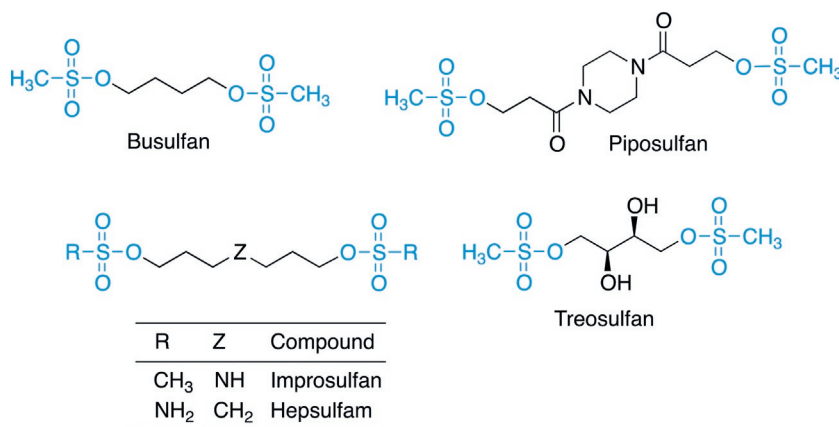


FIGURE 5.25

DNA cross-linking by azinomycin B.



The formation of interstrand DNA cross-links has been demonstrated for busulfan<sup>60</sup> and treosulfan.<sup>61</sup> Busulfan also produces DNA intrastrand cross-links, mainly at the 5'-GA-3' sequence.<sup>62</sup> In contrast with nitrogen mustards, in which the rate-limiting step is the unimolecular formation of the aziridinium ion, busulfan reacts with guanine N-7 by a S<sub>N</sub>2 mechanism (Figure 5.26), in which the rate-limiting step depends on the concentration of both reaction partners.<sup>63</sup>

The study of metabolites of busulfan suggests that it is also able to alkylate cysteine residues. The urinary excretion of compound 5.32 can be explained by the mechanism summarized in Figure 5.27, which involves a double nucleophilic attack by this amino acid.

## 6 NITROSOUREAS

In a random screening carried out by the National Cancer Institute in 1959, 1-methyl-3-nitro-1-nitrosoguanidine showed a weak antileukemic activity. Assays with analogs of this compound led to the discovery of the antitumor activity of 1-methyl-1-nitrosourea, the lead compound of the nitrosourea group. It was soon discovered that introduction of a 2-chloroethyl chain on the nitrogen atom