



FIGURE 13.11

Release of alkylating species through reductive bioactivation of quinones.

to the reduction step because of the electron-withdrawing effect of the quinone moiety on the indole nitrogen (Figure 13.11).

2.2.3 Aromatic Nitro Derivatives

Nitroaromatic compounds are reduced by several nitroreductases, which are flavoprotein enzymes that catalyze the stepwise addition of up to six electrons. The major metabolite is normally the hydroxylamine, which is formed by addition of four electrons. Its stability is due to the very low reduction potential required for its further reduction to an amine. In nitroaromatic compounds with suitable reduction potentials (approximately -330 to -450 mV), the first radical anion formed by one-electron addition can be scavenged efficiently by molecular oxygen, and consequently its formation is restricted to hypoxic cells. Compounds with reduction potentials outside this range are less useful, normally for one of the following reasons: They are too easily reduced and therefore they show little selectivity for hypoxic tissues (reduction potentials higher than -330 mV), or they are too difficult to activate (reduction potentials below -450 mV).

The main nitroaromatic compounds used in cancer chemotherapy were nitroimidazoles. Although they were first introduced as radiosensitizers, it was later shown that they are able to induce cell death in hypoxic environments in the absence of radiation. This cytotoxic activity is mainly due to the formation of nitro radical anion **13.6** and hydroxylamine (**13.8**) metabolites. Compounds **13.6**, or their protonated derivatives **13.7**, can oxidize DNA chains, whereas the *O*-acetyl derivative of the hydroxylamine derivatives **13.8** may give covalent DNA adducts (Figure 13.12).¹²

The observation of cytotoxic activity in the absence of radiation normally requires concentrations of the nitro derivative that are too high to be found in clinical situations, but the presence of two alkylating moieties can lead to improved activity. For instance, RSU-1069 behaves as a DNA monoalkylator in