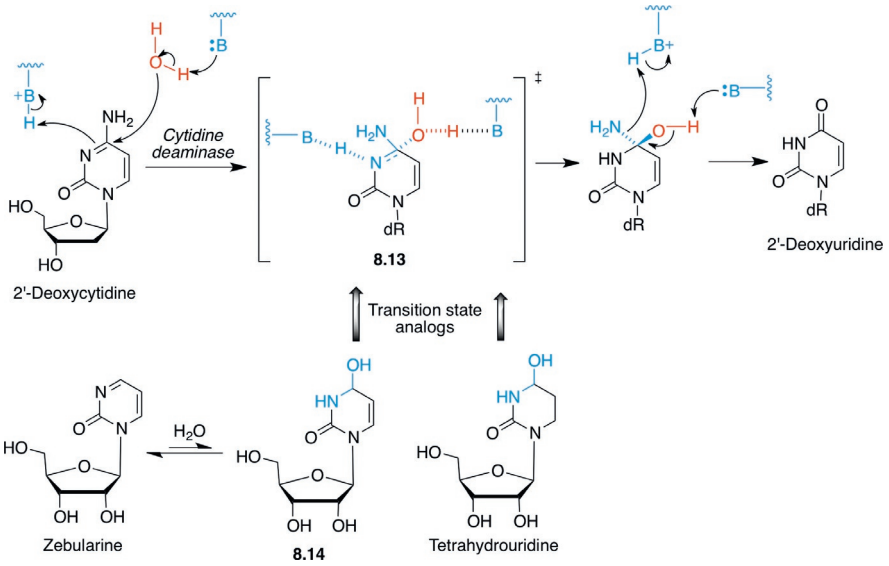

FIGURE 8.9

Inhibition of cytidine deaminase by zebularine hydrate due to its analogy with the reaction transition state.

zebularine to be sequestered by this enzyme and not available for DNMT. In addition, inhibition of cytidine deaminase results in increased levels of deoxycytidine, which competes with zebularine for incorporation into DNA, a necessary step for DNMT inhibition. Despite the promising preclinical results of zebularine, this drug has not entered clinical trials, and emphasis has been placed on identifying prodrugs that circumvent its bioavailability and metabolic limitations as well as on finding less toxic analogs.

2.2 NON-NUCLEOSIDE INHIBITORS OF DNA METHYLTRANSFERASE

These inhibitors have the advantage of binding directly to the catalytic region of the enzyme without needing to be first incorporated into DNA, but their effects on cellular viability have not been analyzed systematically. One of these compounds is psammaplin A, a symmetric, dimeric hydroxyiminotyrosine-based natural product, isolated from various *Verongid* sponges and characterized in 1987, whose physiologic instability precluded its direct clinical development.[25] This compound was initially characterized as a dual inhibitor of DNMT and HDAC, the two main epigenetic modifiers of tumor suppressor gene activity, but recent studies have failed to show significant DNMT inhibitory activity in the natural product[26] and in a number of its analogs.[27]

Another natural DNMT inhibitor isolated from green tea is the polyphenol (–)-epigallocatechin-3-gallate (EGCG).[28] Various clinical studies have revealed that treatment with this compound inhibits tumor incidence in different organs, and several workers have demonstrated that it has potential in cancer prevention because it reduces the activity of DNMTs, proteases, and dihydrofolate reductase. Other