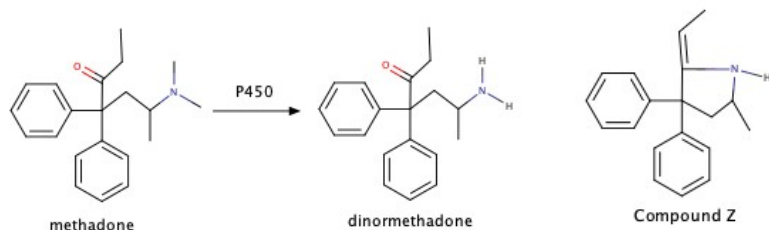


MOQ 3 solutions

You are doing an internship at a drug abuse rehabilitation clinic. A former heroin addict was admitted to the methadone maintenance therapy program at the clinic a few months ago and has been receiving methadone with no relapses to date. Methadone is a synthetic opioid that is used to treat pain and to treat addiction to heroin or other opioids. One of the primary metabolic pathways of methadone is cytochrome P450-mediated formation of dinormethadone. Yesterday, the patient's urine sample showed Compound Z, which may indicate possible illegal drug use.



a. The N in methadone and in dinormethadone is a base. The approximate pK_a of the conjugate acid of this amine group is ___. At pH 7.4 (physiological pH), the amine group has a charge of ___. Give the sign and a number.

$pK_a = 11$ for primary amine.

At $pH = 11 = pK_a$ (half-way point), there would be 50% conjugated acid of the amine and 50% base form of the amine. So at pH 7.4 (lower than pH at $\frac{1}{2}$ way point), the charge on the amine is +1.

b. In methadone and dinormethadone, an intramolecular nucleophilic addition can occur in which the N nucleophile reacts at the ___ electrophile. The N in methadone does not have good access to the electrophile in Blank 1 because ___.

Blank 1: state the atom first and the atom(s) bonded to it, e.g., "O bonded to H and C" or state the bond, e.g., "C=C".

C=O (carbonyl C)

Blank 2: give reasons.

The two methyl groups bonded to N are much larger than H.

c. Compound Z, which was detected in the patient's urine sample, formed from dinormethadone.

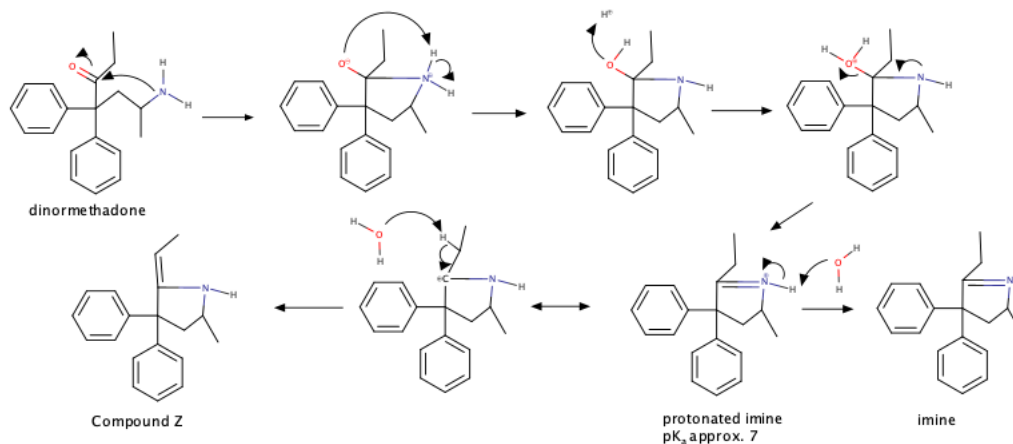
(i) Use curved arrows to show how dinormethadone forms the protonated imine. Use H_2O and H^+ as needed.

Step 1: nucleophilic addition. Step 2: acid-base. Step 3: acid-base. Step 4: elimination.

(ii) Draw the resonance structure of the protonated imine.

(iii) Use curved arrows to show how the resonance structure of the protonated imine forms Compound Z. Use H_2O and H^+ as needed.

Elimination reaction.



Compound Z is an enamine.

(iv) The protonated imine can lose its proton to form an imine. At physiological pH of 7.4, the amount of protonated imine will be ___ the imine because ___.
greater than (blank 1)
equal to (blank 1)

less than (blank 1)

Blank 2: give reasons.

At pH 7 (the approximate pKa of the protonated imine), there will be 50% of protonated imine and 50% imine. So at pH 7.4 (past the ½ way point), there will less protonated imine and more imine.

d. You ___ notify the clinic director and the patient's probation officer about illicit opioid abuse because ___.

Blank 1: answer "should" or "should not".

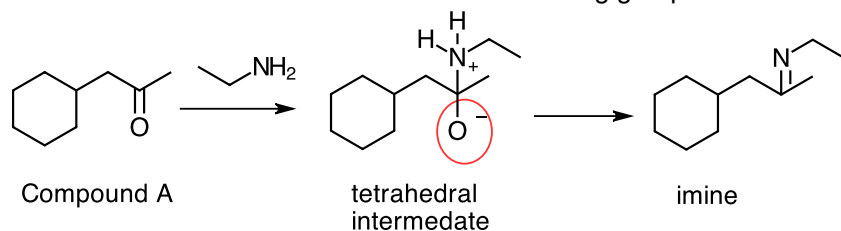
Blank 2: Give reasons.

Compound Z in urine forms from dinormethadone and is a metabolic product, not an illegal drug.

Quiz 8 solutions

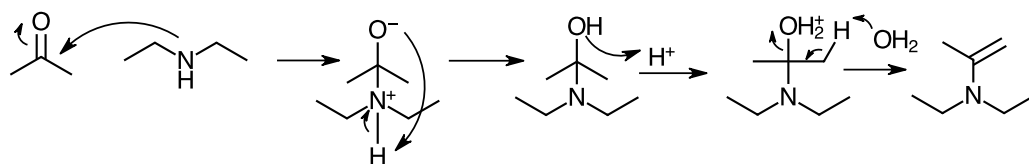
1. Ethyl amine has a fishy smell. You think you can get rid of this smell by reacting Compound A with ethyl amine.

a. Draw the structures of the tetrahedral intermediate and imine product. Circle the atom or group in the tetrahedral intermediate that behaves like a leaving group to form the imine.

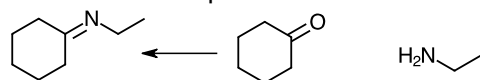


The O⁻ group is a poor leaving group and is made into a better leaving group to form the imine.

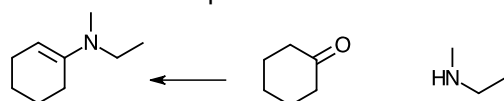
b. Acetone reacts with diethyl amine to form an enamine. Use curved arrows to show how acetone reacts with diethyl amine to form the enamine.



2. a. The compound shown below is an imine. Draw the structures of the carbonyl compound and amine to make this compound.

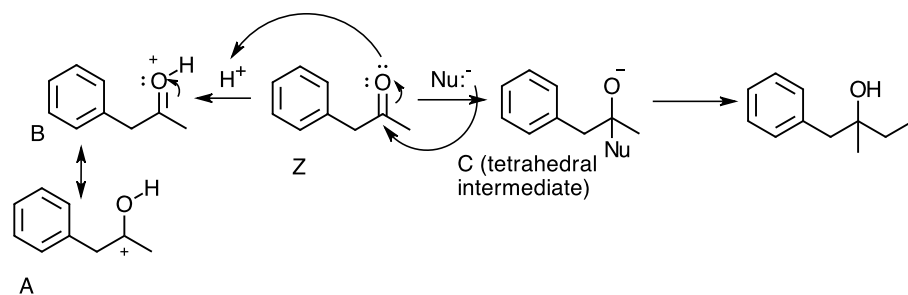


b. The compound shown below is an enamine. Draw the structures of the carbonyl compound and amine to make this compound.



Quiz 7 solutions

1. a. Draw the structures of A and B (resonance structures).



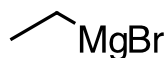
b. (i) Which resonance structure, A or B, shows why reacting H^+ with the ketone makes the **carbonyl carbon** more reactive? (Fill in the blank.)

Need to specify carbonyl carbon. The carbonyl group is $C=O$ so stating carbonyl could mean carbonyl carbon or carbonyl oxygen.

(ii) Explain why H^+ does not react with a pi bond in the ring in Compound Z.

$C=C$ pi bond is a weaker nucleophile than the lone pair on O. Best nucleophile reacts with best electrophile.

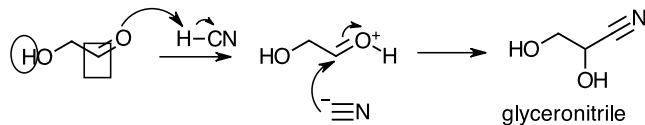
c. (i) Draw the structure of the Nu^- you would use to make Compound D.



Need a nucleophilic carbon, e.g., Grignard reagent, to react with the electrophilic carbonyl carbon.

(ii) Draw the structure of C (tetrahedral intermediate). Use curved arrows to show how C and D are formed.

2. Glyceronitrile is formed from smoke from burning vegetation.



a. The reactant has 2 electrophilic atoms. Circle the best electrophilic atom. Box the other electrophilic atom.

The acidic proton in the alcohol group is a better electrophile than the carbonyl carbon.

b. Use curved arrows to show how the reactant reacts with HCN to form glyceronitrile.