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Synthesis of 2,6-difluorodopamine and 3-(2,6-difluoro-3,4-dihydroxyphenyl)alanine

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Abstract

2,6-Difluorodopamine and 3-(2,6-difluoro-3,4-dihydroxyphenyl)alanine were prepared by side-chain elaboration of 2,6-difluoroveratraldehyde, followed by removal of protecting groups.

Keywords: Synthesis; Difluorodopamine; Difluorodihydroxyphenylalanine; NMR spectroscopy; Mass spectrometry

1. Introduction

Early in our research on the biochemistry and pharmacology of ring-fluorinated biogenic amines, we found that the presence of fluorine on the aromatic ring of dopamine (DA) (**1a**) had little effect on the binding of this amine to either dopaminergic or noradrenergic receptors [1]. In contrast, ring-fluorination markedly effects the binding of norepinephrine (NE) (**2a**) to noradrenergic receptors, in that fluorine in the 2-position of the aromatic ring (2-*F*-NE) (**2b**) inhibits binding to α-adrenergic receptors whereas fluorine in the 6-position (6-*F*-NE) (**2c**) inhibits binding to β-adrenergic receptors [2]. This observation was extended to other adrenergic agonists such as epinephrine. In our efforts to delineate the mechanism(s) of these fluorine-induced adrenergic selectivities, we prepared 2,6-difluoronorepinephrine (2,6-Di*F*-NE, **2d**) and found this compound to be relatively inactive at both the α- and β-adrenergic receptors [3].

Taken together, the contrasting effects of fluorine substitution on DA and NE suggest an approach to a prodrug directed selectively to dopaminergic systems. Thus, the action of aromatic amino acid decarboxylase on 3-(2,6-difluoro-3,4-hydroxyphenyl)alanine (2,6-Di*F*-DOPA) (**3d**) should produce 2,6-difluorodopamine (2,6-Di*F*-DA) (**1d**) in vivo. If disubstitution with fluorine has little effect on the interaction of 2,6-Di*F*-DA with dopaminergic receptors, this amine should retain substantial dopaminergic agonist properties. However, in vivo β-hydroxylation of 2,6-Di*F*-DA to give 2,6-Di*F*-NE (**2d**) would not produce significant adrenergic responses, owing to the relative inactivity of **2d** at noradrenergic receptors.

An additional factor prompted our efforts to synthesize 2,6-Di*F*-DOPA (**3d**). Several laboratories have prepared [^{18}F]-6-*F*-DOPA by electrophilic fluorination of DOPA. We have provided to several research group authentic samples of 6-*F*-DOPA, as well as the isomeric 2-*F*- and 5-*F*-DOPA, for chromatographic analyses of product mixtures produced by these electrophilic fluorinations. There have been indications that a difluorination product [presumably 2,6-Di*F*-DOPA (**3d**)] is produced by the electrophilic fluorination of DOPA [4]. The availability of an authentic sample of **3d** would thus provide another internal standard for analyses of products obtained during this radiochemical fluorination procedure.

Based on these considerations, we have prepared 2,6-Di*F*-DA (**1d**) (Scheme 1) and 2,6-Di*F*-DOPA (**3d**) (Scheme 2) from 2,6-difluoroveratraldehyde (**4**). We are presently examining the binding affinity of **1d** with a series of dopaminergic receptors. The facility with which **3d** is decarboxylated with aromatic amino acid decarboxylase is also being investigated. Results of biochemical and pharmacological experiments will be published separately.

2. Chemistry

We had prepared initially 2,6-difluoroveratraldehyde (**4**) in seven steps (17% overall yield) from 2,4-difluorophenol [3]. We recently have developed a much more efficient route

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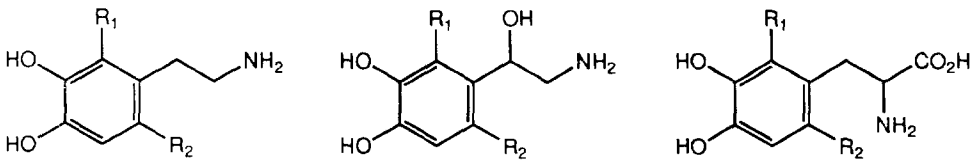


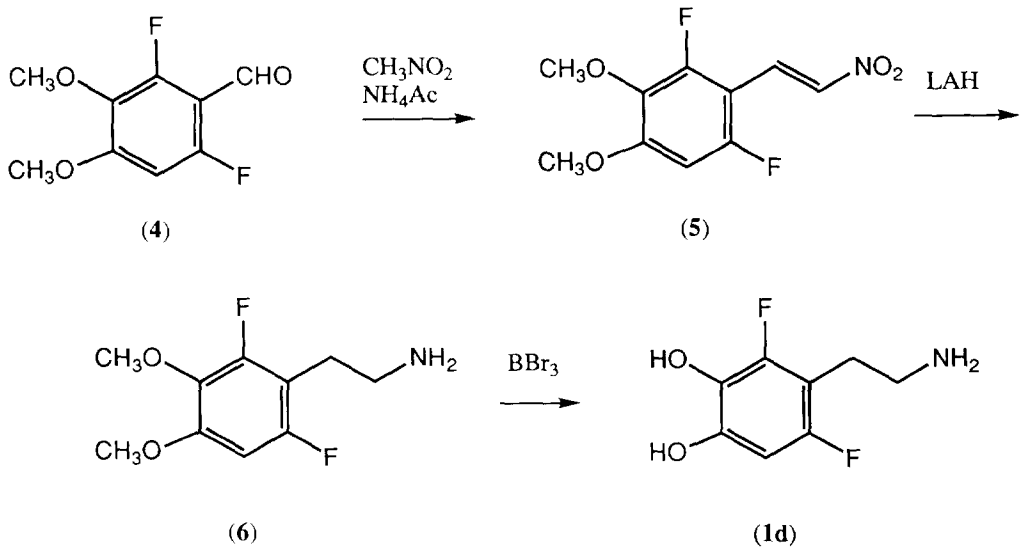
(1) (2) (3)

Series **a**: $R_1 = R_2 = H$
b: $R_1 = F, R_2 = H$
c: $R_1 = H, R_2 = F$
d: $R_1 = R_2 = F$

based on selective lithiation [5] of the oxazoline derived from 2-fluoro-4,5-dimethoxybenzoic acid, followed by reductive hydrolysis to give **4** in good yield [6].

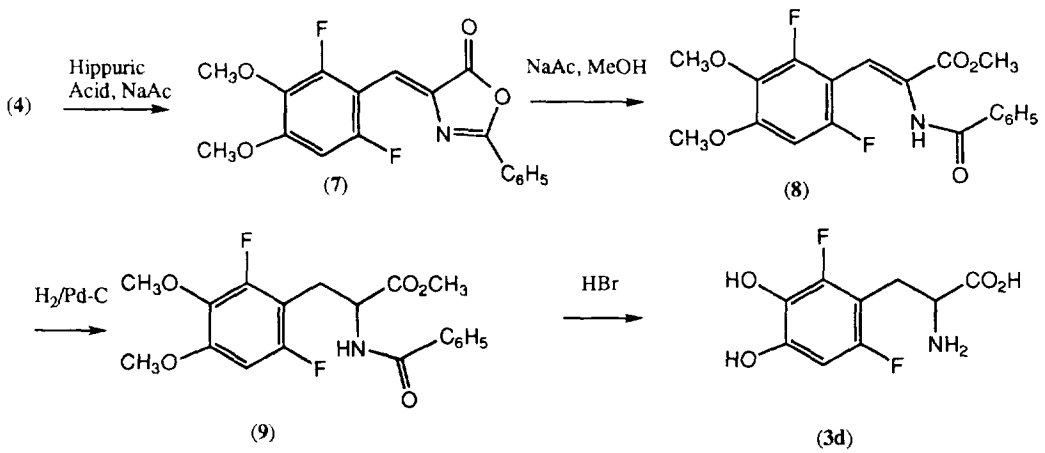
Ammonium acetate-catalyzed condensation of **4** with nitromethane gave the nitrostyrene **5**, reduction of which with lithium aluminum hydride produced 3-(2,6-difluoro-3,4-dimethoxyphenyl)ethylamine (**6**). Cleavage of the methyl ethers with boron tribromide gave **1d**, isolated as the hydrobromide salt (Scheme 1).

Sodium acetate-catalyzed condensation of **4** with hippuric acid gave the azlactone **7**. This was treated with methanolic sodium acetate to give the substituted methyl acrylate **8**. Hydrogenolysis of **8** over Pd–C in methanol gave *N*-benzoyl-2-(2,6-difluoro-3,4-dimethoxyphenyl)alanine methyl ester



(4) (5) (6) (1d)

Scheme 1.



(4) (7) (8) (9) (3d)

Scheme 2.

(**9**) which was converted to **3d** by treatment with refluxing 50% HBr (Scheme 2).

3. Experimental details

3.1. General

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. NMR spectra were performed on a Varian Gemini 300 MHz spectrometer. CI mass spectra were performed on a Finnigan 1015 mass spectrometer by the staff of the Laboratory of Analytical Chemistry, NIDDK.

3.2. 1-(2,6-Difluoro-3,4-dimethoxyphenyl)-2-nitroethylene (5)

A mixture of 233 mg (1.15 mmol) of 2,6-difluoroveratraldehyde (**4**) and 195 mg (2.53 mmol) of ammonium acetate in 15 ml of nitromethane was refluxed for 5 h. To the yellow reaction solution was added 10 ml of water and the mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with water and brine, dried over Na_2SO_4 and evaporated to give a yellow solid. This was purified by preparative thin layer chromatography (TLC) (silica gel, 20% ethyl acetate/petroleum ether) to give 180 mg (0.74 mmol, 64%) of nitroethylene **5** as a yellow solid, m.p. 102–104 °C. MS (CI NH_3) *m/z*: 280 ($M^+ + 35$, $N_2H_7^+$); 263 ($M^+ + 18$, NH_4^+); 245 (M^+). ^{1}H NMR ($CDCl_3$) δ: 3.91 (s, 3H, CH_3O); 3.94 (s, 3H, CH_3O); 6.61–6.57 (d, 1H, $J = 12.6$ Hz, Ar*H*); 7.81–7.76 (d, 1H, $J = 3.9$ Hz, C*H*NO_2); 8.13–8.08 (d, 1H, $J = 3.89$ Hz, ArC*H*) ppm. Analysis: Calc. for $C_{10}H_9F_2NO_3$: C, 48.99; H, 3.70; F, 15.50; N, 5.71%. Found: C, 49.27, H, 3.77; F, 15.62; N, 5.76%.

3.3. 2-(2,6-Difluoro-3,4-dimethoxyphenyl)ethylamine (6)

A solution of 180 mg (0.74 mmol) of nitroethylene **5** in 4 ml of dry THF was added dropwise to a stirred suspension of 142 mg (3.67 mmol) of lithium aluminum hydride in 15 ml of anhydrous ether at ice-bath temperature. The cooling bath was removed after 15 min and the stirring continued for 3 h at room temperature. The reaction mixture was cooled in an ice bath, treated with slow dropwise addition of 0.14 ml of water and stirred for 15 min, 0.14 ml of 15% sodium hydroxide and stirred for 15 min, and then with 0.42 ml of water and stirred for 30 min at room temperature. The white solid was removed by filtration and the filtrate dried over Na_2SO_4. Evaporation gave 140 mg of a yellow oil. Purification of the crude product by preparative TLC (silica gel, 10% methanol/chloroform) gave as a ninhydrin-positive band 82 mg (51%) of **6** as a pale oil. MS (CI NH_3) *m/z*: 235 ($M^+ + 18$, NH_4^+); 218 (M^+). ^{1}H NMR ($CDCl_3$) δ: 2.77–2.72 (t, 2H, $J_1 = 6.5$ Hz, $J_2 = 6.9$ Hz, CH_2N); 2.93–2.88 (t, 2H, $J_1 = J_2 = 6.8$ Hz, ArCH_2); 3.84 (s, 3H, CH_3O); 3.9 (s, 3H, CH_3O); 6.49–6.44 (d–d, 1H, $J^o_{HP} = 13.5$ Hz, Ar*H*) ppm. A sample was converted to the hydrochloride and was recrystallized from methanol/ether for analysis, m.p. 187–190 °C. Calc. for $C_{10}H_{14}ClF_2NO_2 + H_2O$: C, 46.93; H, 5.61; Cl, 13.85; F, 14.71; N, 5.47%. Found: C, 46.77; H, 5.36; Cl, 14.22; F, 14.71; N, 5.38%.

3.4. 2,6-Difluorodopamine (1d)

To a stirred solution of 80 mg (0.37 mmol) of **10** in 5 ml of anhydrous dichloromethane, cooled in a Dry Ice/acetone bath under an argon atmosphere, was added 0.175 ml of BBr_3 (1.84 mmol). After 15 min the cooling bath was removed and the stirring continued overnight at room temperature. The mixture was then chilled in an ice bath and an excess of absolute methanol added slowly. Evaporation of the brown solution under vacuum removed solvent and trimethyl borate to give 108 mg of a dark solid. The residue was taken up in 3 ml of 1 N HCl and added to a column of Dowex (50×8–400, strongly acidic cation) resin. The column was eluted with distilled water, 25 ml of 0.5 N HCl, 75 ml of 1 N HCl and 200 ml of 3 N HCl. The concentration of the 3 N HCl fractions produced the 2,6-difluorodopamine hydrochloride in the second fraction, 40 mg (0.21 mmol, 46%). MS (CI NH_3) *m/z*: 190 ($M^+ + 1$); 207 ($M^+ + 18$). ^{1}H NMR (CD_3OD) δ: 2.96–2.92 (t, 2H, $J_1 = 7.3$ Hz, $J_2 = 7.2$ Hz, NCH_2); 3.11–3.06 (t, 2H, $J_1 = 7.1$ Hz, $J_2 = 7.6$ Hz, ArCH_2); 6.45 (d, 1H, $J^o_{HF} = 10.7$ Hz, Ar*H*) ppm.

3.5. 2-Benzoylamino-3-(2,6-difluoro-3,4-dimethoxyphenyl)acrylic acid azlactone (7)

A mixture of 324 mg (1.58 mmol) of **4**, 319 mg (1.79 mmol) of hippuric acid and 147 mg (1.79 mmol) of anhydrous sodium acetate in 0.8 ml of acetic anhydride was heated for 2 h at 95 °C. The yellow reaction solution was cooled in an ice bath and triturated with 3 ml of ethanol. The solution was allowed to stand for 30 min at 0 °C and then poured into 15 ml of water and stored at 0 °C for 2 h. The yellow crystalline solid which formed was collected by filtration, washed with a small amount of water and dried in vacuum. This produced 490 mg (90%) of **7** that was used in the next step without further purification. MS (CI NH_3) *m/z*: 346 ($M^+ + 1$); 363 ($M^+ + 18$).

3.6. Methyl 2-benzoylamino-3-(2,6-difluoro-3,4-dimethoxyphenyl)acrylate (8)

A mixture of 490 mg (1.42 mmol) of **7** in a solution of 126 mg (1.53 mmol) of sodium acetate in 80 ml of methanol was briefly heated on a water bath to effect dissolution. After being stirred for 1 h at room temperature, no more starting material could be detected by TLC (silica gel: 20% ethyl acetate/petroleum ether). The methanol was removed by evaporation and the yellow solid taken up in chloroform. The chloroform solution was washed with water, dried over Na_2SO_4 and evaporated to give 373 mg of a pale solid. Puri-

fication of the crude product over a silica gel column (30% ethyl acetate/petroleum ether) gave 287 mg (0.76 mmol, 53.6% based on crude starting material) of **8** as a white solid, m.p. 165–168 °C. MS (EI) *m/z*: 377 (M^+). ^{1}H NMR ($CDCl_3$) δ: 3.78 (s, 3H, CH_3O); 3.84 (s, 3H, CH_3O); 3.91 (s, 3H, CH_3O); 6.48–6.45 (dd, 1H, J^o_{HF} = 11.7 Hz, J^m_{HF} = 2.0 Hz, ArH_5); 7.54–7.34 (m, 3H, Ar*H*); 8.19 (s, 1H, C*H*); 7.83–7.81 (d, 2H, *J* = 7.2 Hz, Ar*H*) ppm. Analysis: Calc. for $C_{19}H_{17}O_5F_2N + H_2O$: C, 59.77; H, 4.62; F, 9.95; N, 3.67%. Found: C, 59.84; H, 4.61; F, 9.68; N, 3.65%.

*3.7. N-Benzoyl-3-(2,6-difluoro-3,4-dimethoxyphenyl)-alanine methyl ester (**9**)*

A solution of 449 mg (1.19 mmol) of **8** in 70 ml of methanol was hydrogenated over 200 mg of 10% Pd–C at atmospheric pressure for 24 h. Removal of the catalyst by filtration and evaporation of the solvent gave 385 mg of a white solid. Recrystallization from methanol/hexane gave 342 mg (0.90 mmol, 75%) of **9** as a white crystalline solid. MS (CI NH_3) *m/z*: 380 ($M^+ + 1$); 397 ($M^+ + 18$). M.p. 127–128 °C. ^{1}H NMR ($CDCl_3$) δ: 3.10–3.17, 3.33–3.40 (2q, 2H, CH_2); 3.78 (s, 3H, CH_3O); 3.80 (s, 3H, CH_3O); 3.83 (s, 3H, CH_3O); 5.03–5.06 (dd, 1H, C*H*); 6.46, 6.66 (dd, 1H, *J* = 8.6, 8.9 Hz, ArH_5); 7.40–7.50 (m, 3H, Ar*H*); 7.74 (d, 2H, *J* = 7.0 Hz, Ar*H*) ppm. Analysis: Calc. for $C_{19}H_{19}O_5NF_2$: C, 60.16; H, 5.05; N, 3.69; F, 10.01%. Found: C, 59.77; H, 5.05; N, 3.67; F, 9.90%.

*3.8. (3-(2,6-Difluoro-3,4-dihydroxyphenyl)alanine (**3d**)*

A suspension of 264 mg (0.70 mmol) of **9** in 25 ml of 48% hydrobromic acid was refluxed for 9 h at 145–150 °C (bath temperature). A slow stream of hydrogen was bubbled through the solution during the reaction. After cooling, the solvent was removed under vacuum and additional HBr was removed by the addition of water and evaporation. To remove the final traces of HBr, the residue was placed in a vacuum desiccator over potassium hydroxide. Brown crystals were obtained, homogeneous by TLC. ^{1}H NMR (D_2O) δ: 3.19–3.02 (m, 2H, CH_2); 4.11–4.06 (t, 1H, J_1 = 7.0 Hz, J_2 = 6.5 Hz, C*H*); 6.44–6.40 (d–d, 1H, J^o_{HF} = 10.7 Hz. ArH_5) ppm.

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