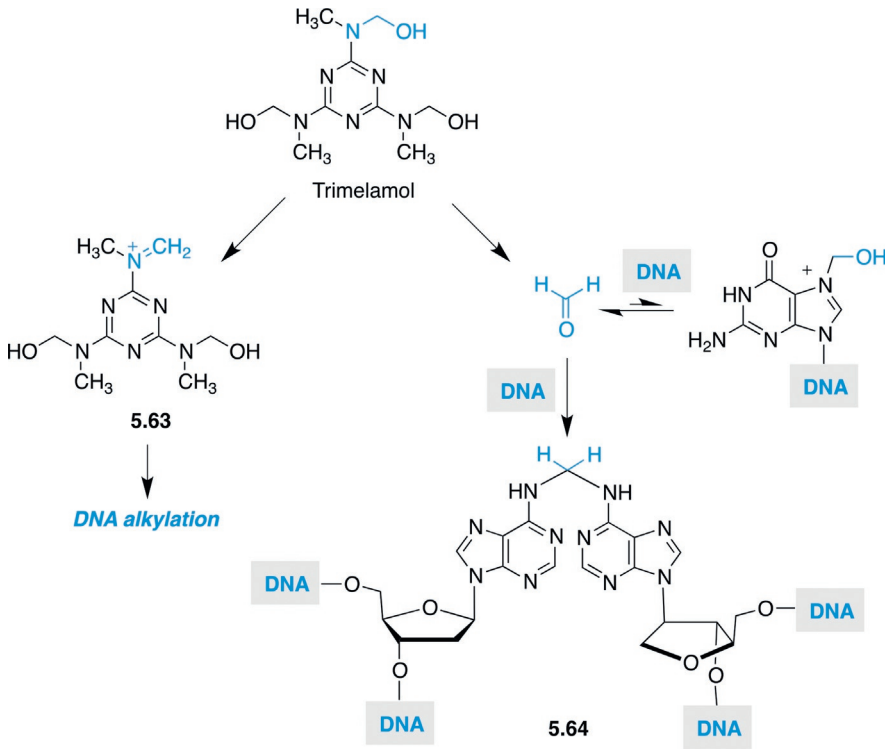

FIGURE 5.38

DNA alkylation by trimelamol.

interactions with renal components leading to tubular necrosis of both proximal and distal renal tubules, can be reduced to some degree through the use of saline hyperhydration before and after treatment. Other side effects limit the dose delivered to patients, which can be sublethal to tumors (particularly ovarian cancers), and this may stimulate the development of resistance to further drug treatment. Mechanisms of drug resistance include reduced drug uptake and/or increased drug efflux, degradation and deactivation by intracellular thiols such as glutathione, and improved repair or tolerance of DNA–cisplatin adducts.[87]

Cisplatin is a square–planar complex, containing two labile chlorines and two relatively inert ammonia molecules coordinated to the central Pt(II) atom in a *cis* configuration. When this compound enters the cell, it reacts with water to give the positively charged active species **5.65** and especially **5.66**, a process that is favored by the relatively low intracellular chloride concentration. These species enter the nucleus and are responsible for the formation of DNA Pt complexes that account for the antitumor activity (see below). Cytoplasmic deactivation of cisplatin is also possible and is mainly due to its reaction with mercapto groups in glutathione because the "soft" nature of both Pt and S favors their mutual binding. In plasma, the high chloride concentration somewhat hampers this reaction, but nevertheless the extracellular hydrolysis of cisplatin followed by the formation of Pt adducts with mercapto