There are some safeguards in the body capable of capturing reactive metabolites before they cause damage, such as glutathione, a scavenger of electrophiles, but these systems are far from perfect and can be overwhelmed by candidate compounds, especially when cells are in a state of oxidative stress.

Alternatively, a compound or metabolite may be capable of forming an adduct with a biomolecule that will elicit an immune response. Compounds of this type are referred to as haptens. In the absence of a carrier protein, a hapten will not evoke an immune response, but once it is linked a suitable protein, the resulting adduct is no longer recognized by the body. Antibodies for the hapten–protein adduct are generated, and an immune response is launched targeting the "foreign" compound. The clinical manifestation of this type of response can range from a simple skin rash to anaphylaxis and death. Allergic reactions to β-lactam are a well-known example of the interaction of a hapten with normal proteins leading to an adverse reaction (Figure 8.5).[12]

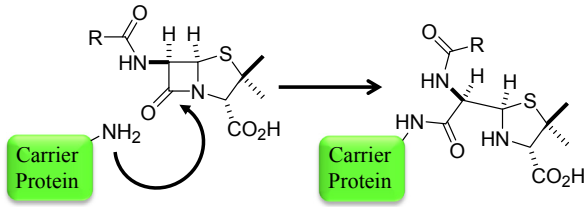

FIGURE 8.5 The reaction of β-lactam containing compounds with a protein is a well-known example of how a small molecule can act as a hapten and elicit an immune response. Nucleophilic functional groups on a protein (e.g., amines) can react with a β-lactam. The resulting hapten–protein adduct is not be recognized as "self" leading to an immune response.

Clearly, understanding the metabolism of a candidate compound can play a key role in minimizing the risk of safety and toxicity issues. Metabolic process, however, often produces multiple metabolites, and determining which compound is responsible for observed negative effects is often problematic. Preparation and testing of the proposed metabolite can provide insight into its potential role in safety and toxicity, but this can be a time and resource intensive process. Fortunately, a great deal of information is available regarding the metabolism of a wide range of functional groups and substructures that may initiate toxicity through the formation of reactive intermediates. Aryl nitro groups, for example, are well known for their propensity to undergo metabolic activation. Tasmar® (Tolcapone), an inhibitor of catechol-*O*-methyl transferase (COMT) useful for the Parkinson's disease, for example, is converted to a quinone imine that reacts with available nucleophiles (Figure 8.6(a)).[13] As a result, this