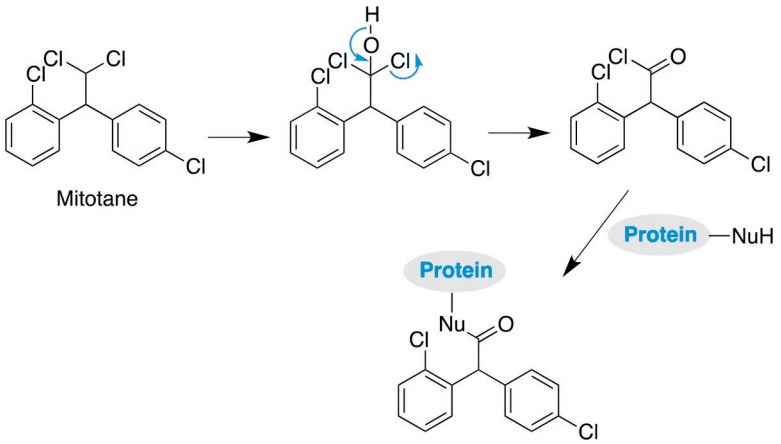

FIGURE 3.39

Biotransformations of mitotane.

proteins, leading to direct necrosis and atrophy of the adrenal cortex and, hence, inhibition of glucocorticoids, mineralocorticoids, and adrenal gland-produced sex hormone synthesis (Figure 3.39). Another possible mechanism is oxidative damage through the production of free radicals.[87]

9 COMPOUNDS ACTING ON OTHER PROTEINS OF THE NUCLEAR RECEPTOR SUPERFAMILY: RETINOIDS

Vitamin A and its analogs, collectively known as retinoids, have profound effects on cell growth and differentiation, and the loss of retinoid function is linked to carcinogenesis. Several retinoids have shown promising activity as antitumor and cancer chemopreventive agents by inhibiting carcinogenesis at the initiation, promotion, and progression stages.[88] The anticancer activity of the retinoids is mainly due to their binding to nuclear receptors that act as hormone receptors activating target genes. They are classified as classical retinoic acid receptors (RARs) and nonclassical retinoid X receptors (RXRs), each of which has three isoforms (α, β, and γ). Because they have different ligand-binding domains, they can be targeted separately. The diet-derived all-*trans* retinoic acid (ATRA, tretinoin), which is the main retinoid in humans, selectively activates the RARs, whereas 9-*cis*-retinoic acid can activate both RARs and RXRs (Figure 3.40). Retinoids with selectivity for RXRs are known as rexinoids. RARs can heterodimerize with RXRs, and the latter can also form heterodimers with other nuclear receptors, including the vitamin D receptors, thyroid hormone receptors, and peroxysome proliferator-activating receptors (PPARγ).

The RAR–RXR heterodimers bind to specific DNA sequences, known as retinoic acid response elements. In the absence of ligands, the heterodimer–DNA complex is linked to corepressors and histone deacetylases, inducing chromatin compaction and silencing the promoter region of the target genes (gene repression). However, the binding of ligands to the heterodimers induces a conformational change that destabilizes the interaction with corepressors and allows the union to coactivators, leading to gene transcription (Figure 3.41).