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Quinine Revisited ... Again

Historical research helps untangle the complex mythology of quinine synthesis

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IF MOLECULES were mythical figures, quinine would be chemistry's Helen of Troy—the structure that launched a thousand research projects. Louis Pasteur, William Henry Perkin, Robert Burns Woodward, Gilbert Stork—quinine has bewitched chemistry's brightest lights for more than 150 years.

Bethany Halford/C&EN
Collector Seeman shows one of his photos of famous chemists.

Now, the antimalarial alkaloid has captured the imagination of chemical history researcher Jeffrey I. Seeman. By combing through old letters, research publications, and news clippings, Seeman has tried to unravel the so-called myth of the first total synthesis of quinine, reported by Woodward and William von Eggers Doering in 1944.

The fruit of his three-year effort, a 38-page paper published this month in *Angewandte Chemie,* reads like a novel, brimming over with passions and power struggles of the scientific enterprise (*Angew. Chem. Int. Ed.* **2007**, 46, 1378).

"To be honest, once I started to read this paper, I found it difficult to put it down," says Princeton University's Erik J. Sorensen. "There is a wealth of wonderful new information about a subject of great importance in organic chemistry. I had no idea the story was so interesting."

Seeman, an organic chemist and tobacco alkaloid expert, has spent 30 years documenting renowned organic chemists of the 20th century. He is probably best known for editing Profiles,

Pathways, and Dreams, a 20-volume series of autobiographies written by eminent chemists such as Carl Djerassi and Derek H. R. Barton, and has also produced a number of short films profiling chemical researchers (C&EN, July 28, 1997, page 34).

Visitors to Seeman's home get their first hint of his fascination with the human side of chemistry as soon as they enter his office. Photographs of eminent organic chemists, many of them autographed, surround the work space: Vladimir Prelog, Ernest L. Eliel, Woodward, Elias J. Corey, and many more. These are Seeman's heroes, watching over him as he works.

If anyone else owned the tidy house in suburban Richmond, Va., this large, sunlit space would probably be the formal dining room. But you don't have to spend much time with Seeman to figure out that he's not hung up on formalities. He'd rather entertain friends in the kitchen and give the grander room to the photographic pantheon of organic chemists.

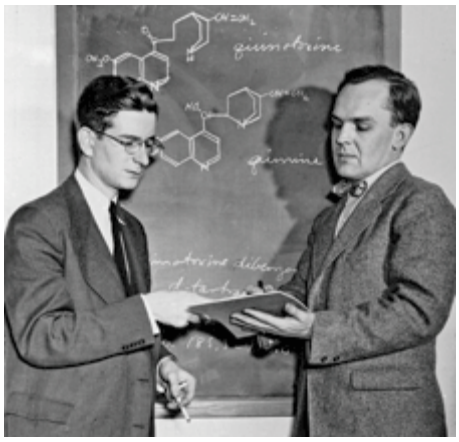

Fritz Goro
Reaction Doering (left) and Woodward re-create the quinine synthesis for the camera.

Seeman first fell under quinine's spell while poking around personal files of one of his heroes, the legendary Woodward, who won the 1965 Nobel Prize in Chemistry for "his outstanding achievements in the art of organic synthesis." Woodward began his long and distinguished career in the chemical construction of natural products, and also achieved worldwide fame, when he and Doering published their communication "The Total Synthesis of Quinine" (*J. Am. Chem. Soc.* **1944**, 66, 849).

THE ANNOUNCEMENT of the synthesis came at a time when the Allied forces fighting in WWII had been cut off from cinchona trees in Java, their sole source of quinine. Woodward, then an assistant professor at Harvard University, and Doering were hailed as war heroes in news reports. "Synthetic Quinine Produced, Ending Century Search," declared the front page of the *New York Times* on May 4, 1944.

Chemists working today would call Woodward and Doering's report a formal synthesis rather than a total synthesis. That's because they prepared quinotoxine, a molecule that German chemists Paul Rabe and Karl Kindler had used to reconstruct quinine back in 1918 (*Ber. Dtsch. Chem. Ges.* **1918**, 51, 466).

Formal syntheses are still quite common in natural product constructions, notes Steven M. Weinreb, a synthetic organic chemist at Pennsylvania State University. "I think most of us have done a formal synthesis at some point or another. Often it's just not worth the trouble to take your material through a route that a reputable chemist has already taken," he says.



Fritz Goro
Chalk Talk Woodward (left) and Doering discuss the synthetic scheme for quinine.

According to Seeman, the chemical community generally credited Woodward and Doering with the first total synthesis of quinine until 2001. That's when another intellectual giant of organic chemistry, Columbia University's Stork, reported the first stereoselective total synthesis of quinine (*J. Am. Chem. Soc.* **2001**, 123, 3239). C&EN covered the work (May 7, 2001, pages 5 and 54) and highlighted Stork in an editorial titled "Setting the Record Straight."

In that coverage, and in a letter to the editor (C&EN, Sept. 25, 2000, page 8), Stork pointed out that Woodward and Doering had completed a formal synthesis, rather than a total synthesis. That they actually made quinine in 1944 had become a "widely believed myth," Stork said. Furthermore, he noted, Rabe and Kindler's synthesis has scant experimental details and might not be reproducible.


Courtesy of Gilbert Stork
Bright Eyed Stork as a graduate student, ca. 1944.

Tease out the threads of Stork's argument, and two similar but subtly different quinine myths emerge. The first is that Woodward and Doering synthesized quinine. The second is that the duo completed the first total synthesis of quinine.

Contrary to the headlines and breathless press reports, Woodward and Doering did not make quinine. Any assertion that they did likely stems from press reports of the time. There was certainly a lot of media hype, and the distinction between synthesizing quinine and completing a formal synthesis of that alkaloid seems to have been lost on the journalists.

Even C&EN got the story wrong, reporting that "Woodward and Doering first combined and recombined synthetic substances until they had synthesized quinotoxine and then retraced Rabe's steps and prepared quinine" (C&EN, May 10, 1944, page 730).

To their credit, most journalists did point out that the synthesis was complex and costly and would be unlikely to quell the Allies' quinine woes anytime soon. To this day, no chemist's quinine synthesis has been able to compete with that of the cinchona tree. It's still cheaper and easier to

extract the alkaloid from its natural source.

SEEMAN STARTED to question Stork's second assertion—that because Rabe's work had never been reproduced, Woodward and Doering had not completed a synthesis of quinine—when he found an old letter in Woodward's quinine files. The note, handwritten in German, was signed by Rabe and dated Feb. 19, 1948. "I studied your first paper with admiration," Rabe, nearly 80 at the time, wrote to Woodward. "I am delighted that I have lived to see the total synthesis of quinine and I send you my sincere congratulation."


Courtesy of Wittko Francke
Rabe

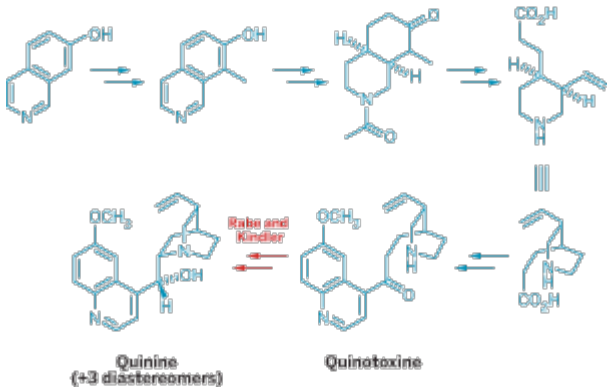
Woodward replied to Rabe on March 16, 1948. "I am sure you can imagine that it was for me a very great pleasure to receive a message from the hand of the chemist who has played the greatest role in the study of the cinchona alkaloids. Your kind letter made me feel that I had established contact with a great tradition." Woodward also sent a care package to Rabe "in token of my respect for and gratitude to one whose work formed the necessary basis upon which I was able to build." That correspondence convinced Seeman that there was more to this story than just a "widely believed myth." As his nuanced *Angewandte Chemie* paper details, there is much, much more.

Ultimately, Seeman concludes that the total synthesis comprising the Woodward-Doering and Rabe-Kindler reports is a valid achievement, not a myth.

"The more I thought about this problem, the more I realized that it was rich in scientific and philosophical issues that are extremely pertinent today," Seeman says, reflecting on his work. "Any explicit claim or hypothesis that Woodward and Doering did not complete a total synthesis is an implicit attack on Rabe and Kindler." To cast doubt upon those final steps, he explains, implies either that Rabe and Kindler were frauds or they were experimental fools. "That's of great seriousness."

Doering, now an emeritus professor at Harvard, is less grave on the matter these days. "I suppose I find the whole thing amusing," he says. "We relied on the work of one of Germany's best organic chemists to complete the conversion. There was no earthly reason to doubt the validity of Rabe's work." Doering adds, "I never felt in need of vindication. The fellow that needs to be vindicated is our old pal Rabe."

"Rabe certainly did what he said, and Woodward certainly was convinced Rabe was right," concludes Roy A. Olofson, a professor emeritus at Penn State. "Should Woodward and Doering have spent extra months optimizing conditions for those last steps for which only cursory experimental directions were available? If this had not been wartime and Germany the enemy, he would probably have written Rabe to get better directions. At that time, when American chemistry was totally mobilized for the war and there was great pressure to get on, it was rational to leave the rest to the potential commercial process optimizers.



Quinine Quest The final steps in Woodward and Doering's formal synthesis of quinine references Rabe and Kindler's 1918 work.

"I wish the present chemistry populace understood that time better—when American chemistry was at the center of the war effort and totally devoted to it," Olofson continues. "At Penn State, everyone worked at least 60 hours a week without vacations. Our dean, Frank Whitmore, who was one of the key coordinators of organic chemistry war research, ultimately died from the overwork and stress. The announcement of his 'heroic' death was a cover of C&E News."

Stork agrees that historical context is important for understanding the whole sticky story of quinine synthesis, but he stands by his assertion. "The whole package of synthetic quinine that was presented to the public was a myth," he says.

He makes a point of saying that this doesn't make Woodward and Doering's synthesis of quinotoxine any less elegant or impressive. "What they did was superb," he says, adding that the work established the synthetic brilliance of a then largely unknown Woodward. But in terms of completing a total synthesis of quinine, he says, "it's a lawyer's synthesis."

Stork doesn't think Rabe and Kindler were fraudulent or incompetent in their chemistry. He simply thinks it's a matter of reproducibility. "I personally believe that if you really know what you're doing, probably you'd get quinine, in maybe 1% yield, from repeating Rabe's steps," he says.

This, it seems, is the knot in the tangle of what is and isn't a myth. For even a 1% yield, says Penn State's Weinreb, the synthesis is valid. "It may be difficult to reproduce, but whether Rabe made it well or not doesn't matter provided he got to the end of the synthesis."

But Princeton's Sorensen adds, "After reading the Seeman article, I don't think I would rely on a formal synthesis. I would reproduce what was reported," he says. "I think any scientist would want to avoid any suspicion that what they did wasn't reproducible."


Fritz Goro
Repose Woodward (left) and Doering contemplate chemistry.

"If the paper were submitted today, it's likely that an editor would require Woodward and Doering to repeat Rabe and Kindler's work or to back off on their claim of a total synthesis," Seeman notes.

PROBABLY the most stunning gem that Seeman unearthed in Woodward's files is a letter written in 1944 by a 22-year-old Stork, then a graduate student at the University of Wisconsin. In that letter, accompanied by a handwritten synthetic scheme, Stork requests that Woodward fill in the yields and conditions for each transformation. In closing, he asks, "Would you also tell me whether Rabe's conversion of quinotoxine into quinine has been repeated by you in your present work?"

In that last sentence, Seeman explains, Stork highlights the most serious deficiency in the Woodward-Doering paper. "It's an early example of Gilbert's brilliance as a chemist," Seeman says.

Woodward did not write back to Stork, but he did provide the requested details of yields and conditions when the young student called him up. "I remember his first words were, 'Do you have a pencil?' " Stork remarks. Stork thinks that phone call is what landed him his first job as an instructor at Harvard.

It's these personal details that Seeman weaves into the paper that truly bring this era of the chemical enterprise to life. There's Rabe and the hardships of living in Germany after two world wars. There's Woodward, Doering, and Stork long before the chemical world knew who they were: young, ambitious, and out to make their marks on the world.

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