Stereocontrolled Conversion of Quinine into 10(*R*),11-Dihydroxydihydroquinine via the Sharpless Osmylation Process

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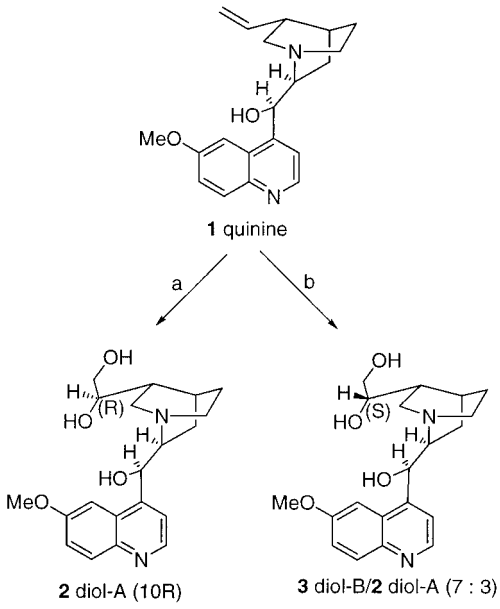
Introduction

Quinine **1** is used for the treatment of malaria, the prevention of nocturnal leg cramps, and the reversal of multidrug resistance during chemotherapy.[1−3] The World Health Organization (WHO) estimates that malaria affects between 300 and 500 million people a year, resulting in death for 2−3 million. Moreover, drug-resistant strains of malaria are now spreading rapidly throughout Southeast Asia, India, and sub-Saharan Africa. The treatment of chloroquinine-resistant malaria with **1** has become important in the past few years;[4] consequently, the products of the metabolism of **1** have been studied.[5,6] Examination of these studies demonstrates that **1** is rapidly metabolized in patients to several oxidized species.[7−11] In addition, when tested as an inhibitor of the MDR pump, quinine-10,11-epoxide was approximately 8-fold more potent than **1**. Bannon identified a number of quinine metabolites in urine after oral dosing in humans;[10] however, the absolute configurations of the two metabolites [10(*R*) and 10(*S*)] of 10,11-dihydroxydihydroquinine were not reported.[10]

Although the structures of a number of metabolites of **1** have been established,[12−17] the absolute configurations of the metabolites **2** and **3** of quinine[18] have not been reported. Recently, it was of interest to prepare the 10-(*R*) (**2**) and 10(*S*) (**3**) diastereomers to carry out the simultaneous determination of quinine and four metabolites in plasma and urine of patients using the technique of HPLC.[11] We wish to report the details here of the synthesis of 10(*R*),11-dihydroxydihydroquinine **2** and the corresponding 10(*S*)-diastereomer **3** as well as confirmation of their structures by single-crystal X-ray analysis.

Scheme 1[a]



[a] Key: (a) *t*-BuOH−H_2O, AD-mix-β, 0 °C, 4 d; $NaHSO_3$, 1 h, 91%; (b) *t*-BuOH−H_2O, AD-mix-α, 0 °C, 4 d; $NaHSO_3$, 1 h, 75%.

Results and Discussion

Treatment of **1** with AD-mix-β under the conditions of the Sharpless dihydroxylation process[19] provided diol-A (mp = 197−198 °C) **2** as the sole diastereomer in 91% yield (Scheme 1). Similar treatment of **1** with AD-mix-α provided the 10(S) diastereomer diol-B (mp=138−140 °C) **3** and the 10(R) isomer **2** in a 7:3 ratio. The two diols **2** and **3** could not be separated from each other by flash chromatography on silica gel nor alumina; however, single pure diastereomers could be obtained by crystallization from CH_2Cl_2/CH_3OH. The absolute configurations of **2** (10*R*) and **3** (10*S*) were established by single-crystal X-ray analysis, the structures of which are depicted in Figures 1 and 2 (see the Experimental Section for details).

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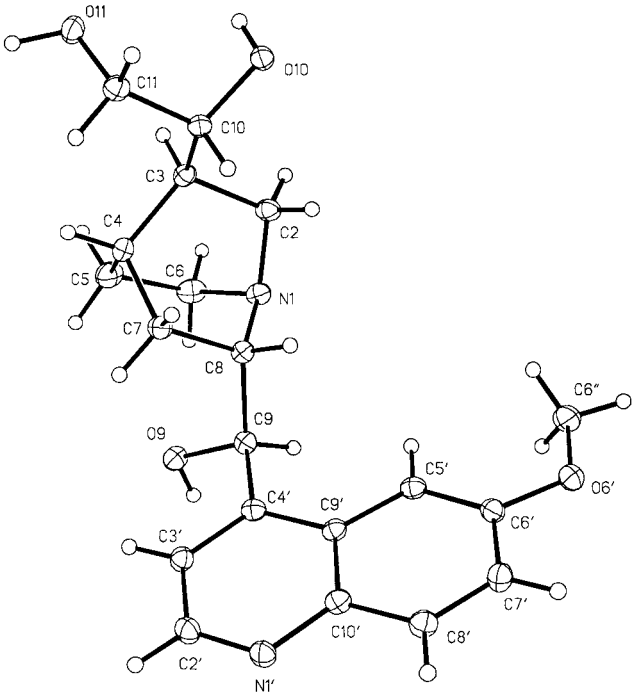

Figure 1. Results of the X-ray study on **2** (diol-A) drawn using experimentally determined coordinates with thermal displacement parameters at the 20% probability level.

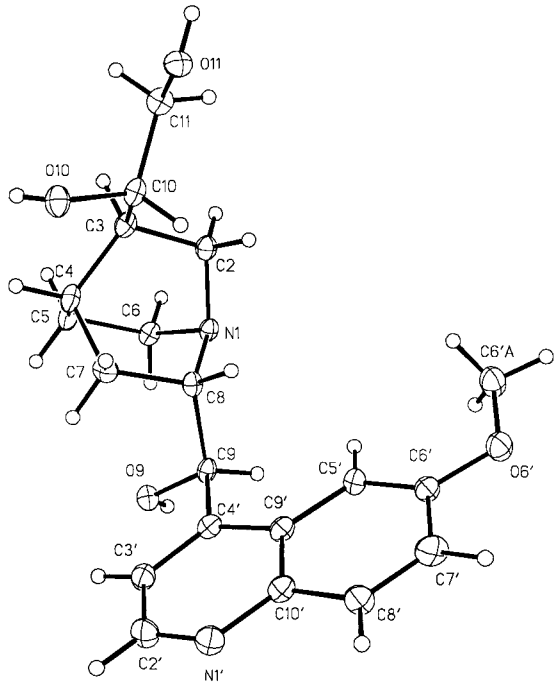

Figure 2. Results of the X-ray study on **3** (diol-B) drawn using experimentally determined coordinates with thermal displacement parameters at the 20% probability level.

Although several metabolites of quinine have been isolated, neither the quantitative importance of these metabolites for the elimination of **1** nor the metabolic pathways have been fully elucidated.[17,20] To our knowledge, this is the first stereospecific formation and characterization of the 10(*R*),11-dihydroxydihydro metabolite **2** of quinine to be reported.[21,22] This makes available the correct structures of these important metabolites to study further transformations in vivo[10,11,17,20] or to predict drug−drug or drug−food interactions, which may be of clinical significance.[5]

Experimental Section

The experimental protocols were carried out as previously reported.[23]

Diastereospecific Preparation of 10(*R*),11-Dihydroxydihydroquinine 2 via the Sharpless Catalytic Asymmetric Dihydroxylation (AD-mix-*β*). To a round-bottom flask (250 mL) that contained a solution of *tert*-butyl alcohol (80 mL) in H_2O (80 mL) were added K_2OsO_4 (100.0 mg, 0.3 mmol), hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQD)_2PYR$, 290.0 mg, 0.31 mmol], potassium ferrocyanide (3.00 g, 9 mmol), and K_2CO_3 (1.25 g, 9 mmol). The solution that resulted was stirred at room temperature for 1 h and was then cooled to 0 °C, after which quinine **1** (1.00 g, 3 mmol) was added to the above solution at 0 °C. The resulting reaction mixture was stirred at 0 °C for 4 d. Analysis by TLC [Al_2O_3, CH_2Cl_2 (90%)−CH_3OH (10%)] indicated the disappearance of starting material. The $NaHSO_3$ (1.2 g, 9 mmol) was then added to this solution, and the reaction mixture was stirred at 0 °C for 1.5 h followed by extraction with CH_2Cl_2 (4 × 30 mL). The combined organic layers were washed with water and brine and dried (K_2CO_3). The solvent was removed under reduced pressure, and the chiral ligand was removed by flash chromatography [Al_2O_3, CH_2Cl_2 (93%)−CH_3OH (7%)] to provide 10(*R*),11-dihydroxydihydroquinine **2** (0.94 g, 91%) as the sole diastereomer. The $(DHQD)_2PHAL$ ligand was used as well in place of $(DHQD)_2PYR$ in this reaction with essentially the same results.

2 (diol-A)10*R*: mp 197−198 °C; R_f = 0.25 (alumina, $CHCl_3$/CH_3OH = 85:15); IR (KBr) 3400−3100 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.32 (1H, m), 1.44 (1H, q, J = 7.14 Hz), 1.50−1.70 (3H, m), 1.73 (1H, m), 2.42 (1H, t, J = 9.99 Hz), 2.64 (2H, d, J = 7.12 Hz), 3.09 (3H, q, J = 7.47 Hz), 3.17−3.21 (2H, m), 3.90 (3H, s), 4.36 (1H, q, J = 5.76 Hz), 5.23 (1H, t, J = 6.32 Hz), 5.60 (1H, d, J = 4.86 Hz), 7.38 (1H, dd, J = 2.65, 9.18 Hz), 7.47−7.56 (2H, m), 7.93 (1H, d, J = 9.17 Hz), 8.67 (1H, d, J = 4.36 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 24.06, 24.51, 28.37, 38.36, 42.01, 53.90, 55.46, 60.71, 65.08, 71.22, 73.93, 102.53, 119.04, 120.91, 127.04, 131.14, 144.00, 147.49, 149.56, 156.73; MS(CI) m/z 359 (M + 1, 100). Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 66.85; H, 7.24; N, 7.80. Found: C, 67.00; H, 7.03; N, 8.11.

Diastereoselective Preparation of 10(*S*),11-Dihydroxydihydroquinine 3 via the Sharpless Catalytic Asymmetric Dihydroxylation. If $(DHQ)_2PYR$ was used instead of $(DHQD)_2$-PYR, a mixture of two diastereomers of 10,11-dihydroxyquinine was obtained in 75% yield and separated by crystallization (**2**/**3** = 3:7). The ligand was again removed by flash chromatography (same system as above), but the two isomers could not be separated from each other by silica gel chromatography or with alumina chromatography. A single pure diastereomer **3** was obtained by crystallization from CH_2Cl_2−CH_3OH. The $(DHQ)_2PYR$ can be replaced with $(DHQ)_2PHAL$ in this process with essentially the same results.

3 (diol-B)10*S*: mp 138−139.5 °C; R_f = 0.25 (alumina, $CHCl_3$−CH_3OH 85:15); IR (KBr):3410−3105 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.20−1.40 (2H, m), 1.55−1.80 (3H, m), 2.03 (1H, m), 2.21 (1H, dd, J = 3.06, 13.05 Hz), 2.40 (1H, td, J = 4.62, 13.94 Hz), 2.65−2.75 (1H, m), 3.03 (1H, q, J = 7.34 Hz), 3.10−3.25 (3H, m), 3.90 (3H, s), 4.40 (1H, d, J = 11.36 Hz), 5.22 (1H, t, J = 6.22 Hz), 5.63 (1H, d, J = 4.69), 7.38 (1H, dd, J = 2.54, 9.18 Hz), 7.50 (2H, d, J = 3.60), 7.92 (1H, d, J = 9.54 Hz), 8.67 (1H, d, J = 4.44 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 22.04, 24.07, 27.84. 37.86, 42.00, 54.23, 55.47, 60.88, 64.56, 71.15, 73.60, 102.53, 119.13, 120.89, 127.01, 131.14, 143.91, 147.48, 149.35, 156.74; MS(CI) m/z 359 (M + 1, 100).

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Single-Crystal X-ray Analysis of Diol-A (2) and Diol-B (3).

2 (diol-A): $C_{20}H_{26}N_2O_4$, (0.04 × 0.04 × 0.10 mm), orthorhombic space group $P2_12_12_1$, a = 11.547(2) Å, b = 11.739(2) Å, c = 27.156(4) Å, V = 3681.09(1) Å^3, Z = 8, ρ_{cacl} = 1.29 mg/mm^3, μ = 0.74 mm^{-1}, $F(000)$ = 1536, 6351 unique data, R1 = 0.046 for 4860 observed data.

3 (diol-B): $C_{20}H_{26}N_2O_4 \cdot 7H_2O$, (0.30 × 0.30 × 0.36 mm), monoclinic space group $P2_1$, a = 17.104(3) Å, b = 11.572(2) Å, c = 21.407(4) Å, β = 110.26(2)°, V = 3974.8(2) Å^3, Z = 2, ρ_{cacl} = 1.30 mg/mm^3, μ = 0.79 mm^{-1}, $F(000)$ = 1676, 20598 unique data, R1 =0.070 for 20249 observed data.

Data for both compounds were collected on a Bruker SMART 6K CCD system mounted on a 6 kW Cu rotating anode with Göbel mirrors to focus the beam. The structure of diol-A **2**, with two molecules per asymmetric unit, was solved by routine application of direct methods as applied in the SHELXTL*PLUS* program package.[24] Crystals of diol-B **3** exhibited non-merohedral twinning (some reflections are not overlapped with reflections from other twin components). Using the CCD, it was possible to collect data sets for both twin components at once, and the program GEMINI[25] was then used to identify the rotation matrix relating the twin components. The structure, with four diol molecules and seven water molecules in the asymmetric, was solved using program *SnB*[26] on the data from the stronger twin. Once the structure was solved, GEMINI was used again to generate a set of reflection data that could be used to do least-squares refinement on both sets of data at the same time. Coordinates for both diols were refined by full-matrix least-squares on F^2 values using programs in the SHELXTL*PLUS* package.[24] The parameters refined included the coordinates and anisotropic thermal parameters for all non-hydrogen atoms and coordinates only for the hydrogen atoms on the hydroxyl oxygens. All other hydrogen atoms were included using a riding model in which the coordinate shifts of their covalently bonded atoms were applied to the attached hydrogens with C−H = 0.96 Å. H angles were idealized and U_{iso} (H) set at fixed ratios of U_{iso} values of bonded atoms. Hydrogen atoms were not found for the water molecules in **3**.

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Supporting Information Available: Crystal data and structural refinement for **2** and **3**. Coordinates are also available from the Cambridge Crystallographic Database.[27] This material is available free of charge via the Internet at http://pubs.acs.org.

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