Studies on 8-Aminoquinoline 1-Oxide Antimalarial Agents

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The synthesis of *N*-oxides of 8-aminoquinolines related to primaquine has been explored in an effort to obtain a less toxic, curative, antimalarial drug. Several side chain *N*-oxide analogs (**2b, 3b**) were prepared as well as the ring *N*-oxide of primaquine with both amines trifluoroacetylated (**13**). All attempts to deblock this material failed. Trifluoroacetylation of primaquine also yielded the novel acyl analog **12** which had curative activity *versus P. cynomolgi* in the monkey about equal to that of primaquine.

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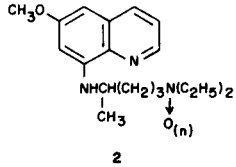
A critical need in malaria chemotherapy is for a curative agent superior to primaquine (**1**). Although substantial effort has been devoted to this problem, the 8-aminoquinolines remain as essentially the sole structural class possessing activity against the extra erythrocytic (the so called tissue stages) of the parasite. Approaches are therefore needed to provide a superior, *i.e.* a less toxic, analog of primaquine.

1

Research in this laboratory has demonstrated that the antiparasitic and antibacterial activity of various basically substituted heterocyclic systems including quinolines, acridines, 1,5-naphthyridines, and benzo[*b*][1,5]naphthyridines is usually retained or enhanced by *N*-oxidation, while toxicity is often concurrently reduced [3-7]. Therefore it was of interest to explore the synthesis of *N*-oxides of 8-aminoquinolines related to primaquine.

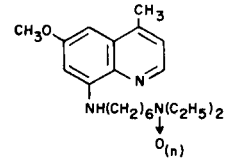
Our primary interest was of course primaquine itself. As was expected from the presence of a primary aliphatic amine in this molecule however, synthetic difficulties appeared early. While solutions were sought for these problems, we investigated a closely related agent pamaquine (**2a**) [8,9] which possesses a tertiary aliphatic amine. Treatment of **2a** with *m*-chloroperoxybenzoic acid provided the terminal amine *N*-oxide derivative **2b**.



2

a, n = 0
b, n = 1

In addition we were able to prepare similarly the *N*-oxide **3b** of the related 8-aminoquinoline which currently is of more interest for its activity against the protozoal leishmanial parasites [10] than for its activity against malarial parasites.

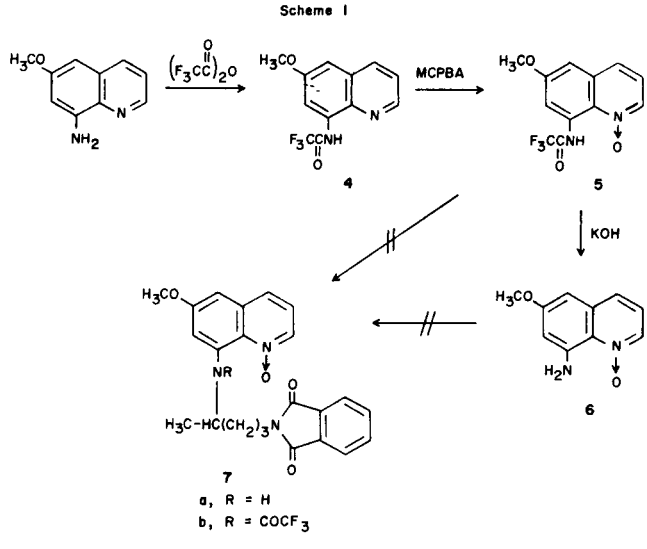


3

a, n = 0
b, n = 1

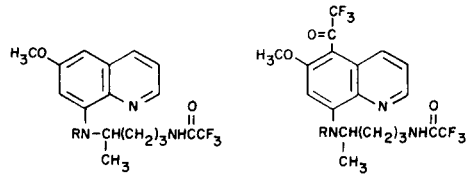
Concerning primaquine itself, all efforts to alkylate either 6-methoxy-8-quinolinamine 1-oxide (**6**) or its trifluoroacetamide (**5**) to provide the key ring *N*-oxidized intermediates **7a,b** were unsuccessful (Scheme I). Therefore our explorations were directed to the route whereby the side chain is first installed and blocked before oxidation is attempted.

Scheme I



Treatment of primaquine **1** with one equivalent of trifluoroacetic anhydride in chloroform at room temperature resulted in acylation of the primary aliphatic amine to pro-

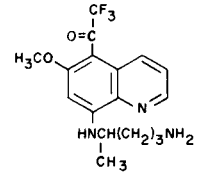
vide **8**. When **1** was treated with 2.2 equivalents of trifluoroacetic anhydride in refluxing chloroform, a bisacylated



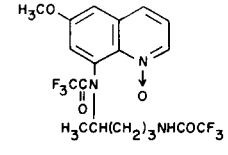
8, R = H
10, R = $COCF_3$

9, R = H
11, R = $COCF_3$

product was isolated, which was identified as **9** rather than the expected **10**. In subsequent experiments in which four or more equivalents of trifluoroacetic anhydride were used, two other acylated products were isolated and characterized as the desired **10** as well as a novel trisacetylated product, **11**. Deblocking of **11** with potassium hydroxide provided the unique primaquine analog **12**. Oxidation of **10** with hydrogen peroxide or *m*-chloroperoxybenzoic acid provided **13**. However, all attempts to remove both trifluoroacetyl groups were unsuccessful.



12



13

Attempts to effect the ring acylation with **3a** were unsuccessful. Moreover attempts to assess the generality of this technique using **1** with other anhydrides such as acetic and methane sulfonic were uniformly unsuccessful.

Ring trifluoroacetylation of primaquine has also been noted in a recent paper dealing with microbial *N*-acetylation of primaquine. In their work, neither the mono **8**, di **10**, or tri **11** trifluoroacetylated, derivatives were obtained, but the bistrifluoroacetylated derivative **9** was obtained in refluxing pyridine [11].

Biology.

The compounds prepared were tested against a normal drug-sensitive strain of *Plasmodium berghei* in mice by the parenteral route [12,13]. The compounds were dissolved and suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 hours postinfection. None of the compounds were active in this test system. This was not unexpected since the majority of 8-aminoquinolines are ineffective against the erythrocytic stages of the malaria parasite as utilized in this model.

The compounds were also tested against *P. cynomolgi* infections in the monkey. In the Schmidt test *vs. P. cynomolgi* [14] **2b** was inactive at 1.0 mg/kg/day while **3** was equal to or somewhat less active than primaquine. Unfortunately, the only ring *N*-oxide analog **13** was not tested in the monkey model. Of most interest is the activity of the novel 5-trifluoroacyl analog **12** which exhibited curative activity at 0.5 mg/kg/day and was thus about equal to primaquine. Further studies are desirable to determine whether this unique substitution pattern might also provide a better therapeutic index than does primaquine.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The nmr spectra were obtained, in most cases, on a Brucker WH-90 spectrometer. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units.

N^1,N^1-Diethyl-N^4-(6-methoxy-8-quinolinyl)-1,4-pentanediamine N^1-Oxide Dihydrochloride Hydrate (1:0.3) (**2b**).

To a stirred solution of 3.28 g (0.01 mole) of *N*,*N*-diethyl-N^4-(6-methoxy-8-quinolinyl)-1,4-pentanediamine (**2a**) (containing 0.15 mole of ethyl acetate of crystallization) in 30 ml of chloroform was added dropwise a solution of 2.1 g (0.01 mole) of 83% pure *m*-chloroperoxybenzoic acid in 60 ml of chloroform. The solution was stirred four hours, washed successively with 5% sodium carbonate solution, water, and saturated sodium chloride solution, dried over sodium sulfate and concentrated to dryness under vacuum. The residual oil was chromatographed over 250 g of alumina (Alcoa, F-20) eluting first with chloroform and then with 2% methanol in chloroform. Those fractions containing the product as determined by tlc (alumina-2% methanol in chloroform, $R_f \cong 0.63$) were combined and evaporated to dryness under vacuum. To a solution of the residual oil in ether containing a little 2-propanol was added a 25% solution of hydrogen chloride in 2-propanol until no more clouding occurred. The mixture was allowed to stand and then the supernatant decanted. The residual gum was extracted three times with ether and then triturated with 2-propanol to give a bright yellow solid. The solid was collected, washed with ether and recrystallized from a 2-propanol:ethanol mixture (10:1) to give 1.1 g (27%) of the N^1-oxide dihydrochloride (**2b**), mp 197-199° dec.

Confirmation that the terminal nitrogen had been oxidized was provided by the nmr spectrum in which the multiplet absorption due to the methylene on either side of the terminal nitrogen was shifted downfield 0.66 ppm from that of the des *N*-oxide, 2.5 ppm to 3.16 ppm. In addition, the uv spectra of the *N*-oxide and the des *N*-oxide were similar, indicating that the ring nitrogen had not been affected.

Anal. Calcd. for $C_{19}H_{29}N_3O_2 \cdot 2HCl$: C, 56.43; H, 7.73; N, 10.39; Cl, 17.53. Found: C, 56.25; H, 7.48; N, 10.44; Cl, 17.53.

N,*N*-Diethyl-*N'*-(6-methoxy-4-methyl-8-quinolinyl)-1,6-hexanediamine, *N*-Oxide, Dihydrochloride, Compound With 2-Propanol (1:0.1), Hydrate (1:0.3) (**3b**).

A solution of 10.4 g (0.025 mole) of *N*,*N*-diethyl-*N'*-(6-methoxy-4-methyl-8-quinolinyl)-1,6-hexanediamine, dihydrochloride [15] (**3a**) in water was made basic with 50% sodium hydroxide and extracted with 250 ml of chloroform. The chloroform was washed with water, dried and filtered. To the stirred filtrate was added dropwise a solution of 5.2 g (0.025 mole) of 84% *m*-chloroperoxybenzoic acid in 250 ml of chloroform. The reaction mixture was stirred two hours, treated with an additional 1 g of *m*-chloroperoxybenzoic acid in 50 ml of chloroform for 0.5 hours, washed with 5% sodium carbonate solution and with water, dried overnight over anhydrous sodium sulfate, filtered, and concentrated to dryness under vacuum. That portion of the black residue that was soluble in ethyl acetate was chromatographed over 400 g of alumina (Alcoa F-20) eluting first with ethyl acetate and then with 10% methanol in ethyl acetate. The eluent which contained product ($R_f \cong 0.14$, alumina - 5% methanol/ethyl

acetate) was evaporated under vacuum to dryness; the residue was immediately dissolved in ether and treated with excess 19% hydrogen chloride in 2-propanol. Trituration of the resulting gum with 2-propanol followed by recrystallization from 2-propanol afforded 2.8 g of product. This was combined with 1.8 g of product obtained similarly from a 0.1 mole run, recrystallized from 2-propanol and dried under vacuum at 49° to afford 3.7 g (24%) of **3b**, mp 148-150°.

The Karl Fisher water titration gave low erratic results. In the ir (potassium bromide) spectrum, strong, broad absorption near 3400 cm^{-1}, indicated the presence of water. Confirmation that the terminal nitrogen had been oxidized was provided by the nmr spectrum (d_6-DMSO) -multiplet absorption due to the methylenes adjacent to the terminal nitrogen was shifted downfield 0.6 ppm from that of the des *N*-oxide, 3.0 ppm to 3.6 ppm. The presence of approximately 0.1 mole of 2-propanol was also confirmed by the nmr (d, 1.05 ppm). Deuterium oxide wash caused a dramatic and unusual change in the nmr spectrum: the two sets of *meta*-coupled doublets at 6.6 and 6.4 ppm (H5 and H7) collapsed to a singlet, integrating for 1 proton. The resulting HDO peak at 3.8 ppm integrated for almost five protons, which would account for one -NH-, two moles of hydrogen chloride, about 0.3 mole of water and the exchange of one aromatic proton. The same aromatic proton exchange phenomenon was observed with the starting material.

Anal. Calcd. for $C_{21}H_{33}N_3O_2 \cdot 0.1C_3H_8O \cdot 2HCl \cdot 0.3H_2O$: C, 57.64; H, 8.27; N, 9.47; Cl, 15.98. Found: C, 57.61; H, 8.34; N, 9.49; Cl, 16.11.

2,2,2-Trifluoro-*N*-(6-methoxy-8-quinolinyl)acetamide (**4**).

A solution of 11.6 g (0.055 mole) of trifluoroacetic anhydride in 25 ml of chloroform was added dropwise to a solution of 8.7 g (0.05 mole) of 6-methoxy-8-quinolinamine in 100 ml of chloroform. When addition was complete the solution was heated under reflux for two hours, cooled and washed successively with water, dilute ammonium hydroxide, water, and saturated sodium chloride solution. The solution was treated with Darco, dried over magnesium sulfate and evaporated leaving 10.6 g of tan solid. Recrystallization from 95% ethanol gave 8.8 g (65%) of cream solid, mp 134-135°.

Anal. Calcd. for $C_{12}H_9F_3N_2O_2$: C, 53.34; H, 3.36; N, 10.37. Found: C, 53.08; H, 3.41; N, 10.43.

2,2,2-Trifluoro-*N*-(6-methoxy-8-quinolinyl)acetamide 1′-Oxide (**5**).

A solution of 6 g (0.026 mole) of 75% *m*-chloroperoxybenzoic acid in 60 ml of chloroform was added to a solution of 6 g (0.022 mole) of 2,2,2-trifluoro-*N*-(6-methoxy-8-quinolinyl)acetamide (**4**) in 70 ml of chloroform. The resulting solution was stirred at room temperature for 1.5 hours, poured into an evaporating dish and the solvent was allowed to evaporate. The solid residue was suspended in water and solid sodium sulfite was added. The mixture was stirred for 20 minutes and filtered. The solid was washed with water, then with ether and air dried to give 2.1 g of bright yellow solid. Recrystallization from ethyl acetate gave 1.4 g (22%) of **5**, mp 192-198° dec.

Anal. Calcd. for $C_{12}H_9F_3N_2O_3$: C, 50.36; H, 3.17; N, 9.79. Found: C, 50.09; H, 3.29; N, 9.73.

6-Methoxy-8-quinolinamine N^1-Oxide Monohydrate (**6**).

To a suspension of 5 g (0.017 mole) of 2,2,2-trifluoro-*N*-(6-methoxy-8-quinolinyl)acetamide 1′-oxide (**5**) in 100 ml of ethanol was added 20 ml of a 1*N* potassium hydroxide solution. The dark solution was stirred at room temperature for 4 hours, chilled overnight, and concentrated to dryness under vacuum. The residue was first triturated with and then recrystallized from water to afford 2.2 g (61%) of **6**, mp 122-124°; nmr (deuteriochloroform): δ 3.7 (s, 3, OCH_3), 6.24, 6.33 (dd, 2, H-5, H-7), 6.99 (dd, 1, H-3), 7.4 (dd, 1, H-4), 8.98 (dd, 1, H-2), (δ of the H-2 and H-4 of 6-methoxyquinolinamine are 8.5 and 7.95).

Anal. Calcd. for $C_{10}H_{10}N_2O_2 \cdot H_2O$: C, 57.68; H, 5.81; N, 13.46; H_2O, 8.65. Found: C, 57.57; H, 5.79; N, 13.42; H_2O, 8.87.

2,2,2-Trifluoro-*N*-[4-[(6-methoxy-8-quinolinyl)amino]pentyl]acetamide (**8**).

A solution of 23 g (0.05 mole) of primaquine phosphate (**1**) in 600 ml of water was treated with 120 ml of 10% sodium hydroxide and extracted with chloroform. The extracts were dried over magnesium sulfate and evaporated leaving 12.2 g (94%) of viscous yellow oil. To a solution of 6.0 g (0.231 mole) of this oil in 20 ml of chloroform was added dropwise 4.85 g (0.231 mole) of trifluoroacetic anhydride. When addition was complete the solution was stirred at room temperature for 1.5 hours, washed with 2% ammonium hydroxide, then with water, dried over magnesium sulfate and evaporated leaving 7.5 g of yellow oil. This oil was chromatographed on 300 g of florisil with chloroform. The first eight 500 ml fractions contained 4.8 g of a green-yellow oil that was crystallized from a mixture of ethyl acetate and hexane to give 2.6 g (32%) of **8** as a light green-yellow solid, mp 87-88° (at 2°/minute, faster heating gives a mp of 94-96°).

Anal. Calcd. for $C_{17}H_{20}F_3N_3O_2$: C, 57.46; H, 5.67; N, 11.82. Found: C, 57.60; H, 5.68; N, 11.88.

2,2,2-Trifluoro-*N*-[4-[[6-methoxy-5-(trifluoroacetyl)-8-quinolinyl]amino]-pentyl]acetamide (**9**).

A solution of 23 g (0.05 mole) of primaquine phosphate (**1**) in 100 ml of water was made basic with 10% sodium hydroxide and extracted with ethyl acetate. The extract was dried over magnesium sulfate, and concentrated under vacuum. A solution of the residue in 125 ml of chloroform was again dried and then treated dropwise with 23.2 g (0.11 mole) of trifluoroacetic anhydride. The mixture was heated under reflux for 7.5 hours, allowed to cool, washed first with water, then with dilute ammonium hydroxide, again with water and finally with brine, dried over magnesium sulfate, and concentrated to dryness under vacuum. The viscous green-yellow oil was recrystallized twice from ethyl acetate-hexane to afford 5.5 g (24%) of **9**, mp 121-122°, lit [11] reports 124-126°. The nmr spectrum of **9** was identical to that reported by Clark *et al.* [11].

Anal. Calcd. for $C_{19}H_{19}F_6N_3O_3$: C, 50.56; H, 4.24; N, 9.31. Found: C, 50.86; H, 4.43; N, 9.31.

2,2,2-Trifluoro-*N*-[6-methoxy-5-(trifluoroacetyl)-8-quinolinyl]-*N*-[1-methyl-4-[(trifluoroacetyl)amino]butyl]acetamide (**11**).

A solution of 45.5 g (0.1 mole) of primaquine, diphosphate (**1**) in water was made basic with 50% aqueous sodium hydroxide and extracted with about 500 ml of chloroform. The extract was washed with water and saturated sodium chloride solution, dried over anhydrous potassium carbonate, and filtered. To the solution was added dropwise 56.4 ml (0.4 mole) of trifluoroacetic anhydride. The reaction mixture was stirred overnight under reflux, evaporated to dryness under vacuum and redissolved in chloroform. Thin layer chromatography (silica-ethyl acetate) indicated that the solution contained mainly 2,2,2-trifluoro-*N*-[4-[(6-methoxy-8-quinolinyl)amino]pentyl]acetamide (**8**, $R_f \cong 0.75$). The solution was washed first with dilute ammonium hydroxide, then with water and finally with saturated sodium chloride solution, dried and returned to a reaction flask. To it was added dropwise 42 ml (0.3 mole) of trifluoroacetic anhydride. The reaction mixture was heated under reflux for eight hours, allowed to cool and evaporated. The residue was dissolved in chloroform, washed and dried as described above and evaporated to give 44 g of an oil which was chromatographed over 460 g of silica gel, eluting with a 50:50 mixture of chloroform and ethyl acetate. Those fractions that contained material with R_f = 0.5-0.6 (silica-ethyl acetate) were combined and evaporated to give 41 g. This was rechromatographed over 400 g of silica gel, eluting with chloroform to give 16.6 g of product, $R_f \cong 0.60$ (silica-ethyl acetate). Recrystallization from 2-propanol/hexane gave 8.8 g (16.1%) of **11**, mp 89-92°. The ir spectrum (potassium bromide disc) indicated the presence of secondary amine (3310 cm^{-1}); nmr (deuteriochloroform): δ 8.82 (2H, q), 8.10 (4H, q), 7.49 (3H, q), 7.32, 7.37 (7H, 2s), 6.78 (NH, broad s), 4.4-4.9 (C*H*, broad m), 4.03, 4.04 (H_3CO, 2s), 3.0-3.7 (CH_2-NH, m), 1.5-2.4 (-CH_2-CH_2, m), 1.03, 1.41 (CH_3, 2d). Presumably, the two sets of methyl doublets, methoxy singlets and 7H singlets are a result of bond fixation due to the trifluoroacetamide group attached to the 8 position of the quinoline ring.

Anal. Calcd. for $C_{21}H_{18}F_9N_3O_4$: C, 46.08; H, 3.31; N, 7.68. Found: C, 45.75; H, 3.48; N, 7.61.

2,2,2-Trifluoro-*N*-(6-methoxy-8-quinolinyl)-*N*-[1-methyl-4-[(trifluoroacetyl)amino]butyl]acetamide (**10**).

Further elution of the second column used to isolate **11** with 10% ethyl acetate in chloroform, followed by concentration and recrystallization from 2-propanol/hexane provided 6.03 g (13%) of **10**, mp 97-100, R_f (silica-ethyl acetate) ≅ 0.5; nmr (deuteriochloroform: δ 8.8 (2H, q), 8.10 (4H, q), 7.49 (3H, q), 7.1-7.3 (5H and 7H, m), 6.8 (NH, br s), 4.4-4.9 (C*H*, br m), 3.95 (H_3CO, s), 3.2-3.6 (CH_2-NH, m), 1.5-2.4 (-CH_2-CH_2, m), and 1.0 and 1.3 (CH_3, 2d, see explanation in preparation of **11**).

Anal. Calcd. for $C_{19}H_{19}F_6N_3O_3$: C, 50.56; H, 4.24; N, 9.31. Found: C, 50.36; H, 4.39; N, 9.41.

In a separate experiment in which 0.1 mole of primaquine base was treated with 0.425 moles of trifluoroacetic anhydride in refluxing chloroform for 20 hours, three products, **9** (11%), **10** (16%) and **11** (20%) were isolated by column chromatography.

1-[8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-5-quinolinyl]-2,2,2-trifluoroethanone Ethanedioate (1:1) (Salt) (**12**).

A solution of 3.73 g (0.00682 mole) of 2,2,2-trifluoro-*N*-[6-methoxy-5-(trifluoroacetyl)-8-quinolinyl]-*N*-[1-methyl-4-[(trifluoroacetyl)amino]butyl]acetamide (**11**) in 35 ml of ethanol and 35 ml of 1*N* potassium hydroxide solution was stirred at room temperature for two hours, concentrated under vacuum to one-half volume, poured into water and extracted with chloroform. The chloroform extract was washed twice with water, dried over anhydrous sodium sulfate, filtered and evaporated. A solution of the residual oil in ether was poured into a solution of 0.9 g (0.0072 mole) of oxalic acid, dihydrate in ethanol. The resulting precipitate was recrystallized from water to afford 0.85 g (28%) of product, mp 190-192° (prior shrinking). This was combined with 0.4 g of material made in a similar manner and analyzed; nmr spectrum of the base (deuteriochloroform): δ 8.63 (4H, q, J = 4 and 1), 8.45 (2H, q, J = 2.5 and 1), 7.35 (3H, q, J = 4 and 2.5), 7.1 (NH, d); 6.19 (7H, s), 3.95 (CH_3O, s), 2.73 (CH_2-NH_2, t), 1.45-2.1 (CH_2-CH_2-, m), 1.55 (NH_2, s), 1.38 (CH_3, d).

Anal. Calcd. for $C_{17}H_{20}F_3N_3O_2 \cdot C_2H_2O_4$: C, 51.23; H, 4.98; N, 9.43; F, 12.80. Found: C, 51.21; H, 5.08; N, 9.69; F, 13.04.

2,2,2-Trifluoro-*N*-(6-methoxy-8-quinolinyl)-*N*-[1-methyl-4-(trifluoroacetyl)amino]butyl]acetamide 1-Oxide Compound With 2-Propanol (1:0.1) (**13**).

A mixture of 2.4 g (0.0053 mole) of 2,2,2-trifluoro-*N*-(6-methoxy-8-quinolinyl)-*N*-[1-methyl-4-[(trifluoroacetyl)amino]butyl]acetamide and 1.3 g (0.006 mole) of 84% *m*-chloroperoxybenzoic acid in 80 ml of chloroform was stirred for 48 hours at room temperature, washed with 5% sodium carbonate solution and with water, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under vacuum. Two recrystallizations from 2-propanol afforded 0.57 g (22%) of the title compound, mp 194-196°. Evidence for oxidation of the ring nitrogen was provided by the nmr (deuteriochloroform) spectrum of the compound. Absorption for the H-2 and H-4 protons was shifted from 8.72 and 8.07 ppm in the des oxide to 8.26 and 7.63 ppm in the product. In addition there was little change in the pattern representing the alkyl portion of the molecule. The presence of 2-propanol was also confirmed by the nmr spectrum.

Anal. Calcd. for $C_{19}H_{19}F_6N_3O_4 \cdot 0.1C_3H_8O$: C, 48.97; H, 4.22; N, 8.88. Found: C, 48.96; H, 4.15; N, 8.71.

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REFERENCES AND NOTES

[1] This is communication 55 of a series on antimalarial drugs. For paper 54 see J. Hung and L. M. Werbel, *J. Heterocyclic Chem.*, **21**, 741 (1984).

[2] This investigation was supported in part by U. S. Army Medical Research and Development Command Contract DADA 17-72-C-2077. This is contribution number 1699 to the Army Research Program on Malaria.

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[13] The parenteral antimalarial screening in mice was carried out in the Leo Rane Laboratory at the University of Miami, and test results were provided through the courtesy of Dr. T. R. Sweeney and Dr. E. A. Steck of the Walter Reed Army Institute of Research.

[14] The *P. cynomolgi* tests were carried out by Dr. L. H. Schmidt and coworkers according to the procedure reported in L. H. Schmidt, *Am. J. Trop. Med. Hyg.*, **32**, 231 (1983).

[15] Provided by the Walter Reed Army Institute of Research.