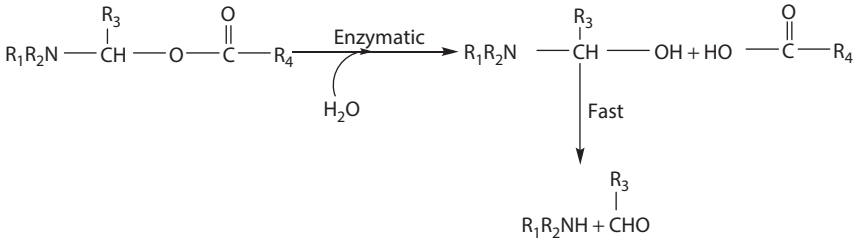

FIGURE 16.4 Drug regeneration from an *N*-Mannich base prodrug by a two-step process.

the corresponding aldehyde and the NH-acidic parent drug. The enzymatic hydrolysis step, then, is the only opportunity to control the drug regeneration rate. Enzymatic hydrolysis can be slowed by steric and electronic factors derived from the carboxylic acid and the R_3 group involved.

An example of a successful prodrug prepared by this method is the hydrochloride salt of the *N*-(*N*′,*N*′-dimethylglycyloxymethyl) derivative of chlorzoxazone (Johansen and Bundgaard, 1981b) that improved the solubility of the parent drug 1000-fold. *N*-acyloxymethyl derivatives of phenytoin, where the acyl group bears an amine group, possess greatly enhanced solubility relative to the parent drug (Varia et al., 1984a). The solubility and the lipophilicity could be modified by the hydrophilic or hydrophobic nature of the acyl moiety. The *N*-acyloxyalkylation can also diminish intermolecular hydrogen bonding in the crystal lattice. It should be noted that formation of the acyloxymethyl prodrugs of phenytoin, where the acyl group had no ionizable functional groups, should also cause diminished hydrogen bonding in the crystal, and indeed these prodrugs possessed a lower melting point, but also a lower solubility in water (Stella et al., 1998).

A second example is allopurinol, a poorly soluble drug, which is also poorly soluble in organic solvents owing to its high melting point (Windholz et al., 1983; Bundgaard and Falch, 1985b). It was found that hydrogen bonding exists between the N_1-H of one molecule and the N_8 of another molecule, and between the N_3 of one and the hydrogen of the N_9-H group of another (Prusiner and Sundaralingam, 1972). *N*-acyloxymethylation blocks intermolecular hydrogen bonding, which can subsequently decrease the melting point and increase both water solubility and lipophilicity (Bundgaard and Falch, 1985a,b; Bundgaard et al., 1990). In particular, the *N,N*-dimethyl- and *N,N*-diethyl-glycyloxymethyl derivatives demonstrated dramatically enhanced solubility and provided a greater partition coefficient over those of the parent drug.

The *N*-butanoyloxymethyl derivative of bupivacaine exhibited pH-independent solubility in excess of 1 g/mL, that is, a 10,000-fold increase in water solubility compared to the parent drug in its base form (Nielsen et al., 2005). Chemical hydrolysis over a pH range of 0.1–9.8 at 37°C followed first-order kinetics and the pH-stability profile was U-shaped. At neutral to slightly alkaline pH, hydrolysis resulted not only in bupivacaine, but also in an aromatic imide that was believed to be formed by an intramolecular acyl transfer involving nucleophilic attack of the amide nitrogen atom on the ester carbonyl carbon. Since this prodrug and other derivatives described in this report were poor substrates for plasma enzymes, the authors tested and confirmed their susceptibility to pancreatic enzymes. The prodrugs possessed sufficient stability in the gastric environment that the authors noted their potential to enhance oral bioavailability of tertiary amines that have pK_a values below about 6 and an intrinsic solubility in the low micromolar range.

A novel technique to prepare water-soluble prodrugs of drugs bearing a tertiary amine group involves a nucleophilic substitution reaction between the amine and di-*tert*-butyl chloromethyl phosphate, resulting in formation of the quaternary ammonium salt (Krise et al., 1999c). The tertiary butyl group is readily removed under acidic conditions using trifluoroacetic acid, giving the *N*-phosphonooxymethyl prodrug in the free phosphoric acid form. This can be subsequently converted to the desired salt form. Included in the studies were quinuclidine, cinnarizine, loxapine, and amiodarone (Krise et al., 1999b,c). The prodrugs would undergo a two-step bioreversion process.