sulfate; and also to Dr. S. R. Hoover for the α-amino nitrogen determinations and Dr. C. L. Ogg for the sulfur determinations.

Summary

Preparation of a crystalline derivative of β-lactoglobulin containing two equivalents of firmly bound dodecyl sulfate is described. The solubility, mobility, titration curve and denaturation temperatures of the derivative are compared with the corresponding properties of β-lactoglobulin.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of Naphthoquinones for Studies of the Inhibition of Enzyme Systems[1]

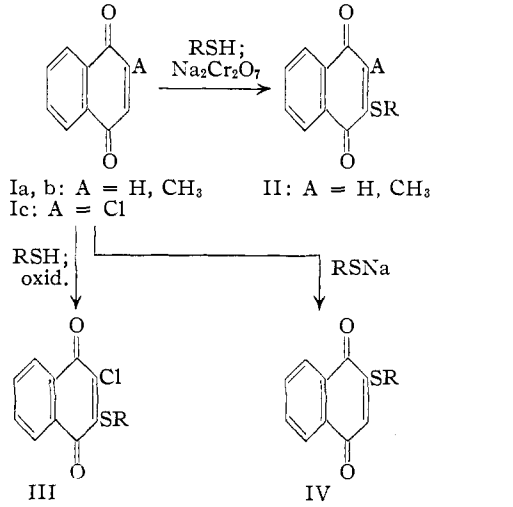
BY LOUIS F. FIESER AND RUSSELL H. BROWN[2]

Bueding, Peters and Waite[3] have reported the interesting finding that 2-methyl-1,4-naphthoquinone has the power to inhibit the anaerobic glycolysis of *Schistosoma mansoni* in *in vitro* tests at low concentrations, and that in experimental schistosomiasis in mice the quinone potentiates the action of subcurative doses of fuadin; the effect apparently vanishes when the dose is increased to the limit of tolerance. In coöperation with the program of pharmacological testing conducted by Dr. E. Bueding and Dr. L. Peters, we synthesized a number of additional naphthoquinones in the search for compounds of value in the chemotherapy of schistosomiasis. The assay data to be reported elsewhere show that, although several of the hydroxyl-free 2,3- and 2,6-disubstituted naphthoquinones described in this paper are considerably more potent than 2-methyl-1,4-naphthoquinone in the inhibition of the glycolytic enzyme concerned; the effect invariably is subject to strong antagonism by plasma proteins and the *in vivo* efficacy is in no instance appreciably greater than that of the simpler quinone.[4] A few of the compounds were tested against *Trichinella spiralis* in rats with completely negative results.[5]

Nachmansohn and Berman[6] observed that 2-methyl-1,4-naphthoquinone effects half-inhibition of choline esterase at dilutions in the order of 5×10^{-4} *M*, and Dr. Nachmansohn has found several of the new quinones here described to be distinctly more potent than methylnaphthoquinone against this enzyme system. The compounds are being studied for antitubercular activity at the Merck Institute for Therapeutic Research, following an observation by Dr. R. Dubos that some of the antimalarial 2-hydroxy-3-alkyl-1,4-naphthoquinones[7] show considerable *in vitro* potency, although the effect is greatly diminished in the presence of plasma proteins. 2-Methyl-6-valeryl-1,4-naphthoquinone appeared particularly promising in the *in vitro* assays but proved to be too toxic for *in vivo* evaluation in infected mice.

Specific naphthoquinones are recognized to influence the synthesis of prothrombin and the respiratory enzymes of malaria parasites, as well as enzymes associated with glycolysis, esterification, and the functioning of the *tubercle bacillus*. The present assay data indicate considerable specificity of action: a naphthoquinone showing high potency against one of the systems is not necessarily active against the others.

One route to compounds possessing enzyme-inhibiting activity was addition of an alkyl or aryl mercaptan to 1,4-naphthoquinone or its 2-methyl (Ia, b) derivative in methanol and oxidation of the resulting substituted hydroquinone by pouring the reaction mixture onto dichromate solution. Quinones of Type II are thus obtained more conveniently and in higher yield than by earlier procedures[8,9]; a similar method has recently been reported for the preparation of 2-thiomethyl-1,4-naphthoquinone, which was found to have high antifungicidal activity.[10] The



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

(3) Bueding, Peters and Waite, *Proc. Soc. Exp. Biol. Med.*, **64**, 111 (1947).

(4) We are indebted to Dr. S. Rajagopalan for the preparation of large samples of fourteen of the quinones for *in vivo* tests.

(5) Oliver-Gonzalez and Bueding, *Proc. Soc. Exp. Biol. Med.*, **69**, 659 (1948).

(6) Nachmansohn and Berman, *J. Biol. Chem.*, **165**, 551 (1946).

(7) Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3151 (1948).

(8) Dimroth, Kraft and Aichinger, *Ann.*, **545**, 124 (1940).

(9) Fieser and Turner, THIS JOURNAL, **69**, 2335 (1947).

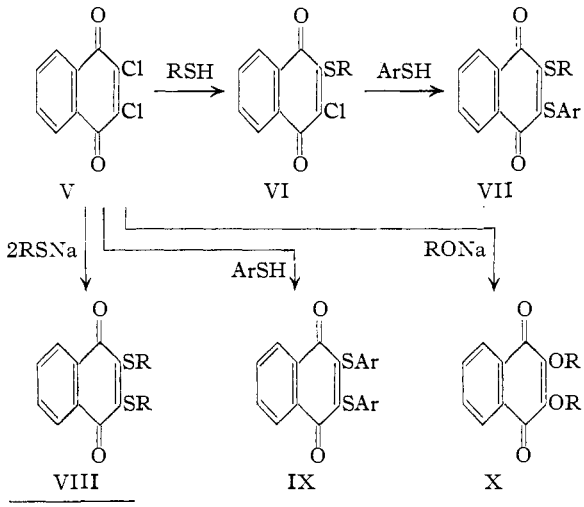
(10) Little, Sproston and Foote, *ibid.*, **71**, 1124 (1949).

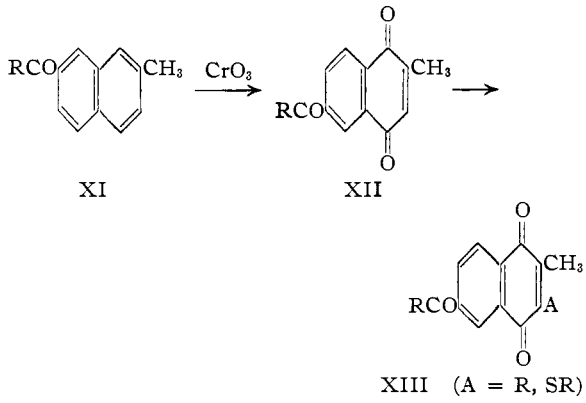
method served well for the preparation of 2-thioalkyl derivatives containing 1–12 carbon atoms in the alkyl group, 2-thioaryl derivatives, 2-methyl-3-thioalkyl and 2-methyl-3-thioaryl derivatives. 2-Chloro-1,4-naphthoquinone (Ic) is known to react with alkali[11] and with aniline[12] not by halogen displacement but by hydroxylation or arylamination at the 3-position, probably through an addition–oxidation mechanism. The reaction with mercaptans follows a similar course and leads to 2-chloro-3-thioalkyl-1,4-naphthoquinones (III). We have found, however, that treatment of the chloroquinone with a sodium mercaptide results in smooth displacement of chlorine to give the 2-thioalkyl derivative (IV). By the same method the chlorine atom of 2-chloro-3-anilino-1,4-naphthoquinone can be replaced by the thioalkyl group; 2-anilino-3-thiomethyl-1,4-naphthoquinone has been prepared previously by a lengthier method.[13] A related observation is that 2-chloro-1,4-naphthoquinone can be converted in good yield into 2-methoxy-1,4-naphthoquinone by reaction with sodium methoxide under anhydrous conditions; the reaction is in contrast to that occurring in aqueous alkali.

Further thio-derivatives were obtained from 2,3-dichloro-1,4-naphthoquinone.[14] When this substance (V) is refluxed in alcoholic solution with an aliphatic mercaptan only one of the chlorine atoms is replaced and the product (VI) is not affected by an excess of reagent. Aryl mercaptans react readily with replacement of both chlorine atoms (IX), and we were unable to isolate a monosubstitution product in experiments utilizing excess dichloronaphthoquinone.[15] Furthermore the chlorine atom of the 2-chloro-3-thioalkyl-1,4-naphthoquinones, although inert to alkyl mercaptans, is easily displaced by reaction with an aryl mercaptan to give VII. As in the examples cited above, the greater reactivity of the sodium salts of the alkyl mercaptans is manifested in the ability of these salts to replace both chlorine atoms of V and afford the 2,3-dithioalkyl derivatives (VIII). 2,3-Dimethoxy-1,4-naphthoquinone (X) was similarly obtained by treatment of dichloronaphthoquinone with sodium methoxide in methanol. The 2,3-diphenoxy derivative has previously been prepared by reaction with potassium phenolate in phenol solution,[16] and the condensation of dichloronaphthoquinone with β-naphthol in pyridine has been shown to proceed with closure of a furan ring.[17] We obtained the isomeric *brazanquinone* by reaction with α-naphthol. An attempt to prepare the thiophene analog led only to 2,3-dithio-β-naphthyl-1,4-naphthoquinone.

Other workers in this Laboratory have attempted without success to introduce the benzyl group into 2-methyl- or 2-hydroxy-1,4-naphthoquinone by peroxide alkylation,[18] but in the present work conditions were found for the satisfactory peroxide benzylation of these compounds and of the 2-chloro derivative by diphenacetyl peroxide. Whereas 2-methyl-3-benzyl-1,4-naphthoquinone was difficultly accessible by previous methods,[19] a 7-g. sample for *in vivo* assay was readily prepared by the present procedure.

A series of 6-acyl-2-methyl-1,4-naphthoquinones (XII) were prepared by oxidation of the 6-acyl-2-methylnaphthalenes (XI) available by Friedel–Crafts acylation of β-methylnaphthalene in nitrobenzene solution according to Haworth.[20] 3-Alkyl and 3-thioalkyl derivatives (XIII) of the 6-acyl quinones were obtained by the methods described above.





(11) Zincke, *Ber.*, **27**, 2758 (1894).

(12) Cleve, *ibid.*, **21**, 93 (1888); Zincke and Kegel, *ibid.*, **21**, 1036 (1888).

(13) Fries and Kerkow, *Ann.*, **427**, 281 (1922).

(14) We are indebted to the Naugatuck Chemical Co. for generous supplies of this chemical and of α-naphthoquinone.

(15) Compare Fries and Ochwat, *Ber.*, **56**, 1291 (1923).

(16) Ullmann and Ettisch, *ibid.*, **54**, 259 (1921).

(17) Eistert, *Chem. Ber.*, **1**, 80 (1947).

(18) Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3197 (1948).

(19) Fieser, Campbell, Fry and Gates, *ibid.*, **61**, 3216 (1939); Fieser and Chang, *ibid.*, **64**, 2043 (1942).

(20) Haworth, Letsky and Mavin, *J. Chem. Soc.*, 1784 (1932); Haworth and Bolam, *ibid.*, 2248 (1932); Kon and Weller, *ibid.*, 792 (1939).

TABLE I

2-THIOALKYL(ARYL)-1,4-NAPHTHOQUINONES

No.	2-Substituent	M. p., °C.	Solv.	Form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	$-SCH_3$[a]	185–186	EtOH–C_6H_6	Needles	$C_{11}H_8O_2S$	64.70	64.67	3.95	4.06
2	$-SC_2H_5$[b]	142–143	MeOH	Needles	$C_{12}H_{10}O_2S$				
3	$-SC_3H_7$-*n*	121–122	MeOH	Leaves	$C_{13}H_{12}O_2S$	67.20	67.04	5.21	5.40
4	$-SC_3H_7$-*i*	103–104	MeOH	Plates	$C_{13}H_{12}O_2S$	67.20	67.31	5.21	5.22
5	$-SC_4H_9$-*n*	102–103	MeOH	Needles	$C_{14}H_{14}O_2S$	68.28	68.39	5.73	5.82
6	$-SCH_2CH(CH_3)_2$	135–136	MeOH	Needles	$C_{14}H_{14}O_2S$	68.28	68.25	5.73	5.55
7	$-SC(CH_3)_3$	150–151	Lig.	Prisms	$C_{14}H_{14}O_2S$	68.28	68.40	5.73	5.72
8	$-SC_5H_{11}$-*n*	112–113	EtOH	Needles	$C_{15}H_{16}O_2S$	69.20	69.30	6.20	6.20
9	$-S(CH_2)_2CH(CH_3)_2$	117–118	MeOH	Leaves	$C_{15}H_{16}O_2S$	69.20	69.34	6.20	6.26
10	$-SC_8H_{17}$-*n*	110–111	MeOH	Leaves	$C_{18}H_{22}O_2S$	71.49	71.63	7.34	7.42
11	$-SC_{12}H_{25}$-*n*	115–116	EtOH–C_6H_6	Leaves	$C_{22}H_{30}O_2S$	73.70	73.51	8.43	8.31
12	$-SC_6H_5$[c]	159–161	Lig.	Prisms					
13	$-SCH_2C_6H_5$	136–137	MeOH	Needles	$C_{17}H_{12}O_2S$	72.83	72.63	4.32	4.47
14	$-SC_6H_4CH_3$-*o*	119–120	MeOH	Plates	$C_{17}H_{12}O_2S$	72.83	73.07	4.32	4.53
15	$-SC_6H_4CH_3$-*m*	142–143	Lig.	Plates	$C_{17}H_{12}O_2S$	72.83	72.81	4.32	4.60
16	$-SC_6H_4CH_3$-*p*	121–122	MeOH	Needles	$C_{17}H_{12}O_2S$	72.83	73.03	4.32	4.41
17	-S-β-Naphthyl	180–181	EtOH	Needles	$C_{20}H_{12}O_2S$	75.91	75.74	3.82	3.69

[a] Little, Sproston and Foote, ref. 10. [b] Ricsei, *Ber.*, **60**, 1836 (1927). [c] Dimroth, Kraft and Aichinger, ref. 8.

TABLE II

2-METHYL-3-THIOALKYL(ARYL)-1,4-NAPHTHOQUINONES

No.	3-Substituent	M. p., °C.	Solvent	Form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
18	$-SCH_3$	91–93	MeOH	Needles	$C_{12}H_{10}O_2S$	66.01	66.03	4.62	4.90
19	$-SC_2H_5$	77–78	MeOH	Needles	$C_{13}H_{12}O_2S$	67.02	67.10	5.21	5.28
20	$-SC_3H_7$-*n*	41–43	MeOH	Prisms	$C_{14}H_{14}O_2S$	68.28	68.43	5.73	5.93
21	$-SC_3H_7$-*i*	66–68	MeOH	Leaves	$C_{14}H_{14}O_2S$	68.28	68.42	5.73	5.70
22	$-SC_4H_9$-*n*	44–46	MeOH	Plates	$C_{15}H_{16}O_2S$	69.20	69.19	6.20	6.25
23	$-SC(CH_3)_3$	125–126	MeOH	Blades	$C_{15}H_{16}O_2S$	69.20	69.42	6.20	6.09
24	$-SC_8H_{17}$-*n*	67–69	MeOH	Leaves	$C_{19}H_{24}O_2S$	72.12	72.12	7.64	7.59
25	$-SC_{12}H_{25}$-*n*	79–80	EtOH	Blades	$C_{23}H_{32}O_2S$	74.15	74.19	8.66	8.63
26	$-SCH_2C_6H_5$[a]	70–71	MeOH	Prisms	$C_{18}H_{14}O_2S$	73.45	73.70	4.79	4.72
27	$-SC_6H_5$	109–110	MeOH	Orange blades	$C_{17}H_{12}O_2S$	72.83	72.78	4.32	4.29
28	$-SC_6H_4CH_3$-*o*	121–122	EtOH	Orange-red plates	$C_{18}H_{14}O_2S$	73.45	73.59	4.79	4.74
29	$-SC_6H_4CH_3$-*m*	103–104	EtOH	Red prisms	$C_{18}H_{14}O_2S$	73.45	73.43	4.79	4.91
30	$-SC_6H_4Cl$-*p*	116–117	EtOH	Red-orange plates	$C_{17}H_{11}O_2SCl$	64.86	65.07	3.52	3.62

[a] Fieser and Turner, ref. 9.

Experimental[21]

2-Thioalkyl-(aryl)-1,4-naphthoquinones (Table I). Example: R = CH_3.[10]—A suspension of 15.8 g. (0.1 mole) of α-naphthoquinone in 140 cc. of methanol was treated at 0° with a cold solution of 5.06 g. (0.125 mole) of methyl mercaptan in 20 cc. of methanol and the mixture allowed to stand at room temperature for two hours, when considerable solid reaction product had separated. The mixture was then poured into a vigorously stirred mixture of 20 g. of sodium dichromate dihydrate, 10 cc. of concentrated sulfuric acid, ice and water. The crude product collected by filtration weighed 17.7 g., m. p. 105–145°. Crystallization from 200 cc. of 95% ethanol and 100 cc. of benzene gave 10.22 g. (51%) of 2-thiomethyl-1,4-naphthoquinone, m. p. 180–184°; the fully purified quinone melted at 185–186° (No. 1).

Other Examples.—A similar preparation conducted with 7.91 g. (0.05 mole) of α-naphthoquinone and 3.10 g. (0.05 mole) of ethyl mercaptan yielded 8.72 g. of crude material, m. p. 97–115°; crystallization from 100 cc. of methanol and 75 cc. of 95% ethanol gave 4.45 g. (41%) of 2-thioethyl-1,4-naphthoquinone (no. 2), m. p. 139–142°. The yield was substantially the same when the amount of ethyl mercaptan was increased to 4.65 g. (0.075 mole): 4.87 g. (45%), m. p. 138–142°. 2-Thioisoamyl-1,4-naphthoquinone was prepared from a mixture of 3.16 g. (0.02 mole) of α-naphthoquinone and 2.08 g. (0.02 mole) of isoamyl mercaptan in 50 cc. of methanol. After standing for eighteen hours at room temperature long colorless needles of the substituted hydroquinone had separated. Oxidation as above and crystallization from 40 cc. of methanol gave 2.15 g. (41%) of large yellow leaves of nearly pure quinone (no. 9).

2-Thioisoamyl-1,4-naphthoquinone was also obtained by adding a solution of 1.04 g. of isoamyl mercaptan and 0.4 g. of sodium hydroxide in 10 cc. of methanol and 1 cc. of water to a solution of 1.93 g. of 2-chloro-1,4-naphthoquinone in 25 cc. of acetone at room temperature. After one hour the solution was diluted and the precipitated material crystallized from methanol (charcoal). A second crystallization from 40 cc. of methanol gave 0.9 g. (35%) of pure no. 9, identical with that of the above synthesis.

2-Thioalkyl-(aryl)-3-methyl-1,4-naphthoquinone (Table II). Example: R = $CH_2C_6H_5$.—A mixture of 3.44 g. (0.02 mole) of 2-methyl-1,4-naphthoquinone and 2.48 g. (0.02 mole) of benzyl mercaptan in 40 cc. of methanol was allowed to stand at room temperature for twenty-four hours and poured with stirring into a mixture of 5 g. of sodium dichromate dihydrate, 5 cc. of 96% sulfuric acid, 50 cc. of water and 150 g. of ice. The crude

(21) All melting points are corrected.

TABLE III

2-HALO-(METHYL)-3-THIOALKYL(ALKOXYL)-1,4-NAPHTHOQUINONES

No.	Substituents 2-	Substituents 3-	M. p., °C.	Solv.	Form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
31	Cl	$-SC_2H_5$	115–116	EtOH	Leaves	$C_{12}H_9O_2SCl$	57.03	56.88	3.59	3.72
32	Cl	$-SC_3H_7$-*n*	50–51	MeOH	Small plates	$C_{13}H_{11}O_2SCl$	58.54	58.64	4.15	4.01
33	Cl	$-SC_4H_9$-*n*	67–68	MeOH	Leaves	$C_{14}H_{13}O_2SCl$	59.88	59.79	4.67	4.78
34	Cl	$-SC_5H_{11}$-*n*	51–52	MeOH	Long leaves	$C_{15}H_{15}O_2SCl$	61.11	61.16	5.13	5.24
35	Cl	$-SC_8H_{17}$-*n*	73–74	MeOH	Small plates	$C_{18}H_{21}O_2SCl$	64.16	64.19	6.28	6.22
36	Cl	$-SC_{12}H_{25}$-*n*	83–84	EtOH	Small plates	$C_{22}H_{29}O_2SCl$	67.23	67.36	7.44	7.47
37	Br	$-SC_4H_9$-*n*	85–86	MeOH	Small plates	$C_{14}H_{13}O_2SCl$	51.70	51.96	4.02	4.00
38	Br	$-OCH_3$	163–164	MeOH	Long needles	$C_{11}H_7O_3Br$	49.46	49.38	2.64	2.53
39	Br	$-OC_2H_5$	116–117	MeOH	Needles	$C_{12}H_9O_3Br$	51.26	51.44	3.23	3.11
40[a]	Cl	$-OC_2H_5$	97–98	MeOH	Feathery needles	$C_{12}H_9O_3Cl$	60.90	61.03	3.83	4.02
41	Br	$-OC_4H_9$-*n*	48–49	EtOH	Fine blades	$C_{14}H_{13}O_3Cl$	54.39	54.32	4.24	4.06
42[b]	CH_3	$-OCH_3$	93–94	MeOH	Long needles					
43	CH_3	$-OC_2H_5$	73–74	MeOH	Needles	$C_{13}H_{12}O_3$	72.22	72.23	5.60	5.78
44	CH_3	$-OCH_2CH{=}CH_2$	62–63	Lig.	Fine blades	$C_{14}H_{12}O_3$	73.67	73.46	5.30	5.63
45	CH_3	$-OC_3H_7$-*n*			Liquid	$C_{14}H_{14}O_3$	73.03	72.74	6.13	6.39
46	CH_3	$-OC_4H_9$-*n*			Liquid	$C_{15}H_{16}O_3$	73.75	73.59	6.60	6.63
47	CH_3	$-CH_2C_6H_5$	53–54	MeOH	Large blades	$C_{18}H_{14}O_3$	77.67	77.43	5.07	5.04

[a] Fieser, THIS JOURNAL, **48**, 2922 (1926). [b] Madinaveitia, *Ann. Soc. Expan. Quim. Fis.*, **31**, 750 (1933).

product (5.33 g.) on crystallization from 40 cc. of methanol yielded 4.11 g. (70%) of 2-methyl-3-thiobenzyl-1,4-naphthoquinone (no. 26), m. p. 68–70°. One more crystallization gave 3.74 g. of product m. p. 71–72°. The compound was obtained previously (Table II, Note *a*) in only 28% yield.

The same procedure was applied to the preparation of the other compounds listed, usually with substantially the same results: 70% yield of once crystallized product. The reaction of 2-methyl-1,4-naphthoquinone (17.2 g.) with *t*-butyl mercaptan (9 g.) in methanol (200 cc.) proceeded less smoothly. After standing for eight days the mixture was refluxed for twenty-four hours and on cooling deposited 3 g. of 2-methyl-3-thio-*t*-butyl-1,4-naphthoquinone.

Derivatives. (a) **Ethyl-(2-methyl-1,4-naphthoquinonyl-3)-sulfoxide.**—2-Methyl-3-thioethyl-1,4-naphthoquinone (2 g.) was covered with 5 cc. of fuming nitric acid and the mixture kept at room temperature for ten minutes and poured into 25 cc. of cold water. Crystallization of the precipitated material from 20 cc. of methanol yielded 1.55 g. (72%) of well-formed red-orange needles, m. p. 140–142°. A recrystallized sample melted at 143–144°.

Anal. Calcd. for $C_{13}H_{12}O_3S$: S, 62.87; H, 4.87. Found: C, 62.99; H, 5.12.

(b) ***n*-Dodecyl-(2-methyl-1,4-naphthoquinonyl-3)-sulfoxide** was obtained by the same method in 70% yield. The compound formed small tan balls from ethanol, m. p. 105–106°.

Anal. Calcd. for $C_{23}H_{32}O_3S$: C, 71.10; H, 8.30. Found: C, 71.46; H, 7.99.

2-Methyl-3-thioethyl-1,4-naphthohydroquinone dibenzoate was prepared in 78% yield (m. p. 138–140°) by the action of benzoyl chloride on the hydroquinone in pyridine. The pure material formed tiny white needles from ethanol–acetone, m. p. 143–145°.

Anal. Calcd. for $C_{27}H_{22}O_4S$: C, 73.26; H, 5.01. Found: C, 73.01; H, 5.28.

2-Halo-3-thioalkyl-1,4-naphthoquinones (Table III). (a) **From 2,3-Dichloro-1,4-naphthoquinone.**—Treatment of the dichloroquinone in alcoholic suspension with as much as two moles of an aliphatic mercaptan results in replacement of only one of the chlorine atoms. Thus 2-chloro-3-thio-*n*-octyl-1,4-naphthoquinone (No. 35) was prepared by heating a mixture of 6.81 g. (0.03 mole) of 2,3-dichloro-1,4-naphthoquinone and 8.76 g. (0.06 mole) of *n*-octyl mercaptan in 100 cc. of 95% ethanol under reflux for two hours. The resulting clear solution when cooled deposited a solid product that when recrystallized from 100 cc. of 95% ethanol afforded 6.30 g. (62%) of the substituted quinone, m. p. 61–65°. Further crystallizations from ligroin and from methanol gave material melting at 73–74°.

(b) **From 2-Chloro-1,4-naphthoquinone.**—2-Chloro-3-thio-*n*-dodecyl-1,4-naphthoquinone was prepared from a suspension of 1.93 g. (0.01 mole) of the monochloroquinone in 50 cc. of methanol, treated with a solution of 2.02 g. (0.01 mole) of *n*-dodecyl mercaptan in 25 cc. of 95% ethanol. After six hours at room temperature a solid reaction product that had separated was collected and recrystallized from 20 cc. of ethanol and afforded 1.0 g. (51%) of the 2-chloro-3-thio-*n*-dodecyl compound (no. 36), m. p. 83–84°.

(c) **By Halogenation.**—A mixture of 0.7 g. of 2-*n*-thiobutyl-1,4-naphthoquinone, 1 g. of fused sodium acetate, and 5 cc. of acetic acid was treated with 15 cc. of a solution of 1 cc. of bromine in 100 cc. of acetic acid. After standing for three hours at room temperature, the mixture was poured into 50 cc. of cold water and the precipitated solid collected, washed and dried: 0.83 g. (90%), m. p. 72–76°. Crystallization from 20 cc. of methanol gave 0.52 g. of 2-bromo-3-thio-*n*-butyl-1,4-naphthoquinone (No. 37), m. p. 82–84°.

2-Halo-3-alkoxy-1,4-naphthoquinones (Table III). (a) **By Halogenation.**—For the preparation of 2-bromo-3-methoxy-1,4-naphthoquinone (no. 38), a mixture of 0.51 g. of 2-methoxy-1,4-naphthoquinone and 1 g. of fused sodium acetate was treated with 15 cc. of a solution of 3.12 g. of bromine in 100 cc. of acetic acid at room temperature. There resulted a clear solution from which a yellow solid separated. Precipitation with 50 cc. of water after eight hours gave 0.68 g. (94%) of crude product, m. p. about 150°. This was crystallized to constant m. p. (163–164°) from methanol. The bromoethoxy and bromobutoxy derivatives (nos. 39–41) were prepared by the same method in comparable high yield. 2-Chloro-3-ethoxy-1,4-naphthoquinone (no. 40, known) was prepared by chlorination of 2.02 g. of 2-ethoxy-1,4-naphthoquinone in 25 cc. of acetic acid in the presence of 3.6 g. of fused sodium acetate with 15 cc. of an acetic acid solution containing 0.48 g. of chlorine for sixteen hours at room temperature. The precipitated product (1.96 g., 83%) melted at 80–85° and afforded pure material, m. p. 97–98°, on one crystallization.

(b) **From 2,3-Dichloro-1,4-naphthoquinone.**—A mixture of 2.27 g. of the dichloroquinone and 0.9 g. of sodium acetate in 60 cc. of absolute ethanol was refluxed for two hours, water was added, and the solid product was crystallized from methanol (charcoal). The resulting 2-chloro-

TABLE IV

2,3-DITHIOALKYL(ARYL)-1,4-NAPHTHOQUINONES AND RELATED COMPOUNDS

No.	Substituents 2-	3-	M. p., °C.	Solvent	Form	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
48	$-SCH_3$	$-SCH_3$	115–116	MeOH	Fine orange-red needles	$C_{12}H_{10}O_2S_2$	57.58	57.22	4.03	4.15
49	$-SC_2H_5$	$-SC_2H_5$	83–84	MeOH	Purple blades	$C_{14}H_{14}O_2S_2$	60.42	60.23	5.07	4.84
50	$-SC_{12}H_{25}$-*n*	$-SC_{12}H_{25}$-*n*	71–73	EtOH	Purple micro-needles	$C_{34}H_{54}O_2S_2$	73.06	73.07	9.74	9.76
51	$-SC_6H_5$	$-SC_6H_5$	151–152	EtOH	Orange needles	$C_{22}H_{14}O_2S_2$	70.55	70.77	3.77	3.82
52	$-SC_6H_4CH_3$-*p*	$-SC_6H_4CH_3$-*p*	173–174	EtOH	Crimson needles	$C_{24}H_{18}O_2S_2$	71.63	71.53	4.51	4.71
53	-S-β-Naphthyl	-S-β-Naphthyl	196–197	EtOH–C_6H_6	Orange needles	$C_{30}H_{18}O_2S_2$	75.93	76.02	3.82	3.98
54	$-SC_2H_5$	$-SC_6H_4CH_3$-*p*	118–119	EtOH	Orange needles	$C_{19}H_{16}O_2S_2$	67.03	66.92	4.74	4.90
55	$-SC_4H_9$-*n*	$-SC_6H_4CH_3$-*p*	105–106	EtOH	Orange needles	$C_{21}H_{20}O_2S_2$	68.45	68.60	5.47	5.75
56	$-SCH_2C_6H_5$	$-SC_6H_4CH_3$-*p*	103–104	EtOH	Red needles	$C_{24}H_{18}O_2S_2$	71.63	71.76	4.51	4.69
57	$-C_4H_9$-*n*	$-SC_6H_5$	112–113	Lig.	Micro cryst.	$C_{20}H_{18}O_2S$	74.50	74.73	5.63	5.72
58	$-NHC_6H_5$	$-SC_5H_{11}$-*n*	114–116	EtOH	Purple needles	$C_{21}H_{21}O_2SN$	71.79	72.05	6.02	5.95
59	$-NHC_6H_5$	$-SC_6H_5$	197–199	EtOH	Purple leaves	$C_{22}H_{15}O_2SN$	73.93	74.07	4.23	4.18
60	-Cl	$-C_2H_5$	111–112	MeOH	Blades	$C_{12}H_9O_2Cl$	65.31	65.54	4.11	4.29
61	-Cl	$-C_{11}H_{23}$-*n*	82–83	Pt. ether	Fine needles	$C_{21}H_{27}O_2Cl$	72.71	72.90	7.85	8.12
62	-Cl	$-CH_2C_6H_5$	130–131	MeOH	Plates	$C_{17}H_{11}O_2Cl$	72.21	72.25	3.92	3.83

3-ethoxy-1,4-naphthoquinone (1.38 g., 58%) melted at 96–98°.

2-Methyl-3-alkoxy-1,4-naphthoquinones (Table III).—For preparation of the 3-methoxy compound (no. 42), 3 g. of the powdered silver salt of phthiocol was covered with 10 cc. of methyl iodide and allowed to stand at room temperature with occasional agitation for one hour. The product was extracted with 100 cc. of ether, the solution was washed three times with 3% ammonia solution, dried and evaporated. Crystallization of the residue from 15 cc. of methanol gave 0.93 g. (45%) of product, m. p. 93–94°.

The ethoxy compound was prepared in the same way in 47% yield (m. p. 72–74°); the silver salt failed to react with ethyl chloride. The alloxy, *n*-propoxy, *n*-butoxy, and benzyloxy derivatives (nos. 44–47) were obtained with use of allyl bromide, *n*-propyl iodide, *n*-butyl iodide and benzyl chloride in yields of 37, 53, 52 and 10%, respectively; the reaction of the silver salt with benzyl chloride was conducted for one-half hour on the steam-bath.

2,3-Dithioalkyl-1,4-naphthoquinones (Table IV).—The dithiomethyl derivative (no. 48) was prepared by treating a suspension of 5.7 g. of 2,3-dichloro-1,4-naphthoquinone in 20 cc. of methanol with a solution prepared from 2 g. of sodium hydroxide, 20 cc. of methanol, and 12 cc. of a solution of 25.3 g. of methyl mercaptan in 100 cc. of methanol. The mixture was refluxed for one-half hour and the resulting clear solution when cooled to 0° deposited 1.55 g. of yellow crystalline product, m. p. 90–100°. The solid was ground to a powder, shaken with 25 cc. of water, dried (1.33 g.) and crystallized from 95% ethanol (charcoal); the yield of long orange-red needles, m. p. 114–117°, was 0.74 g. (12%). 2,3-Dithioethyl-1,4-naphthoquinone (no. 49) was obtained similarly in 19% yield; the substance forms as an orange solution in ethanol, but the crystals that separate are extraordinary for their deep, almost black, purple color.

2,3-Dithioaryl-1,4-naphthoquinones (Table IV).—In a typical case a mixture of 2.27 g. of 2,3-dichloro-1,4-naphthoquinone and 2.48 g. of *p*-thiocresol in 100 cc. of 95% ethanol was refluxed for one hour and the solution cooled to 0°, when 3.68 g. (89%) of red crystals, m. p. 170–172°, separated. Two crystallizations from ethanol (80 cc./g.) gave pure 2,3-di-*p*-thiocresyl-1,4-naphthoquinone (no. 52), m. p. 173–174°. 2,3-Di-β-thionaphthyl-1,4-naphthoquinone was obtained in the same way in 95% yield (m. p. 192–195°).

2,3-Dithiophenyl-5-nitro-1,4-naphthoquinone was prepared by refluxing for one-half hour a mixture of 0.68 g. of 2,3-dichloro-5-nitro-1,4-naphthoquinone[22] in 25 cc. of 95% ethanol with 1.10 g. of thiophenol in 25 cc. of ethanol. A crystalline orange product separated (1.09 g., quantitative; m. p. 130–132°) and when crystallized from 75 cc. of ethanol formed red needles, m. p. 134–135°. A polymorphic form melts at 152°.

Anal. Calcd. for $C_{22}H_{13}O_4S_2N$: C, 63.00; H, 3.13. Found: C, 63.01; H, 3.28.

2-Thioalkyl-3-thioaryl-1,4-naphthoquinones (Table IV).—A solution of 0.25 g. of 2-thioethyl-3-chloro-1,4-naphthoquinone in 10 cc. of 95% ethanol was treated with 0.124 g. of *p*-thiocresol in 5 cc. of 95% ethanol and the mixture was heated gently for fifteen minutes and cooled to 80°, when 0.30 g. (89%) of long needles separated, m. p. 115–117° (no. 54). The homolog no. 55 was prepared similarly in 88% yield (m. p. 105–106°). The less soluble derivative no. 56 was prepared from 1.57 g. of the chloro compound in 20 cc. of 95% ethanol, treated with 0.162 g. of *p*-thiocresol in 25 cc. of 95% ethanol and 15 cc. of benzene; the yield of product, m. p. 98–100°, was 1.60 g. (80%).

2-Anilino-3-thio-*n*-amyl-1,4-naphthoquinone (no. 58) was prepared from a solution of 1.35 g. of 2-anilino-3-chloro-1,4-naphthoquinone[13] in 50 cc. of 95% ethanol mixed with a solution of 0.86 g. of *n*-amyl mercaptan and 0.2 g. of sodium hydroxide in methanol. The mixture was refluxed for two hours, diluted with 50 cc. of water, and the product that separated was crystallized from 20 cc. of methanol to give 1.44 g. (82%) of long, deep-red needles, m. p. 113–115°.

2,3-Disubstituted Naphthoquinones by Peroxide Alkylation

Diphenacetyl Peroxide.—Phenacetyl chloride (5.2 g. 0.0336 mole) was cooled well below 0° in Dry Ice–acetone and treated with 7.5 cc. of 30% hydrogen peroxide, cooled to 0° and added in one portion. The resulting semi-solid mass was treated with a solution of 7 g. of sodium hydroxide in 50 cc. of water that had been cooled almost to its freezing point and the mixture was shaken for ten minutes with intermittent cooling in Dry Ice–acetone, when the peroxide separated as a granular white solid. This was extracted with 100 cc. of ice-cold ether and the ether layer washed with cold saturated sodium chloride solution and used at once.

2-Methyl-3-benzyl-1,4-naphthoquinone.[19]—The above ethereal solution of peroxide was added to a solution of

(22) Fries, Pense and Pectus, *Ber.*, **61**, 1395 (1928).

TABLE V

6-ACYL-2-METHYL-1,4-NAPHTHOQUINONES

No.	Substituents: Position 6	Position 3	M. p., °C.	Solvent	Form	Formula	Analyses, %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
63	$-COCH_3$		126–127	MeOH	Long prisms	$C_{13}H_{10}O_3$	72.90	72.98	4.71	4.82
64	$-COC_2H_5$		153–154	EtOH	Tiny prisms	$C_{14}H_{12}O_3$	73.60	73.45	5.30	5.26
	Hydroquinone		*ca.* 190	Aq. MeOH	Yel. needles	$C_{14}H_{14}O_3$	73.01	73.02	6.13	6.12
	Hydroq. dibenzoate		184–185	EtOH	White needles	$C_{28}H_{22}O_5$	76.40	76.52	4.75	5.09
65	$-COC_2H_5$	$-SC_6H_4CH_3$-*m*	107–108	MeOH	Orange leaves	$C_{21}H_{18}O_3S$	72.00	72.03	5.18	5.27
66	$-COC_3H_7$-*n*		153–154	EtOH	Tiny prisms	$C_{15}H_{14}O_3$	74.36	74.36	5.82	5.79
67	$-COC_3H_7$-*n*	$-SC_2H_5$	64–65	MeOH	Needles	$C_{17}H_{18}O_3S$	67.52	67.60	6.00	5.92
68	$-COC_3H_7$-*n*	$-C_{11}H_{23}$-*n*	73–74	MeOH	Fine needles	$C_{26}H_{36}O_3$	78.74	78.49	9.15	9.29
69	$-COC_4H_9$-*n*		86–87	MeOH	Prisms	$C_{16}H_{16}O_3$	74.98	74.88	6.29	6.20
70	$-COC_5H_{11}$-*n*		85–86	MeOH	Needles	$C_{17}H_{18}O_3$	75.53	75.41	6.71	6.93
71	$-CO(CH_2)_3$–Cyclohexyl		95–96	MeOH	Leaves	$C_{21}H_{24}O_3$	77.77	77.92	7.46	7.40
72	$-CO(CH_2)_2COOH$		198–199	EtOH	Needles	$C_{15}H_{12}O_5$	66.17	66.24	4.44	4.55
73	$-CO(CH_2)_2COOCH_3$		122–123	MeOH	Needles	$C_{16}H_{14}O_5$	67.11	66.90	4.93	4.77
74	$-CO(CH_2)_2COOCH_3$	$-SC_4H_9$-*n*	94–95	MeOH	Needles	$C_{20}H_{22}O_5S$	64.15	64.33	5.92	6.17

0.0167 mole of 2-methyl-1,4-naphthoquinone in 50 cc. of acetic acid and the mixture heated very gently on the steam-bath for one-half-hour and then heated more vigorously for an equal period. The resulting acetic acid solution was diluted and the precipitated product collected and dissolved in 100 cc. of ether. The solution was extracted repeatedly with 2% alkali, shaken for ten minutes with hydrosulfite solution, and starting material was removed by extraction of the ethereal hydroquinone solution with dilute alkali containing hydrosulfite. The solution was washed with brine, shaken for five minutes with 5 g. each of silver oxide and magnesium sulfate, filtered and evaporated. Crystallization of the residue from 20 cc. of methanol gave 0.7 g. (16% based on the acid chloride) of the substituted quinone, m. p. 106–108°, identical with an authentic sample.

Other Examples.—**2-Hydroxy-3-benzyl-1,4-naphthoquinone**[23] was prepared by the same method and the unchanged 2-hydroxy-1,4-naphthoquinone removed by extraction of an ethereal solution of the product with bicarbonate solution; the yield of material m. p. 175–176° was 31%, based on the acid chloride. **2-Chloro-3-methyl-1,4-naphthoquinone**[24] was obtained in 50% yield (m. p. 152–153°) by alkylation of the chloroquinone with diacetyl peroxide. The ethyl and *n*-undecyl and benzyl derivatives (Nos. 60–62) were prepared similarly in yields of 45, 37 and 36%, respectively.

Ethers from Chloroquinones

2,3-Dimethoxy-1,4-naphthoquinone[25] was prepared by refluxing a suspension of 2.27 g. of the dichloro compound and 1.08 g. of sodium methoxide in 50 cc. of absolute methanol for one-half hour. The bright yellow product that separated on cooling (1.8 g., 83%; m. p. 100–105°) on crystallization from methanol gave material m. p. 114–115°. **2-Methoxy-1,4-naphthoquinone** was obtained similarly from the 2-chloroquinone in 37% yield (recrystallized, m. p. 182–183°).

3,4-Benzo-8,11-β-brazanquinone.—A mixture of 9 g. of 2,3-dichloro-1,4-naphthoquinone and 6 g. of α-naphthol in 50 cc. of pyridine was refluxed for five hours and the sparingly soluble product was precipitated with alcohol and crystallized from benzene–alcohol; yield 6.8 g. (58%). The pure substance formed tiny orange needles, m. p. 229–230°.

Anal. Calcd. for $C_{20}H_{10}O_3$: C, 80.54; H, 3.35. Found: C, 80.28; H, 3.30.

6-Acyl-2-methyl-1,4-naphthoquinones (Table V)

The 6-acyl-2-methylnaphthalenes employed as starting materials were prepared by Friedel–Crafts acylation in nitrobenzene solution by the method of Haworth.[20] 6-Acyl derivatives purified to a condition suitable for oxidation have the following melting points: *n*-butyryl, 43–44°; *n*-valeryl, 53–55°; *n*-capryl, 66–68°; γ-cyclohexylbutyryl, 75–76°. Oxidation to the naphthoquinones listed in Table V was conducted with chromic acid in approximately 90% acetic acid solution[26]; the yields varied to 10–40%, depending upon the purity of the starting material. The 3-alkyl derivative No. 68 was prepared by peroxide alkylation; the 3-thioalkyl derivatives were prepared by mercaptan addition and oxidation.

Summary

The preparation of over seventy new naphthoquinones was undertaken in coöperation with investigators who have observed that 2-methyl-1,4-naphthoquinone possesses some power to inhibit the glycolytic enzyme of the schistosome and to inhibit choline esterase. A number of 3-thioalkyl and 6-acyl derivatives of the parent quinone are described, as well as various 2,3-disubstituted-1,4-naphthoquinones and related compounds. The results of assays will be reported elsewhere.

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(24) Fries and Lohmann, *Ber.*, **54**, 2920 (1921).

(25) Fieser, THIS JOURNAL, **50**, 461 (1928).

(26) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath Co., Boston, Mass., 1941, p. 233.