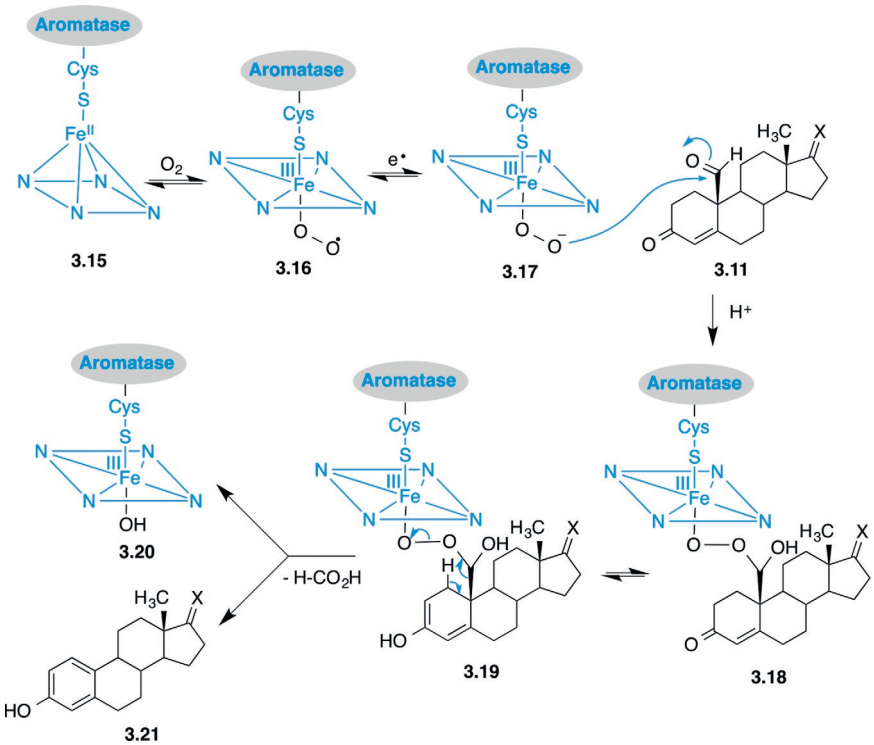

FIGURE 3.18

Alternative mechanism accounting for aromatase activity.

toxicities. For this reason, the steroidal aromatase inhibitors in clinical use behave as mechanism-based irreversible inhibitors.[35] Although the precise chemical details are sometimes unknown, many types of compounds are available that contain latent electrophilic groups intended to be activated by aromatase. The most relevant are summarized here.

4.3 C-19 MODIFIED SUBSTRATE ANALOGS

One example of C-19 modified substrate analogs is the propargyl derivative plomestane, for which two main types of mechanisms have been proposed. The first one postulates its oxidation by aromatase to give the C-19 carbonyl derivative, leading to the Michael acceptor **3.22**, a substrate for nucleophilic attack at the enzyme active site to give **3.23**. The second mechanism is based on the one proposed for the inactivation of cytochrome P450 enzymes by terminal acetylenic compounds and involves epoxidation of the acetylene chain by aromatase to give the unstable oxirene **3.24**, which reacts with aromatase after rearrangement to ketene **3.26** to give **3.27** (Figure 3.19). Although it was found to be effective and produce few adverse effects in preliminary studies, clinical data related to plomestane are very scarce because of the "technical problems" that were encountered in the course of its development.[36]