Fluorinated Benzoic Acid Derivatives

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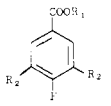
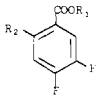
The properties of some fluorinated nitro and aminobenzoic acids and esters are reported.

IN THE COURSE of a program designed to evaluate compounds for their ability to inhibit the enzyme phenylalanine hydroxylase (*1*) the authors were interested in the preparation of 3,4,5-trifluorophenylalanine. Efforts to obtain a key intermediate, 3,4,5-trifluorobenzoic acid, were unsuccessful, however, the properties of some new fluorinated aromatic compounds synthesized as intermediates are reported. 3,5-Dinitro-4-fluorobenzoic acid (I) was hydrogenated to the diamino acid (II), which was immediately esterified with methanolic hydrogen chloride. Treatment of a fluoboric acid solution of the ester (III) with sodium nitrite afforded the bis-diazonium fluoborate salt (IV) identified by its infrared spectrum. When the salt was heated at 150° C. it decomposed as expected, but no product could be isolated from the vapor or residual fraction. The total failure of this pyrolysis is difficult to explain since ethyl 3,5-difluorobenzoate has been prepared in this manner (*5*) and 1,2,3-trifluorobenzene was obtained by pyrolysis of the diazonium fluoborate salt of 2,3-difluoroaniline (*4*).

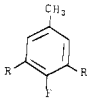
I) $R_1 = H, R_2 = NO_2$
II) $R_1 = H, R_2 = NH_2$
III) $R_1 = CH_3, R_2 = NH_2$
IV) $R_1 = CH_3, R_2 = N_2^+BF_4^-$



V) $R_1 = H, R_2 = NO_2$
VI) $R_1 = H, R_2 = NH_2$
VII) $R_1 = CH_3, R_2 = NH_2$
VIII) $R_1 = CH_3, R_2 = N_2^+BF_4^-$
IX) $R_1 = CH_3, R_2 = F$



X) $R = NO_2$
XI) $R = NH_2$



The nitration of 3,4-difluorobenzoic acid yielded only 2-nitro-4,5-difluorobenzoic acid (V). This was confirmed by conversion to the amino ester (VII) and decomposition of the fluoborate salt (VIII) to afford methyl 2,4,5-trifluorobenzoate (IX) identified by its NMR spectrum. The spectrum clearly showed two nonequivalent aromatic protons as multiplets centered at 2.25 and 3.04 τ with a fine splitting (J = ½ cycle) indicative of para coupling. Spin decoupling by irradiation at the median frequency of the 3.04 τ multiplet removed the splitting. This demonstrates that the coupling was indeed between protons rather than hydrogen and fluorine.

The reaction of 3,5-dinitro-4-chlorotoluene with potassium fluoride in dimethyl formamide yielded the fluoride (X), which was hydrogenated to 3,5-diamino-4-fluorotoluene (XI). The diazonium fluoborate salt of XI could not be isolated.

EXPERIMENTAL

Melting points were taken with a Fischer-Johns apparatus and are corrected.

Methyl 3,5-Diamino-4-fluorobenzoate (III). A mixture of 23.0 grams (0.1 mole) of 3,5-dinitro-4-fluorobenzoic acid (I), 16.7 ml. (0.2 mole) of concentrated hydrochloric acid, 1.0 gram of 5% rhodium-on-carbon, and 250 ml. of tetrahydrofuran was shaken under 3 atm. of hydrogen for 16 hours. Methanol (200 ml.) was added to dissolve the precipitated product and the catalyst was removed by filtration. The filtrate was evaporated and the residual crude acid hydrochloride (II) was directly esterified with saturated methanolic hydrogen chloride at reflux for 24 hours. The solvent was removed, an aqueous solution of the residue was adjusted to pH 8–9, and the product was extracted into ethyl acetate. Evaporation yielded 10.8 grams of white crystals, m.p. 129.5–131° C.

Anal. Calcd. for $C_8H_9FN_2O_2$: C, 52.2; H, 4.92; N, 15.2; F, 10.3. Found: C, 52.4; H, 4.84; N, 15.2; F, 10.2.

A solution of the amino ester in 50% fluoboric acid was treated with sodium nitrite at −15°, followed by dilution with ether. The precipitated diazonium fluoborate salt (IV), yellow crystals, m.p. 155° (dec.), was pyrolyzed at 150° in vacuo to give only a black foam from which no product could be isolated. Dry-Ice traps attached to the system were also devoid of product.

4,5-Difluoro-2-nitrobenzoic Acid (V). To a mixture of 0.40 gram of 3,4-difluorobenzoic acid (*3*) and 3.0 ml. of concentrated sulfuric acid at 0° was added 1.5 ml. of concentrated nitric acid. The reaction was stirred at room temperature for 3 hours, chilled to 0°, and 20 ml. of ice water was added. The aqueous mixture was extracted with three 20-ml. portions of ether and was dried and evaporated in vacuo. Recrystallization from toluene gave 0.24 gram (48%) of white crystals, m.p. 152–154°.

Anal. Calcd. for $C_7H_3F_2NO_4$: C, 41.4; H, 1.49; N, 6.89. Found: C, 41.4; H, 1.54; N, 6.84.

2-Amino-4,5-difluorobenzoic Acid Hydrochloride (VI). 2-Nitro-4,5-difluorobenzoic acid (V) was hydrogenated by a procedure similar to that described for the reduction of I. The product, m.p. 188–189°, was obtained in a 95% yield after recrystallization from 90% acetone.

Anal. Calcd. for $C_7H_5F_2NO_2 \cdot HCl$: C, 40.1; H, 2.40; N, 6.68. Found: C, 40.0; H, 2.46; N, 7.05.

Methyl 2-Amino-4,5-difluorobenzoate Hydrochloride (VII). The ester was obtained by treatment of the acid (VI) with hot saturated methanolic hydrogen chloride for 2 hours. The solvent was evaporated and the residue triturated with ether to afford a 94% yield of white crystals, m.p. 175–183°. A portion was sublimed for analysis, m.p. 179–180°.

Anal. Calcd. for $C_8H_7F_2NO_2 \cdot HCl$: C, 43.0; H, 3.60; N, 6.26. Found: C, 42.7; H, 3.50; N, 6.35.

Methyl 2,4,5-Trifluorobenzoate (IX). To 22.3 grams (0.10 mole) of VII was added 30 ml. of water and 17 ml. of 6*N* hydrochloric acid. A solution of 6.90 grams (0.10 mole) of sodium nitrite in 10 ml. of water was slowly added keeping the temperature below 0°. Sodium fluoborate (12.0 grams, 0.11 mole) was then added and the mixture was stirred at −5° for 15 minutes, filtered, and the cake washed with cold ethanol and ether to yield 3.77 grams (13%) of VIII as pink crystals, m.p. 93–95°. The material was heated in vacuo (ca. 25 mm.) until it had melted (125°) and was then distilled (up to 200°). The distillate was dissolved in ether, washed with saturated sodium bicarbonate,

and the ether was distilled off. The residue was distilled through a short path to yield 1.12 grams, b.p. 130–135° at 100 mm. Gas-liquid chromatography showed approximately 90–95% purity, and a center cut was collected for analysis. The NMR spectrum (100 m.c.s. in $CDCl_3$) had an octet centered at 2.25 τ (H at position 3) and a sextet centered at 3.04 τ (H at position 6) all of which were split (J = ½ c.p.s.). Spin decoupling by irradiation at the median frequency of the peaks at 3.04 τ reduced the split peaks to sharp singlets.

Anal. Calcd. for $C_8H_5F_3O_2$: C, 50.5; H, 2.65. Found: C, 50.9; H, 2.60.

Saponification yielded an acid, m.p. 93–95°; 2,4,5-trifluorobenzoic acid (2) m.p. 97–98°.

Anal. Calcd. for $C_7H_3F_3O_2$: C, 47.7; H, 1.71. Found: C, 47.8; H, 1.77.

4-Fluoro-3,5-dinitrotoluene (X). To 11.6 grams (0.20 mole) of finely divided, anhydrous potassium fluoride was added 10.0 grams (46.3 mmoles) of 4-chloro-3,5-dinitrotoluene (Sherwin-Williams) and 30 ml. of dimethyl formamide. The reaction mixture was heated at 155° for 16 hours, chilled, and diluted with 150 ml. of water. The resulting mixture was partitioned between ether and water. The ether was washed with three 30-ml. portions of 1N NaOH, three 30-ml. portions of 1N HCl, three 30-ml. portions of water, dried, and evaporated in vacuo to dryness to yield a brown solid which was recrystallized from carbon tetrachloride to yield 0.850 gram (11%) of a yellow solid, m.p. 70–72°.

Anal. Calcd. for $C_7H_3FN_2O_4$: C, 42.0; H, 2.52; N, 14.0. Found: C, 41.7; H, 2.69; N, 13.7.

3,5-Diamino-4-fluorotoluene (XI). To 0.50 gram (2.5 mmoles) of 4-fluoro-3,5-dinitrotoluene was added 3.97 grams (21 mmoles) of stannous chloride, 4.3 ml. of concentrated hydrochloric acid, and 15 ml. of water. The mixture was stirred at reflux 2 hours, chilled, and evaporated in vacuo to dryness. The residue was recrystallized from benzene to yield 0.225 gram (64%) of a white solid, m.p. 75.5–77° C.

Anal. Calcd. for $C_7H_9FN_2$: C, 60.0; H, 6.47, N, 20.0. Found: C, 59.9; H, 6.47; N, 19.7.

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An Improved Preparation of Etioporphyrin I

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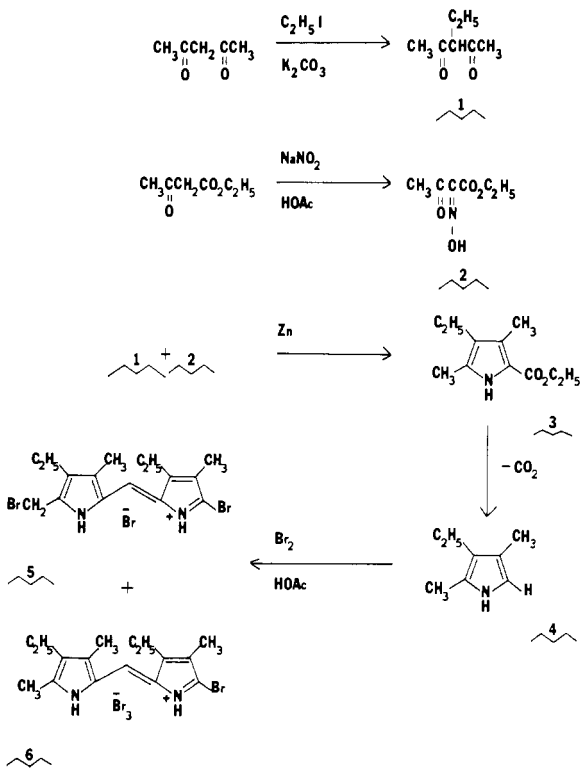
A large quantity of highly purified etioporphyrin I was prepared by an improved method in an over-all yield of about 5% from 3-ethyl-2,4-pentanedione and ethyl acetoacetate.

THE COLLECTION of reliable kinetic data on reactions of etioporphyrin I and its metallo derivatives requires substantial quantities of highly purified reactants. In following the preparative procedures described in the literature for the synthesis of etioporphyrin I, certain of the steps were unsatisfactory or inconvenient.

The authors have not been able to approach yields reported by Treibs and Schmidt (*15*) in the direct synthesis of 2,4-dimethyl-3-ethylpyrrole from ethyl 3,5-dimethyl-4-acetylpyrrole-2-carboxylate. Johnson and coworkers (*10*) report a yield of 8% for a comparable reaction. Yields of the order of 55 to 60% are obtained (*6, 13*) by effecting a high pressure, high temperature autoclave reduction, a procedure requiring special equipment and technique. The use of alkylated pentanediones (*2, 10, 11*) (2,4-pentanedione, Eastman) eliminates the troublesome reduction step. In the synthesis (*11*) of ethyl 3,5-dimethyl-4-ethylpyrrole-2-carboxylate from 3-ethyl-2,4-pentanedione and diethyl malonate, isolation of the intermediate oximinomalonate ester is required. A comparable yield of ethyl 3,5-dimethyl-4-ethylpyrrole-2-carboxylate was obtained by a direct reaction of 3-ethyl-2,4-pentanedione and ethyl acetoacetate by the procedure described herein.

Recently, new methods (*2, 9, 12*) have been described for the synthesis of etioporphyrin I. In two of these pro-



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