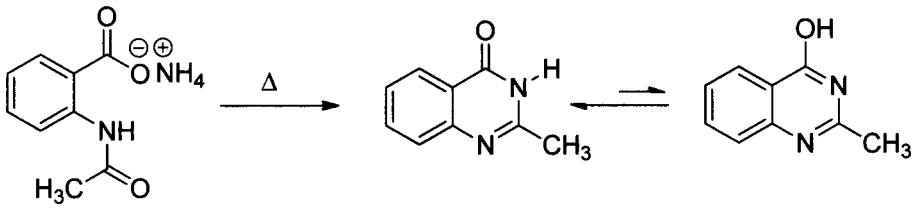
14.3 Quinazoline and Quinazolinone Synthesis

The Bischler and Niementowski syntheses are the most important methods for the synthesis of quinazolines and quinazolinones, with the latter and more well-known reaction being an improvement on the Bischler synthesis. Additional methods for the synthesis of quinazoline and quinazolinone ring systems involve various rearrangement reactions and metal-mediated processes. Examples of these reactions are illustrated below.

14.3.1 Bischler Reaction

The Bischler synthesis, first described in 1893,[15] involves the fusion of *N*-acylanthranilic acid and ammonia to generate the corresponding 2-substituted quinazolinone, which exists in equilibrium with the 4-hydroxy quinazoline tautomer. Bischler's original synthesis, shown below, involved direct conversion of ammonium-*N*-acetylanthranilate to the corresponding 2-alkyl-2,3,4-dihydro-4-quinazolinone under thermal conditions.



The mechanism of the Bischler synthesis is illustrated below. Fusion of ammonium-*N*-acetylanthranilate generates the diamide, which then undergoes cyclodehydration to form the corresponding quinazolinone. The quinazolinone then tautomerizes to the 4-hydroxyquinazoline.[16]