[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

SYNTHESIS OF SOME FLUORINE-CONTAINING ANALOGS AND DERIVATIVES OF MEDICINALS

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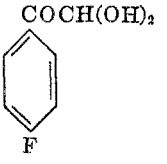
As a continuation of our studies on the effect of substituting fluorine into the molecules of compounds of medicinal interest, we have synthesized fluorine-containing derivatives of N, N-diethylnicotinamide (Nikethamide), a number of other N-substituted nicotinamide derivatives of interest as possible tuberculostatic agents (1), and two isosteres of methyl 3-amino-4-hydroxybenzoate (Orthoform).

The 2-fluoro- and 6-fluoro-N-substituted nicotinamide derivatives (Table I) were prepared from the corresponding acid chlorides by the method of Kushner, *et al.* (1).

The orthoform isosteres, methyl 3-fluoro-4-hydroxybenzoate (V) and methyl 3,4-difluorobenzoate (XVII), were prepared by the synthetic routes shown in charts A and B, respectively. 3-Fluoro-4-methoxyacetophenone (II) was readily converted to 3-fluoro-4-methoxybenzoic acid (III) by the haloform reaction with sodium hypochlorite. On the other hand, 3-fluoro-4-hydroxyacetophenone (VIII) under similar conditions gave as the sole product 3-chloro-4-hydroxy-5-fluorobenzoic acid (IX). The undesired chlorination could not be prevented by the recommended (2) procedure of destroying the excess hypochlorite with acetone before acidification of the reaction mixture.

In an attempted synthesis of the Synephrine isostere 1-(4-fluorophenyl)-2-methylaminoethanol, 4-fluorophenylglyoxal hydrate (XVIII) was obtained in good yield by oxidation of 4-fluoroacetophenone with selenium dioxide. Reductive condensation of XVIII with methylamine according to the method of Fodor and Kovács (3) was, however, unsuccessful.



XVIII

EXPERIMENTAL

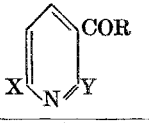
Intermediates. 2- and 6-Fluoronicotinyl chlorides were prepared according to the method of Minor, *et al.* (4). Reaction of the acid chlorides with the various substituted amines was carried out in pyridine according to the general procedures of Kushner, *et al.* (1).

o-Fluoroanisole (I) was obtained from *o*-anisidine in 40% yield by the Schiemann reaction. The Friedel-Crafts reaction of I with acetic anhydride gave 3-fluoro-4-methoxyacetophenone (II) in 87% yield (5). *o-Fluorophenol* (VI) was obtained in 83% yield by demethylation of I with aluminum chloride.

Methyl o-fluorobenzoate (XI) was prepared in 46% yield by application of the Schiemann

TABLE I

SUBSTITUTED NICOTINAMIDES



X	Y	R	YIELD, %	M.P. OR B.P., °C.[a]	FORMULA	ANALYSES					
						Calc'd			Found		
						C	H	N	C	H	N
H	F	Diethylamino	73	131/2 mm.	$C_{10}H_{13}FN_2O$	61.2	6.7	14.3	61.5	6.8	13.9
F	H	Diethylamino	61	136/3 mm.	$C_{10}H_{13}FN_2O$	61.2	6.7	14.3	61.1	6.4	14.2
H	F	2-Thiazolylamino	7	158.6–159.5[b]	$C_9H_6FN_3OS$	48.4	2.7	18.8	48.5	2.5	19.1
F	H	2-Thiazolylamino	97	248.6–249.0[c]	$C_9H_6FN_3OS$	48.4	2.7	18.8	48.6	2.6	18.6
H	F	Dicyandiamido	26	190.2–191.0[d]	$C_8H_6FN_5O$	46.4	2.9	33.8	46.4	3.2	33.7
F	H	2-Pyrimidylamino	95	172.4–173.0[e]	$C_{10}H_7FN_4O$	55.0	3.2	25.7	54.9	3.2	25.6
F	H	2-Pyridylamino	100	145.5–146.3[d]	$C_{11}H_8FN_3O$	60.8	3.7	19.3	60.7	3.8	19.1

[a] Melting points are corrected, boiling points uncorrected. [b] Recrystallized from 50% ethanol. [c] Recrystallized from 70% acetic acid. [d] Recrystallized from 95% ethanol. [e] Recrystallized for water.

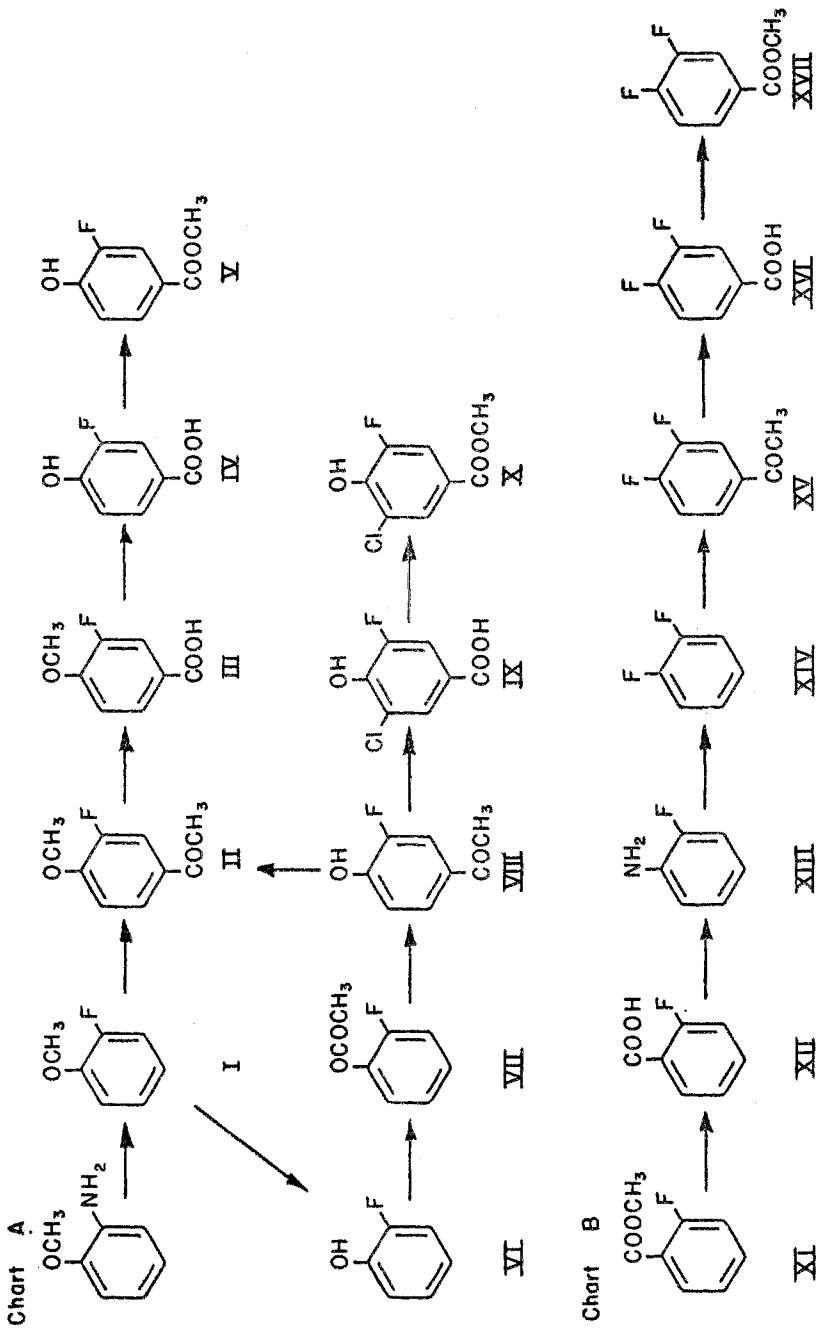


Chart A
Chart B
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII
XIV
XV
XVI
XVII

reaction to methyl anthranilate. Hydrolysis of XI in aqueous potassium hydroxide solution gave *o*-fluorobenzoic acid (XII) in 91% yield.

p-Fluorobromobenzene was obtained in 71% yield by bromination of fluorobenzene according to the method of Schiemann and Pillarsky (6). *p-Fluoroacetophenone* was prepared from fluorobenzene by the Friedel-Crafts reaction according to Renoll (7).

3-Fluoro-4-methoxybenzoic acid (III). To a stirred solution obtained by dissolving 16 g. of chlorine in an ice-cold solution of 22 g. of sodium hydroxide in 155 ml. of water, there was added gradually 8.4 g. (0.050 mole) of II. The temperature was maintained at 80–90° throughout the addition and a subsequent stirring period of 30 minutes. Then 5.0 g. of sodium bisulfite was added to destroy excess hypochlorite, and the solution was acidified with hydrochloric acid and cooled. The precipitated 3-fluoro-4-methoxybenzoic acid (III), after recrystallization from water, weighed 6.5 g. (77%), m.p. 211.6–212.8°; reported (5) m.p. 208–210°.

3-Fluoro-4-hydroxybenzoic acid (IV). A mixture of 6.4 g. (0.038 mole) of III, 40 g. of anhydrous aluminum bromide, and 250 ml. of benzene was refluxed for 5 hours, cooled, and poured onto a mixture of concentrated hydrochloric acid and crushed ice. The product was removed by ether extraction and then extracted from the ether solution with sodium hydroxide solution. The basic solution was made acid with hydrochloric acid, the organic material again taken up in ether, the ether solution dried, and the ether removed by distillation. Sublimation of the dark residue, followed by recrystallization from water, gave 4.3 g. (74%) of colorless IV, m.p. 162.0–163.2°.

Anal. Calc'd for $C_7H_5FO_3$: C, 53.9; H, 3.2.
Found: C, 53.9; H, 3.5.

Methyl 3-fluoro-4-hydroxybenzoate (V). A solution of 4.3 g. (0.028 mole) of IV dissolved in 50 ml. of methanol saturated with dry hydrogen chloride was refluxed on a steam-bath for one hour. The excess methanol was removed by distillation and the residue recrystallized from ligroin to yield 2.3 g. (50%) of V, m.p. 90.0–91.4°.

Anal. Calc'd for $C_8H_7FO_3$: C, 56.5; H, 4.2.
Found: C, 56.5; H, 4.3.

o-Fluorophenyl acetate (VII). A mixture of 112 g. (1 mole) of VI, 125 g. (1.1 moles) of thionyl chloride, and 60 g. (1 mole) of glacial acetic acid was refluxed for several hours. The reaction mixture was then fractionated through a short column to give 148 g. (96.2%) of VII, b.p. 192–194°/737 mm.

Anal. Calc'd for $C_8H_7FO_2$: C, 62.3; H, 4.6.
Found: C, 62.1; H, 4.7.

3-Fluoro-4-hydroxyacetophenone (VIII). A mixture of 148 g. (0.962 mole) of VII, 160 g. of anhydrous aluminum chloride, and 250 ml. of carbon disulfide was refluxed until evolution of hydrogen chloride had ceased. The carbon disulfide was removed by distillation, and the residue heated at 140° for 2 hours. The mass was then pulverized in an ice-cooled solution of hydrochloric acid. The solid was removed, dissolved in ether, the ether removed, and the residue distilled, the fraction boiling at 125–135°/2 mm. being collected. Recrystallized from toluene, the colorless crystals of VIII, m.p. 125.0–126.6°, weighed 78 g. (52%).

Treatment of the product with methyl sulfate in basic solution converted it into II, whose m.p. 90.8–92.0°, was not depressed by an authentic sample.

3-Chloro-4-hydroxy-5-fluorobenzoic acid (IX). Treatment of 7.70 g. (0.05 mole) of VIII at 70° according to the procedure employed for the preparation of III from II afforded 4.0 g. (47%) of a colorless product, m.p. 218.9–220.5°, which, on the basis of analysis and orientation rules, was assigned the structure IX.

Anal. Calc'd for $C_7H_4ClFO_3$: C, 44.1; H, 2.1.
Found: C, 44.3; H, 2.3.

The *methyl ester* (X), prepared in the usual manner, melted at 108.0–109.3° after recrystallization from carbon tetrachloride.

Anal. Calc'd for $C_8H_6ClFO_3$: C, 47.0; H, 3.0; Cl, 17.3.
Found: C, 47.1; H, 3.0; Cl, 17.6.

o-Fluoroaniline (XIII). To a stirred solution of 83 g. (0.59 mole) of XII in 300 g. of concentrated sulfuric acid at 50°, 43 g. (0.66 mole) of sodium azide was added slowly from a funnel designed for the addition of solids out of access to air. The reaction mixture was maintained at 50° for 12 hours. It was then cooled, diluted with water, and neutralized with a cold solution of 240 g. of sodium hydroxide in 500 ml. of water. The solution was extracted with ether, the combined ether extracts dried, the ether removed, and the residual oil distilled under reduced pressure. The yield of XIII, b.p. 74°/24 mm., was 39 g. (59%).

o-Difluorobenzene (XIV). A solution made by the addition of 100 ml. of concentrated hydrochloric acid to 100 ml. of water, and contained in a 500-ml. stainless steel beaker, was cooled to 0° with an ice-salt bath. Then 10 g. of XIII was added. The mixture was again cooled to 0° and diazotization begun by the gradual addition of sodium nitrite in the form of moist balls. Small amounts of XIII and sodium nitrite were added alternately in small portions at 0° until a total of 52.0 g. (0.47 mole) of the former and 35 g. (0.50 mole) of the nitrite had been added.

The solution was transferred to a 1-l. beaker and a cold solution of 110 g. of sodium fluoborate in 150 ml. of water was added at once. Stirring was continued for 30 minutes, and the precipitate which formed was removed by filtration and washed, first with 50 ml. of ice-water, then with 50 ml. of alcohol. It was slurried with 100 ml. of ether and filtered. Dried under a vacuum, the *o*-fluorobenzenediazonium fluoborate weighed 82 g. (83%).

The dried salt was placed in a 1-l. flask attached to an efficient condenser with a receiver cooled in an ice-bath. It was decomposed, first by cautious heating with a small flame, and finally by strong heating. The distilled product was taken up in ether and the ether solution washed with water and then dried. After removal of the ether, distillation of the residue yielded 23 g. (51% based on fluoborate) of XIV, b.p. 91–92°/740 mm.

3,4-Difluoroacetophenone (XV). To a mixture of 23 g. (0.20 mole) of XIV, 57 g. (0.42 mole) of anhydrous aluminum chloride, and 45 ml. of carbon disulfide, 20 g. (0.20 mole) of redistilled acetic anhydride was added dropwise. After the addition was complete, the mixture was stirred for one hour under reflux, then for 6 hours at room temperature. The solvent was removed by distillation, the residue poured onto a mixture of ice and concentrated hydrochloric acid, and the resulting mixture extracted with ether. The combined ether extracts were dried, the ether removed, and the residue distilled under reduced pressure to give 16.1 g. (50%) of XV, b.p. 94–95°/13 mm., 200–201°/734 mm., m.p. 19.5–20.0°.

Anal. Calc'd for $C_8H_6F_2O$: C, 61.4; H, 3.9.

Found: C, 61.8; H, 4.0.

3,4-Difluorobenzoic acid (XVI). To a stirred suspension of 10.5 g. (0.067 mole) of XV in 125 ml. of water at 80°, there was added 31 g. (0.20 mole) of potassium permanganate dissolved in the minimum quantity of water. The reaction mixture was stirred under reflux for 4 hours, the precipitated manganese dioxide removed, and the filtrate evaporated to 150 ml., acidified with 6 *N* sulfuric acid, cooled, and filtered. Recrystallized from water, the precipitate of XVI, m.p. 119.2–120.1°, weighed 3.1 g. (35%).

Anal. Calc'd for $C_7H_4F_2O_2$: C, 53.2; H, 2.6.

Found: C, 53.4; H, 2.8.

Methyl 3,4-difluorobenzoate (XVII). Esterification of XVI with methyl alcohol in the usual manner gave a 75% yield of XVII, b.p. 69°/23 mm., m.p. 23.5°.

Anal. Calc'd for $C_8H_6F_2O_2$: C, 55.8; H, 3.5.

Found: C, 55.9; H, 3.7.

4-Fluorophenylglyoxal hydrate (XVIII). To a solution of 69 g. (0.63 mole) of resublimed selenium dioxide in 360 ml. of dioxane and 12 ml. of water at 60°, there was added 93 g. (0.67 mole) of *p*-fluoroacetophenone. The mixture was refluxed for 18 hours, after which the precipitated selenium was removed and the solvent distilled under reduced pressure. Then 450 ml. of water was added to the residue and the resulting mixture was allowed to stand for several hours. The precipitate was filtered and recrystallized from water to yield 91.5 g. (85%) of colorless *XVIII*, m.p. 80.0–82.4°. The ketone was converted to the

corresponding *quinoxaline*, m.p. 121.8–122.3° after recrystallization from ethanol, by condensation with *o*-phenylenediamine and was analyzed in that form.

Anal. Calc'd for $C_{14}H_9FN_2$: C, 75.0; H, 4.1; N, 12.5.

Found: C, 75.0; H, 4.1; N, 12.5.

Similarly prepared by oxidation of VIII, *3-fluoro-4-hydroxyphenylglyoxal hydrate* was obtained as an amorphous, difficulty crystallizable solid. The corresponding *quinoxaline* melted at 221.8–222.9°.

Anal. Calc'd for $C_{14}H_9FN_2O$: C, 69.9; H, 3.8; N, 11.7.

Found: C, 69.5; H, 4.0; N, 12.0.

Attempted reductive condensation of the glyoxal with both methylamine and isopropylamine by the method of Fodor and Kovács (3) was unsuccessful.

Pharmacological data. The various N-substituted nicotinamides listed in Table I exhibit only slight tuberculostatic activity. Testing of the other products is in progress.

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SUMMARY

1. Synthesis of the following fluorine-containing compounds of pharmacological interest is described: methyl 3-fluoro-4-hydroxybenzoate, methyl 3,4-difluorobenzoate, and a series of 2-fluoro- and 6-fluoro-N- substituted derivatives of nicotinamide.

2. The preparation of a number of new aromatic fluorine-containing intermediates is reported.

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