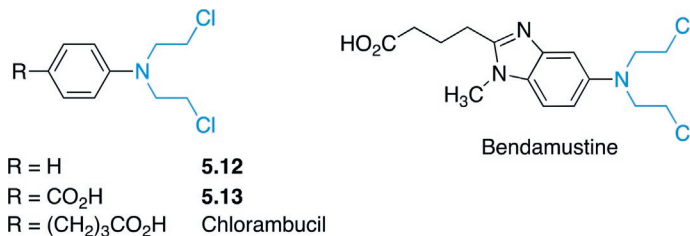


FIGURE 5.4

Other DNA fragmentation processes that take place following guanine alkylation.

nitrogen atom. The increased stability gives enough time for absorption and distribution before alkylation takes place and therefore allows oral administration. The simplest aromatic nitrogen mustard is compound **5.12**, which has the disadvantage of not being water-soluble. Addition of a carboxyl group led to the soluble analog **5.13**, which was inactive. However, simple separation of the carboxylic group from the aromatic ring by a spacer yielded active compounds such as chlorambucil (Leukeran[®]). This compound, approved in 1957, is an orally administered alkylating agent mainly used to treat chronic lymphocytic leukemia and lymphomas. Bendamustine (Ribomustin[®], Treandra[®], Levact[®]) is a related nitrogen mustard in which the benzene ring has been replaced by a benzimidazole. It is sometimes used to treat chronic lymphocytic leukemia, B-cell non-Hodgkin's lymphoma, and myeloma, and its use has undergone a recent renaissance.¹⁰



The butyric acid moiety of chlorambucil and bendamustine modulates not only their aqueous solubility and reactivity as alkylating agents but also their metabolism. Thus, a significant fraction of