

Quinine: Controversy in Synthesis

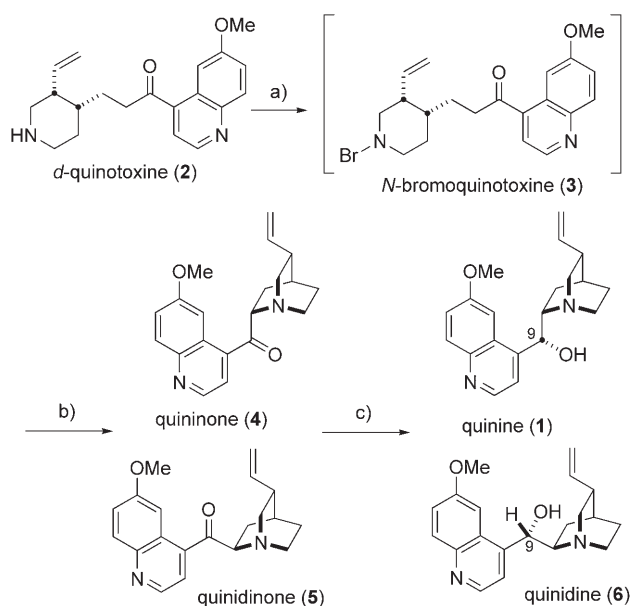
Rabe Rest in Peace: Confirmation of the Rabe–Kindler Conversion of *d*-Quinotoxine Into Quinine: Experimental Affirmation of the Woodward–Doering Formal Total Synthesis of Quinine**

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Dedicated to Professor William von Eggers Doering on the occasion of his 90th birthday

Robert Burns Woodward and William von Eggers Doering of Harvard University published a communication in 1944 and a full paper in 1945 in the *Journal of the American Chemical Society* both entitled “*The Total Synthesis of Quinine*”.^[1] This now famous full paper has been the subject of much attention over the years, particularly recently. It is now well-understood, that the Woodward–Doering “total synthesis” was actually a “formal” total synthesis of quinine (**1**) that relied on a seminal 1918 publication by Paul Rabe and Karl Kindler, wherein *d*-quinotoxine (**2**), the final synthetic substance in the Woodward–Doering work, was converted into quinine by a three-step sequence (Scheme 1).^[2] This sequence involved: 1) oxidation of *d*-quinotoxine with sodium hypobromite to produce “*N*-bromoquinotoxine” (**3**); 2) base-mediated cyclization of **3** to produce “quininone” (**4**); and 3) aluminum-powder reduction of “quininone” to produce quinine (**1**) and quinidine (**6**, as a minor product). The 1918 paper, termed a “preliminary notice” by the authors, provided only a terse summary of this three-step process. This paper referenced Rabe’s 1911 conversion of cinchotoxine into cinchoninone and cinchonidinone (employing the analogous reactions for the quinotoxine to quininone and quinidinone conversion)^[3] but subsequently in 1932, complete experimental details for the reduction protocol were published.^[4]

Despite the significant fanfare accompanying the publication of the Woodward–Doering paper during World War II,



Scheme 1. Conversion of *d*-quinotoxine (**2**) to quinine (**1**). a) NaOBr, NaOH, HCl (aq), Et₂O, 55% yield of crude product; b) NaOEt, EtOH, 88% yield of crude product; c) aluminum powder, NaOEt, EtOH, 5% yield (as the tartrate salt).

and the ensuing rich history of quinine and the *Cinchona* alkaloids in modern medicine,^[5] it is surprising that apparently no one has reported efforts to simply attempt to repeat the Rabe–Kindler conversion of *d*-quinotoxine into quinine. This is particularly significant since concomitant with their relatively recent total synthesis of quinine,^[6] Gilbert Stork and co-workers raised some possible doubts about the validity of this conversion, referring to Woodward and Doering’s “total synthesis” as a “widely believed myth.”^[7] Consequently, the Woodward–Doering claim for a “total synthesis” albeit as a “formal” total synthesis by relay through *d*-quinotoxine based on the Rabe–Kindler sequence, has been besmirched.^[7]

This fascinating saga, spanning more than eighty years, was meticulously researched very recently by Seeman whose 2007 publication entitled: “*The Woodward–Doering/Rabe–Kindler Total Synthesis of Quinine: Setting the Record Straight*”,^[8] helped kindle our own interest in this story. In his analysis of all the available data in the literature and in archival materials, Dr. Seeman stated: “*I conclude that Paul Rabe and Karl Kindler did convert d-quinotoxine into quinine*

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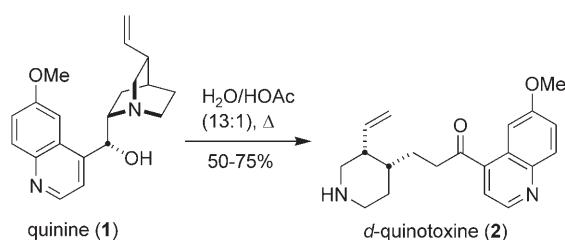
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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

as they reported in 1918.” and: “I therefore also conclude that the Woodward–Doering/Rabe–Kindler total synthesis of quinine is a valid achievement.” This insightful and perhaps even bold conclusion, based on a painstaking and meticulous review of a large body of published and unpublished material, still lacked unambiguous experimental data to back up the purported *d*-quinotoxine to quinine conversion originally reported in 1918 and so significantly relied upon by Woodward and Doering.^[8]

In connection with our laboratory’s work on a novel approach, which relies on an intramolecular S_N2' reaction at C3/4, to the total synthesis of quinine and the related *Cinchona* alkaloids,^[9] we became very interested in this controversial, historically potent, yet from the perspective of the 21st century, straightforward semisynthesis of quinine from *d*-quinotoxine. We have carefully examined this conversion as described by Rabe and Kindler in 1918^[2] and in associated papers by Rabe and co-workers published in 1911,^[3] 1932,^[4] and 1939.^[10] We report herein the successful conversion of *d*-quinotoxine into quinine deploying the experimental protocols originally described by Rabe and his co-workers. This further serves to re-affirm the (formal) total synthesis claimed by Woodward and Doering in 1944.^[1]

We prepared our *d*-quinotoxine (**2**) on a 29-gram scale from commercially available quinine (Aldrich, 90 %) as described by Biddle in 1912 (Scheme 2).^[11] Heating quinine



Scheme 2. Preparation of *d*-quinotoxine (**2**) from natural quinine (**1**).^[11]

in H_2O /acetic acid (13:1) at 100 °C for 35 h provided between 50–75 % yield of pure *d*-quinotoxine. Thus, according to Rabe and Kindler,^[2] *d*-quinotoxine (**2**) was treated with a solution of freshly made sodium hypobromite (Scheme 1). The resultant product, “*N*-bromoquinotoxine” (**3**), proved to be an unstable substance recalcitrant to purification and was immediately treated with sodium ethoxide in ethanol under the same conditions described by Rabe and Kindler to effect quinuclidine cyclization and provided a mixture of quinone (**4**) and quinidine (**5**). As documented in the literature, the product that Rabe and Kindler assumed to be quinone, was in fact its less-soluble epimer, quinidine (**5**).^[6,8,12,13] Quinidine, when dissolved, spontaneously epimerizes at the position α to the ketone moiety at C8 immediately establishing an equilibrium mixture of quinone (**4**) and quinidine (**5**).^[12] The mixture thus obtained was treated with newly purchased aluminum powder (Aldrich)^[14] in a solution of sodium ethoxide and ethanol at reflux temperature to effect reduction of the carbonyl moiety but only provided quinine (**1**) in trace amounts as detected by the appropriate signatures in the 1H NMR spectrum.

We were struck by the initial low yield of quinine obtained from the aluminum-powder reduction and the trace material which we were able to isolate mandated the use of silica gel chromatography, a purification technique not yet discovered at the time of the Rabe–Kindler work nor available in 1944 to Woodward and Doering. It is of course impossible now to determine where Rabe and Kindler had obtained their aluminum powder or the level of purity of the reagent that they had employed in their work. We thus set out to examine other methods to reduce the quinidine/quinone mixture into quinine, to establish the robustness of this general transformation, before returning to the issue of the quality of the aluminum powder. This was achieved through a relay synthesis of quinidine (formed through oxidation of quinine)^[13,15] to provide adequate quantities of pure material to study the reduction step.

As shown in Table 1, in 1973 Uskokovic and co-workers, had reported that quinone could be reduced to quinine through the agency of diisobutylaluminum hydride (entry 1, Table 1).^[12] This protocol provided a mixture of quinine and

Table 1: Conditions for reducing quinidine/quinone to quinine.

Entry	Reducing conditions	T [°C]	Yield of isolated quinine/quinidine	Yield of quinine ^[f]
1 ^[a]	DIBAL-H benzene	20	72 %	33 %
2 ^[b]	$NaBH_4$, EtOH	0	11 %	4 %
3	Al powder (new) ^[c] $NaOEt$, EtOH	reflux	trace	trace
4	Al powder (new) ^[d] $NaOEt$, EtOH	reflux	30 % (1.1:1)	16 %
5	Al powder + Al_2O_3 $NaOEt$, EtOH	reflux	26 % (1.1:1)	14 %
6	Al powder (aerated) ^[c] $NaOEt$, EtOH	reflux	24 % (1.1:1)	13 %
7	Al powder MeOH, $NaOMe$	reflux	8 % (1.2:1)	4 %
8	Al powder (sonication) $NaOEt$, EtOH	reflux	22 % (1.1:1)	12 %
9	Al powder, $Na(OiPr)$, <i>i</i> PrOH	reflux	32 % (1:1.2)	15 %
10	$Al(OiPr)_3$, <i>i</i> PrOH	reflux	28 %	16 %
11	$LiAlH_4$, ether	–78	45 %	trace
12	$LiAlH_4$, ether	0	59 %	trace
13	$LiAlH_4$, ether	20	56 %	trace
14	$LiAlH_4$, ether ^[e]	0	40 % (1:1.5)	16 %

[a] Experiment from Ref. [11]. [b] General reaction conditions here. [c] Bottle #1. [d] Bottle #2. [e] After epimerization. [f] Calculated based on 1H NMR spectra.

quinidine in 72 % yield (33 % yield of quinine as calculated by 1H NMR spectroscopy). Sodium borohydride also effects this reduction but in much lower yield (entry 2, Table 1). These control experiments provided us with authentic mixtures of quinine and quinidine for use as comparison standards to evaluate the aluminum-powder reductions in more detail.

When a new bottle of aluminum powder (“bottle #1”)^[14] was employed in the Rabe–Kindler protocol, quinine was evident in trace amounts by analysis of the 1H NMR spectrum of the crude mixture after workup (entry 3, Table 1). When a

different batch of fresh aluminum powder was examined ("bottle #2", entry 4 in Table 1),^[14] we obtained a mixture of quinine and quinidine in 30% combined yield of which quinine made up roughly half ($\approx 16\%$ overall yield) by ^1H NMR analysis. We reasoned that it was possible that the material used by Rabe and Kindler in 1918 may have contained significant Al^{III} impurities, either as a consequence of the manufacture of elemental aluminum in the early 1900s or as a consequence of their bulk reagent becoming "stale" through exposure to air. To test this speculative hypothesis, we added Al_2O_3 to the aluminum-powder reduction using bottle #1 and observed a significant improvement in the yield (26% combined yield of quinine and quinidine; $\approx 14\%$ overall yield of quinine; entry 5, Table 1).

Next, we took our initial batch of aluminum powder (bottle #1), and aerated this material for 72 h by passing a stream of air over a beaker containing the metal. Resubjecting the quinidinone (**5**) to the "aerated" aluminum powder yielded quinine in $\approx 15\%$ yield (entry 6, Table 1). Several variations on these reductions were also employed and provided similar results (entries 7–9, Table 1). These results clearly establish that the "aluminum powder" reagent that is deployed in these reductions must contain some Al^{III} impurities to give significant conversion of the ketone substrates to the secondary-alcohol products. A further inference from these studies is that the Rabe–Kindler aluminum-powder reduction may be viewed as an early, "activated" progenitor of the Meerwein–Ponndorf–Verley (MPV) reduction.^[16] We also conducted a classical MPV reduction^[13,16] (entry 10, Table 1) to compare the reactivity of that system to that of the aluminum powder. The MPV reaction did provide quinine (16%), but the reaction took 48 h compared to just 2 h for the other conditions employed.

Finally, lithium aluminum hydride was investigated (entries 11–13, Table 1). When pure quinidinone (**5**) was utilized as the substrate, LiAlH_4 provided quinidine (**6**) as the major reduction product in most cases with only a trace amount of quinine detectable by ^1H NMR spectroscopy (entries 11–13, Table 1). This shows that minimal epimerization of quinidinone takes place under these reaction conditions. When epimerization of quinidinone is effected prior to exposure to LiAlH_4 , and a mixture of quinone and quinidinone is employed as the substrate mixture, quinine was formed in 16% yield, which comports with that obtained with the Rabe–Kindler aluminum-powder-reduction conditions. Therefore, we can speculate that, had Woodward and Doering attempted to repeat the Rabe–Kindler reduction protocol and experienced difficulties (i.e., because of the absence of sufficient Al^{III} impurities in their reagent), they could have (and in our view, would have) reasonably turned to other reducing agents available in 1944; lithium aluminum hydride being one such reasonable alternative and the MPV reaction^[13,16] as another that, as demonstrated here, provides quinine (see below).

The bulk of the experiments that we performed to ascertain the molecular validity of the Rabe–Kindler conversion of *d*-quinotoxine into quinine relied on the utilization of all of the modern separation, analytical, and spectroscopic techniques available to us today. We of course realize that

these powerful tools were not available to Rabe and Kindler in 1918 and that most of these tools were likewise still not available to Woodward and Doering in 1944. It then remained for us to repeat the Rabe–Kindler work under conditions and using techniques that would have been available in 1944 to reasonably validate the relay conversion of their synthetic *d*-quinotoxine into quinine had Woodward and Doering chosen to do so. In our hands, the oxidation of quinotoxine with sodium hypobromite was performed on a multigram scale and the crude *N*-bromoquinotoxine product was directly used for the subsequent steps without purification. This substance proved to be somewhat unstable to handling and we were unable to crystallize this material as reported.^[2] This notwithstanding, the crude *N*-bromoquinotoxine was successfully converted into a mixture of quinone and quinidinone through the action of sodium ethoxide in ethanol.^[2] Rabe and Kindler reported that: "*The N-bromoquinotoxine, prepared in the same way as the bromo compound obtained from cinchotoxine, crystallizes from ether as colorless needles with m.p. 123°. The quinone obtained from it with m.p. 108° is in all respects identical to quinone obtained from quinine.*"^[2a] Unfortunately in our hands, and despite extensive efforts, neither quinone nor its epimer, quinidinone, could be purified from the aforementioned reaction mixture using crystallization techniques.^[17] We nevertheless continued to carry the crude material forward as a mixture of quinone and quinidinone which also contained several, unidentified impurities. In the event, treatment of the crude ketone mixture with aluminum powder^[14] in the presence of sodium ethoxide in ethanol at reflux temperature according to the protocol described by Rabe and Kindler^[2] delivered a diastereomeric mixture of alcohols from which pure quinine tartrate (5% yield of isolated product; see Figure 1) could be crystallized as described below.

Thus, the entire three-step sequence originally reported by Rabe and Kindler in 1918 was validated, from *d*-



Figure 1. Crystals of quinine tartrate obtained directly from quinotoxine according to the Rabe–Kindler protocol^[2] without the use of any modern isolation, chromatographic, or analytical techniques.

quinotoxine to quinine, without needing to purify any intermediates nor resorting to any modern separation, purification, or analytical technologies. This sequence was found to be consistently reproducible and was done under laboratory conditions that existed in 1944.

The most difficult step of the Rabe–Kindler protocol in our hands proved to be the isolation of pure quinine from the reaction mixture obtained from the aluminum–powder reduction. We were able to readily isolate a mixture of quinine and quinidine from the aluminum–powder reductions by silica gel chromatography as the crude reaction mixture, which consisted of at least four products: quinine, quinidine, 9-*epi*-quinine, and 9-*epi*-quinidine, was complex as evidenced in the crude ^1H NMR spectrum. Identification of quinine in the reaction mixture served to validate the Rabe–Kindler conversion, and our isolation of this material by silica gel chromatography provided further corroboration. Rabe and Kindler state in their 1918 paper: “16.3 g synthetic quinone 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 $[\alpha]_D^{14} = -158.7^\circ$ ($c = 2.1432$ at 20°C), while Rabe for the natural alkaloid had found $[\alpha]_D^{15} = -158.2^\circ$ ($c = 2.1362$ at 15°C).” [2b, 8] Based on these experimental disclosures, Rabe and Kindler reported obtaining a 12.3 % yield of analytically pure quinine from the aluminum–powder reduction of quinone (now known to be quinidine [6,8,12,13]). Owing to the low and variable yields of the final reduction step in our hands, which we conclude is a function of the quality of the aluminum powder used, Rabe and Kindler may have found it difficult to isolate pure quinine from the reduction reaction mixture in a reproducible manner. This would be particularly true if a new batch of aluminum powder were used that contained less Al^{III} impurities. The reduction conditions used in our studies deployed aluminum powder that had been left open to the air as well as newly opened bottles that were not exposed to the air; the quality of the reagent apparently varied significantly from batch to batch.

We were able to obtain pure quinine from the crude aluminum powder reduction reaction mixture through the use of the selective crystallization protocol first described by Rabe in 1939 [10] and successfully employed by Doering in 1947. [18] The crude aluminum reduction mixture, constituted of quinine and the corresponding C9 and quinidine diastereomers, was purified by selective formation of the di-quinine L-tartaric acid monohydrate salt from 95 % ethanol in 5 % yield (923 milligrams of white needles were isolated from 13.7 grams of the crude quinone:quinidine mixture). The quinine tartrate thus obtained, had a melting point of $212\text{--}214^\circ\text{C}$ (recryst. 95 % ethanol; lit. [6,12] m.p. $211\text{--}212.5^\circ\text{C}$; see Figure 1) and had an optical rotation of $[\alpha]_D^{25} = -160$ ($c = 0.90$, MeOH) (lit. [12] $[\alpha]_D^{25} = -156.4$, $c = 0.97$, MeOH).

Pure quinine could then be prepared from these crystals of the tartrate salt by simple aqueous base extraction. The quinine thus obtained, had a melting point of 178°C (recryst. benzene; lit. [2] m.p. = 177°C) and an optical rotation of $[\alpha]_D^{25} = -155^\circ$ ($c = 0.95$, ethanol; lit. [19] $[\alpha]_D^{25} = -160.4$, $c = 1.05$, ethanol; lit. [6] $[\alpha]_D^{25} = -150.1$, $c = 0.995$, ethanol) and thus matches

the data for the natural alkaloid. To further corroborate this procedure, we asked two additional co-workers (see Acknowledgement) to repeat and check this sequence in its entirety as just described (the optimal conditions were employed using entry 6, Table 1; see Supporting Information) starting with 9–15 grams of quinotoxine and culminating with the isolation of pure, crystalline quinine tartrate. In the event, both individuals were able to successfully repeat and confirm the Rabe–Kindler conversion of quinotoxine into quinine.

In conclusion, we have demonstrated that the originally reported conversion of quinotoxine to quinine as described by Rabe and Kindler in 1918 [2] is readily reproducible and can be conducted under laboratory conditions and with literature available to Woodward and Doering in the early 1940s [2,3,4,10] without the use of any modern separation, purification, analytical or spectroscopic methods or techniques. The entire sequence can be conducted on crude material and analytically pure quinine can be isolated from the final reaction mixture by selective crystallization of the corresponding tartrate salt; this isolation protocol was disclosed by Rabe and Kindler in 1939 [10] and readily available to Woodward and Doering in 1944. We have discovered that the aluminum–powder reduction, when fresh, non-aerated reagent is employed, typically gives only trace amounts of quinine and that “synthetically meaningful” yields are apparently only obtainable when “aged” aluminum powder is utilized that contains Al^{III} surface impurities. We note that the quality of commercial-grade aluminum powder varies in substantial ways with respect to the Rabe–Kindler protocol from batch to batch and in some instances, freshly opened bottles of aluminum powder work satisfactorily while others do not provide sufficient quinine for selective isolation based on crystallization. Further, we have provided solid experimental support for the notion that had Woodward and Doering chosen to follow the Rabe and Kindler protocol and had they had difficulty reproducing the reported 12.3 % yield of quinine isolated from this last step, then other reducing agents known at the time (1944), such as lithium aluminum hydride or the MPV reduction, could have been alternatively deployed to reach quinine. Indeed, Woodward and co-workers actually published the reduction of quinone under MPV conditions to provide quinine (30 % yield) along with quinidine (60 %) in a full paper in 1945. [13] Woodward states in this paper: “The only previous successful reduction of the carbonyl group of quinone was that of Rabe [ref. [2] here] who obtained 12 % of quinine and 6 % of quinidine by reducing the ketone with aluminum and ethanol in the presence of sodium ethoxide. It is worthy of note that this reaction constitutes the last step in the total synthesis of the cinchona alkaloid [ref. to the 1945 paper, ref. [1b] here], which has thus been noticeably improved.”

Finally, the conclusions reached by Seeman [8] on the validity of the Rabe–Kindler work now have firm experimental support which vanquishes any resilient doubts initially raised by Stork in a letter to Woodward in 1944 [8] (apparently unanswered), [8] in which he queried whether the Rabe–Kindler procedure had been repeated at Harvard; these concerns were then made more visible in his series of

publications in 2000 and 2001^[6,7] questioning the 1918 Rabe–Kindler publication^[2] and the ensuing Woodward–Doering (formal) total synthesis.^[1] The Woodward and Doering paper concludes unambiguously: “*In view of the established conversion of quinotoxine to quinine, with the synthesis of quinotoxine (emphasis ours) the total synthesis of quinine was complete.*”^[1] The experimental facts reported herein reaffirm that assertion. Our validation of the formal total synthesis of quinine as originally reported by Woodward and Doering in 1944^[1] should serve to remove the blemish asserted^[6,7] on the reputations of Rabe and Kindler as well as those of Woodward and Doering. The Supporting Information to the present work provides the complete experimental details to the chemical literature of the Rabe–Kindler *d*-quinotoxine into quinine conversion in both a modern experimental setting as well as a pre-1944 setting; may Paul Rabe and Karl Kindler *requiescant in pace*.

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