Photochemistry of Diazonium Salts. 4. Synthesis of Ring-Fluorinated Tyramines and Dopamines[1]

Kenneth L. Kirk

Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

Received October 24, 1975

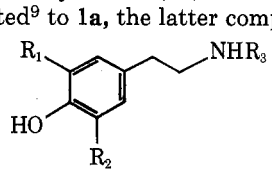
3-Fluorotyramine, 3,5-difluorotyramine, and 6-fluorodopamine were synthesized from ring-hydroxylated *N*-trifluoroacetylphenethylamine precursors by sequences involving ring nitration, catalytic reduction, diazotization of the resulting arylamine, photochemical decomposition of the diazonium fluoroborate in fluoroboric acid, and, finally, removal of the *N*-trifluoroacetyl protecting group. Photochemical decomposition of *N*-trifluoroacetyl-3-fluoro-4-hydroxyphenethylamine-5-diazonium fluoroborate in fluoroboric acid produced, in addition to the 3,5-difluorotyramine derivative, *N*-trifluoroacetyl-3,4-dihydroxy-5-fluorophenethylamine, the result of competitive solvolysis of the presumed arylcarbonium ion intermediate. Removal of the protecting group from the product afforded 5-fluorodopamine. 2-Fluorodopamine was synthesized by elaboration of 2-fluoro-3,4-dimethoxybenzaldehyde, this aldehyde being obtained by an analogous photochemical ring fluorination. As a result of the electronic effect of fluorine, phenol acidity is markedly enhanced in the fluorinated analogues, to the extent that considerable concentrations of phenolate anion will be present at physiological pH.

Ring-hydroxylated phenethylamines (tyramine, dopamine) play a central role in cellular function, particularly in the sympathetic nervous system;[2] accordingly, the biosynthesis, mechanism and sites of action, and transformations of these compounds have received much attention.[3] Several fluorinated derivatives of phenethylamine have been synthesized and tested pharmacologically; in these compounds, however, the fluorine substituent(s) appear on the side chain or on a nonhydroxylated benzene ring.[4-6]

Several considerations prompted our interest in the preparation of phenethylamines with the ring both hydroxylated and fluorinated. The ubiquity of the phenolic function in biogenic amines suggests a unique role for this group in specificity and physiological action. The fluorine atom, through induction and hydrogen bonding, should effect strong perturbation in such properties of the phenolic groups as pK and oxidation potential. The several possible ring positions for the fluorine atom would also provide a series in which each isomer possesses a unique electron density distribution. The value of studying such a series is indicated by the large differences in biological behavior already observed for 2- and 4-fluorohistidine.[7]

The fluorination procedure involves the photochemical decomposition of an aryldiazonium ion in aqueous fluoroboric acid, the diazonium ion being generated in situ from the corresponding arylamine and nitrous acid. Photodecomposition generates, presumably, a carbonium ion which reacts competitively with fluoride ion and with water. Except for one case (see below), the products of the water reaction were not isolated in the present work. The fluorine atom is considered to occupy the same ring position as its precursor functions, the absence of any rearrangements being supported by NMR spectral data, as discussed below.

Illustrative of the general procedure is the conversion of tyramine to 3-fluorotyramine (**1d**). *N*-Trifluoroacetyltyramine[8] was nitrated[9] to **1a**, the latter compound was hydrogenated, and the resulting amine (**1b**) was diazotized in 50% aqueous fluoroboric acid. Irradiation of the solution of diazonium ion afforded *N*-trifluoroacetyl-3-fluorotyramine (**1c**) in 36% yield (based on **1a**). The trifluoroacetyl protecting group was removed by acid hydrolysis, and **1d** was isolated as its hydrochloride.

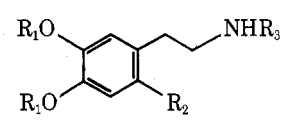


	R_1	R_2	R_3		R_1	R_2	R_3		R_1	R_2	R_3
1a	H	NO_2	$COCF_3$	**2a**	NO_2	F	$COCF_3$	**3a**	OH	F	$COCF_3$
b	H	NH_2	$COCF_3$	**b**	NH_2	F	$COCF_3$	**b**	OH	F	H
c	H	F	$COCF_3$	**c**	F	F	$COCF_3$				
d	H	F	H	**d**	F	F	H				

N-Trifluoroacetyl-3-fluorotyramine (**1c**), in turn, was nitrated in the available ortho position to give **2a**, and the sequence of steps repeated, as above, to produce *N*-trifluoroacetyl-3,5-difluorotyramine (**2c**) in 40% yield, which was converted to 3,5-difluorotyramine hydrochloride (**2d** HCl) by acid hydrolysis. The hydroxylated compound **3a** was isolated as a by-product of the irradiation procedure, and was converted into the hydrochloride of 5-fluorodopamine (**3b**) by methanolysis of **3a**. Attempts to produce *o,o'*-difluorophenols by utilization of the corresponding dinitrophenols were thwarted because of the instability of the intermediate diaminophenol.

In this study, no attempt was made to compare directly the photochemical procedure with thermal methods for decomposition of diazonium fluoroborates.[10,11] While higher yields have been reported for the pyrolysis of certain structurally related diazonium fluoroborates,[6b] the photochemical method was chosen for its reliability (yields of aryl fluoride are consistently 20–40%) and convenience—reaction times of 0.5–1.5 h are sufficient, the diazonium ion is generated and decomposed in situ, and the desired products are isolated with relative ease.

Of the three isomeric ring-fluorinated dopamines, the 6-fluoro isomer (**4d**) is the most readily accessible, because mononitration of *N*-trifluoroacetyl-3,4-dimethoxyphenethylamine[8] occurs exclusively in the 6 position to give **4a**. This result, clearly shown by the absence of any detectable coupling of the two aromatic protons in the NMR spectrum of **4a**, is in agreement with an earlier report of the mononitration of



	R_1	R_2	R_3
4a	CH_3	NO_2	$COCF_3$
b	CH_3	NH_2	$COCF_3$
c	CH_3	F	$COCF_3$
d	H	F	H
e	H	F	$COCF_3$

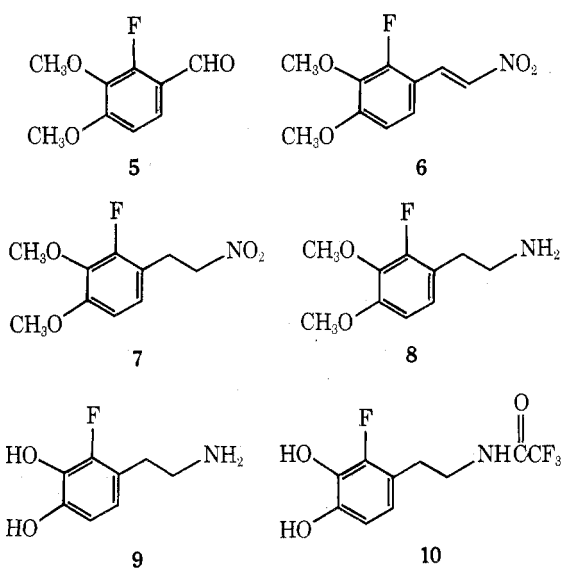
Table I. Aromatic Proton and Fluorine NMR Parameters

Compd	^{1}H, ppm[a]	^{19}F, ppm[b]	J, Hz
1d HCl	6.97–7.30 (m), H-2, H-5, H-6	29.7 (m), F-3	
2d HCl	6.88 (m), H-2, H-6	33.5 (m), F-3, F-5	J_{HF}^{ortho} = +11.3, J_{HF}^{para} = −2.1,[c] J_{HH}^{meta} = 2.6 J_{FF}^{meta} = 12.6
3b HCl	6.55 (q), H-6;[d] 6.51 (q), H-2	31.0 (m), F-5	J_{HH}^{meta} = 2.2, J_{HF}^{ortho} = +10.8,[c] J_{HF}^{para} = −1.6
4d HBr	6.78 (d), H-2;[d] 6.66 (d), H-5	37.0 (dd), F-6	J_{HF}^{meta} = 7.6, J_{HF}^{ortho} = 11.0
9 HCl	6.61 (q), H-6; 6.57 (q), H-5	26.3 (m), F-2	J_{HH}^{ortho} = 8.6, J_{HF}^{meta} = +8.2,[c] J_{HF}^{para} = −1.8

[a] Proton spectra were measured at 60 MHz in CD_3OD. Chemical shifts are relative to $(CH_3)_4Si$. [b] Fluorine spectra were measured at 100 MHz in D_2O. Chemical shifts are recorded in parts per million downfield from hexafluorobenzene. [c] The two HF coupling constants are of opposite sign. The assignment of the negative value to the para coupling constant is arbitrary. [d] The numbering of the ring is such that the fluorine is assigned the 5 position in **3b** HCl and the 6 position in **4d** HBr.

3,4-dimethoxyphenethylamine.[12] Reduction of **4a**, followed by diazotization and photolysis as before, produced **4c** in 20% yield (based on **4b**). Deacylation and demethylation[6b] of **4c** with hydrobromic acid afforded 6-fluorodopamine (**4d**) as its hydrobromide.

The compounds to this point were prepared by ring functionalization of preexisting phenethylamines. No such direct route was obvious for the synthesis of the remaining isomer, 2-fluorodopamine (**9**).[13] 2-Nitro-3,4-dimethoxybenzaldehyde[14] was chosen as a starting point for the synthesis of **9**. Protection of the aldehyde as the dimethyl acetal, hydrogenation, diazotization in situ, and photochemical decomposition afforded 2-fluoro-3,4-dimethoxybenzaldehyde (**5**) in 20% yield, based on the nitrobenzaldehyde acetal. The fluoroaldehyde was condensed with nitromethane to give the nitrostyrene **6**, which was reduced to **7** with sodium borohydride.[15] Catalytic hydrogenation reduced **7** smoothly to the ethylamine **8**, from which the hydrobromide of 2-fluorodopamine (**9**) was produced by demethylation with hydrobromic acid. Because **9** was difficult to purify as its hydrobromide, it was converted to its trifluoroacetyl derivative **10**, purified by sublimation. Acid-catalyzed methanolysis of **10** regenerated **9** as its hydrochloride.



Structural assignments for the ring-fluorinated products are based, in part, on the structures of known precursors. Although replacement of the amino group by the fluorine atom had occurred without rearrangement in all our previous cases, ^{1}H and ^{19}F NMR analyses of the fluorinated products were used as additional support for structural assignments (Table I). Both the ^{1}H and ^{19}F spectra of **1d** HCl are quite complex, and no attempt is made to interpret them at this time.[16] While these spectra do not place the fluorine uniquely adjacent to the hydroxyl group (2-fluorotyramine would probably exhibit similar coupling), the conversion of **1a** to the **3** series (the structures of which are unambiguously assigned below) appears to rule out this alternate structure. The ^{1}H spectrum of **2d** HCl displays a symmetrical multiplet of some ten lines, consistent with an AA′XX′ system and from which the parameters given in Table I were derived.[17] Again, while the coupling pattern does not in itself accommodate only structure **2d** HCl, the symmetry implied by the spectrum, together with the known structure of precursor **1a**, render alternatives untenable. The ^{19}F spectrum of **2d** HCl is in complete agreement with the interpretation given the ^{1}H spectrum, but owing to difficulty in identifying low-intensity lines, it was not further analyzed. The ^{1}H spectrum of **3b** HCl appears as an unsymmetrical multiplet comprised of two overlapping quartets, from which coupling constants consistent with meta proton–proton and ortho and para proton–fluorine spin interactions were extracted,[17] and thus establishes the position of the fluorine atom in this series. A similar analysis of the ^{1}H spectrum of **9** HCl, also an ABX system, revealed ortho proton–proton coupling and meta and para proton–fluorine coupling, confirming the assignment of the fluorine substituent to the 2 position. The para proton–fluorine coupling constants of **3b** HCl and **9** HCl (as well as of **2d** HCl) and the companion proton–fluorine interactions are of opposite signs, with the para coupling constant arbitrarily being assigned the negative value. The appearance of the ^{19}F spectra of **3b** HCl and **9** HCl reflects these sign differences, in that the two most intense peaks are separated by the sum of the two proton–fluorine coupling constants. Thus, the fluorine signal of **3b** HCl is an unresolved singlet, while that of **9** HCl appears as a symmetrical doublet separated by 9 Hz. No attempt was made to identify and analyze additional lines in the ^{19}F spectra of these compounds because of their low intensity and tendency to coalesce. Finally, the presence of ortho and meta hydrogen–fluorine coupling in both the ^{1}H and ^{19}F spectra of **4d** HBr, readily extracted by first-order analysis, requires that the fluorine substituent be in the 6 position.

pK_a values were obtained spectrophotometrically for the fluorophenols: 3-fluorotyramine (**1d**), 8.35; 3,5-difluorotyramine (**2d**), 7.03; *N*-trifluoroacetyl-2-fluorodopamine (**10**), 7.52; *N*-trifluoroacetyl-5-fluorodopamine (**3a**), 7.42. Reliable values for 6-fluorodopamine (**4d** or **4e**) could not be obtained, possibly owing to air oxidation of the catechol system. Literature values for related compounds are: phenol, 9.98;[18] tyramine, 9.50;[19] catechol, 9.45,[20] dopamine, 8.90;[19] *o*-fluorophenol, 8.81;[18] and *m*-fluorophenol, 9.28.[18] As a result of the acid-strengthening effect of fluorine substitution, the phenolic groups of these fluorinated phenethylamines will be significantly ionized at physiological pH, a factor which may be significant in the interaction of these compounds with biomembranes and receptor sites.[21] It is also clear that in the isomeric 2- and 5-fluorodopamines, different phenolic groups, relative to the aminoethyl side chain, will be ionized under physiological conditions.

The likelihood of side-chain hydrogen bonds to fluorine in **4d** and **9** may have physiological significance and conformational studies are in progress. At present, it is impossible to predict the biological properties of these fluoro analogues; a variety of studies are in progress, however, and results will be reported separately.

Experimental Section

Microanalyses, NMR spectra, and mass spectra were provided by the Microanalytical Services and Instrumentation Section of this Laboratory, under the direction of Dr. David F. Johnson. Homogeneities of all compounds were confirmed by TLC; identities of all compounds were checked by mass spectrometry. Physical data are given in Table II.

Fluorination Procedure. The arylamine (10–20 mmol) was dissolved in 150 ml of 50% fluoroboric acid; the solution was cooled to 0 °C and was treated dropwise with a 10% molar excess of aqueous sodium nitrite (~2 M). After 1 h at 0 °C, the solution of diazonium fluoroborate was diluted to 200 ml with ice-cold 50% fluoroboric acid and was irradiated in the apparatus previously described[22] (equipped with a Pyrex filter), until absence of color formation with an alkaline solution of β-naphthol indicated complete decomposition of the diazonium ion. The cold solution was neutralized with concentrated sodium hydroxide and was extracted with ether until TLC showed complete absence of product in the aqueous phase. After drying and removal of solvent, the product was purified by column chromatography or sublimation.

***N*-Trifluoroacetyl-3-nitrotyramine (1a).** To a stirred solution of 8 g (0.034 mol) of *N*-trifluoroacetyltyramine[8] in 40 ml of acetic acid, cooled to 5 °C, was added dropwise 1.8 ml of fuming nitric acid.[9] Following addition, the solution was stirred in an ice bath for 1 h, then poured over ice. The yellow precipitate was filtered and recrystallized from aqueous ethanol to give 8.9 g (94%) of **1a.**

***N*-Trifluoroacetyl-3-fluorotyramine (1c).** A solution of **1a** (2.78 g, 10 mmol) in 100 ml of ethanol was hydrogenated at atmospheric pressure over 10% Pd/C. Removal of catalyst and solvent produced *N*-trifluoroacetyl-3-aminotyramine (**1b**). Without further purification, **1b** was diazotized and irradiated (1 h) to give, after chromatography on silica gel (1% methanol–chloroform), 0.904 g (36%) of **1c,** which was further purified by crystallization from aqueous ethanol.

3-Fluorotyramine Hydrochloride (1d HCl). A solution of 122 mg (0.5 mmol) of **1c** in 5 ml of 3 N hydrochloric acid and 1 ml of ethanol was heated on a steam bath for 20 h. After thorough evaporation of solvent, the residue was dissolved in methanol. Addition of ether effected precipitation of 57 mg of 3-fluorotyramine hydrochloride (**1d** HCl) (60%), recrystallized from methanol–ether.

***N*-Trifluoroacetyl-3-fluoro-5-nitrotyramine (2a).** Nitration as above of a solution of 1.47 g (5.85 mmol) of **1c** in 30 ml of acetic acid with 0.30 ml of fuming nitric acid afforded 1.55 g (89%) of **2a,** recrystallized from aqueous ethanol.

3,5-Difluorotyramine Hydrochloride (2d HCl). Hydrogenation at atmospheric pressure of 1.50 g (5.06 mmol) of **2a** in ethanol produced *N*-trifluoroacetyl-3-fluoro-5-aminotyramine (**2b**). Without further purification, **2b** was subjected to diazotization and irradiation as described. The crude product was chromatographed over silica gel, elution with 1% methanol in chloroform giving 529 mg (40%) of *N*-trifluoroacetyl-3,5-difluorotyramine (**1c**), which was recrystallized from aqueous ethanol. This material was hydrolyzed by heating (steam bath) its solution in 6 N hydrochloric acid for 10 h to give **2d** HCl in 67% yield, recrystallized from methanol–ether.

3,4-Dihydroxy-5-fluorophenethylamine Hydrochloride (5-Fluorodopamine Hydrochloride) (3b HCl). Further elution of the crude product obtained in the photolysis of the diazonium fluoroborate derived from **2b,** with 3% methanol in chloroform, gave 461 mg (34%) of *N*-trifluoroacetyl-3,4-dihydroxy-5-fluorophenethylamine (**3a**), purified by sublimation. Compound **3a** was dissolved in 10 ml of methanol saturated with dry hydrogen chloride, and the solution was stored for 4 days, after which time TLC showed complete deacylation. (This procedure was found to give a cleaner product than hydrolysis in aqueous acid.) Removal of solvent and recrystallization from methanol–ether afforded **3b** HCl in 72% yield.

***N*-Trifluoroacetyl-2-nitro-4,5-dimethoxyphenethylamine (4a).** Nitration of a solution of 22.5 g (0.081 mol) of *N*-trifluoroacetyl-3,4-dimethoxyphenethylamine[8] in 100 ml of acetic acid, with 4.0 ml of fuming nitric acid, was carried out as above, to give 19.6 g (74%) of **4a.**

***N*-Trifluoroacetyl-2-fluoro-4,5-dimethoxyphenethylamine (4c).** A solution of **4a** (3.22 g, 10 mmol) in 250 ml of ethanol was hydrogenated over 500 mg of 10% Pd/C to give the arylamine **4b.** This amine, without purification, was diazotized and irradiated for 1 h to give, after chromatography over silica gel (1% methanol in chloroform), 650 mg of **4c** (22%).

Table II. Yields and Physical Data

Compd	Yield, %	Mp, °C	Formula[b]
1a	94	130–131	$C_{10}H_9F_3N_2O_4$
1c	36	107–108	$C_{10}H_9F_4NO_2$
1d HCl	60	268–270 dec	$C_8H_{11}ClFNO$
2a	89	133–134	$C_{10}H_8F_4N_2O_4$
2c	40	113–114	$C_{10}H_8F_5NO_2$
2d HCl	67	260–273 dec	$C_8H_{10}ClF_2NO$
3a	34	132–133	$C_{10}H_9F_4NO_3$
3b HCl	72	205–215 dec	$C_8H_{11}ClFNO_2$
4a	74	143–144	$C_{12}H_{13}F_3N_2O_5$
4c	22	130–131	$C_{12}H_{13}F_4NO_3$
4d HBr	95	207–209	$C_8H_{11}BrFNO_2$
4e		100–101	$C_{10}H_9F_4NO_3$
5	20	52.5–53.5	$C_9H_9FO_3$
6	75	62–63	$C_{10}H_{10}FNO_4$
7	93	42–43	$C_{10}H_{12}FNO_4$
8 HBr	63	174–177	$C_{10}H_{15}BrFNO_2$
9 HBr[a]	78	158–160	$C_8H_{11}BrFNO_2$
9 HCl	78	158–160	$C_8H_{11}ClFNO_2$
10	76	127–127	$C_{10}H_9F_4NO_3$

[a] Could not be recrystallized. See text. [b] Satisfactory analytical data (±0.35% for C, H, N) were reported for all compounds except **9** HBr (no data), **5** (no N), **1c, 2d** HCl, **9** HCl (C 0.6% low), and **7** (C 0.6% high). Ed.

2-Fluoro-4,5-dimethoxyphenethylamine Hydrobromide (6-Fluorodopamine Hydrobromide) (4d HBr). A solution of 300 mg (1.02 mmol) of **4c** in 10 ml of 48% hydrobromic acid was heated in an oil bath at 140 °C for 4 h.[6b] A stream of hydrogen was bubbled through the solution during the reaction. The solvent was removed under vacuum and traces of hydrogen bromide were removed by addition and evaporation of water, this process being repeated three times. After drying the residue over potassium hydroxide, white crystals were obtained. Recrystallization from methanol–ether gave 260 mg of **4d** HBr (95%).

A small sample of **4d** HBr was treated with excess trifluoroacetic anhydride. After 2 h of storage at room temperature, removal of excess anhydride, addition of methanol, and evaporation, sublimation of the residue produced *N*-trifluoroacetyl-2-fluoro-4,5-dihydroxyphenethylamine (**4e**).

2-Fluoro-3,4-dimethoxybenzaldehyde (5). Hydrogen chloride was bubbled briefly into a solution of 4.22 g (20 mmol) of 2-nitro-3,4-dimethoxybenzaldehyde[14] in 250 ml of methanol. After 1 day, TLC indicated the absence of aldehyde. The solution was neutralized with methanolic potassium hydroxide and evaporated. Water was added and the resulting solution was extracted three times with ether. After drying and removal of solvent, the product, 2-nitro-3,4-dimethoxybenzaldehyde dimethyl acetal, was dissolved in 250 ml of ethanol containing 0.2 ml of triethylamine and the solution was hydrogenated over platinum at 40 psi for 6 h. Removal of catalyst and solvent afforded 2-amino-3,4-dimethoxybenzaldehyde dimethyl acetal, 3.53 g (78%). This amine, 2.27 g (10 mmol), was diazotized and irradiated for 1 h to yield, after chromatography over silica gel (chloroform–carbon tetrachloride, 1:1), 359 mg (20%) of the fluoro aldehyde **5,** purified further by sublimation.

1-(2-Fluoro-3,4-dimethoxyphenyl)-2-nitroethylene (6). A solution of 560 mg (3.04 mmol) of **5** and 500 mg of ammonium acetate in 30 ml of nitromethane was heated on a steam bath for 5 h. Water was added and the solution was extracted three times with ether. After drying, solvent was removed to give 525 mg (75%) of **6,** crystallized from aqueous ethanol.

1-(2-Fluoro-3,4-dimethoxyphenyl)-2-nitroethane (7). Sodium borohydride, 105 mg (2.8 mmol), was dissolved in 3.5 ml of ethanol. The solution was cooled in an ice bath and stirred under nitrogen while a solution of 285 mg (1.25 mmol) of the nitrostyrene **6** in 10 ml of ethanol was added over 2 h.[15] After storage overnight in a refrigerator, the solution was made slightly acidic with 3 N hydrochloric acid, water was added, and the solution was extracted three times with ether. After drying and removal of solvent, the residue was sublimed to give 267 mg of **7** (93%).

Table III. Ultraviolet Spectral Data [a]

Compd-(solvent) [b]	λ_{max}, nm	ϵ	Compd-(solvent) [b]	λ_{max}, nm	ϵ
1d (A)	271	1476	**3a** (C)	277	2407
1d (B)	288	2558	**4e** (A)	281	3162
2d (A)	262	552	**4e** (C)	290	5260
2d (B)	277	2016	**10** (A)	270	866
3a (A)	270	991	**10** (C)	276	2227

[a] Spectra were measured on a Cary Model 15 recording spectrophotometer. [b] Solvents: A, 0.05 N HCl; B, 0.05 N NaOH; C, 0.05 M phosphate buffer, pH 9.40.

2-Fluoro-3,4-dimethoxyphenethylamine Hydrobromide (8 HBr). A solution of 267 mg (1.16 mmol) of the nitroethane **7** in 50 ml of ethanol was hydrogenated overnight over 300 mg of PtO_2 at 40 psi. Removal of catalyst, addition of 1.3 ml of 1 N hydrobromic acid, and removal of solvent gave, after recrystallization from methanol–ether, 205 mg of **8** HBr (63%).

2-Fluoro-3,4-dihydroxyphenethylamine Hydrobromide (2-Fluorodopamine Hydrobromide) (9 HBr). Compound **8**, 100 mg (0.5 mmol), was demethylated as described above for the preparation of **4d**, with a 6-h reaction time. Removal of solvent and drying of the residue over potassium hydroxide gave 76 mg (85%) of **9** HBr as off-white crystals. Repeated attempts to recrystallize this material were unsuccessful.

***N*-Trifluoroacetyl-2-fluoro-3,4-dihydroxyphenethylamine (10).** Using the procedure described above for the preparation of **4e**, **9** HBr, 60 mg (0.21 mmol), was converted to the trifluoroacetyl derivative **10** in 76% yield (after sublimation).

2-Fluoro-3,4-dihydroxyphenethylamine Hydrochloride (9 HCl). A solution of 44 mg (0.16 mmol) of **10** in 10 ml of methanol was saturated with dry hydrogen chloride and stored. After 6 days, TLC demonstrated complete deacylation. Removal of solvent and excess hydrogen chloride produced **9** HCl, 26 mg (78%), recrystallized from methanol–ether.

pK_a Determinations. The uv spectra of the fluorinated phenols and catechols display the expected increase in intensity and bathochromic shift when their solutions are made alkaline (Table III). Aliquots (100 μl) of a stock solution of the material being investigated were diluted to 3.00 ml with 0.05 M phosphate buffers and the degree of ionization determined as a function of pH by measurement of the optical density at that wavelength corresponding to the largest spectral difference between the neutral species and monoanion. Determinations were made at no less than five pH values, with agreement of at least ±0.05 pH unit.

Acknowledgment. The author is grateful to Drs. Louis A. Cohen and Cyrus R. Creveling of this laboratory for many helpful discussions during the course of this work, and to Dr. Herman J. C. Yeh of this Laboratory and Mr. Edward A. Sokolowski and Dr. Robert J. Highet of the National Heart and Lung Institute for valuable help in obtaining and interpreting the NMR spectra.

Registry No.—**1a**, 59043-60-6; **1c**, 59043-61-7; **1d**, 404-84-2; **1d** HCl, 458-33-3; **2a**, 59043-62-8; **2c**, 59043-63-9; **2d**, 59043-64-0; **2d** HCl, 59043-65-1; **3a**, 59043-66-2; **3b** HCl, 59043-67-3; **4a**, 59043-68-4; **4c**, 59043-69-5; **4d** HCl, 59043-70-8; **4e**, 59043-71-9; **5**, 37686-68-3; **6**, 59043-72-0; **7**, 59043-73-1; **8** HBr, 59043-74-2; **9** HBr, 59043-75-3; **9** HCl, 59043-76-4; **10**, 59043-77-5; *N*-trifluoroacetyltryamine, 13230-73-4; nitric acid, 7697-37-2; HCl, 7647-01-0; *N*-trifluoroacetyl-3,4-dimethoxyphenethylamine, 13230-71-2; HBr, 10035-10-6; 2-nitro-3,4-dimethoxybenzaldehyde, 55149-84-3.

References and Notes

(1) For part 3 see K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **38**, 3647 (1973).
(2) L. L. Iverson, Ed., *Br. Med. J.*, **29**, 91 (1973).
(3) For example, A. Rotman, J. Lundstrom, E. McNeal, J. Daly, and C. R. Creveling, *J. Med. Chem.*, **18**, 138 (1975), and references cited therein.
(4) (a) R. W. Fuller, H. D. Snoddy, B. B. Mollow, and K. M. Hauser, *Psychopharmacologia*, **28**, 205 (1973); R. W. Fuller and B. B. Mollow, Abstracts, 170th National Meeting of the American Chemical Society, Chicago, Ill., August 1975, No. FLUO-5; (b) H. Bercher, H. Blayer, and A. Grisk, *Acta Biol. Med. Ger.*, **33**, 335 (1974); H. Bercher and A. Grisk, *ibid.*, **34**, 667 (1975).
(5) A preliminary report has appeared on the preparation of [^{18}F]-6-fluorodopamine: A. P. Wolf, Proceedings of the 21st Annual Meeting of the Society of Nuclear Medicine, *J. Nucl. Med.*, **15**, 513 (1974). A series of polyfluorophenylalkylamines, including a 4-methoxy-2,3,5,6-tetrafluoro analogue of (+)-amphetamine, has been reported: W. L. White and R. Filler, *J. Chem. Soc.*, 2062 (1971).
(6) (a) Aromatic amino acids having both fluoro and hydroxy functionality in the ring are well known: F. Weygand and W. Oettmeier, *Russ. Chem. Rev. (Engl. Transl.)*, **39**, 290 (1970). (b) 3,4-Dihydroxy-5-fluoro-DL-phenylalanine (5-fluoro-Dopa) and [^{18}F] -5-fluoro-Dopa have been reported: G. Firnau, C. Nahmias, and S. Garnett, *J. Med. Chem.*, **16**, 419 (1973).
(7) K. L. Kirk and L. A. Cohen, ACS Symposium Series: "Biochemistry of the Carbon–Fluorine Bond", in press.
(8) D. D. Clarke, S. Wilk, and S. E. Gillow, *J. Gas Chromatogr.*, **4**, 310 (1966).
(9) K. C. Roberts and J. A. Rhys, *J. Chem. Soc.*, 39 (1937).
(10) M. Hudlicky, "Organic Fluorine Chemistry", Plenum Press, New York, N.Y., 1970, p 42.
(11) Initial efforts to decompose diazonium fluoroborates in this series thermally gave disappointing results, either because of difficulties in isolation of the diazonium fluoroborate (from **1b**) or inability to effect clean pyrolytic decomposition (fluoroborate derived from **4b**). A direct comparison of the thermal and photochemical decomposition procedures would require a study of structural parameters affecting each procedure, a study beyond the scope of the present work.
(12) J. Harley-Mason, *J. Chem. Soc.*, 200 (1953).
(13) Preliminary experiments designed to direct nitration of *N*-trifluoroacetyl-3,4-dimethoxyphenethylamine to the 2 position, by prior blocking of the 6 position by halogenation, were unrewarding. Apparently steric and electronic effects combine to prevent ring nitration of the 6-bromo or 6-chloro derivative.
(14) A. Butenandt and H. G. Schlossberger, *Chem. Ber.*, **85**, 565 (1952).
(15) J. Gal, L. D. Gruenke, and N. Castagnoli, Jr., *J. Med. Chem.*, **18**, 683 (1975).
(16) Computer-assisted analyses of the NMR spectra of this and other fluorinated phenols and catechols are in progress.
(17) E. D. Becker, "High Resolution NMR", Academic Press, New York, N.Y., 1969, pp 152–170.
(18) V. M. Vlasov and G. G. Yakobson, *Russ. Chem. Rev. (Engl. Transl.)*, **43**, 781 (1974).
(19) R. B. Martin, *J. Phys. Chem.*, **75**, 2657 (1971).
(20) C. F. Timerlake, *J. Chem. Soc.*, 4987 (1957).
(21) The physiological properties of β,β-difluorophenethylamines may be due, in part, to the reduced basicity of the side chain amino groups (ref 4a).
(22) K. L. Kirk, W. Nagal, and L. A. Cohen, *J. Am. Chem. Soc.*, **95**, 8389 (1973).