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FLUORINE-CONTAINING CATECHOLAMINES. SYNTHESIS OF DL-2, 5, 6-TRIFLUORODOPA

ROBERT FILLER and ROBERT C. RICKERT

Department of Chemistry, Illinois Institute of Technology, Chicago, Ill. 60616 (U.S.A.)

SUMMARY

DL-2,5,6-trifluoro-3,4-dihydroxyphenylalanine (trifluorodopa) hydroiodide has been synthesized from hexafluorobenzene in a six-step procedure. The key step is the methoxylation of p-methyl tetrafluoroanisole. This reaction affords the desired 2,5,6-trifluoro-3,4-dimethoxytoluene, which is separated by preparative glc from 3,5,6-trifluoro-2,4-dimethoxytoluene. Attempts to obtain trifluorodopa by ether cleavage of the appropriately substituted dihydrobenzodioxin have not been successful.

INTRODUCTION

Ring-hydroxylated phenylethylamines and α-amino acids are important biological substances. Those biogenic amines which possess a 3,4-dihydroxyphenyl moiety are called catecholamines, which play a central role in the activity of the sympathetic nervous system. Thus, L-DOPA (3,4 dihydroxyphenylalanine) has been used with efficacy in the treatment of Parkinson's disease.

A number of phenylethylamines with the ring both hydroxylated and fluorinated have been described. Kirk [1] prepared 3-fluorotyramine, 3,5-difluorotyramine, and 6-fluorodopamine. The introduction of fluorine was accomplished by photochemical decomposition of the corresponding aryldiazonium ions. Earlier, Firnau [2] had reported the synthesis of DL-5-fluoro-DOPA and its ^{18}F analogue, using the conventional Schiemann procedure. Recently,

L-6-fluoro-DOPA [3] was obtained by direct fluorination with XeF_2 [4] of L-3-methoxy-4-hydroxyphenylalanine, followed by ether cleavage using 48% HBr.

In order to synthesize a trifluoro analogue, a stepwise Schiemann approach is not practicable. It should be far better to start with a polyfluoroaromatic compound and to introduce the nuclear hydroxyl groups and the amine side chain. In this paper we describe the synthesis of DL-2,5,6-trifluoro-3,4-dihydroxyphenylalanine (trifluoro-DOPA) (I) from hexafluorobenzene.

RESULTS AND DISCUSSION

A. The Benzodioxin Approach

In order to assure the introduction of the required oxygen-containing functions in vicinal positions of the aromatic ring, we adopted a method described by Burdon [5], involving the use of a bifunctional nucleophile. Pentafluorotoluene, prepared by reaction of hexafluorobenzene with methyllithium, was treated with ethylene glycol in alkali to afford 2-(2,3,5,6-tetrafluoro-4-methylphenoxy) ethanol (II) in 23% yield, as well as a 3% yield of a by-product, 1,2-bis (2,3,5,6-tetrafluoro-4-methylphenoxy) ethane (III), as shown in Figure 1. Compound II was converted, in low yield, by a second nucleophilic attack by alkoxide, to 5,7,8-trifluoro-6-methyl-2,3-dihydro-1,4-benzodioxin (IV), on refluxing with potassium carbonate in dimethylformamide.

Light-catalyzed bromination of crude IV provided the bromomethyl compound V in 81% yield. Compound V was converted to the acetamido derivative VI. It was anticipated that treatment with 47% hydriodic acid would yield the hydroiodide of trifluorodopa (I) by hydrolysis of the carboxylates, deacetylation, decarboxylation, and cleavage of the ether linkages. All of these processes occurred, except the cleavage of the ether, to give the hydroiodide of the substituted dihydrobenzodioxyl alanine, VII, from which the amino acid VIII could be isolated by careful neutralization. The failure to cleave these dioxin ether linkages led us to an intensive examination of a variety of reagents and conditions for the cleavage of these ether bonds, as well as

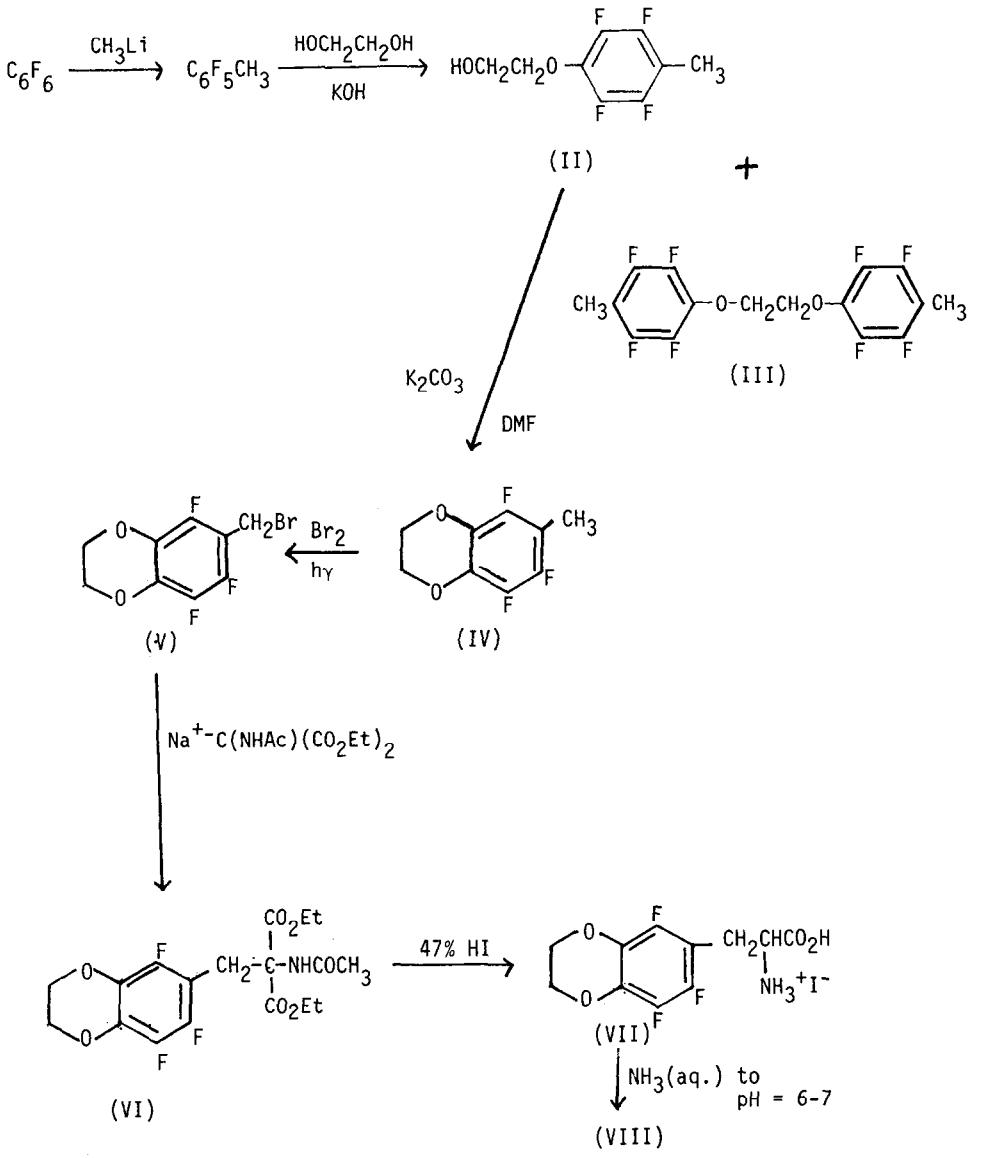

Fig.1. Attempted synthesis of trifluorodopa

structural variations of these compounds (ring size and α-branching). These studies will not be discussed here, since we failed to identify a satisfactory method to effect the cleavage to give the vicinal dihydroxy compound (catecholamine).

B. The Dimethoxylation Route

Our inability to produce the substituted catechol by the dioxin approach led us to examine the vicinal dimethoxy compounds, which should undergo cleavage by hydriodic acid, based on our previous success in synthesizing DL-tetrafluorotyrosine [6]. Reaction of pentafluorotoluene with methoxide ion gave 2,3,5,6-tetrafluoro-4-methylanisole in 82% yield. This compound was then converted to a mixture of two dimethoxy isomers, on refluxing with sodium methoxide in diglyme. The isomers, the desired 2,5,6-trifluoro-3,4-dimethoxytoluene (IX) and 3,5,6-trifluoro-2,4-dimethoxytoluene (X) could not be separated by fractional distillation or column chromatography. However, preparative glc proved successful and compound (IX) was isolated in 19% conversion. The two isomers were differentiated by assigning the multiplicities associated with the methyl and methoxyl hydrogens in the pmr spectra of the mixture and a purified sample of IX. Thus, IX exhibits a triplet at δ 2.1, which is attributed to spin-spin coupling of the methyl hydrogens with the two ortho fluorines. The hydrogens of the two methoxy groups also exhibit coupling with their respective ortho fluorines to afford two doublets centered at δ 3.9. Analysis of the mixture revealed the methyl triplet of IX, as well as a doublet ascribed to the methyl hydrogens of X coupled with its one ortho fluorine. The mixture also showed extensive multiplicity in the methoxyl hydrogen region, including a triplet and doublet, absent in pure IX, which are due to coupling of the ortho fluorines with the respective methoxy protons of X.

The subsequent steps toward the successful preparation of trifluorodopa hydroiodide proceeded uneventfully by following the steps described earlier for the dioxin and for tetrafluorotyrosine [6]. However, the final hydrolysis and cleavage of the methyl ether linkages required more than four days under reflux with 47% hydriodic acid, as observed previously [6]. These reactions are summarized in Figure 2.

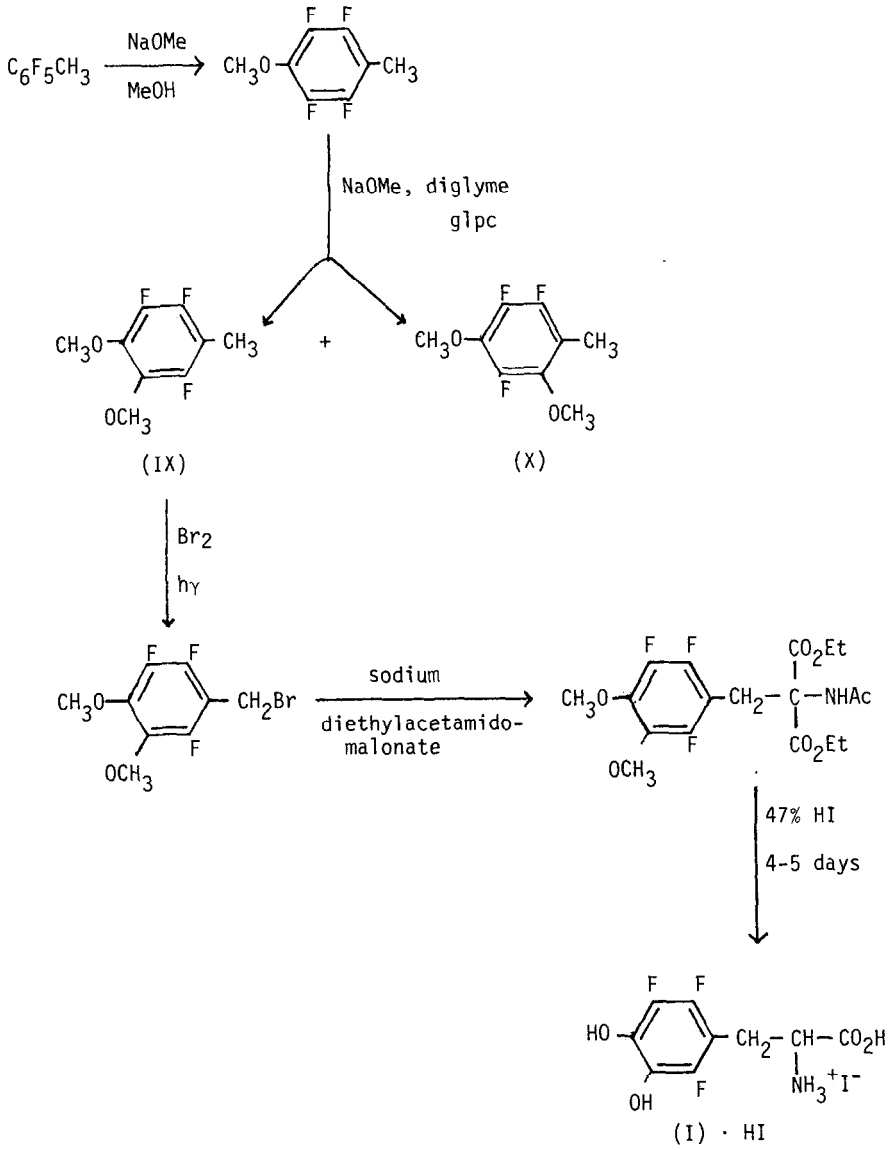

Fig.2. Synthesis of trifluorodopa

EXPERIMENTAL

2,3,4,5,6-Pentafluorotoluene.

This compound was prepared in 70% yield according to a previously reported procedure [7]. The product was isolated by distillation at ambient pressure

through a 5-cm, vacuum-jacketed vigreux column and the fraction that distilled in the range 110^0-120^0 was collected. NMR: doublet (J_p = 1.4) of triplet (J_o = 2.3) at δ 2.3; mass spec.: m/e 182.

2-(2,3,5,6-Tetrafluoro-4-methylphenoxy)ethanol (II) (nc).

Pentafluorotoluene (53.17g, 0.292 mole) was heated under reflux for 22 hrs. under a nitrogen atmosphere, with stirring, in 80 ml of reagent grade ethylene glycol containing KOH (16.37g, 0.292 mole). The hot mixture was poured into 100 ml of water containing 24 ml of concentrated HCl. On cooling, the organic layer was separated and the aqueous layer extracted four times with 25 ml portions of ether. The combined organic layers were washed twice with 25 ml portions of 5% aqueous NaOH and then once with a 15 ml portion of water to remove any phenolic by-products. The organic phase was dried over anhydrous $MgSO_4$ and filtered. Ether was removed on a rotary evaporator. The remaining liquid was vacuum distilled at 0.1 torr through a 5-cm, vacuum-jacketed vigreux column and the fraction that distilled in the range 55^0-60^0 was collected. This material melted very close to ambient temperature and clogging of the condenser caused problems during distillation. Anal. Calcd. for $C_9H_8F_4O_2$: C, 48.23; H, 3.60. Found: C, 47.87; H, 3.42. The IR showed hydroxyl absorption at 3320 cm^{-1}. NMR: triplets at δ 2.2 (J=2.2), δ 3.4 (J=5.5), δ 4.3 (J=4.5), and a multiplet at δ 3.9. The shift value for the triplet with J=5.5 varied with concentration. The most intense peak in mass spec was at m/e 180 (224-CH_2CH_2O). The yield was 14.8g (23%). The pot residue was dissolved in 95% ethanol, treated with decolorizing charcoal, filtered, and recrystallized by cautious addition of water to the heated solution to yield 1,2-bis(2,3,5,6-tetrafluoro-4-methylphenoxy)ethane (III), m.p. 76^0 (nc); Anal. Calcd. for $C_{16}H_{10}F_8O_2$: C, 49.76; H, 2.61; F, 39.35. Found: C, 48.80; H, 2.30; F, 37.34. No further attempt was made to purify the compound. NMR: triplets at δ 2.2 (J=2.2) and δ 4.5 (J=0.5). The most intense peak in the mass spec was at m/e 207 (386-$CH_3C_6F_4O$). Yield was 1.68g (3%).

5,7,8-Trifluoro-6-methyl-2,3-dihydro-1,4-benzodioxin (IV) (nc).

The compound was prepared according to a previously reported procedure [5]. Compound II (36.91g, 0.165 mole) was heated under reflux for 24 hours under a nitrogen atmosphere, with stirring, in 400 ml of dimethylformamide containing potassium carbonate (15g, 0.105 mole). The hot solution was poured into 200 ml of ice-water containing 10 ml of concentrated HCl. The solution was stirred until all of the ice had melted and then filtered. The solid was crystallized from ethanol-water and then sublimed at 100° and 0.1 torr, m.p. 108°, Anal. Calcd. for $C_9H_7F_3O_2$: C, 52.95; H, 3.46; F, 27.92. Found: C, 50.31; H, 2.83; F, 27.82. The product was taken on to the next step in the sequence without further purification. NMR: triplet (J=2.2) at δ 2.2 and a singlet at δ 4.3; m/e 204 (M^+). Yield was 4.34g (13%).

5,7,8-Trifluoro-6-bromomethyl-2,3-dihydro-1,4-benzodioxin (V) (nc).

Under an atmosphere of nitrogen, compound IV (3.67g, 0.018 mole) was dissolved in 20 ml of carbon tetrachloride, contained in a round-bottom flask fitted with a reflux condenser, addition funnel, and mounted above a 100-watt incandescent bulb. Several carborundum boiling chips were introduced and the solution was brought to reflux by heating with the light bulb. A solution of bromine (3.12g, 0.0195 mole) in 20 ml of carbon tetrachloride was then added dropwise at such a rate as to observe decolorization. Upon completion of addition, the mixture was refluxed for an additional hour. After cooling to ambient temperature, carbon tetrachloride was removed on the rotary evaporator. The resulting viscous oil was vacuum distilled at 0.1 torr through a 5-cm, vacuum-jacketed vigreux column and the fraction distilling in the range of 134°-136° was collected. Anal. Calcd. for $C_9H_6BrF_3O_2$: C, 38.19; H, 2.14; Br, 28.23. Found: C, 37.48; H, 2.24; Br, 27.91. The product was used in the next step of the sequence without further purification. NMR: Singlet at δ 4.3 and a triplet (J=1.4) at δ 4.5. The most intense peak in the mass spec was at m/e 203 (M^+-Br). Yield was 4.15g (81%).

Diethyl-dl-acetamido-(5,7,8-trifluoro-2,3-dihydro-1,4-benzodioxyl) malonate (VI) (nc).

Under an atmosphere of nitrogen, metallic sodium (0.30g, 0.0131g atom) reacted with 30 ml of absolute ethanol contained in a round-bottom flask fitted with a reflux condenser, addition funnel, and magnetic stirrer. Upon completion of dissolution of the sodium, solid diethylacetamidomalonate (2.292g, 0.0134 mole) was added and the mixture brought to reflux. A solution of V (3.80g, 0.0134 mole) in 9 ml of absolute ethanol was rapidly added through the funnel and the heterogeneous mixture was refluxed for two (2) hours. The solution was cooled and the ethanol removed on the rotary evaporator to yield a white solid, which was dissolved in a mixture of 27 ml of chloroform and 17 ml of water to yield a two-phase liquid. The chloroform layer was separated and the aqueous layer extracted four times with 10 ml portions of chloroform. The chloroform was removed from the combined organic extracts on a rotary evaporator at ambient temperature and aspirator pressure, to give a white solid, m.p. 201^0, which was recrystallized from ethanol-water to yield the product. Anal. Calcd. for $C_{18}H_{20}F_3NO_7$: C, 51.56; H, 4.81; F, 13.59; N, 3.34. Found: C, 51.86; H, 4.77; F, 13.36; N, 3.14. The IR exhibited two carbonyl absorptions at 1680 and 1730 cm^{-1}. The NMR showed a triplet (J=7.2) at δ 1.3, singlets at δ 2.01, δ 3.7, δ 4.4, δ 6.6, and a quartet (J=7.2) at δ 4.3. The most intense peaks in the mass spec were at m/e 360 and 174, with a weaker parent peak (M^+) at m/e 419. Yield was 4.01g (71%).

dl-2,3,6-Trifluoro-2,3-dihydro-1,4-benzodioxylalanine hydroiodide (VIII) (nc).

Compound VI (0.980g, 0.00234 mole) was refluxed under a nitrogen atmosphere with stirring in 6 ml of 47% HI for 100 hours. The resulting, clear solution was reduced to a gum on the rotary evaporator at 75^0 and aspirator pressure. The gum was triturated in ether to form a suspension of white solid which was transferred to a centrifuge tube and spun down. The ether was decanted. The

solid was repeatedly suspended in ether, spun down, and decanted until the decanted ether was colorless. The resulting product was dried over P_2O_5 at ambient temperature and 0.1 torr for several hours to yield product, decomposition temperature 78°-81°. The elemental analysis corresponded well for the monohydrate. Calcd. for $C_{11}H_{13}F_3INO_5$: C, 31.22; H, 3.10; F, 13.47; I, 29.99; N, 3.31. Found: C, 31.54; H, 2.76; F, 13.70; I, 30.00; N, 3.27. Iodine was liberated when the solid was dissolved in water and mixed with chlorine water and carbon tetrachloride. The $FeCl_3$ test for phenolic groups was negative. Yield was 0.436g (46%).

dl-2,3,6-Trifluoro-2,3-dihydro-1,4-benzodioxylalanine (VIII) (nc).

Compound VII was dissolved in the minimum amount of water and the pH was raised to approximately 6-7, as measured by pH indicating paper, with several drops of concentrated ammonium hydroxide solution. The purple solid that separated was filtered and recrystallized from 95% ethanol to yield a white solid, decomposition at 270°-280°. An aqueous solution gave a positive ninhydrin test, but a negative $FeCl_3$ test (for phenolic OH).

2,3,5,6-Tetrafluoro-4-methylanisole [8].

Pentafluorotoluene (264.8g, 1.454 mole) was refluxed with stirring under a nitrogen atmosphere for 136 hours in 1800 ml of methanol containing solid sodium methoxide (90.0g, 1.667 mole). The solution was cooled to ambient temperature and poured into 2000 ml of water. The two phase mixture was filtered and the pH was lowered to 6 with concentrated HCl. The bottom layer was separated and the upper aqueous layer was extracted twice with 500 ml portions of ether. The combined organic layers were washed once with a 50 ml portion of water and dried 30 minutes over anhydrous $MgSO_4$. The mixture was filtered and ether was removed on the rotary evaporator. The remaining liquid was distilled through a 5-cm, vacuum-jacketed vigreux column and the fraction that distilled in the range 171°-174° was collected, yield: 82%.

2,5,6-Trifluoro-3,4-dimethoxytoluene (IX) (nc).

2,3,5,6-Tetrafluoro-4-methylanisole (74.18g, 0.382 mole) was refluxed with stirring under a nitrogen atmosphere for 23 hours in 170 ml of purified diglyme containing solid sodium methoxide (24.00g, 0.444 mole). The reaction mixture was cooled and poured into 500 ml of water containing 5 ml of concentrated HCl. The lower layer, consisting of a yellow, organic emulsion containing the product, was drawn off and the aqueous phase extracted twice with 200 ml portions of ether. The combined organic layers were washed with a 200 ml portion of water and then with a 50 ml portion of water. The organic phase was dried for five minutes over 15g of anhydrous $MgSO_4$ and filtered. Ether was removed on the rotary evaporator. GLPC and NMR indicated that the remaining liquid was composed of a trace of starting material, diglyme, and predominantly a mixture of IX and 3,5,6-trifluoro-2,4-dimethoxytoluene (X). Compound IX was isolated from the mixture by preparative GLPC. The machine parameters are listed in Table I.

TABLE I

MACHINE PARAMETERS FOR GLPC SEPARATION OF IX and X

Instrument	Hewlett-Packard Prepmaster Jr. 776
Column	5 feet long by 4 inch diameter
Packing	20% Carbowax 20M on 30-60 chromsorb P
Nitrogen Flow	3.5 LPM Air
Column Temp.	192^0 (6.2)
Injector Temp.	261^0 (8.0)
Detector Temp.	255^0 (8.0)
Manifold Temp.	259^0 (7.5)
Attenuation	5×10^4
Trap Coolant	Ice-Water
Sample Size	15 ml
Splitter	Closed as much as possible

A test run with diglyme at a much lower flow rate indicated that the splitter diverted 25% of the sample to the detector. This, coupled with the poor trapping efficiency at higher flow rates, accounts for the poor yield observed after separation.

GLPC analysis of IX after separation indicated an isomeric purity greater than 95%, b.p. 204° (760 torr.), sp. gr. 1.280 (21°), n_D^{21} 1.459; nmr (CCl_4): δ 2.1 (t, CH_3, J 2.2 Hz), δ 3.86 (d, 3-MeO, J 0.8 Hz), δ 3.94 (d, 4-MeO, J 1.0 Hz). Anal. Calcd. for $C_9H_9F_3O_2$: C, 52.43; H, 4.40; F, 27.65. Found: C, 52.55; H, 4.42; F, 27.77. Mass spec: m/e 206. While the other isomer was not isolated, nmr analysis of the mixture of IX and X revealed the following bands characteristic of X, in addition to the aforementioned bands for IX: δ 1.88 (d, CH_3, J 1.6 Hz), δ 3.87 (d, 3-MeO, J 0.9 Hz), and δ 3.98 (t, 4-MeO, J 1.0 Hz). A substantial amount of starting material was also detected in the glpc analysis. The yield of 15.18g of IX corresponded to a conversion of about 19%.

2,5,6-Trifluoro-3,4-dimethoxybenzyl bromide (nc).

Under an atmosphere of nitrogen, compound IX (12.56g, 0.0609 mole) was dissolved in 110 ml of carbon tetrachloride. The solution was placed in a round-bottom flask fitted with a reflux condenser, addition funnel, and mounted over a 100-watt incandescent bulb. Several carborundum boiling chips were introduced and the solution brought to reflux by heating with the bulb. A solution of liquid bromine (10.30g, 0.0645 mole) in 110 ml of carbon tetrachloride was then added dropwise at such a rate as to observe decolorization. When addition was complete, the mixture was refluxed an additional hour. After cooling, the carbon tetrachloride was removed on the rotary evaporator. The resulting viscous oil was vacuum distilled at 0.1 torr through a short-bore still and the colorless liquid distilling in the range 86°-88° was collected, sp.gr. 1.598 at 26°, n_D^{25} 1.510. Anal. Calcd. for $C_9H_8BrF_3O_2$: C, 37.92; H, 2.83; Br, 28.03; F, 19.99. Found: C, 38.06; H, 2.74; Br, 27.91; F, 20.14. Yield was 16.27g (94%).

Diethyl dl-acetamido-(2,5,6-trifluoro-3,4-dimethoxy-benzyl) malonate (nc).

Under an atmosphere of nitrogen, metallic sodium (1.10g, 0.0479 g-atom) reacted with 105 ml of absolute ethanol contained in a round-bottom flask fitted with a reflux condenser, addition funnel, and magnetic stirrer. Upon complete dissolution of the sodium, diethylacetamidomalonate (10.25g, 0.0472 mole) was added and the mixture was brought to reflux. A solution of the aforementioned benzyl bromide (13.45g, 0.0472 mole) in 32 ml of absolute ethanol was added rapidly and the heterogeneous mixture refluxed for 2 hours. The solution was cooled and ethanol was removed on the rotary evaporator at 50^0 and aspirator pressure. The resulting white solid was dissolved in a mixture of 95 ml of chloroform and 60 ml of water. The lower organic layer was separated and the aqueous layer extracted twice with 40 ml portions of chloroform. The organic extracts were combined and the chloroform removed on the rotary evaporator. The solid which remained was recrystallized twice from ethanol-water and then dried for 20 hours over P_2O_5 at ambient temperature and 0.1 torr., to give white crystals, m.p. 109^0. Anal. Calcd. for $C_{18}H_{22}F_3NO_7$: C, 51.31; H, 5.26; F, 13.53; N, 3.32. Found: C, 51.42; H, 5.05; F, 13.36; N, 3.32. Yield was 15.14g (76%).

dl-2,5,6-Trifluorodopa Hydroiodide (nc).

Under an atmosphere of nitrogen, the acetamidomalonate (14.80g, 0.0351 mole) was refluxed with stirring in 47% HI (960 ml, excess) for 5 days. The solution was cooled and all volatile components were removed on the rotary evaporator at 70^0 and aspirator pressure. The resulting gum was slurried with ether until a yellow solid formed. After filtration, the material was recrystallized twice from a minimal amount of water to yield a slightly off-white product, which gave a positive $FeCl_3$ test for the phenolic functions and a positive ninhydrin test for the amino acid function. Anal. Calcd. for $C_9H_9F_3INO_4$: C, 28.52; H, 2.39; F, 15.04; I, 33.48; N, 3.69. Found: C, 28.03; H, 2.42; F, 14.74; I, 32.47; N, 3.35. Yield was 2.458g (18%).

An effort to isolate the free amino acid from this salt by careful neutralization of an aqueous solution with concentrated aqueous ammonia, was unsuccessful.

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