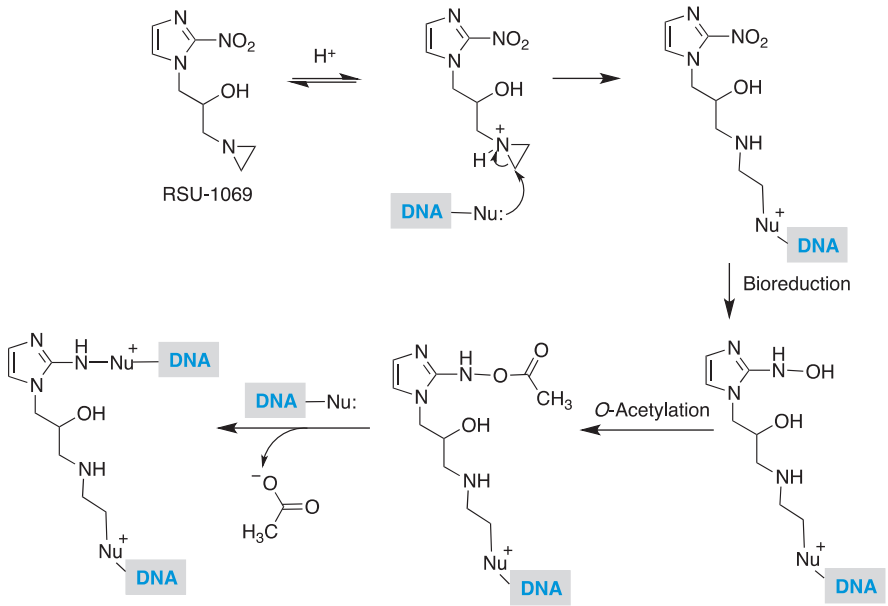
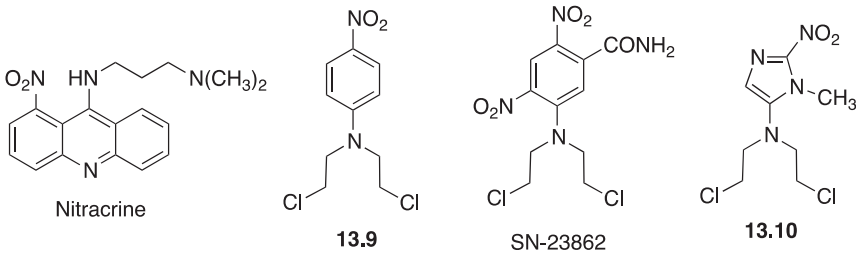


FIGURE 13.13

Enhanced cytotoxicity of RSU-1069 in hypoxic environments.



The problems associated with the presence of several nitro groups attached to the benzene ring of a nitrogen mustard are due to metabolic side reactions that contribute to its deactivation. Thus, reduction of the nitro group *ortho* to a mustard moiety may result in intramolecular alkylation, which is considered to be an inactivation pathway. For instance, the reductive metabolism of SN-23862 affords a mixture of hydroxylamino (**13.11**) and amino (**13.12**) *ortho*-reduced metabolites, which undergo a fast intramolecular cyclization to tetrahydroquinoxaline derivatives **13.13**,[13] where most antitumor activity has been lost (Figure 13.14).

However, reduction of the nitro group *para* to the mustard moiety normally generates potential DNA cross-linking cytotoxins, as is the case of the 3,5-dinitrobenzamide mustard PR-104, a hypoxia-activated DNA cross-linking agent with marked activity against human tumor xenografts,