Although clinically useful antimetabolites ultimately inhibit DNA (and sometimes RNA) synthesis, their site of action may be separated many steps away from these reactions. Specific interference with the *de novo* nucleic acid pathways in cancer cells is probably not possible because tumoral and normal cells use the same biosynthetic routes. Nevertheless, some antimetabolites are remarkably effective against some human cancers and are still one of the bases of cancer chemotherapy.

2 INHIBITORS OF THE BIOSYNTHESIS OF URIDYLIC ACID

The biosynthesis of pyrimidine nucleotides starts with the construction of the heterocyclic system by carbamoylation of aspartate followed by cyclization to dihydroorotate. Its dehydrogenation gives orotate, which then reacts with phosphoribosyl pyrophosphate (PRPP) to give orotidylate. Finally, uridylic acid (uridine monophosphate (UMP)) is generated by decarboxylation (Figure 2.2). UMP is the precursor to other pyrimidine nucleotides, after its conversion to the corresponding nucleoside triphosphate (UTP).

Among the many compounds known to inhibit reactions of this pathway, we mention only *N*-phosphonoacetyl-L-aspartate (PALA), an inhibitor of aspartate transcarbamoylase that acts as a

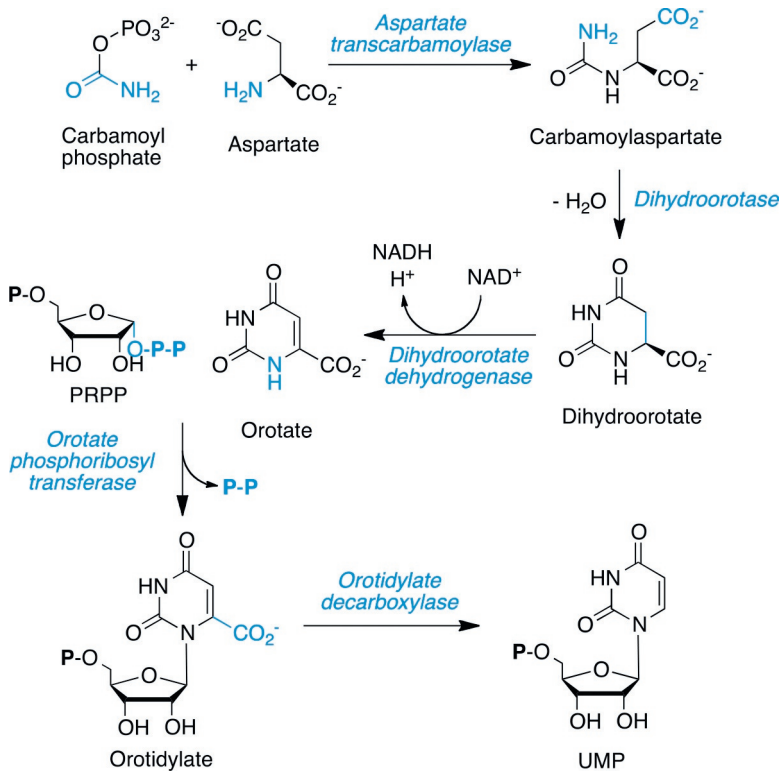

FIGURE 2.2

Biosynthesis of pyrimidine nucleotides.