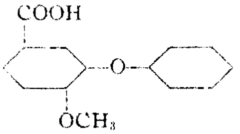
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MISSOURI]

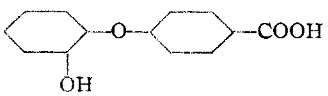
The Gattermann Reaction in the Mono-methoxydiphenyl Ethers[1]

BY H. E. UNGNADE AND E. F. ORWOLL[2]

When the Gattermann aldehyde synthesis is carried out with 4-methoxydiphenyl ether the product is 4-(4-methoxyphenoxy)-benzaldehyde. The yields are poor[3] and difficult to reproduce. When the same reaction is carried out with the 2- and 3-isomers, the yields are good (40–50%), but the products in each case are mixtures of aldehydes which so far have not been separated. The position of the aldehyde group in each isomer has, however, been determined from the oxidation products.

Oxidation of the aldehyde mixture from 2-methoxydiphenyl ether with potassium permanganate gave a mixture of methoxy acids from which the known *m*-phenoxy-*p*-methoxybenzoic acid (I)[4] could be isolated by fractional crystallization.

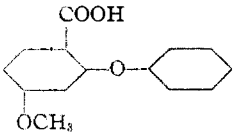

I

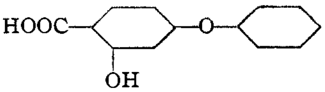

II

Demethylation of the acid mixture with hydriodic acid gave a mixture of the acids (I) and (II), which after esterification could be separated by extraction with alkali. The known acid (II)[5] was obtained from the hydrolysis of the alkali-soluble fraction. *m*-Phenoxy-*p*-methoxybenzoic acid (I) was stable toward hydriodic acid but could be demethylated by use of hydrobromic acid at 150° or aluminum chloride in benzene.

When the mixture of methoxy acids was demethylated with potassium hydroxide in ethylene glycol, the product consisted of approximately equivalent amounts of 2-hydroxydiphenyl ether and *p*-(*o*-hydroxyphenoxy)-benzoic acid (II). The pure methoxy acid (I) was demethylated and decarboxylated to give 2-hydroxydiphenyl ether with the same reagent whereas the isomeric *p*-(*o*-methoxyphenoxy)-benzoic acid was demethylated to the hydroxy acid (II).

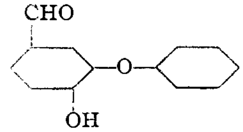
The mixture of methoxy aldehydes from 3-methoxydiphenyl ether was oxidized with potassium permanganate. When the resulting mixture of methoxy acids was treated with acetyl chloride or with sulfuric acid 3-methoxyxanthone was obtained in yields of 16–23%. The only two 3-methoxy acids of diphenyl ether which can cyclize in this fashion are *o*-phenoxy-*p*-methoxybenzoic acid (III) and *o*-(*m*-methoxyphenoxy)-benzoic acid. The latter acid was not expected in the reaction mixture since the formation of the corresponding aldehyde is contrary to the normal orientation. The experimental data are therefore taken as evidence that one of the isomeric acids corresponded to structure (III).


III


IV

The acid (IV) was obtained in yields of 76% by demethylation of the mixture of 3-methoxy acids with aluminum chloride. The small amount of acid (III) was lost during the demethylation.

Both mixtures of methoxy aldehydes have been studied in respect to their behavior toward aluminum chloride. When the mixture from 2-methoxydiphenyl ether was treated with aluminum chloride in benzene, the aldehyde (V) and 2-hydroxydiphenyl ether were the only products.


V

The structure of the hydroxy aldehyde (V) was established by methylation and oxidation to the acid (I). The formation of an equivalent amount of 2-hydroxydiphenyl ether indicates that *p*-(*o*-methoxyphenoxy)-benzaldehyde lost carbon monoxide in the demethylation with aluminum chloride. A sample of the pure compound treated in the same way gave 2-hydroxydiphenyl ether in good yield. The loss of carbon monoxide in

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(1) Presented before the Division of Organic Chemistry at the 105th meeting of the American Chemical Society, Detroit, Michigan, April 13, 1943.

(2) Summary of the investigation undertaken by Mr. E. F. Orwoll in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Present address, Sharples Chemicals, Inc., Wyandotte, Michigan.

(3) Harington and Pitt Rivers, *J. Chem. Soc.*, 1101 (1940).

(4) Faltis, Holzinger, Ita and Schwarz, *Ber.*, **74B**, 79 (1941).

(5) Ungnade, THIS JOURNAL, **63**, 2091 (1941).

this case was unexpected but is not without precedent.[6] The aldehyde (V) was converted to 3-phenoxytyrosine, a new isomer of thyronine.

Aluminum chloride in benzene acted upon the aldehyde mixture from 3-methoxydiphenyl ether with formation of 3-hydroxydiphenyl ether as the only alkali-soluble product. Since *o*-methoxybenzaldehyde under identical conditions gave a 45% yield of phenol it may be assumed that the 3-hydroxydiphenyl ether was formed from *p*-phenoxy-*o*-methoxybenzaldehyde. In all cases the action of aluminum chloride on methoxy aldehydes led to by-products which will be the subject of future studies.

Experimental

Preparation of the Methoxy Aldehydes.—Anhydrous aluminum chloride (11.8 g.) was added to a solution of the methoxydiphenyl ether in 30 cc. of dry, thiophene-free benzene. To the cooled solution was added with stirring 7.8 cc. of freshly prepared anhydrous hydrogen cyanide. Stirring was continued for thirty minutes. Then a stream of dry hydrogen chloride was passed into the solution with vigorous stirring for thirty minutes at 0°, thirty minutes at room temperature and one and one-half hours at 40–50°. At this time 1.0 g. of aluminum chloride was added and the reaction continued for one and one-half hours. After cooling and decomposition with ice and hydrochloric acid the benzene was removed by steam distillation. The ether extract of the remaining aqueous solution was stirred with excess saturated sodium bisulfite solution for three hours. The bisulfite addition compound was filtered, washed with ether and decomposed with sodium carbonate solution. The combined ether solutions usually contained some starting material and some hydroxydiphenyl ether. 2-Methoxydiphenyl ether gave 40–50% yield of aldehydes, 3-methoxydiphenyl ether 40–45% and 4-methoxydiphenyl ether 6% yield of the 4'-aldehyde. The products separated as oils except in the case of the 4-isomer. All attempts to separate the aldehyde mixtures by the usual methods failed.

***m*-Phenoxy-*p*-methoxybenzoic Acid.**—The mixture of aldehydes from 2-methoxydiphenyl ether (0.75 g.) was dissolved in 6.7 cc. of acetone and the solution was treated in the cold with 3.8 g. of potassium permanganate in small portions with shaking. The manganese dioxide was filtered off and extracted with hot water. The combined filtrates were freed from acetone and acidified. Numerous fractional crystallizations from benzene–petroleum ether (86–100°) gave a pure acid melting at 186.0–186.4°. A mixture with an authentic specimen of *m*-phenoxy-*p*-methoxybenzoic acid melted at 186–186.5°.

Synthesis of *m*-Phenoxy-*p*-methoxybenzoic Acid: 3-Bromo-4-hydroxytoluene.—3-Bromo-4-aminotoluene (37.6 g.) was dissolved in a mixture of 36 cc. of concd. sulfuric acid and 96 g. of ice. A fine precipitate of the amine sulfate separated when the mixture was cooled and stirred and treated with 90 g. of ice. To the cold mixture was added a solution of 16.1 g. of sodium nitrite in 39 cc. of water. Excess nitrous acid was destroyed by addition of 1.5 g. of urea and the mixture diluted to 625 cc. with ice-water. The cold diazonium solution was added from a dropping funnel to a boiling solution of 75 g. of sodium sulfate, 100 g. of concentrated sulfuric acid and 50 g. of water at such a rate that the temperature in the solution was maintained at 130–135°. After all the diazonium solution was in, 200 cc. of water was added at the same rate. The steam-distillate was extracted with ether. The phenol was taken up in 10% sodium hydroxide solution and liberated with hydrochloric acid. The ether extract left upon evaporation 93–96% of crude 3-bromo-4-hydroxytoluene. The pure product boils at 102–104° (20 mm.).

3-Bromo-4-methoxytoluene.—Methylation of 3-bromo-4-hydroxytoluene with dimethyl sulfate[7] gave a yield of 78% of a colorless oil boiling at 126–127° (25 mm.).

3-Phenoxy-4-methoxytoluene.—Potassium phenoxide was prepared from 9.4 g. of phenol and 5.05 g. of powdered potassium hydroxide. The mixture was heated *in vacuo* for three hours at 160°. To the dry salt was then added 4.7 g. of phenol, 0.03 g. of copper powder and 18.4 g. of 3-bromo-4-methoxytoluene. The mixture was heated under reflux for three hours at 200°. The product (11.6 g.), isolated by steam distillation, melted at 38.5–39° after crystallization from aqueous alcohol and petroleum ether (28–38°).

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.56; H, 6.66.

3-Phenoxy-4-hydroxytoluene.—A mixture of 3-phenoxy-4-methoxytoluene (1.4 g.), 13.5 cc. of glacial acetic acid, 13.5 cc. of 47% hydriodic acid and 5 cc. of acetic anhydride was refluxed for fifty minutes. The product solidified when the mixture was poured into water. The crude hydroxy compound weighed 1.2 g. It melted at 69.7–70° after crystallization from petroleum ether.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 78.00; H, 6.00. Found: C, 78.00; H, 6.30.

***m*-Phenoxy-*p*-methoxybenzoic Acid.**—3-Phenoxy-4-methoxytoluene (1.6 g.) was added to a solution of 2.36 g. of potassium permanganate in 12 cc. of water and 23 cc. of pyridine. The mixture was refluxed for two hours, then filtered. The acid, liberated upon acidification, melted at 186–186.5° after crystallization from petroleum ether.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.92. Found: C, 68.95; H, 4.95.

***m*-Phenoxy-*p*-hydroxybenzoic Acid.**—Demethylation of the methoxy acid (0.2 g.) was unsuccessful with hydriodic acid (2 cc., 47%) in acetic acid (15 cc.) and varying amounts of acetic anhydride even with refluxing for one to five hours. The methoxy acid was always recovered unchanged. The hydroxy acid could be obtained by demethylation with hydrobromic acid (48%) in acetic acid by heating in a Carius tube for four hours at 150°, or by demethylation with aluminum chloride in benzene upon refluxing for two hours (0.17 g. of the methoxy acid, 1.5 g. of aluminum chloride and 35 cc. of benzene). The *m*-phenoxy-*p*-hydroxybenzoic acid after crystallization from

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(6) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," A. C. S. Monograph No. 87, Reinhold Publ. Corp., New York, N. Y., 1941, p. 645.

(7) "Organic Syntheses," Coll. Vol. I, p. 50.

benzene–petroleum ether (86–100°) melted at 187.6–188°. It gave a melting point depression when mixed with the methoxy acid (m. p. 186–186.5°). Remethylation with dimethyl sulfate gave *m*-phenoxy-*p*-methoxybenzoic acid, melting point and mixed melting point 186–186.5°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 67.82; H, 4.35. Found: C, 67.70; H, 4.35.

***m*-Phenoxy-*p*-hydroxybenzaldehyde.**—The mixture of methoxy aldehydes from 2-methoxydiphenyl ether (2.5 g.) was dissolved in 60 cc. of dry, thiophene-free benzene. Aluminum chloride (5.6 g.) was then added with stirring. Stirring was continued during two and one-quarter hours at 70°. After cooling the mixture was poured into water and the benzene distilled off. Addition of excess hydrochloric acid to the aqueous solution precipitated a red oil which was extracted with ether. The sodium carbonate extract of this ether solution gave upon acidification 0.7 g. (30%) of a solid product melting at 117–118°. The pure hydroxy aldehyde after crystallization from benzene-petroleum ether (60–80°) melted at 121.5–122°.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.67. Found: C, 72.56; H, 4.85.

The sodium hydroxide extract of the ether solution, after acidification, gave a brown solid (0.8 g.) which, after decolorization and crystallization from aqueous alcohol, melted at 105.0–105.5°. The mixed melting point with 2-hydroxydiphenyl ether (104.5–105°) was 104.5–105°.

***m*-Phenoxy-*p*-methoxybenzaldehyde.**—Methylation of the hydroxyaldehyde with dimethyl sulfate in the usual way gave *m*-phenoxy-*p*-methoxybenzaldehyde, m. p. 49–50°, yield 91%.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.68; H, 5.26. Found: C, 73.53; H, 5.28.

Oxidation of this aldehyde with potassium permanganate in acetone gave *m*-phenoxy-*p*-methoxybenzoic acid, melting point and mixed melting point 186–186.5°, yield 63%.

The semicarbazone, crystallized from aqueous alcohol, melted at 172.4–173°.

Anal. Calcd. for $C_{15}H_{15}O_2N_3$: C, 63.00; H, 5.32. Found: C, 62.81; H, 5.14.

Demethylation of *p*-(*o*-Methoxyphenoxy)-benzaldehyde.—This aldehyde, reported previously,[5] formed a semicarbazone melting at 207–208° after crystallization from aqueous acetic acid.

Anal. Calcd. for $C_{15}H_{15}O_2N_3$: C, 63.00; H, 5.32. Found: C, 63.24; H, 5.50.

Demethylation of the aldehyde with aluminum chloride in benzene as described previously gave 2-hydroxydiphenyl ether as the only product; melting point and mixed melting point 104.5–105°.

4′-Carboxy-2-hydroxydiphenyl Ether.—This acid which has been described in an earlier paper[5] was obtained from the oxidation products of the aldehyde mixture from 2-methoxydiphenyl ether in two ways.

1. The mixture (1.2 g.) was refluxed with 18 cc. of acetic acid, 13 cc. of hydriodic acid and 5 cc. of acetic anhydride for one hour Then the reaction mixture was poured into water and the products extracted with ether. The sodium carbonate extract liberated on acidification 1.0 g. of an oily acid mixture which was converted to the corresponding silver salts. The salts (1.15 g.) were converted to the ethyl esters by refluxing with excess ethyl iodide in ether. This ether solution was then extracted with sodium hydroxide. Acidification gave 0.25 g. of an oil which after hydrolysis with 5% alcoholic potassium hydroxide yielded 0.18 g. of a crystalline solid melting at 120–121°. The melting point was raised to 138.5–138.8° by crystallizing from water and from benzene–petroleum ether. Mixed melting point with 4′-carboxy-2-hydroxydiphenyl ether (138.2–139°) was 138.2–129°.

2. The acid mixture (0.95) was refluxed for five hours with a solution of 8.3 g. of potassium hydroxide in 40 cc. of ethylene glycol in a copper flask. The mixture was then poured into water and acidified with hydrochloric acid. After extraction with ether the acid fraction was taken up in sodium carbonate solution, acidified with hydrochloric acid and crystallized from benzene–petroleum ether (86–100°), m. p. 136–137°, yield 34%; mixed melting point with 4′-carboxy-2-hydroxydiphenyl ether (m. p. 138–139°) 136–137°. The sodium hydroxide extract of the ether solution gave 0.28 g. (39%) of 2-hydroxydiphenyl ether, m. p. 104–105.5° (mixed m. p. 104–105.5°).

Demethylation of the Pure Methoxy Acids.—A specimen of each of the pure methoxy acids was demethylated with potassium hydroxide in ethylene glycol according to the above procedure. 4′-Carboxy-2-methoxydiphenyl ether gave a 53% yield of 4′-carboxy-2-hydroxydiphenyl ether, m. p. 138–139°, whereas *m*-phenoxy-*p*-methoxybenzoic acid gave a 75% yield of 2-hydroxydiphenyl ether, m. p. 103–104°.

3-Phenoxytyrosine.—*m*-Phenoxy-*p*-hydroxybenzaldehyde was converted to the corresponding oxazolone by the usual method. The product after crystallization from benzene–petroleum ether melted at 183.4–184°, yield 75%.

Anal. Calcd. for $C_{22}H_{15}NO_4$: N, 3.92. Found: N, 3.77.

Hydrolysis of the azlactone was carried out according to the customary procedure.[8] The yield of amino acid amounted to 50%. The amino acid melted at 236° when heated rapidly in a melting point block pre-heated to 200°.

Anal. Calcd. for $C_{15}H_{15}O_4N$: N, 4.68. Found: N, 5.12.

The absorption curve[9] shows a maximum at 2970 Å. ($\log \epsilon = 3.62$) and a minimum at 2750 Å. ($\log \epsilon = 3.4$) where ϵ = molecular extinction coefficient.

3-Methoxyxanthone.—The aldehyde mixture from 3-methoxydiphenyl ether was oxidized with potassium permanganate in acetone in the usual way. The acid mixture obtained in 59.5% yield was heated with sulfuric acid according to the procedure of Ullmann and Wagner[10] and gave a 16.7% yield of 3-methoxyxanthone, m. p. 122–123°. Cyclization with acetyl chloride[11] gave 23% of the xanthone, m. p. 125–127°. An authentic specimen of *o*-phenoxy-*p*-methoxybenzoic acid treated in the same way yielded 84% of 3-methoxyxanthone, m. p. 125–126°; mixed melting point 124–126°.

3-Hydroxyxanthone.—Demethylation with aluminum chloride of the above 3-methoxyxanthone gave 3-hydroxy-

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(8) "Organic Syntheses," Vol. XIV, p. 80.

(9) Absorption spectrum by V. R. Ells, Spectrographic Service University of Missouri.

(10) Ullmann and Wagner, *Ann.*, **355**, 369 (1907).

(11) Gottesmann, *Ber.*, **66**, 1168 (1933).

xanthone, m. p. 249–250°. Ullmann and Wagner[10] report 243°.

***o*-Phenoxy-*p*-hydroxybenzoic Acid.**—Demethylation of *o*-phenoxy-*p*-methoxybenzoic acid with aluminum chloride in benzene gave 54% of the hydroxy acid which melted at 163–164° after vacuum sublimation and crystallization from water.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.84; H, 4.27. Found: C, 67.64; H, 4.54.

***p*-Phenoxy-*o*-hydroxybenzoic Acid.**—The acid mixture resulting from the oxidation of the 3-methoxy aldehydes was demethylated with aluminum chloride in benzene. The product melted at 162–167°, yield 76%. Vacuum sublimation at 150–170° of 0.126 g. of this product gave 0.122 g. melting at 167–168°. Crystallization from benzene-petroleum ether raised the melting point to 180.8–181.4°. Mixed with an authentic specimen of *p*-phenoxy-*o*-hydroxybenzoic acid (182.4–183°) the melting point was 180.4–181.2°.

Synthesis of *p*-Phenoxy-*o*-hydroxybenzoic Acid: 2-Amino-4-chlorotoluene.—2-Nitro-4-chlorotoluene (100 g.) in 100 cc. of methanol was reduced in the presence of 3 g. of Raney nickel at 60° (2000 lb.). The pure amine boiled at 120–125° (40 mm.), yield 83%.

4-Chloro-2-hydroxytoluene.—Diazotization and hydrolysis of the above amine according to the procedure described for 3-bromo-4-hydroxytoluene (above) gave 85% of the chlorocresol melting at 67–68°. Methylation with dimethyl sulfate[7] gave 80% of 4-chloro-2-methoxytoluene boiling at 104–106° (25 mm.).

***p*-Methoxy-*o*-methoxytoluene.**—A mixture of potassium phenoxide (4.3 g.), 5.0 g. of 4-chloro-2-methoxytoluene and 0.1 g. of copper powder was heated for two and one-half hours at 250–270°. The products were taken up in ether and vacuum distilled. The desired diphenyl ether boiled at 275–276°, yield 10%. It was oxidized to the methoxy acid without further purification.

***p*-Phenoxy-*o*-hydroxybenzoic Acid.**—The above compound was oxidized with permanganate in aqueous pyridine. The crude acid melted at 74–75°, yield 31%; it was used without further purification for the preparation of the hydroxy acid, which was obtained by demethylation with hydriodic acid in acetic acid. The pure acid, crystallized from benzene–petroleum ether, melted at 182.4–183.0°.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.84; H, 4.27. Found: C, 67.54; H, 3.93.

3-Hydroxydiphenyl Ether.—Demethylation of 3-methoxydiphenyl ether with potassium hydroxide in ethylene glycol gave a 76% yield of the hydroxydiphenyl ether. A 70% yield was obtained by demethylation with hydriodic acid (sp. gr. 1.5) in acetic acid. The liquid product was used without special purification.

The aryloxyacetic acid formed from this ether melted at 67–67.4° (from petroleum ether (86–100°)).

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.80; H, 4.95. Found: C, 68.91; H, 4.65.

Demethylation of the aldehyde mixture (2 g.) from 3-methoxydiphenyl ether with aluminum chloride (6 g.) in benzene (60 cc.) gave 0.4 g. of alkali-soluble material which was found to be 3-hydroxydiphenyl ether by conversion to its aryloxyacetic acid, m. p. 65–66°, mixed with an authentic specimen (67–67.4°), m. p. 66–67°.

Summary

1. The Gattermann aldehyde synthesis applied to the three mono methoxydiphenyl ethers gives good yields of aldehydes with the 2- and 3-isomers but not with the 4-isomer.

2. 2-Methoxydiphenyl ether yields a mixture of approximately equal amounts of the 5- and 4′-aldehydes. The structures of these aldehydes have been established by two independent methods.

3. The aldehydes from 3-methoxydiphenyl ether consist of a mixture of the 4- and 6-isomers in which the 4-isomer predominates.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Reaction between Quinones and Metallic Enolates. XVII. Dibromo-*p*-xyloquinone and Sodiomalonic Ester[1]

BY LEE IRVIN SMITH AND JOSEPH NICHOLS[2]

Previous work[1,3,4] has shown that a brominated methylquinone may react with a metallic enolate to produce either a coumarin derivative by reaction at a methyl group, or a quinonemalonic ester by direct replacement of a bromine atom. Thus, trimethylbromoquinone is converted by action of sodiomalonic ester into the coumarin I; in this case, no replacement of the bromine atom occurs, and the reaction is confined entirely to the methyl group which is in the meta position to the bromine atom. In a similar fashion, dibromo-*m*-xyloquinone is converted into the coumarin II, and no product could be isolated which was derived by replacement of a bromine atom. However, dibromo-*o*-xyloquinone reacts entirely by replacement of a bromine atom, and the primary

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[1] XVI. Smith and Austin, THIS JOURNAL, **64**, 528 (1942).

[2] Abstracted from a thesis by Joseph Nichols, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, February, 1943.

[3] Smith and Byers, *ibid.*, **63**, 612 (1941).

[4] Smith and Johnson. *ibid.*, **59**. 673 (1937).