance when it approaches $H_a$. Instead, it removes $H_b$ to form the less stable product / less substituted alkene.

logical explanation involving steric argument
identifies $H_a$ and $H_b$ clearly

**(ii)** Rate of **II** is directly proportional to concentration of NaOH.

**(b) (i)** A narcotic analgesic is a drug that relieves pain by depressing the activity of the central nervous system.

Agonist is a drug that mimics the natural ligand for a receptor. It will dock sufficiently to a binding site for the receptor to change shape adequately for the active site or ion-channel to open.

**(ii)** Phenol – hydrogen bonding
Aromatic ring – Van de Waals forces
Ammonium – ionic bonding

**(iii)** I All have the essential groups to bind at binding site in vitro.

Ease of passing through blood brain barrier which is lipophilic:
C > morphine > B > A
Because order of polarity: C < morphine < B < A (most polar)

II Esterase presence in vivo studies hydrolysed the ester groups /metabolized D to release essential groups (phenol).

**(iv)** pKa = pH –lg [M]/[MH]
14 – 5.79 = 7.4 – lg [M]/[MH]
-0.81 = lg [M]/[MH]
$[M]/[MH] = 10^{-0.81} = 0.154$

**2 (c) (i)** HPLC should be used because the three compounds have very high boiling points (due to high molecular mass/no. of electrons) such that they are unlikely to form vapour easily. Thus, they cannot be analysed with GLC directly.

**(ii)** X contain alcohol group which gives white fumes with $PCl_5$. X must be either morphine or E.

X cannot be morphine as X should be either the most polar or the least polar compounds of the three thus X should be E.

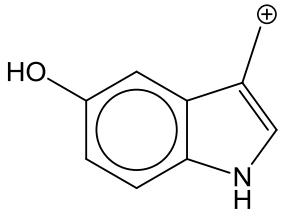
**(iii)** Mobile phase should be polar and the stationary phase should be non-polar, because the most polar compound was eluted first.

Y is morphine and Z is C as the most polar compound will be eluted first.

**3 (a) (i)** L-dopa
Its mass spectrum will show a strong absorption at ~ 1700 $cm^{-1}$ due to the C=O stretch

**(ii)** 2 eq. $CH_3Br$

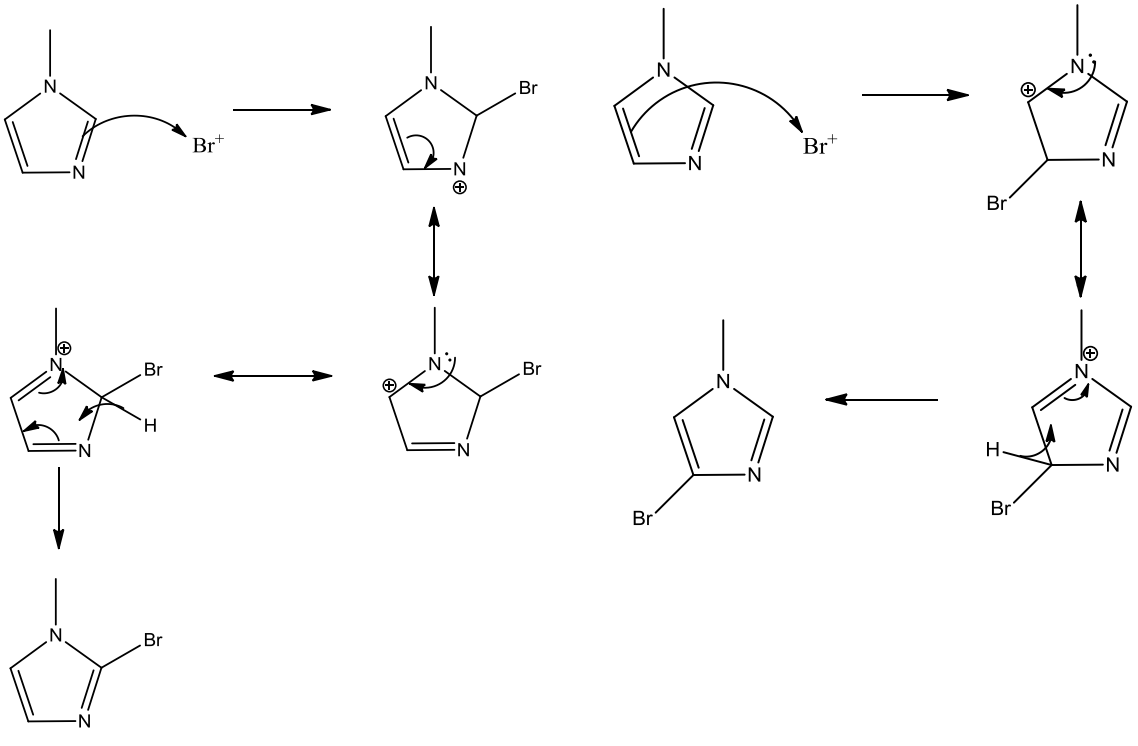
**(iii)** The structure is:




The carbocation is resonance-stabilised due to the overlap between the empty p-orbital on the C atom and the π-system of indole / pyridine.

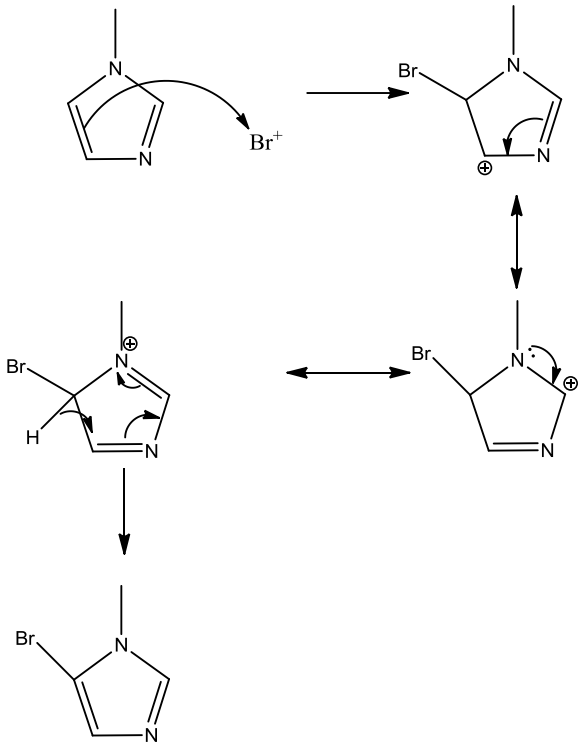
**(iv)** 0.78 = 24 500 x 1.0 x [L-dopa]
[L-dopa] = $3.18 \times 10^{-5}$ mol $dm^{-3}$

**(b) (i)** **Formation of 1** **Formation of 2**



**3**

**Formation of 3**

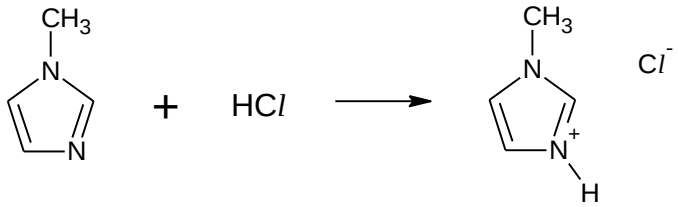



The formation of product ***1*** is not as favourable because one of the mesomeric structures formed is unstable since the positive charge resides on the electronegative N as indicated.

The formation of product ***2*** is not as favourable since there are only two possible mesomeric structures.

The major product is ***3.***

**(ii)**



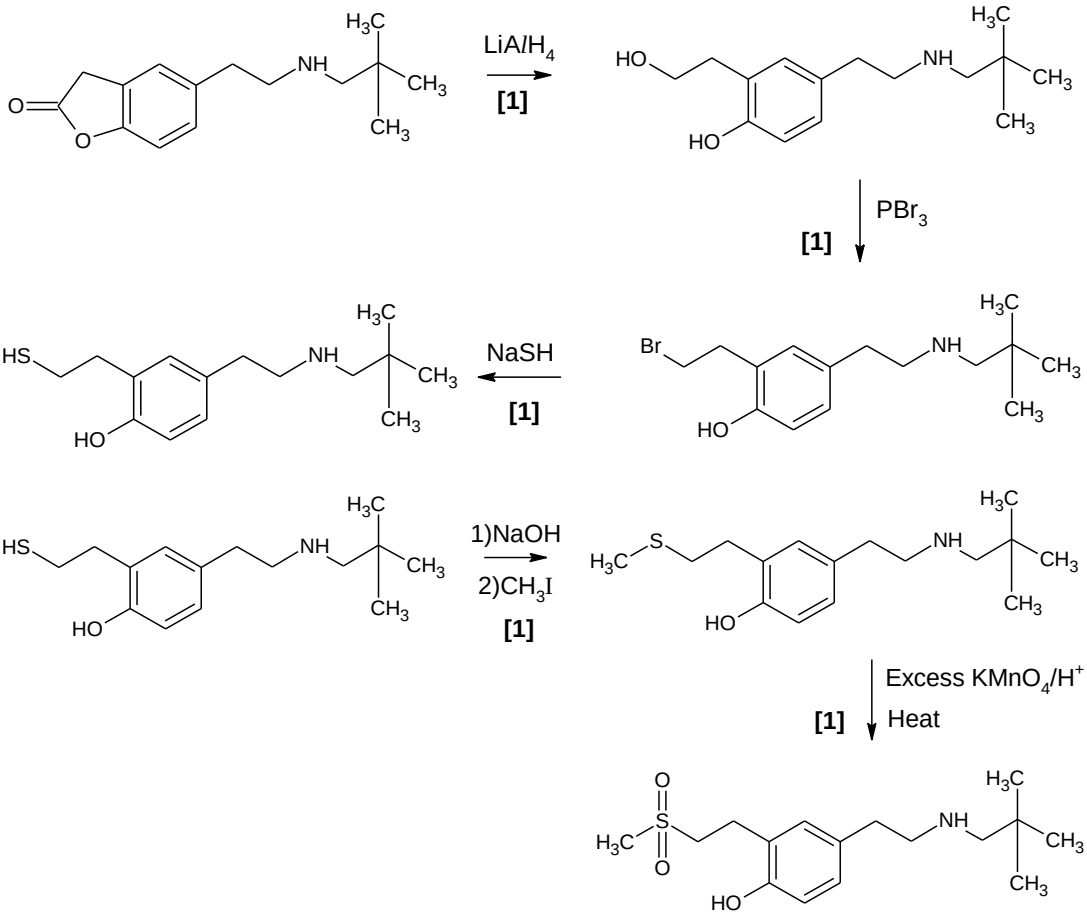

**(iii)** 1–methylimidazole is less aromatic than benzene

as the electronegative nitrogen exerts its electron withdrawing effect on its lone pair and reduce extent of delocalization of π electrons in the ring.

**(c)** **(i)** Similar effect: increase heart rate, blood pressure, respiration rate, adrenaline levels increase ; any two

Differences: blood sugar increase in caffeine, no effect n nicotine; sleep pattern disturb in caffeine, no effect in nicotine, urine flow increase in caffeine, reduce in nicotine; appetite not affected in caffeine, depressed in nicotine ; any two

**3** **(ii)**




**(iii)**




**4** **(a)** Mass spectrum

$$\frac{A_M}{A_{M+1}} = \frac{100}{1.1n}$$

$$\frac{7.51}{1} = \frac{100}{1.1n}$$

$n$ = 12

The molecular ion loses 28 mass units, corresponding to a CO unit, to form the base peak.

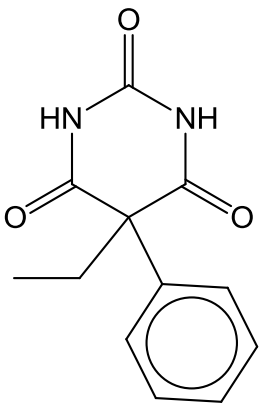
NMR spectrum

| $\delta$ / ppm | splitting | Number of protons | Deductions |
|---|---|---|---|
| 0.99 | t | 3 | $CH_3$ protons split by adjacent $–CH_2-$ |
| 2.49 | q | 2 | $CH_2$ protons split by adjacent $CH_3$<br>Structure contains a $–CH_2CH_3$ chain |
| 7.36 | m | 5 | aromatic protons on mono-substituted benzene ring |
| 8.79 | s | 2 | Labile amide protons |

Stereochemical information

C=C with different groups on each C atom is absent and chiral C is absent

IR spectrum




A series of sharp absorptions ~1650 to 1800 $cm^{-1}$
- A series of C=O stretches

Broad absorption ~3100 $cm^{-1}$
- Amide N-H stretch

Since the $M_r$ = 232, and the molecule contains 12 C atoms and 12 H atoms, the total number of N and O atoms contribute a total of 232 – (12 x 12) – 12 = 76 mass units. By trial and error, the molecule contains 2 N atoms and 3 O atoms.

The molecular formula of phenobarbital is $C_{12}H_{12}N_2O_3$
Structure of phenobarbital

**(b)** Aspirin (carboxylic acid) undergoes acid-base reaction with $NaHCO_3$ to form sodium salt containing the $–COO^-$ which can form strong ion-dipole interactions with the water molecules. This makes aspirin more soluble in water.

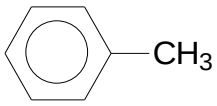
Addition of dilute HCl forms the molecular form of aspirin that has low solubility in water. Hence, precipitation occurs. Filtration and collection of residue yield aspirin.

Paracetamol being neutral will not react with the base remains in molecular form and dissolved in the organic layers. Even though the –OH and –CONH can form hydrogen bonds with the water molecules, the energy from these limited hydrogen bonds released is not enough -to break the large van der Waals forces between the non-polar groups of the amide and organic solvent.

Evaporation of organic layer yields paracetamol.

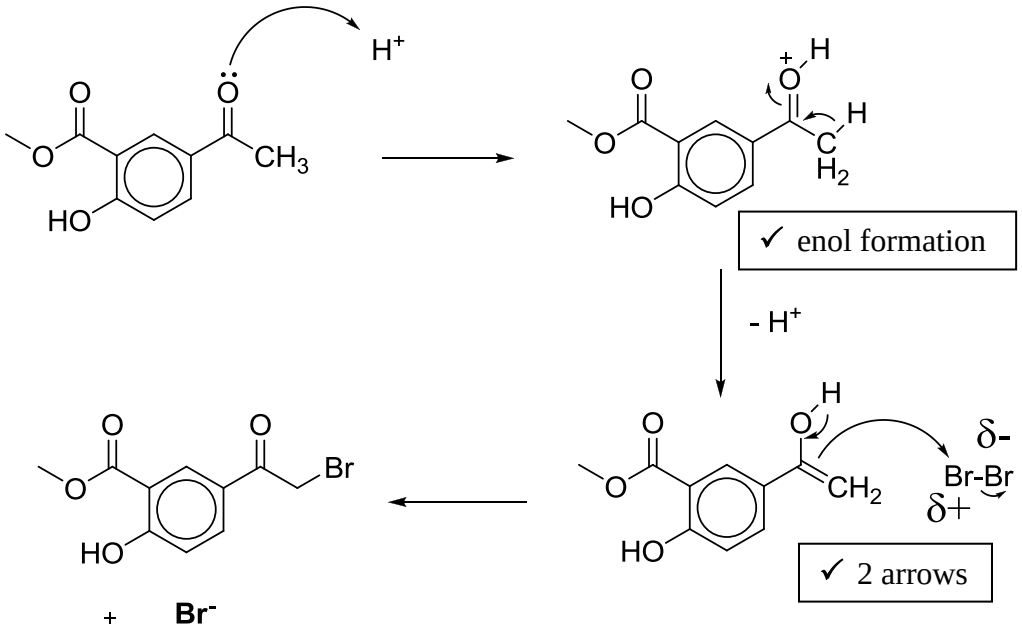
**4 (c) (i)** Step **A**: $CH_3OH$, conc $H_2SO_4$, reflux
Step **C**: $(CH_3)_3CNHCH_2Ph$, reflux

**(ii)**

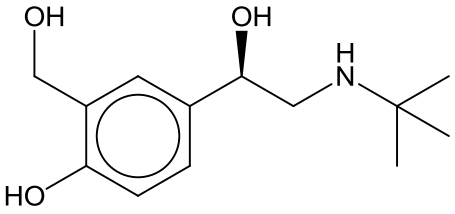



**(iii)** The C=O bond is stronger than the C=C bond, thus the keto form is much more stable.

**(iv)**




**(d)** **(i)**



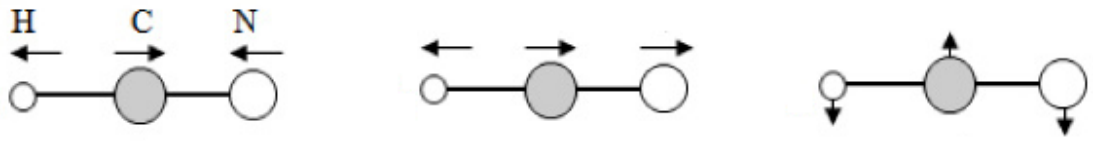

**(ii)** The other enantiomer may result in undesired side-effects, or even be toxic.

and

Manufacturing a racemic mixture is a waste of chemicals and increases the cost of production.

[Note: S-isomer can be hydrolyse in the body into R-isomer. S-isomer is non-toxic.]

**5** **(a)**




asymmetric stretch



symmetric stretch



bend

712 $cm^{-1}$

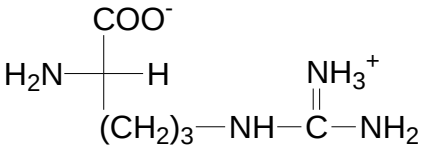
*Note: Stretches involving H, C and N atoms occur at higher wavenumbers. The symmetric stretch and asymmetric stretch of HCN occurs at 2089 $cm^{-1}$ and 3312 $cm^{-1}$ respectively.*

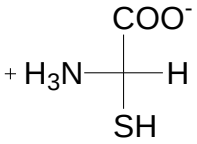
**(b)** The sample mixture is placed in a gel and is separated into its constituents by applying an electric field to the gel, which is soaked in a liquid buffer.

The components in the sample mixture like amino acids have either zero, overall positive or overall negative charge depending on the pH of buffer.

The molecules move in response to the electrical field and the rate of progress depends on their size, charge and shape.

**(c)** **(i)** Sulfur atom in the $-CH_2SH$ in Cys makes the side chain higher in priority than $-CO_2H$.

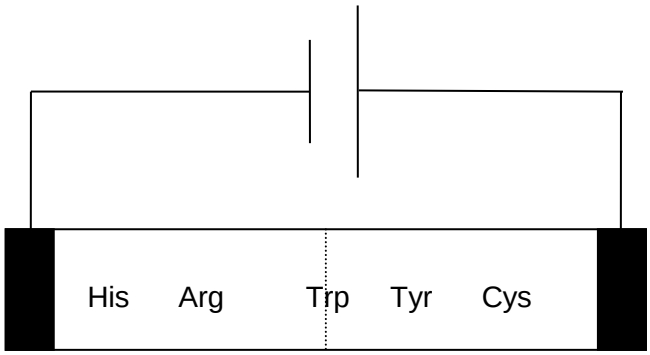



also accept resonance structures

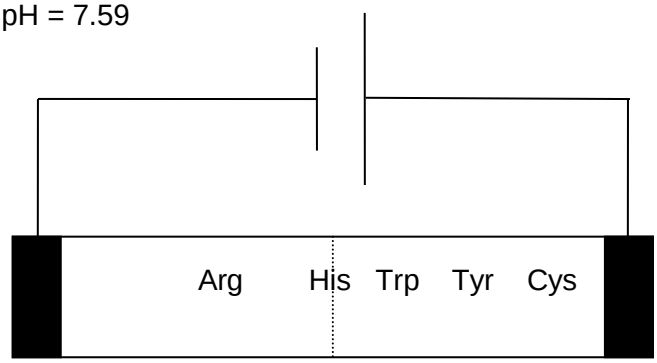
correct Fischer projections
correct ionized in Arg

**(ii)** pH = 5.89




starting point

(I) pH = 7.59

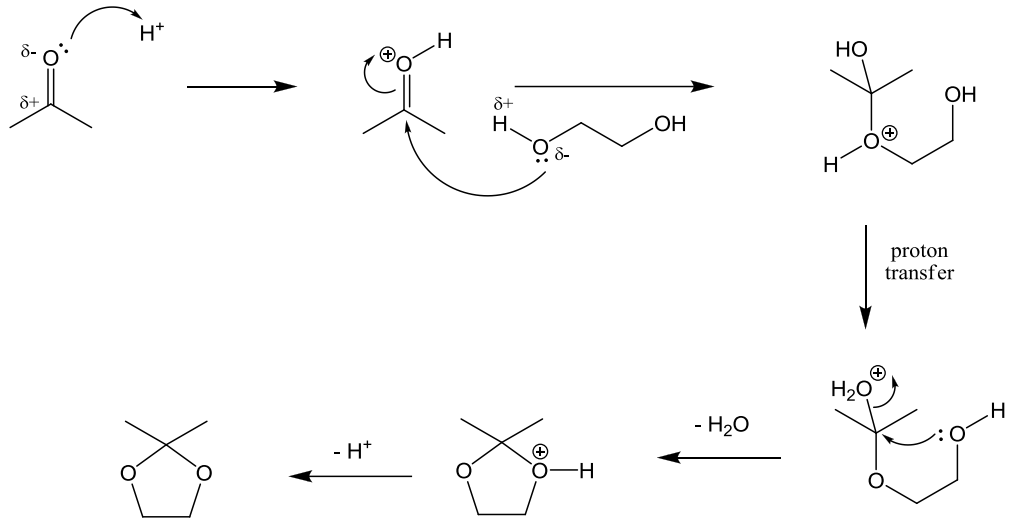



starting point

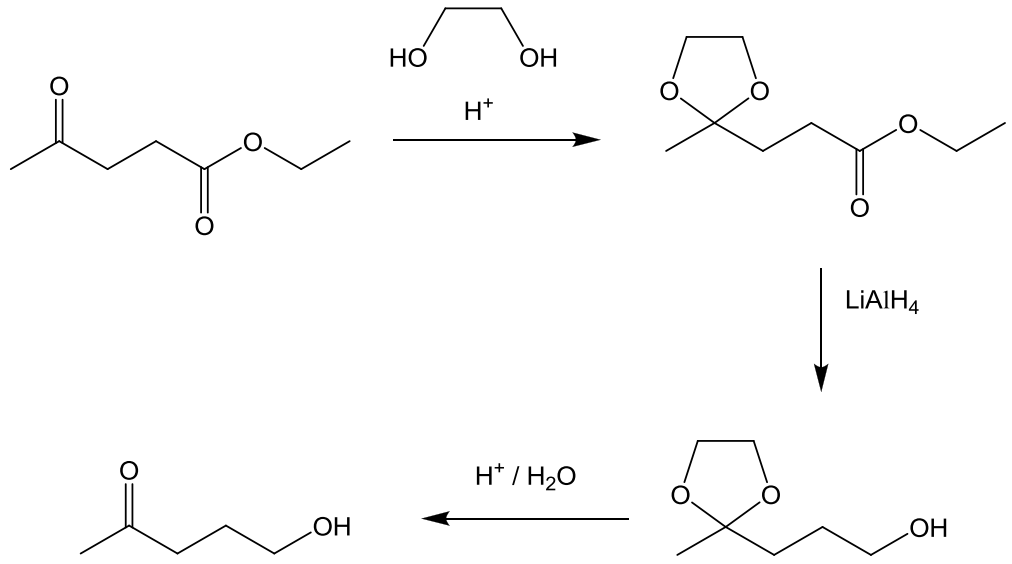
**(iii)** Ninhydrin

**(d)** **(i)** Nucleophilic addition

**(ii)**




**(iii)**

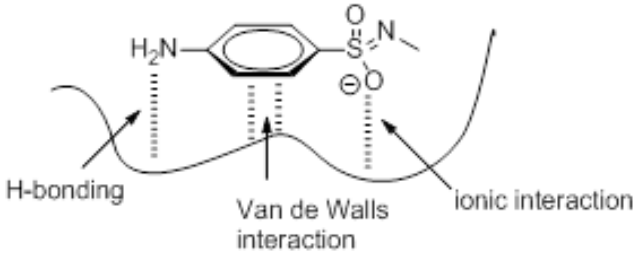



**6 (a) (i)** Competitive inhibitor acts as the natural substrate and <u>binds reversibly</u> at the <u>active site of the enzyme</u> to stop the action of the enzyme.

**(ii)** Gut wall is <u>lipophilic</u>. The <u>carboxylic acid group in the amide side chain is ionised</u> at physiology pH of 7 in the intestine. This makes the drug more polar.

[Note: Ionisation of -$SO_2NH$- is not acceptable as these drugs will all consist of this group.

**(iii)**




Sulfonamide in the active site

Structure of sulfathiazole in the anionic form.
Diagram needs to illustrate the three groups involved in interaction.

**(b)** **(i)**

$$rate = rate_{\max}\left(\frac{[S]}{[S]+K_M}\right)$$

$$rate = \frac{1}{2}rate_{\max} \text{ when } [S] = [S]_{\frac{1}{2}rate\max}$$

$$\frac{1}{2}rate_{\max} = rate_{\max}\left(\frac{[S]_{\frac{1}{2}rate\max}}{[S]_{\frac{1}{2}rate\max}+K_M}\right)$$

$$[S]_{\frac{1}{2}rate\max} + K_M = 2[S]_{\frac{1}{2}rate\max}$$

$$K_M = [S]_{\frac{1}{2}rate\max} \quad \text{shown}$$

**(ii)**

$$rate = rate_{\max}\left(\frac{[S]}{[S]+K_M}\right)$$

$$\frac{1}{rate} = \frac{[S]+K_M}{[S]\times rate_{\max}}$$

$$\frac{1}{rate} = \frac{K_M}{rate_{\max}}\frac{1}{[S]} + \frac{1}{rate_{\max}}$$

**(iii)** Graph A
Same y-intercepts (=1/$rate_{max}$) for both graphs that shows $rate_{max}$ the same.

At high [S] where 1/[S] is low, substrate is able to compete with and displace inhibitors at all the active sites. This results to the same maximum rate obtained in the presence or absence of inhibitor.
The maximum rate should be the same with or without inhibitor when all active sites are occupied by natural substrate.

**(c)** (least basic) B, C, A, D (most basic)

$N_B$ is least basic nitrogen as its lone pair of electrons can simultaneously delocalise into 2 aromatic rings as a result of continuous overlapping of the p orbital on N with the π orbitals of the 2 adjacent rings.

Amide nitrogen $N_c$, is of lower basicity than $N_A$ due to poor availability of lone pair of electrons as it can delocalise over N-C=O bonds.

$N_A$ is less basic than $N_D$ as the lone pairs on pyridine are in $sp^2$ hybridised orbitals, and are thus held more strongly to the nucleus as $sp^2$ hybridised orbitals have more s character compared to the lone pairs in $sp^3$ hybridised orbitals of the amine.

**(d)** Proton NMR

**C** does not contain any labile protons

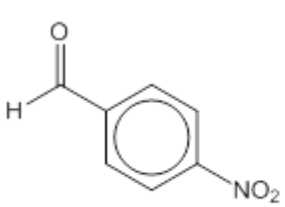
| $\delta$ / ppm | Relative intensity | Deductions |
|---|---|---|
| 8.1 | 2 | - Aromatic protons<br>- Symmetrically substituted phenyl ring |
| 8.4 | 2 | |
| 10.2 | 1 | - Highly deshielded aldehyde proton |

Chemical reactions

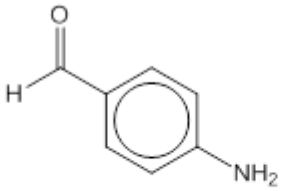
| Evidence | Type of reaction | Deduction |
|---|---|---|
| **C** reacts with Sn / conc HC*l* to form **D** | Reduction | - **C** contains a nitrobenzene<br>- **D** contains a phenylamine |
| Both **D** and **F** dissolve in dilute acid. | Acid-base / neutralisation | - Both **D** and **F** contain basic amine groups |
| Both **E** and **F** react with Na. | Redox | - Both **E** and **F** contain alcohol groups |
| Both **E** and **F** do not react with NaOH. | Acid-base / neutralisation | |
| Both **C** and **D** react with Tollen's regent to give a silver mirror. | Oxidation | - Both **C** and **D** contain aldehyde functional groups |

$M_r$ of **F**

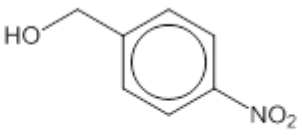
- **C** only contains 5 protons and 1 aromatic ring
- The chemical formula of **F** is $C_7H_{15}NO$.



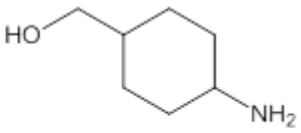
**C**



**D**



**E**



**F**