



CANDIDATE  
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CT GROUP 13S

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## PHARMACEUTICAL CHEMISTRY

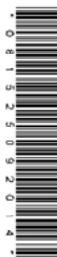
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Paper 1

25 September 2014

2 hours 30 minutes

Additional Materials:      Answer Paper  
   Insert  
   Data Booklet



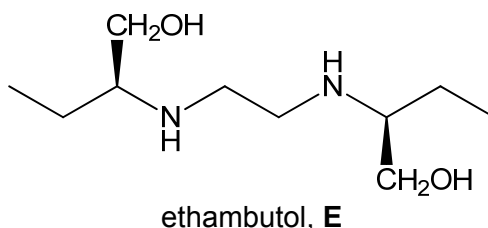
### READ THESE INSTRUCTIONS FIRST

Write your index number, name and CT on all the work you hand in.  
Begin each question on a **fresh** sheet of writing paper. A **nil return** is necessary for any unattempted question.  
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.

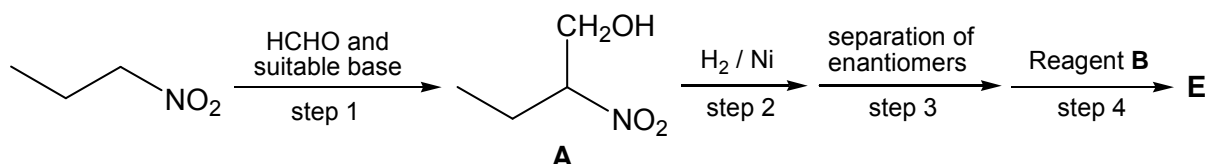
Answer any **five** questions.  
The Insert provides the spectra required in question 3(c)(iv),(v).  
At the end of the examination, fasten all your work securely together.

The number of marks is given in brackets [ ] at the end of each question or part question.  
You may use a calculator.  
You are reminded of the need for good English and clear presentation in your answers.

1 Ethambutol (**E**) is an anti-bacterial drug used to treat tuberculosis.

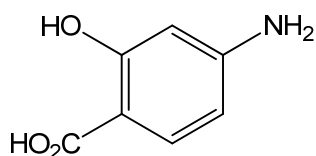


(a) Ethambutol may be synthesised as follows.

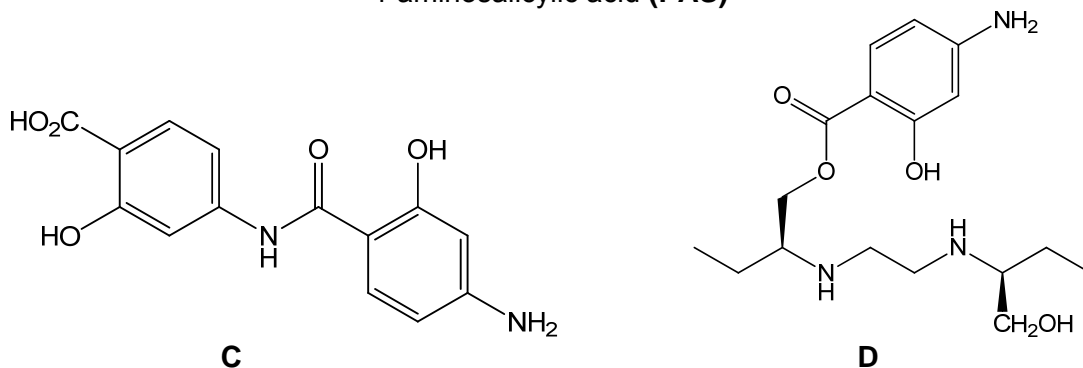


- (i) Suggest a mechanism for step 1, consistent with the observation that a racemic mixture of **A** was formed. [2]
- (ii) Step 3 involves the use of (+)-tartaric acid. Briefly describe the method used for separation of enantiomers in this step. [2]
- (iii) Suggest the structure of reagent **B**. [1]

4-aminosalicylic acid (**PAS**) and its prodrugs **C** and **D** are also antibacterials used for tuberculosis treatment. In particular, **C** is obtained by combining two molecules of **PAS**.



4-aminosalicylic acid (**PAS**)



- (b) (i) What do you understand by the term *prodrug*? [1]
- (ii) Similar to many penicillins, **PAS** can cause the undesirable side-effect of diarrhoea. However, this side-effect is appreciably reduced in **C**. Suggest an explanation. [2]
- (iii) In synthesising **C** from **PAS**, a C=O stretch at  $1590\text{ cm}^{-1}$  was observed in the IR spectrum of the product, showing that **C** has been formed. Explain the relatively low wavenumber for the C=O stretch with the aid of a suitable diagram. [1]
- (iv) Some tuberculosis-causing bacteria have developed a resistance to **PAS**. Explain why although **C** is completely ineffective against such bacteria, **D** still shows anti-bacterial activity in vivo. [1]



An experiment was conducted to study the in-vitro hydrolysis of **C**. A  $5 \mu\text{g cm}^{-3}$  solution of **C** ( $M_r=288$ ) was prepared in synthetic gastric fluid and its absorbance was monitored at a particular wavelength where the molar absorptivities of **C** and **PAS** may be taken to be equal. The absorbance was found to be 0.160 and 0.260 at time  $t = 0$  and 30 min respectively.

- (c) (i) Find the molar absorptivity of **C** at the wavelength of the experiment. [1]
- (ii) Find the percentage of **C** that had been hydrolysed by time  $t = 30$  min. [2]

**E** and **PAS** are examples of competitive inhibitors of enzymes.

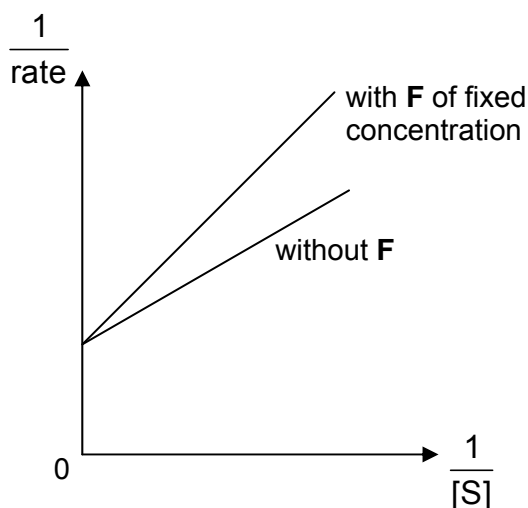
- (d) Suggest the structural features of ethambutol (**E**) that might allow it to bind to relevant amino acid residues at the active site of the enzyme. What kind of interactions would be involved? [2]

The kinetics of an enzyme-catalysed reaction may be described by the Michaelis-Menten equation:

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

where  $\text{rate}_{\max}$  is the maximum rate of reaction,  $[\text{S}]$  is the substrate concentration and  $K_M$  is a constant.

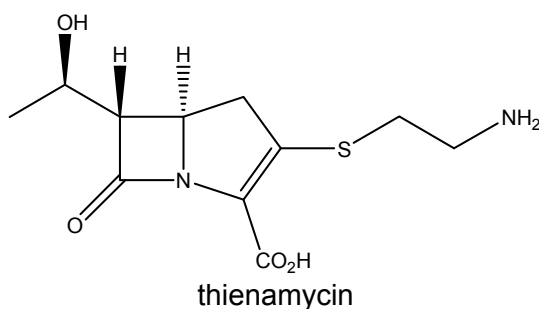
- (e) (i) Show that  $K_M$  represents the concentration of substrate at which the rate of reaction is half of its maximum. [1]
- (ii) Express the Michaelis-Menten equation in a linear form relating  $\frac{1}{\text{rate}}$  to  $\frac{1}{[\text{S}]}$ . [1]
- (iii) An experiment was conducted to investigate the rate of a particular enzyme-catalysed reaction, both with and without compound **F**. The results are shown in the following graph.



Explain why the experiment shows that compound **F** is a competitive inhibitor. [3]

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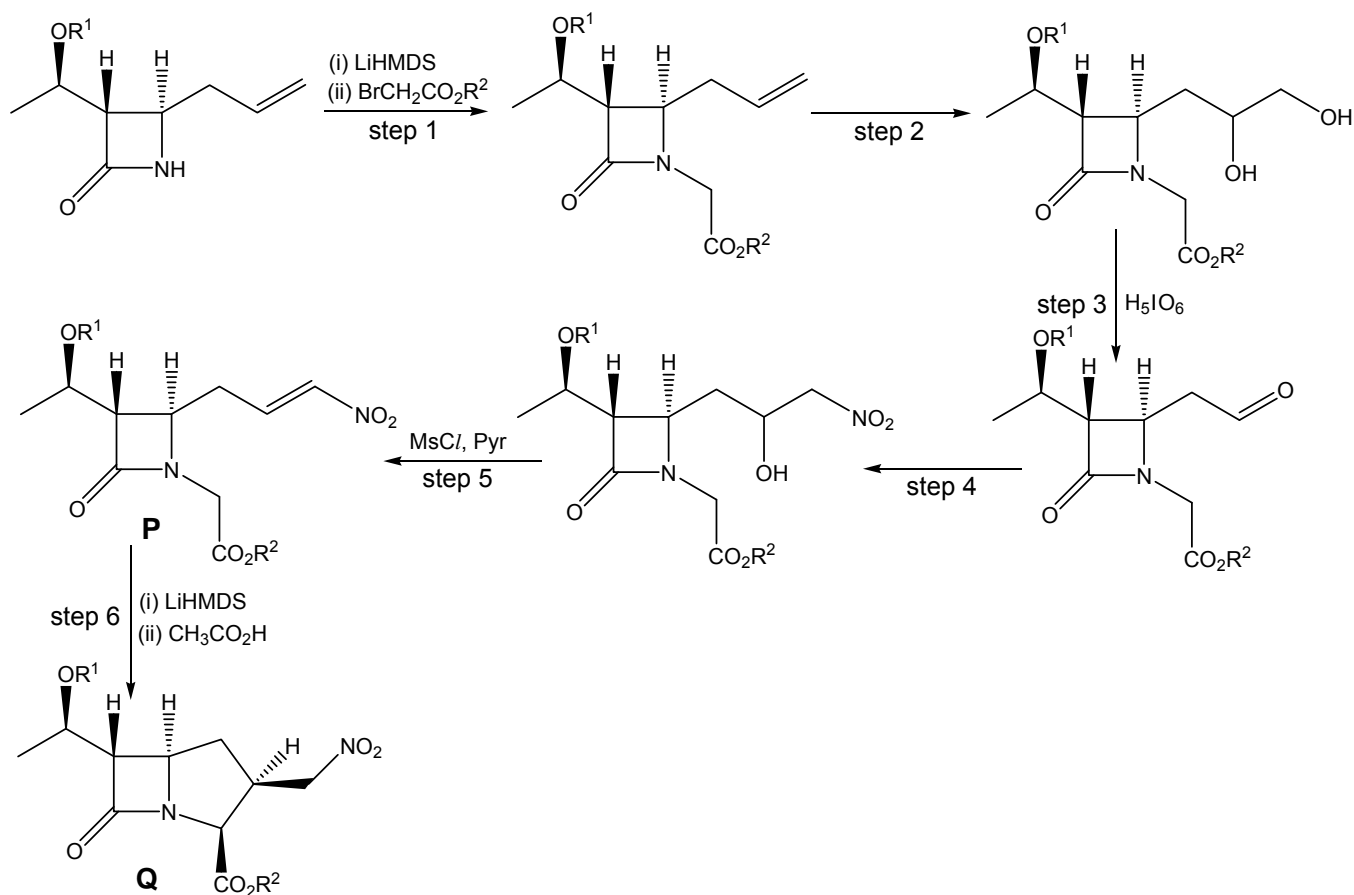
- 2 Thienamycin was discovered in fermentation broths of *Streptomyces cattleya* and showed exceptional antibacterial potency and spectrum. It disrupts the cell wall synthesis of various Gram-positive and Gram-negative bacteria.



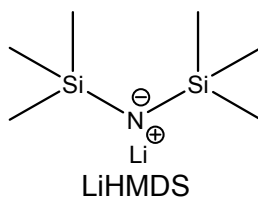
(a) State **two** other ways in which antibacterials work.

[2]

The asymmetric synthesis of thienamycin was achieved in early 1990 and the reaction scheme below shows part of the synthetic route leading to intermediate **Q**.



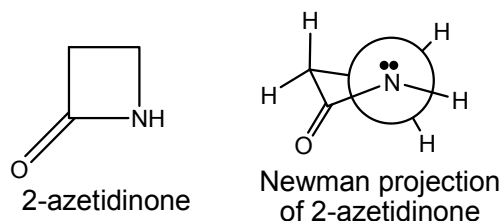
(b) (i) LiHMDS acts as a base in the initial stage and its structure can be represented as follow.



Illustrate the mechanism to step 1 of the synthesis and explain why LiHMDS is unlikely to attack the carbonyl carbon during the course of the reaction. [2]



- (ii) Suggest reagents and conditions for steps 2 and 4. [2]
- (iii) Thienamycin contains the 2-azetidinone moiety and its Newman projection is shown below.



Draw the Newman projection of **P** and **Q**.

[2]

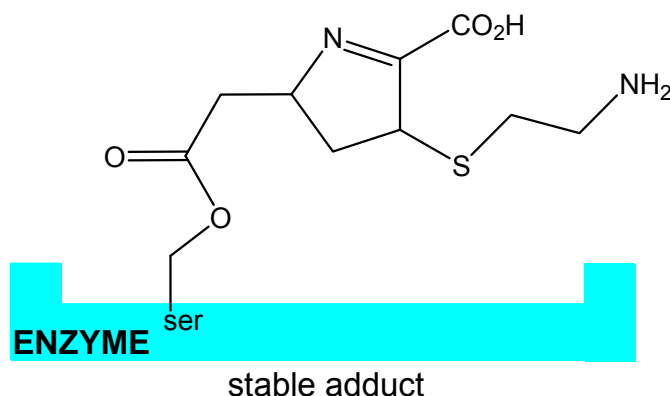
- (iv) Step 6 involves the following reactions.

- deprotonation (using LiHMDS)
- conjugate addition
- work up (using  $\text{CH}_3\text{CO}_2\text{H}$ )

Using your answer to **b(iii)**, suggest the mechanism of this transformation, showing **clearly** how the two new stereogenic centres are obtained. [2]

- (c)  $\beta$ -lactamases are a major antibiotic resistance mechanism employed by bacteria; these periplasmic enzymes hydrolyse typical  $\beta$ -lactam antibiotics, preventing the drug from reaching the penicillin binding proteins target. One unique feature of thienamycin is that not only is it able to perform its role as antibiotics, it can also act as inhibitors of certain classes of  $\beta$ -lactamases.

Upon reaction with  $\beta$ -lactamase, thienamycin releases a small molecule **Q** and forms a stable adduct shown below.



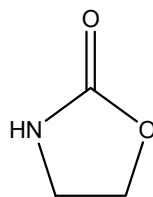
- (i) Suggest the identity of the small molecule **Q**, given that it gives a brick red precipitate when subjected to Fehling's solution. [1]

Some bacteria have been known to develop resistance against thienamycin by producing enzymes known as carbapenemases that are able to hydrolyse thienamycin. This is especially so if patients fail to complete the course of antibiotics.

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



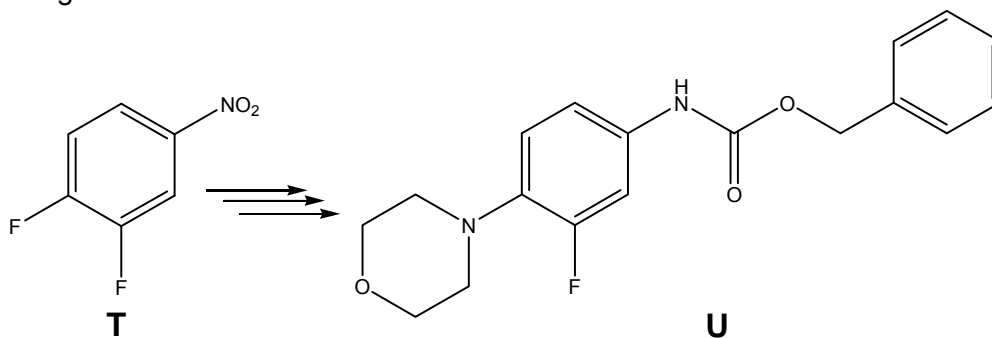
- (d) Antibiotics of last resort are drugs that are administered after all other treatment options have failed to produce an adequate response in the patient. Linezolid is one such antibiotics and it contains an oxazolidinone ring.



oxazolidinone ring

- (i) Suggest a mechanism for the acid hydrolysis of oxazolidinone. This reaction involves initial protonation and carbon dioxide is evolved after the reaction. [3]
- (ii) Explain why oxazolidinone is more susceptible to hydrolysis as compared to lactam. [1]

The commercial synthesis of linezolid requires the synthesis of an important intermediate **U**, using **T** as the starting material.



- (iii) Suggest how **U** could be synthesised from **T**, showing clearly the reagents (and conditions employed) and the intermediate compounds formed. [2]

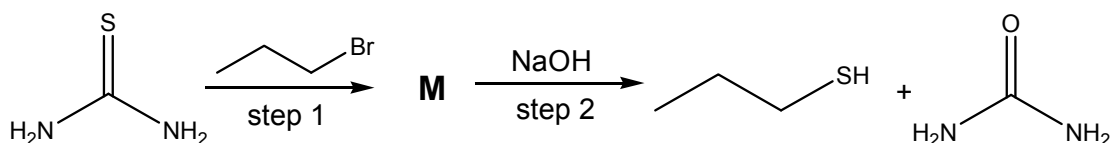
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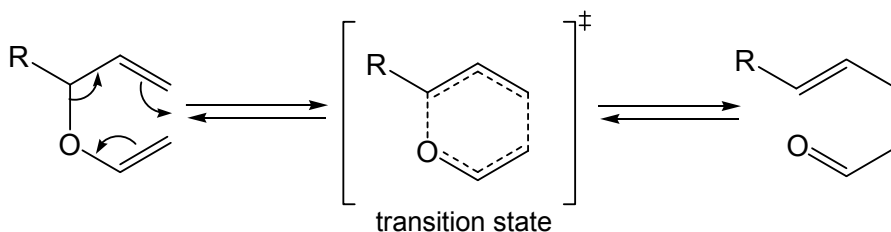
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- 3 Sulfides and disulfides are important in biological systems (e.g. synthons in natural product synthesis, protein structure and so on). Disulfides can be formed via the oxidation of thiols and thiols themselves can be prepared from thiourea.

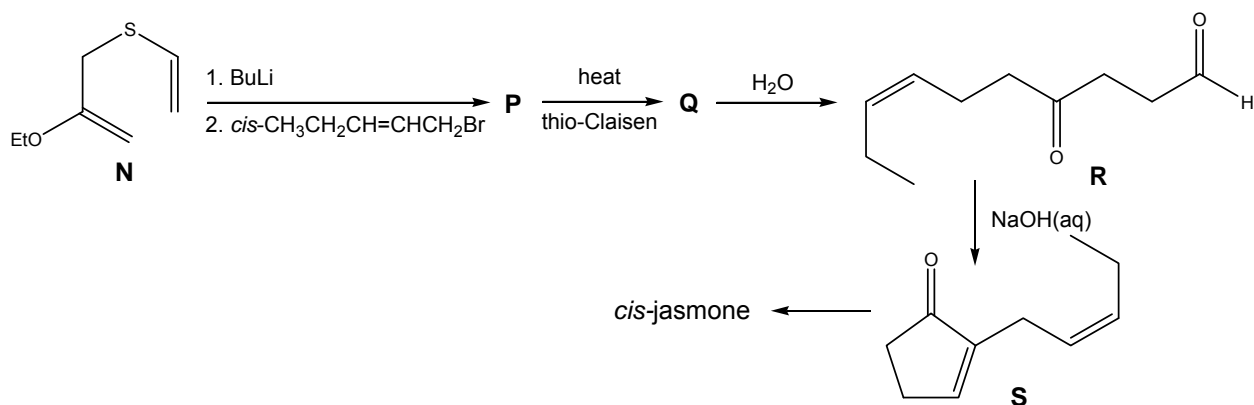
(a) The first step of the synthesis of thiols involves a nucleophilic substitution reaction followed by hydrolysis.



- (i) Draw the structure of the intermediate salt **M**. [1]
- (ii) Propose the mechanism for step 2. [2]
- (iii) When 1-bromopropane used in step 1 is replaced with 2-bromo-2-methylpropane, the reaction yields only 2-methylpropene instead of the corresponding intermediate salt. Account for this observation and support your answer with a relevant reaction mechanism. [2]
- (b) (i) By considering the relative polarisability of the relevant lone pairs, explain why thiolates are better nucleophiles than alkoxides. [2]
- (ii) Describe how propane thiol formed in (a) may be converted to ethylpropyl sulfide. [2]
- (iii) Suggest a suitable reagent for the oxidation of ethylpropyl sulfide and draw the structures of the two products you would expect. [2]
- (c) Claisen rearrangement is one of the most renowned rearrangements in organic chemistry. When heat is applied to an enol ether, it will undergo Claisen rearrangement as illustrated below.

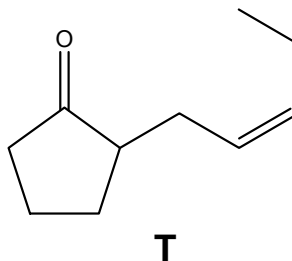


Allyl sulfides are precursors to important aliphatic natural products such as *cis*-jasmane, a volatile compound extracted from jasmine flowers. It is used widely in the perfume industry as well as in plant defence and it can be synthesised via the route shown below.





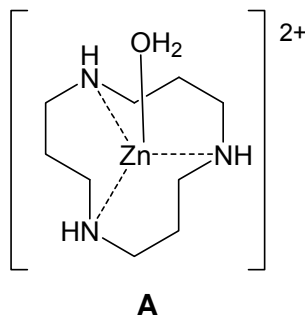
- (i) The allyl sulfide **N** is first reacted with a strong organic base, butyllithium (BuLi), forming a carbanion which is then alkylated with *cis*-CH<sub>3</sub>CH<sub>2</sub>CH=CHCH<sub>2</sub>Br to produce the compound **P**. Draw the structure of **P**. [1]
- (ii) **P** then undergoes thio-Claisen rearrangement forming **Q**. Draw the structure of **Q**. [1]
- (iii) **Q** is then hydrolysed to produce the  $\gamma$ -ketoaldehyde **R**, which subsequently undergoes a base catalysed cyclisation to form **S**. Suggest the mechanism for the formation of **S** from **R**. [3]
- (iv) The NMR spectrum of **S** (with a missing signal) is shown in the Insert. Assign **all** the signals to particular protons in the molecule by completing the table below the NMR spectrum. [3]
- (v) Compound **S** was made to undergo selective hydrogenation to give compound **T**. The IR spectrum of **S** is provided in the Insert. Predict how the C=O stretch in **S** will be different from that in **T** by drawing the peak corresponding to the C=O stretch in **T** directly onto the insert. Briefly explain your sketch by providing appropriate annotation near the peak that you have drawn. [1]



[Total: 20]

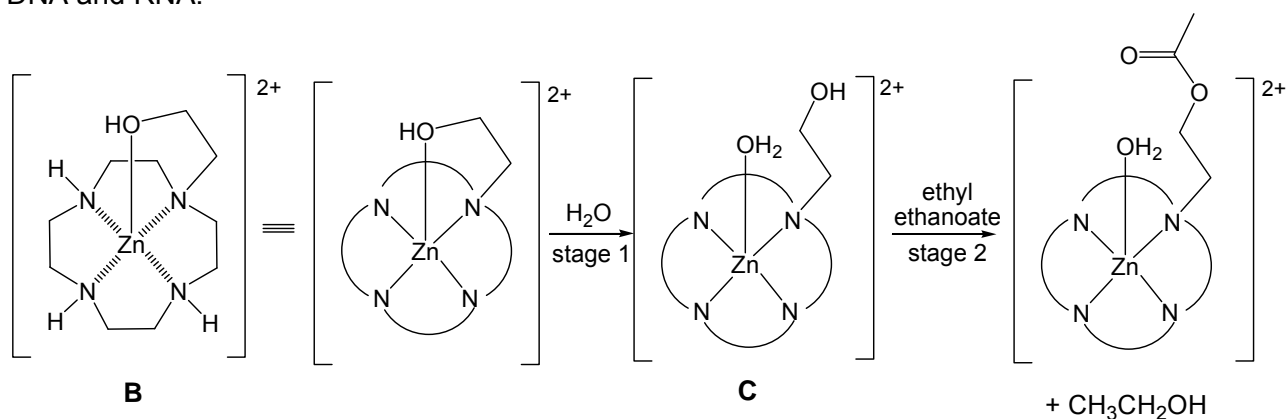


4 Complex **A** can be used extensively as enzyme mimics.



The acidity of the bound water molecule in **A** is enhanced by its coordination to the Zn metal centre ( $pK_a = 7.30$ ).

- (a) Suggest why the acidity of the water molecule is enhanced in **A**. [1]
- (b) Complex **B** is another Zn(II) complex that mimics the action of esterases. The complex hydrolyses ester groups, which is of significant interest because of the hydrolysis of phosphate esters found in DNA and RNA.



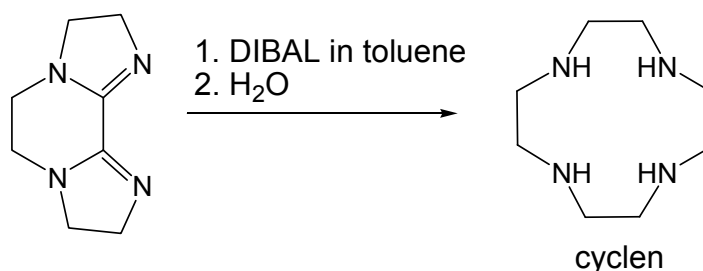
In the hydrolysis of the ester ethyl ethanoate by **B**, **B** first undergoes a ligand exchange reaction with water in stage 1 to form complex **C** ( $pK_a = 7.60$ ). The subsequent hydrolysis of the ester is described by the rate equation as follows:

$$\text{rate} = k[\mathbf{C}][\text{ethyl ethanoate}]$$

It was also found that when the side arm ( $-\text{CH}_2\text{CH}_2\text{OH}$  group on the amine) was absent, the reaction occurs ten times slower.

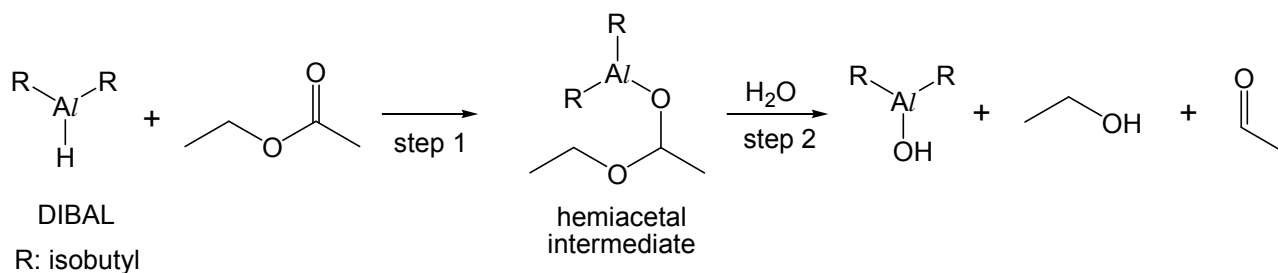
By considering the information given above, describe the mechanism in stage 2 for the hydrolysis of ethyl ethanoate starting with complex **C**, indicating the slow step clearly in your mechanism. [3]

- (c) **B** is an example of a complex formed by a cyclen derivative and Zn(II) ions. Cyclens are useful ligands that bind selectively to cations. The scheme below shows part of the synthesis of cyclen.



Diisobutyl aluminium hydride (DIBAL) is an “electrophilic” reducing agent used in the synthesis that can also reduce esters to aldehydes.

In the presence of an ester such as ethyl ethanoate, DIBAL accepts an electron pair from the ester. Subsequently, a stable hemiacetal intermediate is formed.

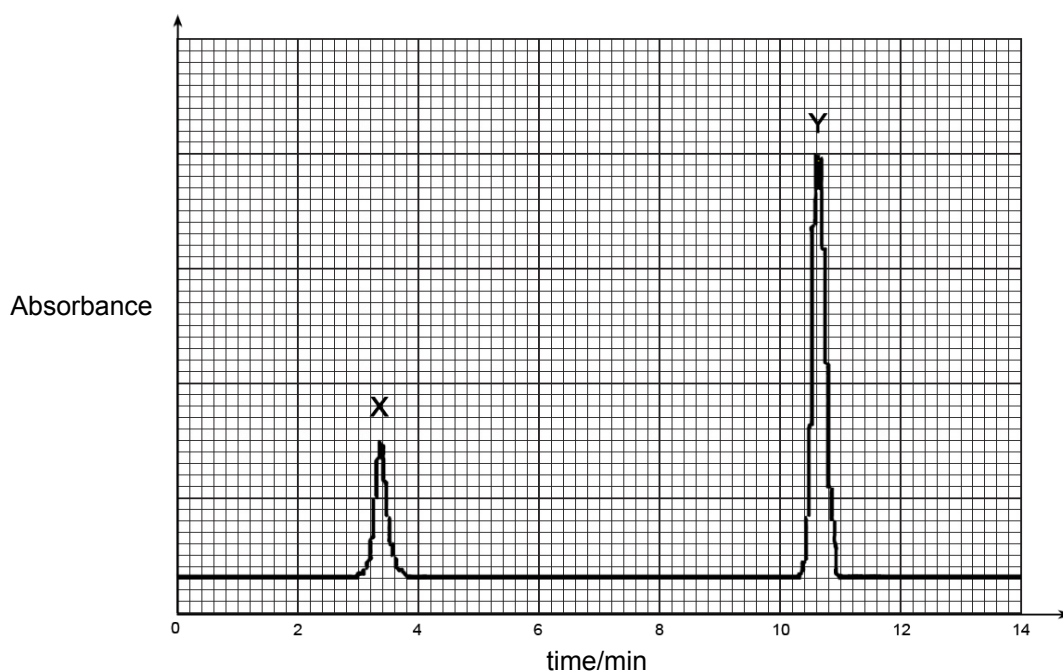


- (i) Outline the mechanism for step 1. [1]
- (ii) In step 2, the hemiacetal intermediate is hydrolysed to give ethanal. Draw the mechanism for the hydrolysis, given that the first step in the mechanism involves a nucleophilic attack on the Al centre. [2]

Ethanal is also derived from oxidation of ethanol in the body by enzymes. The determination of the small concentration of ethanal formed in the blood is of interest in the studies of alcohol effects. This can be achieved using reverse-phased HPLC with a UV spectrometry detector.

A sample of ethanal extracted from human blood was reacted with excess 2,4-dinitrophenylhydrazine (2,4-DNPH) and the resulting mixture was injected into the HPLC.

- (iii) Suggest a reason why ethanal was first reacted with 2,4-DNPH to give a hydrazone before injection into the HPLC. [1]
- (iv) The following chromatogram was obtained for the injected sample. The two peaks correspond to 2,4-DNPH and the hydrazone in the sample. [2]



Explain which peak in the HPLC chromatogram corresponds to 2,4-DNPH. [2]

- (v) Assuming that the peak areas were found to be proportional to the concentration of the compounds, determine the ratio of 2,4-DNPH to ethanal that was used in the reaction. [2]



- (d) Compound **X** ( $M_r = 432$ ) is a derivative of cyclen that contains only carbon, hydrogen, nitrogen and oxygen.

The NMR spectrum of **X** shows the following signals.

$\delta_H$	No. of protons	splitting
2.4	8	t
2.5	8	t
3.3	4	s
3.4	4	s
3.7	6	s
11.0	2	s

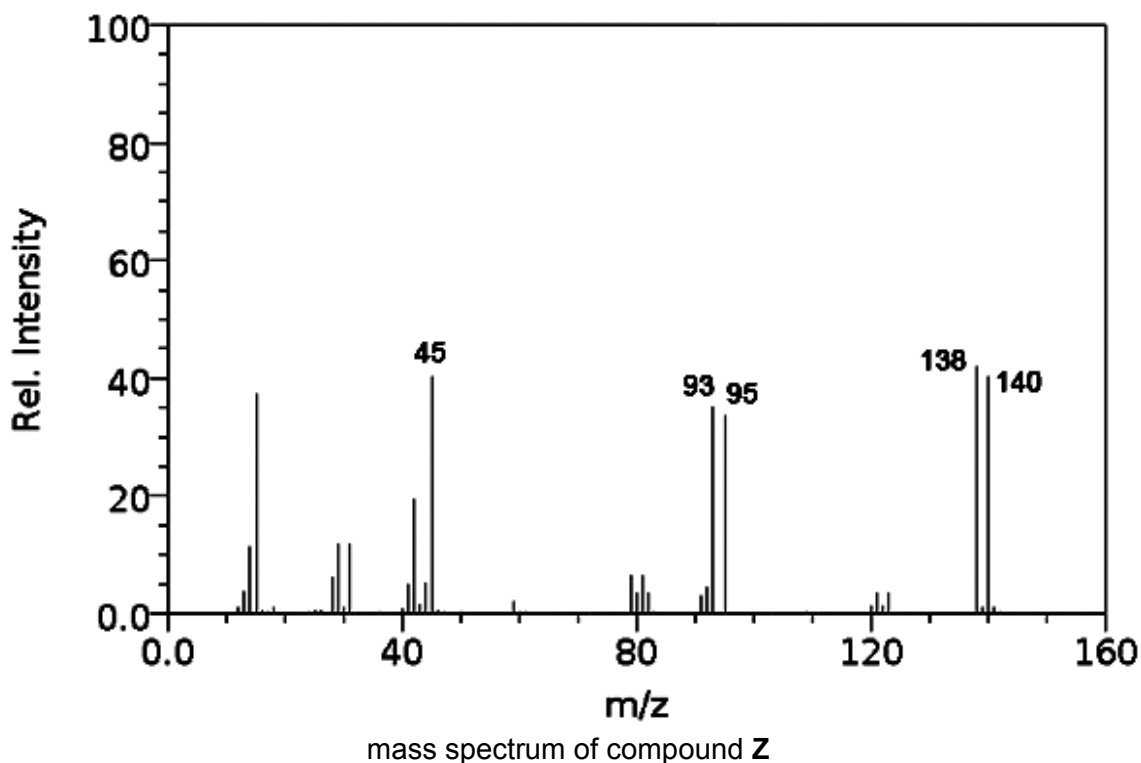
The peak at  $\delta$  11.0 disappears on shaking the sample with  $D_2O$ .

The IR spectrum of **X** also shows a strong and broad absorption at  $3200\text{ cm}^{-1}$  (O–H stretch).

Upon treatment of **X** with hot aqueous hydrochloric acid, the NMR spectrum of the compound **Y** that was formed showed several differences from that of **X**.

- The peak at  $\delta$  3.7 disappeared.
- The peak at  $\delta$  11.0 now showed an integral of 4 protons.
- The peaks at  $\delta$  2.4 and  $\delta$  2.5 have collapsed into a singlet 16-proton peak at  $\delta$  2.5.
- The peaks at  $\delta$  3.3 and  $\delta$  3.4 have collapsed into a singlet 8-proton peak at  $\delta$  3.4.

Compound **Y** can also be formed by reacting cyclen with compound **Z**. The mass spectrum of **Z** is shown below:



Interpret these data and suggest the structures of **X** and **Z**.

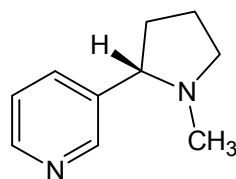
[8]

[Total: 20]





- 5 Nicotine is a natural alkaloid found in tobacco leaves where it acts as a botanical insecticide.



nicotine

- (a) (i) The  $pK_b$  values of nicotine are 6.1 and 11.0.

Explain which of the two nitrogen atoms in nicotine is more basic, and hence suggest the structure of the form in which nicotine exists at physiological pH 7.4. [2]

- (ii) The bioavailability of a drug is the fraction of an administered dose of the drug that reaches the blood circulation. When administered intravenously, the bioavailability of nicotine is 100 %.

Give two reasons to explain why the bioavailability of nicotine is only 20 % when administered orally. [2]

- (iii) Discuss the short- and long-term effects of nicotine consumption. [2]

- (b) Figure 1 shows the release of adrenaline from chromafin cells of the adrenal gland under physiological conditions (left) and in the presence of nicotine (right).

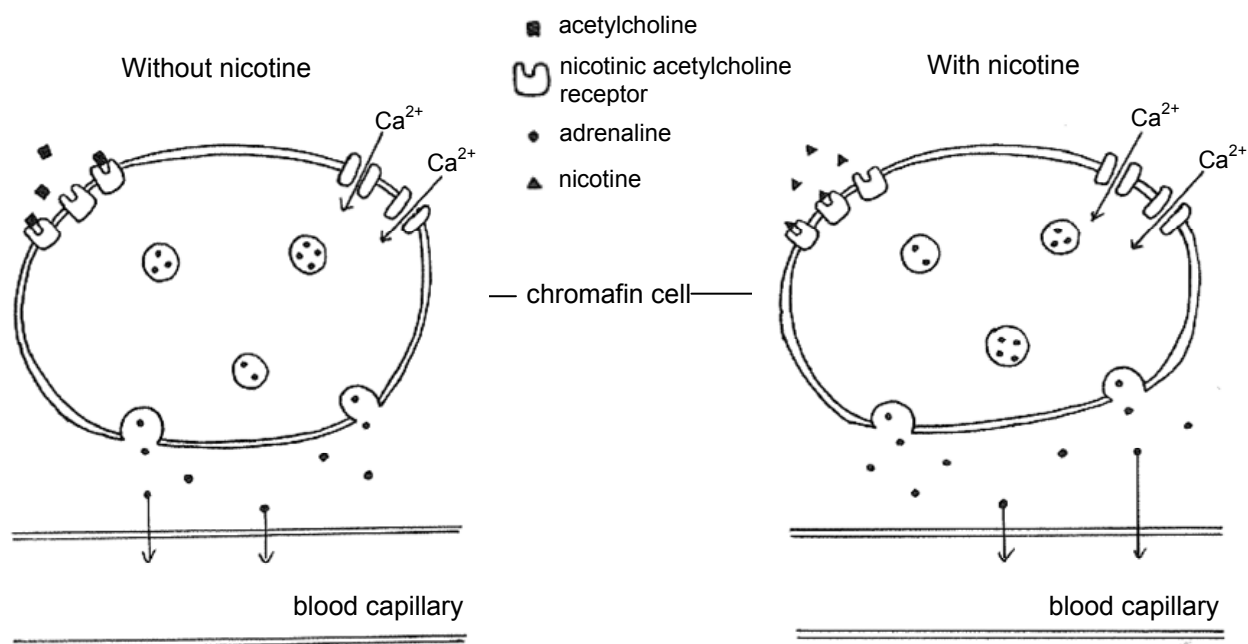


Figure 1.

- (i) With reference to Figure 1, briefly describe the mode of action of nicotine. [2]



Nicotine was found to have an effect on the transmission of impulses in dopaminergic neurons in the brain as well.

Under physiological conditions, the dopamine neurotransmitter is released from storage vesicles into the synapse upon binding of acetylcholine, *Ac*, to receptors, *nAcR*, at the pre-synaptic nerve. Eventually, the dopamine is re-absorbed into the pre-synaptic nerve via dopamine transporters, *DT*.

The process of nerve transmission is illustrated in Figure 2 (the key to the abbreviations is given below).

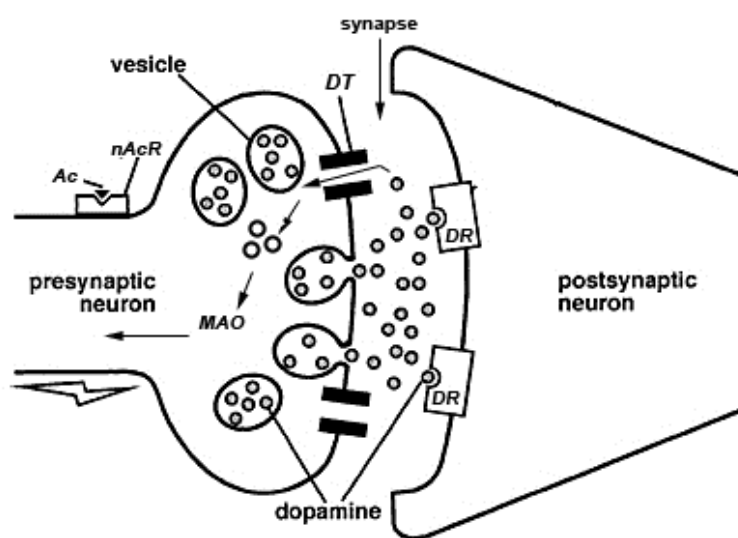


Figure 2.

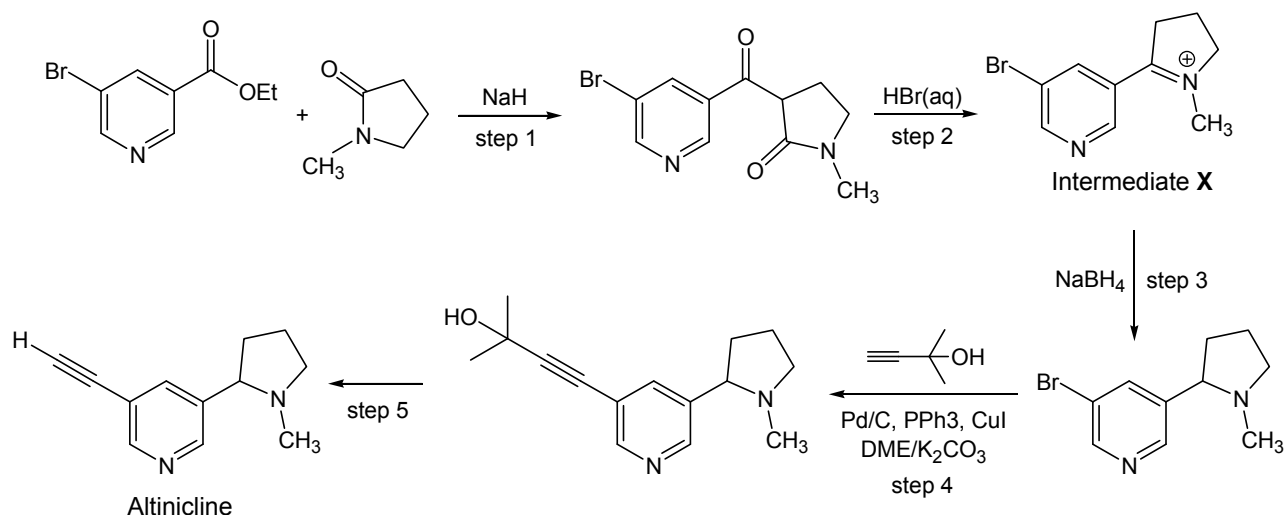
The following drugs affect the process of nerve transmission in dopaminergic neurons in the following ways:

Drug	Effect
cocaine	block presynaptic dopamine transporter, <i>DT</i>
bupropion	antagonist at nicotinic acetylcholine receptor, <i>nAcR</i>
altinicline	agonist at nicotinic acetylcholine receptor, <i>nAcR</i>
haloperidol	antagonist at dopamine receptor, <i>DR</i>
apomorphine	agonist at dopamine receptor, <i>DR</i>
nornicotine	inhibitor of the enzyme mono-amine oxidase, <i>MAO</i> , which metabolises dopamine into inactive molecules

- (ii) What is meant by the terms *agonist* and *antagonist*? [2]
- (iii) State which of the drugs above **increase** the transmission of a nerve signal. [2]



(c) The synthetic route of the nicotinic agonist, altinicline, is shown below.



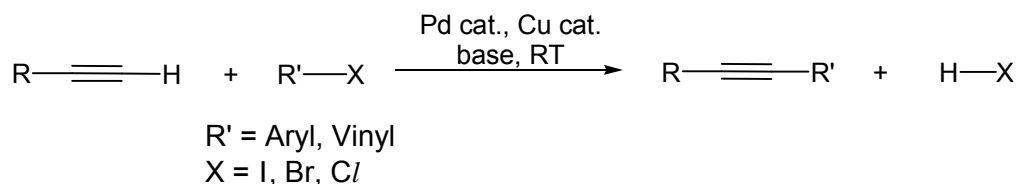
(i) State the type of reaction that has occurred in step 1. [1]

In step 2, the reaction was thought to occur via the hydrolysis of the amide followed by a decarboxylation reaction.

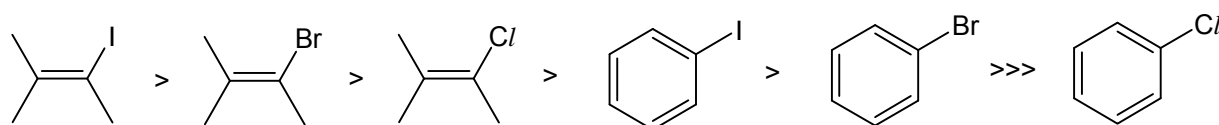
(ii) Draw the structure of the hydrolysed product. [1]

(iii) Suggest the mechanism for the formation of intermediate X from the hydrolysed product. [3]

Step 4 is an example of the Sonogashira coupling reaction which is a cross-coupling reaction used in organic synthesis to form carbon–carbon bonds. It employs a palladium catalyst to form a carbon–carbon bond between a terminal alkyne and an aryl or vinyl halide.

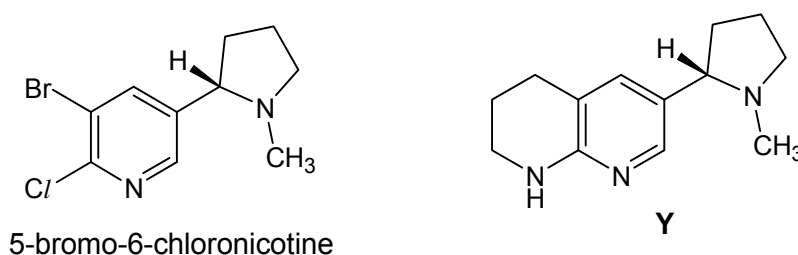


The rate of reaction of the aryl or vinyl halide varies as follows:



Similar to alkenes, alkynes can be reduced to the corresponding alkanes via catalytic reduction.

(iv) Suggest how the nicotine derivative, Y, can be synthesized from 5-bromo-6-chloronicotine. [3]



[Total: 20]





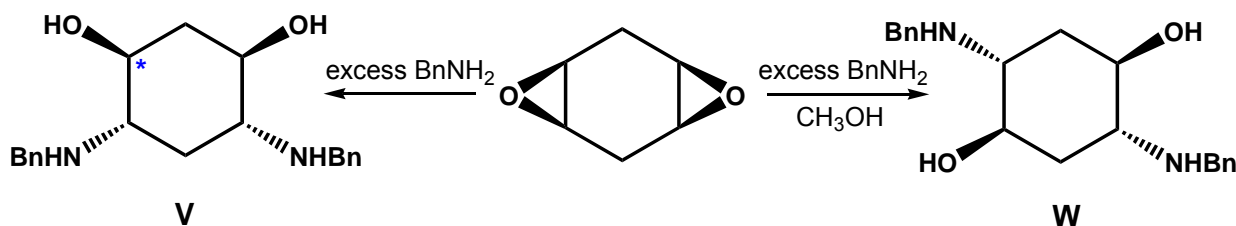


- 6 The laborious process of lead discovery and optimisation has been aided by combinatorial chemistry to generate collections of test compounds for screening. Since 2001, the emergence of "click chemistry", popularised by Nobel laureate Barry Sharpless, greatly accelerated the drug discovery process.

Click chemistry facilitates the process of drug discovery by making use of a few near-perfect chemical reactions for the synthesis and assembly of specially designed building blocks that have *high built-in energy content*. Reactions employed in click chemistry tend to be *insensitive to oxygen and water* as well.

- (a) By considering the phrases in *italics*, suggest two properties that are typical to reactions used in "click chemistry". [2]

One such reaction is the nucleophilic ring opening of 3-membered heterocycles such as epoxides as illustrated below.



Note: ( $\text{C}_6\text{H}_5\text{CH}_2-$ ) is represented by ( $\text{Bn}-$ )

- (b) (i) State the isomeric relationship between **V** and **W**. [1]
- (ii) Deduce the stereochemistry (*R* or *S*) at the carbon atom marked with an asterisk in **V**, explaining your answer. [1]
- (iii) By drawing appropriate chair conformations, deduce whether **V** or **W** is the more stable compound. [2]

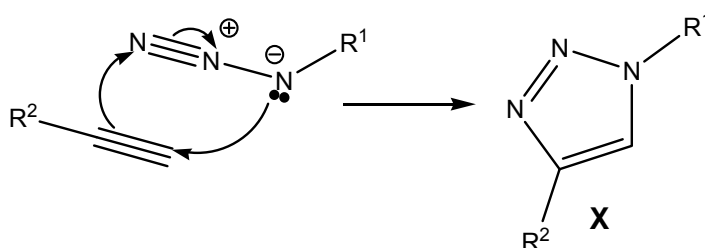
As illustrated in the reaction scheme above, when the reaction was carried out without any solvent, **V** was obtained whereas in the presence of methanol as the solvent, **W** was obtained.

- (iv) For both reactions, the first step involves the nucleophilic attack on one of the 3-membered epoxide ring to produce the same intermediate amino alcohol, with the other epoxide intact. Suggest the structure of the intermediate amino alcohol. [1]
- (v) It was postulated that the alcohol group in the intermediate amino alcohol will activate the epoxide intramolecularly when the reaction is carried out without any solvent. This results in the intermediate amino alcohol taking on a near boat-like conformation.

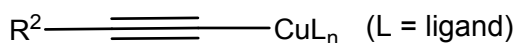
Hence illustrate the mechanism from the intermediate amino alcohol leading to **V** and explain why in the presence of methanol, **W** is the product preferentially formed. [4]



- (c) The most regularly employed reaction in click chemistry thus far is the Huisen cycloaddition as shown in the reaction mechanism below.

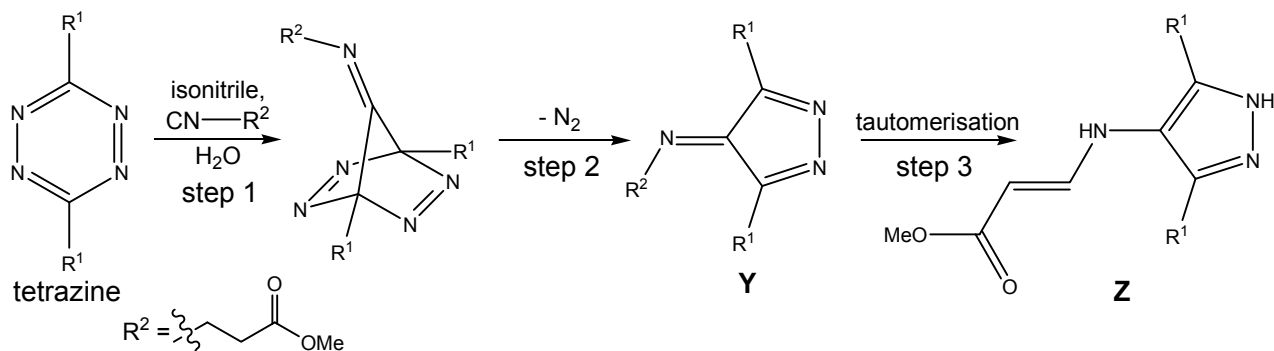


- (i) Suggest the identity of another isomer of **X** that will be formed in this reaction. [1]
- (ii) In order to control which isomer is formed from the Huisen cycloaddition, Cu(I) salt is often used as the catalyst and **X** will often be formed almost exclusively, regardless of the steric demand of  $R^1$  and  $R^2$ . It is known that the Cu(I) ion coordinates to the end of the alkyne as shown below.



Suggest why the use of Cu(I) salt gives **X** almost exclusively. [1]

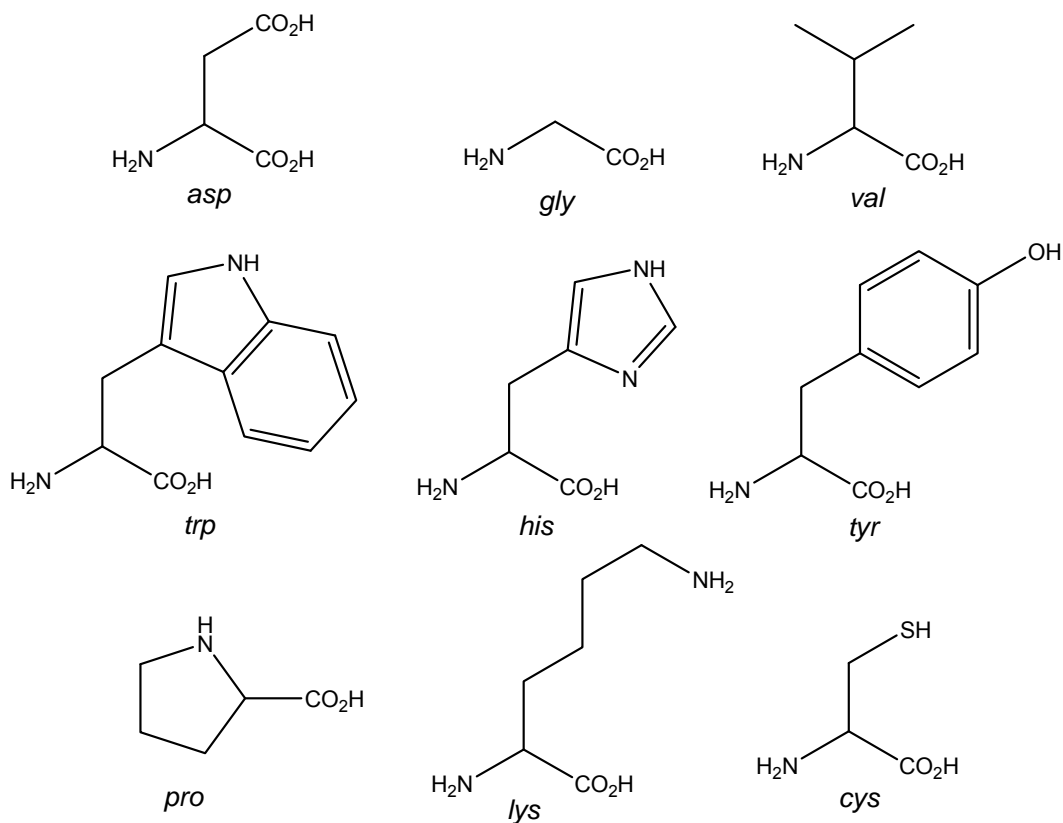
- (d) Recently, another efficient "click" reaction was identified and it involves the cycloaddition of tetrazines and isonitriles in aqueous medium. A generic scheme involving the formation of **Z** is shown below.



- (i) Use curly arrows to suggest the mechanism of step 2. [1]
- (ii) Explain the driving force which causes **Y** to quickly tautomerise to give **Z**. [1]
- (iii) It was observed via IR spectroscopy that **Z** slowly isomerises to give its *cis* analogue. By using a suitable diagram, suggest why its *cis* analogue is more stable and predict a value for its N–H stretch, explaining briefly. [2]



(e) Nine amino acids are shown below in their non-ionised forms.



Use a **selection of these** to describe how the behaviour of amino acids is influenced by the pH of the mobile phase in paper chromatography. [3]

[Total: 20]

