Summary

From the 3,3,3-trifluoropropyl Grignard reagent several new compounds have been prepared, including methyl and ethyl esters of 4,4,4-trifluorobutyric acid, 4,4,4-trifluorobutyraldehyde, 5,5,5-trifluoro-2-pentanol, 1,1,1,5,5,5-hexafluoro-2-pentanone and its hydrate and 1,1,1,7,7,7-hexafluoro-4-heptanone.

Some of the compounds thus prepared have been used to synthesize 4,4,4-trifluoro-1-butanol, 4-iodo-1,1,1-trifluoropentane and 5,5-bis-(3′,3′,3′-trifluoropropyl)-hydantoin.

3-Iodo-1,1,1,-trifluoropropane has been prepared.

LAFAYETTE, IND. RECEIVED OCTOBER 24, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

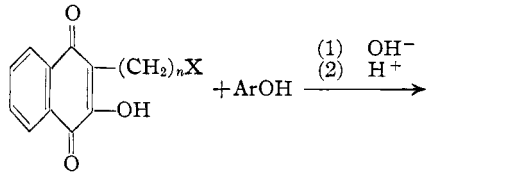
Naphthoquinone Antimalarials. XXV.[1] Naphthoquinones with Oxygen in the Side Chain

BY MARVIN PAULSHOCK[2] AND CARL M. MOSER[3]

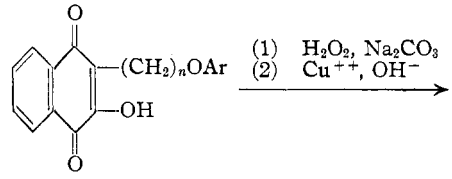
The discovery that 2-alkyl-3-hydroxy-1,4-naphthoquinones with a hydroxylated side chain are resistant to metabolic degradation[4] suggested the synthesis of other 2-alkyl-3-hydroxy-1,4-naphthoquinones with oxygen in the side chain in order to determine the potency of these compounds as antimalarial agents. Previous work[5,6] had indicated that quinones with an oxygenated side chain containing less than twelve carbon atoms are for the most part inactive or only feebly active. The most potent quinones contained about twenty carbon atoms in the side chain.

A number of ethers of suitable side chain length were synthesized by condensation between an ω-halo quinone (I) and a phenolic compound in the presence of base in a manner analogous to the method used for the preparation of thioether naphthoquinones.[6] Some of the 2-aryloxyalkyl-3-hydroxy-1,4-naphthoquinones were prepared from ω-aryloxyacids *via* the peroxide alkylation[7,8] of lawsone (2-hydroxy-1,4-naphthoquinone). Norhomologs of some of these aryloxyalkyl derivatives of lawsone were prepared by the two-step[9] Hooker oxidation[10] of alkyl hydroxynaphthoquinones. Attempts to perform the oxidation on ω-haloquinones (I) were unsuccessful.

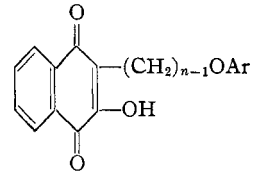
The relative anti-respiratory activities[11] of these quinones have been determined (see Table I, Experimental section), and on the basis of this *in vitro* assay it appears that some of these aryloxyalkyl quinones possess potency as antimalarial drugs. This conclusion has been confirmed in duck assays.[4]



I

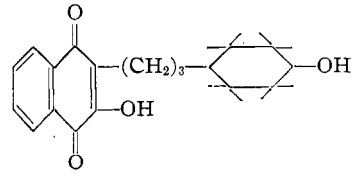


II

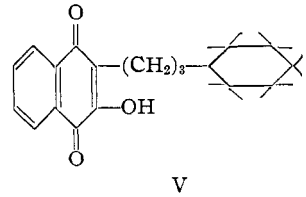


III

Although the quinone IV, which is a metabolite of V, is stable to further metabolic degradation,



IV



V

(1) 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. For the previous paper in this series see Fawaz and Fieser, THIS JOURNAL, **72**, 996 (1950).

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(4) Fieser, Heymann and Seligman, *J. Pharmacol. Exp. Therap.*, **94**, 112 (1948).

(5) Fieser and Richardson, THIS JOURNAL, **70**, 3156 (1948).

(6) See Moser and Paulshock, "Naphthoquinone Antimalarials XXVI," to be published in THIS JOURNAL.

(7) Fieser and Oxford, *ibid.*, **64**, 2060 (1942).

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

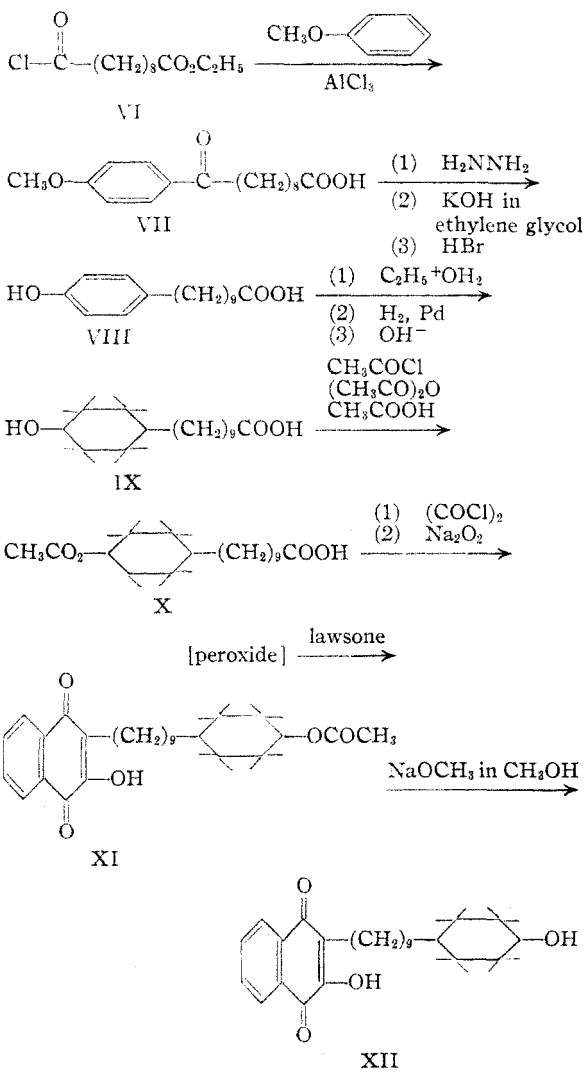
(9) Fieser and Fieser, *ibid.*, **70**, 3215 (1948).

(10) Hooker, *ibid.*, **58**, 1163, 1174, 1179 (1936).

(11) Fieser and Heymann, *J. Biol. Chem.*, **176**, 1363 (1948).

it possesses only feeble activity.[11] The quinone IV is more hydrophilic than V—the pE[12] value of V is 9.4, whereas the pE of IV is 6.4. The pE value for satisfactory potency of a quinone should be in the range of 9.8–11.8. This desired balance of hydrophilic and lipophilic character could be achieved by the synthesis of a higher homolog of IV.

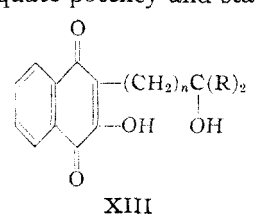
The following synthesis was carried out in order to prepare such a compound



The reduction of VIII[13] proved to be troublesome. Reduction with platinum in acetic acid at low pressure resulted in partial loss of the hydroxyl group, presumably through hydrogenolysis; the separation of the complex reaction mixture did not prove to be feasible. Reduction with Raney nickel at high pressure and temperature gave similarly unpromising results. Reduction could not be effected at room temperature with Raney nickel and an aqueous sodium carbonate solution of the acid, although this method was satisfactory for a lower homolog of VIII.[14] Reduction of the ethyl ester with palladium on strontium carbonate in ethyl acetate solution at 230° and 2800 lb. pressure proved to be successful.

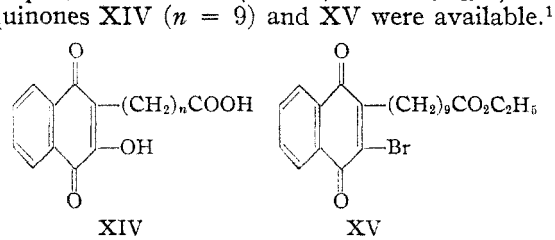
The separation of the quinone XI from the by-products of the alkylation reaction seemed to be impossible until it was discovered that the sodium salt of XI is lipophilic and can be extracted with ether from a strong brine solution. Deacetylation of XI with sodium methoxide in absolute methanol failed, but the reaction proceeded readily when ordinary commercial methanol was used. From this observation it appears that the mechanism of the transformation XI→XII is one of hydrolysis rather than transesterification. The quinone XII possessed low antirespiratory activity and a pE of 10.1.

The results of previous experimentation on the use of 2-alkyl-3-hydroxy-1,4-naphthoquinones as anti-malarial agents[15] had indicated that the quinone XIII (n = 8, R = C_5H_{11}-n) (lapinone)[16] possesses adequate potency and stability and



XIII

shows promise when tested in human beings as an agent against *Plasmodium vivax*. This discovery suggested the synthesis of other tertiary alcohols of similar structure. From a large scale preparation of XIII (n = 8, R = C_5H_{11}-n) two quinones XIV (n = 9) and XV were available.[16]



XIV XV

The quinone XIV (n = 9) was esterified, the ester was reductively acetylated, and the triacetate ester was treated with an excess of a suitable Grignard reagent.[8] The quinone XV was transformed into the hydroxy quinone XIV (n = 8) by the two-step Hooker oxidation,[9,16] and this acid was carried through similar transformations. In this manner several tertiary alcohols XIII (n = 8 and 9, R = C_3H_7-n to C_5H_{11}-n and -i) were prepared. On the basis of anti-respiratory assay none of the alcohols

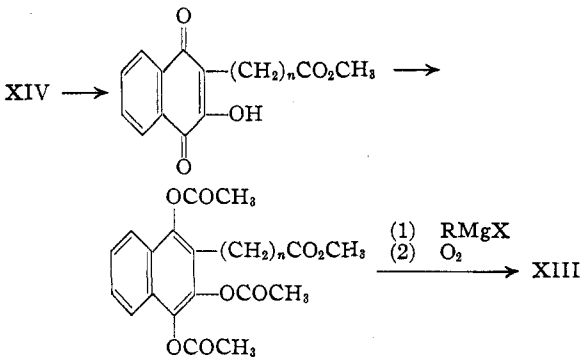
(12) For a discussion of the critical extraction value, the precise definition and the method of determination, see Fieser, Ettlinger and Fawaz, THIS JOURNAL, **70**, 3228 (1948).

(13) Papa, Schwenk and Hankin, *ibid.*, **69**, 3018 (1947).

(14) Fieser, Leffler and co-workers, *ibid.*, **70**, 3195 (1948).

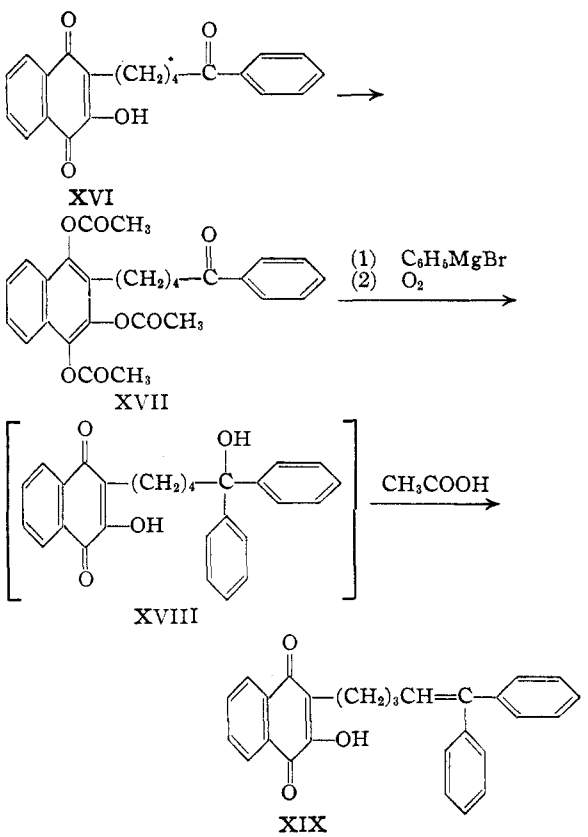
(15) Fieser, Leffler and co-workers, *ibid.*, **70**, 3151 (1948).

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



prepared is significantly more active than lapinone.

An attempt was made to prepare a diphenyl carbinol by the scheme



The carbinol XVIII could not be isolated. The crystallization of the reaction product from dilute acetic acid led to dehydration and formation of the diphenyl ethylene XIX.

Acknowledgment.—We are grateful to Professor Louis F. Fieser for the suggestion of this problem and for helpful discussions held during the course of the investigation.

Experimental[17]

ω-Bromodecanoic Acid.—The following procedure for the preparation of this acid does not appear to have been previously reported. A solution of 33.7 g. (0.115 mole) of ethyl ω-bromoundecylate[18] in 100 cc. of dry ether was added dropwise over a period of one hour to 100 cc. of an ethereal solution of phenylmagnesium bromide (0.23 mole), which had been filtered free from magnesium. The ethereal solution was refluxed overnight and then was poured into a mixture of 200 cc. of 10% sulfuric acid and 100 g. of ice. The ether layer was separated and dried. On distillation under reduced pressure, 32.6 g. (70.3%) of **1,1-diphenyl-ω-bromononylethylene** was obtained, b. p. 190° (0.5 mm.), $n^{25}D$ 1.557. *Anal.*[19] Calcd. for $C_{23}H_{29}Br$: C, 71.68; H, 7.58. Found: C, 71.76; H, 7.82.

The oxidation of the diphenylethylene was carried out in the usual manner.[20] A 71% yield of acid, m. p. 35–38°, was obtained (reported[21] m. p. 43°).

2-(9′-Bromononyl)-3-hydroxy-1,4-naphthoquinone (I, n = 9, X = Br). **Procedure A.**—A peroxide was prepared from the acid chloride of ω-bromodecanoic acid by the use of the sodium peroxide method described by Fieser, Leffler and co-workers.[22] The solid thus obtained was approximately 75% peroxide, as determined by iodometric titration. Alkylation of lawsone with this peroxide was carried out in warm acetic acid solution essentially according to a procedure previously described.[22] The quinone was obtained (30% yield) as yellow prisms from ligroin (b. p. 90–100°), m. p. 68.5–69.5°.

Anal. Calcd. for $C_{19}H_{23}O_3Br$: C, 60.16; H, 6.05. Found: C, 60.16; H, 6.25.

The preparation of other ω-haloalkyl quinones used to prepare the ethers reported in this paper has been reported in another paper.[6]

ω-*p*-Xenoxyundecylic Acid.—A solution of 43.8 g. (0.167 mole) of ω-bromoundecylic acid, 31.3 g. (0.184 mole) of *p*-hydroxydiphenyl and 14.1 g. of sodium hydroxide in 500 cc. of methanol was refluxed for five hours; a white precipitate gradually settled out of solution. The cooled mixture was slowly stirred into 1300 cc. of 5% hydrochloric acid; the precipitate that formed was filtered and dried. Two recrystallizations from benzene gave 35.8 g. (60.5%) of white platelets, m. p. 129.5–130°.

Anal. Calcd. for $C_{32}H_{30}O_3$: C, 77.94; H, 8.57. Found: C, 77.96; H, 8.64.

ω-Phenoxyundecylic acid was prepared in a similar manner and was obtained as white platelets (55% yield) from ligroin (b. p. 90–120°), m. p. 75.5–76.5°.[23] The **amide** was prepared in the usual manner. After two recrystallizations from dilute methanol and one from benzene the pure amide was obtained, m. p. 100–100.5°.

Anal. Calcd. for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81. Found: C, 73.60; H, 9.43.

ω-*p*-Methylphenoxyundecylic acid was obtained in 43% yield as white platelets from ligroin (b. p. 75–90°), m. p. 79–79.5°.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.01; H, 9.92.

2-(10′-*p*-Chlorophenoxydecyl)-3-hydroxy-1,4-naphthoquinone (II, n = 10, Ar = C_6H_4Cl-*p*). **Procedure B.**—A solution of quinone I (n = 10, X = Br) (0.00635 mole) and 0.42 g. (0.00635 mole) of potassium hydroxide in 35 cc. of 75% ethanol was added slowly to a refluxing solution of 1.28 g. (0.01 mole) of *p*-chlorophenol and 0.66 g. (0.01 mole) of potassium hydroxide in 15 cc. of 75% ethanol. The solution was refluxed for eight hours and then cooled. Acidification with concentrated hydrochloric acid followed by extraction with ether gave a yellow ethereal solution, which was dried over *Drierite*.

(17) All melting points are corrected.

(18) Svugusawa, *J. Pharm. Soc. Japan*, No. **550**, 1050 (1927); *C. A.*, **22**, 1572 (1928).

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

(20) See, *e. g.*, Marker, THIS JOURNAL, **59**, 1367 (1937).

(21) Chuit, *Helv. Chim. Acta*, **12**, 463 (1929).

(22) Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3178 (1948).

(23) Newman and Rapoport, *ibid.*, **69**, 471 (1947).

The ether was removed with a blast of air. Recrystallization of the yellow residue from methanol gave 1.8 g. of beautiful long silky yellow needles, m. p. 88.5–89.5° (65%).

The Hooker oxidation of II ($n = 10$, Ar = C_6H_4Cl-*p*) was carried out using the procedure of Fieser and Fieser.[9] From 0.5 g. of this quinone there was obtained 0.3 g. of yellow needles (from methanol), m. p. 96–97°.

Synthesis of 2-(ω-4′-Hydroxycyclohexylnonyl)-3-hydroxy-1,4-naphthoquinone (XII). Ethyl ω-*p*-Hydroxyphenylcaprate.—ω-*p*-Methoxybenzoylpelargonic acid was prepared from the Friedel–Crafts reaction between anisole and ω-carbethoxypelargonyl chloride. This reaction had been carried out prior to the publication of the results of Papa, Schwenk and Hankin,[13] but as there is essential agreement there seems to be no point in repeating the details here. The keto acid (VII) was reduced by the modification of the Wolff–Kishner reaction introduced by Huang-Minlon,[24] and, as observed by Papa, Schwenk and Hankin, the product from this reaction is a mixture of the methyl ether and the phenolic acid. The pure phenolic acid could be obtained by demethylation of the reaction product with 48% hydrobromic acid, the pure methoxy acid by methylation of the reaction mixture with dimethyl sulfate and alkali.

A solution of 57 g. of ω-*p*-hydroxyphenylcapric acid (VIII) in 90 cc. of absolute ethanol, 100 cc. of benzene and eight drops of concentrated sulfuric acid was refluxed in a water-separator esterification apparatus until no more water would separate. Distillation under reduced pressure gave 49 g. of colorless, viscous oil, b. p. 195–197° (1.4 mm.), $n^{25}D$: 1.499.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.11; H, 9.70.

ω-4′-Hydroxycyclohexylcapric Acid (IX).—A suspension of palladium hydroxide on strontium carbonate[25] was prepared by warming 1 g. of palladium chloride and 15 g. of strontium carbonate in distilled water for one hour. The solid was filtered and dried in a vacuum oven at 65°.

The ester (5 g.), 55 cc. of ethyl acetate and 1.5 g. of the 4% catalyst were placed in a steel bomb, capacity 130 cc. The initial pressure of hydrogen was 1800 lb. Shaking was begun and the temperature was raised to 230° (pressure of hydrogen at this temperature was 2790 lb.). Shaking was continued at this temperature for eighteen hours as the pressure slowly dropped to 2300 lb. The bomb was allowed to cool to room temperature (pressure 1200 lb.) After filtration the solvent was evaporated and 50 cc. of 25% sodium hydroxide solution was added. The mixture was refluxed for five hours; the alkaline solution was poured into a mixture of ice and concentrated hydrochloric acid, and the precipitate that formed was collected and dried. The product weighed 2.6 g., m. p. 119–127°. On crystallization from benzene 1.8 g. (40%) of white platelets, m. p. 125–127°, was obtained.

Anal. Calcd. for $C_{16}H_{30}O_3$: C, 71.06; H, 11.18. Found: C, 71.33; H, 11.15.

ω-4′-Acetoxycyclohexylcapric Acid (X).—To 3.96 g. of XI there were added 100 cc. of glacial acetic acid, 20 cc. of acetic anhydride, and 2 cc. of acetyl chloride. The solution was refluxed for six hours, and then poured into 200 cc. of water. The product was collected and dried. Crystallization from ligroin (b. p. 90–100°) gave 3.7 g. (78%) of white platelets, m. p. 88–89°.

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.15; H, 10.30.

2-(ω-4′-Acetoxycyclohexylnonyl)-3-hydroxy-1,4-naphthoquinone (XI).—The acid X was converted into the acid chloride by warming with oxalyl chloride. The oily acid chloride remaining after removal of excess oxalyl chloride was dissolved in a small quantity of dioxane and added to cold sodium peroxide solution.[22] A 67% yield of peroxide was obtained in this manner. The alkylation of lawsone was carried out in warm glacial acetic acid solution as previously described,[22] but a special purification procedure was adopted in order to separate the quinone from the acid (IX or X) that is formed as a by-product. The reaction mixture remaining after the removal of unreacted lawsone was taken up in hot ligroin (b. p. 90–120°). On cooling a yellow solid, m. p. 70–100°, was deposited. This precipitate was taken up in ether and extracted several times with 1.2% aqueous sodium hydroxide. Both aqueous and ethereal layers were red, but, upon the addition of salt, the red color was completely driven into the ether layer. In the aqueous layer there remained a suspension of a white precipitate. The aqueous layer was drawn off; the ether layer was acidified and then washed with water. The ethereal solution was dried and then the ether was evaporated. The yellow residue was recrystallized twice from ligroin, and there was obtained a 30% yield of a yellow powder, m. p. 114–117°.

Anal. Calcd. for $C_{27}H_{36}O_5$: C, 73.60; H, 8.24. Found: C, 73.89; H, 8.11.

2-(ω-4′-Hydroxycyclohexylnonyl)-3-hydroxy-1,4-naphthoquinone (XII).—The acetate XI was hydrolyzed according to the procedure used for the hydrolysis of 2-hydroxy-3-(4′-acetoxycyclohexyl)-propyl-1,4-naphthoquinone to 2-hydroxy-3-(4′-hydroxycyclohexyl)-propyl-1,4-naphthoquinone.[8] The quinone was obtained in 90% yield as a yellow powder (from ligroin (b. p. 90–120°)), m. p. 100–101°, with softening around 90°.

Anal. Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.58; H, 8.85.

2-(9′-Carbomethoxynonyl)-3-hydroxy-1,4-naphthoquinone.—The quinone XIV ($n = 9$) was converted into the methyl ester with the use of boron fluoride-etherate as catalyst (thirty minutes reflux). The crude ester obtained on dilution with water[16] was not sufficiently pure for the next step. The crude material was dissolved in ether, and this solution was extracted with 5% bicarbonate solution until the aqueous layer was no longer colored red. The ether was evaporated, and the residue was crystallized from ligroin. The ester was obtained as small golden needles (64% yield), m. p. 90–91°.

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.63; H, 7.38.

1,3,4-Triacetoxy-2-(9′-carbomethoxynonyl)-naphthalene.—The reductive acetylation of XIV ($n = 9$) was carried out in the usual manner[26] with acetic anhydride, zinc dust and freshly fused sodium acetate. The yield of small white prisms (from a mixture of ether and ligroin (b. p. 70–90°)), m. p. 87–88°, was 79%.

Anal. Calcd. for $C_{27}H_{34}O_8$; C, 66.66; H, 7.04. Found: C, 66.72; H, 7.34.

1,3,4-Triacetoxy-2(8′-carbomethoxyoctyl)-naphthalene.—The quinone XV was transformed into the hydroxy quinone XIV ($n = 8$) by the two-step Hooker oxidation.[16] With the use of *freshly* purified dioxane[27] it was found that the red solution was decolorized *within one minute*. The yield of pure acid (m. p. 124–125°) XIV ($n = 8$) was 72%. The acid was esterified as described above (m. p. 83–84°), and the methyl ester was reductively acetylated. The triacetate was obtained (86% yield) as small white prisms, m. p. 71–72°, from a mixture of ether and ligroin (b. p. 70–90°).

Anal. Calcd. for $C_{26}H_{32}O_8$: C, 66.09; H, 6.83. Found: C, 66.30; H, 6.89.

2-(10′-Hydroxy-10′-*n*-amylpentadecyl)-3-hydroxy-1,4-naphthoquinone (XIII, $n = 9$, R = C_5H_{11}-*n*).—The Grignard reaction was carried out with the triacetate ester and *n*-amylmagnesium bromide according to the procedure of Fieser, *et al.*[8] The product was obtained as a viscous orange-red oil in 46% yield.

1,3,4-Triacetoxy-2(4′-benzoylbutyl)-naphthalene (XVII).—The quinone XVI[28] was reductively acetylated

(24) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(25) Busch and Stove, *Ber.*, **49**, 1064 (1916).

(26) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., p. 399.

(27) Fieser, *ibid.*, p. 389.

(28) Fieser, THIS JOURNAL, **70**, 3237 (1948).

TABLE I

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

2-Substituent	Procedure	M. p., °C.	Solvent	Form	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	R. A. A.[b]	pE[c]
$-(CH_2)_{10}OC_6H_5$	A and B	87.5–88	Methanol	Yellow needles	$C_{26}H_{30}O_4$	76.82	76.80	7.44	7.46	6.3	11.4
$-(CH_2)_{10}OC_6H_4C_6H_5$-$p$	A and B	123–124	Methanol	Yellow needles	$C_{32}H_{34}O_4$	79.63	79.62	7.10	7.40		
$-(CH_2)_{10}OC_6H_4CH_3$-p	A	93–94	Ligroin[a]	Yellow needles	$C_{27}H_{32}O_4$	77.11	77.12	7.67	7.96	2.7	
$-(CH_2)_{10}OC_6H_4Cl$-p	B	88.5–89.5	Methanol	Yellow needles	$C_{26}H_{29}O_4Cl$	70.82	71.04	6.63	6.66	6.4	11.6
$-(CH_2)_{10}OC_6H_4C_6H_{11}$-$p$	B	92.5–93.5	Methanol	Yellow powder	$C_{32}H_{40}O_4$	78.65	78.89	8.25	8.40		
$-(CH_2)_{10}OC_{10}H_7$-α	B	103–104	Methanol	Yellow powder	$C_{30}H_{32}O_4$	78.92	78.67	7.23	7.19		
$-(CH_2)_8OC_6H_5$	B	83.5–84.5	Methanol	Yellow prisms	$C_{24}H_{26}O_4$	76.16	75.98	6.93	6.96	0.47	10.4
$-(CH_2)_8OC_6H_4Cl$-p	B	95–96	Methanol	Yellow rosettes	$C_{24}H_{25}O_4Cl$	69.81	70.09	6.10	6.39	4.7	11.1
$-(CH_2)_8OC_6H_4CH_3$-p	B	89–90	Methanol	Yellow needles	$C_{25}H_{28}O_4$	76.50	76.59	7.19	7.30	3.3	11.0
$-(CH_2)_7OC_6H_5$	B	88–89	Methanol	Yellow prisms	$C_{23}H_{24}O_4$	75.86	75.87	6.64	6.84	0.34	9.1
$-(CH_2)_7OC_6H_4Cl$-p	B	95.5–96.5	Ligroin[a]	Yellow platelets	$C_{23}H_{23}O_4Cl$	69.25	69.17	5.81	5.91	0.6	10.2
$-(CH_2)_7OC_6H_4CH_3$-p	B	105.5–107	Methanol	Yellow platelets	$C_{24}H_{26}O_4$	76.16	75.93	6.92	6.84	2.1	10.1
$-(CH_2)_9OC_6H_4Cl$-p	C and B	95–96	Methanol	Yellow needles	$C_{25}H_{27}O_4Cl$	70.33	70.13	6.38	6.38	9.1	11.4
$-(CH_2)_9OC_6H_5$	C	87.5–88	Methanol	Yellow needles	$C_{25}H_{28}O_4$	76.50	76.84	7.36	7.70	0.66	11.1

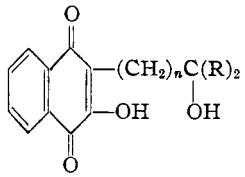
[a] B. p. 90–120°. [b] For the determination of the relative anti-respiratory activity of these quinones we are indebted to Miss Shirley Katz and Mrs. Grace Nahm. [c] Critical extraction constant ref. 12.

in the usual manner.[26] From 1 g. of XVI there was obtained 1 g. (76%) of XVII, m. p. 123–125°.

Anal. Calcd. for $C_{27}H_{26}O_7$: C, 70.12; H, 5.67. Found: C, 70.32; H, 5.84.

TABLE II

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



n[a]	R	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	R. A. A.[b]
9	C_4H_9-n	$C_{28}H_{42}O_4$	75.98	75.70	9.57	9.77	2.7
9	C_5H_{11}-n	$C_{30}H_{46}O_4$	76.55	76.66	9.85	9.93	2.9
9	C_5H_{11}-i	$C_{30}H_{46}O_4$	76.55	76.33	9.85	9.94	2.9
9	C_4H_9-i	$C_{28}H_{42}O_4$	75.98	75.82	9.57	9.40	1.25
9	C_3H_7-n	$C_{26}H_{38}O_4$	75.32	75.20	9.48	9.32	1.3
8	C_5H_{11}-i	$C_{29}H_{44}O_4$	76.28	76.08	9.71	9.82	1.9
8	C_4H_9-i	$C_{27}H_{40}O_4$	75.65	75.60	9.53	9.60	0.77

[a] All of these compounds were obtained as viscous oils. [b] The relative antirespiratory activity of quinone XV (n = 8, R = C_5H_{11}-n) (lapinone) is 3.4.

2-(5′,5′-Diphenylpentene-4′)-3-hydroxy-1,4-naphthoquinone (XIX).—A solution of 0.39 g. of XVII in 75 cc. of dry benzene was added dropwise over a period of twenty minutes to a stirred solution of phenylmagnesium bromide, prepared from 3.14 g. (0.02 mole) of freshly distilled bromobenzene and 0.48 g. (0.02 mole) of magnesium in 75 cc. of dry ether. The light orange solution was refluxed for four hours and then decomposed with 50 cc. of 20% sulfuric acid. The ether layer was separated, and the ether was removed. All attempts at crystallization from ligroin (b. p. 90–100°) or methanol gave only an oil. When the product stood in aqueous acetic acid in the cold room there was obtained 0.1 g. of thick yellow needles, m. p. 132–134°.

Anal. Calcd. for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62. Found: C, 82.20; H, 5.87.

Summary

A number of 2-alkyl-3-hydroxy-1,4-naphthoquinones have been synthesized with oxygen in the side chain (either hydroxyl oxygen or ether oxygen) to be tested as antimalarial agents. Several of the aryloxy ethers possess high activity on the basis of *in vitro* assay.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Restricted Rotation in Aryl Amines. XIV. Isopropyl Derivatives of Dibenzenesulfonamidomesitylene

BY ROGER ADAMS AND NILS K. NELSON[1]

The synthesis of various N,N′-alkylated dibenzenesulfonamidomesitylenes and separation of *cis* and *trans* forms have been previously described.[2] All of the compounds reported are *n*-alkyl derivatives. The synthesis of the mono- and diisopropyl homologs has now been undertaken. Steric factors not existent in the preparation of the *n*-alkyl derivatives were encountered.

Mono-isopropylation of diaminomesitylene was accomplished by prolonged boiling of an ethanolic solution of diaminomesitylene with a large excess of isopropyl bromide. More drastic conditions were required to prepare the diisopropyl derivative. When an ethanolic solution of diaminomesitylene and isopropyl bromide was heated in a bomb at 100° for forty-eight hours, a mixture of the mono- and diisopropyl derivatives resulted. When this mixture was subjected to similar treatment, the diisopropyl derivative was formed in 44% yield. At temperatures as high as 180°, a large amount of propylene was evolved and no

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(2) Adams and Tjepkema, THIS JOURNAL, **70**, 4204 (1948); Adams, *et al.*, *ibid.*, **71**, 1620 (1949); **72**, 128, 132, 135, 2454, 2458, 4606 (1950).