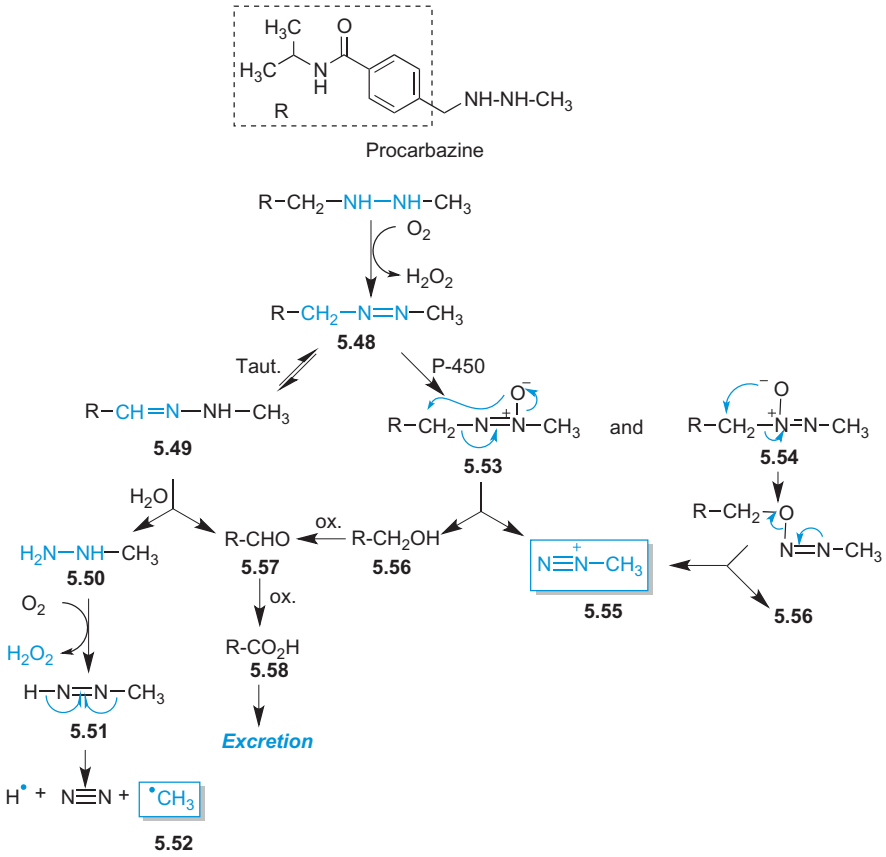

FIGURE 5.36

Generation of methyldiazonium during procarbazine metabolism.

9 1,3,5-TRIAZINES: HEXAMETHYLMELAMINE AND TRIMELAMOL

Altretamine (hexamethylmelamine, Hexalen®) was originally prepared as a resin precursor, but it was studied as an antitumor compound because of its structural analogy with the previously mentioned aziridine derivative triethylenemelamine (TEM). Although it is active in several types of tumors, its main therapeutic role is in the treatment of recurrent ovarian cancer, following first-line treatment with cisplatin.[82] The precise mechanism of altetramine cytotoxicity is unknown, although several proposals have been made. The main metabolic pathway is oxidative cytochrome P450-catalyzed *N*-demethylation, with carbinolamine **5.59** as an intermediate, which yields the pentamethyl derivative **5.62**, formaldehyde, and smaller amounts of inactive compounds arising from further demethylation. Alternatively, elimination of the hydroxy group from **5.59** gives the iminium species **5.60** that appears to be the alkylating species[83] rather than the formaldehyde generated in the demethylation process, which then reacts with DNA to give **5.61** (Figure 5.37).