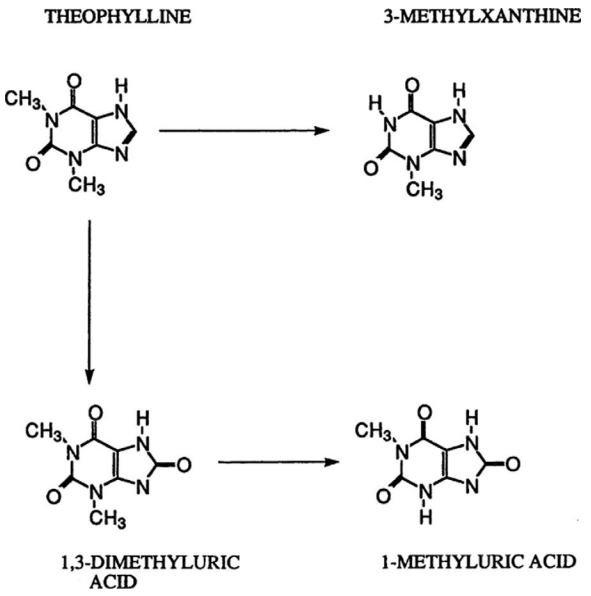

FIGURE 33.4 Pathways of theophylline metabolism.

or absence of food in the gastrointestinal tract. Using both human skin samples and its microsomes, Ademola et al. determined that theophylline was metabolized with the production of 1,3-dimethyl uric acid, 3-methyl uric acid, and 3-methylxanthine from the skin samples. These metabolites of theophylline are produced via cytochrome P450–dependent metabolism in the liver, and the authors proposed that a similar mechanism may occur in skin (Figure 33.4).

33.6 METABOLISM OF ENVIRONMENTAL XENOBIOTICS

An important consideration in this subject is the metabolism by the skin of compounds it is exposed to in the environment. The skin forms a barrier against our environment and is constantly exposed to compounds both natural and manmade. In this section, we address the effects of their metabolism.

33.6.1 Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are produced by the incomplete combustion of fossil fuels and other organic matter. Their potential role in human carcinogenesis is suggested by their presence in the environment and the carcinogenicity of their metabolites.

Cutaneous metabolism of PAH is capable of forming carcinogenic metabolites (see Ref. 17 for review). Studies with model compounds such as benzo[a]pyrene have demonstrated that cutaneous metabolism of PAHs can lead to the formation of phenols, quinones, dihydrodiols, and reactive diol epoxides. The diol epoxides are thought to be responsible for the carcinogenic effect, binding covalently to macromolecules. Covalent binding with DNA correlates well with the tumorigenicity of the metabolites of benzo[a]pyrone (18).

The PAHs are present in crude coal tar, which is extensively used in dermatological practice. Merk et al. (19) demonstrated that exposure of crude coal tar to the human hair follicle results in the induction of aromatic hydrocarbon hydroxylase (AHH), which is a cytochrome P450–dependent enzyme. This resulted in the production of benzo[a]pyrene derivatives that were shown to bind to DNA.