drolysate contained two ninhydrin-positive substances with R_f's identical to those of arginine (R_f = 0.82) and glutamic acid (R_f = 0.06).

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

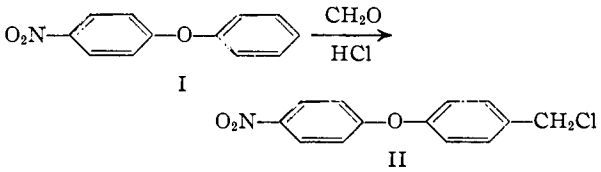
A Synthesis of *dl*-Thyronine *via* 4-Chloromethyl-4′-nitrodiphenyl Ether[1]

BY PHILIP L. SOUTHWICK, GEORGE E. FOLTZ AND WILLIAM E. MCINTYRE, JR.[2]

RECEIVED JULY 20, 1953

dl-Thyronine has been prepared in 30% yield from 4-nitrodiphenyl ether by means of a sequence of reactions (four separate steps) beginning with chloromethylation to give 4-chloromethyl-4′-nitrodiphenyl ether, and condensation of the latter compound with the sodium derivative of diethyl acetamidomalonate.

In the compound 4-nitrodiphenyl ether (I) the ring holding the nitro group should be relatively inert toward electrophilic reagents for aromatic substitution, whereas the other ring should show a higher reactivity and ortho and para orientation of an entering group. Previous investigations of the reactions of this substance have, in fact, shown that halogenation in the 4′-position is strongly favored.[3] It seemed likely, therefore, that chloromethylation of this compound, if it occurred at all, would lead almost exclusively to the formation of 4-chloromethyl-4′-nitrodiphenyl ether (II), a potentially useful synthetic intermediate. We were particularly interested in the utility of this substance as a starting point for the preparation of compounds related to thyroxine. In the present investigation satisfactory conditions were found for the preparation of compound II by means of the proposed chloromethylation reaction, and a useful synthesis was developed for *dl*-thyronine (V), the desiodo derivative of *dl*-thyroxine. The new thyronine synthesis produced a considerably better over-all yield than methods previously reported.[4]



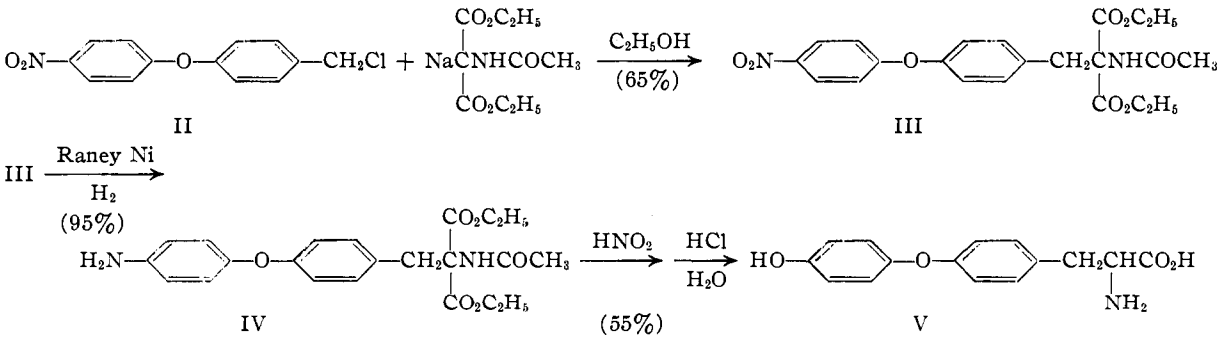
I

II

The best conditions found for the chloromethylation of 4-nitrodiphenyl ether (I) involved the use of a glacial acetic acid–phosphoric acid mixture as the reaction medium and a 60-hour heating period on a steam-bath. In this way the crystalline chloromethyl derivative II, m.p. 54–55° when fully purified, was obtained in 90% yield. The use of higher reaction temperatures reduced the time required for complete reaction but resulted in lower yields because of the decomposition of the product. That the chloromethyl group had been introduced into the 4′-position of 4-nitrodiphenyl ether (I) was established by oxidation of the chloromethyl derivative II with potassium permanganate solution to give a sample of 4-(4′-nitrophenoxy)-benzoic acid which was identical with a sample prepared by oxidizing 4-nitro-4′-methyldiphenyl ether.[5]

For the synthesis of *dl*-thyronine (V) from the chloromethyl derivative II a method based on the use of diethyl acetamidomalonate was developed. A 65% yield of the key intermediate, the malonic ester derivative III, was obtained from the reaction of compound II with the sodium derivative of diethyl acetamidomalonate in absolute ethanol solution.

A number of routes for the conversion of the malonic ester derivative III into *dl*-thyronine (V) were investigated. The one which proved most satisfactory was that involving the transformations indicated below.



II

III

IV

V

Analytical results, the melting point and the melting points of derivatives confirmed the identification of the product as *dl*-thyronine. A new

(1) Abstracted from a thesis submitted by William E. McIntyre, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Carnegie Institute of Technology, December, 1952.

(2) Institute Fellow in Organic Chemistry, 1951–1952.

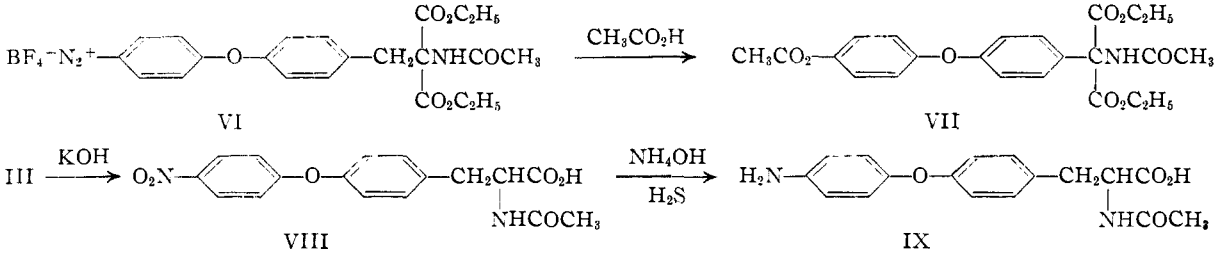
(3) (a) R. Q. Brewster and R. Slocombe, THIS JOURNAL, **67**, 562 (1945); (b) H. A. Scarborough, *J. Chem. Soc.*, 2361 (1929).

(4) (a) G. R. Harington, *Biochem. J.*, **20**, 300 (1926); (b) C. R. Harington and W. McCartney, *ibid.*, **21**, 852 (1927); (c) A. Canzanilli, C. R. Harington and S. S. Randall, *ibid.*, **28**, 68 (1934); (d) C. R. Harington and R. V. Pitt Rivers, *J. Chem. Soc.*, 1101 (1940).

(5) Both samples of the acid melted at 236–237° and a mixed melting point showed no depression. C. Haussermann and E. Bauer, *Ber.*, **29**, 2083 (1896), gave the m.p. 236–237°, and C. M. Suter and E. Oberg, THIS JOURNAL, **53**, 1566 (1931), gave the m.p. 235–236°, but H. A. Scarborough and J. L. Sweeten, *J. Chem. Soc.*, 52 (1934), recorded a value of 245°.

derivative of *dl*-thyronine, the methyl ester in the form of the free base, was prepared and characterized. The yield of *dl*-thyronine obtained from 4-nitrodiphenyl ether by this method is 30%, as compared to the 11.6% over-all yield (from ethyl *p*-hydroxybenzoate and *p*-bromoanisole) obtained by Harington and Pitt Rivers[4d] by the best method previously described.

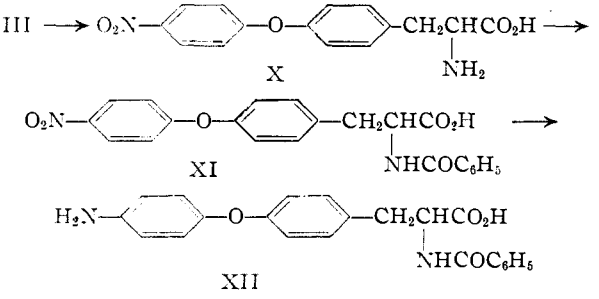
The most consistently troublesome step in the various reaction sequences investigated was the replacement of the aromatic amino group by the phenolic hydroxyl through diazotization and hydrolysis. An important advantage of the route described above over others dependent upon conducting these reactions with such intermediates as the amino acids IX or XII was a higher yield in this step. It should be mentioned that an effort was made to improve upon the 55% yield in the conversion of the amine IV into the *dl*-thyronine (V) by isolating the diazonium fluoborate VI and decomposing this salt in glacial acetic acid to give the acetate VII (not isolated), which yielded *dl*-thyronine when hydrolyzed.[6]



However, the over-all yield of *dl*-thyronine from the amino ester IV obtained by means of this procedure was only 52%, or slightly less than by the direct hydrolysis of the diazonium chloride. The similarity of the results from the two different procedures is in marked contrast to the divergence in results obtained in model experiments on the conversion of 4-aminodiphenyl ether into 4-hydroxydiphenyl ether. In that instance the decomposition of the diazonium fluoborate in glacial acetic acid led to a 67% yield of the phenol, whereas direct hydrolysis of the diazonium chloride gave only about 8%, as had previously been reported.[7]

The amino acid IX was prepared by saponification and decarboxylation of the malonic ester derivative III, followed by reduction of the resulting nitro acid VIII. Before the discovery of the advantages of the reaction sequence previously described, conversion of the acid IX into *dl*-thyronine was attempted by means of a variety of diazotization and hydrolysis procedures. All produced much tar and very little thyronine. When the diazonium chloride was hydrolyzed in aqueous hydrochloric acid, for example, the yield of thyronine was only 5%. The maximum yield obtained from IX was 22%, produced by diazotizing and decomposing the diazonium salt in glacial acetic acid containing a small amount of sulfuric acid.

At that stage of the investigation the diazotization and hydrolysis of the benzoyl derivative XII was also studied, for the conversion of the *l*-form of this compound into *d*-thyronine had been reported[4c] to give a yield (*ca.* 40%) higher than any we had obtained up to that time. The most convenient preparation of the benzoyl derivative was by means of complete hydrolysis and decarboxylation of the malonic ester derivative III, followed by benzoylation and reduction. The intermediate compounds X, XI and XII were isolated but not fully characterized. The yield of *dl*-thyronine (V) which we obtained from XII by diazotization and hydrolysis was 30%.



Experimental[8,9]

4-Chloromethyl-4′-nitrodiphenyl Ether (II).—A solution of 100 g. (0.465 mole) of 4-nitrodiphenyl ether,[10] 30 g. of paraformaldehyde, 55 ml. of sirupy phosphoric acid and 140 ml. of concentrated hydrochloric acid in 300 ml. of glacial acetic acid was heated on a steam-bath under a reflux condenser. The temperature of the reaction mixture remained at about 85°. After 48 hours, 20 g. of paraformaldehyde and 100 ml. of concentrated hydrochloric acid were added and heating was continued for 12 hours. The reaction mixture was cooled, then poured into 300 ml. of cold water. The layer of heavy oil was separated and the aqueous layer was extracted with two 150-ml. portions of ether. The ether extracts were combined with the heavy oil, and the solution was washed with water, then with 5% sodium carbonate solution until neutral and finally with water. After the solution had been dried over calcium chloride, the ether was removed by evaporation over a steam-bath and the residue was vacuum distilled. The product distilled at 190–210° (4 mm.)[11] and solidified on standing to give 110 g. (90%) of light yellow crystals, m.p. 52–54°. Two crystallizations from 95% ethanol gave tiny white prisms, m.p. 54–55°.

Anal. Calcd. for $C_{13}H_{10}O_3NCl$: C, 59.21; H, 3.82. Found: C, 59.45; H, 3.93.

Oxidation of the compound with hot potassium permanganate solution yielded an acid of m.p. 236–237°, which did not depress the m.p. of a sample of 4-(4′-nitrophenoxy)-benzoic acid[5] of the same m.p. prepared by alkaline permanganate oxidation of 4-methyl-4′-nitrodiphenyl ether.

(6) *Cf.* H. L. Haller and P. S. Schaffer, THIS JOURNAL, **55**, 4954 (1933).

(7) G. Loch, *Monatsh.*, **56**, 183 (1930).

(8) Microanalyses by Drs. G. Weiler and F. B. Strauss, Oxford, England, by Micro Tech Laboratories, Skokie, Illinois, and by Clark Microanalytical Laboratories, Urbana, Illinois.

(9) Melting points are corrected.

(10) R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 445.

(11) The residue in the distillation flask must be allowed to cool before air is admitted to the system; otherwise vigorous decomposition occurs.

Diethyl 4-(4′-Nitrophenoxy)-benzylacetamidomalonate (III).—In an apparatus protected from atmospheric moisture, 9.3 g. (0.403 gram atom) of sodium was dissolved in 1 l. of absolute ethanol. To this solution were added 87.5 g. (0.403 mole) of diethyl acetamidomalonate[12] and 105.2 g. (0.4 mole) of 4-chloromethyl-4′-nitrodiphenyl ether (II). The mixture was refluxed for 5 hours, then cooled and allowed to stand in the refrigerator overnight. The white crystalline product was separated from the pasty mixture by filtration with suction and was washed thoroughly with cold 95% ethanol and with warm water. It was crystallized from 95% ethanol to give 115 g. (65%) of fluffy white leaflets melting at 152–153°. Recrystallization raised the m.p. to 153.5–154°.

Anal. Calcd. for $C_{22}H_{24}O_8N_2$: C, 59.46; H, 5.44. Found: C, 59.45; H, 5.59.

Preparation of *dl*-Thyronine (V) *via* Compound IV. Preparation of Diethyl 4-(4′-Aminophenoxy)-benzylacetamidomalonate (IV).—To a solution of 8.88 g. (0.02 mole) of diethyl 4-(4′-nitrophenoxy)-benzylacetamidomalonate (III) in 200 ml. of dry, thiophene-free benzene was added 1 g. of Raney nickel catalyst, and the mixture was shaken for 2 hours at room temperature under a hydrogen pressure of 40 lb. per sq. in. The catalyst was removed by filtration and dry hydrogen chloride was passed through the filtrate to precipitate the hydrochloride of the amino ester. The white precipitate (9 g., m.p. 115–120°) was dissolved in 200 ml. of water and the solution was made alkaline by addition of concentrated ammonium hydroxide. The white powder which was precipitated weighed 7.9 g. (95% yield) and melted over a range of several degrees, beginning at about 142°. After recrystallization from 60% ethanol, the compound was obtained as white needles, m.p. 147–148°.

Anal. Calcd. for $C_{22}H_{26}O_6N_2$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.94; H, 6.28; N, 6.55.

Diazotization and Hydrolysis of Compound IV. Method A.—A solution prepared from 4.14 g. (0.01 mole) of diethyl 4-(4′-aminophenoxy)-benzylacetamidomalonate (IV), 200 ml. of water and 2 ml. of concentrated hydrochloric acid was cooled to 10°, and 0.8 g. (0.012 mole) of sodium nitrite was added with stirring. The solution was allowed to stand in the refrigerator for 12 hours and was filtered to remove a small amount of insoluble material. The filtrate was refluxed for three hours and the volume of the solution was reduced to 50 ml. by distillation. An equal volume of concentrated hydrochloric acid was added, and heating under reflux was resumed for an additional three hours. The resulting red solution was neutralized with concentrated ammonium hydroxide, filtered while hot to remove a black precipitate and allowed to stand overnight in the refrigerator. The tan precipitate which formed was washed with 95% ethanol and ether to give 1.51 g. (55%) of *dl*-thyronine as a light tan powder melting at 257–259° with decomposition. When dissolved in dilute sulfuric acid, treated with decolorizing charcoal and precipitated with ammonia, the product was obtained as a white crystalline powder, m.p. 259–260°.[13]

Anal. Calcd. for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.55; H, 5.47; N, 5.20.

Thyronine hydrochloride was prepared by crystallizing the amino acid from hot 6 *N* hydrochloric acid. White plates, m.p. 235–238°, were obtained. Harington and Randall[14] reported the m.p. 237–240°. The hydrochloride of thyronine methyl ester was prepared by refluxing a solution of the amino acid in methanolic hydrogen chloride. The hydrochloride was obtained as a fine white powder, m.p. 206–208°.[15] Since the amino ester hydrochloride was difficult to purify by crystallization, it was converted into the dibenzoyl derivative by treatment with benzoyl chloride and pyridine. The dibenzoyl derivative was crystallized from a methanol–water mixture to give white plates, m.p. 132–133°. Harington and Pitt Rivers[4d] report the m.p. 132–134°.

Anal. Calcd. for $C_{30}H_{25}O_8N$: C, 72.71; H, 5.08; N, 2.83. Found: C, 72.59; H, 5.10; N, 2.60.

dl-Thyronine methyl ester was obtained as the free base by dissolving 0.2 g. of crude *dl*-thyronine methyl ester hydrochloride in 20 ml. of water and making the solution slightly alkaline by addition of ammonia. Silvery white plates, m.p. 135°, crystallized from the solution.

Anal. Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96. Found: C, 66.64; H, 6.22.

Method B.—A solution prepared from 4.14 g. (0.01 mole) of the amino ester IV in 100 ml. of water and 4 ml. of concentrated hydrochloric acid was cooled to 10° and 0.8 g. (0.012 mole) of sodium nitrite was added with stirring. The solution was allowed to stand in the refrigerator for 24 hours, then was filtered to remove small amounts of insoluble impurities and was treated with 2.7 g. (0.012 mole) of 40% fluoboric acid solution. The precipitated diazonium fluoborate was allowed to settle for 30 minutes, then was removed by filtration and air dried. The resulting white powder was added to 100 ml. of glacial acetic acid and the green solution was heated on a steam-bath for 18 hours. The acetic acid was removed under reduced pressure and the residue was dissolved in 100 ml. of 95% ethanol containing 2 g. of potassium hydroxide. The solution was refluxed for 2 hours, the ethanol was removed by distillation and 100 ml. of 6 *N* hydrochloric acid solution was added to the residue. The mixture was refluxed for 2 hours, most of the hydrochloric acid was removed under reduced pressure, 50 ml. of water was added and the solution was filtered to remove suspended tarry materials. The filtrate was neutralized with ammonium hydroxide and allowed to stand overnight in the refrigerator. The precipitate which separated was washed with 95% ethanol to give 1.41 g. (52%) of *dl*-thyronine as a light buff powder melting at 256–257° with decomposition.

Preparation of *dl*-Thyronine (V) *via* Compound IX. Preparation of α-Acetamido-β-[4-(4′-nitrophenoxy)-phenyl]-propionic Acid (VIII).—A solution of 44.4 g. (0.1 mole) of diethyl 4-(4′-nitrophenoxy)-benzylacetamidomalonate (III) and 11.2 g. (0.2 mole) of potassium hydroxide in 250 ml. of 95% ethanol was refluxed for one hour. Most of the ethanol was distilled away, the residue was dissolved in 200 ml. of water and the solution was filtered to remove a small amount of insoluble material. Acidification of the filtrate with concentrated hydrochloric acid produced a sticky white precipitate and abundant evolution of carbon dioxide. After removal from the solution the precipitate fully solidified and was powdered and dried to give 30 g. (an 87% yield) of a white product, m.p. 158–159°. After crystallization from 60% ethanol, shiny white plates were obtained, m.p. 162–163°.

Anal. Calcd. for $C_{17}H_{16}O_6N_2$: C, 59.30; H, 4.68. Found: C, 58.98; H, 4.80.

Preparation of α-Acetamido-β-[4-(4′-aminophenoxy)-phenyl]-propionic Acid (IX).—A solution of 17.2 g. (0.05 mole) of α-acetamido-β-[4-(4′-nitrophenoxy)-phenyl]-propionic acid (VIII) in 500 ml. of concentrated ammonium hydroxide was treated for two hours with a stream of hydrogen sulfide. The pasty mixture which resulted was heated for six hours on a steam-bath, and the precipitated sulfur was removed by filtration. Another 6 hours on the steam-bath precipitated more sulfur and expelled most of the ammonia and hydrogen sulfide. The solution was filtered again, acidified with glacial acetic acid and allowed to stand in the refrigerator for 12 hours. The hard, white cake of material obtained was crystallized from 60% ethanol to give 10.2 g. (65% yield) of a fine, white powder melting at 206–207°. Two further crystallizations from 60% ethanol gave tiny white prisms, m.p. 210–211°.

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: C, 64.96; H, 5.77; N, 8.92. Found: C, 64.83; H, 5.79; N, 8.80.

Diazotization and Hydrolysis of Compound IX.—A solution of 3.14 g. (0.01 mole) of compound IX in 100 ml. of glacial acetic acid was cooled to 20° and 1.0 g. (0.015 mole) of sodium nitrite was added in small portions. The green solution was allowed to stand at room temperature for 24 hours, 2 ml. of concentrated sulfuric acid was added and the solution was refluxed for 4 hours. After the acetic acid was removed under reduced pressure, the red residue was dissolved in 50 ml. of 5% sodium hydroxide solution and the solution was refluxed for 2 hours. An equal volume of con-

(12) H. R. Snyder and C. W. Smith, THIS JOURNAL, **66**, 350 (1944).

(13) A number of melting points within the range 250–260° have been given for *dl*-thyronine (see ref. 4). Melting occurs with decomposition; in the present work melting point samples were placed in a block preheated to about 250°.

(14) C. R. Harington and S. S. Randall, *Biochem. J.*, **23**, 373 (1929).

(15) C. R. Harington and R. V. Pitt Rivers, ref. 4d, report the m.p. 215° for a fully purified sample.

centrated hydrochloric acid was added and the refluxing was continued for 2 hours more. Most of the hydrochloric acid was removed under reduced pressure, 50 ml. of water was added and the solution was filtered to remove insoluble tar. The filtrate was brought to a *p*H of 4 with concentrated ammonium hydroxide and allowed to stand overnight in the refrigerator. The brown precipitate which formed was removed by filtration, washed with 95% ethanol and ether and redissolved in dilute sulfuric acid. Neutralization with ammonium hydroxide gave 0.6 g. (22%) of *dl*-thyronine as a tan powder which melted with decomposition at 255–257°.

Preparation of *dl*-Thyronine from Compound III *via* Compound XII. Hydrolysis.—A solution of 8.88 g. (0.02 mole) of diethyl 4-(4′-nitrophenoxy)-benzylacetamidomalonate (III) in a mixture of 200 ml. of 95% ethanol, and 200 ml. of concentrated hydrochloric acid was refluxed for 12 hours. The solution was concentrated by distillation to remove the alcohol, and water was added to dissolve the precipitated amino acid hydrochloride. This solution was filtered free of a trace of insoluble material and brought to *p*H 4 with concentrated ammonium hydroxide. When the cloudy solution was cooled overnight in the refrigerator, 5.4 g. (90%) of white needles were deposited, m.p. 187–188°. The product is evidently α-amino-β-[4-(4′-nitrophenoxy)-phenyl]-propionic acid (X).

Benzoylation.—A solution of 3.02 g. (0.01 mole) of this substance and 0.4 g. (0.01 mole) of sodium hydroxide in 100 ml. of water was cooled to 5° in an ice-bath. Alternate additions of 10% aqueous sodium hydroxide and benzoyl chloride were made until 12.0 ml. (0.03 mole) of the sodium hydroxide solution and 3.2 ml. (0.03 mole) of the acid chloride had been added. The solution was stirred for 30 minutes, filtered and acidified with concentrated hydrochloric acid. The resulting precipitate was thoroughly extracted with low-boiling (30–60°) petroleum ether to remove benzoic acid, then was crystallized from 95% ethanol to give 2.44 g. (60%) of white needles melting at 91–92°, evidently α-benzamido-β-[4-(4′-nitrophenoxy)-phenyl]-propionic acid (XI).

Reduction.—To a solution prepared from 4.06 g. (0.01 mole) of the above product, 200 ml. of water and 4.0 g. (0.1 mole) of sodium hydroxide was added 25 g. (0.09 mole) of hydrated ferrous sulfate in 100 ml. of water. The resulting suspension was heated on a steam-bath for 1 hour and filtered while hot. The ferric hydroxide collected was washed with 50 ml. of hot water and the combined filtrate was acidified with glacial acetic acid. A white powder was deposited when the cloudy solution was allowed to stand overnight in the refrigerator. This was dissolved in 200 ml. of hot 1% hydrochloric acid and the solution was filtered while hot, then brought to *p*H 4 by addition of concentrated ammonium hydroxide. When the solution was cooled, 3.1 g. (80%) of a white powder was deposited, m.p. 181–182°, which was evidently α-benzamido-β-[4-(4′-aminophenoxy)-phenyl]-propionic acid (XII).

Diazotization and Hydrolysis.—A solution of 3.76 g. (0.01 mole) of the above product in 200 ml. of water containing 5 ml. of concentrated hydrochloric acid was cooled to 10° and 0.8 g. (0.012 mole) of sodium nitrite was added with stirring. The solution was allowed to stand at room temperature for 2 hours, filtered to remove the small amount of insoluble material and refluxed for 3 hours. The volume of the solution was then reduced to 50 ml. by distillation, an equal volume of concentrated hydrochloric acid was added and the mixture was refluxed for 4 hours. Most of the hydrochloric acid was removed under reduced pressure, 50 ml. of water was added and the solution was filtered to remove the insoluble tar. The filtrate was neutralized with concentrated ammonium hydroxide and allowed to stand overnight in the refrigerator. The precipitate which formed was removed by filtration and washed with 95% ethanol and ether to give 0.8 g. (30%) of *dl*-thyronine as a tan powder melting at 251–254° with decomposition. Dissolving the powder in dilute sulfuric acid and precipitating with ammonia raised the m.p. to 256–257°.

Conversion of 4-Aminodiphenyl Ether into 4-Hydroxydiphenyl Ether.—A solution of 1.5 g. (0.022 mole) of sodium nitrite in 200 ml. of water was added to a cold solution of 3.7 g. (0.02 mole) of 4-aminodiphenyl ether[16] in 150 ml. of water containing 10 ml. of concentrated hydrochloric acid. The solution was stirred for 15 minutes with the temperature remaining below 10°, and 5.5 g. (0.025 mole) of 40% fluoboric acid solution was added. The precipitate which formed was allowed to settle for 15 minutes, removed by filtration and air dried. The dry white powder was added to 150 ml. of hot glacial acetic acid and the red solution was refluxed for 1 hour. The acetic acid was removed under reduced pressure and the red residue was dissolved in 100 ml. of 95% ethanol containing 3.0 g. of potassium hydroxide. The solution was refluxed for 1 hour, the ethanol was distilled away and the residue was dissolved in 50 ml. of water. The solution was filtered to remove the small amount of insoluble material and the filtrate was acidified with hydrochloric acid. The brown precipitate which formed was crystallized from hot water to give 2.5 g. (67%) of white needles melting at 81–82°. Another crystallization raised the m.p. to 83–84°. Osterlin[17] reported a m.p. of 84° for this compound.

(16) Prepared from 4-nitrodiphenyl ether by reduction with zinc dust and calcium chloride in an ethanol–water solution. See C. M. Suter, THIS JOURNAL, **51**, 2581 (1929).

(17) M. Osterlin, *Monatsh.*, **57**, 31 (1931).

PITTSBURGH 13, PENNA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

Betaine Esters. A Study of their Reactions[1]

BY WERNER V. COHEN[2] AND ALSOPH H. CORWIN

RECEIVED JUNE 3, 1953

In betaine esters, the effect of the formal positive charge is not sufficient to cause the loss of a proton from the methylene group in alkaline solutions. It is sufficient, however, to bring about alkyl–oxygen bond fission in the ester group. This reaction is reversible so that esterification can be accomplished by the action of alcohol on the sodium salt of the betaine. Identification of certain betaine salts is complicated by the fact that they form molecular complexes with sodium and potassium bromide.

It has been recognized that loss of a proton from a methylene group can be promoted either by electron attracting substituents or by unsaturated groups capable of yielding double resonance in the ion of the conjugate base. Earlier work indicates that the resonance effect may be of the greater importance. In order to learn how the proximity of a formally charged nitrogen atom will modify the chemistry of neighboring methylene and carbalkoxy groups we have investigated the chemistry of certain betaine esters of type I.

Betaine esters may be compared to esters of sulfuric and sulfonic acids in that there exists an essentially positive charge distribution around the hetero-atoms in both classes of compounds. In the betaine esters, however, the charge is separated

(1) From the doctoral dissertation of Werner V. Cohen, The Johns Hopkins University.

(2) United States Public Health Service Research Fellow 1950-1951.