stirring for one-half hour, the mixture was carbonated to give a 60% yield of acid melting at 296°. The identity of the acid as 4,6-dimethoxy-1-dibenzofurancarboxylic acid was established by converting it to the methyl ester and comparing this ester with an authentic specimen.[10]

1,9-Dibromo-2,8-dimethoxydibenzofuran.—This dibromo compound was prepared by bromination of 2,8-dihydroxydibenzofuran and subsequent methylation.[12] The 1,9-positions of the bromine atoms are assigned provisionally on the basis of the behavior of the related 2-hydroxydibenzofuran upon bromination.[13]

To 1.5 g. (0.00389 mole) of the dibromo compound dissolved in 120 cc. of benzene was added an ether solution of *n*-butyllithium (0.035 mole). The mixture was refluxed and stirred for two hours and then carbonated to yield 820 mg. (66.6%) of acid melting at 210–220°. Two recrystallizations from glacial acetic acid raised the melting point to 270–271°, and a mixed melting point with the acid obtained from direct dimetalation of 2,8-dimethoxydibenzofuran[12] followed by carbonation was not depressed. The methyl ester, prepared from the acid, methanol and dry hydrogen chloride melted at 128–129° after crystallization from methanol.

This dimethyl 2,8-dimethoxy-1,9-dibenzofurandicarboxylate did not depress the melting point of the dimethyl ester[12] obtained from the 2,8-dimethoxydibenzofurandicarboxylic acid resulting from direct dimetalation of 2,8-dimethoxydibenzofuran.

3,7-Dibromo-2,8-dimethoxydibenzofuran.—To 0.7 g. (0.00183 mole) of the dibromo-2,8-dimethoxydibenzofuran melting at 260–261° and tentatively designated as the 3,7-isomer,[12] dissolved in 60 cc. of benzene was added an ether solution of 0.018 mole of *n*-butyllithium. After stirring and refluxing for seven hours, the mixture was carbonated. The resulting acidic material weighed 650 mg. and from this was isolated by sublimation several tenths of a gram of benzoic acid.[14] The residual acid, 2,8-dimethoxy-3,7-dibenzofurandicarboxylic acid, was recrystallized three times from glacial acetic acid to yield 0.1 g. (17.5%) of needles which melted at 290° with decomposition.

Anal. Calcd. for $C_{16}H_{12}O_7$: methoxyl, 19.62. Found: methoxyl, 19.62.

Thirty milligrams of the dimethoxy-dibasic acid was esterified by methanol and dry hydrogen chloride to yield 18 mg. (50%) of dimethyl 2,8-dimethoxy-3,7-dibenzofurandicarboxylate. This ester crystallized from methanol as needles melting at 183–184°.

Anal. Calcd. for $C_{18}H_{16}O_7$: methoxyl, 36.05. Found: methoxyl, 36.50.

(12) Unpublished studies.

(13) Gilman and Van Ess, THIS JOURNAL, **61**, 1365 (1939).

Summary

The halogen–metal interconversion reaction has been shown to be the predominant reaction with a series of bromo-ethers of dibenzofuran in which a bromine is not only *ortho*, *meta* and *para* to a methoxy group, but also *ortho* and *meta* to the oxygen bridge.

Although no organomagnesium or organolithium compound can be prepared from 1-bromo-3,4-dimethoxydibenzofuran with magnesium or lithium, respectively, under ordinary conditions, a reaction takes place readily and satisfactorily with *n*-butyllithium to give 3,4-dimethoxy-1-dibenzofuryllithium.

(14) It is known that benzene and *n*-butyllithium give on protracted refluxing small quantities of phenyllithium, the carbonation of which yields benzoic acid.

AMES, IOWA RECEIVED DECEMBER 7, 1939

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 754]

The Synthesis of 3,5-Difluoro- and 3-Fluoro-5-iodo-*dl*-tyrosine

BY JAMES ENGLISH, JR., JAMES F. MEAD AND CARL NIEMANN

Tyrosine and thyronine are different from all other amino acids in that they alone are found in nature as nuclear substituted halogen derivatives and in all cases it has been observed that the halogen atoms are contiguous to either a phenolic or aryloxy group.[1] Until recently the only halogenated amino acid of unambiguous physiological importance was the hormone thyroxine. However, the synthesis of 3-fluorotyrosine by Schiemann and Winkelmuller[2] and the subsequent pharmacological investigations of G. Litzka, K. Kraft, and W. May[3] have shown that other halogenated amino acids must be added to this category. As part of a study on the halogenated tyrosines and thyronines this communication describes the synthesis of 3,5-difluoro- and 3-fluoro-5-iodo-*dl*-tyrosine.[4]

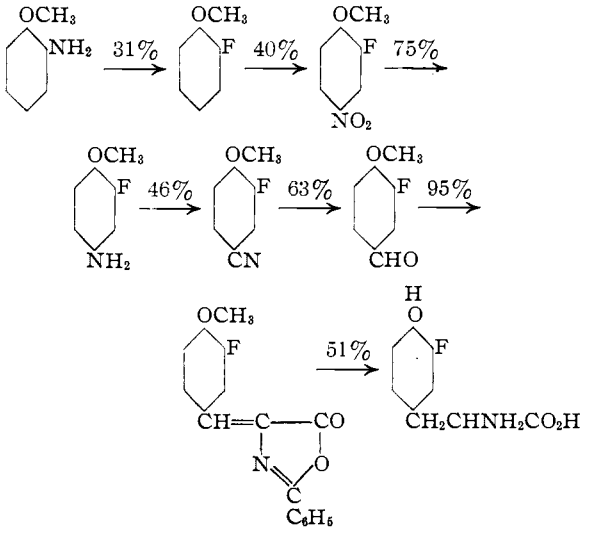
(1) (a) C. R. Harington, *Fortschritte Chem. organ. Naturstoffe*, **2**, 103 (1939); (b) C. L. A. Schmidt, "The Chemistry of the Amino Acids and Proteins," C. Thomas, Springfield, Ill., 1938.

(2) G. Schiemann and W. Winkelmuller, *J. prakt. Chem.*, **135**, 101 (1932).

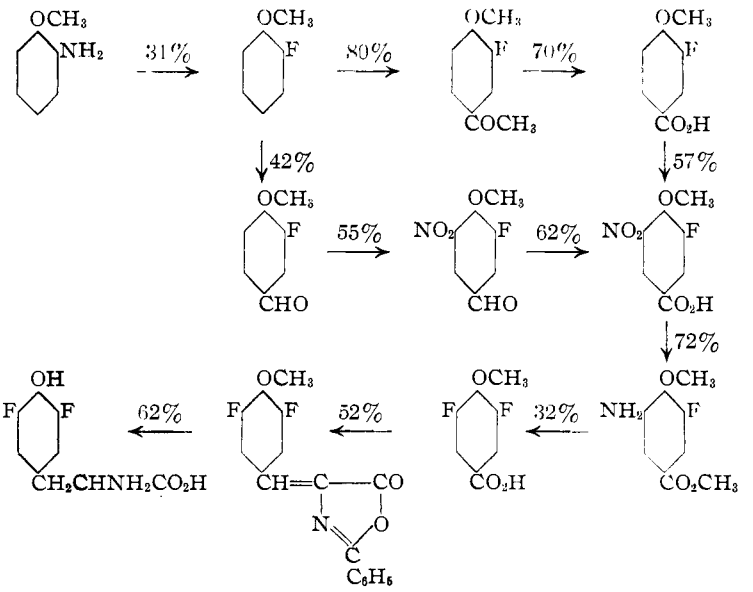
(3) (a) G. Litzka, *Arch. exptl. Path. Pharmakol.*, **183**, 427, 436 (1936); (b) *Klin. Wochschr.*, **15**, 1568 (1936); (c) *Z. ges. exptl. Med.*, **99**, 518 (1936); (d) *Deut. med. Wochschr.*, **63**, 1037 (1937); (e) H. May and G. Litzka, *Z. Krebsforsch.*, **48**, 376 (1939); (f) K. Kraft, *Z. physiol. Chem.*, **245**, 58 (1936); (g) K. Kraft and R. May, *ibid.*, **246**, 233 (1937); (h) W. May, *Klin. Wochschr.*, **14**, 790 (1935); **16**, 562 (1937).

(4) This research is being conducted as a coöperative project with Professor Paul Phillips of the University of Wisconsin.

3-Fluoro-5-iodo-*dl*-tyrosine was prepared by the direct iodination of 3-fluoro-*dl*-tyrosine. The latter amino acid was prepared by two methods. The first was a modification of a synthesis described by Schiemann[2,5] and differed only in starting with *o*-anisidine rather than *o*-phenetidine. A second synthesis was based upon the reactions



The synthesis of 3,5-difluoro-*dl*-tyrosine was attended with some difficulty; however, after several unsuccessful attempts this amino acid was obtained in a 0.73% yield from *o*-anisidine by the following series of reactions



(5) (a) G. Schiemann, *Z. physik. Chem.*, **A156**, 397 (1931); (b) *J. prakt. Chem.*, **140**, 97 (1934).

Experimental

I. Synthesis of 3-Fluoro-*dl*-tyrosine

***o*-Fluoroanisole.**[5,6]—To 2.60 kg. of freshly distilled *o*-anisidine in 5.2 l. of concd. hydrochloric acid was added 1.53 kg. of sodium nitrite in 2 l. of water. Throughout the above and succeeding operation the reaction mixture was stirred vigorously and the temperature was not allowed to rise above 0°. Five liters of fluoboric acid, prepared from 4.05 l. of technical 52% hydrofluoric acid and 1.86 kg. of boric acid,[7] was added to the clear solution of the diazotized amine and the mixture maintained at −10° for one hour. The precipitate was then recovered, washed successively with water, ethanol, and ether, and dried *in vacuo* over sulfuric acid. The yield of diazonium fluoborate was 2.70 kg. or 57.5% of the theoretical amount. The diazonium salt was then decomposed, in 540-g. portions, in a manner identical with that described in *Organic Syntheses*.[7] The crude fluoroanisole was taken up in ether, the ethereal solution washed successively with dilute sodium hydroxide and water and finally dried over sodium sulfate. Fractional distillation gave 820 g. of *o*-fluoroanisole, b. p. 69–70° (26 mm.), a yield of 53.5% from the diazonium fluoborate or an over-all yield of 30.8% from *o*-anisidine.

Anal. Calcd. for C_7H_7OF (126): C, 66.7; H, 5.6. Found: C, 66.8; H, 5.9.

2-Fluoro-4-nitroanisole.[5b,6]—The nitration of *o*-fluoroanisole according to the directions given by Schiemann and Miau[6b] consistently gave 39–40% of the theoretical amount of 2-fluoro-4-nitroanisole, m. p. 104.5°, instead of the 70% reported by these authors. All attempts to improve the yield by modification of the procedure with respect to temperature, duration of the reaction, and concentration of the nitric acid were without effect. In no case was the compound of m. p. 53° described by Holmes and Ingold[6a] as a 2-fluoro-4-nitro-anisole obtained.

2-Fluoro-4-aminoanisole.[5b,6b]—The reduction of 2-fluoro-4-nitroanisole with hydrochloric acid and stannous chloride as described by Schiemann and Miau[6b] gave 65–75% of the theoretical amount of 2-fluoro-4-aminoanisole, m. p. 82.0°, which confirms the observations of these authors.

2-Fluoro-4-cyanoanisole.—To 51 g. of 2-fluoro-4-aminoanisole in 110 ml. of concd. hydrochloric acid and 100 ml. of water was added 26 g. of sodium nitrite in 50 ml. of water. The diazonium salt was then added, with vigorous stirring, to a solution, maintained at 60–70°, of 105 g. of potassium cyanide and 92 g. of copper sulfate in 500 ml. of water layered with 100 ml. of benzene. The reaction product was taken up in an additional quantity of benzene and the solution dried over sodium sulfate. Fractional distillation gave 25 g. (46%) of the nitrile,

(6) (a) E. L. Holmes and C. K. Ingold, *J. Chem. Soc.*, **129** 1328 (1926); (b) G. Schiemann and T. Miau, *Ber.*, **66**, 1179 (1933).

(7) *Organic Syntheses*, **13**, 46 (1933).

b. p. 96–98° (1.5 mm.), m. p. 95–96°. After repeated recrystallization the substance melted at 96.5°.

Anal. Calcd. for C_8H_6ONF (151): N, 9.3; Found: N, 9.4.

3-Fluoroanisaldehyde.[2]—(A) To a solution of 15 g. of stannous chloride in 80 ml. of ether, previously saturated with hydrogen chloride, was added 8 g. of 2-fluoro-4-cyanoanisole in 100 ml. of ether.[8] The reaction mixture was allowed to stand overnight after hydrogen chloride had been passed through it, with stirring, for four hours. The precipitate was recovered, decomposed with warm water, the aldehyde taken up in ether and the ethereal solution dried over sodium sulfate. Fractional distillation gave 63% of the theoretical amount of 3-fluoroanisaldehyde, b. p. 93° (4.5 mm.), m. p. 29–30°.

Anal. Calcd. for $C_8H_7O_2F$ (154): C, 62.4; H, 4.5. Found: C, 62.4; H, 4.6.

(B) Twenty grams of *o*-fluoroanisole was added to 27 g. of zinc cyanide[9] suspended in 100 ml. of benzene. After the solution was saturated with hydrogen chloride, 24 g. of aluminum chloride was added and the reaction mixture was heated at 40–50° for four hours. The complex, after standing overnight, was decomposed by refluxing with 10% hydrochloric acid and the crude aldehyde was isolated as described above. Fractional distillation gave 6.5 g. of *o*-fluoroanisole and 7.0 g. of 3-fluoroanisaldehyde, m. p. 29–30°. The yield of aldehyde was therefore 29% of the theoretical amount, based on the original starting material, or 42% on the basis of *o*-fluoroanisole consumed.

4-(3'-Fluoro-4'-methoxybenzal)-2-phenyl-oxazolone-5.[2]—Six grams of 3-fluoroanisaldehyde was condensed with hippuric acid in the presence of acetic anhydride and sodium acetate,[2,10] and 11 g. (95%) of 4-(3-fluoro-4-methoxybenzal)-2-phenyl-oxazolone-5, m. p. 207° (cor.), was obtained.

3-Fluoro-*dl*-tyrosine.[2]—Thirty grams of the above azlactone gave, on reduction and hydrolysis,[2] 10.3 g. of 3-fluoro-*dl*-tyrosine, dec. p. 275–278° with rapid heating. The yield of amino acid from 3-fluoroanisaldehyde was 49% of the theoretical amount.

Anal. Calcd. for $C_9H_{10}O_3NF$ (199): C, 54.3; H, 5.0; N, 7.0. Found: C, 54.4; H, 5.2; N, 6.9.

3-Fluoro-5-iodo-*dl*-tyrosine.—To 7 g. of 3-fluorotyrosine in 8 *N* ammonium hydroxide was added 9 g. of iodine dissolved in the minimum amount of potassium iodide solution and the mixture was allowed to stand overnight. The crystalline precipitate was then recovered, dissolved in alkali and reprecipitated by the careful addition of acid. The mother liquors were concentrated *in vacuo* to remove the excess ammonia and carefully acidified, whereupon a further quantity of 3-fluoro-5-iodo-*dl*-tyrosine was obtained. After recrystallization from 50% ethanol the compound melted with decompn. at 192°. The yield was 5.4 g. or 47% of the theoretical amount.

Anal. Calcd. for $C_9H_9O_3NFI$ (324.9): C, 32.9; H, 2.8; N, 4.3. Found: C, 32.9; H, 3.1; N, 4.1.

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

(9) (a) R. Adams and J. Levine, THIS JOURNAL, **45**, 2373 (1923); (b) R. Adams and E. Montgomery, *ibid.*, **46**, 1518 (1924).

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

II. Synthesis of 3,5-Difluoro-*dl*-tyrosine

3-Fluoro-4-methoxyacetophenone.—To 750 g. of *o*-fluoroanisole in 2.4 l. of carbon disulfide was added, with cooling, 1.80 kg. of aluminum chloride and 6.5 g. of acetic anhydride.[11] The reaction mixture was refluxed for one hour and then poured into ice water. The solid was recovered and recrystallized (charcoal) from ethanol. The yield of 3-fluoro-4-methoxyacetophenone, m. p. 92° was 700–800 g. or 70–80% of the theoretical amount.

Anal. Calcd. for $C_9H_9O_2F$ (168): C, 64.3; H, 5.4. Found: C, 64.1; H, 5.3.

3-Fluoro-4-methoxy-5-nitroacetophenone.—Twenty-two and one-half ml. of nitric acid, sp. gr. 1.5 in 45 ml. of concd. sulfuric acid was added, with stirring, at −10°, to 90 g. of 3-fluoro-4-methoxyacetophenone in 270 ml. of sulfuric acid. After thirty minutes the mixture was poured onto ice and the product isolated by extraction with ether and distillation *in vacuo;* 50 g. (44%) of 3-fluoro-4-methoxy-5-nitroacetophenone, b. p. 144–147° (4 mm.), was obtained. The crystalline phenylhydrazone, m. p. 160–161° dec., was prepared for analysis.

Anal. Calcd. for $C_{15}H_{14}O_3N_3F$ (303): N, 13.9. Found: N, 13.9.

3-Fluoro-5-nitroanisaldehyde.—Fourteen grams of 3-fluoroanisaldehyde was dissolved in 200 ml. of concd. sulfuric acid at −10° and while maintaining this temperature there was added 8.8 g. of nitric acid, sp. gr. 1.5. The resulting solution was allowed to stand at −10° for three hours and then poured into ice water. A white crystalline solid was recovered. This product was recrystallized from isopropyl ether, yielding 10 g. (55%) of 3-fluoro-5-nitroanisaldehyde m. p. 57–58°. Reaction of the aldehyde with hydroxylamine gave an oxime m. p. 138–139°.

Anal. Calcd. for $C_8H_7O_4N_2F$ (214): N, 13.1. Found: N, 13.1.

3-Fluoroanisic Acid.[2]—Two hundred and seventy-five grams of potassium permanganate dissolved in the minimum quantity of hot water was added to 100 g. of 3-fluoro-4-methoxyacetophenone suspended in 1 l. of water (at 80°) containing 2 g. of potassium hydroxide. After the reaction was completed the manganese dioxide was removed and the filtrate acidified with sulfuric acid. The solution was then heated to 95–98° and sufficient ethanol was added to dissolve the precipitate, 70.3 g. (70%) of 3-fluoroanisic acid, m. p. 208–210°, crystallized from this solution on standing at 0° for twenty-four hours.

Anal. Calcd. for $C_8H_7O_3F$ (170): C, 56.5; H, 4.1. Found: C, 56.6; H, 4.2.

3-Fluoro-5-nitroanisic Acid.—(A) Forty-eight grams of 3-fluoroanisic acid was added in small portions to 250 ml. of nitric acid, sp. gr. 1.5, with efficient stirring at −5°. The clear solution was allowed to stand at 0° for two hours and then poured into ice water. The 3-fluoro-5-nitroanisic acid separated as a white solid which was recovered, washed with cold water, and recrystallized from benzene, m. p. 166°. The yield was 35 g. or 57% of the theoretical amount.

Anal. Calcd. for $C_8H_6O_5NF$ (215): C, 44.7; H, 2.8; N, 6.5. Found: C, 44.7; H, 2.9; N, 6.6.

(11) C. R. Noller and R. Adams, THIS JOURNAL, **46**, 1892 (1924).

(B) Three grams of 3-fluoro-5-nitroanisaldehyde was refluxed for one hour with 25 ml. of water and 1.5 g. of potassium permanganate. The reaction product was filtered and upon acidification 2.0 g. (62%) of 3-fluoro-5-nitroanisic acid of m. p. 165° was obtained. After recrystallization the substance melted at 166°.

(C) Oxidation of 3-fluoro-4-methoxy-5-nitroacetophenone with potassium permanganate at 100° (see B above) gave 3-fluoro-5-nitroanisic acid of m p. 164–165°, recrystallized 166°. The yield was poor.

Methyl 3-Fluoro-4-methoxy-5-nitrobenzoate.—The esterification of 3-fluoro-5-nitroanisic acid was conducted in the usual manner with methanol and hydrogen chloride. From 200 g. of the acid 160 g. (80%) of the ester b. p. 128–131° (3 mm.), m. p. 50°, was obtained.

Anal. Calcd. for $C_9H_8O_5NF$ (229): N, 6.1 Found: N, 6.4.

Methyl 3-Fluoro-4-methoxy-5-aminobenozate.—One hundred and forty grams of the above nitro compound was dissolved in methanol and reduced catalytically with the aid of platinic oxide. Upon evaporation of the solvent, 110 g. (90%) of the amine, m. p. 53°, was obtained. After recrystallization from isopropyl ether the compound melted at 55°.

Anal. Calcd. for $C_9H_{10}O_3NF$ (199): N, 7.0. Found: N, 7.2.

3,5-Difluoroanisic Acid.—To 30 g. of methyl 3-fluoro-4-methoxy-5-aminobenzoate in 25 ml. of concd. hydrochloric acid was added, at −5°, 11 g. of sodium nitrite dissolved in the minimum quantity of water; 60 ml. of fluoboric acid (see above) was then added to the clear solution of the diazotized amine, still maintaining the temperature at −5°. After the reaction mixture had stood for some time at 0°, the insoluble diazonium fluoborate was recovered, washed in the usual manner and dried *in vacuo* over sulfuric acid. The yield was 38 g. or 89% of the theoretical amount. The diazonium fluoborate (38 g.) was then decomposed by dry distillation and 13 g. of methyl 3,5-difluoro-4-methoxybenzoate, was obtained. Without further purification the ester was saponified with alcoholic potassium hydroxide and upon acidification of the reaction mixture 9.0 g. (32%) of crude 3,5-difluoroanisic acid was obtained. Several recrystallizations from benzene gave 8.0 g. (28%) of pure difluoroanisic acid, m. p. 162°.

Anal. Calcd. for $C_8H_6O_3F_2$ (188): C, 51.1; H, 3.2. Found: C, 51.3; H, 3.3.

4-(3′,5′-Difluoro-4′-methoxybenzal)-2-phenyloxazolone-5.—Eight grams of 3,5-difluoroanisic acid was heated on a steam-bath for three hours with thionyl chloride. The excess reagent was removed by distillation *in vacuo* at 100° and the crude acid chloride, m. p. 15–20°, was converted into 3,5-difluoroanisaldehyde without further purification. The reduction was accomplished by refluxing a solution of the acid chloride in 25 ml. of xylene, containing 1 g. of 5% palladium barium sulfate and 45 mg. of quinoline sulfur poison,[12] while passing in hydrogen for three hours. At the end of this time no more hydrogen chloride was being evolved and the reaction mixture was filtered, extracted with a small quantity of dilute hydrochloric acid, washed with water, dried over sodium sulfate, and the xylene removed *in vacuo*. The residual liquid aldehyde was converted into the azlactone in the usual manner and from this reaction 7.0 g. (52%) of 4-(3′,5′-difluoro-4′-methoxybenzal)-2-phenyloxazolone-5, m. p. 165–169° dec., was obtained.

Anal. Calcd. for $C_{17}H_{11}O_3NF_2$ (315): N, 4.4. Found: N, 4.6.

α-N-Benzoylamino-3,5-difluoro-4-methoxycinnamic Acid.—The above azlactone was saponified with alcoholic sodium hydroxide and after acidification of the reaction mixture α-N-benzoylamino-3,5-difluoro-4-methoxycinnamic acid, m. p. 200–201°, was obtained.

Anal. Calcd. for $C_{17}H_{13}O_4NF_2$ (333): C, 61.2; H, 3.9; N 4.2. Found: C, 61.0; H, 4.2; N, 4.1.

3,5-Difluoro-*dl*-tyrosine.—Seven grams of 4-(3′,5′-difluoro-4′-methoxybenzal)-2-phenyloxazolone-5 and 7 g. of red phosphorus in 65 ml of hydriodic acid, sp. gr. 1.7, and 50 ml. of acetic anhydride, was refluxed for five hours. The reaction mixture was then worked up in the usual manner and 3.7 g. of the crude amino acid was obtained. Recrystallization from water gave 3.0 g. (62%) of 3,5-difluoro-*dl*-tyrosine, m. p. 263–265° dec.

Anal. Calcd. for $C_9H_9O_3NF_2$ (217): C, 49.8; H, 4.2; N, 6.5. Found: C, 49.7; H, 4.3; N, 6.3.

3-Fluoro-4-methoxy-5-aminobenzyl Alcohol.—(A) Four grams of 3-fluoro-5-nitroanisaldehyde in 30 ml. of ethanol was shaken with 50 mg. of platinic oxide and 0.1 ml. of 0.1 *M* ferrous chloride, in the presence of 3–4 atm. of hydrogen, for thirty minutes. After removing the catalyst and solvent the residual dark oil was distilled *in vacuo;* 0.95 g. (27%) of 3-fluoro-4-methoxy-5-aminobenzyl alcohol, b. p. 141° (2 mm.), m. p. 55°, was obtained.

Anal. Calcd. for $C_8H_{10}O_2NF$ (171): N, 8.2. Found: N, 8.2.

(B) 3-Fluoro-5-nitroanisaldehyde (6.3 g.) dissolved in 25 ml. of dry isopropyl alcohol was treated with 2 g. of aluminum isopropoxide and the mixture slowly distilled until no more acetone could be detected in the distillate. The residue was poured into water, extracted with ether and the ethereal solution dried over sodium sulfate. Fractional distillation gave 65% of the theoretical amount of 3-fluoro-4-methoxy-5-nitrobenzyl alcohol, b. p. 155–159° (3 mm.). The alcohol thus obtained was reduced quantitatively with platinic oxide and hydrogen to give 3-fluoro-4-methoxy-5-aminobenzyl alcohol, m. p. 55°.

All attempts to convert 3-fluoro-4-methoxy-5-aminobenzyl alcohol to the corresponding diazonium fluoborate, either by diazotization in the usual manner or by diazotization in fluoboric acid,[13] were unsuccessful. In a control experiment 3-amino-4-methoxybenzyl alcohol gave a 60% yield of the diazonium fluoborate.

3-Fluoro-4-methoxy-5-aminoacetophenone.—This substance was prepared by the reduction of the corresponding nitro compound in ethanol solution with platinic oxide and hydrogen. The amine, b. p. 138° (2.5 mm.), was converted into the hydrochloride which did not exhibit a true m. p. but decomposed slowly from 160–175°.

(12) K. W. Rosenmund and F. Zetsche, *Ber.*, **54**, 425 (1921).

(13) C. M. Suter, E. J. Lawson and P. G. Smith, THIS JOURNAL, **61**, 161 (1939).

Anal. Calcd. for $C_9H_{11}O_2NFCl$ (219.5): N, 6.4. Found: N, 6.5.

All attempts to prepare the diazonium fluoborate from this amine by the usual procedures were unsuccessful.

Methyl 3,5-Diamino-4-methoxybenzoate.—The methyl ester of 3,5-dinitroanisic acid[14] was reduced catalytically in an ethanol solution and a quantitative yield of the diamine, m. p. 157°, was obtained.

On tetrazotizing the diamine according to the method given by Schiemann and Pillarsky,[15] 55% of the theoretical amount of crystalline tetrazonium fluoborate separated very slowly from the reaction mixture. It was found impossible to control the decomposition of this salt so as to give a practical yield of difluoroanisic acid.

2,6-Diamino-4-nitrophenol.[16]—Hydrogen sulfide was passed into a solution of 75 g. of picric acid in 500 ml. of 28% ammonia and 500 ml. of water. Heat was evolved and cooling was necessary to prevent the temperature from rising above 75°. When the solution cleared and when heat was no longer evolved, the passage of hydrogen sulfide was stopped and the mixture evaporated *in vacuo* until the residue was practically free of ammonia. After filtration the solution was acidified, the precipitate extracted with dilute hydrochloric acid and the extract filtered. Careful addition of acid to the filtrate gave, on cooling, 45% of the theoretical amount of 2,6-diamino-4-nitrophenol, m. p. 169° dec.

Anal. Calcd. for $C_6H_7O_3N_3$ (169): N, 24.8. Found: N, 24.6.

Eight grams of the diamine heated on a steam-bath for one hour with 100 ml. of acetic acid and 9.5 g. of acetic anhydride gave a 65% yield of 2,6-diacetoamino-4-nitrophenol, m. p. 235° with decompn.

2,6-Diamino-4-nitroanisole.—Finely powdered 2,6-diacetamino-4-nitrophenol was treated, at 0° for twenty-four hours with an ethereal solution of diazomethane. A 75% yield of 2,6-diacetamino-4-nitroanisole, m. p. 211°, was obtained by recrystallizing the precipitate with ethyl acetate. 2,6-Diamino-4-nitroanisole, m. p. 180–181°, was obtained in an 85% yield from the diacetyl derivative by saponification with 5 *N* sodium hydroxide.

Anal. Calcd. for $C_7H_9O_3N_3$ (183): N, 22.9. Found: N, 23.0.

A 52% yield of the tetrazonium fluoborate was obtained from the above diamine but it was found that the salt decomposed explosively giving a very small amount of oily product.

2,6-Difluoro-4-nitroanisole.—To 2.4 g. of 2-fluoro-4-nitro-6-aminoanisole,[6b] m. p. 108°, in 3.6 ml. of concd. hydrochloric acid was added 0.9 g. of sodium nitrite in 2 ml. of water and the resulting filtered solution treated with 4 ml. of fluoboric acid. The diazonium fluoborate was obtained in a 60% yield. The decomposition of this salt was difficult to control and it was found impossible to obtain more than a 10% yield of 2,6-difluoro-4-nitroanisole, m. p. 35°.

Anal. Calcd. for $C_7H_5O_3NF_2$ (189): N, 7.4. Found: N, 7.5.

Summary

The synthesis of 3,5-difluoro- and 3-fluoro-5-iodo-*dl*-tyrosine from *o*-anisidine has been described.

PASADENA, CALIFORNIA RECEIVED DECEMBER 1, 1939

(14) F. Ullmann, *Ann.*, **366**, 94 (1909).
(15) G. Schiemann and R. Pillarsky, *Ber.*, **62**, 3039 (1929).
(16) P. Griess, *Ann.*, **154**, 202 (1870).

[CONTRIBUTION FROM THE KENT AND GEORGE HERBERT JONES CHEMICAL LABORATORIES, UNIVERSITY OF CHICAGO]

dl-Threonic Acid from 3-Hydroxy-crotonic Acid

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While *dl*-erythronic lactone can be prepared without difficulty and in quantity directly from 3-hydroxy-isocrotonic lactone[2] which itself is easily obtained in good yield as a by-product in the synthesis of *dl*-2,3-dihydroxybutyric acid,[3] the epimeric tetronic acid, *dl*-threonic acid, is still a rare chemical. The only synthesis of the last-named acid that is reported in the literature was accomplished by Braun.[4] Glycerol-1,3-dichlorohydrin is the starting material and this is converted into *dl*-threonic acid by a procedure consisting of six steps. While the yield in each step is good (varying from 25 to 81%) the over-all yield is only about 2% of the theoretical.[5] As none of the intermediates is available commercially, it becomes necessary to start with glyceroldichlorohydrin in each attempt to synthesize *dl*-threonic

(1) The material in this article is taken from a dissertation submitted by E. C. Lee in August, 1936, to the faculty of the Division of the Physical Sciences in the University of Chicago in partial fulfilment of the requirements for the Ph.D. degree. Dr. Lee died in June, 1939. This article has been prepared by the senior author.
(2) Braun, THIS JOURNAL, **51**, 235 (1929).
(3) Glattfeld, Leavell, Spieth and Hutton, *ibid.*, **53**, 3164 (1931).
(4) Braun, *ibid.*, **52**, 3167 (1930); **54**, 1133 (1932).
(5) Braun also prepared one of the intermediates, 2-hydroxy-3-chloro-butyronitrile from epichlorohydrin and hydrogen cyanide (Lespieau) in 65% yield as against 25% from glycerol-1,3-dichlorohydrin. This would make the over-all yield of *dl*-threonic acid from the former 6.5% as against 2% from the latter. In spite of the lower yield, Braun seems to consider the dichlorohydrin as the starting material in this procedure for he says [*ibid.*, **52**, 3168 (1930)] "Lespieau's method has the great disadvantage that the handling of anhydrous hydrogen cyanide above its boiling point is very inconvenient. The *new procedure* (italics the author's) avoids this; it involves the treatment of dichlorohydrin with sodium cyanide in aqueous suspension."