Journal of Natural Products
Vol. 53, No. 1, pp. 112-124, Jan-Feb 1990

SYNTHESIS OF 10,11-DIHYDROXYDIHYDROQUINIDINE *N*-OXIDE, A NEW METABOLITE OF QUINIDINE. PREPARATION AND ^{1}H-NMR SPECTROSCOPY OF THE METABOLITES OF QUININE AND QUINIDINE AND CONFORMATIONAL ANALYSIS VIA 2D COSY NMR SPECTROSCOPY

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ABSTRACT.—The first synthesis of 10,11-dihydroxydihydroquinidine *N*-oxide [**7b**], a recently isolated metabolite of quinidine, was accomplished in three steps from **1b**. The related congener **7a** in the quinine series was also prepared, as well as two other analogues **3a** and **4a**. In addition, the previously reported human metabolites **2a**, **5a**, and **6a** of quinine [**1a**] and those **2b**, **3b**, **4b**, **5b**, and **6b** of quinidine [**1b**] were synthesized. The chemical shift and coupling constants for all of the metabolites of quinine and quinidine were assigned via 2D COSY ^{1}H-nmr spectroscopy. Moreover, the conformations of these metabolites in solution were found to parallel those of the parent alkaloids, quinine [**1a**] and quinidine [**1b**], respectively.

Quinine and quinidine have been employed extensively in medicine as antimalarial (1) and antiarrhythmic (2) drugs, respectively. Unfortunately both demonstrate in certain individuals adverse side effects that operate through an immunologic mechanism implicated in the disease state, drug-induced immunologic thrombocytopenia (DITP) (3–7). This drug-induced reaction is characterized by formation of drug-dependent antibodies (DDAB) that in the presence of the offending drug and/or its metabolites destroy platelets in the blood. The molecular events responsible for the drug interaction with platelets that culminates in the formation of antigenic determinants recognized by DDAB are unknown. To date, it is not possible to predict who will respond to the drug with the production of the destructive antibodies. Nevertheless, the antibodies have been classified into at least three different groups (8). The first class of antibodies, termed "non-cross-reactive," binds to platelets in the presence of the drug (quinine [**1a**] or quinidine [**1b**]) and, for recognition is dependent upon the stereochemistry at C-8 and C-9 in these molecules. The second group of antibodies recognizes the aforementioned stereochemical centers (C-8, C-9) but is also dependent upon the presence of the C-6′ methoxyl group for efficient binding to platelets. The third class of antibodies is not stereoselective; the members react with either epimer (C-8 and C-9) and are therefore termed "cross-reactive."

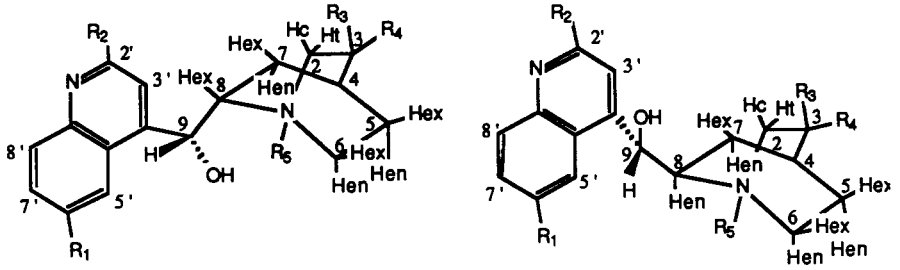
In order to understand the molecular basis for DITP, the various binding interactions among drug, platelets, and DDAB must be determined. This rests on studies of the role of drug metabolites in provoking formation of the platelet antigens and metabolite-specific antibodies involved in the pathogenesis of DITP, as well as determination of the conformation of the parent drug and metabolites in solution. In short, the potential binding conformation of metabolites or agents in question must be determined.

Although extensive nmr studies have been reported in the literature with regard to the structures of quinine [**1a**] and quinidine [**1b**] (9–11), only rarely has this involved their metabolites (12). This is especially relevant with respect to the assignment of the ^{1}H-nmr spectrum of the quinuclidine ring, which exhibits a large degree of signal overlap and complex coupling patterns. The metabolites of quinine and quinidine have

been isolated and characterized by several authors (12–15). As part of our research on the role of quinine, quinidine, and their metabolites in DITP, the preparation of a number of metabolites of quinine [**1a**] and quinidine [**1b**] has been carried out. In addition, the first synthesis of the recently isolated metabolite 10,11-dihydroxydihydroquinidine *N*-oxide [**7b**] (15) has been completed. The preferred conformation of these metabolites in solution was established by ^{1}H-nmr spectroscopy with particular emphasis on proton correlated two-dimensional nmr spectroscopy (2D-COSY).

RESULTS AND DISCUSSION

The synthesis of the metabolites of quinine [**1a**] and quinidine [**1b**] and their related derivatives (Figure 1) was accomplished by either following directly or modifying

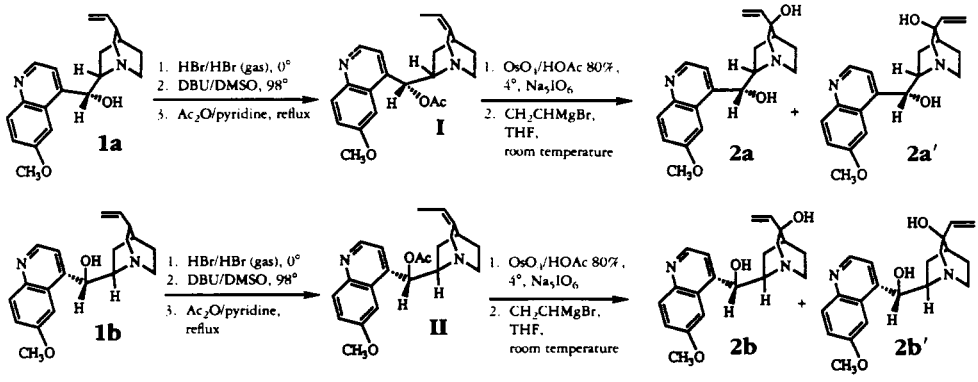


a **b**

1a, 1b R_1=MeO, R_2=R_4=H, R_3=CH_2CH
2a, 2b R_1=MeO, R_2=H, R_3=CH_2CH, R_4=OH
3a, 3b R_1=MeO, R_2=R_4=H, R_3=CH_2CH, R_5=O
4a, 4b R_1=OH, R_2=R_4=H, R_3=CH_2CH
5a, 5b R_1=MeO, R_2=OH, R_3=CH_2CH, R_4=H
6a, 6b R_1=MeO, R_2=R_4=H, R_3=$CH_2OHCHOH$
7a, 7b R_1=MeO, R_2=R_4=H, R_3=$CH_2OHCHOH$, R_5=O

FIGURE 1. Derivatives of quinine (a) and quinidine (b).

procedures reported previously in the literature. A brief description follows. The preparation of 3-hydroxyquinidine [**2b**] was reported by Coleman *et al.* (16), and this chemistry was extended to 3-hydroxyquinine [**2a**] (Scheme 1). When either quinine [**1a**] or quinidine [**1b**], individually, was treated with concentrated hydrobromic acid, the corresponding 10,11-hydrobromides were produced; they were then subjected to dehydrohalogenation with DBU to provide the apoquinidine and apoquinine analogues, respectively. Both apo-analogues were directly acetylated to generate the apoquinine acetate **I** and apoquinidine acetate **II** intermediates (Scheme 1). The inter-

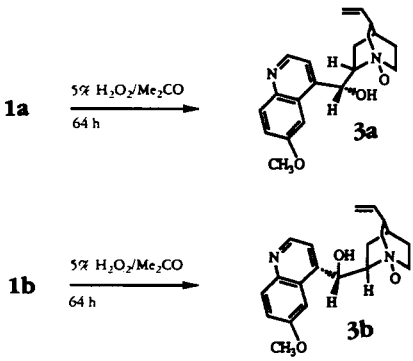


SCHEME 1

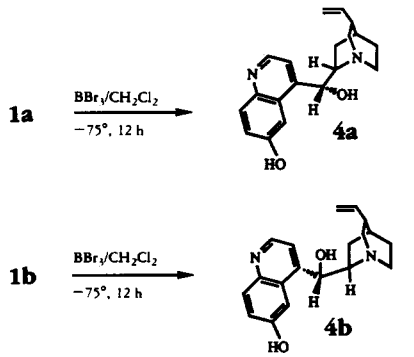
mediates **I** and **II** were oxidized with OsO_4 and sodium paraperiodate to furnish the corresponding quinine ketoacetate and quinidine ketoacetates. The ketoacetates were stirred separately with vinyl magnesium bromide to provide a mixture of the two epimeric 3-hydroxyquinidines and the related 3-hydroxyquinines. The epimeric alcohols (C-3) in both series were separated by flash chromatography. The desired 3-hydroxyquinidine [**2b**] was obtained in 45% yield. The related alcohol in the quinine series, 3-hydroxyquinine [**2a**], was obtained in 35% yield (Scheme 1).

Regioselective *N*-oxidation of the tertiary amine of the quinuclidine ring of both quinine [**1a**] and quinidine [**1b**] was performed with H_2O_2 (Scheme 2). The quinine *N*-oxide derivative **3a** and the quinidine metabolite **3b** were prepared following the procedure of Guentert *et al.* (17).

The early attempts to prepare the metabolite *O*-desmethyl quinidine [**1b**] with hot concentrated mineral acids were unsuccessful (18). The action of these reagents on **1b** readily brings about isomerization of the $\Delta^{11\text{-}10}$ doublet bond to the $\Delta^{3\text{-}10}$ position. Successful cleavage of the methyl group from the 6′ position of the methyl ether **1b** was achieved by the method of Small *et al.* (18). Both *O*-desmethylquinine [**4a**] and *O*-desmethylquinidine [**4b**] were prepared in 60% yield, individually (Scheme 3).

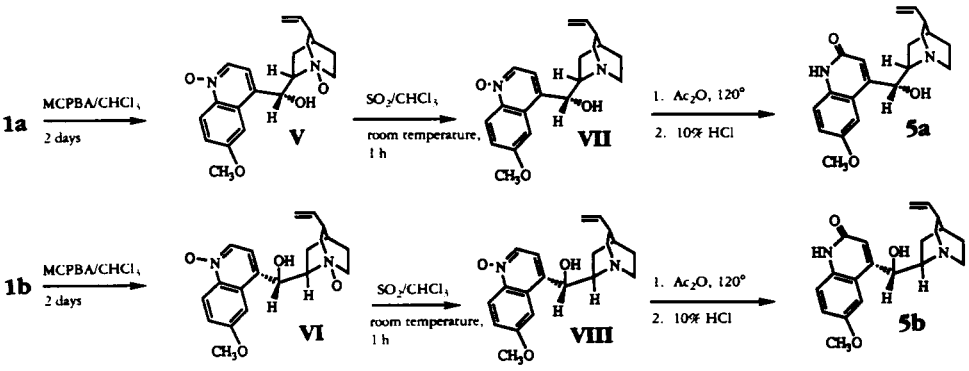


SCHEME 2



SCHEME 3

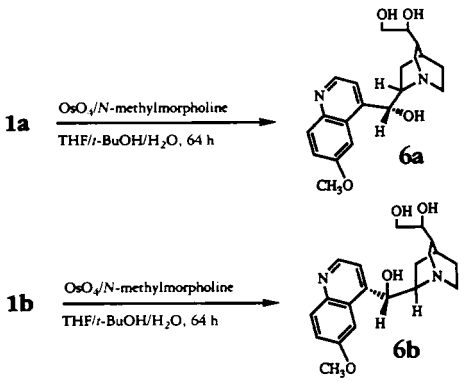
The synthesis of the metabolites represented by the pyridones, 2′-quinone [**5a**] and 2′-quinidone [**5b**], was executed according to published procedures (19) (Scheme 4). Quinine [**1a**] and quinidine [**1b**] were initially converted into the corresponding bis-*N*-oxide intermediates **V** and **VI**, respectively, on treatment with *m*-chloroperbenzoic acid (7 equiv). Originally 30% H_2O_2/HOAc was employed, but low yields were obtained. Comparison of the pKa values of aliphatic and aromatic nitrogen (pyridine)



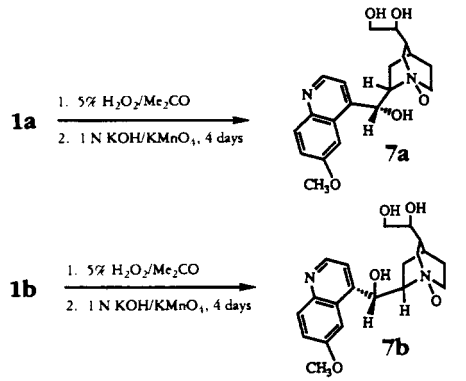
SCHEME 4

functions (19) indicates that formation of the *N*-oxide of the quinuclidine ring could be accomplished regioselectively via use of a mild oxidizing agent (aqueous 5% H_2O_2). Stronger oxidizing agents such as *m*-chloroperbenzoic acid and 30% H_2O_2/HOAc effect *N*-oxidation at both nitrogen centers. The bis-*N*-oxides **V** and **VI** were then regioselectively reduced with SO_2 to the mono-*N*-oxides **VII** and **VIII** without reduction of the quinoline *N*-oxide. The N-O bond of aromatic *N*-oxides is more stable due to mesomeric effects and is unaffected by the SO_2-mediated reduction. The conversion of the mono-*N'*-oxides into the quinone metabolite **5a** and the quinidone metabolite **5b** with Ac_2O is considered to proceed via 1,2 addition of the reagent to the quinoline ring. Thus, mono-*N'*-oxide analogues **VII** and **VIII** were treated with an excess of Ac_2O at 120–130°. The excess Ac_2O was removed by distillation, and the acetate which remained was hydrolyzed with aqueous HCl (reflux, 4 h). This process furnished quinidone [**5b**] and quinone [**5a**] (individually) in 75% yield.

The synthesis of 10,11-dihydroxydihydroquinine [**6a**] and 10,11-dihydroxydihydroquinidine [**6b**] was carried out either by the use of OsO_4 oxidation (Scheme 5) or by the procedure of Rakhit *et al.* (20) (Scheme 6). The structures of **6a** and **6b** were confirmed by ir, nmr, and mass spectroscopy.



SCHEME 5



SCHEME 6

Recently Imai *et al.* (15) isolated a new metabolite of quinidine, 10,11-dihydroxydihydroquinidine *N*-oxide [**7b**], the structure of which was determined by hplc and ms. The synthesis of **7b** and the related quinine analogue **7a** was recently completed as outlined in Scheme 6. Quinine [**1a**] and quinidine [**1b**] (individually) were reacted with H_2O_2 5% in Me_2CO for 64 h at room temperature to provide regioselective *N*-oxidation at the quinuclidine nitrogen atom (17). The structure of this *N*-oxide was confirmed by ms *m/z* 341 $[M + 1]^+$ (ci, CH_4). Close examination of the ^{1}H-nmr spectrum of the *N*-oxide derivatives **3a** and **3b** indicated that the protons at C-2, C-6, and C-8 which were located α to the *N*-oxide group were shifted downfield about 1 ppm relative to those of **1a** and **1b**. In addition, the proton located at H-9 was deshielded approximately 1.5 ppm, while the protons of the methoxyl group were shifted upfield about 1 ppm. Normally, the methyl function of arylmethyl ethers in this series appears at a chemical shift of δ 3.9. The chemical shifts of the protons in **3a** and **3b** support a conformation in solution (Figures 2 and 3) in which the proton located at H-9 is perpendicular to the N-O bond, while the protons of the methoxyl group are parallel to this N-O bond. The distance between the groups is small enough to permit the protons at H-9 and of the MeO-group to experience the effect of anisotropy from the roughly equidistant positions of the N-O bond. The two *N*-oxides **3a** and **3b** were then (individually) oxidized at the olefinic position (C-10 and C-11) according to the procedure of

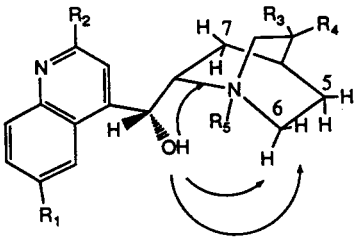


FIGURE 2. Conformation of the derivatives of quinine in solution.

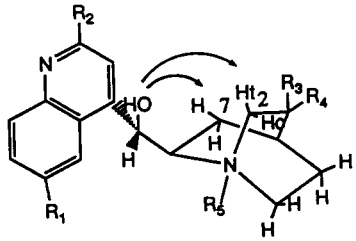


FIGURE 3. Conformation of the derivatives of quinidine in solution.

Rakhit *et al.* (20), as shown in Scheme 6. After chromatography, 10,11-dihydroxydihydroquinine *N*-oxide [**7a**] was obtained in 50% overall yield (mp 169°), and the corresponding analogue **7b** of quinidine was isolated in 48% overall yield from the analogous oxidation (mp 154°).

Examination of the ^{1}H-nmr spectrum of both **7a** and **7b** clearly indicated that the desired hydroxylation had taken place. The triplet located at δ 5.16 ppm attributed to H-11 and the doublet of quintets found at 6.14 ppm (H-10) due to the double bond of the *N*-oxide **3b** had disappeared, followed by the upfield appearance of multiplets at δ 3.44 and 3.39 ppm for **7b** (H-11). A multiplet at δ 3.79 ppm also appeared and was assigned as H-10 in the spectrum of 10,11-dihydroxydihydroquinidine *N*-oxide **7b**. In similar fashion, the triplet at δ 4.96 ppm for H-11 and the doublet of quintets at 5.53 ppm for H-10 of the quinine *N*-oxide analogue **3a** disappeared, followed by the appearance of multiplets at δ 3.22 ppm (H-11) and δ 3.34 ppm for H-10 in the spectrum of

TABLE 1. ^{1}H-nmr Data of the Metabolites of Quinine (chemical shift assignments in ppm).

Proton	Compound						
	1a[a]	**2a**[b]	**3a**[b]	**4a**[b]	**5a**[a]	**6a**[b]	**7a**[b]
H-2′	8.42 d	8.77 d	8.74 d	8.57 d	—	8.66 d	8.66 d
H-3′	7.38 d	7.63 d	7.69 d	7.48 d	7.12 m	7.48 d	7.59 d
H-5′	7.14 d	7.47 s	7.13 d	7.46 d	6.88 m	7.47 d	7.99 s
H-7′	7.19 d	7.45 dd	7.08 dd	7.26 dd	7.02 m	7.37 dd	7.33 dd
H-8′	7.83 dd	7.98 d	7.89 d	7.84 d	6.85 m	7.91 d	7.88 d
H-11	4.48 t	5.28 dd	4.96 t	4.94 t	4.90 t	3.19 m	3.22 m
H-10	5.65 dq	6.05 dd	5.53 dq	5.85 dq	5.67 dq	3.34 s	3.34 m
H-9	5.42 m	6.17 s	6.98 s	5.12 m	5.44 s	5.20 d	6.62 s
H-8	3.02 m	3.62 m	3.18 m	3.05 m	3.06 m	3.03 m	3.22 m
H-2t	2.57 m	3.38 m	3.62 m	2.24 m	3.12 m	2.62 m	3.34 m
H-2c	2.95 m	3.2 m	3.00 m	2.87 m	2.68 m	2.21 m	2.90 m
H-3	2.18 m	—	2.80 m	2.18 m	2.29 m	1.40 m	2.16 m
H-4	1.72 s	1.94 s	1.96 s	1.63 m	1.79 m	1.61 s	1.87 s
H-5en	1.66 m[c]	1.85 m[c]	2.30 m[c]	2.02 m[c]	1.79 m[c]	1.57 m[c]	2.05 m[c]
H-5ex	1.42 m	1.85 m	1.93 m	1.86 m	1.45 m	1.30 m	1.83 m
H-6en	3.38 m[c]	4.12 m[c]	4.56 m[c]	3.96 m[c]	3.68 m[c]	3.15 m[c]	3.81 m[c]
H-6ex	2.54 m	3.32 m	3.23 m	3.12 m	2.68 m	2.42 m	3.10 m
H-7en	1.63 m[c]	1.19 m[c]	2.38 m[c]	2.02 m[c]	1.79 m[c]	1.71 m[c]	2.16 m[c]
H-7ex	1.42 m	1.56 m	1.54 m	1.45 m	1.45 m	1.57 m	1.60 m
MeO	3.80 s	3.99 s	2.96 s	—	3.74 s	3.88 s	3.70 s

[a]Spectrum in $CDCl_3$.
[b]Spectrum in DMSO.
[c]Unusually deshielded protons.

10,11-dihydroxydihydroquinine *N*-oxide [**7a**]. The chemical shifts of the protons present in the spectra of **7a** and **7b** are listed in Tables 1 and 2. These were established from analysis of their 2D-COSY nmr spectra.

TABLE 2. ^{1}H-nmr Data of the Metabolites of Quinidine (chemical shift assignments in ppm).

Proton	Compound						
	1b[a]	**2b**[b]	**3b**[b]	**4b**[b]	**5b**[a]	**6b**[b]	**7b**[b]
H-2′	8.52 d	8.73 d	8.56 d	8.64 d	—	8.67 d	8.64 d
H-3′	7.47 d	7.57 d	7.74 d	7.53 d	7.11 m	7.49 d	7.59 d
H-5′	7.13 d	7.42 s	7.10 d	7.47 d	6.88 m	7.48 d	7.77 s
H-7′	7.24 dd	7.44 dd	7.02 dd	7.38 dd	7.11 m	7.38 dd	7.35 dd
H-8′	7.89 d	7.96 d	7.85 d	7.88 d	6.88 m	7.92 d	7.89 d
H-11	5.00 t	5.45 dd	5.16 t	5.17 t	5.07 t	3.30 m	3.44 m
H-10	5.99 dq	6.17 dd	6.14 dq	5.98 dq	6.00 dq	3.68 s	3.79 m
H-9	5.52 m	6.09 s	7.13 s	6.08 m	5.17 s	5.26 d	7.00 s
H-8	3.00 m	3.53 m	3.13 m	3.46 m	3.06 m	2.96 m	3.24 m
H-2t	3.27 m[c]	4.53 m[c]	4.61 m[c]	3.93 m[c]	3.28 m[c]	3.14 m[c]	3.99 m[c]
H-2c	2.96 m	3.31 m	3.26 m	3.34 m	3.06 m	2.54 m	3.23 m
H-3	2.18 m	—	2.72 m	2.63 m	2.33 m	1.46 m	2.06 m
H-4	1.72 s	1.92 s	1.88 s	1.99 m	1.70 m	1.70 s	1.85 s
H-5en	1.45 m	1.57 m	1.93 m	1.76 m	1.61 m	1.46 m	1.77 m
H-5ex	1.54 m	2.05 m	1.80 m	1.76 m	1.61 m	1.43 m	1.77 m
H-6en	2.73 m	3.09 m	3.37 m	3.34 m	3.06 m	2.57 m	3.31 m
H-6ex	2.73 m	3.09 m	3.10 m[c]	3.20 m	2.91 m	2.52 m	3.12 m
H-7en	1.10 m	1.25 m	1.34 s	1.13 m	1.22 m	1.46 m	1.21 m
H-7ex	1.99 m[c]	2.13 m[c]	1.71 m	2.22 m[c]	2.15 m[c]	1.91 m[c]	2.45 m[c]
MeO	3.81 s	3.98 s	2.66 s	—	3.79 s	3.89 s	3.99 s

[a]Spectrum in $CDCl_3$.
[b]Spectrum in DMSO.
[c]Unusually deshielded protons.

The ^{1}H 2D COSY spectrum of **7a** is illustrated in Figure 4. It was anticipated that H-2′ and H-8′ (see Figure 1 for numbering) would be observed at low magnetic fields with H-2′ resonating at a lower frequency than H-8′ because H-2′ is α and H-8′ is β to the nitrogen atom of the quinoline ring. Hence the doublet at 8.66 ppm was assigned to H-2′, for this has the lowest chemical shift of the signals in the spectrum. It is α to the nitrogen atom in the quinoline ring and experiences a strong deshielding effect. It is also coupled to H-3′ at 7.59 ppm with a $J_{2'\text{-}3'}$ value of 4.5 Hz. In addition, the H-3′ proton is cross-coupled to the singlet at H-9 which resonates at 6.62 ppm. The doublet at 7.88 ppm has been assigned to H-8′ (β to the quinoline nitrogen) and is coupled to a signal present as a doublet of doublets attributable to H-7′ (7.33 ppm) with a $J_{8'\text{-}7'}$ of 9 Hz. Moreover, H-7′ is coupled to H-5′ at 7.99 ppm with a $J_{7'\text{-}5'}$ value of 2.7 Hz. The methoxyl protons (OMe) are observed as a singlet at 3.70 ppm.

In the quinuclidine ring, the protons at H-2c, H-2t, H-6en, H-6ex, and H-8 were expected to resonate at lower magnetic fields than H-3, H-7ex, H-7en, H-5en, H-5ex, and H-4, because the former set are α to the nitrogen atom of the quinuclidine ring. The protons of the multiplet at δ 3.22 ppm were assigned to H-8, which is cross-coupled both to H-7ex located at δ 1.60 ppm and to H-7en found at 2.16 ppm. Both H-7ex and H-7en are cross-coupled to the signal for H-4 observed at 1.87 ppm. The protons designated H-5ex and H-5en are cross-coupled to each other (1.83 ppm and 2.05 ppm), as well as to both H-6ex and H-6en located at 3.10 ppm and 3.81 ppm, re-

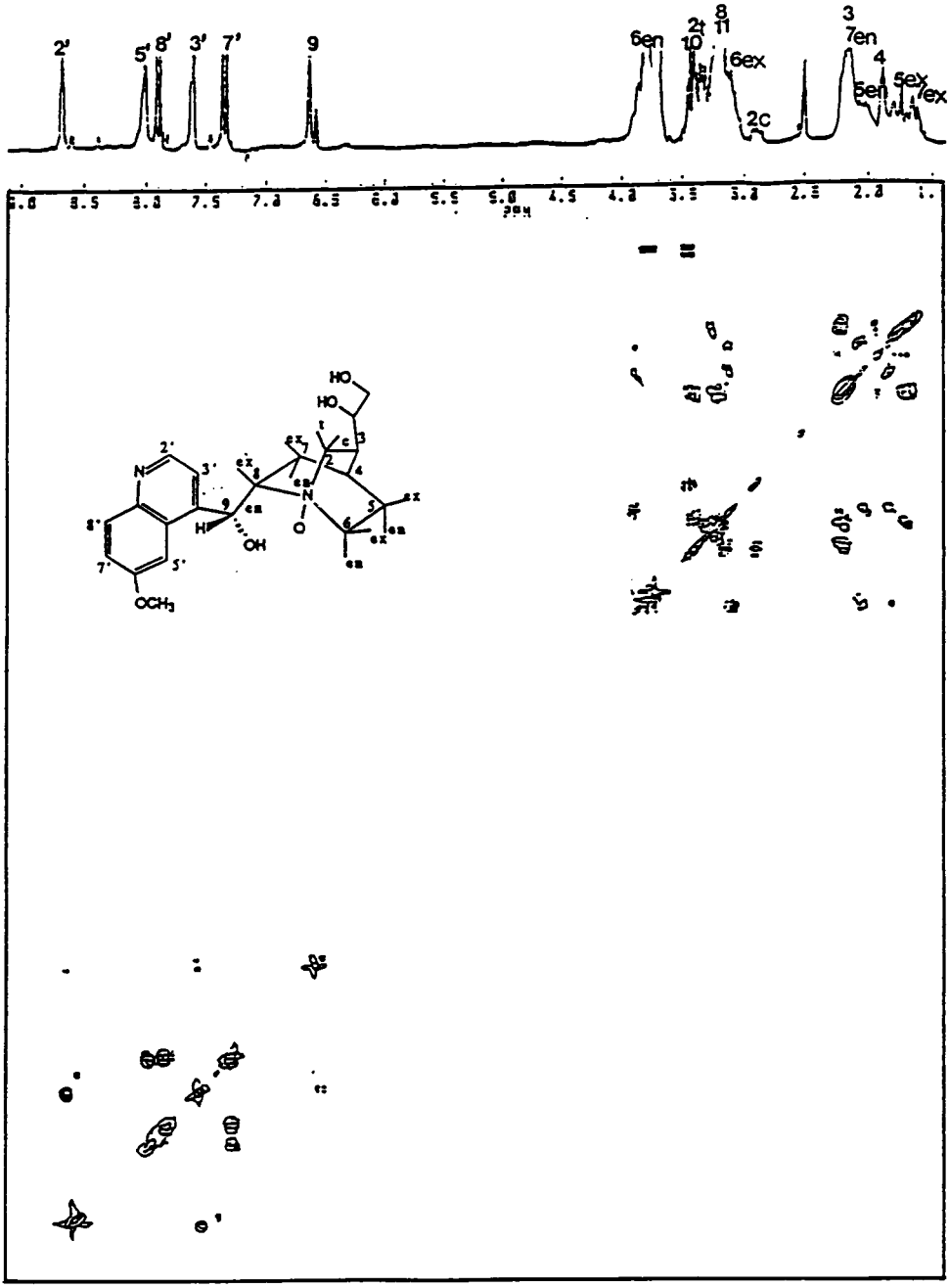


FIGURE 4. 2D COSY of 10,11-dihydroxydihydroquinine *N*-oxide [**7a**] [Me_2SO-d_6, $f_1 = -0.5$, $f_2 = 9.5$ ppm, NS = 64, NE = 512, DO = 0.000005, $SF_1 = 250.204$, $SF_2 = 250.204$].

spectively, and also to proton H-4 found at δ 1.87 ppm. The proton designated H-3 was assigned the signal at 2.16 ppm and is cross-coupled to H-2c at 2.90 ppm and to H-2t at 3.34 ppm.

The ^{1}H 2D COSY nmr spectrum of **7b** is outlined in Figure 5. The chemical shifts of the ring protons of the quinoline nucleus are similar to those assigned for **7a**, with which they are related: H-2′ and H-8′ are expected to resonate at lower magnetic field

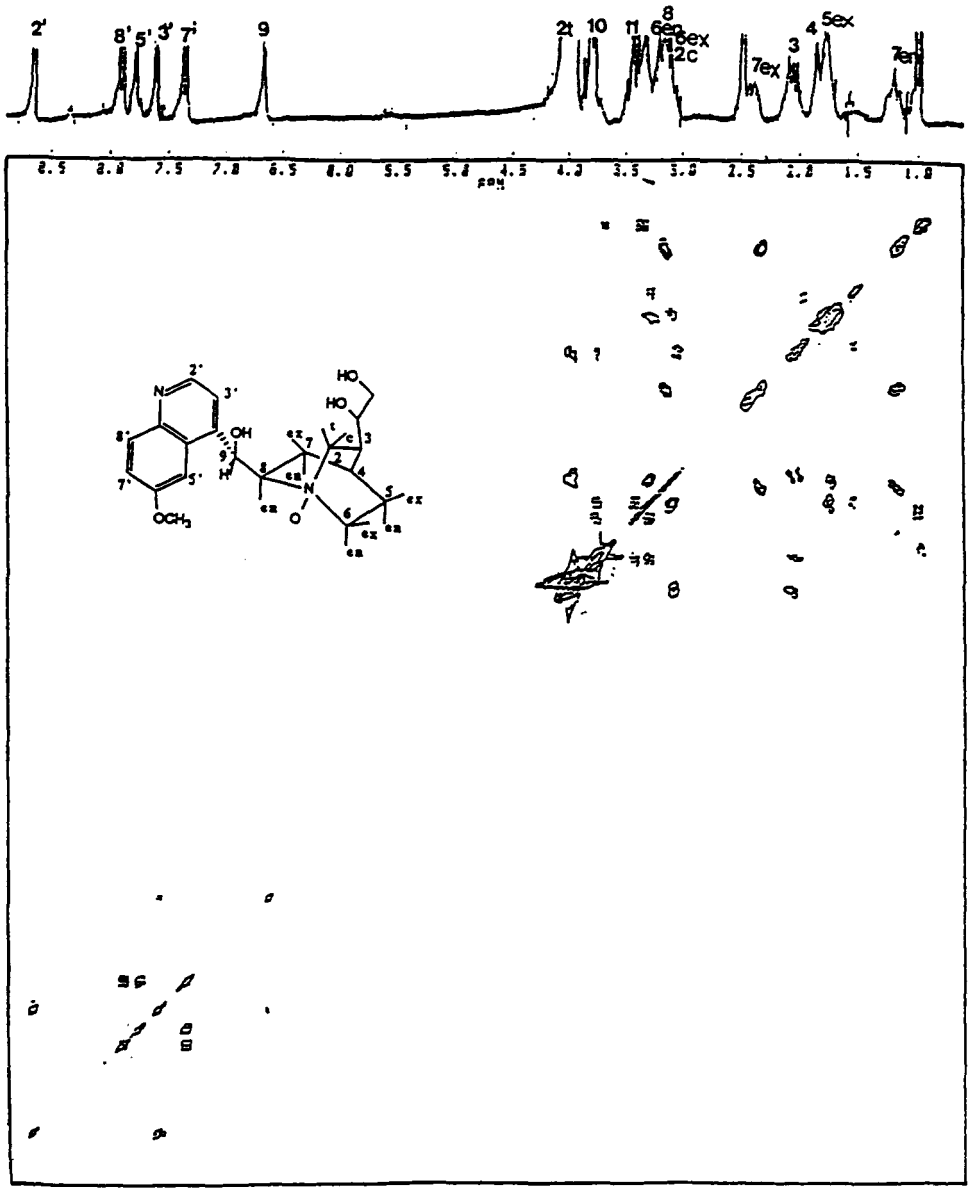


FIGURE 5. 2D COSY of 10,11-dihydroxydihydroquinidine *N*-oxide [**7b**] [Me_2SO-d_6, $f_1 = -0.5$, $f_2 = 9.5$ ppm, NS = 64, NE = 512, DO = 0.000005, $SF_1 = 250.204$, $SF_2 = 250.204$].

and in that consecutive order. The H-2′ proton observed at 8.64 ppm is coupled with H-3′ located at 7.59 ppm, which is also cross-coupled to H-9 at 7.00 ppm. The signal for H-8′ is found at 7.89 ppm and is coupled to H-7′ observed at 7.35 ppm. The latter proton is also coupled to H-5′ (7.77 ppm). The protons for the methoxyl group are observed as a singlet at δ 3.99 ppm. In the quinuclidine ring of **7b** the proton designated H-6en is found as a multiplet at 3.31 ppm and is cross-coupled to H-6ex observed at 3.12 ppm and also to H-5en and to H-5ex located at 1.77 ppm. The H-7ex proton at 2.45 ppm is cross-coupled to H-7en located at 1.21 ppm and to H-8 at 3.24 ppm. The multiplet at 3.99 ppm was assigned to H-2t which is cross-coupled to H-2c found at 3.23 ppm and to H-3 at 2.06 ppm. Comparison of the chemical shifts for the quinuclidine protons of metabolite **7a** and derivative **7b** is particularly informative. Protons

2t and 7ex in **7b** and the protons 6en, 7en and 5en in **7a** are unusually deshielded. These effects are also true for the other metabolites which were studied (Tables 1 and 2). These changes in chemical shift reflect the differences in the configurations at C-8 and C-9 of the quinine and quinidine molecules and provide information in regard to the relative preferred conformations of these molecules in solution.

In quinine, quinidine, and their metabolites, only limited rotational freedom is expected about the bonds in the single atom bridge (C-9) because of adverse steric interactions. This results in a preferred conformation of these molecules even though they contain two rigid heterocyclic rings. Two reports of conformational analysis have been published for quinine and quinidine. The first was reported by Yehuda *et al.* (10); the second was by Chazin and Colebrook (11).

From data based on the ^{1}H-nmr resonances generated from the correlation analysis it was found that the hydroxyl group at C-9 and the bond between C-9 and C-8 (because it is from the exo position) render the protons located at H-2t and H-7ex closer to the hydroxyl group, and they are, therefore, deshielded in the quinidine series. That is to say, the hydroxyl group is located spatially in the environment of the upper-left portion of the quinuclidine ring, as illustrated in Figure 3. In the quinine series the effects of deshielding are due to the same hydroxyl group at C-9, but the bond between C-9 and C-8 is spatially located from the endo position of the quinuclidine ring. The hydroxyl group is, therefore, closer to the protons designated H-6en, H-7en, and H-5en and deshields them. In other words, the hydroxyl group is located below the quinuclidine ring, in the quinine series (Figure 2). For these reasons, as well as from consideration of molecular models, it is felt that the preferred conformations of the metabolites of quinine and quinidine are represented as illustrated in Figures 2 and 3. These conformations are in agreement with those proposed earlier by Chazin and Colebrook (11) for quinine [**1a**] and quinidine [**1b**] based on nOe and ^{1}H spin-lattice relaxation experiments. Because the molecules in solution adopt a preferred conformation with a specific orientation for the two rings (quinoline and quinuclidine) and the hydroxy group (Figures 2 and 3), the deshielding experienced by the protons located at H-9 and of the methoxyl group of **7a** and **7b** can be understood.

In conclusion, the previously reported metabolites **2a**, **5a**, and **6a** of quinine were synthesized, as well as the metabolites **2b**, **3b**, **4b**, **5b**, and **6b** of quinidine. In addition, the first synthesis of the recently isolated metabolite 10,11-dihydroxydihydroquinidine *N*-oxide [**7b**] was accomplished, as well as preparation of the related quinine diastereomer **7a**, both of which are now available in gram quantities for biological studies. A number of related derivatives **3a**, **4a**, and **7a** of interest in the quinine series were also synthesized.

The ^{1}H-nmr chemical shifts and coupling constants of all metabolites (Tables 1 and 2) were defined by 2D COSY ^{1}H-nmr spectroscopy. Moreover, it was found that the conformations of the metabolites of quinine and quinidine in solution were similar to those reported for quinine and quinidine, respectively, by Chazin and Colebrook (11). The conformations of these metabolites, as well as those of the parent alkaloids **1a** and **1b**, are considered extremely important in regard to the study of drug-platelet-antibody interactions in DITP (8,21). Further work in this area is in progress and will be reported in due course.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H-nmr spectra were taken on a Bruker 250 MHz and General Electric 500 MHz spectrometer. Ir spectra were run on either a Beckman Acculab-1 or a Nicolet MX-1 spectrophotometer. Low-resolution mass spectral data (ei/ci) were obtained on a Hewlett-Packard 5855 GC-mass spectrometer. High-resolution mass spectra were taken on a Finnigan HR mass spectrometer at

NIH. Analytical tlc plates employed were E. Merck Brinkman uv active Si gel 60 F_{254} or alumina on plastic. Si gel 60 and aluminum oxide for chromatography were purchased from J.T. Baker. Unless otherwise specified, all chemicals were purchased from Aldrich Chemical Co.

(3*S*)-HYDROXYQUININE [**2a**].—Mp 148° (Et_2O) [lit. (13) mp 147–148°]; ir (KBr) 3350, 1615, 1500, 1240, 1015 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ (ppm, Hz) 8.77 (d, 1H, $J_{2'-3'}=4.4$), 7.98 (d, 1H, $J_{8'-7'}=9.0$), 7.63 (d, 1H, $J_{3'-2'}=4.4$), 7.47 (s, 1H), 7.45 (dd, 1H, $J_{7'-5'}=2.1, J_{7'-8'}=9.0$), 6.17 (s, 1H), 6.05 (dd, 1H, $J_{10-11t}=10.5, J_{10-11c}=17$), 5.28 (dd, 2H, $J_{11t-10}=10.5, J_{11c-10}=17$), 4.12 (m, 1H), 3.99 (s, 3H), 3.62 (m, 1H), 3.38 (m, 1H), 3.32 (m, 1H), 3.20 (m, 1H), 1.99 (m, 1H), 1.94 (m, 1H), 1.85 (m, 2H), 1.56 (m, 1H); cims (CH_4) *m/z* $[M+1]^+$ 341 (100%), $[M+29]^+$ 369 (25%), $[M+1-18]^+$ 323 (25%). The undesired isomer **2a′**: mp 157° (Et_2O); ir (KBr) 3350, 1610, 1500, 1248, 1225, 1010 cm^{-1}; cims (CH_4) *m/z* $[M+1]^+$ 341 (100%), $[M+29]^+$ 369 (25%), $[M+1-18]^+$ 323 (27%).

(3*S*)-HYDROXYQUINIDINE [**2b**].—Mp 211° (Et_2O) [lit. (12) mp 211–212°]; ir (KBr) 3350, 1650, 1500, 1228, 1035 cm^{-1}; cims (CH_4) *m/z* $[M+1]^+$ 341 (100%), $[M+29]^+$ 369 (25%), $[M-17]^+$ 323 (30%). Isomer **2b′**: mp 187 ° (Et_2O) [lit. (16) mp 188–190°]; ir (KBr) 3350, 1518, 1500, 1249, 1232, 1012 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ (ppm, 250 Hz) 8.73 (d, 1H, $J_{2'-3'}=4.4$), 7.96 (d, 1H, $J_{8'-7'}=9.0$), 6.57 (d, 1H, $J_{3'-2'}=4.4$), 7.44 (dd, 1H, $J_{7'-8'}=9.0, J_{7'-5'}=2.1$), 7.42 (s, 1H), 6.17 (dd, 1H, $J_{10-11t}=10.5, J_{10-11c}=17$), 6.09 (s, 1H), 5.35 (dd, 2H, $J_{11t-10}=10.5, J_{11c-10}=17$), 4.53 (m, 1H), 3.98 (s, 3H), 3.53 (m, 1H), 3.31 (m, 1H), 3.09 (m, 2H), 2.13 (m, 1H), 2.05 (m, 1H), 1.92 (s, 1H), 1.57 (m, 1H), 1.25 (m, 1H); cims (CH_4) *m/z* $[M+1]^+$ 341 (100%), $[M+29]^+$ 369 (25%), $[M-17]^+$ 323 (30%).

QUININE *N*-OXIDE [**3a**].—Quinine [**1a**] (1.5 g, 4.6 mmol) was dissolved in Me_2CO (200 ml), and 5% aqueous H_2O_2 (750 ml) was added. The mixture was stirred in the dark at room temperature for 64 h, and the reaction was followed by tlc [MeOH-$CHCl_3$ (0.5:9.5) on Si gel]. Excess H_2O_2 was destroyed by addition of 10% palladium on charcoal until starch iodide paper no longer turned blue. The solution was filtered and extracted with $CHCl_3$ (150 ml). The solvent was removed under reduced pressure to yield **3a** (1.26 g, 60% yield): mp 96°; ir (KBr) 947 cm^{-1}; ^{1}H nmr (Me_2SO-d_6) δ (ppm, 250 Hz) 8.74 (d, 1H, $J_{2'-3'}=4.4$), 7.69 (d, 1H, $J_{3'-2'}=4.4$), 7.13 (d, 1H, $J_{5'-7'}=2.7$), 7.08 (dd, 1H, $J_{7'-5'}=2.7, J_{7'-8'}=9$), 7.89 (d, 1H, $J_{8'-7'}=9$), 4.96 (t, 2H, $J_{11t-11c}=1.2, J_{11t-10}=10.5, J_{11c-1}=17$), 5.53 (dq, 1H, $J_{10-11t}=10.5, J_{10-11c}=17$), 6.98 (s, 1H), 3.18 (m, 1H), 3.62 (m, 1H), 3.00 (m, 1H), 2.30 (m, 1H), 1.93 (m, 1H), 4.56 (m, 1H), 3.23 (m, 1H), 2.38 (m, 1H), 1.54 (m, 1H), 2.96 (m, 1H), 2.96 (s, 3H); cims (CH_4) *m/z* $[M+1-16]^+$ 325 (100%), $[M+1]^+$ 341 (85%), $[M+29]^+$ 369 (20%). *Anal.* calcd for $C_{20}H_{24}N_2O_3$, C 67.02, H 7.312, N 7.81; found C 68.34, H 7.08, N 7.65.

QUINIDINE *N*-OXIDE [**3b**].—Quinidine [**1b**] (2 g, 6.1 mmol) was dissolved in Me_2CO (200 ml), and 5% aqueous H_2O_2 (750 ml) was added. The mixture was stirred in the dark at room temperature for 64 h, and the reaction was followed by tlc [MeOH-$CHCl_3$ (0.5:9.5) on Si gel]. Excess H_2O_2 was destroyed by addition of 10% palladium on charcoal until the solution was negative to starch iodide paper. The solution was filtered and extracted with $CHCl_3$ (150 ml), and the solvent was removed under reduced pressure to yield **3b** (1.28 g, 60% yield): mp 149–152° dec. [lit. (17) mp 150–152°]; ir (KBr) 949 cm^{-1}; ^{1}H nmr (Me_2SO-d_6) δ (ppm, 250 Hz) 8.56 (d, 1H, $J_{2'-3'}=4.4$), 7.74 (d, 1H, $J_{3'-2'}=4.4$), 7.10 (d, 1H, $J_{5'-7'}=2.7$), 7.02 (dd, 1H, $J_{7'-5'}=2.7, J_{7'-8'}=9$), 7.85 (d, 1H, $J_{8'-7'}=9$), 5.16 (t, 2H, $J_{11t-11c}=1.2, J_{11t-10}=10.5, J_{11c-10}=17$), 6.14 (dq, 1H, $J_{10-11t}=10.5, J_{10-11c}=17$), 7.13 (s, 1H), 3.13 (m, 1H), 4.61 (m, 1H), 3.26 (m, 1H), 1.93 (m, 1H), 1.80 (m, 1H), 3.37 (m, 1H), 3.10 (m, 1H), 1.34 (m, 1H), 1.71 (m, 1H), 2.66 (m, 1H), 2.66 (s, 3H); cims (CH_4) *m/z* $[M+1-16]^+$ 325 (100%), $[M+1]^+$ 341 (90%), $[M+29]^+$ 369 (22%). *Anal.* calcd for $C_{20}H_{24}N_2O_3$, C 63.81, H 6.95, N 7.44; found C 63.30, H 6.78, N 6.96.

O-DESMETHYLQUININE [**4a**].—Quinine [**1a**] (3.42 g, 10.6 mmol) was dissolved in 50 ml of CH_2Cl_2 and cooled to −78° (dry ice/Me_2CO bath). Boron tribromide (10.4 g, 42.4 mmol) in 50 ml of CH_2Cl_2 was then added dropwise to the stirred solution over 1 h. After the solution was stirred for 1 h at −78°, the reaction mixture was stirred for an additional 12 h at 5° and at room temperature for 3 h. H_2O was cautiously added to decompose excess boron tribromide, and the mixture was made basic with 1 N NaOH (pH 11–12). The solution was then extracted with CH_2Cl_2 which was discarded. To the aqueous layer, dry ice was added slowly to bring the pH to approximately 8–9, and the precipitate which resulted was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to provide **4a** (2.1 g, 65% yield): tlc [MeOH-$CHCl_3$ (1:9) on Si gel] indicated the presence of a homogeneous single spot. The sample was purified by flash chromatography (SiO_2) to yield **4a**: mp 155–175°; ir (KBr) 3100–3600, 1330, 1227, 1075 cm^{-1}; ^{1}H nmr (Me_2SO-d_6) δ (ppm, 250 Hz) 8.64 (d, 1H, $J_{2'-3'}=4.5$), 7.53 (d, 1H, $J_{3'-2'}=4.5$), 7.47 (d, 1H, $J_{5'-7'}=2.7$), 7.38 (dd, 1H, $J_{7'-5'}=2.7, J_{7'-8'}=9.0$), 7.88 (d, 1H, $J_{8'-7'}=9.0$), 5.17 (t, 2H, $J_{11c-11t}=1.2, J_{11t-10}=10.5, J_{11c-10}=17$), 5.98 (dq,

1H, $J_{10\text{-}11t}$ = 10.5, $J_{10\text{-}11c}$ = 17), 6.08 (m, 1H), 3.46 (m, 1H), 3.93 (m, 1H), 3.34 (m, 1H), 1.76 (m, 2H), 3.34 (m, 1H), 3.20 (m, 1H), 1.13 (m, 1H), 2.22 (m, 1H); cims (CH_4) *m/z* $[M+1]^+$ 310 (100%), $[M+29]^+$ 339 (23%). *Anal.* calcd for $C_{19}H_{22}O_2N_2Cl$, C 59.53, H 6.30, N 7.30; found C 58.87, H 6.17, N 7.14.

O-DESMETHYLQUINIDINE [**4b**].—Quinidine [**1b**] (3.42 g, 10.6 mmol) was dissolved in 50 ml of CH_2Cl_2 and cooled to −78° (dry ice/Me_2CO bath). Boron tribromide (10.4 g, 42.4 mmol) in 50 ml of CH_2Cl_2 was then added dropwise to the stirred solution over 1 h. After the mixture was allowed to stir for 1 h at −78°, the reaction mixture was stirred for an additional 12 h at 5° and then at room temperature for 3 h. H_2O was cautiously added to decompose excess boron tribromide, and the mixture was made basic with NaOH (pH 11–12, 1 N). The solution was then extracted with CH_2Cl_2, and the organic layer was discarded. To the aqueous layer, dry ice was added slowly to bring the pH to approximately 8–9, and the precipitate that resulted was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to provide **4b** (2.12 g, 64% yield). Tlc [MeOH-$CHCl_3$ (1:9) on Si gel] indicated the presence of a single homogeneous spot. The sample was purified by flash chromatography (SiO_2) to yield **4b**: mp 167–175° (Et_2O) [lit. (18) mp 167–171°]; ir (KBr) 3100–3600, 1380, 1240, 1032 cm^{-1}; ^1H nmr (Me_2SO-d_6) δ (ppm, Hz) 8.57 (d, 1H, $J_{2'\text{-}3'}$ = 4.5), 7.48 (d, 1H, $J3'\text{-}2'$ = 4.5), 7.46 (d, 1H, $J_{5'\text{-}7'}$ = 2.7), 7.26 (dd, 1H, $J_{7'\text{-}5'}$ = 2.7, $J_{7'\text{-}8'}$ = 9), 7.84 (d, 1H, $J_{8'\text{-}7'}$ = 9), 4.94 (t, 2H, $J_{11c\text{-}11t}$ = 1.2, $J_{11t\text{-}10}$ = 10.5, $J_{11c\text{-}10}$ = 17), 5.85 (dq, 1H, $J_{10\text{-}11t}$ = 1.2, $J_{10\text{-}11c}$ = 17), 5.12 (m, 1H), 3.05 (m, 1H), 2.24 (m, 1H), 2.87 (m, 1H), 2.02 (m, 2H), 1.86 (m, 1H), 3.96 (m, 1H), 3.14 (m, 1H), 1.45 (m, 1H); cims (CH_4) *m/z* $[M+1]^+$ 311 (100%), $[M+29]^+$ 339 (21%). *Anal.* calcd for $C_{19}H_{22}O_2N_2Cl$, C 58.53, H 6.30, N 7.30; found C 58.83, H 6.13, N 7.13.

2'-OXOQUININE (2'-QUINONE) [**5a**].—Mp 248° ($CHCl_3$/Et_2O) [lit. (13) mp 248°]; ir (KBr) 1655, 1622, 1241 cm^{-1}; ^1H nmr ($CDCl_3$) δ (ppm, 250 Hz) 7.12 (m, 1H), 7.07 (s, 1H), 6.88 (m, 1H), 6.85 (m, 1H), 5.44 (s, 1H), 5.67 (dq, 1H, $J_{10\text{-}11t}$ = 10.5, $J_{10\text{-}11c}$ = 17), 4.90 (t, 2H, $J_{11t\text{-}11c}$ = 1.2, $J_{11t\text{-}10}$ = 10.5, $J_{11c\text{-}10}$ = 17), 3.74 (s, 3H), 3.68 (m, 1H), 3.06 (m, 1H), 3.12 (m, 1H), 2.68 (m, 2H), 2.29 (s, 1H), 1.79 (m, 3H), 1.45 (m, 2H); cims (CH_4) *m/z* $[M+1]^+$ 341 (100%), $[M+29]^+$ 369 (19%).

2'-OXOQUINIDINE (2'-QUINIDONE) [**5b**].—Mp 259° ($CHCl_3$/Et_2O) [lit. (13) mp 235–260°]; ir (KBr) 1658, 1621, 1259, 1040 cm^{-1}; ^1H nmr ($CDCl_3$) δ (ppm, 250 Hz) 7.12 (m, 1H), 7.09 (m, 1H), 6.90 (m, 1H), 6.86 (m, 1H), 6.00 (dq, 1H, $J_{10\text{-}11t}$ = 10.5), 5.17 (s, 1H), 5.07 (t, 2H, $J_{11t\text{-}11c}$ = 1.2, $J_{11t\text{-}10}$ = 10.5, $J_{11c\text{-}10}$ = 17), 3.79 (s, 3H), 3.68 (m, 1H), 3.06 (m, 3H), 2.91 (m, 1H), 2.33 (m, 1H), 2.15 (m, 1H), 1.80 (s, 1H), 1.61 (m, 2H), 1.22 (m, 1H); cims (CH_4) *m/z* $[M+1]^+$ 341 (100%), $[M+29]^+$ 369 (21%).

10,11-DIHYDROXYDIHYDROQUININE [**6a**].—Quinine [**1a**] dihydrochloride (1 g, 2.7 mmol) was dissolved in 3 ml of THF–*t*-BuOH (2:1) and was added dropwise (40 min) to a solution of OsO_4 (3 mg, 0.012 mmol) and *N*-methylmorpholine *N*-oxide (0.6 g, 5.12 mmol) which had been dissolved in 32 ml of solvent [THF (10 ml), *t*-BuOH (20 ml), and H_2O (2 ml)] at 0°. The mixture was allowed to warm to room temperature and was stirred until the reaction was complete (20 h). The progress of the reaction was followed by tlc [EtOAc-MeOH (9:1), SiO_2].

A slurry of sodium hydrosulfite (250 mg) and H_2O (10 ml) was added to the reaction mixture, and the filtrate from celite (3 g) was extracted with CH_2Cl_2 (100 ml). The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to give **6a** (0.33 g, 30% yield): mp 80° (Et_2O); ir (KBr) 3100–3400, 1430, 1250, 1098 cm^{-1}; ^1H nmr (Me_2SO-d_6) δ (ppm, Hz) 8.66 (d, 1H, $J_{2'\text{-}3'}$ = 4.4), 7.48 (d, 1H, $J_{3'\text{-}2'}$ = 4.4), 7.47 (d, 1H, $J_{5'\text{-}7'}$ = 2.7), 7.37 (dd, 1H, $J_{7'\text{-}5'}$ = 2.7, $J_{7'\text{-}8'}$ = 9.1), 7.91 (d, 1H, $J_{8'\text{-}7'}$ = 9.1), 3.34 (m, 2H), 3.19 (m, 1H), 5.20 (d, 1H, $J_{9\text{-}8}$ = 5.7), 3.03 (m, 1H), 2.62 (m, 1H), 2.21 (m, 1H), 1.40 (m, 1H), 1.60 (m, 1H), 1.57 (m, 1H), 1.30 (m, 1H), 3.15 (m, 1H), 2.42 (m, 1H), 1.71 (m, 1H), 1.57 (m, 1H), 3.88 (s, 3H), 5.58 (s, 1H, D_2O exch.), 4.37 (s, 1H, D_2O exch.), 4.35 (s, 1H, D_2O exch.); cims (CH_4) *m/z* $[M+1]^+$ 359 (100%), $[-H_2O]^+$ 341 (80%), $[M+29]^+$ 387 (24%).

10,11-DIHYDROXYDIHYDROQUINIDINE [**6b**].—Quinidine [**1b**] dihydrochloride (1 g, 2.7 mmol), which had been dissolved in 3 ml of THF–*t*-BuOH (2:1), was added dropwise (40 min) at 0° to a solution of OsO_4 (3 mg, 0.012 mmol) and *N*-methylmorpholine *N*-oxide (0.6 g, 5.12 mmol) which had been dissolved in 32 ml of solvent [THF (10 ml), *t*-BuOH (20 ml), and H_2O (2 ml)]. The mixture was allowed to warm to room temperature and stirred until the reaction was complete (20 h); the progress of the reaction was followed by tlc [EtOAc-MeOH (9:1) SiO_2]. A slurry of sodium hydrosulfite (250 mg) and H_2O (10 ml) was added to the reaction mixture, and the solution was filtered over celite (3 g) and extracted with CH_2Cl_2 (100 ml). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to furnish **6b** (0.28 g, 30% yield): mp 226° (pentane) [lit. (10) mp 225–227°]; ir (KBr) 3200–3500, 1430, 1250, 1005 cm^{-1}; ^1H nmr (Me_2SO-d_6) δ (ppm, 250 Hz) 8.60 (d, 1H, $J_{2'\text{-}3'}$ = 4.4), 7.49 (d, 1H, $J_{3'\text{-}2'}$ = 4.4), 7.48 (d, 1H, $J_{5'\text{-}7'}$ = 2.5), 7.38 (dd, 1H, $J_{7'\text{-}5'}$ = 2.5, $J_{7'\text{-}8'}$ = 9.1), 7.92 (d, 1H, $J_{8'\text{-}7'}$ =

9.1), 3.40 (m, 1H), 3.28 (m, 1H), 3.68 (s, 1H), 5.68 (s, 1H, 5.26 (d, 1H), $J_{9\text{-}8}$ = 5.7), 2.96 (m, 1H), 3.14 (m, 1H), 2.54 (m, 1H), 1.70 (s, 1H), 1.46 (m, 3H), 1.43 (m, 1H), 2.57 (m, 1H), 2.52 (m, 1H), 1.91 (m, 1H), 3.89 (s, 3H), 5.64 (s, 1H, D_2O exch.), 4.53 (s, 1H, D_2O exch.), 4.51 (s, 1H, D_2O exch.); cims (CH_4) *m/z* $[M + 1]^+$ 359 (100%), $[M + 1 - 18]^+$ 341 (48%), $[M + 29]^+$ 387 (23%).

10,11-DIHYDROXYDIHYDROQUININE *N*-OXIDE [**7a**].—To quinine *N*-oxide [**3a**] (0.5 g, 1.46 mmol), which had been dissolved in THF (20 ml), aqueous KOH (1 N, 35 ml) at 5° was added until the solution became alkaline (pH 12). Aqueous $KMnO_4$ (0.71 g, 0.5 N) was then added to the reaction mixture, and it was stirred at room temperature for 4 days. The mixture was then filtered to remove the MnO_2, and the THF was removed under reduced pressure. The solution which remained was extracted with CH_2Cl_2 (3 × 20 ml) and brought to pH 8 with dry ice (CO_2), and the H_2O was removed under reduced pressure followed by purification (flash chromatography) to provide **7a** in 53% yield: mp 169–171° (Et_2O); ir (KBr) 3400, 1053, 948 cm^{-1}; ^1H nmr (DMSO-d_6) δ (ppm, 250 Hz) 8.66 (d, 1H, $J_{2'\text{-}3'}$ = 4.4), 7.99 (s, 1H), 7.88 (d, 1H, $J_{8'\text{-}7'}$ = 9.0), 7.59 (d, 1H, $J_{3'\text{-}2'}$ = 4.4), 7.33 (dd, 1H, $J_{7'\text{-}8'}$ = 9.0, $J_{7'\text{-}5'}$ = 2.1), 6.62 (s, 1H), 3.81 (m, 1H), 3.70 (s, 3H), 3.34 (m, 2H), 3.22 (m, 2H), 3.12 (m, 1H), 2.90 (m, 1H), 1.87 (s, 1H), 2.16 (m, 2H), 2.05 (m, 1H), 1.83 (m, 1H), 1.60 (m, 1H); cims (CH_4) *m/z* $[M + 1 - 16]^+$ 359 (100%), $[M + 1 - 34]^+$ 341 (74%), $[M + 1]^+$ 375 (41%), $[M + 29]^+$ 403 (11%). *Anal.* calcd for $C_{20}H_{26}N_2O_4$, C 67.04, H 7.26, N 7.82; found C 67.23, H 7.03, N 7.95.

10,11-DIHYDROXYDIHYDROQUINIDINE *N*-OXIDE [**7b**].—To quinidine *N*-oxide [**3b**] (0.5 g, 0.00146 mol), which had been dissolved in THF (20 ml), aqueous KOH (1N, 35 ml) at 5° was added until the solution became alkaline (pH 12). Aqueous $KMnO_4$ (0.71 g, 0.5 N) was added to the reaction mixture, and it was stirred at room temperature for 4 days. The mixture was then filtered to remove the MnO_2, and the THF was removed under reduced pressure. The solution that remained was extracted with CH_2Cl_2 (3 × 20 ml) and brought to pH 8 with CO_2 (dry ice), and the H_2O was removed under reduced pressure to provide **7b** in 50% yield: mp 151–155° (Et_2O); ir (KBr) 3400, 1049, 954 cm^{-1}; ^1H nmr (DMSO-d_6) δ (ppm, 250 Hz) 8.64 (d, 1H, $J_{2'\text{-}3'}$ = 4.4), 7.89 (d, 1H, $J_{8'\text{-}7'}$ = 9.0), 7.77 (d, 1H, $J_{5'\text{-}7'}$ = 2.1), 7.59 (d, 1H, $J_{3'\text{-}2'}$ = 4.4), 7.35 (dd, 1H, $J_{7'\text{-}5'}$ = 2.1, $J_{7'\text{-}8'}$ = 9.0), 3.99 (m, 1H), 3.99 (s, 3H), 3.79 (m, 1H), 3.44 (m, 1H), 3.39 (m, 1H), 3.34 (m, 1H), 3.24 (m, 1H), 3.12 (m, 2H), 2.48 (m, 1H), 2.06 (m, 1H), 1.85 (m, 1H), 1.77 (m, 2H), 1.21 (m, 1H); cims (CH_4) *m/z* $[M + 1 - 16]^+$ 359 (100%), $[M - 33]^+$ 341 (76%), $[M + 1]^+$ 375 (24%), $[M + 29]^+$ 403 (4%). *Anal.* calcd for $C_{20}H_{26}N_{20}O_4$, C 67.04, H 7.26, N 7.82; found C 67.21, H 7.04, N 7.97.

ACKNOWLEDGMENTS

We wish to thank NIH (NS 22287) and NIMH (MH 36644) for generous financial support. We also wish to acknowledge Mr. Frank Laib and Mr. Keith Krumnow for their technical assistance and Dr. Susan Wehrli for valuable comments. We are greatly indebted to Ms. Liesl Schindler for her contributions in preparation of this manuscript.

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Received 17 July 1989