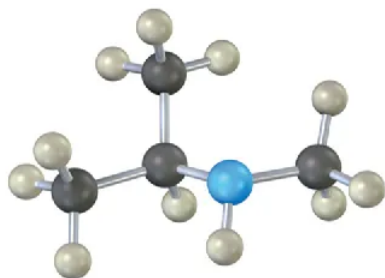


## 10.12: Additional Problems

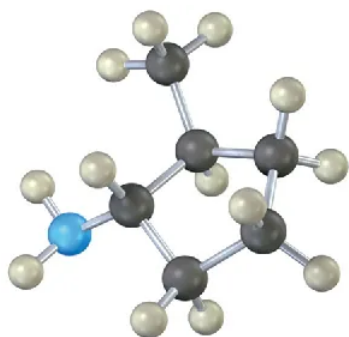
24 • Additional Problems 24 • Additional Problems

### Visualizing Chemistry

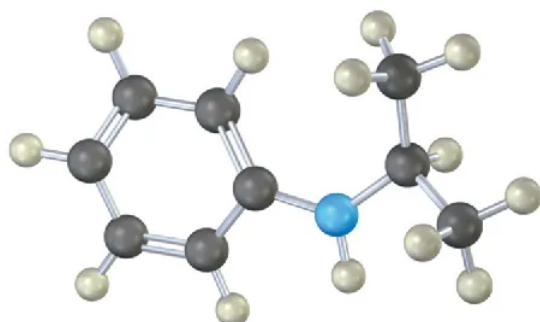
Name the following amines, and identify each as primary, secondary, or tertiary: (a)



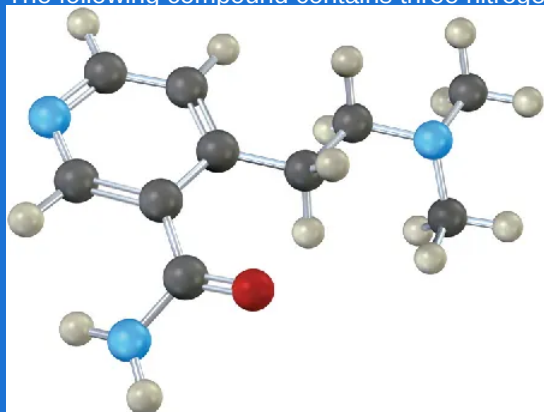
(b)



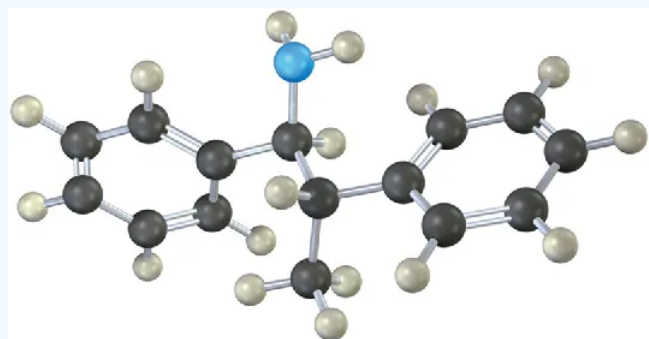
(c)



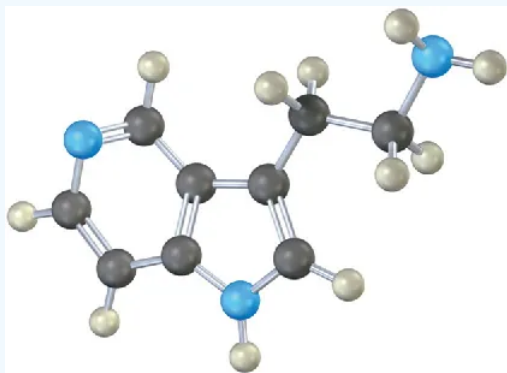
The following compound contains three nitrogen atoms. Rank them in order of increasing basicity.



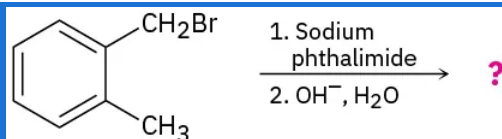
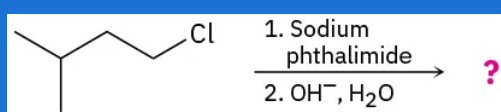
Name the following amine, including *R,S* stereochemistry, and draw the product of its reaction with excess iodomethane followed by heating with  $\text{Ag}_2\text{O}$  (Hofmann elimination). Is the stereochemistry of the alkene product *Z* or *E*? Explain.



Which nitrogen atom in the following compound is most basic? Explain.



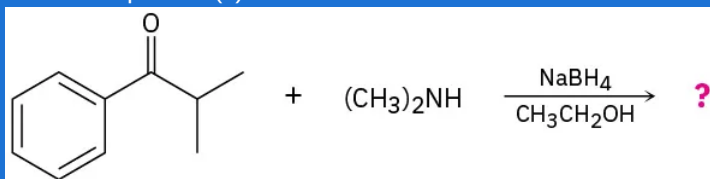
### Mechanism Problems



(b)

Problem 24-31

Predict the product(s) and write the mechanism for each of the following reactions: (a)



Problem 24-32

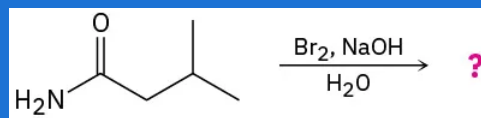
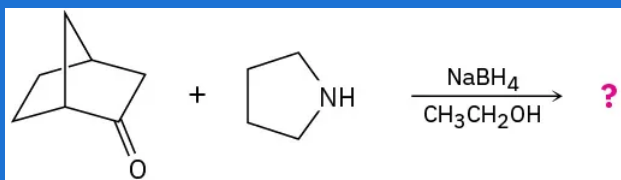
Predict the product(s) and write the mechanism for each of the following reactions: (a)

Problem 24-33

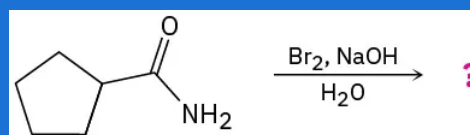
Predict the product(s) and write the mechanism for each of the following reactions: (a)

Problem 24-34

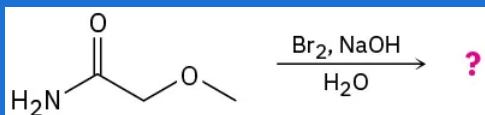
(b)



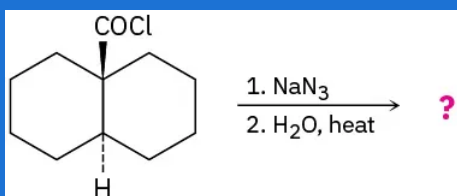
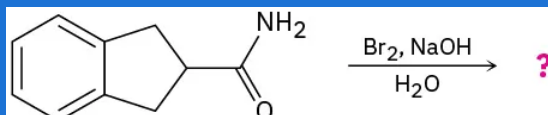
(b)



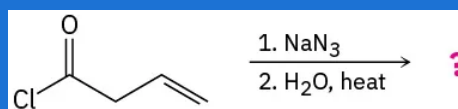
(c)



(d)

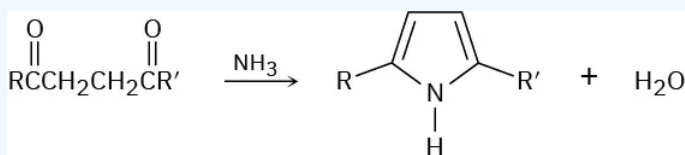


(b)

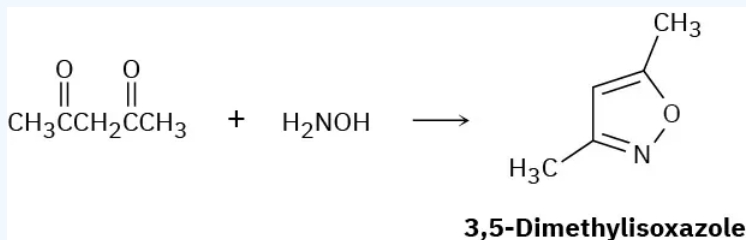


The diazotization of aniline first involves the formation of  $\text{NO}^+$  (nitrosonium ion) by the dehydration of nitrous acid with sulfuric acid. The aniline nitrogen then acts as a nucleophile and eventually loses water. Propose a mechanism for the formation of the dizonaion salt of aniline using curved arrows to show all electron movement.

Substituted pyrroles are often prepared by treatment of a 1,4-diketone with ammonia. Propose a mechanism.

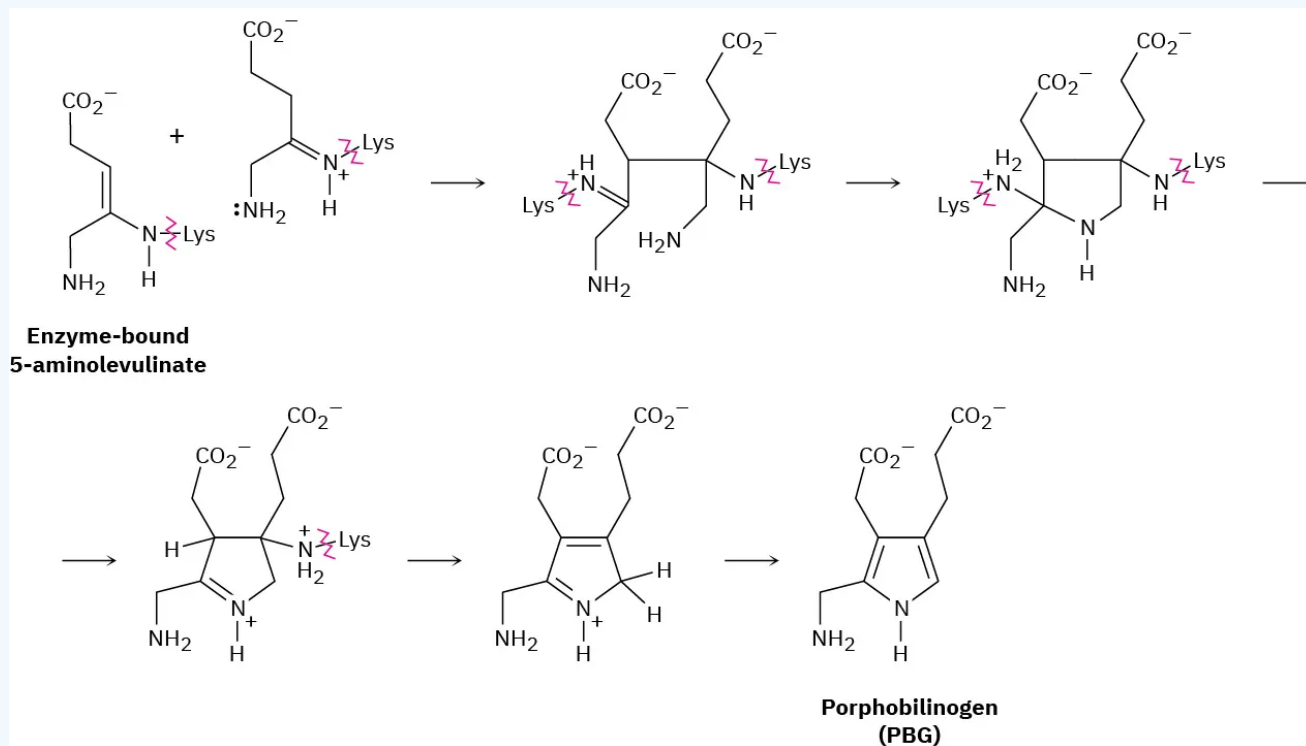


3,5-Dimethylisoxazole is prepared by reaction of 2,4-pentanedione with hydroxylamine. Propose a mechanism.

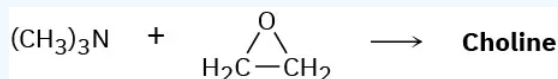


One problem with reductive amination as a method of amine synthesis is that by-products are sometimes obtained. For example, reductive amination of benzaldehyde with methylamine leads to a mixture of *N*-methylbenzylamine and *N*-methylaldibenzylamine. How do you suppose the tertiary amine by-product is formed? Propose a mechanism.

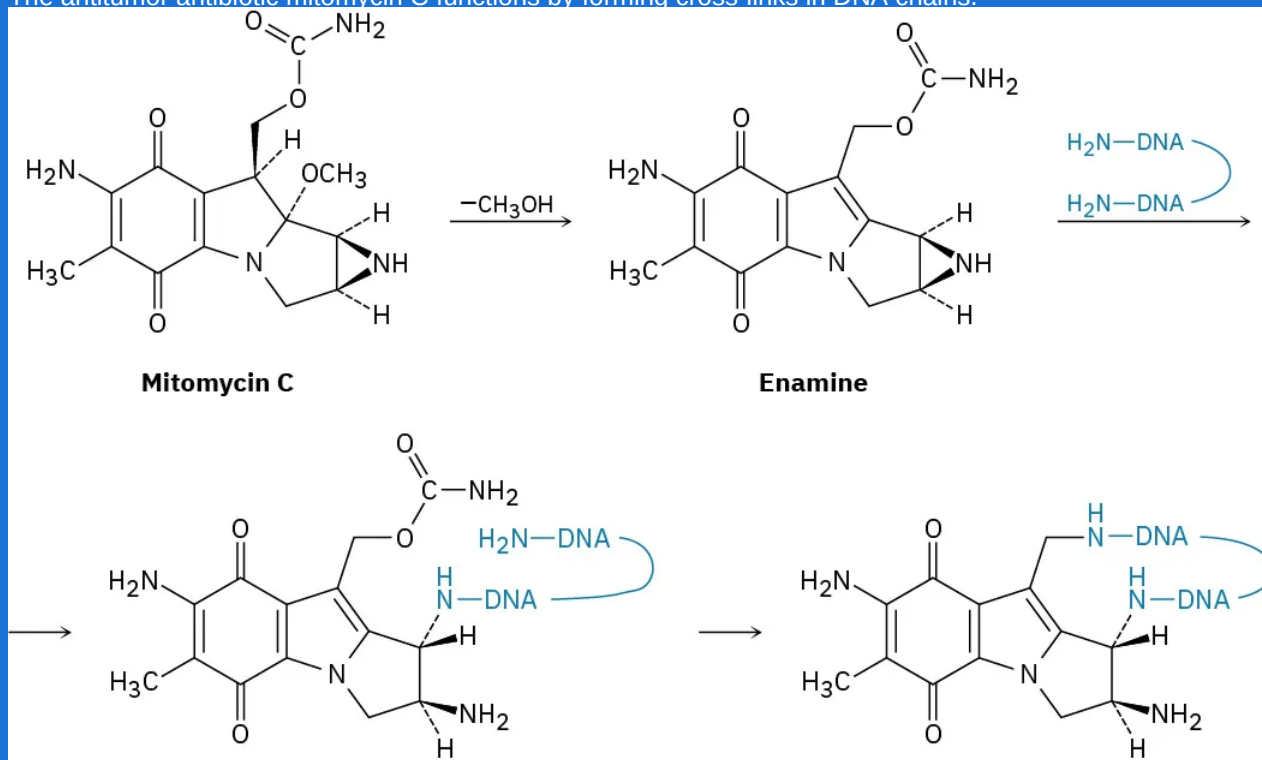
Chlorophyll, heme, vitamin B<sub>12</sub>, and a host of other substances are biosynthesized from porphobilinogen (PBG), which is itself formed from condensation of two molecules of 5-aminolevulinate. The two 5-aminolevulinates are bound to lysine (Lys) amino acids in the enzyme, one in the enamine form and one in the imine form, and their condensation is thought to occur by the following steps. Use curved arrows to show the mechanism of each step.



Choline, a component of the phospholipids in cell membranes, can be prepared by S<sub>N</sub>2 reaction of trimethylamine with ethylene oxide. Show the structure of choline, and propose a mechanism for the reaction.



The antitumor antibiotic mitomycin C functions by forming cross-links in DNA chains.

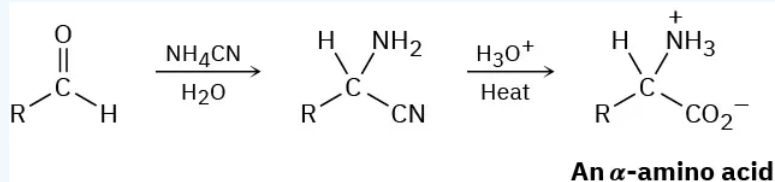


(a)

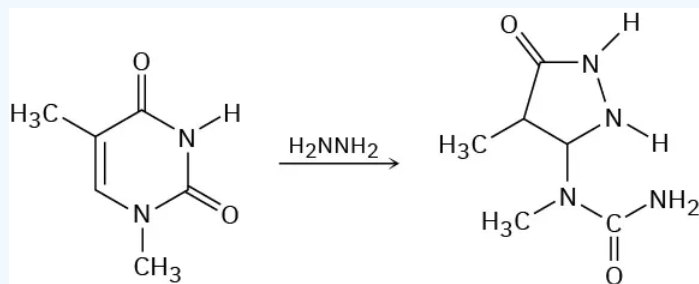
The first step is loss of methoxide and formation of an iminium ion intermediate that is deprotonated to give an enamine. Show the mechanism.

(b) The second step is reaction of the enamine with DNA to open the three-membered, nitrogen-containing (aziridine) ring. Show the mechanism. (c) The third step is loss of carbamate ( $\text{NH}_2\text{CO}_2^-$ ) and formation of an unsaturated iminium ion, followed by a conjugate addition of another part of the DNA chain. Show the mechanism.

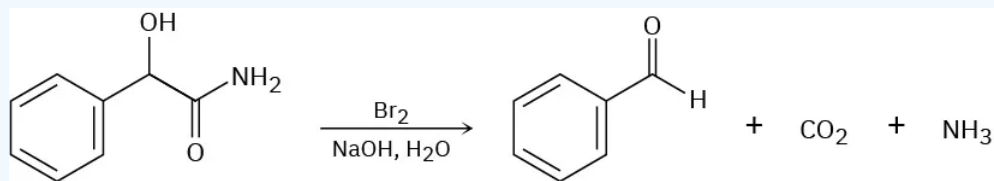
$\alpha$ -Amino acids can be prepared by the Strecker synthesis, a two-step process in which an aldehyde is treated with ammonium cyanide followed by hydrolysis of the amino nitrile intermediate with aqueous acid. Propose a mechanism for the reaction.



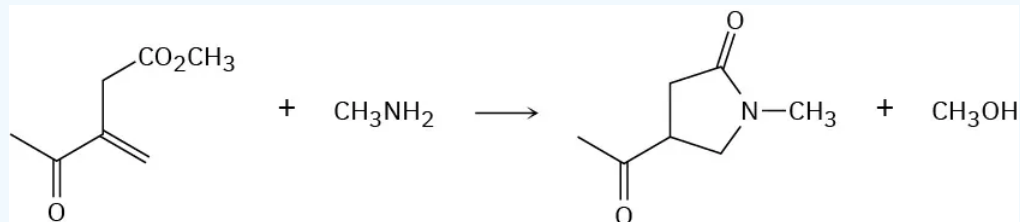
One of the reactions used in determining the sequence of nucleotides in a strand of DNA is reaction with hydrazine. Propose a mechanism for the following reaction, which occurs by an initial conjugate addition followed by internal amide formation.



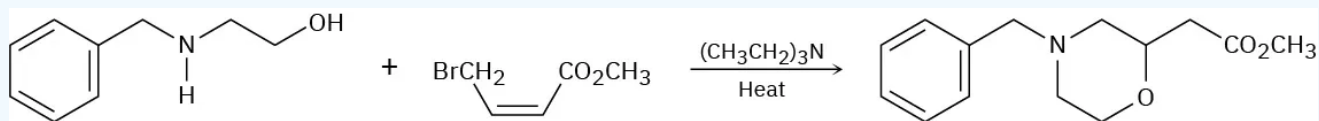
When an  $\alpha$ -hydroxy amide is treated with  $\text{Br}_2$  in aqueous  $\text{NaOH}$  under Hofmann rearrangement conditions, loss of  $\text{CO}_2$  occurs and a chain-shortened aldehyde is formed. Propose a mechanism.



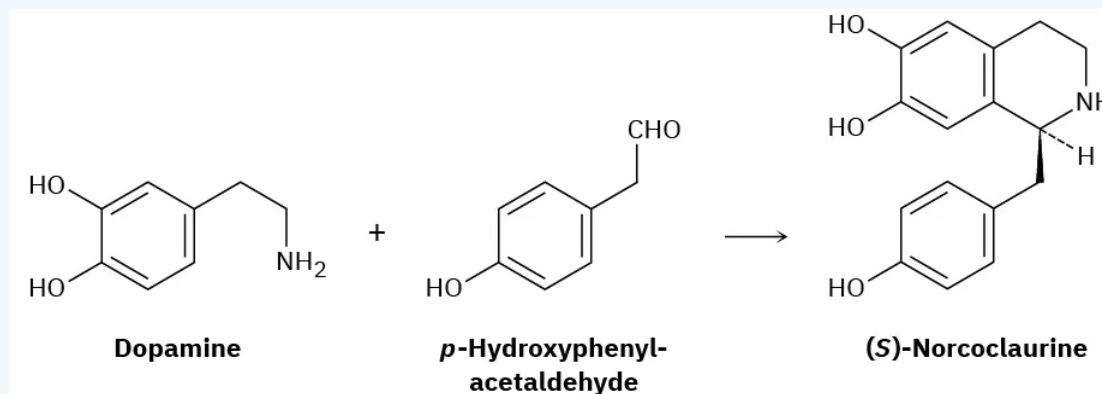
The following transformation involves a conjugate nucleophilic addition reaction (Section 19.13) followed by an intramolecular nucleophilic acyl substitution reaction (Section 21.2). Show the mechanism.



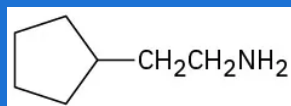
Propose a mechanism for the following reaction:



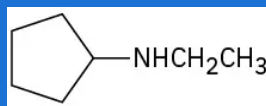
One step in the biosynthesis of morphine is the reaction of dopamine with  $p$ -hydroxyphenylacetaldehyde to give ( $S$ )-norcoclaurine. Assuming that the reaction is acid-catalyzed, propose a mechanism.



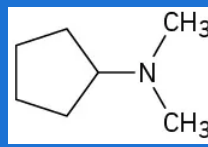
## Naming Amines



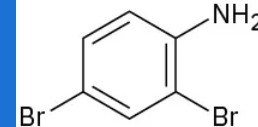
(c)



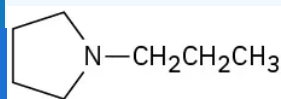
(d)



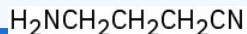
(e)



(b)



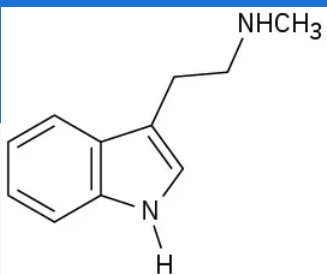
(f)



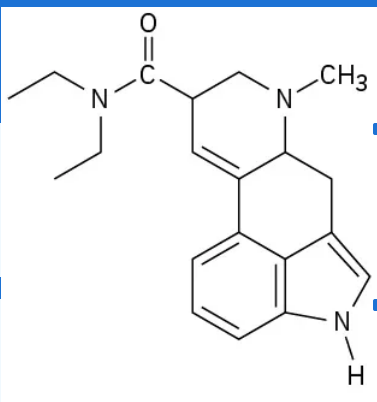
(b)

(Cyclohexylmethyl)amine

(c) *N*-Methylcyclohexylamine (d) (2-Methylcyclohexyl)amine (e) 3-(*N,N*-Dimethylamino)propanoic acid

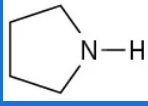


(c)



**Lysergic acid diethylamide**

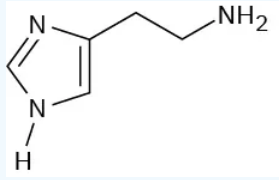
**Amine Basicity**



(b)

Although pyrrole is a much weaker base than most other amines, it is a much stronger acid ( $pK_a \approx 15$  for the pyrrole versus 35 for diethylamine). The N-H hydrogen is readily abstracted by base to yield the pyrrole anion,  $C_4H_4N^-$ . Explain.

Histamine, whose release in the body triggers nasal secretions and constricted airways, has three nitrogen atoms. List them in order of increasing basicity and explain your ordering.



**Histamine**

Account for the fact that *p*-nitroaniline ( $pK_a = 1.0$ ) is less basic than *m*-nitroaniline ( $pK_a = 2.5$ ) by a factor of 30. Draw resonance structures to support your argument. (The  $pK_a$  values refer to the corresponding ammonium ions.)

### Synthesis of Amines

#### Butylamine

(b) Dibutylamine (c) Propylamine (d) Pentylamine (e) *N,N*-Dimethylbutylamine (f) Propene

#### Pentanamide

(b) Butylamine (c) Pentylamine (d) 2-Bromopentanoic acid (e) Hexanenitrile (f) Hexylamine

#### Benzene

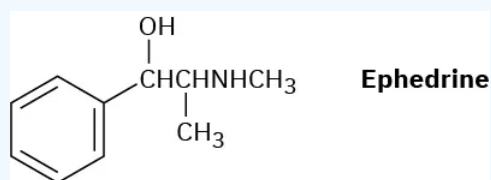
(b) Benzamide (c) Toluene

How would you prepare benzylamine,  $C_6H_5CH_2NH_2$ , from benzene? More than one step is needed.

#### Pentanamide

(b) Pentanenitrile (c) 1-Butene (d) Hexanamide (e) 1-Butanol (f) 5-Decene (g) Pentanoic acid

How might a reductive amination be used to synthesize ephedrine, an amino alcohol that was widely used for the treatment of bronchial asthma?



## Reactions of Amines

### Benzene

(b) Benzamide (c) Toluene

m-toluidine (*m*-methylaniline) with the following reagents: (a)

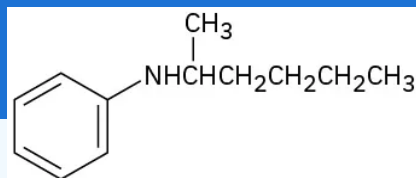
Br<sub>2</sub> (1 equivalent)

(b) CH<sub>3</sub>I (excess) (c) CH<sub>3</sub>COCl in pyridine (d) The product of (c), then HSO<sub>3</sub>Cl

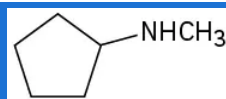
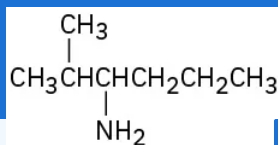
p-bromoaniline with the following reagents: (a)

CH<sub>3</sub>I (excess)

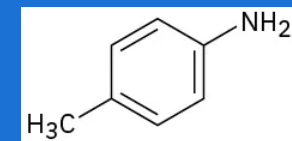
(b) HCl (c) HNO<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub> (d) CH<sub>3</sub>COCl (e) CH<sub>3</sub>MgBr (f) CH<sub>3</sub>CH<sub>2</sub>Cl, AlCl<sub>3</sub> (g) Product of (c) with CuCl, HCl (h) Product of (d) with CH<sub>3</sub>CH<sub>2</sub>Cl, AlCl<sub>3</sub>



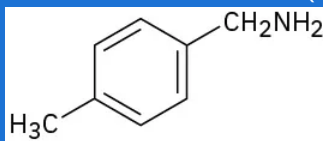
(c)



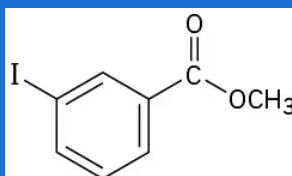
(b)



(b)

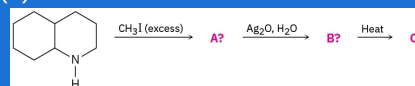


(c)

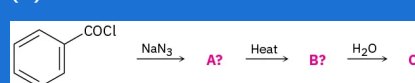


Problem 24-64  
Predict the product(s) of the following reactions. If more than one product is formed, tell which is major.

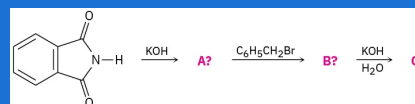
(a)



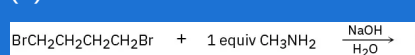
(b)



(c)

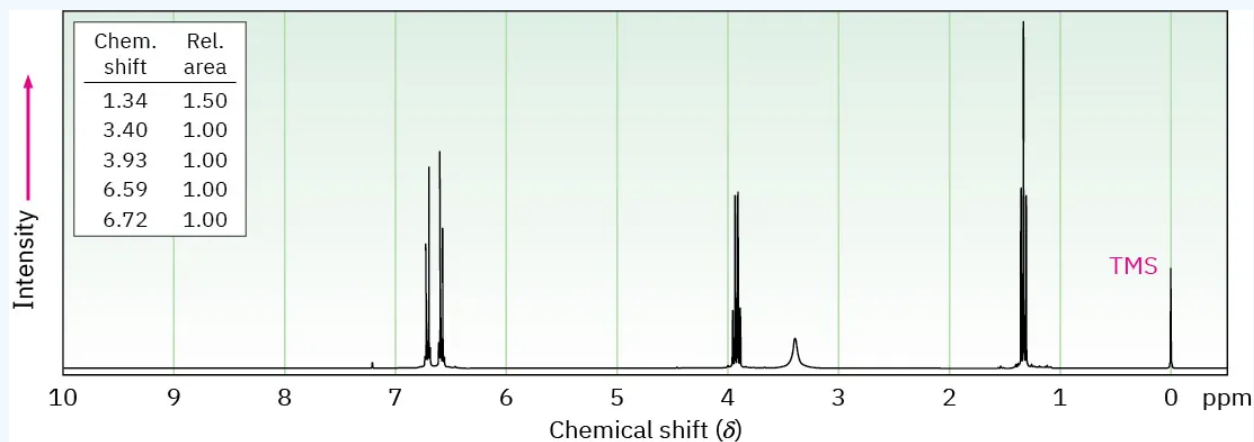


(d)



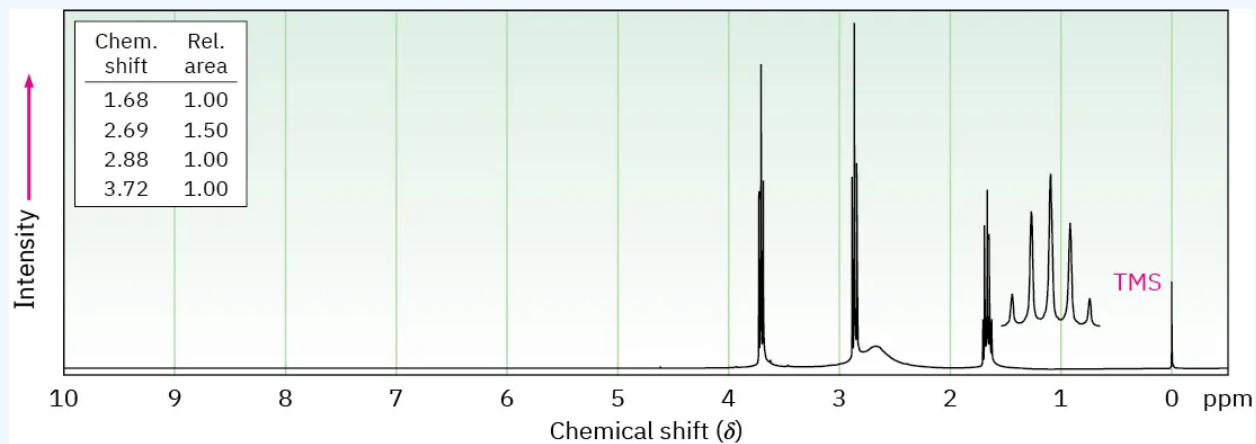
### Spectroscopy Problem 24-65

Phenacetin, a substance formerly used in over-the-counter headache remedies, has the formula  $C_{10}H_{13}NO_2$ . Phenacetin is neutral and does not dissolve in either acid or base. When warmed with aqueous NaOH, phenacetin yields an amine,  $C_8H_{11}NO$ , whose  $^1H$  NMR spectrum is shown. When heated with HI, the amine is cleaved to an aminophenol,  $C_6H_7NO$ . What is the structure of phenacetin, and what are the structures of the amine and the aminophenol?



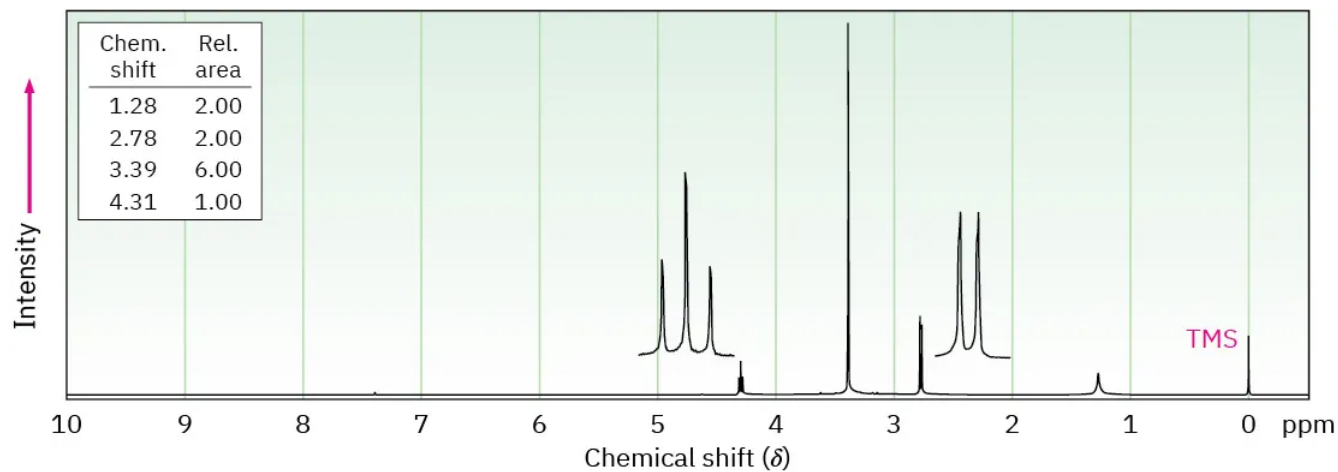
1H NMR spectra: (a)

$C_3H_5NO$



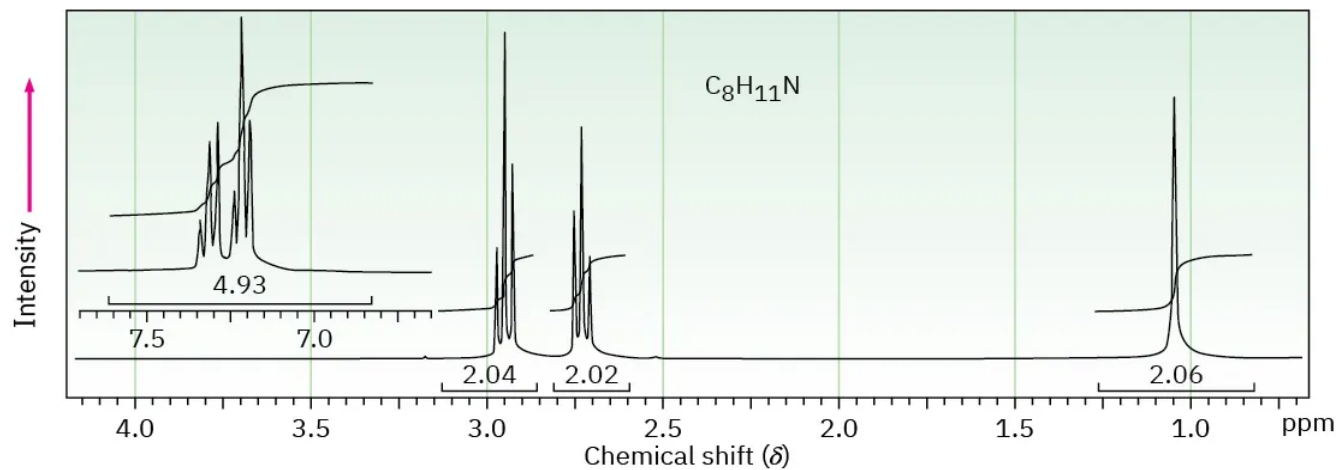
(b)

$C_4H_{11}NO_2$



(c)

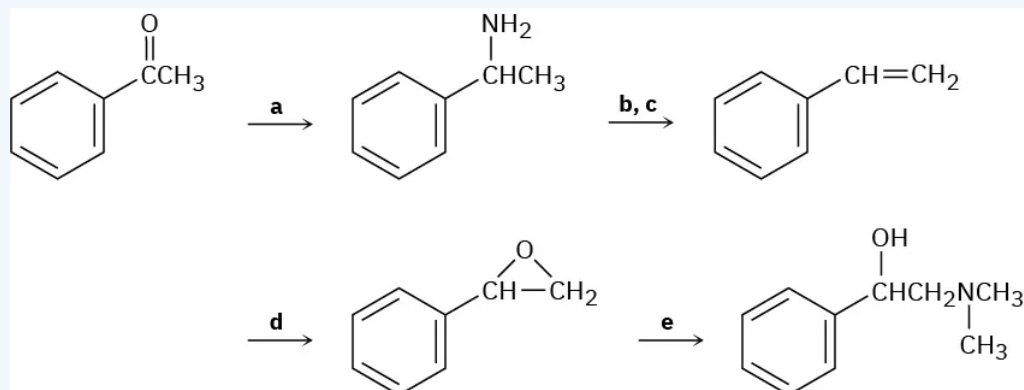
$C_8H_{11}N$



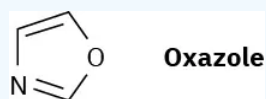
Draw the structure of the amine that produced the  $^1\text{H}$  NMR spectrum shown in Problem 24-66(c). This compound has a single strong peak in its IR spectrum at  $3280\text{ cm}^{-1}$ .

### General Problems

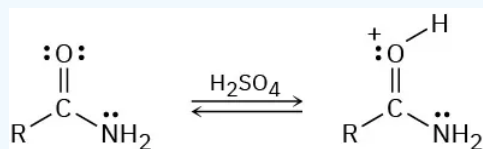
Fill in the missing reagents a–e in the following scheme:



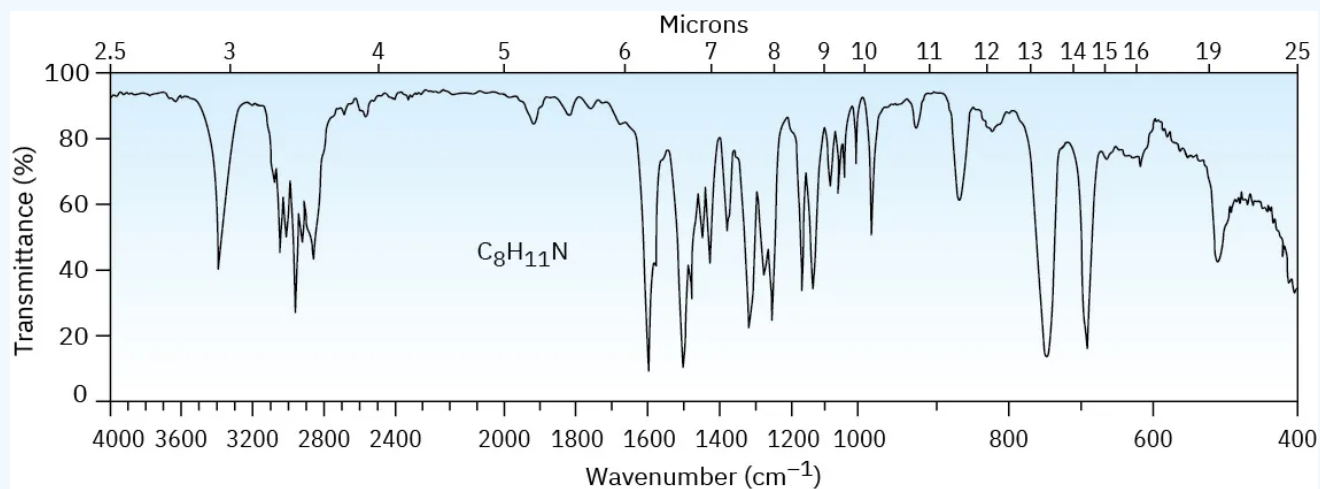
Oxazole is a five-membered aromatic heterocycle. Would you expect oxazole to be more basic or less basic than pyrrole? Explain.



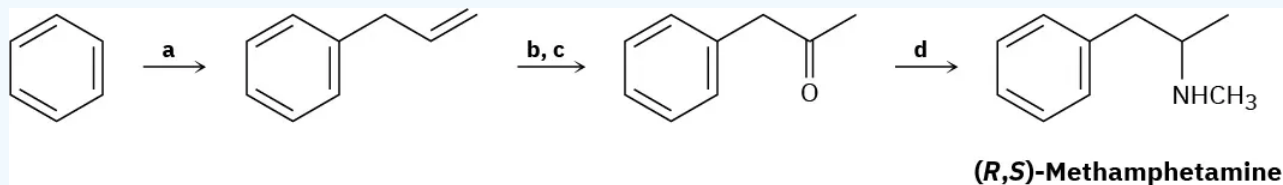
Protonation of an amide using strong acid occurs on oxygen rather than on nitrogen. Suggest a reason for this behavior, taking resonance into account.



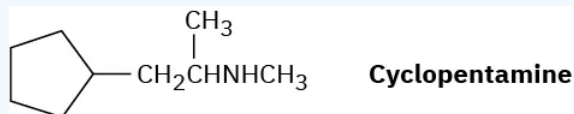
What is the structure of the compound with formula  $\text{C}_8\text{H}_{11}\text{N}$  that produced the following IR spectrum?



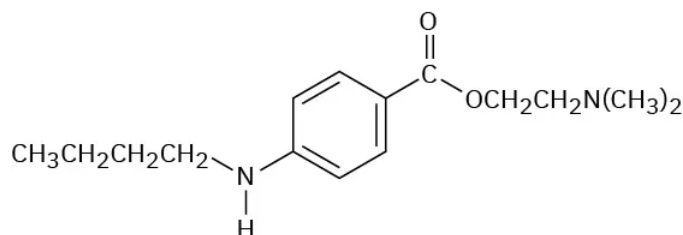
Fill in the missing reagents a–d in the following synthesis of racemic methamphetamine from benzene.



Cyclopentamine is an amphetamine-like central nervous system stimulant. Propose a synthesis of cyclopentamine from materials of five carbons or less.



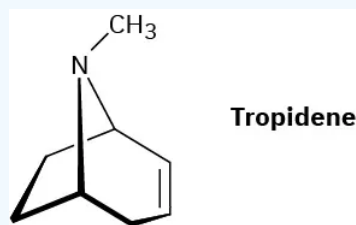
Tetracaine is a substance used as a spinal anesthetic.



**Tetracaine**

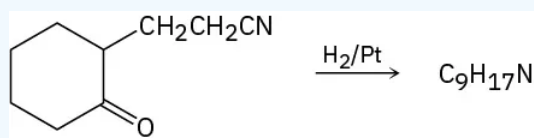
(a) How would you prepare tetracaine from the corresponding aniline derivative,  $\text{ArNH}_2$ ? (b) How would you prepare tetracaine from *p*-nitrobenzoic acid? (c) How would you prepare tetracaine from benzene?

Atropine,  $\text{C}_{17}\text{H}_{23}\text{NO}_3$ , is a poisonous alkaloid isolated from the leaves and roots of *Atropa belladonna*, the deadly nightshade. In small doses, atropine acts as a muscle relaxant; 0.5 ng (nanogram,  $10^{-9}$  g) is sufficient to cause pupil dilation. On basic hydrolysis, atropine yields tropic acid,  $\text{C}_6\text{H}_5\text{CH}(\text{CH}_2\text{OH})\text{CO}_2\text{H}$ , and tropine,  $\text{C}_8\text{H}_{15}\text{NO}$ . Tropine is an optically inactive alcohol that yields tropidene on dehydration with  $\text{H}_2\text{SO}_4$ . Propose a structure for atropine.



Tropidene (Problem 24-75) can be converted by a series of steps into tropilidene (1,3,5-cycloheptatriene). How would you accomplish this conversion?

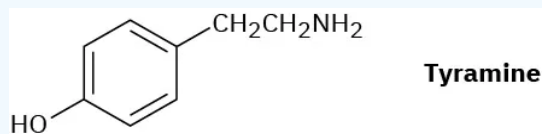
Propose a structure for the product with formula  $\text{C}_9\text{H}_{17}\text{N}$  that results when 2-(2-cyanoethyl)cyclohexanone is reduced catalytically.



Coniine,  $C_8H_{17}N$ , is the toxic principle of the poison hemlock drunk by Socrates. When subjected to Hofmann elimination, coniine yields 5-(*N,N*-dimethylamino)-1-octene. If coniine is a secondary amine, what is its structure?

How would you synthesize coniine (Problem 24-78) from acrylonitrile ( $H_2C=CHCN$ ) and ethyl 3-oxohexanoate ( $CH_3CH_2CH_2COCH_2CO_2Et$ )? (See Problem 24-77.)

Tyramine is an alkaloid found, among other places, in mistletoe and ripe cheese. How would you synthesize tyramine from benzene? From toluene?

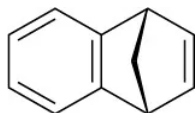


o-aminobenzoic acid) with  $HNO_2$  and  $H_2SO_4$  yields a diazonium salt that can be treated with base to yield a neutral diazonium carboxylate. (a)

What is the structure of the neutral diazonium carboxylate?

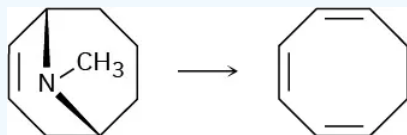
(b)

Heating the diazonium carboxylate results in the formation of  $CO_2$ ,  $N_2$ , and an intermediate that reacts with 1,3-cyclopentadiene to yield the following product:



What is the structure of the intermediate, and what kind of reaction does it undergo with cyclopentadiene?

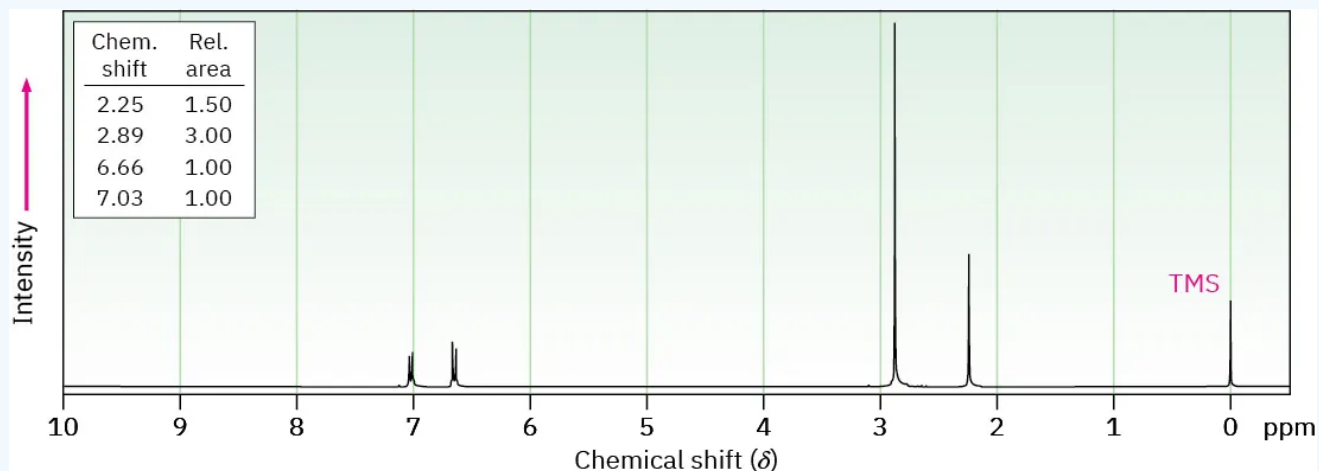
Cyclooctatetraene was first synthesized in 1911 by a route that involved the following transformation:



How might you use the Hofmann elimination to accomplish this reaction? How would you finish the synthesis by converting cyclooctatriene into cyclooctatetraene?

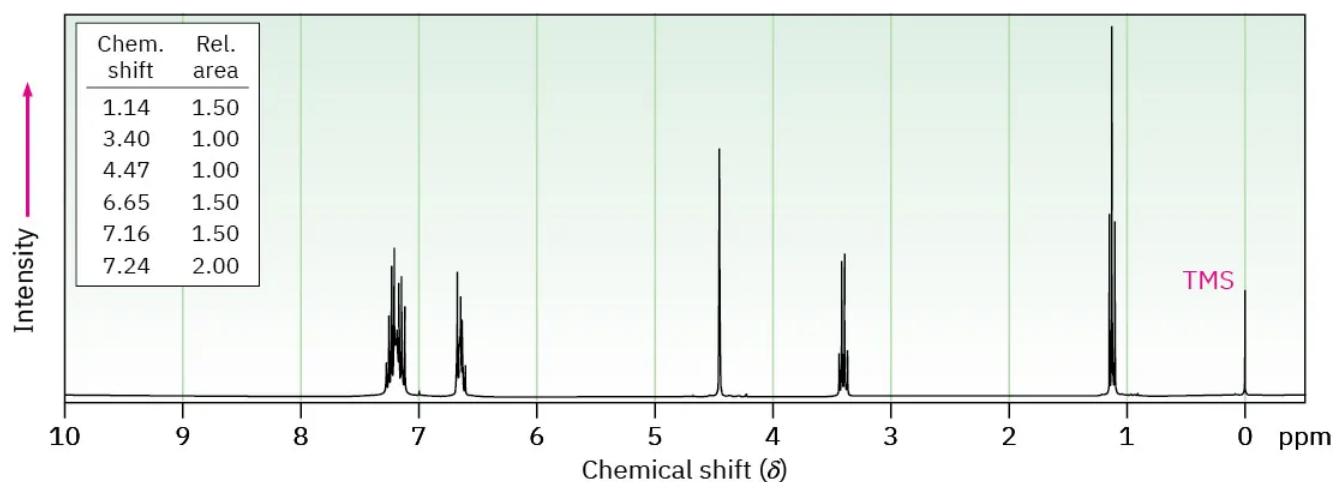
**<sup>1</sup>H NMR spectra. (a)**

$C_9H_{13}N$

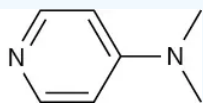


(b)

$C_{15}H_{17}N$



**4-Dimethylaminopyridine (DMAP) acts as a catalyst in acyl transfer reactions. DMAP's catalytic activity stems from its nucleophilic character at the pyridine nitrogen, not the dimethylamino group. Explain this behavior, taking resonance into account.**



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