in CNS panels at contract research organizations that specialize in *in vitro* screening services such as EMD Millipore,[7] Perkin Elmer,[8] and Cerep.[9] The National Institute of Mental Health also provides *in vitro* screening services specifically focused on CNS targets through the Psychoactive Drug Screening Program at the University of North Carolina at Chapel Hill.[48]

At the *in vivo* stage, candidate compounds can be assessed for their impact on central nervous system using several of the animal models described in Chapter 7. The novel object recognition model,[49] the contextual fear conditioning model,[50] and the Morris water maze[51] are all capable of identifying compounds that have a deleterious effect on memory formation. Separately, compounds capable of acting as a sedative can be identified with the rotarod test.[52] Animals that are under the influence of a sedative are more likely to fall off of the rotating wheel than those that are not suffering from the lethargy produced by a sedative. These and other *in vivo* CNS safety and toxicology studies are, of course, significantly more resource intensive than their *in vitro* counterparts.

## IMMUNE SYSTEM MEDIATED SAFETY ISSUES

Safety and toxicity issues can also occur as a result of a candidate compound's interaction with the immune system or macromolecules that regulate the immune system. In some cases, an immune response is initiated as a result of the formation of covalent bond between a candidate compound and an otherwise normal biomolecule. Although neither the candidate compound, which is referred to in this context as a hapten (a small molecule that can elicit an immune response, but only when bound to a carrier protein), nor the carrier macromolecule are noticed by the immune system, the combination of the two creates a hapten-carrier adduct that is recognized by the immune system as foreign material. In response, the immune system generates antibodies and launches an allergic response. The severity of the response will increase with each exposure to the candidate compound and can be as severe as anaphylactic shock.[53] Penicillin allergy[12a,54] is a well-known example (Figure 8.22),

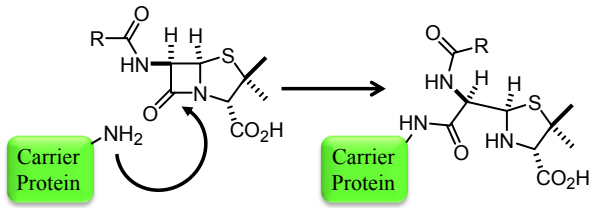


**FIGURE 8.22** The reaction of β-lactam containing compounds with a protein is a well-known example of how a small molecule can act as a hapten and elicit an immune response. Nucleophilic functional groups on a protein (e.g., amines) can react with a β-lactam. The resulting hapten–protein adduct may not be recognized as "self" leading to an immune response.