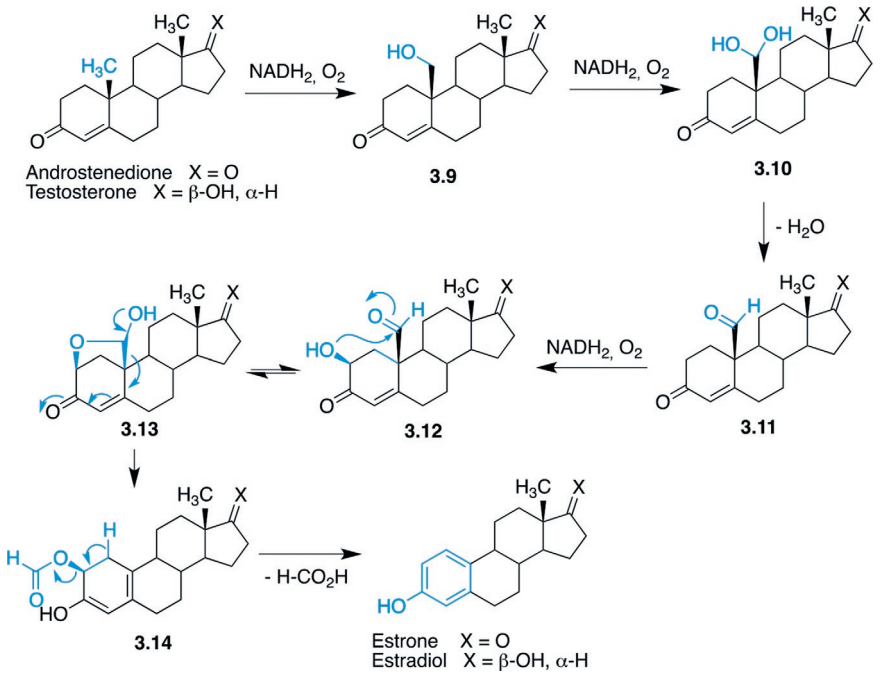

FIGURE 3.17

Initial mechanistic proposal to explain aromatase activity, which was falsified by isotopic labelling experiments.

An alternative mechanism involves chemical changes in the heme group at the catalytic site. Similarly to other cytochrome P450 enzymes, the catalytic site of aromatase contains an Fe(III) heme group that, after reduction to Fe(II) affording species **3.15**, binds to an oxygen molecule that becomes activated, giving **3.16**. A further one-electron reduction leads to peroxide anion **3.17**, which can undergo a nucleophilic attack onto the formyl group of aldehyde **3.11**. The adduct **3.18** thus generated, probably as its enol tautomer **3.19**, evolves to **3.20** and **3.21** by loss of a molecule of formic acid via the ionic mechanism shown in Figure 3.18, or perhaps through a radical pathway, yielding the estrogen hormones. This mechanism is consistent with all experimental data and is considered more likely than the one via 2-hydroxylation previously discussed and other alternatives that have been proposed.[33]

4.2 STEROIDAL AROMATASE INHIBITORS (TYPE I INHIBITORS)

Aromatase inhibitors are normally classified as steroidal (type I) or nonsteroidal (type II). Numerous steroidal agents that exhibit competitive, irreversible, or mechanism-based inhibition of aromatase have been developed.[34] Mechanism-based inhibitors, known as *aromatase inactivators*, are bound to the catalytic site, where they are transformed into electrophilic intermediates that become irreversibly attached to the enzyme, blocking its activity. These inhibitors have distinct advantages in drug design because they are highly enzyme specific, produce prolonged inhibition, and exhibit minimal