ency for the olefins formed to polymerize in substantial amounts.

Methyl, ethyl and *n*-propyl alcohols were dehydrated to the corresponding ethers with little or no olefin formation.

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[CONTRIBUTION FROM THE LABORATORIES OF WALLACE & TIERNAN CO., BELLEVILLE, N. J.]

Substituted *p*-Aminobenzoic Acids

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The bacteriostasis brought about by the sulfonamides has been attributed to the competitive inhibition by these compounds of a metabolic process involving the essential nutrilite *p*-aminobenzoic acid.[2,3] Attempts have been made to correlate the bacteriostatic effectiveness of a given sulfonamide with its structural relationship to *p*-aminobenzoic acid.[4,5] It seemed of interest to us to investigate derivatives of *p*-aminobenzoic acid itself from this point of view. The bacteriological evaluation of the compounds prepared for this study has been reported elsewhere.[6] It is of interest that several of the non-sulfur containing compounds studied exhibited *in vitro* "sulfonamide" activity of the order of the active sulfonamides. That this bacteriostatic activity was in reality of the true "sulfonamide" type was indicated by its complete inhibition by *p*-aminobenzoic acid. During the course of this work the "sulfonamide" activity of *p*-aminobenzamide,[7] and *p*-aminophenyl ketones,[8] and other sulfur-free derivatives and analogs of *p*-aminobenzoic acid[9,10] was reported. The preparation of the new compounds reported in our previous study[6] is described below.

Of the various possible monohalogenated derivatives of 4-aminobenzoic acid, the only ones which have not been previously described were the 2- and 3-fluoro- and the 3-chloro-4-aminobenzoic acids. As the starting material for the 2-fluoro-4-aminobenzoic acid, 2-fluoro-4-nitrotoluene was prepared from diazotized 2-amino-4-nitrotoluene by the method of Schiemann.[11] It was observed that if all of the alcohol used in the preparation of the diazofluoborate were not carefully removed, partial deamination with formation of 4-nitrotoluene occurred on the thermal decomposition of the diazofluoborate. A similar deamination of a substituted benzidine by decomposition of a *bis*-diazofluoborate in absolute ethanol has been recorded.[12] Since traces of *p*-aminobenzoic acid interfere seriously with the "sulfonamide" assay of these compounds, it is essential that possible precursors of this material be eliminated in the preparation of the necessary intermediates.

Experimental Part

All melting points and boiling points are uncorrected.

2-Fluoro-4-nitrotoluene.—The diazofluoborate of 2-amino-4-nitrotoluene, prepared by the method of Schiemann from diazotized 2-amino-4-nitrotoluene[13] was washed with methanol and ethyl ether and dried by standing in a vacuum desiccator over phosphorus pentoxide overnight. Thermal decomposition in the usual manner[14] was best carried out on material that had been diluted with five volumes of sand. The product was extracted with ether, the ether extracts dried with anhydrous magnesium sulfate, concentrated, and the residue distilled, b. p. 65–68° (2 mm.); m. p. 34–35° from low boiling petroleum; yield 60%. *Anal.* Calcd. for $C_7H_6O_2NF$: C, 54.19; H, 3.90. Found: C, 54.76; H, 4.14. If the methanol was not completely removed from the diazofluoborate, the product of the thermal decomposition was difficult to crystallize. Oxidation of this material with neutral permanganate in the manner described below for the preparation of 3-chloro-4-acetamidobenzoic acid gave a mixture from which *p*-nitrobenzoic acid could be obtained on fractional crystallization from boiling water; m. p. 239–240°. There was no depression on mixed melting point with an authentic sample of *p*-nitrobenzoic acid. It is evident that the starting material was contaminated with *p*-nitrotoluene.

2-Fluoro-4-aminotoluene.—The reduction of 20 g. of 2-fluoro-4-nitrotoluene with tin and hydrochloric acid in the usual way gave 13 g. of 2-fluoro-4-aminotoluene (80.5%), b. p. 200–205°. *Anal.* Calcd. for C_7H_8NF: C, 67.18; H, 6.44. Found: C, 68.82; H, 6.92.

2-Fluoro-4-acetotoluidide.—The amine on treatment with acetic anhydride gave a quantitative yield of 2-fluoro-4-acetotoluidide which melted at 133.5–134° after recrystallization from water. *Anal.* Calcd. for $C_9H_{10}ONF$: C, 64.65; H, 6.03. Found: C, 64.67; H, 6.05.

2-Fluoro-4-acetamidobenzoic Acid.—Oxidation of 16.7 g. of 2-fluoro-4-acetotoluidide with neutral permanganate, as described below for the preparation of 3-chloro-4-acetamidobenzoic acid, gave 15.8 g. (80%) of the acid (m. p. 256–257°) on recrystallization from water. *Anal.* Calcd. for $C_9H_8O_3NF$: C, 54.82; H, 4.09. Found: C, 55.02; H, 4.19.

2-Fluoro-4-aminobenzoic Acid.—The hydrolysis of 10 g. of 2-fluoro-4-acetamidobenzoic acid was complete after twenty minutes of refluxing in 100 cc. of ethanol and 15 cc. of concentrated hydrochloric acid. After distillation of the

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alcohol *in vacuo* the acid was neutralized with sodium carbonate solution and the amino acid precipitated by the addition of acetic acid. After standing overnight in the ice box, the amino acid was filtered, extracted six times with 20-cc. portions of boiling benzene and twice recrystallized from water, m. p. 216–216.5°. *Anal.* Calcd. for $C_7H_6O_2NF$: C, 54.19; H, 3.90; N, 9.09. Found: C, 54.04; H, 4.07; N, 9.25.

2-Fluoro-4-nitrobenzoic Acid.—The oxidation of 45.6 g. of 2-fluoro-4-nitrotoluene with neutral permanganate gave 13.7 g. of acidic product, m. p. 170–174°. On recrystallization from water 2-fluoro-4-nitrobenzoic acid melted at 176–177°; yield 25%. *Anal.* Calcd. for $C_7H_4O_4NF$: C, 45.44; H, 2.18. Found: C, 45.92; H, 2.29.

2-Fluoro-4-aminobenzoic Acid.—Reduction of 1.0 g. of 2-fluoro-4-nitrobenzoic acid effected by boiling two hours in 10 cc. of concentrated ammonia solution with 8 g. of ferrous sulfate in 25 cc. of water, followed by filtration and acidification of the clear filtrate with acetic acid, gave 0.6 g. (71%) of 2-fluoro-4-aminobenzoic acid, m. p. 215–216° on recrystallization from water. A mixed melting point with a sample of the acid prepared through 2-fluoro-4-acetotoluidide as described above gave no depression in melting point. *Anal.* Calcd. for $C_7H_6O_2NF$: C, 54.19; H, 3.90. Found: C, 54.39; H, 4.25.

3-Fluoro-4-nitrobenzoic Acid.—A mixture of 20 g. of 3-fluoro-4-nitrotoluene,[15] 51 g. of potassium permanganate and 2000 cc. of water was refluxed until the aqueous solution was colorless (four hours). The manganese dioxide was removed by filtration, the clear filtrate extracted with ether to remove unchanged starting material, and the nitro acid precipitated by acidification with hydrochloric acid. Two recrystallizations of the product from hot water gave 7 g. (29.4%) of material melting at 174–175°. *Anal.* Calcd. for $C_7H_4O_4NF$: C, 45.45; H, 2.16. Found: C, 45.67; H, 2.52. A mixture of 1 g. of 3-fluoro-4-nitrobenzoic acid, 0.5 g. of potassium hydroxide and 10 cc. of absolute methanol was refluxed for two hours. After the addition of 10 cc. of water, the methanol was removed by distillation. The aqueous residue was filtered and acidified with hydrochloric acid. The precipitated acid melted at 231–233°. It gave no depression in melting point when mixed with an authentic specimen of 3-methoxy-4-nitrobenzoic acid.[16]

3-Fluoro-4-aminobenzoic Acid.—To a solution of 2 g. of 3-fluoro-4-nitrobenzoic acid in 20 cc. of concentrated ammonia solution was added 20 g. of ferrous sulfate dissolved in 50 cc. of water. After one hour of reflux the mixture was filtered, the filtrate boiled with charcoal, filtered again and concentrated to 25 cc. Acidification of the clear solution with acetic acid resulted in the precipitation of the amino acid. After standing overnight in the refrigerator, the product was recrystallized from hot water; 1.1 g. (66%) of fine needles, m. p. 215–216° was obtained. *Anal.* Calcd. for $C_7H_6O_2NF$: C, 54.19; H, 3.88. Found: C, 54.31; H, 4.17.

3-Chloro-4-acetamidobenzoic Acid.—To a solution of 10.3 g. of magnesium sulfate and 14.6 g. of potassium permanganate in 800 cc. of water, was added 6 g. of 3-chloro-4-acetotoluidide.[17] After refluxing for five hours the solution was cooled and 14 g. of sodium carbonate added with vigorous stirring. The mixture was filtered and the clear filtrate acidified with concentrated hydrochloric acid. Recrystallization of the precipitate from water gave 4.0 g. (56.4%) of product melting at 237–238°. *Anal.* Calcd. for $C_9H_8O_3NCl$: C, 50.59; H, 3.65. Found: C, 51.07; H, 3.76.

3-Chloro-4-aminobenzoic Acid.—A mixture of 4.0 g. of 3-chloro-4-acetamidobenzoic acid, 20 cc. of 95% ethanol and 4 cc. of concentrated hydrochloric acid was refluxed for fifteen minutes. The hydrochloride of the amino acid, which precipitated on concentration of the alcoholic solution to a volume of 10 cc., was dissolved by the addition of 30 cc. of water. The solution was filtered and brought to a *p*H of 4 to 5 by the addition of sodium acetate solution. The precipitated amino acid melted at 225.5 to 227° on recrystallization from water; yield 2.5 g. (61%). *Anal.* Calcd. for $C_7H_6O_2NCl$: Cl, 20.70; Found: Cl, 20.56.

3-Chloro-4-benzamidobenzoic Acid.—Oxidation of 4.6 g. of 3-chloro-4-benzotoluidide[17] with neutral permanganate solution, as described above for 3-chloro-4-acetamidobenzoic acid, gave 4.0 g. of product melting at 234–235° after recrystallization from water. *Anal.* Calcd. for $C_{14}H_{10}O_3NCl$: C, 60.99; H, 3.68. Found: C, 61.18; H, 3.87.

Hydrolysis with alcoholic hydrochloric acid was carried out as described above for the corresponding acetamido acid. The acid solution was filtered to remove the precipitated benzoic acid and the 3-chloro-4-aminobenzoic acid precipitated from the clear filtrate by the addition of sodium acetate solution. On recrystallization from water, the product melted at 225.5–227°. It gave no depression on mixed melting point with the material derived from 3-chloro-4-acetamidobenzoic acid.

Substituted *p*-nitrobenzamides were prepared by the addition of equimolar quantities of *p*-nitrobenzoyl chloride in small portions to the appropriate amine dissolved in excess pyridine. When the addition was complete, the mixture was warmed gently for fifteen minutes and then poured into ice and water. The precipitated product was filtered, washed with water and cold dilute sodium carbonate solution and finally recrystallized from ethyl alcohol.

2-(*p*-Nitrobenzoyl)-aminopyridine was obtained in 90% yield by this procedure and melted at 242.5–243.5°. *Anal.* Calcd. for $C_{12}H_9O_3N_3$: N, 16.87. Found: N, 16.84. This product has been previously reported,[9] m. p. 244°.

2-(*p*-Nitrobenzoyl)-aminothiazole was prepared in 88% yield, m. p. 297–298°. *Anal.* Calcd. for $C_{10}H_7O_3N_3S$: C, 48.19; H, 2.99. Found: C, 48.61; H, 3.48.

2-(*p*-Nitrobenzoyl)-aminopyrimidine melted at 206.5–207.5°; yield 85%. *Anal.* Calcd. for $C_{11}H_8O_3N_4$: N, 22.95. Found: N, 22.76.

Substituted *p*-aminobenzamides were prepared from the corresponding nitro compounds by catalytic reduction with platinum oxide at three atmospheres and room temperature. The reductions were complete in one to two hours. The products were purified by recrystallization from ethanol.

2-(*p*-Aminobenzoyl)-aminopyridine melted at 166–167°; yield, 90%. *Anal.* Calcd. for $C_{12}H_{11}ON_3$: C, 67.59; H, 5.20. Found: C, 68.01; H, 5.52. This compound has been previously reported,[9] m. p. 168°.

2-(*p*-Aminobenzoyl)-aminothiazole melted at 257–258°; yield, 95%. *Anal.* Calcd. for $C_{10}H_9ON_3S$: N, 19.26. Found: N, 18.92. A melting point of 257–258° has been recorded.[10]

2-(*p*-Aminobenzoyl)-aminopyrimidine melted at 240–241°; yield, 80%. *Anal.* Calcd. for $C_{11}H_{10}ON_4$: N, 26.02. Found: N, 25.92.

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Summary

1. The preparation of 2- and 3-fluoro and 3-chloro-4-aminobenzoic acids has been described.

2. The *p*-aminobenzoic acid analogs of sulfapyridine, sulfathiazole, and sulfadiazine have been prepared.

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