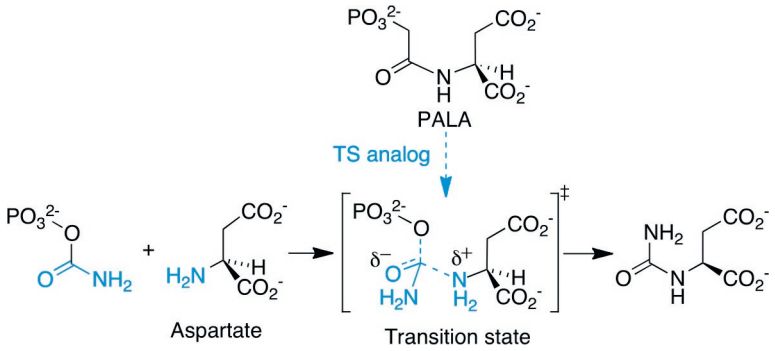

FIGURE 2.3

Inhibition of aspartate transcarbamoylase by PALA.

transition state analog (Figure 2.3). This compound has undergone some clinical trials, normally in combination with 5-fluorouracil, another pyrimidine antimetabolite.[1]

3 INHIBITORS OF RIBONUCLEOTIDE REDUCTASE

The biosynthesis of 2′-deoxyribonucleotides, the immediate precursors of DNA, involves the replacement of the 2′-OH group by a hydrogen atom (Figure 2.4). This reaction takes place on ribonucleoside-5′-diphosphates and is catalyzed by the enzyme ribonucleotide reductase (RNR), also known as nucleoside diphosphate reductase (NDPR). RNR is the rate-determining enzyme in the supply of deoxynucleotides, and its substrates are ADP, GDP, CDP, and UDP. Deoxythymidine diphosphate (dTDP) is synthesized by another enzyme (thymidylate kinase) from deoxythymidine monophosphate (dTMP). Ribonucleotide reductase thus plays a central role in cell growth and proliferation by ensuring a balanced supply of nucleotide precursors for DNA synthesis, and it has been identified as an important target for hematologic malignancies.[2]

3.1 STRUCTURE AND CATALYTIC CYCLE OF RIBONUCLEOTIDE REDUCTASE

The most extensively studied ribonucleotide reductase is that from *Escherichia coli*, which is considered as a suitable prototype for the mammalian enzyme. In eukaryotes, ribonucleotide reductase has two subunits, with each containing a dinuclear iron center that generates an essential stable tyrosyl

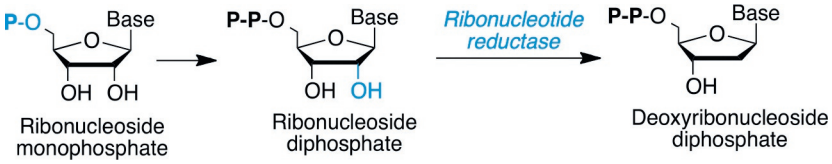

FIGURE 2.4

Biosynthesis of 2-deoxyribonucleotides.