History of Chemistry

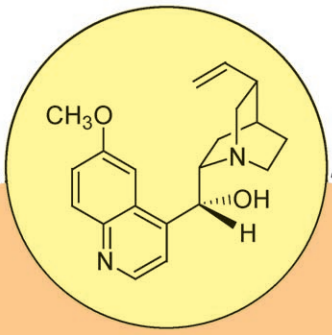
DOI: 10.1002/anie.200601551

The Woodward–Doering/Rabe–Kindler Total Synthesis of Quinine: Setting the Record Straight

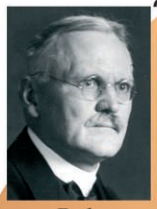
*Jeffrey I. Seeman**

Keywords:
alkaloids · heterocycles · history of science · quinine · total synthesis

Dedicated to Professors Otto Theodor Benfey, Ernest L. Eliel, and Rolf Huisgen.



1918



Rabe

48. Paul Rabe und Karl Kindler: Über die partielle Synthese des Chinins. Zur Kenntnis der China-Alkaloide XIX.

[Vorläufige Mitteilung aus dem Chem. Staatslaboratorium zu Hamburg.]

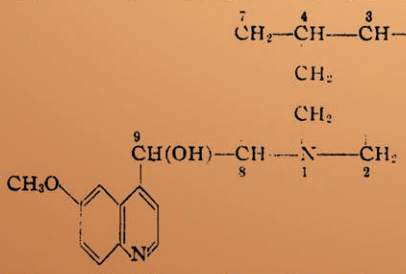
Kindler

The Total Synthesis of Quinine

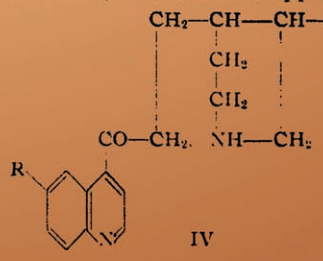
BY R. B. WOODWARD AND W. E. DOERING

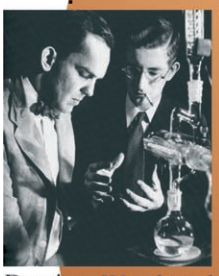
1945

The culmination of the structural investigations on quinine in the proposal of the correct structure (I) in 1908[1] may be considered the point at which rational efforts toward total synthesis could be initiated.[2] These efforts first took the form of an attack on the synthesis of substances containing the quinoline moiety of the quinine molecule. First success was achieved independently by Pictet and Misner,[3a] and by Kaufmann and Peyer,[3b] in 1912 with the synthesis of quininic acid



had shown[6] in 1853 that the cinchona alkaloids, on heating with tartaric or sulfuric acid, were transformed into isomeric substances, *e. g.*, cinchotoxine (cinchonicine) and quinotoxine[7] (quinicine) from cinchonine and quinine, respectively. Subsequent investigations by other workers resulted in the verification of these early results,[8] in improvements in the mode of effecting the isomerization,[9] and in the successful formulation[10] of quinotoxine as (IV, R = OCH_3) and cinchotoxine as (IV, R = H). It was now apparent that these





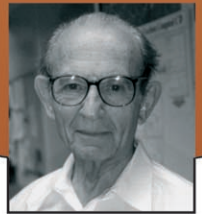
Doering Woodward

2001

The First Stereoselective Total Synthesis of Quinine

Gilbert Stork,* Deqiang Niu, A. Fujimoto,† Emil R. Koft,‡ James M. Balkovec,§ James R. Tata,§ and Gregory R. Dake⊥

Contribution from the Department of Chemistry, Columbia University, New York, New York



Stork

In 1918, Paul Rabe and Karl Kindler reported the three-step conversion of d-quinotoxine into quinine. In 1944 Robert B. Woodward and William von Eggers Doering reported the total synthesis of homomeroquinene and d-quinotoxine from 7-hydroxyisoquinoline. Based on the transformations by Rabe and Kindler, Woodward and Doering asserted the "Total Synthesis of Quinine" (the title of their 1944 and 1945 papers). In 2000 and 2001, Gilbert Stork concluded that the claim by Woodward and Doering is a "myth" because they had synthesized only homomeroquinene and d-quinotoxine; no synthetic quinine had been made in Cambridge. In fact, Rabe and Kindler never published the experimental details of their conversion of d-quinotoxine into quinine. This Review presents the results of a detailed examination of the synthesis of cinchona alkaloids, and previously unpublished material combined with unpublished material and numerous interviews give insight into the lives of the personalities in this nearly 100-year saga.

From the Contents

1. The Context

In the *Chemical & Engineering News* editorial of May 7, 2001 entitled, "Setting the Record Straight," the Editor-in-Chief wrote:

> "Many people believe that Harvard University chemists Robert B. Woodward and William von Eggers Doering achieved the synthesis of quinine in 1944. Aided and abetted by the *New York Times* and *Science News Letter*, this idea became part of the literature and has been repeated in many biographies, exhibitions, and articles. In fact, what the Harvard scientists synthesized was an intermediate many steps away from quinine."[1]

This editorial then appropriately praised "The First Stereoselective Total Synthesis of Quinine," a remarkable feat of synthetic organic chemistry just published[2] in 2001 by Gilbert Stork:

> "… a riveting tale of one man's 55-year quest to carry out a particularly difficult and challenging synthesis. That man is Gilbert Stork … a towering figure in synthetic organic chemistry. Stork is legendary in the chemical world. Now, at almost 80, he is still a formidable researcher, tackling problems that would daunt a person half his age …"[1]

Gilbert Stork (Figure 1; born December 31, 1921) first became actively interested in the synthesis of quinine as an undergraduate in 1940. In this same issue of *C&EN* as the above referenced editorial, a detailed news article entitled "Quinine Revisited" by Maureen Rouhi appeared.[3] According to the article, "Stork refers to [the] 'quasiuniversal impression'"[3] that Woodward and Doering achieved the total synthesis of quinine (Scheme 1). In fact, in 2000, some months prior to the publication of his total synthesis of quinine,[2] Stork characterized the impression of the achievement of the synthesis of quinine by Woodward and Doering as a "widely believed myth."[4]

> "According to Stork, the myth began with the title of a paper published in 1944 [*J. Am. Chem. Soc.* **1944**, *66*, 849]: 'The Total Synthesis of Quinine.' A full paper with the exact same title was published the following year [*J. Am. Chem. Soc.* **1945**, *67*, 860]. In these two papers, Woodward and Doering describe primarily the synthesis of *cis*-3-vinyl-4-piperidinopropionic acid. 'This was,' Stork says, 'an impressive achievement. But it wasn't quinine.'"[3]

The publications by Woodward and Doering[5,6] clearly indicated that they had performed what in today's parlance is termed a "formal" total synthesis of quinine. Woodward and Doering (Figure 2) had actually synthesized racemic homo-

[*] Dr. J. I. Seeman
SaddlePoint Frontiers
12001 Bollingbrook Place, Richmond, VA 23236-3218 (USA)
E-mail: jiseeman@yahoo.com

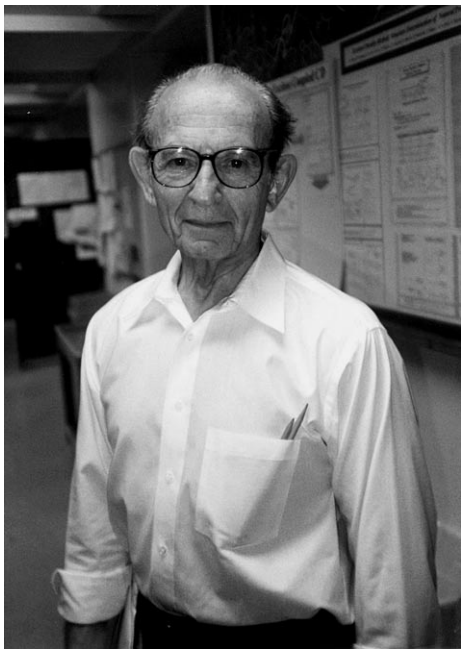


Figure 1. Gilbert Stork at Columbia University in 1996.

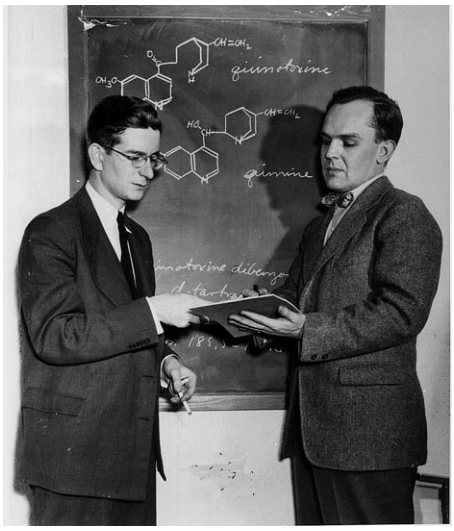
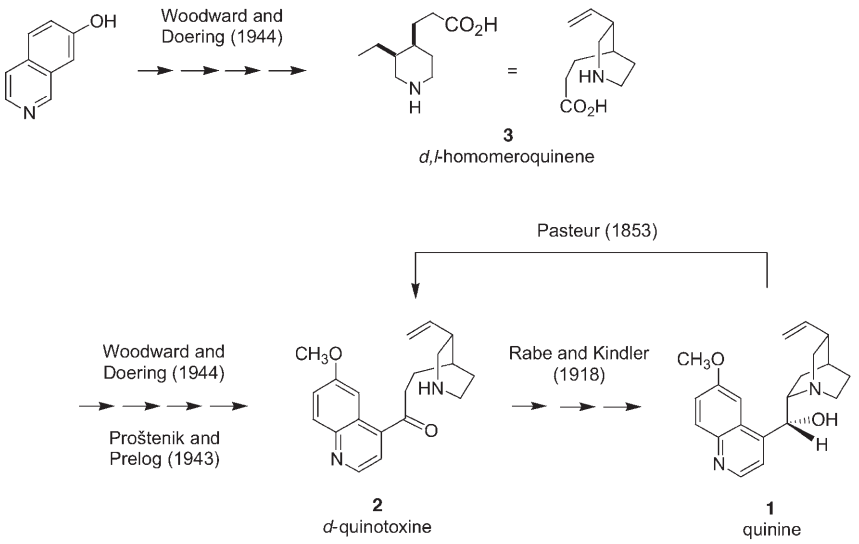


Figure 2. R. B. Woodward and William Doering at the blackboard at Harvard in May 1944. Reproduced with permission from the Fritz Goro archives.



Scheme 1. The Woodward–Doering/Rabe–Kindler total synthesis of quinine.[5–7]

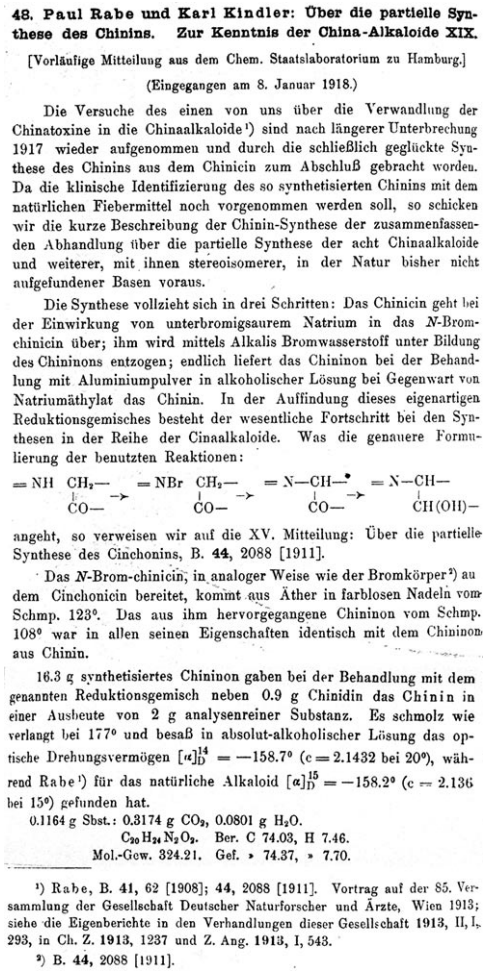
meroquinene (**3**) and resolved and isolated *d*-quinotoxine (**2**; Scheme 1),[5,6] they had not obtained synthetic quinine in Cambridge. Twenty six years earlier, in 1918, Paul Rabe (August 24, 1869–August 28, 1952) and Karl Kindler (September 7, 1881–September 29, 1967) had reported the transformation of *d*-quinotoxine to quinine (Scheme 2 and Figure 3).[7] Of historical note and of significant relevance to this story, in 1853 Louis Pasteur (December 27, 1822–September 28, 1895) heated quinine with acid and obtained *d*-quinotoxine (Scheme 1).[8] As Woodward and Doering stated:

> "In view of the established conversion of quinotoxine to quinine,[7] with the synthesis of quinotoxine [in this publication] the total synthesis of quinine was complete."[6]

Thus, taken together (Scheme 1), the total synthesis of *d*-quinotoxine by Woodward and Doering in 1944[5] and the conversion of *d*-quinotoxine into quinine by Rabe and Kindler in 1918[7] constitute the Woodward–Doering/Rabe–Kindler total synthesis of quinine. This order of names is used to reflect chemical chronology, in that the transformations by Woodward and Doering are sequentially before those of Rabe and Kindler.

According to Rabe and Kindler, their 1918 paper was a "preliminary notice" or communication in today's parlance. In 1932, Rabe said of his 1918 publication that it "ist noch nicht eingehend beschrieben worden" ("is not described yet in detail").[9] Rabe and Kindler did not publish either the "clinical identification" nor the full experimental details of their 1918 "preliminary notice", although Rabe did publish

Jeffrey I. Seeman received his PhD from the University of California, Berkeley. After a two-year staff fellowship at the National Institutes of Health, he joined Philip Morris in Richmond, Virginia where, during a 27-year career, he published over 100 papers and patents on tobacco alkaloids and physical organic chemistry. He initiated and was editor of the 20-volume series of autobiographies of eminent chemists, Profiles, Pathways and Dreams. He currently serves as Chair of the Division of History of Chemistry of the American Chemical Society. He is a consultant and an independent video producer.



48. Paul Rabe und Karl Kindler: Über die partielle Synthese des Chinins. Zur Kenntnis der China-Alkaloide XIX.

[Vorläufige Mitteilung aus dem Chem. Staatslaboratorium zu Hamburg.]

(Eingegangen am 8. Januar 1918.)

Die Versuche des einen von uns über die Verwandlung der Chinatoxine in die Chinaalkaloide[1]) sind nach längerer Unterbrechung 1917 wieder aufgenommen und durch die schließlich geglückte Synthese des Chinins aus dem Chinicin zum Abschluß gebracht worden. Da die klinische Identifizierung des so synthetisierten Chinins mit dem natürlichen Fiebermittel noch vorgenommen werden soll, so schicken wir die kurze Beschreibung der Chinin-Synthese der zusammenfassenden Abhandlung über die partielle Synthese der acht Chinaalkaloide und weiterer, mit ihnen stereoisomerer, in der Natur bisher nicht aufgefundener Basen voraus.

Die Synthese vollzieht sich in drei Schritten: Das Chinicin geht bei der Einwirkung von unterbromigsaurem Natrium in das *N*-Bromchinicin über; ihm wird mittels Alkalis Bromwasserstoff unter Bildung des Chininons entzogen; endlich liefert das Chininon bei der Behandlung mit Aluminiumpulver in alkoholischer Lösung bei Gegenwart von Natriumäthylat das Chinin. In der Auffindung dieses eigenartigen Reduktionsgemisches besteht der wesentliche Fortschritt bei den Synthesen in der Reihe der Cinaalkaloide. Was die genauere Formulierung der benutzten Reaktionen:

$$=NH \;\; \underset{\underset{CO-}{|}}{CH_2-} \;\rightarrow\; =NBr \;\; \underset{\underset{CO-}{|}}{CH_2-} \;\rightarrow\; =N-\overset{\bullet}{C}H- \;\; \underset{\underset{CO-}{|}}{} \;\rightarrow\; =N-CH- \;\; \underset{\underset{CH(OH)-}{|}}{}$$

angeht, so verweisen wir auf die XV. Mitteilung: Über die partielle Synthese des Cinchonins, B. **44**, 2088 [1911].

Das *N*-Brom-chinicin, in analoger Weise wie der Bromkörper[2]) aus dem Cinchonicin bereitet, kommt aus Äther in farblosen Nadeln vom Schmp. 123°. Das aus ihm hervorgegangene Chininon vom Schmp. 108° war in allen seinen Eigenschaften identisch mit dem Chininon aus Chinin.

16.3 g synthetisiertes Chininon gaben bei der Behandlung mit dem genannten Reduktionsgemisch neben 0.9 g Chinidin das Chinin in einer Ausbeute von 2 g analysenreiner Substanz. Es schmolz wie verlangt bei 177° und besaß in absolut-alkoholischer Lösung das optische Drehungsvermögen $[\alpha]_D^{14} = -158.7°$ ($c = 2.1432$ bei 20°), während Rabe[1]) für das natürliche Alkaloid $[\alpha]_D^{15} = -158.2°$ ($c = 2.136$ bei 15°) gefunden hat.

0.1164 g Sbst.: 0.3174 g CO_2, 0.0801 g H_2O.

$C_{20}H_{24}N_2O_2$. Ber. C 74.03, H 7.46.
Mol.-Gew. 324.21. Gef. » 74.37, » 7.70.

[1]) Rabe, B. **41**, 62 [1908]; **44**, 2088 [1911]. Vortrag auf der 85. Versammlung der Gesellschaft Deutscher Naturforscher und Ärzte, Wien 1913; siehe die Eigenberichte in den Verhandlungen dieser Gesellschaft **1913**, II, I, 293, in Ch. Z. **1913**, 1237 und Z. Ang. **1913**, I, 543.

[2]) B. **44**, 2088 [1911].

Figure 3. P. Rabe, K. Kindler, *Ber. Deutsch. Chem. Ges.* **1918**, *51*, 466–467 (see Box 1 for translation by O. T. Benfey).

Box 1 (see Figure 3).

48. Paul Rabe and Karl Kindler: Partial Synthesis of Quinine. The Cinchona Alkaloids XIX

[Preliminary notice from the Chemische Staatslaboratorium, Hamburg.]

(Received 8 January 1918)

The studies by one of us of the conversion of cinchonatoxines into the cinchona alkaloids[1]) were resumed in 1917 after a long break. They were finally brought to a successful conclusion through the successful synthesis of quinine from quinotoxine. Since the clinical identification of the thus synthesized quinine with the natural antipyretic has yet to be carried out, we are submitting this brief description of the quinine synthesis prior to the comprehensive paper on the partial synthesis of the eight cinchona alkaloids, together with their stereoisomeric bases that have not so far been found in nature.

The synthesis proceeds in three stages: quinotoxine when treated with sodium hypobromite is converted into *N*-bromquinotoxine; by use of alkali, hydrogen bromide is removed and quininone is formed; finally the quininone when treated with aluminum powder in alcohol in the presence of sodium ethoxide yields quinine. The use of this unusual reducing mixture represents the real advance in the synthesis of the series of cinchona alkaloids. Regarding the more detailed formulation of the reactions we have used:

[see Figure 3 for structural formulas]

we refer to paper XV: The partial synthesis of cinchonine. *Ber.* **44**, 2088 [1911].

The *N*-bromquinotoxine, prepared in the same way as the bromo compound obtained from cinchotoxine,[2]) crystallizes from ether as colorless needles with m.p. 123°. The quininone obtained from it with m.p. 108° is in all respects identical to the quininone obtained from quinine.

16.3 g synthetic quininone when treated with the aforementioned reducing mixture yielded, besides 0.9 g quinidine, 2 g of analytically pure quinine. Quinine melted as required at 177° and had an optical rotation in absolute alcohol of $[\alpha]_D^{14} = 158.7°$ ($c = 2.1432$ at 20 °C) while Rabe[1]) for the natural alkaloid had found $[\alpha]_D^{15} = 158.2°$ ($c = 2.1362$ at 15 °C).

Sample 0.1164 g: 0.3174 g CO_2, 0.0801 g H_2O

$C_{20}H_{24}N_2O_2$. Observed C 74.03, H 7.46.
Mol. Wt. 324.21 Calculated C 74.37, H 7.70.

[1]) Rabe, Ber. **41**, 62 [1908]; **44**, 2088 [1911]. Lecture at the 85th Meeting of the Gesellschaft Deutscher Naturforscher und Ärzte (Society of German Scientists and Physicians), Vienna 1913; see the reports in the Proceedings of this Society **1913**, II, I, 293; Ch. Z. **1913**, 1237, and Zeitschrift für angewandte Chemie **1913**, I, 543.[2]) Ber. **44**, 2088 [1911].

experimental details of the same transformations of other cinchona alkaloids related to quinine.[9,10] The lack of direct and complete experimental information has been the basis for the current recent, public and widely held conclusion that the claim of a total synthesis of quinine by Woodward and Doering is, in fact, not complete[2,11–15] and a myth.[2–4] As stated by Stork:

"The problem is that Rabe's minuscule description included no experimental details, except for a vague reference to work done with a different alkaloid."[4]

Furthermore, as reported in the *C&EN* news article:

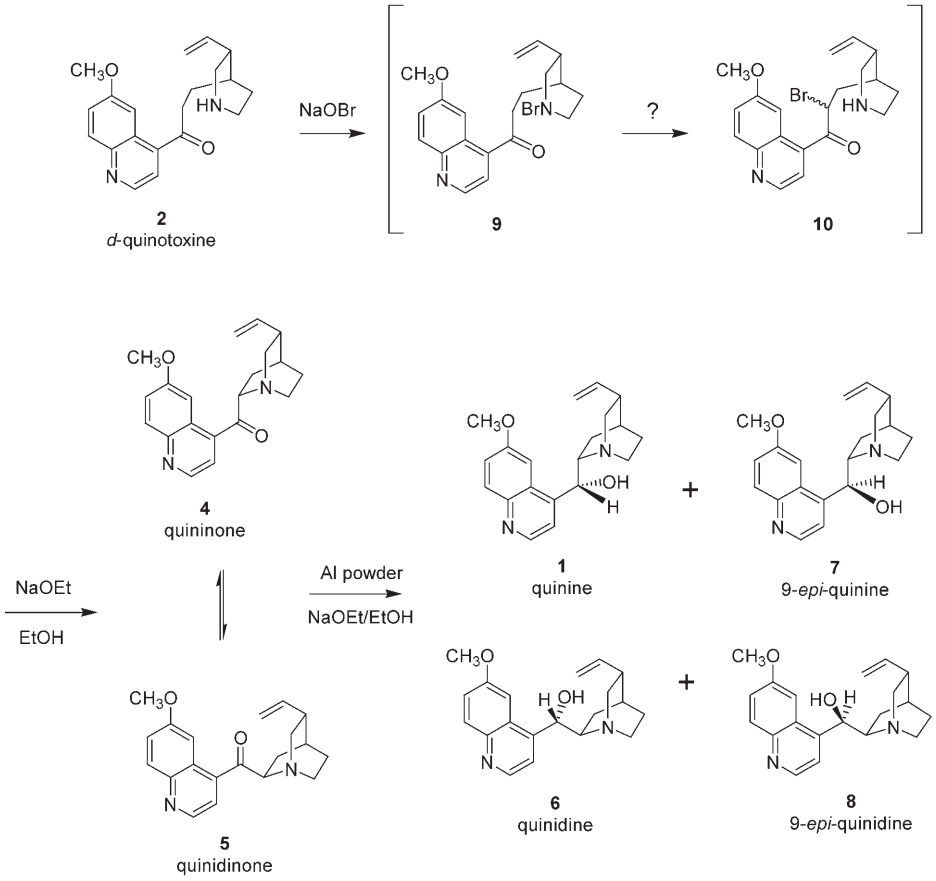
"The literature shows that those accolades [to Woodward and Doering] were 'in part based on wishful thinking,' Stork says, … The final steps that Woodward and Doering assumed would take that intermediate to quinine likely would not have worked had they tried them."[3]

Today there is a new quasiuniversal impression that Woodward and Doering in fact failed to complete the (formal) total synthesis of quinine. As demonstrated in this Review, one myth has been replaced by another. On the basis of a number of pieces of newly uncovered information reported herein, I conclude that Rabe and Kindler did convert *d*-quinotoxine into quinine in 1918.[7] There has never been any question that Woodward and Doering completed a total synthesis of *dl*-homomeroquinene and *d*-quinotoxine in 1944. I therefore conclude that the Woodward–Doering/Rabe–Kindler claim of the total synthesis of quinine is valid. The overriding goal of this historical review is to set the record straight.[*]

2. Introduction

QUININE! This single-word first-sentence construction is borrowed from the style of one of the greatest chemists ever

[*] Note: Throughout this Review, the now-obsolete[16] *dl* nomenclature is retained rather than (±) or *rac*, as well as *d*- for (+)- or dextrorotatory, in keeping with the historical context of the subject.



Scheme 2. Details of the conversion of *d*-quinotoxine into quinine and its isomers **6**–**8** by Rabe and Kindler.[7,77] In 1918 quinine was isolated and identified; **6**–**8** as well as additional quantities of quinine were isolated and identified in 1939 from the reaction residues from 1918. The intermediacy of the α-bromoketone **9** has not been established but suggested based on the failure of analogous intermediates to react with methyl iodide. Sodium ethoxide causes epimerization about C8 of the quininone/quinidinone mixture, possibly isomerization of the bromoketones **9** and **10** as suggested by Gutzwiller and Uskoković[119] as well as Nicolaou and Snyder,[15] and cyclization.

to have lived, Robert Burns Woodward (Figure 4; April 10, 1917–July 8, 1979), to honor both the man and this natural product. Quinine has remarkable antimalarial properties, and has outlasted modern synthetic therapeutic agents which have, one by one, fallen to drug resistance. "The Total Synthesis of Quinine" was proclaimed by Woodward and William E. Doering (born June 22, 1917) in a one-page communication in 1944[5] followed by a full paper in 1945.[6] This announcement was the first of many Woodward total syntheses.[17–19]

Nearly 20 years later, Woodward et al. would herald the total synthesis of another alkaloid natural product by exclaiming, "STRYCHNINE!" as the first sentence of that publication.[20] Of course, Woodward could have equally well proclaimed, at various times in his splendid career, "CHOLESTEROL!", "RESERPINE!", "CHLOROPHYLL!", "CEPHALOSPORIN C!", and "VITAMIN B_{12}!" Who else but Woodward had both the courage and the right to such acts of public display of scientific plumage? Who else would be carried in celebratory fashion in a sedan chair by his own students (Figure 4)?[19] Who else would lecture for hours into the evening, ending only when the entire blackboard was precisely filled with his perfectly drawn, multicolored structures, without erasures?

As stated by Albert Eschenmoser (born August 5, 1925), the eminent chemist, philosophically oriented scholar, and collaborator with Woodward on the total synthesis of vitamin B_{12}:

> "What he did was to put up one masterpiece after the other, masterpieces that were universally recognized as such by his fellow chemists, achievements that were chemically inspiring but also captivated the young."[21]

Figure 4. Birthday celebration: Woodward being carried in a sedan chair by members of his research group at Harvard, April 10, 1978. The photograph is reproduced with permission from Anton Fliri.

Woodward was the man against whom the greatest chemists of his day measured themselves and their research. I remember a remarkable event subsequent to giving a lecture on the history of chemistry at the University of Wisconsin at Madison. One of the staff, with pride, ran to show me a glass container—preserved for decades—containing cigarette butts collected and saved from the great man. One of the most remarkable salutes to Woodward appeared in a 1982 editorial in the journal *Accounts of Chemical Research* which discussed

> "… the leaders of the respective fields of chemistry. (In my own field, these are sometimes irreverently called the Cardinals; the late R. B. Woodward was the Pope.)"[22]

For their total synthesis of quinine, which was announced during World War II, Woodward and Doering were hailed as

war heroes, and youthful war heroes at that. When their experimental work was completed, Woodward was 27 years and one day old,[19] Doering only 26. The newspaper and magazine accounts were highly exuberant. For the next 60 years, popular encyclopedias as well as professional chemistry reviews and books heralded the total synthesis of quinine by Woodward and Doering.[2,12,19] According to Niles Trammell, President of the National Broadcasting Company, Woodward and Doering was celebrated on radio in a broadcast "which originated in the studios of our key station WEAF in New York [and] was also heard from coast to coast over the NBC network"[23] on May 8, 1944. According to the script, Robert St. John reported:

> "I have an exciting story for you, today … a story with war as its background … but a story about the saving of lives, rather than the taking of lives!!! …
>
> "The Polaroid Corporation was interested in quinine, because they used quinine in manufacturing light-polarizing material. And so they set Bob Woodward to work, trying to create synthetic quinine … Woodward chose as his collaborator on the project 26-year-old Bill Doering … These two mere boys set to work, with common chemicals, and just a few days ago they were proudly able to announce that they had succeeded, where generations of great scientists had failed!! They had succeeded in creating synthetic quinine!! A substance which may snatch whole hospitals' full of malaria-ridden soldiers in Pacific jungles out of the shadow of death!!! Bob Woodward, 27! Bill Doering, 26! Mere boys! I wish you could meet them, face to face!"[24]

Is the Woodward–Doering/Rabe–Kindler total synthesis of quinine a "myth"?

I wanted to know the answer to this most interesting controversy involving a famous natural product and important therapeutic drug, quinine. Perhaps the earliest attempted synthesis of quinine[12,15] resulted in the totally unintended yet remarkably successful synthesis of mauve in 1856 by William Henry Perkin (March 12, 1838–July 14, 1907) and the beginning of the chemical industry.[25,26] In the 19th Century, a number of other eminent scientists worked on quinine (for example, Liebig, Skraup, and, as mentioned earlier, Pasteur). Also, the "quinine myth" brings together several preeminent chemists who published classic research in organic chemistry, including Woodward, Doering, Rabe, Kindler, and Vladimir Prelog (July 23, 1906–January 7, 1998), as well as a distinguished and beloved chemist who described the 1944 claim of a total synthesis of quinine as a "myth" and who published his own "First Stereoselective Total Synthesis of Quinine" in 2001,[2] namely Gilbert Stork. As a consequence of Stork's recent statements,[2,4,11] the organic chemical community reversed its previously widely held opinion from praise to rejection. The scientific media, in particular *Chemical & Engineering News*,[1,3] added to the momentum and certification of rejection.

My own interest in quinine began in 2001 with my production of a video documentary on antimalarial drugs for the Johns Hopkins School of Public Health. About 20 years ago, my interest in the history and sociology of chemistry emerged, first with an article on the Curtin–Hammett principle in *Chemical Reviews* that contained a historical section.[27] I then originated and edited a series of 20 autobiographies of eminent organic chemists.[28–30] The *Profiles, Pathways and Dreams* series immersed me firmly into the world of the elite scholars of our profession. As I continued my own research that focused on tobacco plant alkaloids,[31–36] the coalescence and focus on quinine and Woodward came about quite naturally.

When I started my inquiries, I could not have imagined the most fascinating detective investigation that was waiting. The paths I followed to decipher this riddle stretched around the world and into the lives of chemists from a hundred years ago. Amazing finds were ripe for discovery in Woodward's files, carefully and safely preserved in the Harvard University archives. Within those files are papers from the quinine research, unknown—or long thought to be lost—by one of the key participants whose office is still only minutes away, Bill Doering. Bit by bit, piece by piece, after almost three years, the puzzle became whole and the understanding became clear.

My goal in this Review is to share the excitement of these revelations with you. Please join me in this adventure of understanding the synthesis of the target molecule, the process of science, and the people involved in the myths and realities of the total syntheses of quinine. In this tour, I shall:

1) review the various recent criticisms in light of the documented chemistry and related background of the Rabe–Kindler and Woodward–Doering publications;
2) disentangle some of the interwoven clutter regarding almost 100 years of events, and focus on the specific issues involved;
3) examine the role of editors, reviewers, and scientists of the 1910s and the 1940s to the present day in determining the "acceptability" of publications;
4) present historically important documentation—much of which has not been previously known—dealing with Rabe, Kindler, Woodward, Doering, Stork, and quinine;
5) compare Woodward's use of *d*-quinotoxine as a "relay compound" in his and Doering's formal total synthesis of quinine with Woodward's use of cobyric acid as a relay compound in his and Eschenmoser's formal total synthesis of vitamin B_{12};
6) place these issues in the context of the time periods involved; and
7) set the record straight, by providing compelling direct and indirect evidence of the total synthesis of quinine by Woodward–Doering/Rabe–Kindler.

3. Praise: The View from 1944 to 2001 of the Woodward–Doering Total Synthesis of Quinine

3.1. Praise and Accolades within the Scientific Community: 1944 to 2001

Various authoritative scientific publications accepted the Woodward–Doering/Rabe–Kindler total synthesis of quinine. Many editions of *The Merck Index* state, under the listing for quinine:

> "Synthesis: Woodward, Doering, *J. Am. Chem. Soc.* **1944**, *66*, 849; **1945**, *67*, 860 … "[37]

Other notable examples[19,38,39] which credit Woodward and Doering for the total synthesis of quinine include the major history text *The Development of Modern Chemistry* by Aaron J. Ihde ("The total synthesis of quinine was finally accomplished by Woodward and Doering in 1944."[40]); *Organic Chemistry* by Louis F. Fieser and Mary Fieser ("the achievement of Woodward and Doering (1944) in effecting total synthesis of quinine"[41]); *Chemistry of Organic Compounds* by Carl R. Noller ("The last phase of a total synthesis of quinine was completed successfully in 1944."[42]); and the 2002 book *Alkaloids. Nature's Curse or Blessing?* by Manfred Hesse ("Woodward … Synthesized numerous natural products, notably the alkaloids quinine and strychnine."[43]). In his 1981 book *Introduction to Alkaloids*, Cordell, who was later to edit many volumes of Manske's "The Alkaloids," wrote:

"Quinine itself was first synthesized by Woodward and Doering in 1944, and is a classic achievement in synthetic organic chemistry … The subsequent steps had been worked out previously by Rabe in 1911."[44]

The published evidence clearly demonstrates that the broad chemical community had, until June of 2001, accepted—in fact, praised—the formal total synthesis of quinine by Woodward and Doering.

3.2. Praise and Accolades by the News Media: 1944

Many articles appeared in the news media, including a front-page article in *The New York Times* on May 4, 1944[45] as well as another article and an editorial a few days later.[46,47] Further articles appeared in *Life* magazine,[48] *The New Yorker*,[49] *Business Week*,[50,51] *Newsweek*,[52] *Time*,[53] *Reader's Digest*,[54] *Science News Leader*,[55] as well as the Virginia *Gazette*, Alexandria,[56] the Philadelphia *Inquirer*,[57] *Drug Trade News*,[58] Kentucky *Messenger*,[59] and a remarkable cartoon from the *Oregon Journal* (Figure 5).[60] Most of the news reports were overwhelmingly positive, as the following excepts illustrate:

Figure 5. Cartoon from the Portland *Oregon Journal*, May 28, 1944. Reproduced with permission from the National Archives.

"Two 27-year-old chemists, Robert Burns Woodward and William von Eggers Doering announced last month that they had made quinine by a laboratory process from synthetic chemicals derived from coal tar. This is the first time quinine has been produced outside the life processes of the tropical Cinchona tree … Although responsible war agencies have not yet decided on its necessity, the Woodward–Doering synthesis does open the possibility of mass production of quinine … "[48] (from *Life* magazine; included in the article were photographs of crystals of "synthetic quinotoxine" and "quinine … in actual crystals.")

"a notable peace victory … of great benefit to mankind … a victory for science … "[56] (from the Virginia *Gazette*, Alexandria)

"a promise of life and health for millions now suffering and dying from malaria"[57] (from the Philadelphia *Inquirer*)

"one of the greatest scientific achievements of our time"[59] (from the Kentucky *Messenger*, Owensboro)

"The final step—commercial production—still remained to be taken. Chemists Woodward & Doering had made only 1/100 of an ounce from five pounds of expensive, involved chemicals."[53] (from *Time* magazine)

In contrast, the article in *Drug Trade News* was skeptical if not coldly realistic. In an article entitled "Synthetic Quinine Actual Use Doubted. Cost Seen Prohibited," P. H. Van Itallie said:[58]

"… editors of daily newspapers nevertheless negated this [warning of commercial infeasibility] to caution by insinuating that this synthesis was curtains for [Emperor] Tojo … a careful study of the details shows that, while every step is perfectly straightforward and feasible, there are so many steps involved and the yields obtainable are likely to be so small, that the commercialization is definitively very remote, unless price were considered no object."[58]

In 2001, Stork et al. in footnote [14] of their paper "The First Stereoselective Synthesis of Quinine", stated:

"This was wartime, and the U.S. had been cut off from the Dutch East Indies, its major sources of cinchona bark. The resulting anxiety may explain press accounts, notable for enthusiasm rather than for sober analysis, which created the quasiuniversal impression that the construction of homomeroquinene in 1944 [by Woodward and Doering] meant that quinine had been synthesized … Remarkably, the confusion produced by these and hundreds of other contemporary reports has persisted to this day."[2]

3.3. Praise and Accolades Outside Professional Circles

A number of major general reference books (for example, *The Random House Encyclopedia*,[61] *The Encyclopaedia Britannica*,[62] *The Columbia Encyclopedia*,[63] *The Grolier Library of Scientific Biography*,[64] and Wikipedia—*The Free Encyclopedia*[65]) all highlight that Woodward and Doering completed the total synthesis of quinine.

3.4. Woodward Believed and Doering Believes in the Woodward–Doering Total Synthesis of Quinine

It would have been disingenuous and perhaps even unethical had either Woodward or Doering not believed that they had completed "the total synthesis of quinine." That was, in fact, the title of both their communication[5] and their

full paper.[6] The extent of Woodward's own belief in his work and his capabilities are noteworthy.

The notoriety bestowed upon Woodward by the news media (see the section immediately above) led a number of individuals to write directly to Woodward. One letter[66] dated May 24, 1944 came from William M. S. Myers, Jr. from Fire Station No. 1 in Indianapolis. Woodward's response,[67] dated July 6, 1944, leaves little doubt that he believed that he completed the synthesis of quinine:

Myers to R.B.W.: "Is your discovery of 'Quinine' the first 'synthetic' quinine?"[66]

R.B.W.'s answer: "Prior to the completion of the investigation carried out in this laboratory, no method was available by which quinine could be prepared artificially, that is, by synthesis from materials available—in the last analysis—from the elements carbon, hydrogen, oxygen, and nitrogen, without the (unconscious) intervention of a living organism, plant, or animal. The only previous source of quinine was from the cinchona tree."[67]

Myers to R.B.W.: "Is your recent discovery now called a synthetic or, is it called a real quinine?"[66]

R.B.W.'s Answer: "The new material is real quinine, prepared by synthesis. It is indistinguishable from the natural material."[67]

Woodward's answer to at least this latter question was not rigorously accurate. As he and Doering never converted their synthetic *d*-quinotoxine into quinine, the comparison "indistinguishable" was not possible.[67] One explanation: Woodward's firm belief that Rabe and Kindler did convert *d*-quinotoxine into quinine would mean therefore that Woodward's representation to Myers was "formally" valid, as was their "formal" total synthesis. Clearly, Woodward had firm belief in his work and his capability to synthesize quinine. Parenthetically, it is noteworthy that the "synthetic" quinine made by Rabe and Kindler must be "indistinguishable from the natural material" in that their starting material, *d*-quinotoxine, was derived from quinine itself using Pasteur's precedent without epimerization (Scheme 1)![68]

Woodward and Doering surely were enormously pleased if not outright jubilant upon the completion of the synthesis of *d*-quinotoxine. These joyful memories persisted for years, and in his address to honor Doering on the occasion of Doering's receipt of the Richards Medal on April 9, 1979, Woodward said of his friend:

"The completion of the synthesis of quinine attracted a certain amount of notoriety. At that precise time I became the victim, or beneficiary, of some of the lurid aspects of one of the earlier instances of a not inconsiderable train of melancholy events which have molded my character, or vice versa. In consequence, Doering had to bear the brunt of dealing with our public relations, which he did with aplomb, charm, and revealing, I think, a certain amount of pleasure.

"These days were not without their hilarious aspects. One of the radical news organs of the day, happily now defunct, hurled sensational charges that Doering and I had taken the tainted gold of the Dutch quinine cartel in return for keeping the benefits of our discovery from the public. Alas, such was not so. We had to find our tainted gold later and elsewhere, a task no doubt made easier by the notoriety we had achieved as a consequence of those reckless charges."[69]

At then age of 88, Doering's resilience and adamantness can be seen from the following exchange I had with him in 2005:

Question: "Did you and R.B.W. discuss what is described above at all, either in the 1940s or subsequently, regarding Rabe and Kindler?"

Answer: "No; I might say, 'Of course not.' It was never an issue."

Question: "If not, had you known the perspective of science in 2005 as opposed to the perspective of science from 1918–2002, would you have discussed this with RBW in the 1940s?"

Answer: "No—see above!!!"[70]

4. Acceptance of the 1944 Woodward–Doering Research Results

4.1. On the Correspondence between Weller, Rabe, and Woodward

On July 24, 1947, Dr. Richard Weller wrote to Woodward from Lüneburg, British Zone, Germany:

"In the Manchester Guardian Weekly of June 17th, I read a report about your interesting success in producing protein-like molecules. There also was mentioned that three years ago you succeeded to produce synthetic quinine. As an old quinine-expert—I was 7 years chemist and manager in the Vereinigten Chininfabriken Zimmer & Co., Frankfurt/M–Stuttgart and later 10 years Director of a quinine-factory in Netherland—I am very interested to hear details about that synthesis and also the old friend of my famil[y] Prof. Dr. Rabe from the University Hamburg, who also succeeded many years ago in producing quinine although only at scientifi[c] scale. We are sorry that we can not get here since many years any chemical literature from abroad and I would be very glad if you could send me your publications about the quinine synthesis."[71]

On December 18, 1947, Woodward sent reprints with the request that copies be forwarded to

"Professor Dr. Rabe, whom you mentioned as a friend, and who of course was the acknowledged master in the chemistry of the cinchona alkaloids, both in the determination of structure, and in laying the basic foundation for successful synthetic work."[72]

On February 10, 1948, Weller responded:

"With cordial thanks, I confirm today your kind letter … One of each [reprint] I have sent to Professor Rabe. The two papers were of great interest to me. I tried again to improve the yield of [this word, unfortunately, is unintelligible but the last letters appear to be 'ininone'] following Rabe's procedure without satisfactory result however. I assume that Professor Rabe will write to you.

"If you want to do something good, it would be great when one of your excellent organizations would send a care package to Professor Dr. Paul Rabe Hamburg Parkallee 54. The creative thinkers are not usually in the situation to acquire additional food by barter. With some coffee, tea, cheese and meat, you would certainly make happy the about 80-year old researcher."[73]

On February 19, 1948, Rabe (Figure 6), then 79 and afflicted with an eye illness that seriously limited his sight, wrote to Woodward (Figure 7) in his own handwriting:[74]

Rabe also forwarded to Woodward reprints of five of his papers published since 1939. On March 16, 1948, Woodward responded:

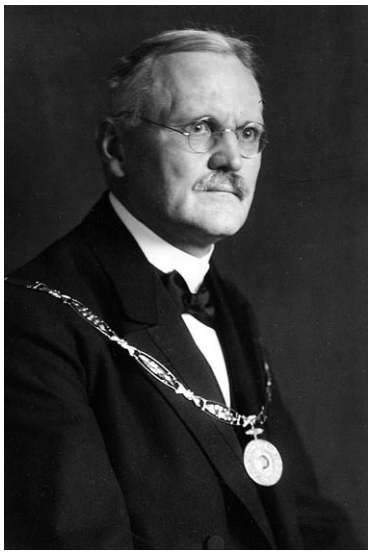
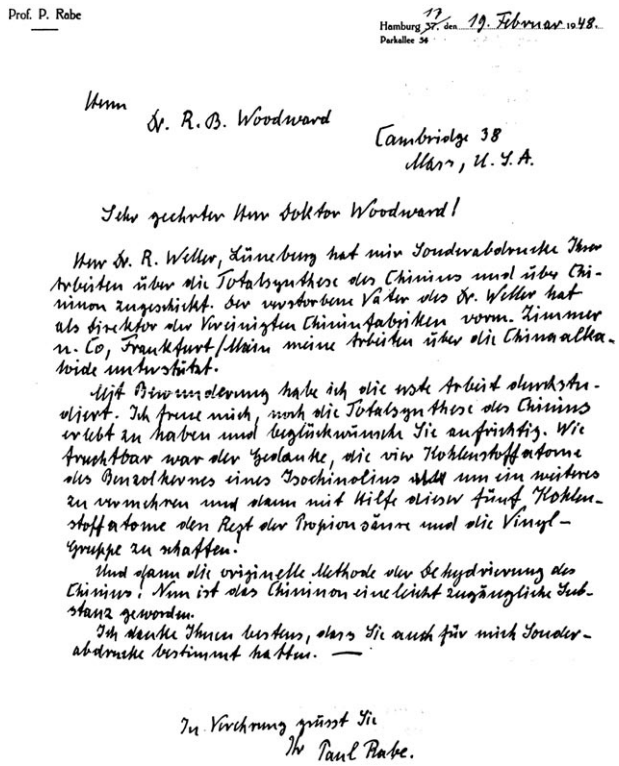


Figure 6. Paul Rabe. The photograph is reproduced with permission from Wittko Francke.



Prof. P. Rabe

Hamburg 17, den 19. Februar 1948.
Parkallee 36

Herrn
Dr. R. B. Woodward
Cambridge 38
Mass., U. S. A.

Sehr geehrter Herr Doktor Woodward!

Herr Dr. R. Weller, Lüneburg hat mir Sonderabdrucke Ihrer Arbeiten über die Totalsynthese des Chinins und über Chinin zugeschickt. Der verstorbene Vater des Dr. Weller hat als Direktor der Vereinigten Chininfabriken vorm. Zimmer u. Co, Frankfurt/Main meine Arbeiten über die Chinaalkaloide unterstützt.

Ihre Bemerkung habe ich als sehr starke Anerkennung meiner Arbeit überhaupt. Ich freue mich, noch die Totalsynthese des Chinins erlebt zu haben und beglückwünsche Sie aufrichtig. Wie fruchtbar war der Gedanke, die vier Kohlenstoffatome des Benzolkernes eines Isochinolins stets um ein weiteres zu vermehren und dann mit Hilfe dieser fünf Kohlenstoffatome den Rest der Propionsäure und die Vinyl-Gruppe zu schaffen.

Und dann die originelle Methode der Dehydrierung des Chinins! Nun ist das Chinin ein leicht zugängliche Substanz geworden.

Ich danke Ihnen bestens, dass Sie auch für mich Sonderabdrucke bestimmt hatten. —

In Verehrung grüsst Sie
Ihr Paul Rabe.

Figure 7. Excerpt from a 1948 letter[74] from Paul Rabe to R. B. Woodward, congratulating Woodward on the first total synthesis of quinine. The translation shown in Box 2 is by O. T. Benfey and R. Huisgen.

"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. Please permit me to thank you most warmly for your generous comments on my work …

"The news I receive from Germany suggest very strongly that those things which make life pleasant, not to mention essentials, are very hard to come by. I hope you will forgive me for taking the liberty of arranging to have sent to you a small package of useful materials, in token of my respect for and gratitude to one whose work formed the necessary basis upon which I was able to build in making what contributions to the chemistry of the cinchona alkaloids it has been my good fortune to make."[75]

Box 2 (see Figure 7).
"Dr. Weller of Lüneburg sent me reprints of your work on the total synthesis of quinine and about quininone. Dr. Weller's father, now deceased, as director of the Vereinigten Chininfabriken (united quinine works), formerly Zimmer & Co. of Frankfurt/Main, supported my work on the cinchona alkaloids.

"I studied your first paper with admiration. I am delighted that I have lived to see the total synthesis of quinine and I send you my sincere congratulations. Your thought was certainly a fruitful one to increase the four carbon atoms of the benzene nucleus of isoquinoline by an additional one and then with the help of these five carbon atoms to create the rest of the propionic acid and the vinyl group!

"And then the original method of dehydrating the quinine! Now quininone has become an easily obtainable substance.

With my cordial greetings,
Paul Rabe"

Rolf Huisgen, who provided for this Review the translations of many of Rabe's publications and letters, wrote to me on July 24, 2006:

"The presently active generation has no idea about the food situation in the German postwar years. Hans Meerwein told me once that he received several CARE packages from Paul D. Bartlett [Woodward's colleague at Harvard] whom he had never met before nor had he corresponded with him. Isn't this great?"[76]

4.2. The Acceptance of the 1918 Rabe–Kindler Research Results

4.2.1. Editors and Reviewers of the Publications from Rabe and Kindler (1918 and 1939) and Rabe (1932)

The *d*-quinotoxine to quinine transformation by Rabe and Kindler was published in 1918 (Scheme 2).[7] Rabe continued to publish papers on cinchona alkaloids for 30 more years. There were numerous opportunities for Rabe to be asked, to be required to, and to publish the full experimental information. A 1939 paper, also authored by Rabe and Kindler (Figure 8), specifically followed up on their 1918 publication and contained experimental details regarding the isolation and purification of quinine, quinidine, *epi*-quinine, and *epi*-quinidine but not experimental details of the *d*-quinotoxine to quinine transformation.[77] A 1932 publication of Rabe's consisted of 25 pages and is an accumulation of bits-and-pieces of experimental procedures not previously published that related to many earlier cinchona alkaloid publications.[9] In fact, that paper presents experimental details from at least seven other co-workers from three locations (Jena, Prague, and Hamburg); some results were from 21 years earlier. In that 1932 paper Rabe specifically acknowledged that the experimental details of the reduction of quininone to quinine with aluminum powder (the last step in Scheme 2) had not been reported by Kindler and him in 1918. Yet Rabe describes the reduction of hydrocinchoninone and not quininone:

Figure 8. Karl Kindler. The photograph is reproduced with permission from the Kommissionsverlag der Osterreichischen Kommissionsbuchhandlung and Helmut Schmidhammer.

"Just like the 25th report, this one relates to investigations which go back to 1911… The noncatalytic reduction succeeded through the use of aluminum powder and sodium ethylate in alcoholic solution. This method introduced by Rabe and Kindler[7] has not yet been described in detail. Therefore, we shall illustrate it with the example of hydrocinchoninone."[9]

Thus, the lack of experimental details was clearly pointed out by Rabe himself. There were several opportunities for journal editors or journal reviewers to require, or the scientific community to inquire, or Rabe himself to publish full experimental details of the 1918 conversion of *d*-quinotoxine into quinine. He apparently never was asked; he certainly never did.

4.2.2. *The Reliance of Prelog on Rabe and Kindler*

In their 1943 paper, Mihovil Proštenik (1916–1994) and Prelog (Figure 9) prepared *d*-quinotoxine by condensation of a derivative of optically active homomeroquinene (**3**) with ethyl quininate (Scheme 3).[78] The claim by Proštenik and Prelog of a partial synthesis of quinine[78] also relied on the 1918 report of Rabe and Kindler.[7] In 1991, 48 years later, Prelog would confirm his reliance on the 1918 chemistry of Rabe and Kindler without hesitation in his autobiography, *My 132 Semesters of Chemistry Studies*,":

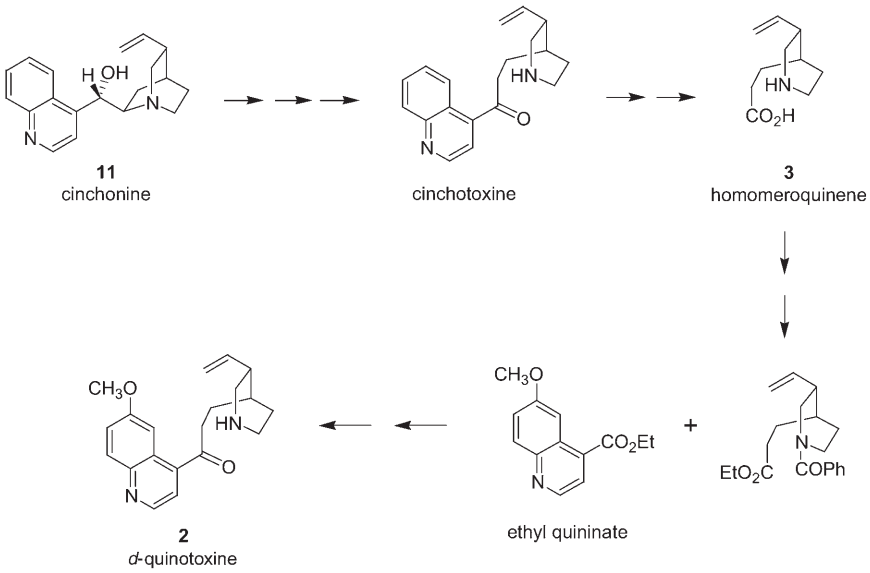
"As an exercise, we made quinotoxine by starting with pure homomeroquinene that we had obtained by degradation of cinchonine and thus accomplished a partial synthesis of quinine".[78,79]

In fact, Proštenik and Prelog were the first (1943) to convert homomeroquinene into *d*-quinotoxine.[78] This transformation is a chemical "requisite" step in the Woodward–Doering formal total synthesis of quinine (1944; Scheme 1). Stork has suggested that, "if you wish to be consistent, you would have to add the name of Prelog to your list",[80] that is,

Figure 9. Vladimir Prelog, Mrs. Kamila Prelog, and Mihovil Proštenik in Zagreb on May 22, 1989. Reproduced from Kruno Kovačević.

the Woodward–Doering/Proštenik–Prelog/Rabe–Kindler total synthesis of quinine.

The conversion of homomeroquinene into *d*-quinotoxine involves a Claisen condensation to form a β-keto ester that is subsequently hydrolyzed and decarboxylated to form the ketone. Similar reactions were performed previously within the cinchona alkaloid system. For example, the condensation of ethyl 4-quinolinecarboxylates with both aliphatic esters by Rabe and Pasternack (1913)[81] and with a protected dihydromeroquinene ester by Rabe and Kindler (1918)[82] serve as direct precedents for the condensation reported by Proštenik and Prelog[78] (Scheme 3). Thus, the attachment of two more names to the total synthesis serves only in "nomenclatorial play" and adds insufficiently to the sciences of chemistry and history of chemistry.



Scheme 3. The partial synthesis of quinine by Proštenik and Prelog in 1943 involved the conversion of homomeroquinene into *d*-quinotoxine. Optically active (nonracemic) homomeroquinene was obtained from degradation of the natural product cinchonine (**11**). The condensation of the protected homomeroquinene with ethyl quininate was based on analogous condensations by Rabe and Pasternack in 1913[81] as well as by Rabe and Kindler in 1918.[82] The claim of Proštenik and Prelog for a partial synthesis of quinine relied on the conversion of *d*-quinotoxine into quinine by Rabe and Kindler (Scheme 2).[78]

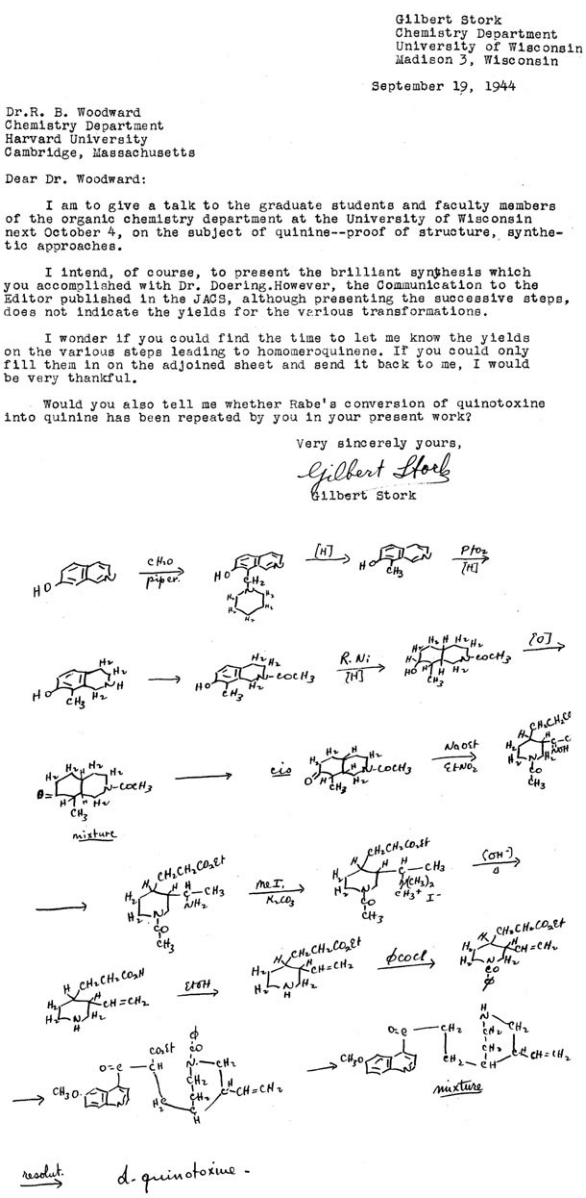
4.3. The Acceptance of the 1944 and 1945 Woodward–Doering Total Synthesis of Quinine

4.3.1. Reviewers' Comments

Any discussion of the validity of the Woodward–Doering claim of a total synthesis of quinine should also be made within the context of the chemistry that Woodward and Doering (Figure 10) did unambiguously achieve. The Woodward–Doering synthesis is shown in Stork's 1944 handwritten graphics in Figure 11. As stated by Stork in 2001:

Figure 10. Doering blowing glass, Harvard in 1944. The photograph is reproduced from the Fritz Goro archives.

"The Woodward–Doering synthesis of homomeroquinene (*cis*-3-vinyl-4-piperidinepropionic acid referred to above) deserves our admiration, not because of its putative relationship to Rabe's work, but for its own sake. It is beautiful and inspiring … the inspired cleavage of a cyclohexanone ring to produce not a ketoacid, as others might well have planned, but the related oximino acid, thereby avoiding the likely danger of losing the painfully acquired *cis* relationship of the piperidine substituents. This and Doering's superb and insufficiently acknowledged mastery of the far from trivial experimental difficulties is what makes the homomeroquinene synthesis a masterpiece."[11]



Gilbert Stork
Chemistry Department
University of Wisconsin
Madison 3, Wisconsin

September 19, 1944

Dr.R. B. Woodward
Chemistry Department
Harvard University
Cambridge, Massachusetts

Dear Dr. Woodward:

I am to give a talk to the graduate students and faculty members of the organic chemistry department at the University of Wisconsin next October 4, on the subject of quinine--proof of structure, synthetic approaches.

I intend, of course, to present the brilliant syn$hesis which you accomplished with Dr. Doering.However, the Communication to the Editor published in the JACS, although presenting the successive steps, does not indicate the yields for the various transformations.

I wonder if you could find the time to let me know the yields on the various steps leading to homomeroquinene. If you could only fill them in on the adjoined sheet and send it back to me, I would be very thankful.

Would you also tell me whether Rabe's conversion of quinotoxine into quinine has been repeated by you in your present work?

Very sincerely yours,

Gilbert Stork

Gilbert Stork

Figure 11. Letter[103] from the then graduate student Gilbert Stork to the then Harvard instructor Robert Burns Woodward asking for information about the Woodward–Doering total synthesis of quinine following the publication of their 1944 communication[5] but prior to the submission on November 8, 1944 of their full paper.[6]

The details of the Woodward–Doering synthesis of *d*-quinotoxine from 7-hydroxyisoquinoline have been discussed elsewhere.[12,13,15,83] Suffice it to say, subsequent to the publication of the communication and full paper, a new era in organic synthesis began (see Section 3.1 and the comments of Nicolaou et al.[17] in Section 5).

Beyond the remarkable chemistry achieved by Woodward and Doering, what was said contemporaneously about their reliance on Rabe and Kindler? Two detailed reviewers' comments on the 1945 Woodward–Doering full paper "Total Synthesis of Quinine" are available in the Harvard University archives.[84] One reviewer, arbitrarily named Reviewer A herein, provided a very specific three-pages long commentary (excerpts are shown in Figure 12). The second, Reviewer B, wrote a shorter review, about half that in length, although it contained numerous detailed recommendations (Figure 13). Neither reviewer criticizes the use of the Rabe–Kindler precedent by Woodward and Doering to assert the total synthesis of quinine. The communication on the Woodward–Doering total synthesis had appeared in the previous year and was clearly well known—it was an extraordinarily highly publicized research result. Thus, the reviewers and editor understood the national and international significance of this submission.

Reviewer A rejected the full paper, criticizing the paper for its inclusion of historical material, its duplication of presentation of, and in some cases excess amount of, experimental details, the amount of "rationalization of the syntheses chosen", the authors' literary style and pedantic

The accompanying manuscript entitled "The Total Synthesis of Quinine" by Woodward and Doering is an excellent paper, but I do not believe it is suitable for publication in the Journal.

(3) A considerable portion of the discussion is devoted to rationalization of the syntheses chosen. The authors take some pains to point out why they expected each reaction to proceed as it subsequently was found to do. This is interesting material, but again an expert in the field does not require such step by step guidance; confronted with the necessity for making the prediction, an expert would doubtless produce the same one the authors do. The authors undoubtedly

(4) An author's literary style is his own concern even in a scientific paper, but fine writing prejudices me against any paper. This is particularly the case when an unusual synonym or phrase is used where a common word would serve just as well. A few examples from many that might be cited, may serve to show how much a return to simplicity could be made in this paper.

p. 1, "moiety", but half, is commonly used. Another expression in the same sentence "more highly organized and consequently simpler" appears to have been used more for literary effect than for any real meaning it contains.

p. 2, "took on prime importance because of a correlative line of investigation", = was important because it indicated how (for instance) the two halves of the cinchona bases could be joined.

p. 2, "along the lines adumbrated in" = using the method developed in ...

p. 4, "to implement" and "apposite", also p. 16, "apposite", are words characteristic of fine writing.

p. 15, "proximate later" = subsequent.

(5) It is my opinion that the paper can be condensed to not more than half its present length, and that this condensation could be done to the advantage of the paper. Such condensation could be achieved through the omission of (a) most of the historical part, (b) duplication in the discussion and experimental parts, (c) some of the explanations why the reactions were expected to succeed, (d) some of the material on mechanisms of the reactions, and (e) some of the unnecessary experimental details. Whether these omissions are made or not requires some judgment from Dr. Lamb as to editorial policy, since as previously noted the paper is an excellent one, in some respects, but differs from the type usually published in the Journal.

Figure 12. Excerpts from one of two journal reviews[84] (see Figure 13) of the 1945 full paper by Woodward and Doering.[6]

Page

1 Delete note 2 (not a rational effort)

" more highly organized, and consequently simpler" (not clear)

Segment for moiety

2 Delete note 5 (not relevant)

Delete note 7 (interesting but not essential)

Adumbrated could be substituted by suggested or foreshadowed.

Appropriate for apposite

" relatively disorganized quinuclidine part of the cinchona alkaloid molecule." (not clear)

5 Delete well known

Figure 13. Excerpt from one of two journal reviews[84] (see Figure 12) of the 1945 full paper by Woodward and Doering.[6]

quality. Reviewer A states that the paper's length "can be condensed to not more than half its present length".[84] However, Reviewer A does not point to any substantive chemistry weaknesses.

The criticisms from reviewer B are threefold:[84] Two deal with the authors' writing style. In fact, both reviewers criticize the use of the words "moiety," "adumbrated", and "apposite" by Woodward and Doering, and both make suggestions for replacement words; nevertheless, these three words remained in the publication. The most relevant comment of reviewer B deals with the use of literature precedents—but not that of Rabe and Kindler,[7] rather of Prošťenik and Prelog.[78] As shown in Scheme 3, Prošťenik and Prelog prepared homomeroquinene (**3**) by chemical degradation of natural cinchonine (**11**) and converted it into *d*-quinotoxine.[78] Reviewer B states:

"It seems to me that more cognizance should be taken of the work of Prošťenik and Prelog [who converted homomeroquinene to quinotoxine and claimed "a partial synthesis of quinine"[78,79] in 1943, prior to Woodward and Doering; see Section 4.2.2] and that this can be done in all fairness to them without any lessening of your own contribution in some such way as this,—

"'In this regard P. and P., by duplicating the synthetic scheme of Rabe, effected a partial synthesis of quinine by employing homoeroquinine obtained from natural sources. Thereby these workers demonstrated that the general method for combining the two portions of the quinine molecule involving *dihydro*homomeroquinine was also applicable in the case of homomeroquinine itself. However, the obtainment of homomeroquinine synthetically still remained to be accomplished and so consequently the total synthesis of quinine. The achievement of that goal is described in this communication.'"[84]

Thus, Reviewer B is fully cognizant of the contributions of both Rabe and Prelog, accepts the report by Rabe and Kindler on the conversion of *d*-quinotoxine into quinine, and criticizes Woodward and Doering for not sufficiently crediting the directly related significant precedent. There is no hint from either Reviewer A or Reviewer B that the Rabe and Kindler 1918 results were incomplete or unacceptable, or needed to be repeated or confirmed by Woodward and Doering. The editor of the *Journal of the American Chemical Society* at that time was Arthur Lamb, a colleague of Woodward's at Harvard. Lamb had a reputation for being an extremely thorough editor; he also was a pioneer in requiring peer review for publication.[85,86] Lamb accepted the Woodward–Doering full paper without requiring the major changes recommended by the reviewers.

4.3.2. Industry, the US Government, and the National Research Council during and just after World War II

Quinine was of interest to the Polaroid Corporation as a light polarizer.[19] Polaroid, then based in Cambridge, was led by Edwin Land (Figure 14), one of American industry's most technically focused leaders. Land was surely prescient regarding scientific talent that would enhance Polaroid's future profitability. In the early 1940s, he engaged Woodward as a consultant for the Polaroid Corporation:

"in the fields of chemistry and optics, and more particularly the field comprising the manufacture of light-polarizers, light absorbers, and optical plastics, and of materials useful in the same … Polaroid agrees to pay to Woodward the sum of One Thousand ($1000.00) Dollars for a period of one year commencing June 1, 1942 … "[87]

Figure 14. Richard Kriebel (head of Polaroid's public relations department), Edwin Land, and Woodward in Cambridge, ca. 1946. Reproduced with permission from the Polaroid Corporation and the Chemical Heritage Foundation.

Two years later, the revised consulting agreement showed an increased yearly fee of $4000.[88] Within the Woodward collection in the Harvard archives, there are numerous letters, contracts, and research memos and notes dealing with his consultations with Polaroid on novel polarizers.

The address lines for both the communication and the full paper of the total synthesis of quinine by Woodward and Doering list the "Research Laboratory [of the] Polaroid Corporation" first and the "Converse Memorial Laboratory [of] Harvard University" second. This prioritization reflects the funding source of the research and the ownership of patent rights; none of this laboratory work was performed at Polaroid. Rather, the experimental work occurred at both the Harvard and Columbia Universities.

Woodward must surely have been pleased to receive a congratulatory letter from the Polaroid Corporation. On April 13, 1944, A. B. Lamb and Edwin H. Land wrote:

"We would like to express our appreciation of your splendid achievement in the solution of this classic problem of organic chemistry and we take great satisfaction in having been associated administratively in this achievement … We want you to know that in our minds the only significant point is that at long last your dream of synthesizing quinine has been realized."[89]

One can only speculate if Lamb and Land understood at that time that Woodward and Doering had not, in fact, physically obtained any quinine.

There were several other industrial and governmental contemporaneous evaluations of the Woodward–Doering claim of the total synthesis of quinine. A major program of high US national security priority was initiated in 1941 aimed at securing adequate supplies of antimalarial drugs for American soldiers in the Pacific war theater.[90] In a series of letters and meetings beginning in 1942, Woodward proposed to the United States government the large-scale synthesis of quinine for possible use as an antimalarial by the troops in the South Pacific. Woodward's interactions were with the National Research Council, the Committee on Medical Research, the Office of Production Research and Development, and the Chemical Industries Branch of the War Production.

While it was clear, at least to those providing recommendations to the War Department, that the commercial-scale synthesis of quinine was not going to be feasible during the war, Woodward's proposal was highly regarded. For example, one of the reviewers for the Chemical Industries (War) Branch was the then-renowned Frank C. Whitmore, who wrote on May 16, 1944:

"the Woodward–Doering total synthesis of quinine … involves a real triumph in academic organic chemistry. It involves some of the cleverest work which has been done in the past twenty-five years … The steps of the Woodward–Doering synthesis are complete as far as laboratory experimentation goes. The next steps should be on the development of a production scale … "[91]

In the early 1940s, Woodward also participated in correspondence with US industrial corporations other than Polaroid on the commercial synthesis of quinine.[92,93] These corporations included American Cyanamid, Ciba Pharmaceutical Products, Eli Lilly and Company, Merck & Company, Monsanto Chemical Company, The New York Quinine and Chemical Works, and The Squibb Institute. A full discussion of the interactions with Polaroid, these chemical and pharmaceutical companies, as well as with the War Production Board is outside the scope of the present Review and will be reported elsewhere.[94] Nevertheless, it should be noted that Woodward understood and represented that, in a letter to Squibb dated April 24, 1944:

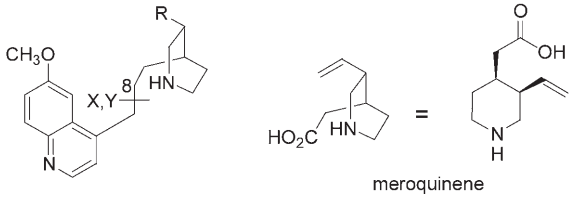
"The synthesis of so complex a molecule is long, and the task of producing the product on a large scale is a formidable one. The decision as to whether development for production should be attempted is one which lies properly with Governmental authorities and we are awaiting their reaction."[95]

In response to various requests for information,[96,97] Woodward wrote:

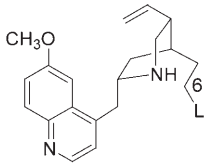
"No quinine is being manufactured synthetically in this country at the present time and it is unlikely that the situation will change in the future. This circumstance arises from the much greater cost of synthetic quinine as compared with the natural product … "[95]

4.3.3. *Other Quinine Syntheses*

In the 1970s and 1980s a number of formal and total syntheses of quinine were reported, all involving N–C8 cyclization to the quinine ring system (see **12**). While this cyclization mode is based on the 1911 work of Rabe[10] and the



12 **13**



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1918 model of Rabe and Kindler,[7] cyclization methods other than NaOBr halogenations were involved. In some syntheses of quinine, the key target was meroquinene (**13**).[98–101] The first total stereoselective synthesis of quinine was reported by Stork et al.[2] who were the first to apply the N–C6 cyclization route (see **14**). These syntheses of quinine were recently reviewed in 2003 by Nicolaou and Snyder[15] and in 2004 by Kaufman and Rúveda.[13]

5. Criticism: The Current View of the Woodward–Doering Total Synthesis of Quinine

Today, 60 years subsequent to the Woodward and Doering publications[5,6] and 90 years since the Rabe and Kindler

report,[7] serious doubts have been raised about the assertion of the first total synthesis of quinine.[2,11–15] Some of these questions appear in Section 1 of this Review. Additional criticisms are now presented.

In 2001, Stork and colleagues reported an elegant "First Stereoselective Total Synthesis of Quinine".[2] In that publication, they said:

"Woodward and Doering did not claim to have confirmed Rabe's 1918 report,[7] in a few lines, that [Rabe] had succeeded in converting quinotoxine to quinine (although the basis of [Woodward and Doering's] characterization of Rabe's claim as 'established' is unclear), nor is there any evidence that [Woodward and Doering] produced any quinine in their own laboratories."[2]

In fact, Woodward and Doering did not produce any quinine in their laboratory nor did they attempt to convert *d*-quinotoxine into quinine. The Rabe and Kindler[7] study of 1918 does not include sufficient experimental details to replicate their reported conversion of *d*-quinotoxine into quinine (Figure 3). Rabe and Kindler categorized their publication as a "preliminary notice"[7] "since the clinical identification of the thus synthesized quinine with the natural antipyretic has yet to be carried out."[7] In the 21st Century, this study has been characterized as "a very laconic publication,"[12] an "extremely abbreviated announcement,"[2] and "very terse."[2]

Other criticisms rapidly followed Stork's evident sharp focus on the shortcomings of the Rabe–Kindler publication and the reliance of Woodward and Doering on this publication. In his review in *Nature* on "Synthetic Lessons from Quinine", Steven Weinreb stated:

"In addition, the Stork paper is written with an insight and historical perspective (as well as correcting some myths) rarely seen in the primary chemical literature, and should be required reading for all students of organic chemistry."[14]

In the book *Napoleon's Buttons*, Penny Le Couteur and Jay Burreson stated:

"The quest to synthesize the actual quinine molecule was supposedly fulfilled in 1944 when Robert Woodward and William Doering of Harvard University converted a simple quinoline derivative into a molecule that previous chemists, in 1918, had allegedly been able to transform into quinine. The total synthesis of quinine was finally presumed complete. But this was not the case."[102]

In their 2005 review "The Quest for Quinine" in *Angewandte Chemie*, Theodoro Kaufman and Edmundo Rúveda stated:

"Rabe's procedure from his 1918 report was not cautiously reviewed and his claims were not fully substantiated … Unfortunately, Rabe's method would prove to be unreliable … ."[12]

In their authoritative book on Woodward, Benfey and Morris are somewhat ambivalent. They simultaneously state:

"The synthesis of quinine, with William von Eggers Doering, was Woodward's first total synthesis … "[19]

Benfey and Morris also state:

"Moveover, it has not been found possible to repeat Rabe's conversion of quinotoxine to quinine, and questions linger as to whether he was successful."[19]

Most remarkably, the reliability of the Rabe–Kindler *d*-quinotoxine into quinine conversion was first raised on September 19, 1944, shortly after the communication by Woodward and Doering[5] and months before their submission of their full paper.[6] In a letter to "Dr. Woodward", the then 22-year-old graduate student from the University of Wisconsin Gilbert Stork wrote (Figure 11):

"Would you also tell me whether Rabe's conversion of quinotoxine into quinine has been repeated by you in your recent work."[103]

Within the Harvard archives, I found no evidence that Woodward replied to Stork. Also within the Woodward archives are many examples in which copies of Woodward's responses are found immediately behind the letters sent to him, even in instances in which the response was written months later. According to the Harvard archivists, the placement of the documents within the Woodward files is exactly the order in which they were found following Woodward's death in 1979.

Interestingly, Stork does not recall writing to Woodward in 1944. As he told *Chemical & Engineering News*:

"As a young graduate student at the University of Wisconsin, Madison, also working on constructing quinine, Stork was very impressed with the Harvard work … 'I never questioned it. But over the years, it became likely that they never made any quinine by the Rabe route.'"[28]

In an authoritative reference on total synthesis, Nicolaou and Snyder leave the validity of the Woodward–Doering claim of total synthesis open to question:

"There has been some debate in the current literature concerning the validity of Rabe's reconstitution of quinine (**1**) from quinotoxine (**2**) in regards to the final reduction using aluminum powder … This issue is clearly of consequence because if this reaction did not proceed as written, then the Woodward/Doering route would not constitute a formal synthesis of quinine, but merely a synthesis of quinotoxine since the Harvard researchers did not repeat Rabe's chemistry. While we do not wish to engage directly in revisionist commentary about whether or not this conversion is valid, we do think it important to note that Woodward and Doering were not alone [see Prelog's autobiography[79]] in basing their synthetic work on the assumption that the Rabe route indeed led to the generation of quinine."[78],[15]

6. The Substance of the Controversy: Good or Bad Science? Poor Judgment? Fraud in Science? Scientific Incompetence?

That Woodward and Doering based their formal total synthesis of quinine[5,6] on the report by Rabe and Kindler[7] is clear and unambiguous. That Rabe and Kindler never reported the full experimental details of their *d*-quinotoxine to quinine transformation (Scheme 2) is also clear and unambiguous. Did Woodward and Doering use poor judgment by not repeating the *d*-quinotoxine to quinine transformation or developing one themselves? Perhaps the answer

to that question depends on the answer to another question, namely, did Rabe and Kindler actually succeed in their claim to have completed this transformation?

- If Rabe and Kindler did, in fact, convert *d*-quinotoxine into quinine, then Woodward and Doering did, in fact, complete the first formal total synthesis of quinine.
- If Rabe and Kindler did not convert *d*-quinotoxine into quinine as they claimed, then either Rabe and Kindler committed scientific fraud by misrepresenting their experimental results, or they were experimentally incompetent and honestly thought that they had prepared "quinine" but in fact did not.

7. The Personal and Scientific Qualities of Paul Rabe and Karl Kindler

Over a 40-year period, Paul Rabe and his students published over 40 papers on the structure, chemical and physical properties, and synthesis of quinine and other cinchona alkaloids including dihydroquinine.[12,83,104–108] Rabe received his "Habilitation" in May 1900 at the University of Jena, where he subsequently began his independent academic career. In 1907, he published three papers[109–111] involving the cinchona alkaloids, including the first[109] of his series "The Cinchona Alkaloids"; numbers XXXII and XXXIII were published in the early 1940s.[112,113] A number of papers involving cinchona alkaloids were published as part of other series, for example, "1,2-Hydramines. III. Splitting of alkyl halides of quinine alkaloids in ethylene oxides"[114] was published in 1948 when Rabe was almost 80 years old. Most of these publications include detailed experimental procedures. Indeed, the procedures published by Rabe to isolate and purify the cinchona alkaloids before the days of chromatography involved elegant use of differential solubility. Doering and other Woodward students made excellent use of the Rabe experimental procedures.

To my knowledge, there has not been a single publication challenging the accuracy or validity of Rabe's scientific work—except for statements that point out the lack of experimental details for the synthesis of quinine from *d*-quinotoxine. Quite the contrary: In a tribute paid to Rabe by two colleagues 15 years after his death,[115] Rabe was celebrated for his personal and professional integrity:

> "Science represented for [Rabe] the pure quest for knowledge, far from any utilitarian deviations. His dedication to science was high and he always pursued the search for knowledge through experimental results and high-level research. This attitude greatly influenced his publication standards, and placed severe limits to what he considered a novelty and publishable. If he did not feel confident enough with a result, then he would wait to secure the data … "[12,115]

Rabe was also praised for his personal and professional conduct. During Rabe's career, "the students flocked around their adored teacher … "[12,115] while after World War II, "his friends and students tried to ameliorate the hunger and cold of the Rabe's; some of them visited, bringing potatoes and cabbages in their rucksacks, instead of flowers … "[12,115] In 1935, Rabe was forced by the Nazis into early retirement from his position as Director of the Institute in Hamburg. This was retaliation because Rabe had "removed a notice from the notice board notifying of a boycott against Jewish students at his Institute."[12,115] Rabe continued to do research at the bench with limited resources. These are descriptions of an honorable man and a competent and professional scholar/scientist. There has never been any suggestion of scientific fraud in Rabe's career, quite the reverse.[12,115]

Karl Kindler received his PhD in 1916 in Breslau and his "Habilitation" in 1923 in Hamburg[116–118] He published six papers with Rabe, five in the years 1917–1922 and one in 1939. In 1928, Kindler was appointed the position of Extra-Ordinarius (Hamburg). In 1936, he became the head of the newly founded Department of Pharmaceutical Chemistry (Chemische Staatsinstitute) in Hamburg, and when this institute was closed by order of the Nazi Ministry, Kindler became in 1941 head of the Pharmaceutical Chemistry in Innsbruck. In 1945 Kindler returned to Hamburg as Extra-Ordinarius where he founded an Institute of Pharmacy, and retired in 1959 as Director of the Pharmaceutical Institute.

During the 1920s and 1930s in Hamburg, Kindler published numerous papers, particularly in the series "New and improved methods for the synthesis of pharmacologically important amines" and "Mechanism of chemical reactions". Kindler was scientifically and physically close to Rabe in 1939. That was the year in which the follow-up Rabe–Kindler paper on isolating additional quinine from the 1918 reaction residues was published.[77] As an established, independent colleague of Rabe's, Kindler had the opportunity to provide influential input to Rabe regarding the need to publish additional experimental details of their 1918 paper. Whether any discussions were held in Hamburg regarding this matter are lost in time.

Thus, both Paul Rabe and Karl Kindler were established academic and research leaders in the first half of the 20th Century. Both held major professorships, and both continued to publish late in their lives. In the absence of definitive evidence to the contrary, it is just unreasonable to speculate that the 1918 and 1939 papers[7,77] of Rabe and Kindler were fraudulent.

Is it possible that Rabe and Kindler honestly but carelessly, in some fashion, failed to perform the experiments properly or mistakenly identified another compound as quinine?

Of course, errors are always possible, but at least four arguments speak against this possibility:

1) Paul Rabe focused almost exclusively on the chemistry of the cinchona alkaloids over a very long and productive career. He was arguably the world's expert in cinchona alkaloids and quinine in particular. Rabe had a reputation for being a careful, conservative scientist and an ethical human being. Had Rabe considered there was an experiment issue, he had more than sufficient time and resources to either correct the errors or report them.
2) Karl Kindler himself was a renowned academic researcher who devoted his career to natural products and pharmacologically active amines and related compounds.
3) The Rabe–Kindler sequence or modifications thereof were used in other related series of compounds, in both

Rabe's laboratory and that of other researchers (see Sections 8.3 and 8.4).

4) The final synthetic compound in the Rabe–Kindler sequence was quinine itself. To misjudge another compound, and far less likely a mixture, for quinine is most unlikely. As discussed in Section 8.1, the physical properties of quinine are significantly different from those of its isomers: quinidine, *epi*-quinine, and *epi*-quinidine (Scheme 2).

8. On the Scientific Validity of the 1918 Rabe–Kindler Reported Conversion of d-Quinotoxine into Quinine

8.1. The 1918 Experimental Results of Rabe and Kindler

Rabe and Kindler reported the three-step conversion of *d*-quinotoxine into quinine (Figure 3 and Scheme 2). In the first step, reaction of *d*-quinotoxine with sodium hypobromite (NaOBr) formed a brominated derivative of quinotoxine, **9** and/or **10**. Rabe and Kindler proposed **9** as the structure for this crystalline compound (m.p. 128 °C), based primarily on the observation that the analogous compound in the cinchotoxine series (desmethoxyquinine; see Section 8.4.1) did not react with methyl iodide.[10] Treatment with sodium ethoxide in ethanol in the second step had two effects: first, to cause the cyclization to quininone (**4**) and quinidinone (**5**), and, second, to establish an equilibrating mixture of these two ketones. Rabe and Kindler did not fully understand in 1918 that both quininone and quinidinone are formed and interconvert under the basic conditions.[7] However, the NaOEt-catalyzed interconversion of **4** and **5** is critical for the next step, the reduction with aluminum powder, also performed in the presence of sodium ethoxide in ethanol. Rabe and Kindler isolated only the less-soluble crystalline "quininone", now known to be quinidinone (Schemes 2 and 4).[2,83,119] In a 1945 publication entitled "Quininone"[120] Woodward et al. point out that their results

"seem to justify the assignment of the name quinidinone to the known [less soluble, isolated] isomer. In order to avoid confusion and since in any event the other isomer has not yet been obtained, the change in nomenclature has not been made in this paper."[120]

Quotation marks are placed around the word "quininone" in this publication to indicate that that was the identification made of the isolated crystalline compound in the 1910s–1940s. However, this compound was actually quinidinone, the epimer of quininone (see Scheme 2).

The hesitancy of Woodward et al.[120] to assign quinidinone to the less-soluble, isolated ketone in 1945 was overcome by the time of the review of Woodward and Turner in 1953. In that review, they state:

Scheme 4. Isomerization of cinchona alkaloid ketones at C8.[119]

"the reconversion of quinotoxine into quinidinone was similarly accomplished [by Rabe and Kindler in 1918],[7] and reduction of the latter compound with aluminum powder and ethyl alcohol in the presence of sodium ethoxide afforded a mixture of stereoisomeric alcohols, from which quinine and quinidine were isolated."[83]

The melting point of the "quininone" obtained by Rabe and Kindler in 1918 from *d*-quinotoxine was 108° and was in all respects identical to the "quininone" obtained from quinine.[7] Rabe and Kindler did not provide a reference to "quininone" nor did they state what identical "in all respects" meant even though Rabe had worked extensively with "quininone" previously.[121] Woodward et al. later reported a melting point range of 107–108.5 °C for this compound.[120]

The interconversion between quininone and quinidinone (Scheme 2) was suggested by experimental observations of Rabe et al. in 1910.[121] They observed changes in the optical rotations of a solution containing quininone and quinidinone which leveled out at $[\alpha]_D^{14} = 66°$. They also observed mutarotation in the cinchonine and cinchonidine series.[121] Milan Uskoković (born July 14, 1924) led a team of scientists at Hoffmann-La Roche who studied the chemistry and total synthesis of quinine and its relatives. In 1973, Jürg Gutzwiller (born August 29, 1937) and Uskoković similarly observed a change in the optical rotation for their mixture of quininone and quinidinone; in their case the value leveled out at $[\alpha]_D^{25} = 72.6°$ (both rotations taken in ethanol).[119] Rabe knew that "mutarotation" was occurring, he simply did not know the structural details—even Woodward et al., over two decades later, were uncertain.[120] Gutzwiller and Uskoković[119] had a clear understanding of the identity of the two compounds and pointed out that cinchona ketones can readily undergo epimerization. Since Rabe used sodium ethoxide for the cyclization step, both **4** and **5** could be considered the initial products. The less-soluble **5** was then obtained in the crystallization process.

For the third step in the conversion of *d*-quinotoxine into quinine, Rabe and Kindler reduced "quininone" with aluminum powder in the presence of sodium ethoxide in ethanol. Whether Rabe and Kindler started with pure **5** or a mixture of **4** and **5** in the reduction step is immaterial, as the reduction to form quinine was performed in the presence of sodium ethoxide,[119] which ensured the interconversion of quininone and quinidinone. In 1918, Rabe and Kindler isolated a substantial quantity of quinine (2 g), which was characterized as being "analytically pure."[7] The physical properties of their product provided very strong evidence that they had, indeed, synthesized quinine. Elemental analysis gave the correct empirical formula for quinine. In addition, the isolated product:

"melted as required at 177° and had an optical rotation in absolute alcohol of $[\alpha]_D^{14} = -158.7°$ ($c = 2.1432$ at 20°) while Rabe for the natural alkaloid had found $[\alpha]_D^{15} = -158.2°$ ($c = 2.136$ at 15°)."[7]

As shown in Table 1, of quinine, quinidine, *epi*-quinine, and *epi*-quinidine, only quinine is levorotatory; its diastereomers are either slightly dextrorotatory (+43°) or substantially

Table 1: Physical properties of quinine and three of its diastereomers.

	Specific rotation[a,b] $[\alpha]_D$ (ethanol) [°]	Specific rotation[c] $[\alpha]_D^{25}$ (ethanol) [°]	M.p.[a] [°C]	M.p.[c] [°C]
quinine (**1**)	−158.2 (−158.7[d])	–	177	–
9-*epi*-quinine (**7**)	+43.3	+43.8	"oily"[e]	amorphous
quinidine (**6**)	+243.5	+263.6	168	170–171.5
9-*epi*-quinidine (**8**)	+102.4	+108	113	111–112

[a] Values from Rabe.[9] [b] Values from the review of Turner and Woodward.[83] [c] Values from Gutzwiller and Uskoković.[119] [d] Value from Rabe.[7] [e] In the original, "ölig."[9]

dextrorotatory (+103° and +254°). A 5% contamination of quinine with the least dextrorotatory isomer would have resulted in $[\alpha]_D^{14} = \approx -148°$, a readily observable experimental distinction. Furthermore, Rabe and Kindler were comparing a synthetic sample believed to be quinine with the natural quinine—a key comparison with a classical plant alkaloid that Rabe had, by 1918, been studying for over a decade.

While it is true that Rabe and Kindler failed to provide the experimental details for the three-step conversion of *d*-quinotoxine into quinine, Rabe did report the experimental procedures for analogous reactions (for the bromination and cyclization reactions, see Section 8.4.1; for the reduction reaction, see Section 8.4.2).

8.2. The 1939 Experimental Results of Rabe and Kindler

The most compelling data that supports the assertion by Rabe and Kindler that they did, in fact, obtain quinine in 1918 are presented in this section and in Sections 8.3 and 8.4. In 1939, 21 years after their preliminary communication, Rabe and Kindler published "Cinchona alkaloids. Syntheses in the series of the cinchona alkaloids".[77] In this brief publication (1939) with experimental details, Rabe and Kindler report the isolation of additional quantities of quinine from the "preserved" two-decades-old reaction residues from the aluminum powder reduction of "quininone" (Scheme 2).[77]

Excerpts from this paper are shown in Figure 15. At the time of its publication, however, the main point of this paper, however, was the isolation of quinidine, *epi*-quinine, and *epi*-quinidine. For the purposes of this historical investigation, however, obtaining quinine in 1939 from the 1918 residues is persuasive that quinine was present 21 years earlier. Interestingly, the abstract that appears in *Chemical Abstracts* does not include the isolation of quinine![122]

The use of reaction residues from 20 years previous is a rare if not a unique event in synthetic organic chemistry. Could Rabe and Kindler have been experimentally incompetent in 1939? Unlikely. A further 21 years of experimental work on the cinchona alkaloids were performed by Rabe and his co-workers. In that time, they completed the unquestioned total synthesis of dihydroquinine (1931).[123] Rabe also published full experimental details regarding the isolation and purification, as well as the physical data of quinine,

46. Paul Rabe und Karl Kindler: Zu Synthesen in der Reihe der China-Alkaloide (Zur Kenntnis der China-Alkaloide, XXX. Mitteil.*)).

[Aus d. Chem. Staats-Institut d. Universität Hamburg.]
(Eingegangen am 10. Januar 1939.)

Die partielle Synthese des Chinins[1]) und die Totalsynthese des noch wirksameren Hydrochinins[2]) — bekanntlich ist dieses Alkaloid der China-Rinde im Chinin des Handels stets (zu etwa 10%) vorhanden — bestehen beide in ihrer letzten Stufe in der Hydrierung eines Ketons zu einem sekundären Alkohol, nämlich des Chininons zum Chinin und des Hydro-chininons zum Hydro-chinin. Außer diesen Heilmitteln läßt die Theorie im Sinne des Schemas die Bildung von je 3 weiteren sekundären Alkoholen voraussehen[3]).

Wir hatten die damals übrig gebliebenen Rückstände von solchen Reduktionsversuchen verwahrt. Jetzt gelang aus ihnen auch die Isolierung des Epichinins wie des Epichinidins.

Beschreibung der Versuche.

Das hinterbliebene obige Basengemisch mit wenig Lösungsmittel wog 214 g. Seine Auflösung in verd. Salzsäure, die eben lackmus-sauer reagierte, wurde wiederholt ausgeäthert. Die ausgeätherte Lösung wurde mit Natronlauge und Äther behandelt, wobei sich der kleinere Teil der in Freiheit gesetzten Basen in Äther löste, der größere sich als Schmiere absetzte. Die abgetrennte ätherische Lösung hinterließ nach dem Trocknen 57.3 g eines zähen Öls. Aus ihm wurde in der üblichen Weise noch vorhandenes Chinin als in Alkohol schwer lösliches neutrales Tartrat (3.3 g Salz) und darauf noch vorhandenes Chinidin als in Wasser schwer lösliches saures Tartrat (13.5 g Salz) entfernt. Aus der weinsauren Mutterlauge wurden die restlichen Basen freigemacht und dann mittels wäßriger Schwefelsäure in das neutrale Sulfat übergeführt. Aus der hinreichend konzentrierten wäßrigen Lösung (71 g) krystallisierten allmählich 14.1 g eines Salzes aus, das wie erwartet mit dem von Rabe aufgefundenen Doppelsalz[4]) identisch war, nämlich mit dem neutralen Epichinin-Epichinidin-sulfat der Formel $C_{20}H_{24}O_2N_2.C_{20}H_{24}O_2N_2.H_2SO_4 + 6H_2O$. Diese Verbindung erkennt und identifiziert man außerordentlich leicht

*) Hierüber werden Rabe u. Helmut Höter an andrer Stelle in einer Mitteilung „Zur Charakterisierung und Herstellung des Epichinins und Epichinidins" eingehender berichten.

Figure 15. Excerpts from the 1939 paper of Rabe and Kindler[77] in which they report the isolation of additional quantities of quinine from the "leftover residues" from their research reported in 1918. See Box 3 for translation.

Box 3 (see Figure 15).

"The partial synthesis of quinine and the total synthesis of the pharmacologically even more active dihydroquinine—as well known, this alkaloid is present at a 10% level in commercial quinine—involved, in the last stage, the reduction of a ketone to a secondary alcohol, namely, of quininone to quinine and of hydroquininone to hydroquinine. In addition to these pharmaceuticals, theory predicts the formation of three additional secondary alcohols".[77]

[see structures in Figure 15]

"We had preserved the leftover residues of the various reduction experiments from the past. Now we succeeded in isolating from them *epi*-quinine as well as *epi*-quinidine."

"**Description of the Experiment**"

"The above left-over mixture of bases with a little solvent weighed 214 g. Its solution in dilute HCl slightly acid to litmus was repeatedly extracted with ether. The extracted aqueous solution was treated with aqueous sodium hydroxide and ether whereby a small part of the liberated bases dissolved in ether, whereas the larger part precipitated as a grease. The ethereal solution was dried and evaporated and yielded 57.3 g of a viscous oil. From this in the usual way, the still present quinine was removed as the poorly soluble neutral tartrate (3.3 g) followed by isolation of the still present quinidine as an acid tartrate that was poorly soluble in water (13.5 g). The remaining bases were liberated from the mother liquors containing tartrate and then converted into the neutral sulfate by means of aqueous sulfuric acid. After some concentration of the aqueous solution (71 g), 14.1 g of a salt gradually crystallized. This salt, as expected, was identical to the double salt, namely the neutral epiquinine-epiquinidine sulfate ... "[77] [emphasis added]

quinidine, *epi*-quinine, and *epi*-quinidine (Table 1).[9] The isolation procedures and physical chemical parameters characterizing these compounds have been used by others decades later. It is simply unreasonable to consider that in 1939, Rabe and Kindler misidentified a compound as quinine in a reaction mixture in which they simultaneously obtained and identified the other three quinine isomers, quinidine, *epi*-quinine, and *epi*-quinidine. It is simply unreasonable to conclude that Rabe and Kindler were experimentally incompetent.

I conclude that Rabe and Kindler did convert *d*-quinotoxine into "quininone" and then to quinine in 1918.

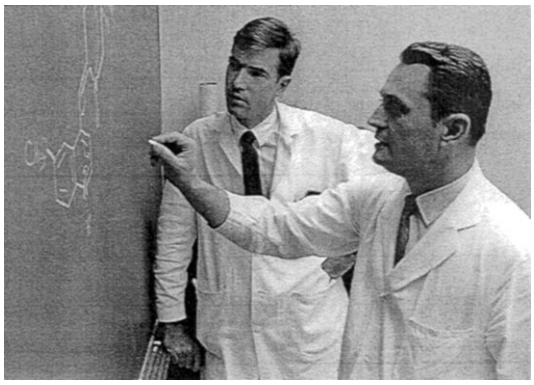


Figure 16. Jürg Gutzwiller and Milan Uskoković at Hoffmann-La Roche, New Jersey, ca. 1970. The photograph is reproduced with permission from Milan Uskoković.

8.3. The 1973 Experimental Results of Gutzwiller and Uskoković[104]

The chemical literature does not describe any attempt to repeat the exact transformations of Rabe and Kindler from 1918,[7] be it in published research or review articles, books, or within the Woodward archives at Harvard University. I carried a handwritten note to Vladimir Prelog in July of 1997 in which Gilbert Stork wrote:

"Dear Vlado, a question: do you know whether anyone repeated or tried to repeat (you?) the Rabe claim of converting quinotoxine to quinine? Doering says he does not know and you are the only one who might."[80]

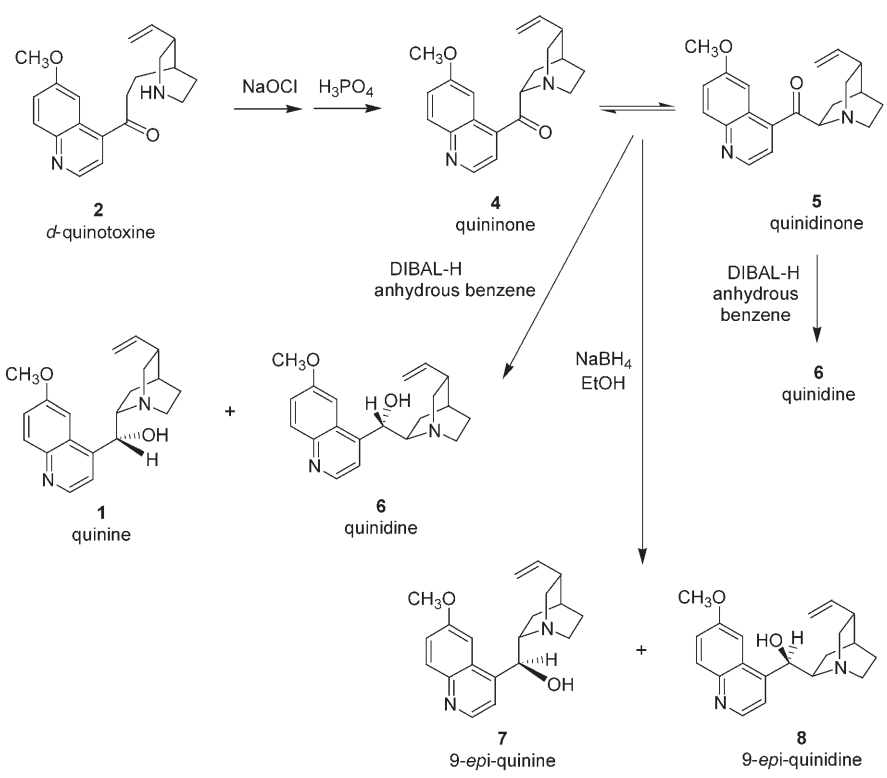
A few days later in Zürich, after Prelog had read Stork's note, I saw him give his characteristic enigmatic smile and slowly shake his head, "no."

In 1973, Jürg Gutzwiller and Milan Uskoković (Figure 16) reported[119] the closest analogous chemistry to that of Rabe and Kindler[7] (compare Scheme 5 with Scheme 2). Gutzwiller and Uskoković did not specifically state in their publication whether they had tried the reagents reported by Rabe and Kindler;[7] in fact, Gutzwiller and Uskoković used NaOCl as the halogenating reagent instead of NaOBr as used by Rabe and Kindler, phosphoric acid instead of sodium ethoxide for the cyclization, and DIBAL-H and $NaBH_4$ instead of aluminum powder. Rouhi interviewed Uskoković in April 2001, and in her *Chemical & Engineering News* article quoted Uskoković:

"'When we have a new project, we recheck the syntheses reported in the literature to prove the validity of published procedures,' says Milan Uskoković, the leader of [the Hoffmann–La Roche] team. Rabe's recipe, he says, was not suitable for their purposes until they changed it in major ways. Eventually, the team developed several quinine syntheses independent of the Rabe sequence … The Hoffmann–La Roche team had different objectives. 'Our goal was to produce both quinine and quinidine, because both were useful to us,' Uskoković says."[124]

This author had been in contact with both Uskoković and Rouhi. I asked Rouhi about information not contained in her article but pertinent to the Rabe–Kindler 1918 paper. On February 23, 2005, Rouhi informed me[125] that in her April 1, 2001 interview with Uskoković, he said:

"In the very last phase of the Rabe pathway, one has to reduce a ketone, quininone and quinidinone, to alcohol … . We tried to repeat it but we were not successful to obtain quinine in a yield that one can consider successful. One obtained a mixture: quinine was one of the



Scheme 5. Gutzwiller and Uskoković published[119] the closest analogous modern transformation of *d*-quinotoxine to quinine to that used by Rabe and Kindler[7,77] (Scheme 2). In both the diisobutylaluminum hydride (DIBAL-H) and sodium borohydride reductions, an equilibrated mixture of quininone and quinidinone was prepared prior to their exposure to the reductant. Furthermore, reduction of quinidinone by DIBAL-H (under conditions in which there is no equilibration with quininone) resulted in 94% yield of quinidine exclusively.

components but not in substantial amount that in my point of view we could call a practical yield."[126]

At that time, these Roche scientists had a goal of an "economic synthesis of these alkaloids,"[127] not just a synthesis that was academically successful. That Gutzwiller and Uskoković did, in fact, obtain quinine was not included in Rouhi's *Chemical & Engineering News* article[3] at Uskoković's stipulation and thus, this revelation was not referred to in the editorial "Setting the Record Straight."[1, 128]

On February 27, 2006, Uskoković agreed to allow that quote to be reported herein:

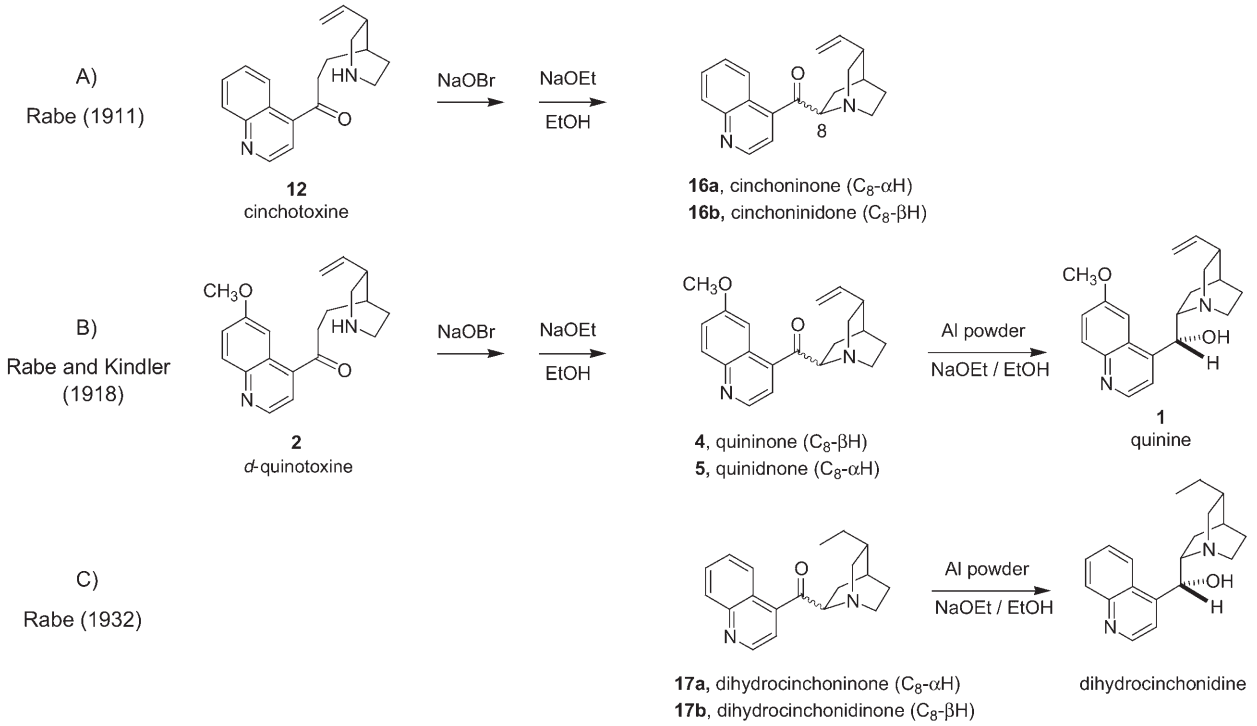
"That is about what we found repeating the Rabe conditions in the last step of the quinine synthesis … "[129]

Unfortunately, Uskoković was unable to locate the Hoffmann-La Roche laboratory notebooks from that time, as I had requested.[130] However, Uskoković and co-workers had, on at least two other occasions in the literature,[131,132] reiterated their belief that the total synthesis of quinine (and quinidine) had been accomplished by Woodward–Doering/Rabe–Kindler. For example, in 1978, five years after Gutzwiller and Uskoković's publication of alternative halogenation/cyclizations and reduction steps,[119] Uskoković, Gutzwiller, and co-workers stated:

"The medically important alkaloids quinine and quinidine have long been subjects of one of the most intensive structural and synthetic investigations in classical chemistry.[83] The original and quite elegant syntheses of these alkaloids[5–7,120] [by Rabe and Kindler and by Woodward and Doering] … "[131]

8.4. Additional Literature Results Supporting the Rabe–Kindler Reports: Experimental Conditions for Analogous Transformations

Rabe and Kindler did not provide experimental details of the three steps in the conversion of *d*-quinotoxine into quinine (Equation B in Scheme 6).[7] However, Rabe did provide the experimental conditions for three analogous reactions: the experimental details for the halogenation and cyclization reactions were described by him in 1911 (Equation A in Scheme 6) and for the reduction with aluminum powder in 1932 (Equation C in Scheme 6). Rabe unambiguously stated that the reactions were the same by referencing and comparing the transformations of the quinine series with those of the cinchotoxine and dihydrocinchonidinone series.[7,9,10] Details for these analogous reactions are discussed in the following two sections. It can be argued that experimental details for these analogous reactions are not



Scheme 6. In 1918 Rabe and Kindler published the three-step conversion of *d*-quinotoxine into quinine (Equation B) without providing experimental details.[7] In two other papers, Rabe presented the experimental conditions for analogous reactions within the cinchona alkaloids. In their 1918 paper, Rabe and Kindler referred to the 1911 publication (Equation A) of Rabe[10] for the method of bromination and cyclization of cinchotoxine **12** to cinchoninone **16a** (and likely its more-soluble C8 isomer **16b**). These bromination/cyclization steps are analogous to the two-step transformation of *d*-quinotoxine to "quninone" (first two steps in Equation B; see Figure 17 for the experimental portion of this 1911 publication). In his 1932 publication, Rabe referred to the lack of experimental information on the reduction of "quininone" to *d*-quinotoxine with aluminum powder (Equation C)[9] and experimental conditions were therein reported (see Figure 18). In 1939, Rabe and Kindler reported that this reduction of the quininone–quinidinone mixture with aluminum powder led to quinine and its three C8 and C9 stereoisomers[77] (quinidine, *epi*-quinine, and *epi*-quinidine are not shown in Equation B; see Scheme 2). See Figure 15.

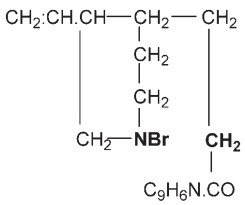
applicable because the presence of the methoxy and vinyl groups in quinine differentiates quinine from its analogues. Indeed, the quinoline methoxy group is conjugated with the ketones in *d*-quinotoxine, quininone, and quinidinone, thus making the carbonyl carbon atom in these three compounds somewhat less electrophilic. The double bond in the quinine series could also lead to undesirable side reactions.

8.4.1. ***The Halogenation/Cyclization Steps***

In the 1918 Rabe and Kindler publication on the three-step conversion of *d*-quinotoxine into quinine (Scheme 2) the authors state (Figure 3):

"quinotoxine when treated with sodium hypobromite is converted to N-bromoquinotoxine; by use of alkali, hydrogen bromide is removed and quininone is formed … Regarding the more detailed formulation of the reactions we have used, we refer to paper XV: The partial synthesis of cinchonins, B. **44**, 2088 (1911)."[7]

The experimental section of the above referenced 1911 paper is shown in Figure 17. The formation of the *N*-bromo intermediate **18** is discussed, and its correct elemental analysis is presented.[10]



18

The text of the 1911 paper states that hypobromous acid is the brominating agent; however, the experimental section indicates that sodium hypobromite is the actual reactant.[10] In their full paper, Woodward and Doering state that the bromination is effected by sodium hypobromite[6] while, in their review, Turner and Woodward refer to the brominating agent as hypobromous acid.[83] Interestingly, the abstract of this 1911 paper published in *Chemical Abstracts* incorrectly refers to the starting material as "quinotoxine" and the brominated product as "*N*-Bromoquinotoxine."[133,134]

Rabe et al. and other research groups performed similar halogenations/cyclizations in the cinchona alkaloid series. For example, in 1913, Rabe converted dihydrocinchotoxine (**19**) into dihydrocinchonidinone (**17a**) by treating **19** with NaOBr followed by cyclodehydrobrominaton with sodium ethoxide (Scheme 7).[135] In 1913 and 1917 Kaufmann et al. converted **19** into **17a** using Br_2/48% HBr followed by cyclizations of the intermediate α-bromoketone with sodium ethoxide (also shown in Scheme 7).[136,137] Again, in the case of quinidinone and quininone (see Section 8.1), a time-dependent variation was observed in the optical rotation of "**17a**" and after three days a value of $[\alpha]_D^{21} = 75.8°$ (ethanol) was reached; the isolation of one cinchona ketone is due to selectivity in the crystallization rather than selectivity in their formation.

Experimentelles.

***N*-Brom-cinchotoxin (Formel II).**

Eine Auflösung von 58 g Cinchotoxin (1 Mol.) in 200 ccm *n*.-Salzsäure (enthaltend 1 Mol. Salzsäure) wird mit 500 ccm Äther überschichtet. Hierzu läßt man bei Zimmertemperatur unter lebhaftem Turbinieren eine kalte Lösung von unterbromigsaurem Natrium, bereitet aus 32 g Brom (1 Mol.) und 400 g 6-prozentiger Natronlauge (3 Mol. Natronlauge), im dünnen Strahl einlaufen. Nach insgesamt 10 Minuten wird die ätherische Lösung rasch abgehoben und mit wasserfreiem Natriumsulfat versetzt. Allmählich scheidet sich ein Salz ab. Nach 24-stündigem Stehen wird abfiltriert.

Bei einem solchen Versuche wurde aus dem Rückstande das organische Salz durch Auskochen mit Alkohol isoliert. Es enthielt 24 g unverändertes Cinchotoxin. Aus der abfiltrierten ätherischen Lösung krystallisierten nach dem Einengen 23 g des Bromkörpers in analysenreinem Zustande aus. Es betrug daher die Ausbeute ca. 54 %.

0.1925 g Sbst.: 13.2 ccm N (22°, 746 mm). — 0.1740 g Sbst.: 0.0869 g AgBr.

$C_{19}H_{21}ON_2Br$. Ber. N 7.51, Br 21.44.
Gef. » 7.78, » 21.25.

Das *N*-Brom-cinchotoxin ist unlöslich in Wasser, ziemlich schwer löslich in Äther und in kaltem Alkohol, sehr leicht löslich in heißem Alkohol. Aus Äther oder aus Alkohol erscheint es in farblosen, langgestreckten Prismen vom Schmp. 153°. Das Verhalten gegenüber Lackmus und gegenüber Methyljodid ist schon in der Einleitung erwähnt.

Überführung des *N*-Brom-cinchotoxins in Cinchoninon.

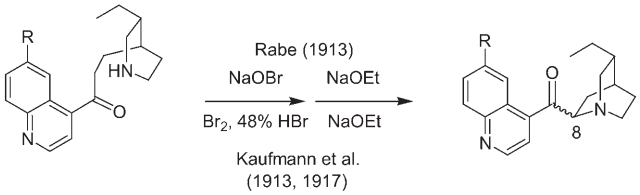
Die unten mitgeteilten Versuchsbedingungen gaben die beste Ausbeute. Warum unter anderen Verhältnissen die Ausbeute zurückging und die Aufarbeitung so erschwert wurde, soll noch näher geprüft werden.

Eine kochende Lösung von 10 g Bromkörper und 250 ccm Alkohol wurden nach der Entfernung der Wärmequelle mit 30 ccm kalter Natriumäthylatlösung, enthaltend 1.5 g Natrium, versetzt, wobei anfangs eine gelbliche, später eine rotbraune Färbung auftrat. Nach dem freiwilligen Erkalten wurde verdünnte Salzsäure bis zur schwach sauren Reaktion auf Lackmus hinzugefügt, durch Wasserdampf der Alkohol abgeblasen und mit Äther ausgeschüttelt. Die so behandelte wäßrige Lösung gab nach dem Versetzen mit Alkali an Äther das gebildete Cinchoninon als ein erstarrendes Öl ab. Die Rohausbeute betrug 3.5 g oder 46 % der Theorie. Das Keton wurde aus möglichst wenig heißem absolutem Alkohol umkrystallisiert. Es schmolz — ebenso wie eine Mischprobe — bei 126—127° und besaß alle die früher angegebenen Eigenschaften[1]).

0.1695 g Sbst.: 0.4802 g CO_2, 0.1040 g H_2O.

$C_{19}H_{20}ON_2$. Ber. C 78.08, H 6.85.
Gef. » 78.25, » 6.87.

Figure 17. Excerpt from the experimental section of Rabe's 1911 publication[10] describing the bromination with NaOBr and cyclization reactions shown in Scheme 6A. See Box 4 for translation.



19, R = H, dihydrocinchotoxine

17a, R = H, dihydrocinchoninone (C_8-αH)

17b, R = H, dihydrocinchonidinone (C_8-βH)

Scheme 7. Additional cyclizations of the toxins.[135–137] Kaufmann et al. performed the bromination/cyclization on both dihydrocinchotoxine and dihydroquinotoxine (R = MeO).

Box 4 (see Figure 17).

Experimental

***N*-Bromo-cinchotoxine**

A solution of 58 g cinchotoxine (1 mol) in 200 cc 1 N hydrochloric acid (1 mol) is layered with 500 cc of ether. To this mixture a cold solution of NaOBr (prepared from 32 g of bromine (1 mol) and 400 g of 6% sodium hydroxide solution (3 mol)) is added in a thin stream with vigorous stirring. After a total of 10 min, the ethereal layer is quickly separated and dried with sodium sulfate. After some time, a salt separates. It is filtered after 24 h.

In one of these experiments, the organic salt was isolated from the residue by extracting with boiling ethanol. It contained 24 g of unchanged cinchotoxine. From the separated ethereal solution, after concentration, 23 g (54%) of the bromo compound crystallized analytically pure.

0.1925 g material: 13.2 cc N (22°, 746 mm).—0.1740 g material: 0.0869 g

$C_{19}H_{21}ON_2Br$.	Calculated	N 7.51, Br 21.44
	Found	N 7.78, Br 21.25

N-Bromocinchotoxine is insoluble in water, poorly soluble in ether and cold alcohol, readily soluble in hot alcohol. From ether or alcohol, it crystallizes in colorless long prisms m.p. 153°. Its behavior towards litmus paper and towards methyl iodide has already been mentioned.

Conversion of *N*-bromocinchotoxine into Cinchoninone.

Best yields were obtained under the experimental conditions described below. We still have to ascertain why under other conditions the yield was diminished and the workup became difficult.

A boiling solution of 10 g of the bromine compound in 250 cc ethanol was treated, after removal of the source of heating, with 30 cc of a cold solution of sodium ethylate, prepared from 1.5 g of sodium. At the beginning, the color turned to yellow, later to reddish brown. The solution was allowed to cool, then dilute hydrochloric acid was added until the solution was just acidic to litmus paper. The alcohol was removed by steam and the remaining aqueous layer extracted with ether. The aqueous solution was treated with alkali, and ether yielded the cinchoninone which formed as a solidifying oil. The crude yield was 3.5 g (46%). The ketone was recrystallized from a minimum volume of hot absolute alcohol, its m.p., as well as its mixed m.p., was 126–127°C and had all its previously described properties (Ref. 1).

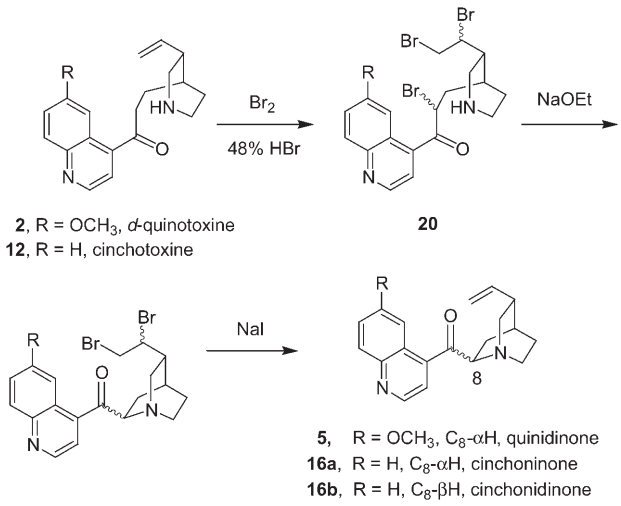
0.1695 g Material: 0.4802 g CO_2, 0.1040 g H_2O

$C_{19}H_{21}ON_2$.	Calculated,	C 78.08, H 6.85
	Found	C 78.25, H 6.87

Ludwiczakówna[138,139] performed reactions analogous to those shown in the previous section, by using toxine derivatives **20** devoid of the vinyl group by the then very clever use of a masked vinyl group (Scheme 8).

Perhaps Uskoković and co-workers at Hoffmann-La Roche in New Jersey made the most significant contributions to the chemistry and synthesis of the cinchona alkaloids in the 1970s.[104,105] The single most direct analogy to the bromination-cyclization sequence used by Rabe and Kindler outside of the Rabe group is found in the comprehensive study by Gutzwiller and Uskoković.[104] In 1973 these authors reported:

"After extensive experimentation with different halogenating agents, we found that *N*-chloroquinotoxine could be readily prepared by treatment [of quinotoxine] with sodium hypochlorite. The *N*-chloramine was cyclized by treatment with a strong non-nucleophilic mineral acid [phosphoric acid] and subsequent work-up under basic conditions."[119] (See Scheme 5.)



Scheme 8. Cyclizations in the cinchotoxine and *d*-quinotoxine series by Ludwiczakówna.[138,139] Compare these halogenation/cyclizations reactions with those shown in Schemes 2 and 7. Note that equilibrium mixtures of the ketones are obtained, as indicated in Scheme 4.

8.4.2. ***The Reduction Step: Literature Analogies***

The third and final step in the 1918 Rabe–Kindler partial synthesis of quinine is the reduction of "quininone"[7] with aluminum powder and sodium ethylate in ethanol. As shown in Figure 3, the experimental conditions were not provided at that time, yet the 1918 paper states:

"The use of this unusual reducing mixture represents the real advance in the synthesis of the series of cinchona alkaloids."[7]

In a lengthy paper published in 1932 with experimental data from three universities over almost 30 years, Rabe undertook to provide experimental details not provided by him and his co-workers in previous publications. Regarding the 1918 reduction method with aluminum powder, Rabe said in 1932:,

"This method introduced by P. Rabe and K. Kindler[7] has not yet been described in detail. Therefore, we shall illustrate it with the example of hydrocinchoninone."[9]

Figure 18 presents the relevant experimental details for this reduction with aluminum powder. Yields are not provided. Furthermore, Rabe had the opportunity of providing the experimental results for "quininone" (and ultimately for quinine) rather than for hydrocinchoninone. One can only speculate as to why Rabe did not report the results in the quinine series or the yields in the hydrocinchoninone system.

In 1908, Rabe treated "cinchoninone"—likely to be the less soluble cinchonidinone (**16a**) or an equilibrating mixture of the two ketones **16a** and **16b**—with sodium/ethanol as well as iron/acetic acid.[140] Low yields of cinchonine (**11**) were obtained, but its "identity was established beyond doubt by many of its reactions"[140] and by its melting point.

The first and most comprehensive modern study of the reduction of the quininone–quinidinone system was reported

Die nicht-katalytische Hydrierung gelingt mit Hilfe von Aluminiumpulver und Natriumäthylat in alkoholischer Lösung. Diese von P. Rabe und K. Kindler[2]) eingeführte Methode ist noch nicht eingehend beschrieben worden. Sie wird daher am Beispiel des Hydro-cinchoninons erläutert.[3])

100 g Keton wurden in 1 Liter 99,5-proc. Alkohol gelöst und mit einer Auflösung von 84 g Natrium in 1280 ccm abs. Alkohol versetzt. Unter Turbinieren wurden 84 g Aluminiumpulver hinzugefügt. Die zuerst lebhafte Reaktion wurde durch zweistündiges Erwärmen bis zum schwachen Sieden unter Zusatz von etwa 400 ccm absolutem Alkohol zu Ende geführt. Dann wurde heiß filtriert, die Lösung mit verdünnter Salzsäure kongosauer gemacht und der Alkohol abdestilliert. Die entstandenen Reduktionsprodukte wurden mit 30-proc. Natronlauge in Freiheit gesetzt und mit Äther ausgeschüttelt.

[1]) Siehe Fußnote 3, S. 242.
[2]) B. 51, 466 (1918).
[3]) Nach Versuchen von Elisabeth Müller, Diss. Hamburg 1920. Siehe auch *Vereinigte Chininfabriken Zimmer & Co.*, Frankfurt a. M., D. R. P. Nr. 330813.

Figure 18. Excerpts from Rabe's 1932 paper[9] in which the experimental details are provided for the reduction reaction with aluminum powder shown in Scheme 6C. See Box 5 for translation.

Box 5 (see Figure 18).
The non-catalytic reduction succeeded through use of aluminum powder and sodium ethylate in alcoholic solution. This method introduced by P. Rabe and K. Kindler[2)] has not yet been described in detail. Therefore, we shall illustrate it with the example of the hydrocinchoninones.[3)]

100 g of ketone [hydrocinchoninone, see Scheme 6C] were dissolved in 1 liter of 99.5% alcohol and treated with a solution of 84 g of sodium in 1280 cc absolute alcohol. Aluminum powder, 84 g, was added with vigorous stirring. The reaction, at first vigorous, is completed by warming to light boiling for two hours with addition of about 400 cc of absolute alcohol. After being filtered when hot, the solution was made acid to Congo Red with dilute hydrochloric acid, and the alcohol was distilled off. The reduction products so obtained were liberated with 30% aqueous sodium hydroxide and extracted with ether.

[2)] B. **51**, 466 (1918).
[3)] From the Experimental details of Elisabeth Müller, Dissertation Hamburg 1920. See also *Vereinigte Chininfabriken Zimmer & Co.*, Frankrut a. M., D. R. P. No. 330813.

by Gutzwiller and Uskoković in 1973 (Scheme 5).[119] Reduction of a preformed mixture of quininone and quinidinone with DIBAL-H yielded a mixture of quinine and quinidine. A 94% yield of quinidine was isolated when freshly prepared pure quinidinone was reduced with DIBAL-H. In contrast, reduction of a preformed mixture of quinidinone and quinidinone with sodium borohydride resulted in a high yield of a mixture of *epi*-quinine and *epi*-quinidine.

8.5. On Repeating the Rabe–Kindler Synthesis of Quinine from d-Quinotoxine

Why is it that no systematic study has been reported that repeats the Rabe and Kindler transformations?[7,77] Today there is only one type of project that would use Rabe's reagent of aluminum powder as a reducing agent: historical research, trying to replicate the Rabe and Kindler transformations of 1918.[7]

Uskoković published[119] the closest analogous chemistry to that of Rabe and Kindler (compare Scheme 2 and Scheme 5[7]). Uskoković remembered[126] that he had obtained quinine from the reduction of a quinidinone/quininone mixture with aluminum powder (see Section 8.3.). I contacted the organic chemistry laboratory at the University of Hamburg, but the Rabe–Kindler laboratory notebooks are not available. I have made no effort to locate laboratory notebooks from Jena or Prague, other locations where Rabe conducted research on the Cinchona alkaloids.

What would the value be in a 21st Century attempt to repeat the 1918 report from Rabe and Kindler?[7] As summarized by Stork:

"This was a no-win situation: the transformation is not simple, even if feasible. And there are practically no details. If one should make the attempt, and it failed, there would be inter alia, two possibilities: what Rabe did was not followed exactly; or, the checker is a lousy chemist."[141]

In 2005, Doering confirmed that he had not tried to repeat the Rabe and Kindler conversion of *d*-quinotoxine into quinine:

"Both [Woodward] and Prelog, who had a special interest in the synthesis of quinine, believed without question in the reliability of Rabe's published work …"

"It is almost never possible to reproduce published details. They assume an indefinable amount of experience and cannot be written for the first time cook who has never mastered the elementary techniques! The premise that the best, detailed descriptions suffice to guarantee reproducibility is contrary to universal experience. Try writing two sets of directions for playing a piano composition—the one to reproduce the performance according to Ogdon, the second Horowitz!"[70]

Doering remains firm in his convictions, stating:

"We all know that, for decades, many organic chemistry publications appeared in journals such as *Tetrahedron Letters*, *JOC*, and *JACS* in the form of preliminary communications in which a series of compounds were, for example, stated to undergo a new reaction, X(i)→Y(i), where i = large number of examples, and where the experimental conditions for a single example was given. This was a common practice. Now, most (all?) major communication journals require full experimental details in the supplementary sections."[70]

I asked Stork if he had ever tried to repeat the Rabe procedure. Stork replied:

"No. Incidentally, the cost/benefit ratio would not be very favorable: most of the details one would need are not in the Rabe one page paper of 1918. One would be left to surmise what he did—and then one would either be successful or not. If the former, all that would be accomplished would be to buttress the case that what has become known as the Woodward synthesis should have been called the Rabe–Woodward synthesis, since a good half of the synthesis would be due to Rabe. Or, one would fail … and then, a reasonable conclusion would be that the attempting duplicator was not as good a chemist as Rabe or Kindler."[142]

Would attempting to reproduce Rabe–Kindler have been worthwhile? As Stork said:

"When one claims total synthesis on the basis of previously established transformations, one should at least verify that the transformations proceed as one believes. For whatever reason, Woodward and Doering never tried the Rabe steps."[124,142]

Indeed, as summarized by Scott Snyder, the identicalness of the reagents is open to question:

"… would a pre-World War I sample of 'powder' produced in Germany be the same as a sample produced during/after World War II in the States? … if perhaps Rabe on a given day did actually have success, and fifteen years later, using another bottle, might he have gotten a different result? There are so many examples of reagent contamination, different quality across different samples, and related factors affecting chemical outcomes … "[143]

Even had Woodward and Doering (or anyone else) succeeded in converting *d*-quinotoxine into "quininone" and then "quininone" into quinine with the reagents reported by Rabe and Kindler, we would still not know for certain if these were the exact conditions used by Rabe and Kindler.

9. The Human Side of Science

9.1. The Personalities and Circumstances of Woodward, Doering, and Stork

By the age of 20, Woodward had earned his BSc and PhD from MIT. He joined Harvard in 1937, first as a postdoctoral fellow and then as a member of the elite Society of Fellows. Woodward published four breakthrough papers in 1941 and 1942 that correlated UV spectra with molecular structure, that is, the relative orientation and position of 1,3-dienes and α,β-unsaturated ketones in steroids and the number and types of substituents and the relative orientation of the bonds.[144–147] Soon known as the "Woodward Rules", these were well publicized in the Fieser and Fieser book, *Steroids*.[148]

A confluence of events were to sweep Woodward, Doering, and Stork together, in the early 1940s and, as it turned out, fatefully so in the early 2000s. Quite independently, Woodward and Stork were both interested in quinine in their youth. To illustrate this, on November 30, 1948, the young then postgraduate student but one-day eminent organic chemist Yoshiro Kobayashi wrote Woodward and inquired about his quinine synthesis:

"By what motive or idea started [sic] you study in this particular work?"[149]

Woodward responded on February 16, 1949:

"The synthesis of quinine was a project which I had dreamed about from the time of my first interest in chemistry as a child. Indeed, I learned much of my organic chemistry during the elaboration of paper schemes for the synthesis of the alkaloid. You will not find it difficult to imagine that my earliest schemes were very unrealistic; none the less each subsequent scheme served its purpose in sharpening my knowledge of the field to which I was (and am) devoted. Much later, when the opportunity presented itself of actually embarking on the attempt to carry out a synthesis of quinine, I seized it, with the results known to you."[150]

Stork's interest in the synthesis of quinine can be traced to his years as an undergraduate student in 1940–1941. His first publication in the quinine area occurred as a graduate student (Figure 19) in 1946 with a publication with his PhD advisor

Figure 19. Gilbert Stork as a graduate student at the University of Wisconsin, ca. 1944. The photograph is reproduced with permission from Gilbert Stork.

Samuel M. McElvain on the synthesis of (±)-*cis*-3-ethyl-4-piperidineacetic acid (meroquinene, **13**).[151] As recounted by Stork:

"I started getting interested in quinine in 1940–41: when an undergraduate at the University of Florida, I saw in *Chemical Abstracts* an abstract of a paper by Rabe on the structure of Quinine. This included the 'structure' (essentially no stereochemistry) deduced for quinine, and it fascinated me. I convinced the chemistry department at Florida to let me have a lab, and worked there (dangerously alone) until I left for graduate school in 1942. I continued on my quinine project, with McElvain's consent, until I heard, through the newspapers and magazines of Woodward and Doering's achievement. A call to Woodward convinced me (I was only 22 at the time, and easy to convince) that he had made homomeroquinene, very closely related to the meroquinene I was attempting to synthesize. I then stopped my own work, but I claim that the pathway I established for the construction of dihydromeroquinene was the first stereospecific construction of a natural product precursor. (The word should really be stereorational, to distinguish a successful, planned, stereocontrolled construction from an unplanned happenstance)."[80]

The similarities and contrasts between Woodward and Stork are remarkable. Both began working on the total synthesis of quinine in their early youth. Woodward, an instructor in the Chemistry Department at Harvard from 1941–1944,[19] published "The Total Synthesis of Quinine"[5] in 1944 at the age of 27. Stork published his first paper dealing with quinine[151] as a graduate student in 1946 at the age of 24, and "The First Stereoselective Synthesis of Quinine"[2] in 2001 at the age of 79, a 55-year spread. Synthetic organic chemistry and total synthesis are their fields of expertise. Stork began his own academic career at Harvard (1944–1953) as an untenured instructor and assistant professor alongside Woodward (Associate Professor 1946–1950). Stork joined Columbia University in 1953 where he continues to conduct research today.

Woodward in the 1940s was a strong competitor. He was beginning to rock the foundations of the then conservative elite in organic chemistry with his new style: a seminal grasp of physical properties that would control chemical reactions;

a way of constructing organic molecules that would revise synthetic organic chemistry; a style of writing and a language more suited to prose than the chemical literature; a flamboyance in presentation—a blend of a musical maestro, a movie star, and a Nobel Prize winner—and a hard-hitting lifestyle which included many-hour, colored-chalk seminars accompanied by a bottle of liquor, the performance ending simultaneously with the last drops of the refreshment finished and the last open space on the chalkboard used. Some say there was never an erasure! As recalled by Frank Westheimer, Woodward's colleague at Harvard for nearly 30 years:

"Woodward's own lectures are famous, or perhaps *notorious* would be a more suitable adjective … He would start in the upper left-hand corner of a large blackboard and present his synthesis, ending at the lower right-hand corner, with a display that would have been perfect for publication. Every square inch of the board was neatly covered with elegant formulas … His lectures often lasted for three hours and occasionally for more … Woodward would show off by drinking an entire pitcher of daiquiris while he lectured, without noticeable effect … But Bob's megalectures were not displays of arrogance—or anyway not primarily so. They were based on Bob's need for perfection. If a subject required three hours to explain properly, then he would give it three hours and expected his audience to do likewise."[152]

John D. Roberts spent a year (1945) at Harvard on a National Research Council Fellowship. He recalls from that time:

"Our postdoctoral group loved to congregate in Woodward's office after seminars … Many of these sessions were Socratic, with problems posed, discussed, and solved. Others were more Delphic. [Paul D.] Bartlett accused us of going to the horse's mouth, and observed (correctly), 'He will practically neigh for you.' We generated three axioms about Woodward: He never got drunk, he never got tired, and he never perspired. Each of these became less axiomatic on one occasion or the other, but they held up very well indeed for many years."[153]

As summarized by Doering:

"A lot of people were put out by Woodward's style which could have been accused of being pretentious … He prided himself of writing in a way that was different than others … his ego, it differentiated himself from country rock …"[154]

Nobelist Vladimir Prelog was one of Woodward's closest personal friends and professional colleagues. Prelog was also a soft spoken, a highly liked and admired man of interesting tales and quiet demeanor. Somewhat uncharacteristically,[79] Prelog was rather open in his oral history for the Chemical Heritage Foundation when he similarly described Woodward's relationship with other chemists:

"Woodward first came [to Switzerland] in 1948 … At that time he was about 31 years old. He had had some conflicts with American chemists, especially the older ones, because he was very self-confident. He realized that he knew much more chemistry than these people and he irritated them. Some of them, of course, recognized him, but the others just thought that he was not a pleasant fellow."[155]

Westheimer described the young Woodward as follows:

"After graduating from MIT, Bob spent a summer at the University of Illinois, where he managed to alienate—well, to outrage—two of the most powerful of America's chemists. A number of explanations have been advanced for his social failure; my explanation rests on the assumption that Bob failed to conceal adequately that he was much brighter than the Illinois professors."[152]

As overtly dominating was the personality of Woodward, Stork's personality is one of subdued yet extraordinary scientific excellence, quiet persistence, understated charm, and impressive persuasiveness. I feel it necessary at this point to make a "conflict of interest" statement regarding Gilbert Stork. When I was developing the *Profiles, Pathways and Dreams* series, I made a special, personal trip to the home university of only one potential author: Gilbert Stork. Gilbert is not noted for his enjoyment of writing—in contrast, for example, to one of his closest friends Carl Djerassi. I felt that the only chance I could obtain Gilbert's autobiography was through a personal plea. I knew it would be hopeless, and it was. However, a decade later, I was able to persuade Stork to "star" in one of six documentary videos I produced in the series *In the Pursuit of Discovery*, the other five interviewees being Djerassi, Derek Barton, Marye Anne Fox, Dudley Herschbach, and Koji Nakanishi.[28] Thus, I acknowledge my own professional admiration of and personal affection for Gilbert Stork (Figure 20).

Figure 20. Jeffrey I. Seeman and Stork at a *Chemical & Engineering News* celebration "Top 75 Distinguished Contributors to the Chemical Enterprise" in Boston in 1996. Note the medal around Stork's neck.

Bill Doering's short career in synthetic organic chemistry with Woodward and quinine was handsomely received by much positive acclaim and recognition. Comfortably enjoying emeritus status at Harvard, in 2000 and 2001 Doering once again found himself in the center of "quinine fame", this time with the word "myth" associated with his work and not "glory". Doering, of course, had received much praise as a result of his own major and independent successes in physical organic chemistry: carbene chemistry, non-benzenoid aromatic compounds, radical chemistry, and that remarkable compound bullvalene, to name just a few.

In the early 1940s, Doering's relationship with Woodward was as a postdoctoral colleague and a friend. According to Doering, "there was no intellectual input on my part in that original [synthetic] scheme."[156] Woodward spent many hours in the laboratory talking with and watching Doering but, according to Doering's memory, did no laboratory work (Figure 21).

Figure 21. Doering and Woodward at Harvard in 1944. The photograph is reproduced with permission from the Fritz Goro archives.

"Laboratory work really wasn't Bob's strength, and he had no liking for it … Bob could boil water, but I think it was pretty tough to boil an egg. He just was totally impossible … He'd be in [the laboratory] watching most of the time. He was a very sharp observer, with a very, very sharp eye. He was able to direct later graduate students through what he had seen, an experimental experience which he had acquired vicariously rather than though his own hands.

"Woodward became interested in organic chemistry when he was ten years old and at some point after that taught himself German so that he could read *Beilstein.* He would read *Beilstein* in order to find either the mistakes that people had made or problems that hadn't been solved. Much of his early work comes from and clearly is stimulated by having pored through *Beilstein*."[156]

I have seen two sides of Bill Doering. During our first interactions involving many e-mails, he was short, crisp, and on rare occasions, even biting. Then, during our first face-to-face meeting, I showed him copies of items from the Harvard archives. These included pages from his laboratory notebooks[157] that he had not seen in over 50 years and was certain had been lost forever.[156] I can recall the moment clearly; it was like those sultry summer afternoons when suddenly, the dark clouds unexpectedly pass by and the powerful sunlight hits our face. Exuberant smiles arrived! Doering was capable of warmth and humor.

A few days later, on October 1, 2005, I escorted Doering to the Harvard archives where I showed him the originals, discovered during days of searching and research. Doering's appreciation and amazement increased, and with it, his attitude toward me softened. He held his lab notebooks with childlike joy and appreciation, savoring events 60 years previous (Figure 22). Many of the other documents he had never seen: the reviewers' comments for Woodward's and his 1945 quinine paper; the correspondence between Rabe and Woodward; the 1944 letter from Stork to Woodward (Figure 11).

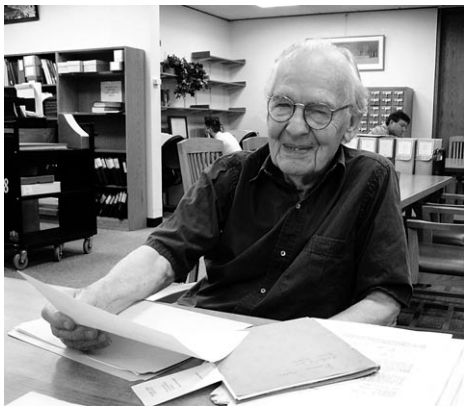


Figure 22. Doering reviewing his 1944 laboratory notebooks at the Harvard archives in September 2005. The photograph is reproduced with permission from Toshi Ueta.

The letter from Stork clearly affected Doering the most. It was clear to Doering that Stork's concern about the 1918 Rabe and Kindler precedent began well before Woodward and Stork had ever met. Stork's inquiry in 1944 preceded whatever interactions Stork and Woodward would subsequently have during Stork's brief nontenured professorship at Harvard shortly thereafter and for the following 30 years. Doering said of Stork:

"He raises a fundamental question. Can you be sure of Rabe? Our synthesis depended on the reproducibility of Rabe's claims. There is no question about that. It has to be reproducible. If it's wrong, if it's fabricated, if it's virtual, then [it is not] quinine … Woodward and Prelog considered Rabe to be reliable, without question … I have no idea how I would have responded at the time. Had there been any question voiced about the reliability of Rabe's work, I would have repeated the work … ."[154]

I hesitate to speculate what might have transpired had Doering been aware of Stork's questioning of the Rabe work in 1944.

Doering continued:

"[Today] my reputation can't be damaged, and it can't be enhanced. Paul Rabe, rest in peace.

"The purpose of [repeating today] the synthesis is to remove the blot on his reputation. The old man should be allowed to rest in peace."[154]

The same sentiments go to Karl Kindler.

9.2. On Woodward's Youthful Impatience and Immense Ego: Motivations to Advance His Career

"The Total Synthesis of Quinine" was of far greater importance to Woodward than to Doering. Doering was the student; hence, this work was critical for him to obtain his first

independent academic position. His career would then depend on his own independent achievements. Doering did receive the 1966 ACS Award for Creative Work in Synthetic Organic Chemistry. As mentioned in Section 9.1, Doering is noted primarily for his research in physical organic chemistry, for which he received the 1989 James Flack Norris Award in Physical Organic Chemistry and the 1990 Robert A. Welch Award. Once quinine was completed, Doering would not return to natural products chemistry or total synthesis.

In the very early 1940s, Woodward's future at Harvard University, in particular, and in the academic world, in general, was still very uncertain. On July 21, 1942, Linus Pauling (Figure 23) wrote from Caltech to Woodward, who had been at Harvard since 1937:

Figure 23. Linus Pauling at Caltech in 1942. From the Linus Pauling collection, Special Collections, Oregon State University.

"I have learned from Dr. E. R. Buchman that there is the possibility that you might be interested in accepting appointment as Research Fellow at this Institute for the coming year. Would you please let me know whether or not this is so, since I think that it might well be that we could arrange for you to fit into our program."[158]

The Woodward papers at the Harvard archives show that Woodward typically answered inquiries after some months delay, often with an apologetic opening paragraph. Thus, atypical for Woodward, he promptly responded on August 3, 1942:

"My position here affords me an adequate research fund, as many graduate students as care to enroll in my research course, a congenial teaching schedule, and an increase slightly in excess of $4000 per year. On the other hand, my present appointment runs only until July, 1943, and it is not yet clear whether there will be a vacancy in another grade, for which I would be eligible, at that time. Consequently, I am interested in any opportunities elsewhere with approximately equivalent advantages and the possibility of relative permanence. I should appreciate further details about the appointment you have in mind."[159]

Woodward was surely concerned about obtaining a tenured faculty position. He would have to wait more than two months before hearing from Pauling. On October 5, 1942, Pauling declined offering a position to Woodward (Figure 24).[160] At that moment in time, Caltech lost a rare

CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA

GATES AND CRELLIN LABORATORIES OF CHEMISTRY — October 5, 1942

Dr. R. B. Woodward
Division of Chemistry
12 Oxford Street
Cambridge, Massachusetts

Dear Dr. Woodward:

I thank you for your letter of August 3, the answer to which has been delayed because of my absence from Pasadena.

We do not have at present any opening which would interest you, and the times are so upset that it is not possible to make plans for the future. I hope that it will at some time turn out that you can do some work in our Laboratories. If you ever happen to be in the neighborhood, please come to see us.

Sincerely yours,

Linus Pauling

Figure 24. Pauling wrote to Woodward on July 21, 1942, inquiring if he was interested in a position at Caltech. On August 3, 1942, Woodward answered in the affirmative. Pauling then responded with the letter shown above.[160]

opportunity to recruit a scientist who would change the face of science. Caltech's rejection surely would have increased Woodward's anxiety and frustrated his ego.

What strategy for tenure at Harvard and international recognition would be best for Woodward? (Are the answers to these two questions the same?) What strategy for research would be best for Woodward? Doering, retrospectively, speaks of the strategies used by Woodward in choosing his synthetic targets:

"[Woodward] certainly already knew that if you were to become a synthetic organic chemist, targets that were not recognized widely might be just as difficult to synthesize as targets that *were* widely recognized. So if you ask how he chose his problems (the synthetic targets), a necessary condition for his target was that it should be widely known natural product … It falls into the same category as the old saying, 'Well, if you're going to marry for love, she might as well be rich.' [laughter] If you're going to choose a target, it might as well be an easily recognizable one … Certainly, selecting quinine during the war, with malaria a concern—can you imagine a better choice?"[156]

So, Woodward chose quinine as his synthetic target; he also chose Doering who had already built a reputation as someone who "got around a laboratory pretty well."[156] To further build his reputation, Woodward began to promise quinine to the US War Department. This strategy reminds me of a saying Woodward's close friend, Derek Barton (Figure 25) said to me in the early 1990s,

Figure 25. Albert Eschenmoser, Stork, Woodward, and Derek H. R. Barton, ca. 1977.

"Speculate as widely and wildly as possible. People only remember when you are right."

10. Good, Not so Good, and Bad Science: Shared Responsibilities

10.1. Judgments and Scientific Standards

The art of science relies on and builds upon a continuous flow of conscious and subconscious judgments. Scientists make judgments about what they do, what others do, and what has been done in the past. This Review is fundamentally about the judgments made, not only by Rabe, Kindler, Woodward, Doering, and Stork, but also by the editors and reviewers of the papers involved and by the interested scientific community. Albert Eschenmoser, who collaborated with Woodward on the "total synthesis of vitamin B_{12}, in response to questions from me said:

"It is the question about good, not so good, and bad science. And it must be accepted and admitted: it is possible, and happens often, that an unquestionably good scientist can happen to produce a piece of not so good if not of bad science. If a synthetic chemist accomplishes a synthesis of a relay compound and declares that his work amounts to a total synthesis of a natural product, he is expected to apply his own scientific standards to the question whether the conversion of the relay to the final product described in the literature is good or bad science. If he wants his contribution to be good science, he will oblige himself to repeat the relay-to-final product synthesis in the specific case where he considers the corresponding series of reactions described as being bad science. Pretty simple, and so far so good.

"But I can imagine young R.B.W. and W.v.E.D., having arrived in 1944 at the relay compound toward quinine, were psychologically in a situation in which, first, the temptation was overwhelming to believe that Rabe's work was good science and, second, it must have been R.B.W.'s conviction that the heart of the problem of a quinine synthesis, the essence and the novelty of the problem's solution, lay in the synthesis of quinotoxine and not in the classical chemistry supposed to lead from there to quinine itself."[161,162]

The following sections will discuss various aspects of good, not so good, and bad science and shared responsibilities within the scientific community.

10.2. On Woodward's Understanding of the Incompleteness of Rabe and Kindler's Experimental Information

10.2.1. Woodward's Literature Search on Quinine and Rabe Before 1944

The question raised by Stork in his 1944 letter to Woodward ("Would you also tell me whether Rabe's conversion of quinotoxine into quinine has been repeated by you in your present work?"[103]) put Woodward on notice that the Rabe and Kindler relay-precedent might be considered inadequate. Figure 26 reproduces a portion of Woodward's literature search results, written in his own distinctive handwriting. Regarding the Rabe and Kindler 1918 paper, Woodward wrote:

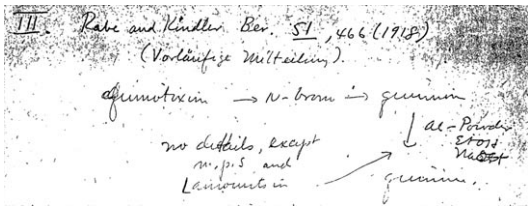


Figure 26. Excerpt from handwritten literature search notes (ca. 1943) of Robert B. Woodward on the 1918 Rabe and Kindler article.[7] Note the words, "no details, except m.p.s and amounts in".[159]

"no details, except m.p.s and amounts in … "[159]

Regarding Rabe and Kindler's 1919 paper,[163] Woodward wrote:

"meritous, but not details partial synthetic dihydroquinotoxine"[159]

Clearly, Woodward recognized papers of Rabe's without experimental details. Later on this page of his literature search, Woodward writes:

"V. final synthesis art[icle]—gives many details for hydroquinine case …"

"aluminum red. Cf. Rabe. Ann. *49*, 253 (1932) case of Hydrocinchoninone"[159]

In this latter quote, Woodward emphasizes examples where Rabe does include experimental details. Also of note on this literature search page is Woodward's record of the Rabe citation in which details of the reduction of the ketone to the alcohol with aluminum powder is reported, although in the case of hydrocinchoninone, not quininone and quinidinone.[9]

In summary, the literature search notes by Woodward clearly indicate his awareness of Rabe's failure to provide complete experimental details for critical transformations. In addition, Woodward reveals in his literature search notes that Rabe does provide experimental details for the key reaction steps in the *d*-quinotoxine to quinine transformation (bromination, cyclization, and reduction) but for transformations of analogues only.

10.2.2. Inconsistent Documentation by Woodward and Doering in Their 1945 Paper Regarding Publications with Incomplete Experimental Information

Woodward and Doering were certainly conscious of cases in which scientists published their chemical research without experimental details. Woodward and Doering were aware of Pasteur's resolution of *dl*-tartaric acid via their diastereomeric salts with *d*-quinotoxine[8] as they, 100 years later, attempted to resolve *dl*-quinotoxine via its diastereomeric salts with *d*-tartaric acid. In footnote [48] of their 1945 full paper,[6] Woodward and Doering specifically point out that in his extraordinarily historic paper on the first resolution of a racemic mixture via diastereomers, Pasteur[8] failed to provide experimental details. Inconsistently, Woodward and Doering do not point out that Rabe and Kindler failed to provide experimental details in their publication which included the

essential last steps in the Woodward–Doering formal total synthesis of quinine.

The publications by Pasteur and by Rabe and Kindler are different in an important sense. Pasteur provided an example of a resolution that would be emulated, over and over again, but with different racemic mixtures and hence different diastereomers.[8] In this case, there is little necessity for an exact recipe as few would specifically be repeating the resolution of *dl*-quinotoxine with *d*-tartaric acid. On the other hand, Rabe and Kindler[7] provided the basis for the relay compound for Woodward and Doering.[5] In this latter case, omission of the experimental details for any one transformation—and there were three in the report by Rabe and Kindler—places into doubt the reproducibility if not the validity of the entire total synthesis.

10.3. Woodward's Evolution: Relay Compounds and the Total Synthesis of Vitamin B_{12}: A Comparison with the Total Synthesis of Quinine

Three decades separate the publication of the total synthesis of quinine[5] and the completed synthesis of vitamin B_{12}.[164] These two syntheses represent the major bookends of the career of Robert Burns Woodward. According to Doering, the synthesis of *d*-quinotoxine was completed on Woodward's birthday, April 10, 1944[156] although April 11, 1944 is cited in the authoritative volume by Benfey and Morris [19] as well as in a contemporaneous quote of Doering in the *New Yorker* magazine published on May 13, 1944.[49,165] The total synthesis of vitamin B_{12} was completed on March 17, 1976,[19] just three years before Woodward's untimely death.

The synthesis of the left side (or "western half") of the corrin system, the backbone of vitamin B_{12}, at Harvard and the right side (or "eastern half") in Zürich is a wonderfully complex story which is told elsewhere. For leading references and commentary, see the essay in the book by Benfey and Morris[19] and the essay by Eschenmoser (Figure 27) in that same volume.[21] For our purposes, attention is focussed on the total synthesis of cobyric acid, the relay compound for the vitamin B_{12} synthesis, and the conversion of cobyric acid into vitamin B_{12}.

Figure 27. Woodward and Eschenmoser on March 5, 1979. The photograph is reproduced with permission from Albert Eschenmoser.

According to Woodward:

"In late 1972 we put down the last segments of paths which constituted, actually three variants of syntheses of vitamin B_{12}. And, in saying that *we put down at that time the last segments,* I choose my language carefully. Because, in fact, the paths to synthetic vitamin B_{12} had been laid down at that time, but no actual synthetic vitamin B_{12} had been made. Professor Eschenmoser and I felt that the final stages of the synthesis of vitamin B_{12} deserved every bit as much attention and care as had been lavished on all the earlier stages, and so it seemed to us that there was still work to be done at the end of 1972 … It had been shown by Professor Friedrich, Professor Bernhauer, and their collaborators that cobyric acid, the natural substance, could be converted into vitamin B_{12}"[164] [Emphasis from the original.]

Woodward then repeats himself:

"In the light of the fact that we had not made [in 1972] any actual synthetic cobyric acid or vitamin B_{12}, I think you will realize that the situation as I have presented it could be said to include some lacunae which we felt should be obliterated."[164]

As recounted and proposed by Eschenmoser:

"The very same is to be said for R.B.W.'s synthesis of chlorophyll, where the 'well trodden path' to chlorophyll itself was by no means so well trodden (the insertion of magnesium!). It may well be that the matured R.B.W., after the accomplishment of the synthesis of cobyric acid [the vitamin B_{12} relay compound], had in the back of his mind those potential imperfections in his *oeuvre* that he insisted in what at the time I myself could not understand at all, namely, that the Bernhauer-conversion of cobyric acid to vitamin B_{12} should be repeated with synthetic cobyric acid. I remember my opposition to this standpoint, saying, 'I participate in such a project only if we can think of new chemistry to achieve this conversion.' I decided at that time to accept cobyric acid as the relay. But R.B.W. with [Mark] Wuonola repeated Bernhauer's conversion by hard work, and they did so successfully."

"About a decade later, long after R.B.W.'s death, we actually discovered in Zürich a truly novel two-step conversion [of cobyric acid to vitamin B_{12}] that was stimulated by asking a question referring to the etiology of the vitamin B_{12} structure. It would have been impossible to think of such a question before. I tell this story in order to illustrate that I myself had potentially accepted the (very small) risk that Bernhauer's conversion might be incorrect. I knew Bernhauer personally, and I knew that he was the top expert in isolating and characterizing vitamin B_{12} samples. It was he who discovered cobyric acid to be a natural product."[163]

In a 47-page essay published in 1979, Woodward described in extraordinary detail the exquisite conversion of cobyric acid into vitamin B_{12} in which his students, primarily Mark Wuonola (Figure 28), substantially modified the literature report to achieve the final synthesis. Woodward's descriptions are like those of a museum curator displaying his own internationally acclaimed art. Woodward even included photographic comparisons of the crystals of synthetic cobyric acid, the furanose and pyranose molecules, and ultimately totally synthetic vitamin B_{12} and natural vitamin B_{12}.

Woodward then concluded:

"I believe it will be agreed that our synthetic vitamin B_{12} has been well identified and characterized … we considered that we should at least have one biological test. In Figure 34, it will be seen that in the standard assay the totally synthetic vitamin B_{12} shows full biological activity … against natural U.S.P. cyanocobalamin in the standard permissive growth assay, using *Lactobacillus leichmannii* … "[164]

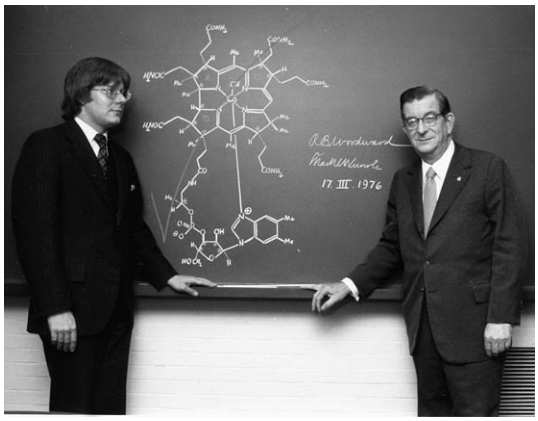


Figure 28. Woodward and Mark Wuonola on March 17, 1976, the day that the synthesis of Vitamin B_{12} was completed. Note the check mark to the left of the structure, apparently indicating the successful completion of the total synthesis. The photograph is reproduced with permission from Albert Eschenmoser.

Perhaps even more insightful is Woodward's vision:

"I hope that [our synthetic and analytical research on the conversion of cobyric acid to vitamin B_{12}] sets a standard in the establishment of identity in synthetic work."[164]

I inquired of Mark Wuonola, did he believe that Woodward, having not synthesized quinine in his own laboratory but rather stopping at *d*-quinotoxine, was driven to obtain totally synthetic vitamin B_{12}. Wuonola recalled:

"Woodward never said anything explicit about why. We [his students] all thought this had to do with his quinine work. He did not want to get criticized. Did we ask him? No, that would have been impertinent."[166]

Thirty five years earlier, in 1944, the youthful Woodward did not demand of himself even an unoptimized conversion of *d*-quinotoxine into quinine.

Ironically, there is one artistic similarity between Woodward's experiences with quinine and vitamin B_{12}. Woodward's 1979 essay on the total synthesis of vitamin B_{12} includes numerous photographs of crystals.[164,167] This is more than matched by the photographic glory published in the June 5, 1944 issue of *Life* magazine. On pages 85–88 of that magazine, 28 photographs appear. These include a photograph of Woodward sitting on a lab bench, reading a notebook with Doering looking over his shoulder; photographs of many molecular models and chemical apparatus with hands likely belonging to Doering; and five photographs of crystals, including crystals of quinine and quinotoxine. Woodward clearly loved crystals: indeed, one of Woodward's daughters was named Crystal.

The photographer, Fritz Goro, spent a week at Harvard taking hundreds of photographs of the quinine researchers, their equipment, and their crystals. Goro was later to become extremely well known for photographing many aspects of science and his invention of macrophotography.[168,169] While Woodward and Doering provided Goro with crystals of quinine, and while the article states that "[Rabe's] process also converts synthetic quinotoxine to quinine,"[48] the fact that Woodward and Doering did not produce quinine in Cambridge was not mentioned.

At least one perturbing question remains. If Woodward was plagued by the memory of a substandard performance in his "total synthesis of quinine" and responded with extraordinary overachievement in his total synthesis of vitamin B_{12}, why did he not return to quinine? When compared to the structures of Woodward's subsequent synthetic targets, quinine is simple indeed. By 1976, Woodward had set the standards in total synthesis and had enormous resources which could have been applied to any project. What would have been the result had Woodward placed his considerable energy, focus, determination, mastery, and resources once again to the total synthesis of quinine? One can only imagine.

11. The Evolution of Scientific Practices and Standards: Open Questions

11.1. Poor Judgment in Reporting or Obtaining Full Experimental Details

To what extent did Rabe and Kindler demonstrate poor judgment in the publication of their work, by not reporting sufficient experimental details to allow the replication of their research?

Rabe and Kindler might have believed that they did provide experimental details for each of the reactions in the *d*-quinotoxine to quinine transformation, although the details were for analogous compounds (see Section 8.4.1 and 8.4.2). Even with what would have been acceptable experimental details to today's reviewers, an exact replication of Rabe and Kindler may not be possible because of ambiguities regarding the exact nature of their "aluminum powder" in the reduction step (Scheme 2 and Figure 3). Would the current quasiuniversal view that Woodward and Doering did not complete the total synthesis of quinine been otherwise had Rabe included all details except for the source and physical characterization of the aluminum powder?

To what extent did Woodward and Doering demonstrate poor judgment by not seeking experimental details from Rabe and Kindler?

Woodward could have requested these details from Rabe during their brief but substantive correspondence in 1948. Kindler continued to publish from Hamburg for some years following Rabe's death, so these questions could also have been addressed to him. Apparently, they were not.

To what extent did Woodward and Doering demonstrate poor judgment in the experimental design of their work, by not demonstrating the conversion of d-quinotoxine into quinine?

It is worth pointing out again that in 1944, subsequent to the publication of their communication but some months prior to the submission of their full paper, Woodward was alerted to the possibility that the broader outside chemical community would one day be as aware as he was, and as Stork was, that Rabe and Kindler failed to provide the experimental details of their work, possibly invalidating the use of *d*-

quinotoxine as a relay compound. Thus, to some large extent, the editors and reviewers failed Woodward and Doering, and perhaps failed Rabe and Kindler as well, by not requiring a higher standard for publication.

One can imagine a number of reasons that Woodward did not question Rabe and Kindler: 1) Rabe was an internationally recognized expert in quinine chemistry and a German professor: Rabe's publications were not to be questioned; 2) Woodward did not wish to open Pandora's box—"the one experiment too many" phenomenon—and unleash an abundant source of experimental burden; 3) Doering had already left Harvard, was on the staff of Columbia University, and had completed the *d*-quinotoxine research under trying part-time conditions; 4) there were pressures caused by World War II which encouraged rapid completion and publication of their work; 5) there were tenure incentives at Harvard for Woodward (and at Columbia for Doering) to complete the synthesis and publish the results; and 6) as suggested by Eschenmoser:

"In the R.B.W. era of natural product synthesis, the central challenge was to accomplish strategically new synthetic chemistry. Relay questions, important as they are in principle, in the context of being obliged to do, are good science but were in the background of attention."[163]

Rabe and Kindler were not alone in failing to publish experimental details in their publications. Ironically, Woodward was criticized for the same shortcoming. To celebrate the centennial of the American Chemical Society, *Chemical & Engineering News* published a special issue on April 6, 1976. Therein, the eminent historian D. Stanley Tarbell wrote an article entitled "Organic Chemistry: The Past 100 Years".[170] Tarbell wrote of the then still-living Woodward:

"An impartial appraisal of Woodward would admit that his failure to publish the details of his later work has deprived the chemical community of the benefits of his new synthetic methods. However, his influence, through his work, both experimental and theoretical, and through the students and postdoctorates he has trained, has made him the dominant figure in his generation of organic chemists, with the stature Sir Robert Robinson and Emil Fischer had in their day."[170]

11.2. Shared Responsibilities in Science Publishing

Are the authors of a publication solely responsible for that publication, or are there shared responsibilities in the world of science publishing?

A peripheral response to these questions leads to a trivial conclusion: Only the authors can be responsible for the content of their publication. This conclusion is surely valid in terms of a publication's substantive, technical material. Reviewers and editors can examine, criticize, and make recommendations about a publications data, experimental design and methods, assumptions, and conclusions, but fundamentally the authors are responsible for their publication. On the other hand, if the editors and reviewers allow a manuscript to be published without requiring full experimental details, then there is a shared responsibility. There is a balance, if not a tension, between editorial policy, reviewers' judgments, and authors' inclination toward compliance.

For decades, a large proportion of chemical manuscripts were published without full experimental details. In many cases, a single experimental procedure was provided for an "example" of a series of a single transformation. This practice was normal in the practice of chemistry. Journals such as *Tetrahedron Letters* and *Chemical Communications* specialized in short reports with minimal, if any, experimental detail. Even the archival quality *Journal of the American Chemical* Society and the *Journal of Organic Chemistry* for many years published communications with scant experimental information. There was the inherent expectation by the editors and the readers, if not the explicit promise from the authors, that full papers with complete experimental detail would subsequently be published.

The incentive of "to publish or perish" led to the not-always-met expectation of a full paper. Indeed, some illustrious chemists were well-known (and continue) to hardly ever publish full papers; yet, the journal editors, reviewers, and the scientific community did not provide sufficient peer pressure to require the publication of full experimental details. Many journals now require experimental details to be supplied with communications.

11.3. On the Acceptance of Representations in the Literature

On February 7, 2005, I asked Gilbert Stork the question,

"If we discount Rabe's 1918 paper on the basis of a lacking in experimental details, are we to discount all papers published by organic chemists over the past 40 years that likewise do not include experimental details?"[171]

Gilbert responded on the next day:

"Checking data in Communications is not the issue, and would be absurd, as I am sure you would agree. On the other hand, if a particular Communication reported something like a method for accomplishing a sought-after transformation of much interest, such as the suitability of palladium doped with some lead acetate for the reduction of disubstituted alkyne[s] to *Z* olefins, it should be checked, and certainly would be."[172]

Is Stork suggesting that, if and only if the report reaches a specific type of significance, then full experimental details are required? Does it then become a judgment call? What is that threshold, beyond which experimental data are required or the publication will be discounted? Can this criterion be quantified and applied consistently in the various subdisciplines of chemistry? What if the original researchers are not alive or are otherwise unable to provide the information, does this automatically devalue the work? These almost unanswerable questions point to the futility of arbitrary standards.

11.4. Our Reliance on "Experts"

What lessons can be learned from this sharp transition in judgment from (referring to Rabe and Kindler) "highly significant"[15] and (referring to Woodward and Doering) "classical design to brilliant execution"[15] to (explicitly

referring to Woodward and Doering but implicitly referring to Rabe and Kindler synthesis of quinine) "myth."[2,3] What was the basis for this abrupt and rather uniform change in peer opinion? What are the relationships between peer opinion, expert opinion, and the facts? To what extend do the facts matter? The issues discussed in this Review are not limited to the specifics of quinine but rather are important to all of us in the 21st Century.

Standards within the academic community are operationally set by the decision makers, of which there are many. These include university and industrial managers, when they decide who to hire; scientists, when they decide what positions to accept; students, when they choose with whom to work; journal editors and reviewers; funding agencies; faculty tenure committees; industrial pay/promotion managers; each of us, when we decide what research projects to undertake, with whom we will collaborate, and what we will publish.

So many decisions are made on a daily basis that, more and more, we have begun to depend on shortcuts, reliable or otherwise. We cannot be an expert in all matters. We identify those subjects which absolutely require the investment of our own the time and energy to gather, interpret, and evaluate the data. Otherwise, one shortcut is the reliance on experts—individuals in whom we trust, for their integrity, and value, for their capabilities. Who are the experts? How serious are the issues (risk versus reward) that we place our reliance for our opinions or our actions on them?

When a Nobel Prize winner, or individuals of the highest esteem (for example, Stork in 2001, Woodward in 1944; Prelog in 1943; Rabe and Kindler in 1918), present that they completed a synthesis of quinine (whether total, formal total, or partial), do we not accept that representation? When such an eminent individual (Stork in 2001) represents that someone else, 57-years earlier, did not synthesize quinine, do we not accept that representation at face value?

Are our judgments consistent? If we turned these questions upon ourselves, how would we judge our own work? Did we always report all the experimental data for all of our published research? Would we agree if others concluded that some of our published work is a "myth" because our experimental data is incomplete or unpublished?

12. Historical Interpretations and Conclusions

12.1. The Woodward–Doering/Rabe–Kindler Total Synthesis of Quinine: A Significant Achievement

In 1944, Woodward and Doering obtained homomeroquinene (**3**) and *d*-quinotoxine (**2**), not quinine (**1**), by total synthesis.[5] Their claim of the formal total synthesis of quinine relies on Rabe's and Kindler's transformation of *d*-quinotoxine to quinine.[7] As discussed in this Review, I conclude that Paul Rabe and Karl Kindler did convert *d*-quinotoxine into quinine as they reported in 1918. The conclusion is based on the following facts:

1) In 1918 Rabe and Kindler published the conversion of *d*-quinotoxine into quinine in a prestigious journal.[7] The physical properties of the isolated quinine matched those of the natural product. Even a small percentage of any one of the C8 and/or C9 diastereomers of quinine would have been observed.
2) In their 1939 study Rabe and Kindler isolated additional quantities of quinine from the residues of the reaction mixture saved from 20 years earlier.[77] Given the vast experience of Rabe in quinine chemistry, it is simply unreasonable to believe that their identification of quinine in both 1918 and 1939 was incorrect.
3) Rabe and Kindler never reported the exact experimental details of their conversion of *d*-quinotoxine into quinine although Rabe did report experimental conditions for analogous transformations. In 1911 and 1932 Rabe published transformations with full experimental details in the cinchona alkaloid system directly analogous to the conversion of *d*-quinotoxine into "quininone" and then into quinine. Rabe referred to these reactions as the same conditions as for the halogenation/cyclizations of quinotoxine[10] and the reduction of "quininone".[9]
4) Rabe and others performed very similar halogenations/cyclizations and reductions in other cinchona alkaloid systems.
5) Rabe and Kindler were both eminent scholars who led major academic research oriented departments for decades. Rabe's research on cinchona alkaloids was a lifetime endeavor. He was the leader in cinchona alkaloid chemistry in the first half of the 20th Century. Paul Rabe was known to be a highly ethical scientist. Karl Kindler published research for 40 years. After his habilitation with Rabe in 1923, Kindler became head of two pharmaceutical academic departments and later founded the Institute of Pharmacy in Hamburg. It is unreasonable to believe that both Rabe and Kindler were guilty of scientific fraud, intentional misrepresentation, or scientific incompetence. It is also unreasonable to believe that Rabe and Kindler mistook some other material for quinine in their synthetic work.
6) While not proof, I consider it significant that Rabe wrote to Woodward in 1948 saying (Figure 7): "I am delighted that I have lived to see the total synthesis of quinine".[74]

I therefore also conclude that the Woodward–Doering/Rabe–Kindler total synthesis of quinine is a valid achievement.

12.2. Achieving Exceptional Science

Could, and should, Rabe and Kindler have anticipated that their failure to produce the full experimental details of their 1918 paper would throw in doubt 80 years later their reported results?

Between 1918 and 1944 when the Woodward–Doering publication appeared, Rabe and his co-workers authored numerous publications on various aspects of the cinchona alkaloids. The editors, reviewers, and scientists of the time did not influence Rabe to publish the experimental details of the 1918 report. However, as events would unfold, science would

have best been served had Rabe and Kindler followed through on their implicit promise to publish the experimental details.

Could, and should, Woodward and Doering have reasonably anticipated the controversies that would arise 60 years after their 1944 and 1945 publications?

The two independent reviewers of the Woodward–Doering full paper provided very lengthy, critical reviews but neither of them questioned the use of the relay compound from the work of Rabe and Kindler. In fact, Woodward declined to follow most of the reviewers' recommendations. Lamb, then editor of the *Journal of the American Chemical Society* and Harvard chemistry professor, accepted the full paper, even though one reviewer rejected it outright. Interestingly, as a young graduate student, Gilbert Stork questioned Woodward on the reliability of the Rabe–Kindler report. As events would unfold, science would have best been served had Woodward and Doering provided a reproducible transformation of *d*-quinotoxine to quinine.

Could the interested scientific community have been more diligent before their reversal of opinion from the "total synthesis of quinine" to "myth" in 2001?

As argued above, any explicit judgment that Woodward and Doering did not rise to the highest standards because they failed to reproduce Rabe and Kindler carries with it an implicit judgment that Rabe and Kindler were either fraudulent or experimentally incompetent. Otherwise, one accepts the report of Rabe and Kindler at face value and values the total synthesis of Woodward and Doering. The scientific community understands that charges of scientific misconduct or incompetence are serious; unfortunately, an interested yet peripheral examination of the facts would lead only the most attentive of us to understand the full impact of implicit judgments. In these times of demanding schedules, there is a tendency to rely on experts rather than on our own searching for and evaluation of the data.

The scientific community is acutely aware that, with time, higher standards of quality have melded into the profession. Perhaps nowhere in chemistry is that more evident than in organic synthesis: one would not even need to know any organic chemistry to visually discern the increased complexity of synthetic targets as a function of time.[17] As stated by Eschenmoser:

> "In a rapidly advancing field, the standards of quality change in such a way that in later times, the quality which was acceptable for the pioneers would no longer be sufficient in the advanced state."[163]

Many standards do not change': ethical standards dealing with fabrication of data, for example. The *Chemist's Code of Conduct* from the American Chemical Society provides an excellent, yet simple, set of guidelines.[173] On the one hand, providing experimental details is a fundamental requirement for scientific progress. It might well be argued that the experimental portion of a publication is more important that the discussion section. The *Code* advocates caution regarding statements made in public, be they letters to the editor or journal articles:

> "Public comments on scientific matters should be made with care and precision, without unsubstantiated, exaggerated, or premature statements."[173]

In all these issues, good science requires adhering to the highest of standards—a fine lesson for all of us, whatever level of achievement we may have already reached in our profession.

I thank the staff of the Harvard archives, in particular Barbara Meloni, Tim Driscoll, and Robin McElheny for their enthusiastic assistance. I thank Crystal Woodward for granting permission to cite and duplicate materials from the Woodward collection in the Harvard archives.[174] I thank William von E. Doering, Gilbert Stork, and Albert Eschenmoser for their continuous series of helpful communications over more than two years; Otto Theodor Benfey, Ernest L. Eliel, and Rolf Huisgen for their enormously helpful translations of many of Rabe's papers and for their technical insights, Benfey, Doering, Eliel, Eschenmoser, Carmen Giunta, Jürg Gutzwiller, Roald Hoffmann, Koji Nakanishi, Albert Padwa, Will Pearson, Gary H. Posner, Scott A. Snyder, Stork, and Milan Uskoković for reviewing a draft of the manuscript; Wittko Francke, Gutzwiller, Huisgen, Eric N. Jacobsen, George B. Kauffman, Teodoro S. Kaufman, Maureen Rouhi, Helmut Schmidhammer, Uskoković, Steven M. Weinreb, Mark Wuonola, and several reviewers for helpful discussions; Alan I. Goldsmith for technical information assistance; and Anthony Barrett, Padwa, and Posner for their encouragement and wise council. I thank the Chemical Heritage Foundation for access to and permission to cite two oral histories. I thank Thomas Goreau, grandson of Fritz Goro, for permission to use Goro's photographs, and to Margaret Goreau for her critical patience and assistance during our search through through the Goro archives. The following organizations are acknowledged and thanked the for permission to reprint copyrighted material: The American Chemical Society, Verlag Walter de Gruyter, Elsevier, and the Nature Publishing Group. I thank Jonathan and Lauren Shea for their hospitality in Boston during my several lengthy visits to Harvard University. This work was entirely funded by SaddlePoint Frontiers to which I am deeply indebted.

Received: April 19, 2006
Revised: August 17, 2006

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