Recall that the reaction of an amine with an acid chloride or an anhydride requires either two equivalents of the amine or one equivalent of the amine and an additional equivalent of another base such as a tertiary amine or hydroxide ion. These and other aspects of amine acylation can be reviewed in Sec. 21.8.

PROBLEMS

23.13 Suggest two syntheses of N-ethylcyclohexanamine by reductive amination.
23.14 Outline a second synthesis of N-ethyl-N-methylaniline (the target molecule in Study Problem 23.3) by reductive amination.
23.15 Outline a synthesis of the quaternary ammonium salt (CH₃)₃NCH₂Ph Br⁻ from each of the following combinations of starting materials.
   (a) dimethylaniline and any other reagents  (b) benzylamine and any other reagents
23.16 (a) A chemist Caleb J. Cookbook heated ammonia with bromobenzene expecting to form tetraphenylammonium bromide. Can Caleb expect this reaction to succeed? Explain.
   (b) What type of catalyst might be used to bring about this reaction under relatively mild conditions? (See Sec. 23.11C.)
23.17 Continue the sequence of reactions in Eqs. 23.16a–c to show how trimethylammonium iodide is formed as one of the products in Eq. 23.15.
23.18 Outline a preparation of each of the following from an amine and an acid chloride.
   (a) N-phenylbenzamide  (b) N-benzyl-N-ethylpropanamide

23.8 HOFMANN ELIMINATION OF QUATERNARY AMMONIUM HYDROXIDES

The previous section discussed ways to make carbon–nitrogen bonds. In these reactions, amines react as nucleophiles. The subject of this section is an elimination reaction used to break carbon–nitrogen bonds. In this reaction, which involves quaternary ammonium hydroxides (R₄N⁺ OH⁻) as starting materials, amines act as leaving groups.

When a quaternary ammonium hydroxide is heated, a β-elimination reaction takes place to give an alkene, which distills from the reaction mixture.

![Hofmann Elimination Reaction](image)

This type of elimination reaction is called a Hofmann elimination, after August Wilhelm Hofmann (1818–1892), a German chemist who became professor at the Royal College of Chemistry in London and later, at the University of Berlin. Hofmann was particularly noted for his work on amines.

A quaternary ammonium hydroxide used as the starting material in Hofmann eliminations is formed by treating a quaternary ammonium salt with silver hydroxide (AgOH), which is essentially a hydrated form of silver (I) oxide (Ag₂O).

![Hofmann Reaction](image)
Alkenes, then, can be formed from amines by a three-step process: exhaustive methylation (see Eq. 23.21, p. 1132), conversion of the ammonium salt to the hydroxide (Eq. 23.34), and Hofmann elimination (Eq. 23.33).

The Hofmann elimination is conceptually analogous to the E2 reaction of alkyl halides (Sec. 9.5), in which a proton and a halide ion are eliminated; in the Hofmann elimination, a proton and a tertiary amine are eliminated. Because the amine leaving group is very basic, and therefore a relatively poor leaving group, the conditions of the Hofmann elimination are typically harsh.

Like the analogous E2 reaction of alkyl halides, the Hofmann elimination generally occurs as an anti-elimination (Sec. 9.5D).

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{R} & \quad \text{R} \\
\text{C} & \quad \text{C} \\
\text{NMe}_3 & \quad \text{NMe}_3 \\
\end{align*}
\]

\[
\text{H} \quad \text{H} \\
\text{R} & \quad \text{R} \\
\text{C} & \quad \text{C} \\
\text{NMe}_3 & \quad \text{NMe}_3 \\
\]

PROBLEMS

23.19 What product (including its stereochemistry) is expected from the Hofmann elimination of each of the following stereoisomers?

(a) \[\text{N(CH}_3)_3 \text{OH} \]

(b) \[\text{N(CH}_3)_3 \text{OH} \]

23.20 Give the major product formed when each of the following amines is treated exhaustively with methyl iodide and then heated with \( \text{Ag}_2\text{O} \). Explain your reasoning.

(a)

(b)

23.21 \((+)-\text{Coniine}\) is the toxic component of poison hemlock, the plant believed to have killed Socrates. Coniine has the molecular formula \( \text{C}_8\text{H}_{17}\text{N} \). When coniine is exhaustively methylated, and the resulting product is then heated with \( \text{Ag}_2\text{O} \), the mixture of compounds \( A-C \) is formed. (Compounds \( A \) and \( B \) are the \((E)\) stereoisomers.)

\[
\begin{align*}
\text{Me}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 & \equiv \text{CHCH}_2\text{CH}_3 \\
\text{Me}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 & \equiv \text{CHCH}_2\text{CH}_2\text{CH}_3 \\
\text{H}_2\text{C} & \equiv \text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{NMe}_2 & \equiv \\
\end{align*}
\]

Propose a structure for coniine. (The absolute configuration of coniine cannot be determined from the data.)