found to be 119 (calcd., 116). The fourth fraction was butyl chloroacetate. It was changed in 80% yield to chloroacetamide, m. p. 119–120°, and no trace of dichloroacetamide (m. p. 98–99°) could be found.

Summary

The C—O—C grouping in aldehyde-acid combinations is an acylal function. Fourteen new acylals were synthesized having the general formula: $RCH\langle^{OR}_{OCOR}$, wherein R represents methyl, ethyl, propyl, or butyl radicals. These were prepared by reaction of a sodium salt with a 1-alkoxyalkyl chloride.

Ethylidene acetate was selected as a typical acylal for study with three new reactions, namely, with aniline, hydroxylamine, and chlorine. Reaction products with aniline were acetanilide, acetic acid, and acetaldehyde. Reaction products with hydroxylamine were acetohydroxamic acid, hydroxylammonium acetate, and acetaldoxime. Reaction products with chlorine were chloral, dichloroacetaldehyde, acetic acid, chloroacetic acid, 2-chloroethylidene acetate, and 2,2-dichloroethylidene acetate. The significance of these results is discussed briefly.

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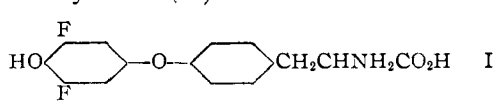
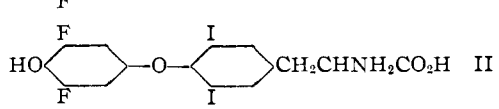
The Synthesis of 3′,5′-Difluoro-*dl*-thyronine and 3,5-Diiodo-3′,5′-difluoro-*dl*-thyronine

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

Recent studies reported by Boyer, Evans and Phillips[1] have shown marked differences in the toxicity and physiological behavior of 3-fluoro- and 3,5-difluoro-*dl*-tyrosine.[2] In order to provide suitable compounds for an analogous study in the thyronine series, we previously synthesized 3′-fluoro-*dl*-thyronine and some of its iodinated derivatives.[3] In continuation of this phase of our work we now wish to report the synthesis of 3′,5′-difluoro-*dl*-thyronine (I) and 3,5-diiodo-3′,5′-difluoro-*dl*-thyronine (II).[4]



I



II

The synthesis of these two compounds demanded as an intermediate 3,5-difluoro-4-methoxyphenol which was prepared in a 3.3% over-all yield by a series of reactions: anethole $\xrightarrow{74\%}$ 3-nitro-4-methoxybenzoic acid $\xrightarrow{86\%}$ methyl 3-nitro-4-methoxybenzoate $\xrightarrow{91\%}$ methyl 3-amino-4-methoxybenzoate $\xrightarrow{49\%}$ methyl 3-fluoro-4-methoxybenzoate $\xrightarrow{72\%}$ methyl 3-fluoro-4-methoxy-5-nitrobenzoate $\xrightarrow{92\%}$ methyl 3-fluoro-4-methoxy-5-aminobenzoate $\xrightarrow{30\%}$ methyl 3,5-difluoro-4-methoxybenzoate $\xrightarrow{98\%}$ 3,5-difluoro-4-methoxybenzoic acid $\xrightarrow{91\%}$ 3,5-difluoro-4-methoxybenzamide $\xrightarrow{77\%}$ 3,5-difluoro-4-methoxyaniline $\xrightarrow{86\%}$ 3,5-difluoro-4-methoxyphenol. A second synthesis, giving an over-all yield of 9.0% was based on the following reactions: *o*-fluoroanisole $\xrightarrow{37\%}$ 2-fluoro-6-nitrophenol $\xrightarrow{86\%}$ 2-fluoro-6-nitroanisole $\xrightarrow{84\%}$ 2-fluoro-6-aminoanisole $\xrightarrow{48\%}$ 2,6-difluoroanisole $\xrightarrow{88\%}$ 2,6-difluoro-4-nitroanisole $\xrightarrow{93\%}$ 3,5-difluoro-4-methoxyaniline $\xrightarrow{86\%}$ 3,5-difluoro-4-methoxyphenol.

This phenol was condensed with triiodonitrobenzene and the resulting substituted diphenyl ether converted into 3,5-diiodo-3′,5′-difluoro-*dl*-thyronine (II) by following the general method used by Harington and Barger[5] for the synthesis of 3,5-diiodo-*dl*-thyronine. Partial dehalogenation of 3,5-diiodo-3′,5′-difluoro-*dl*-thyronine (II) gave 3′,5′-difluoro-*dl*-thyronine (I).

In the second synthesis of 3,5-difluoro-4-meth-

(1) P. D. Boyer, R. J. Evans and P. H. Phillips, Proceedings of the American Society of Biological Chemists, 35th Annual meeting, Chicago, 1941, p. xx.

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

(3) C. Niemann, J. F. Mead and A. A. Benson, *ibid.*, **63**, 609 (1941).

(4) This research is being conducted as a coöperative project with Professor Paul Phillips of the University of Wisconsin who has undertaken a pharmacological investigation of the compounds reported in this and earlier communications.[1,2]

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

oxyphenol an indirect procedure was required for the preparation of 2-fluoro-6-nitroanisole. When *o*-fluoroanisole is nitrated in the usual manner[2,3,6] the principal reaction product is 2-fluoro-4-nitroanisole and not 2-fluoro-6-nitroanisole as claimed by Holmes and Ingold.[6c] In fact we have been unable to prepare 2-fluoro-6-nitroanisole by direct nitration of *o*-fluoroanisole. To overcome this difficulty *o*-fluoroanisole was sulfonated to give 2-fluoroanisole-4-sulfonic acid, which upon nitration gave 2-fluoro-6-nitroanisole-4-sulfonic acid. Hydrolysis of the latter compound gave 2-fluoro-6-nitrophenol which was methylated, with dimethyl sulfate, to give the desired 2-fluoro-6-nitroanisole.

As 3-fluoroanisic acid and 3,5-difluoroanisic acid are very satisfactory intermediates for the synthesis of 3-fluoro- and 3,5-difluoro-*dl*-tyrosine[2,6a,b] it should be pointed out that with the development of the improved procedures for the preparation of 3-fluoroanisic acid and 3,5-difluoroanisic acid, described in this communication, these two amino acids can now be prepared in yields substantially greater than those previously reported.[2] In addition we have found that the McFadyen–Stevens reaction[7] provides an alternative method for the conversion of 3-fluoroanisic acid and 3,5-difluoroanisic acid into the corresponding aldehydes.

Experimental[8]

3-Nitroanisic Acid (III).[9]—U. S. P. oil of anise (200 g.) was added dropwise, from the top of a reflux condenser, to a well stirred suspension, maintained at 90°, of 2.5 g. of vanadium pentoxide in 2 liters of concd. nitric acid. After all of the oil had been added the solution was refluxed for five hours, cooled, and poured into 4 liters of ice and water. The granular precipitate was collected, dissolved in warm ammonium hydroxide, the solution filtered with the aid of filter-cel, and the acid precipitated by the addition of hydrochloric acid to the filtrate. The yield of crude III, m. p. 170–185°, was 148 g.

Methyl 3-Nitro-4-methoxybenzoate (IV).[10]—Crude III (2.88 kg.) was refluxed for ten hours with 13.5 liters of 5% methanolic hydrogen chloride; 2.65 kg. (86%) of IV, m. p. 108–109°, was recovered from the reaction mixture.

Methyl 3-Amino-4-methoxybenzoate (V).[11]—The catalytic reduction of IV with hydrogen and platinic oxide gave a 91% yield of V upon evaporation of the solvent (methanol). After recrystallization from methanol V melted at 85–86°.

Methyl 3-Fluoro-4-methoxybenzoate (VI).—To 536 g. of V in 1.2 l. of concd. hydrochloric acid was added, at −2°, 210 g. of sodium nitrite dissolved in the minimum amount of cold water; 600 ml. of fluoroboric acid, made from 52% hydrofluoric acid,[12] was then added to the clear, filtered solution of the diazotized amine and the mixture cooled to −25°. The precipitated diazonium fluoroborate was collected, washed,[12] and dried *in vacuo* over sulfuric acid; yield, 732 g. (88%). The diazonium fluoroborate was decomposed in 200-g. portions by dry distillation under reduced pressure (50 mm.) to give an average yield of 56% of VI, m. p. 70–71°, b. p. 116° (5 mm.).

Anal. Calcd. for $C_9H_9O_3F$ (184.2): C, 58.7; H, 4.9. Found: C, 58.8; H, 5.2.

Methyl 3-Fluoro-4-methoxy-5-nitrobenzoate (VII).[2]—VI (423 g.) was added slowly, with vigorous stirring, to 1.17 liters of fuming nitric acid (d. 1.5) maintained at 0–5°. The clear solution was allowed to stand at 0° for several hours and then poured onto ice to give 461 g. of solid material after the latter had been washed with water and dilute ammonium hydroxide and dried *in vacuo* over sulfuric acid. Recrystallization of the crude product from isopropyl ether gave 380 g. (72%) of VII, m. p. 49.3–49.5°.

Methyl 3-Fluoro-4-methoxy-5-aminobenzoate (VIII).[2]—The catalytic reduction of VII with platinic oxide and hydrogen gave, after removal of the solvent (methanol) and subsequent distillation, 92% of VIII, m. p. 51–54°, b. p. 117° (0.1 mm.).

Methyl 3,5-Difluoro-4-methoxybenzoate (**IX**).—VIII was converted into IX as previously described.[2] The yield of crude difluoro ester was 35% of the theoretical amount. The crude difluoro ester was fractionated, by distillation, to give pure IX, m. p. 37.5°, b. p. 55° (0.2 mm.), and methyl 3-fluoro-4-methoxybenzoate (XXVII), m. p. 70–71°, b. p. 78° (0.2 mm.).

Anal. Calcd. for $C_9H_8O_3F_2$ (202.2): C, 53.5; H, 4.0. Found: C, 53.3; H, 4.0.

3,5-Difluoroanisic Acid (**X**).[2]—Saponification of IX with alcoholic potassium hydroxide gave X, m. p. 164–165° after repeated recrystallization from aqueous acetic acid.

3,5-Difluoro-4-methoxybenzamide (**XI**).—X (25.2 g.) was refluxed with 30 ml. of thionyl chloride for three hours. The excess thionyl chloride was removed by distillation at reduced pressure and the acid chloride taken up in dry ether. The addition of anhydrous ammonia to the ethereal solution of the acid chloride resulted in the precipitation of the amide, which was recovered, washed with dilute ammonium hydroxide and water, and dried. Recrystallization of the crude amide from ethanol gave 44.3 g. (91%) of XI, m. p. 158–160°.

Anal. Calcd. for $C_8H_7O_2NF_2$ (187.1): C, 51.3; H, 3.8; N, 7.5. Found: C, 51.4; H, 3.9; N, 7.7.

(6) (a) G. Schiemann and T. Miau, *Ber.*, **66**, 1179 (1933); (b) G. Schiemann, *J. prakt. Chem.*, **140**, 97 (1934); (c) E. L. Holmes and C. K. Ingold, *J. Chem. Soc.*, 1328 (1926); (d) H. H. Hodgson and D. E. Nicholson, *ibid.*, 810 (1940).

(7) J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.*, 584 (1936).

(8) Microanalyses by Dr. G. Oppenheimer, G. A. Swinehart and H. Lanz, Jr.

(9) H. Salkowski, *ibid.*, **163**, 6 (1872).

(10) (a) Cahours, *Ann.*, **56**, 315 (1845); (b) H. Goldschmidt and N. Polonowska, *Ber.*, **20**, 2407 (1887).

(11) (a) Cahours, *Ann.*, **109**, 26 (1859); (b) K. Auwers, *Ber.*, **30**, 1473 (1897).

(12) "Organic Syntheses," **13**, 46 (1933).

o-Fluoroanisole (**XII**).[2,13]—This compound was prepared as previously described[2,13] with the exception that technical sodium fluoborate was used in the preparation of the diazonium fluoborate. The over-all yield of XII from *o*-anisidine was 64%.

Sodium 3-Fluoro-4-methoxybenzenesulfonate (**XIII**).—XII was dissolved in five times its weight of concd. sulfuric acid and after standing at room temperature for six hours. the solution was poured onto ice. The addition of sodium chloride to this solution precipitated XIII which was then recrystallized from water for analysis.

Anal. Calcd. for $C_7H_6O_4FSNa$ (228.2): C, 36.8; H, 2.7; Na, 10.1. Found: C, 36.8; H, 2.9; Na, 10.1.

Sodium 3-Fluoro-4-methoxy-5-nitrobenzenesulfonate (**XIV**).—XII (2 g.) was added to 25 ml. of concd. sulfuric acid and the solution allowed to stand at room temperature overnight. This solution was then chilled to 0° and 3.2 g. of fuming nitric acid (d. 1.5) added with vigorous stirring. Dilution of the reaction mixture with water followed by the addition of sodium chloride gave white crystals of XIV.

Anal. Calcd. for $C_7H_5O_6NFSNa$ (273.2): N, 5.1; Na, 8.4. Found: N, 5.2; Na, 8.4.

2-Fluoro-6-nitrophenol (**XV**).—To a chilled solution of 250 g. of XII in 1 liter of concd. sulfuric acid, which previously had been allowed to stand at 25° overnight, was slowly added, with vigorous stirring, 130 g. of fuming nitric acid (d. 1.5). After standing at 0° for a total of seven hours the reaction mixture was poured onto 2 kg. of ice and the clear orange solution steam distilled, with superheated steam (170–190°), in 1-liter batches. The oil-bath surrounding the distilling flask was maintained at 180°. The product, which appeared in the distillate as a yellow solid, was collected, dried, and recrystallized from isopropyl ether to give 37% of large yellow prisms of XV, m. p. 90–91°.

Anal. Calcd. for $C_6H_4O_3NF$ (157.1): C, 45.9; H, 2.6; N, 8.9. Found: C, 45.9; H, 2.4; N, 8.9.

2-Fluoro-6-nitroanisole (**XVI**).[6c]—XV was added to a hot aqueous solution of sodium carbonate (15%) and upon cooling the sodium phenolate crystallized from the solution in the form of long red needles. A mixture of 55.4 g. of sodium 2-fluoro-6-nitrophenolate and 40 g. of dimethyl sulfate was heated in an oil-bath (110–120°), with sufficient toluene to make a stirrable paste, until the reaction mixture was decolorized. Water was then added, the solution made alkaline, and extracted with ligroin. Evaporation of the solvent and subsequent distillation gave 45.6 g. (86%) of XVI, m. p. 9°, b. p. 93° (3 mm.).

Anal. Calcd. for $C_7H_6O_3NF$ (171.1): N, 8.2; OCH_3, 18.1. Found: N, 8.1; OCH_3, 18.2.

2-Fluoro-6-aminoanisole (**XVII**).—XVI was reduced catalytically with platinic oxide and hydrogen to give an 84% yield of XVII, b. p. 94° (10 mm.).

Anal. Calcd. for C_7H_8ONF (141.1): N, 9.9. Found: N, 10.1.

Acylation of XVII with *p*-nitrobenzoyl chloride gave, after recrystallization from ethanol, 2-fluoro-6-*p*-nitrobenzoylaminoanisole, yellow needles, m. p. 147–148.5°.

Anal. Calcd. for $C_{14}H_{11}O_4N_2F$ (290.2): C, 57.9; H, 3.8; N, 9.7. Found: C, 58.2; H, 3.8; N, 9.5.

2,6-Difluoroanisole (**XVIII**).—Sodium nitrite (10.5 g.) in 19 ml. of water was added to a chilled solution prepared by slowly dropping 20 g. of XVII into 34 ml. of vigorously stirred cold concd. hydrochloric acid. During the above operations pellets of dry-ice were added to reduce oxidative discoloration. The diazo solution was extracted with ether, filtered and to the clear filtrate was added 30 g. of technical sodium fluoborate in 30 ml. of water. After cooling the reaction mixture to −20° the precipitate was collected and dried to give 28.8 g. (85%) of the diazonium fluoborate, which was then decomposed by dry distillation, under reduced pressure. The distillate was washed with water and dilute alkali and then carefully redistilled to give 56% of XVIII, b. p. 62° (40 mm.). The over-all yield from XVII to XVIII was 48%.

Anal. Calcd. for $C_7H_6OF_2$ (144.0): C, 58.4; H, 4.2. Found: C, 58.2; H, 4.2.

2,6-Difluoro-4-nitroanisole (**XIX**).—Fuming nitric acid (19.2 ml. of d. 1.5) was added slowly, with vigorous stirring, to a well-cooled solution of 40 g. of XVIII in 250 ml. of concd. sulfuric acid. After standing for two hours in an ice–salt-bath the reaction mixture was poured onto ice and the light crystalline reaction product recovered. The crude nitro compound was taken up in ligroin, washed with water, dried, and distilled to give 46.2 g. (88%) of XIX, m. p. 37–38°, b. p. 71° (0.6 mm.).

Anal. Calcd. for $C_7H_5O_3NF_2$ (189.1): C, 44.5; H. 2.7; N, 7.4. Found: C, 44.2; H, 2.6; N, 7.2.

2,6-Difluoro-4-aminoanisole (**XX**).—(A) The reduction of 29.3 g. of XIX with platinic oxide and hydrogen, followed by removal of the solvent (methanol) and subsequent distillation gave 23.1 g. (93%) of XX, m. p. 73–74°, b. p. 80° (0.1 mm.). After recrystallization from aqueous methanol XX was recovered in the form of thin platelets. m. p. 78.5–79°.

Anal. Calcd. for $C_7H_7ONF_2$ (159.1): C, 52.8; H. 4.4; OCH_3, 19.5. Found: C, 52.9; H, 4.7; OCH_3, 19.3.

In several instances a slightly soluble crystalline substance precipitated during the catalytic reduction of XX. This compound, m. p. 163–164°, was shown to be 3,5,3′,5′-tetrafluoro-4,4′-dimethoxyazoxybenzene (XXVIII) by the fact that it could be reduced to XX with stannous chloride.

Anal. Calcd. for $C_{14}H_{10}O_3N_2F_4$ (330.2): C, 50.9; H, 3.1; N, 8.5; OCH_3, 18.8. Found: C, 51.0; H, 3.0; N, 8.7; OCH_3, 18.8.

Acylation of XX with *p*-nitrobenzoyl chloride gave 2,6-difluoro-4-*p*-nitrobenzoylaminoanisole, colorless needles, m. p. 207–207.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{10}O_4N_2F_2$ (308.2): C, 54.6; H, 3.3; N, 9.1. Found: C, 54.3; H, 3.4; N, 9.4.

(B) Pulverized XI (21.5 g.) was added to a solution prepared by dissolving 19 g. of bromine in 110 ml. of water, at −10°, containing 22 g. of sodium hydroxide. The temperature of the reaction mixture was allowed to rise to 25° whereupon the amide dissolved completely, and, after adding, with stirring, 17.7 g. of powdered sodium hydroxide the solution was heated on a steam-bath for one hour. The reaction mixture was diluted with water, chilled, ex-

(13) G. Schiemann, *Z. physik. Chem.*, **A156**, 397 (1931).

tracted with ether, the ethereal extract dried, the solvent removed and the residue distilled to give 14 g. (77%) of XX, b. p. 80° (0.1 mm.). After recrystallization from aqueous methanol XX melted at 78.5–79°, and a mixed m. p. with XX prepared by the reduction of XIX showed no depression.

3,5-Difluoro-4-methoxyphenol (XXI).—As the method previously used for the preparation of 3-fluoro-4-methoxyphenol[3] failed to give satisfactory results when applied to the preparation of XXI the following procedure was devised. Ice was added to a solution of 23 g. of XX in 36 ml. of concd. sulfuric acid to give a fine paste of the amine hydrogen sulfate, to which was added dropwise, in the course of three hours, a solution of 10.6 g. of sodium nitrite in 100 ml. of water. The resulting diazo solution was filtered, and the filtrate added to, and beneath the surface of, a hot, well-stirred, solution of 750 g. of cupric sulfate pentahydrate in 1 liter of water. The cupric sulfate solution was covered with 500 ml. of xylene, to take up the phenol as it was formed, and was maintained at refluxing temperature throughout the addition of the 200 ml. of diazo-solution, which required three hours. Upon completion of the reaction, the reaction mixture was cooled, the xylene phase separated, and the phenol transferred to an aqueous sodium hydroxide solution, which was then extracted with ether. The ether-extracted alkaline solution was acidified, extracted with ether, the ethereal solution dried, the solvent removed, and the residue distilled to give 20.0 g. (86%) of XXI, b. p. 71° (0.2 mm.). Recrystallization of XXI from benzene and ligroin gave colorless platelets, m. p. 69–70°.

Anal. Calcd. for $C_7H_6O_2F_2$ (160.1): C, 52.5; H, 3.8; OCH_3, 19.4. Found: C, 52.8; H, 3.8; OCH_3, 19.2.

3,5-Diiodo-4-(3',5'-difluoro-4'-methoxyphenoxy)-nitrobenzene (XXII).—A mixture of 72.6 g. of 3,4,5-triiodonitrobenzene,[14] 32.2 g. (1.4 mole proportion) of XXI, 50 g. of freshly dehydrated, powdered potassium carbonate and 230 ml. of freshly distilled 2-pentanone was refluxed for eight hours. Water was then added to the reaction mixture and the 2-pentanone and other volatile products removed by steam distillation. The supernatant liquid was decanted from the tarry residue which crystallized upon standing overnight. Recrystallization of the latter product from isopropyl ether gave 56.6 g. (73%) of XXII, colorless crystals, m. p. 127–128°.

Anal. Calcd. for $C_{13}H_7O_4NI_2F_2$ (533.0): C, 29.3; H, 1.3; N, 2.6. Found: C, 29.3; H, 1.4; N, 2.7.

3,5-Diiodo-4-(3',5'-difluoro-4'-methoxyphenoxy)-aniline Hydrochloride (XXIII).—To a hot solution of 97 g. of XXII in 480 ml. of glacial acetic acid was added, in small portions, 136 g. (10% excess) of powdered stannous chloride dihydrate. The reaction was conducted as previously described[3,5,14] and upon passing dry hydrogen chloride into the ethereal solution of the amine, 81.3 g. (82%) of XXIII, m. p. 185–200°, was obtained.

Anal. Calcd. for $C_{13}H_{10}O_2NF_2ClI_2$ (539.5): N, 2.6. Found: N, 2.9.

The free base, liberated from XXIII, was acetylated with acetic anhydride. Recrystallization of the crude acetyl compound, from ethanol, gave 3,5-diiodo-4-(3',5'-difluoro-4'-methoxyphenoxy)-acetanilide, small colorless needles, m. p. 219–220°.

Anal. Calcd. for $C_{15}H_{11}O_3NF_2I_2$ (545.1): C, 33.0; H, 2.0; N, 2.6. Found: C, 33.0; H, 2.2; N, 2.6.

3,5-Diiodo-4-(3',5'-difluoro-4'-methoxyphenoxy)-benzonitrile (XXIV).—To a well-stirred suspension of 21.8 g. of XXIII in 200 ml. of glacial acetic acid was added, at 20–25°, 5.5 ml. (15% excess) of *s*-butyl nitrite. After standing for an additional thirty minutes, the resulting clear solution was poured, with vigorous stirring, into a solution (at 25°) prepared by adding 124 g. of potassium cyanide in 220 ml. of water to 109 g. of cupric sulfate pentahydrate in 430 ml. of water. Stirring was continued for an hour, and, after warming to 90° and cooling, the precipitate was collected and dried by distillation with benzene. The residual benzene solution, containing the nitrile, was filtered and the filtrate decolorized by passing it through a 15-cm. column of animal charcoal. The solvent was removed and the residue distilled at 0.1 mm. pressure, with a bath temperature of 200–300°. Crystallization of the glassy distillate, 13.7 g. (66%), from ethanol gave XXIV, small colorless rosets, m. p. 129–134°.

Anal. Calcd. for $C_{14}H_7O_2NF_2I_2$ (513.0): C, 32.8; H, 1.4; N, 2.7. Found: C, 33.0; H, 1.4; N, 2.9.

A specimen of XXIV was hydrolyzed with a 1:1 mixture of glacial acetic acid and hydriodic acid (d. 1.7) to give 3,5-diiodo-4-(3',5'-difluoro-4'-hydroxyphenoxy)-benzoic acid, small colorless needles, m. p. 232–234°, after recrystallization from 30% aqueous ethanol.

Anal. Calcd. for $C_{13}H_6O_4I_2F_2$ (518.0): C, 30.1; H, 1.2. Found: C, 30.4; H, 1.3.

3,5-Diiodo-4-(3',5'-difluoro-4'-methoxyphenoxy)-benzaldehyde (XXV).—XXIV (35.8 g.) in 190 ml. of dry chloroform was added to 63 g. of anhydrous stannous chloride dissolved in 325 ml. of a dry ethereal solution of hydrogen chloride.[3,5,14,15] The solution was saturated with dry hydrogen chloride and allowed to stand overnight,[3] whereupon the aldimine hydrochloride–stannic chloride double salt began to precipitate. After evaporation of most of the solvent the double salt was collected and hydrolyzed with 6 *N* hydrochloric acid. The crude hydrolysis product was recrystallized from isopropyl ether to give 25.8 g. (72%) of XXV, colorless prisms, m. p. 124–126°.

Anal. Calcd. for $C_{14}H_8O_3I_2F_2$ (516.0): C, 32.6; H, 1.6. Found: C, 32.7; H, 1.7.

XXV was converted into the *p*-nitrophenylhydrazone, small yellow needles, m. p. 280–281° (decomp.) after recrystallization from acetic acid.

Anal. Calcd. for $C_{20}H_{13}O_4N_3I_2F_2$ (651.2): C, 36.9; H, 2.0; N, 6.5. Found: C, 36.8; H, 2.3; N, 6.3.

4-[3',5'-Diiodo-4'-(3'',5''-difluoro-4''-methoxyphenoxy)-benzal]-2-phenyloxazolone-5 (XXVI).—An intimate mixture of 10 g. of XXV, 10 g. of freshly fused sodium acetate, 4.84 g. of hippuric acid, and 36 ml. of acetic anhydride was heated for one hour on a steam-bath. The crude azlactone (13 g.) was recovered as previously described,[3,5,14] and recrystallized from acetic acid, containing 5% acetic anhydride, to give 7.8 g. of XXVI, bright orange needles, m. p. 216–217°, with preliminary sintering at 214.5°

(14) C. Niemann and C. E. Redemann, THIS JOURNAL, **63**, 1549 (1941).

(15) H. Stephen, *J. Chem. Soc.*, **127**, 1874 (1925).

Anal. Calcd. for $C_{28}H_{13}O_4NF_2I_2$ (659.2): C, 41.9; H, 2.0; N, 2.1. Found: C, 42.0; H, 2.0; N, 2.2.

3,5-Diiodo-3′,5′-difluoro-*dl*-thyronine (II).—A mixture of 7.7 g. of recrystallized XXVI, 46 ml. of acetic anhydride, 46 ml. of hydriodic acid (d. 1.7) and 4.6 g. of red phosphorus was refluxed for three hours. The hydrolyzate was cooled, filtered, and the filtrate evaporated to incipient dryness. The residue was taken up in 60 ml. of hot 2 *N* hydrochloric acid, filtered, and the filtrate neutralized with concd. ammonium hydroxide. The precipitated crude amino acid was collected, washed with ethanol, suspended in hot 70% aqueous ethanol and dissolved by adding the minimum quantity of 8% sodium hydroxide solution. The rapid addition of an equivalent amount of 10% acetic acid to the hot solution gave 3.6 g. (60%) of II, clusters of colorless needles, m. p. 248° (decomp.).

Anal. Calcd. for $C_{15}H_{11}O_4NI_2F_2$ (561.1): C, 32.1; H, 2.0; N, 2.5. Found: C, 32.1; H, 2.3; N, 2.2.

3′,5′-Difluoro-*dl*-thyronine (I).—II (1 g.) in 200 ml. of *N* aqueous sodium hydroxide was reduced with hydrogen and palladized calcium carbonate (2%), following the procedure described by Harington.[16] After several recrystallizations from alcoholic sodium hydroxide (*vide supra*) I, m. p. 242–244°, possessed the following composition.

Anal. Calcd. for $C_{15}H_{13}O_4NF_2$ (309.3): C, 58.3; H, 4.2; N, 4.5. Found: C, 58.0; H, 4.4; N, 4.5.

3-Fluoro-4-methoxybenzhydrazide (**XXIX**).—The reaction of methyl 3-fluoro-4-methoxybenzoate (XXVII) with 85% hydrazine hydrate (10% excess) gave 92% of XXIX, colorless flakes, m. p. 178–179° (decomp.), after recrystallization from ethanol.

Anal. Calcd. for $C_8H_9O_2N_2F$ (184.2): C, 52.2; H, 4.9; N, 15.2. Found: C, 52.1; H, 4.8; N, 15.4.

sym-**3-Fluoro-4-methoxybenzoylbenzenesulfonhydrazide** (**XXX**).—XXIX was treated with benzenesulfonyl chloride, in pyridine solution,[7] to give 93% of XXX, colorless needles, m. p. 176–177°, after recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{13}O_4N_2S$ (324.5): C, 51.8; H, 4.0. Found: C, 51.6; H, 4.1.

3-Fluoro-*dl*-tyrosine (**XXXI**).[2,17]—XXX was decomposed with sodium carbonate, in ethylene glycol, at 155°,[7] to give a 67% yield of crude 3-fluoroanisaldehyde, which was converted without further purification into 4-(3′-fluoro-4′-methoxybenzal)-2-phenyloxazolone-5 in a 73% yield.[2,17,18] Hydrolysis of the azlactone with alcoholic sodium hydroxide gave 55% of α-N-benzoylamino-3-fluoro-4-methoxycinnamic acid, small needles, m. p. 221–222°, after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{17}H_{14}O_4NF$ (315.3): C, 64.8; H, 4.5; N, 4.4. Found: C, 64.6; H, 4.4; N, 4.4.

The simultaneous hydrolysis and reduction of 6.36 g. of the above benzoylaminocinnamic acid, with hydriodic acid, acetic anhydride and red phosphorus,[2,17] gave 2.1 g. (52%) of XXXI, dec. p. 275–278°, with rapid heating.

Anal. Calcd. for $C_9H_{10}O_3NF$ (199.2): C, 54,3; H, 5.0; N, 7.0. Found: C, 54.2; H, 5.2; N, 6.7.

The over-all yield from methyl 3-fluoro-4-methoxybenzoate to 3-fluoro-*dl*-tyrosine was 12%.

3,5-Difluoro-4-methoxybenzhydrazide (**XXXII**).—Methyl 3,5-difluoro-4-methoxybenzoate (IX) was converted into XXXII, platelets, m. p. 189–190° (decomp). in a 93% yield by following the procedure described above.

Anal. Calcd. for $C_8H_8N_2O_2F_2$ (202.2): C, 47.5; H, 4.0; N, 13.9. Found: C, 47.8; H, 4.2; N, 14.0.

sym-**3,5-Difluoro-4-methoxybenzoylbenzenesulfonhydrazide** (**XXXIII**).—XXXIII was prepared in a manner similar to that described above and was recrystallized from ethanol to give a 92% yield of colorless prisms, m. p. 179–180°.

Anal. Calcd. for $C_{14}H_{12}N_2O_4F_2S$ (342.3): C, 49.2; H, 3.5; N, 8.2. Found: C, 49.1; H, 3.7; N, 8.5.

3,5-Difluoro-*dl*-tyrosine[2] (**XXXIV**).—XXXIII, upon decomposition at 155°, in the presence of sodium carbonate and ethylene glycol,[7] gave 62% of crude 3,5-difluoroanisaldehyde which was converted, without further purification, into 4-(3′,5′-difluoro-4′-methoxybenzal)-2-phenyloxazalone-5, in a 50% yield. Hydrolysis of the above azlactone with alcoholic sodium hydroxide gave 65% of α-N-benzoylamino-3,5-difluoro-4-methoxycinnamic acid,[2] thin flakes, m. p. 202–203°. The simultaneous hydrolysis and reduction of the above benzoylaminocinnamic acid, with hydriodic acid, acetic anhydride and red phosphorus,[2] gave 77% of XXXIV, needles, dec. p. 280° with rapid heating.[19]

Anal. Calcd. for $C_9H_9O_3NF_2$ (217.2): C, 49.8; H, 4.2; N, 6.5. Found: C, 50.0; H, 4.5; N, 6.3.

The over-all yield from methyl 3,5-difluoro-4-methoxybenzoate to 3,5-difluoro-*dl*-tyrosine was 13%, as compared to the 31% yield obtained by preparing the aldehyde by the reduction of 3,5-difluoro-4-methoxybenzoyl chloride.[2]

Summary

The synthesis of 3,5-diiodo-3′,5′-difluoro-*dl*-thyronine and 3′,5′-difluoro-*dl*-thyronine and a new synthesis of 3-fluoro-*dl*-tyrosine and 3,5-difluoro-*dl*-tyrosine have been described.

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

(17) G. Schiemann and W. Winkelmüller, *J. prakt. Chem.*, **135**, 101 (1932).

(18) E. Erlenmeyer, Jr., *Ann.*, **275**, 1 (1893).

(19) The dec. p. reported in this communication is 15° higher than the previously reported value.[2] We do not believe that the higher dec. p. is indicative of a purer product, but is merely the result of a combination of physical circumstances, *i. e.*, size of crystals, degree of packing, rate of heating, etc.