Disputed total synthesis of quinine by Woodward and Doering confirmed

January 31 2008

Drugs derived from cinchona bark, known as cinchona alkaloids, have been used in healing from ancient times. The most prominent representative of this group is quinine, a bitter substance contained in beverages such as tonic water and used in modern medicine to combat malaria.

As early as 1945, Robert Burns Woodward and William von Eggers Doering (Harvard University) described how to synthesize quinine in the laboratory. The last step of this “formal” total synthesis, a three-step reaction procedure previously described by Paul Rabe and Karl Kindler in 1918, has continued to be the subject of much controversy to this day.

Aaron C. Smith and Robert M. Williams at Colorado State University (USA) have now successfully reproduced the Rabe–Kindler protocol. As described in an *Angewandte Chemie* article dedicated to Doering on his 90th birthday, they repeated the entire procedure without employing any modern methods.

Had they done it or not? That has been the question for decades. Woodward and Doering published the synthesis of d-quinotoxine in 1944. Based on the conversion of d-quinotoxine into quinine described by Rabe and Kindler in 1918, they claimed to have derived the total synthesis of quinine, though they had not actually completed this last step themselves before publishing. Their “formal” total synthesis was strongly challenged and was even dismissed as a “myth” by Gilbert Stork (Columbia University) in 2001.

“Quinine and the cinchona bark alkaloids play an important role in modern medicine. It is thus amazing that no attempts to reproduce the Rabe–Kindler conversion of quinotoxine into quinine have been published,” marvels Williams. Smith and Williams reviewed the old publications, researched further references, and set themselves the task of repeating the procedure outlined by Rabe and Kindler—and with techniques available at the time. Initially, the yield of quinine they obtained was far too low.

The key turned out to be the aluminum powder used as a reducing agent in the last step. It must not be too fresh, instead it must be exposed to air for a while first to produce a small amount of aluminum oxide. This results in yields of quinine in agreement with those in the old publications.

“Analytically pure quinine can be isolated from this reaction by the selective crystallization of the corresponding tartrate salt, just as described by Rabe in 1939,” says Williams. “We have thus corroborated Rabe and Kindler’s 1918 publication. Woodward and Doering could theoretically also have followed this procedure in 1944.”

Citation: Robert M. Williams, Rabe Rest in Peace: Confirmation of the Rabe-Kindler Conversion of d-Quinotoxine to Quinine: Experimental Affirmation of the Woodward-Doering Formal Total Synthesis of Quinine, *Angewandte Chemie International Edition*, doi: 10.1002/anie.200705421

Source: Angewandte Chemie

quinine-woodward.html