### [CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# Naphthoquinone Antimalarials. XXVI.<sup>1</sup> Thioether Naphthoquinones<sup>2</sup>

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Previous communications<sup>6</sup> on the use of 2alkyl-3-hydroxy-1,4-naphthoquinones as antimalarial drugs have shown that quinones with a hydrocarbon side chain suffer rapid metabolic degradation to less active compounds. When the side chain contains a hydroxyl group, quinones of reasonable potency and stability can be obtained. For example, lapinone  $(I)^{6a}$  exhibits



potentialities as a chemotherapeutic agent against *Plasmodium vivax*.

It seemed of interest to synthesize other naphthoquinones with a hetero atom in the side chain. This paper reports the results of efforts to synthesize hydroxynaphthoquinones that contain the thioether structure in the side chain; a summary of the biological activity as determined by *in vitro* assay is included.

Thioether sulfur was introduced into the side chain by two general methods: (1) condensation of a haloalkyl hydroxynaphthoquinone with a mercaptan or thiophenol in the presence of base; (2) addition of mercaptan or thiophenol to a 2alkenyl-3-hydroxy-1,4-naphthoquinone. An alternate route to thioether quinones might consist in the alkylation of lawsone with peroxides prepared from aryl-(or alkyl)-mercapto acids. However, attempts to prepare a peroxide from pchlorophenylmercaptoacetic acid<sup>7</sup> failed.

2- $\omega$ -Haloalkyl-3-hydroxy-1,4-naphthoquinones II (n = 2, 3, 4, 7, 8 and 10) (X = Cl or Br) were prepared by the alkylation<sup>8,9</sup> of lawsone (2-hydroxy-1,4-naphthoquinone) with a peroxide prepared from an  $\omega$ -halo acid. The chloroquinone II (n = 2, X = Cl) was obtained in low yield

(1) For the previous paper in this series see Paulshock and Moser. THIS JOURNAL, **72**, 5073 (1950).

(2) This paper represents a part of the dissertations submitted by the authors in partial fulfillment of the requirements for the degree Doctor of Philosophy to the Faculty of Arts and Sciences, Harvard University, May, 1948.

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(6) Fieser, Leffler, and co-workers, This Journal,  $\textbf{70},\,3153$  (1948) and succeeding papers.

(6a) Fawaz and Fieser, *ibid.*, **72**, 996 (1950).

(7) We are indebted to the Cooper Union, New York City, for a supply of this compound.

(8) Fieser and Oxford, THIS JOURNAL, 64, 2060 (1942).

(9) Fieser, Leffler, and co-workers, ibid., 70, 3206 (1948).



by this method, but it could be purified only with considerable loss. Attempts to prepare this chloroquinone by the addition of hydrochloric acid to 2-vinyl-3-hydroxy-1,4-naphthoquinone (III)<sup>10</sup> were fruitless. The addition of hydro-



bromic acid to IV in the presence of peroxide resulted in the formation of a dibromo napthoquinone that is probably V.

The preparation of thioethers from the haloquinones II (n = 0,<sup>11</sup> 4, 7, 8 and 10) and VI (X = Cl)<sup>12</sup> was smoothly carried out by con-



densation of the quinone in methanol solution with a mercaptan or thiophenol in the presence of base. The haloquinone II (n = 3, X = Cl)reacted very rapidly with base to form the chromane quinone VII.<sup>13</sup>

Previous work in this Laboratory<sup>14</sup> had indicated that it was not possible to prepare II (n = 1, X = Cl) by the alkylation of lawsone with the peroxide prepared from chloroacetic acid. Thioethers II (n = 1, X = SR) were prepared by the

- (10) Hooker, ibid., 58, 1179 (1936).
- (11) Diel and Merz, Ber., 11, 1066 (1878).
- (12) Fieser, This Journal, 48, 3201 (1936).

(13) Cf. the cyclization of chlorohydrolapachol to  $\alpha$ -lapachone, Hooker, J. Chem. Soc., **61**, 611 (1892); **69**, 1355 (1896).

(14) Mao-i Wu, Ph.D. Dissertation, Radcliffe College, 1942.



condensation of lawsone with formaldehyde and a thiophenol or mercaptan. The product from this reaction is assigned the structure II (n = 1, X = SR) rather than the isomeric structure VIII



on the following grounds: (1) potentiometric titration indicates that the quinone is monobasic; (2) the condensation with an aliphatic mercaptan proceeds under the same conditions to give apparently the same type of product as with a thiophenol; (3) reductive acetvlation gave a compound whose composition more closely corresponds to a tri- rather than a tetraacetate. This condensation is analogous to the Mannich reaction<sup>15</sup> that has been carried out with lawsone, aldehydes and amines.<sup>16</sup> From the results of a few preliminary experiments it appears that phthiocol (2-methyl-3-hydroxy-1,4naphthoquinone) cannot replace lawsone and the benzaldehyde cannot be used in place of formaldehyde in the condensation with thiols.

The addition of mercaptans or thiophenols to olefins has often been a useful method for the preparation of thioethers.<sup>17</sup> This method has proved to be satisfactory with some alkenyl hydroxynaphthoquinones. Addition of mercaptans and thiophenols to IV takes place under specific reaction conditions. Addition does not



take place in methanol or ethanol solution even in the presence of benzoyl peroxide. Addition products were obtained in fair yield by reaction in warm acetic acid solution catalyzed by a small amount of benzoyl peroxide. The structure II follows from the observation that the thioethers are isomeric with, but different from, the thio-

(16) (a) Leffler and Hathaway, THIS JOURNAL, 70, 3222 (1948);
(b) Dalgleish, *ibid.*, 71, 1697 (1949).

(17) Connor, in Gilman's "Organic Chemistry," Vol. I, p. 835, 1943.

ethers VI (X = SR). A dihydrotriacetate could be readily obtained from IX.



The addition of mercaptans to lapachol (X) proved to be interesting. A priori the structure of the product might correspond either to XI or XII. From the results of previous investigations<sup>18</sup> the prediction could be made that addition should take place in a manner contrary to Markownikoff's rule. The weight of evidence in this instance favors XII over XI. The peroxide catalyzed addition of p-chlorothiophenol to isolapachol (XIII) yields an addition product isomeric with, but different from, the product



(18) Cunneen, J. Chem. Soc., 36 (1947); Posner, Ber., 38, 646 (1905); Ashworth and Burkhardt, J. Chem. Soc., 1791 (1928).

<sup>(15)</sup> Blicke, "Organic Reactions," Vol. I. p. 303, 1942.

obtained from lapachol and this mercaptan. The structure of this addition product is almost certainly XIV rather than XV. To support this contention it has been found that the product formed from the addition of p-chlorothiophenol to the quinone XVI<sup>19</sup> is identical with the quinone



prepared by condensation of VI (X = Cl) with the same mercaptan. By analogy the structure of the addition product from isolapachol is established, and, therefore, the structure of the product obtained from lapachol has been reasonably well determined.

Conditions could not be found for the addition of mercaptans to III. Invariably only tarry products resulted.

**Biological Activity.**—The inhibition of the respiration of parasitized red blood cells drawn from a duck infected with *P. lophurae*<sup>20</sup> has been found satisfactory for screening quinones for antimalarial activity.<sup>21</sup> In Table II (Experimental section) the relative antirespiratory molar activity (the activity of quinone XVII is arbi-



trarily set equal to unity) of the thioethers is listed. On the one hand, the quinones with shorter side chains (II, n = 0, 1, 3 and 4, X =SR) are either completely inactive or possess only moderate activity. The same observation holds true for most of the branched chain quinones. On the other hand, the quinones with longer side chains (II, n = 10, X = SR) show rather high activity in the *in vitro* tests.

This variation in activity can be accounted for on the basis of previous work in this Laboratory.<sup>22</sup> Effective drug action may be dependent upon a proper balance between lipophilic and hydrophilic characteristics. This balance can be ex-

- (19) Hooker, This Journal, 58, 1202 (1936).
- (20) Wendel, Federation Proc., 5, 406 (1946).
- (21) Fieser and Heymann, J. Biol. Chem., 176, 1363 (1948).
- (22) Fieser, Ettlinger and Fawaz, THIS JOURNAL, 70, 3228 (1948).



Fig. 1.—The variation of critical extraction values with molecular weight. The value for *n* refers to the number of methylene groups in formula II: \_\_\_\_\_, X = SC\_6H\_5; \_\_\_\_\_, X = SC\_6H\_4CH\_3-p; \_\_\_\_\_, X = SC\_6H\_4Cl-p.

pressed by pE, the critical extraction value.<sup>22</sup> For maximum antimalarial activity the pE for several series of hydroxynaphthoquinones has been found to lie between 9.8 and 11.8. Figure 1 shows a plot of pE vs. molecular weight for three series of thioethers. It will be seen that only the longer chain compounds possess a pE value in the desired range.<sup>23</sup>

The thioethers were not extensively tested in duck assays, but there is the probability that thioether naphthoquinones are toxic. All of the ducks treated with quinone VI ( $X = SC_6H_5$ ) died although the same dosage of other quinones was usually harmless.<sup>24</sup>

Acknowledgment.—We wish to acknowledge our indebtedness to Professor Louis F. Fieser for his suggestion of this problem and for many helpful suggestions and stimulating discussions during the prosecution of this work.

## Experimental<sup>25</sup>

2-(8'-Bromoöctyl)-3-hydroxy-1,4-naphthoquinone (II, n = 8, X = Br). Procedure A.—The preparation of a peroxide from  $\omega$ -bromopelargonic acid<sup>26</sup> proved to be troublesome. After the acid had been warmed with ex-

(23) Some of the pE values reported in this paper may appear to be low in comparison with the pE values previously reported (ref. 22) for quinones of comparable molecular weight; the reasons for this are not entirely clear at the present time. The average deviation from the mean of the values obtained in this investigation is  $\pm 0.2$ pE unit; previously (ref. 22) the a. d. has been reported to be  $\pm 0.05$ pE unit.

- (24) Communication from Dr. A. P. Richardson.
- (25) All melting points are corrected.
- (26) Hunsdiecker, Ber., 75, 291 (1942).

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TABLE I	
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2-Haloalkyl-3-hydroxy-1,4-naphthoguinones

						- Analyses, %					
						Car	bon	Hydrogen			
2 Substituent	Procedure	M. p., °C.	Solvent	I <sup>7</sup> orm <sup>c</sup>	Formula	Caled,	Found	Caled.	Found		
$-(CH_2)_{10}Br^a$	A	83.7-84.5	Ligroin <sup>b</sup>	Platelets							
$-(CH_2)_8Br$	А	69.5 - 70.5	Ligroin	Prisms	$\mathrm{C_{18}H_{21}O_{3}Br}$	59.19	59.40	5.80	5.98		
$-(CH_2)_7Br$	Α	86-88	Ligroin	Platelets	$C_{17}H_{19}O_{3}Br$	58.13	58.45	5.45	5.55		
$-(CH_2)_4Cl$	В	101 - 102	Methanol	Needles	$C_{14}H_{13}O_{3}Cl$	63.51	63.34	4.95	5.19		
$-(CH_2)_8C1$	в	128 - 129	Methanol	Needles	$\mathrm{C}_{13}\mathrm{H}_{11}\mathrm{O}_3\mathrm{Cl}$	62.28	62.33	4.42	4.55		
$-(CH_2)_2Cl$	В	126 - 127	Ligroin	Microcrystals	$C_{12}H_9O_8C1$	60.90	61.07	3.83	4.06		
$-\mathrm{Br}^d$		203 - 204	Ethanol	Orange prisms							

<sup>*a*</sup> Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3206 (1948). <sup>*b*</sup> B. p. 90–120°. <sup>*c*</sup> The color of these compounds is yellow unless otherwise stated. <sup>*d*</sup> Diel and Merz, *Ber.*, **11**, 1066 (1878).

#### TABLE II

2-Arvl-(alkyl)-mercaptoalkyl-3-hydroxy-1,4-naphthoguinones

						C	-Analys	es. 70		10 4	
2-Substituent	Proced.	M. p., °C.	Solvent	Form	Formula	Caled.	Found	Caled.	Found	A. 6	$pE^d$
$-(CH_2)_{10}SC_6H_5$	C	80-81	MeOH	Yell. prisms	$C_{26}H_{50}O_3S$	73.90	73.90	7.16	7.27	7.3	11.8
$-(CH_2)_{10}SC_6H_4Cl-p$	С	108-109	Ligr."	Yell, platelets	C25H29O3SC1	68.33	68.55	6.41	6.58	4.9	11.8
-(CH2)10SC6H4CH3-p	С	98.5-99	MeOH	Or. platelets	C27H22O3S	74.28	74.62	7.39	7.56	4.7	11.7
-(CH2)8SC6H4Cl-p	С	111.5-112.5	Ligr.	Oryell. plates	C24H25O4SCI	67.19	67.29	5.87	5.87	2.7	11.7
-(CH2)8SC6H4CH3-p	С	104-105	MeOH	Vell, prisms	$C_{25}H_{28}O_3S$	73.50	73.57	6.91	6.86	2.5	11.6
$-(CH_2)_8SC_6H_5$	C	75 - 76	MeOH	Or, ndls. or	$C_{24}H_{26}O_3S$	73.06	72.79	6.64	6.72	1.05	11.2
				yell, plates							
$-(CH_2)_7SC_6H_5$	С	89~90	MeOH	Or. udls.	$C_{23}H_{24}O_3S$	72.60	72.87	6.36	6.59	0.36	10.9
$-(CH_2)_7SC_6H_4Cl-p$	¢	115.5 - 116.5	MeOH	Or. ndls.	C23H28O3SC1	66.57	66.65	5.59	5.84	0.51	11.4
-(CH2)7SC6H4CH3-p	С	107.5-108.5	MeOH	Or. ndls.	$C_{24}H_{26}O_3S$	73.06	73.05	6.64	6.58	0.42	10.9
-(CH2)10SC10H21-n	С	79-80	MeOH	Yell. ndls.	$C_{30}H_{46}O_3S$	74.02	74.10	9.53	9.58		
-(CH2)10SC8H17-n	С	78-79	MeOH	Yell, ndls.	$C_{28}H_{42}O_3S$	73.32	73.47	9.24	9.27		
-(CH2) 8SC10H21-n	С	80.5-81.5	MeOH	Yell, ndls.	$C_{28}H_{42}O_3S$	73.32	73.58	9.24	9.43		
- (CH2)8SC8H17-11	С	69.5 - 70.5	Ligr.	Yell, ndls.	$C_{26}H_{38}O_8S$	72.51	72.76	8.89	8.92		
$-CH_2SC_6H_4Cl-p$	D	172-173 E	tOH→Bz	Or. ndis.	$C_{17}H_{11}O_3SC1$	61.73	61.90	3.35	3.58	nil	6.6
Triacetate	ь	152 - 153	MeOH	White prisms	$C_{23}H_{19}O_6SC1$	60.19	60.32	4.27	4.71		
$-CH_2SC_6H_{\delta}$	D	137-138	MeOH	Searl, ndls.	$C_{17}H_{12}O_3S$	68.90	68.67	4.08	4.25	nil	5.6
-CH2SC6H4CH3-p	D	144 - 145	MeOH	Or. ndls.	C18H14O3S	69.59	69.26	4.56	4.86	nil	6.7
-CH2SC14H29-12	D	82-83	HAc	Yell, ndfs.	$C_{25}H_{55}O_8S$	72.07	72.16	8.71	8.96	nil	
-CH2CH(CH3)SC6H5	c	108.5-109.5	MeOH	Yell, ndis.	$C_{19}H_{16}O_8S$	70.37	70.24	5.00	5.06	0.65	
-CH2CH(CH3)SC6H4Cl-p	С, Е	124-125	MeOH	Or. ndls.	CisH15O3SC1	63.60	63.58	4.21	3.99	1.5	8.4
-(CH2)2SC6H4Cl-p	Ε.	150 - 151	EtOH	Yell. ndls.	$C_{19}H_{15}O_3SCl$	63.60	63.86	4.21	4.01	nil	
Triacetate	ь	144 - 145	MeOH	White prisms	$C_{25}H_{23}O_6SC1$	61.66	61.80	4.76	4.74		
$-(CH_2)_3SC_6H_5$	E	121-122	MeOH	Or. ndls.	$C_{19}H_{16}O_8S$	70.34	70.14	4.97	5.19	nil	
-(CH2)3SC6H4CH3-p	E	135 - 136	MeOH	Yell, ndls.	$C_{20}H_{18}O_{0}S$	70.98	70.80	5.36	5.44	nil	
-(CH2)3SC8H17-n	E	93-94	MeOH	Yellor. prisms	$C_{21}H_{28}O_3S$	69.96	70.11	7.83	7.81	0.29	
$-(CH_2)_2C(CH_3)_2SC_6H_4Cl-p$	Е	119 - 120	MeOH	Oryell, prisms	$C_{21}H_{19}O_2SC1$	65.19	65.48	4.95	5.09	nil	
$-(CH_2)_2C(CH_3)_2SC_6H_4CH_3-p$	E	136 - 137	MeOH	Oryell. prisms	C22H22O3S	72.10	72.04	6.05	5.83	níl	
$-(CH_2)_2C(CH_3)_2SC_6H_5$	Е	128-130	MeOH	Yell, ndls.	$C_{21}H_{20}O_0S$	71.57	71.34	5.72	5.82	nil	
$-(CH_2)_2C(CH_3)_2SC_{10}H_{21}-n$	Е	129-130	MeOH	Oryell, plates	$\mathrm{C}_{25}\mathrm{H}_{36}\mathrm{O}_2\mathrm{S}$	72.07	72.28	8.71	8.82	0.066	
$-(CH_2)_2C(CH_3)_2SC_{12}H_{25}-n$	E	135 - 136	MeOH	Or. ndls.	$C_{27}H_{40}O_3S$	72.93	73.15	9.07	8.75	nil	
$-(CH_2)_2C(CH_3)_2SC_{14}H_{29}-n$	E	129-131	MeOH	Yell, ndls,	$C_{29}H_{44}O_3S$	73.68	73.41	9.38	9.10	nil	
$-CH_2CH(SC_6H_4Cl-p)CH(CH_3)_2$	E	177 - 178	MeOH	Yell, ndis.	$C_{21}H_{19}O_3SC1$	65.19	65.33	4.95	4.95	nil	
$(CH_2)_4SC_6H_4Cl-p$	¢	127-128	Ligr.	Yell, prisms	$C_{20}H_{17}O_8SC1$	64.46	64.75	4.60	4.60	0.8	8.95
$-(CH_2)_4SC_6H_5$	c	105-106	Ligr.	Yell, prisms	$C_{20}H_{18}O_8S$	70.98	71.00	5.36	5.64	0.42	8.6
$-(CH_3)_4SC_6H_4CH_3-p$	С	9899	Ligr.	Yell, prisms	$C_{21}H_{22}O_3S$	71.56	71.82	5.72	5.86	0.75	8.8
-SC6H4Cl-p	С	160161 dec.	MeOH	Or. plates	C16H9O3SCi	60.68	60.77	2.86	2.91	0.09	4.1
-SC6H4CH3-p	C	158–159 dec.	MeOH	Or. red. ndls.	$C = H_{12}O_3S$	68.90	68.70	3.99	4.13	nil	4.3
SC6H5	C	149-150 dec.	MeOH	Red ndls.	$\mathrm{C}_{46}\mathrm{H}_{10}\mathrm{O}_3\mathrm{S}$	68.07	68.21	3.57	3.85	0.13	4.0
SC13H27-11	C	65-66	HAc	Red ndls.	$C_{23}H_{32}O_3S$	71.11	70.88	8.33	8.71	nil	
$-SC_8H_{17}-n$	C	61 - 62	HAe	Red ndls.	$C_{18}H_{22}O_{\delta}S$	68.33	68.63	7.01	7.07		

<sup>a</sup> B. p. 90-100°. <sup>b</sup> Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., p. 399. <sup>c</sup> For the determination of the relative antirespiratory activity of these quinones we are indebted to Miss Shirley Katz and Mrs. Grace Nahm. <sup>d</sup> Critical extraction constant.

cess thionyl chloride for about an hour, dry benzene was added and the mixture evaporated to an oil under reduced pressure. The procedure was repeated, and then Norit together with a small amount of benzene (about one-half of the original weight of acid used) was added, the suspension heated for fifteen minutes and then filtered. A peroxide was prepared by adding the benzene solution to a stirred, cold solution of sodium peroxide.<sup>27</sup> The peroxide

(27) Fieser, Leffler and co-workers. THIS JOURNAL, 70, 3178

(1948).

was filtered, washed with water and dried. The alkylation of lawsone with this peroxide was carried out in warm acetic acid solution.<sup>27</sup> The quinone was obtained (28% yield) as yellow prisms from ligroin (b. p. 90–120°), m. p. 69.5–70.5°.

 $2^{-\gamma}$ -Chloropropyl-3-hydroxy-1,4-naphthoquinone (II, n = 3, X = Cl). Procedure B.—A peroxide was prepared from  $\gamma$ -chlorobutyryl chloride<sup>28</sup> in ether solution according to the "hydrogen peroxide method" of Fieser, *et al.*<sup>27</sup> Al-

(28) Lipp and Casper, Ber., 58, 1013 (1925).

kylation of lawsone with the ethereal solution of peroxide was carried out in warm acetic acid solution.<sup>27</sup> The quinone was obtained as brilliant yellow needles (41%yield) from dilute methanol, m. p. 128–129°.

 $2-\gamma$ -Bromopropyl-3-bromo-1,4-naphthoquinone (V).— The quinone IV (1 g.) was dissolved in 5 cc. of warm glacial acetic acid. Benzoyl peroxide (ca. 10 mg.) was added and then gaseous hydrogen bromide was bubbled into the solution for one minute. During this addition the solution became warm. After cooling, the flask was stoppered and allowed to remain at room temperature overnight. The solution was cooled in an ice-bath and 25 cc. of 48% hydrobromic acid was added. The dark black precipitate that formed was filtered and washed with water. Recrystallization of this material (0.35 g.) from ligroin (b. p. 90-100°) and a small amount of benzene (Norit) gave 0.25 g. of beautiful yellow needles, m. p. 130-131°. This compound gives a pale orange color with alcoholic alkali that slowly changes to deep red on boiling for one minute.

Anal.<sup>23</sup> Calcd. for  $C_{13}H_{10}O_2Br_2$ : C, 43.61; H, 2.82. Found: C, 43.70; H, 2.96.

2-(10'-Phenyimercaptodecyl)-3-hydroxy-1,4-naphthoquinone (II, n = 10,  $X = C_6H_5$ ). Procedure C.—A solution of 2.3 g. (0.0059 mole) of II (n = 10, X = Br), 0.98 g. (0.0089 mole) of thiophenol (Eastman Kodak Co. White Label) and 0.66 g. (0.0165 mole) of sodium hydroxide in 25 cc. of 95% methanol was refluxed under nitrogen for four hours. The red solution was acidified with concentrated hydrochloric acid, and the yellow precipitate was extracted with ether. The ethereal solution was dried over "Drierite," and the ether was removed in an air blast. The yellow residue was taken up in 100 cc. of hot methanol. On cooling, 1.9 g. (76%) of beautiful yellow prisms, m. p. 80-81°, crystallized. 2,3-(5,6-Dihydropyrano-2',3')-1,4-naphthoquinone

2,3-(5,6-Dihydropyrano-2',3')-1,4-naphthoquinone (VII).—In an attempt to prepare a thioether from the quinone II (n = 3, X = Cl), 1 g. (0.004 mole) of the quinone, 0.75 g. of *p*-chlorothiophenol and 0.35 g. of sodium hydroxide in 50 cc. of 75% ethanol solution was refluxed in a nitrogen atmosphere for three hours. Upon acidification there was obtained an oil that was taken up in ether, the ether evaporated, and the residue dissolved in hot ligroin (b. p. 90-120°). On cooling, 350 mg. of yellow needles, m. p. 216-218° was obtained. Recrystallization

(29) We are indebted to Mrs. M. Reese and Miss S. Katz for the microanalyses reported in this paper.

from ligroin gave 280 mg. of yellow needles (31%), m. p. 220-221°. This compound is not immediately soluble in dilute alkali, but on shaking for two or three minutes the quinone does dissolve slowly to produce a red solution.

Anal. Calcd. for  $C_{13}H_{10}O_3$ : C, 72.89; H, 4.71. Found: C, 72.66; H, 4.83.

2-p-Chlorophenylmercaptomethyl-3-hydroxy-1,4naphthoquinone (II, n = 1,  $X = C_6H_4C1-p$ ). Procedure D.—A mixture of 2.5 g. (0.14 mole) of lawsone and 1.9 g. of p-chlorothiophenol was dissolved in 50 cc. of warm dioxane; 2 drops of 36% hydrochloric acid and 4 g. of 37% formalin solution were added, and the dark solution was refluxed under nitrogen for an hour. The mixture was poured into 250 cc. of water, and the tarry precipitate that formed was taken up in ether. Evaporation of the ether left a gummy residue that was dissolved in warm methanol. On cooling 3.8 g. of brown needles, m. p. 162-168° were deposited. One recrystallization from ethanolbenzene (Norit) gave 3.0 g. (65%) of long orange needles, m. p. 172-173°. This compound gives an orange-red color in alcoholic alkali.

2-(3'-p-Chlorophenylmercapto)-propyl-3-hydroxy-1,4naphthoquinone (II, n = 3,  $X = C_6H_4Cl-p$ ). Procedure **E**.—A mixture of 1.6 g. (0.0075 mole) of IV and 1.2 g. of p-chlorothiophenol was dissolved in 30 cc. of warm glacial acetic acid. A pinch of benzoyl peroxide was added, and the yellow solution was gently heated on the steam-bath for 2.5 hours, after which time the solution was red. The solution was poured into water, and the mixture was twice extracted with 30-cc. portions of ether. The ethereal extracts were combined and the ether evaporated. The yellow residue was crystallized from ethanol, and 1.1 g. of product, m. p. 146–148°, was obtained. One recrystallization from ethanol gave 0.9 g. (33%) of beautiful yellow needles, m. p. 150–151°. This compound gives a red color when a drop of alkali is added to a warm methanolic solution.

#### Summary

Forty 2-aryl-(alkyl)-mercaptoalkyl-3-hydroxy-1,4-naphthoquinones have been synthesized as potential antimalarial drugs. Some of these quinones showed activity in *in vitro* assay, but it is probable that these compounds have a low therapeutic index.

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# Photochemistry of Proteins. X. The Influence of Reagents and Conditions on the Quantum Yield for the Inactivation-denaturation of Chymotrypsin

## By A. D. McLaren and Paul Finkelstein<sup>1</sup>

Recently quantum yields for the inactivation of enzymes, proteins and viruses have appeared in the literature.<sup>2,3</sup> The apparent relationship between quantum yields ( $\Phi$ ) and molecular weights (M) is given roughly by

$$\Phi = Q M^{-2/2} \tag{1}$$

where Q is a constant.<sup>4</sup> In this laboratory we have begun investigating factors which may influence the value of  $\Phi$  for a given protein.<sup>5</sup> The quantum

(2) Landen, THIS JOURNAL, 62, 2465 (1940).

(5) The literature up to 1949 has been summarized and reviewed

yield has been found to be dependent on hydrogen ion activity and wave length. As previously reported for chymotrypsin,<sup>6</sup>  $\Phi$  is independent of intensity, the presence or absence of oxygen, and concentration in the range previously investigated (2 × 10<sup>-8</sup> to 8 × 10<sup>-9</sup> mole per ml; the molecular weight has been taken as 41,000). Since the quantum yield for inactivation is not dependent on the presence or absence of oxygen by McLaren in "Advances in Enzymology," Interscience Publishers, Inc., New York, N. Y., 1949, Vol. IX, p. 75. The photochemistry of amino acids and peptides is also reviewed here.

(6) Finkelstein and McLaren, J. Polymer Sci., 4, 573 (1949). We wish to report a printer's error in this paper: the graph on p. 578 is Fig. 2 and that on p. 577 is Fig. 3; *ibid.*, 5, 267 (1950).

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<sup>(3)</sup> Mandl and McLaren, Arch. Biochem., 21, 408 (1949).

<sup>(4)</sup> McLaren, Acta Chim. Scand., 4, 386 (1950).