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The Synthesis of 2-Fluoro-DL-tyrosine and 2-Fluoro-4-methoxy-DL-phenylalanine

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In extending our studies on the fluorinated α-amino acids[2] two new monofluoro-α-amino acids, *viz.*, 2-fluoro-DL-tyrosine and 2-fluoro-4-methoxy-DL-phenylalanine, have been prepared by the series of reactions: 2-amino-4-nitrotoluene $\xrightarrow{92\%}$ 2-methyl-5-nitrobenzenediazonium fluoroborate $\xrightarrow{58\%}$ 2-fluoro-4-nitrotoluene $\xrightarrow{93\%}$ 2-fluoro-4-aminotoluene $\xrightarrow{86\%}$ 2-fluoro-4-hydroxytoluene $\xrightarrow{85\%}$ 2-fluoro-4-methoxytoluene $\xrightarrow{55\%}$ 2-fluoro-4-methoxybenzoic acid $\xrightarrow{97\%}$ 2-fluoro-4-methoxybenzoyl chloride $\xrightarrow{81\%}$ 2-fluoro-4-methoxybenzyl chloride $\xrightarrow{85\%}$ diethyl α-acetamido-α-(2-fluoro-4-methoxybenzyl)-malonate $\xrightarrow{62\%}$ N-acetyl-2-fluoro-4-methoxy-DL-phenylalanine. The latter compound was deacetylated to give 63% of 2-fluoro-4-methoxy-DL-phenylalanine or simultaneously deacetylated and demethylated to give 80% of 2-fluoro-DL-tyrosine. The over-all yields of 2-fluoro-4-methoxy-DL-phenylalanine and 2-fluoro-DL-tyrosine were 5.0 and 6.3%, respectively.

The principal features of the ultraviolet absorption spectra of 0.1 *M* aqueous sodium chloride solutions of the above two compounds and those of L-tyrosine and 3-fluoro-DL-tyrosine[2] are given in Table I. Whereas replacement of a nuclear hydrogen atom in phenylalanine by a fluorine atom causes a bathochromic displacement of the benzenoid (B) absorption of *ca.* 10 mμ[3] the same replacement in tyrosine leads to a hypsochromic displacement of *ca.* 3 mμ. Further the notable hyperchromic effect associated with the presence of a nuclear fluorine atom in the case of phenylalanine[3] appears to be very much less prominent for the monofluorotyrosines.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SUBSTITUTED DL-TYROSINE IN 0.1 *M* AQUEOUS SODIUM CHLORIDE

Compound	λ (mμ)		ε
L-Tyrosine	223	(max.)	8600
	245	(min.)	165
	275	(max.)	1400
2-Fluoro-DL-tyrosine	220.5	(max.)	8925
	242	(min.)	185
	272	(max.)	1580
3-Fluoro-DL-tyrosine	221	(max.)	8250
	243	(min.)	200
	272	(max.)	1520
2-Fluoro-4-methoxy-DL-phenylalanine	222	(max.)	11000
	243	(min.)	200
	271	(max.)	1730

The apparent ionization constants of 2-fluoro-4-methoxy-DL-phenylalanine in 0.1 *M* aqueous sodium chloride at 23° were found to be, pK'_{CO_2H} = 2.12; $pK'_{NH_3^+}$ = 9.03 as compared with pK'_{CO_2H} = 2.12; $pK'_{NH_3^+}$ = 9.01 for *o*-fluoro-DL-phenylalanine.[3]

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Experimental[4]

2-Methyl-5-nitrobenzenediazonium Fluoroborate (I).[5]—I, decomp. point 129–130°, was prepared in 92% yield by the diazotization of 4-nitro-2-aminotoluene.

2-Fluoro-4-nitrotoluene (II).[5]—Fifty grams of I was placed in a 1-l. RBST flask attached to an upright 40-cm. air condenser and a 40-cm. downward water cooled condenser assembled in the form of an inverted U. A 250-ml. flask was connected at the bottom of the downward condenser, and this in turn connected to another 250-ml. flask with an inlet projecting one-half way into the water with which this latter flask was partially filled. The decomposition was initiated by gently heating I at a small spot near the surface with a micro burner or a match. As soon as the reaction had started, heating was discontinued and the reaction allowed to proceed spontaneously. After the reaction had subsided, the decomposition flask was heated gently until no more gases were evolved. The contents of the decomposition flask, condensers and traps were taken up in ether, the ethereal extract washed with water, dried and fractionally distilled to give 121 g. (58%) of II, b. p. 94–95° (8 mm.), m. p. 33.5–34.8°, from 338 g. of I; lit.[5] b. p. 65–68° (2 mm.), m. p. 34–35°. The above method of decomposition was found to be more satisfactory than that described previously.

2-Fluoro-4-aminotoluene (III).[5]—Catalytic reduction of II in absolute ethanol over platinum oxide gave 93% of III, b. p. 97° (15 mm.); lit.[5] b. p. 200–205°.

2-Fluoro-4-hydroxytoluene (IV).—A solution of 77 g. of III in 2 *M* sulfuric acid was diazotized at 0° with 43 g. of sodium nitrite in 100 ml. of water, the excess nitrite destroyed with urea, and the diazo solution slowly added to 500 ml. of boiling water with simultaneous removal of IV from the reaction mixture by steam distillation. The distillate was extracted with ether, the ethereal extract dried, and fractionally distilled to give, 67 g. (86%) of IV, b. p. 88–89° (10 mm.).

Anal. Calcd. for C_7H_7OF (126): C, 66.7; H, 5.6. Found: C, 66.5; H, 5.6.

2-Fluoro-4-methoxytoluene (V).—The methylation of IV with sodium hydroxide and dimethyl sulfate gave 85% of V, b. p. 81–82.5° (24 mm.).

Anal. Calcd. for C_8H_9OF (140): C, 68.6; H, 6.4. Found: C, 68.6; H, 6.4.

2-Fluoro-4-methoxybenzoic Acid (VI).—V (24 g.) was oxidized with potassium permanganate,[6] the reaction mix-

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(2) For previous studies from this Laboratory see THIS JOURNAL, **62**, 350 (1940); **63**, 609, 2204 (1941); **68**, 1671 (1946); **69**, 1232 (1947); **70**, 2610 (1948); **71**, 3024 (1949).

(3) E. L. Bennett and C. Niemann, *ibid.*, **72**, 1804 (1950).

(4) All melting points are corrected.

(5) F. Schmelkes and M. Rubin, THIS JOURNAL, **66**, 1631 (1944).

(6) H. Clarke and E. Taylor, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 135.

ture steam distilled to remove unreacted V, freed of manganese dioxide and the solution acidified to give 16.2 g. (55%) of VI, m. p. 190–193°. A portion of this product was recrystallized from toluene to give VI, m. p. 192–193.5°.

Anal. Calcd. for $C_8H_7O_3F$ (170): C, 56.5; H, 4.2. Found: C, 56.7; H, 4.2.

2-Fluoro-4-methoxybenzoyl Chloride (VII).[7]—VI (29.9 g.) was refluxed with 40 ml. of thionyl chloride for ten hours[8] and the reaction mixture fractionally distilled to give 32 g. (97%) of VII, b. p. 120–122° (3 mm.), m. p. 37–40°.

2-Fluoro-4-methoxybenzyl Chloride (VIII).[7]—A solution of 30.8 g. of VII in 300 ml. of absolute ether was reduced with 200 ml. of 0.5 *M* lithium aluminum hydride.[9] When the reduction had been completed, 10 ml. of water was added, the mixture poured into a slurry of ice in dilute sulfuric acid, the ethereal phase collected, the aqueous phase repeatedly extracted with ether, the ethereal extracts combined, washed with water until neutral, dried and the solvent removed to give 30 g. of crude 2-fluoro-4-methoxybenzyl alcohol. This latter product was taken up in 25 ml. of thionyl chloride, the solution allowed to stand overnight and then warmed at 90° for one hour. The excess thionyl chloride was removed by distillation *in vacuo* and the residue fractionally distilled to give 23 g. (81%) of VIII, b. p. 110–112° (7 mm.), d. 1.22.

Anal. Calcd. for C_8H_8OFCl (174.5): C, 55.0; H, 4 6. Found: C, 55.1; H, 4.6.

Diethyl α-Acetamido-α-(2-fluoro-4-methoxybenzyl)-malonate (IX).—To a solution of 3.1 g. of sodium and 30 g. of diethyl acetamidomalonate in 250 ml. of absolute ethanol was added 21.8 g. of VIII, the mixture refluxed for four hours,[10,11] the sodium chloride removed and 600 ml. of water added to the filtrate. The crystalline product was collected, washed with 30% aqueous ethanol and then with water to give 36.8 g. (85%) of IX, m. p. 118–120°. A portion of this product was recrystallized from absolute ethanol to give IX, m. p. 120–121.5°.

Anal. Calcd. for $C_{17}H_{22}O_6NF$ (355): C, 57.5; H, 6.2; N, 3.9. Found: C, 57.6; H, 6.3; N, 3.9.

N-Acetyl-2-fluoro-4-methoxy-DL-phenylalanine (X).—IX (35.5 g.) was refluxed for six hours with 175 ml. of 2.5 *M* sodium hydroxide, 95 ml. of 5 *M* hydrochloric acid added and the mixture refluxed for an additional two hours[10,11] to give, after standing at 4° overnight, 15.8 g. (62%) of X, m. p. 162–170° which was then recrystallized from ethanol to give 13.7 g. of X, m. p. 169.5–171.5°.

Anal. Calcd. for $C_{12}H_{14}O_4NF$ (255): C, 56.5; H, 5.5; N, 5.5. Found: C, 56.5; H, 5.5; N, 5.6.

2-Fluoro-4-methoxy-DL-phenylalanine (XI).—X (1.0 g.) was refluxed with 40 ml. of 3 *M* hydrochloric acid for seven hours, the hydrolysate concentrated *in vacuo*, the residue taken up in 20 ml. of water, an excess of ammonium hydroxide added, the excess expelled by boiling, and 15 ml. of ethanol added to the cold solution to give 0.53 g. (63%) of XI, long needles, dec. point 218–226°. Recrystallization of this latter product from 50% aqueous ethanol gave XI, dec. point 217–221°.

Anal. Calcd. for $C_{10}H_{12}O_3NF$ (213): C, 56.3; H, 5.7; N, 6.6. Found: C, 56.4; H, 5.8; N, 6.6.

2-Fluoro-DL-tyrosine (XII).—A solution of 1.4 g. of X in 20 ml. of aqueous hydrobromic acid was refluxed for seven hours, the excess hydrogen bromide removed by distillation *in vacuo*, and the residue crystallized from aqueous ammonia to give 0.87 g. (80%) of XII, dec. point 280–285°, which was recrystallized from water to give XII, dec. point 280–285°.

Anal. Calcd. for $C_9H_{10}O_3NF$ (199): C, 54.3; H, 5.1; N, 7.0. Found: C, 54.2; H, 5.0; N, 7.1.

Ultraviolet Spectra and Ionization Constants.—The methods used have been described previously.[12]

Summary

The synthesis of 2-fluoro-DL-tyrosine and 2-fluoro-4-methoxy-DL-phenylalanine has been described and their ultraviolet absorption spectra determined.

(7) VII was prepared with the intent to reduce it to 2-fluoro-4-methoxybenzaldehyde. Difficulties encountered in this reduction led to the procedure described. It is clear that the benzoic acid could have been reduced directly to the alcohol.

(8) B. Helferich and W. Schaefer, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 147.

(9) R. Nystrom and W. Brown, THIS JOURNAL, **69**, 1197 (1947).

(10) N. Albertson and S. Archer, *ibid.*, **67**, 308 (1945).

(11) H. Snyder, J. Shekleton and C. Lewis, *ibid.*, **67**, 310 (1945).

(12) J. C. Nevenzel, W. Shelberg and C. Niemann, *ibid.*, **71**, 3024 (1949).

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Some Reactions of *cis*-3,5-Dibromocyclopentene

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A survey of the literature reveals that 3,5-dihalocyclopentenes have been virtually neglected as intermediates in the synthesis of substituted cyclopentenes. This paper reports several studies, mainly carried out on the *cis*-dibromide, directed toward the synthesis of 3,5-dialkylcyclopentenes, and especially 3,5-di-*s*-butylcyclopentene, which is the ring system reported to be present in the two plant hormones, auxins a and b.[2] Although attempts to effect substitution of both bromine atoms failed, *cis*-3,5-dibromocyclopentene proved very efficient for the introduction of the cyclopentadienyl unit by means of alkylation and Barbier-type[3] reactions.

Despite the fact that Grignard reagents have been shown to react with 3-halocyclopentenes[4,5,6] in the normal Brooks–Humphrey fashion,[7] our efforts to extend this type of reaction to either *cis*- or *trans*-3,5-dibromocyclopentene were without success. Although many attempts were made under various conditions and with different Grignard reagents, deep polymerization inevitably resulted, and no monoalkyl or dialkyl product

(1) From the doctoral dissertation of John F. Yost, The Johns Hopkins University.

(2) Kögl, Erxleben, Michaelis and Visser, *Z. physiol. Chem.*, **235**, 181 (1935).

(3) Barbier, *Compt. rend.*, **128**, 110 (1899).

(4) Braun, Kamp and Kopp, *Ber.*, **70B**, 1750 (1937).

(5) Braun and Reitz-Kopp, *ibid.*, **74B**, 1105 (1941).

(6) Crane, Boord and Henne, THIS JOURNAL, **67**, 1237 (1945).

(7) Brooks and Humphrey, *ibid.*, **40**, 822 (1918).