[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY][1]

THE MONOFLUOROCATECHOLS

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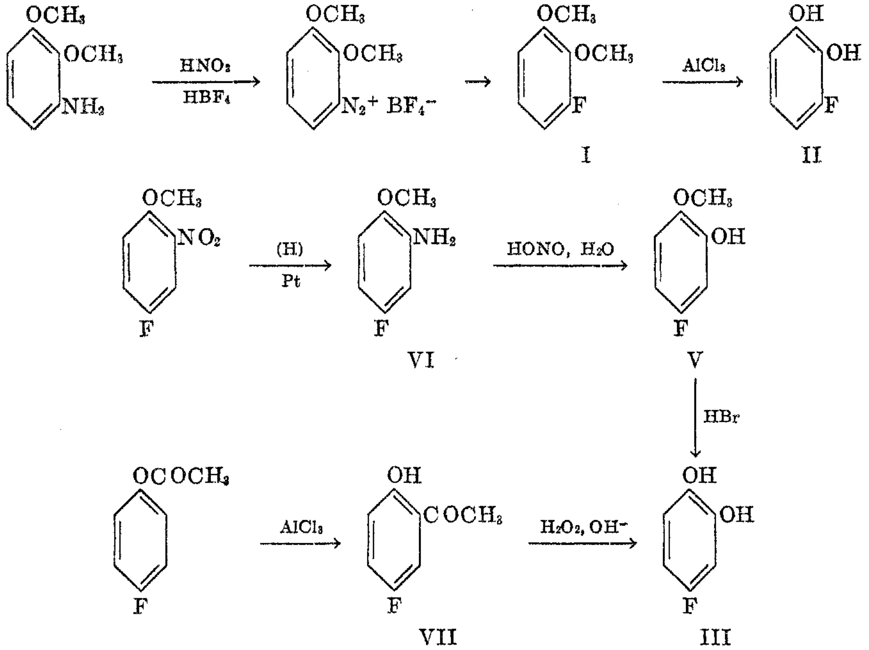
Received April 3, 1951

During the study of the effect of ring substituents on the oxidation of catechol by polyphenolase it became desirable to have both 3- and 4-fluorocatechol available.

3-Fluoroveratrole (I), prepared by the Schiemann reaction (1), was demethylated with hydriodic acid or aluminum chloride to give 3-fluorocatechol (II).

Several methods were investigated for the synthesis of 4-fluorocatechol (III). The most direct synthesis was the analogous method used above for 3-fluorocatechol, using 4-aminoveratrole. Dry distillation of 3,4-dimethoxybenzenediazonium fluoborate gave 40–50% yields of 4-fluoroveratrole (IV), which afforded the desired 4-fluorocatechol (III) upon demethylation with hydriodic acid. 4-Fluoroveratrole was characterized further by formation of its mononitro derivative, presumably 4-fluoro-5-nitroveratrole. This, on catalytic reduction, yielded 2-fluoro-4,5-dimethoxyaniline. Smith and Haller (2) obtained a small yield of 4-fluoroveratrole from the decomposition of 3,4-dimethoxybenzenediazonium fluoborate in acetic acid. The chief product they obtained was 4,5-



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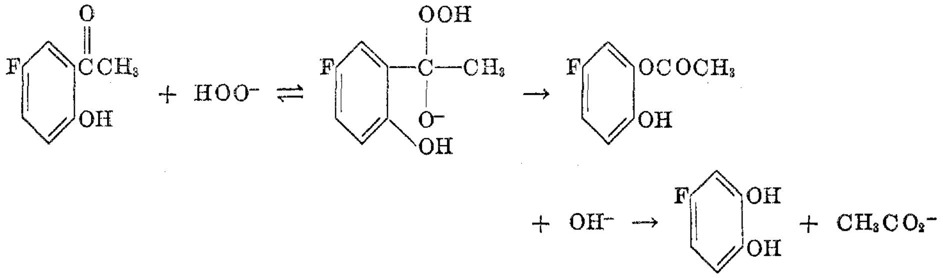
dimethoxy-2-hydroxyacetophenone, formed by the boron-trifluoride-induced Fries rearrangement of the 3,4-dimethoxyphenyl acetate initially produced. A second synthesis of III involved the formation of 5-fluoroguaiacol (V) from 5-fluoro-2-methoxyaniline (VI) and demethylation of the guaiacol with hydrobromic acid (3). The intermediate anisidine (VI) was prepared by the catalytic reduction of 4-fluoro-2-nitroanisole (4). The over-all yield was lower in this synthesis and there were more steps involved than in the preparation from 4-aminoveratrole.

The Dakin oxidation (5) of 5-fluoro-2-hydroxyacetophenone (VII) gave 63% of 4-fluorocatechol. This is in line with the lower yields that Dakin found when ketones were oxidized, in contrast to the excellent yields from aldehydes. It was found advisable to add a second equivalent of base during the reaction. This may facilitate peroxide ion addition to the carbonyl group, or may be necessary for the hydrolysis of the resulting ester (6–9).



Acknowledgment. We wish to thank Mr. L. M. White, Miss Geraldine Secor, and Mrs. Mary Kilpatrick for the microanalyses reported herein.

EXPERIMENTAL

All melting points are corrected.

3-Fluoroveratrole (I). First, 47 g., (0.25 mole) of 3-aminoveratrole hydrochloride (10, 11), suspended in 25 ml. of conc'd hydrochloric acid, was chilled and diazotized with 18 g. of sodium nitrite in 18 ml. of water. The resulting diazonium salt was poured into 80 ml. of cold 42% fluoboric acid. The crystals which separated were collected and washed successively with cold portions of water, alcohol, and ether. Drying was effected *in vacuo* over phosphorus pentoxide and potassium hydroxide. The dry salt (31.5 g., 50% yield) was pyrolyzed by gentle heating and the residue was subjected to steam-distillation. The combined distillate and steam-distillate was extracted with ether, washed with dilute sodium hydroxide and water, and dried. The yield of 3-fluoroveratrole was 11.4 g. (58%); b.p. 96–97° at 20 mm.; $\eta_D^{22.5}$ 1.4958.

Anal. Calc'd for $C_8H_9FO_2$: C, 61.5; H, 5.81.

Found: C, 61.7; H, 5.84.

3-Fluorocatechol (II). A mixture of 22 g. (0.141 mole) of 3-fluoroveratrole, 200 ml. of chlorobenzene, and 35 g. of anhydrous aluminum chloride was refluxed for three hours and then poured onto an ice-hydrochloric acid mixture. The organic layer was separated and the aqueous layer extracted three times with ether. The combined chlorobenzene portion and ether extracts were dried over magnesium sulfate. The ether and chlorobenzene were removed by vacuum-distillation and the residue was vacuum-sublimed. The 3-fluorocatechol (14.1 g., 77%) was recrystallized from ether-petroleum ether (b.p. 30–60°); m.p. 71–71.5°.

Anal. Calc'd for $C_6H_5FO_2$: C, 56.3; H, 3.93.
Found: C, 56.5; H, 4.15.

4-Fluorocatechol (III). 3,4-Dimethoxybenzenediazonium fluoborate was prepared according to the directions of Smith and Haller (2). Pyrolysis of the dry salt gave 40–50% yields of 4-fluoroveratrole. This could be demethylated in comparable yields with aluminum chloride as was done for 3-fluorocatechol or by refluxing for two hours with hydriodic acid (*sp. gr.* 1.7). After sublimation and recrystallization from ether-petroleum ether, 4-fluorocatechol melted at 90–91°.

Anal. Calc'd for $C_6H_5FO_2$: C, 56.3; H, 3.93.
Found: C, 56.4; H, 4.13.

4-Fluoro-5-nitroveratrole. Nitration of 3.25 g. of 4-fluoroveratrole with 2.3 ml. of conc'd nitric acid diluted with 2.3 ml. of water, after the method of Cardwell and Robinson for veratrole (12), gave, on dilution, a product which did not crystallize well. The material was dissolved in benzene and chromatographed on activated alumina (Alorco grade F, 80–200 mesh). The principal band was eluted with a benzene-alcohol mixture. Removal of the solvent gave 1.32 g. of material, presumably 4-fluoro-5-nitroveratrole; after recrystallization from benzene-petroleum ether it melted at 144–144.5°.

Anal. Calc'd for $C_8H_8FNO_4$: C, 47.8; H, 4.01; N, 6.96.
Found: C, 48.2; H, 4.18; N, 6.95.

2-Fluro-4,5-dimethoxyaniline hydrochloride. A solution of 1.12 g. of 4-fluoro-5-nitroveratrole in 20 ml. of ethanol was reduced with hydrogen and platinum oxide at 60 p.s.i. After the catalyst was removed, excess anhydrous hydrogen chloride was bubbled into the solution, which was then evaporated. The resulting compound was recrystallized from alcohol-ether; on heating, it decomposed at 240–245° (sealed tube).

Anal. Calc'd for $C_8H_{12}ClFNO_2$: C, 46.3; H, 5.34; N, 6.75.
Found: C, 46.5; H, 5.53; N, 6.53.

5-Fluoro-2-methoxyaniline hydrochloride (VI). 4-Fluoro-2-nitrophenol (13) was readily methylated with methyl sulfate in sodium carbonate solution to give 4-fluoro-2-nitroanisole (14). Then 10 g. (0.058 mole) of the nitroanisole in 100 ml. of alcohol was reduced at 60 p.s.i. with hydrogen and platinum oxide catalyst. An excess of dry hydrogen chloride was then added and the solution filtered and evaporated. Recrystallization of the resulting solid from alcohol-ether gave 5-fluoro-2-methoxyaniline hydrochloride, m.p. 141–142°, in essentially quantitative yield.

Anal. Calc'd for C_7H_9ClFNO: C, 47.3; H, 5.11; N, 7.89.
Found: C, 47.5; H, 5.28; N, 7.72.

5-Fluoroguaiacol (V). A solution of 5-fluoro-2-methoxyaniline sulfate, prepared from 32 g. (0.18 mole) of the hydrochloride, in a mixture of 19.2 ml. of conc'd sulfuric acid and 200 g. of ice, was diazotized with 12.5 g. of sodium nitrite in 30 ml. of water. The resulting diazonium salt solution was diluted to about 500 ml. with water and added slowly to a boiling solution of 100 g. of hydrated cupric sulfate and 50 ml. of conc'd sulfuric acid in 700 ml. of water in a steam-distillation apparatus. Steam was passed through the reaction flask during the addition, and the distillate was collected. The distillation was stopped when no further 5-fluoroguaiacol came over and the distillate was extracted several times with ether. The combined ether extracts were dried over magnesium sulfate and distilled *in vacuo;* yield 17.1 g. (67%); b.p. 94–95° at 16 mm.; η_D^{27} 1.5082.

Anal. Calc'd for $C_7H_7FO_2$: C, 59.2; H, 4.97.
Found: C, 59.1; H, 5.16.

Demethylation with hydrobromic acid (3) gave an excellent yield of 4-fluorocatechol.

2-Amino-4-fluorophenol. Hydrogenation of 15.7 g. (0.1 mole) of 4-fluoro-2-nitrophenol in 130 ml. of ethanol with hydrogen and platinum oxide at 60 p.s.i., gave a quantitative yield of 2-amino-4-fluorophenol. For analysis, the material was recrystallized from methanol-petroleum ether; m.p. 145–146°.

Anal. Calc'd for C_6H_6FNO: C, 56.7; H, 4.76; N, 11.02.
Found: C, 57.2; H, 5.00; N, 11.0.

p-Fluorophenyl acetate. *p*-Fluorophenol (71 g., 0.63 mole) was dissolved in 75 ml. of acetic anhydride. Several drops of conc'd sulfuric acid were added and the solution was allowed to cool. It was then poured into cold water to which 5 g. of potassium bicarbonate had been added. The oily layer was taken up in ether and washed thoroughly with potassium bicarbonate solution and water and then dried over magnesium sulfate. Distillation gave 79 g. of *p*-fluorophenyl acetate (81% yield); b.p. 61° at 2 mm.

Anal. Calc'd for $C_8H_7FO_2$: C, 62.3; H, 4.58.

Found: C, 61.8; H, 4.75.

5-Fluoro-2-hydroxyacetophenone (VII). *p*-Fluorophenyl acetate (50 g., 0.32 mole) was mixed with 75 g. of anhydrous aluminum chloride. After standing for ten minutes, the mixture was heated on a steam-bath for ten minutes and then decomposed with ice and hydrochloric acid. Steam-distillation gave 44.5 g. (89%) of 5-fluoro-2-hydroxyacetophenone which melted at 56.5–57° on recrystallization from ether-petroleum ether.

Anal. Calc'd for $C_8H_7FO_2$: C, 62.4; H, 4.58.

Found: C, 62.1; H, 4.74.

Dakin oxidation of 5-fluoro-2-hydroxyacetophenone. A solution of 15.4 g. (0.1 mole) of 5-fluoro-2-hydroxyacetophenone in 100 ml. of *N* sodium hydroxide and 50 ml. of ethanol was warmed to about 40°. Then 140 ml. of 3% hydrogen peroxide was added. The temperature immediately rose to about 70°; gentle cooling was necessary. Over the course of an hour an additional 16 ml. of 6 *N* sodium hydroxide was added, and the reaction mixture was allowed to stand overnight. Acetic acid was added to *p*H 6 and a small amount of unchanged ketone was removed. The filtrate was evaporated to dryness *in vacuo* and the residue was extracted with three 100-ml. portions of boiling toluene. The toluene extracts were evaporated and the residue was vacuum-sublimed; yield of 4-fluorocatechol 8.1 g. (63%).

SUMMARY

The synthesis of the two monofluorocatechols is described.

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