

Chapter 24 – Amines and Heterocycles

Chapter Outline

I. Facts about amines (Section 24.1 – 24.5).

A. Naming amines (Section 24.1).

1. Amines are classified as primary (RNH_2), secondary (R_2NH), tertiary (R_3N) or quaternary ammonium salts (R_4N^+).
2. Primary amines are named in two ways:
 - a. For simple amines, the suffix *-amine* is added to the name of the alkyl substituent.
 - b. For more complicated amines, the $-\text{NH}_2$ group is an amino substituent on the parent molecule.
3. Secondary and tertiary amines:
 - a. Symmetrical amines are named by using the prefixes *di-* and *tri-* before the name of the alkyl group.
 - b. Unsymmetrical amines are named as *N*-substituted primary amines.
The largest group is the parent.
4. The simplest arylamine is aniline.
5. Heterocyclic amines (nitrogen is part of a ring) have specific parent names.
The nitrogens receive the lowest possible numbers.

B. Properties and sources of amines (Section 24.2).

1. The three amine bonds and the lone pair occupy the corners of a tetrahedron.
2. An amine with three different substituents is chiral.
 - a. The two amine enantiomers interconvert by pyramidal inversion.
 - b. This process is rapid at room temperature.
3. Amines with fewer than 5 carbons are water-soluble and form hydrogen bonds.
4. Amines have higher boiling points than alkanes of similar molecular weight.
5. Amines smell really bad.

D. Amine basicity (Sections 24.3 – 24.5).

1. The lone pair of electrons makes amines both nucleophilic and basic (Section 24.3).
2. The basicity constant K_b is the measure of the equilibrium of an amine with water.
The larger the value of K_b (smaller $\text{p}K_b$), the stronger the base.
3. More often, K_a is used to describe amine basicity.
 - a. K_a is the dissociation constant of the conjugate acid of an amine.
 - b. $\text{p}K_a + \text{p}K_b = 14$ (for aqueous media).
 - c. The smaller the value of K_a (larger $\text{p}K_a$), the stronger the base.
4. Base strength.
 - a. Primary, secondary, and tertiary alkylamines have similar basicities.
 - b. Arylamines and heterocyclic amines are less basic than alkylamines.
 - i. The sp^2 electrons of the pyridine lone pair are less available for bonding.
 - ii. The pyrrole lone pair electrons are part of the aromatic ring π system.
 - c. Amides are nonbasic.
 - d. Amine basicity can be used as a means of separating amines from a mixture.
An amine can be converted to its salt, extracted from a solution with water, neutralized, and re-extracted with an organic solvent.
 - e. Some amines are very weak acids.
LDA is formed from diisopropylamine and acts as a strong base.

5. Basicity of substituted arylamines (Section 24.4).
 - a. Arylamines are less basic than alkylamines for two reasons:
 - i. Arylamine lone-pair electrons are delocalized over the aromatic ring and are less available for bonding.
 - ii. Arylamines lose resonance stabilization when they are protonated.
 - b. Electron-donating substituents increase arylamine basicity.
 6. Biological amines and the Henderson-Hasselbalch equation (Section 24.5).
 - a. The Henderson-Hasselbalch equation (Section 20.3) can be used to calculate the percent of protonated vs. unprotonated amines.
 - b. At physiological pH, most amines exist in the protonated form.
- II. Synthesis of amines (Section 24.6).
- A. Reduction of amides, nitriles and nitro groups.
 1. S_N2 displacement with ^-CN , followed by reduction, turns a primary alkyl halide into an amine with one more carbon atom.
 2. Amide reduction converts an amide or nitrile into an amine with the same number of carbons.
 3. Arylamines can be prepared by reducing aromatic nitro compounds.
 - a. Catalytic hydrogenation can be used if no other interfering groups are present.
 - b. SnCl_2 can also be used.
 - B. S_N2 reactions of alkyl halides.
 1. It is possible to alkylate ammonia or an amine with RX .
Unfortunately, it is difficult to avoid overalkylation.
 2. An alternative is displacement of ^-X by azide, followed by hydrogenation.
 3. Also, reaction of an alkyl halide with phthalimide anion, followed by hydrolysis, gives a primary amine (Gabriel amine synthesis).
 - C. Reductive amination of aldehydes and ketones.
Treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent yields an amine
 - a. The reaction proceeds through an imine, which is reduced.
 - b. NaBH_3CN is the reducing agent most commonly used.
 - D. Rearrangements.
 1. Hofmann rearrangement.
 - a. When a primary amide is treated with Br_2 and base, CO_2 is eliminated, and an amine with one less carbon is produced.
 - b. The mechanism is lengthy and proceeds through an isocyanate intermediate.
 - c. In the rearrangement step, the $-\text{R}$ group migrates at the same time as the Br^- ion leaves.
 2. The Curtius rearrangement starts with an acyl azide and occurs by a mechanism very similar to that of the Hofmann rearrangement.
- III. Reactions of amines (Sections 24.7 – 24.9).
- A. Alkylation and acylation (Section 24.7).
 1. Alkylation of primary and secondary amines is hard to control.
 2. Primary and secondary amines can also be acylated.
 - B. Hofmann elimination.
 1. Alkylamines can be converted to alkenes by the Hofmann elimination reaction.
 - a. The amine is treated with an excess of methyl iodide to form a quaternary ammonium salt.
 - b. Treatment of the quaternary salt with Ag_2O , followed by heat, gives the alkene.
 2. The elimination is an E_2 reaction.
 3. The less substituted double bond is formed because of the bulk of the leaving group.
 4. The reaction was formerly used for structure determination and is rarely used today.

C. Reactions of arylamines (Section 24.8).

1. Electrophilic aromatic substitution.
 - a. Electrophilic aromatic substitutions are usually carried out on *N*-acetylated amines, rather than on unprotected amines.
 - i. Amino groups are *o,p*-activators, and polysubstitution sometimes occurs.
 - ii. Friedel–Crafts reactions don't take place with unprotected amines.
 - b. Aromatic amines are acetylated by treatment with acetic anhydride.
 - c. The *N*-acetylated amines are *o,p*-directing activators, but are less reactive than unprotected amines.
 - d. Synthesis of sulfa drugs was achieved by electrophilic aromatic substitution reactions on *N*-protected aromatic amines.
2. The Sandmeyer reaction.
 - a. When a primary arylamine is treated with HNO_2 , an arenediazonium salt is formed.
 - b. The diazonio group of arenediazonium salts can be replaced by many types of nucleophiles in radical substitution reactions.
 - i. Aryl halides are formed by treatment with CuCl , CuBr or NaI .
 - ii. Aryl nitriles are formed by treatment with CuCN .
 - iii. Phenols are formed by treatment with Cu_2O and $\text{Cu}(\text{NO}_3)_2$.
 - iv. H_3PO_2 converts a diazonium salt to an arene, and is used when a substituent must be introduced and then removed.
3. Diazonium coupling reactions.
 - a. Diazonium salts can react with activated aromatic rings to form colored azo compounds.
 - b. The reaction is an electrophilic aromatic substitution that usually occurs at the *p*-position of the activated ring.
 - c. The extended π system of the azo ring system makes these compounds brightly colored.

IV. Heterocyclic amines (Section 24.9).

A. Pyrrole, imidazole and other 5-membered ring unsaturated heterocycles.

1. Structures of pyrrole, furan and thiophene.
 - a. All are aromatic because they have six π electrons in a cyclic conjugated system.
 - b. Pyrrole is nonbasic because all 5 nitrogen electrons are used in bonding.
 - c. The carbon atoms in pyrrole are electron-rich and are reactive toward electrophiles.
2. Electrophilic substitution reactions.
 - a. All three compounds undergo electrophilic aromatic substitution reactions readily.
 - b. Halogenation, nitration, sulfonation and Friedel–Crafts alkylation can take place if reaction conditions are modified.
 - c. Reaction occurs at the 2-position because the reaction intermediate from attack is more stable.
3. Imidazole and thiazole.

A nitrogen in these compounds is basic.

B. Pyridine and pyrimidine.

1. Structure of pyridine.
 - a. Pyridine is the nitrogen-containing analog of benzene.
 - b. The nitrogen lone pair isn't part of the π electron system.
 - c. Pyridine is a stronger base than pyrrole but a weaker base than alkylamines.

2. Electrophilic substitution of pyridine.
Electrophilic substitutions take place with great difficulty.
 - i. The pyridine ring is electron-poor due to the electron-withdrawing inductive effect of nitrogen.
 - ii. Acid-base complexation between nitrogen and an electrophile puts a positive charge on the ring.

C. Polycyclic heterocycles.

1. The reactivity of polycyclic heterocyclic compounds is related to the type of heteroatom and to the size of the ring.
2. Indole has a pyrrole-like nitrogen and undergoes electrophilic aromatic substitutions in the heterocyclic ring.
3. Purines have 4 nitrogens (3 pyridine-like, and one pyrrole-like) in a fused-ring structure.

IV. Spectroscopy of amines (Section 24.10).

A. IR spectroscopy.

1. Primary and secondary amines absorb in the region $3300\text{--}3500\text{ cm}^{-1}$.
 - a. Primary amines show a pair of bands at 3350 cm^{-1} and 3450 cm^{-1} .
 - b. Secondary amines show a single band at 3350 cm^{-1} .
 - c. These absorptions are sharper than alcohol absorptions, which also occur in this range.
2. Adding a small amount of HCl causes a broad band in the range $2200\text{--}3000\text{ cm}^{-1}$ that is due to the ammonium ion.

B. NMR spectroscopy.

1. ^1H NMR.
 - a. Amine protons are hard to identify because they appear as broad signals.
 - b. Exchange with D_2O causes the amine signal to disappear and allows identification.
 - c. Hydrogens on the carbon next to nitrogen are somewhat deshielded.
2. ^{13}C NMR.
Carbons next to nitrogen are slightly deshielded.

C. Mass spectrometry.

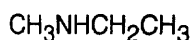
1. The nitrogen rule: A compound with an odd number of nitrogens has an odd-numbered molecular weight (and molecular ion).
2. Alkylamines undergo α -cleavage and show peaks that correspond to both possible modes of cleavage.

Solutions to Problems

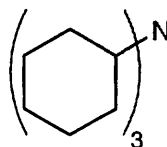
24.1 Facts to remember about naming amines:

- (1) Primary amines are named by adding the suffix *-amine* to the name of the alkyl substituent.
- (2) The prefix *di-* or *tri-* is added to the names of symmetrical secondary and tertiary amines.
- (3) Unsymmetrical secondary and tertiary amines are named as *N*-substituted primary amines. The parent amine has the largest alkyl group.

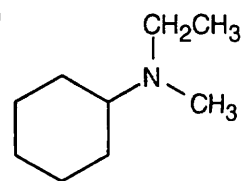
(a)

***N*-Methylethylamine**

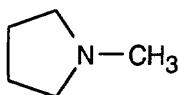
(b)

**Tricyclohexylamine**

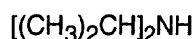
(c)

***N*-Ethyl-*N*-methylcyclohexylamine**

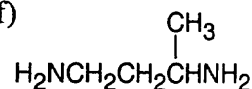
(d)

***N*-Methylpyrrolidine**

(e)

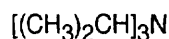
**Diisopropylamine**

(f)

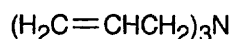
**1,3-Butanediimine**

24.2

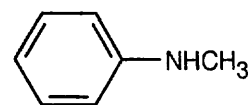
(a)

**Triisopropylamine**

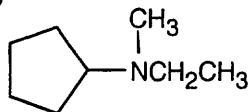
(b)

**Triallylamine**

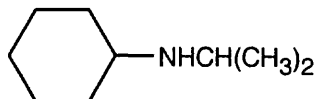
(c)

***N*-Methylaniline**

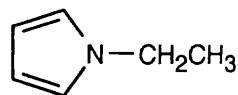
(d)

***N*-Ethyl-*N*-methylcyclopentylamine**

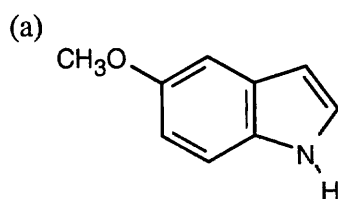
(e)

***N*-Isopropylcyclohexylamine**

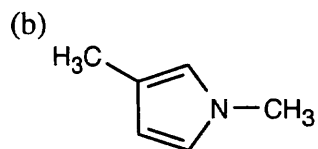
(f)

***N*-Ethylpyrrole**

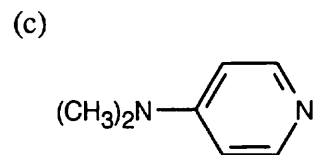
24.3 The numbering of heterocyclic rings is described in Section 24.1.



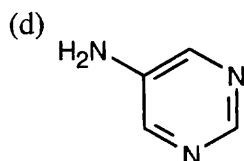
5-Methoxyindole



1,3-Dimethylpyrrole



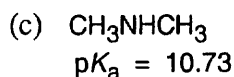
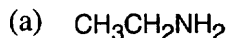
4-(N,N-Dimethylamino)-pyridine



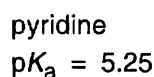
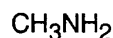
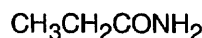
5-Aminopyrimidine

24.4 Amines are less basic than hydroxide but more basic than amides. The pK_a values of the conjugate acids of the amines in (c) are shown. The larger the pK_a , the stronger the base.

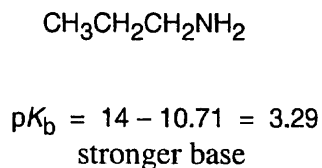
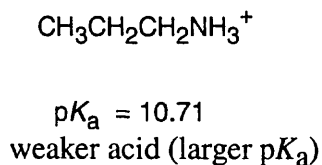
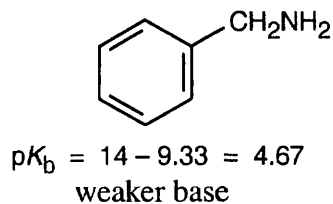
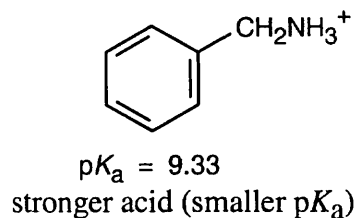
More Basic



Less Basic



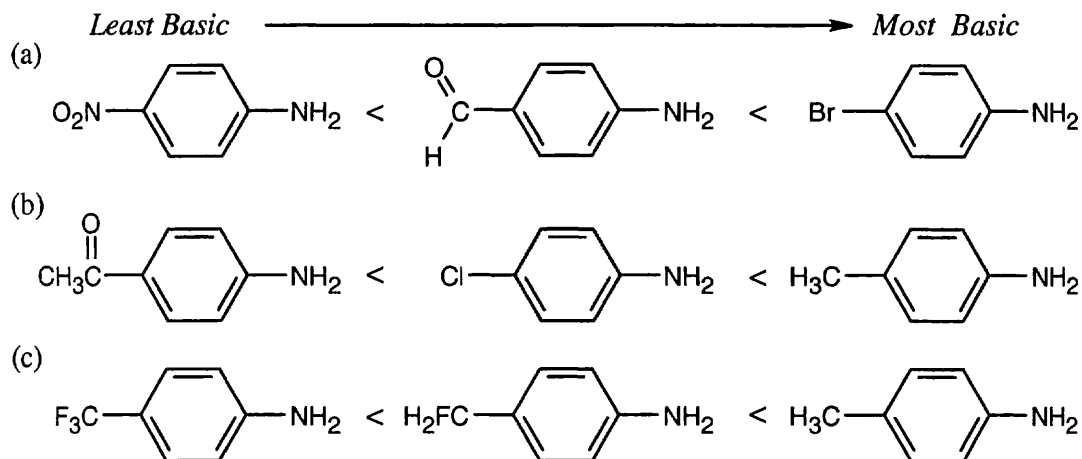
24.5



The stronger base (propylamine) holds a proton more tightly than the weaker base (benzylamine). Thus, the propylammonium ion is less acidic (larger pK_a) than the benzylammonium ion (smaller pK_a).

To calculate pK_b : $K_a \cdot K_b = 10^{-14}$, $pK_a + pK_b = 14$ and $pK_b = 14 - pK_a$.

- 24.6** The basicity order of substituted arylamines is the same as their reactivity order in electrophilic aromatic substitution reactions because, in both cases, electron-withdrawing substituents make the site of reaction more electron-poor and destabilize a positive charge.



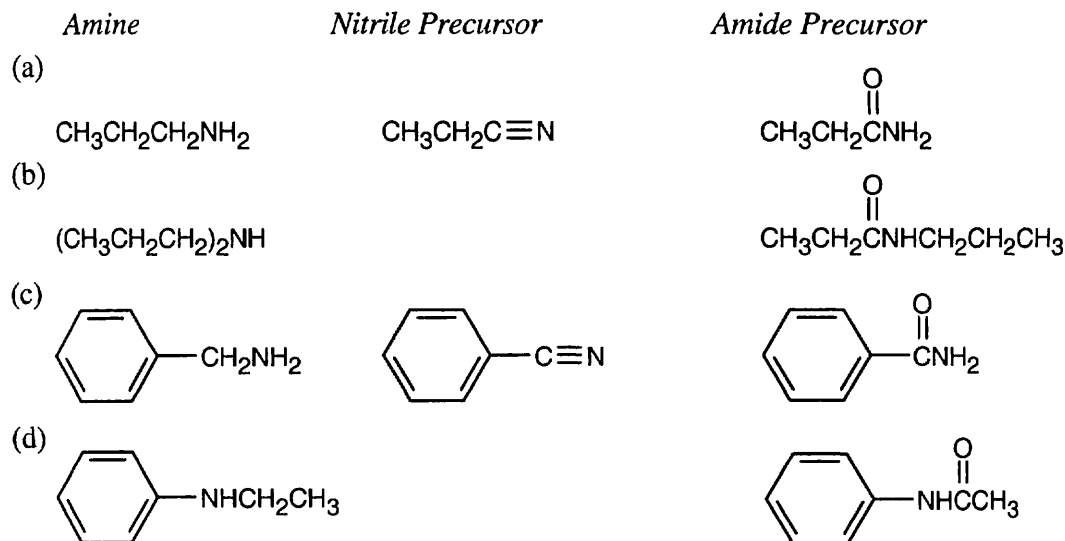
- 24.7** Use the expressions shown in Section 24.5.

$$\log \frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \text{pH} - \text{pK}_a = 7.3 - 1.3 = 6.0$$

$$\frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \text{antilog}(6.0) = 10^6: [\text{RNH}_2] = 10^6 [\text{RNH}_3^+]$$

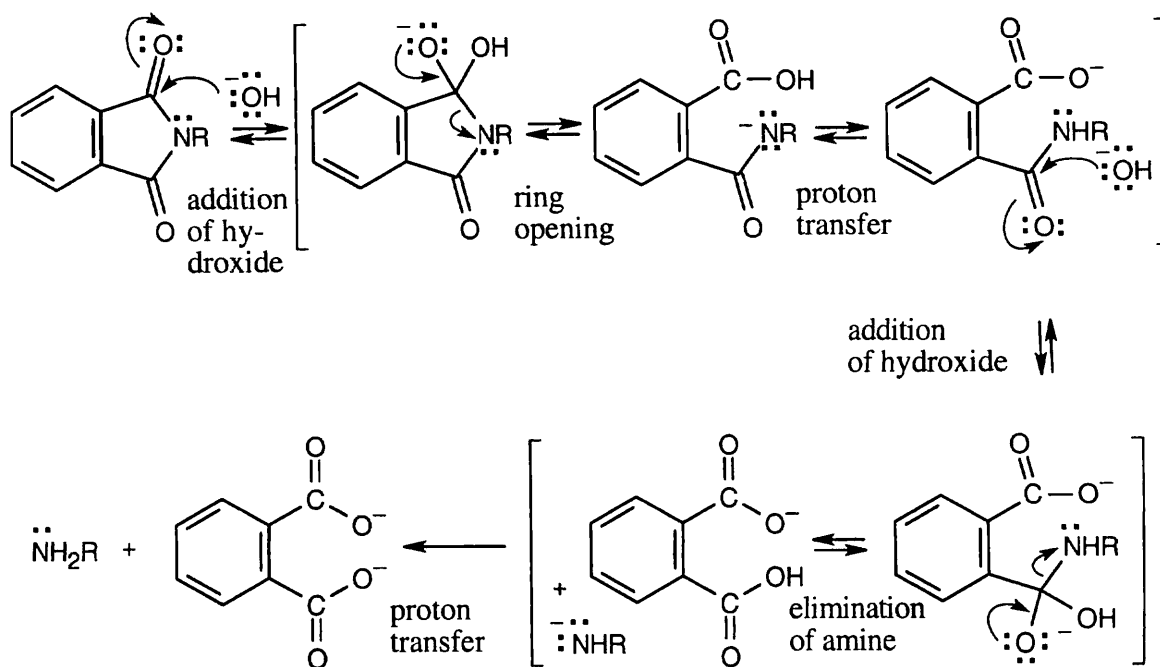
At pH = 7.3, virtually 100% of the pyrimidine molecules are in the neutral form.

- 24.8** Amide reduction can be used to synthesize most amines, but nitrile reduction can be used to synthesize only primary amines. Thus, the compounds in (b) and (d) can be synthesized only by amide reduction.

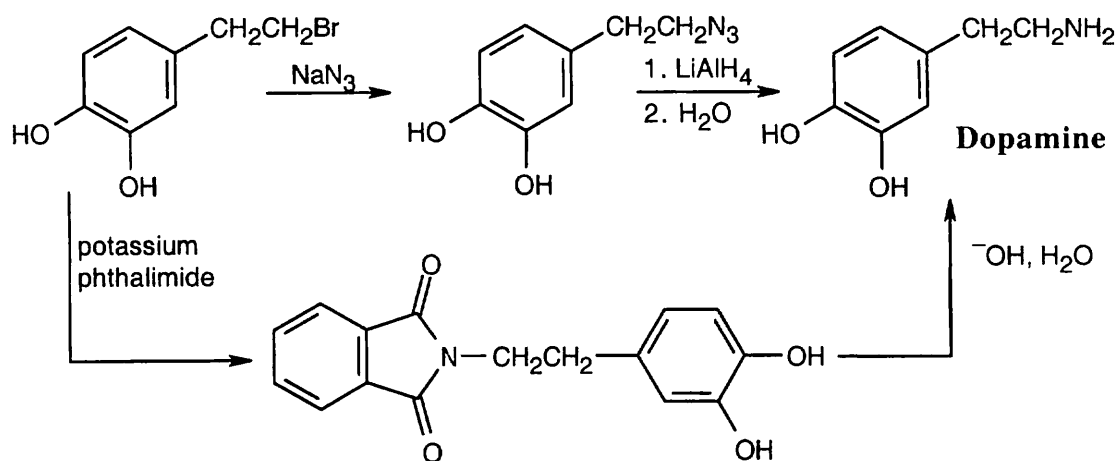


The compounds in parts b and d can't be prepared by reduction of a nitrile.

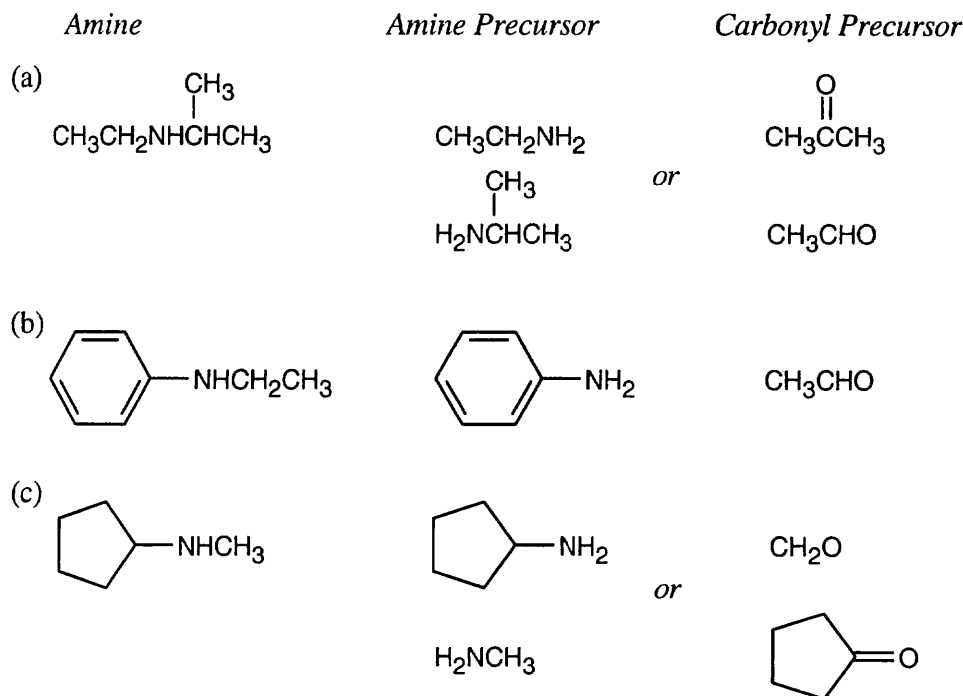
24.9



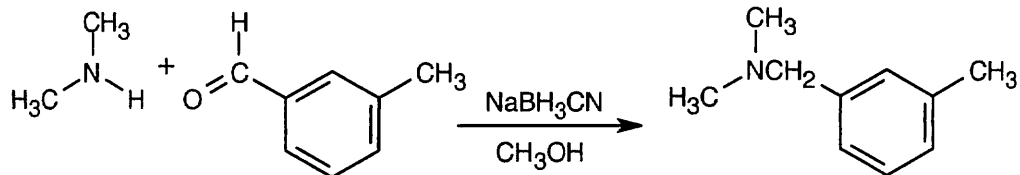
24.10



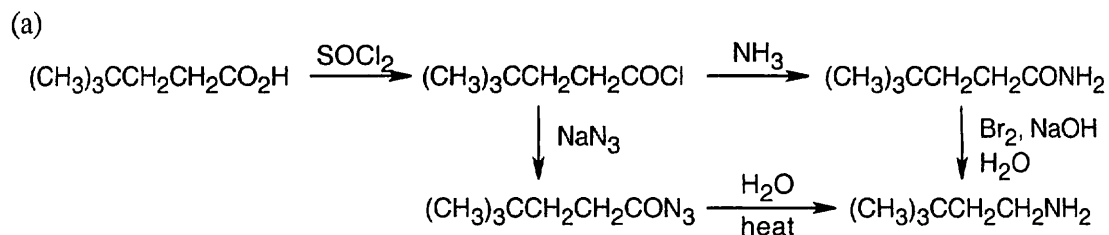
24.11 Look at the target molecule to find the groups bonded to nitrogen. One group comes from the aldehyde/ketone precursor, and the other group comes from the amine precursor. In most cases, two combinations of amine and aldehyde/ketone are possible.

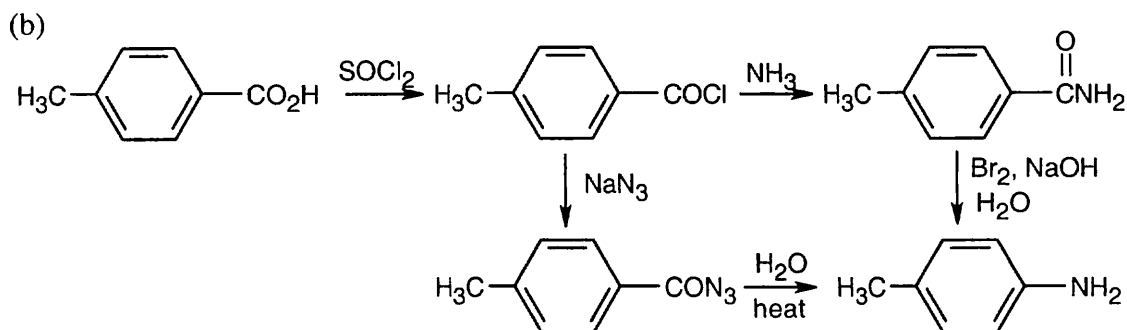


24.12

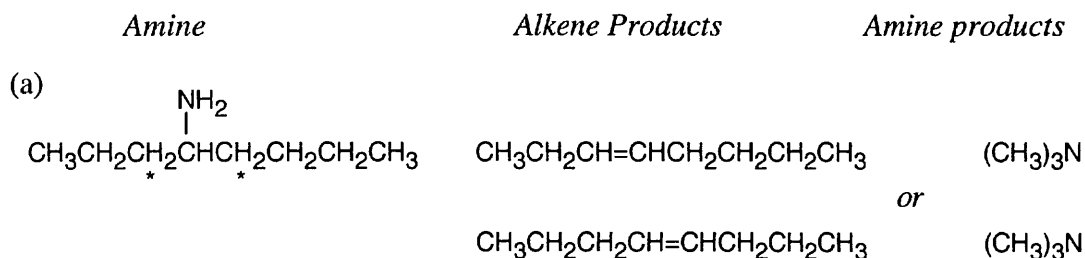


24.13 In both of these reactions, the product amine is formed from a carboxylic acid derivative precursor that has one more carbon than the amine. In the Hofmann rearrangement, the precursor is an amide, which is treated with Br_2 , NaOH and H_2O . In the Curtius rearrangement, the precursor is an acid chloride, which is treated with NaN_3 , then with H_2O and heat.

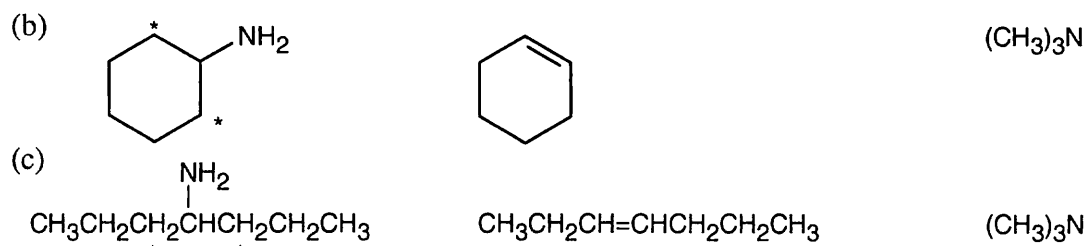




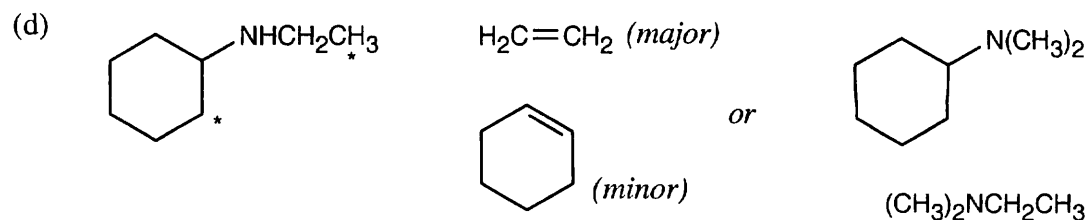
24.14 The Hofmann elimination yields alkenes and amines from larger amines. The major alkene product has the less substituted double bond, but all possible products may be formed. The hydrogens that can be eliminated are starred. When possible, cis and trans double bond isomers are both formed.



Both hydrogens that might be eliminated are secondary, and both possible products should form in approximately equal amounts.

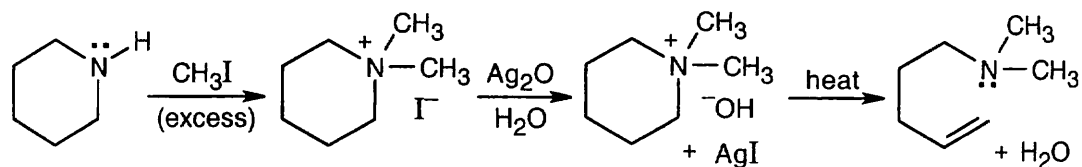


In each of the above reactions, only one product can form.

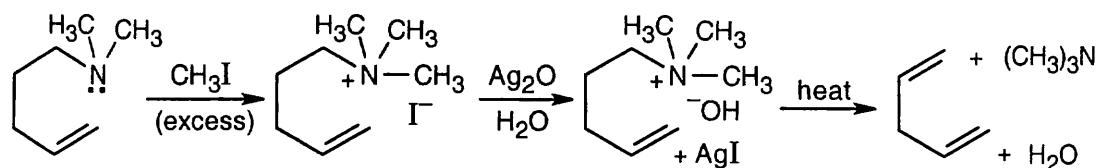


The first pair of products in (d) results from elimination of a primary hydrogen and are the major products. the second pair of products results from elimination of a secondary hydrogen.

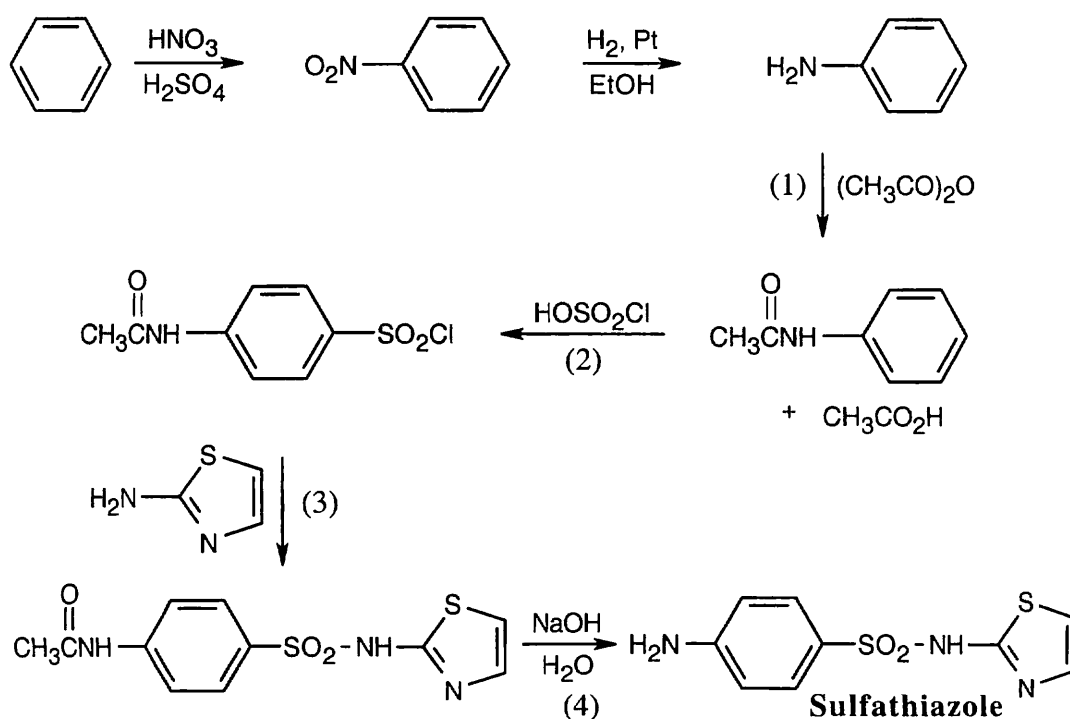
24.15



The product, which contains both the double bond and the tertiary amine in an ring-opened structure, can undergo a second Hoffmann elimination.

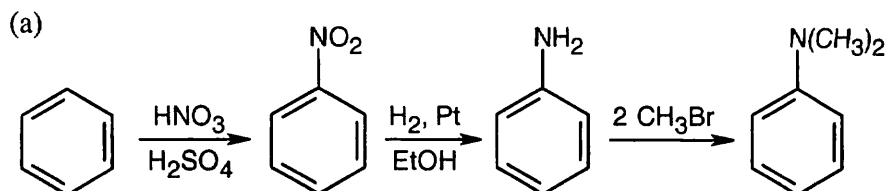


24.16 This reaction sequence is similar to the sequence used to synthesize sulfanilamide. Key steps are: (1) treatment of aniline with acetic anhydride to modulate reactivity, (2) reaction of acetanilide with chlorosulfonic acid, (3) treatment of the chlorosulfonate with the heterocyclic base, and (4) removal of the acetyl group.

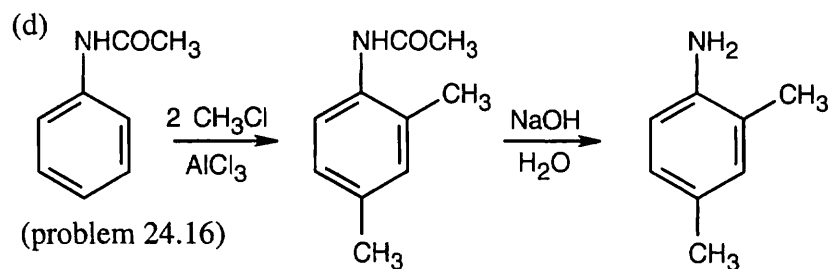
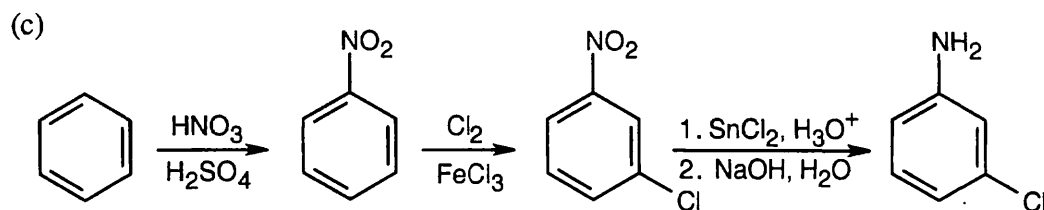
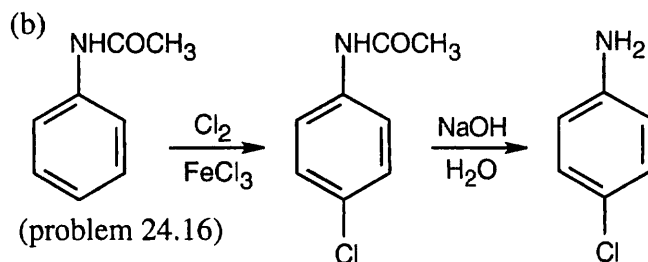


24.17 In all of these reactions, benzene is nitrated and the nitro group is ultimately reduced, but the timing of the reduction step is important in arriving at the correct product. In (a), nitrobenzene is immediately reduced and alkylated. In (c), chlorination occurs before reduction so that chlorine can be introduced in the *m*-position. In (b) and (d), nitrobenzene is reduced and then acetylated in order to overcome amine basicity and to control reactivity. In both cases, the acetyl group is removed in the last step.

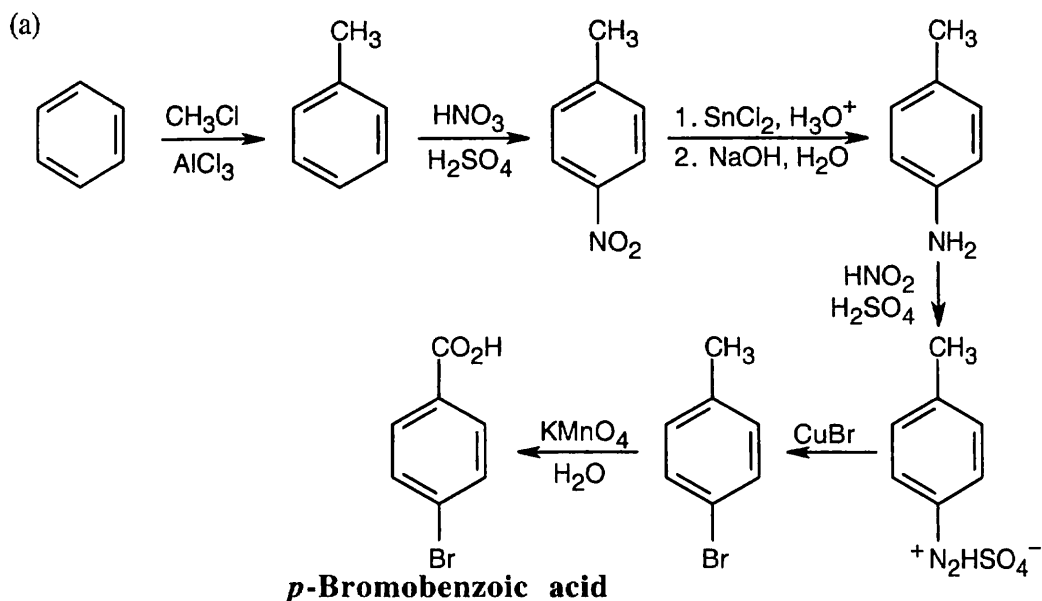
Either method of nitro group reduction (SnCl_2 , H_2) can be used in all parts of this problem; both methods are shown.



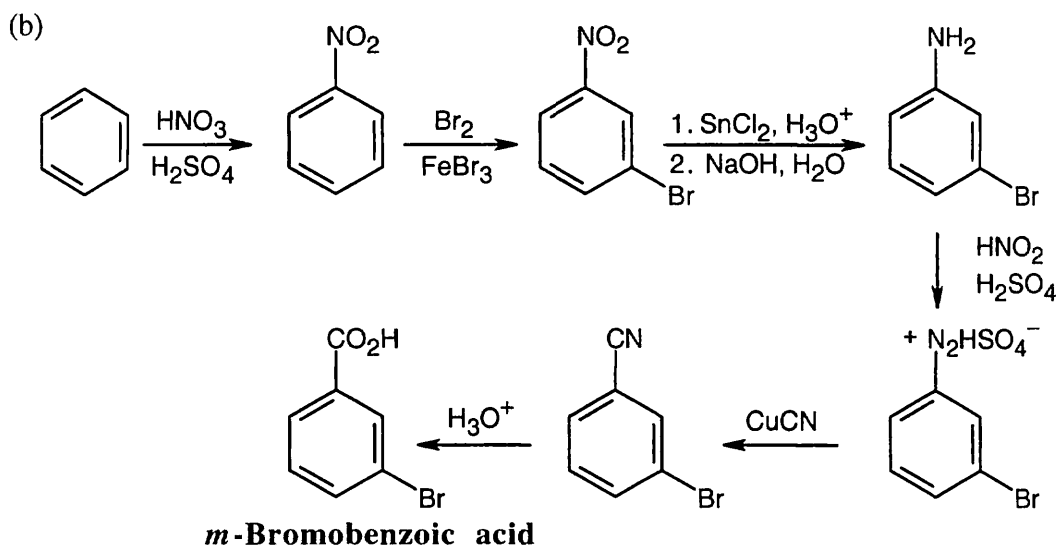
Mono- and trialkylated anilines are also formed.



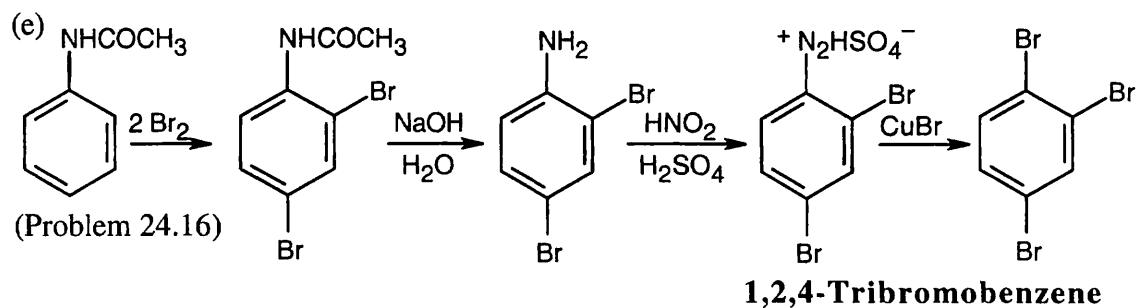
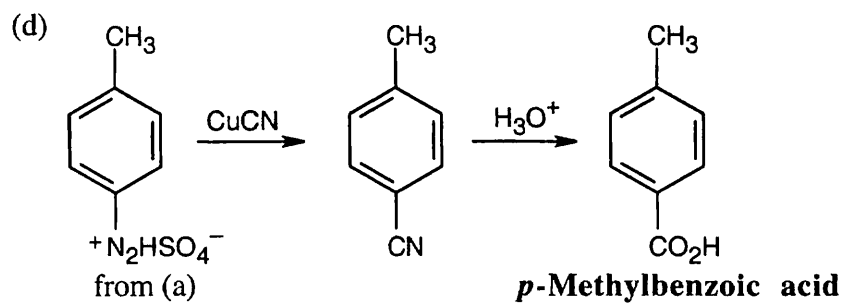
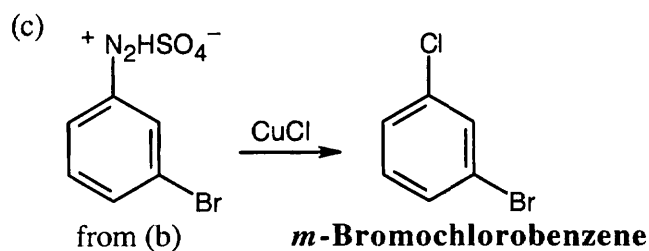
24.18



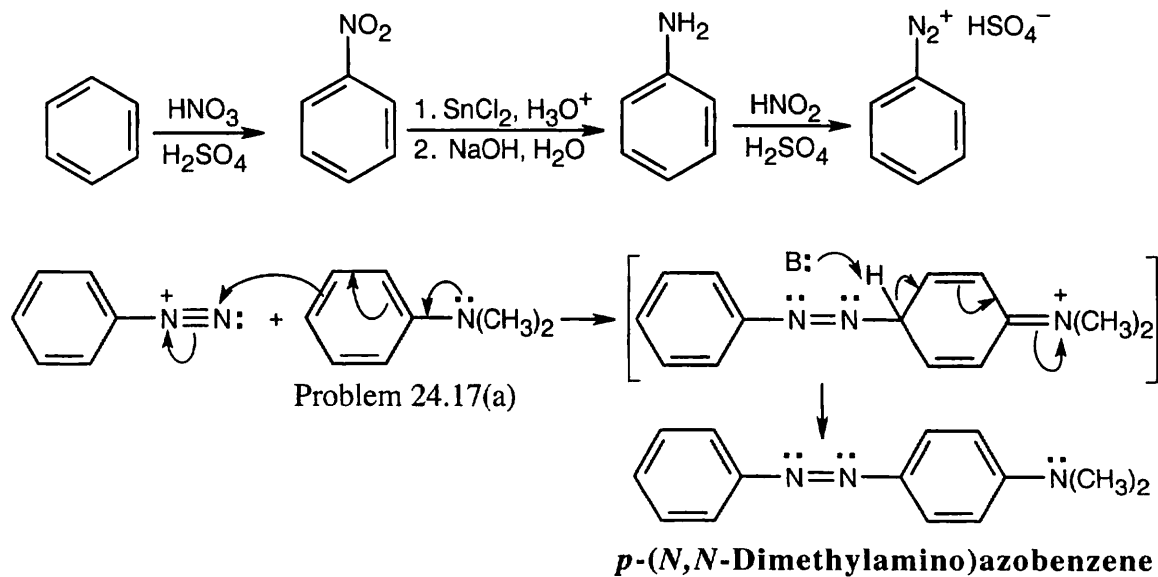
The route shown above is one of several ways to synthesize *p*-bromobenzoic acid and is definitely not the simplest way. (The simplest route is Friedel–Crafts alkylation → bromination → oxidation). The illustrated synthesis shows the use of the diazonium replacement reaction that substitutes bromine for a nitro group. Oxidation of the methyl group yields the substituted benzoic acid.



Again, this isn't the easiest route to this compound. In this case, nitration is followed by bromination, then by diazotization, treatment with CuCN, and hydrolysis of the nitrile.

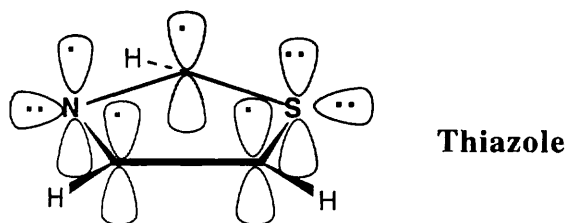


24.19



Coupling takes place between *N,N*-dimethylaniline and a benzenediazonium salt to yield the desired product.

24.20



Thiazole contains six π electrons. Each carbon contributes one electron, nitrogen contributes one electron, and sulfur contributes two electrons to the ring π system. Both sulfur and nitrogen have lone electron pairs in sp^2 orbitals that lie in the plane of the ring.

24.21

$$\log \frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \text{pH} - \text{pK}_a = 7.37 - 6.00 = 1.37$$

$$\frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \text{antilog}(1.37) = 23.4: [\text{RNH}_2] = 23.4 [\text{RNH}_3^+]$$

$$[\text{RNH}_3^+] + 23.4 [\text{RNH}_3^+] = 24.4 [\text{RNH}_3^+] = 100\%$$

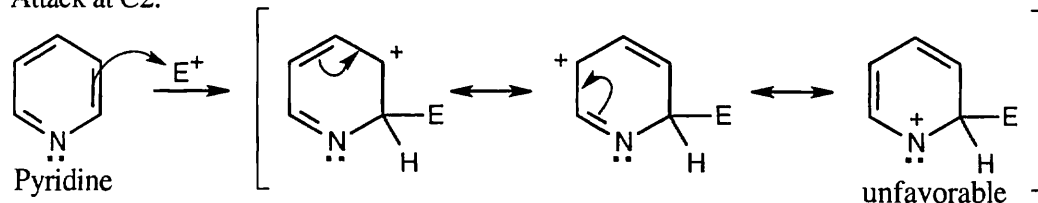
$$[\text{RNH}_3^+] = 100\% \div 24.4 = 4.1\%$$

$$[\text{RNH}_2] = 100\% - 4.1 = 95.9\%$$

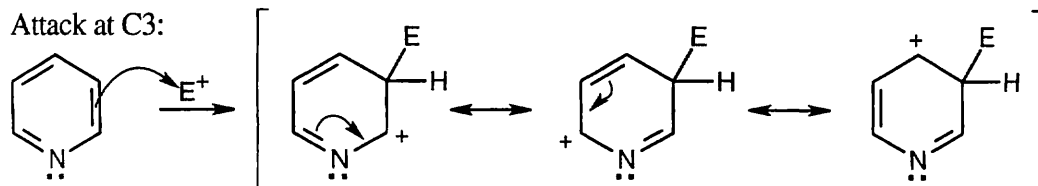
4.1% of histidine molecules have the imidazole nitrogen in the protonated form at physiological pH.

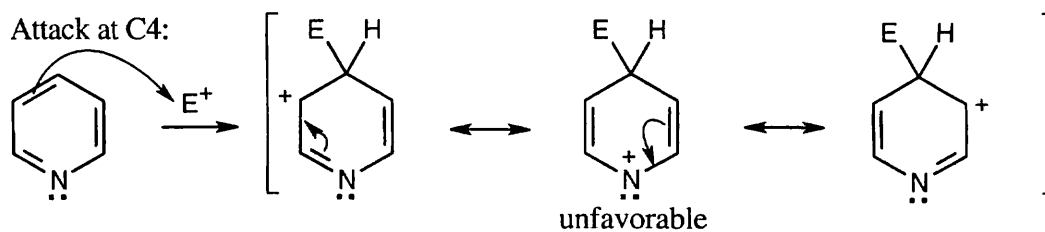
24.22

Attack at C2:



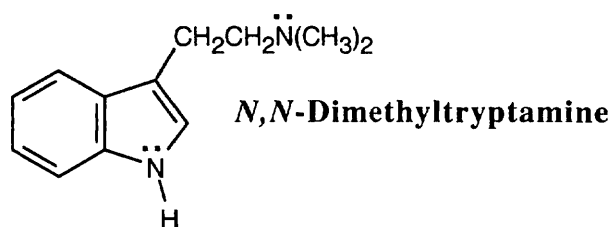
Attack at C3:





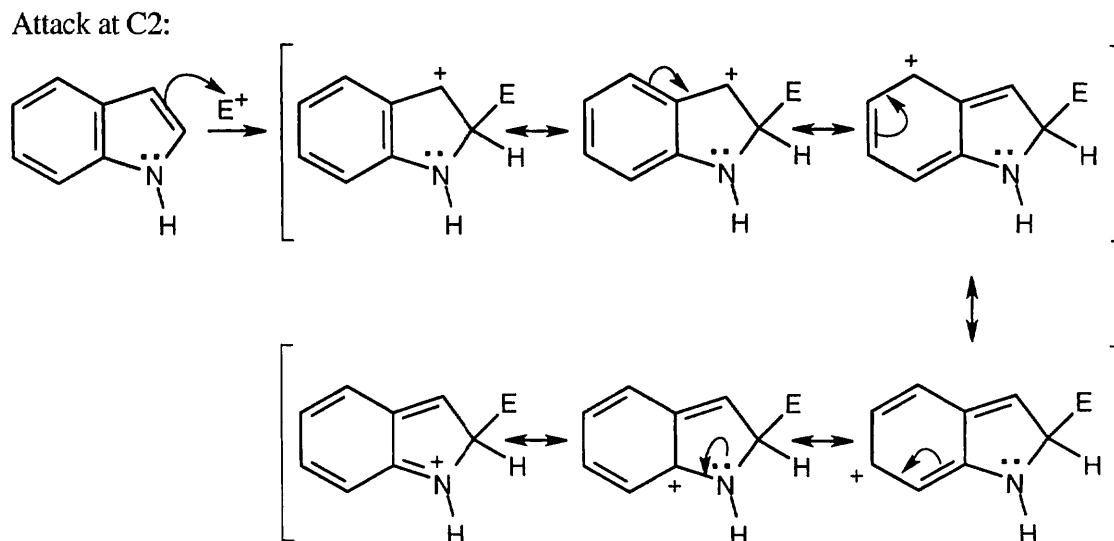
Reaction at C3 is favored over reaction at C2 or C4. The positive charge of the cationic intermediate of reaction at C3 is delocalized over three carbon atoms, rather than over two carbons and the electronegative pyridine nitrogen.

24.23

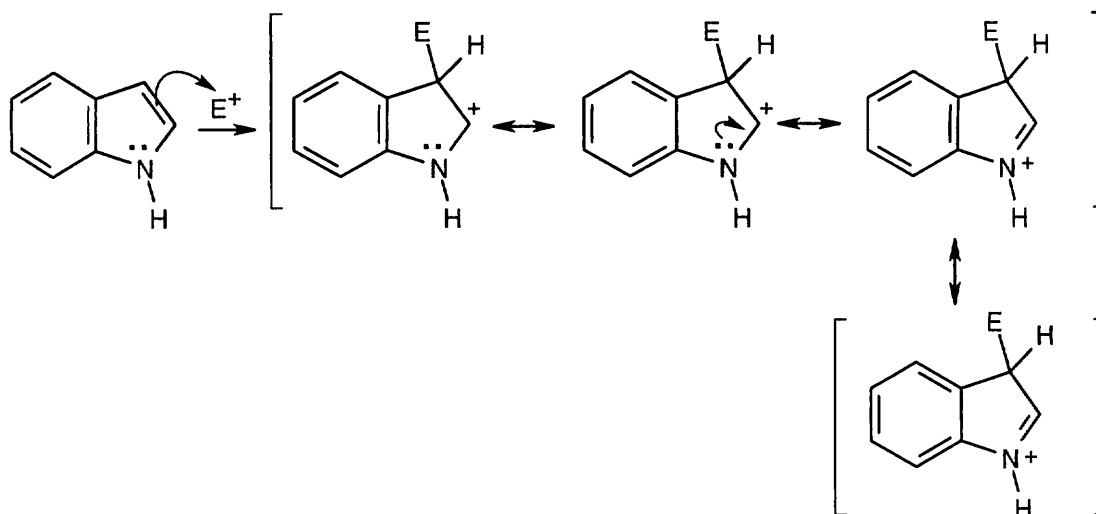


The side chain nitrogen atom of *N,N*-dimethyltryptamine is more basic than the ring nitrogen atom because its lone electron pair is more available for donation to a Lewis acid. The aromatic nitrogen electron lone pair is part of the ring π electron system.

24.24

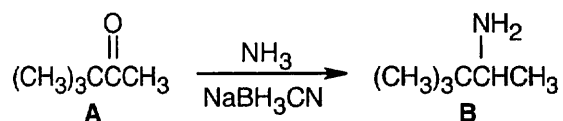


Attack at C3:



Positive charge can be stabilized by the nitrogen lone-pair electrons in reaction at both C2 and C3. In reaction at C2, however, stabilization by nitrogen destroys the aromaticity of the fused benzene ring. Reaction at C3 is therefore favored, even though the cationic intermediate has fewer resonance forms, because the aromaticity of the six-membered-ring is preserved.

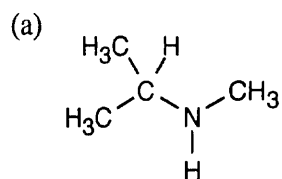
24.25



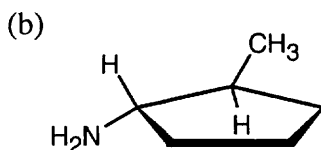
The IR spectrum shows that **B** is a primary amine, and the ^1H NMR spectrum shows a 9-proton singlet, a one-proton quartet, and a 3-proton doublet. An absorption due to the amine protons is not visible.

Visualizing Chemistry

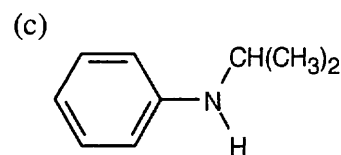
24.26

**N-Methylisopropylamine**

secondary amine

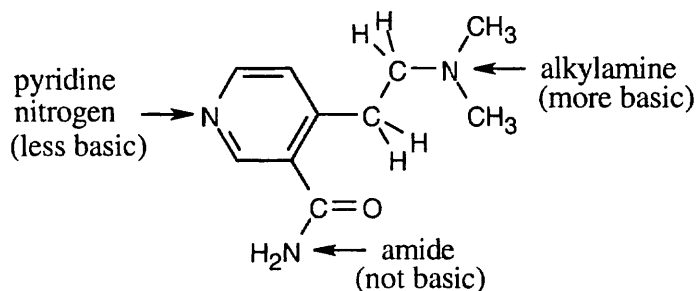
**trans-(2-Methylcyclopentyl)amine**

primary amine

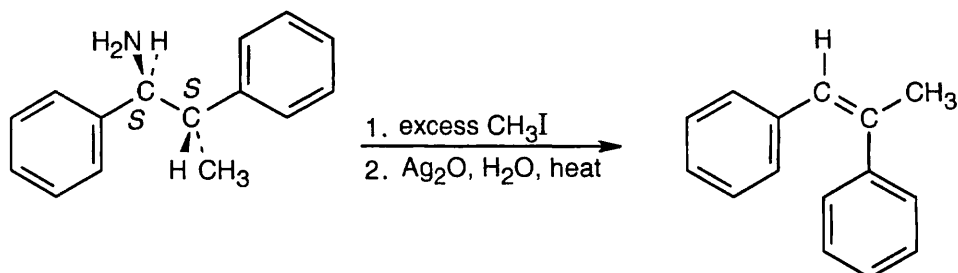
**N-Isopropylaniline**

secondary amine

24.27



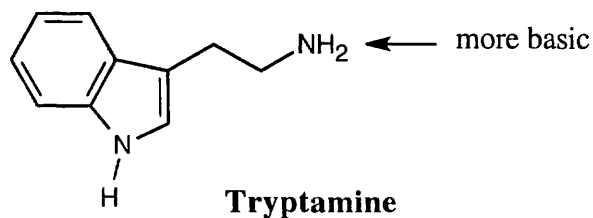
24.28



(1*S*,2*S*)-(1,2-Diphenylpropyl)amine (Z)-1,2-Diphenyl-1-propene

Hofmann elimination is an E_2 elimination, in which the two groups to be eliminated must be 180° apart. The product that results from this elimination geometry is the *Z* isomer.

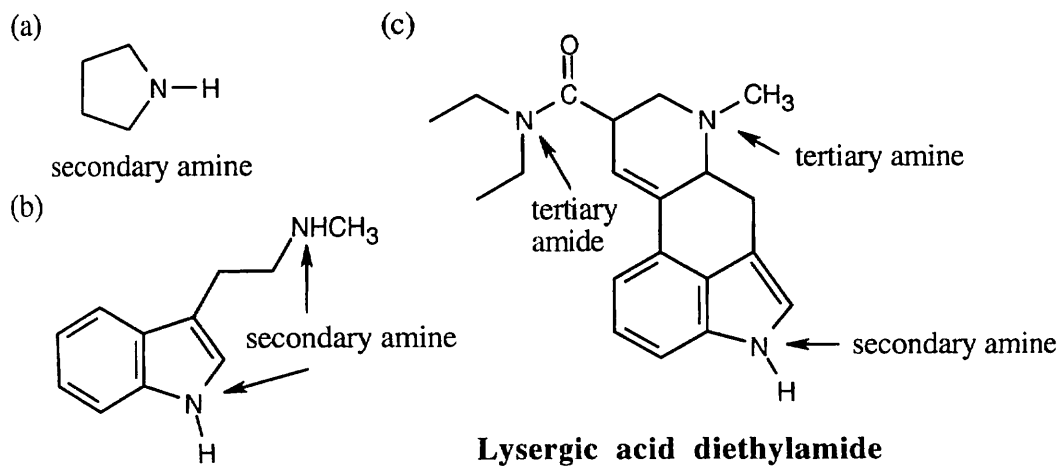
24.29



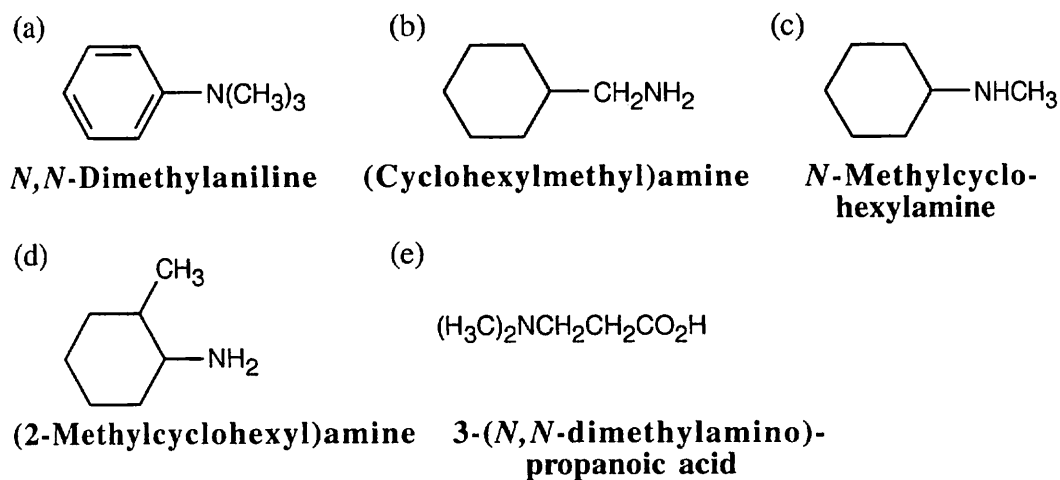
The indicated nitrogen is more basic because it is more electron-rich. The electrons of the other nitrogen are part of the fused-ring π system and are not available for donation to a Lewis acid.

Additional Problems

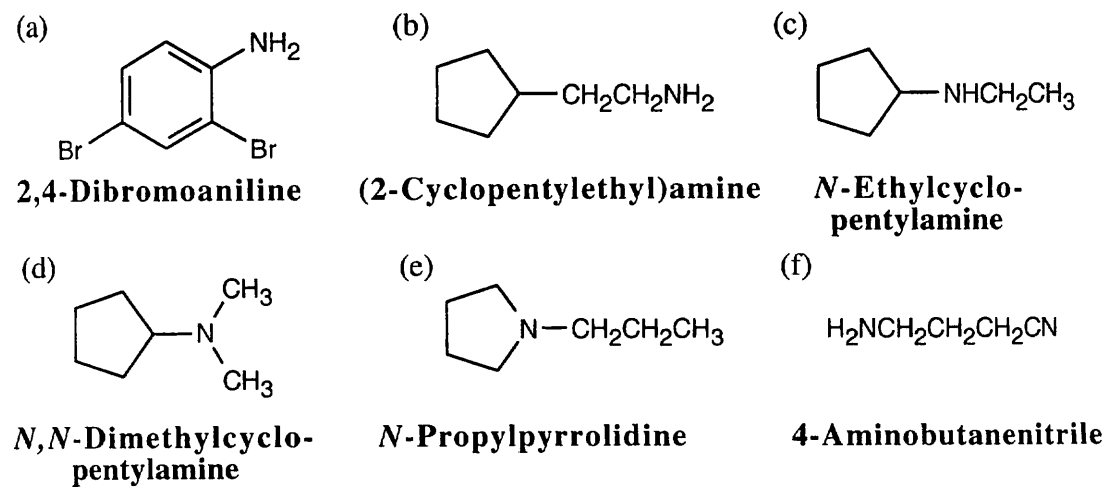
24.30



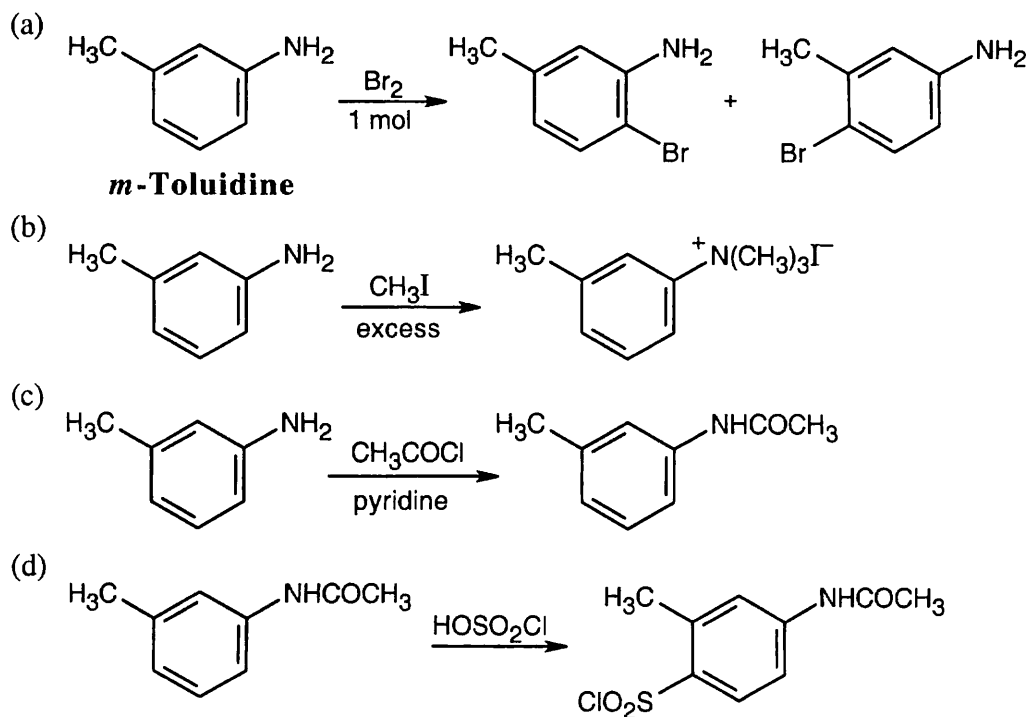
24.31



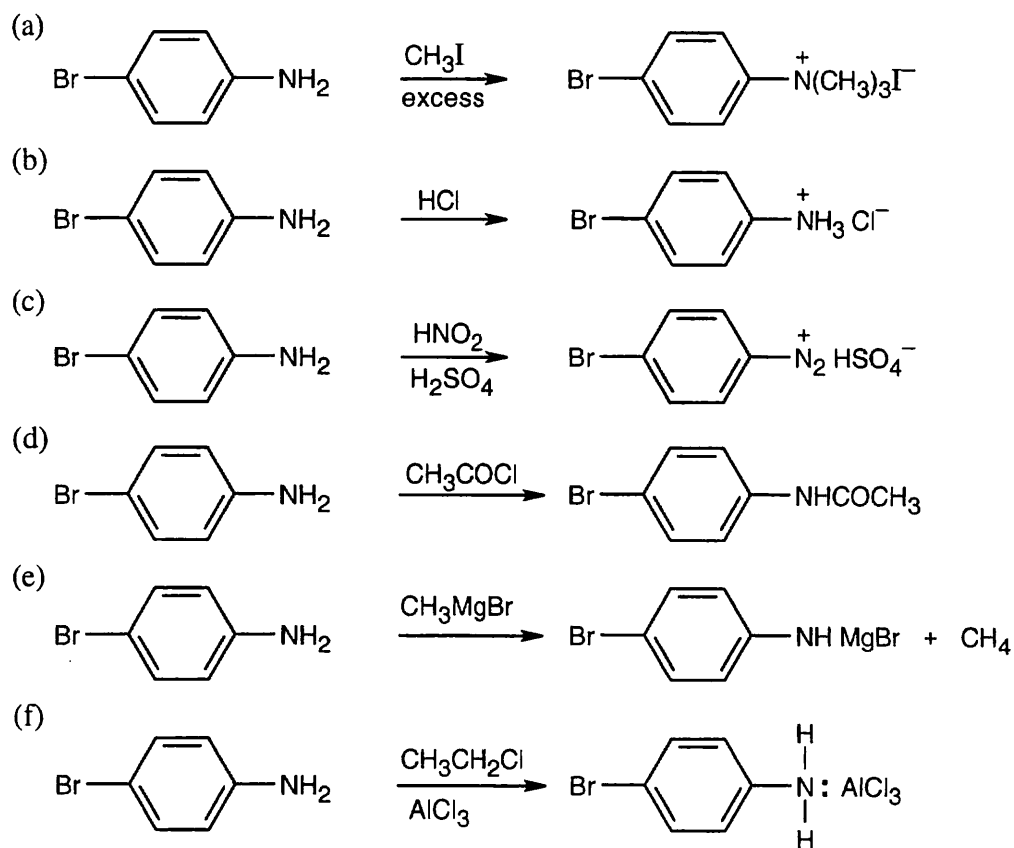
24.32

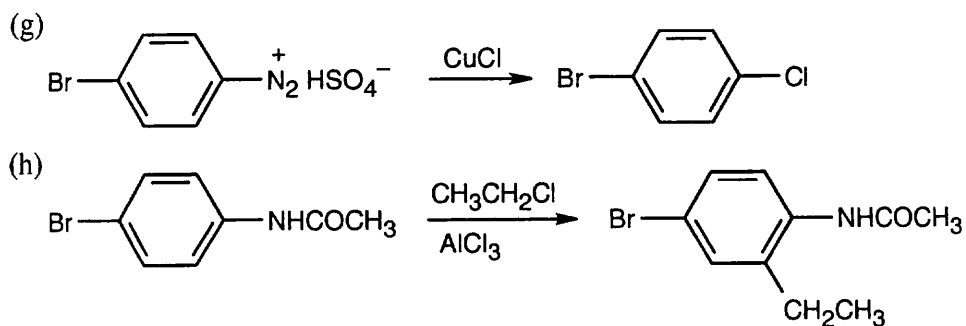


24.33

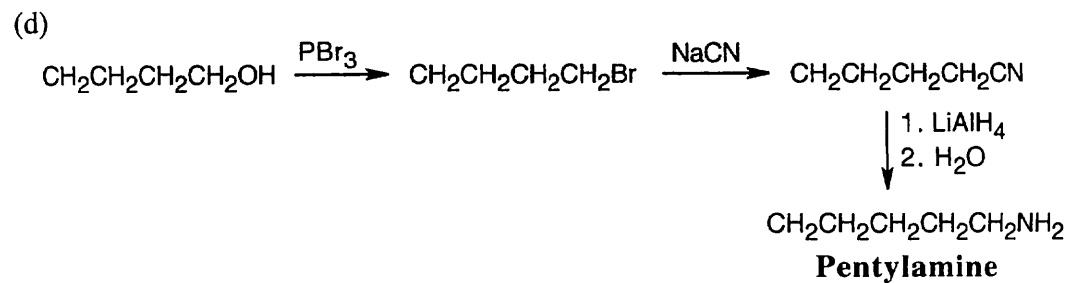
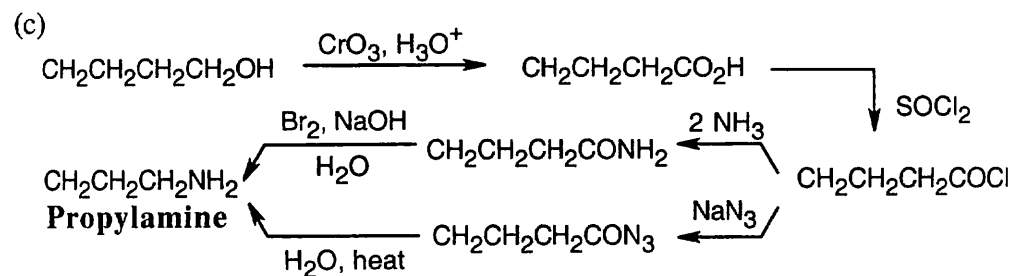
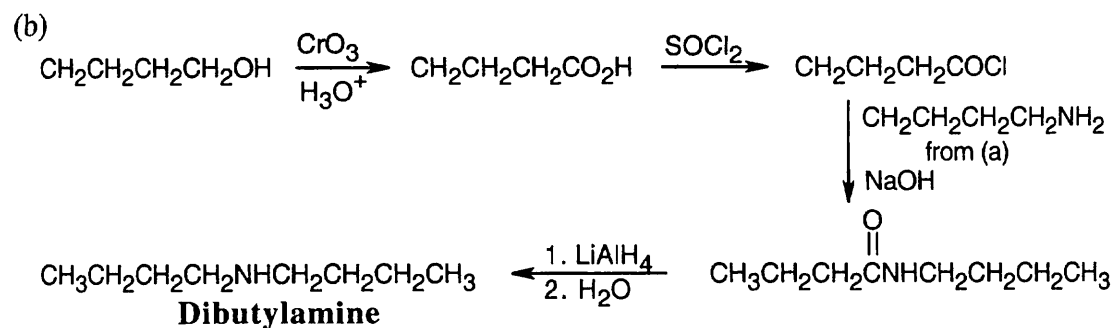
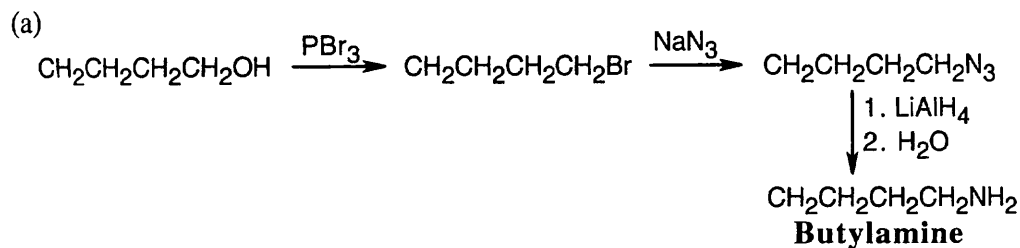


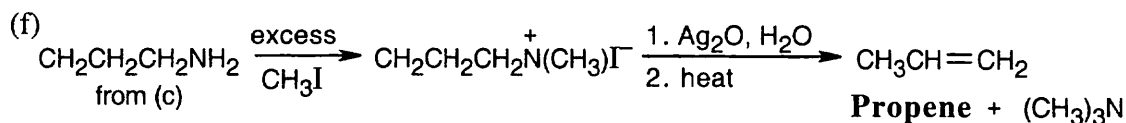
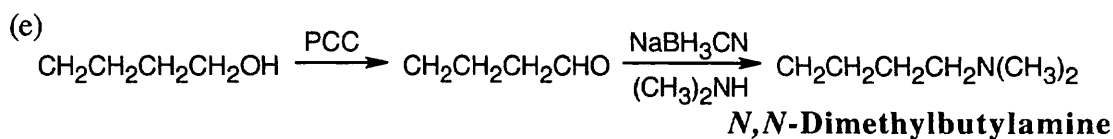
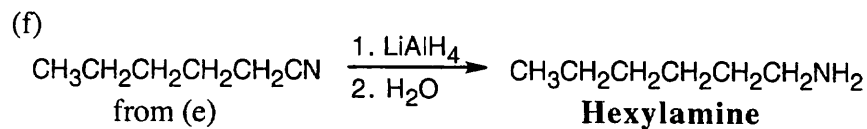
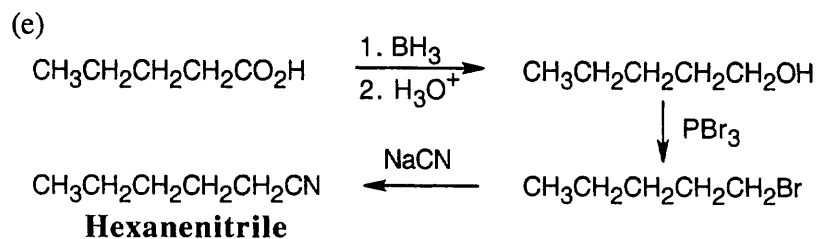
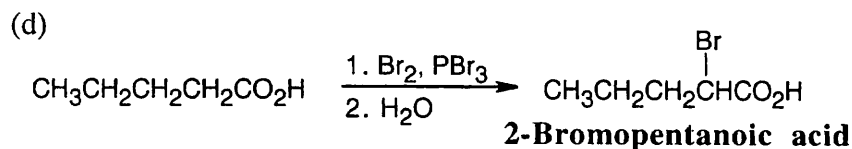
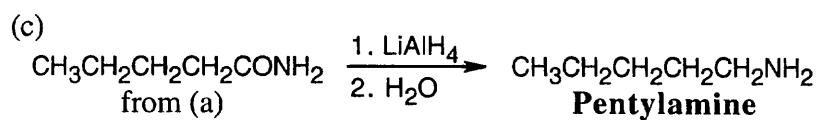
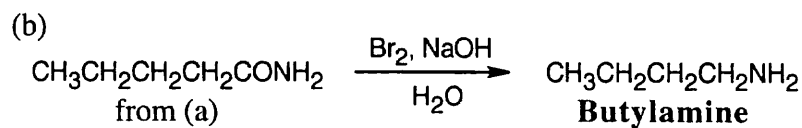
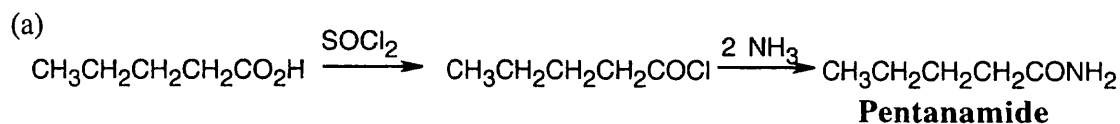
24.34



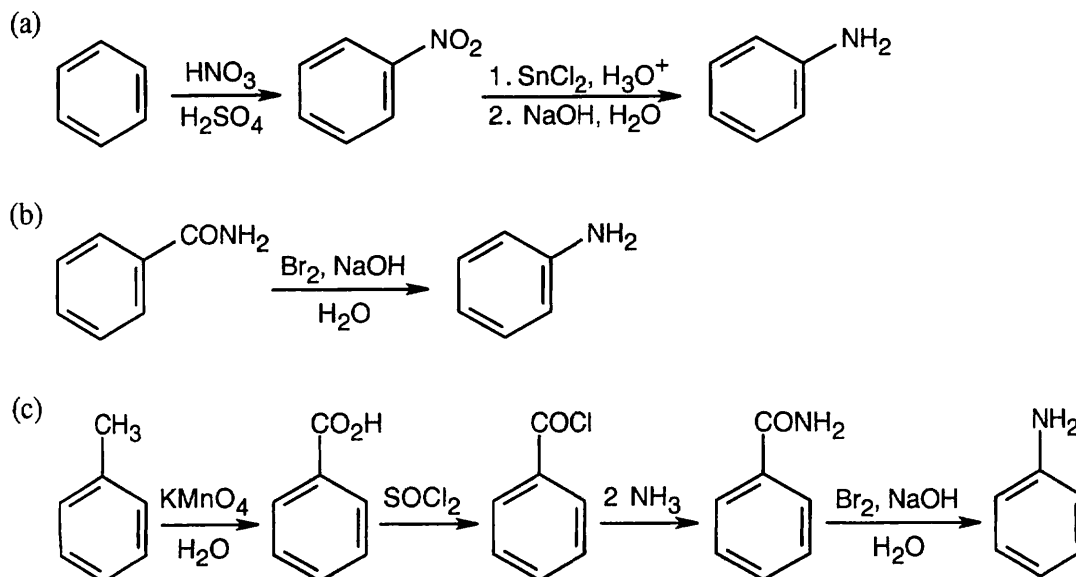


24.35

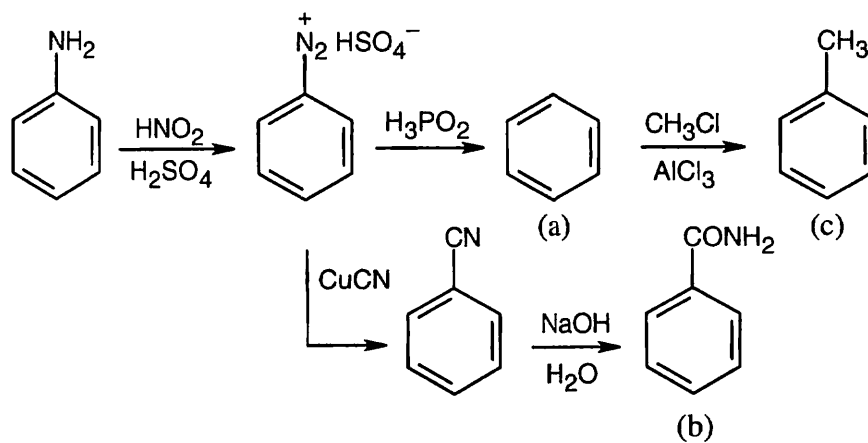


**24.36**

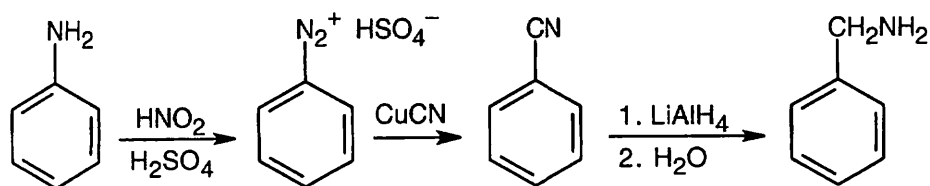
24.37



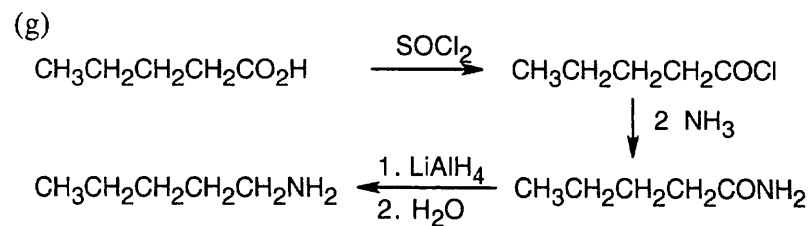
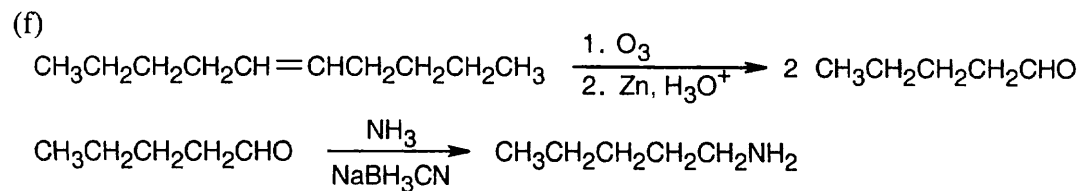
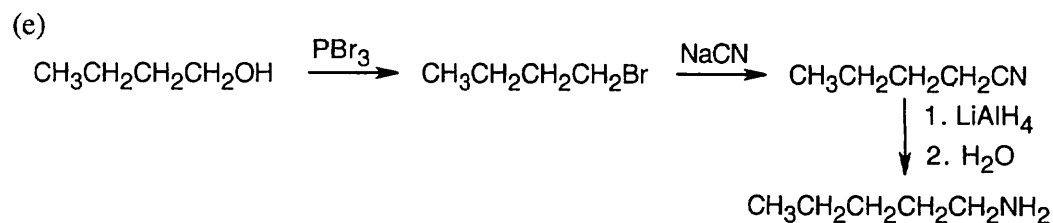
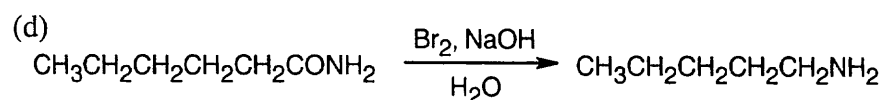
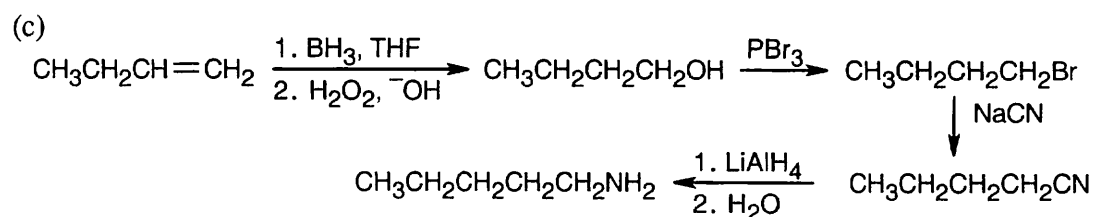
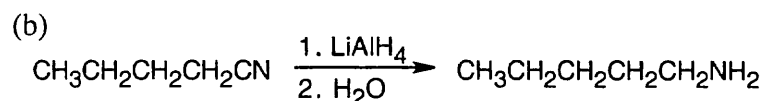
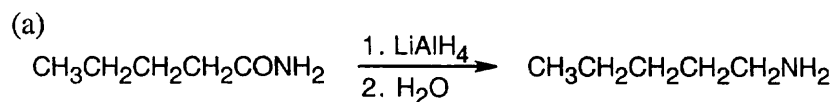
24.38



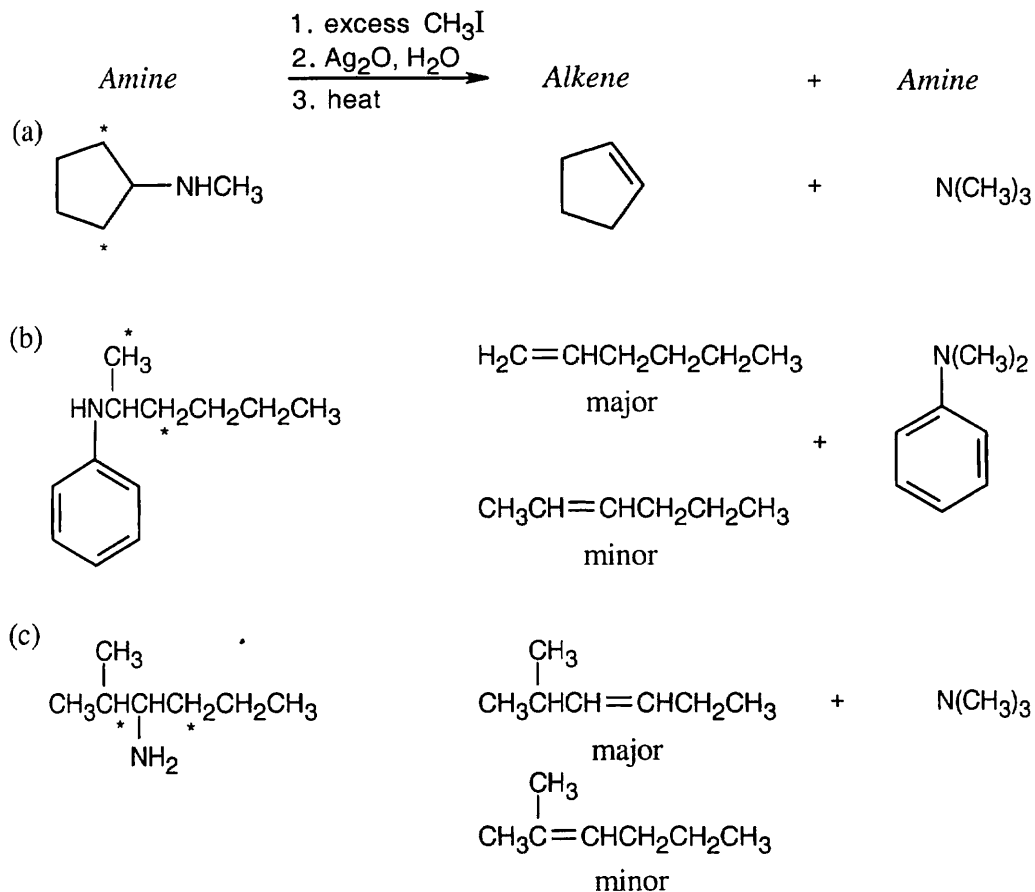
24.39 First, synthesize aniline from benzene, as shown in Problem 24.37 (a).



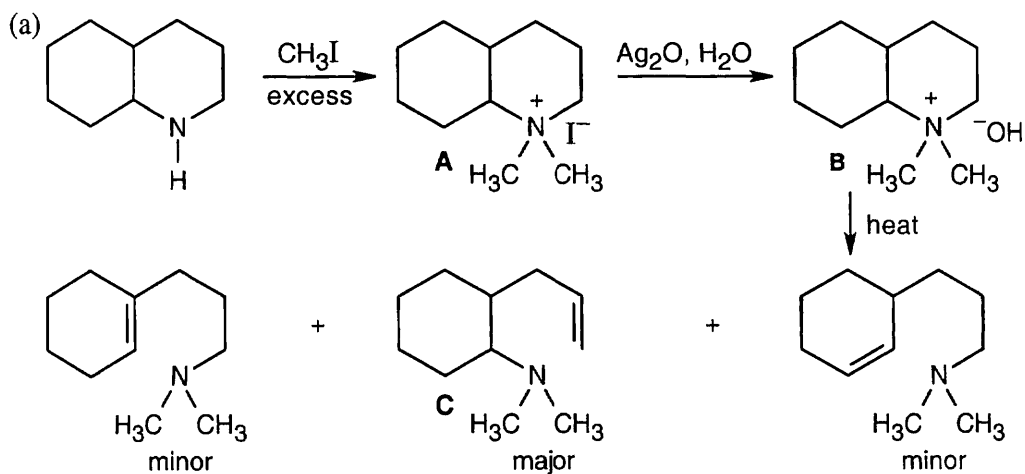
24.40

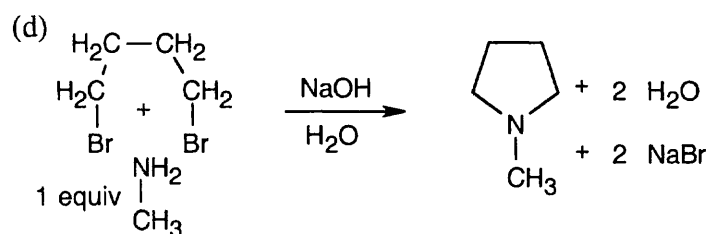
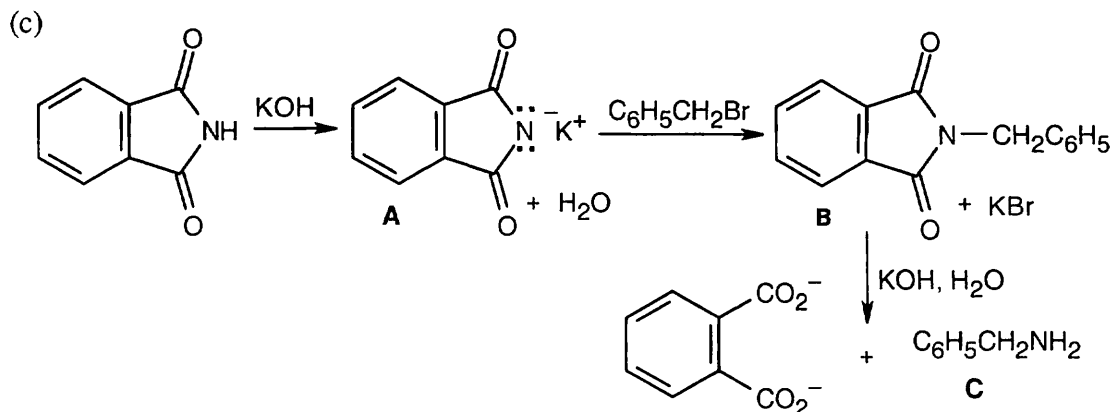
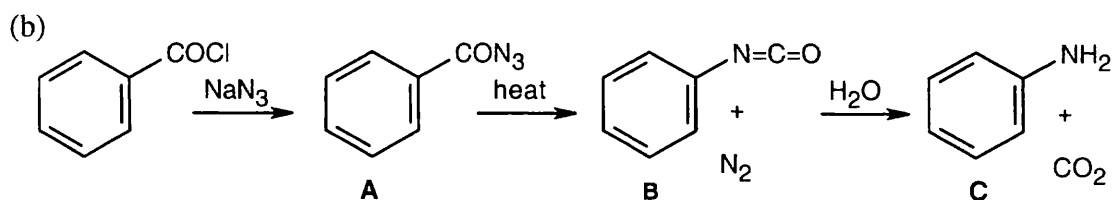


24.41 Hydrogens that can be eliminated are starred. In cases where more than one alkene can form, the alkene with the less substituted double bond is the major product..

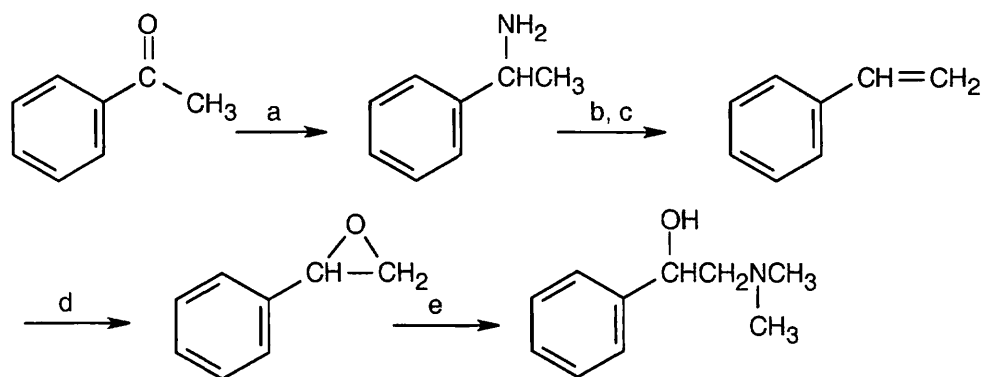


24.42





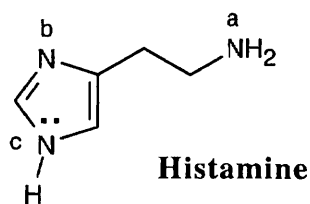
24.43



(a) NH_3 , NaBH_3CN ; (b) excess CH_3I ; (c) Ag_2O , H_2O , heat; (d) RCO_3H (e) $(\text{CH}_3)_2\text{NH}$. Step (e) is an $\text{S}_{\text{N}}2$ ring opening of the epoxide by nucleophilic substitution of the amine at the primary carbon.

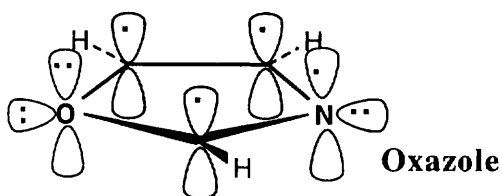
24.44 The pyrrole anion, $\text{C}_4\text{H}_4\text{N}^-$, is a 6π electron species that has the same electronic structure as the cyclopentadienyl anion. Both of these anions possess the aromatic stability of 6π electron systems.

24.45



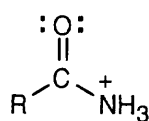
The "a" nitrogen is most basic because its electron pair is most available to Lewis acids. The "c" nitrogen is the least basic because the lone-pair electrons of the pyrrole nitrogen are part of the ring π electron system.

24.46

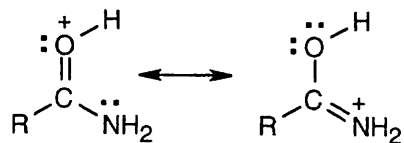


Oxazole is an aromatic 6π electron heterocycle. Two oxygen electrons and one nitrogen electron are in p orbitals that are part of the π electron system of the ring, along with one electron from each carbon. An oxygen lone pair and a nitrogen lone pair are in sp^2 orbitals that lie in the plane of the ring. Since the nitrogen lone pair is available for donation to acids, oxazole is more basic than pyrrole.

24.47



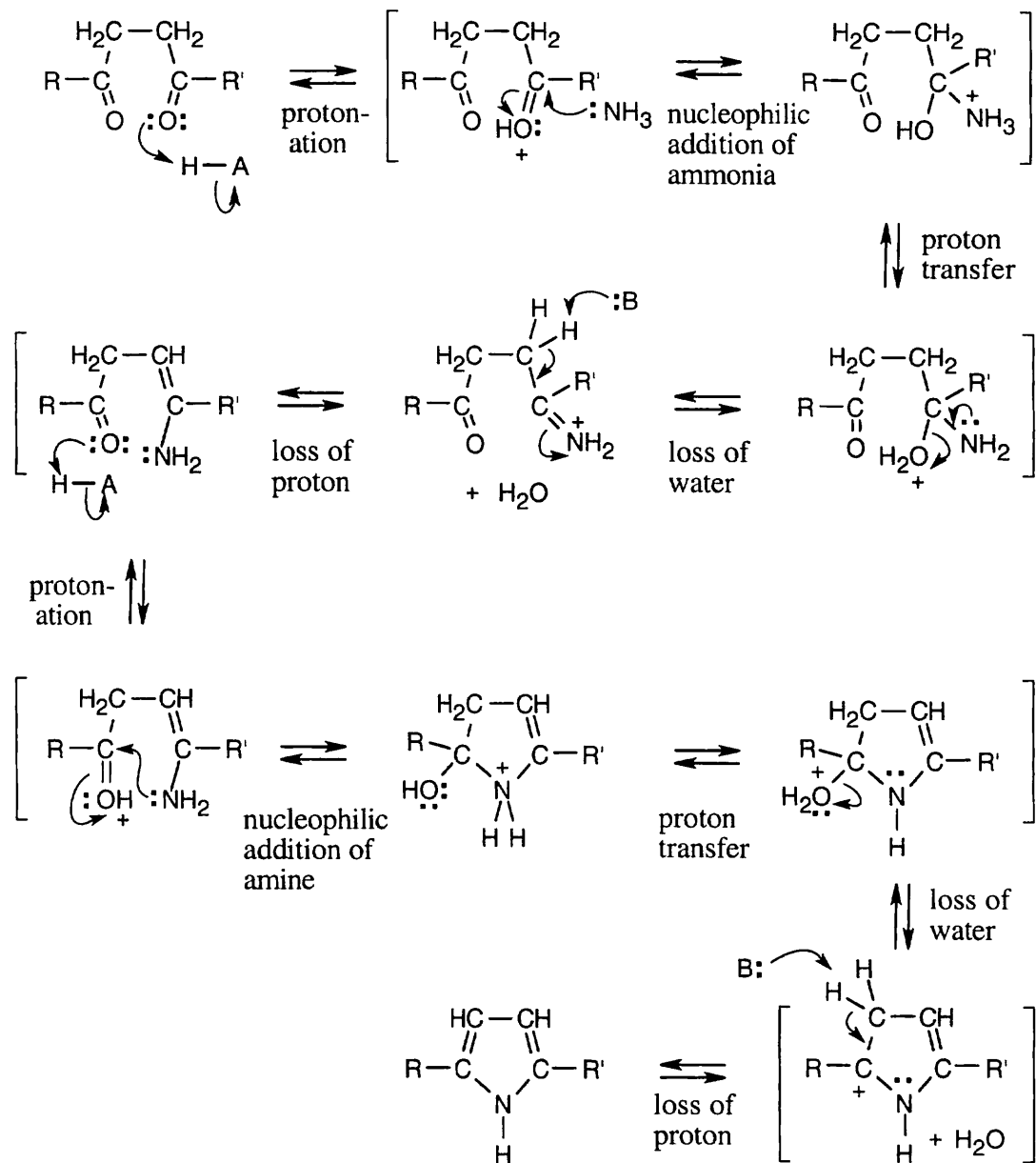
N-Protonation
(no resonance stabilization)



O-Protonation
(resonance stabilization)

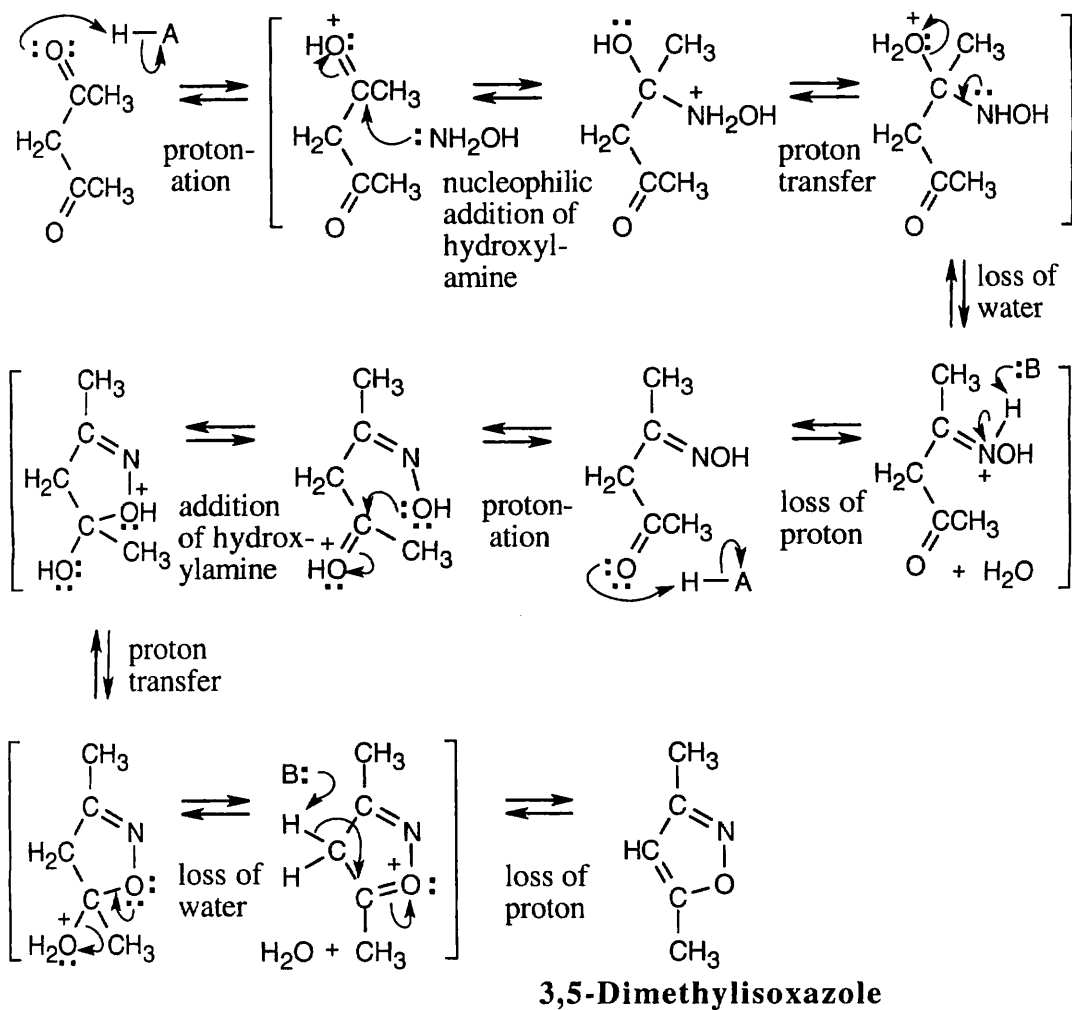
Protonation occurs on oxygen because an *O*-protonated amide is stabilized by resonance.

24.48



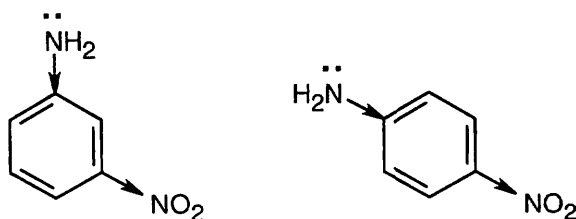
The mechanism consists of the nucleophilic addition of ammonia, first to one of the ketones, and then to the other, with loss of two equivalents of water.

24.49

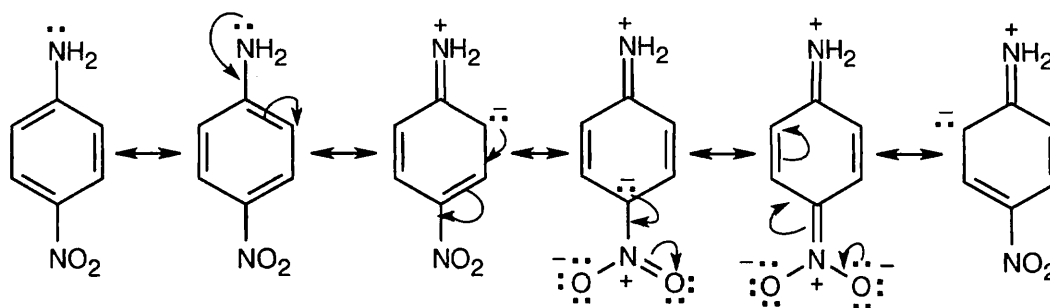


This mechanism is virtually identical to the mechanism illustrated in the previous problem, and involves two nucleophilic additions to carbonyl groups.

24.50

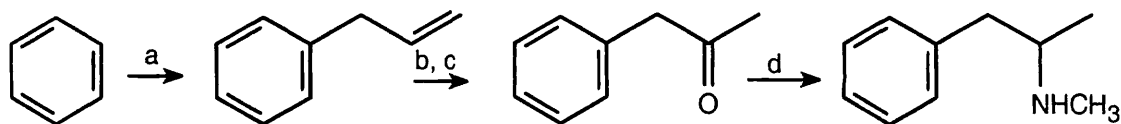


The inductive effect of the electron-withdrawing nitro group makes the amine nitrogens of both *m*-nitroaniline and *p*-nitroaniline less electron-rich and less basic than aniline.



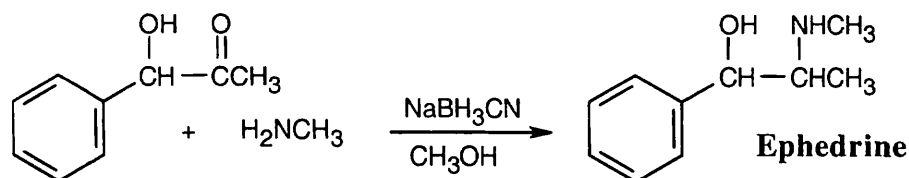
When the nitro group is para to the amino group, conjugation of the amino group with the nitro group can also occur. *p*-Nitroaniline is thus even less basic than *m*-nitroaniline.

24.51

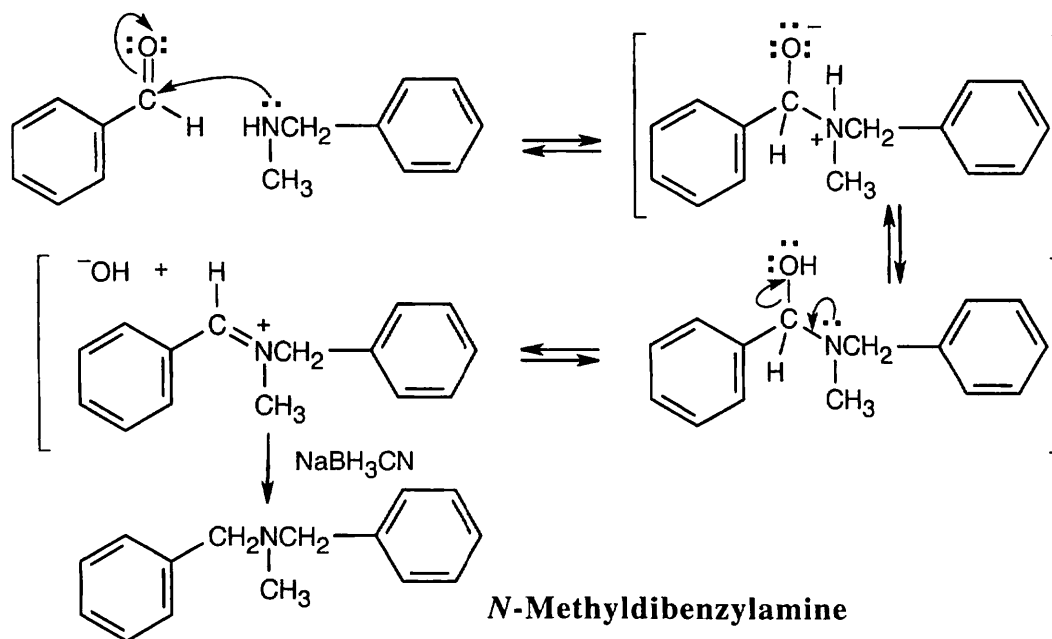


(a) $\text{CH}_2=\text{CHCH}_2\text{Cl}$, AlCl_3 ; (b) $\text{Hg}(\text{OAc})_2$, H_2O ; NaBH_4 ; (c) CrO_3 , H_3O^+ (d) CH_3NH_2 , NaBH_3CN .

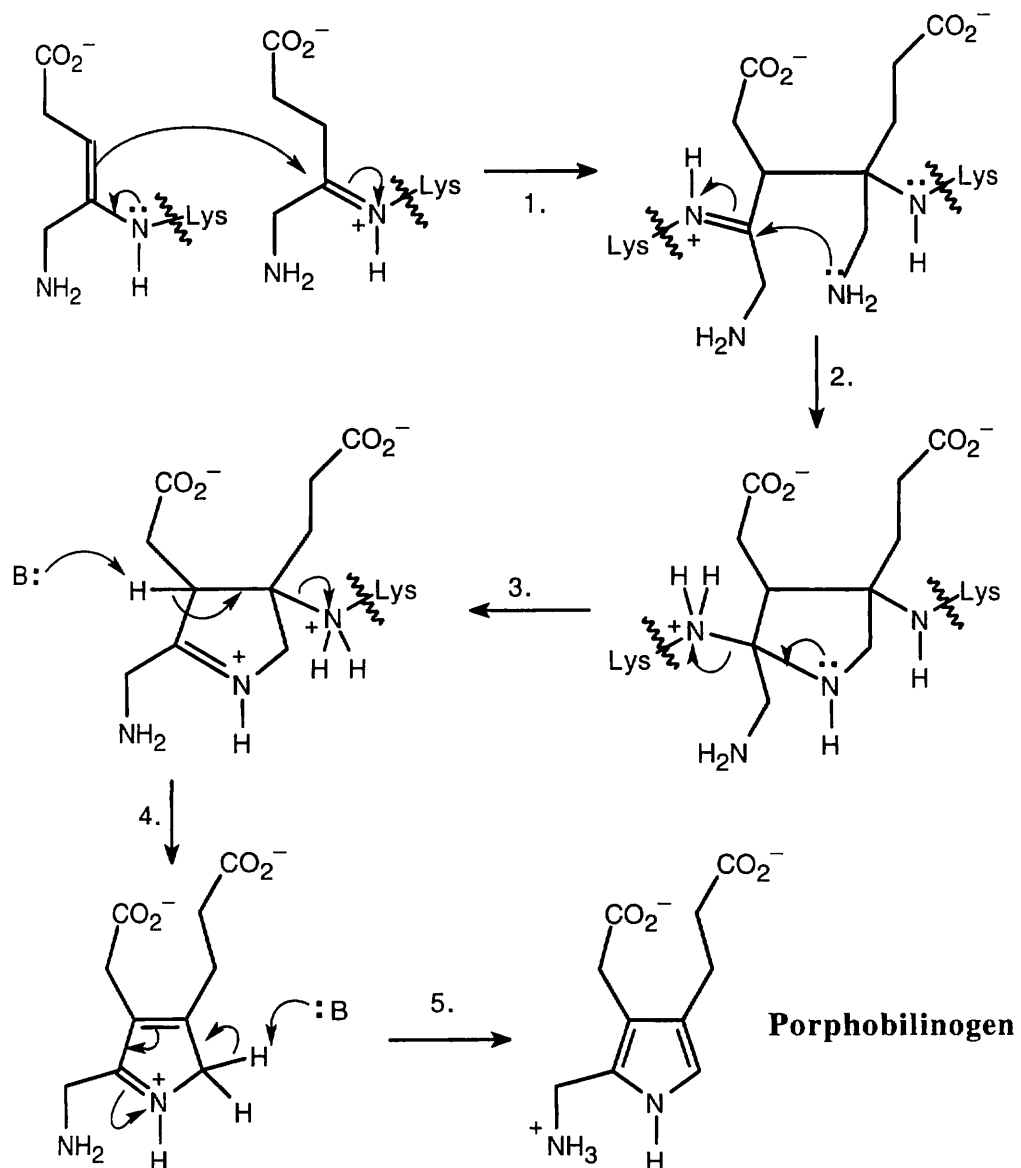
24.52



24.53 Benzaldehyde first reacts with methylamine and NaBH_3CN in the usual way to give the reductive amination product *N*-methylbenzylamine. This product then reacts further with benzaldehyde in a second reductive amination to give *N*-methyldibenzylamine.



24.54



Step 1: Nucleophilic addition.

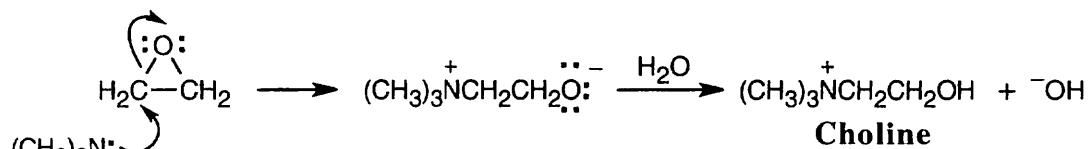
Step 2: Cyclization.

Step 3: Elimination of lysine.

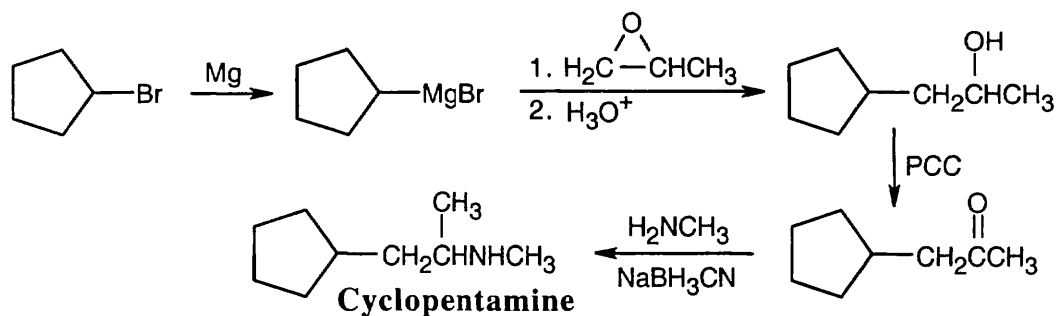
Step 4: Elimination of the other lysine.

Step 5: Tautomerization.

24.55 The reaction of trimethylamine with ethylene oxide is an S_N2 reaction that opens the epoxide ring.

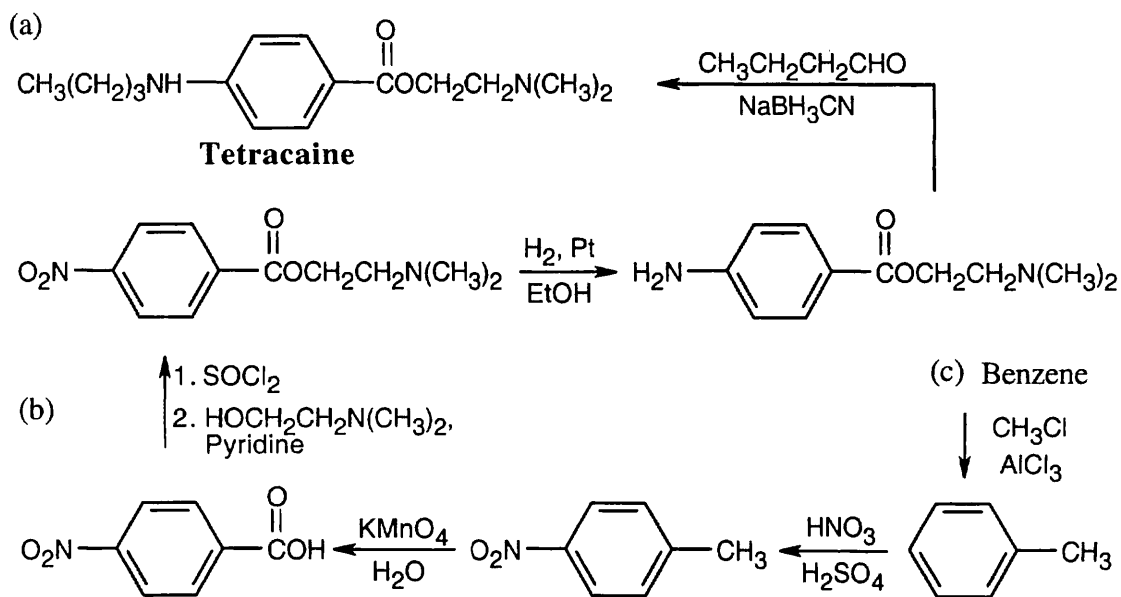


24.56



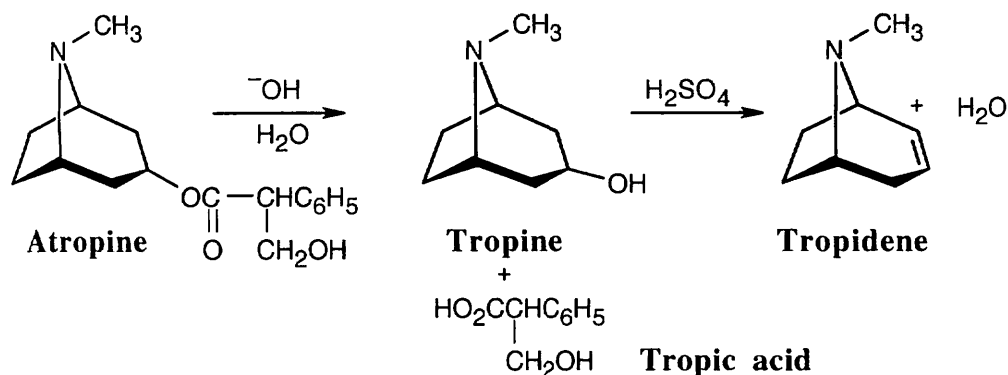
The last step of the synthesis is a reductive amination of a ketone that is formed by oxidation of the corresponding alcohol. The alcohol results from the Grignard reaction between cyclopentylmagnesium bromide and propylene oxide.

24.57



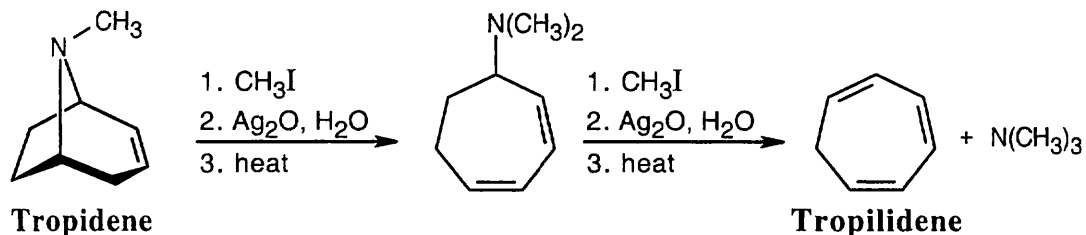
The synthesis in (a) is achieved by a reductive amination reaction. Reactions in (b) include formation of an acid chloride, esterification, and reduction of the nitro group.

24.58



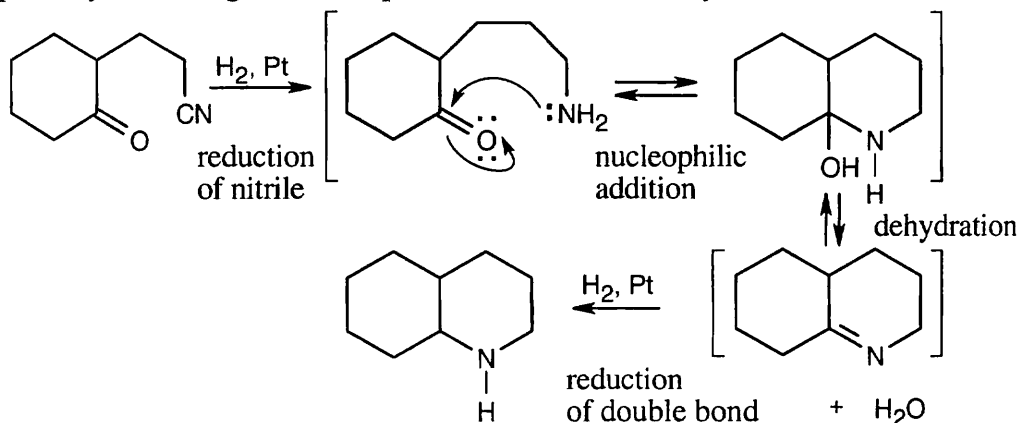
We know the location of the OH group of tropine because it is stated that tropine is an optically inactive alcohol. This hydroxyl group results from basic hydrolysis of the ester that is composed of tropine and tropic acid.

24.59

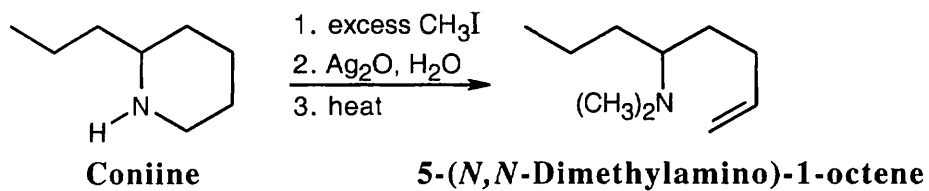


Tropilidene results from two cycles of Hofmann elimination on tropidene.

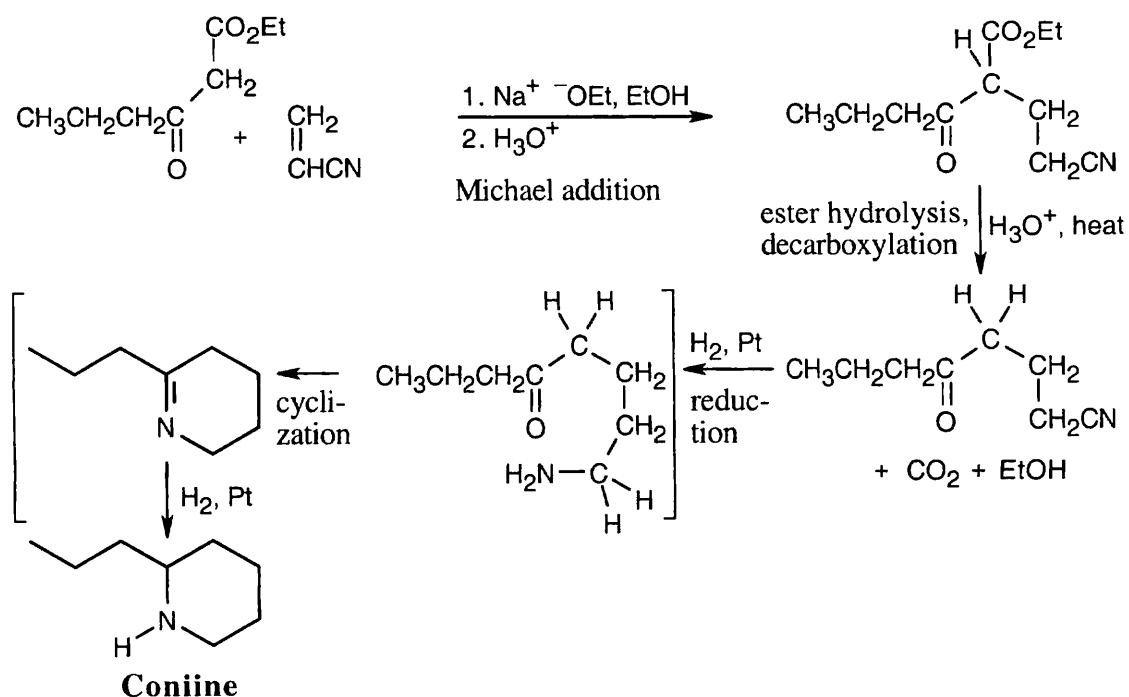
24.60 The formula $\text{C}_9\text{H}_{17}\text{N}$ indicates two degrees of unsaturation in the product. Both are probably due to rings since the product results from catalytic reduction.



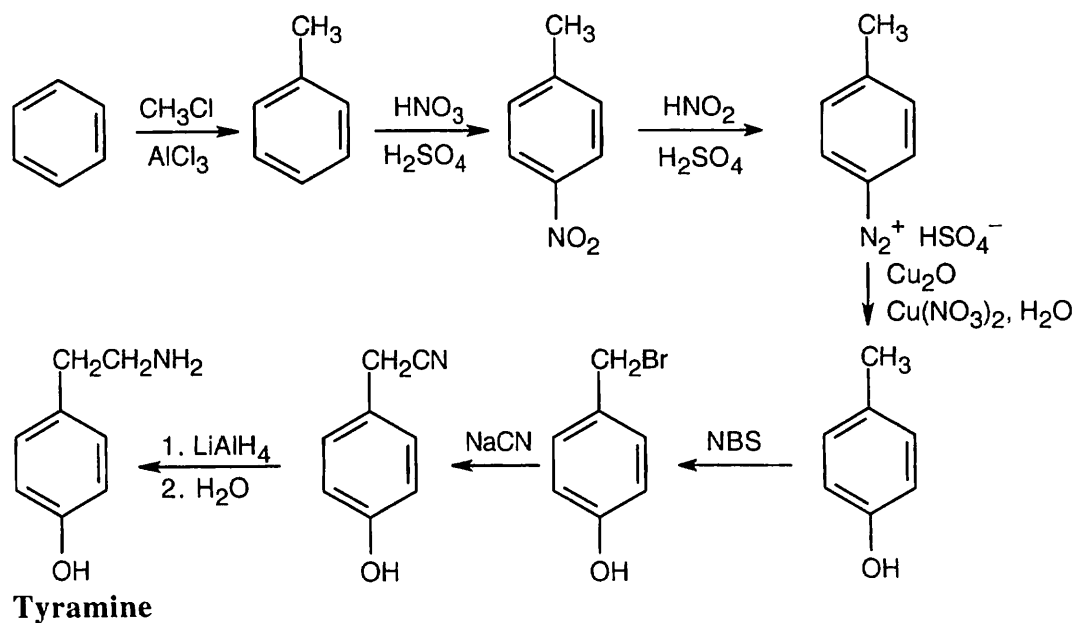
24.61 The molecular formula indicates that coniine has one double bond or ring, and the Hofmann elimination product shows that the nitrogen atom is part of a ring.



24.62



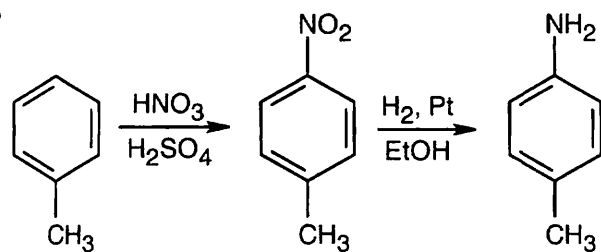
24.63



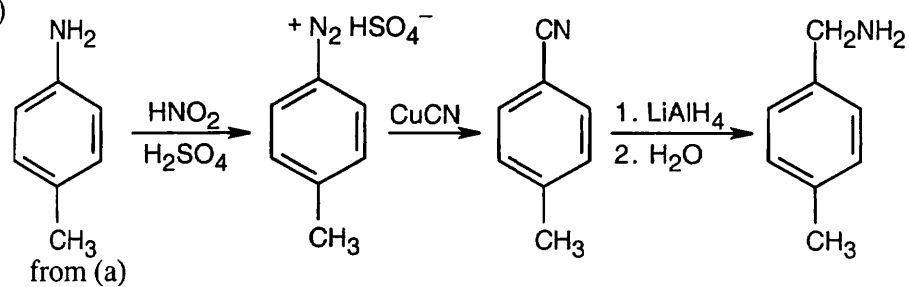
When you see $-\text{CH}_2\text{NH}_2$, think of the reduction of a nitrile. The nitrile comes from substitution of a benzylic bromide by ^-CN .

24.64

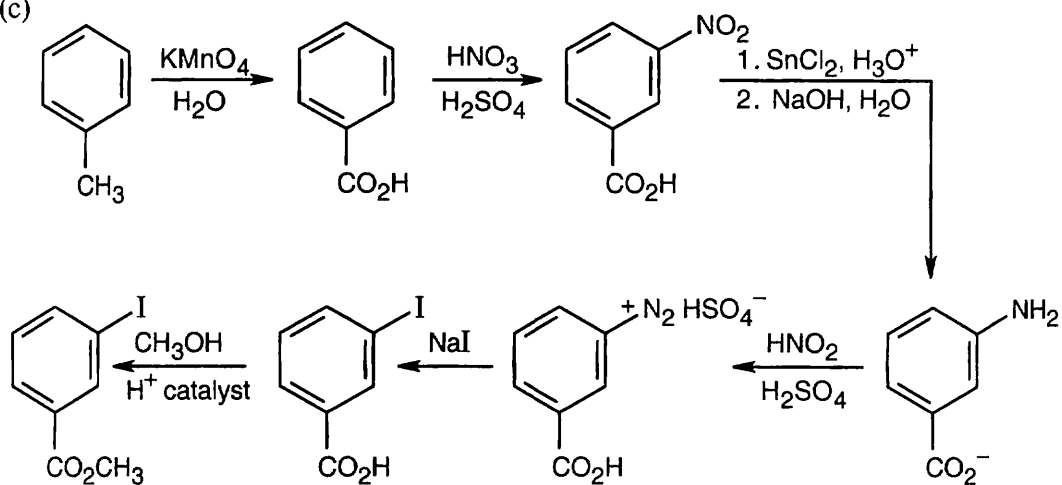
(a)



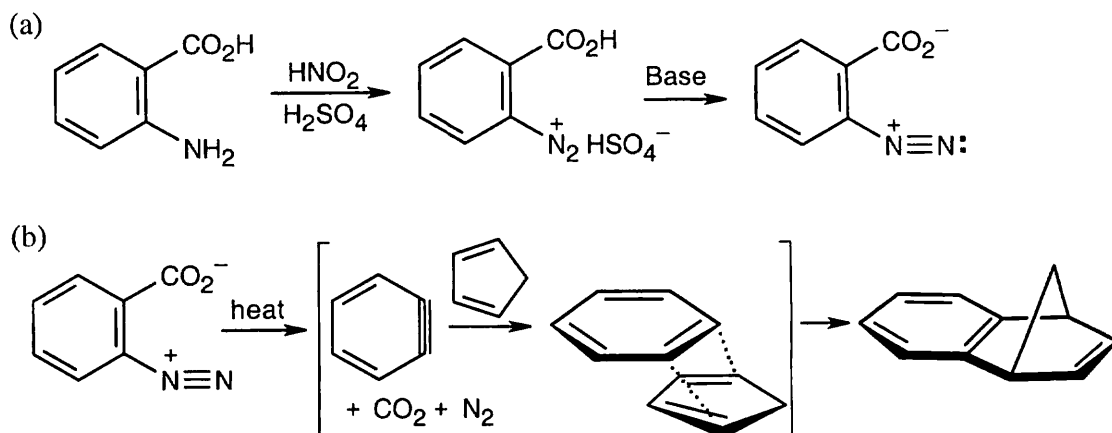
(b)



(c)

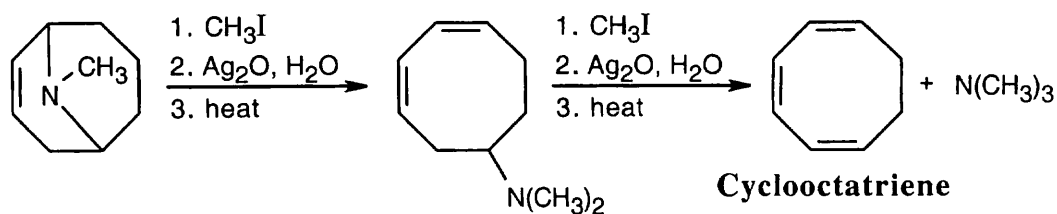


24.65

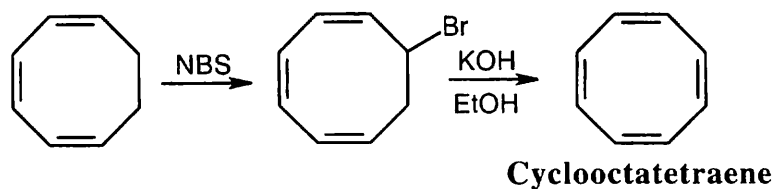


The reactive intermediate is benzyne, which undergoes a Diels Alder reaction with cyclopentadiene to yield the observed product.

24.66

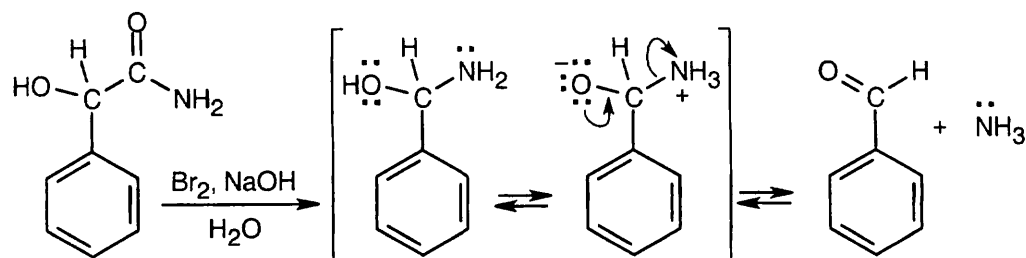


Two successive cycles of Hofmann elimination lead to formation of cyclooctatriene.



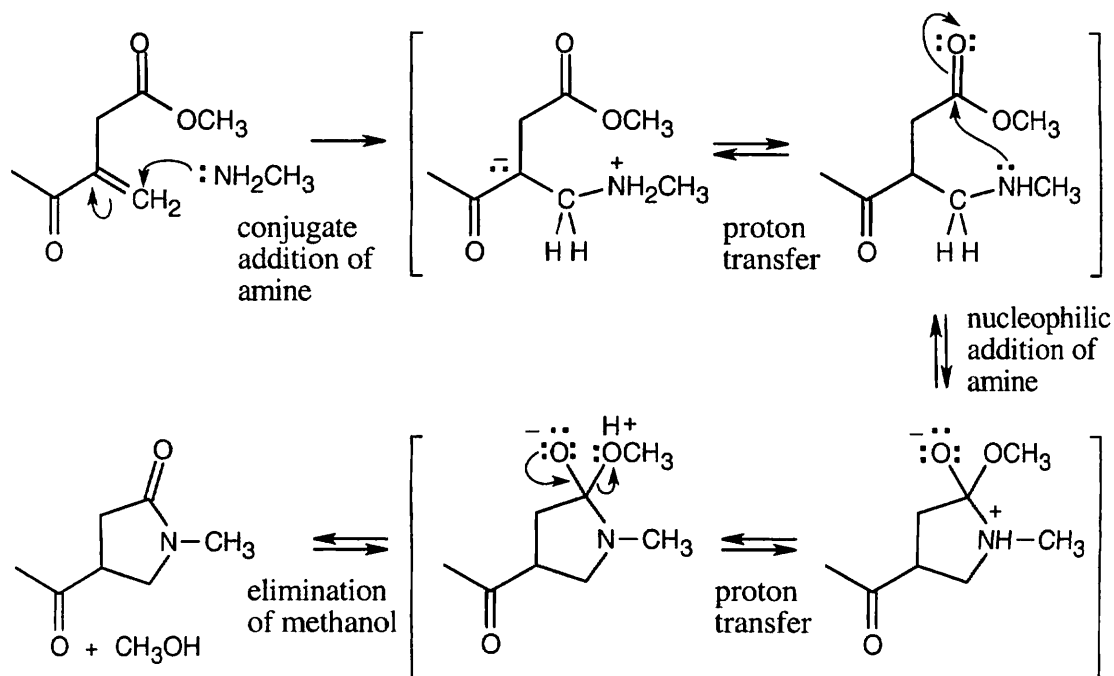
Allylic bromination followed by elimination yield cyclooctatetraene.

24.67

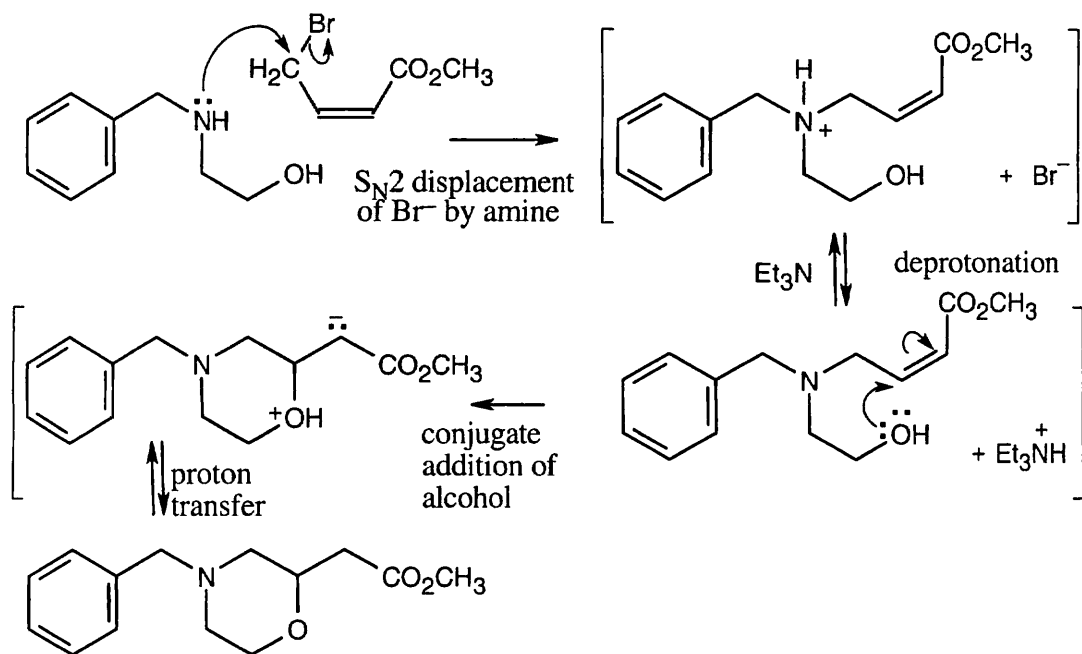


Hofmann rearrangement (the mechanism is shown in Section 24.6) of an α -hydroxy amide produces a carbinolamine intermediate that expels ammonia to give an aldehyde.

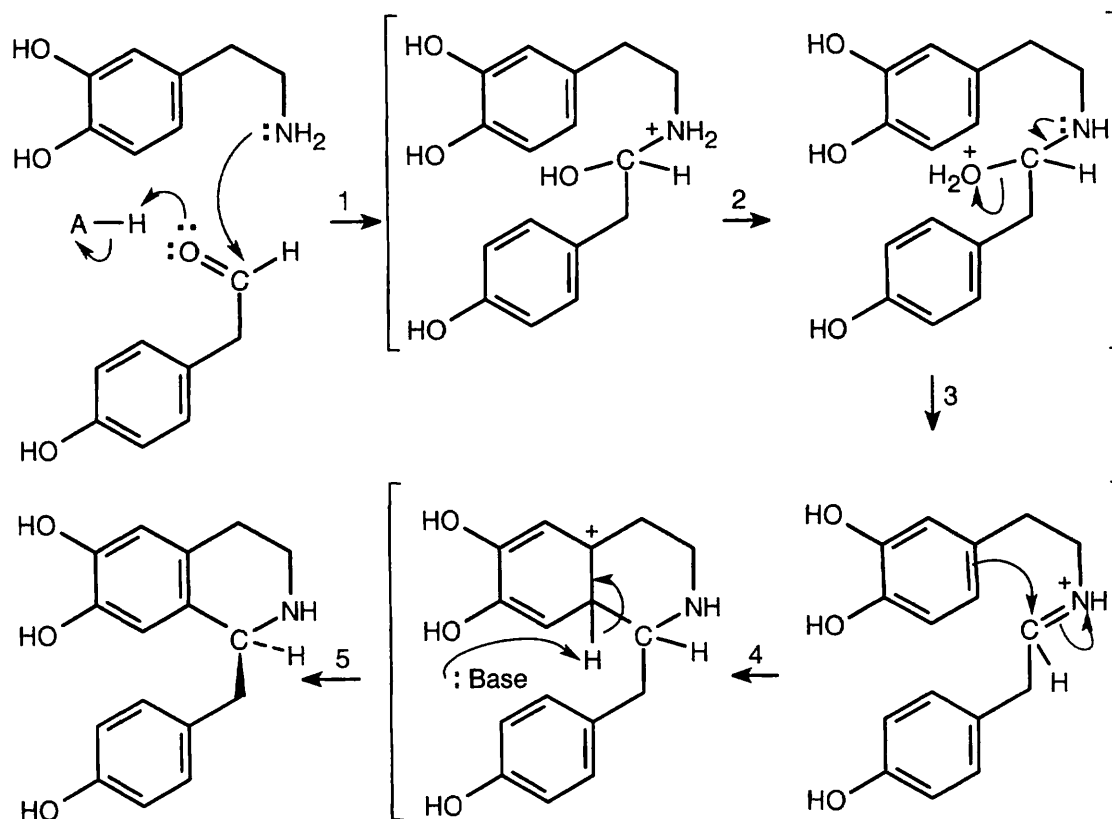
24.68



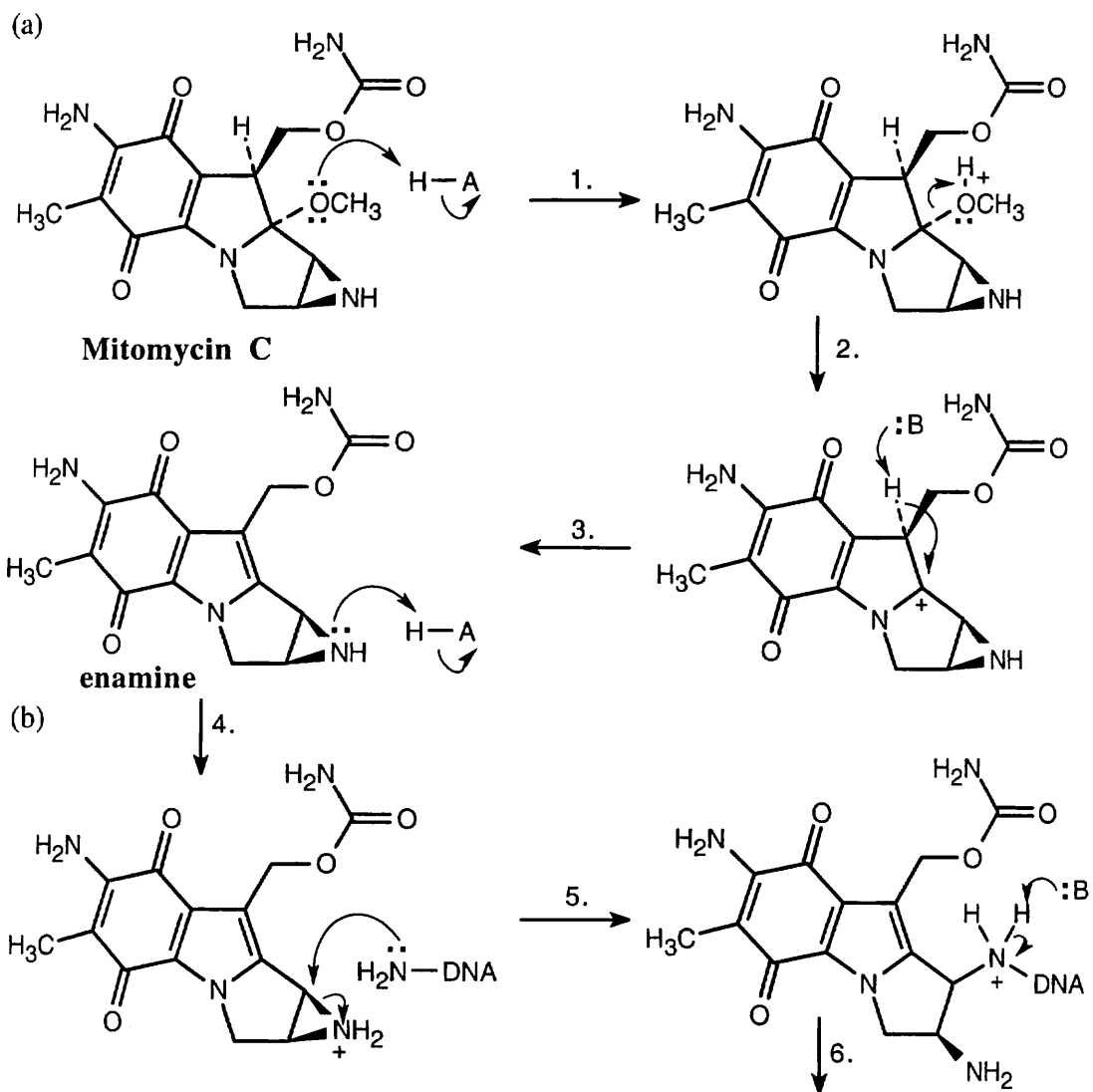
24.69

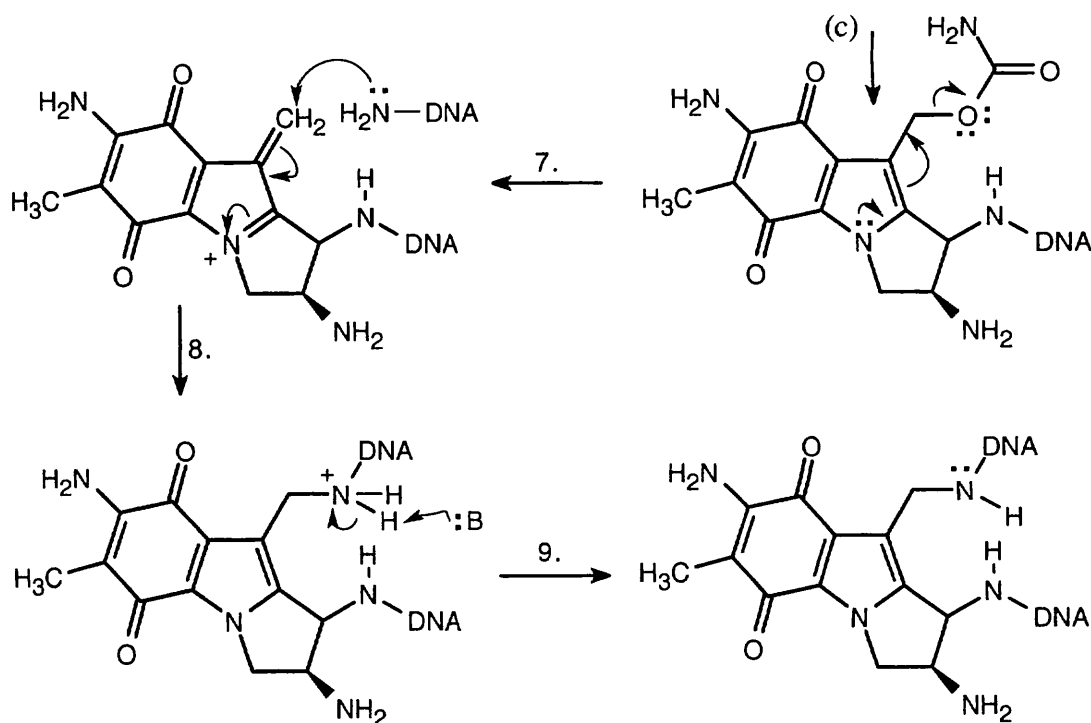


24.70

**(S)-Norcoclaurine****Step 1:** Nucleophilic addition of the amine to the protonated aldehyde.**Step 2:** Proton transfer.**Step 3:** Loss of water.**Step 4:** Electrophilic aromatic substitution.**Step 5:** Loss of proton.

24.71





Steps 1 – 3: E1 elimination (protonation, loss of HOCH₃, deprotonation).

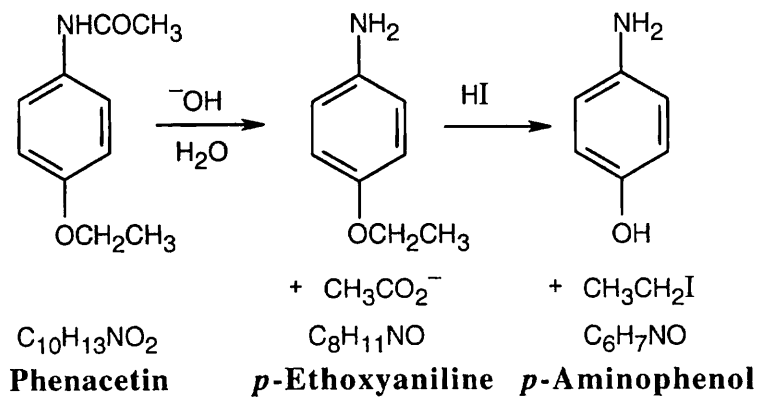
Steps 4 – 6: S_N2 substitution (protonation, substitution, deprotonation).

Step 7: E1 elimination of carbamate.

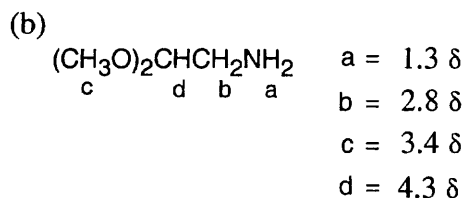
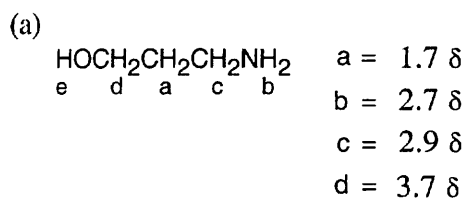
Steps 8 – 9: conjugate addition of DNA (addition, deprotonation).

Notice that five of the nine steps are either protonations or deprotonations.

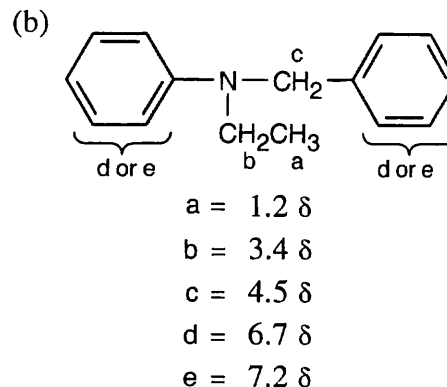
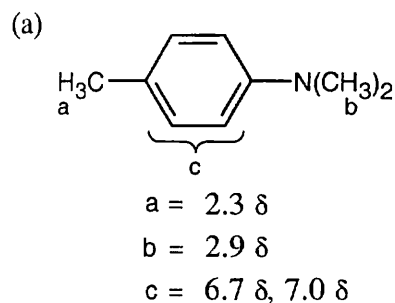
24.72 The ¹H NMR of the amine shows 5 peaks. Two are due to an ethyl group bonded to an electronegative element (oxygen), two are due to 4 aromatic ring hydrogens, and the peak at 3.4 δ is due to 2 amine hydrogens.



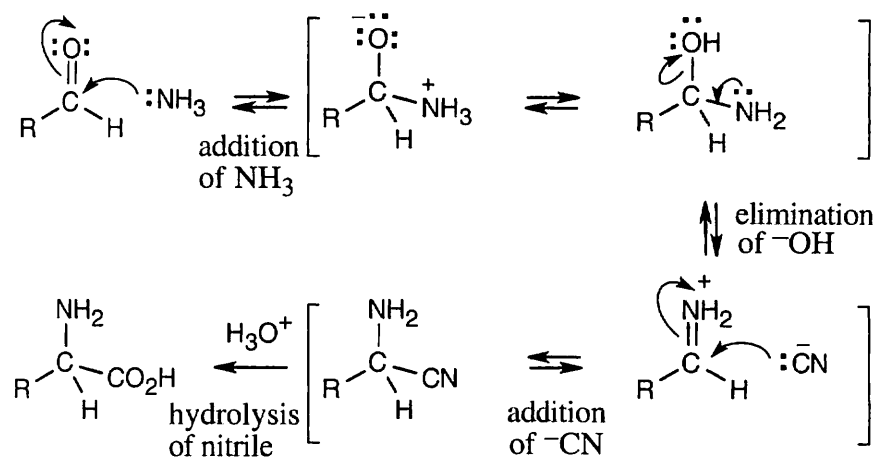
24.73



24.74

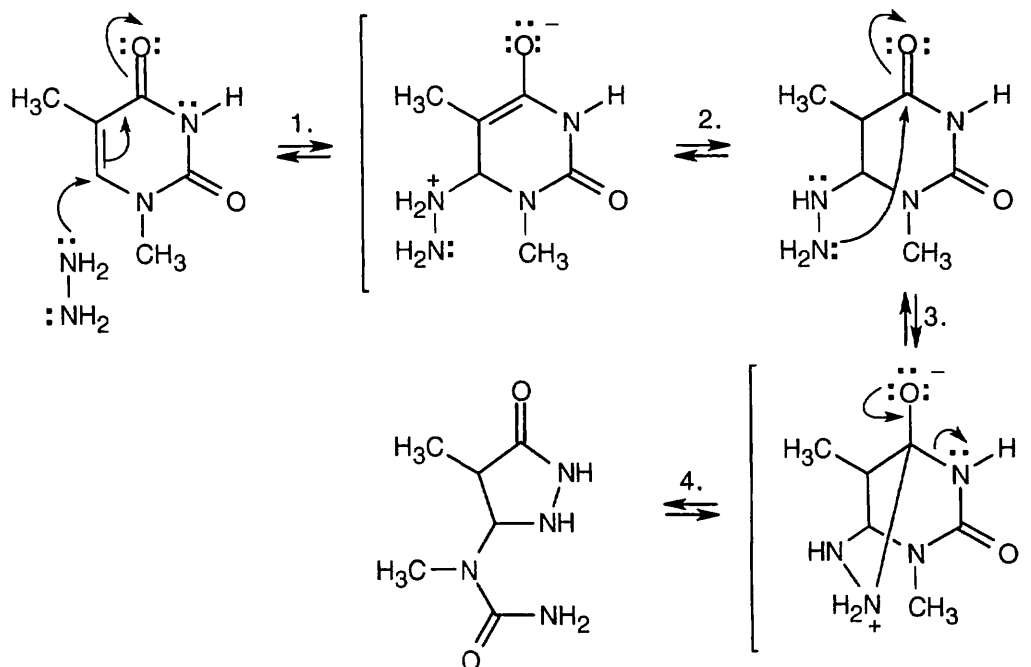


24.75



The mechanism of acid-catalyzed nitrile hydrolysis is shown in Problem 20.45.

24.76



Step 1: Conjugate addition of hydrazine.

Step 2: Proton transfer.

Step 3: Nucleophilic acyl substitution, forming the cyclic amide.

Step 4: Proton transfer.

Review Unit 9: Carbonyl Compounds II

Reaction at the α Carbon; Amines

Major Topics Covered (with vocabulary):

Carbonyl α -substitution reactions:

α -substitution reaction tautomerism tautomer enolate ion Hell-Volhard-Zelinskii reaction
 β -diketone β -keto ester malonic ester synthesis acetoacetic ester synthesis LDA

Carbonyl condensation reactions:

carbonyl condensation reactions aldol reaction enone mixed aldol reaction
Claisen condensation reaction Dieckmann cyclization Michael reaction Michael acceptor
Michael donor Stork enamine reaction Robinson annulation reaction

Amines:

primary, secondary, tertiary amine quaternary ammonium salt arylamine heterocyclic amine
pyramidal inversion K_b azide synthesis Gabriel amine synthesis reductive amination
Hofmann rearrangement Curtius rearrangement Hofmann elimination reaction
arenediazonium salt diazotization Sandmeyer reaction azo compound
diazonium coupling reaction pyrrole thiophene furan pyridine fused-ring heterocycle
pyrimidine purine nitrogen rule

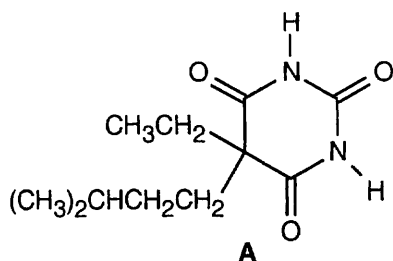
Types of Problems:

After studying these chapters, you should be able to:

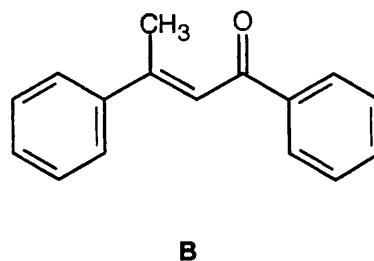
- Draw keto-enol tautomers of carbonyl compounds, identify acidic hydrogens, and draw the resonance forms of enolates.
- Formulate the mechanisms of acid- and base-catalyzed enolization and of other α -substitution reactions.
- Predict the products of α -substitution reactions.
- Use α -substitution reactions in synthesis.
- Predict the products of carbonyl condensation reactions.
- Formulate the mechanisms of carbonyl condensation reactions.
- Use carbonyl condensation reactions in synthesis.
- Name and draw amines, and classify amines as primary, secondary, tertiary, quaternary, arylamines, or heterocyclic amines.
- Predict the basicity of alkylamines, arylamines and heterocyclic amines.
- Synthesize alkylamines and arylamines by several routes.
- Predict the products of reactions involving alkylamines and arylamines.
- Use diazonium salts in reactions involving arylamines, including diazo coupling reactions.
- Draw orbital pictures of heterocycles and explain their acid-base properties.
- Explain orientation and reactivity in heterocyclic reactions, and predict the products of reactions involving heterocycles.
- Propose mechanisms for reactions involving alkylamines, arylamines, and heterocycles.
- Identify amines by spectroscopic techniques.

Points to Remember:

- * It is unusual to think of a carbonyl compound as an acid, but the protons α to a carbonyl group can be removed by a strong base. Protons α to two carbonyl groups are even more acidic: in some cases, acidity approaches that of phenols. This acidity is the basis for α -substitution reactions of compounds having carbonyl groups. Abstraction by base of an α proton produces a resonance-stabilized enolate anion that can be used in alkylations involving alkyl halides and tosylates.
- * Alkylation of an unsymmetrical LDA-generated enolate generally occurs at the less hindered α carbon.
- * When you need to synthesize a β -hydroxy ketone or aldehyde or an α,β -unsaturated ketone or aldehyde, use an aldol reaction. When you need to synthesize a β -diketone or β -keto ester, use a Claisen reaction. When you need to synthesize a 1,5-dicarbonyl compound, use a Michael reaction. The Robinson annulation is used to synthesize polycyclic molecules by a combination of a Michael reaction with an aldol condensation.
- * In many of the mechanisms in this group of chapters, the steps involving proton transfer are not explicitly shown. The proton transfers occur between the proton and the conjugate base with the most favorable pK of those present in the solution. These steps have been omitted at times to simplify the mechanisms.
- * In the Claisen condensation, the enolate of the β -dicarbonyl compound is treated with H_3O^+ to yield the neutral product.
- * For an amine, the larger the value of pK_a of its ammonium ion, the stronger the base. The smaller the value of pK_b of the amine, the stronger the base.
- * The Sandmeyer reaction allows the synthesis of substituted benzenes that can't be formed by electrophilic aromatic substitution reactions. These reactions succeed because N_2 is a very good leaving group.

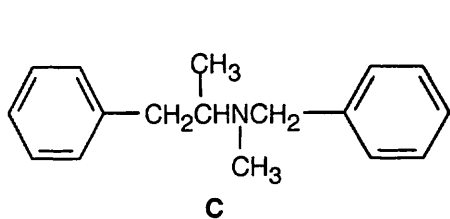
Self-Test:

Pentymal
(a sedative)

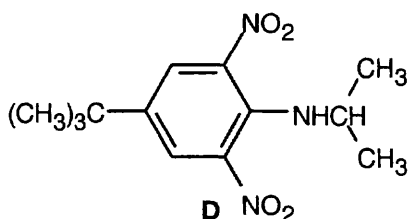


Dyprone
(sunscreen)

The six-membered ring in **A** is formed by the cyclization of two difunctional compounds. What are they? What type of reaction occurs to form the ring? The two alkyl groups are introduced into one of the difunctional compounds prior to cyclization. What type of reaction is occurring, and how is it carried out? What type of reaction occurs in the formation of Dyprone (**B**)? Why might **B** be effective as a sunscreen?



Benzphetamine
(an appetite suppressant)



Butralin
(an herbicide)

What type of amine is **C**? Do you expect it to be more or less basic than ammonia? Than aniline? What product do you expect from Hofmann elimination of **C**? What significant absorptions might be seen in the IR spectrum of **C**? What information can be obtained from the mass spectrum? Plan a synthesis of **D** from benzene.

Multiple Choice:

- Which of the following compounds has four acidic hydrogens?
(a) 2-Pentanone (b) 3-Pentanone (c) Acetophenone (d) Phenylacetone
- In which of the following reactions is an enol, rather than an enolate, the reacting species?
(a) acetoacetic acid synthesis (b) malonic ester synthesis (c) LDA alkylation (d) Hell-Volhard-Zelinskii reaction
- Cyclobutanecarboxylic acid is probably the product of a:
(a) malonic ester synthesis (b) acetoacetic ester synthesis (c) LDA alkylation (d) Hell-Volhard-Zelinskii reaction
- An LDA alkylation can be used to alkylate all of the following, except:
(a) aldehydes (b) ketones (c) esters (d) nitriles
- If you want to carry out a carbonyl condensation, and you don't want to form α -substitution product, you should:
(a) lower the temperature (b) use one equivalent of base (c) use a catalytic amount of base (d) use a polar aprotic solvent
- Which reaction forms a cyclohexenone?
(a) Dieckmann cyclization (b) Michael reaction (c) Claisen condensation (d) intramolecular aldol condensation
- All of the following molecules are good Michael donors except:
(a) Ethyl acetoacetate (b) Nitroethylene (c) Malonic ester (d) Ethyl 2-oxocyclohexanecarboxylate
- The ammonium ion of which of the following amines has the smallest value of pK_a ?
(a) Methylamine (b) Trimethylamine (c) Aniline (d) *p*-Bromoaniline
- All of the following methods of amine synthesis are limited to primary amines, except:
(a) Curtius rearrangement (b) reductive amination (c) Hofmann rearrangement (d) azide synthesis
- To form an azo compound, an aryldiazonium salt should react with:
(a) CuCN (b) benzene (c) nitrobenzene (d) phenol