

made from benzene both with a mixture of hydrogen fluoride and sulfuric acid and with fluorosulfonic acid. *p*-Tolyl phenyl sulfone was made both from benzenesulfonyl chloride and toluene and *p*-toluenesulfonic acid and benzene by the

action of hydrogen fluoride. Benzene was nitrated at a temperature below 0° by nitric acid aided with hydrogen fluoride.

STATE COLLEGE, PENNSYLVANIA

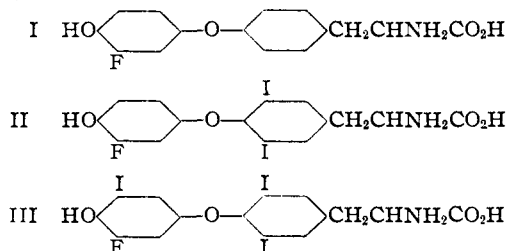
RECEIVED DECEMBER 19, 1940

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 800]

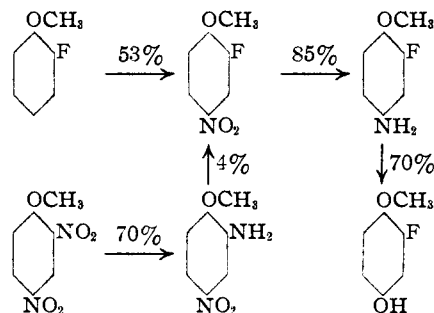
The Synthesis of 3'-Fluoro-*dl*-thyronine and Some of its Iodinated Derivatives

BY CARL NIEMANN, JAMES F. MEAD AND ANDREW A. BENSON

In continuation of our investigations upon the halogenated tyrosines and thyronines,^{1,2} we now wish to report the synthesis of 3'-fluoro-*dl*-thyronine (I), 3'-fluoro-3,5-diiodo-*dl*-thyronine (II), and 3'-fluoro-5'-iodo-3,5-diiodo-*dl*-thyronine (III).



The synthesis of these three compounds demanded as an intermediate 3-fluoro-4-methoxyphenol which was prepared by the following series of reactions



This phenol was condensed with triiodonitrobenzene and the resulting substituted diphenyl ether was converted into 3'-fluoro-3,5-diiodo-*dl*-thyronine (II) by following the general procedure used by Harington and Barger³ for the

synthesis of 3,5-diiodo-*dl*-thyronine. Partial dehalogenation of 3'-fluoro-3,5-diiodo-*dl*-thyronine (II) gave 3'-fluoro-*dl*-thyronine (I); 3'-fluoro-5'-iodo-3,5-diiodo-*dl*-thyronine (III) was obtained by the direct iodination of 3'-fluoro-3,5-diiodo-*dl*-thyronine (II). The authors wish to express their indebtedness to Messrs. H. Lanz, Jr., and G. A. Swinehart for the microanalyses reported in this paper.

Experimental

2-Amino-4-nitroanisole.⁴—To a mechanically stirred suspension of 189 g. of 2,4-dinitroanisole⁵ in one l. of water, maintained at 80–85°, was added, in the course of twenty minutes, 389 g. of sodium sulfide and 141 g. of sodium bicarbonate dissolved in 2.9 l. of water. After forty minutes the reaction mixture was cooled, the solid recovered and dissolved in dilute hydrochloric acid. The addition of ammonium hydroxide to this solution gave 70–80% of crude 2-amino-4-nitroanisole, m. p. 107–111°. Upon repeated recrystallization from aqueous methanol the m. p. was raised to the maximum value of 117–118°.

2-Fluoro-4-nitroanisole.^{1,6}—(A) Diazotization of crude 2-amino-4-nitroanisole, m. p. 111°, and precipitation of the diazonium fluoborate as described by Schiemann and Miao^{6a} gave 70–75% of the diazonium fluoborate. This salt was mixed with two volumes of fine sand and decomposed by dry distillation at 30 mm. pressure. The distillate was taken up in ether, the ethereal phase washed with aqueous sodium carbonate solution and the crude fluoronitroanisole (10–14%, based on diazonium fluoborate), recovered from the ethereal extract, purified by steam distillation. Recrystallization of this product from a 1:1 methanol-ethanol mixture and finally from isopropyl ether gave pure 2-fluoro-4-nitroanisole, m. p. 104.0–104.5°. The over-all average yield from amine to pure fluoro compound was approximately 4%.

(B)^{1,6} To a vigorously stirred solution of 250 g. of *o*-fluoroanisole¹ in 825 ml. of acetic anhydride was added, over a period of four hours, a solution of 87 ml. of nitric

(1) J. English, Jr., J. F. Mead and C. Niemann, *THIS JOURNAL*, **62**, 350 (1940).

(2) This research is being conducted as a cooperative project with Professor Paul Phillips of the University of Wisconsin who has undertaken a pharmacological investigation of the compounds reported in this and a previous communication.¹

(3) C. R. Harington and G. Barger, *Biochem. J.*, **21**, 169 (1927).

(4) I. I. Vorontzov, *J. Chem. Ind. (Moscow)*, **7**, 2145 (1930).

(5) H. Vermeulen, *Rec. trav. chim.*, **25**, 12 (1906).

(6) (a) G. Schiemann and T. Miao, *Ber.*, **66**, 1179 (1933); (b) G. Schiemann, *J. prakt. Chem.*, **140**, 97 (1934); (c) E. L. Holmes and C. K. Ingold, *J. Chem. Soc.*, **129**, 1938 (1926); H. H. Hodgson and D. E. Nicholson, *ibid.*, 810 (1940).

acid (d. 1.5) in 40 ml. of acetic acid, the temperature being maintained at -10° . The reaction mixture was stirred an additional two hours, while the temperature was allowed to rise to 25° , and was then poured into a large excess of ice water and left overnight in order to complete the hydrolysis of the acetic anhydride. The crystalline precipitate was recovered and recrystallized from a 1:1 methanol-ethanol mixture to give 130 g. of 2-fluoro-4-nitroanisole, m. p. $101-103^{\circ}$. Upon recrystallization from the above solvent or from isopropyl ether the m. p. was raised to $104.0-104.5^{\circ}$.

The residual oil, obtained as a by-product in the above nitration, was cooled to -30° and an additional 20 g. of pure nitrofluoroanisole was recovered, thereby raising the yield of this latter compound to 45% of the theoretical amount. The 180 g. of oil recovered from the above operation was reduced catalytically and, after solution of the basic compounds in dilute hydrochloric acid, 40 g. of *o*-fluoroanisole was obtained. Thus the total yield of 2-fluoro-4-nitroanisole, based on starting materials used, was 53%.

2-Fluoro-4-aminoanisole.^{1,6a,b}—This compound was obtained by the catalytic reduction, with platinum oxide, of 2-fluoro-4-nitroanisole dissolved in a 1:1 methanol-ethanol mixture. The crude product was recrystallized from methanol yielding 85% of 2-fluoro-4-aminoanisole, m. p. $83.0-83.5^{\circ}$.

3-Fluoro-4-methoxyphenol.—2-Fluoro-4-aminoanisole (21 g.) was suspended in a solution prepared by adding 20 ml. of concd. sulfuric acid to 60 g. of ice. After the addition of a second 60-g. portion of ice, the amine was diazotized by introducing 12 g. of sodium nitrite dissolved in the minimum quantity of water. The excess nitrous acid was removed with urea and the solution, diluted to 500 ml., was dropped slowly into a distilling flask containing a boiling solution of 75 g. of anhydrous sodium sulfate in 100 g. of concd. sulfuric acid and 50 ml. of water. The solution contained in the flask was maintained at $130-135^{\circ}$ during the addition of the diazonium solution by regulating the rate of addition of the latter solution. After all the diazonium solution had been added, 200 ml. of water was introduced into the flask, in a similar manner, the temperature still being maintained at $130-135^{\circ}$. The phenol was then recovered from the distillate by extracting the latter with ether. The ethereal extract was dried, the solvent removed and the residual 15 g. of crude phenol (70%) distilled at 90° (0.4 mm.). Upon recrystallization from a mixture of benzene and ligroin, 3-fluoro-4-methoxyphenol, m. p. $54-55^{\circ}$, was obtained.

3,5-Diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-nitrobenzene.^{3,7}—A mixture of 100 g. of triiodonitrobenzene,⁷ 41 g. (1.4 mole proportion) of 3-fluoro-4-methoxyphenol, 60 g. of freshly dehydrated anhydrous potassium carbonate and 275 ml. of freshly distilled 2-pentanone was refluxed in an oil-bath for six hours. Water was added to dissolve the salts and the 2-pentanone and other volatile products removed by steam distillation. When 1.5 l. of distillate had been collected, the mixture was allowed to cool and the water poured off the solid but somewhat

(7) A more detailed account of this condensation and of the preparation of triiodonitrobenzene will be described in the near future. We are indebted to Dr. C. E. Redemann for the use of this unpublished information.

tarry mass. The latter was treated with 100 ml. of methanol, which dissolved out the tar and caused the condensation product to become crystalline. The light brown solid was collected and recrystallized from 2-butanone, giving 80 g. (79%) of a light yellow product, m. p. $126-127^{\circ}$. Upon repeated recrystallization from the same solvent the m. p. was raised to $127-129^{\circ}$.

Anal. Calcd. for $C_{13}H_9O_4NI_2F$ (515.0): C, 30.3; H, 1.6; N, 2.7. Found: C, 30.4; H, 1.5; N, 2.9.

3,5-Diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-aniline Hydrochloride.—To a hot solution of 75 g. of 3,5-diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-nitrobenzene in 385 ml. of acetic acid was added, in small portions, 117 g. of powdered stannous chloride dihydrate. The reaction was conducted as previously described³ and, upon passing dry hydrogen chloride into the ethereal solution of the amine, 53 g. (70%) of 3,5-diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-aniline hydrochloride, m. p. 200° (after preliminary sintering) was obtained.

Anal. Calcd. for $C_{13}H_{11}O_2NI_2FCl$ (521.5): C, 29.9; H, 2.1; N, 2.7. Found: C, 29.9; H, 2.3; N, 3.0.

3,5-Diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-acetanilide.—The free base was liberated from the above hydrochloride by shaking an ethereal suspension of the latter with *N* aqueous sodium hydroxide. The base recovered from the ethereal solution was acetylated with acetic anhydride and, after several recrystallizations from ethanol, the acetamino compound was obtained as colorless platelets, m. p. $199-200^{\circ}$.

Anal. Calcd. for $C_{15}H_{12}NO_3I_2F$ (527.1): C, 34.2; H, 2.3; N, 2.7. Found: C, 34.2; H, 2.5; N, 2.6.

3,5-Diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-benzonitrile.—To a well-stirred suspension of 41 g. of 3,5-diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-aniline hydrochloride in 410 ml. of glacial acetic acid was added, at $15-20^{\circ}$, 8 g. of butyl nitrite. After stirring for an additional thirty minutes, the resulting clear solution was poured, with vigorous stirring, into a hot solution prepared by adding 235 g. of potassium cyanide in 410 ml. of water to 215 g. of copper sulfate pentahydrate in 820 ml. of water. The stirring was continued for one hour and, after cooling, the precipitate was collected. The solid was dehydrated with the aid of benzene and then extracted with three 200-ml. portions of boiling benzene. Upon evaporation of the solvent a dark brown crystalline solid was obtained which was distilled at 0.1 mm. pressure and a bath temperature of 250° . The distillate was taken up in chloroform and washed with aqueous sodium bisulfite. Removal of the solvent gave 26 g. (67%) of a light yellow crystalline solid, which after two recrystallizations from ethanol, melted at $115-117^{\circ}$.

Anal. Calcd. for $C_{14}H_8O_2NI_2F$ (495.0): C, 34.0; H, 1.6; N, 2.8. Found: C, 34.2; H, 1.9; N, 2.6.

3,5-Diiodo-4-(3'-fluoro-4'-hydroxyphenoxy)-benzoic Acid.—A specimen of 3,5-diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-benzonitrile was hydrolyzed with a 1:1 mixture of acetic acid and hydriodic acid (d. 1.7) for thirty minutes. The hydrolyzate was diluted with cold water, the precipitate recovered, extracted with dilute ammonium hydroxide, the extract filtered and the filtrate acidified with 6 *N* hydrochloric acid. The precipitated acid was

collected and recrystallized from 50% aqueous ethanol giving a white crystalline compound, m. p. 237–238°.

Anal. Calcd. for $C_{13}H_7O_4I_2F$ (500.0): C, 31.2; H, 1.4. Found: C, 31.4; H, 1.7.

3,5 - Diiodo - 4 - (3' - fluoro - 4' - methoxyphenoxy)-benzaldehyde.—Sixty grams of anhydrous stannous chloride was suspended in 300 ml. of anhydrous ether and dry hydrogen chloride was passed into the suspension, at 0°, until all of the solid had dissolved and only a single liquid phase remained. To this solution was added a solution of 25 g. of 3,5-diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-benzoxonitrile in 175 ml. of dry chloroform. Hydrogen chloride was passed into the reaction mixture for an additional two hours, during which time a heavy yellow liquid separated. Upon standing overnight exposed to the atmosphere through a calcium chloride tube, the liquid was transformed into the solid stannic chloride double salt of the aldimine hydrochloride.⁸ This was collected and hydrolyzed by boiling with 6 *N* hydrochloric acid. The aldimine double salt hydrochloride hydrolyzed rapidly, leaving a yellow glassy solid which was crystallized from 70% aqueous acetic acid giving 17 g. (68%) of 3,5-diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-benzaldehyde, m. p. 106–108°.

Anal. Calcd. for $C_{14}H_9O_3I_2F$ (498.0): C, 33.8; H, 1.8. Found: C, 33.8; H, 1.9.

The *p*-nitrophenylhydrazone of the above aldehyde was prepared by adding 0.2 g. of the aldehyde to an equivalent amount of *p*-nitrophenylhydrazine dissolved in hot glacial acetic acid. Upon recrystallization from glacial acetic acid, the hydrazone formed clusters of microscopic needles, m. p. 263–264°.

Anal. Calcd. for $C_{20}H_{14}O_4N_2I_2F$ (633.2): C, 37.9; H, 2.2; N, 6.6. Found: C, 37.8; H, 2.6; N, 6.8.

4 - [3',5' - Diiodo - 4' - (3' - fluoro - 4' - methoxyphenoxy)-benzal]-2-phenyloxazolone-5.—An intimate mixture of 16 g. of 3,5-diiodo-4-(3'-fluoro-4'-methoxyphenoxy)-benzaldehyde, 8 g. of hippuric acid, 16 g. of anhydrous sodium acetate and 60 ml. of acetic anhydride was heated on a boiling water-bath for one hour. The reaction mixture was poured, with stirring, into 800 ml. of ice water and allowed to stand until the acetic anhydride had hydrolyzed. The yellow solid was collected, washed with water and dried *in vacuo*. The 20 g. of azlactone, m. p. 180–190°, thus obtained is satisfactory for subsequent operations.

α - Benzoylamino - β - [3,5 - diiodo - 4 - (3' - fluoro - 4' - methoxyphenoxy)-phenyl]-acrylic Acid.—A portion of the above azlactone was added to 100 parts of a boiling solution of 1% sodium hydroxide in 70% ethanol and the reaction mixture was boiled for ten minutes before acidification with dilute hydrochloric acid. The precipitated acid was collected and recrystallized several times from ethanol to give the crystalline acid, needles, m. p. 238–240°.

Anal. Calcd. for $C_{23}H_{16}O_6NI_2F$ (659.2): C, 41.9; H, 2.4; N, 2.1. Found: C, 41.8; H, 2.5; N, 2.4.

***dl* - α - Amino - β - [3,5 - diiodo - 4 - (3' - fluoro - 4' - hydroxyphenoxy)-phenyl]-propionic Acid.**—A mixture of

30 ml. of acetic anhydride, 30 ml. of hydriodic acid (d. 1.7), 3 g. of red phosphorus and 5.0 g. of azlactone was refluxed for three hours. The hot solution was filtered through a sintered glass filter and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in 40 ml. of 2 *N* hydrochloric acid, the solution decolorized with carbon, filtered and the amino acid precipitated by neutralization with 15 *N* ammonium hydroxide. The average yield was 1.8 g., or 42% of the theoretical amount. The precipitated amino acid was dissolved in 70% aqueous ethanol with the aid of a small quantity of dilute aqueous sodium hydroxide, the solution filtered and the filtrate rapidly acidified with dilute acetic acid^{9,9} to give 3'-fluoro-3,5-diiodo-*dl*-thyronine, platelets, m. p. 248° (decompn.). Prior to analysis the amino acid was again recrystallized from alcoholic sodium hydroxide.

Anal. Calcd. for $C_{15}H_{12}O_4NI_2F$ (543.1): C, 33.2; H, 2.2; N, 2.6; I, 46.8. Found: C, 33.3; H, 2.6; N, 2.5; I, 47.0.

***dl* - α - Amino - β - [4 - (3' - fluoro - 4' - hydroxyphenoxy)-phenyl]-propionic Acid.**—3'-Fluoro-3,5-diiodo-*dl*-thyronine (2 g.) dissolved in 150 ml. of 1 *N* aqueous potassium hydroxide was reduced with hydrogen and palladized calcium carbonate following the procedure described by Harington.¹⁰ After removing the catalyst, the solution was acidified with acetic acid and the precipitated amino acid was recovered. After several recrystallizations from alcoholic sodium hydroxide (see above), the amino acid, platelets, m. p. 238° (decompn.), possessed the following composition.

Anal. Calcd. for $C_{15}H_{14}O_4NF$ (291.3): C, 62.0; H, 4.8; N, 4.8. Found: C, 62.1; H, 5.1; N, 4.8.

***dl* - α - Amino - β - [3,5 - diiodo - 4 - (3' - fluoro - 5' - iodo - 4' - hydroxyphenoxy) - phenyl] - propionic Acid.**—The stoichiometrical quantity of 1 *M* potassium triiodide solution was added slowly to a well-cooled solution of 2 g. of 3'-fluoro-3,5-diiodo-*dl*-thyronine in 40 ml. of 7 *N* aqueous ammonium hydroxide. During the course of the addition a precipitate appeared. After standing for one hour at 0°, the solution was diluted with 50 ml. of water and sufficient sodium bisulfite was added to remove any excess iodine. The reaction mixture was made acid to litmus by the addition of dilute hydrochloric acid. The precipitated amino acid was recovered, washed with water and alcohol and recrystallized several times from alcoholic sodium hydroxide (see above). The final product, m. p. 201° (decompn.), possessed the following composition.

Anal. Calcd. for $C_{15}H_{11}O_4NI_3F$ (669.0): C, 26.9; H, 1.7; N, 2.1; I, 56.9. Found: C, 26.8; H, 2.1; N, 1.9; I, 58.0.

Summary

The synthesis of 3'-fluoro-*dl*-thyronine, 3'-fluoro-3,5-diiodo-*dl*-thyronine and 3'-fluoro-5'-iodo-3,5-diiodo-*dl*-thyronine has been described. PASADENA, CALIFORNIA RECEIVED NOVEMBER 12, 1940

(8) It is of interest to note that very poor yields of the aldehyde are obtained when this operation is conducted in a sealed vessel.

(9) K. Schuegraf, *Helv. Chim. Acta*, **12**, 405 (1929).

(10) C. R. Harington, *Biochem. J.*, **20**, 293, 300 (1926).