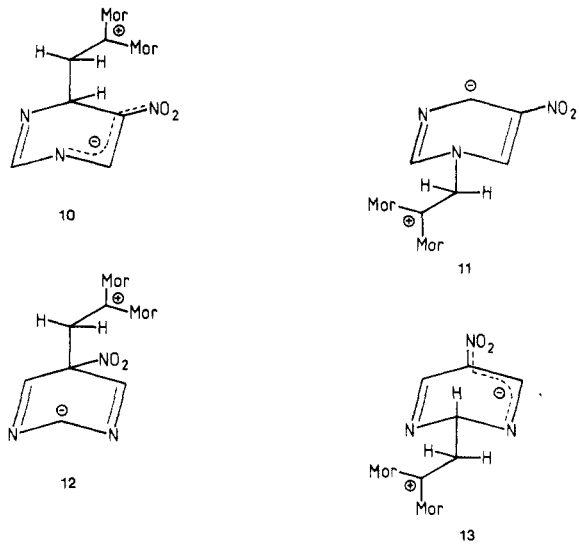
Scheme III



In conclusion, the regiospecificity of the present reactions appears to be a clear-cut example of superjacent orbital control.[7] It has been reported[8] that 5-nitropyrimidine (2) and some of its 2-substituted derivatives give with 1-(diethylamino)prop-1-yne the 2:1 adducts 9. This reaction has been proposed to involved the 4 + 2 cycloadduct 8, which after rearrangement and addition of a second molecule of the propyne yields 9. The regioselectivity of the cycloaddition leading to 8 would appear to constitute a "normal" HOMO/LUMO controlled situation since C_4 (C_6) and the nitro group oxygen carry large LUMO coefficients (cf. Figure 1).

Stereospecificity. The various FMO interaction energies calculated above do not only predict an exclusive regiospecific addition of the enamine across N_1,C_4—as observed—but also indicate that a considerable preference should exist for the $N_1,C_{1'}/C_4,C_{2'}$ mode over the $N_1,C_{2'}/C_4,C_{1'}$ mode, since the former provides both stronger HOMO/LUMO and stronger HOMO/(LUMO + 1) interaction. The experimental observation that only the product 4 derived from 3 is formed fully corroborates the predicted regiospecificity of the addition process.

Concluding Remarks

While the results discussed above nicely demonstrate that FMO perturbation theory correctly predicts the observed course of the cycloaddition between 2 and electron-rich olefins, it should be noted that this does not automatically imply that the cycloaddition occurs in a concerted manner.

The presence of strongly electron-withdrawing and electron-donating substituents not only induces a highly polar character in the transition-state for a concerted pathway but might even stabilize a zwitterionic structure sufficiently to make it an actual reaction intermediate. Experimental support for the possible existence of a zwitterionic intermediate is the fact that the reaction of 2 with 1 occurs readily and in good yield in the polar solvent ethanol but poorly in an apolar solvent. As usual the most stable transition state in a concerted pathway also sets the stage for formation of a stable zwitterionic intermediate as may be seen upon comparison of the mesomeric option available to the zwitterions 10 – 13 depicted in Scheme III, that are related to 3, 5, 6, and 7, respectively. Consideration of the stability of such zwitterions, i.e., 10 > 11 and 13 > 12, readily leads to prediction of regioselectivity. However, prediction of the correct regioisomers 10 or 13 cannot easily be achieved on this basis.

Experimental Section

The radical anion of 2 was measured on a Varian 4502-10A; X band. The electrolysis was performed with a 10^{-4} M solution of 2 in dimethylformamide with tetra-*n*-butylammonium iodide as a supporting electrolyte, 10 μA at −1.45 V. The cell used in these experiments was deoxygenated in a glovebox.

Registry No. 1, 14212-87-4; 2, 14080-32-1; $2^{-\cdot}$, 34515-84-9.

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New Syntheses of 2-Fluoroisovanillin and 5-Fluorovanillin

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Received March 14, 1986

The addition of fluorine to give the three different positional isomers on the aromatic ring of the neurotransmitter norepinephrine has provided new drugs with very selective actions on the adrenergic nervous system.[1] We have been interested in the synthesis of new drug molecules incorporating fluorine into the aromatic ring and have thus investigated the synthesis of potential fluorinated aldehyde precursors.

A previous report of the synthesis of 5-fluorovanillin (1) involved a photochemical–Schiemann reaction of 5-aminovanillin (2).[1] This reaction gave 1 in low yields (10–12%) and involved a tedious chromatographic step. Since the reaction also does not lend itself to the preparation of significant quantities of 1, we sought a method for preparation of 1 that would be amenable to large scale reactions and be carried out in a minimum number of steps. We now report a new method for the formation of 1. During this investigation, a new route to 2-fluoroisovanillin (3) was also discovered. The synthetic pathways for the formation of 1 and 3 are outlined in Scheme I.

Our first attempt at the formation of 1 involved treatment of 2-fluoro-6-methoxyphenol[2] (4) with hexamethylenetetraamine (HMTA) and trifluoroacetic acid. This is a modification of the Duff reaction[3] and under these mild reaction conditions, a high para regioselectivity has been observed.[4] However, upon completion of the reaction, the major product of the reaction was 2-fluoro-3-hydroxy-4-methoxybenzaldehyde (2-fluoroisovanillin, 3) (75%), rather than 1. Compound 3 had previously been formed in 4% yield by partial demethylation of 2-fluoroveratraldehyde.[5,6]

The second approach to 1 involved the oxidation of a *N,N*-dimethylbenzylamine. Phenols are easily aminomethylated by reaction with formaldehyde and a secondary

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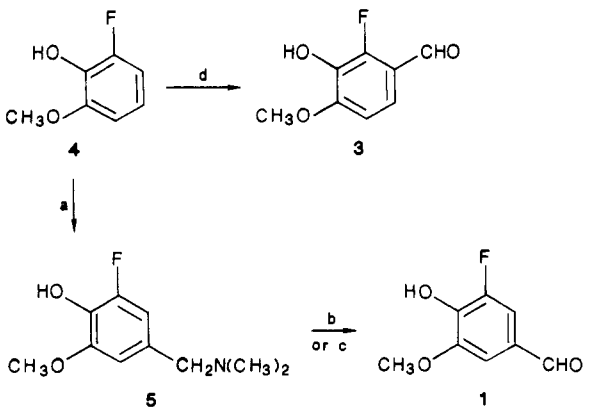
Scheme I[a]



[a] (a) 37% CH_2O, 40% $(CH_3)_2NH$; (b) HMTA, HOAc; (c) 1. CH_2I; 2. HMTA, HOAc/H_2O; (d) HMTA, TFA.

amine.[7] Treatment of **4** with formaldehyde and *N,N*-dimethylamine afforded, *N,N*-dimethyl-3-methoxy-4-hydroxy-5-fluorobenzylamine (**5**, 95%) as the sole regioisomer. A standard method for the conversion of tertiary amines into aldehydes involves a transamination with HMTA, followed by hydrolysis.[8] Treatment of **5** with HMTA in acetic acid gave a 20% yield of **1**. In order to increase the yield, we sought a better leaving group. Treatment of **5** with methyl iodide, followed by reaction with HMTA in a 50% aqueous acetic acid and hydrolysis with concentrated HCl, afforded **1** in 91% yield, after purification.

In summary, we have developed new pathways for the formation of both 2-fluoroisovanillin and 5-fluorovanillin from a common intermediate. Each step of the reaction sequence can be scaled up and involves a modest to very good yield of the product. We also report a new method for the formation of benzaldehydes via a transamination and hydrolysis of quaternary salts of *N,N*-dimethylbenzylamines.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared data were collected on a Beckman 4230 spectrophotometer. The ^1H and ^{19}F NMR were recorded on a Bruker HX-90E or a IBM 270 spectrometer with tetramethylsilane as the internal standard for ^1H NMR and hexafluorobenzene as the external standard for ^{19}F NMR. The mass spectra were obtained at the Ohio State University Chemical Instrument Center, by use of a Kratos MS-30 mass spectrometer. Chemical analyses were determined by Galbraith Laboratories, Inc., Knoxville, TN. TLC was performed on silica gel 60 F precoated aluminum-backed plated from EM Reagents. Column chromatography was performed on silica gel 60, 70–230 mesh, from EM Reagents. Flash chromatography was performed on flash silica gel 60, 230–400 mesh, from EM Reagents. All organic solvents were appropriately dried prior to use.

2-Fluoro-3-hydroxy-4-methoxybenzaldehyde (3). To a heated solution (80 °C) of hexamethylenetetraamine (HMTA) (2.8 g, 20 mmol) in trifluoroacetic acid (10 mL) was added dropwise over a 50-min period 2-fluoro-6-methoxyphenol[2] (1.42 g, 10 mmol) in TFA (10 mL). The mixture was heated for an additional 1 h and concentrated, and H_2O (50 mL) was added. The mixture was stirred for 10 min and solid potassium carbonate was added until the solution was neutral. The mixture was stirred for 20 min and extracted with ether (3 × 50 mL), washed with H_2O (3 × 50 mL), dried with anhydrous $MgSO_4$, and evaporated under reduced pressure to give 1.4 g (75%) of **3** which was purified by sublimation (113 °C) to give 1.1 g (63%) of pure **3**; mp 180–181 °C (lit.[5,6] mp 180–195 °C).

***N,N*-Dimethyl-3-hydroxy-4-methoxy-5-fluorobenzylamine (5).** 2-Fluoro-6-methoxyphenol[2] (10 g, 70 mmol) was added to a solution of 40% dimethylamine (15 g, 124 mmol) and 37% formaldehyde (9 mL, 124 mmol) in absolute ethanol (70 mL). The mixture was heated at reflux for 2 h, cooled, and concentrated under reduced pressure to give a solid. The solid was triturated with ether (100 mL) to give 13.2 g of **5** (95%); mp 140–142 °C; IR (KBr) 3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 6.56–6.68 (m, 2 H, 2 × ArH), 3.74 (s, 3 H, $ArOCH_3$), 3.35 (s, 2 H, $ArCH_2N$), 2.24 (s, 6 H, $N(CH_3)_2$).

Anal. Calcd for $C_{10}H_{14}FNO_2$: C, 59.67; H, 4.50; N, 7.73. Found: C, 59.37; H, 4.35; N, 7.68.

3-Methoxy-4-hydroxy-5-fluorobenzaldehyde (1). Iodomethane (40 mL) was added to a solution of *N,N*-dimethyl-3-methoxy-4-hydroxy-5-fluorobenzylamine (**5**) (4 g, 20 mmol) in $CHCl_3$ (200 mL). The mixture was stirred at 25 °C for 18 h and filtered to give 7.8 g of a white solid. Without further purification, the solid was heated to 120 °C in HOAc (20 mL) and H_2O (20 mL). At that time, HMTA (12 g, 30 mmol) was added to the reaction mixture. The mixture was stirred at 120 °C for 2 h and concentrated HCl (5 mL) was added. The mixture was heated an additional 5 min, cooled, and extracted with ether (3 × 50 mL). The organic layer was washed with H_2O (3 × 50 mL), dried with $MgSO_4$, and evaporated under reduced pressure to give 3.12 g (91%) of **1** which was purified by sublimation: mp 113–114 °C (lit.[1] mp 113–114 °C); ^1H NMR ($CDCl_3$) δ 9.8 (d, 1 H, J_{HF} = 1.3 Hz, CHO), 7.3 (m, 2 H, ArH), 6.1 (b, 1 H, OH), 4.0 (s, 3 H, OCH_3); ^{19}F NMR ($CDCl_3$) δ − 138.47.

Acknowledgment. We thank the NIH for financial support (GM29358 and HL22533) and Mr. Jack Fowble for NMR spectra on the 270-MHz instrument.

Registry No. **1**, 79418-78-3; **3**, 79418-73-8; **5**, 103905-49-3; 2-fluoro-6-methoxyphenol, 73943-41-6.

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An Improved Synthesis of 4-Fluoroveratrole. Efficient Route to 6-Fluoroveratraldehyde and 6-Fluoro-D,L-DOPA

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Received March 14, 1986

Fluorinated analogues of catecholamines and amino acids have received recent attention as pharmacological tools and as mechanistic probes and biological tracers.[1] For example, the utility of 6-fluoronorepinephrine (6FNE) (**1**) as a specific α-adrenergic agonist has been demonstrated in several studies of both central and peripheral systems.[2] The study of the pharmacology of 6-fluoro-D,L-DOPA (6FDOPA) (**2**) has increased importance due to the potential of ^{18}F-labeled 6FDOPA as a scanning agent in positron emission transaxial tomography.[3] Both of these analogues, as well as other 6-fluoro analogues of amines and metabolites related to DOPA, have been synthesized from a common precursor, 6-fluoroveratraldehyde (**3**).[4,5] Our previous synthesis of **3** was based on our

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