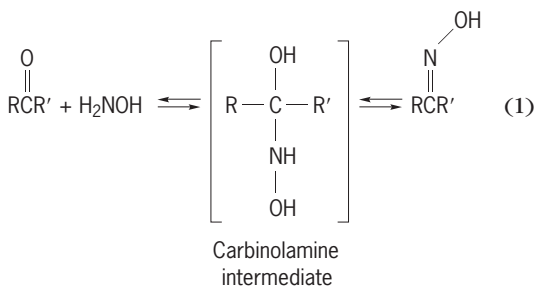


Oxime

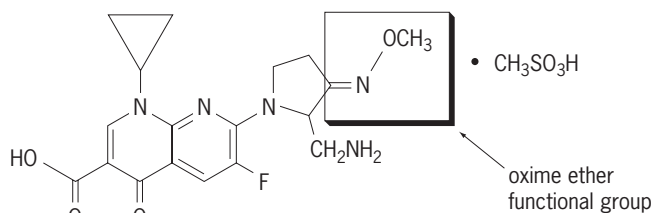
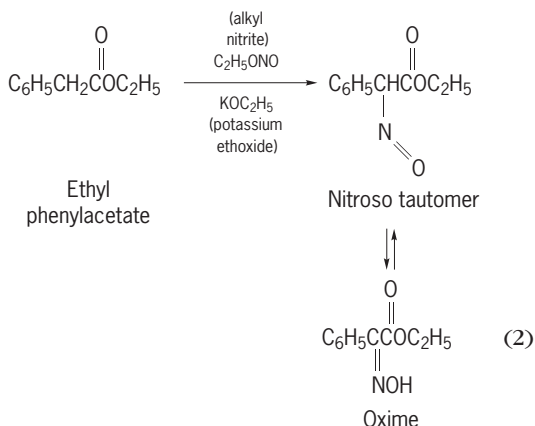
One of a group of chemical substances with the general formula $RR'C=N-OH$, where R and R' represent any carbon group or hydrogen. Oximes are derived from aldehydes (aldoximes, $RHC=NOH$) and ketones (ketoximes, $RR'C=NOH$, where R and R' are not hydrogen). Oximes and oxime ethers ($RR'C=N-OR''$) have important pharmaceutical and synthetic applications. The oxime (and oxime ether) functional group is incorporated into many organic medicinal agents, including some antibiotics, for example, gemifloxacin mesylate (see structure); and pralidoxime chloride (see structure) and obidoxime chloride are used in the treatment of poisoning by organophosphate insecticides malathion and diazinon. See ALDEHYDE; KETONE.

Hydroxylamine (H_2NOH) reacts readily with aldehydes or ketones to give oximes. The rate of the reaction of hydroxylamine with acetone is greatest at pH 4.5. Oximes are formed by nucleophilic attack of hydroxylamine at the carbonyl carbon ($C=O$) of an aldehyde or ketone to give an unstable carbinolamine intermediate [reaction (1)]. Since the breakdown of

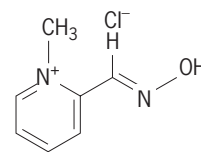


the carbinolamine intermediate to an oxime is acid-catalyzed, the rate of this step is enhanced at low pH. If the pH is too low, however, most of the hydroxylamine will be in the nonnucleophilic protonated form (NH_3OH^+), and the rate of the first step will decrease. Thus, in oxime formation the pH has to be such that there is sufficient free hydroxylamine for the first step and enough acid so that dehydration of the carbinolamine is facile. See REACTIVE INTERMEDIATES.

Oximes can also be prepared by acid- or base-catalyzed oximation of active methylene compounds with alkyl nitrites [reaction (2)]. The nitroso com-



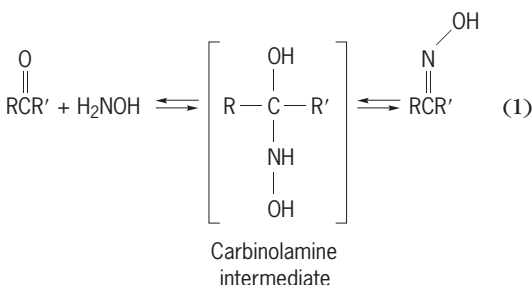
Gemifloxacin mesylate



Pralidoxime chloride

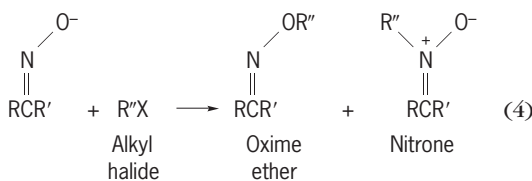
ound that is first formed in this reaction rapidly rearranges to the more stable oxime tautomer. See TAUTOMERISM.

Photolysis of alkyl nitrite esters [reaction (3)] is useful in conformationally rigid systems, and leads to oxime formation at a δ -carbon atom. Again, a ni-



troso tautomer rearranges to the oxime. This reaction has been used to convert cortisone acetate into aldosterone acetate oxime. See NITRO AND NITROSO COMPOUNDS.

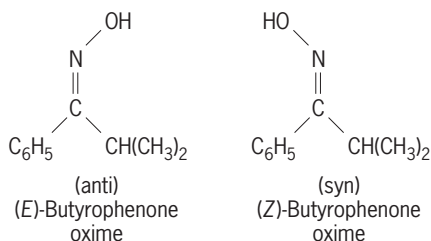
An oxime can act as both a weak acid and a weak base ($pK_b \cong 12$ and $pK_a \cong 11$). Oxime anions are capable of reacting at two different sites with alkyl halides ($R''X$). Anions of this type are referred to as ambident (literally, two-sided tooth) nucleophiles. In the case of oxime anions, the reaction with an alkyl halide (an alkylation reaction) can give an oxime ether or a nitron [reaction (4)].



See ACID AND BASE.

The *Z* and *E* isomers (formerly referred to as *syn* and *anti* isomers) of many oximes, such as butyro-

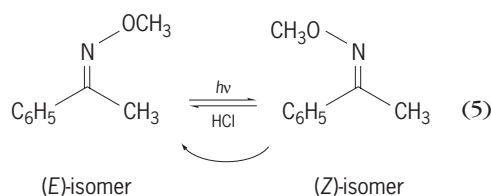
phenone oxime (see structure), are known. The *E*



and *Z* isomers of oxime ethers ($RR'C=NOR''$) are particularly resistant to thermal isomerization.

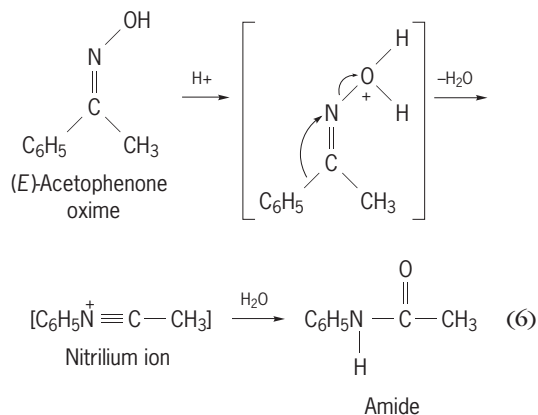
Many of the original (prior to 1921) assignments of configuration of the *Z* and *E* isomers were based on chemical reactions (the Beckmann rearrangement) and were in error because of incorrect assumptions concerning the stereochemistry of these reactions. The assignment of configurations of oximes, when both isomers are available, can be made from ^1H and ^{13}C nuclear magnetic resonance spectra. See MOLECULAR ISOMERISM; STEREOCHEMISTRY.

The *O*-methyloxime prepared from reaction of acetophenone with hydroxylamine followed by alkylation with methyl iodide has the *E* configuration (OCH_3 and C_6H_5 on opposite sides of the double bond) [reaction (5)]. Ultraviolet irradiation of benzene solution of the *E* isomer gives a mixture of the *E* and *Z* isomers from which the *Z* isomer is obtained by chromatography. Reversion to the more stable *E* isomer can be accomplished by acid-catalyzed isomerization (hydrogen chloride in dioxane) of the *Z* from [reaction (5)].



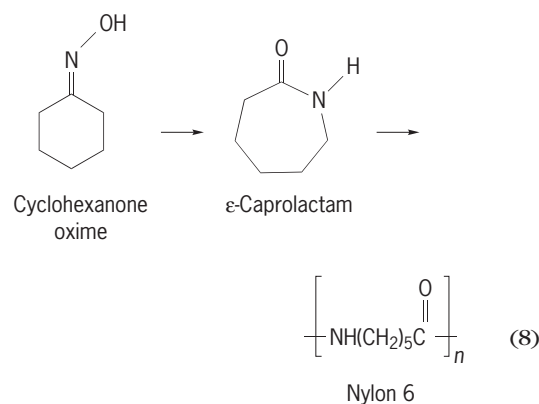
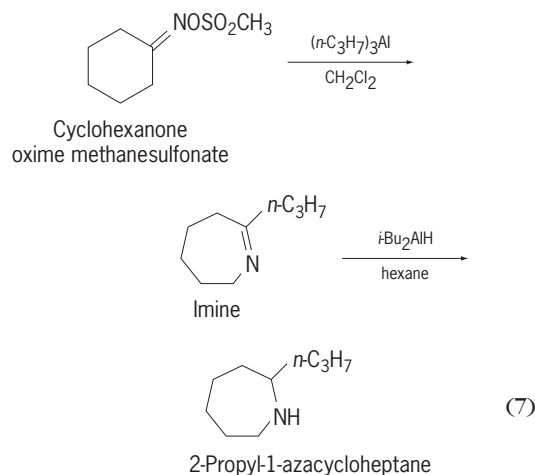
One of the best-known reactions of oximes is their rearrangement to amides. This reaction, the Beckmann rearrangement, can be carried out with a variety of reagents [such as phosphorus pentachloride (PCl_5), concentrated sulfuric acid (H_2SO_4), and perchloric acid (HClO_4)] that induce the rearrangement by converting the oxime hydroxyl group into a group of atoms that easily departs in a displacement reaction (a good leaving group) by either protonation or formation of a derivative. The Beckmann rearrangement has been shown to be a stereospecific process in which the group anti to the leaving group undergoes a 1, 2-shift to give a nitrilium ion. The nitrilium ion reacts with water to form the amide [reaction (6)].

tion (6)].

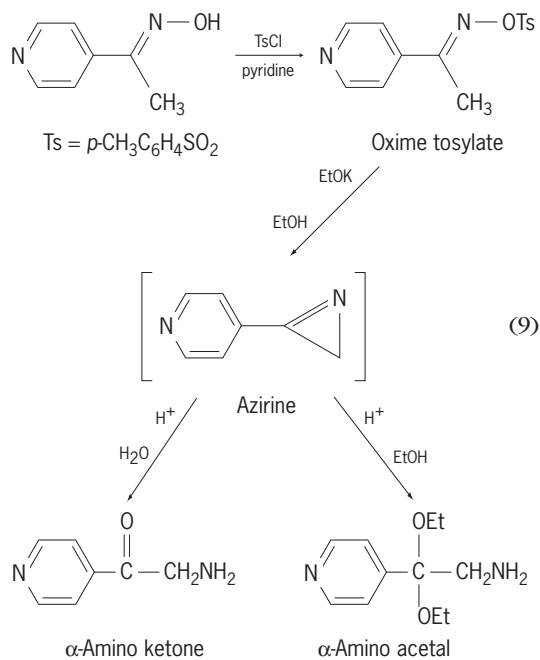


The Beckmann rearrangement can be carried out with a trialkylalane, which provides a Lewis acid for the rearrangement as well as a nucleophile to react with the intermediate nitrilium ion. For example, the tosylate of cyclohexanone oxime methanesulfonate reacts with tri-*n*-propylalane [$(n\text{-C}_3\text{H}_7)_3\text{Al}$] to give an imine, which is reduced with diisobutylaluminum hydride to 2-propyl-1-azacycloheptane [reaction (7)].

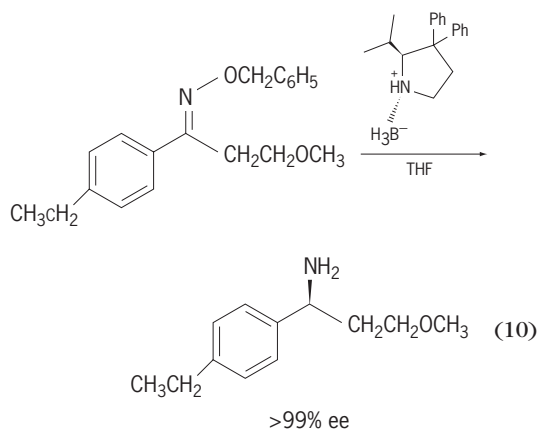
The industrial synthesis of ϵ -caprolactam is carried out by a Beckmann rearrangement on cyclohexanone oxime. ϵ -Caprolactam is polymerized to the polyamide known as nylon 6, which is used in tire cords [reaction (8)].



The conversion of oxime tosylates into α -amino ketones is known as the Neber rearrangement [reaction (9)]. The intermediate azirine is usually not

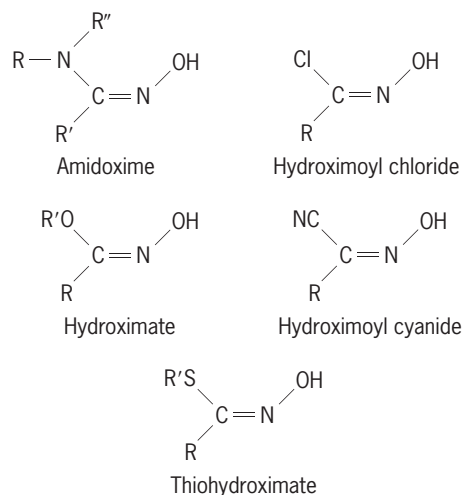


isolated and is reacted with aqueous acid to give the α -amino ketone. Reaction of the azirine with acid in anhydrous ethanol gives an α -amino acetal.



Aldoximes are dehydrated with acetic anhydride to nitriles ($RC\equiv N$). Oxidation of oximes with trifluoroperacetic acid at controlled pH gives nitro compounds ($RR'/CHNO_2$). Oximes can be reduced to amines with lithium tetrahydridoaluminate ($LiAlH_4$) or by catalytic hydrogenation. Reductions of oxime ethers with a chiral oxazaborolidine give optically active amines with high enantioselectivity [reaction (10)]. Reduction of oximes with sodium cyanotrihydrideborate ($NaBH_3CN$) gives hydroxylamines. See HYDROGENATION.

There are many more complex functional groups that contain the oxime moiety, including:



See ORGANIC SYNTHESIS. James E. Johnson
Bibliography. B. R. Brown, *The Organic Chemistry of Aliphatic Nitrogen Compounds*, 1994; F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 4th ed., 2001; J. P. Freeman (ed.), *Organic Syntheses Collective Volume*, 8, pp. 568-572, 1993; J. P. Freeman (ed.), *Organic Syntheses Collective Volume 7*, pp. 149-152, 1990; R. E. Gawley, The Beckmann reaction: Rearrangements, elimination-additions, fragmentations, and rearrangement-cyclizations, *Org. React.*, 35:1-420, 1988; L. S. Hegedus (ed.), *Organic Syntheses*, 79:130-138, 2002; M. B. Smith and J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed., 2001.