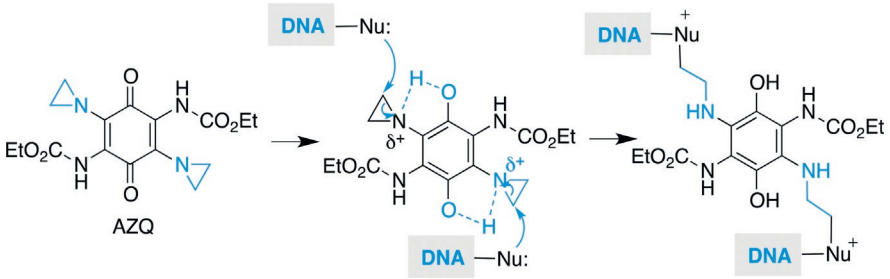
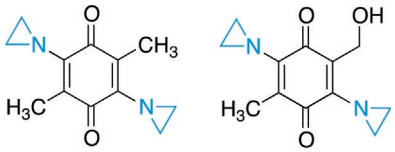


FIGURE 5.19

Bioreductive activation of aziridinylbenzoquinones.

partially overcome by introduction of hydrophilic hydroxyl groups in the side chains. For instance, RH1[43] is an excellent substrate for DTD, which has potent DNA cross-linking activity and high antitumor potency *in vitro* and *in vivo*[44] with reduced toxicity in normal tissues. It underwent phase I clinical studies in patients with solid tumors under the auspices of Cancer Research UK,[45,46] although because of its limited aqueous stability and solubility, it will require a suitable formulation for more advanced clinical trials.



In addition to alkylation, other reactions are possible on the hydroquinone form of aziridinylquinones such as **5.23**. One of them, which leads to its inactivation, is a 1,5-sigmatropic shift of hydrogen to give **5.24**,[47] which is then transformed into ethylaminoquinone **5.25** by tautomerism or into aminoquinone **5.26** through a second 1,5-sigmatropic shift followed by hydrolysis (Figure 5.20).

An additional transformation that inactivates **5.23** takes place by loss of the aziridine ring on its tautomer **5.27**, leading to quinone **5.28** (Figure 5.21).

One-electron metabolic reduction of aziridinylquinones is also possible, leading to semiquinones. Their protonated derivatives **5.29** also undergo a 1,5-sigmatropic shift, leading to inactive compounds **5.25** and **5.26**, the same as in the two-electron reduction process (Figure 5.22). As expected, semiquinone intermediates can also generate oxygen radical species upon reaction with O_2.[48]

These degradation pathways have therapeutic implications because the lower pharmacokinetic stability of indoloquinone aziridines, such as EO-9, with regard to their benzoquinone analogs is due to higher concentrations of the corresponding protonated semiquinone **5.29** due to the fact that the electron-releasing effect of the indole nitrogen leads to a low acidity for **5.29**. The pK_a of the semiquinone derived from EO-9 is 9.3, whereas the corresponding pK_a values of benzosemiquinones are below neutrality. For this reason, benzosemiquinones are mostly deprotonated, and the hydrogen sigmatropic shift mentioned previously cannot occur.[49]

Several natural products, including the mitomycins, FR-900482, and FR-69979, contain one fused aziridine ring,[50] but because of their specificity toward the minor groove, they are discussed in Chapter 6.