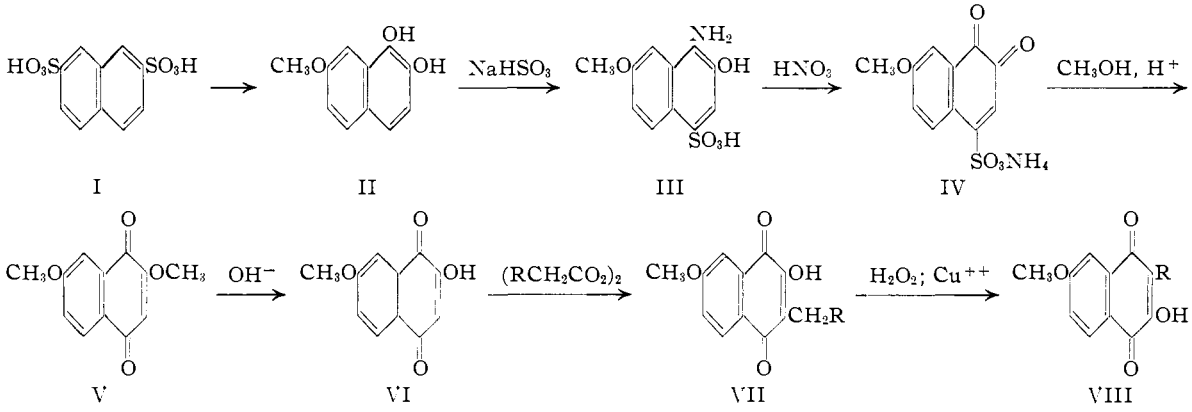
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Naphthoquinone Antimalarials. XXIII. Bz-Substituted Derivatives[1]

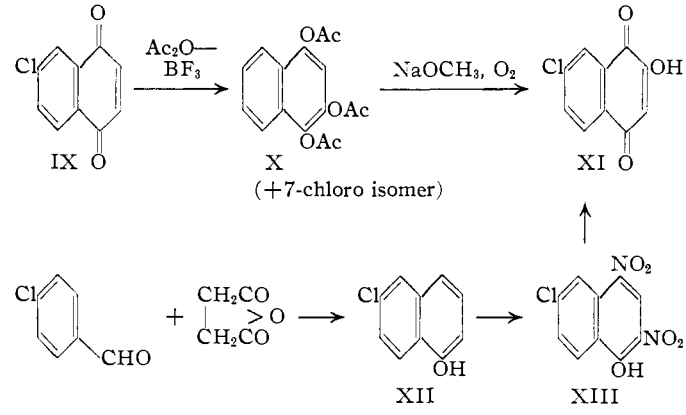
BY LOUIS F. FIESER AND RUSSELL H. BROWN[2]

In the few instances previously investigated the substitution of alkyl or hydroxyl groups in the benzenoid ring of a 2-hydroxy-3-alkyl-1,4-naphthoquinone has been found to practically obliterate antimalarial activity.[3] Since the case of atabrine would suggest the possibility of a more favorable result from the introduction of β-methoxy or β-chloro substituents into the aromatic ring, several new compounds of this type have been examined.



Two series of β-bz-methoxyquinones were prepared starting with 7-methoxy-1-nitroso-2-naphthol (II), available from naphthalene-2,7-disulfonic acid in three known steps. By procedures worked out for 1-nitroso-2-naphthol, II was converted through the aminonaphtholsulfonic acid III, the quinone sulfonate IV, and the dimethoxy quinone V into 2-hydroxy-7-methoxy-1,4-naphthoquinone (VI). By the peroxide alkylation reaction this was converted into 3-alkyl derivatives having from seven to eleven carbon atoms in the side-chain. These were converted by the modified Hooker oxidation[4] reaction into the next lower homologs in which, in consequence of the opening and reclosing of the quinone ring, the methoxy group is transposed to the 6-position (VIII). None of the compounds tested showed any antirespiratory activity,[5] whereas the corresponding methoxyl-free compounds are all active, even though the methoxyl substitution produces little change in the extraction constants.[6]

Related compounds carrying a chlorine atom at the 6- or 7-position were prepared starting with 6-chloro-1,4-naphthoquinone (IX), available from chloroprene and benzoquinone. The Thiele reaction afforded a separable mixture of the two hydroquinone triacetates, each of which was converted into the corresponding hydroxychloronaphthoquinone. One of these was identified as



the 2-hydroxy-6-chloro isomer by synthesis from the known 6-chloro-1-naphthol (XII) through the dinitro derivative XIII; this on reduction and oxidation afforded 6-chloro-2-amino-1,4-naphthoquinone-4-imine, which yielded XI on hydrolysis. The two hydroxychloroquinones were then alkylated with the peroxide from γ-cyclohexylbutyric acid, but neither product showed appreciable antirespiratory activity.

Experimental[7]

2-Hydroxy-3-alkyl-7(6)-methoxy-1,4-naphthoquinones

1-Nitroso-2-hydroxy-7-methoxynaphthalene.—Additional data on previously described procedures are as follows. Naphthalene (128 g.) was sulfonated with 95%

(1) This work was supported in part by grants from the Rockefeller Foundation and Research Corporation.

(2) Abbott Laboratories postwar Fellow, 1945–1948.

(3) Fieser and Richardson, THIS JOURNAL, **70**, 3156 (1948); Fieser, Leffler and co-workers, *ibid.*, **70**, 3212 (1948).

(4) Fieser and Fieser, *ibid.*, **70**, 3215 (1948).

(5) Heymann and Fieser, *J. Pharmacol. Exp. Therap.*, **94**, 97 (1948); Fieser and Heymann, *J. Biol. Chem.*, **176**, 1363 (1948).

(6) Fieser, Ettlinger and Fawaz, THIS JOURNAL, **70**, 3228 (1948).

(7) The melting points are all corrected.

TABLE I

1,4-NAPHTHOQUINONES

No.	Substituents	M. p., °C.	Solvent	Form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	2,7-$(OCH_3)_2$	214–215	EtOH	Orange needles	$C_{12}H_{10}O_4$	66.05	66.32	4.62	4.95
2	2-OH-7-OCH_3	220–222	EtOH	Orange needles	$C_{11}H_8O_4$	64.71	64.93	3.95	4.09
3	2-OH-7-OCH_3-3-$(CH_2)_3$-cyclohexyl	119–120	MeOH	Yellow needles	$C_{20}H_{24}O_4$	73.12	73.41	7.37	7.48
4	2-OH-7-OCH_3-3-CH_2-cyclohexyl	164–165	Pet. ether	Fine needles	$C_{18}H_{20}O_4$	72.00	72.36	6.71	7.03
5	2-OH-7-OCH_3-3-$C_{11}H_{23}$-*n*	94–95	MeOH	Leaves	$C_{22}H_{30}O_4$	73.70	73.86	8.44	8.28
6	2-OH-7-OCH_3-3-C_9H_{19}-*n*	97–98	MeOH	Leaves	$C_{20}H_{28}O_4$	72.71	72.97	7.93	8.07
7	2-OH-6-OCH_3-3-$(CH_2)_2$-cyclohexyl	137–138	MeOH	Large leaves	$C_{19}H_{22}O_4$	72.58	72.67	7.06	6.79
8	2-OH-6-OCH_3-3-cyclohexyl	142–143	MeOH	Fine blades	$C_{17}H_{18}O_4$	71.30	71.57	6.33	6.21
9	2-OH-6-OCH_3-3-$C_{10}H_{21}$-*n*	110–111	MeOH	Blades	$C_{21}H_{28}O_4$	73.23	73.15	8.19	8.32
10	2-OH-6-Cl	210–212	MeOH	Micro cryst.	$C_{10}H_5O_3Cl$	57.55	57.53	2.42	2.49
11	2-OH-6-Cl-3-$(CH_2)_3$-cyclohexyl	164–165	MeOH	Small leaves	$C_{19}H_{21}O_3Cl$	68.58	68.72	6.36	6.37
12	2-OH-7-Cl	205–207	MeOH	Micro cryst.	$C_{10}H_5O_3Cl$	57.55	57.57	2.42	2.40
13	2-OH-7-Cl-3-$(CH_2)_3$-cyclohexyl	132–133	MeOH	Leaflets	$C_{19}H_{21}O_3Cl$	68.58	68.39	6.36	6.20
14	2-OH-3-$(CH_2)_7CH{=}CH_2$	70–71	MeOH	Leaflets	$C_{19}H_{22}O_3$	76.47	76.60	7.43	7.61
15	2-OH-3-$(CH_2)_6CH{=}CH_2$	62–63	MeOH	Leaflets	$C_{18}H_{20}O_3$	76.01	75.95	7.09	7.39
16	2-OH-3-$(CH_2)_5CH{=}CH_2$	86–87	MeOH	Leaflets	$C_{17}H_{18}O_3$	75.54	75.35	6.71	6.98
17	2-OH-3-$(CH_2)_4CH{=}CH_2$	78–79	MeOH	Leaflets	$C_{16}H_{18}O_3$	74.99	75.00	6.29	6.77
18	2-OH-3-$(CH_2)_3CH{=}CH_2$	101–102	MeOH	Leaflets	$C_{15}H_{14}O_3$	74.35	74.52	5.82	6.05
19	2-OH-3-$(CH_2)_2CH{=}CH_2$	98–100	MeOH	Tiny plates	$C_{14}H_{12}O_3$	73.69	73.77	5.30	5.40

sulfuric acid (350 cc.) for four hours at 160°[8,9] and the cooled solution poured onto 500 g. of ice and 1.5 l. of water and neutralized with 450 g. of powdered calcium carbonate or 300 g. of quicklime. The mixture was filtered at 40° and the residual calcium sulfate extracted twice with 500-cc. portions of boiling water. The combined filtrates were evaporated to dryness and the mixture of 2,6- and 2,7-sulfonates was dried to constant weight at 200°; yield 263–285 g. Three parts of the crude calcium salt was treated with 5 parts of boiling water and the mixture was filtered by suction at the boiling point and the solid washed with a little hot water. Evaporation of the filtrate and dehydration as above gave 190 g. (58%) of **calcium 2,7-disulfonate**. Conversion to **2,7-dihydroxynaphthalene**[8] was effected by fusing 100 g. of calcium salt with 200 g. of crude potassium hydroxide flakes and 50 cc. of water for four hours at 250°. The granular mixture was added while hot in small portions with stirring to 800 cc. each of 36% hydrochloric acid and water and the granular 2,7-dihydroxynaphthalene that separated after cooling at 0° overnight was crystallized twice from water (100 cc.); yield 21.8–24.0 g. (44–49%), m. p. 189–190°.

2-Hydroxy-7-methoxynaphthalene[10] was prepared as outlined by Fischer and Hammerschmidt[11] by slowly adding 5.6 g. of potassium hydroxide in 100 cc. of water to a stirred mixture of 16 g. of 2,7-dihydroxynaphthalene; 150 cc. of water, and 20 cc. of dimethyl sulfate at 40°. After fifteen minutes 10% alkali was added to the point of distinct alkalinity, the solution was filtered by suction into dilute hydrochloric acid containing sodium sulfite and the residual diether washed repeatedly with warm alkali. The monomethyl ether separated as large white leaflets and was crystallized from ligroin; yield 9.76 g. (56%), m. p. 116–117°.

The 1-nitroso derivative[11] was prepared by slowly adding 20.3 g. of sodium nitrite in 150 cc. of water to a stirred solution at 0° of 51 g. of 2-hydroxy-7-methoxynaphthalene in 300 cc. of acetic acid containing 30 cc. of water. The resulting slurry was allowed to stand at room temperature for several hours, diluted with water, and the solid collected, washed, dried, and crystallized from 400 cc. of methanol. The yield of bright red needles, m. p. 124–125°, was 41 g. (69%).

7-Methoxy-1,2-naphthoquinone was obtained from the nitroso derivative by reduction and oxidation; it formed crimson microprisms from ethanol, m. p. 143–145°.

Anal. Calcd. for $C_{11}H_8O_3$: C, 70.20; H, 4.28. Found: C, 70.01; H, 4.18.

2,7-Dimethoxy-1,4-naphthoquinone (Table I).—By reaction with sodium bisulfite and acidification by a procedure worked out for the methoxyl-free compound,[12,13] 67 g. of 1-nitroso-2-hydroxy-7-methoxynaphthalene yielded 74 g. (84%) of 1-amino-7-methoxy-2-naphthol-4-sulfonic acid as a light gray granular solid. Oxidation of 83 g. of this material with nitric acid by the procedure of Fieser and Martin[14] gave 73 g. (83%) of ammonium 7-methoxy-1,2-naphthoquinone-4-sulfonate. Treatment of this substance with methanol and sulfuric acid according to Fieser and Martin afforded satisfactory 2,7-dimethoxy-1,4-naphthoquinone in 72% yield (No. 1, Table I).

The dimethoxy compound dissolved rapidly in hot dilute alkali, and acidification of the red solution gave **2-hydroxy-7-methoxy-1,4-naphthoquinone** in 82.5% yield (No. 2).

Alkyl Derivatives.—The 2-hydroxy-7-methoxy-3-cyclohexylpropyl and 3-undecyl derivatives Nos. 3 and 5 were prepared by peroxide alkylation in the usual manner.[15] A succession of Hooker oxidations[3] then gave, alternately, members of the 6-methoxy and the 7-methoxy series; thus: 3 → 7 → 4 → 8, and 5 → 9 → 6.

2-Hydroxy-3-alkyl-6(7)-chloro-1,4-naphthoquinones

6-Chloro-1,4-naphthoquinone[16] was prepared by the procedure described by Fieser for the parent quinone.[17] *p*-Benzoquinone (108 g.) was condensed with chloroprene[18] (89 g.) in acetic acid (500 cc.) at room temperature

(8) Weber, *Ber.*, **14**, 2206 (1881).

(9) Haller and Lynch, *Ind. Eng. Chem.*, **16**, 274 (1924).

(10) Bungly and Decker, *Ber.*, **38**, 3272 (1905).

(11) O. Fischer and Hamnerschmidt, *J. prakt. Chem.*, **94**, 25 (1916).

(12) Fieser, *Org. Syn.*, Coll. Vol. II, 42 (1943).

(13) Fieser, THIS JOURNAL, **48**, 2929 (1926); Martin and Fieser, *Org. Syn.*, **21**, 91 (1941).

(14) Fieser and Martin, *Org. Syn.*, **21**, 56 (1941).

(15) Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3175 (1948).

(16) Carothers and Collins, U. S. Patent 1,967,862 (1934) [*C. A.*, **28**, 5994 (1934)]; Koslov and Talybov, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 1827 (1939).

(17) Fieser, THIS JOURNAL, **70**, 3165 (1948).

(18) Obtained by fractionation of a stabilized chloroprene-xylene solution kindly supplied by the du Pont Company.

for forty-eight hours. Isomerization with hydrochloric acid–stannous chloride resulted in crystallization of 149 g. (76%) of light gray 6-chloro-5,8-dihydro-1,4-naphthoquinone (recrystallized sample, m. p. 197–198°). Oxidation in acetic acid with nitrous acid and then dichromate mixture gave bright yellow 6-chloro-1,4-naphthoquinone, m. p. 102–105°, in 77% yield from the dihydronaphthohydroquinone. Crystallization from ether raised the m. p. to 106–107°.

6- and 7-Chloro-1,2,4-triacetoxynaphthalene.—A suspension of 58 g. of 6-chloro-1,4-naphthoquinone in 120 cc. of acetic anhydride was cooled to 0° and treated with 6 cc. of boron fluoride etherate. After standing at room temperature for several hours, the mixture was warmed briefly on the steam-bath and again let stand. The suspension of crystals in dark brown liquor was poured into water and the product collected as a tan solid, m. p. 120–135°; yield 65 g. (63%). Fractionation from methanol was tedious but afforded substantial amounts of the less soluble 7-chloro compound, m. p. 163–164°, and of the more soluble 6-chloro isomer, m. p. 143–144°.

Anal. Calcd. for $C_{16}H_{13}O_6Cl$: C, 57.08; H, 3.89. Found: (164°) C, 57.34; H, 3.88; (144°) C, 57.31; H, 3.95.

6- and 7-Chloro-2-hydroxy-1,4-naphthoquinone (Table I) was prepared by the hydrolysis procedure of Fieser.[17] Thus 8.4 g. of 7-chloro-1,2,4-triacetoxynaphthalene was added in ten minutes to a suspension of 7 g. of sodium methoxide in 70 cc. of methanol, stirred in an ice-bath. After one hour the red salt was collected (more from mother liquor with air), dissolved in hot water, and the filtered solution acidified; yield of bright yellow microcrystalline product 4.5 g. (91%). The isomer was obtained in 81% yield.

The properties and analyses of the products of peroxide alkylation are listed in Table I.

Synthesis of 2-Hydroxy-7-chloro-1,4-naphthoquinone

7-Chloro-1-naphthol.—In the preparation of this substance according to Erdmann and Kirchhoff[19] the reaction mixture from 70 g. of *p*-chlorobenzaldehyde, 41 g. of fused sodium acetate and 50 g. of succinic anhydride was treated with water and 10 g. of the unchanged aldehyde was removed by steam distillation. The residue was diluted with water to about 2 liters, filtered, and acidified with hydrochloric acid. The crude precipitated *p*-chlorophenylparaconic acid [containing *p*-chlorobenzoic acid and β-(*p*-chlorobenzal)-propionic acid] weighing 40 g. was heated in a distilling flask until the evolution of carbon dioxide had subsided and distilled; the yellow, solidified distillate was dissolved in dilute alkali. The solution was extracted with ether to remove oily material and neutralized with carbon dioxide, when the 7-chloro-1-naphthol separated as almost colorless, fine needles, m. p. 125–130°; yield 8 g. (22%). One crystallization from water raised the m. p. to 130–131°.

2,4-Dinitro-7-chloro-1-naphthol was prepared by the exact procedure described for the chlorine-free substance[20] and obtained as the ammonium salt in 67% yield. The free phenol after several crystallizations from alcohol melted at 169–170°, dec.

Anal. Calcd. for $C_{10}H_5O_5N_2Cl$: C, 44.71; H, 1.88. Found: C, 44.70; H, 1.75.

2-Hydroxy-7-chloro-1,4-naphthoquinone.—By the procedure indicated,[20] 4 g. of the ammonium salt of the dinitro phenol yielded 2.0 g. (59%) of 2-amino-7-chloro-1,4-naphthoquinone-4-imine hydrochloride as deep red crystals. A suspension of 1.5 g. of this salt in 50 cc. of 5% aqueous potassium hydroxide solution was boiled for fifteen minutes and the resulting deep red solution was acidified. The amorphous precipitate of the hydroxyquinone (0.72 g.) was purified in the form of the hydroquinone triacetate, which crystallized from 40 cc. of methanol in the form of colorless needles, m. p. 140–143°. After five recrystallizations the analytical sample melted at 143–144° and gave no depression when mixed with the **7-chloro-1,2,4-triacetoxynaphthalene** described above.

Anal. Calcd. for $C_{16}H_{13}O_6Cl$: C, 57.08; H, 3.89. Found: C, 57.14; H, 3.73.

Other Observations

The **2-hydroxy-3-Δ$^{\omega}$-alkenyl-1,4-naphthoquinones** listed as Nos. 14–19 in Table I were all prepared from 2-hydroxy-3-Δ^{9}-decenyl-1,4-naphthoquinone[21] by the modified Hooker oxidation procedure.[4] We attempted to determine the nature of the water-soluble products obtainable[22] by the action of acetyl sulfuric acid in acetic acid solution on the homologs having 8, 7 and 6 methylene groups in the side-chain. The results were not fully conclusive but suggested that the products have the side-chain structure: $-(CH_2)_nCHOHCH_2SO_3H$. Thus the product from No. 7 yielded an aniline salt, m. p. 152–154°, and a *p*-toluidine salt, m. p. 163–165° (from alcohol–water) of the following analyses.

Anal. **Aniline salt.** Calcd. for $C_{25}H_{31}O_7NS$: C, 61.33; H, 6.38. Found: C, 61.61; H, 6.38. ***p*-Toluidine salt.** Calcd. for $C_{26}H_{33}O_7NS$: C, 62.00; H, 6.61. Found: C, 62.54; H, 6.67.

These substances were completely devoid of antirespiratory activity, as was a sulfonation product obtained in crude form from an oil resulting from alkylation of hydroxynaphthoquinone with the peroxide from oleic acid.

Oxidation of 3-Alkyl-1-tetralones with Selenium Dioxide.—The method of Weygand and Schröder[23] for the synthesis of 2-hydroxy-3-alkyl-1,4-naphthoquinones was briefly investigated with the following results. 3-Ethyl-1-tetralone, b. p. 112–114° at 2 mm., on reaction with selenium dioxide in ethanol afforded 2-hydroxy-3-ethyl-1,4-naphthoquinone, m. p. 137–138°, in 35% yield; the substance was compared with an authentic sample from the Hooker collection.[24]

2-Hydroxy-3-methyl-1,4-phenanthrenequinone was obtained by the same method in comparable yield; it formed bright orange needles from benzene, m. p. 215–217°.

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.61; H, 4.23. Found: C, 75.44; H, 4.25.

Summary

Substances related to actively antimalarial 2-hydroxy-3-alkyl-1,4-naphthoquinones but having methoxyl or chloro substituents in the β-positions of the benzenoid ring were synthesized and found to be devoid of activity.

Converse Memorial Laboratory
Cambridge 38, Massachusetts Received May 12, 1949

(19) Erdmann and Kirchhoff, *Ann.*, **247**, 366 (1888).

(20) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath Co., Boston, Mass., 1941.

(21) Fieser, Leffler and co-workers, This Journal, **70**, 3195 (1948).

(22) Fieser, *ibid.*, **70**, 3232 (1948).

(23) Weygand and Schröder, *Ber.*, **74**, 1844 (1941).

(24) Hooker, This Journal, **58**, 1174 (1936).