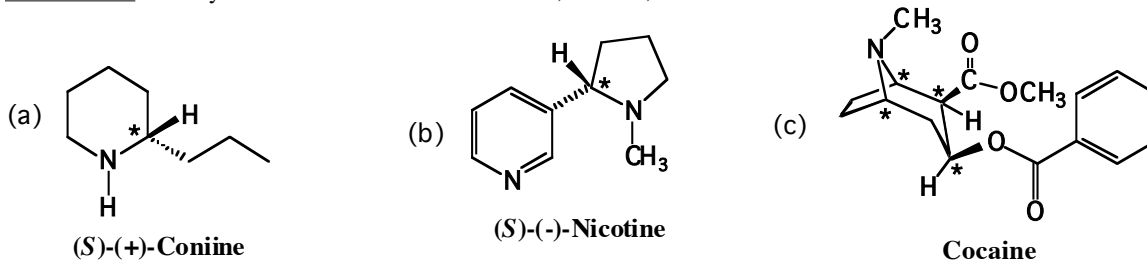


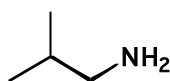
CHAPTER 23
Solutions to the Problems

Problem 23.1 Identify all carbon chiral centers in coniine, nicotine, and cocaine.

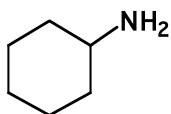


Problem 23.2 Write structural formulas for these amines.

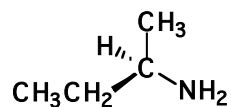
(a) 2-Methyl-1-propanamine



(b) Cyclohexanamine

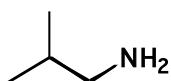


(c) (R)-2-Butanamine

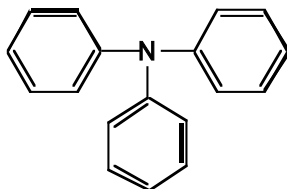


Problem 23.3 Write structural formulas for these amines.

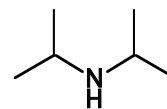
(a) Isobutylamine



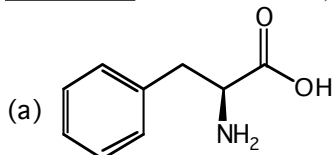
(b) Triphenylamine



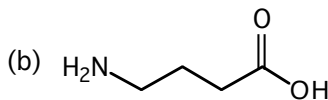
(c) Diisopropylamine



Problem 23.4 Write IUPAC and, where possible, common names for each compound.



(S)-2-Amino-3-phenylpropanoic acid
(L-Phenylalanine)

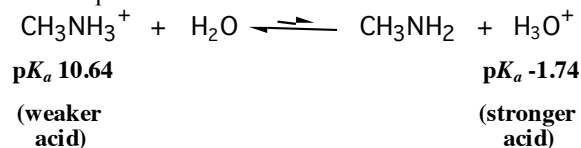


4-Aminobutanoic acid
(γ -Aminobutyric acid)



2,2-Dimethylpropanamine
(Neopentylamine)

Problem 23.5 Predict the position of equilibrium for this acid-base reaction.



Because equilibrium favors formation of the weaker acid, equilibrium will be to the left as shown.

MCAT Practice: Questions

The Planarity of -NH_2 Groups on Heterocyclic Rings

A. The angle found in *p*-nitroaniline means that the amine group is planar and in the same plane as the benzene ring. Why is this the case?

1. The nitro group withdraws the lone pair electron from the amine, primarily via induction, making the N atom sp^2 hybridized and hence trigonal planar.

2. The nitro group withdraws the lone pair electrons from the amine, primarily via resonance, making the N atom sp^2 hybridized and hence trigonal planar.

3. The lone pair of the N atom of the NH_2 must be in a *p* orbital to make the system aromatic.

4. The nitrogen of an amine is usually planar, and aniline and methylamine are exceptions.

B. What is the hybridization of the nitrogen in aniline?

1. The nitrogen is sp^2 hybridized.

2. The nitrogen is sp^3 hybridized.

3. The nitrogen is between sp^2 and sp^3 hybridized, but closer to sp^3 .

4. The nitrogen is between sp^2 and sp^3 hybridized, but closer to sp^2 .

C. What accounts for the geometry (pyramidalization) of the NH_2 group in aniline?

1. Resonance between the NH_2 group and the benzene ring.

2. The electronic withdrawing nature of the sp^2 carbons in the phenyl group.

3. Participation of the nitrogen lone pair to make the system aromatic.

4. Both 1 and 3.

D. The pK_a s of the conjugate acids of aniline and methylamine are 4.6 and 10.7, respectively. What accounts for the greater acidity of the conjugate acid of aniline?

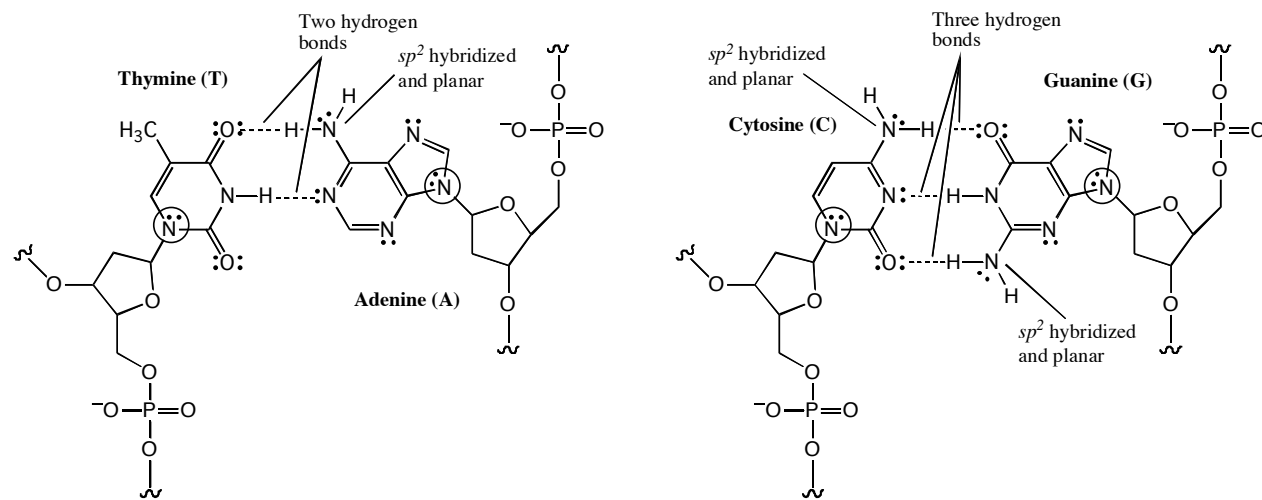
1. Resonance between the NH_2 group and the benzene ring.

2. The electronic withdrawing nature of the sp^2 carbons in the phenyl group.

3. Participation of the nitrogen lone pair to make the system aromatic.

4. Both 1 and 2.

The geometry of -NH_2 groups on heterocyclic rings has a profound influence on the properties and folding of nucleic acids. Three of the four common nucleic acid bases have amino groups (see next page). In each case, the angle between the bisector of the -NH_2 group and the attached ring is 180° (such as drawn above for *p*-nitroaniline). Not only does the hybridization of the amino group allow for an overall flat structure, but also the geometry of the planar amino group is ideal for making specific, highly directional hydrogen bonds with the complementary base.



The structures of the T–A and C–G base pairs showing the locations of planar -NH_2 groups bonded to the aromatic bases as well as the specific patterns of hydrogen bonds responsible for recognition between complementary strands of DNA.

E. In the structures of T–A and C–G base pairs, there are three amino groups specifically labeled as “ sp^2 hybridized and planar”. What is the primary difference between these structures and that of aniline that lead to their planarity?

1. In contrast to aniline, the amino groups on the DNA bases are necessary to make the heterocyclic rings aromatic.

2. In contrast to aniline, the contributing structures that delocalize the nitrogen lone pairs onto the rings creates partial negative charges on electronegative atoms.

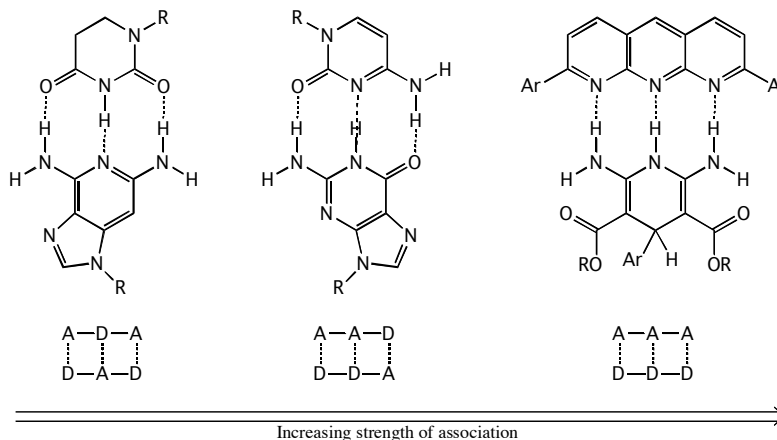
3. In contrast to aniline, the hydrogen bond accepting ability of the lone pairs on the -NH_2 groups of the DNA bases is better when these amino groups are sp^2 hybridized.

4. Both 2 and 3.

F. In the structures of T—A and C—G base pairing, four nitrogens are circled. Given your knowledge of organic functional group names, which of the following is the most appropriate descriptor for the kind of functional group that these nitrogens are part of?

1. An *N*-heterocyclic ester.
2. An *N*-acetal.
3. An imide.
4. An imine.

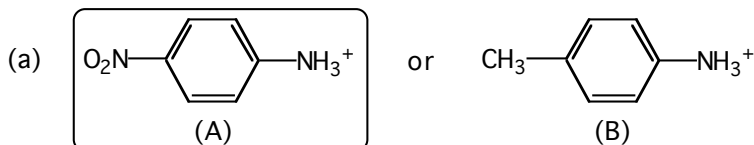
Chemists have studied base pairings analogous to those found in DNA in order to shed light on the strength of the hydrogen bonds. For example, the strength of the association of the following three base pairs increases in the order given (as an abbreviation, the pattern can be written with D = hydrogen bond Donor and A = hydrogen bond Acceptor).



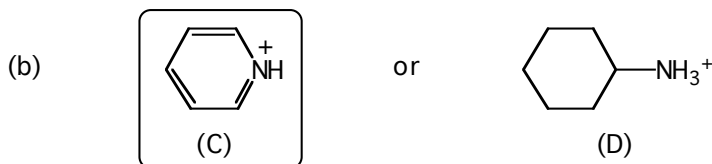
G. Which of the following is the most likely explanation for the order of association found experimentally?

1. A trend is not expected, and hence the result is random.
2. The overall number of hydrogen bond donating and hydrogen bond accepting interactions increases from left to right.
3. The hydrogen bonds are increasingly more linear in the complexes from the left to the right.
4. By decreasing the alternation of hydrogen bond donors and acceptors on the same molecule, the hydrogen bonds becomes stronger due to less repulsive interactions between neighboring hydrogen bonds.

Problem 23.6 Select the stronger acid from each pair of compounds.

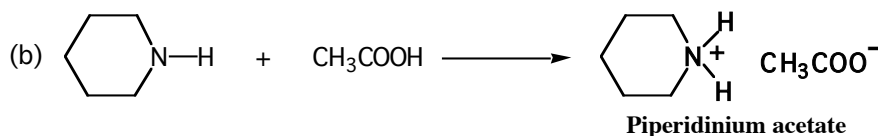
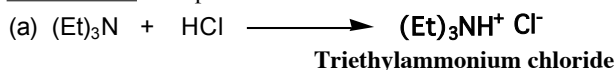


4-Nitroaniline (pK_b 13.0) is a weaker base than 4-methylaniline (pK_b 8.92). The decreased basicity of 4-nitroaniline is due to the electron-withdrawing effect of the *para* nitro group. Because 4-nitroaniline is the weaker base, its conjugate acid (A) is the stronger acid.

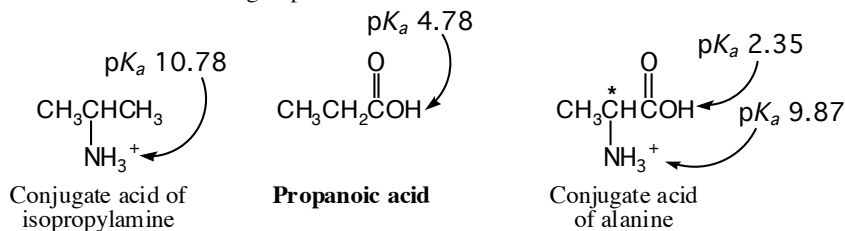


Pyridine (pK_b 8.75) is a much weaker base than cyclohexanamine (pK_b 3.34). The lone pair of electrons in the sp^2 orbital on the nitrogen atom of pyridine (C) has more *s* character, so these electrons are less available for bonding to a proton. Because pyridine is a weaker base, its conjugate acid, (C), is the stronger acid.

Problem 23.7 Complete each acid-base reaction and name the salt formed.



Problem 23.8 Following are structural formulas for propanoic acid and the conjugate acids of isopropylamine and alanine, along with $\text{p}K_a$ values for each functional group:



(a) How do you account for the fact that the $-\text{NH}_3^+$ group of the conjugate acid of alanine is a stronger acid than the $-\text{NH}_3^+$ group of the conjugate acid of isopropylamine?

The electron-withdrawing properties of the carboxyl group adjacent to the amine of alanine make the conjugate acid of alanine more acidic than the conjugate acid of isopropylamine.

(b) How do you account for the fact that the $-\text{COOH}$ group of the conjugate acid of alanine is a stronger acid than the $-\text{COOH}$ group of propanoic acid?

The $-\text{NH}_3^+$ group is electron-withdrawing, so the adjacent $-\text{COOH}$ group is made more acidic by an inductive effect. This situation is analogous to the electron-withdrawing effects of halogens adjacent to carboxylic acids in molecules such as chloroacetic acid, which has a $\text{p}K_a$ of 2.86. In addition, deprotonation of the carboxylic acid function of alanine results in formation of an overall neutral zwitterion. Thus, the carboxylate form of alanine can be thought of as being neutralized by the adjacent positively-charged ammonium ion.

Problem 23.9 In what way(s) might the results of the separation and purification procedure outlined in Example 23.9 be different if the following conditions exist?

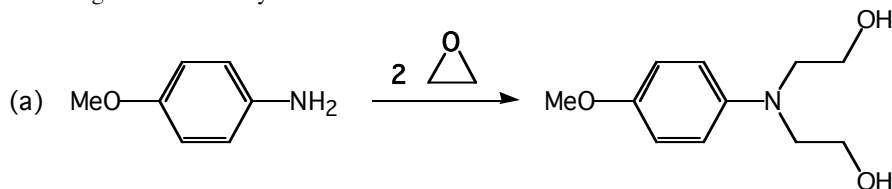
(a) Aqueous NaOH is used in place of aqueous NaHCO_3 ?

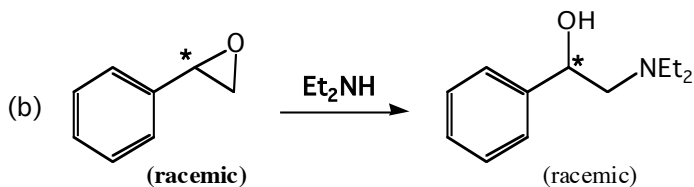
If NaOH is used in place of aqueous NaHCO_3 , then the phenol will be deprotonated along with the carboxylic acid, so they will be isolated together in fraction A.

(b) The starting mixture contains an aromatic amine, ArNH_2 , rather than an aliphatic amine, RNH_2 ?

If the starting mixture contains an aromatic amine, ArNH_2 , rather than an aliphatic amine, RNH_2 , then the results will be the same. The aromatic amine will still be protonated by the HCl wash, and deprotonated by the NaOH treatment.

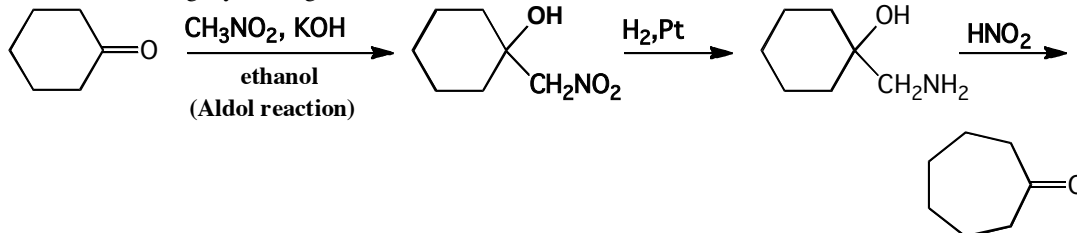
Problem 23.10 Show how to bring about each conversion in good yield. In addition to the given starting material, use any other reagents as necessary.





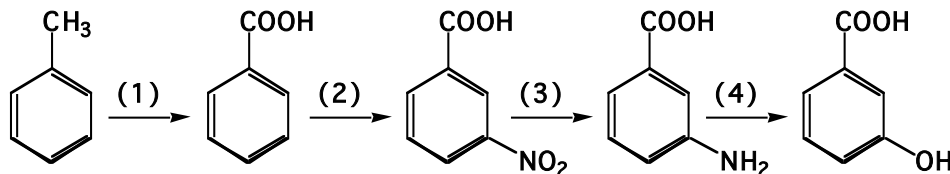
The stereochemistry of the product will be determined by the stereochemistry of the starting material; if the product is racemic, the starting material must have been racemic as well.

Problem 23.11 How might you bring about this conversion?



The synthesis begins with an aldol reaction using nitromethane, followed by reduction to give a β -aminoalcohol that then undergoes the ring expansion reaction.

Problem 23.12 Show how to convert toluene to 3-hydroxybenzoic acid using the same set of reactions as in Example 23.12, but changing the order in which two or more of the steps are carried out.



The key to this question is that the methyl group is converted to a meta-directing carboxyl group before the nitration reaction. This leads to the desired product with the hydroxy group in the 3 position.

Step (1) Oxidation at a benzylic carbon (Section 20.6A) can be brought about using chromic acid to give benzoic acid.

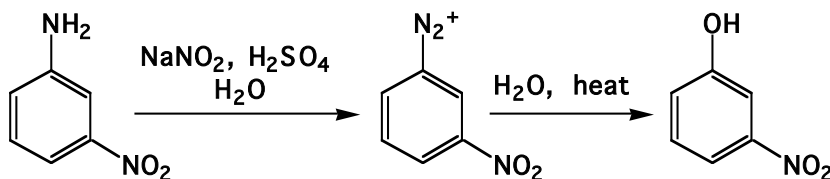
Step (2) Nitration of the aromatic ring using HNO_3 in H_2SO_4 . The meta-directing carboxyl group gives predominantly the desired 3-nitrobenzoic acid product.

Step (3) Reduction of the nitro group to 3-aminobenzoic acid can be brought about using H_2 in the presence of Ni or other transition metal catalyst. Alternatively, it can be brought about using Zn, Sn, or Fe metal in aqueous HCl.

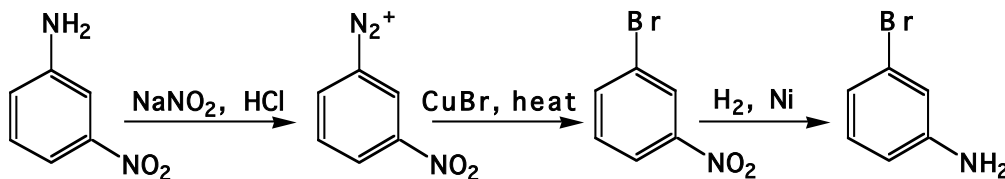
Step (4) Reaction of the aromatic amine with HNO_2 followed by heating in water gives 3-hydroxybenzoic acid.

Problem 23.13 Starting with 3-nitroaniline, show how to prepare the following compounds.

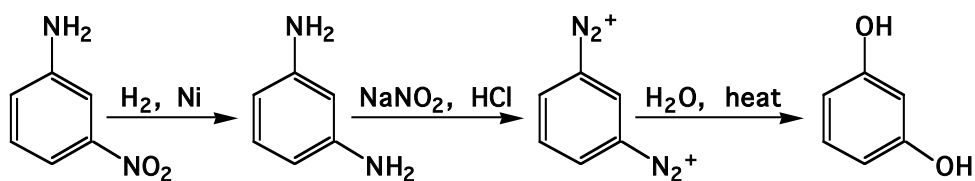
(a) 3-Nitrophenol



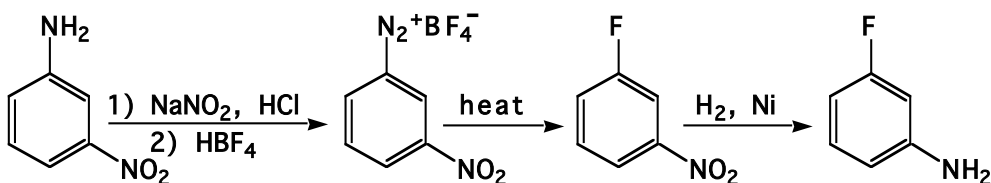
(b) 3-Bromoaniline



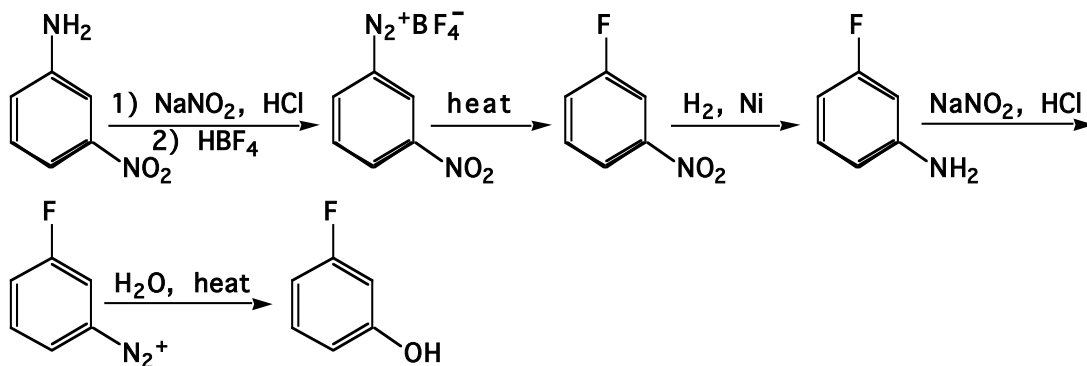
(c) 1,3-Dihydroxybenzene (resorcinol)



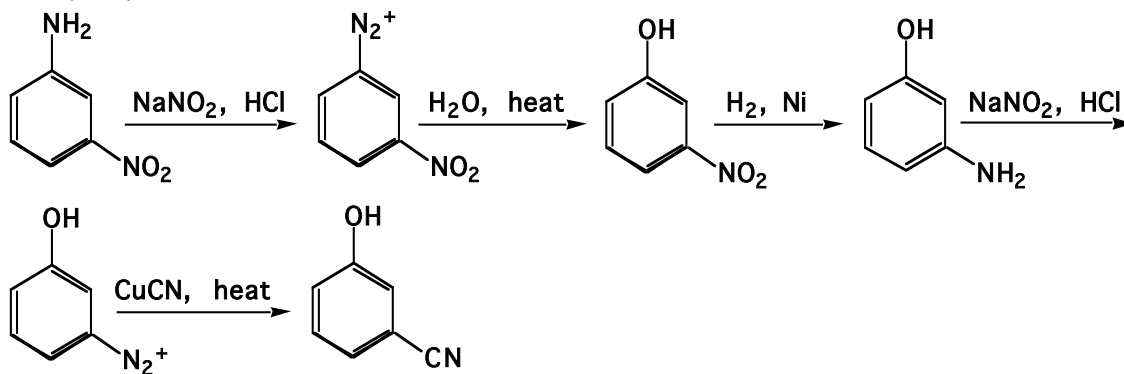
(d) 3-Fluoroaniline



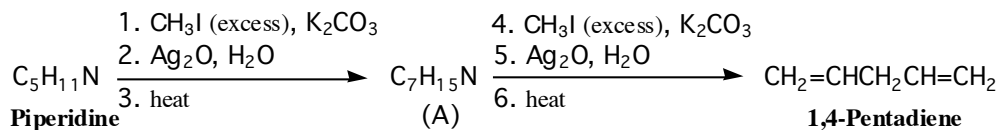
(e) 3-Fluorophenol



(f) 3-Hydroxybenzoxonitrile

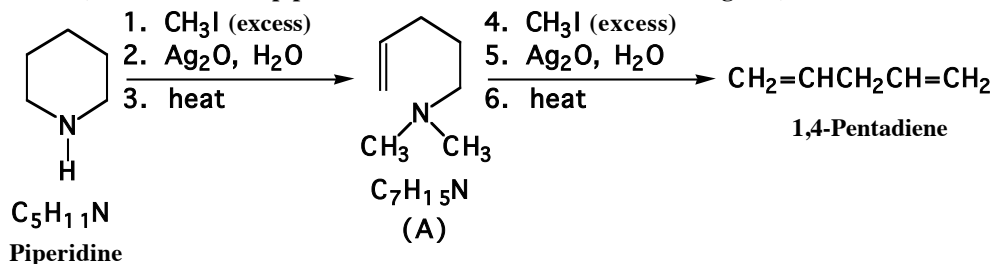


Problem 23.14 The procedure of methylation of amines and thermal decomposition of quaternary ammonium hydroxides was first reported by Hofmann in 1851, but its value as a means of structure determination was not appreciated until 1881 when he published a report of its use in determining the structure of piperidine. Following are the results obtained by Hofmann:



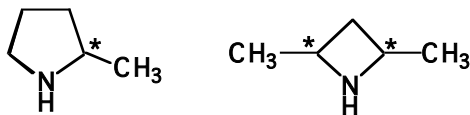
(a) Show that these results are consistent with the structure of piperidine (Section 23.1).

As shown below, the structure of piperidine is consistent with the formulas given, as well as the final product.



(b) Propose two additional structural formulas (excluding stereoisomers) for $\text{C}_5\text{H}_{11}\text{N}$ that are also consistent with the results obtained by Hofmann.

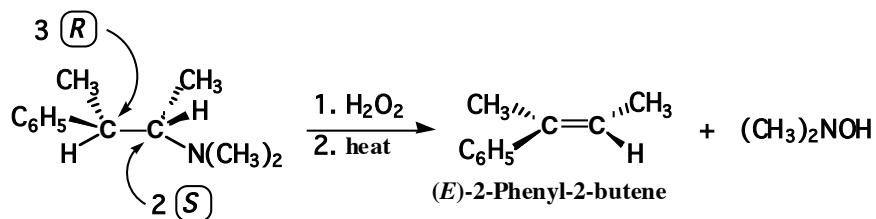
The following two molecules also have structures that are consistent with the formulas given, as well as the final product. Remember that in Hofmann eliminations, the least substituted alkene is formed predominantly.



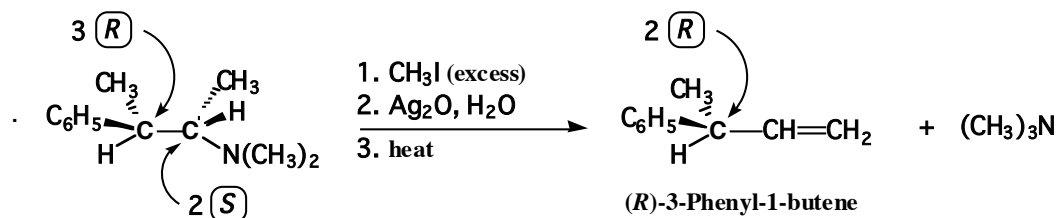
Problem 23.15 In Example 23.15, you considered the product of Cope elimination from the $2R,3S$ stereoisomer of 2-dimethylamino-3-phenylbutane. What is the product of Cope elimination from the following stereoisomers? What is the product of Hofmann elimination from each stereoisomer?

(a) $(2S,3R)$ stereoisomer?

The Cope elimination gives predominantly (*E*)-2-phenyl-2-butene.

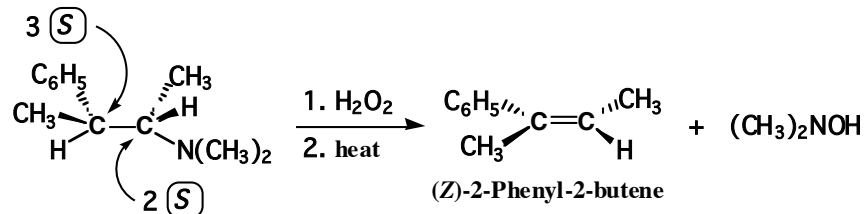


The Hofmann elimination gives predominantly (*R*)-3-phenyl-1-butene.

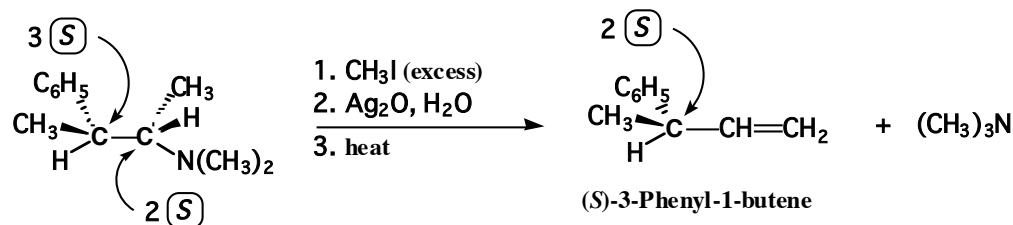


(b) (2*S*, 3*S*) stereoisomer?

The Cope elimination gives predominantly (*Z*)-2-phenyl-2-butene.



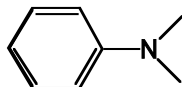
The Hofmann elimination gives predominantly (*S*)-3-phenyl-1-butene.



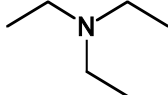
Structure and Nomenclature

Problem 23.16 Draw structural formulas for each amine and amine derivative.

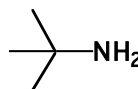
(a) *N,N*-Dimethylaniline



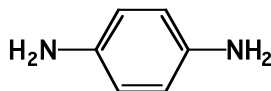
(b) Triethylamine



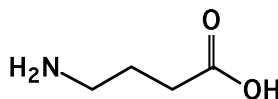
(c) *tert*-Butylamine



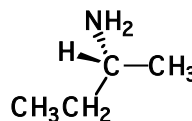
(d) 1,4-Benzenediamine



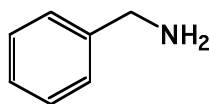
(e) 4-Aminobutanoic acid



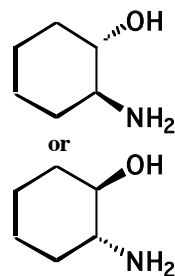
(f) (*R*)-2-Butanamine



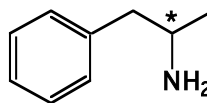
(g) Benzylamine



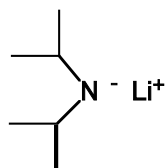
(h) *trans*-2-Aminocyclohexanol



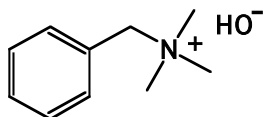
(i) 1-Phenyl-2-propanamine (amphetamine)



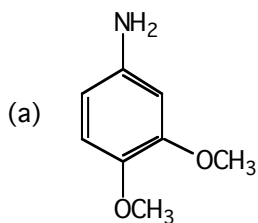
(j) Lithium diisopropylamide (LDA)



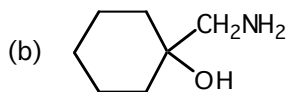
(k) Benzyltrimethylammonium hydroxide (Triton B)



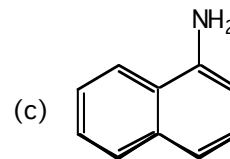
Problem 23.17 Give an acceptable name for these compounds.



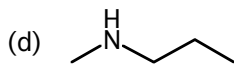
3,4-Dimethoxyaniline



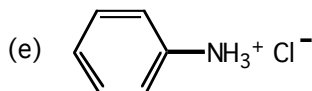
1-Aminomethylcyclohexanol



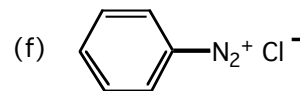
1-Naphthylamine



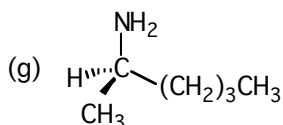
Methylpropylamine



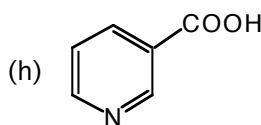
Aniline hydrochloride



Benzenediazonium chloride

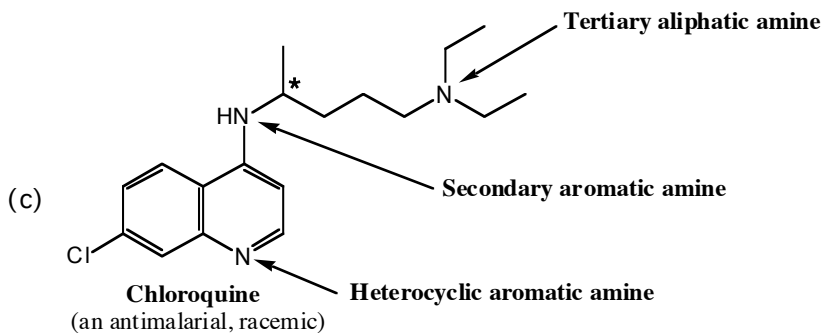
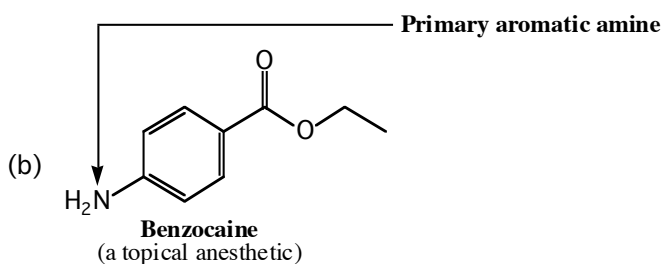
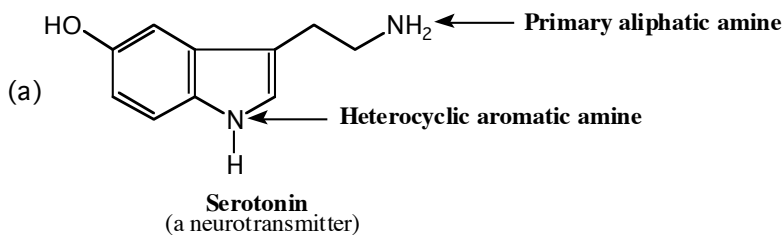


(R)-2-Hexanamine

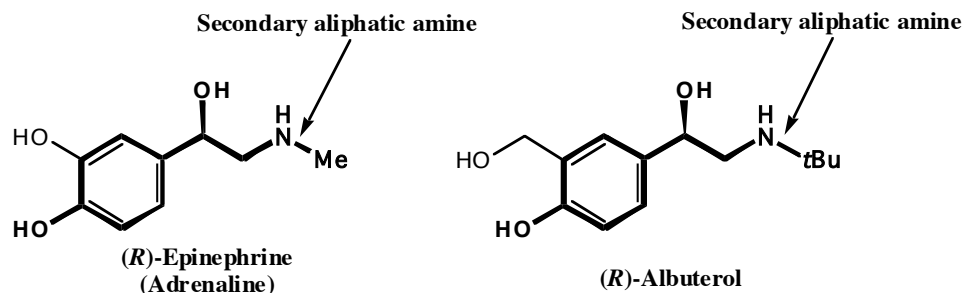


3-Pyridinecarboxylic acid

Problem 23.18 Classify each amine as primary, secondary, or tertiary; as aliphatic or aromatic.



Problem 23.19 Epinephrine is a hormone secreted by the adrenal medulla. Among its actions, it is a bronchodilator. Albuterol, sold under several trade names, including Proventil and Salbumol, is one of the most effective and widely prescribed antiasthma drugs. The *R* enantiomer of albuterol is 68 times more effective in the treatment of asthma than the *S* enantiomer.

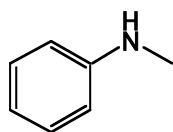


- (a) Classify each as a primary, secondary, or tertiary amine.
 (b) Compare the similarities and differences between their structural formulas.

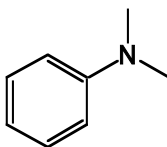
The parts of the molecules that are identical are indicated in bold on the above structures. As far as differences are concerned, epinephrine possesses a second hydroxyl group on the aromatic ring and a methyl group on the amine, while (*R*)-albuterol has a hydroxymethyl group on the ring and a *tert*-butyl group on the amine.

Problem 23.20 Draw the structural formula for a compound with the given molecular formula.

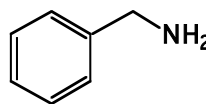
(a) A 2° arylamine, C_7H_9N



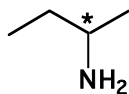
(b) A 3° arylamine, $C_8H_{11}N$



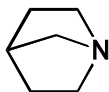
(c) A 1° aliphatic amine, C_7H_9N



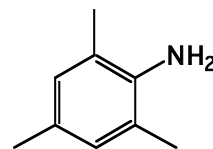
(d) A chiral 1° amine, $C_4H_{11}N$



(e) A 3° heterocyclic amine, $C_6H_{11}N$

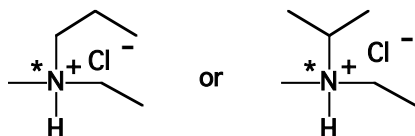


(f) A trisubstituted 1° arylamine, $C_9H_{13}N$

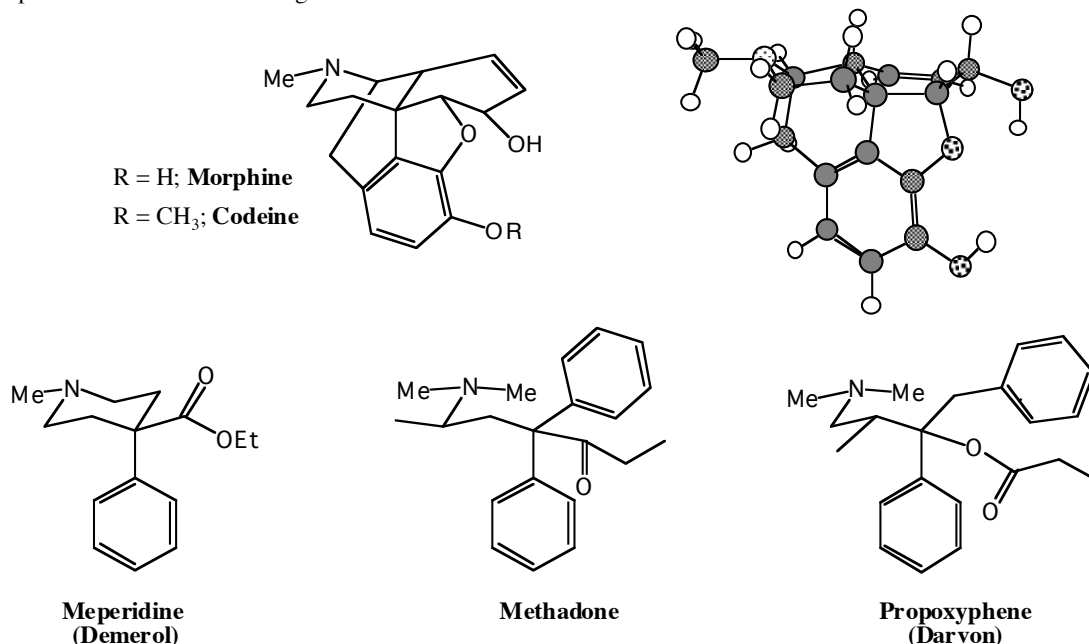


(Other isomers are possible)

(g) A chiral quaternary ammonium salt, $C_6H_{16}NCl$

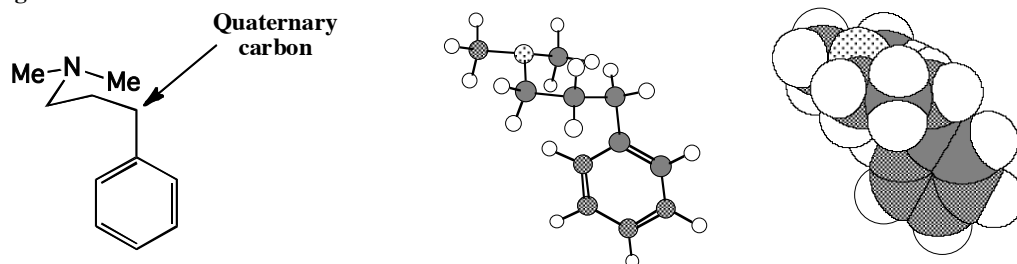


Problem 23.21 Morphine and its *O*-methylated derivative codeine are among the most effective pain killers known. However, they possess two serious drawbacks: they are addictive, and repeated use induces a tolerance to the drug. Increasingly larger doses become necessary; these doses can lead to respiratory arrest. Many morphine analogs have been prepared in an effort to find drugs that are equally effective as pain killers but that have less risk of physical dependence and potential for abuse. Following are several of these.



(a) List the structural features common to each of these molecules.

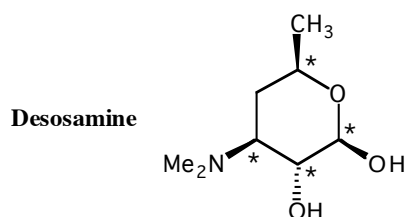
Each of the above molecules contains a tertiary amine and a phenyl ring that is three sp^3 carbons away from the nitrogen atom of the amine.



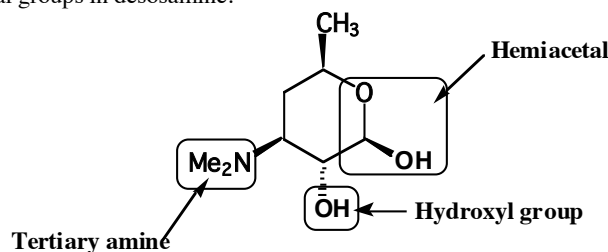
(b) The Beckett-Casey rules are a set of empirical rules to predict the structure of molecules that bind to morphine receptors and act as analgesics. According to these rules, to provide an effective morphine-like analgesia, a molecule must have (1) an aromatic ring attached to (2) a quaternary carbon and (3) a nitrogen at a distance equal to two carbon-carbon single bond lengths from the quaternary center. Show that these structural requirements are present in the molecules given in this problem.

By inspection of the structures, it can be seen that all of these three structural requirements are present in the molecules mentioned in this problem.

Problem 23.22 Following is a structural formula of desosamine, a sugar component of several macrolide antibiotics, including erythromycins. The configuration shown is that of the natural or D isomer. Erythromycin is produced by a strain of *Streptomyces erytheus* found in a soil sample from the Phillipine archipelago.



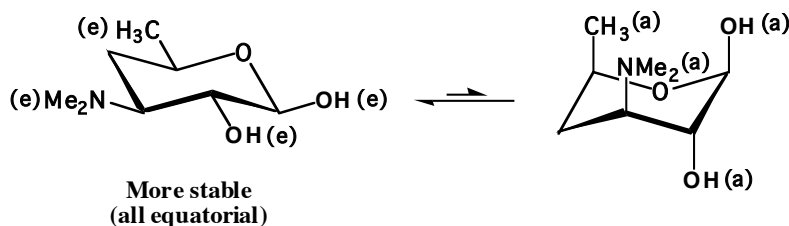
(a) Name all the functional groups in desosamine.



(b) How many chiral centers are present in desosamine? How many stereoisomers are possible for it? How many pairs of enantiomers are possible for it?

Desosamine has 4 chiral centers, marked with asterisks on the uppermost structure. There are $2 \times 2 \times 2 \times 2 = 16$ possible stereoisomers as 8 pairs of enantiomers.

(c) Draw alternative chair conformations for desosamine. In each, label which groups are equatorial and which are axial.



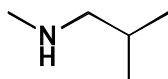
(d) Which of the alternative chair conformations for desosamine is the more stable? Explain.

The chair structure on the left is by far the more stable because all of the groups are equatorial, thereby minimizing non-bonded interaction strain.

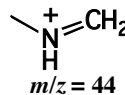
Spectroscopy

Problem 23.23 Account for the formation of the base peaks in these mass spectra.

(a) Isobutylmethylamine, m/z 44



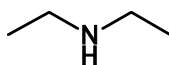
Isobutylmethylamine



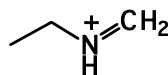
$m/z = 44$

As shown above, the peak at $m/z = 30$ is the result of the characteristic β -cleavage reaction often observed as the base peak in the mass spectra of amines.

(b) Diethylamine, m/z 58



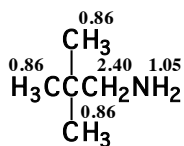
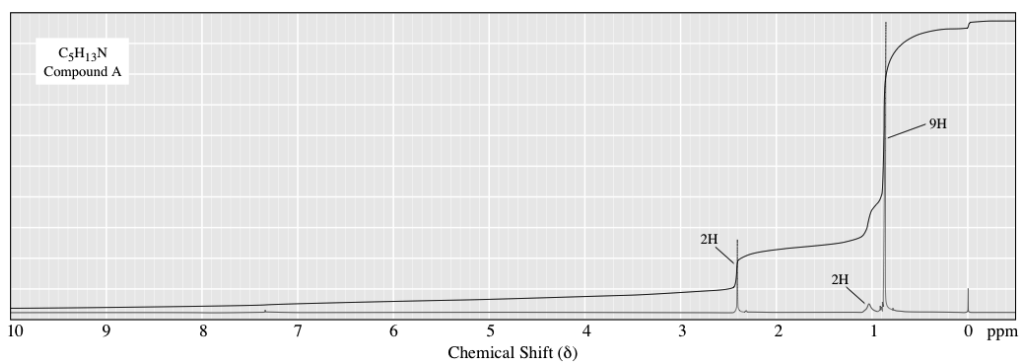
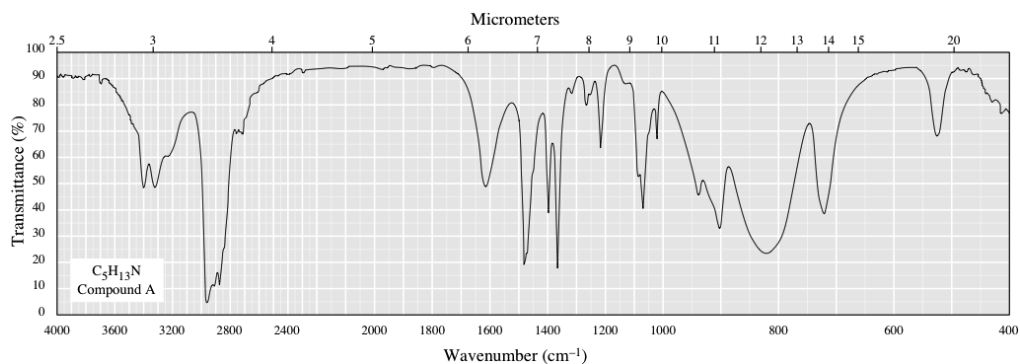
Diethylamine



$m/z = 58$

As shown above, the peak at $m/z = 58$ is the result of the characteristic β -cleavage reaction often observed as the base peak in the mass spectra of amines.

Problem 23.24 Propose a structural formula for compound (A), molecular formula $C_5H_{13}N$, given its IR and 1H -NMR spectra.

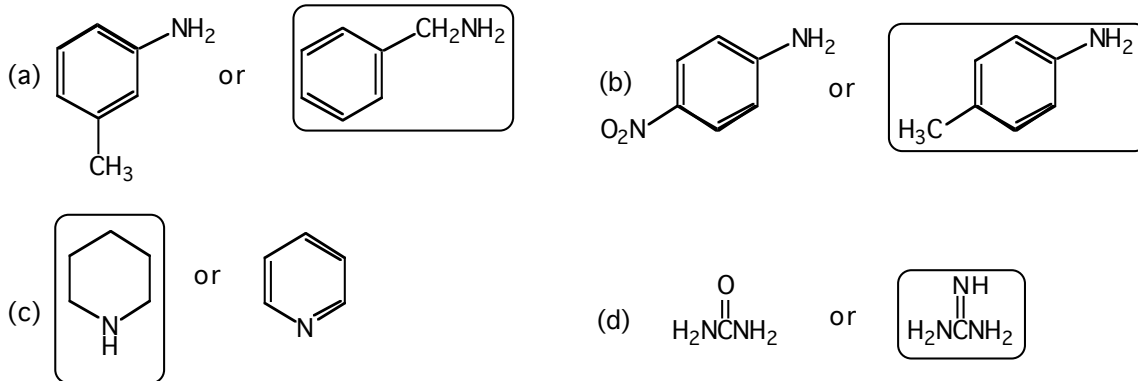


Compound A
1-Amino-2,2-dimethylpropane
(Neopentylamine)

The presence of two absorptions near 3300 to 3400 cm^{-1} in the IR spectrum indicates that compound A is a primary amine. Furthermore, in the 1H -NMR, there are two sharp singlets at $\delta 0.86$ and $\delta 2.40$ integrating to 9H and 2H, respectively. The above structure is consistent with the index of hydrogen deficiency of zero, because there are no rings or π bonds.

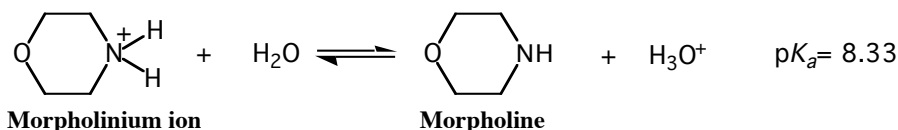
Basicity of Amines

Problem 23.25 Select the stronger base from each pair of compounds.





Problem 23.26 The pK_a of morpholine is 8.33.



(a) Calculate the ratio of morpholine to morpholinium ion in aqueous solution at pH 7.0.

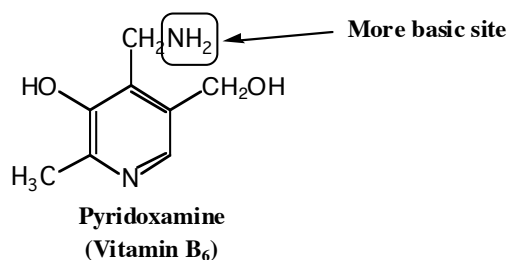
$$K_a = \frac{[\text{Morpholine}][\text{H}^+]}{[\text{Morpholinium Ion}]} = 10^{-8.33} \quad \text{At pH 7.0} \quad [\text{H}^+] = 10^{-7}$$

$$\frac{[\text{Morpholine}]}{[\text{Morpholinium Ion}]} = \frac{10^{-8.33}}{[\text{H}^+]} = \frac{10^{-8.33}}{10^{-7.0}} = 10^{-1.33} = \boxed{0.047}$$

(b) At what pH are the concentrations of morpholine and morpholinium ion equal?

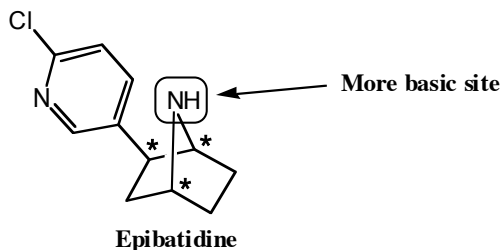
The concentrations of morpholine and morpholinium ion will be equal when the pK_a is equal to the pH, that is, at pH 8.33.

Problem 23.27 Which of the two nitrogens in pyridoxamine (a form of vitamin B₆) is the stronger base? Explain your reasoning.



The nitrogen atom of the primary amine is more basic than the pyridine nitrogen atom. This is because the primary amine nitrogen atom is sp^3 hybridized, while the pyridine nitrogen is sp^2 hybridized. The sp^2 hybridized nitrogen atom has a greater percentage s character, so the electrons are held closer to the nucleus and are less available for interactions with protons.

Problem 23.28 Epibatidine, a colorless oil isolated from the skin of the Ecuadorian poison frog *Epipedobates tricolor* has several times the analgesic potency of morphine. It is the first chlorine-containing, nonopioid (nonmorphine-like in structure) analgesic ever isolated from a natural source.



(a) Which of the two nitrogen atoms of epibatidine is the more basic?

The nitrogen atom of the secondary amine is more basic than the pyridine nitrogen atom. This is because the secondary amine nitrogen atom is sp^3 hybridized, while the pyridine nitrogen is sp^2 hybridized. The sp^2 hybridized nitrogen atom has a greater percentage s character, so the electrons are held tighter and are less available for interactions with protons.

(b) Mark all chiral centers in this molecule.

The three chiral centers are marked with an asterisk (*).

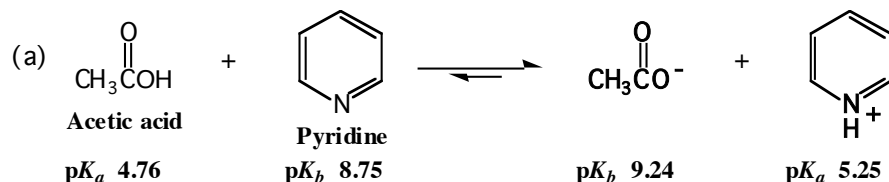
Problem 23.29 Aniline (conjugate acid pK_a 4.63) is a considerably stronger base than diphenylamine (pK_a 0.79). Account for these marked differences.

$C_6H_5NH_2$	$(C_6H_5)_2NH$
Aniline	Diphenylamine
Conjugate acid pK_a	pK_a
pK_a 4.63	0.79

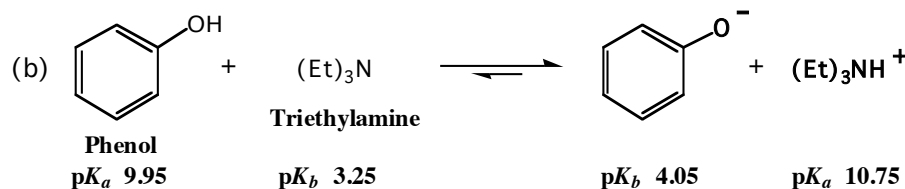
Diphenylamine is a weaker base because the nitrogen lone pair is delocalized by interaction with the π system of both aromatic rings, as opposed to aniline in which the lone pair on nitrogen is only delocalized by interaction with a single aromatic ring. This delocalization (resonance stabilization) cannot take place when the amine is protonated. Thus, the diphenylammonium ion is a stronger acid because loss of the proton results in greater resonance stabilization (delocalization into two aromatic rings instead of one).

Problem 23.30 Complete the following acid-base reactions and predict the direction of equilibrium (to the right or to the left) for each. Justify your prediction by citing values of pK_a for the stronger and weaker acid in each equilibrium. For values of acid ionization constants, consult Table 23.2 (Acid Strengths, pK_a , of the Conjugate Acids of Selected Amines), and Appendix 2 (Acid Ionization Constants for the Major Classes of Organic Acids). Where no ionization constants are given, make the best estimate from the information given in the reference tables and sections.

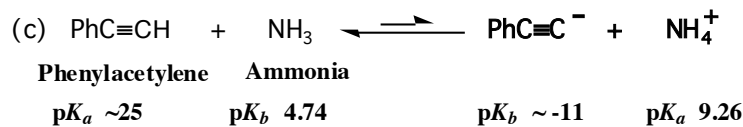
In all cases, the equilibrium favors formation of the weaker acid (higher pK_a) and weaker base (higher pK_b). Recall that $pK_a + pK_b = 14$ for any conjugate acid-base pair.



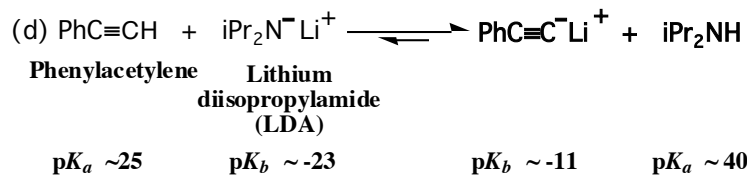
Equilibrium lies to the right, because the acetate anion and pyridinium ion are the weaker acid and base, respectively.



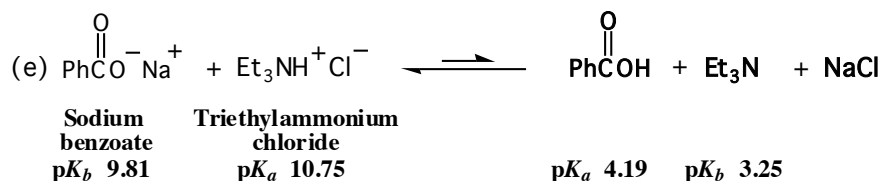
Equilibrium lies to the right, because the phenoxide anion and the triethylammonium species are the weaker base and acid, respectively.



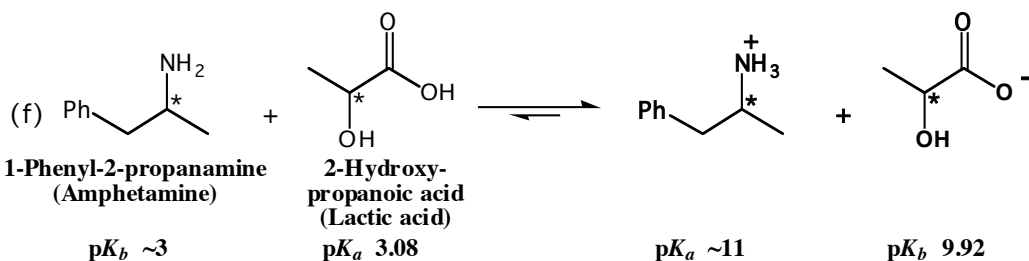
Equilibrium lies to the left, because the alkyne and ammonia are the weaker acid and base, respectively.



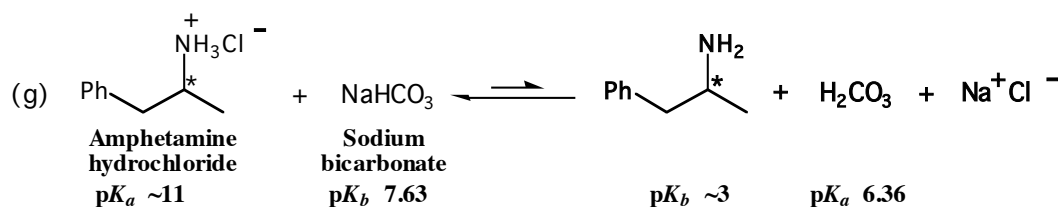
Equilibrium lies to the right, because the alkyne anion and the amine are the weaker base and acid, respectively.



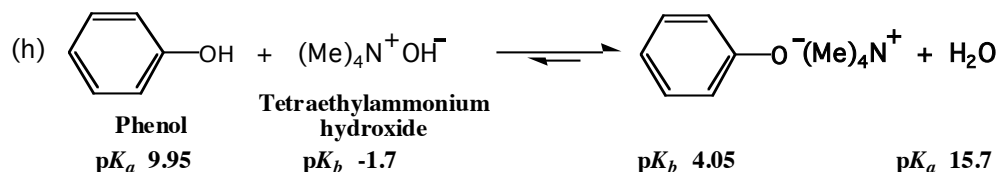
Equilibrium lies to the left, because the carboxylate anion and the triethylammonium ion are the weaker base and acid, respectively.



Equilibrium lies to the right, because the 1-phenyl-2-propanammonium ion and the carboxylate ion are the weaker acid and base, respectively.

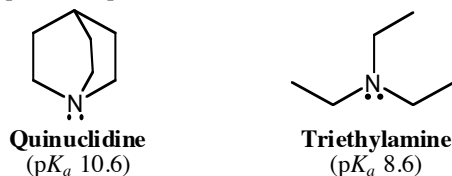


Equilibrium lies to the left, because the amphetamine ammonium ion and the bicarbonate ion are the weaker acid and base, respectively.



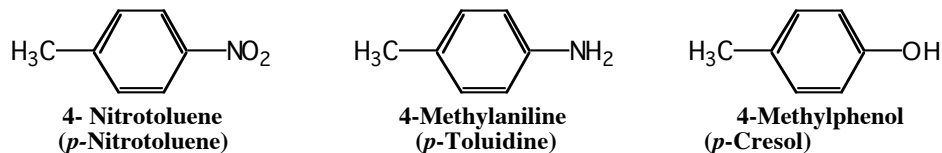
Equilibrium lies to the right, because phenoxide and water are the weaker base and acid, respectively.

Problem 23.31 Quinuclidine and triethylamine are both tertiary amines. Quinuclidine, however, is a considerably stronger base than triethylamine. Stated alternatively, the conjugate acid of quinuclidine is a considerably weaker acid than the conjugate acid of triethylamine. Propose an explanation for these differences in acidity/basicity.



The protonated form of quinuclidine is more compact than protonated triethylamine, because the alkyl groups of quinuclidine are "tied back" allowing it to be solvated better. For this reason, protonated quinuclidine is a weaker acid, so quinuclidine is a stronger base.

Problem 23.32 Suppose that you have a mixture of these three compounds. Devise a chemical procedure based on their relative acidity or basicity to separate and isolate each in pure form.

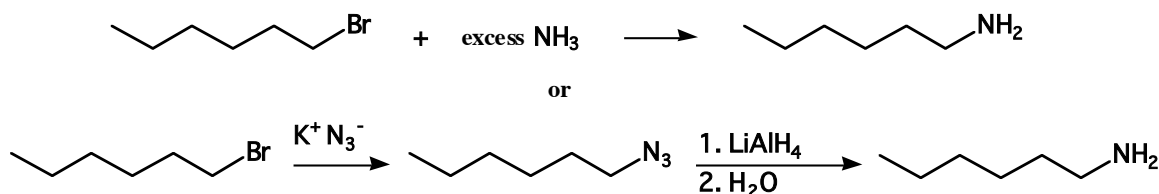


These molecules can be separated by extraction into different aqueous solutions. First, the mixture is dissolved in an organic solvent such as ether in which all three compounds are soluble. Then, the ether solution is extracted with dilute aqueous HCl. Under these conditions, 4-methylaniline (a weak base) is converted to its protonated form and dissolves in the aqueous solution. The aqueous solution is separated, treated with dilute NaOH, the water-insoluble 4-methylaniline precipitates, and is recovered. The ether solution containing the other two components is then treated with dilute aqueous NaOH. Under these conditions, 4-methylphenol (a weak acid) is converted to its phenoxide ion and dissolves in the aqueous solution. Acidification of this aqueous solution with dilute HCl forms water-insoluble 4-methylphenol that is then isolated. Evaporation of the remaining ether solution gives the 4-nitrotoluene, which is neither acidic or basic.

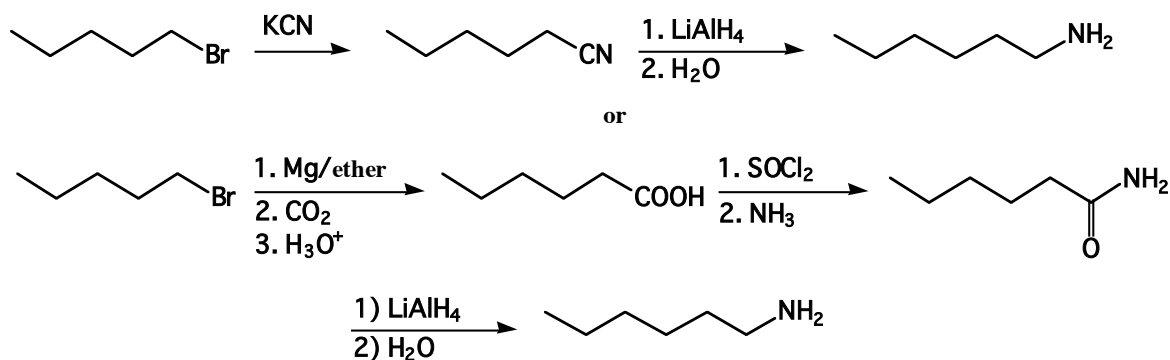
Preparation of Amines

Problem 23.33 Propose a synthesis of 1-hexanamine from the following:

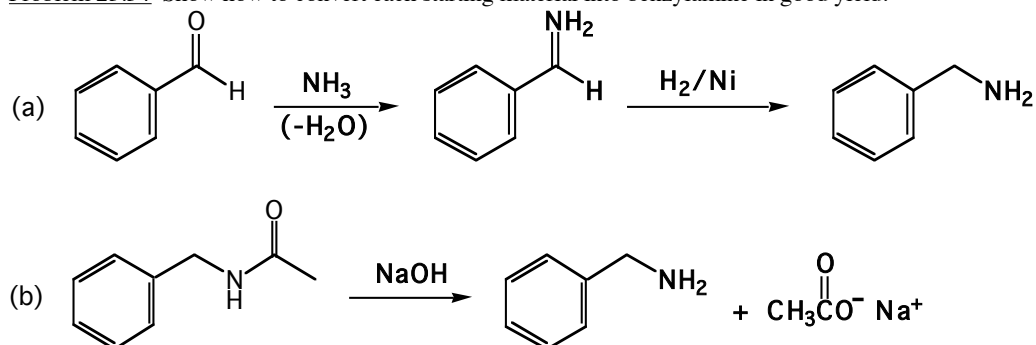
(a) A bromoalkane of six carbon atoms

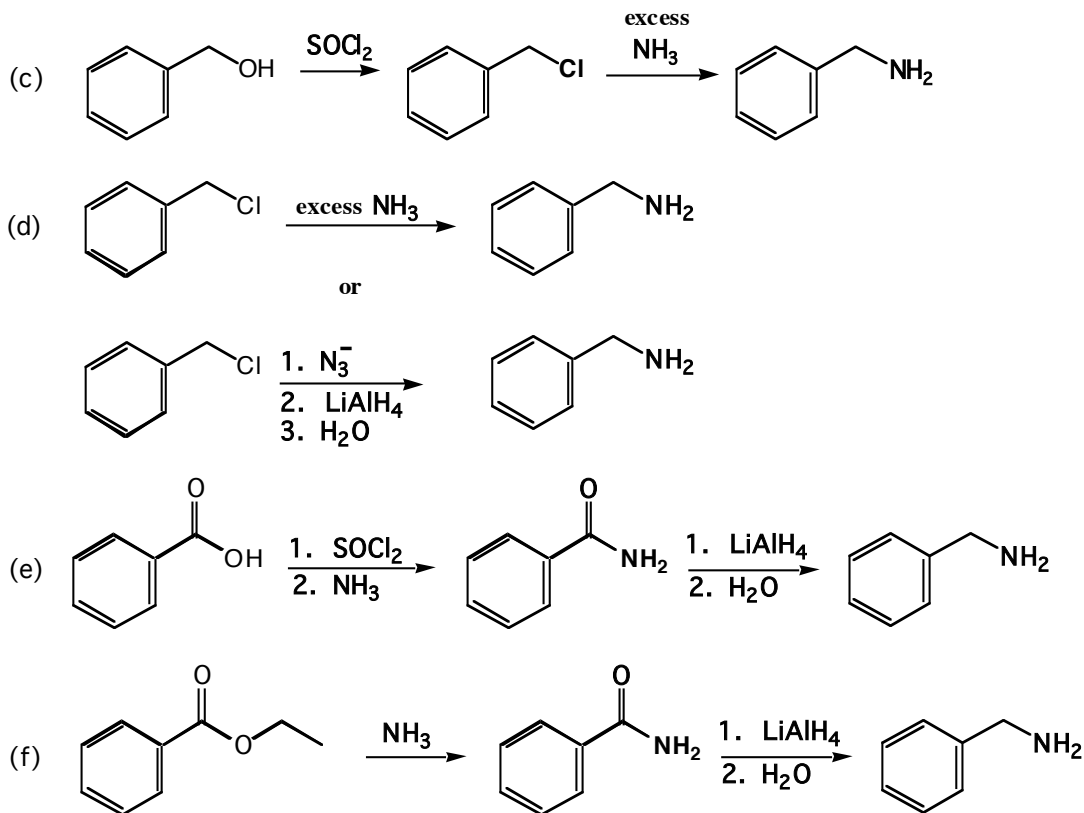


(b) A bromoalkane of five carbon atoms



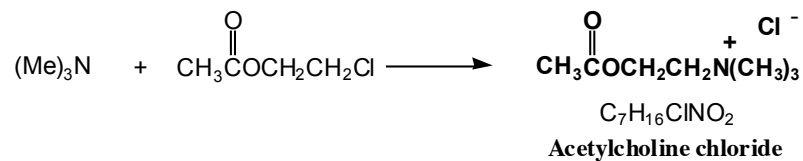
Problem 23.34 Show how to convert each starting material into benzylamine in good yield.





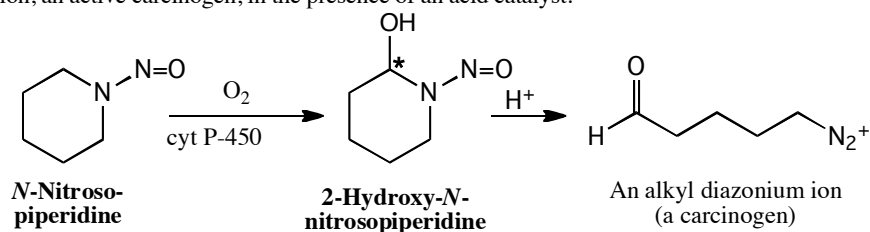
Reactions of Amines

Problem 23.35 Treating trimethylamine with 2-chloroethyl acetate gives acetylcholine as its chloride. Acetylcholine is a neurotransmitter. Propose a structural formula for this quaternary ammonium salt and a mechanism for its formation.

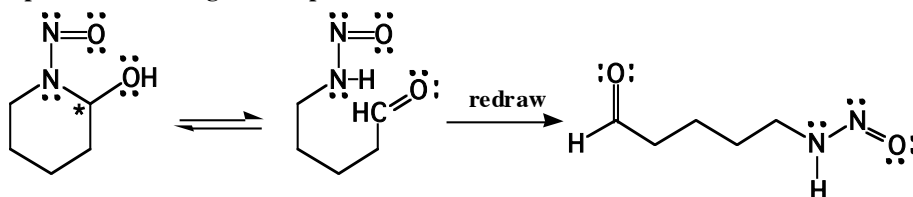


Acetylcholine is formed through an $\text{S}_{\text{N}}2$ reaction between trimethylamine and the alkyl chloride, giving the structure shown.

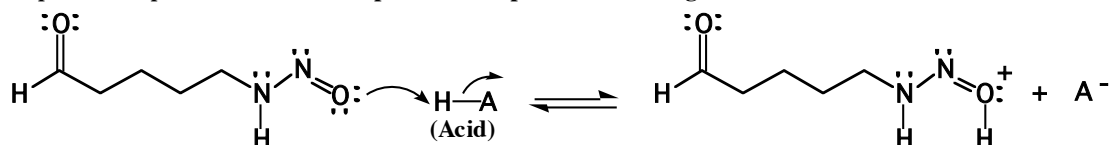
Problem 23.36 *N*-Nitrosamines by themselves are not significant carcinogens. However, they are activated in the liver by a class of iron-containing enzymes (members of the cytochrome P-450 family). Activation involves the oxidation of a C-H bond next to the amine nitrogen to a C-OH group. Show how this hydroxylation product can be transformed into an alkyl diazonium ion, an active carcinogen, in the presence of an acid catalyst.



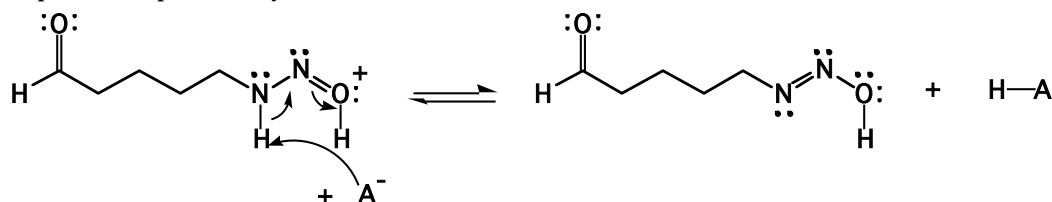
Step 1: Break a bond to give stable molecules or ions-add a proton-take a proton away. These three steps occur in rapid succession to give the open chain molecule shown.



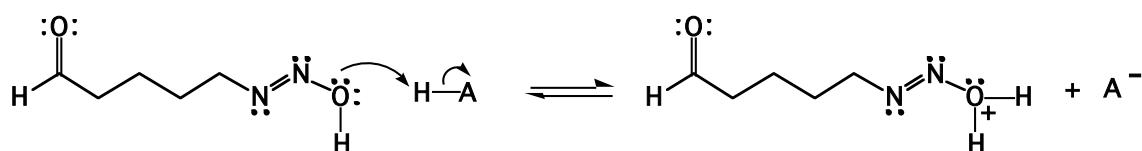
Step 2: Add a proton. Note that steps 2 and 3 represent an analog of keto-enol tautomerization.



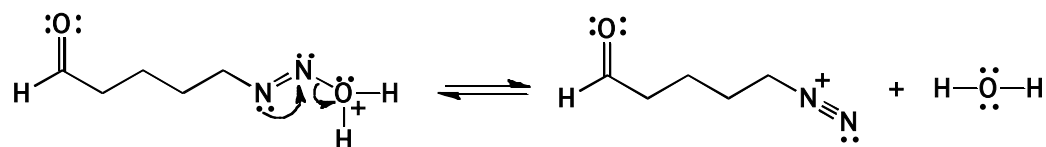
Step 3: Take a proton away.



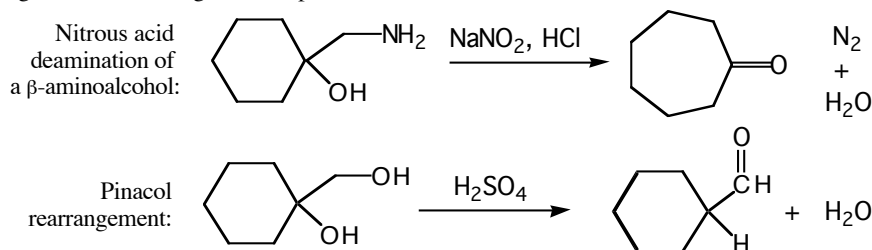
Step 4: Add a proton.



Step 5: Break a bond to give stable molecules or ions.



Problem 23.37 Marked similarities exist between the mechanism of nitrous acid deamination of β -aminoalcohols and the pinacol rearrangement. Following are examples of each.



(a) Analyze the mechanism of each rearrangement and list their similarities.

The nitrous acid deamination of a β -aminoalcohol (Section 23.8D) involves formation of a diazonium ion that loses N_2 in concert with a 1,2 shift to create a cation that loses a proton to give the ring expanded ketone.

In the pinacol rearrangement of 1,2 diols (Section 10.7), protonation of one of the alcohol groups leads to departure of water to create a carbocation, followed by migration of a hydride to generate a resonance-stabilized cation that loses a proton to give the ketone product.

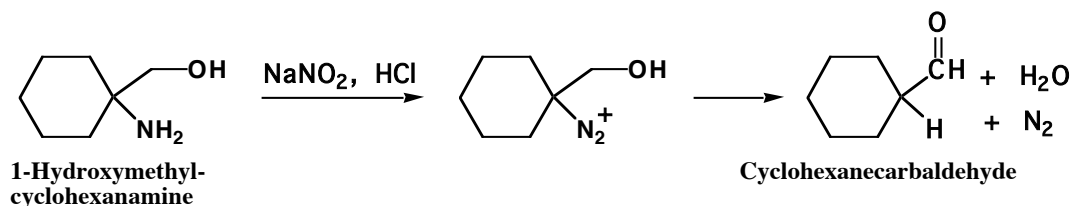
The similarities between the two mechanisms are that in both cases a 1,2 shift of an alkyl group or hydride ion produces a cation, that loses a proton to create the final product.

(b) Why does the first reaction, but not the second, give ring expansion?

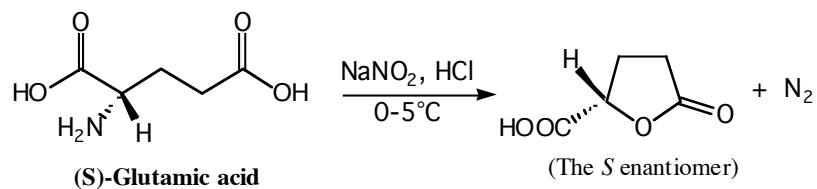
In the case of the β -aminoalcohol shown above, the N_2 departs from the primary center not in the ring, requiring a concerted ring expansion for the subsequent alkyl migration step. In the case of the pinacol rearrangement, the tertiary $-OH$ group on the cyclohexane ring departs, precluding the possibility of a ring expanding rearrangement.

(c) Suggest a β -aminoalcohol that would give cyclohexanecarbaldehyde as a product?

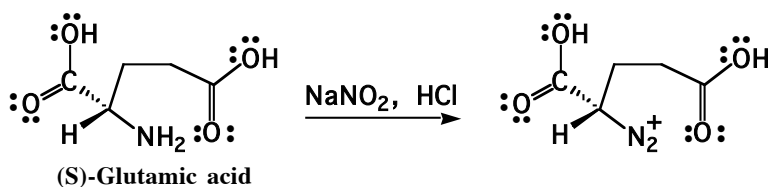
1-Hydroxymethylcyclohexanamine would undergo reaction to give cyclohexanecarbaldehyde as shown.



Problem 23.38 (*S*)-Glutamic acid is one of the 20 amino acid building blocks of polypeptides and proteins (Chapter 27). Propose a mechanism for the following conversion.

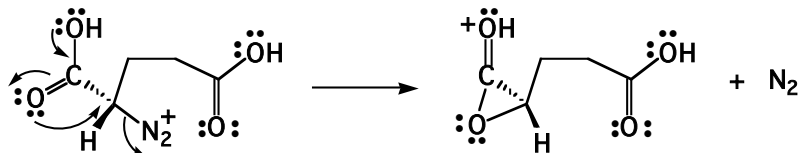


Several Steps:

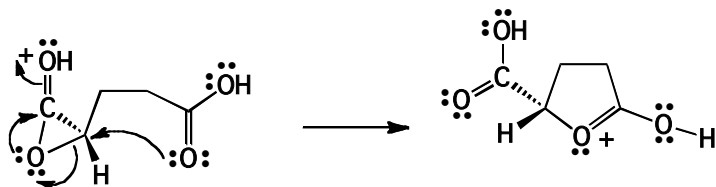


Step 2: Make a bond between a nucleophile and an electrophile and simultaneously break a bond to give stable

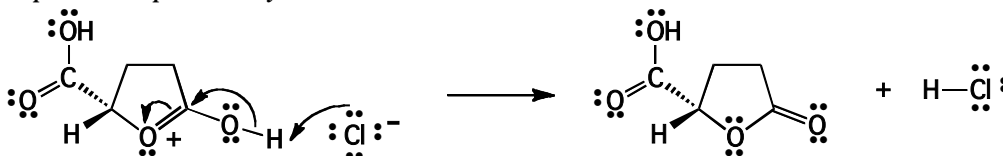
molecules or ions. The intriguing part of the mechanism is that there is no racemization. This means that it is unlikely that N_2 departs leaving a free cation behind. Such a cation would be sp^2 hybridized, would be planar and thus would lead to racemization. Therefore, propose the adjacent carbonyl group reacts to form a short-lived three membered ring intermediate that then reacts with the other carboxyl group to make the more stable, five-membered ring intermediate. The chiral center undergoes double inversion, resulting in net retention of stereochemistry.



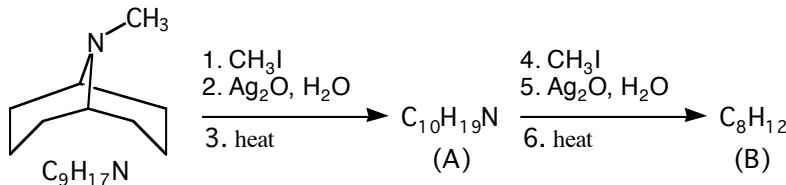
Step 3: Make a bond between a nucleophile and an electrophile and simultaneously break a bond to give stable molecules or ions.



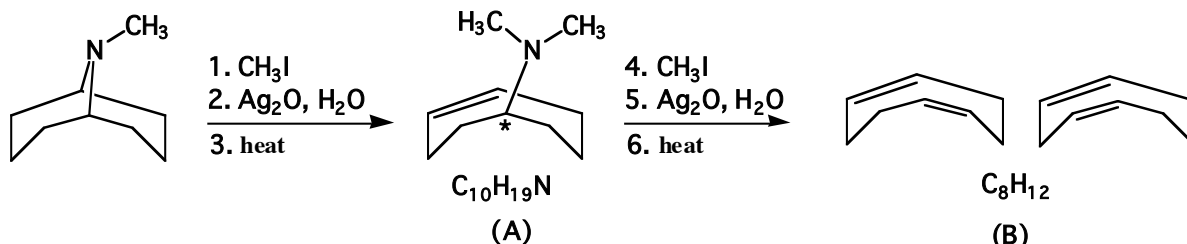
Step 4: Take a proton away.



Problem 23.39 The following sequence of methylation and Hofmann elimination was used in the determination of the structure of this bicyclic amine. Compound B is a mixture of two isomers.



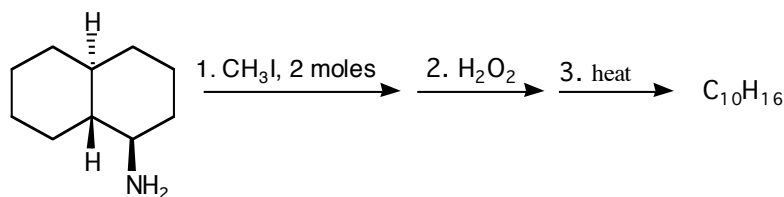
(a) Propose structural formulas for compounds (A) and (B).



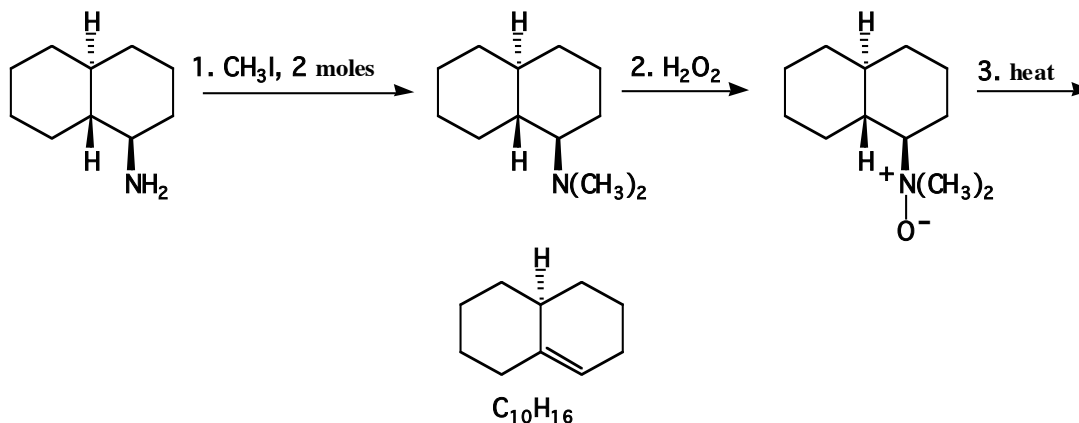
(b) Suppose you were given the structural formula of compound B but only the molecular formulas for compound A and the starting bicyclic amine. Given this information, is it possible, working backward, to arrive at an unambiguous structural formula for compound A? For the bicyclic amine?

Simply knowing the structural formula of compound (B) does not unambiguously establish the structure of compound (A), because the amine could be bonded at either end of what is a double bond in compound (B). Given this, the starting bicyclic amine cannot be unambiguously identified either, because two different structures are possible. One structure contains the bridging nitrogen atom in a [3.3.1] ring system (shown above), and the other structure contains the bridging nitrogen atom in a [4.2.1] ring system.

Problem 23.40 Propose a structural formula for the compound, $C_{10}H_{16}$, and account for its formation.

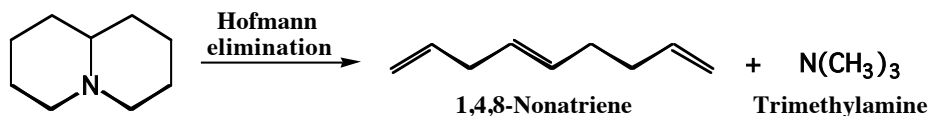


Note how, in the following example of a Cope elimination, the syn stereoselectivity of the transition state allows formation of the more substituted alkene, as shown. Note that, because the starting material is chiral and a single enantiomer, only a single enantiomer of the product will be created in the reaction sequence.

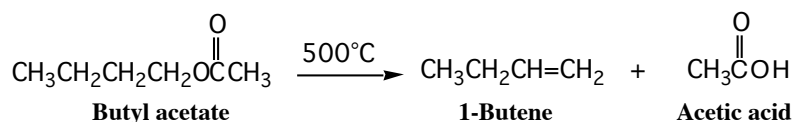


Problem 23.41 An amine of unknown structure contains one nitrogen and nine carbon atoms. The ^{13}C -NMR spectrum shows only five signals, all between 20 and 60 ppm. Three cycles of Hofmann elimination sequence [(1) CH_3I ; (2) Ag_2O , H_2O ; (3) heat] give trimethylamine and 1,4,8-nonatriene. Propose a structural formula for the amine.

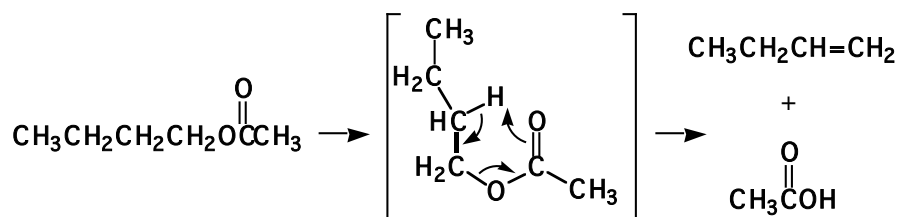
The bicyclic amine shown below is the only structure that would explain the five signals in the ^{13}C spectrum as well as the location of the double bonds in 1,4,8-nonatriene.



Problem 23.42 The pyrolysis of acetic esters to give an alkene and acetic acid is also thought to involve a planar transition state and cyclic redistribution of $(4n + 2)$ electrons. Propose a mechanism for pyrolysis of the following ester.



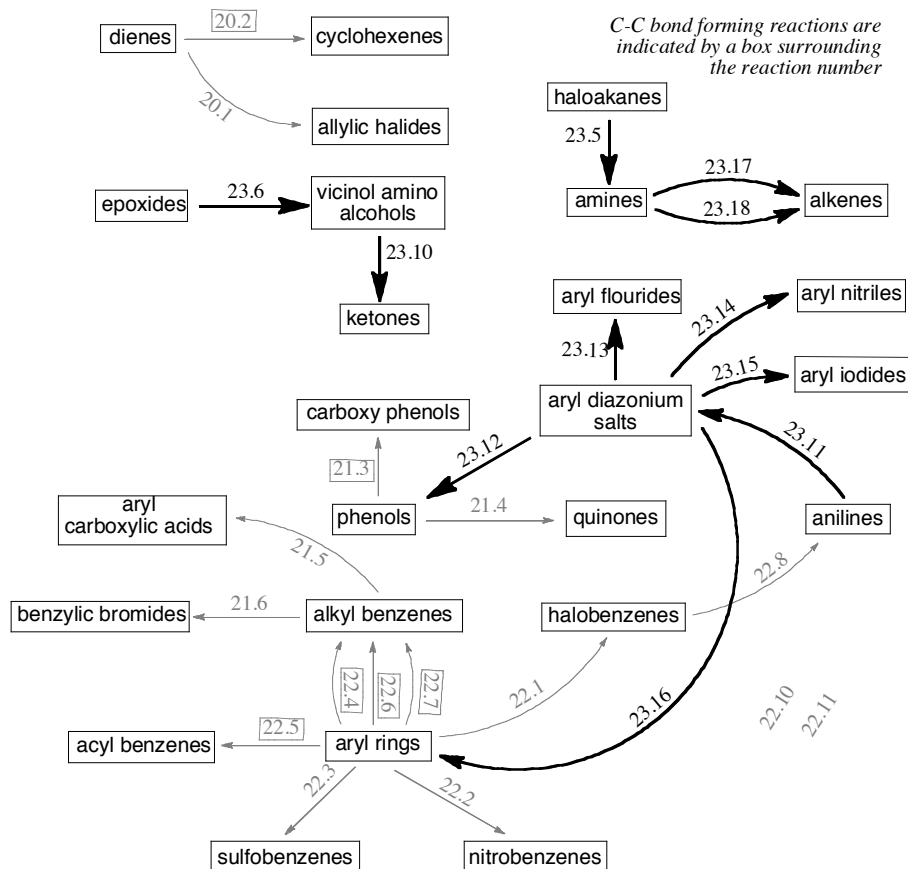
A reasonable transition state structure including the likely flow of electrons is shown below:



Organic Chemistry Roadmap

Problem 23.43 Use the roadmap you made for problems 20.55, 21.49, and 22.30 and update it to contain the reactions in the Key

Reactions section of this chapter. Because of their highly specific nature, do not use reactions, 1, 2, 3, 4, 7, 8, and 9 on your roadmap.



Chapter 23 Roadmap Reaction Legend (Numbers correspond to “Key Reactions” summary section)

Reaction 23.5

RNH_2 or NH_3

- This method is seldom used because of overalkylation

Reaction 23.10

HNO_2

- Treating a cyclic vicinal amino alcohol with HNO_2 gives ring expansion and a ketone

Reaction 23.12

H_2O , heat

- Important method for creating phenols

Reaction 23.14

CuCN , KCN

- The Sandmeyer reaction
- Also works with CuCl and CuBr to give aryl halides

Reaction 23.16

H_3PO_2

Reaction 23.6

1. KN_3 2. H_2O 3. LiAlH_4 4. H_2O

- The azide anion reacts with an epoxide to give a vicinal azido alcohol with anti stereochemistry, that is reduced by the LiAlH_4 to give a vicinal amino alcohol

Reaction 23.11

HNO_2 , HCl

- Important method because it converts an aniline to the highly reactive arenediazonium
- The key reactive intermediate is HONO

Reaction 23.13

HBF_4

- The Schiemann reaction
- Important method for creating aryl fluorides

Reaction 23.15

KI

- Important method for creating aryl iodides

Reaction 23.17

Conversion to ammonium hydroxide, heat

- Important method for removing nitrogen from an aryl ring

- The Hoffman elimination
- Anti stereoselective elimination of quaternary ammonium hydroxides occurs preferentially to form the least substituted carbon-carbon double bond (Hofmann's rule)

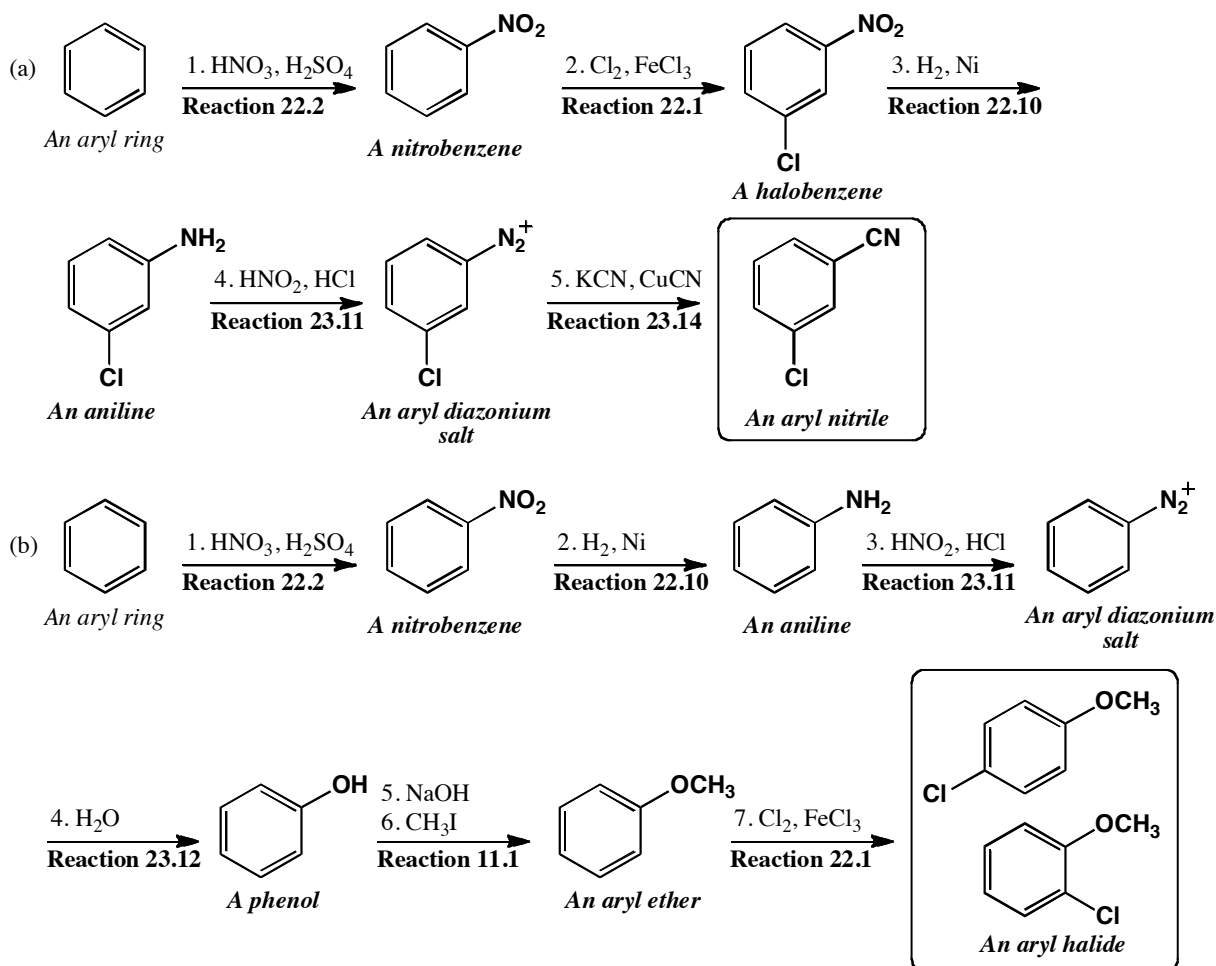
Reaction 23.18

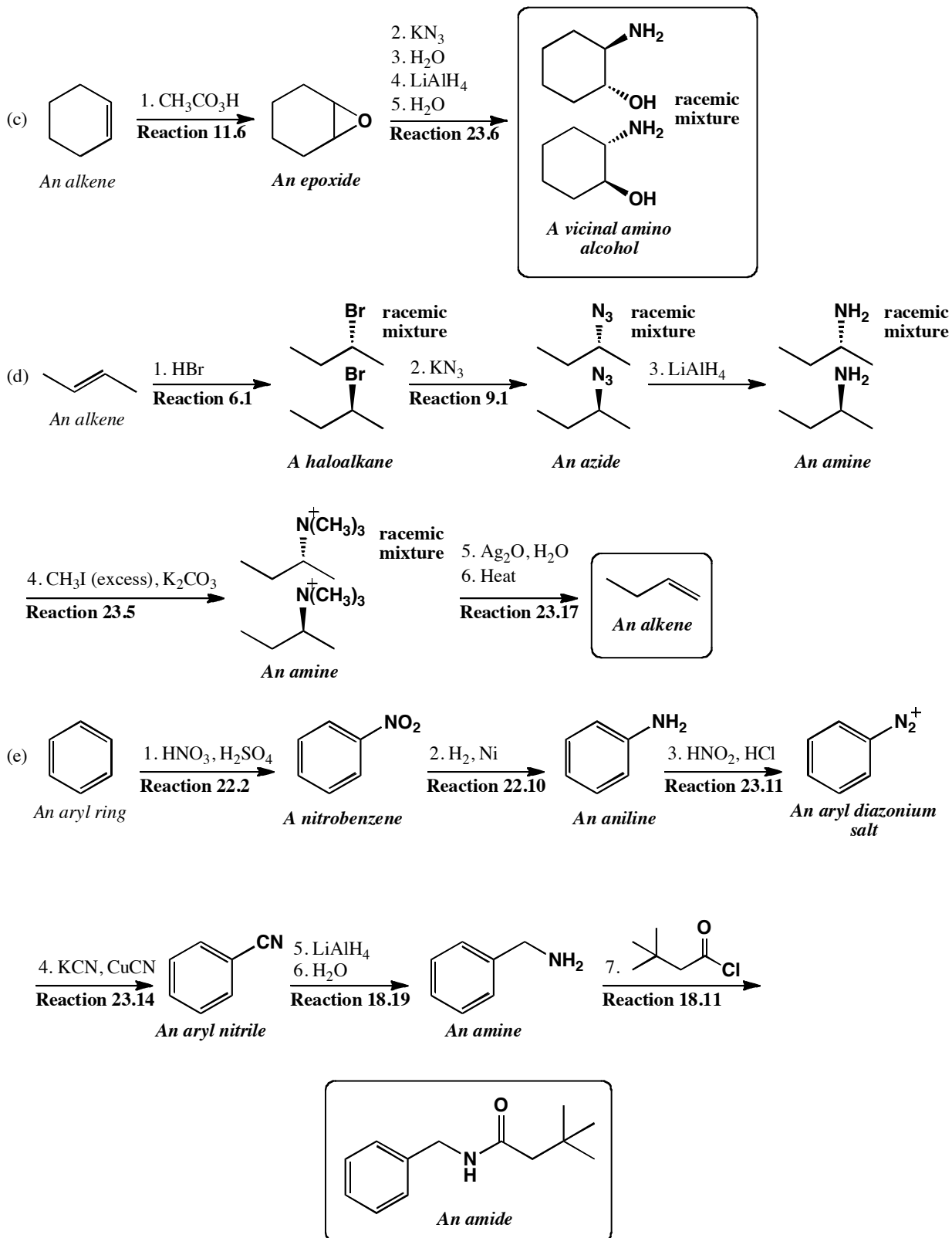
Conversion to amine oxide, heat

- The Cope elimination

- Elimination is syn stereoselective and involves a cyclic flow of six electrons in a planar transition state

Problem 23.44 Write the products of the following sequences of reactions. Refer to your roadmaps to see how the combined reactions allow you to "navigate" between the different functional groups. Note that you will need your old Chapters 6–11, Chapters 15–18 and Chapter 19 roadmaps along with your new Chapters 20–23 roadmap for these.

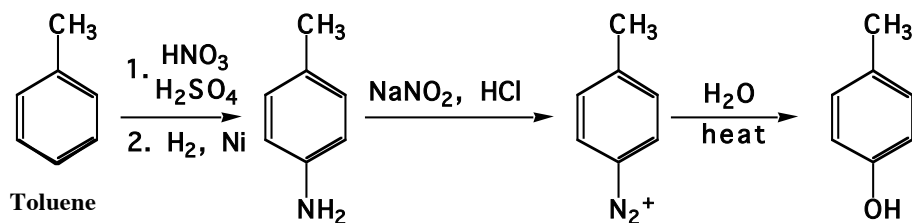




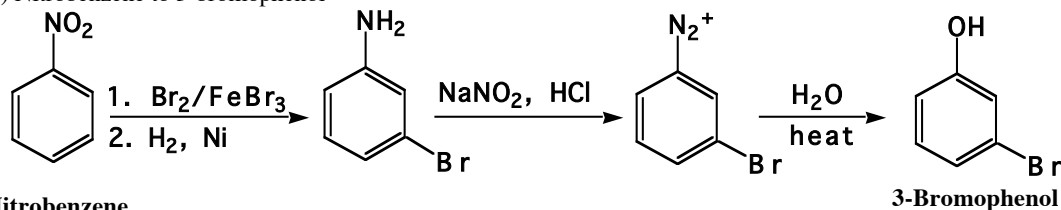
Synthesis

Problem 23.45 Propose steps for the following conversions using a reaction of a diazonium salt in at least one step of each conversion.

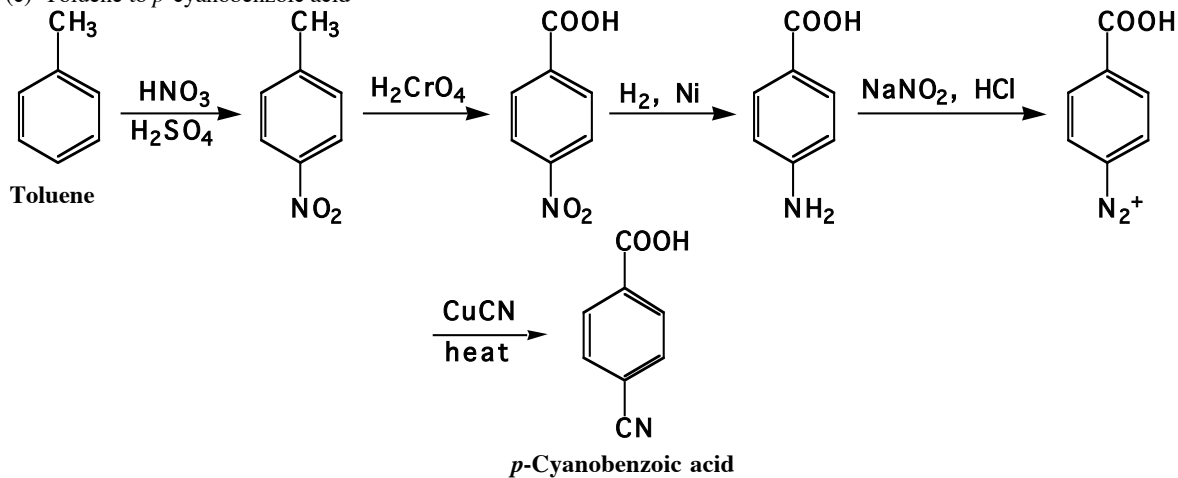
(a) Toluene to 4-methylphenol (*p*-cresol)



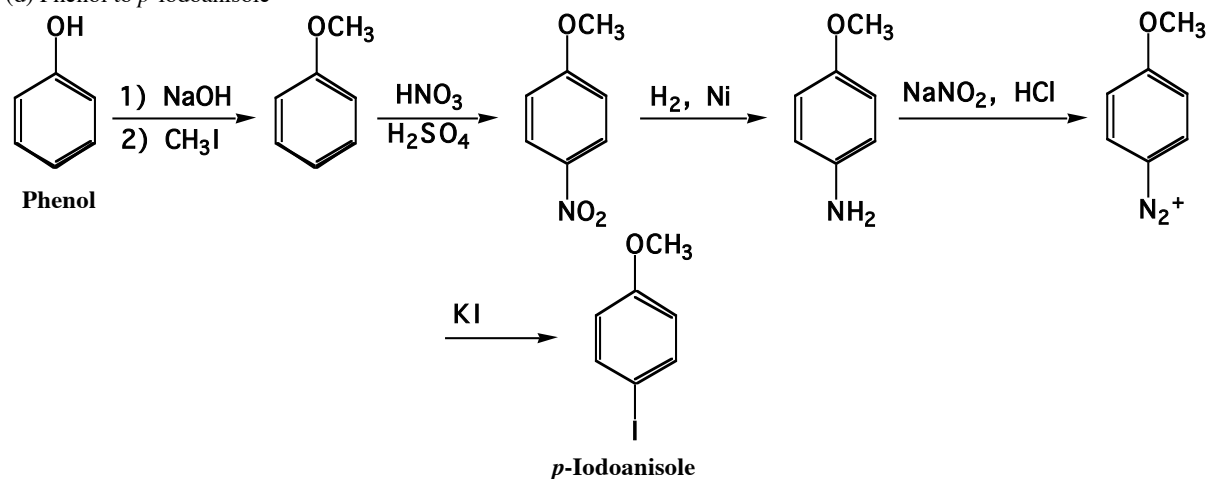
(b) Nitrobenzene to 3-bromophenol



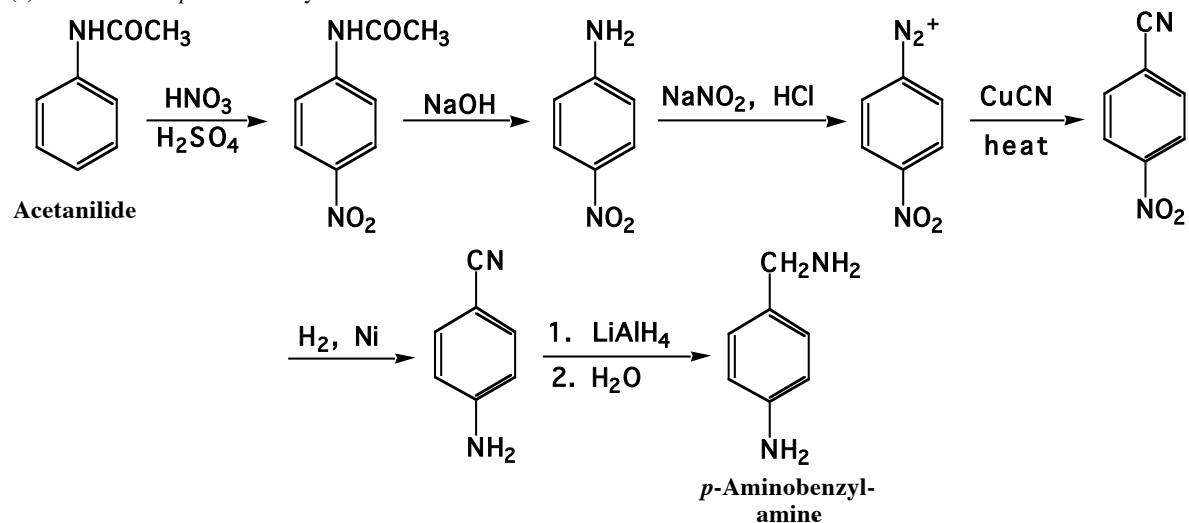
(c) Toluene to *p*-cyanobenzoic acid



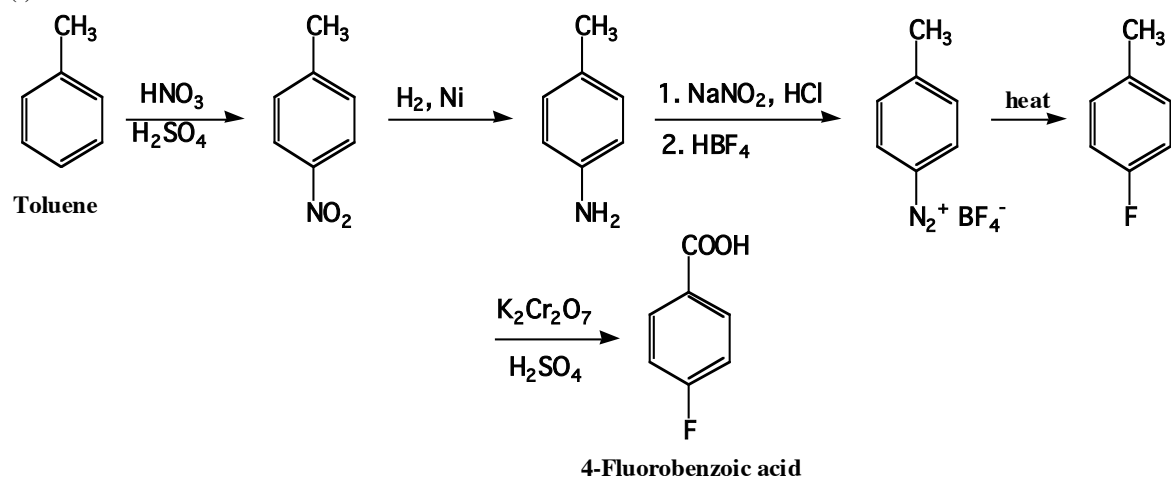
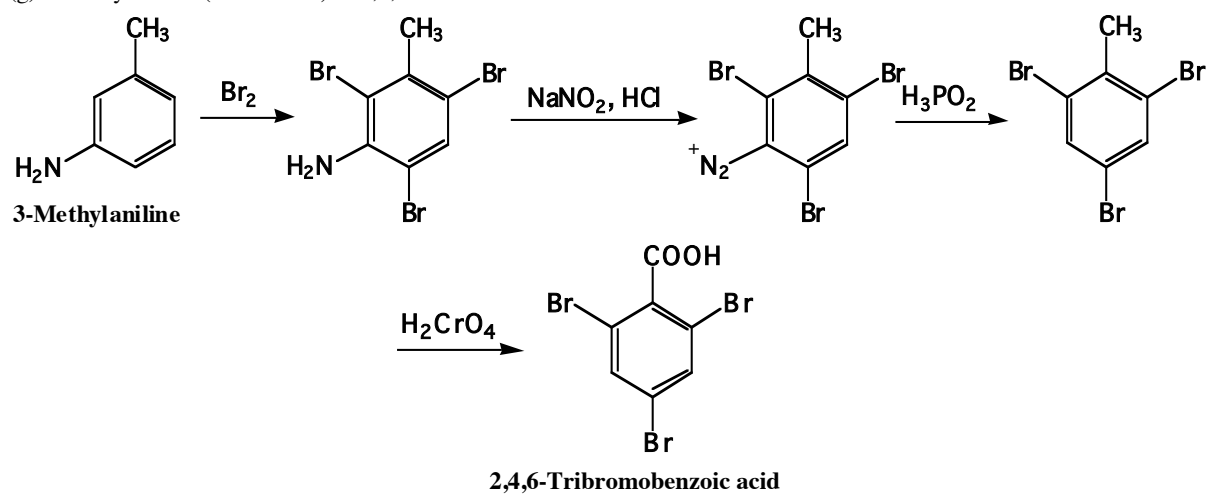
(d) Phenol to *p*-iodoanisole



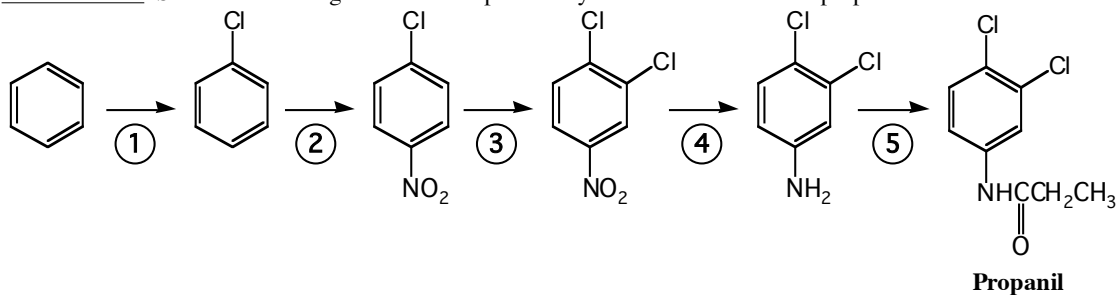
Note that dimethyl sulfate could be used in place of CH_3I to give the methyl ether in the first step of the synthesis.

(e) Acetanilide to *p*-aminobenzylamine

(f) Toluene to 4-fluorobenzoic acid

(g) 3-Methylaniline (*m*-toluidine) to 2,4,6-tribromobenzoic acid

Problem 23.44 Show how to bring about each step in this synthesis of the herbicide propanil.



The reagents that can be used in each step are listed below:

Step (1) Aromatic chlorination reaction using Cl_2 and FeCl_3 .

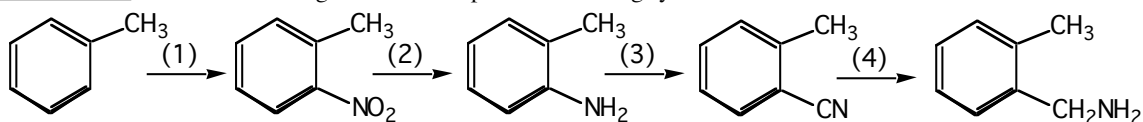
Step (2) Aromatic nitration reaction using HNO_3 and H_2SO_4 .

Step (3) Another aromatic chlorination reaction using Cl_2 and FeCl_3 . The new Cl atom is directed to the correct position by the groups already present on the ring.

Step (4) This reduction can be carried out using H_2 and a transition metal catalyst.

Step (5) Propanoic acid is first converted to the acid chloride by treatment with SOCl_2 and then reacted with the 3,4-dichloroaniline to give the desired propanil.

Problem 23.47 Show how to bring about each step in the following synthesis.



The reagents that can be used in each step are listed below:

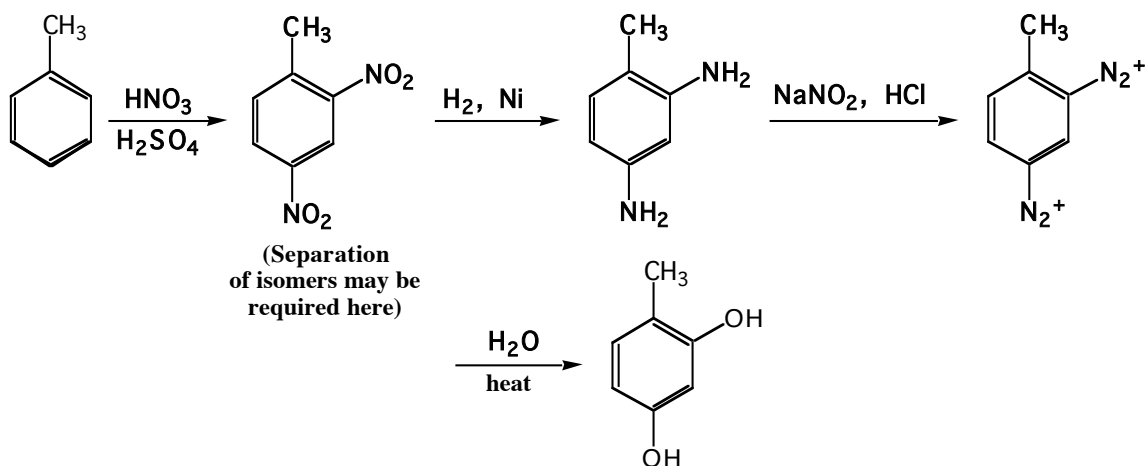
Step (1) Aromatic nitration reaction using HNO_3 and H_2SO_4 .

Step (2) This reduction can be carried out using H_2 and a transition metal catalyst.

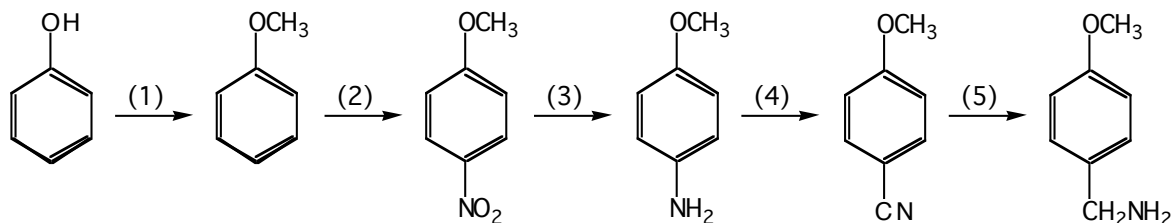
Step (3) This transformation can be accomplished by first turning the amino group into a diazonium salt by reaction with NaNO_2 and HCl , followed by a Sandmeyer reaction using CuCN and heat.

Step (4) This reduction can be carried out using LiAlH_4 followed by H_2O .

Problem 23.48 Show how to bring about this synthesis.



Problem 23.49 Show how to bring about each step in the following synthesis.



The reagents that can be used in each step are listed below:

Step (1) Reaction with NaOH to produce the phenoxide, followed by treatment with CH_3I .

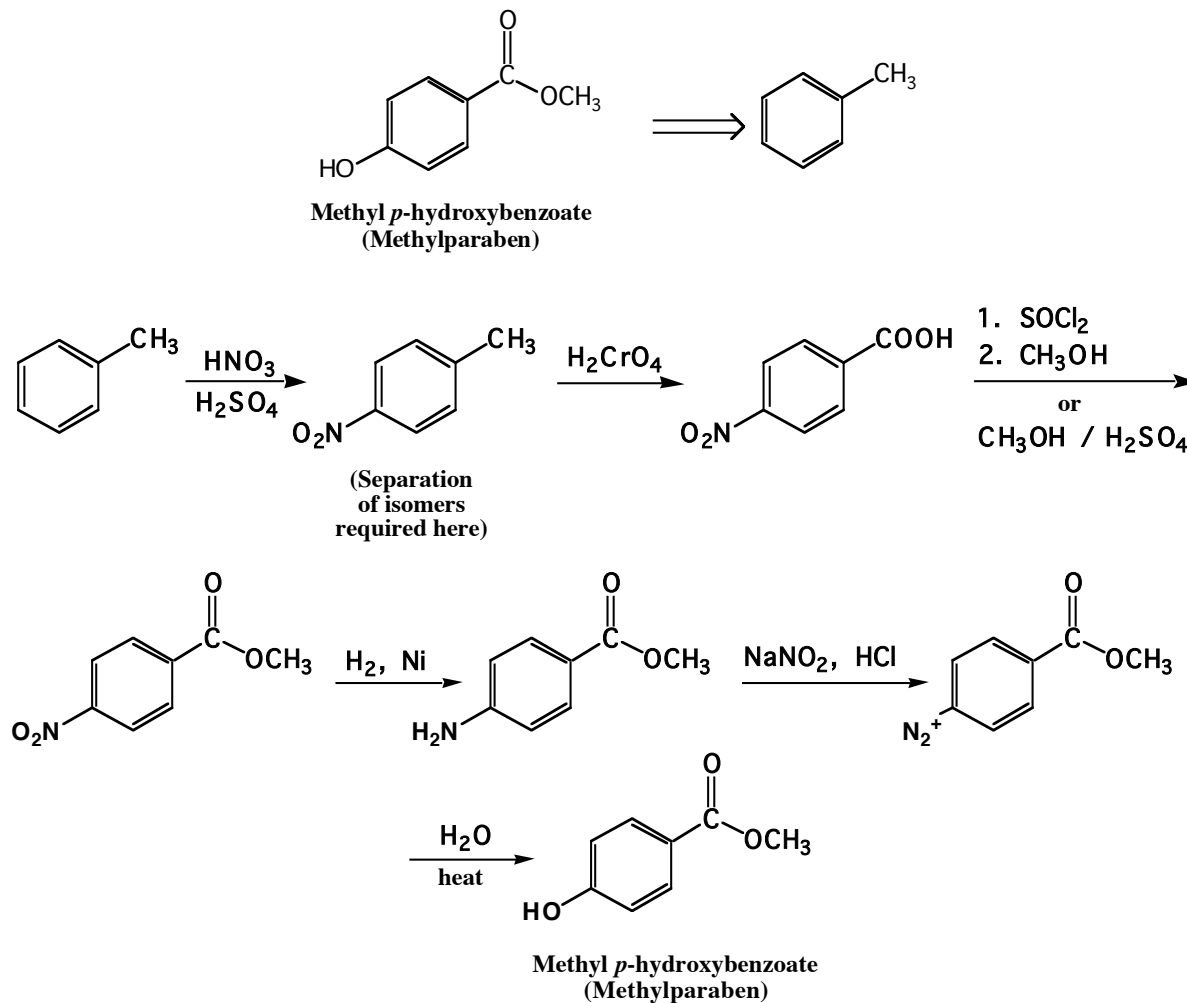
Step (2) Aromatic nitration reaction using HNO_3 and H_2SO_4 .

Step (3) This reduction can be carried out using H_2 and a transition metal catalyst.

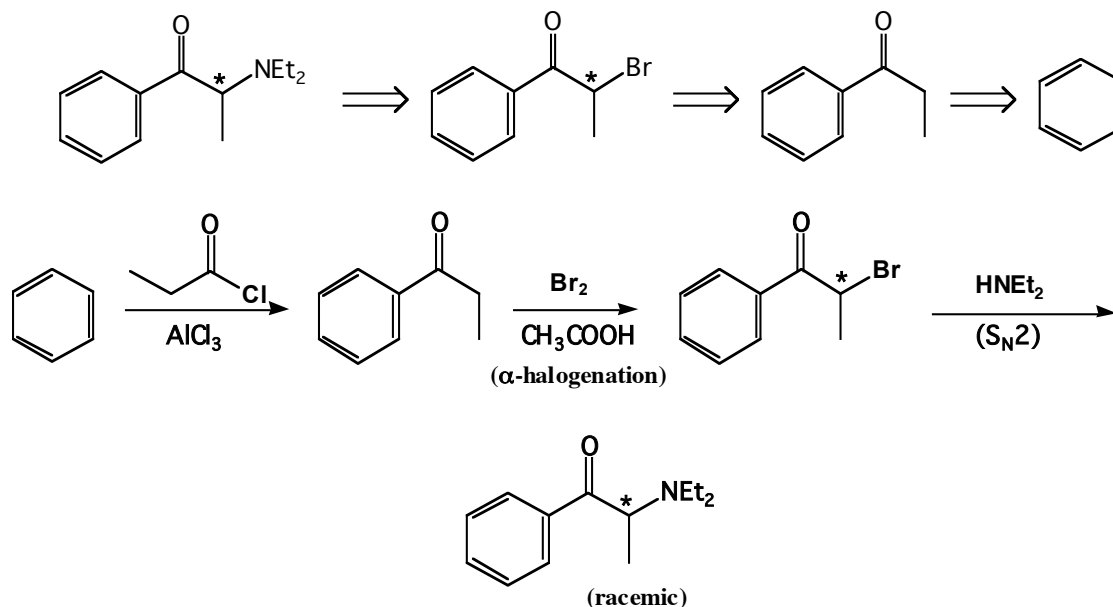
Step (4) This transformation can be accomplished by first turning the amino group into a diazonium salt by reaction with NaNO_2 and HCl, followed by a Sandmeyer reaction using CuCN and heat.

Step (5) This reduction can be carried out using (1) H_2 and a transition metal or (2) LiAlH_4 followed by H_2O .

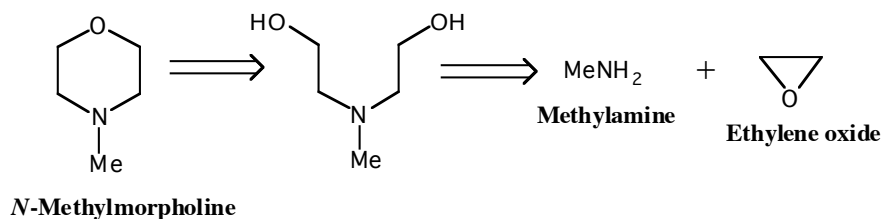
Problem 23.50 Methylparaben is used as a preservative in foods, beverages, and cosmetics. Provide a synthesis of this compound from toluene.



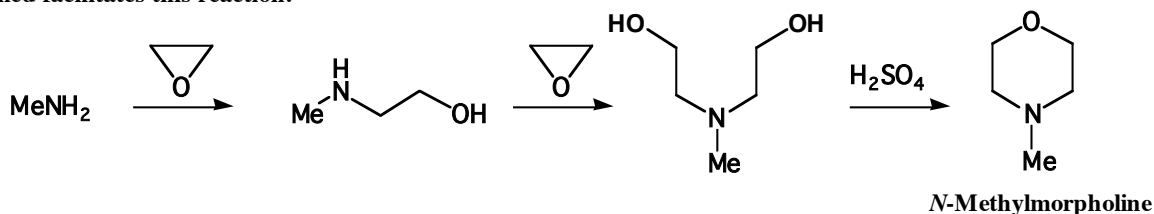
Problem 23.51 Given the following retrosynthetic analysis, show how to synthesize the following tertiary amine as a racemic mixture from benzene and any necessary reagents.



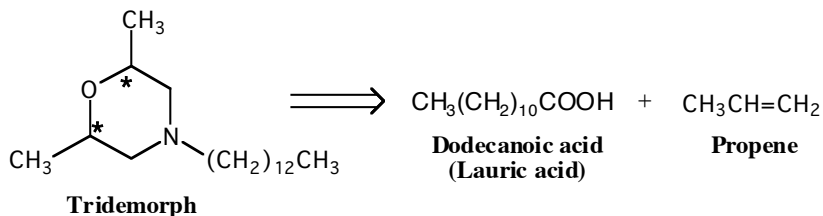
Problem 23.52 *N*-Substituted morpholines are building blocks in many drugs. Show how to synthesize *N*-methylmorpholine given this retrosynthetic analysis.



The key step in this synthesis is the last one, in which acid is used to form the morpholine ring. The reaction involves protonation of one of the hydroxyl groups, that then leaves as water. The fact that a six-membered ring is being formed facilitates this reaction.

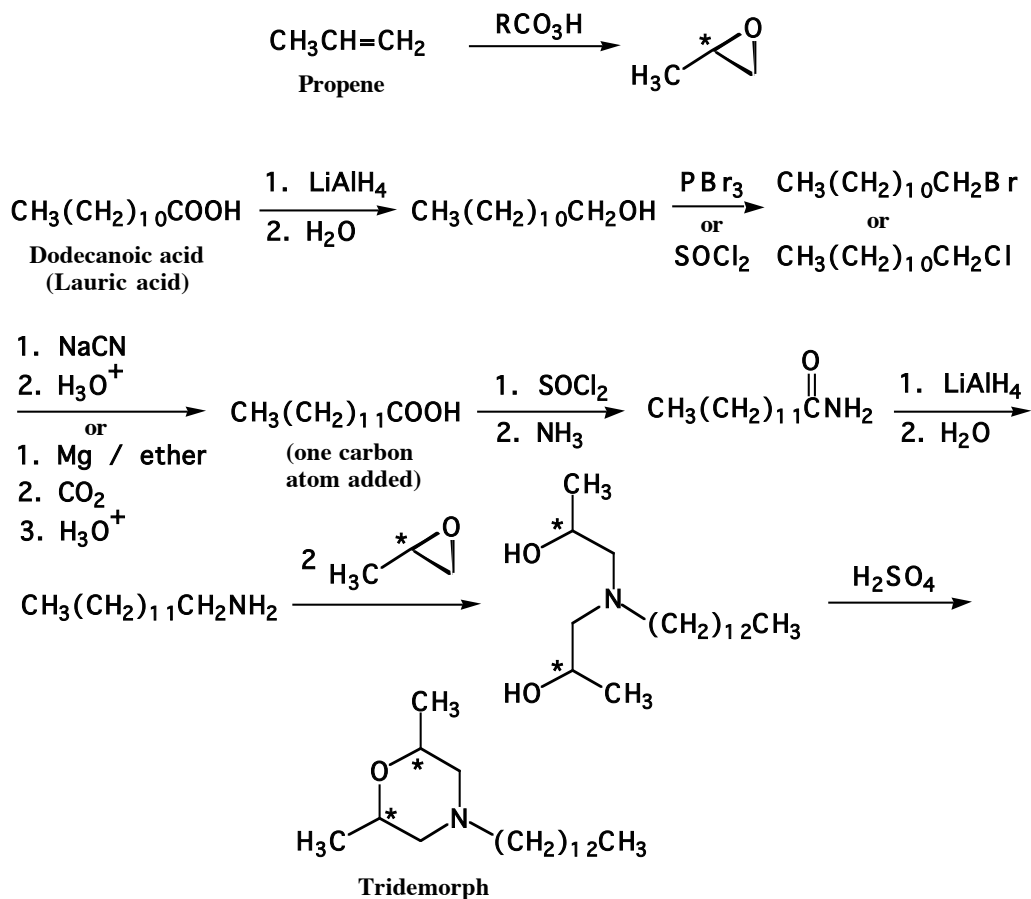


Problem 23.53 Propose a synthesis for the systemic agricultural fungicide tridemorph from dodecanoic acid (lauric acid) and propene. How many stereoisomers are possible for tridemorph?



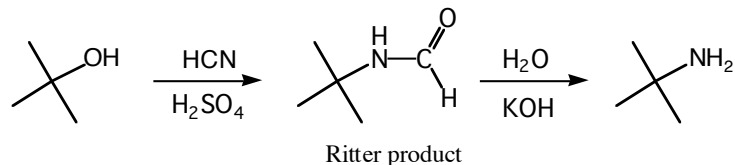
There are two keys to this synthesis. The first is to recognize that the morpholine ring is constructed from an acid-catalyzed reaction between two alcohol groups analogous to that used in problem 23.52. Note that the required diol can be prepared from reaction of an aliphatic amine and the epoxide derived from propene. The second key of the

synthesis is to notice that dodecanoic acid must be lengthened by one carbon atom before it is turned into an amine function.



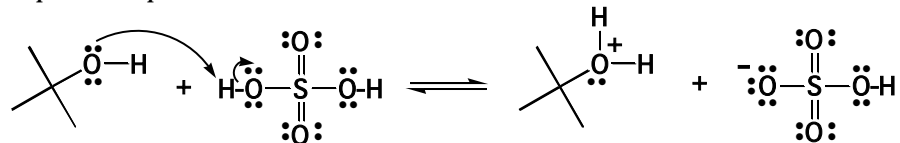
Note that Tridemorph has two chiral centers. Assuming racemic epoxide is used as starting material, a racemic mixture of three stereoisomers (one meso form and two enantiomers) will be formed as the product of the above reaction sequence.

Problem 23.54 The Ritter reaction is especially valuable for the synthesis of 3° alkanamines. In fact, there are few alternative routes to them. This reaction is illustrated by the first step in the following sequence. In the second step, the Ritter product is hydrolyzed to the amine.

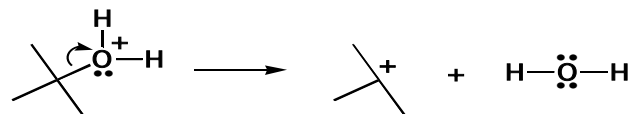


(a) Propose a mechanism for the Ritter reaction.

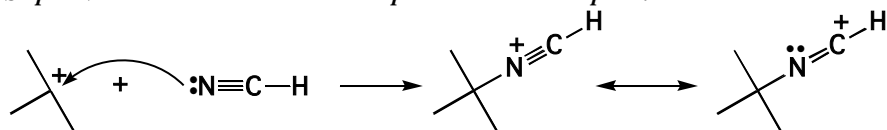
Step 1: Add a proton.



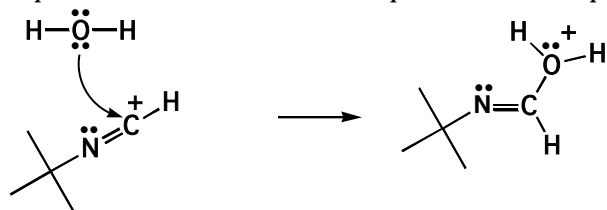
Step 2: Break a bond to give stable molecules or ions.



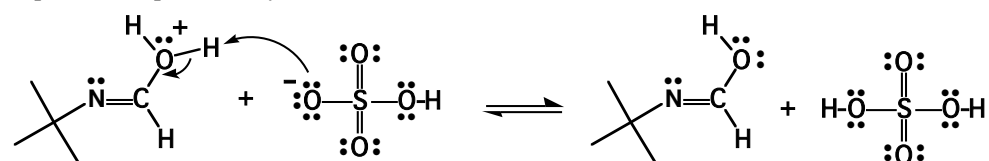
Step 3: Make a bond between a nucleophile and an electrophile.



Step 4: Make a bond between a nucleophile and an electrophile.



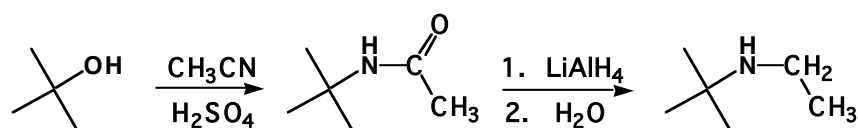
Step 5: Take a proton away.



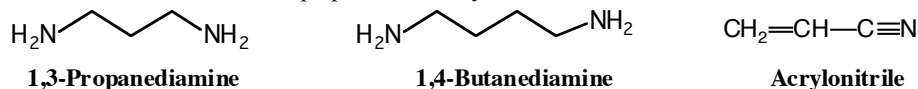
Step 6: Keto-enol tautomerism.



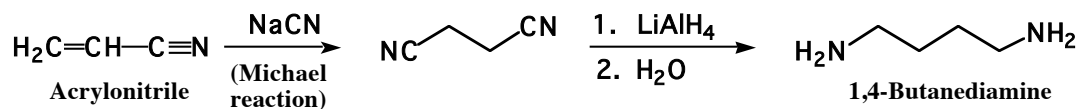
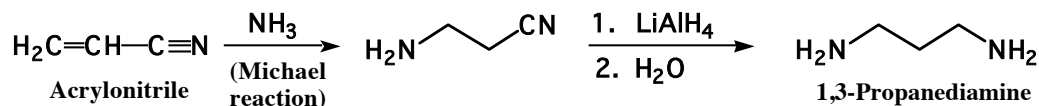
(b) What is the product of a Ritter reaction using acetonitrile, CH_3CN , instead of HCN followed by reduction of the Ritter product with lithium aluminum hydride?



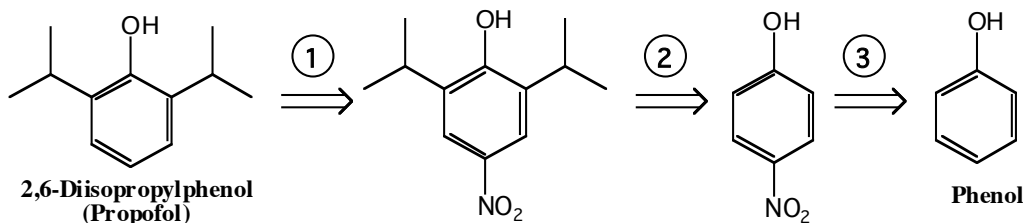
Problem 23.55 Several diamines are building blocks for the synthesis of pharmaceuticals and agrochemicals. Show how both 1,3-propanediamine and 1,4-butanediamine can be prepared from acrylonitrile



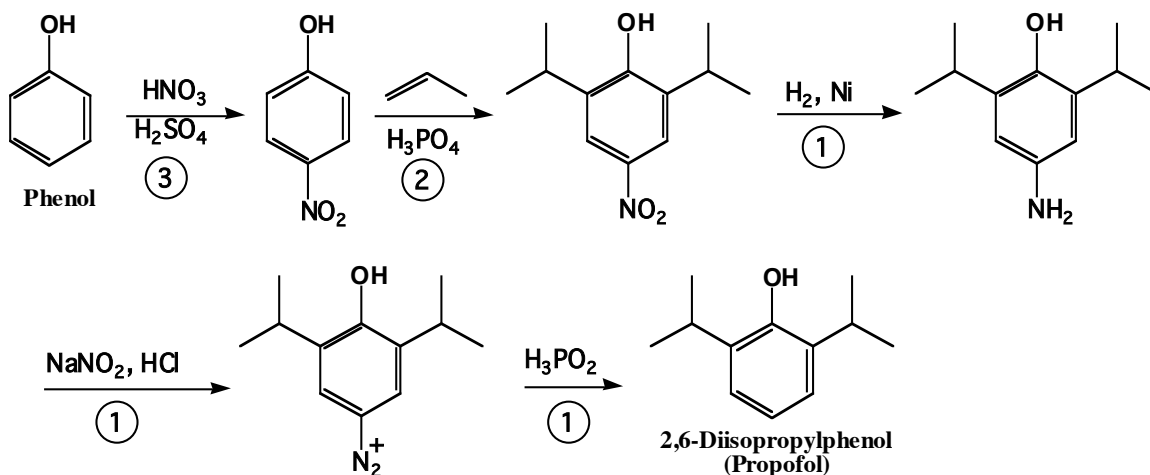
Acrylonitrile is a Michael acceptor that can react with amines (ammonia) or the cyanide anion.



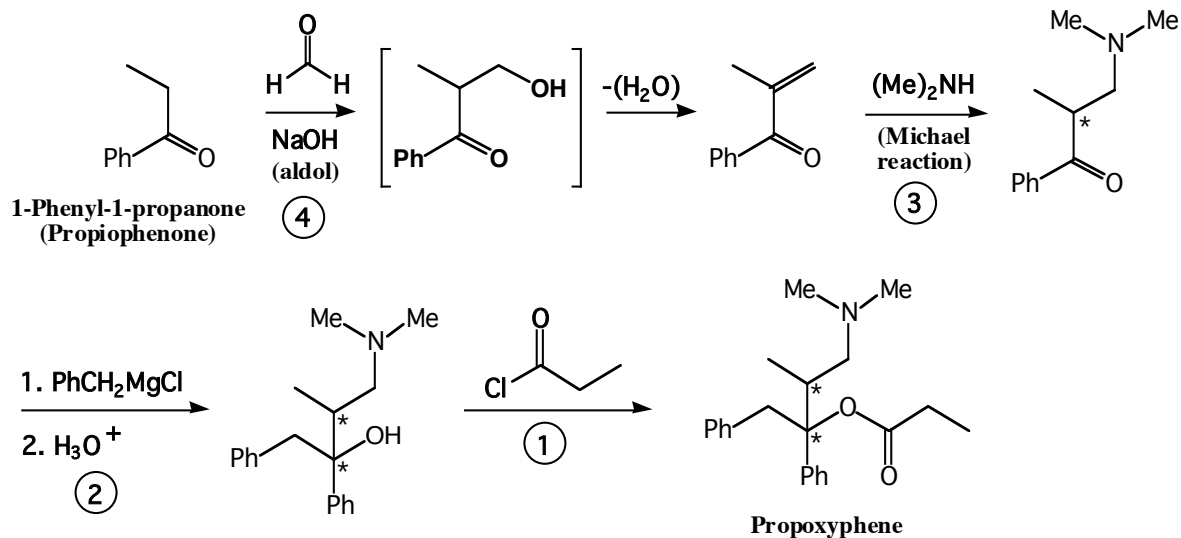
Problem 23.56 Given the following retrosynthetic analysis, show how the intravenous anesthetic 2,6-diisopropylphenol (Propofol) can be synthesized from phenol.



In the following synthetic scheme, note how the overall yield of product is increased by having the temporary nitro group insure that the alkylation will occur only in the desired positions ortho to the methyl group.



Problem 23.57 Following is a retrosynthetic analysis for propoxyphene, the hydrochloride salt of which is Darvon. The naphthalenesulfonic acid salt of propoxyphene is Darvon-N. The configuration of the carbon in Darvon bearing the hydroxyl group is *S*, and the configuration of the other chiral center is *R*. Its enantiomer has no analgesic properties, but it is used as a cough suppressant.



(a) Propose a synthesis for propoxyphene from 1-phenyl-1-propanone and any other necessary reagents.

Step (4) A crossed aldol reaction using formaldehyde followed by dehydration gives the α,β -unsaturated ketone (Section 19.2).

Step (3) A Michael reaction using dimethylamine (Section 19.8) gives the second key intermediate.

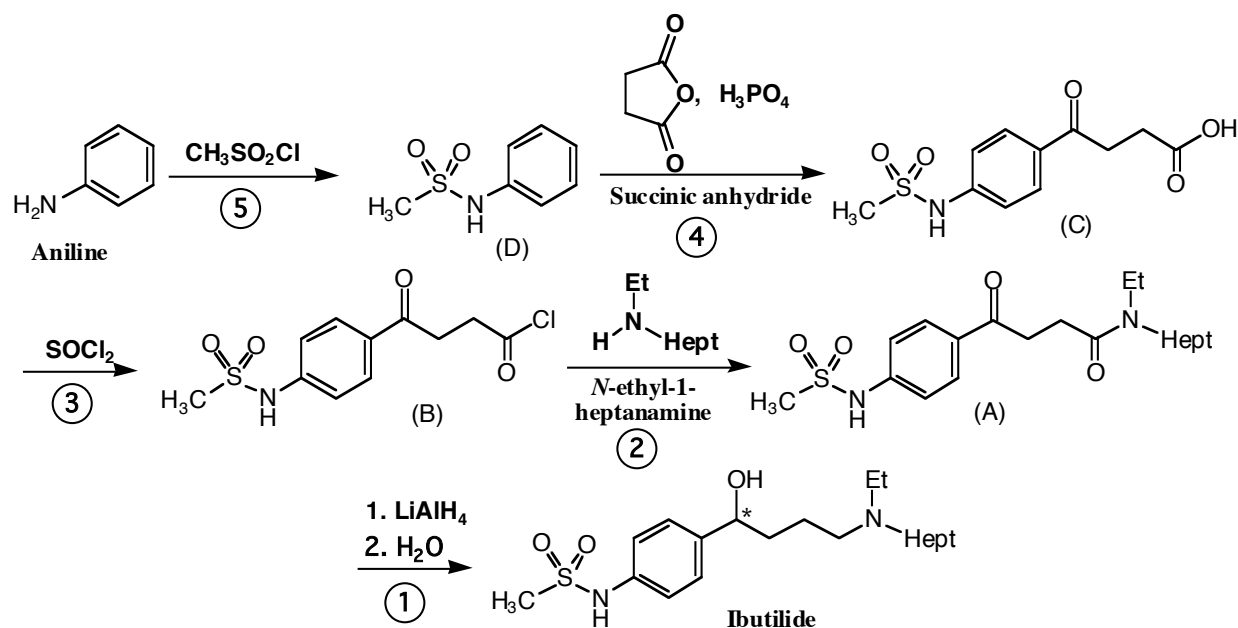
Step (2) Reaction of the ketone with a benzyl Grignard reagent (Section 16.5) gives the alcohol product.

Step (1) Reaction with propanoyl chloride (Section 18.5) gives propoxyphene ether.

(b) Is propoxyphene chiral? If so, which of the possible stereoisomers are formed in this synthesis?

Propoxyphene has two chiral centers, so a racemic mixture of four stereoisomers is produced in this synthesis.

Problem 23.58 Following is a retrosynthetic analysis for ibutilide, a drug used to treat cardiac arrhythmia. In this scheme, Hept is an abbreviation for the 1-heptyl group.



(a) Propose a synthesis for ibutilide starting with aniline, methanesulfonyl chloride, succinic anhydride, and *N*-ethyl-1-heptanamine.

Step (5) Treatment of a primary or secondary amine with methanesulfonyl chloride (Section 18.1) gives a sulfonamide.

Step (4) This reaction is a type of electrophilic aromatic substitution (Section 22.1) that results in acylation of the aromatic ring. For a mechanism of this type of acylation, review the solution to Problem 22.27.

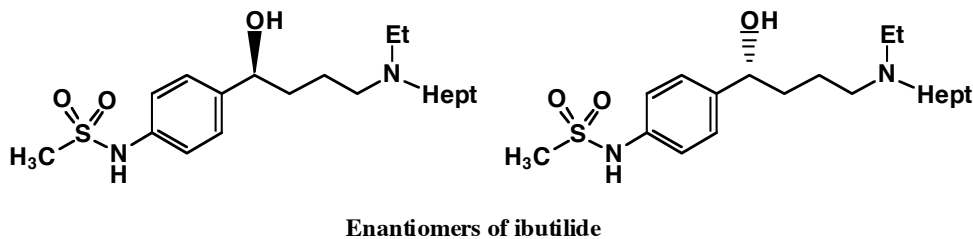
Step (3) Treatment of the carboxylic acid with thionyl chloride gives an acid chloride (Section 17.8).

Step (2) Treatment of the acid chloride with *N*-ethyl-1-heptanamine gives (a secondary amine) gives an amide (Section 18.6).

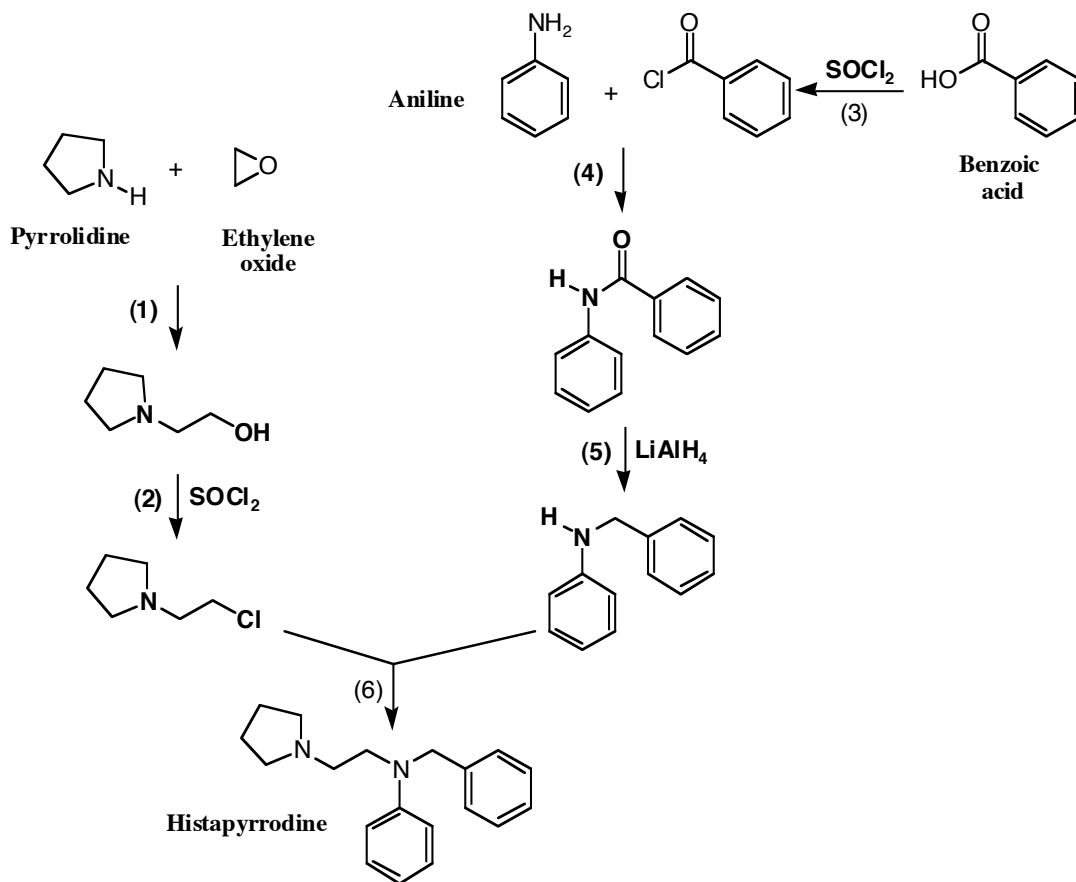
Step (1) Reduction with lithium aluminum hydride gives a secondary alcohol (Section 16.11) and amine (Section 18.10).

(b) Is ibutilide chiral? If so, which of the possible stereoisomers are formed in this synthesis?

Ibutilide has one chiral center, so it is produced as a racemic mixture of enantiomers.



Problem 23.59 Propose a synthesis for the antihistamine histapyrrodine.



Step (1) Nucleophilic opening of the epoxide (Section 11.9) gives an aminoalcohol.

Step (2) Treatment of the alcohol with thionyl chloride (Section 10.5) gives an alkyl chloride.

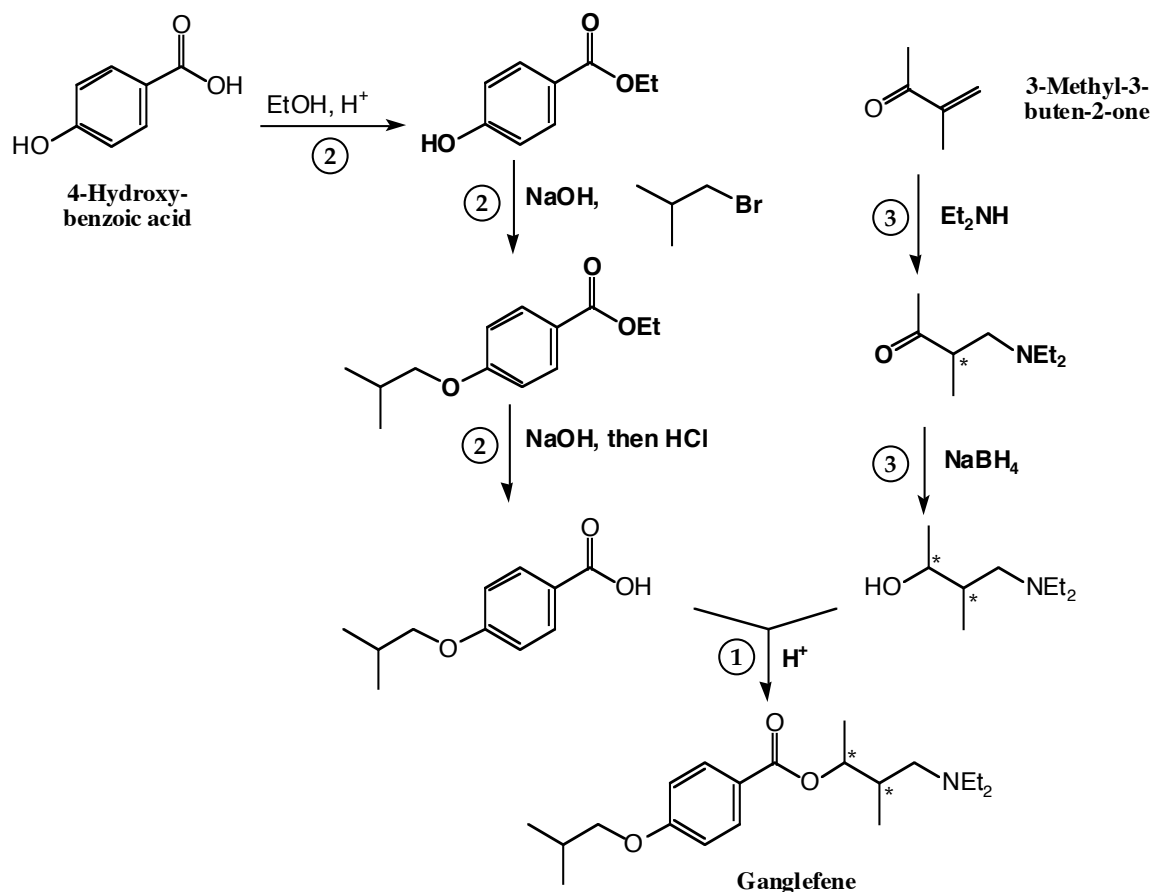
Step (3) Treatment of benzoic acid with thionyl chloride (Section 17.8) gives benzoyl chloride.

Step (4) Reaction of benzoyl chloride and aniline (Section 18.6) gives *N*-phenylbenzamide.

Step (5) LiAlH_4 reduction of the amide (Section 18.10) gives a secondary amine.

Step (6) Because of participation by the neighboring nitrogen atom (Section 9.11), this primary chloride undergoes reaction with the secondary amino group of *N*-methylbenzylamine to give histapyrrodine.

Problem 23.60 Following is a retrosynthesis for the coronary vasodilator ganglefene.



(a) Propose a synthesis for ganglefene from 4-hydroxybenzoic acid and 3-methyl-3-buten-2-one.

Step (3) Michael addition (Section 19.8) of diethylamine to this α,β -unsaturated ketone gives a β -aminoketone.

Sodium borohydride reduction of the ketone gives a secondary alcohol (Section 16.11).

Step (2) A carboxylic acid (pK_a 4-5) is a stronger acid than a phenol (pK_a 9-10). Therefore, if 4-hydroxybenzoic acid were treated with one mole of NaOH, the carboxyl proton would be removed preferentially. Treatment of this anion with 1-bromo-2-methylpropane (isobutyl bromide) would then give an isobutyl ester. To ensure that alkylation takes place on the phenolic oxygen, first convert the carboxyl group to an ethyl ester by Fischer esterification (Section 17.7). Then treat this ester with one mole of NaOH followed by isobutyl bromide to form the phenolic ether. Finally remove the carboxyl protecting group by base-promoted hydrolysis (Section 18.4) followed by acidification to give 4-isobutoxybenzoic acid.

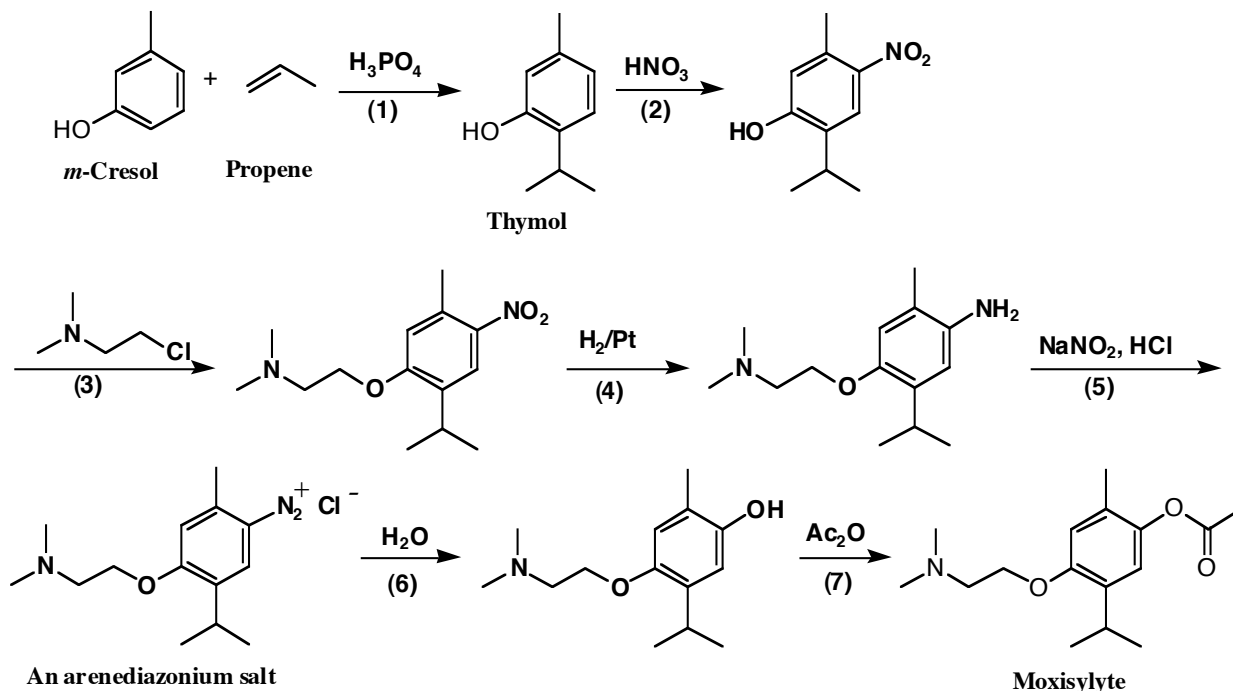
Step (1) Fischer esterification (Section 17.7) of the carboxylic acid with the secondary alcohol gives ganglefene.

Alternatively, the carboxyl group may be converted to its acid chloride using thionyl chloride (Section 17.8) and the acid chloride reaction with the alcohol to give ganglefene.

(b) Is ganglefene chiral? If so, which of the possible stereoisomers are formed in this synthesis?

Ganglefene has two chiral centers, so it is produced as a racemic mixture of four stereoisomers.

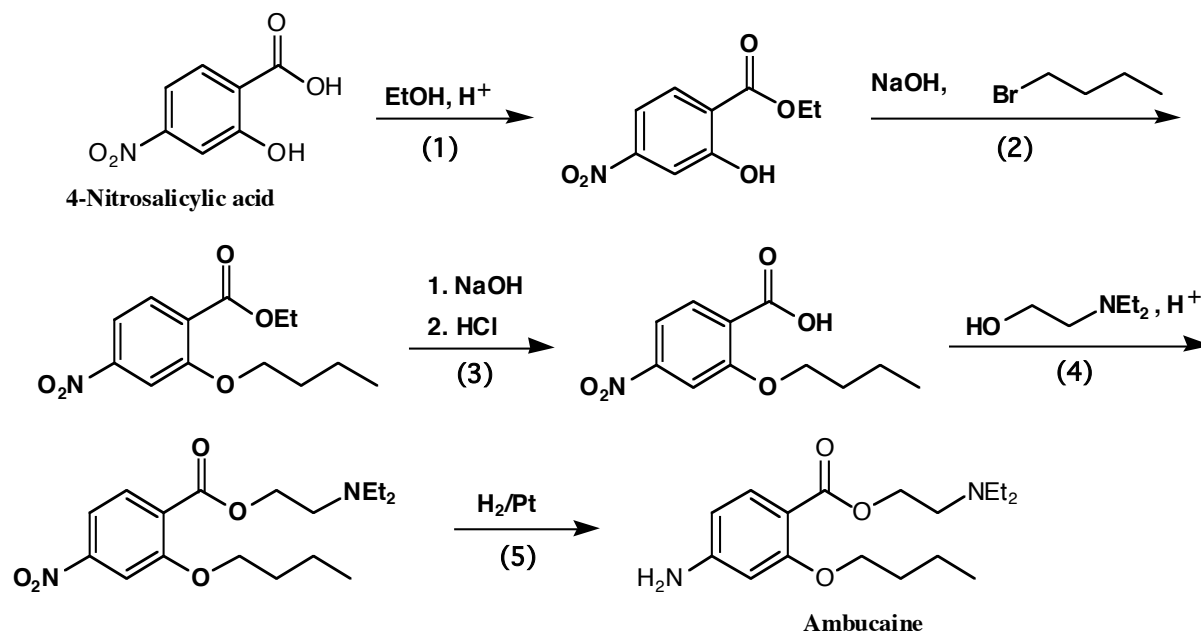
Problem 23.61 Moxisylyte, an α -adrenergic blocker, is used as a peripheral vasodilator. Propose a synthesis for this compound from thymol, which occurs in the volatile oils of members of the thyme family. Thymol is made industrially from *m*-cresol.



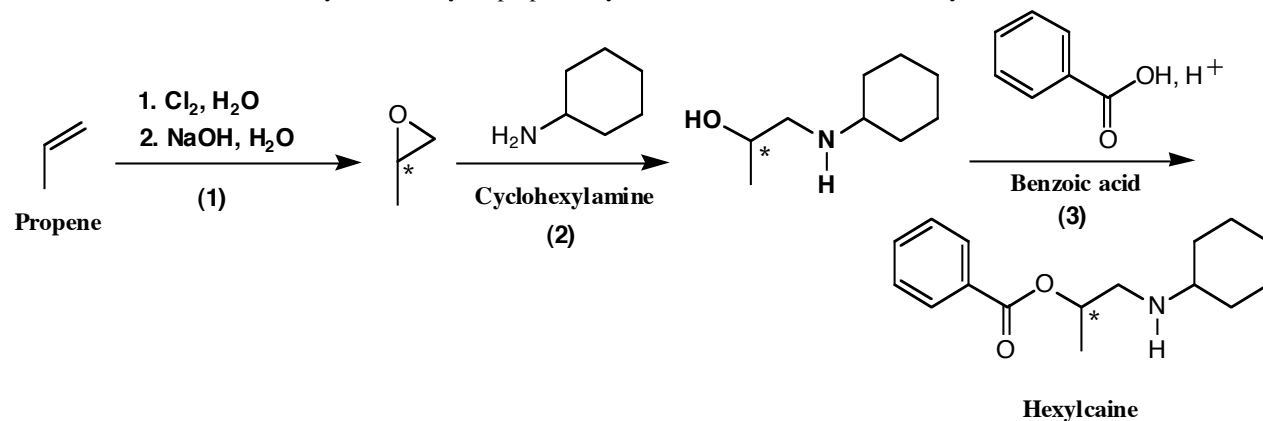
- An arenediazonium salt**
- Step (1)** A phenol may be alkylated using an alkene and a phosphoric acid catalyst (Section 21.4), or an alcohol and a phosphoric acid catalyst (Section 21.4).
- Step (2)** Nitration (Section 22.1) is directing by the strongly activating phenolic -OH group.
- Step (3)** Reaction with this chloramine gives the ether intermediate (Section 9.11).
- Step (4)** Catalytic reduction of the nitro group (Section 22.1) gives a primary aromatic amine.
- Steps (5 and 6)** Treatment of the primary aromatic amine with nitrous acid gives an arenediazonium salt (Section 23.8). Warming this salt in water results in evolution of N_2 and formation of a phenol.
- Step (7)** Treatment of the phenol with acetic anhydride (Section 18.5) gives moxisylyte.

Problem 23.62 Propose a synthesis of the local anesthetic ambucaine from 4-nitrosalicylic acid, ethylene oxide, diethylamine, and 1-bromobutane.

- Steps (1-3)** The synthetic problem here is to alkylate the phenolic -OH group while retaining the -COOH group. This can be accomplished by protection of the -COOH group as its methyl ester (Fischer esterification, Section 17.7), alkylation the phenolic -OH group using NaOH and 1-bromobutane, and finally base-promoted hydrolysis of the ethyl ester followed by acidification with aqueous HCl followed to regenerate the carboxyl group (Section 18.4).
- Step (4)** Fischer esterification (Section 17.7) using the β -aminoalcohol gives the ester. The β -amino alcohol is derived by treating ethylene oxide with diethylamine.
- Step (5)** Catalytic reduction of the nitro group gives the primary aromatic amine (Section 21.1) and completes the synthesis of ambucaine.



Problem 23.63 Given this retrosynthetic analysis, propose a synthesis for the local anesthetic hexylcaine.

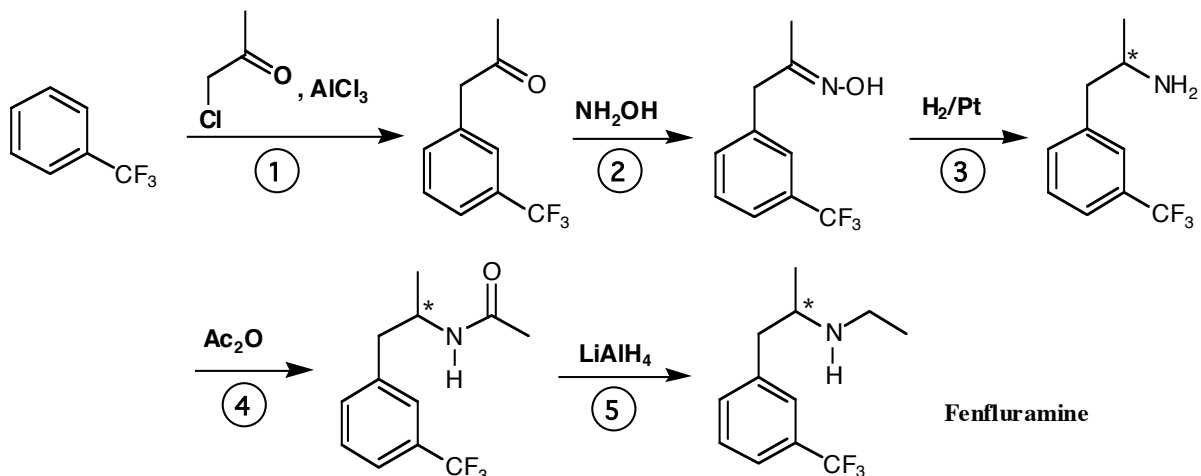


Step 1: This synthesis of methyloxirane (propylene oxide) is described in Section 11.8.

Step 2: Treatment of the epoxide with cyclohexylamine results in regioselective nucleophilic opening of the epoxide ring (Section 11.9).

Step 3: Fischer esterification with benzoic acid gives hexylcaine (Section 17.7). Note that the acid chloride method can not be used here because of secondary amine of the β -aminoalcohol is a stronger nucleophile than the hydroxyl group.

Problem 23.64 Following is an outline for a synthesis of the anorexic (appetite suppressant) fenfluramine. This compound was one of the two ingredients in Phen-Fen, a weight-loss preparation now banned because of its potential to cause irreversible heart valve damage.



(a) Propose reagents and conditions for Step 1. Account for the fact that the $-\text{CF}_3$ group is meta directing.

This step is a Friedel-Crafts acylation (Section 22.1) using an α -chloroketone. For the reason the trifluoromethyl group is meta directing, review your answer to Problem 22.17.

(b) Propose reagents and experimental conditions for Steps 2 and 3.

Step 2: Treatment of the ketone with hydroxylamine (Section 16.8) gives an oxime.

Step 3: The chemistry of this portion of the problem is not presented in the text, but relies on principles similar to those you have seen. Under these reaction conditions, the $\text{C}=\text{N}$ double bond is reduced to $\text{C}-\text{N}$. In addition, the $\text{N}-\text{O}$ bond of the oxime is cleaved. The result is reduction of the oxime to a primary amine. You have already seen an example of catalytic reduction of an $\text{N}-\text{O}$ bond to an $\text{N}-\text{H}$ bond in the catalytic reduction of a $-\text{NO}_2$ group to a $-\text{NH}_2$ group (Section 22.1).

(c) An alternative procedure for preparing the amine of Step 3 is reductive amination of the corresponding ketone. What is reductive amination? Why might the two-step route for formation of the amine be preferred over the one-step reductive amination?

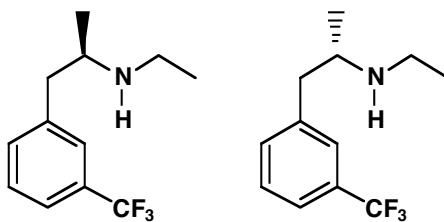
Reductive amination refers to the process in which an amine is added along with hydrogen and a transition metal. An imine is formed temporarily, then the $\text{C}=\text{N}$ bond is reduced by hydrogenation. A potential problem with the reductive amination procedure is that the imines are not that stable, and during the reduction step some imine can revert to the ketone, which is reduced, lowering the yield. The oxime is more stable, so with this procedure, it is easier improve the yield of the overall process.

(d) Propose reagents for Steps 4 and 5.

Step 4: Treatment of the primary amine with acetic anhydride (Section 18.6) gives the amide.

Step 5: Lithium aluminum hydride reduction of the amide (Section 18.10) gives the secondary amine and completes the synthesis of fenfluramine.

(e) Is fenfluramine chiral? If so, which of the possible stereoisomers are formed in this synthesis?

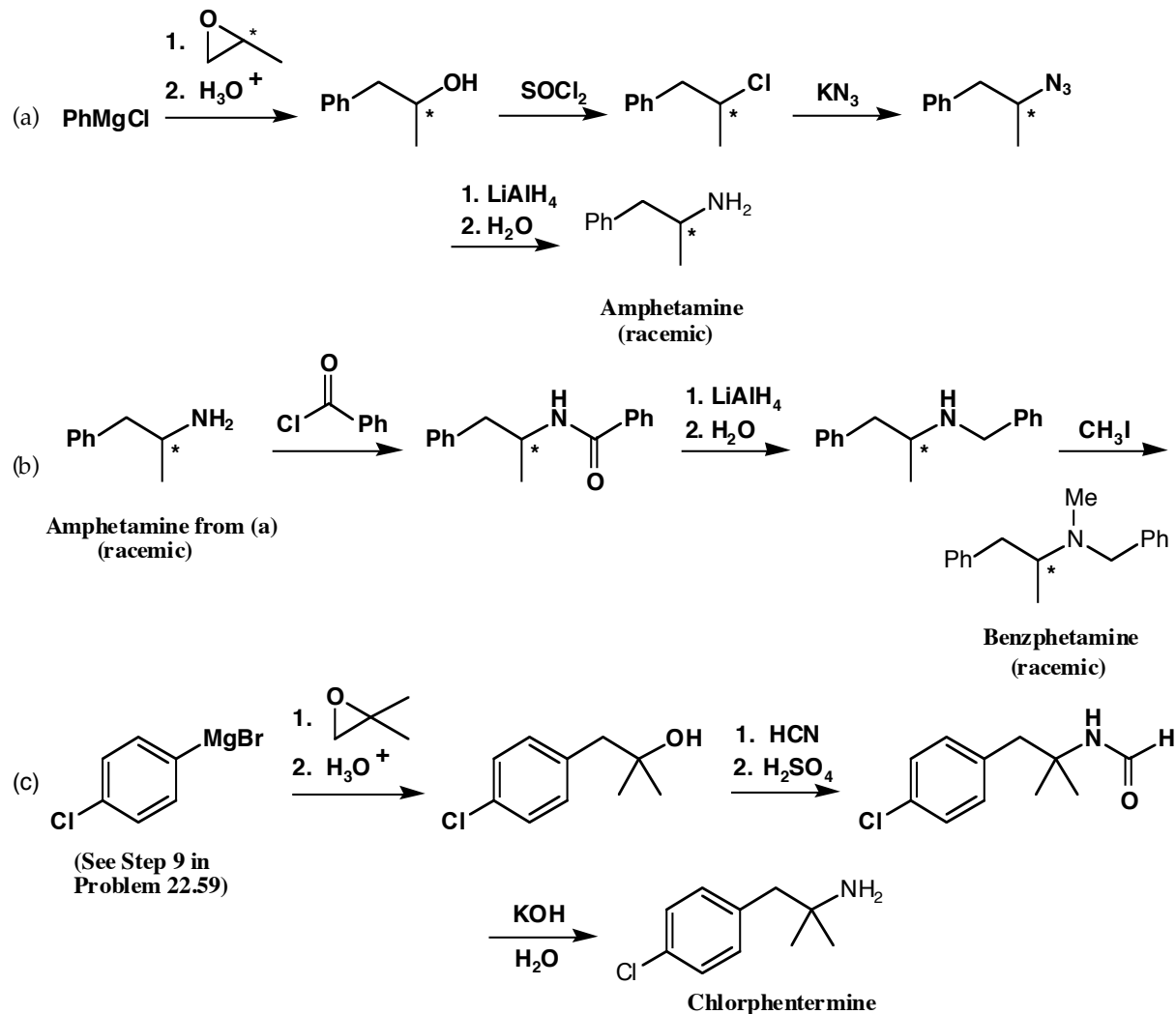


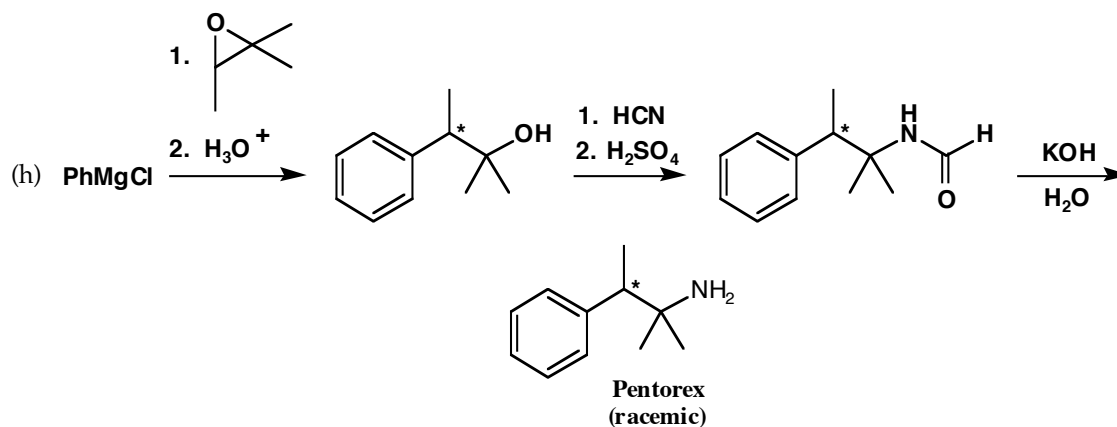
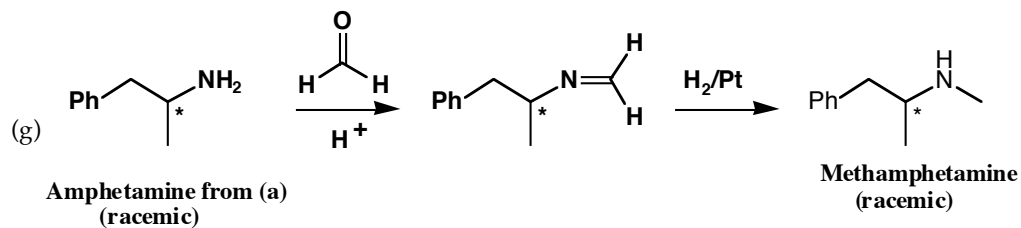
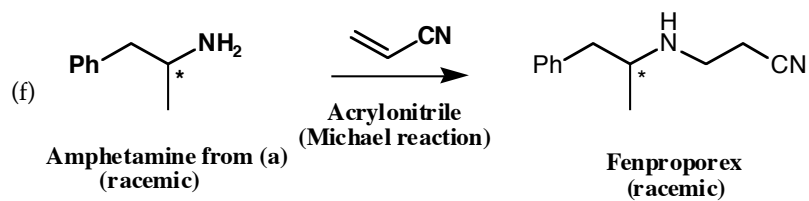
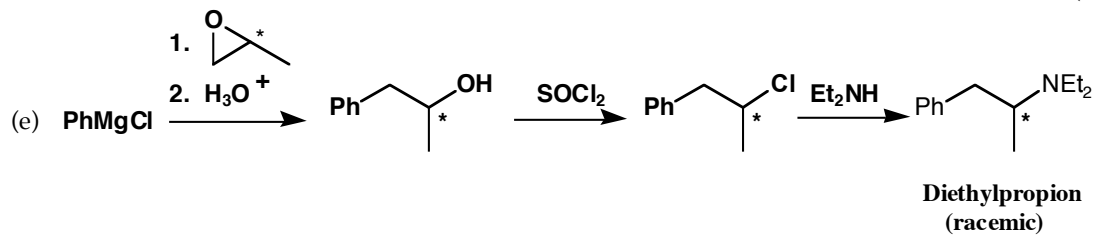
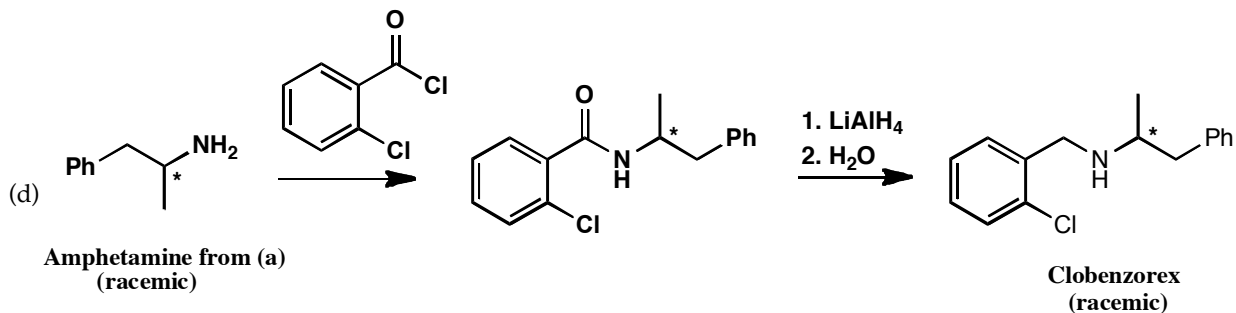
Enantiomers of fenfluramine

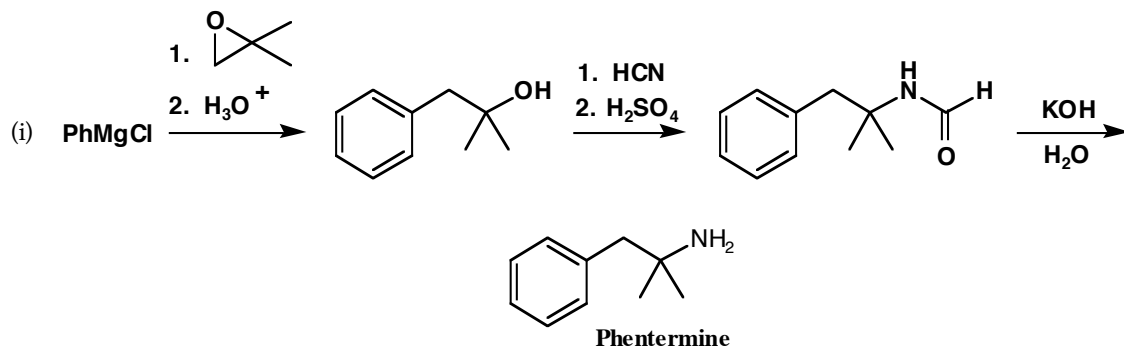
Problem 23.65 Following is a series of anorexics (appetite suppressants). As you study their structures, you will surely be struck by the sets of characteristic structural features.

(a) Knowing what you do about the synthesis of amines, including the Ritter reaction (Problem 23.52), suggest a synthesis for each compound.

An important observation is that the amine of amphetamine is on a secondary carbon and can be synthesized from an alkyl halide using the azide route. Amphetamine can be used as starting material for several other derivatives (b),(d),(f),(g). Others are on tertiary carbons and can be synthesized by the Ritter reaction (c),(h),(i). In most cases, reaction of a phenyl Grignard reagent with an epoxide will give the required alcohol for Ritter reactions (c),(h),(i), or conversion to an alkyl chloride with SOCl_2 for the azide route (a). In other cases, various methods such as reduction of amides (b),(d), Michael reactions (f), or reductive aminations (g) are used to avoid overalkylation of the primary amine of amphetamine.



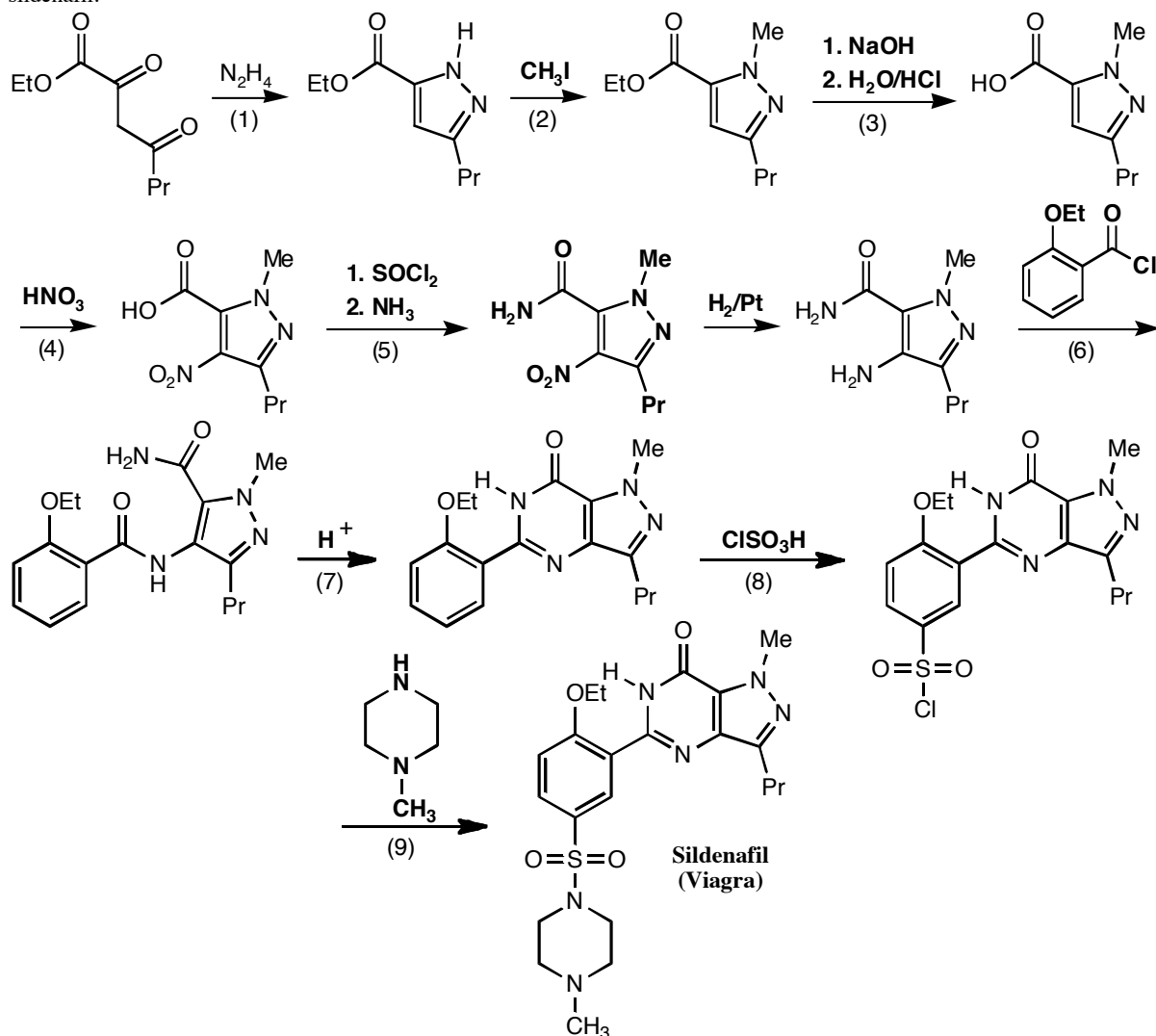




(b) Which of these compounds are chiral?

As labeled on the structures above, (a), (b), (d), (e), (f), (g), and (h) are chiral because they each have one chiral center. They are produced as racemic mixtures in the proposed syntheses.

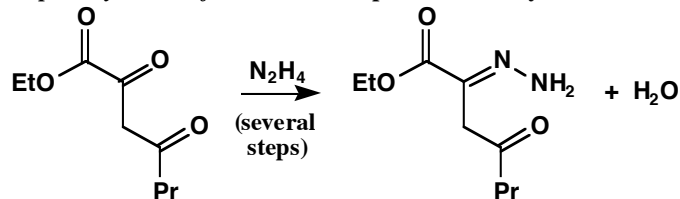
Problem 23.66 The drug sildenafil, sold under the trade name Viagra, is a potent inhibitor of phosphodiesterase V (PDE V), an enzyme found in high levels in the corpus carvenosum of the penis. Inhibitors of this enzyme enhance vascular smooth muscle relaxation and are used for treatment of male impotence. Following is an outline for a synthesis of sildenafil.



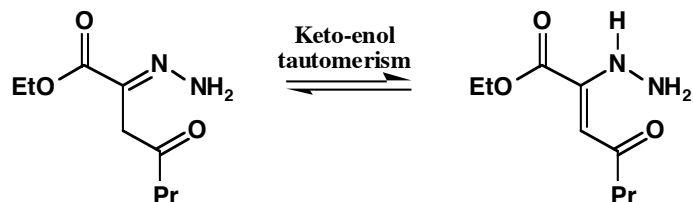
(a) Propose a mechanism for Step 1.

The mechanism for this step involves formation of a hydrazone (Section 16.8) followed by tautomerization to give the fully conjugated system, then another C=N bond forming process.

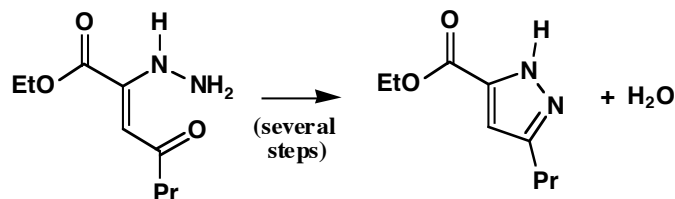
Step 1: Hydrazone formation This process actually takes several steps.



Step 2: Keto-enol tautomerism. This process actually takes several steps.

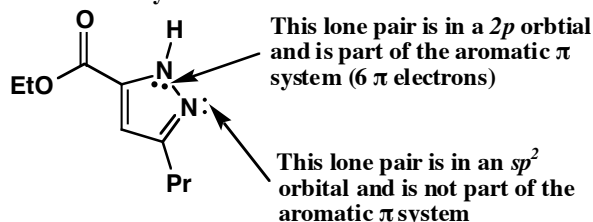


Step 3: Hydrazone formation This process actually takes several steps.



(b) The five-membered nitrogen-containing ring formed in Step 1 is named pyrazole. Show that, according to the Hückel criteria for aromaticity, pyrazole can be classified as an aromatic compound.

The pyrazole is aromatic by virtue of the 4 π electrons from the two C=C π bonds, and the lone pair from one of the N atoms (the one in the $2p$ orbital) as shown in the diagram. The other N atom lone pair is in an sp^2 orbital and is not part of the aromatic π system.



(c) Propose a reagent or reagents for Steps 2-7 and 9.

Step (2) Methylation of the N atom with methyl iodide (Section 9.3).

Step (3) The ester is hydrolyzed by saponification followed by acidification to reprotonate the carboxylic acid function (Section 18.4).

Step (4) Nitration of the aromatic ring using HNO_3 (Section 22.1).

Step (5) The carboxylic acid group is converted to the acid chloride, then reacted with ammonia to give the primary amide (Section 18.6). The nitro group is then reduced with hydrogenation (Section 22.1). Note the nitro group is not reduced until after amide formation, because an aromatic amine would react with the acid chloride.

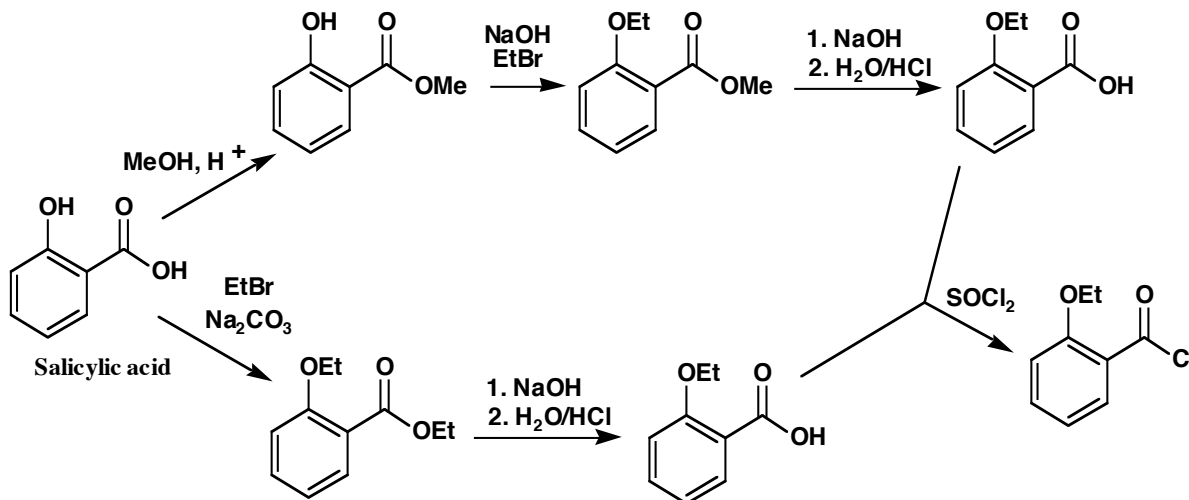
Step (6) An aromatic acid chloride is reacted with the aromatic amine to give the amide (Section 18.6).

Step (7) Anhydrous acid causes dehydration and formation of the purine ring system.

Step (9) Reaction of the sulfonyl chloride with the appropriate amine completes the synthesis and gives Sildenafil.

(d) Show how the reagent for Step 6 can be prepared from salicylic acid (2-hydroxybenzoic acid). Salicylic acid, the starting material for the synthesis of aspirin and a number of other pharmaceuticals, is readily available by the Kolbe carboxylation of phenol (Section 21.4E).

The synthetic problem here is to alkylate the phenolic -OH group while retaining the -COOH group. There are two solutions to this problem. The first solution involves protection the -COOH group as its methyl ester (Fischer esterification, Section 17.7), alkylation the phenolic -OH group using NaOH and ethyl bromide, and finally base-promoted hydrolysis of the methyl ester followed by acidification with aqueous HCl followed to regenerate the carboxyl group (Section 18.4). The second solution is to alkylate both the phenolic -OH and the -COOH groups using ethyl bromide in the presence of sodium carbonate, and then hydrolyze the ester. Both synthetic strategies have been used to alkylate the -OH group of salicylic acid and substituted salicylic acids. For the present synthesis, the acid is converted to the acid chloride with SOCl_2 (Section 17.8).

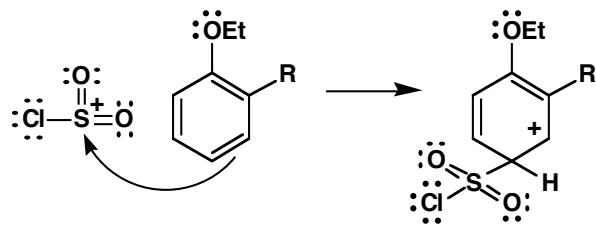


(e) Chlorosulfonic acid, ClSO_3H , the reagent used in Step 8 is not described in the text. Given what you have studied about other types of electrophilic aromatic substitutions (Section 22.1), propose a mechanism for the reaction in Step 8.

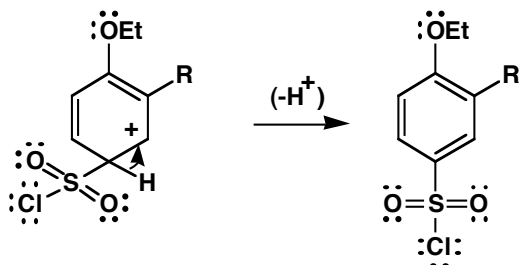
Step 1: Hydrolysis This process actually takes several steps.



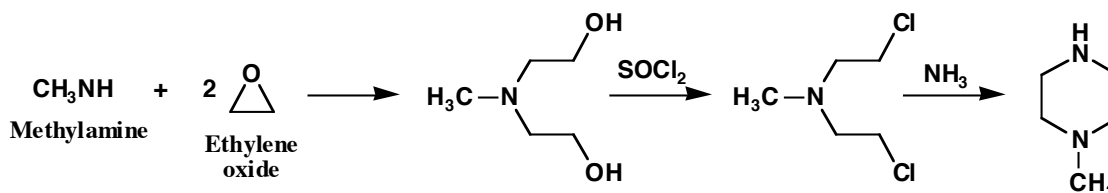
Step 2: Make a new bond between a nucleophile (π bond) and an electrophile.



Step 3: Take a proton away.



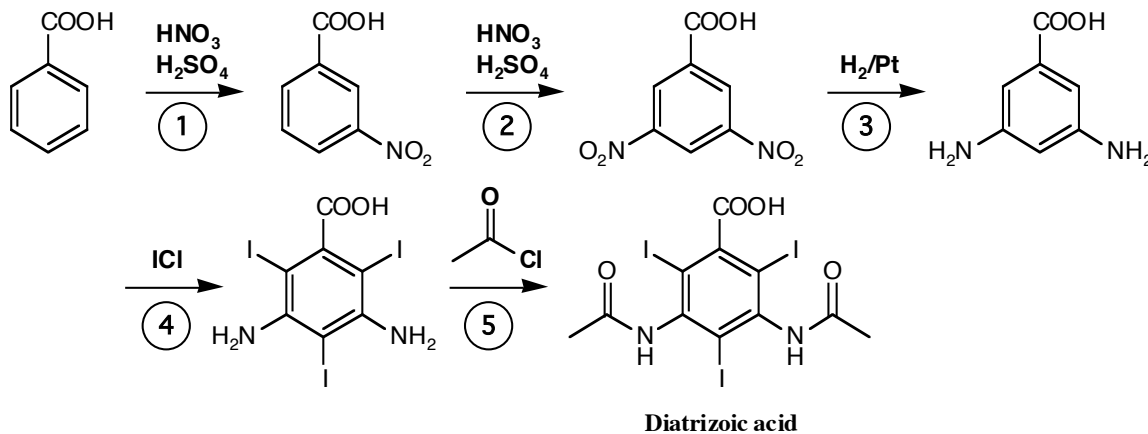
(f) Propose a structural formula for the reagent used in Step 9 and show how it can be prepared from methylamine and ethylene oxide.



(g) Is sildenafil chiral? If so, which of the possible stereoisomers are formed in this synthesis?

No, sildenafil is not chiral.

Problem 23.67 Radiopaque imaging agents are substances administered either orally or intravenously that absorb x-rays more strongly than body material. One of the best known of these is barium sulfate, the key ingredient in the so-called barium cocktail for imaging of the gastrointestinal tract. Among other x-ray contrast media are the so-called triiodoaromatics. You can get some idea of the imaging for which they are used from the following selection of trade names: Angiografin, Gastrografin, Cardiografin, Cholegrafrin, Renografrin, and Urografrin. Following is a synthesis for diatrizoic acid from benzoic acid.



(a) Provide reagents and experimental conditions for steps (1), (2), (3), and (5).

Steps (1) and (2) are nitration reactions (Section 22.1). The -COOH group is meta directing. Note the Step (2) will require some heating because the ring is relatively deactivated.

Step (3) Reduction of the nitro groups using hydrogenation (Section 22.1).

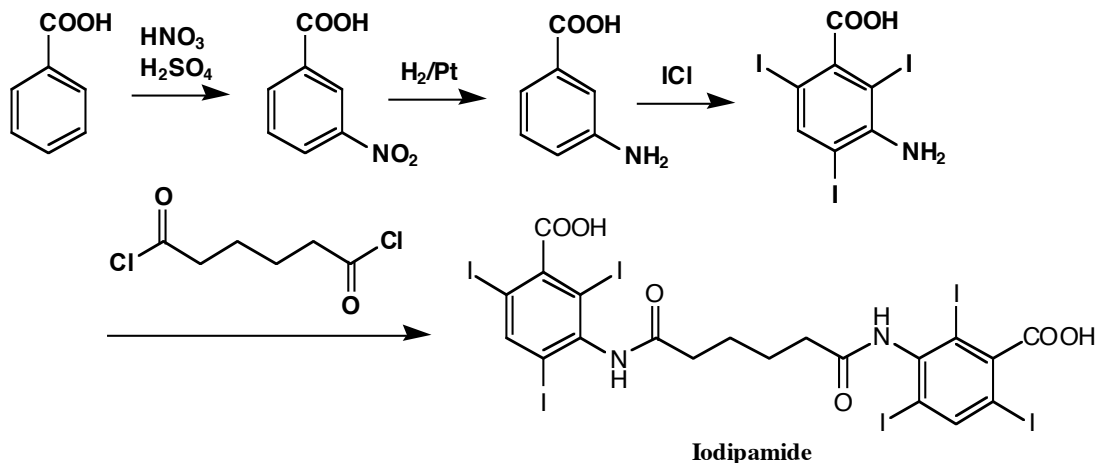
Step (5) Amide formation using excess acetyl chloride (Section 18.6).

(b) Iodine monochloride, ICl, a black crystalline solid with a mp of 27.2°C and a bp of 97°C, is prepared by mixing equimolar amounts of I₂ and Cl₂. Propose a mechanism for the iodination of 3,5-diaminobenzoic acid by this reagent.

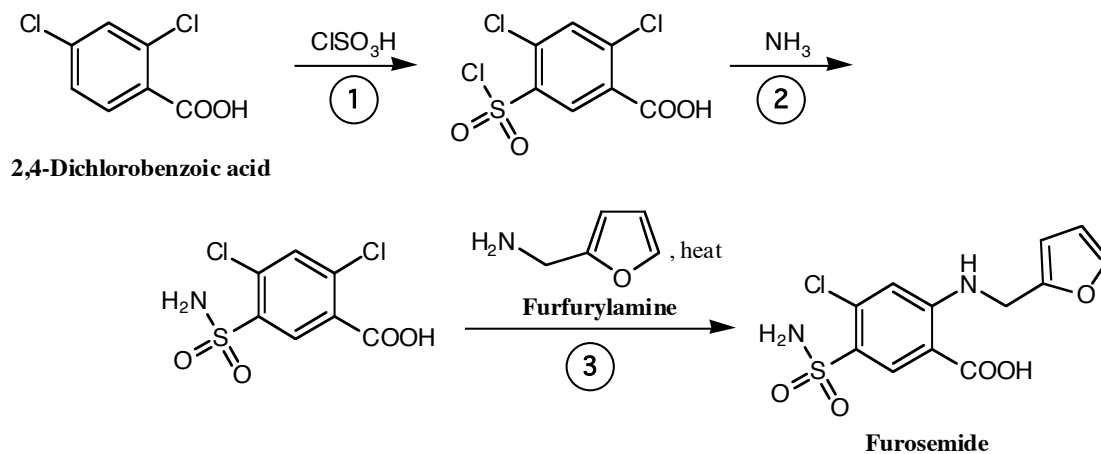
This reaction is a standard electrophilic aromatic substitution reaction (Section 22.1). The iodine monochloride reacts with the I because the electrophilic atom because Cl is the more electronegative of the two.

Problem 23.68 Show how the synthetic scheme developed in problem 23.65 can be modified to synthesize this triiodobenzoic acid x-ray contrast agent.

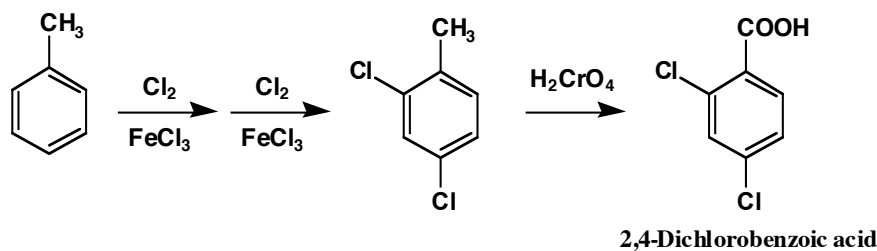
Only mononitration would be used, and a diacid chloride would be used in the final step. The other steps are the same. However, in the final coupling step two equivalents of the aromatic amine would be reacted with a single equivalent of the diacid chloride.



Problem 23.69 A diuretic is a compound that causes increased urination and thereby reduces fluid volume in the body. An important use of diuretics in clinical medicine is in the reduction of the fluid build up, particularly in the lungs, that is associated with congestive heart failure. It is also used as an antihypertensive; that is, to reduce blood pressure. Furosemide, an exceptionally potent diuretic, is prescribed under 30 or more trade names, the best known of which is Lasix. The synthesis of furosemide begins with treatment of 2,4-dichlorobenzoic acid with chlorosulfonic acid in a reaction called chlorosulfonation. The product of this reaction is then treated with ammonia, followed by heating with furfurylamine.



(a) Propose a synthesis of 2,4-dichlorobenzoic acid from toluene.



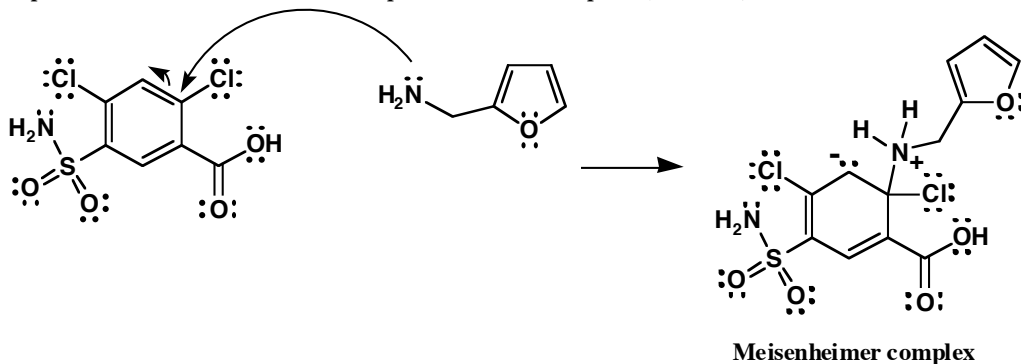
(b) Propose a mechanism for the chlorosulfonation reaction in Step (1).

See the answer to Problem 23.64 (e) for this mechanism.

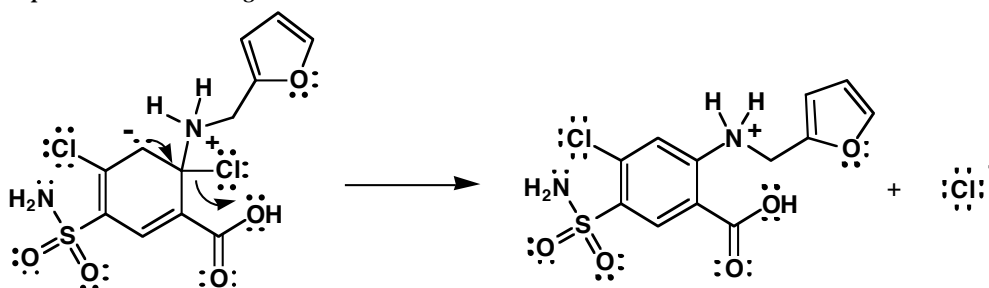
(c) Propose a mechanism for Step (3).

This is an nucleophilic aromatic substitution reaction. The aromatic ring is extremely electron deficient by virtue of the four electron withdrawing groups. Note that the last two steps could occur in either order.

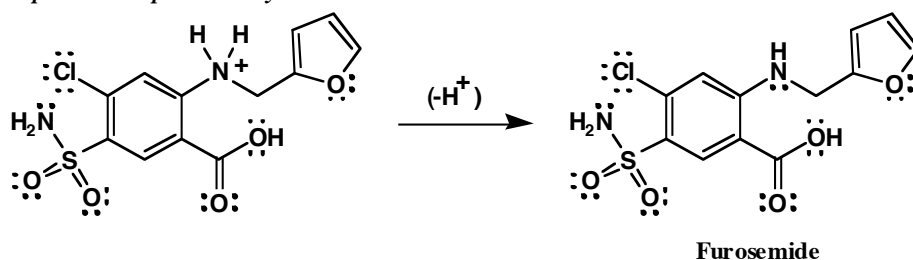
Step 1: Make a bond between a nucleophile and an electrophile (aromatic).



Step 2: Break a bond to give stable molecules or ions.



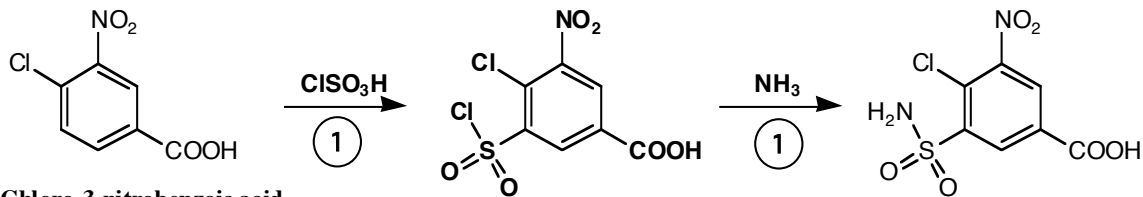
Step 3: Take a proton away.

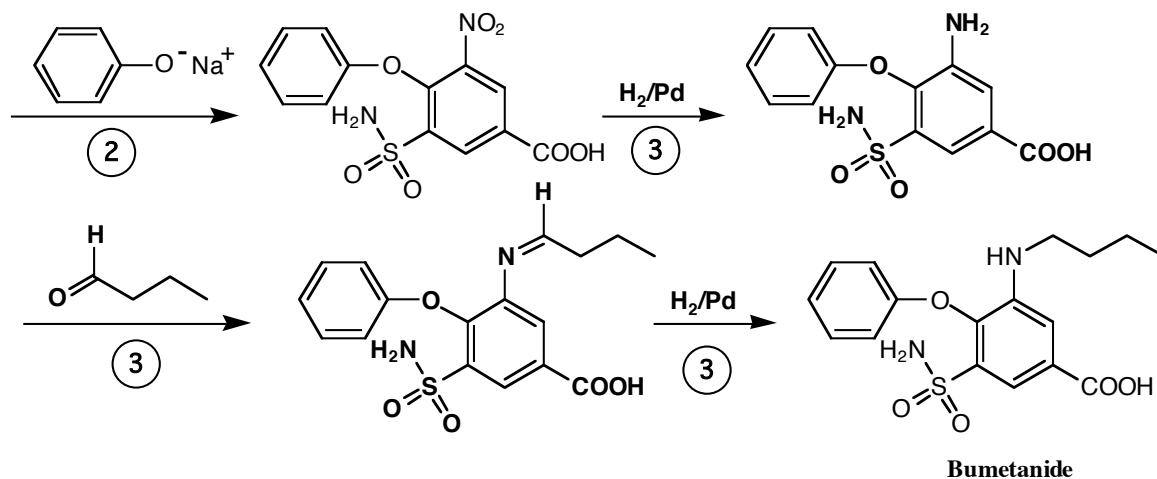


(d) Is furosamide chiral? If so, which of the possible stereoisomers are formed in this synthesis?

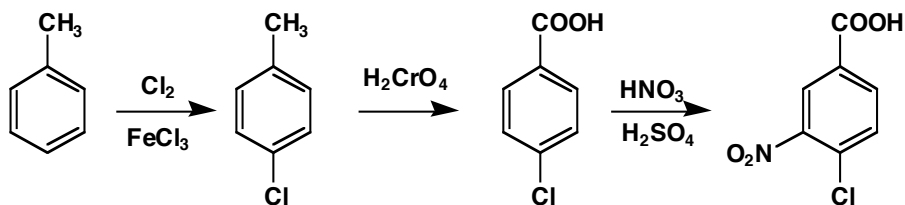
No, furosamide is not chiral.

Problem 23.70 Among the newer generation diuretics is bumetanide, prescribed under several trade names, including Bumex and Fordiuran. Following is an outline of a synthesis of this drug.





(a) Propose a synthesis of 4-chloro-3-nitrobenzoic acid from toluene.



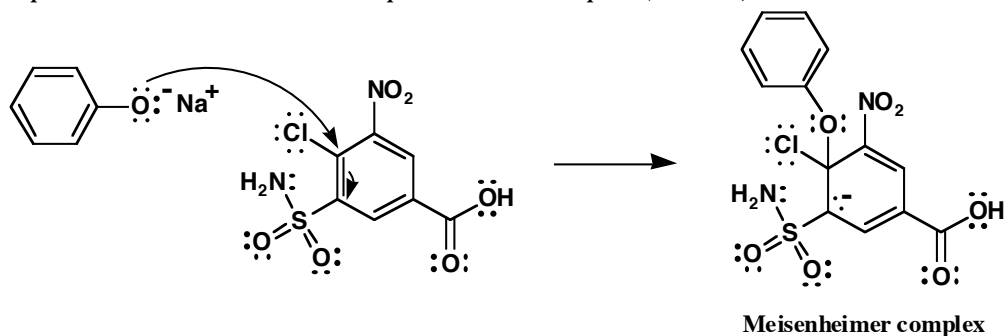
(b) Propose reagents for Step (1). (*Hint*: It requires more than one reagent.)

Chlorosulfonation followed by reaction with ammonia gives the desired sulfonamide.

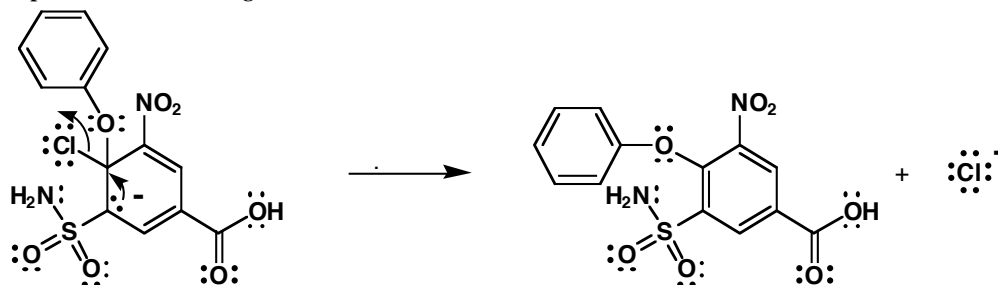
(c) Propose a mechanism for reaction (2).

This is an nucleophilic aromatic substitution reaction. The aromatic ring is extremely electron deficient by virtue of the four electron withdrawing groups.

Step 1: Make a bond between a nucleophile and an electrophile (aromatic).



Step 2: Break a bond to give stable molecules or ions.



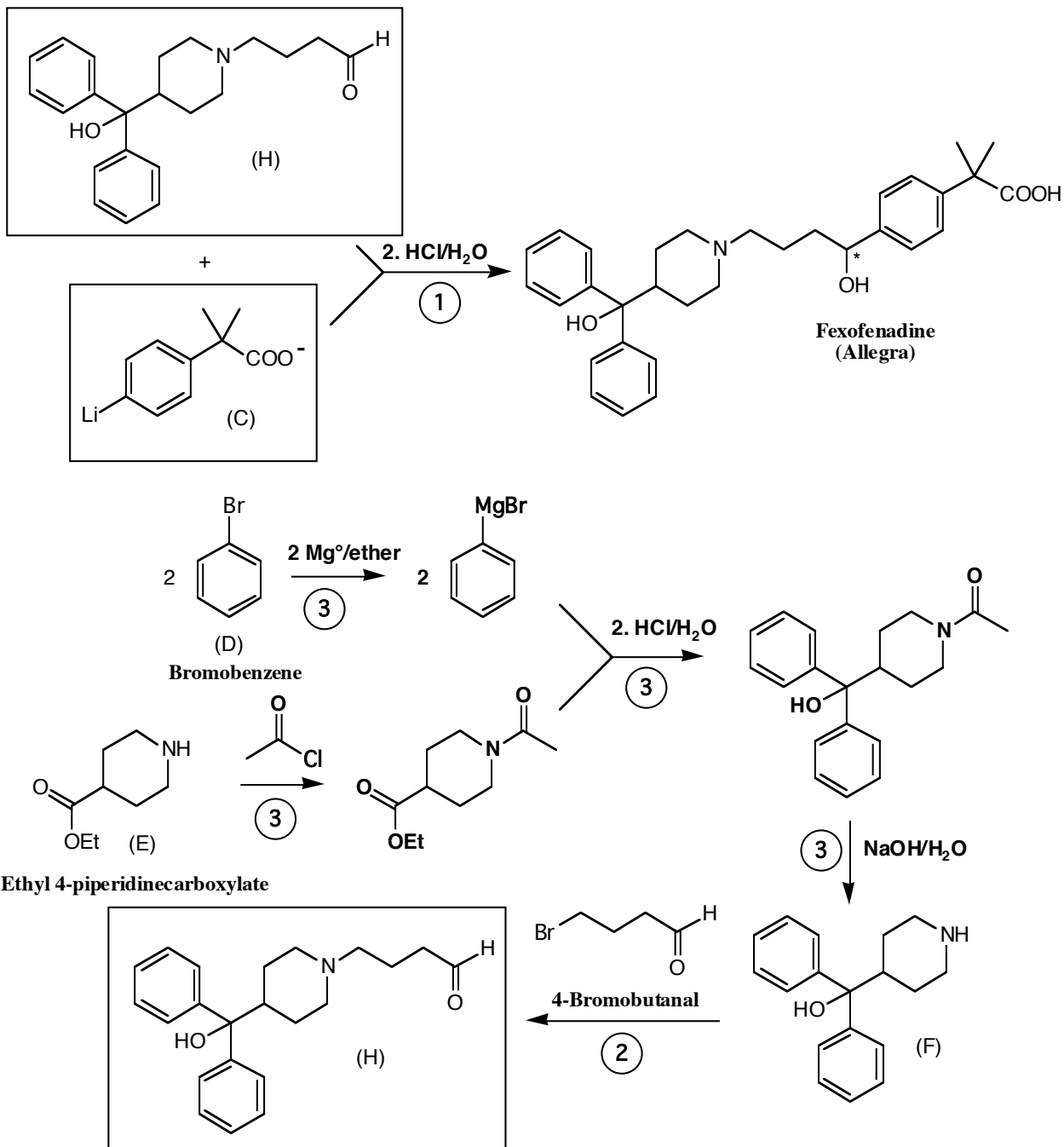
(d) Propose reagents for Step (3). (*Hint*: It too requires more than one reagent.)

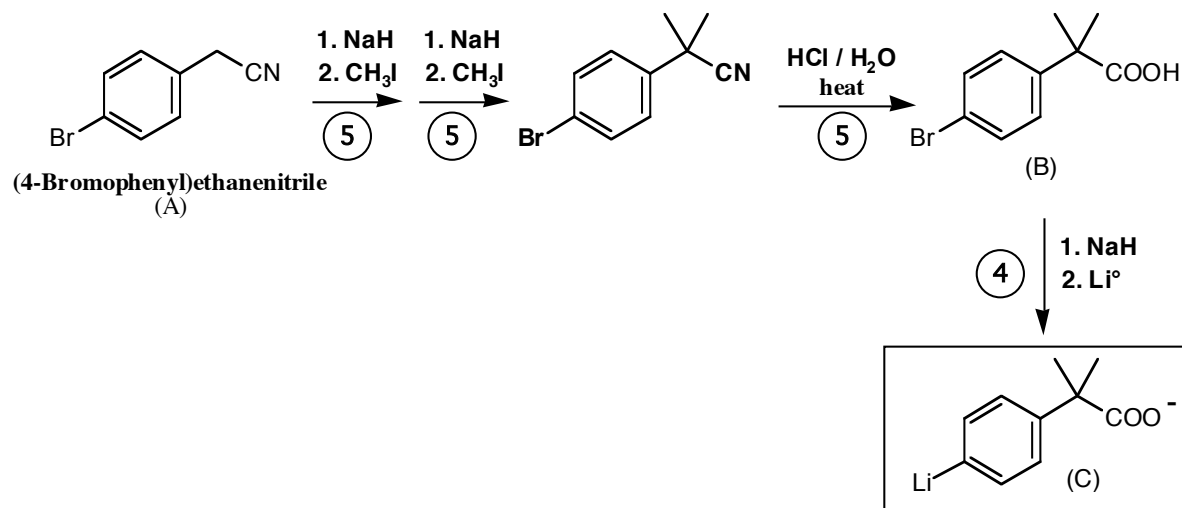
First the nitro group is reduced to an amino group using hydrogenation. Next, a reductive amination is carried out using butanaldehyde to give the final product in high yield.

(e) Is bumetanide chiral? If so, which of the possible stereoisomers are formed in this synthesis?

No, bumetanide is not chiral.

Problem 23.71 Of the early antihistamines, most had a side effect of mild sedation; they made one sleepy. More recently, there has been introduced a new generation of nonsedating antihistamines known as histamine H_1 receptor antagonists. One of the most widely prescribed of these is fexofenadine (Allegra). This compound is nonsedating because the polarity of its carboxylic anion prevents it from crossing the blood-brain barrier. Following is a retrosynthetic analysis for the synthesis of fexofenadine.





(Note: The organolithium reagent C cannot be made directly from B because the presence of the carboxyl group in B would lead to intermolecular destruction of the reagent by an acid-base reaction. In practice, B is first converted to its sodium salt by treatment with sodium hydride, NaH, and then the organolithium reagent is prepared.)

(a) Given this retrosynthetic analysis, propose a synthesis for fexofenadine from the four named starting materials.

Step (1) The organolithium reagent reacts with the aldehyde function followed by an aqueous workup to give the racemic alcohol product (fexofenadine) (Section 15.1).

Step (2) The 4-bromobutanol reacts with the secondary amine of the piperidine group in an S_N2 reaction to give (H) (Section 9.3).

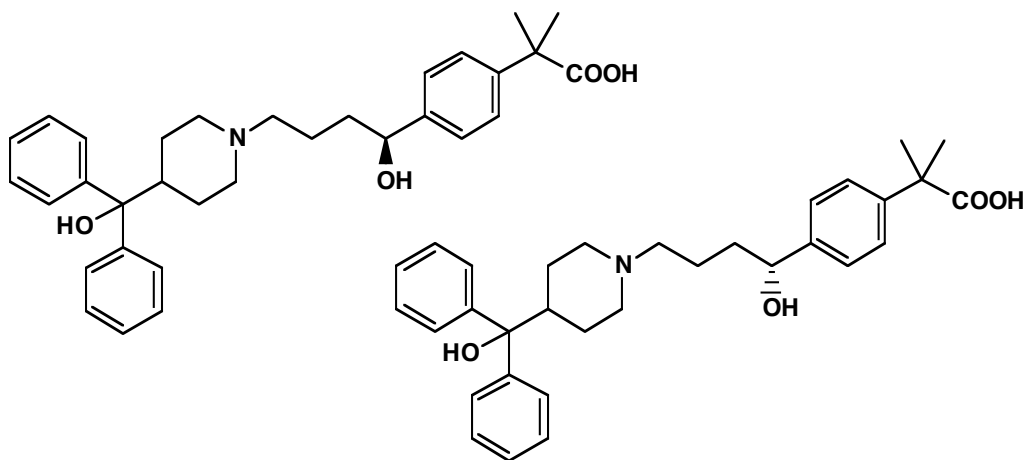
Step (3) This conversion requires multiple steps. The piperidine amino group must be protected as the acetamide in preparation for the Grignard reaction (Section 18.9). If left unprotected, it would become deprotonated by the basic Grignard reagent (Section 15.1). The Grignard reaction is made from bromobenzene by reaction with Mg⁰ in ether. The Grignard reagent adds twice to the ester function to give the tertiary alcohol (Section 18.9). The acetamide group is removed in aqueous base (Section 18.4). Note acid is not used here as the tertiary alcohol is sensitive to acid (β-elimination).

Step (4) The organolithium reagent is prepared by first removing the carboxylic acid proton with NaH, followed by reaction with Li⁺ to give (C).

Step (5) 4-(bromophenyl)ethanamide is alkylated with CH₃I two times at the position α to the nitrile through formation of an enolate using NaH or other strong base (Section 19.1). The nitrile is hydrolyzed in aqueous acid to give the carboxylic acid (Section 18.4).

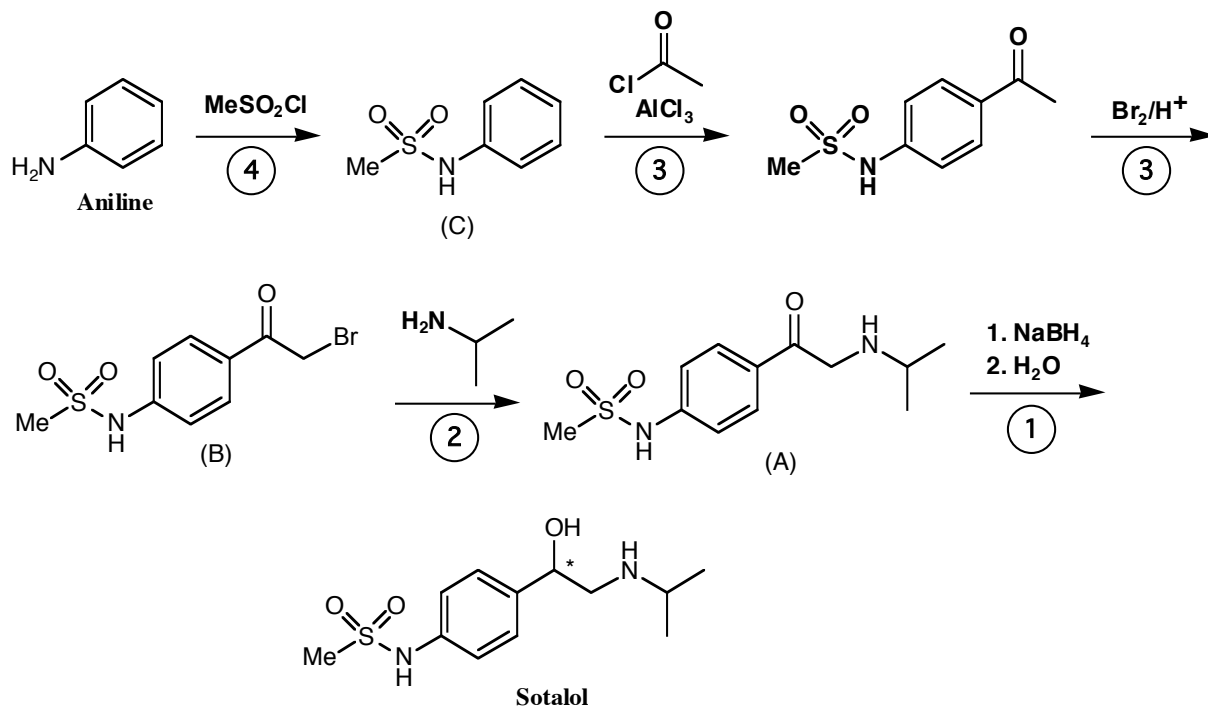
(b) Is fexofenadine chiral? If so, which of the possible stereoisomers are formed in this synthesis?

Fexofenadine has one chiral center, so a racemic mixture of enantiomers is produced in this synthesis.



Enantiomers of fexofenadine (Allegra)

Problem 23.72 Sotalol is a β -adrenergic blocker used to treat certain types of cardiac arrhythmias. Its hydrochloride salt is marketed under several trade names, including Betapace. Following is a retrosynthetic analysis.

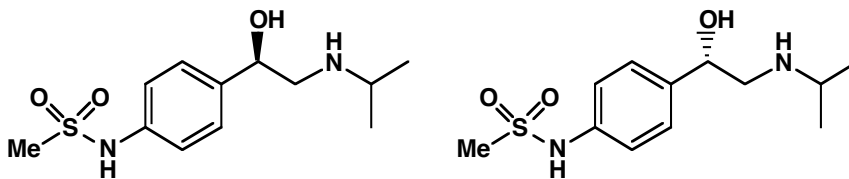


(a) Propose a synthesis for sotalol from aniline.

Step (1) Reduction of the ketone (A) using NaBH_4 gives the racemic alcohol, sotalol (Section 16.11).
Step (2) Reaction of (B) with isopropyl amine gives intermediate (A) through an $\text{S}_{\text{N}}2$ reaction (Section 9.3).
Step (3) This transformation can be accomplished in high yield using a combination of a Friedel-Crafts acylation with acetyl chloride (Section 22.1) followed by α -halogenation in acid using Br_2 (Section 16.12).
Step (4) Reaction of aniline with mesyl chloride (MeSO_2Cl) gives (C).

(b) Is sotalol chiral? If so, which if the possible stereoisomers are formed in this synthesis?

Sotalol has one chiral center, so a racemic mixture of enantiomers is produced in this synthesis.



Enantiomers of sotalol