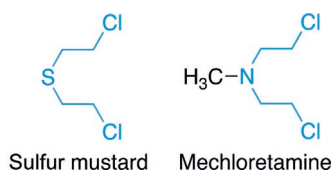


Prompted by this report and by their own previous work on the effects of mustard gas on animals, the Yale pharmacologists Louis Goodman and Alfred Gilman tested mechlorethamine (chlormethine, mustine), a nitrogen analog of mustard gas, on animals and then humans and found it to be effective as a treatment for lymphoma, including Hodgkin's lymphoma and acute lymphoblastic leukemia. This study was classified at that time and was not published until 1946, when it started the modern era of cancer chemotherapy.<sup>6</sup> Even at this early stage, it was soon apparent that the therapeutic effect of nitrogen mustards was limited by marrow toxicity and the development of resistance, which are still a source of problems in cancer chemotherapy today. These problems notwithstanding, mechlorethamine (Mustargen<sup>®</sup>) was approved in 1949, and it is still used as part of some antitumor regimes for the chemotherapy of Hodgkin's lymphoma.<sup>7</sup> In 2013, a mechlorethamine gel (Valchlor<sup>®</sup>) was approved for the topical treatment of stage IA/IB mycosis fungoides-type cutaneous T-cell lymphoma.



## 2.2 DNA ALKYLATION BY NITROGEN MUSTARDS AND CYTOTOXICITY MECHANISMS

Due to the relative unreactivity of alkyl chlorides as electrophiles, direct attack of DNA nucleophilic centers by nitrogen mustards under physiological conditions is too slow to be of therapeutic relevance. The reason why nitrogen mustards have a high reactivity as alkylating agents under mild conditions is the anchimeric assistance from the nitrogen atom—that is, the formation through an intramolecular nucleophilic substitution of the aziridinium cation **5.1**, which is highly reactive because of the positive charge at the leaving group and the high strain of the three-membered ring, which is relieved in the alkylation process. Because the most nucleophilic atom in DNA is the N-7 nitrogen of guanine, the most common species arising from alkylation is **5.2** (Figure 5.2).

As mentioned previously, one consequence of alkylation is the alteration of the normal pairing of DNA bases between adenine–thymine and guanine–cytosine (Watson–Crick base pairs). For instance, the three hydrogen bonds normally linking guanine and cytosine require the existence of a carbonyl group at the purine C-6 position. Because alkylation at N-7 creates a positive charge on this center, which is adjacent to the partial positive charge at C-6 due to the electron deficiency of the carbonyl group, the tautomeric equilibrium is displaced to the more stable 6-hydroxy form.<sup>8</sup> This change in the normal tautomeric form converts hydrogen bond acceptor groups into donors and vice versa.

