an overarching question that must be considered as any compound moves into animal models and eventually human studies is where does a compound go when it enters the bloodstream? Stated in another manner, how is the compound distributed?

The distribution of a compound in the body refers to the reversible transfer of a drug between the various tissues, organs, cells, etc. of the body. Compound distribution can be the key to having a successful drug rather than a failed compound as highlighted by nitrofurantoin and desmethylprodine (MPPP). Macrobid® (nitrofurantoin) was originally introduced in 1957 as a treatment for urinary tract infections (Figure 6.18). It

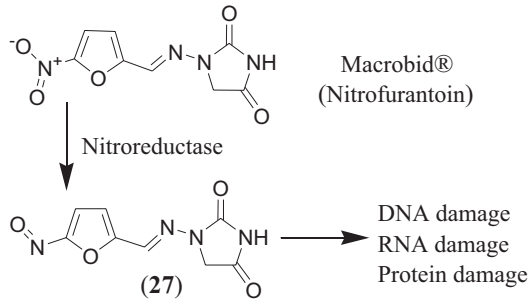

FIGURE 6.18 Macrobid® (nitrofurantoin) is useful for the treatment of urinary tract infections, despite its potential for conversion into (**27**) by nitroreductase. Its potential for toxicity via DNA damage, RNA damage, and protein damage is mitigated by its rapid excretion into the bladder.

has been highly successful, despite the fact that it contains an aryl nitro group which is usually associated with mutagenicity, teratogenicity, and carcinogenicity.[25a,b] The successful application of this drug is a direct result of its limited distribution in the body. Although it is capable of causing significant DNA, RNA, and protein damage, Nitrofurantoin is rapidly distributed to the bladder and excreted in the urine. This prevents any untoward effect on the body, and places the drug exactly where it needs to be in order to eliminate urinary tract infections.[26]

In a similar manner, but in the opposite sense, the failure of desmethylprodine, also known as MPPP, is in part a result of compound distribution (Figure 6.19). MPPP is an opioid analgesic originally brought to market by Hoffmann-La Roche in the 1940s, but is no longer used in clinical practice. Although MPPP itself is not dangerous, it is metabolized to another compound, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which crosses the blood–brain barrier. Once inside the brain, MPTP is absorbed by glial cells which convert it to 1-methyl-4-phenylpyridinium (MPP^+). This charged species is incapable of exiting the brain, is absorbed by the dopaminegic cells of the substantia nigra (the region of the brain that