sively from 450 ml of *i*-PrOH and 300 ml of MeOH. The pale yellow solid weighed 22.0 g (52%), mp 255–257°. *Anal.* ($C_{20}H_{28}F_3N_3O \cdot HCl$) C, H, N, Cl.

1,1'-[Azobis(5,6,7,8-tetrahydro-1,4-naphthyleneiminotrimethylene)]dipiperidine (XIVa).—A solution of 11.0 g (0.026 mole) of XII in 300 ml of H_2O containing 8 ml of concentrated HCl was diazotized at 0° with 26 ml of 1 *N* $NaNO_2$. The diazonium solution was added at 0–5° to a cold solution of 7.1 g (0.026 mole) of 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}piperidine (**101**) in 100 ml of EtOH, 200 ml of H_2O, and 12.5 ml of concentrated HCl. The purple solution was stirred overnight and made alkaline with NH_4OH, and the sticky product was washed with H_2O. The crude amide XIIIa was dissolved in 500 ml of Me_2CO–MeOH, 20 ml of 2 *N* methanolic NaOH was added, and the mixture was stirred overnight. The solid was collected by filtration, dried, and crystallized from $CHCl_3$ to give 7.5 g (51% over-all) of red needles, mp 235–237°. *Anal.* ($C_{36}H_{54}N_6$) C, H, N.

1-[3-(4-{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthylazo}-2,3-xylidino)propyl]piperidine (XIVb).—N-(4-Amino-5,6,7,8-tetrahydro-1-naphthyl)-2,2,2-trifluoro-N-(3-piperidinopropyl)acetamide hydrochloride (XII) (28.1 g, 0.067 mole) was coupled with 1-[3-(2,3-xylidino)propyl]piperidine (**98**) (16.5 g, 0.067 mole) using the procedure described for XIVa. The crude amide (XIIIb) was hydrolyzed without purification and the product was crystallized from $CHCl_3$–petroleum ether (bp 30–60°) to give orange crystals, mp 199.5–201°, yield 18.0 g (49% over-all). *Anal.* ($C_{34}H_{52}N_6$) C, H, N.

1,1'-Decamethylenebis{1-[3-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamino)propyl]piperidinium Bromide} (XV).—A solution of 10.0 g (0.027 mole) of 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)amino]propyl}piperidine (**14**) and 3.9 g (0.013 mole) of 1,10-dibromodecane in 150 ml of MeCN was heated under reflux for 74 hr. Some solid had formed. Me_2CO was added to induce further precipitation and the solid was removed by filtration. The crude quaternary salt was triturated with boiling Me_2CO, filtered, and dried to give 7.5 g (53%) of an orange-red solid, mp 209–213° *Anal.* ($C_{58}H_{84}Br_2N_8$) H, N, Br; C: calcd, 66.14; found, 65.67.

1-Methyl-1-[3-(5,6,7,8-tetrahydro-4-phenylazo-1-naphthylamino)propyl]piperidinium Iodide (XVI).—A mixture of 10.0 g (0.027 mole) of 1-{3-[(5,6,7,8-tetrahydro-4-phenylazo-1-naphthyl)amino]propyl}piperidine (**14**) and 50 ml of MeI was stirred briefly. Solution began followed by an exothermic reaction and precipitation of an orange solid. The reaction mixture was warmed on a steam bath for 15 min, and the product was collected by filtration and recrystallized from 1.2 l. of EtOH. The orange needles thus obtained weighed 11.3 g (82%), mp 210–212°. *Anal.* ($C_{25}H_{35}N_4I$) C, H, N.

1-{3-[(4-Chloro-5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}-piperidine Hydrochloride (XVIIa).—To a solution of 41.6 g (0.229 mole) of 4-chloro-5,6,7,8-tetrahydro-1-naphthylamine in 1 l. of dry toluene was added 50.0 g (0.25 mole) of 1-(3-chloropropyl)piperidine hydrochloride and 64 g of anhydrous K_2CO_3, and the mixture was heated under reflux with stirring for 24 hr. Excess aqueous NaOH was added and the mixture was stirred for 2 hr. The toluene layer was separated and dried (K_2CO_3), and volatile materials were removed *in vacuo*. The product was purified as the HCl salt, off-white crysals from *i*-PrOH, mp 204–207°, yield 18.5 g (24%). *Anal.* ($C_{18}H_{27}ClN_2 \cdot HCl$) C, H, N.

1-{3-[(5,6,7,8-Tetrahydro-4-methoxy-1-naphthyl)amino]propyl}piperidine Hydrochloride (XVIIb).—Alkylation of 4-methoxy-5,6,7,8-tetrahydro-1-naphthylamine (50.0 g, 0.283 mole) with 1-(3-chloropropyl)piperidine hydrochloride (56.0 g, 0.283 mole) according to the procedure described for the preparation of XVIIa gave 45.8 g (48%) of the desired product as off-white crystals from EtOH, mp 208–211°. *Anal.* ($C_{19}H_{30}N_2O \cdot HCl$) C, H, N.

Acknowledgments.—The authors wish to express their appreciation to Dr. Loren M. Long for encouragement in this investigation and to Dr. Y. T. Chang, Dr. D. H. Kaump, and co-workers for their assistance in the biological evaluation of these compounds. We also thank Dr. David B. Capps, Miss Joan Multhaup, Mrs. Dianne Kurtz, and Mr. Donald F. Worth for the preparation of several of the compounds described herein, Mr. William Pearlman for the performance of the hydrogenations described, and Mr. Charles E. Childs and associates for the microanalyses.

Antiprotozoal Quinones. I. Synthesis of 2-Hydroxy-3-alkyl-1,4-naphthoquinones as Potential Coccidiostats[1]

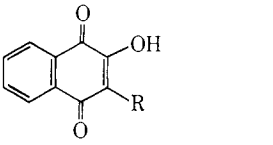
F. J. BULLOCK[2]

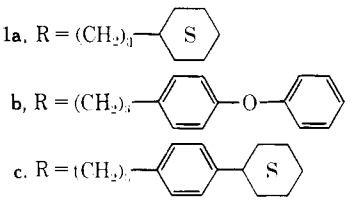
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02139

Received August 10, 1967

A series of 2-hydroxy-3-alkyl-1,4-naphthoquinones has been synthesized; the compounds have been screened as potential coccidiostats. Six of the new quinones have activity against *Eimeria brunetti* infections in chickens with 0.0125% of compound in the feed. The alkyl groups imparting greatest activity are 3-(4-cyclopentylphenyl)propyl, 3-(4-cycloheptylphenyl)propyl, 3-[4-(3-pentyloxy)phenyl]propyl, and 3-[4-(4-heptyloxy)phenyl]-propyl. In a series of quinones having 3-(4-alkoxyphenyl)propyl side chains, the activity increases with increasing lipophilicity of the alkoxy group. This parallels the effect first observed by Fieser, *et al.*, for the antimalarial activity of 2-hydroxy-3-alkyl-1,4-naphthoquinones.

The 2-hydroxy-3-alkyl-1,4-naphthoquinones have been extensively studied by Fieser and his coworkers[3,4] as potential antimalarials. In 1960 a number of hydroxyquinones selected from Fieser's extensive collection (Table I) were screened by Merck Sharp and Dohme as potential coccidiostats.[5] Several of the





compounds, especially **1a–c**, showed a significant level of coccidiostat activity in chickens infected with

(1) This work was supported by a predoctoral fellowship from the U. S. Public Service, Division of General Medicinal Sciences, during the period 1961–1963.

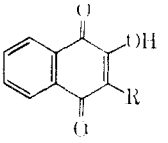
(2) Arthur D. Little, Inc., Acorn Park, Cambridge, Mass. 02140.

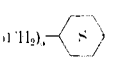
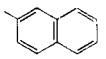
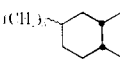
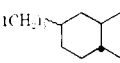
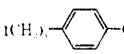
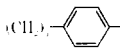
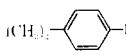
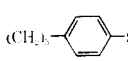
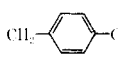
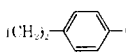
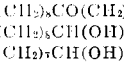
(3) L. F. Fieser, *et al.*, *J. Am. Chem. Soc.*, **70**, 3151–3244 (1948).

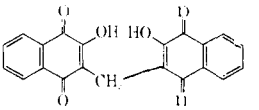
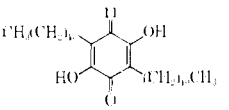
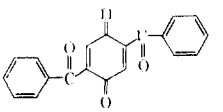
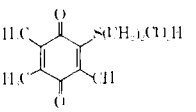
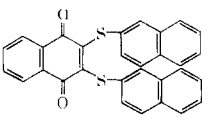
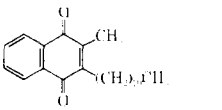
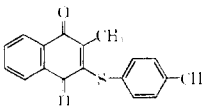
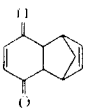
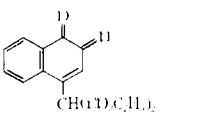
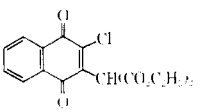
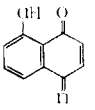
(4) (a) L. F. Fieser, J. P. Shirmer, S. Archer, R. L. Lorenz, and P. I. Pfaffenbach, *J. Med. Chem.*, **10**, 513 (1967); (b) L. F. Fieser, M. Z. Nazer, S. Archer, D. A. Berbarian, and R. G. Slighter, *ibid.*, **10**, 517 (1967).

(5) The selection of most of the compounds in Table I was made by E. F. Rogers, Merck Sharp and Dohme.

TABLE I
PRELIMINARY BIOLOGICAL RESULTS[a]



No.	R	Activity[b] E_t	E_m	E_a
1		I, 0.2	I, 0.01	I, 0.05
2	$CH_2CH{=}C(CH_3)_2$		I, 0.05	I, 0.025
3	$(CH_2)_{10}CH_3$	I, 0.2	I, 0.05	
4		A, 0.1	A, 0.05	A, 0.05
5	$(CH_2)_3C_6H_4Br$-p	I, 0.1	I, 0.05	I, 0.05
6	$(CH_2)_3C_6H_4CH_3$-p	I, 0.063	I, 0.026	
7	$(CH_2)_3$- 	I, 0.033	T, 0.026	
8		I, 0.25	I, 0.05	I, 0.025
9	$(CH_2)_4$- 	I, 0.063	I, 0.025	
10	$CH_2CH(CH_3)CH_2$- 	A, 0.063	I, 0.025	
11	$(CH_2)_3C_6H_4F$-p	I, 0.025	I, 0.05	
12	$(CH_2)_2$-$CH(CH_3)$- 	I, 0.063	I, 0.025	
13	$(CH_2)_3C_6H_4Cl$-p	I, 0.033	T, 0.025	
14	$(CH_2)_3$- 	I, 0.2	I, 0.05	
15	$(CH_2)_9CH(CH_3)_2$		I, 0.05	
16	$(CH_2)_3$- 	I, 0.063	I, 0.025	I, 0.025
17	$(CH_2)_3$- 	A, 0.05	A, 0.025	A, 0.025
18	$(CH_2)_3$- 	A, 0.05	A, 0.05	A, 0.05
19	$(CH_2)_4$- 	I, 0.063		
20	$(CH_2)_3$- 		I, 0.0125	
21	$(CH_2)_{18}CH_3$		I 0.05	
22	$(CH_2)_8C(OH)[(CH_2)_4CH_3]_2$	I, 0.1	I, 0.05	I, 0.05
23	$(CH_2)_4$- 	I, 0.063	I, 0.025	
24	$(CH_2)_3$- 		MA, 0.016	
25	CH_2- 		I, 0.05	
26	$(CH_2)_2$- 		I, 0.05	
27	$(CH_2)_8CO(CH_2)_7CH_3$		I, 0.037	
28	$(CH_2)_8CH(OH)(CH_2)_7CH_3$		MA, 0.05	
29	$(CH_2)_7CH(OH)(CH_2)_7CH_3$		I, 0.05	

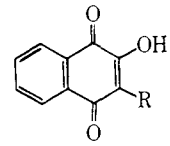
No.	R or structure	Activity[b] E_t	E_m	E_a
30	$(CH_2)_{10}CH(OH)(CH_2)_5CH_3$		I, 0.05	
31	$(CH_2)_2C(OH)(CH_3)_2$	I, 0.025	I, 0.05	I, 0.025
	Miscellaneous Compounds			
32			I, 0.05	I, 0.025
33			I, 0.05	I, 0.025
34			I, 0.05	
35			I, 0.05	I, 0.025
36			I 0.05	
37			I 0.05	
38			I, 0.05	
39			I, 0.05	I, 0.025
40			I, 0.025	
41			I, 0.025	
42			I, 0.025	

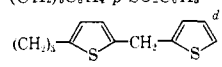
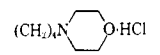
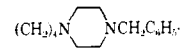
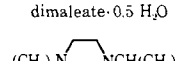
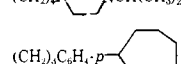
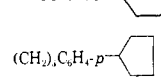
[a] The compounds in this table were donated by Professor L. F. Fieser. The biological data were made available by Dr. Edward F. Rogers of Merck Sharp and Dohme before the work reported in this paper began. [b] The abbreviations are: I, inactive; T, toxic; A, active; MA, moderately active; E_t, *E. tenella;* E_m, *E, maxima;* E_a, *E. acervalina.* The numerical values are percentages of compound incorporated into the bird feed during the assay (see text). The limited amounts of material available prohibited testing at higher quinone concentrations, as well as any retesting.

Eimeria tenella, Eimeria maxima, or *Eimeria acervulina.* The work reported here was undertaken to prepare further structural modifications of these three compounds for screening as coccidiostats.

Scheme I illustrates the general synthetic route used in this work.[6] Although the diacyl peroxide alkylation was generally carried out in hot acetic acid as described by Fieser, *et al.*,[3] it is possible to use reflux-

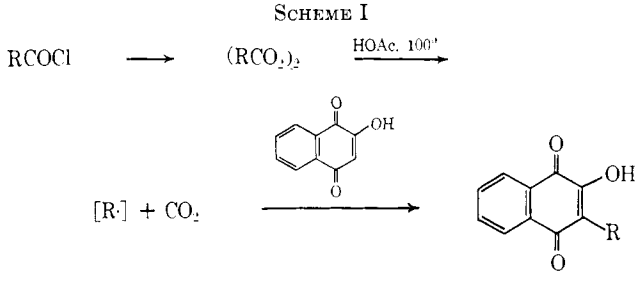
TABLE II
2-HYDROXY-3-ALKYL-1,4-NAPHTHOQUINONES



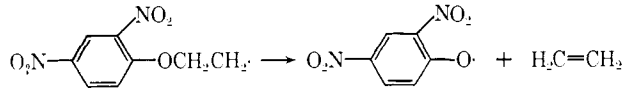
No.	R	Mp, °C	RS[a]	Yield, %	Formula	Analyses	Activity[b] Et	Activity[b] Eb
1	$(CH_2)_3C_6H_4$-*p*-$OCOCH_3$	118–119	EtOH	25	$C_{21}H_{18}O_5$	C; H[e]		
2	$(CH_2)_3C_6H_4$-*p*-NO_2[c]	149–150	MeOH	19	$C_{19}H_{15}NO_5$	C, H	I, 0.05	
3	$(CH_2)_3C_6H_4$-*p*-OH	131–132	C_6H_6	75	$C_{19}H_{16}O_4$	C, H	I, 0.05	
4	$(CH_2)_3C_6H_4$-*p*-$SO_2C_6H_5$	160.5–161	EtOH	35	$C_{25}H_{20}SO_5$	C, H	I, 0.05	
5	 [d]	100–101	Ligroin	10	$C_{22}H_{18}S_2O_3$	C, H	I, 0.05	
6		245–247	EtOH	69	$C_{18}H_{22}NO_4Cl$	C, H, N	I, 0.05	
7	 dimaleate·0.5 H_2O	193–194	EtOH	29	$C_{33}H_{36}N_2O_{11}\cdot 0.5H_2O$	C, H, N		I, 0.05
8		174–175	EtOH	29	$C_{29}H_{34}N_2O_{11}\cdot 0.5H_2O$	C, N; H		I, 0.05
9		123–124	MeOH	34	$C_{26}H_{28}O_3$	C, H		A, 0.0125
10		110–111	Ligroin	21	$C_{24}H_{24}O_3$	C, H		A, 0.0125
11	$(CH_2)_3C_6H_4$-*p*-$OCH_2C_6H_5$	144–145	Et_2O–petr ether	15	$C_{26}H_{22}O_4$	C, H	I, 0.05	
12	$(CH_2)_3C_6H_4$-*p*-$OCH(CH_3)_2$	100–101	Petr ether	22	$C_{22}H_{22}O_4$	C, H	I, 0.05	
13	$(CH_2)_3C_6H_4$-*p*-$OCH(C_2H_6)_2$	74–75	Petr ether	24	$C_{24}H_{26}O_4$	C, H		A, 0.025 MA, 0.0125
14	$(CH_2)_3C_6H_4$-*p*-$OCH[(CH_2)_2CH_3]_2$	65.6–65.6	Pentane	20	$C_{26}H_{30}O_4$	C, H		A, 0.0125 MA, 0.006
15	$(CH_2)_3C_6H_4$-*p*-OC_6H_3-2,4-$(NO_2)_2$	144–145	C_6H_6	27	$C_{25}H_{18}N_2O_8$	C, H	I, 0.05	
16	$(CH_2)_3C_6H_2$-3,5-$(NO_2)_2$-4-$C_6H_4NO_2$-*p*	158.5–159	HOAc	19	$C_{25}H_{20}N_2O_9$	C, H	I, 0.05	
17	$(CH_2)_2$—OC_6H_3-2,4-$(NO_2)_2$	179–180	HOAc	low	$C_{18}H_{12}N_2O_8$	C, H, N		I, 0.025
18	$(CH_2)_3C_6H_4$-*p*-$CH(CH_2)_2CH_3$ (C_2H_5, CH_3)	67–68	Petr ether	39	$C_{26}H_{28}O_3$	C, H		MA, 0.0125
19	$(CH_2)_3C_6H_4$-*p*-$CH(CH_2)_3CH_3$	84.5–85.5	Ligroin	30	$C_{28}H_{28}O_3$	C, H		A, 0.0125

[a] Recrystallizing solvent. [b] Abbreviations: I, inactive; A, active; MA, moderately active; Et, *E. tenella;* Eb, *E. brunetti.* Numerical values represent percentage of compound added to the bird feed during the assay. [c] 4-(*p*-Nitrophenyl)butyric acid prepared according to J. Van der Sheer, *J. Am. Chem. Soc.*, **56**, 744 (1934). [d] 4-[5-(2-Thenyl)-2-thienyl]butyric acid prepared according to Ya. L. Goldfarb and M. L. Krimalova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 479 (1957); *Chem. Abstr.*, **51**, 1590*f* (1958). [e] *Anal.* H: calcd, 5.18; found, 5.62. [f] *Anal.* H: calcd, 5.92; found, 6.39.

SCHEME I



ing benzene as the reaction solvent without alkylating the solvent. The unusually low yield of quinone **17** (Table II) containing the 2,4-dinitrophenoxyethyl side chain is almost certainly due to the rapid decomposition of the radical intermediate formed by thermolysis of the



corresponding diacyl peroxide. A similar decomposition of a β-alkoxy radical has been reported.[6]

The *p*-alkyl- and cycloalkyl-4-phenylbutyric acids required for the synthesis of quinones **9**, **10**, **18**, and **19** (Table II) were readily obtained by Friedel–Crafts succinoylation of the appropriate alkylbenzene followed by Huang-Minlon reduction.[7] Cycloalkylbenzenes were prepared from the cycloolefins by modification of the procedure of Pines, *et al.*[8] The isomeric 2- and 3-phenylhexanes were obtained by reaction of phenylmagnesium bromide with the appropriate hexanone. This does not require isomerically pure olefins as previous methods do. An acid work-up of the reaction mixture followed by distillation of the tertiary alcohol at ordinary pressure served to accomplish dehydration and yielded the phenylhexenes directly. Catalytic hydrogenation gave the required hydrocarbons.

The butyric acids needed for quinones **11**–**14** (Table II) were prepared by alkylation of methyl 4-*p*-hydroxyphenylbutyrate[9] under Williamson conditions followed by base hydrolysis. Sodium 4-*p*-hydroxyphenylbutyrate may be used in this alkylation but separation of product from unreacted starting phenol is more difficult. At the time this work was carried out the only aryloxyphenylbutyric acids obtained from the above ester took advantage of a particularly reactive aryl halide or *p*-toluenesulfonate. Under the usual conditions for the Ullman aryl ether synthesis[10] methyl

(6) W. A. Waters, "Free Radicals," Oxford University Press, London, 1946, p 145.

(7) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(8) H. Pines, A. Edeleanu, and V. Ipatieff, *ibid.*, **67**, 2193 (1945).

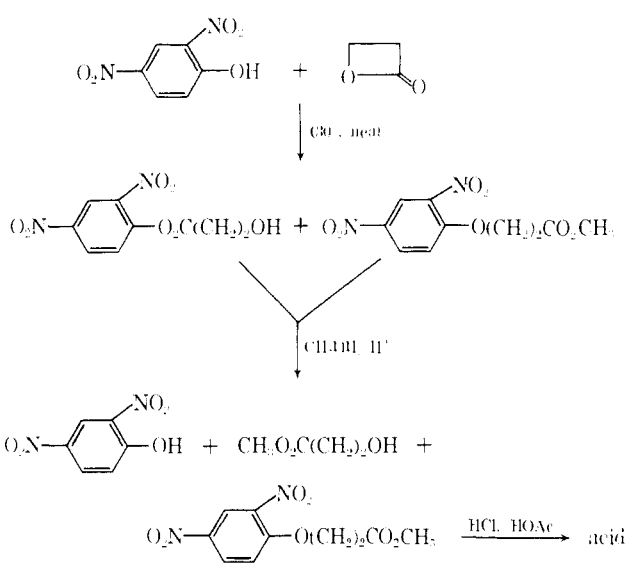
(9) Prepared by esterification of the acid: L. F. Fieser, M. T. Leffler, *et al.*, *ibid.*, **70**, 3195 (1948).

(10) F. Ullmann and B. Sponagel, *Chem. Ber.*, **38**, 2212 (1905); *Ann.*, **350**, 83 (1906).

4-*p*-hydroxyphenylbutyrate undergoes extensive degradation. The use of dimethylformamide as solvent in this reaction[11] apparently permits aryl ether formation under less drastic conditions, but this was not attempted here.

An efficient synthesis of β-aryloxypropionic acids from propiolactone is outlined in Scheme II. Subjecting the entire crude reaction mixture to Fischer esterification conditions simultaneously accomplishes esterification of the desired product and transesterification of the undesired ester to starting phenol. The phenol is easily removed from the neutral products and recycled.

SCHEME II



Quinone **3** (Table II) bearing the free phenolic group was obtained either by hydrolysis of the acetate ester **1** (Table II) or by removal of the 2,4-dinitrophenyl residue of quinone **15** (Table II) by reaction with sodium methoxide in refluxing methanol. The 2,4-dinitrophenyl residue can be a useful protecting group for phenolic groups in preparing this class of quinones. Quinones **6–8** (Table II) were obtained by reaction of the appropriate amine with 2-hydroxy-3-(4-bromobutyl)-1,4-naphthoquinone.[12]

Discussion

The biological test data for the hydroxyquinones prepared during this work are for *E. tenella* or *E. brunetti* and are presented in Table II. Six new quinones (**9**, **10**, **13**, **14**, **18**, **19** of Table II) have activity against these protozoa at a dosage level of 0.0125% of compound in the feed. Quinone **14** shows moderate activity at 0.006%.

Several conclusions may be drawn from the biological data in Tables I and II. In Table I is seen a general correlation between the structural types of side chain imparting anticoccidial activity and those known to impart maximal antimalarial activity.[3] Quinones **1a–c** were also among the better antimalarial compounds. An exception to this finding is lapinone (**22**, Table I) which has been reported to cure malaria,[3] but which is inactive as a coccidiostat. The limited comparable data available on the effect of chain length on coccidiostatic activity in a homologous series (quinones **17**, **23**, **25**, Table I) indicate that maximal activity is observed with propyl, as was seen in the antimalarial work.[3] This fact as well as the activity of **1a** and **1c** led us to preserve the propyl moiety in most of the new compounds prepared.

Introduction of polar groups such as amino or nitro into the side chain abolishes coccidiostatic activity. Similarly, conversion of the thioether of **24** (Table I) to a sulfone (**4**, Table II) abolishes the marginal activity of **24**. The increasing coccidiostatic activities in the quinone series **3** ≈ **12** < **13** < **14** (Table II) demonstrates the importance of lipophilicity in the side chain of the hydroxyquinone nucleus. This trend is quite reminiscent of the relationship between lipophilicity and antimalarial activity of the hydroxynaphthoquinones already documented by Fieser and coworkers.[13] They observed increasing antimalarial activity with increasing chain length in several homologous series. They also observed a relationship between antimalarial activity and hydrophilic–lipophilic balance, quantitated by an "extraction coefficient"[14] characteristic of the distribution of quinone between organic solvents and aqueous buffers. Insufficient quantitative test data are available to attempt a similar correlation among the coccidiostatic quinones. A detailed discussion of the possible relationship between the ability of 2-hydroxy-3-alkyl-1,4-naphthoquinones to block oxidative phosphorylation[15] and their anticoccidial and antimalarial activity has been presented elsewhere.[16]

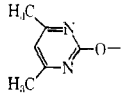
The biological evaluations reported in Tables I and II were carried out by Dr. E. C. McManus and his coworkers at Merck Sharp and Dohme Research Laboratories, Rahway, N. J. The assays were carried out as described in previous publications from those laboratories,[17,18] except that the 1958 concept of activity has been refined and the scores described there are now rated as follows: 0–3, active; 4–7, moderately active; 8–10, slightly active; >10, inactive.

Experimental Section[19]

Only typical procedures are described here. The diacyl peroxides needed for the alkylation[3] of 2-hydroxy-1,4-naphthoquinone (lawsone)[20] were prepared by (a) reaction of the acid chloride with Na_2O_2, as described by Fieser, *et al.*,[3] (b) reaction

(11) N. Kornblum and D. L. Kendall, *J. Am. Chem. Soc.*, **74**, 5782 (1952).
(12) L. F. Fieser and M. T. Leffler, *et al.*, *ibid.*, **70**, 3206 (1948).
(13) L. F. Fieser, M. Ettlinger, and G. Fanaz, *ibid.*, **70**, 3228 (1948).
(14) Fieser's definition of "extraction coefficient" is equivalent to the linear free-energy expression, $-\log E = \log K + pK_a + (\text{constant})$, where K is the distribution coefficient. This appears to be one of the earliest successful correlations of biological data with such a relationship.
(15) (a) C. Marcus and D. Nitz-Litzow, *Biochim. Biophys. Acta*, **12**, 131 (1965); (b) E. Ball, C. B. Anfinsen, and O. Cooper, *J. Biol. Chem.*, **168**, 257 (1947); (c) C. Widmer, H. Clark, H. Needfel, and E. Sholtz, *ibid.*, **210**, 861 (1958).
(16) F. J. Bullock, Ph.D. Thesis, Harvard University, 1963.
(17) A. C. Cuckler, L. R. Chapin, C. M. Malanga, E. F. Rogers, H. J. Becker, R. L. Clark, W. J. Leanza, A. A. Pessolano, T. T. Shen, and L. H. Sarett, *Proc. Soc. Exptl. Biol. Med.*, **98**, 167 (1958).
(18) E. F. Rogers, R. L. Clark, H. J. Becker, A. A. Pessolano, W. J. Leanza, E. C. McManus, F. J. Andriuli, and A. C. Cuckler, *Proc. Soc. Exptl. Biol. Med.*, **117**, 488 (1964).
(19) Melting points were taken in unsealed capillaries with a calibrated Mel-Temp apparatus. Microanalyses were performed by Dr. S. M. Nagy and his associates, Microchemical Laboratory, Massachusetts Institute of Technology. Ir spectra were recorded on a Perkin-Elmer Model 21 recording spectrophotometer and calibrated vs. atmospheric CO_2. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.
(20) L. F. Fieser, *J. Am. Chem. Soc.*, **70**, 3168 (1948).

TABLE III
SUBSTITUTED BUTYRIC ACIDS

R	Method[a]	% yield	Mp, °C	Bp, °C (mm)	Recrystn solvent	Analyses
			R-C6H4-(CH2)3CO2H			
$C_6H_5CH_2O$	A	70	108–109		C_6H_6–ligroin	C, H
$(CH_3)_2CHO$	A	47	41–42	219–221 (9)	Petr ether	C, H
$(CH_3CH_2)_2CHO$	A	31		160–165 (0.9)		C, H
$(CH_3CH_2CH_2)_2CHO$	A	35		176–177 (0.5)		C, H
	A	46	113–114		C_6H_6	C, H, N
	HM	55	70–71	205–210 (1)	Ligroin	C, H
$CH_3(CH_2)_3CH(CH_3)$	HM	81		157–158 (0.6)		C, H
$CH_3(CH_2)_2CH(CH_2CH_3)$	HM	83		148–149 (0.6)		C, H
			R-C6H4-CO(CH2)2CO2H			
	FC	82	145–146		C_6H_6	C, H
$CH_3(CH_2)_3CH(CH_3)$	FC	61	73.2–74		Ligroin	C, H
$CH_3(CH_2)_2CH(CH_2CH_3)$	FC	63	78–79		Ligroin	C, H

[a] Identification of abbreviations and general procedures are given in the Experimental Section.

of the acid chloride with H_2O_2, as described by Fieser, *et al.*;[3] or (c) the following method, which is generally superior. H_2O_2 (30%, 1.1 equiv) and pyridine (2.2 equiv) were covered with 30 ml of dry Et_2O and cooled to 0°. To this vigorously stirred mixture was added the crude acid chloride dissolved in Et_2O. The rate of addition was such that the temperature did not rise above 5° After addition of the acid chloride solution, the mixture was stirred vigorously at 0° for 3 hr. If the diacyl peroxide separated as a solid, it was filtered after neutralization of the excess pyridine with cold dilute HCl (cooling) and washed with ice water, and the bulk of the water was removed by suction. The alkylation was carried out immediately using this slightly moist peroxide. When the diacyl peroxide remained in the ether solution, the pyridine was removed by washing the ether layer with cold dilute HCl. The ether layer was then dried by filtration through a cone of Na_2SO_4 and titrated for peroxide content.[21] All acid chlorides were prepared from the acid and $SOCl_2$ in the usual way and were used directly without purification.

Benzene as Solvent in the Alkylation of Lawsone.—In a typical procedure a dried ether solution containing 7.2 mmoles of di-4-phenylbutyryl peroxide was evaporated *in vacuo* and the residual peroxide was dissolved in 50 ml of benzene. This solution in a vented dropping funnel was slowly added through the condenser to a well-stirred, refluxing suspension of 6 g (3.4 mmoles) of lawsone in 200 ml of C_6H_6. During the addition the lawsone gradually dissolved. After 30 min further of refluxing, the solvent was removed *in vacuo* and the residue was extracted with 200 ml of Et_2O. The bulk of the unreacted lawsone was removed by filtration and the ether solution was thoroughly washed with saturated aqueous $NaHCO_3$ to remove the remainder of the lawsone and other acidic by-products. The ether solution was then washed with dilute HCl, dried, and evaporated. Crystallization of the product from EtOH containing 1 drop of HCl gave 4.9 g (43%) of 3-(3-phenylpropyl)-2-hydroxy-1,4-naphthoquinone, mp 131–132° (lit.[3] mp 133–134°).

Cyclopentylbenzene has previously been prepared by a variety of other methods.[22] Dry C_6H_6 (35 g) and 50 g of HF were stirred in a polyethylene bottle, cooled to −10°, while a solution of cyclopentene (37 g, 0.545 mole) in 45 g of C_6H_6 was added slowly (1.5 hr). The bottle was capped and the solution was allowed to gradually warm to 15° with continued stirring and occasional release of any pressure built up (1.5 hr). The HF was then removed in a hood with a stream of air and the colored residue distilled fractionally, the fraction boiling at 90–105° (20 mm) being collected (49.5 g). Redistillation gave 47.8 g (60%) of product, bp 97–100° (17 mm) [lit.[22] bp 116–117° (37 mm)]. Cycloheptylbenzene was prepared similarly.

***dl*-3-Phenylhexane.**—Hexan-3-one (32 g, 0.32 mole) was added slowly to an Et_2O solution of C_6H_5MgBr[23] (prepared from 0.43 mole of Mg). After 1 hr of gentle refluxing, the reaction mixture was decomposed with excess dilute HCl, and the ether layer was separated and evaporated without drying. Distillation gave 39.4 g (78%) of the phenylhexene mixture, bp 210–225° (765 mm). This was reduced over Pt–C without solvent. After filtration of the catalyst and distillation, 36.3 g (91%) of material was obtained, bp 203–206° (768 mm) (lit.[24] bp 209–212°). *dl*-2-Phenylhexane was obtained in a similar manner.

4-*p*-Alkoxyphenylbutyric Acids.—Methyl 4-*p*-hydroxyphenylbutyrate [bp 200–205° (12 mm)][9] was converted to the phenoxide salt with 1 equiv of freshly prepared NaOEt in EtOH. After addition of 1 equiv of the appropriate iodoalkane, the mixture was stirred and heated at 60–65° overnight. Filtration of the precipitated salt and removal of solvent generally yielded an oil which was then dissolved in ether. Thorough extraction of the ether solution with 1 *N* NaOH removed unreacted phenolic material. Acidification of the basic extract enables recovery of 4-*p*-hydroxyphenylbutyric acid. The crude ester obtained by removal of the ether was hydrolyzed with methanolic KOH. Final purification of the desired acid was accomplished by vacuum distillation or crystallization as was appropriate. If necessary small amounts of 4-*p*-hydroxyphenylbutyric acid may be removed before final purification by dissolving the crude product in petroleum ether (bp 30–60°) and filtering the insoluble residue. The compounds prepared in this way are listed in Table III (method A).

Friedel–Crafts Succinoylations.—Succinoylations of alkyl and cycloalkylbenzenes were accomplished by the procedure of Fieser and Desreux.[25] The compounds prepared in this way are listed in Table III (method FC).

Reduction of Benzoylpropionic Acids.—The various β-(4-alkyl)benzoylpropionic acids obtained were readily reduced by Huang-Minlon's modification[7] of the Wolff–Kishner procedure. After dilution of the reaction mixture with water, acidification, and extraction with Et_2O, the products were purified by vacuum distillation, then recrystallization if possible. The compounds prepared are listed in Table III (method HM).

4-*p*-Acetoxyphenylbutyric Acid.—4-*p*-Hydroxyphenylbutyric acid[9] (47 g, 0.26 mole) was dissolved in 260 g of pyridine and the

(21) V. Kokatnur and M. Jelling, *J. Am. Chem. Soc.*, **63**, 1432 (1941).
(22) F. H. Case, *ibid.*, **56**, 716 (1934), and references therein.
(23) C. F. H. Allen and S. Converse, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 227.
(24) L. Spiegler and J. M. Tinker, *J. Am. Chem. Soc.*, **61**, 1002 (1939).
(25) L. F. Fieser and V. Desreux, *ibid.*, **60**, 2255 (1938).

solution was chilled to ice-bath temperature while Ac_2O (39 g) was added. The solution was then allowed to stand in the refrigerator for 5 days, then poured with stirring onto a mixture of 1 kg of chipped ice and 300 ml of concentrated HCl. The oily precipitate was extracted with C_6H_6, the solution was dried (Na_2SO_4), and the solvent was removed. The residue was fractionally distilled and the product (24.5 g, 42%) was collected at bp 195–200° (4 mm) as a pale yellow oil. This slowly solidified and was crystallized once from C_6H_6–ligroin; mp 62–63°. *Anal.* ($C_{12}H_{14}O_2$) C, H.

4-[*p*-(Benzenesulfonyl)phenyl]butyric Acid.—Methyl 4-phenylbutyrate, bp 115–117° (3 mm) (20 g, 0.17 mole), and benzenesulfonyl chloride (30 g, 0.17 mole) were dissolved in 250 ml of CS_2 at 0°. To this was added all at once 56 g (0.4 mole) of anhydrous $AlCl_3$. A vigorous but not uncontrolled reaction ensued. After the reaction subsided the solution was warmed to room temperature and stirred overnight. The reaction mixture was then poured into 350 ml of dilute iced HCl and the CS_2 was removed by heating the mixture on a steam bath. The aqueous mixture was cooled and extracted with C_6H_6 which was then evaporated to give the crude ester. This was hydrolyzed by refluxing in methanolic KOH, treated with active charcoal, and poured into excess dilute HCl. The acid, which separated as a semisolid, was extracted with $CHCl_3$, which was dried (Na_2SO_4) and evaporated to give a viscous oil. The product was obtained crystalline by slow cooling of a C_6H_6 solution or, better, an AcOH solution of the oil. The yield was 34 g (60%), mp 110–111°. *Anal.* ($C_{16}H_{16}SO_4$) C, H.

4-[4-(4-Methoxyphenoxy)-3,5-dinitrophenyl]butyric Acid.—Methyl 4-[4-(4-methoxyphenoxy)-3,5-dinitrophenyl]butyrate, mp 64–65°, was prepared by the route used for preparation of the ethyl ester.[25] Into 200 ml of pyridine was dissolved 19 g (0.062 mole) of the ester, and *p*-toluenesulfonyl chloride (12.5 g, 0.66 mole) was added. After the solution had been stirred overnight, hydroquinone monomethyl ether (17.5 g, 0.14 mole) was added and the solution refluxed 2 hr. After cooling, the pyridine was evaporated *in vacuo*, the oily residue was poured into 200 ml of dilute HCl, and the mixture was extracted with three 100-ml portions of C_6H_6. After dilution with an equal volume of Et_2O, the C_6H_6 solution was washed with two 25-ml portions of 1 *N* NaOH, then once with H_2O. The organic solvents were then evaporated and the residual oil was dissolved in 100 ml of AcOH. Concentrated HCl (45 ml) was added and the solution refluxed for 2.5 hr. H_2O (30 ml) was added to the hot solution and this was allowed to stand at 4° overnight. The product (19 g, 76% over-all) crystallized directly from the reaction mixture as pale green plates, mp 152–154°. Further crystallization from AcOH yielded pale yellow needles, mp 153–154°. *Anal.* ($C_{17}H_{16}N_2O_8$) C, H.

4-[4-(2,4-Dinitrophenoxy)phenyl]butyric acid was prepared from methyl 4-(4-hydroxyphenyl)butyrate and 2,4-dinitrophenyl *p*-toluenesulfonate in a similar manner, mp 110–111°, yield 61%, recrystallized from AcOH. *Anal.* ($C_{16}H_{14}N_2O_6$) C, N.

3-(2,4-Dinitrophenoxy)propionic Acid.—The following procedure is generally useful for preparing 3-aryloxypropionic acids. 2,4-Dinitrophenol (24 g, 0.13 mole) and β-propiolactone (13.2 g, 0.18 mole) were heated at 130° for 12 hr. After the heating period 200 ml of MeOH was added and the mixture was subjected to esterification conditions (1 ml of concentrated H_2SO_4, 6 hr of reflux). The mixture was then poured into 1 l. of H_2O and extracted thoroughly with Et_2O. After washing (four 75-ml portions of 0.5 *N* NaOH and once with H_2O) and drying (Na_2SO_4), the ether was evaporated to yield crude methyl 3-(2,4-dinitrophenoxy)-propionate of adequate purity for subsequent steps; yield 9.2 g (85% based on unrecovered 2,4-dinitrophenol). The material crystallized from Et_2O as long pale yellow needles, mp 72.5–73.2°. *Anal.* ($C_{10}H_{10}N_2O_7$) C, H, N.

The crude ester (9 g, 0.033 mole) was hydrolyzed by refluxing in a mixture of 25 ml of concentrated HCl and 20 ml of H_2O for 4 hr. The product (6.9 g, 80%) was isolated by cooling. Crystallization from Et_2O gave nearly colorless material, mp 118–119°. *Anal.* ($C_9H_8N_2O_7$) H, N; C: calcd, 42.19; found, 42.83.

Reaction of Amines with 3-(4-Bromobutyl)-2-hydroxy-1,4-naphthoquinone.—The quinone[10] was dissolved in $CHCl_3$, 4 equiv of amine was added, and the red solution was heated at 75° for 20 hr. The $CHCl_3$ was evaporated, the resulting red oil was treated with *exactly* 2 equiv of 1.0 *N* NaOH, and the resulting red solution again was evaporated *in vacuo*. The red quinone salt was washed thoroughly with dry Et_2O to remove unreacted amine, suspended in a small amount of H_2O, and treated with *exactly* 2 equiv of 1.0 *N* HCl. When morpholine was the reacting amine, addition of 1 further equiv of HCl caused precipitation of the hydrochloride of the product directly. Dimaleates were isolated by dilution of the carefully neutralized quinone solution with 1 vol of H_2O and addition of a 20-fold excess (based on starting quinone) of maleic acid. The precipitate was digested until it was completely yellow and then filtered after the mixture was cooled to 0°. Recrystallization from H_2O containing a small amount of maleic acid and EtOH, then from EtOH, yielded the pure dimaleates.

3-(3-*p*-Hydroxyphenylpropyl)-2-hydroxy-1,4-naphthoquinone. Procedure A.—3-{3-[*p*-(2,4-Dinitrophenoxy)phenyl]propyl}-2-hydroxy-1,4-naphthoquinone (2 g, 4.2 mmoles) prepared by the usual alkylation reaction was suspended in 40 ml of MeOH, NaOMe (1.75 g) was added, and the red solution refluxed for 6 hr. The methanolic solution was then acidified at the boiling point with HCl, poured into 100 ml of H_2O, and extracted with Et_2O. The quinone obtained after drying (Na_2SO_4) and evaporation was crystallized from C_6H_6; yield 0.7 g (54%), mp 130–131°.

Procedure B.—3-[3-(*p*-Acetoxyphenyl)propyl]-2-hydroxy-1,4-naphthoquinone (0.5 g, 1.4 mmoles) prepared by the usual alkylation was dissolved in 25 ml of MeOH, 0.4 g of KOH in 2 ml of H_2O was added, and the solution refluxed for 2 hr. The solvent was evaporated, the red residue was acidified with dilute HCl, and the quinone was extracted with 25 ml of Et_2O. Drying ($CaCl_2$), evaporation of solvent, and crystallization of the product from C_6H_6 gave 0.33 g (75%) of golden yellow needles, mp 131–132°. *Anal.* ($C_{19}H_{18}O_4$) C, H.

Acknowledgment.—I am grateful to Professor L. F. Fieser for having suggested work on this problem and to both Mrs. Fieser and him for considerable kind encouragement while the work was in progress. Considerable patient correspondence from Dr. E. F. Rogers of Merck Sharp and Dohme on certain biological aspects of the work is also gratefully acknowledged.

[25] N. Kharasch and S. H. Kalfayan, *J. Org. Chem.*, **21**, 929 (1956).