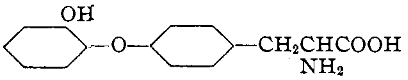
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

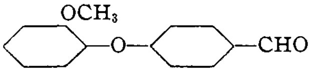
The Synthesis of *dl*-"Ortho"-Thyronine[1]

BY HERBERT E. UNGNADE

Although thyronine has been thoroughly investigated,[2] its isomers with hydroxyl groups ortho or meta to the ether oxygen are at present unknown. Of the two compounds, the ortho isomer (I) may be of importance as a reference substance for studies of the physiological formation of thyroxine. Since the Erlenmeyer synthesis of amino acids is very satisfactory for compounds of this type, the problem consisted essentially in the preparation of *p*-(*o*-methoxyphenoxy)-benzaldehyde (II). The usual method of preparation from the nitro compound: $NO_2 \rightarrow NH_2 \rightarrow C \equiv N \rightarrow CHO$ proved unsatisfactory since the Stephen reduction gave only traces of aldehyde. Likewise unsuccessful were attempts to introduce the formyl group into 2-methoxydiphenyl ether by means of chloromethylation or the Gattermann synthesis. Mixtures of isomers were obtained in both of these reactions.[3] Attempts to oxidize 2-methoxy-4′-methyldiphenyl ether (III) with chromic oxide, acetic acid and acetic anhydride resulted apparently in complete decomposition.



(I)



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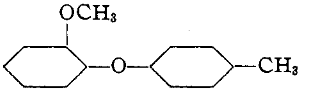
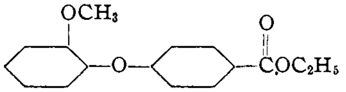


(III)

The aldehyde (II) could be obtained by reduction of ethyl *p*-(*o*-methoxyphenoxy) benzoate (IV) using the method of McFayden and Stevens.[4]



(IV)

The ester was readily converted to the hydrazide, the *p*-toluenesulfonate of which gave the aldehyde (II) on decomposition.

The ultraviolet absorption spectra of "ortho" and "para" thyronine have been determined and are shown in Fig. 1.[5] The curves obtained can be used for identification of either of the pure compounds. In view of the relative position of the minima and maxima, mixtures of the two compounds may be estimated from their absorption spectra.

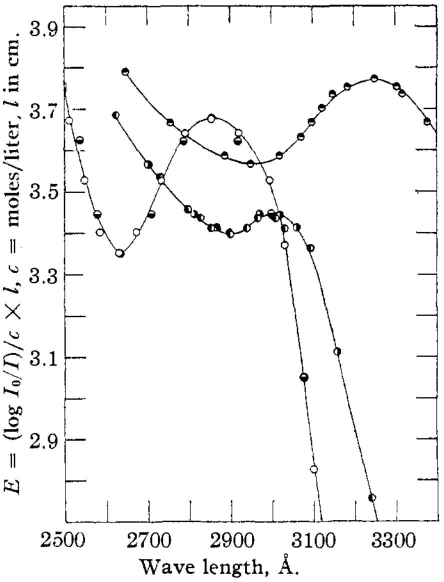


Fig. 1.—○, 0.081 mg./cc., *dl*-"ortho"-thyronine; ◒, 0.0486 mg./cc., *dl*-"ortho"-thyronine; ◐, 0.095 mg./cc., *dl*-thyronine (synthetic); ◑, 0.127 mg./cc., *dl*-thyronine (synthetic); ◓, 0.2 mg./cc., *dl*-thyroxine.[6]

Upon iodination of *o*-thyronine in concentrated ammonia, absorption was rapid at first but ceased entirely when two molar equivalents of iodine had been added. The iodination product was found to be devoid of thyroid activity in doses of one hundred times the effective thyroxin dose (tadpole test).

It is interesting to note that diiodo-"ortho"-tyrosine obtained by iodination of *o*-hydroxyphenylalanine is devoid of thyroid activity as measured by the tadpole metamorphosis test, whereas diiodotyrosine shows some activity when

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[1] Presented before the Division of Organic Chemistry at the 101st Meeting of the American Chemical Society, St. Louis, Missouri, April 7-11, 1941.

[2] Harington, *et al.*, *Biochem. J.*, **20**, 300 (1926); **21**, 852 (1927); **28**, 68 (1934); *J. Chem. Soc.*, 1101 (1940).

[3] Unpublished work by E. Orwoll in this Laboratory.

[4] McFayden and Stevens, *J. Chem. Soc.*, 584 (1936); Harington and Pitt Rivers, *ibid.*, 1101 (1940).

[5] The absorption spectra were determined by V. R. Ells, Spectrographic Service, University of Missouri.

[6] I wish to thank Dr. C. W. Turner of the Dairy Department, University of Missouri, for a sample of synthetic thyroxine (Hoffman-La Roche, Basel).

given at the same level as the ortho isomer (one hundred times the effective thyroxine dose).[7]

Acknowledgment.—The author wishes to express his thanks to the University Research Council for funds to purchase apparatus used in this investigation.

Experimental[8]

4'-Nitro-2-methoxydiphenyl Ether.—Application of the Ullmann reaction[9] gave a 64% yield of a product boiling at 160–161° (1 mm.) (from a sausage flask). One crystallization from ethanol gave a product melting at 106–107° which agrees with the value reported by Buchan and Scarborough.[10]

4'-Amino-2-methoxydiphenyl Ether.—Reduction of the above nitro compound took place readily at 100° and 2000 lb. pressure in the presence of 3% Raney nickel. Distillation gave an 86% yield of the amine, b. p. 149–150° (1 mm.) (sausage flask), which melted at 96–97° after one crystallization from dilute methanol.

Acetyl Derivative.—M. p. 115–115.5° (after repeated crystallizations alternately from dilute acetic acid and petroleum ether). The melting point has been reported as 118°.[10]

*Anal.** Calcd. for $C_{15}H_{15}O_3N$: C, 70.03; H, 5.88; N, 5.44. Found: C, 69.80; H, 5.85; N, 5.48.

4'-Cyano-2-methoxydiphenyl Ether.—Gattermann reaction: The usual procedure of diazotization and replacement with cuprous cyanide gave only a 30% yield of a product boiling at 145–150° (1 mm.) which after numerous crystallizations melted at 93–94°.

Anal. Calcd. for $C_{14}H_{11}O_2N$: C, 74.67; H, 4.89; N, 6.22. Found: C, 74.71; H, 5.14; N, 6.22.

A product of greater purity could be obtained through the Rosenmund–v. Braun synthesis.[11]

A mixture of 6.8 g. of 4'-amino-2-methoxydiphenyl ether, 8.2 cc. of concentrated hydrochloric acid and 20 cc. of water was treated at 0° with 2.2 g. of sodium nitrite. The diazonium solution was poured into a slight excess of aqueous potassium iodide solution and, after standing, heated on a water-bath to complete decomposition. The ether extract was washed with water and bisulfite, dried and freed from solvent. The iodo compound was distilled from a Hickman still; b. p. 150–151° (2 mm.); yield 4.46 g., colorless oil.

A mixture of 4.46 g. of this iodide and 1.50 g. of dry cuprous cyanide was heated for four hours at 250°. The cold solid reaction mixture was ground in a mortar and then extracted with acetone. The extract was concentrated and then allowed to crystallize after addition of water. The product melted at 92–93°, yield 95–98%.

4'-Carboxy-2-hydroxydiphenyl Ether.—4'-Cyano-2-methoxydiphenyl ether (0.13 g.), 2 cc. of acetic acid and 2 cc. of 47% hydriodic acid were refluxed for six hours. Then the reaction mixture was poured into water. The acid crystallized on cooling, yield 0.08 g. One crystallization from benzene–petroleum ether (86–100°) gave a product melting at 139–139.5°.

*Anal.** Calcd. for $C_{13}H_{10}O_4$: C, 67.80; H, 4.03 Found: C, 67.84; H, 4.27.

Synthesis of 4'-Carboxy-2-hydroxydiphenyl Ether: 4'-Methyl-2-methoxydiphenyl Ether.—Guaiacol potassium was prepared from 25 g. of guaiacol and 9.8 g. of powdered potassium hydroxide. The mixture was heated *in vacuo* for two hours at 150°. To the dry salt was then added 0.1 g. of copper powder and 30 g. of *p*-bromotoluene. The mixture was heated under reflux for four hours at 200°. The product (20.2 g.), isolated by steam distillation, melted at 50–51°. Recrystallization from aqueous ethanol or petroleum ether (30–60°) gave the pure substance melting at 51.8–52.5°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.5; H, 6.74. Found: C, 78.67; H, 6.74.

4'-Methyl-2-hydroxydiphenyl Ether.—A mixture of 1.04 g. of the methyl ether (above), 10 cc. of acetic acid, 10 cc. of hydriodic acid (d. 1.50) and 5 cc. of acetic anhydride was refluxed for one hour. The product solidified when the mixture was poured into water. The crude hydroxy compound weighed 0.85 g. It melted at 63–63.8° after one crystallization from petroleum ether.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 78.00; H, 6.00. Found: C, 78.05; H, 5.91.

4'-Carboxy-2-methoxydiphenyl Ether.—Oxidation of 4'-methyl-2-methoxydiphenyl ether with permanganate was found to be unsatisfactory in water, acetone, aqueous acetone, and in pyridine. The following procedure gave satisfactory yields. A mixture of 6.6 g. of the methyl compound, 9.74 g. of potassium permanganate, 50 cc. of water and sufficient pyridine to produce a homogeneous solution was refluxed for two hours. The manganese dioxide was filtered off and extracted with hot water, and the filtrate acidified with hydrochloric acid. The crude acid melted at 159–160°, yield 88%. Crystallization from benzene–petroleum ether (86–100°) did not change the melting point.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.91. Found: C, 68.80; H, 5.08.

4'-Carboxy-2-hydroxydiphenyl Ether.—The methoxy acid (0.18 g.) was treated with 2 cc. of acetic acid and 2 cc. of hydriodic acid and the mixture refluxed for six hours. The hydroxy acid separated when the mixture was poured into water. After crystallization from benzene–petroleum ether (86–100°) the acid melted at 138–139°. It did not depress the melting-point of a sample prepared by the hydrolysis of the nitrile.

4-[*p*-(*o*-Methoxyphenoxy)-benzal]-2-phenyloxazolone-5.—Attempts to reduce 4'-cyano-2-methoxydiphenyl ether by the method of Stephen[12] gave disappointing yields. Stannous chloride (4.66 g.) in 35 cc. dry ether was saturated with dry hydrogen chloride. The nitrile (2.5 g.) was added and the mixture stirred for one hour. The reaction mixture was allowed to stand overnight and then the addition

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[7] I am indebted to E. P. Reinecke of the Dairy Department, University of Missouri, for the thyroid assays.

[8] Starred microanalyses by E. E. Hardy, University of Minnesota, all others by the microlaboratory of the University of Missouri.

[9] Weston and Adkins, THIS JOURNAL, **50**, 859 (1928).

[10] Buchan and Scarborough, *J. Chem. Soc.*, 705 (1934).

[11] Rosenmund and Struck, *Ber.*, **52**, 1749 (1918); von Braun and Manz, *Ann.*, **488**, 111 (1931); C. F. Koelsch, private communication.

[12] Stephen, *J. Chem. Soc.*, **127**, 1874 (1925).

product filtered with suction and washed with dry ether. Decomposition with warm water gave an oily product which was taken up in ether, washed and dried. A solid remained after removal of the ether which could be crystallized from petroleum ether but did not give any sharp-melting fractions. Conversion of the various fractions into the oxazolone[13] gave a total yield of 20 mg. One crystallization from acetic acid yielded the pure oxazolone, m. p. 184–185°.

Anal. Calcd. for $C_{23}H_{17}O_4N$: C, 74.39; H, 4.58; N, 3.77. Found: C, 74.17; H, 4.85; N, 3.86.

4′-Carbethoxy-2-methoxydiphenyl Ether.—Ethyl *p*-hydroxybenzoate (24 g.) and 8.4 g. of powdered potassium hydroxide were intimately mixed and heated *in vacuo* at 140–150° for two hours. To the dry salt was added 300 mg. of copper powder and 42 g. of *o*-bromoanisole (93.8–94° (10 mm.), $n^{20}\text{D}$ 1.5737). The mixture was then heated under reflux in a metal bath. The bath temperature was raised to 240° and maintained at 240° for one hour. Finally the temperature was raised to 260° during ten minutes and the mixture allowed to cool. The reaction products were taken up in water and ether and dried over calcium chloride. Acidification of the water layer with hydrochloric acid gave 0.15 g. of a solid, m. p. 156–157°, after one crystallization from benzene–petroleum ether, which did not depress the melting point of 4′-carboxy-2-methoxydiphenyl ether.

Distillation of the alkali-insoluble material gave 17.07 g. recovered *o*-bromoanisole, b. p. 70–71° (1 mm.), and a solid fraction which crystallized in the side-arm. The material melted at 72–72.5° after one crystallization from petroleum ether and did not depress the melting point of 2-methoxydiphenyl ether. Demethylation with hydriodic acid (d. 1.50) gave an 88% yield of the known 2-hydroxydiphenyl ether, m. p. 106–107°. The remainder of the alkali-insoluble product boiled at 145–147° (1 mm.); yield 16.47 g., colorless liquid which could not be crystallized.

Hydrazide.—A mixture of 16.17 g. of the above ester, 9 cc. of hydrazine hydrate (85%) and 28 cc. of absolute ethanol was heated in a pressure bottle for sixteen hours at 100°. The product crystallized on cooling, m. p. 128–129°, yield 11.83 g. Recrystallization from methanol gave a product melting at 130.5–131.5°. The hydrazide obtained from the ethyl ester prepared from 4′-carboxy-2-methoxydiphenyl ether by way of the silver salt (overall yield 78%) did not depress the melting point of the above compound.

Anal. Calcd. for $C_{14}H_{14}O_3N_2$: C, 65.11; H, 5.43. Found: C, 65.05; H, 5.66.

Toluenesulfonyl Derivative.—The hydrazide (11.83 g.) was dissolved in 100 cc. of dry pyridine, the solution cooled with ice and treated, in small portions, with 9.1 g. of *p*-toluenesulfonyl chloride. After standing for two hours at room temperature, the solution was poured into an ice-cold mixture of 130 cc. of concentrated hydrochloric acid and 130 cc. of water. The product crystallized on cooling. One crystallization from acetic acid gave the pure sulfonyl derivative, m. p. 205–206°, yield 14.15 g.

Anal. Calcd. for $C_{21}H_{20}N_2O_5S$: C, 61.16; H, 4.85. Found: C, 61.16; H, 5.32.

***p*-(*o*-Methoxyphenoxy)-benzaldehyde.**—The above *p*-toluenesulfonyl derivative (6.75 g.) was dissolved in ethylene glycol by heating to 160° and stirring. The hot solution was treated with 3.5 g. anhydrous sodium carbonate. Effervescence persisted for sixty seconds. Heating was continued for thirty seconds longer and then the mixture was cooled to 100° by immersing the flask in boiling water. Then 240 cc. of hot water was added and the mixture shaken. The ether extract left 2.94 g. of a pale yellow viscous oil which could not be crystallized. It was used without further purification for the preparation of the oxazolone.

The pure crystalline aldehyde, melting at 56–56.5°, was obtained by conversion into the bisulfite addition compound, regeneration and crystallization from petroleum ether (86–100°).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.68; H, 5.26. Found: C, 73.78; H, 5.45.

Ortho-thyronine.—*p*-(*o*-Methoxyphenoxy)-benzaldehyde was converted to the corresponding oxazolone by the usual method. The product separated in yellow needles, melting point and mixed melting point with the previous sample 184–185°, yield 63%.

Hydrolysis of the azlactone was carried out according to the customary procedure.[14] The yield of *o*-thyronine amounted to 62.5%, m. p. 240° (dec.).[15]

Anal. Calcd. for $C_{15}H_{15}O_4N$: N, 5.12. Found: N, 5.19.

Iodination in concentrated ammonia according to Datta and Prosad[16] ceased after addition of two molar equivalents of iodine. The iodination product was filtered, washed and dried. It has not been obtained entirely pure.[17]

Summary

1. Various synthetic routes for the preparation of *p*-(*o*-methoxyphenoxy)-benzaldehyde have been investigated. The structures of the new compounds have been established.

2. *dl*-*o*-Thyronine has been synthesized and characterized by its ultraviolet absorption spectrum. Its direct iodination product is devoid of thyroid activity.

COLUMBIA, MISSOURI RECEIVED MAY 21, 1941

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[13] "Organic Syntheses," Vol. XIII, p. 8.

[14] "Organic Syntheses," Vol. XIV, p. 80.

[15] The bath was preheated to 200° and then heated rapidly with the sample. Sintering occurred at 238°.

[16] Datta and Prosad, THIS JOURNAL, **39**, 441 (1917).

[17] According to Harington, "The Thyroid Gland," London, 1933, p. 145, 3′,5′-diiodothyronine has not been prepared in pure state.