folded is the molecule and the lower its entropy.

Equation 3 is based upon the free-space intramolecular conformational entropy. If the effects of solvent are included in the estimation of S, the relationship between pC and S partly breaks down. In essence, the highly folded, energetically preferred conformations found in free space for flexible substituents, lose their energetic preference in a simulated solvent medium, and the entropy increases. This was observed when the aqueous hydration shell model[3] was used to take into account solvation energetics as part of the conformational analysis.

It is difficult to speculate why the entropy associated with free-space conformational behavior best correlates with inhibition potency. Perhaps the shape of the receptor site limits the conformational behavior of the substituents upon initial binding and keeps them restricted throughout the binding process.

The role of electrostatic and hydrogen-bonding interactions on intramolecular entropy can be realized by comparing compounds 4 and 21 of Table I. These compounds differ by R_2 = OH for 4 vs. R_2 = OCH_3 for 21. The lower entropy of compound 4 is a result of combined electrostatic–hydrogen bond interaction between the hydroxyl and the SO_2 oxygens. This stabilizing set of interactions, which are not possible for the methoxy group of compound 21, limits conformational flexibility and, consequently, lowers entropy relative to compound 21.

The examples cited above illustrate that molecular modeling can sometimes lead to results that are different from our intuitive feelings. At the same time, modeling calculations can be dissected to identify the reasons why the calculations are not consistent with intuition. In so far as the reasons found in the calculations are valid, molecular modeling may offer us an unbiased, new way of looking at some of our structure-activity problems.

Acknowledgment. We very much appreciate the assistance of Professor W. J. Dunn III (UIC) during the course of this investigation and Dr. C. Compadre (UIC) for useful comments. All computational chemistry calculations were done with the CHEMLAB-II molecular modeling package. M. Wiese, M. Piper, G. Krüger, K. R. Noll, and J. Keck are acknowledged for making some of the inhibition measurements reported in Table I that are not yet published.

Registry No. 1, 34332-19-9; 2, 107114-72-7; 3, 107114-73-8; 4, 14571-23-4; 5, 80-03-5; 6, 107114-74-9; 7, 35880-91-2; 8, 107114-75-0; 9, 80-08-0; 10, 35880-83-2; 11, 51688-26-7; 12, 25963-47-7; 13, 107114-76-1; 14, 86552-09-2; 15, 93427-46-4; 16, 107114-77-2; 17, 107114-78-3; 18, 107114-79-4; 19, 51688-31-4; 20, 101513-28-4; 21, 35881-03-9; 22, 27147-69-9; 23, 3572-34-7; 24, 107114-80-7; 25, 107114-81-8; 26, 46948-43-0; 27, 107114-82-9; 28, 565-20-8; 29, 17078-72-7; 30, 4094-38-6; 31, 107134-58-7; 32, 34037-45-1; 33, 7019-01-4; 34, 86552-10-5; 35, 7146-68-1; 36, 1948-92-1; dihydropteroate synthase, 9055-61-2.

Synthesis and Antimalarial Effects of 4-[(7-Chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl]-6-alkylphenols and Their N^{ω}-Oxides[1,2]

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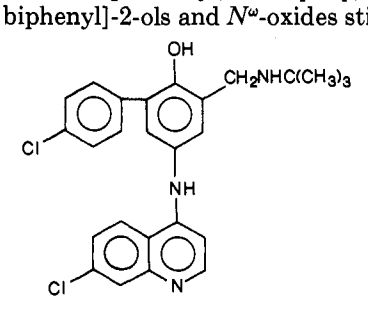
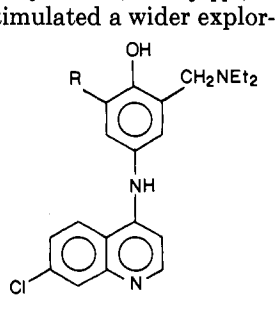
Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105. *Received April 17, 1986*

A series of 4-[(7-chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl]-6-alkylphenols and their N^{ω}-oxides were synthesized by the condensation of 4,7-dichloroquinoline and 4,7-dichloroquinoline N^{ω}-oxide with appropriately substituted 4-amino-2-[(diethylamino)methyl]-6-alkylphenol dihydrochlorides. The latter precursors were prepared in a six-step synthesis starting from available 2-alkylphenols. Several of the title compounds display potent antimalarial activity in mice.

Our recent report[1] of the potent antimalarial activity and unique properties of tebuquine (1) and related 5-[(7-chloro-4-quinolinyl)amino]-3-[(alkylamino)methyl][1,1'-biphenyl]-2-ols and N^{ω}-oxides stimulated a wider exploration of the effects of structural modification on antimalarial activity. Of particular concern was the nature of the requirement for a biphenylol system. We now report, therefore, the synthesis and biological activity of a series of 4-[(7-chloro-4-quinolinyl)amino]-2-[(diethylamino)-methyl]-6-alkylphenols and their N^{ω}-oxides (**2a–o**) as well as several closely related analogues.



1



2

Chemistry. The synthetic scheme for the preparation of 4-[(7-chloro-4-quinolinyl)amino]-2-[(diethylamino)-methyl]-6-alkylphenols is outlined in Scheme I. The readily available appropriate 2-alkylphenols were treated with sodium nitrite and hydrochloric acid[3] to afford the corresponding 2-alkyl-2,5-cyclohexadiene-1,4-dione 4-oximes (**4**) in 22–65% yield (Table I). These were reduced catalytically with Raney nickel under ~50 psi of hydrogen, or in one case with sodium dithionite, and immediately acetylated with acetic anhydride to generate the corresponding N-(3-alkyl-4-hydroxyphenyl)acetamides (**5**) in 30–95% overall yields (Table II). These compounds were then treated with aqueous formaldehyde and diethylamine to provide the N-[5-[(diethylamino)methyl]-3-alkyl-4-hydroxyphenyl]acetamides (**6**) in 23–87% yields (Table III). Acidic hydrolysis gave the corresponding 4-amino-

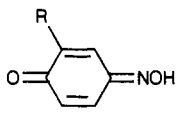
(1) This is paper 61 of a series on antimalarial drugs. For paper 60, see: Werbel, L. M.; Cook, P. D.; Elslager, E. F.; Hung, J. H.; Johnson, J. L.; Kesten, S. J.; McNamara, D. J.; Ortwine, D. F.; Worth, D. F. *J. Med. Chem.* **1986**, *29*, 924.

(2) This investigation was supported by U.S. Army Medical Research and Development Command Contract DADA17-72-C-2077. This is contribution No. 1788 to the Army Research Program in Parasitic Diseases.

(3) Norris, R. K.; Sternhill, S. *Aust. J. Chem.* **1966**, *19*, 617.

0022-2623/87/1830-0906$01.50/0

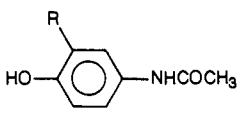
Table I. Properties of 2-Alkyl-2,5-cyclohexadiene-1,4-dione 4-Oximes



no.	R	mp, °C	% yield practical	purif sol	formula	anal.
4b	$(CH_3)_3C$	132–134	65	toluene–hexane	$C_{10}H_{13}NO_2$	C, H, N
4c	C_6H_{11}	164–166	62	toluene	$C_{12}H_{15}NO_2$	C, H, N
4d	$C_6H_5CH_2$	160–162	32	toluene	$C_{13}H_{11}NO_2$	C,[a] H, N
4e	C_2H_5	95–97	44	Et_2O–pet. ether	$C_8H_9NO_2$	C, H, N
4f	$CH(CH_3)_2$	102–104	34	Et_2O–hexane	$C_9H_{11}NO_2$	C, H, N
4g	CH_3	116–118	41	none	$C_7H_7NO_2$	C,[b] H, N
4h	$CH(CH_3)C_2H_5$	54–59	22	Et_2O–hexane	$C_{10}H_{13}NO_2$	C, H, H

[a] C: calcd, 73.22; found, 73.64. [b] C: calcd, 61.31; found, 61.89.

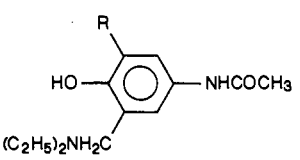
Table II. Properties of *N*-(3-Alkyl-4-hydroxyphenyl)acetamides



no.	R	mp, °C	% yield practical (two steps)	purif sol	formula	anal.
5b	$(CH_3)_3C$	147	30[a]	toluene	$C_{12}H_{17}NO_2$	C, H, N
5b	$(CH_3)_3C$	147–149	97[b]	none	$C_{12}H_{17}NO_2$	none[c]
5c	C_6H_{11}	129–130	87	toluene	$C_{14}H_{19}NO_2$[d]	C, H, N
5d	$C_6H_5CH_2$	110–112	91	none	$C_{15}H_{15}NO_2$	none[c]
5e	C_2H_5	140–141	62	none	$C_{10}H_{13}NO_2$	C, H, N
5f	$CH(CH_3)_2$	116–117	47	Et_2O–CH_2Cl_2	$C_{11}H_{15}NO_2$	C, H, N
5g	CH_3	177–178	62[e]	MeOH–Et_2O	$C_9H_{11}NO_2$	C, H, N
5h	$CH(CH_3)C_2H_5$	106–107	49	none	$C_{12}H_{17}NO_2$	C, H, N
5i	SC_6H_4-4-Cl	143–144	95	toluene	$C_{14}H_{12}ClNO_2S$	C, H, N, Cl, S
11	2,3-$(CH_2)_4$	188	82[f]	THF–Et_2O	$C_{12}H_{15}NO_2$	C, H, N

[a] Via sodium dithionite. [b] Catalytically. [c] Sample was identical with analytical material prepared previously. [d] With 0.1 mol of toluene. [e] Crude yield. [f] One-step yield from fully aromatized compound.

Table III. Properties of *N*-[3-[(Diethylamino)methyl]-5-alkyl-4-hydroxyphenyl]acetamides



no.	R	mp, °C	% yield practical	purif sol	formula	anal.
6b	$(CH_3)_3C$	155	26	acetone	$C_{17}H_{28}N_2O_2 \cdot 1.5HCl \cdot 0.1H_2O$	C, H, N, Cl^-, H_2O
6c	C_6H_{11}	(gum)	59	none	$C_{19}H_{30}N_2O_2$	none[a]
6d	$C_6H_5CH_2$	104–106	23	toluene–hexane	$C_{20}H_{26}N_2O_2$	C, H, N
6e	C_2H_5	113–115	60	Et_2O	$C_{15}H_{24}N_2O_2$	C, H, N
6f	$CH(CH_3)_2$	113–114	87	Et_2O–hexane	$C_{16}H_{26}N_2O_2$	C, H, N
6g	CH_3	91–93	60[b]	Et_2O	$C_{14}H_{22}N_2O_2$	C, H, N
6h	$CH(CH_3)C_2H_5$	(gum)	100	none	$C_{17}H_{28}N_2O_2$	*c*
6i	SC_6H_4-4-Cl	97–105	76[b]	toluene	$C_{19}H_{23}ClN_2O_2S$	C, H, N, S
12	5,6-$(CH_2)_4$	153–155	71	none	$C_{17}H_{26}N_2O_2$	C, H, N[d]

[a] Structure confirmed by NMR. [b] Crude yield. [c] The product was homogeneous by TLC. [d] C: calcd, 70.31; found, 69.33.

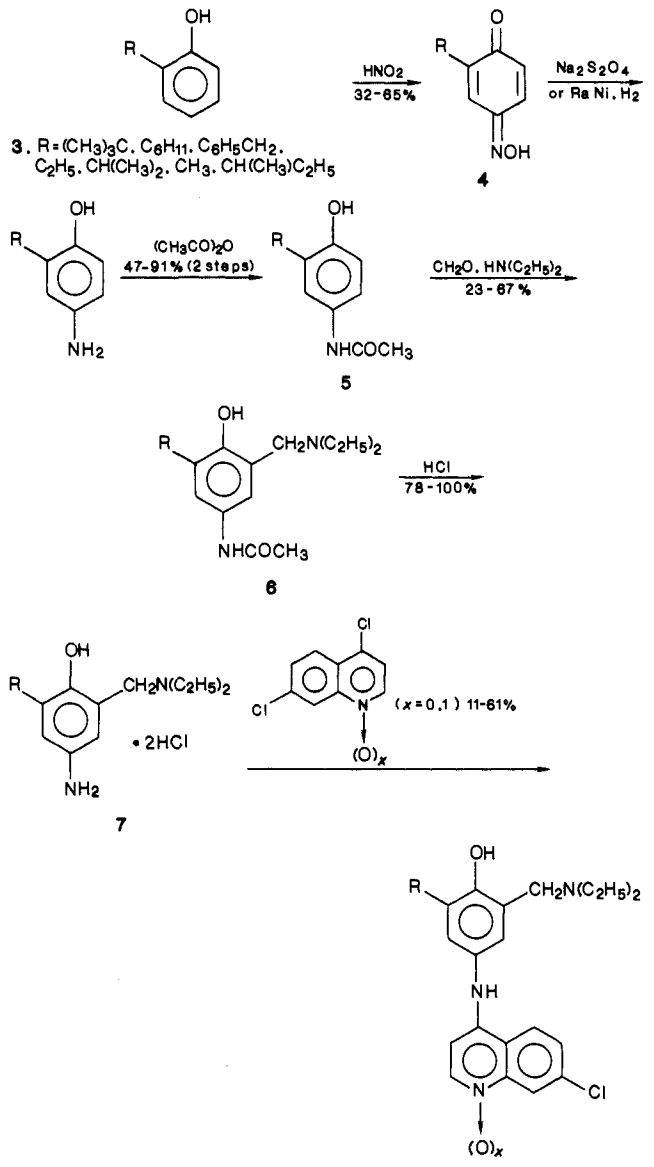
2-[(diethylamino)methyl]-6-alkylphenol dihydrochlorides (**7**) and these were condensed separately with 4,7-dichloroquinoline and 4,7-dichloroquinoline 1-oxide to furnish the desired **2b–g**, in 11–81% yields (Table IV).

Introduction of a sulfur spacer was achieved (Scheme II) by condensation of [(4-chlorophenyl)thio]-2-propanone[4] with sodium nitromalonaldehyde hydrate[6] to provide 2-[(4-chlorophenyl)thio]-4-nitrophenol (**8**). Catalytic hydrogenation over Raney nickel followed by treatment with acetic anhydride afforded *N*-[3-[(4-chlorophenyl)thio]-4-hydroxyphenyl]acetamide, which was utilized as described above to give **2p,q**.

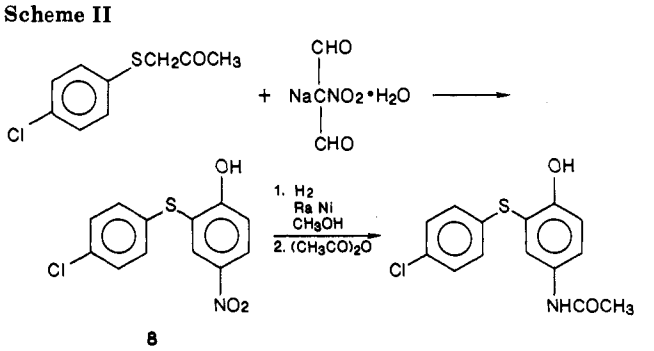
A variant of the basic structure (1) where the 5- and 6-positions of the phenol ring are linked by way of a four-carbon chain was synthesized as outlined in Scheme III. The product, 4-[(7-chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl]-5,6,7,8-tetrahydro-1-naphthalenol, is essentially a reduced naphthyl analogue of amodiaquine. The starting point in its synthesis[5] is the commercially available 4-nitro-1-naphthalenamine, which is hydrolyzed in base to afford 4-nitro-1-naphthalenol (**9**) in 89% yield. This underwent Raney nickel reduction and subsequent acetylation to provide *N*-(4-hydroxy-1-naphthalenyl)-acetamide (**10**) in an overall 80% yield. A further reduction in the presence of Raney nickel gave *N*-(5,6,7,8-tetrahydro-4-hydroxy-1-naphthalenyl)acetamide (**11**) in

(4) Procedure according to Anjaneyulu, B.; Govindachari, T. R.; Sathe, S. S.; Viswanathau, N. *Tetrahedron* **1969**, *25*, 3091.
(5) Modified procedure of Nabih, I.; Nasr, M.; Badawi, M. A. *J. Pharm. Sci.* **1972**, *61*, 1500.
(6) Provided by Ash Stevens, Inc., Detroit, MI.

Scheme I



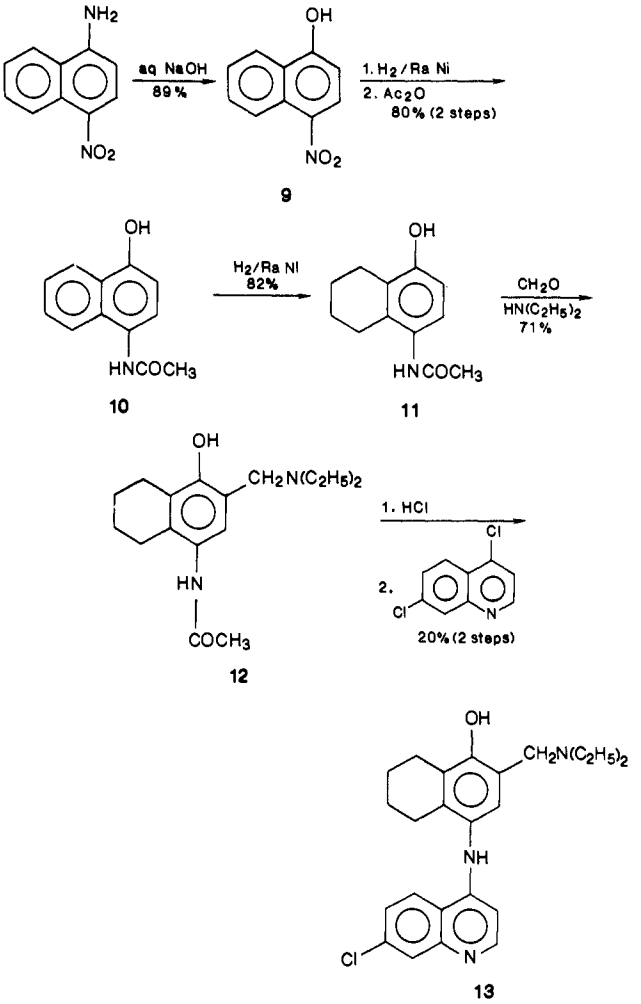
Scheme II



82% yield. The remainder of the scheme was analogous to that of the 6-alkyl compounds. *N*-[3-[(Diethylamino)-methyl]-5,6,7,8-tetrahydro-4-hydroxy-1-naphthalenyl]-acetamide (**12**) was obtained in 71% yield and the target compound, **13**, was generated in a 20% yield (over two steps). An attempt to prepare the N^{ω}-oxide of **13** resulted in the formation of an intractable gum from which none of the desired product could be obtained.

Suppressive Antimalarial Screening in Mice. The target compound **2** and their N^{ω}-oxides were tested against a normal drug-sensitive strain of *Plasmodium berghei* in

Scheme III



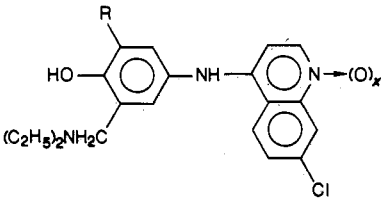
mice by the parenteral route.[7] The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 h postinfection. Extension of the mean survival time of the treated mice is interpreted as evidence of antimalarial activity.[8] Compounds are arbitrarily considered to be "active" when they produce at least a 100% increase in the mean survival time of mice. Animals that survive to 60 days are considered "cured". The mean survival time of control mice in this study ranged from 6.1 to 6.3 days. Six intermediates, **4c**, **6b**, **6d**, **6f**, **7e**, and **7g**, were tested and found to be inactive at 640 mg/kg. Other results are summarized in Table V.

Insertion of a methylene spacer between the two phenyl rings of the biphenylol system (**2d**, **2k**) clearly deletes most of the antimalarial activity. A sulfur spacer (**2p**, **2q**) has the same effect. To determine if a purely spatial effect was operative, the 6-phenyl group was replaced by the *tert*-butyl group (**2b**, **2i**). This was also counterproductive and led to a dramatic loss of activity. Use of cyclohexyl in place of *tert*-butyl, however, restored a substantial portion of the activity, and other straight or branched chain substituents at the 6-position led to compounds (**2e**, **2l**, **2f**, **2n**, **2g**, **2h**, **2o**) with reasonable antimalarial activity.

(7) The parenteral antimalarial screening in mice was carried out by the laboratory of Dr. Leo Rane, and test results were provided through the courtesy of Drs. T. R. Sweeny and E. A. Steck of WRAIR.

(8) Osdene, T. S.; Russell, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.

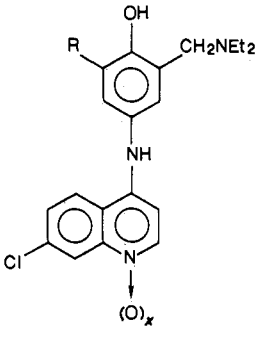
Table IV. Properties of 4-[(7-Chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl]-6-alkylphenols and Their *N*-Oxides



no.	R	x	mp, °C	% yield practical	purif sol	formula	anal.
2b	$(CH_3)_3C$	0	224–226	61	2-PrOH–MeCN	$C_{24}H_{30}ClN_3O$	C, H, N
2i	$(CH_3)_3C$	1	222–224	11	MeOH	$C_{24}H_{30}ClN_3O_2$	C, H, N, Cl
2c	C_6H_{11}	0	232–234	40	EtOH	$C_{26}H_{32}ClN_3O$	C, H, N
2j	C_6H_{11}	1	220–223	25	MeOH–AcOEt	$C_{26}H_{32}ClN_3O_2$	C, H, N, Cl
2d	C_6H_5-CH_2	0	153–155	50	MeCN	$C_{27}H_{28}ClN_3O$	C, H, N, Cl
2k	C_6H_5-CH_2	1	191–193	30	2-PrOH–MeCN	$C_{27}H_{28}ClN_3O_2$	C, H, N
2e	C_2H_5	0	174–176	81	MeOH	$C_{22}H_{26}ClN_3O$	C, H, N, Cl
2l	C_2H_5	1	202–203	50	MeOH–Et_2O	$C_{22}H_{26}ClN_3O_2$	C, H, N, Cl
2f	$CH(CH_3)_2$	0	209–212	78	MeOH	$C_{23}H_{28}ClN_3O$	C, H, N, Cl
2m	$CH(CH_3)_2$	1	197–199	39	CH_2Cl_2–MeOH	$C_{23}H_{28}ClN_3O_2$	C, H, N, Cl
2g	CH_3	0	226–228	67	MeOH	$C_{21}H_{24}ClN_3O$	C, H, N, Cl
2n	CH_3	1	211	47	MeOH–2-PrOH	$C_{21}H_{24}ClN_3O_2$	C, H, N, Cl
2h	$CH(CH_3)C_2H_5$	0	206–207	60	MeOH	$C_{24}H_{30}ClN_3O$	C, H, N, Cl
2o	$CH(CH_3)C_2H_5$	1	206–208	29	MeOH–2-PrOH	$C_{24}H_{30}ClN_3O_2$	C, H, N, Cl
2p	SC_6H_4-4-Cl	0	180–183	45	toluene	$C_{26}H_{25}Cl_2N_3OS$	C, H, N
2q	SC_6H_4-4-Cl	1	125–133	47	chromatog	$C_{26}H_{25}Cl_2N_3O_2S{\cdot}0.2H_2O$	C, H, N, S
13	5,6-$(CH_2)_4$	0	210–212	20	CH_2Cl_2–$(2\text{-}Pr)_2O$	$C_{24}H_{28}ClN_3O$	C, H, N, Cl

[a] Except for the cases where R = C_2H_5 and SC_6H_4-4-Cl, these yields are based on crude yields obtained in the previous step and may actually be higher than stated.

Table V. Effects of 4-[(7-Chloro-4-quinolinyl)amino]-2-[(alkylamino)methyl]-6-alkylphenols and N^{ω}-Oxides against Trophozoite-Induced *P. berghei* in Mice



			ΔMST after single dose (sc),[a] mg/kg						
no.	R	x	640	320	160	80	40	20	10
1	tebuquine		17.1	1C (16.4)	2C (14.9)	3C (14.9)	4C (19.9)	3C (14.9)	
2a	H (camoquine)	0	5C	5C	5C	2C	11.9	8.3	
2b	$(CH_3)_3C$	0	6.3	5.9	1.9	1.7	0.5	0.1	
2c	C_6H_{11}	0	5C	5C	5C	2C (10.6)	5.7	0.5	
2d	$C_6H_5CH_2$	0	7.9	7.8	3.7	3.4	1.7	0.2	
2e	C_2H_5	0	4C (27.4)	4C (34.4)	4C (14.4)	2C (20.7)	1C (12.4)	12.1	6.1
2f	$CH(CH_3)_2$	0	5C	5C	5C	4C (25.4)	3C (27.9)	18.1	11.1
2g	CH_3	0	5C	3C (17.2)	4C (20.7)	4C (13.7)	1C (13.0)	10.4	7.0
2h	$CH(CH_3)C_2H_5$	0	5C	5C	1C (40.2)	2C (29.4)	2C (27.7)	18.0	9.8
2i	$(CH_3)_3C$	1	6.1	6.7	4.1	2.9	1.7	0.1	3.7
2j	C_6H_{11}	1	5C	4C (24.9)	3C (22.4)	8.5	3.9	0.5	
2k	$C_6H_5CH_2$	1	14D	14D	5.4	4.2	2.0	0.4	
2l	C_2H_5	1	4C (1.4)	3C (13.4)	2C (13.4)	3C (10.9)	1C (13.2)	5.5	3.7
2m	$CH(CH_3)_2$	1	4C (23.7)	1C (29.7)	1C (21.7)	1C (15.5)	1C (15.5)	11.8	3.0
2n	CH_3	1	5C	3C (19.0)	3C (13.0)	1C (11.5)	2C (14.3)	7.6	1.4
2o	$CH(CH_3)C_2H_5$	1	5C	3C (39.7)	2C (30.0)	21.9	20.9	12.6	4.6
2p	4-ClC_6H_4S	0	13.1	--	10.1	8.8	7.3	3.0	
2q	4-ClC_6H_4S	1	14.4	9.0	7.6	3.4	4.1	0.5	
13	5,6-$(CH_2)_4$	0	3C	3C (28.3)	2C (15.1)	2C (14.8)	2C (12.8)	12.6	6.8

[a] ΔMST is the change in mean survival time of the treated mice, in days, calculated by subtracting the mean survival time of the control mice (an average of 6.2 days in these experiments) from the mean survival time of the treated mice. In calculating the mean survival time of the treated mice, 60-day survivors are not included. C indicates the number of mice surviving at 60 days postinfection and termed "cured". Each compound was administered as a single sc dose 72-h postinfection. Each entry at each dose represents results with a five-animal group.

The tetrahydronaphthyl analogue **13** was prepared because of a report[9] that it had curative activity and in addition provided chemoprophylaxis against massive parasite challenge. This material did show good activity but once

again was clearly less potent than the biphenyl-2-ols.

Conclusions. Although simple 6-alkyl analogues of the biphenyl-2-ol type 1 did retain substantial antimalarial activity, their lower potency in the murine model and the advanced stage of the testing of Tebuqine suggested it would be prudent to defer further studies on these materials in favor of the compound of choice to date, i.e., 1.

Experimental Section

Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. The ^1H NMR spectra were obtained with a Varian EM390 or Bruker WH90 spectrometer at 90 MHz or a Varian XL-200 spectrophotometer at 200 MHz. The IR spectra were obtained on Digilab DP-1-15 or Beckman IR-9 spectrophotometers. The IR and NMR spectra of all compounds and intermediates were consistent with the assigned structures. Analyses for C, H, N, and Cl were within 0.4% and for H_2O (method of Karl Fisher) within 0.5% of calculated values, unless otherwise noted.

2-Alkyl-2,5-cyclohexadiene-1,4-dione 4-Oximes (Table I, 4). 2-Ethyl-2,5-cyclohexadiene-1,4-dione 4-Oxime (4e). A light orange solution of 24.4 g (0.2 mol) of 2-ethylphenol in 150 mL of 95% aqueous ethanol and 150 mL of concentrated aqueous hydrochloric acid was cooled to −5 °C and 20.7 g (0.3 mol) of sodium nitrite was added portionwise. The resulting dark green mixture was stirred at 0 °C for 5 h and was then poured into 1250 mL of cold water. The brown solid that separated was collected and washed with water. It was taken up in saturated aqueous sodium carbonate. The resulting solution was treated with charcoal, filtered through Celite, and then acidified slowly with concentrated aqueous hydrochloric acid to pH ca. 2. The oil that separated soon solidified. The solid was collected, washed with water, and recrystallized from ether–petroleum ether. Drying in vacuo at 50 °C for 4 h afforded 13.4 g of **4e**, mp 95–97 °C.

***N*-(3-Alkyl-4-hydroxyphenyl)acetamides (Table II, 5) (See Alternate Route). *N*-(3-Ethyl-4-hydroxyphenyl)acetamide (5e).** A solution of 13.0 g (0.086 mol) of 2-ethyl-2,5-cyclohexadiene-1,4-dione 4-oxime in 150 mL of methanol was hydrogenated over 1.5 g of Raney nickel at an initial pressure of 51.5 psi for 5.5 h or until 2 mol of hydrogen was taken up. The solution was filtered into a flask containing 7.1 mL (0.086 mol) of acetic anhydride, and about 500 mL of tetrahydrofuran was added to dissolve the product. The resulting dark solution was heated under reflux for 30 min. The solvents were removed in vacuo leaving a dark red semisolid residue. The residue was suspended in a mixture of methanol–ether (1:5, 50 mL) and the suspension was filtered. The solid product was washed carefully with small amounts of methanol to remove colored material and leave behind an off-white product. The product was dried in vacuo at 50 °C for 3 h to give 9.5 g of **5e**, mp 140–141 °C.

***N*-(3-Alkyl-4-hydroxyphenyl)acetamides (Alternate Route). *N*-[3-(1,1-Dimethylethyl)-4-hydroxyphenyl]acetamide (5b).** A 28.0-g (0.187 mol) sample of sodium dithionite was added to a stirred solution of 7.3 g (0.041 mol) of 2-(1,1-dimethylethyl)-2,5-cyclohexadiene-1,4-dione 4-oxime in 200 mL of 1 N sodium carbonate. Black clumps separated from the mixture as the temperature rose to 35 °C. Stirring was continued for about 3 h and the solid was collected and taken up in ethyl acetate. The solution was washed with water and dilute sulfuric acid consecutively. The acidic layer was allowed to stand overnight during which time its blue color darkened. It was rendered alkaline and extracted with ethyl acetate. The extract was washed with water followed by saturated sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to dryness. The residual dark red oil was taken up in toluene and treated with 2.2 mL of acetic anhydride. The resulting solution was treated with charcoal and filtered. The cooled filtrate deposited 3.0 g of a purple solid, mp 145–147 °C. Recrystallization from toluene followed by drying afforded 2.5 g of **5b**, mp 147 °C.

***N*-[3-[(Diethylamino)methyl]-5-alkyl-4-hydroxyphenyl]acetamides (Table III, 6). *N*-[3-[(Diethylamino)methyl]-5-ethyl-4-hydroxyphenyl]acetamide (6e).** A dark solution of 9.3 g (0.052 mol) of *N*-(3-ethyl-4-hydroxyphenyl)acetamide, 5.9 mL (0.0572 mol) of diethylamine, and 5.8 mL (0.078 mol) of 37% formaldehyde solution in 250 mL of ethanol was heated to reflux. Additional amounts of *diethylamine* and formaldehyde, each equal to those originally added, were added at the following intervals during refluxing: (a) 6 h, (b) 30 h, (c) 45 h. After 48 h of refluxing the solution was allowed to stir at room temperature for 16 h and filtered. The filtrate was concentrated in vacuo to a dark red oil. Trituration with a small amount of ether induced crystallization. The pale pink solid was collected and dried in vacuo at 50 °C for 3 h to afford 3.5 g of the analytical sample of **6e**, mp 113–115 °C. A second crop of 4.7 g, mp 111–113 °C, was obtained by evaporating the ether filtrate and triturating the residue with petroleum ether; total yield 8.2 g.

4-Amino-2-[(diethylamino)methyl]-6-alkylphenol Dihydrochlorides (7). 4-Amino-2-[(diethylamino)methyl]-6-ethylphenol Dihydrochloride (7e). A solution of 8 g (0.03 mol) of *N*-[3-[(diethylamino)methyl]-5-ethyl-4-hydroxyphenyl]acetamide in 50 mL of 6 N aqueous hydrochloric acid was heated under reflux for 1 h. The solvent was removed in vacuo, leaving a thick residual oil. The oil was dissolved in ethanol and this solution was concentrated in vacuo to a gum. Trituration of the gum with ether gradually induced crystallization. Recrystallization from methanol–2-propanol and drying in vacuo at 60 °C for 3 h afforded 8.1 g (89%) of **7e**, mp 213–214 °C.

The other requisite 4-amino-2-[(diethylamino)methyl]-6-alkylphenol dihydrochlorides were prepared in a similar manner, but they generally resisted attempts at crystallization. Except for the methyl analogue (**7g**), mp 199–201 °C, which analyzed correctly, the others were assumed to be sufficiently pure for the next step by displaying a homogeneous TLC. **7g**: Anal. Calcd for $C_{12}H_{20}N_2O\cdot 2HCl$: C, 51.25; H, 7.89; N, 9.96; Cl^-, 25.21. Found: C, 51.09; H, 8.12; N, 10.13; Cl^-, 25.13.

4-[(7-Chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl]-6-alkylphenols (Table IV, 2). 4-[(7-Chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl]-6-ethylphenol (2e). A solution of 2 g (0.0068 mol) of a 4-amino-2-[(diethylamino)methyl]-6-ethylphenol dihydrochloride and 1.34 g (0.0068 mol) of 4,7-dichloroquinoline in 75 mL of ethanol was heated under reflux for 1.5 h. Approximately 50 mL of solvent was removed in vacuo and the residual viscous solution was poured slowly into 500 mL of cold water containing 20 mL of concentrated aqueous ammonium hydroxide. The off-white solid that separated was collected and washed thoroughly with water. It was recrystallized from methanol and dried in vacuo at 65 °C for 3 h to give 2.1 g of **2e**, mp 174–176 °C.

4-[(7-Chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl]-6-alkylphenol N^{ω}-Oxides (Table IV, 2). 4-[(7-Chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl]-6-ethylphenol N^{ω}-Oxide (21). A solution of 4 g (0.0136 mol) of 4-amino-2-[(diethylamino)methyl]-6-ethylphenol dihydrochloride and 2.9 g (0.0136 mol) of 4,7-dichloroquinoline 1-oxide in 125 mL of ethanol was heated under reflux for 2 h. The solution was concentrated in vacuo to approximately 15 mL and diluted with 500 mL of water. The resulting turbid solution was filtered and 20 mL of concentrated aqueous ammonium hydroxide was added to the filtrate. The yellow-green solid that separated was collected and washed with water. Recrystallization from a mixture of methanol and ether and drying in vacuo at 70 °C for 4 h afforded 2.7 g of **21**, mp 202–203 °C.

The crude products, in most cases, were contaminated with trace amounts of the des-*N*-oxides. Recrystallization generally removed this impurity. However, the benzyl and isopropyl analogues required chromatography. The procedure for the latter compound is shown.

4-[(7-Chloro-4-quinolinyl)amino]-2-[(diethylamino)methyl]-6-(1-methylethyl)phenol N^{ω}-Oxide (2m). A solution of 5.6 g (0.018 mol) of 4-amino-2-[(diethylamino)methyl]-6-(1-methylethyl)phenol dihydrochloride as a crude semisolid and 3.9 g (0.018 mol) of 4,7-dichloroquinoline 1-oxide in 200 mL of ethanol was heated under reflux for 2 h. The mixture was reduced in volume in vacuo to about 25 mL and the viscous solution was poured into 1 L of water. The resulting solution was filtered, and 20 mL of concentrated aqueous ammonium hydroxide was added dropwise to the clear, cold, stirred filtrate. A yellow solid separated and was collected. The solid was washed thoroughly with water

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and then was dissolved in a mixture of 125 mL of dichloromethane and 125 mL of ethyl acetate. The solution was absorbed on 300 g of silica gel 60 (70–230 mesh) in a column 1.5 in. in diameter. The column was eluted with the following mixtures: (a) ethyl acetate, 1200 mL, (b) ethyl acetate, 540 mL, and methanol, 60 mL, (c) ethyl acetate, 1050 mL, and methanol, 1050 mL, (d) methanol, 500 mL, and dichloromethane, 500 mL, (e) methanol, 225 mL, and *N,N*-dimethylformamide, 25 mL. The eluates were collected and combined according to their TLC patterns. The initial 2250 mL collected contained only a trace of the desired product. The next 500 mL contained pure *N*-oxide and no additional product could be obtained from successive eluates. Evaporation in vacuo of the solvent from the fractions containing the product left a green-yellow solid residue. This solid was recrystallized from a mixture of dichloromethane and methanol containing a trace of ammonium hydroxide and dried in vacuo at 85 °C for 6 h to provide 2.9 g of **2m**, mp 197–199 °C.

2-[(4-Chlorophenyl)thio]-4-nitrophenol (8). A mixture of 20 g (0.127 mol) of sodium nitromalonaldehyde monohydrate in 220 mL of water and 80 mL of 10% sodium hydroxide solution was combined with a solution of 30 g (0.136 mol) of [(4-chlorophenyl)thio]-2-propanone in 250 mL of ethanol, allowed to stand overnight, concentrated in vacuo to remove the ethanol, and cooled to afford a gold precipitate. This was collected, washed with a little 1 N sodium hydroxide and then with ether, and then dissolved in 1 L of hot water. The hazy solution was filtered through Supercel and poured into iced dilute hydrochloric acid. The resulting precipitate was recrystallized from toluene to afford 25.2 g (70%) of the desired product, mp 140–144 °C. Anal. Calcd for $C_{12}H_8ClNO_3S$: C, 51.16, H, 2,86; N, 4.97. Found: C, 51.03; H, 2.97; N, 5.04.

4-Nitro-1-naphthalenol (9). A mixture of 40 g (0.213 mol) of 4-nitro-1-naphthalenamine and 400 mL of 10% aqueous sodium hydroxide was heated on a steam bath for 5 h. The resulting solution was filtered from a small amount of suspended impurity, and the filtrate was cooled to 5 °C and acidified with concentrated hydrocholoric acid. The yellow solid that separated was collected, washed with water, and then recrystallized from dichloromethane–isopropyl ether. Drying in vacuo at 70 °C for 16 h afforded 36 g (89%) of **9**, mp 161–164 °C. Anal. Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.26; H, 3.83; N, 7.42.

***N*-(4-Hydroxy-1-naphthalenyl)acetamide (10).** A mixture of 29.2 g (0.154 mol) of 4-nitro-1-naphthalenol in 300 mL of methanol was hydrogenated over 1.0 g of Raney nickel at an initial pressure of 51 psi for 17.5 h and filtered into 17 mL of acetic anhydride. The resulting purple solution was heated under reflux for 40 min, treated with charcoal, and filtered through Celite. The filtrate was concentrated in vacuo to a thick puple gum, which was triturated with a mixture of 20 mL of methanol and 100 mL of ethyl acetate to induce crystallization. The white solid was collected and dried in vacuo at 50 °C for 18 h to afford 24.8 g (80%) of **10**, mp 186–187 °C. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.16; H, 5.31; N, 7.12.

***N*-(5,6,7,8-Tetrahydro-4-hydroxy-1-naphthalenyl)acetamide (11).** A mixture of 24.4 g (0.12 mol) of *N*-(4-hydroxy-1-naphthalenyl)acetamide in 120 mL of methanol and 120 mL of tetrahydrofuran was hydrogenated over 2.0 g of Raney nickel at a constant pressure of 1500 psi for 23.5 h and filtered. The filtrate, which included several tetrahydrofuran washings of the catalysts, was concentrated to dryness in vacuo. The residual white solid was recrystallized from tetrahydrofuran–ether and dried in vacuo at 90 °C for 16 h to afford 20.5 g (82%) of **11**, mp 188 °C.

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Leukotriene Receptor Antagonists. 2. The [[(Tetrazol-5-ylaryl)oxy]methyl]acetophenone Derivatives

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A series of [[(tetrazol-5-ylaryl)oxy]methyl]acetophenones was synthesized and evaluated as antagonists of leukotriene D_4 induced contractions of guinea pig ileum. Substitutions at the 3-position of the acetophenone with ethyl (**66**), propyl (**68**), butyl (**83**), and isobutyl (**84**) gave $-\log IC_{50}$ values of 7.9, 8.0, 7.8, and 7.7, respectively. Equally potent compounds were obtained when the tetrazol-5-yl group was connected to the second benzene ring in the para position with a chemical bond (**67**), methylene (**68**), or ethylene (**71**). For retention of high antagonist activity, the acetophenone should be substituted in the 2-position by a hydroxyl group and the tetrazole ring should have an acidic hydrogen atom. 1-[2-Hydroxy-3-propyl-4-[[4-(1*H*-tetrazol-5-ylmethyl)phenoxy]methyl]phenyl]ethanone (**68**, LY163443) has undergone extensive pharmacologic evaluation for its potential as an antiasthma agent.

The metabolism of arachidonic acid via the lipoxygenase pathway gives rise to a group of important biological mediators, the sulfidopeptide leukotrienes. Since their identification as the constituents of SRS-A,[1] these eicosanoid products, leukotrienes C_4, D_4, and E_4, have been chemically synthesized[2] and their biological effects have been investigated.[3] These efforts have led to an increased understanding of the physiological role of these important mediators and their possible role in pathological conditions such as asthma,[4] ischemia,[5] and shock.[6] A potent antagonist would be useful in identifying the importance of sulfidopeptide leukotrienes in these diseases and might be useful clinically in treating them.

One of the first recognized antagonists of LTD_4 was FPL55712.[7] Historically, it has served as the standard LTD_4 antagonist throughout the scientific community. Unfortunately, FPL55712 has the disadvantage of a short biological half-life and minimal oral bioavailability.[8]

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