Supporting Information

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Rabe Rest in Peace: Confirmation of the Rabe-Kindler Conversion of \( d \)-Quinotoxine to Quinine. Experimental Affirmation of the Woodward-Doering Formal Synthesis of Quinine.

Aaron C. Smith\(^1\) and Robert M. Williams\(^1,2\*)

\(^1\)Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523
\(^2\)University of Colorado Cancer Center, Aurora, Colorado 80045

This work is dedicated to Professor William von Eggers Doering of Harvard University on the occasion of his 90\(^{th}\) birthday

**General Methods.** Unless otherwise noted, all materials were obtained from commercial sources and used without purification. Quinine (Aldrich, 90\%), acetic acid (Mallinckrodt, glacial), bromine (Aldrich, reagent grade), ethanol (Decon Laboratories, Inc., absolute), and ethyl ether (Fisher, anhydrous) were used as received. Aluminum powder (Aldrich, 99\%, ReagentPlus, <75 micron, Aldrich catalog #21,4752) was used from a freshly-opened bottle unless otherwise noted. Silica gel, Davisil\(^\text{TM}\), grade 643, 200-425 mesh, 150 Å, 99+% (Aldrich) was used for chromatography of the products from the reduction study. Standard silica gel proved incompatible with these compounds and eluent. Flash chromatography of quinotoxine was performed on standard grade silica gel (230 x 400 mesh) from Sorbent Technologies with the indicated solvent. \(^1\)H NMR and \(^13\)C NMR spectra were recorded on Varian 300 or 400 MHz spectrometers as indicated. Infrared spectra were recorded on a Nicolet Avatar 320-FT IR spectrometer. Mass spectra were obtained at the Colorado State University CIF on a Fisons VG Autospec. Melting points were obtained on a Mel-Temp Laboratory Device.

**Quinotoxine:**

A 1 L RB flask was charged with quinine (43 g, 120 mmol). A premixed solution of 43 mL acetic acid and 560 mL water was then added. The mixture was heated to 102 °C with stirring for 36 h. The color gradually turns yellow then darkens into a brownish-red mixture. The solution was cooled to rt and slowly transferred to a solution of ethyl acetate and 1M NaOH (to neutralize AcOH) in a 1L Erlenmeyer flask with stirring. 1M NaOH was added until the pH was basic by pH paper. The mixture was then transferred to a
separatory funnel and the layers separated. The aqueous layer was extracted with ethyl acetate (x3), the organic layers combined, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was then brought up in benzene and cooled for a short time to precipitate some of the unreacted quinine to ease purification. This mixture was filtered and washed with benzene. The filtrate was concentrated and chromatographed using 10% MeOH/89.5% CH₂Cl₂/0.5% NH₄OH. Once all of the product fractions have been concentrated, the purified material was brought up in benzene and concentrated once more to provide pure quinotoxine (Rᶠ = 0.15, 10% MeOH/89.5% CH₂Cl₂/0.5% NH₄OH) as a brown oil (28.9 g, 89 mmol, 75% yield).

¹H NMR (400 MHz, CDCl₃): δ 8.75 (d, J = 4.5 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H), 7.71 (d, J = 2.7 Hz, 1H), 7.47 (d, J = 4.5 Hz, 1H), 7.31 (dd, J = 2.7, 9.2 Hz, 1H), 6.03 (dt, J = 10.1 Hz, 17.0 Hz, 1H), 5.04 (m, 2H), 3.83 (s, 3H), 3.02–2.88 (m, 4H), 2.74 (dd, J = 3.1, 12.2 Hz, 1H), 2.55 (dt, J = 3.4, 11.1 Hz, 1H), 2.20 (m, 1H), 1.63–1.50 (m, 4H), 1.43–1.32 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 204.0, 159.1, 146.8, 145.5, 140.3, 137.2, 131.1, 125.0, 122.6, 119.8, 116.3, 102.8, 55.4, 52.0, 46.3, 42.9, 39.0, 38.1, 29.0, 27.7. IR (cm⁻¹): 3293, 3067, 2930, 2852, 2725, 1690, 1578, 1547, 1491, 1460, 1342, 1291, 1235. [α]₀²¹ (c = 1.00, EtOH): +38. HRMS (ESI-TOF) calcd for C₂₀H₂₄N₂O₂, [M+H]: 325.1911 obs: 325.1906.

Figure 1. Flask containing quinotoxine oil (~9 grams)
Bromoquinotoxine:

A fresh solution of sodium hypobromite was prepared as follows: sodium hydroxide (10.68 g, 267 mmol) was dissolved in 180 mL water in a round bottomed flask. The basic solution was cooled to 0 °C and bromine (4.57 mL, 89 mmol) was added with vigorous stirring. The solution turned yellow upon consumption of the bromine. The solution was then allowed to stir for 15 minutes at 0 °C.

A round-bottomed flask containing d-quinotoxine (28.9 g, 89 mmol) was charged with 1M HCl (89 mL, 89 mmol) and ether (220 mL) and stirred vigorously. The freshly-prepared solution of sodium hypobromite was then added in a thin stream via addition funnel down the side of the flask. During this time, the yellow biphasic mixture became reddish-brown. Stirring was continued for 10 minutes. The ether layer was then separated, dried over sodium sulfate, and filtered into an Erlenmeyer flask. The flask was stoppered and allowed to stand 24 h in the dark. The reddish-brown solution became yellow with a dark brown residue on the bottom of the flask at the end of this period. The ether was filtered and the solvent was removed by rotary evaporation to yield an unstable yellow oil (19.6 g, 48.6 mmol, 55% crude yield) that was immediately brought forward to the next reaction (if left standing, this yellow oil decomposes into a dark residue).

Figure 2. Ether layer after bromination, T=0 hours  Figure 3. Ether layer after bromination, T = 24 h
Quininone/quinidinone:

Crude bromoquinotoxine (19.6 g, 48.6 mmol) was dissolved in absolute ethanol (450 mL) and brought to reflux temperature. The reaction mixture was removed from the heat source and 55 mL of a freshly-prepared solution of sodium ethoxide (a stock solution of 2.16M was made from 4.96 g sodium and 100 mL ethanol) was added in one portion. The reaction color changed from yellow to reddish-brown. The solution was allowed to cool to room temperature and quenched through the addition of 1 M HCl solution until pH <3 is achieved as measured by pH paper. The ethanol was removed through rotary evaporation. The aqueous layer was then made basic through the addition of 1M NaOH solution and extracted with ether (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to yield a brown oil (13.72 g, 42.5 mmol, 88% crude yield). Crude ¹H NMR shows that both quininone and quinidinone are present as the major compounds with a small amount of impurity (see spectra for comparison).

**Figure 4.** Quininone/Quinidinone solution following addition of NaOEt

**Figure 5.** Quininone/Quinidinone after workup
**Quinine!**

The crude mixture of ketones obtained above (13.72 g, 42.5 mmol) was dissolved in absolute ethanol (210 mL) in a 1 L round-bottomed flask. A freshly-prepared solution of sodium ethoxide (510 mmol, made from 11.72 g sodium and 180 mL ethanol) was added in one portion. Aluminum powder (11.7 g, 434 mmol, aerated as described below) was then added and the flask fitted with a reflux condenser. The mixture was vigorously stirred, brought to reflux temperature and allowed to react for 2 h. The unreacted aluminum was filtered while hot through a fritted funnel and rinsed with ethanol. 1M HCl was then added to the filtrate and the ethanol removed through rotary evaporation. After removal of all of the ethanol, 30% aqueous NaOH was then added until pH >10. Ether was then added and the layers separated. The aqueous phase was extracted with ether (x3) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to provide 11.3 g of a crude foaming oil. Next, 18 mL of 95% ethanol (1.6 mL/g crude) was then added and the mixture heated to reflux temperature. A separate solution of L-tartaric acid was prepared with 2.62 g L-tartaric acid and 4.2 mL 95% ethanol (232 mg acid / g crude). This mixture was heated to reflux and then added to the hot crude quinine solution. The material was allowed to cool to room temperature. At this time, a small seed crystal of quinine was added and allowed to stand until crystals formed. The crystals were filtered and washed with cold 95% ethanol and dried under vacuum to afford 923 mg quinine as the diquinine-L-tartaric acid salt (5% yield). A portion of the solid was subjected to recrystallization from 95% ethanol to give fine white needles for characterization.

\[ \alpha \]_D^{21} (c=0.90, MeOH): -160. lit.\(^5\) \[ \alpha \]_D^{21} = -156.4, c = 0.97, MeOH). m.p. = 212-214 °C. lit.\(^6\) m.p. = 211-212.5 °C.

**Diquinine-L-tartaric acid salt:**

\(^1\)H NMR (400 MHz, DMSO-d6): \( \delta \) 8.68 (d, \( J = 3.5 \) Hz, 1H), 7.91 (dd, \( J = 0.6 \) Hz, 9.0 Hz, 1H), 7.55 (d, \( J = 4.0 \) Hz, 1H), 7.48 (bs, 1H), 7.37 (d, \( J = 9.1 \) Hz, 1H), 6.07 (vbs, 1H), 5.78 (ddd, \( J = 7.5, 10.4, 17.5 \) Hz, 1H), 5.71 (bs, 1H), 5.01 (bd, \( J = 7.3 \) Hz, 1H), 4.91 (bd, \( J = 10.3 \) Hz, 1H), 4.03 (bs, 1H), 3.90 (bs, 3H), 3.64 (bs, 1H), 3.32 (bs, 1H), 3.20 (bt, \( J = 11.9 \) Hz, 1H), 2.84 (m, 2H), 1.84 (m, 2H), 1.62 (m, 1H), 1.46 (bt, \( J = 11.1 \) Hz, 1H). \(^{13}\)C NMR (100 MHz, DMSO-d6): \( \delta \) 176.2, 158.0, 148.1, 147.7 144.5, 141.2, 131.9, 126.9, 122.1, 119.7, 115.9, 102.6, 72.9, 68.6, 60.1, 56.6, 54.7, 42.9, 38.6, 27.7, 26.0, 21.0. IR: 3247, 2935, 2807, 2526, 2356, 2331, 1619, 1583, 1506, 1470, 1424, 1235.
Figure 6. Crystals of diquinine tartrate obtained from the crude quininone/quinidinone aluminum powder reduction reaction mixture. This material was obtained directly from α-quinotoxine without the purification of any intermediates at any stage by any modern chromatographic, purification or isolation technologies.

Quinine!

A portion of the tartrate obtained above was shaken with 1M NaOH and ethyl acetate to provide quinine after concentration of the organic layer. \([\alpha]_D^{21}\) (c=0.95, EtOH): -155. lit.\(^5\) [\(\alpha\)]\(_D\)\(^{25}\) = -160.4, c= 1.05, ethanol; lit.\(^2\) [\(\alpha\)]\(_D\)\(^{25}\) = -150.1, c = 0.995, ethanol). m.p. = 178 °C (recryst. benzene); lit.\(^3\) m.p. = 177 °C.

\(^1\)H (400 MHz, DMSO-d6): 8.64 (d, \(J = 4.5\) Hz, 1H), 7.89 (d, \(J = 9.2\) Hz, 1H), 7.47 (d, \(J = 3.8\) Hz, 2H), 7.34 (dd, \(J = 2.6, 9.2\) Hz, 1H), 5.84 (ddd, \(J = 7.7, 10.4, 17.4\) Hz, 1H), 5.60 (bs, 1H), 5.19 (d, \(J = 7.1\) Hz, 1H), 4.95 (bd, \(J = 17.3\) Hz, 1H), 4.90 (bd, \(J = 10.4\) Hz, 1H), 3.86 (s, 3H), 3.15 (m, 1H), 3.02 (q, \(J = 7.8\) Hz, 1H), 2.81 (dd, \(J = 10.0, 13.5\) Hz, 1H), 2.38 (m, 2H), 2.15 (m, 1H), 1.70 (m, 2H), 1.60 (m, 2H), 1.38 (m, 1H). \(^13\)C (100 MHz, DMSO-d6): 157.4, 150.0, 148.2, 144.6, 143.3, 131.8, 127.8, 121.6, 119.8, 114.8, 103.1, 71.6, 61.4, 56.6, 56.1, 42.4, 40.3, 28.2, 28.1, 24.9. IR (cm\(^{-1}\)): 3119, 2930, 2865, 1614, 1588, 1512, 1468, 1451, 1363, 1238, 1227. HRMS (ESI-TOF) caled for C\(_{20}\)H\(_{24}\)N\(_2\)O\(_2\), [M+H]: 325.1911 obs: 325.1912.

In a separate experiment, authentic quinidinone (obtained through oxidation of quinine) was used in the reduction following the same experimental procedure with the following amounts: quinidinone (5 g, 15.5 mmol), Al powder (aerated, 4.18 g, 155 mmol), NaOEt (2.85 M, 69 mL, 187 mmol), EtOH (absolute, 125 mL). Selective crystallization took place with 10 mL 95% ethanol and 1.4 g L-tartaric acid in 95% ethanol. The hot solutions were added together, cooled, and seeded with a trace of commercial quinine to yield 625 mg diquinine-L-tartaric acid (1.56 mmol, 10% yield) upon filtration.
Reduction with new aluminum powder:

**Stock solution of sodium ethoxide (2.85 M in ethanol):** Sodium (1.31 g, 57.0 mmol) was added in portions to a round-bottomed flask containing absolute ethanol (20 mL) and fitted with a reflux condenser. The solution bubbled vigorously and became hot. The solution was warmed to ensure complete consumption of sodium. The solution was then used immediately to prevent decomposition.

Quinidinone (200 mg, 0.62 mmol, obtained through oxidation of quinine) was placed in a 25 mL round-bottomed flask and dissolved in ethanol. Sodium ethoxide (2.6 mL, 7.44 mmol) from a freshly-opened bottle (Aldrich) was then added in one portion and the mixture was heated to reflux temperature with stirring. The reaction was allowed to proceed for 2 hours at which time the material was filtered while hot through a glass fritted funnel. The aluminum was then washed with ethanol. The filtrate was quenched through the addition of 1M HCl until a pH <3 was reached as measured with pH paper. Ethanol was then removed under reduced pressure with warming. 30% sodium hydroxide was then added to the remaining mixture until pH >10 was reached as measured by pH paper. The mixture was then extracted with ether (x3), dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography with Davisil neutral silica gel (3:1:1:1, ethyl acetate:acetonitrile:methanol:water) provided an inseparable mixture of quinine and quinidine (60 mg, 0.18 mmol, 1:1:1 by $^1$H NMR analysis) in combined 30% yield.
Reduction with aerated aluminum powder:

Aluminum powder (Aldrich) was placed in a beaker with a stir bar and was exposed to a thin stream of air for 72 hours. Quinidinone (200 mg, 0.62 mmol) was placed in a 25 mL round-bottomed flask and dissolved in ethanol. Sodium ethoxide (2.6 mL, 7.44 mmol) was then added. Aerated aluminum powder (171 mg, 6.33 mmol) was then added in one portion and the mixture was heated to reflux with stirring. The reaction was allowed to proceed for 2 hours. The reaction was quenched as described above. An intractable mixture of quinine and quinidine (58 mg, 0.18 mmol, 1.1:1 by \(^1\)H NMR analysis) was obtained in combined 29% yield.

Reduction with aerated aluminum powder and added alumina:

Aluminum powder was placed in a beaker with a stir bar and was exposed to a thin stream of air for 72 hours. Quinidinone (200 mg, 0.62 mmol) was placed in a 25 mL round-bottomed flask and dissolved in ethanol. Sodium ethoxide (2.6 mL, 7.44 mmol) was then added. Aluminum powder (171 mg, 6.33 mmol) from a freshly-opened bottle was then added followed by addition of basic alumina (171 mg). The mixture was heated to reflux with stirring. The reaction was allowed to proceed for 2 hours. The reaction was quenched as described above. A mixture of quinine and quinidine (53 mg, 0.16 mmol, 1.1:1 by \(^1\)H NMR analysis) was obtained in combined 26% yield.

Reduction with aerated aluminum powder and sonication:

Aluminum powder was placed in a beaker with a stir bar and was exposed to a thin stream of air for 72 hours. Quinidinone (200 mg, 0.62 mmol) was placed in a 25 mL round-bottomed flask and dissolved in ethanol. Sodium ethoxide (2.6 mL, 7.44 mmol) was then added. Aluminum powder (171 mg, 6.33 mmol) from a freshly-opened bottle was then added in one portion. The mixture was heated to 75 °C with sonication. The reaction was allowed to proceed for 2 hours. The reaction was quenched as described above. A mixture of quinine and quinidine (44 mg, 0.14 mmol, 1.1:1 by \(^1\)H NMR analysis) was obtained in combined 22% yield.

Reduction with aerated aluminum powder, sodium methoxide, methanol:

Quinidinone (200 mg, 0.62 mmol) was placed in a 25 mL round-bottomed flask and dissolved in methanol. Sodium methoxide (2.85 M, 2.6 mL, 7.44 mmol, prepared as described previously, but with methanol) was then added. Aerated aluminum powder (171 mg, 6.33 mmol) was then added in one portion and the mixture was heated to reflux with stirring. The reaction was allowed to proceed for 2 hours. The reaction was quenched as described above. A mixture of quinine and quinidine (16 mg, 0.05 mmol, 1.2:1 by \(^1\)H NMR analysis) was obtained in combined 8% yield.

Reduction with aerated aluminum powder, sodium isopropoxide, isopropanol:

Quinidinone (200 mg, 0.62 mmol) was placed in a 25 mL round-bottomed flask and dissolved in \(iso\)-propanol (20 mL). Sodium \(iso\)-propoxide (0.87 M, 8.5 mL, 7.44 mmol, prepared as described previously, but with \(iso\)-propanol) was then added. Aerated aluminum powder (171 mg, 6.33 mmol) was then added in one portion and the mixture was heated to reflux with stirring. The reaction was allowed to proceed for 2 hours. The
reaction was quenched as described above. A mixture of quinine and quinidine (65 mg, 0.20 mmol, 1:1.2 by $^1$H NMR analysis) was obtained in combined 32% yield.

**Meerwein-Pondorf-Verley conditions:**

Quinidinone (200 mg, 0.62 mmol)$^4$ was placed in a 25 mL round-bottomed flask and dissolved in iso-propanol (10 mL). Aluminum iso-propoxide (1.3 g, 6.2 mmol) was added and the mixture was heated to reflux temperature with stirring. The reaction was allowed to proceed for 48 hours. The reaction was quenched as described above. A mixture of quinine and quinidine (55 mg, 0.17 mmol, 1.4:1 by $^1$H NMR analysis) was obtained in combined 28% yield.

**Lithium Aluminum Hydride Reductions:**

Quinidinone (200 mg, 0.62 mmol)$^4$ was placed in a 25 mL round-bottomed flask, dissolved in ether (10 mL), and cooled to either 0 °C, -78 °C or left at rt depending on the experiment. Lithium aluminum hydride (118 mg, 3.1 mmol) was added and the reaction was allowed to proceed for 1 hour at the temperature. The reaction was then quenched with very slow addition of 1M HCl and stirred to dissolve any salts. 30% NaOH was added and the mixture was extracted with ether (x3). The combined organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. Flash column chromatography as described above provided quinidine (120 mg, 0.37 mmol) in 59% yield for the reaction run at 0 °C; provided quinidine (90 mg, 0.28 mmol) in 45% yield for the reaction run at -78 °C; and provided quinidine (112 mg, 0.35 mmol) in 56% yield for the reaction run at rt.

**Lithium Aluminum Hydride Reduction with epimerization:**

Quinidinone (100 mg, 0.31 mmol)$^4$ was placed in a 25 mL round-bottomed flask, dissolved in ethanol (10 mL), and treated with sodium ethoxide (2.85 M, 1.3 mL, 3.72 mmol). This was allowed to stir for 15 minutes at which time the reaction was quenched as described above. The crude mixture of ketones was then dissolved in ether (10 mL) and cooled to 0 °C. Lithium aluminum hydride (118 mg, 3.1 mmol) was added and the reaction was allowed to proceed for 1 hour. The reaction was then quenched with very slow addition of 1M HCl and stirred to dissolve any salts. 30% NaOH was added and the mixture was extracted with ether (x3). The combined organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. Flash column chromatography as described above provided a mixture of quinine and quinidine (40 mg, 0.12 mmol, 1:1.5 by $^1$H NMR analysis) in combined 40% yield.

**References**

*Note. Repetition of the entire sequence (the protocol involving no chromatographic isolation or modern purification technologies) by Dr. Thomas J. Greshock starting with 9 grams of quinotoxine, yielded 330 mg of analytically pure diquinine tartrate crystals and 268 mg of analytically pure, crystalline quinine (5.9% yield).
SpinWorks 2.5: Quinuclidine from NQET Cyclization 300 MHz DMSO-6
SpinWorks 2.5: commercial quinine, DMSO-6, 400 MHz

Number of scans: 16

Spin-lattice: 158 (0.04 ppm, 0.0000 ppm, 0.000)

Spin-repolarization 6530 complex points

Processed size: 6530 complex points

Time of acquisition: 6200 points

Sample delay: 400.4427 MHz

The CP spectrum and spin-lattice reorientation of NMR data from commercial quinine in DMSO-d6. DMSO-d6 broadening at 0.4 ppm. 400.188 MHz.
Spinsworks 2.5: LAHA Reduction of quinidine at 300 MHz, DMSO-d6

Instruments and Spectral Data:

- Spectrometer: Varian Inova 600 MHz
- Sample: Quinidine
- Solvent: DMSO-d6
- Temperature: 298 K

Spectral Data:

- ppm: 0.00
- Chemical Shifts: 1.00, 1.01, 1.27, 3.73, 5.99, 2.26, 0.00, 0.86, 2.26, 2.26, 2.18, 0.86, 0.86, 0.86, 0.90, 0.90

Analysis:

- Number of scans: 12
- Spectral width: 5000 Hz
- Acquisition time: 31944 sec
- Transform range: 300.16-199.0 Hz
Spinworks 2.5: authentic mixture of 1:1 commercial quinidine:quinidine, 300 MHz, DMSO-δ6
SpinWorks 2.5: authentic sample, commercial quinine:quinidine, 1:2.1; 300 MHz, DMSO-d6