Monarch butterflies are a preeminent example of a toxin-sequestering animal, gaining protection against predators via cardenolides obtained from their milkweed host plants. Although cardenolide sequestration by monarchs has been studied in ecological, physiological, and phylogenetic contexts, relatively little research has surveyed genetic variation in the ability to sequester, nor has monarch sequestration been studied in relation to divergent host plant assemblages or variation in exposure to predation. Here, we use the monarch’s recent global range expansion to test hypotheses about how cardenolide sequestration evolves over relatively contemporary time scales. First, we test for whether sympatric monarch/milkweed combinations have a sequestration advantage by rearing six geographically disparate monarch populations on six associated milkweed host species and measuring sequestered cardenolides in 440 adult butterflies. Second, we use monarchs from Guam—an oceanic island where birds have been functionally extirpated for approximately 40 years—to test hypotheses about how exposure to avian predation affects cardenolide sequestration. We find little overall evidence for increased sequestration on sympatric hosts. However, one monarch population (Puerto Rico) shows strong support for cross-host tradeoffs in sequestration ability, primarily driven by limited sequestration of polar cardenolides from two temperate North American milkweeds (*Asclepias syriaca*and *A. speciosa*). Monarchs from Guam show some evidence for reduced cardenolide sequestration in both a cross-island comparison of wild-caught butterflies as well as population-level comparisons of greenhouse-reared butterflies. Our results suggest that there is substantial genetic variation in sequestration ability and that evolutionary history and contemporary species interactions may influence patterns of cardenolide sequestration.