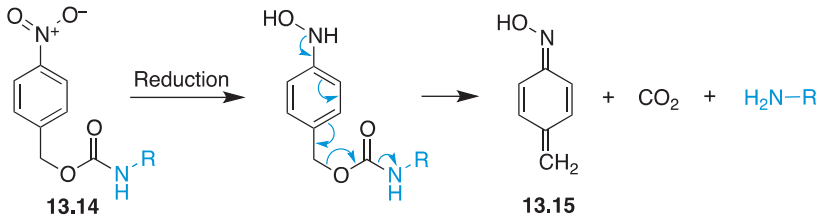

FIGURE 13.16

Reductive bioactivation of nitrobenzyl carbamates.

Similarly, the reduction of *p*-nitrobenzyl carbamates such as **13.14** to its hydroxylamino metabolite generates the electrophilic quinoneimine methide **13.15** together with amine R-NH_2. Compound **13.15** is a DNA cytotoxin, but because the reduction potential of the prodrug **13.14** is too low, this bioreduction is inefficient (Figure 13.16).

The same problem, related to a value that is too low for the reduction potential, has been shown in the bioreductive activation of the fluorouracil prodrug **13.16**, which has been designed to generate the active species together with the electrophilic quinoneimine methide by a "through-space" cyclization-extrusion process in the reduced metabolite **13.17** (Figure 13.17).

2.2.4 Cobalt Complexes

As mentioned in Section 2.4 of Chapter 5, another strategy to design hypoxic selective nitrogen mustards is the complexation of both nitrogen atoms from bidentate mustards with transition metals such as cobalt. Complexes in the low-spin Co(III) oxidation state, such as SN-24771, are very stable and have appropriate reduction potential values to be reduced by cellular reductases. This reduction is competitively inhibited by oxygen, but under hypoxia, the unstable high-spin Co(II) species resulting from reduction rapidly releases its ligands to coordinate with water molecules forming stable hexaaquo Co(II) species (Figure 13.18).[16] The limited activity shown *in vivo* by this prodrug discouraged its further development.

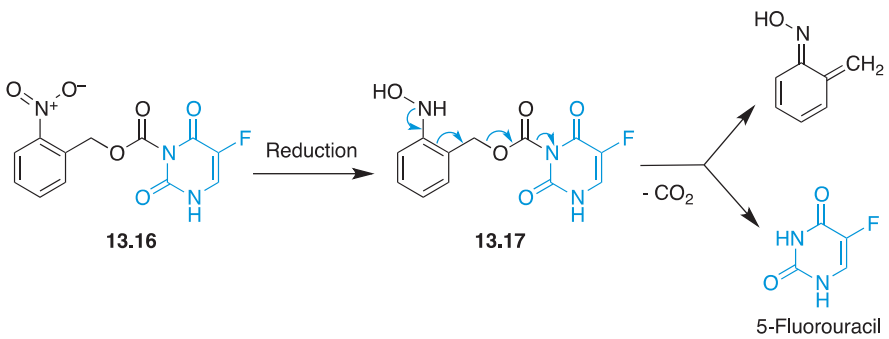

FIGURE 13.17

Reductive bioactivation of a 5-fluorouracil prodrug.