erythematosus; the drug also has immunosuppressant action in smaller doses. Ifosfamide (Mitoxana®), a more recent related compound, is usually used to treat sarcoma, testicular cancer, and some types of lymphomas.

The original assumption about cyclophosphamide hydrolytic bioactivation soon proved to be wrong, and several studies showed that cyclophosphamide is not metabolized by hydrolysis but, rather, by hepatic P450 oxidation to give 4-hydroxycyclophosphamide, which is in equilibrium with its acyclic aldophosphamide form. Hepatic alcohol dehydrogenase transforms these compounds into the inactive metabolites 4-ketocyclophosphamide and carboxyphosphamide, respectively, which explains the low hepatic toxicity of this drug. Some of the hydroxycyclophosphamide is carried throughout the body by the bloodstream and is further activated by a spontaneous elimination reaction that yields acrolein and phosphoramide mustard, the main cytotoxic species. The negative charge on the phosphoramidate oxygen atom balances the electron-withdrawing effect of the P=O group and allows its activation to an aziridinium cation. Phosphoramide mustard can be hydrolyzed to nornitrogen mustard, which is also active (Figure 5.10).

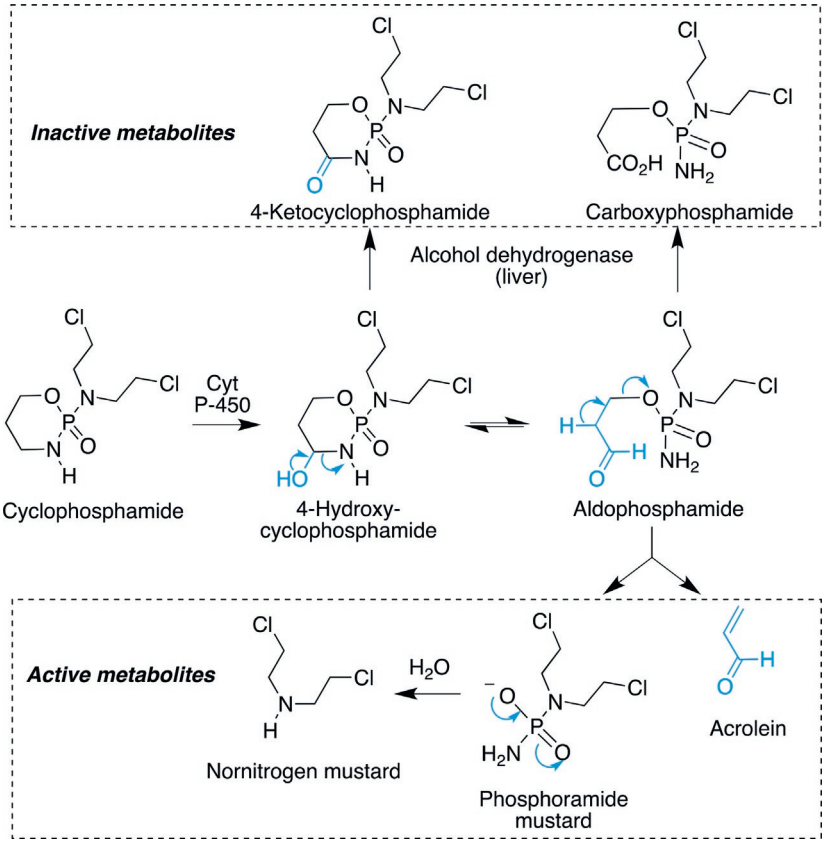


**FIGURE 5.10**

Bioactivation of cyclophosphamide.