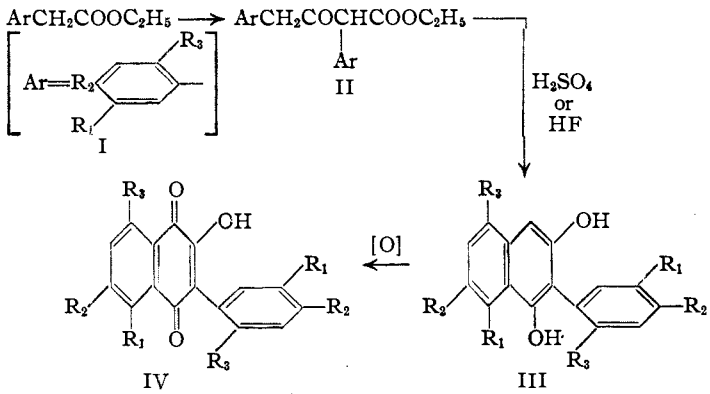
[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

Naphthoquinone Antimalarials. XIV. 2-Hydroxy-3-aryl-1,4-naphthoquinones

BY HAROLD E. ZAUGG, RICHARD T. RAPALA AND MARLIN T. LEFFLER

The observation[1] that 2-hydroxy-3-phenyl-1,4-naphthoquinone[2] (IV, $R_1 = R_2 = R_3 = H$) has an activity approximately one-fourth that of quinine against *P. lophurae* in ducks, prompted further investigation in this series.

It was decided to diversify the method used by Volhard[2] in the preparation of the parent compound, by starting with various substituted phenylacetic esters (I). In this way nine new



hydroxynaphthoquinones have been prepared. The R-substituents in the phenylacetic esters were all restricted to ortho-para orienting groups. Only two disubstituted esters were included, and positions of all substituents were chosen so that cyclization would lead to products of unambiguous structures.

In addition, both α-naphthylacetic ester and β-naphthylacetic ester were carried through the above series. The former led to the 1,4-phenanthrenequinone derivative (V, Table III, experimental section) and the latter either to the phenanthrenequinone (VI) or to the anthraquinone (VII). Since it is known[3] that use of anhydrous hydrogen fluoride can result in linear rather than expected angular cyclization of β-naphthyl derivatives, the choice between these two structures is left open. A comparison of the ultraviolet absorption spectrum of this product (VI or VII) with that of the phenanthrenequinone (V) was found to be inconclusive in the absence of a comparable spectrum of a suitable 1,4-anthraquinone derivative.

Published accounts of the Claisen ester condensation as applied to arylacetic esters (I) seem to be limited to phenylacetic ester itself and to the *p*-chloro derivative.[4] Ivanov and Spassov[4] reported that *p*-chlorophenylacetic ester gave the corresponding β-keto-ester (II) in good yield with isopropylmagnesium bromide as a catalyst[5] but did not react in the presence of sodium ethoxide. Therefore the former reagent was chosen for use in the present work. The general applicability of isopropylmagnesium bromide as a catalyst for Claisen condensations of this type is indicated in Table II (experimental section) describing those β-keto-esters which were obtained as pure crystalline products. All other β-keto-esters were obtained as thick oils which nevertheless, with only one exception, yielded the desired 2-aryl-1,3-naphthalenediols (III) on further treatment.

Since Volhard's original work,[2] concentrated sulfuric acid has been the only reagent used by subsequent investigators,[6,7] to convert α-substituted-γ-phenylacetoacetic esters in satisfactory yields to 2-substituted-1,3-naphthalenediols.[8] In the present work it was observed that in many cases use of concentrated sulfuric acid resulted in sulfonation of the aromatic rings. Indeed, with the α-naphthyl ester (II, Ar-α-naphthyl) it was found that sulfonation (indicated by total water solubility of the product) was complete in one hour at 0°. The simple expedient of diluting the sulfuric acid with half its volume of dry ether served to eliminate sulfonation in some cases without preventing the desired cyclization. However, the most satisfactory reagent to avoid sulfonation proved to be anhydrous hydrogen fluoride. Although not as effective as concentrated sulfuric acid in producing cyclization in β-keto-esters (II) with less active rings, it generally showed increased effectiveness with those β-keto-esters containing aryl rings more susceptible to substitution.

Other conditions for the cyclization reaction, notably boron trifluoride in ether, 100% phosphoric acid at 60°, and sodium acetate in refluxing acetic anhydride, were tried without success.

In the case of the halogenated β-keto-esters (II), treatment with concentrated sulfuric acid resulted in considerable cleavage with formation of the corresponding symmetrical halogenated dibenzyl ketones. Indeed, with the *o*-chloro deriva-

(1) Richardson and Hewitt, University of Tennessee, O. S. R. D. Contract OEMcmr-481.

(2) Volhard, *Ann.*, **296**, 14 (1897).

(3) Johnson and Mathews, THIS JOURNAL, **66**, 210 (1944).

(4) Ivanov and Spassov, *Bull. soc. chim.*, [4] **49**, 375 (1931).

(5) Conant and Blatt, THIS JOURNAL, **51**, 1227 (1929).

(6) Metzner, *Ann.*, **298**, 374 (1897); Ogata, *et al.*, *C. A.*, **33**, 4230 (1939); Wagreich, *et al.*, *Chemist Analyst*, **31**, 59 (1942); Meyer and Bloch, "Organic Syntheses," **25**, 73 (1945).

(7) Soliman and West, *J. Chem. Soc.*, 53 (1944).

(8) Zaki and Iskander, *ibid.*, 68 (1943), prepared 2-(2',4'-dinitrophenyl)-1,3-naphthalenediol by treatment of the corresponding α-substituted-γ-phenylacetoacetic ester with hot 5% sodium hydroxide, but no yield was given.

TABLE I

BACTERIOSTATIC ACTIVITY OF HYDROXYNAPHTHOQUINONES AGAINST *Staph. aureus*

Hydroxynaphthoquinone (IV)	Activity[a] plain broth	Agar cup plate method[b] Plain agar	+10% plasma	+50% plasma	+10% whole blood
$R_1 = R_2 = R_3 = H$	1:5000	2.5[c]	0	0	0
$R_1 = R_3 = H$; $R_2 = CH_3$	<1:5000	2.5[c]	2[c]	0	0
$R_1 = R_3 = H$; $R_2 = CH_3O$-	<1:5000	2.0[c]	0	0	0
$R_2 = H$; $R_1 = CH_3$; $R_3 = CH_3O$-	1:10,000	5.5	4.0	2.0	4.0

[a] Maximum dilution showing complete inhibition in one day. [b] Zone of inhibition in mm., 1:1000 dilution. [c] Only partial inhibition in the zone.

TABLE II

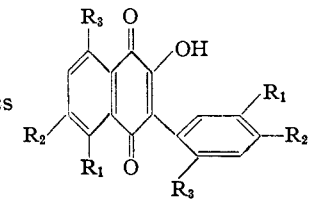
α,γ-BIS-(ARYL)-ACETOACETIC ESTERS[a] FROM ARYLACETIC ESTERS

Moles acetic ester	$ArCH_2COCH(Ar)COOR$ Ar	R	Crude yield, %	M. p. of yield, °C.	M. p. pure, °C.	Recryst. solvent	Crystalline form	Formula	Analyses Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
0.34	*p*-Tolyl	Ethyl	70	75–78	77–78.5	EtOH	Small needles	$C_{20}H_{22}O_3$	77.39	77.66	7.15	7.15
.28	*o*-Tolyl	Ethyl	80	60–68	71–72.5	MeOH	Small prisms	$C_{20}H_{22}O_3$	77.39	77.54	7.15	7.05
.34	*p*-Isopropylphenyl	Ethyl	29[b]	50–55	62–64	MeOH	Small needles	$C_{24}H_{30}O_3$	78.65	78.94	8.25	8.17
.14	β-Naphthyl	Ethyl	95	90–100	102–104	Abs. EtOH	Flat prisms	$C_{28}H_{22}O_3$	81.65	81.68	5.80	5.61
.25	α-Naphthyl	Ethyl	67	105–110	108–109	EtOH	Elongated prims	$C_{28}H_{22}O_3$	81.65	81.70	5.80	5.82
.25	α-Naphthyl	Methyl	37	105–107	119–121	MeOH	Elongated prisms	$C_{26}H_{20}O_3$	81.50	81.67	5.47	5.62

[a] Ethyl α,γ-bis-(*p*-chlorophenyl)-acetoacetate has been reported[4] as a solid, m. p. 119–120°. However, in the present work, crystallization of this compound could not be induced. [b] An additional 21% yield of oil (*Anal.* C, 79.28; H, 8.32; $n^{25}D$ 1.5347; b. p. 205° (0.5 mm.)) was obtained by distillation of residues.

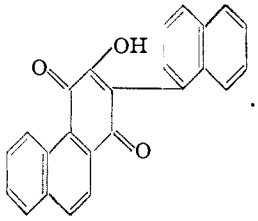
TABLE III

2-HYDROXY-3-ARYL-1,4-NAPHTHOQUINONES

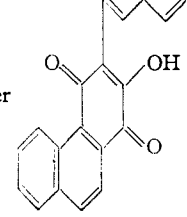


Compound	Ring closure method	Crude yield,[a] %	M. p. of yield, °C.	M. p. pure, °C.	Recryst. solvent	Cryst. form and color	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$R_1 = R_3 = H$; $R_2 = CH_3$	A	97.5[b]	174–175	175.5–176.5	EtOH	Orange needles	$C_{18}H_{14}O_3$	77.68	77.76	5.07	5.12
$R_1 = R_2 = H$; $R_3 = CH_3$	A[c]	45[d]	180–182	183–183.5	EtOH	Yellow powder	$C_{18}H_{14}O_3$	77.68	77.93	5.07	4.96
$R_1 = R_3 = H$; $R_2 = (CH_3)_2CH$	A	64[d]	126–134	137–139	Skelly B	Orange prisms	$C_{22}H_{22}O_3$	79.01	79.29	6.63	6.70
$R_2 = H$; $R_1 = R_3 = CH_3$	B[e]	41	143–145	145–145.5	EtOH	Yellow powder	$C_{20}H_{18}O_3$	78.41	78.56	5.92	5.97
$R_1 = R_3 = H$; $R_2 = Cl$	A	6.7	222–226	236–238	EtOH	Orange needles	$C_{16}H_8O_3Cl_2$	60.21	60.11	2.53	2.70
$R_1 = R_3 = H$; $R_2 = Br$	A	27	225–226	226–228	HOAc	Orange needles	$C_{16}H_8O_3Br_2$	47.09	47.46	1.98	2.01
$R_1 = R_3 = H$; $R_2 = CH_3O$	C	59[f]	157–161	160–162	EtOH	Red needles	$C_{18}H_{14}O_5$	69.67	69.60	4.55	4.91
$R_2 = H$; $R_1 = CH_3$; $R_3 = CH_3O$	C	20	193–195	197–199	MeOH	Orange prisms	$C_{20}H_{18}O_5$	70.99	71.39	5.36	5.40
$R_1 = R_3 = H$; $R_2 =$ phenyl	C[g]	50	208–210	214–215	HOAc	Orange needles	$C_{28}H_{18}O_3$	83.56	83.59	4.51	4.60
V[i]	C	55[d,h]	190–200	204–206	Ether	Red powder	$C_{24}H_{14}O_3$	82.27	82.40	4.03	4.32
VI or VII[j]	C	24[d]	226–227	227–228	HOAc	Red needles	$C_{24}H_{14}O_3$	82.27	82.56	4.03	4.18

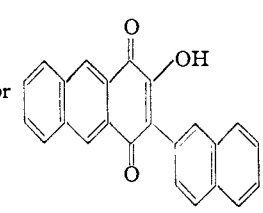
[a] Over-all yield of three steps from the corresponding arylacetic ester, except where otherwise indicated. [b] Based on pure 2-(*p*-tolyl)-7-methyl-1,3-naphthalenediol (m. p. 181–184°). [c] Method C gave a 20% yield,[d] m. p. 182–183°. [d] Yield of two steps based on crude, solid β-keto-ester (Table II). [e] Method A gave a negligible yield; method C gave a 32% yield,[a] m. p. 125–135°. [f] Based on crude 2-(*p*-anisyl)-7-methoxy-1,3-naphthalenediol (m. p. 145–150°). [g] Method A gave a negligible yield. [h] Based on β-keto-ethyl ester; methyl ester gave a 46% yield.[d] [i] Structure of Compound V:



. [j] Ambiguous structure: either



VI or



VII

tive (II, Ar = *o*-chlorophenyl) the only product isolated was the corresponding dibenzyl ketone, although the red color produced by aeration of an alkaline solution of the crude reaction mixture indicated the presence of some of the alkali salt of the desired product (IV, $R_1 = R_2 = H$, $R_3 = Cl$).

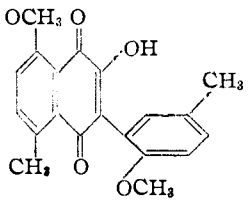
In only two cases were the 1,3-naphthalenediols (III) isolated in pure form. In most in-

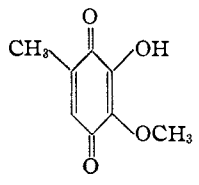
stances these intermediates were observed to oxidize so readily that purification was not even attempted. For example, an impure sample of the *p*-isopropyl derivative (III, $R_1 = R_3 = H$, $R_2 = (CH_3)_2CH—$) allowed to stand for five months in a desiccator under vacuum (50–100 mm.) was completely converted to the corresponding quinone (IV). On the other hand, the unsubstituted 1,3-naphthalenediol[2] (III, $R_1 = R_2 = R_3 = H$), the *p*-methyl- (III, $R_1 = R_3 = H$, $R_2 = CH_3$), and *p*-methoxy- (III, $R_1 = R_3 = H$, $R_2 = CH_3O$-) derivatives were easily purified and found to be stable indefinitely in closed containers.

For preparative purposes the hydroxynaphthoquinones (IV) were formed by simple aeration of alkaline solutions of the 1,3-naphthalenediols (III). In all cases intensely colored solutions of the alkali salts of the products were formed. Acidification yielded the less deeply tinted hydroxyquinones, all of which were easily isolated in crystalline form varying in color from light yellow to dark red.

Biological Activity.—All of the quinones reported in Table III were found[1] to be either very weak or completely lacking in antimalarial activity. However, four representative members of this series were tested for antibacterial activity against *Staph. aureus*. The results are summarized in Table I.

It is seen that the *p*-methyl-methoxy derivative is the only active member of this series. The difference is particularly striking in the agar cup test method and becomes more significant when the structure of the naphthoquinone is compared to that of the naturally produced quinone, fumigatin. Fumigatin has been shown[9] to possess





Fumigatin

complete bacteriostatic activity against *Staph. aureus* in maximum broth dilutions of 1:50,000. Oxford[10] has further extended this series to include a number of hydroxy- and methoxy- substituted toluquinones. Although other structural factors were found to be involved in their relative activities, in general, the toluquinones most active against *Staph. aureus* were those in which a methoxy group was present in a position para to the methyl group.

Experimental

Ethyl Arylacetates from Arylacetonitriles.—The results in the preparation of five arylacetic esters from the corresponding arylacetonitriles are summarized below. The nitriles were all prepared from the corresponding benzyl chlorides. The procedure of Wislicenus[11] for ethanolysis of the nitriles was used with no important alteration. In all cases small quantities of the corresponding amides were obtained as by-products. Smaller amounts of the related acids were also isolated in some cases.

Ethyl 2-methyl-α-toluate,[12] b. p. 68–69° (0.5 mm.), $n^{24}D$ 1.4998, yield 68% + 9.5% of the amide.[13]

Ethyl 4-isopropyl-α-toluate,[13] b. p. 85–87° (0.35 mm.), $n^{27}D$ 1.4910, yield 83% + 5% of the amide.[13]

Ethyl 4-bromo-α-toluate,[13] b. p. 88–90° (0.35 mm.), $n^{24}D$ 1.5310, yield 87% + 4% of the amide.[13]

Ethyl 2-chloro-α-toluate,[13] b. p. 125–128° (13 mm.), $n^{26}D$ 1.5123, yield 75% + 10% of the amide.[13]

Ethyl 2-methoxy-5-methyl-α-toluate,[14] b. p. 94–96° (0.25 mm.), $n^{25}D$ 1.5061, yield 67%.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.74. Found: C, 69.33; H, 7.53.

2-Methoxy-5-methyl-α-toluamide, m. p. 126–127° (from water). *Anal.* Calcd. for $C_{10}H_{13}O_2N$: N, 7.81. Found: N, 7.75.

2-Methoxy-5-methyl-α-toluic acid, m. p. 131–133° (from water). *Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.72. Found: C, 66.78; H, 6.72.

Ethyl Arylacetates through the Modified Willgerodt Reaction.—Five of the arylacetic esters used in this work were prepared from corresponding aryl methyl ketones[15] through the Willgerodt-Kindler reaction as modified by Schwenk and Bloch.[16] The arylthioacetomorpholides obtained in the reaction were hydrolyzed either with 10% potassium hydroxide[16] or with the sulfuric-acetic acid mixture employed by Newman.[17] The arylacetic acids were then esterified in the usual manner.

Results obtained for four of the esters are summarized below. The fifth one, ethyl β-naphthylacetate,[13] was prepared by esterification of the corresponding acid obtained according to Newman.[17]

4-Tolylthioacetomorpholide,[18] m. p. 100–102° (fr. dil. methanol), yield 85% (m. p. 80–90°).

Anal. Calcd. for $C_{13}H_{17}ONS$: N, 5.95. Found: N, 5.84.

4-Methyl-α-toluic acid, by potassium hydroxide hydrolysis, yield[19] 65%, m. p. 86–88° (lit.,[13] m. p. 93°). Ethyl ester,[13] yield 85%, b. p. 116–118° (13 mm.), $n^{26}D$ 1.4935.

2,5-Dimethylphenylthioacetomorpholide, m. p. 128–129.5° (fr. 50% ethanol), yield 63% (m. p. 92–97°).

Anal. Calcd. for $C_{14}H_{19}ONS$: C, 67.43; H, 7.68. Found: C, 67.68; H, 7.50.

2,5-Dimethyl-α-toluic acid, by potassium hydroxide hydrolysis, yield[19] 50%, m. p. 124–126°, (lit.,[13] m. p. 128°). Ethyl ester,[13] yield 90%, b. p. 70–73° (0.2 mm.), $n^{27}D$ 1.4989.

4-Chlorophenylthioacetomorpholide, m. p. 98.5–99° (fr. ethanol), yield 32% (m. p. 78–85°) or 18% (m. p. 94–97°).

Anal. Calcd. for $C_{12}H_{14}ONSCl$: C, 56.34; H, 5.51. Found: C, 56.49; H, 5.43.

4-Chloro-α-toluic acid, by potassium hydroxide hy-

(9) Oxford and Raistrick, *Chem. and Ind.*, **61**, 128 (1942).

(10) Oxford, *ibid.*, p. 189.

(11) Wislicenus, *Ann.*, **296**, 362 (1897).

(12) McElvain, Anthes and Shapiro, THIS JOURNAL, **64**, 2531 (1942).

(13) Beilstein, "Handbook of Organic Chemistry," Vol. IX, 1926.

(14) Both this ester and the nitrile from which it was prepared are unreported. The nitrile was kindly supplied by Dr. M. A. Spielman who prepared it in connection with other work.

(15) Either obtained from the Eastman Kodak Company, or prepared according to Adams and Noller, "Organic Syntheses," Coll. Vol. I, 111 (1941).

(16) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

(17) Newman, *J. Org. Chem.*, **9**, 518 (1944).

(18) Haller and Barthel, U. S. Patent 2,358,925 (1944) describe the preparation of this compound but no physical constants are reported.

(19) Based on crude morpholide.

drolysis, yield[20] 88%, m. p. 99–102° (lit.,[13] m. p. 103–104°).

Xenylthioacetomorpholide, m. p. 139–140° (fr. ethanol), yield 82% (m. p. 130–136°).

Anal. Calcd. for $C_{18}H_{19}ONS$: C, 72.69; H, 6.44. Found: C, 73.06; H, 6.31.

Xenylacetic acid, by sulfuric–acetic acid hydrolysis, yield[19] 80%, m. p. 153–158° (lit.,[21] m. p. 161–162°). Ethyl ester, yield 85%, b. p. 134–136° (0.2 mm.), $n^{25}D$ 1.5781.

Anal. Calcd. for $C_{16}H_{16}O$: C, 79.97; H, 6.71. Found: C, 79.76; H, 6.7.

Other Arylacetic Esters.—The methyl and ethyl α-naphthylacetates were obtained from the Dow Chemical Company. For the ethyl 4-methoxy-α-toluate[22] we are indebted to Mr. W. B. Brownell, who prepared it in connection with other work.

α,γ-bis-(Aryl)-acetoacetic Esters.—The procedure used was exactly the same as that described by Conant and Blatt[5] for the self-condensation of ethyl phenylacetate with the exception that instead of using a theoretical half mole of isopropylmagnesium bromide, one and one-half moles of the Grignard reagent was used for each mole of ester. This undoubtedly resulted in the formation of by-products which may have accounted for the inability to obtain some of the β-keto-esters in crystalline form. However, it seemed that more reproducible results could be obtained in this way.

The reaction mixture was decomposed by pouring the ether suspension into excess cold dilute acetic acid and washing the ether layer with bicarbonate and water. Drying and distillation of the ether gave the product which was either crystallized from an appropriate solvent or used as such in later steps if crystallization could not be induced. In most cases, oily residues from those β-keto-esters which did crystallize were used in later steps with appreciable yields of final products. The results obtained for the crystalline β-keto-esters are summarized in Table II.

2-Aryl-1,3-naphthalenediols.—Three different sets of conditions were used in the ring closure reaction (II → III).

Method A (Concentrated Sulfuric Acid).—Conditions were essentially the same as those described by Soliman and West,[7] namely, one part by weight of β-keto-ester in three volumes of concd. sulfuric acid was allowed to stand overnight at room temperature. The solution was poured into ice-water, and precipitated oil or solid was taken up in ether and washed with water to neutrality. Drying over anhydrous magnesium sulfate followed by distillation of the ether gave a solid or oil which in most cases was used in the next step without further purification.

Method B (Ether–Sulfuric Acid).—One gram of the β-keto-ester dissolved in 10 cc. of dry ether cooled in ice was treated dropwise with 20 cc. of cold concentrated sulfuric acid, keeping the temperature below 15°. Addition was slow at first but could be increased greatly as the exothermic reaction decreased. The mixture was allowed to stand at room temperature for five to eight hours, poured into ice-water and worked up as in Method A.

Method C (Anhydrous Hydrogen Fluoride).—One part by weight of the β-keto-ester was added to 8–10 parts by weight of anhydrous hydrogen fluoride contained in an ice-cooled copper vessel. The mixture was stirred briefly with a copper wire and allowed to stand at room temperature overnight (sixteen to twenty hours) loosely covered and in a well-ventilated hood. The mixture was then poured into ice and worked up as in Method A.

In addition to the parent 1,3-naphthalenediol (III, $R_1 = R_2 = R_3 = H$), only two others were isolated in pure form.

2-(*p*-Tolyl)-7-methyl-1,3-naphthalenediol, prepared by Method A in 75% yield (m. p. 181–184°) based on solid β-keto-ester (Table II). For analysis, recrystallized from chloroform, shiny leaflets, m. p. 182.5–184.5°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.96; H, 6.15.

2-(*p*-Anisyl)-7-methoxy-1,3-naphthalenediol, prepared by Method C in 82% yield (m. p. 145–150°) based on crude liquid β-keto-ester. For analysis, recrystallized from benzene, pink leaflets, m. p. 159.5–161.5°.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.14; H, 5.45.

2-Phenyl-1,3-naphthalenediol,[2] prepared by Method C in 33% yield (m. p. 158–161°) based on pure β-keto-ester. Purification gave m. p. 165–166°.

Halogenated Dibenzyl Ketones.—In the case of the halogenated β-keto-esters considerable cleavage occurred as a side reaction on treatment with concentrated sulfuric acid. The resulting halogenated dibenzyl ketones were separated from the desired 1,3-naphthalenediols by extraction of the latter with warm aqueous 10% sodium hydroxide. The insoluble residues were then recrystallized from the appropriate solvents.

1,3-bis-(*o*-Chlorophenyl)-2-propanone was prepared by Method A in 46% yield (m. p. 90–100°) based on ethyl *o*-chlorophenylacetate; recrystallized from ethanol by addition of a little water, fine needles, m. p. 102–102.5° (lit.[23] m. p. 102°).

1,3-bis-(*p*-Chlorophenyl)-2-propanone was prepared by Method A in 24% yield (m. p. 93–95°) based on ethyl *p*-chlorophenylacetate. Recrystallized from 95% ethanol, large plates, m. p. 98–99° (lit.[23] m. p. 93°).

1,3-bis-(*p*-Bromophenyl)-2-propanone was prepared by Method A in 15% yield (m. p. 100–110°) based on ethyl *p*-bromophenylacetate. For analysis, recrystallized from 95% ethanol, colorless plates, m. p. 116–118°.

Anal. Calcd. for $C_{15}H_{12}OBr_2$: C, 48.94; H, 3.29. Found: C, 48.92; H, 3.30.

2-Hydroxy-3-aryl-1,4-naphthoquinones.[2,24]—The crude naphthalenediol was taken up in 15 to 20 volumes of 5–10% sodium hydroxide, warmed on the steam-bath and, if necessary, ethanol was added in sufficient quantities to produce a homogeneous solution. If an entirely clear solution was not produced, it was filtered through a layer of Nuchar. (In the case of the halogenated derivatives where relatively little, if any, alcohol was used, the filtrates from the dibenzyl ketones were used as the alkaline solutions of the naphthalenediols.)

The alkaline solution was aerated at room temperature overnight by passing air through a fritted glass filter-tube extending to the bottom of the container. The deeply colored solution was then acidified with excess glacial acetic acid. If the precipitated product was a friable solid it was filtered, dried and recrystallized. If it contained considerable gummy impurity it was taken up in ether, washed with bicarbonate, dilute hydrochloric acid and water, and dried over anhydrous magnesium sulfate. The material left after evaporation of the ether was either recrystallized directly or triturated with Skellysolve B to promote solidification, and then recrystallized. The results are summarized in Table III.

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(20) Based on recrystallized morpholide, m. p. 94–97°.

(21) Blicke and Grier, THIS JOURNAL, **65**, 1725 (1943).

(22) Beilstein, "Handbook of Organic Chemistry," Suppl. Vol. X 83 (1932).

(23) Kenner and Morton, *J. Chem. Soc.*, 679 (1934).

(24) Soliman and Latif, *ibid.*, 55 (1944).

Summary

The preparation of eleven substituted derivatives of 2-hydroxy-3-phenyl-1,4-naphthoquinone is described in connection with antimalarial and bacteriostatic studies.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Naphthoquinone Antimalarials. XV. Distribution between Organic Solvents and Aqueous Buffers[1,2]

BY LOUIS F. FIESER, MARTIN G. ETTLINGER AND GEORGE FAWAZ[3,4]

In the investigation of drug metabolism (Paper XVIII) use was made of fractional extraction from ether with a series of buffers of increasing alkalinity for the separation of metabolites from the less hydrophilic starting materials. Approximate estimations of the *p*H at which appreciable extraction begins to occur revealed marked differences among the naphthoquinones examined and suggested that the precise determination of distribution ratios might be of value for purposes of characterization and separation. The present quantitative study was undertaken with this objective in view and also to see whether a correlation could be established between distribution and some biological factor involved in drug action.

The hydroxyalkylnaphthoquinones are all acids (type HA) of about the same acidity (*pKa* 5–5.5). When such a substance is distributed between ether and an alkaline buffer at a total concentration in the order of 5×10^{-4} molar it may be assumed that the ratio of the concentrations of unionized HA in the ether and water phases is a constant, *K*. Since the material found in the aqueous phase is present almost exclusively as the anion, the measurable distribution ratio *C* is given by the expression

$$C = \frac{[\text{Total quinone}]^{\text{ether}}}{[\text{Total quinone}]^{\text{water}}} = \frac{[\text{HA}]^{\text{ether}}}{[\text{A}^-]}$$

Since

$$K = [\text{HA}]^{\text{ether}}/[\text{HA}]^{\text{water}} \text{ and } Ka = [\text{H}^+][\text{A}^-]/[\text{HA}]$$

it follows that

$$C = [\text{H}^+](K/Ka)$$

An **extraction constant E** may be defined as the hydrogen ion concentration corresponding to the ratio $C = 100$ (whence $K/Ka = 100/\text{E}$). The constant is conveniently employed as its negative logarithm, *p*E, which can be calculated from measurement of the distribution ratio at an appropriate *p*H by means of the equation

$$p\text{E} = \log C + p\text{H} - 2$$

The value 100 for *C* is chosen as a basis for comparison because *p*E then defines accurately the roughly determinable *p*H at which, at a total concentration of 20 mg./100 cc., visible color appears in the aqueous phase; *p*E also indicates the upper limit of *p*H at which oxidation products can be safely separated without extracting any more than 1/101 part of starting material (equal volumes of solvents).[5] The theory was tested by calculation of *p*E for hydrolapachol from distribution determinations conducted over wide ranges of hydrogen ion and quinone concentrations (Table I); the results validate the theory with an accuracy of ±0.05 *p*H unit.

TABLE I

DETERMINATION OF *p*E FOR HYDROLAPACHOL

Buffer *p*H	*p*E found at an initial concentration in ether of (mg./100 cc.) 10	20	50
8.65		7.76	7.73
8.95	7.82	7.75	7.72
9.50	7.78	7.77	7.80
10.10		7.82	

*p*E (av.) = 7.77

Extraction Procedure.—A standard solution of the quinone was prepared by dissolving 50 ± 0.2 mg. of material in ether that had been saturated with water and diluting the solution to a volume of 250 cc. with the same solvent. Such a solution is susceptible to autoxidation unless stored in darkness. The buffers were suitable mixtures of 0.2 *N* primary and secondary phosphate or of 0.2 *N* sodium hydroxide and 0.1 *N* glycine–0.1 *N* sodium chloride solutions. The *p*H values were determined with a *p*H meter. The *p*H values of standard solutions of sodium hydroxide were either assumed from the concentrations or determined by the use of a special electrode suitable for high alkalinity.

A dry 125-cc. separatory funnel was shaken with more than enough ether to saturate the vapor space, the excess ether was drained off, and 25 cc. of the standard quinone solution (5 mg.) was transferred to the funnel by pipet. A 30-cc. portion of buffer was saturated with ether in a separatory funnel and 25 cc. of the aqueous layer was shaken with the quinone solution. When fully clear, the aqueous extract was separated and the concentra-

(1) For acknowledgments to CMR and the Rockefeller Foundation, see Paper I.

(2) Preliminary experiments were conducted by C. Heidelberger.

(3) On leave of absence from the American University, Beirut.

(4) With the technical assistance of Eva Fawaz.

(5) The constant *p*E closely resembles the hydrochloric acid number employed by Willstätter in the characterization and separation of porphyrins; see Zeile and Rau, *Z. physiol. Chem.*, **250**, 197 (1937); Keys and Bruegsch, THIS JOURNAL, **60**, 2135 (1938).