5,6-Dehydrovitamin A Methyl Ether (XV).—Dehydration of XIV in glacial acetic acid proved too slow to be practical. Consequently the enynol (7.1 g.) was dissolved in 110 ml. of methanol containing 0.6 cc. of concd. hydrochloric acid and 0.1 g. of hydroquinone and allowed to stand under nitrogen for three days at room temperature. The solution was then diluted with water and the product extracted with petroleum ether, washed with sodium bicarbonate solution and dried with anhydrous potassium carbonate. The extract was concentrated under vacuum to 50 cc. and chromatographed as previously described under *cis*-VII. Under ultraviolet light the column showed a single large red-fluorescent zone preceded by a bright red-fluorescing edge. The column was extruded and the lower two-thirds of the main band was cut out and eluted with methanol. The remainder of the column was rejected although it showed very nearly the same spectrum as the above eluate. After working up in the usual manner, distillation gave 4.1 g. of golden-yellow product at 110–120° (0.001 mm.); $n^{20}D$ 1.5791.

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.52; H, 10.13; methoxyl, 10.40. Found: C, 84.48; H, 9.99; methoxyl, 10.42.

Ozonolysis[1] gave 21% geronic acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE MOUNT SINAI HOSPITAL]

p-Hydroxyphenoxy Aliphatic Acids

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A new series of water-soluble monoethers of hydroquinone has been prepared including the hydroquinone ethers of lactic acid, of β-hydroxypropionic acid, of α- and γ-hydroxybutyric acid, the hydroquinone acetal of ethyl glyoxalate, and some of their derivatives. Four methods of synthesis have been adapted to the specific conditions encountered.

This report describes the synthesis of a number of monoethers of hydroquinone with aliphatic monohydroxy acids. Of this group one representative only has been previously described, namely, the glycolic acid monoether of hydroquinone,[1] also designated as *p*-hydroxyphenoxyacetic acid and, less correctly, as hydroquinone-O-acetic acid.[2] The homologs of this ether-acid include two subseries, the "α-phenoxy" acids of the general formula $HOC_6H_4OCHRCO_2H$ and the "(non-α)-phenoxy" acids, $HOC_5H_4O(CH_2)_nCO_2H$. The formation of *p*-hydroxyphenoxyacetic acid, according to Carter and Lawrence,[1] could not be verified within a wide range of conditions, nor did we find it possible to obtain it by diazotization of *p*-aminophenoxyacetic acid and elimination of nitrogen.

We therefore developed several methods for the condensation of hydroquinone with one molecule of halogenated aliphatic acids. In order to circumvent the condensation with two molecules, one of the hydroxy groups had to be masked by a group that would not be hydrolyzed by the alkaline reaction required for the condensation. At the same time the masking group had to be so selected as to enable its removal under conditions that would not simultaneously open the other ether linkage. All four methods, subsequently described, apply to the α-halogeno acids as well as to the γ-halogeno acid, γ-chlorobutyric acid. β-Halogenated fatty acids tend to dehydrohalogenate to the corresponding acrylic acids, therefore certain precautions had to be applied to the synthesis of β-(*p*-hydroxyphenoxy)-propionic acid.

The condensation of alkali salts of diphenol monomethyl ethers with halogenoacetic acids was claimed in three patents by Majert and Lederer,[3] but they gave as only example the ortho-isomer, the monocatechol ether of glycolic acid. We have succeeded in the synthesis of a series of *p*-methoxyphenoxy aliphatic acids and esters by condensation of hydroquinone monomethyl ether with halogeno-fatty acids and esters; demethylation with concentrated hydrochloric acid yielded the respective *p*-hydroxyphenoxy acids. In order to avoid the heating with hydrochloric acid or dry hydrogen chloride, we used the benzyl group which may be removed by catalytic hydrogenolysis. Reaction of the sodium salt of monobenzyl hydroquinone with ethyl β-bromopropionate in anhydrous medium exemplifies the extension of the method to β-halogenated acids. The method proved also suitable for the condensation of dichloroacetic acid with two molecules of hydroquinone.

An alternative synthesis of β-(*p*-hydroxyphenoxy)-propionic acid might be accomplished by the condensation of β-propiolactone with the methyl- or benzylmonoether of hydroquinone according to Gresham[4] leading to the methoxy acid (IV) or the benzyloxy acid of which we describe the ethyl ester (XI).

The method of widest scope and operative under the mildest conditions is the condensation of the sodium or potassium salt of arbutin, hydroquinone-β-glucopyranoside, with salts of halogenated acids. The primary condensation products could not be isolated in crystalline form. The glucoside linkage is easily opened by dilute acid or by emulsin (β-glucosidase).

As a further alternative, the procedure of Friess[5] was used for the synthesis of γ-(*p*-hydroxyphenoxy)-butyric acid.

A study of the antioxidant properties of these water-soluble hydroquinone monoethers will be reported separately. The influence of the substituent groups on the stability of the ether linkage is under investigation.

We are indebted for the microanalyses to the Schwarzkopf Microanalytical Laboratories, Middle Village, L. I., N. Y. Miss Franca Nunes contrib-

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(2) "Beilstein," Vol. VI, Berlin, 1923, p. 847.

(3) W. Majert and L. Lederer, German Patent 87336 (1895); German Patent 87668 (1895); German Patent 108241 (1896).

(4) T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, W. E. Beears and M. G. Prendergast, THIS JOURNAL, **71**, 661 (1949).

(5) S. L. Friess, *ibid.*, **71**, 14 (1949).

TABLE I

PREPARATION OF *p*-METHOXYPHENOXY ACIDS

Except in example I, the sodium salts were not isolated and the acids were recrystallized from benzene–petroleum ether

	p-Methoxyphenoxy	Method	M.p., °C.	Yield, %	B.p., °C.	Analyses, % Calculated C	Calculated H	Found C	Found H
I	Acetic acid, $C_9H_{10}O_4$	A	110	86	.....	59.33	5.53	59.22	5.88
II	α-Propionic acid, $C_{10}H_{12}O_4$	A	90	53	173–175 at 1 mm.	61.21	6.16	61.81	6.03
III	α-Butyric acid, $C_{11}H_{14}O_4$	A	57	45	150–155 at 1 mm.	62.84	6.71	63.28	6.79
IV	β-Propionic acid, $C_{10}H_{12}O_4$	B	109	23[a]	143–146 at 1 mm. (of ethyl ester)	61.21	6.16	61.63	5.85
V	γ-Butyric acid, $C_{11}H_{14}O_4$	B	101[b]	16[a]	159–161 at 2 mm. (of ethyl ester)	62.84	6.71	63.53	7.15

[a] Yield of parent ester. [b] M.p. of ester 29°. Hydrolyzed with concentrated HCl or alcoholic KOH.

TABLE II

PREPARATION OF *p*-HYDROXYPHENOXY ACIDS BY HYDROLYSIS OF METHOXYPHENOXY ACIDS

	p-Hydroxyphenoxy-	M.p., °C.	Yield, %	Analyses, % Calculated C	Calculated H	Found C	Found H
VI	Acetic acid, $C_8H_8O_4 \cdot {}^1/_3H_2O$	154	54	55.17	5.00	55.14	5.02
	Ethyl ester of VI, $C_{10}H_{12}O_4$	124	..	61.21	6.16	61.40	6.23
VII	α-Propionic acid, $C_9H_{10}O_4$	144	73	59.33	5.53	59.69	5.46
	Amide of VII,[a] $C_9H_{11}O_3N$	140	..	59.66	6.12	59.82	6.46
VIII	α-Butyric acid, $C_{10}H_{12}O_4$	137	75	61.21	6.16	61.74	6.23
IX	β-Propionic acid, $C_9H_{10}O_4$	173	Poor	59.33	5.53	59.86	5.47

[a] Prepared *via* the ethyl ester; recrystallized from chloroform–petroleum ether; calcd. N, 7.73; found N, 7.49.

uted skilful assistance during the earlier part of this work.

Experimental

Condensation of the monomethyl ether of hydroquinone with halogeno acids was carried out with monochloroacetic, α-bromopropionic and α-bromobutyric acids.

***p*-Methoxyphenoxyacetic Acid (I) (Method A).**—A mixture of 12.4 g. (0.1 mole) of hydroquinone monomethyl ether in 80 ml. of 5% sodium hydroxide (0.1 mole) and of 19 g. (0.2 mole) of monochloroacetic acid in 200 ml. of 8% sodium hydroxide (0.4 mole) was heated on a steam-bath for 18 hours. On cooling 11 g. of the sodium salt of *p*-methoxyphenoxyacetic acid crystallized as slightly brownish leaflets; another 6 g. was obtained from the mother liquor; yield 17 g. (83.5% of theory).

Seventeen grams of the sodium salt was dissolved in 250 ml. of boiling water and acidified with 12 ml. of concentrated hydrochloric acid. On cooling 11 g. of crude methoxy acid was obtained and 2 more grams from the mother liquor; yield 13 g. (86% of theory). After Norite treatment and two recrystallizations from 50% ethanol, the acid was obtained as colorless plates; m.p. 110°.

Acids with the halogen atom in positions other than α cannot be condensed in aqueous alkaline solution. In these cases their esters had to be added to the solution of the sodium salt of monomethyl hydroquinone in absolute alcohol.

β-(*p*-Methoxyphenoxy)-propionic Acid (IV) (Method B).—Two and six-tenth grams (0.115 mole) of metallic sodium and 100 ml. of absolute methanol were placed in a three-neck flask fitted with mechanical stirrer, condenser and dropping funnel. The apparatus was kept under nitrogen. When all the metal had dissolved, 14.3 g. (0.115 mole) of hydroquinone monomethyl ether was added and all the alcohol was replaced with dry toluene by constant distillation. Twenty-one grams (0.115 mole) of ethyl β-bromopropionate was added over a period of one hour to the brownish-yellow suspension. Refluxing was continued for 21 hours. Sodium bromide was removed by filtration and washed with 30 ml. of toluene. The combined filtrate and washing were extracted with 3% sodium carbonate solution to remove unchanged hydroquinone monomethyl ether. After further washing with dilute hydrochloric acid and water, the toluene was distilled off and the residual oil distilled under 1.8 mm. pressure. Four and nine-tenths grams of ethyl β-(*p*-methoxyphenoxy)-propionate was obtained as a colorless mobile oil boiling between 143–146°; yield 23%.

Three grams of the ester was warmed with 60 ml. of concentrated hydrochloric acid until a clear solution had formed. On cooling 1.5 g. of the crude acid was obtained. On recrystallization from benzene–petroleum ether, it formed colorless plates of m.p. 109°; reported[4] m.p. 106–107°.

Hydrolysis of the ester with hot alcoholic potassium hydroxide solution gave hydroquinone monomethyl ether. Table I summarizes the condensations carried out by these methods.

The *p*-hydroxyphenoxy acids were prepared from the above *p*-methoxyphenoxy acids by heating with concentrated hydrochloric acid. In the case of the γ-methoxyphenoxybutyric acid this treatment resulted not only in demethylation, but also in considerable hydrolysis of the other ether linkage. Therefore, we reverted in this instance to other methods.

***p*-Hydroxyphenoxyacetic Acid (VI).**—Ten grams of I and 40 ml. of concentrated hydrochloric acid[5] was heated in a sealed tube at 95–100° for 15 hours. On dilution with water, treatment with Norite, and concentration to 40 ml., 5 g. of crude *p*-hydroxyphenoxyacetic acid was obtained; yield 54%. Two recrystallizations from water afforded the pure acid as colorless prisms of m.p. 154°, reported[1] 152°.

Table II summarizes our results with the above method. Since it did not lead to practical yields in the course of the β-propionic compound, the benzyl ether method was resorted to in this case as also in that of the γ-hydroxyphenoxybutyric acid. The practicality of the method was first tested in the following case.

***p*-Benzyloxyphenoxyacetic Acid (X).**—A mixture of 10 g. (0.05 mole) of hydroquinone monobenzyl ether in 200 ml. of 1% sodium hydroxide (0.05 mole) and 9.4 g. (0.1 mole) of monochloroacetic acid in 100 ml. of 8% sodium hydroxide (0.2 mole) was heated on a steam-bath for 8 hours. Precipitation of the sodium salt of the acid started after about 30 min. The suspension was cooled to 0° and the collected sodium salt was dissolved in 750 ml. of hot water. Acidification with 30 ml. of concentrated hydrochloric acid liberated the acid and unreacted hydroquinone monobenzyl ether which were extracted with ether after saturation of the solution with sodium chloride. The ether layer was thoroughly extracted with saturated sodium bicarbonate solution, which was acidified and extracted with ether. The ethereal solution of the acid was dried over sodium sulfate and taken to dryness. Several recrystallizations of the crude acid from absolute methanol yielded 6.4 g. of pure acid, forming colorless needles of m.p. 140°, yield 50%.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.52; H, 5.70.

Hydrogenation of X in 95% ethanol with 5% palladium/charcoal yielded acid VI in theoretical quantity. For those acids whose halogen atom is labile toward aqueous alkali, the "benzyloxy" method was modified as shown in the following example.

Ethyl β-(*p*-Benzyloxyphenoxy)-propionate (XI).—Twenty grams (0.1 mole) of hydroquinone monobenzyl ether was

added to a solution of 2.3 g. (0.1 mole) of metallic sodium in 100 ml. of absolute methanol in a three-neck flask, fitted as described, and the alcohol replaced by dry toluene to a final volume of 200 ml. Eighteen grams (0.1 mole) of ethyl β-bromopropionate was added to the refluxing suspension. Ethyl acrylate was formed in a side reaction and identified by odor. Refluxing was kept up for 72 hours. Fourteen grams of suspended solid was removed by centrifugation. The aqueous solution of this solid was acidified with dilute nitric acid. Ether extraction recovered 5 g. (25%) of hydroquinone monobenzyl ether. The toluene portion was extracted with 10% sodium hydroxide solution until on acidification no more hydroquinone benzyl ether was precipitated (8 g. recovered). The toluene fraction was washed with saturated sodium chloride solution, dried over sodium sulfate and taken to dryness. Nine grams of oil was obtained at room temperature. Recrystallization from absolute ethanol afforded 7.5 g. of the ester; m.p. 67°, yield 25%.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.27; H, 6.78.

Two and nine-tenths grams of the ester XI was hydrogenated in 200 ml. of 95% ethanol containing 0.6 g. of 5% palladium/charcoal; absorbed, 230 ml.; calculated for one mole H_2, 235 ml. The solution was filtered and taken to dryness *in vacuo*. The residual oil was recrystallized from carbon tetrachloride affording the ethyl ester of IX as colorless prisms of m.p. 95°, from which the free acid (IX) of m.p. 173° was easily obtained on hydrolysis.

The homologous **ethyl γ-(*p*-benzyloxyphenoxy)-butyrate (XII)** was prepared analogously from the sodium salt of 20 g. (0.1 mole) of monobenzyl hydroquinone and 15 g. (0.1 mole) of ethyl γ-chlorobutyrate.[6] The resulting ester, recrystallized in absolute alcohol, formed colorless prisms of m.p. 47°, yield 24%.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.58; H, 7.06. Found: C, 73.07; H, 7.03.

γ-(*p*-Benzyloxyphenoxy)-butyric acid (XIII) was prepared from its ethyl ester (XII) by saponification; colorless prisms from 50% ethanol, m.p. 125°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.53; H, 6.46.

Its methyl ester melted at 90°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.01; H, 6.77.

γ-(*p*-Hydroxyphenoxy)-butyric Acid (XIV) by Hydrogenolysis of XII.—Hydrogenation of the ethyl ester of the benzyloxy acid led to the absorption of the theoretical amount of hydrogen. The solution was filtered through Hy-flo and taken to complete dryness *in vacuo*. Ethyl γ-(*p*-hydroxyphenoxy)-butyrate was obtained as colorless prisms. Hydrolysis of this ester with 10% alcoholic potassium hydroxide gave the theoretical yield of γ-(*p*-hydroxyphenoxy)-butyric acid, m.p. (from benzene) 120°.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.16. Found: C, 61.57; H, 6.19.

***p*-Benzyloxyphenoxy Acetal of Ethyl Glyoxalate (XV).**—One-fifth mole (40 g.) of hydroquinone monobenzyl ether was added to a solution of 4.6 g. (0.2 mole) of metallic sodium in 100 ml. of absolute ethyl alcohol in a three-neck flask as described and all the alcohol was replaced by dry toluene to a final volume of 300 ml. One-tenth mole (15.6 g.) of ethyl dichloroacetate in 50 ml. of dry toluene was added to the refluxing suspension over a period of 20 min. and refluxing continued for 24 hours. The mixture was worked up as usual. The product was recrystallized from absolute ethanol, giving 25 g. of the acetal ester XV as white amorphous solid of m.p. 67–68°.

Anal. Calcd. for $C_{30}H_{28}O_6$: C, 74.36; H, 5.82. Found: C, 74.22; H, 5.95.

***p*-Hydroxyphenoxy acetal of ethyl glyoxalate (XVI)** was obtained by catalytic hydrogenolysis. The substance was obtained by several recrystallizations from aqueous ethanol as colorless needles melting at 139°.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.10; H, 5.44.

***p*-Benzyloxyphenoxy Acetal of Glyoxalic Acid (XVII).**—Two grams of XV was dissolved in 50 ml. of normal alcoholic potassium hydroxide. The potassium salt of the acid crystallized in needles on standing at room temperature. The salt was suspended in a small volume of water in a separatory funnel, covered with ether and acidified with hydrochloric acid. The acidified solution was immediately extracted to prevent splitting of the acetal. The ethereal layer was washed with concentrated sodium chloride, dried over sodium sulfate and evaporate to dryness. The residual oil which solidified on refluxing with petroleum ether was twice recrystallized from benzene–petroleum ether, affording the acid as colorless needles of m.p. 92°.

Anal. Calcd. for $C_{28}H_{24}O_6$: C, 73.66; H, 5.29. Found: C, 73.16; H, 5.31.

Hydrogenolysis of XVII in alcoholic solution with palladium/charcoal led to the ester XVI. Hydrolysis of XVI with normal alcoholic potassium hydroxide gave hydroquinone. Hydrogenolysis of the acid XVII and of its potassium salt under various conditions did not furnish the free acid corresponding to the ester XVI.

***p*-Hydroxyphenoxyacetic Acid (VI) from Arbutin.**—A mixture of 13.6 g. (0.05 mole) of arbutin in 80 ml. of 2.5% sodium hydroxide (0.05 mole) and 9.5 g. (0.1 mole) of monochloroacetic acid in 80 ml. of 10% sodium hydroxide (0.2 mole) was heated on a steam-bath for 20 hours. Fifteen ml. of concentrated sulfuric acid was added with stirring and the mixture was refluxed for 12 hours. After cooling and saturation with sodium chloride the solution was extracted with ether, the ether layer evaporated to dryness and the residual oil crystallized from water. Eight grams of the acid of m.p. 154° was obtained; yield 50%.

γ-(*p*-Hydroxyphenoxy)-butyric Acid (XIV) by Friess Method; Ethyl γ-(*p*-Propiophenoxy)-butyrate (XVIII).—Fifteen grams (0.1 mole) of *p*-hydroxyphenoxypropiophenone was added to a solution of 2.3 g. of sodium metal (0.1 mole) in 200 ml. of absolute ethyl alcohol contained in a three-neck flask, fitted in the described manner. The mixture was stirred until everything had gone into solution and 15 g. (0.1 mole) of ethyl γ-chlorobutyrate was added to the refluxing solution over a period of one hour. Refluxing was continued for 72 hours. Three grams of sodium chloride (50% of theory), which had separated, was removed by filtration, the filtrate taken down to a volume of 50 ml. and poured into 200 ml. of ice-water. The resulting emulsion (unreacted ester could be smelled) was saturated with sodium chloride and extracted three times with ether. One-half of the *p*-hydroxypropiophenone was recovered by acidification of the aqueous layer and by extraction with sodium hydroxide from the ethereal layer. The washed and dried ether and unchanged ester were distilled off at 100° and 2 mm. pressure. The residual oil was distilled in a molecular still under 0.1 mm. pressure at 116°. Ethyl γ-(*p*-propiophenoxy)-butyrate was obtained as colorless oil which crystallized in the ice-box; yield 7.3 g.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.42; H, 7.85.

γ-(*p*-Propiophenoxy)-butyric acid (XIX) was obtained by saponification of XVIII, m.p. (from water) 119°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.83; H, 7.41.

Five grams of XVIII was added to 175 ml. of a 0.25 molar dry perbenzoic acid solution (100% excess).[7] The bottles were kept at room temperature for nine days when oxygen absorption had practically stopped at 50% of the theoretical amount. The solution was then extracted with 10% sodium carbonate until on acidification no more benzoic acid was precipitated. Washing with water was followed by drying over sodium sulfate. Five grams of oily residue was left after removal of chloroform. This was hydrolyzed with 30 ml. of 10% alcoholic potassium hydroxide. Part of the alcohol was boiled off and water was added to a volume of 100 ml. The solution was then extracted with ether, the ether layer dried and taken to dryness. The residual oil was repeatedly crystallized from dry benzene. The separation of the hydroxyphenoxy portion from the unchanged propiophenoxy portion could be achieved because of the higher solubility of the latter in benzene. One gram of γ-(*p*-hydroxyphenoxy)-butyric acid (XIV) was obtained of m.p. 120°.

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