H3 Pharmaceutical Chemistry (9812)
2017 Preliminary Examination

1 (a) (i)

Non–Narcotics	**Narcotics**
Paracetamol	Codeine
Aspirin	
Diflunisal	

(ii) A narcotic analgesic is a substance that depresses the activity of the central nervous system (CNS) affecting the brain's capacity to sense pain.

***(Alternative answer:** by binding with pain receptors in the brain and blocking transmission of pain signals between brain cells.)*

A non-narcotic analgesic act as inhibitor of the cyclo-oxygenase (COX) enzyme. This prevents the formation of prostaglandins that send pain messages to the brain.

(iii) Prolonged consumption of aspirin inhibits cyclo-oxygenase, inhibiting the production of stomach lining (gastric mucosa). Hence, exposing the stomach wall and its associated blood supply to attack by strong acid causing ulcers and bleeding respectively.

(iv) Any 2 of the following:

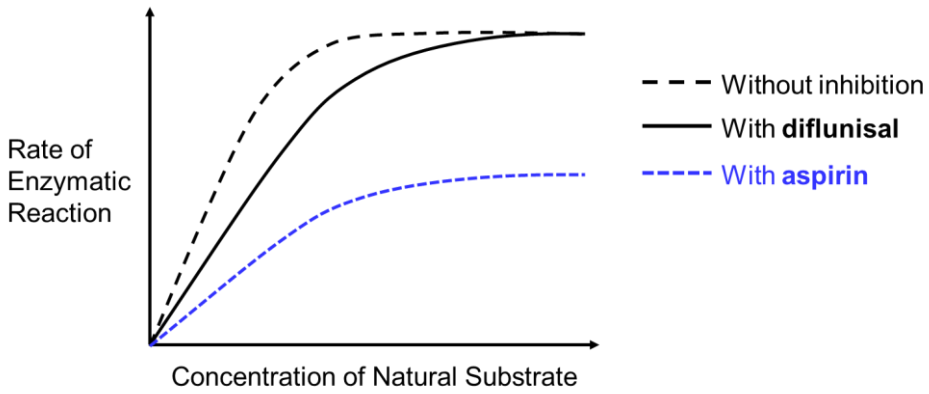
- Paracetamol is safe for children below age of 12 (but dosage has to be different)
- Less irritating sensation than aspirin
- Does not cause blood thinning or prevents clot or prolonged bleeding
- Used when patient has stomach ulcer
- Used when anti–inflammatory action is not required.
- As alternative for patients who are allergic to salicylate derivatives

(v) Competitive reversible inhibition/inhibitor.

With increasing [natural substrate], there is an increased competition by the natural substrate for active site of enzyme, increasing the rate of enzymatic reactions.

At high [substrate], the rate of enzymatic reaction with diflunisal is the same as that without application of the drug indicating natural substrates out compete the diflunisal for the active sites of the enzyme.

(vi)



The rate of enzymatic reaction with aspirin still increases with increasing [natural substrate], **however**, the maximum rate is lower than the case of diflunisal.

This is because aspirin is a non-competitive irreversible inhibitor of COX enzymes, where the drug is permanently bound to the enzyme blocking the access of the natural substrate reducing the maximum reaction possible.

(b) **(i)**

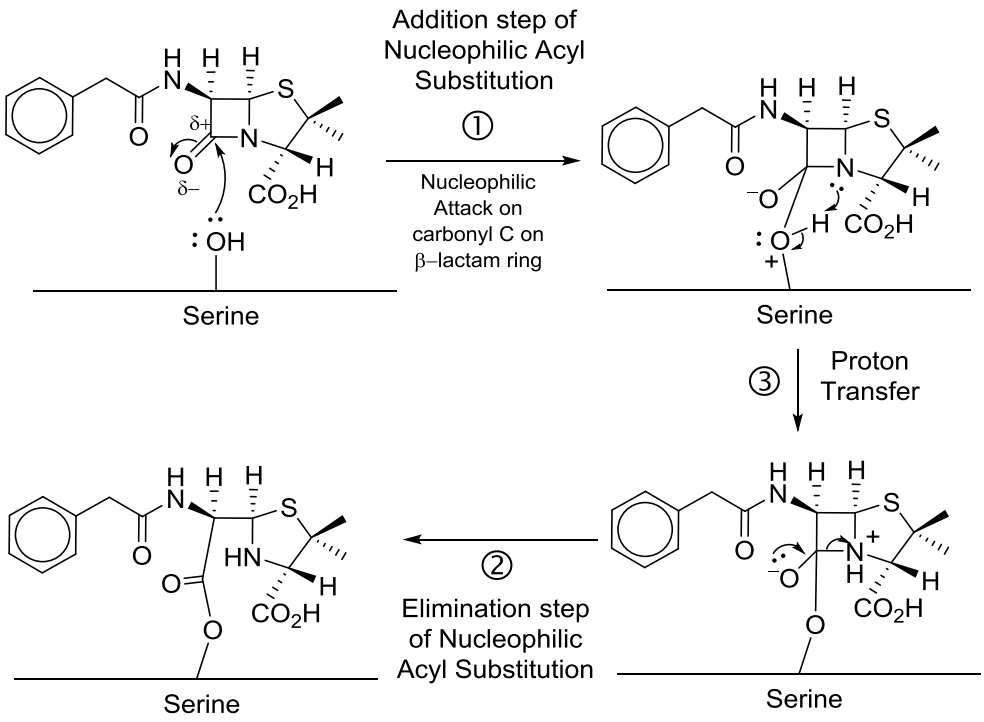
tertiary amine	:	ionic bonding/ion–dipole interaction/ionic interaction
phenolic –OH	:	hydrogen bonding
benzene ring	:	VDWs forces/Hydrophobic interaction

(ii) 6-acetylmorphine is less polar than morphine as one of the polar –OH group is masked as ester. Diamorphine has two polar groups masked as esters making it the least polar among the 3 drugs**.** Hence, diamorphine is most efficient in crossing the non–polar blood–brain barrier and in greater concentration, followed by 6–acetylmorphine and least for morphine**.**

However, 3–acetylmorphine has greater analgesic effect than diamorphine as the phenolic –OH that is needed for binding to invoke analgesic effect is free and will interact immediately with the receptors. However, the 3-acetyl group on the phenol of diamorphine has to be first hydrolysed by esterases in the brain before interacting with the receptors, hence lesser time and lower effect.

- **Compare and link structure to polarity of molecule**
- **Compare efficiency in crossing blood–brain barrier**
- **Free phenolic –OH allows immediate interaction with receptors**
- **Esters need to be broken down first before interaction so reduced effectiveness**

2 (a) (i)



Nucleophilic Acyl Substitution ① + ②
Proton Transfer ③
Correct intermediates

(ii) Penicillin <u>binds irreversibly</u> to the transpeptidase enzyme in bacteria, thus inhibits the formation of structural cross-links (pentaglycine bridge) between peptide chains in (the final stage of) bacterial cell wall biosynthesis. Bacterial cell wall becomes fragile and cell lysis occurs (<u>in low osmotic pressure solutions</u>) and this eventually kills the bacteria.

(iii) The <u>bulky</u> penicillin molecule poses a steric hindrance to the water molecule/ blocks access of water molecule to the active site.

(iv) The β–lactam ring of penicillin G can be easily <u>hydrolysed under the acidic condition</u> of the stomach. This is due to <u>high ring strain</u> in the 4-membered ring, <u>the highly reactive β–lactam carbonyl</u> group and influence of the <u>acyl side</u> chain.

(b) (i) <u>Bulky 2-methoxy groups</u> on the aromatic ring of methicillin act as steric shields which prevents it from binding <u>effectively</u> to active site of penicillase (or β–lactamases), thus methicillin is not hydrolysed to the inactive form, penicilloic acid, by bacterial enzyme.

(ii) Antibacterial activity of the analogue would be higher than methicillin. The analogue is expected to have greater resistance to enzymatic hydrolysis by β–lactamases since the larger ethoxy group provides a larger steric shield.

Or,

Antibacterial activity of the analogue would be lower *t*han methicillin because larger steric shield may hinder its ability to attach to the transpeptidase enzyme, thus inhibiting cell wall cross-linking to a lesser extent than methicillin itself.

(c) Penicillin V has electron–withdrawing O atom while ampicillin has the basic NH_2 group in the acyl side chain. Both these groups reduce the nucleophilic effect of the carbonyl O atom on the acyl side chain thus preventing acid-catalysed hydrolysis of the β–lactam ring in the stomach.

Penicillin G and methicillin are easily hydrolysed in the acidic stomach environment, thus cannot be taken orally (needs to be injected).

(d) The –COOH group being largely deprotonated (or predominantly $–COO^-$) under physiological pH, makes the molecule hydrophilic as it forms favorable ion-dipole interaction with water molecules.

Masking the –COOH group increases lipophilicity (hydrophobicity) of the drug so that absorption through the hydrophobic gut walls is better.

(e) Any two of the following sets. Appropriate examples must be given.

Disruption of cell metabolism:

- Sulphonamides are competitive inhibitors to the enzyme dihydropteroate synthetase**,** competing with natural substrate 4-aminobenzoic acid, disrupting the production of folic acid/ tetrahydrofolate/ coenzyme F needed for DNA synthesis.

Disruption of protein synthesis:

- Inhibits protein synthesis by binding to ribosomal RNA and inhibiting different stages of the translation process.
  - E.g. Tetracyclines (blocks tRNA binding), Chloramphenicol (blocks transfer of peptide), Aminoglycosides-Streptomycin (translocation), Macrolide-Erythromycin (translocation)

Disruption of function of plasma membrane:

- Increase permeability of the bacterial cell membrane towards cation and small hydrophilic molecules, thus upsetting the ionic balance within the cell.
- Providing a hydrophilic channel through the membrane, or by masking cations with a hydrophobic coat
  - E.g. Hydrophilic channel: Amphotericin, Gramicidin A
  - E.g. Hydrophobic coat: Valinomycin, Polymyxin B

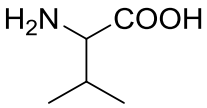
Disruption of nucleic acid transcription:

- Inhibiting topoisomerase enzyme in bacteria cells causing DNA double helix to not be unwound preventing replication and transcription
- E.g. Quinolones, fluoroquinolones

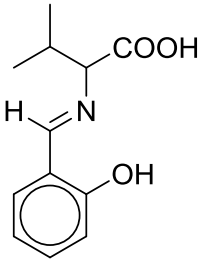
3 **(a)** **(i)** The R groups on the amino acids being alkyl groups would be expected to show signal on the ^{1}H NMR spectrum in the 0–4 region.

Chemical shift / ppm	Splitting pattern	Integral value	Deduction
1.01	doublet	6	Two equivalent –C**H**$_3$ groups joined to a –CH– group (–CH(C**H**$_3$)$_2$)
2.20	multiplet	1	–C**H** attached to two –C**H**$_3$ groups (–C**H**(CH$_3$)$_2$)
3.99	doublet	1	–C**H** attached to –CH(CH$_3$)$_2$ group and to electron withdrawing –N and –COOH group

The only amino acid with R group which will give such pattern will be:



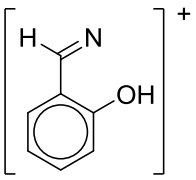
(ii) Schiff base **A**:



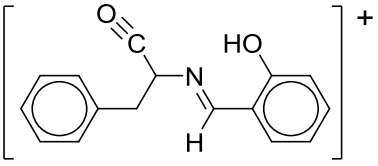
(iii) The two singlet peaks at 5.00 and 11.00 corresponding to labile protons of phenolic –OH and –COOH will be diminished or disappear completely upon undergo proton exchange with D_2O.

(b) **(i)**

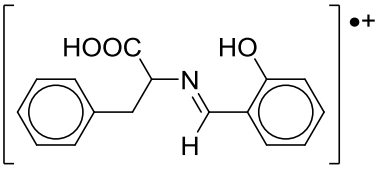
m/e = 120



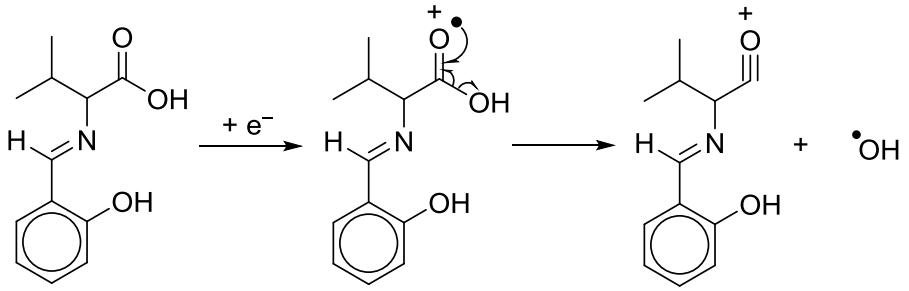
m/e = 252



m/e = 269



(ii)



Correct use of half arrows
Correct structures drawn

(c) **(i)** UV spectroscopy is used to detect organic compounds with <u>extensive conjugation of π electrons</u>. Non–bonding electron (n) or π electrons absorbs UV radiation of the electromagnetic spectrum when excited and promote from π → π*, (*or* n → π*, *n*→σ*) molecular orbitals .

Compound with a more extensive conjugated system of delocalized π electrons, would have a smaller energy gap between the π and the π* molecular orbitals. Hence, these compounds will absorb at a larger λ_{max}.

(ii) Presence of more extended π-conjugated system in **C** resulting in an absorption at lower energy (longer wavelength) resulting in bathochromic shift/ red shift/ shift to a longer wavelength allows additional peak to be observed within the range of the spectrometer for **C**.

(iii) $A_{358,mixture} = A_{358,\mathbf{C}} + A_{358,\mathbf{D}}$

$0.78 = 17200[\mathbf{C}](1) + \frac{0.24}{0.68}(19300)[\mathbf{D}](1) = 17200[\mathbf{C}] + 6812[\mathbf{D}]$

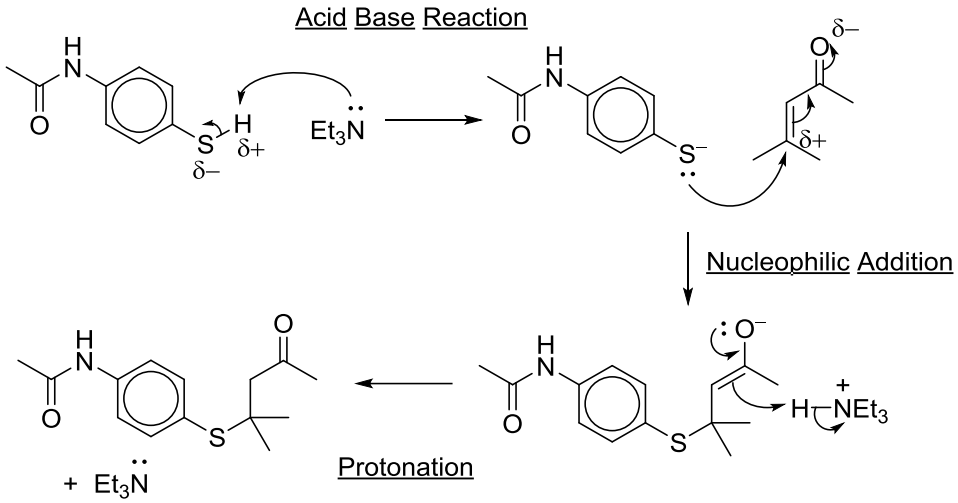
$A_{394,mixture} = A_{394,\mathbf{C}} + A_{394,\mathbf{D}}$

$0.92 = \frac{0.18}{0.53}(17200)[\mathbf{C}](1) + 19300[\mathbf{D}](1) = 5842[\mathbf{C}] + 19300[\mathbf{D}]$

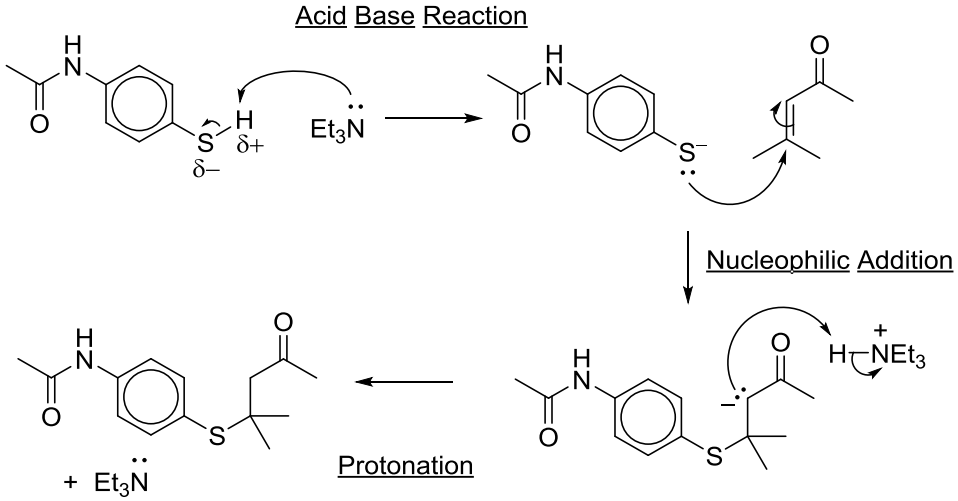
Solving the two equations will give $[\mathbf{C}] = 3.01 \times 10^{-5}$ mol dm^{-3}
and $[\mathbf{D}] = 3.86 \times 10^{-5}$ mol dm^{-3}

(iv) **C** and **D** are the **<u>only</u>** two substances which absorb radiation at 358 nm and 394 nm.

4 (a) (i) Preferred Mechanism



Alternate answer:

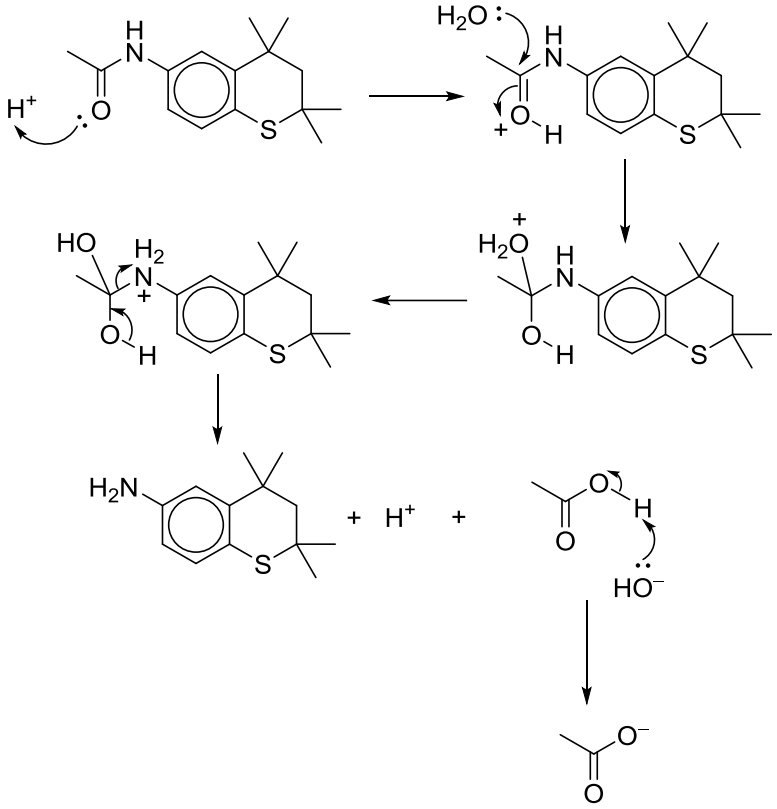


Acid Base reaction
Nucleophilic addiion reaction
Protonation to restore carbonyl

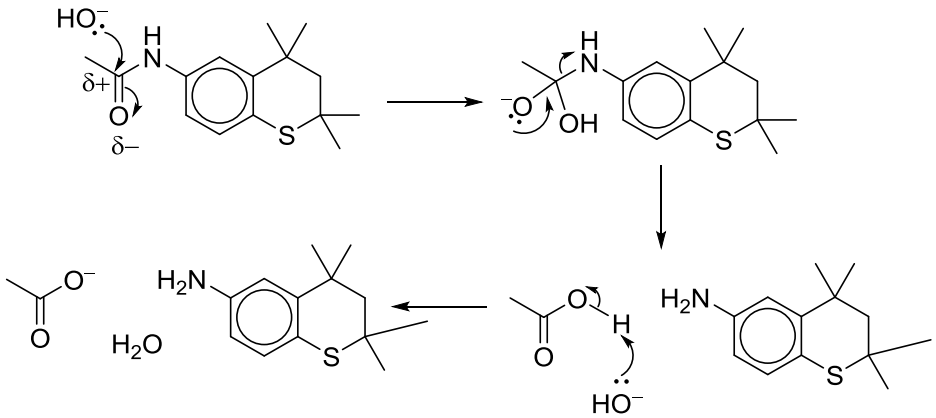
(ii) The amide group in compound **A** serves as a protecting group to prevent competition with the thiol group in step 1 and also with the benzene in step 3, resulting in side reactions.

(iii) Dil. H_2SO_4, (prolonged) heating / dil NaOH, (prolonged) heating

(iv) Acid–catalysed Hydrolysis



Base–catalysed Hydrolysis



Points to look out for:

- Acid catalysis – Protonation and regeneration of H^+
- Correct hydrolysis sequence
- Proton transfer
- Correct use of arrow
- Correct charge and dipole
- Correct intermediate structure

(b) Being metabolized into a molecule with higher hydrophilicity allows the drug dissolve in and **transported** by blood and plasma to the target cancer cell. This increases the level of drug availability.

(c) **(i)** In normal-phase HPLC, the polar silica particles serve as the stationary phase. Non–polar solvent (or low polarity solvent) is used as the mobile phase in this mode of chromatography. The solutes are dissolved in the solvent and carried through the column.

The most polar solute will form a stronger interaction with the polar stationary phase and be eluted out last (longer retention time). The least polar solute will be the first to be eluted out of the column.

(ii) Due to the presence of conjugated pi electron group in the benzene ring and –NC(=S)–, a UV detector will be a suitable detection method.

(iii) Peak 1: SHetA2
Peak 2: **L**
Peak 3: **K**

(iv) Relative composition of:
I (SHetA2) – 34.1/0.54 = 63.1
II (**L**) – 19.2/0.37 = 51.9
III (**K**) – 5.8/0.23 = 25.2

% composition of **I** = 63.1/140.2 = 45.0%

(v) Compound such as **K** may be too polar to dissolve in the non–polar solvent and may have long retention time due to strong interaction with the stationary phase. Hence, normal phased HPLC is not suitable.

Reverse phased HPLC should be used instead.

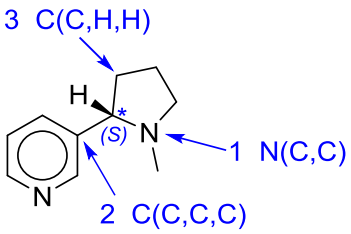
5 (a) (i) Acts as an agonist at the nicotinic acetylcholine receptors (nAChR), increasing the level of adrenaline, which in turns result in elevated energy levels, heart rate, blood pressure and respiration rate.

Dopamine level is also increased, generating a feeling of pleasure.

(ii) Drug addiction is partly attributed to the increased level of dopamine at the reward pathway in the brain which generates a sense of pleasure. Nicotine depresses the brain ability to experience pleasure and users gradually need **regular intake** and **higher dosage** of nicotine to achieve the same stimulatory effects.

***(Alterative answer:** As an agonist, nicotine will **continuously** stimulate the dopaminergic and cholinergic receptors. To maintain a steady level of nervous transmission, the body will reduce the number of receptors at the post–synaptic nerves to reduce stimulation. This decrease in receptors will result in a need of **higher drug dosage** and **regular intake** of the drug **for** same pleasuring effect to be felt.)*

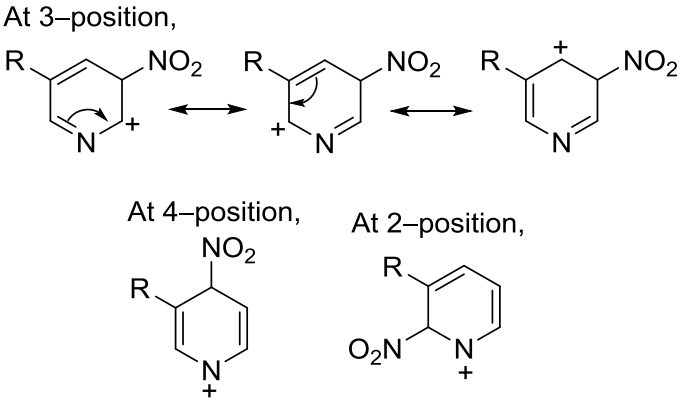
(iii)



The priorities are in clockwise direction, but as the lowest priority group is facing the reader, the stereochemistry is **S.**

(iv) Due to the electron withdrawing effect of the electronegative nitrogen**,** the pyridine is deactivated towards electrophilic substitution.

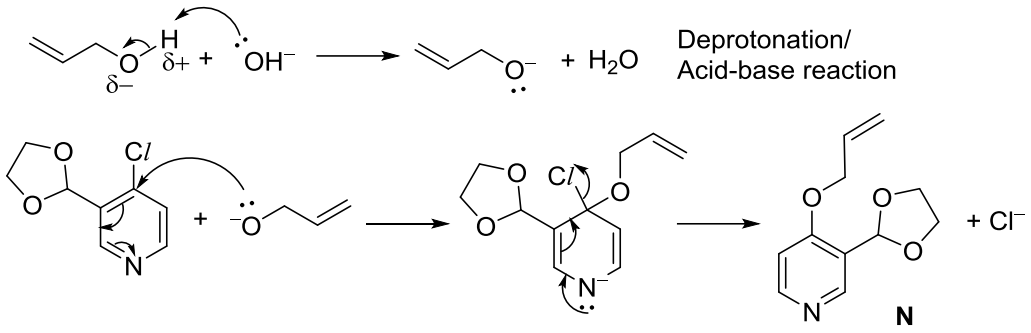
(v)



From the canonical structures shown above, 3–position is favoured as there are no instance where N has only 6 electrons.

(vi) Nucleophilic aromatic substitution

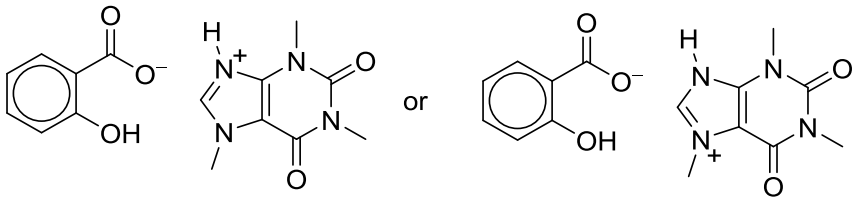
(vii)



Nucleophilic Aromatic Substitution

(b) **(i)** Acid–base reaction

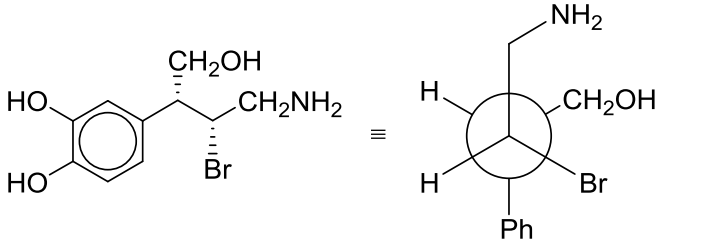
(ii)

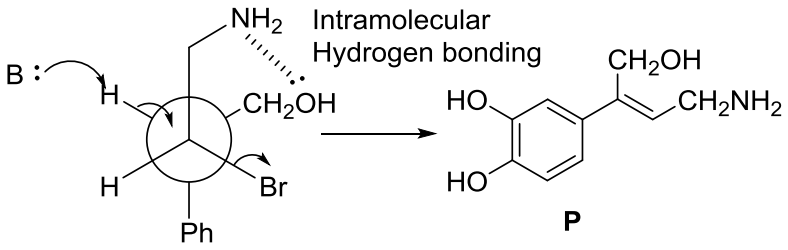


(c) **(i)** **Any 3*

Adrenaline	**Amphetamine**
Rapid metabolism [mins]	Slow metabolism [hrs/days]
No effect on appetite	Suppresses appetite
No effect on sleep	Disrupts sleep patterns
No direct effect on dopamine and serotonine levels	Releases and elevates dopamine and serotonine

(ii) 2nd Order reaction implies that this is a E2 elimination process.





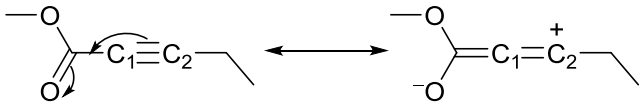
E2 mechanism
Must adopt an antiperiplanar configuration

6 **(a)** From experiment **1** and **2**, it can be observed that atropine can dissolve in both hexane and water but has greater solubility in water than in hexane, hence when ground in water before extraction with hexane in **1**, it will remain dissolve in water rather than crossing over to the hexane phase. But in absence of water (experiment **2**), it can dissolve in hexane.

Addition of excess HC*l* in step **3** resulted in zero activity as the atropine reacts with the H^+ give a positively charged species which remained dissolved in the aqueous layer, rather than moving into the hexane layer. Hence, atropine was not present in the hexane layer for any pharmacological effects. This indicates that atropine is basic in nature. This is further supported by the very high activity of solution **4**. The addition of NaOH in the 3rd step free up the protonated basic group to its neutral form so that it can be extracted by hexane.

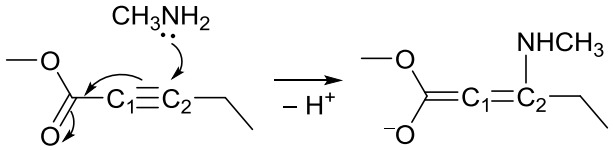
(b) **(i)**

- C_2 is more electron deficient than C_1 as seen from the resonance shown below.



- By using C_2 rather than C_1 as the electrophilic center, an aromatic pyrrole ring is formed. Aromatic compounds have added stability and more likely to be formed. [If C_1 were to be attacked there is no aromatic ring formed.]

- C_2 is preferred over C_1 as the electrophilic center because it has a better electron sink (the carbonyl oxygen in the ester; compared to C_2 as the electron sink.)



(ii) Pseudotropine is capable of intramolecular hydrogen bonding while tropine is not.

(iii) The reducing agent can only approach the ketone from its top face. There is steric hindrance at its bottom face.

(c) **(i)** Tetramethylsilane (TMS)

(ii) TMS is used as the <u>reference compound</u> at 0.0 ppm as it gives a strong singlet signal even *at low concentrations* due to its <u>twelve highly deshielded chemically equivalent protons</u>.

(iii) ' * ' denotes compulsory data of deduction

M_r of **T** = 218

*No. of O atoms = $\frac{218 \times 0.220}{16} = 3$

*N. of C atoms = $\frac{100}{1.1}\left(\frac{9.5}{67.1}\right) = 13$

*NMR data (Max 5 marks)

δ	Splitting pattern	Integral	Deduction
1.54	doublet	3	–CHC**H**$_3$ group
2.90	doublet	2	–CHC**H**$_2$– group
3.74	singlet	3	–C**H**$_3$ group attached to electronegative O atom (more deshielded), hence higher ppm.
3.90	triplet	1	–C**H**CH$_2$– group. –CH– bonded to aromatic ring.
5.57	quartet	1	–C=C**H**(CH$_3$) group. Presence of C=C supported by IR peak at 1650 cm^{-1}.
6.93	doublet	2	Protons on aromatic benzene group. Since only 2 doublets, 1,4-disubstituted bezene.
7.29	doublet	2	

Other acceptable points:

- **Lactone functional group**
  –COOH bond is formed when compound **U** undergoes acidic hydrolysis. Ester is present in the molecule. Since only 1 organic compound is present at the end of the hydrolysis, compound **U** contains a lactone. This is supported by the IR peak at 1725 cm^{-1} which indicates the presence of C=O group.

- **Ether functional group**
  Compound **U** gives a phenol derivatives (indicated by purple colouration when neutral FeC*l*$_3$(aq)) is added to **W** a product from the reaction with HI. This suggest acidic cleavage of ether occurred.

- **Alkene functional group**
  Compound **U** reacts with Br$_2$(aq) despite having phenol –OH masked as an ether. Alkene is present in the compound of **U**.

*Structure of **U**