Mechanism of Autoxidation of 5,7-Dihydroxytryptamine: Effect of Fluorine Substitution at Positions 4 and/or 6[1)]

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Analogs of 5,7-dihydroxytryptamine (5,7-DHT), namely, 4-fluoro-, 6-fluoro-, and 4,6-difluoro-5,7-DHT's (30a—c) were synthesized starting from 4-fluorophenol (7a), 4-fluorobenzyl alcohol (12) and 2,4-difluorophenol (7b), respectively. Regiospecific hydroxylation and formylation *ortho* to fluoro groups, both *via* aryllithium intermediates, were made possible by the blocking effect of *tert*-butyldimethylsilyloxy functions and allowed the conversion of the starting materials to the key intermediates, namely, 3,5-bis(*tert*-butyldimethylsilyloxy)-2-fluoro-, 4-fluoro- and 2,4-difluorobenzaldehydes (11a, b and 19, respectively). The latter were converted in one step to the corresponding benzyloxybenzaldehydes, from which indole-2-carboxylates 22a—c were synthesized *via* azidostyrenes 21a—c, respectively. Decarbonylation of the indole-2-carboxaldehydes (24a—c) produced from 22a—c in two steps gave 2,3-unsubstituted indoles 25a—c, respectively. Introduction of the aminoethyl side chains on C-3 of 25a—c *via* the corresponding indole-3-acetonitriles, and subsequent debenzylation generated the hydroxytryptamines, which were isolated as their creatinine sulfate salts 30a—c, respectively. Cyclic voltammetric studies indicated that like 5,7-DHT, 30a—c undergo electrochemical oxidation in 1 M H_2SO_4 *via* the corresponding *p*-quinoneimine derivatives 31a—c by an electrochemical-chemical-electrochemical (ECE) process. The voltammetrically detectable products of the ECE process appear to be the corresponding 5-hydroxytryptamine-4,7-dione (6) derivatives 33a—c. The nature of the interaction of dissolved O_2 with 30a—c at pH 7.4 appears to be strikingly different from that of 5,7-DHT, which undergoes autoxidation at pH 7.4 *via* the 4-hydroperoxy derivative 4 to the quinone 6. Thus, contrary to expectation and as judged by ultraviolet-visible spectroscopy, 30a undergoes autoxidation *via* the *p*-quinoneimine 31a to give the quinone 6 with loss of fluorine ion while 30b gives an unidentified colorless product(s) and 30c does not react with oxygen at pH 7.4.

Keywords fluoro-5,7-dihydroxytryptamine; autoxidation; cyclic voltammetry; *ortho*-lithiation; *tert*-butyldimethylsilyl ether; silyl ether *O*-alkylation; hydroxyindole; decarbonylation, reductive cyclization

5,7-Dihydroxytryptamine (5,7-DHT, **1**, Chart 1) is a general pharmacological tool used to produce selective chemical denervation of 5-hydroxytryptamine (5-HT)-containing neurons.[3,4)] While the selectivity of 5,7-DHT is due to its high-affinity uptake by the 5-HT membrane pumps, its ability to induce neuronal degeneration is derived from an inherent chemical property, namely, its autoxidizability.[5)] 5,7-DHT, which exhibits pronounced phenol-keto tautomerism at pH 7.4, with **2** being the predominant keto tautomer, undergoes rapid autoxidation at the same pH (Chart 1). The initial product of autoxidation appears to be the hydroperoxide **4**, which breaks down in a time-dependent manner to produce ultimately the quinone **6**. This mechanism was proposed based on the comparison of the kinetics and the nature of the products of autoxidation of 5,7-DHT and its methyl-substituted analogs.[6)] Further investigations, all of which support the mechanism shown in Chart 1, have dealt with the isolation of the quinone **6**,[7)] the confirmation of the structure of **6** by an independent synthesis,[8)] and ^{18}O-labeling studies.[9)]

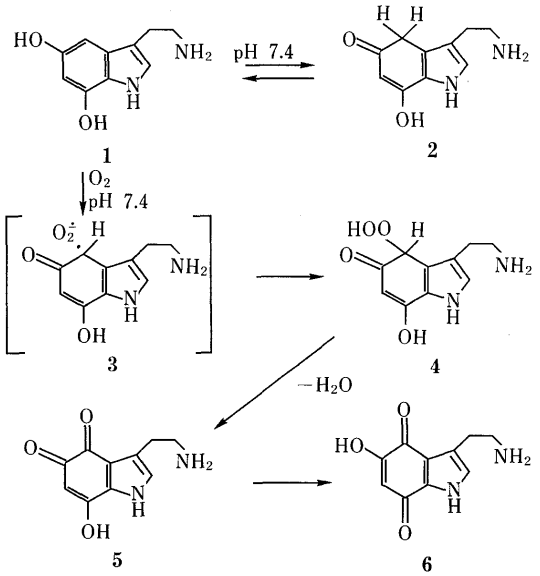
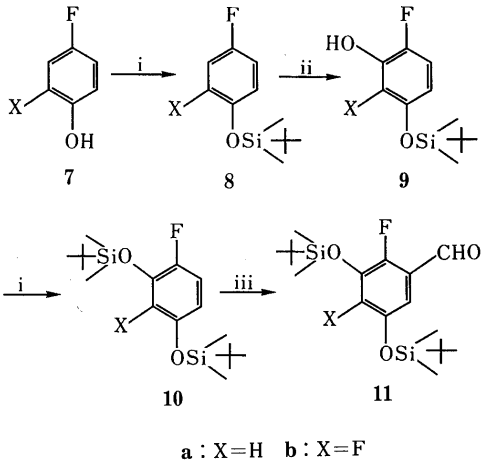


Chart 1

The methyl-substituted analogs of 5,7-DHT mentioned above were 4-methyl-, 6-methyl-, and 4,6-dimethyl-5,7-DHTs, which reacted with O_2 18-fold, 13-fold, and 178-fold faster, respectively, than 5,7-DHT.[6)] These increased rates of autoxidation of the methylated analogs rendered them unsuitable as probes for elucidating the mechanism of biological action of 5,7-DHT. Anticipating that the corresponding fluorine-substituted analogs would be sterically similar to 5,7-DHT, yet would undergo autoxidation at slower rates, we designed 4-fluoro-, 6-fluoro-, and 4,6-difluoro-5,7-DHTs (**30a—c**, respectively) as probes for elucidating the mechanism of biological action of 5,7-DHT. In this paper we present efficient syntheses of these fluorine-substituted 5,7-DHT's and describe the unanticipated effects of fluorine substitution on the mechanism of the autoxidation of 5,7-DHT.

Results and Discussion

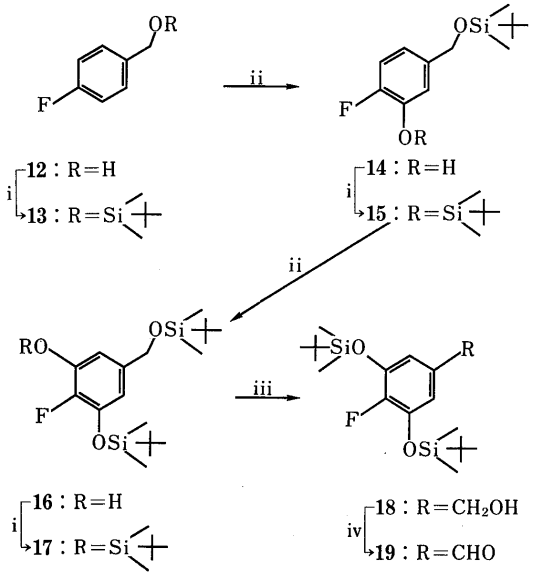
Synthetic Studies The general strategy for the synthesis of **30a—c** was first to construct the corresponding indole nuclei from appropriately substituted benzaldehydes followed by introduction of the aminoethyl side chains. The syntheses of silyloxybenzaldehydes **11a, b**, precursors to **30a** and **30c**, respectively, are shown in Chart 2. Fluorophenol **7** was first protected as its *tert*-butyldimethylsilyl (TBDMS)



a : X=H b : X=F

reagents: (i) *tert*-$BuMe_2SiCl$–imidazole–DMF/25°C; (ii) (a) *sec*-BuLi–THF/−78°C/1 h, (b) $B(OMe)_3$/−78°C, (c) HOAc–H_2O_2/25°C/24 h; (iii) (a) *sec*-BuLi–THF/−78°C, (b) Me_2NCHO

Chart 2

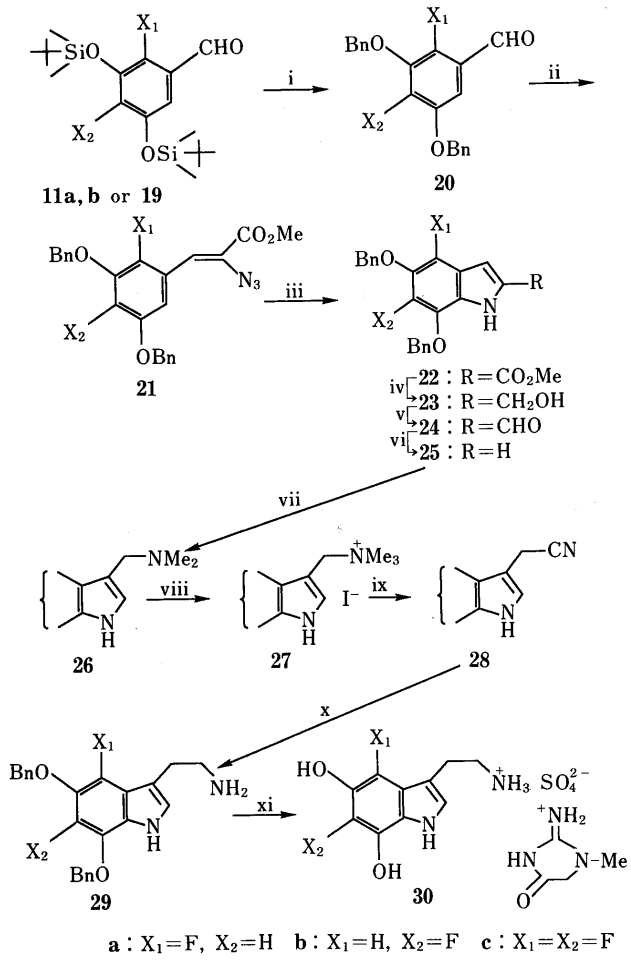


reagents: (i) *tert*-$BuMe_2SiCl$–imidazole–DMF/25°C; (ii) (a) *sec*-BuLi–THF/−78°C, (b) $B(OMe)_3$/−78°C, (c) HOAc–H_2O_2/25°C/24 h; (iii) Dowex50-X8H^+ form–MeOH/25°C/5.5 h; (iv) pyridinium chlorochromate–NaOAc–CH_2Cl_2/25°C/1.2 h

Chart 3

ether to give **8**. Hydroxylation of **8** *via* its aryllithium derivative, generated *in situ*, gave **9**. It was necessary to protect the phenolic hydroxyl group of **9** as its TBDMS ether before the formyl group could be introduced. The formyl group was introduced *via* the aryllithium derivative of **10** to give **11**.

For the synthesis of the aldehyde **19**, a precursor to **30b**, fluorobenzyl alcohol **12** served as the starting material, which was first protected as its TBDMS ether (Chart 3). Hydroxylation of **13** *via* its aryllithium derivative and protection of the resulting phenolic hydroxyl group with a TBDMS group gave **15**. The same procedure for hydroxylation and subsequent silylation of the hydroxyl group was applied to **15** to generate **17**. Selective hydrolysis of the alcoholic TBDMS ether function of **17** and subsequent oxidation of the resulting benzyl alcohol furnished the aldehyde **19**.



a : X_1=F, X_2=H b : X_1=H, X_2=F c : X_1=X_2=F

Bn=CH_2Ph reagents: (i) BnBr–KF–DMF; (ii) $N_3CH_2CO_2Me$–NaOMe–THF–MeOH; (iii) xylene/reflux; (iv) $LiAlH_4$–THF; (v) MnO_2–CH_2Cl_2; (vi) $(Ph_3P)_2Rh(CO)Cl$–$Ph_2P(CH_2)_3PPh_2$–mesitylene/reflux; (vii) CH_2O–Me_2NH–EtOH–HOAc; (viii) MeI–EtOH–EtOAc; (ix) KCN–DMF–H_2O; (x) $LiAlH_4$–Et_2O–PhH; (xi) (a) H_2SO_4–Pd/C–H_2–EtOH, (b) creatinine

Chart 4

The sequence of reactions that was used for the conversion of the aldehydes **11a, b** and **19** to the target tryptamines is shown in Chart 4. The silyloxybenzaldehydes were first converted to benzyloxybenzaldehydes **20** in near quantitative yields using a procedure developed in our laboratory[10] which involved treatment of the silyl ethers with $PhCH_2Br$ in the presence of KF in Me_2NCHO (DMF). Condensation of **20** with methyl azidoacetate gave the azidostyrene **21**, which, upon refluxing in xylene, afforded the indole-2-carboxylate **22**. Conversion of **22** to the corresponding 2,3-unsubstituted indole **25** was accomplished in three steps with minimal purification of the intermediates: reduction of the carboxylate to the alcohol **23**, oxidation of the alcohol to the aldehyde **24**, and, finally, decarbonylation of the aldehyde catalyzed by $(Ph_3P)_2$-(CO)RhCl in the presence of $Ph_2P(CH_2)_3PPh_2$. For the introduction of the aminoethyl side chain on C-3, the indole **25** was first converted to **26**. Quaternization of **26** and subsequent reaction with KCN gave the nitrile **28**. Reduction of **28** to the tryptamine **29** could be effected satisfactorily only in a very dilute solution of 1 : 1 Et_2O : PhH with a 15-fold excess of $LiAlH_4$.[6,11] Catalytic debenzyla-

tion of the hydrogen sulfate salts of **29a—c**, followed by treatment with creatinine furnished the target dihydroxytryptamines **30a—c**, respectively. The synthetic intermediates as well as the target compounds were characterized by obtaining satisfactory spectral (proton nuclear magnetic resonance (^{1}H-NMR), infrared (IR) and mass spectra (MS)) data and elemental analyses.

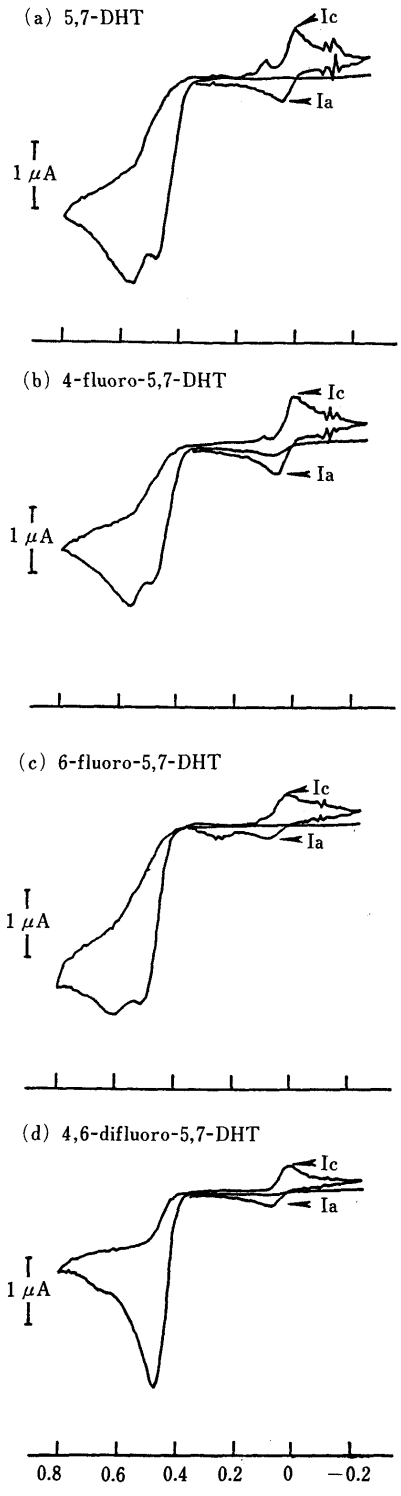


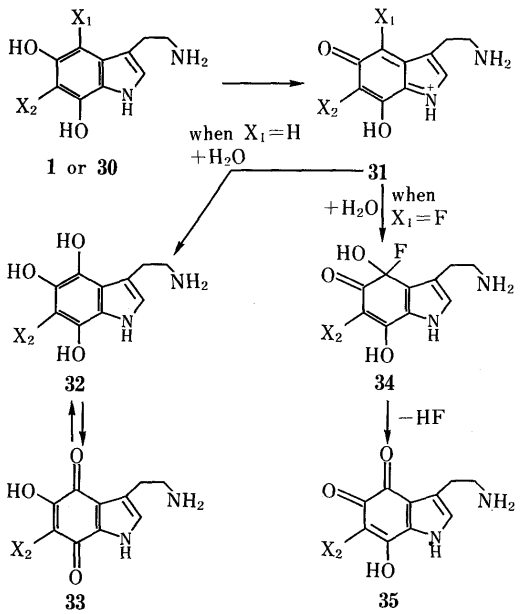
Fig. 1. Cyclic Voltammograms of 5,7-DHT and Its Fluorine-Substituted Derivatives at 0.5 mM in 1 M Sulfuric Acid at a Scan Rate of 100 mV/s at 25°C

The scans were initiated at −0.25 V *vs.* a SCE.

Cyclic Voltammetric Studies Previous cyclic voltammetric studies with 5,7-DHT have indicated that it undergoes electrochemical oxidation by a mechanism that is somewhat different from that of autoxidation (*vide supra*), although the ultimate product of autoxidation, compound **6**, is fortuitously also produced as one of the products of electrochemical oxidation at low pH.[6] The cyclic voltammetric studies with fluorine-substituted 5,7-DHTs were undertaken to determine if this disparity between the two modes of oxidation continues when fluorine substituents are introduced.

The cyclic voltammograms for 5,7-DHT and its fluorine-substituted analogs were generated using the standard three-electrode configuration with a C paste electrode in 1 M H_2SO_4 (Fig. 1). On the first anodic scan, a peak was observed in each case. The values of the peak potentials for 5,7-DHT and **30a—c** were (in mV *vs.* a saturated calomel electrode (SCE)) 563, 570, 667 and 473, respectively. In analogy to 5,7-DHT (and 5-HT and 6-methyl-5,7-DHT[6]), the first anodic peaks of Fig. 1 for **30a—c** correspond, in part, to the formation of the *p*-quinoneimines **31a—c**, respectively (Chart 5). It should be emphasized that at the present time we do not have any information on the extent to which the *p*-quinoneimines **31a—c** account for the respective first anodic peak. The number of electrons involved in each of these electrochemical oxidations also remains to be determined.

On the cathodic scan, at scan rates of up to 5 V/s, none of the test compounds displayed peaks corresponding to the reduction of **31a—d** to **30a—c** and **1**, respectively. The peak labeled Ic, with the peak potential of 5 mV, in Fig. 1a for 5,7-DHT has been ascribed[6] to a classic electrochemical-chemical-electrochemical (ECE) process (**1**→**31d**→**32d**→**33d**→**32d**) with the chemical step being Michael addition of water to **31d**. Confirmation of such a process has been provided by the isolation of **33d** (which is identical to



a : X_1=F, X_2=H **b** : X_1=H, X_2=F **c** : X_1=X_2=F
d : X_1=X_2=H
30d is the same as **1** **33a** and **33d** are same as **6**

Chart 5

structure **6**) from the electrochemical oxidation of 5,7-DHT at acidic pH.[7] Surprisingly, all the fluorine-substituted analogs also displayed similar cathodic peaks. The corresponding peak potentials (labeled Ic in Fig. 1b—d) for **30a—c**, were 5, 10 and 5 mV, respectively. In analogy to 5,7-DHT and 6-methyl-5,7-DHT,[6] the occurrence of an ECE process was expected from the 4-unsubstituted analog 6-fluoro-5,7-DHT (**30b**) with the steps being **30b**→**31b**→**32b**→**33b**→**32b**. The occurrence of the cathodic peaks labeled Ic for 4-fluoro-5,7-DHT (**30a**) and 4,6-difluoro-5,7-DHT (**30c**) is in sharp contrast to the absence of any such cathodic peak under identical conditions for 4-methyl-5,7-DHT and 4,6-dimethyl-5,7-DHT.[6] The similarity of the cyclic voltammograms in Figs. 1b and 1d to those in Figs. 1a and 1c clearly indicate that both **30a** and **30c** undergo ECE processes and that the products of such processes have structures analogous to **32b** and **32d**. Formation of **32a, c** from **30a, c**, respectively, requires the loss of fluorine from C-4 and the most likely mechanism, involving intermediacy of **34**, **35** and **33** and in that order, is indicated in Chart 5.

On the first anodic follow-up scan a peak labeled Ia is observed for each of **1** and **30a—c** with peak potentials of 50, 50, 75 and 65 mV (*vs.* SCE), respectively. Each of these peaks corresponds to a simple oxidation process with the oxidation step being the transformation of **32** to **33** (Chart 5).

Ultraviolet (UV)-Visible Spectroscopic Studies The UV-visible spectra were recorded in the presence or absence of dissolved O_2 at pH 7.4 (phosphate buffer) at regular intervals over a period of time. Selected examples of the absorption curves for 5,7-DHT and the three fluorine-substituted analogs are shown in Fig. 2. In the absence of O_2 or at zero time in the presence of O_2, all four compounds absorb only in the UV region and these absorption curves, in the presence and absence of O_2, for each compound are essentially indistinguishable.

When the autoxidation of 5,7-DHT at pH 7.4 is followed by UV-visible spectroscopy, the absorption band at 348 nm, which is due both to the predominant keto tautomer **2** and the hydroperoxide **4**,[6] is replaced by a flat band at 520 nm and a prominent band at 300 nm, both bands being due to the quinone **6** (Fig. 2a).

Surprisingly, the eventual product of autoxidation of 4-fluoro-5,7-DHT (**30a**) displays UV-visible absorption bands nearly identical to those of 5,7-DHT (Fig. 2b). Thus, the product, which has not yet been isolated, is almost certainly the quinone **6**. These results of autoxidation (like those of electrochemical oxidation, *vide supra*) with **30a** are in sharp contrast to those obtained with 4-methyl-5,7-DHT which reacted with O_2 18-fold faster than 5,7-DHT but formed no colored (quinoidal) product.[6] Based on the results with 5,7-DHT and 4-methyl-5,7-DHT, it was expected that 4-fluoro-5,7-DHT would undergo autoxidation to produce colorless products such as those resulting from the degradation of 4-fluoro analogs of the free radical-$O_2^{\cdot-}$ complex **3** and hydroperoxide **4**. Formation of the quinone **6** from the autoxidation of **30a** requires the loss of F from C-4. The mechanism by which F is lost and **6** is formed is probably identical to the mechanism by which the corresponding processes occur during electrochemical oxidation of **30a**, and is shown in Chart 5. Although the reason is not known, it is apparent that the presence of fluorine on C-4 of 5,7-DHT does not allow formation of the 4-fluoro-4-hydroperoxy analog of **4** but forces autoxidation to proceed *via* the *p*-quinoneimine **31a**. The analogous *p*-quinoneimine **31d** from 5,7-DHT is not formed to any significant extent during the autoxidation of

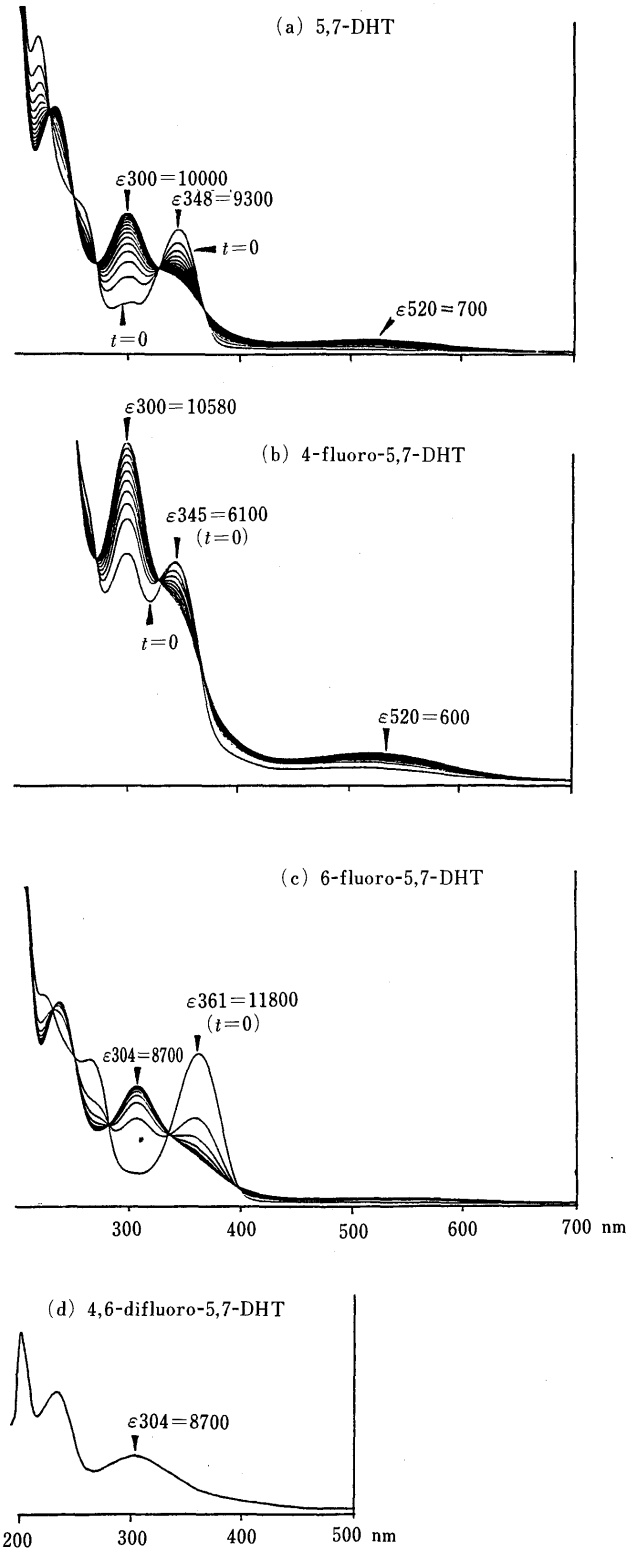
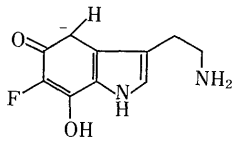


Fig. 2. UV-Visible Absorption Curves of 5,7-DHT and Its Fluorine-Substituted Derivatives at 25°C in 0.05 M Phosphate Buffer at pH 7.4

In Fig. 2a and 2b the repetitive scans were recorded at 45 min intervals while those in Fig. 2c were recorded every 10 min. In each case the curve labeled $t=0$ was recorded at time zero *i.e.* immediately after sample preparation.

5,7-DHT, as has been demonstrated by conducting autoxidation of 5,7-DHT in the presence of either ^{18}O or $H_2{}^{18}O$.

6-Fluoro-5,7-DHT (**30b**) displays a prominent absorption band at 361 nm at pH 7.4 in the absence of O_2 or in the presence of O_2 at zero time (Fig. 2c). In the presence of O_2 and with time this band disappears and is replaced with one at 304 nm. The product(s) responsible for the appearance of the band at 304 nm remains to be characterized. The expected product, the quinone **33b**, clearly was not formed. Based on the established mechanism of autoxidation of 5,7-DHT, its 4-unsubstituted derivatives are expected to undergo autoxidation to the corresponding derivatives of **6**. For example, 6-methyl-5,7-DHT gives a colored quinone which is thought to be 5-hydroxy-6-methyltryptamine-4,7-dione.[6] Lack of formation of a colored, quinoidal product(s) from **30b** indicates that neither the *p*-quinoneimine **31b** nor the 6-fluoro derivative of the hydroperoxide **4** is an intermediate in the autoxidation of **30b**. It is possible that **30b** reacts with O_2 *via* stabilized carbanions such as **36** or **37** which are derived from the 5-keto and 7-keto tautomers, respectively, of **30b**. These reactions can, in theory, lead to colorless 6-fluoro-6-hydroperoxy derivatives of **36** and **37** or to colorless dimeric and polymeric products *via* radical processes.



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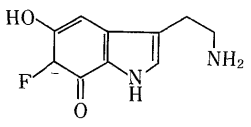

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The UV absorption bands of 4,6-difluoro-5,7-DHT (**30c**) remain virtually unchanged even after prolonged exposure to O_2 at pH 7.4 and these bands are identical to those observed in the absence of dissolved O_2 (Fig. 2d). Thus, in contrast to 4,6-dimethyl-5,7-DHT, which reacts with dissolved O_2 178 times faster than 5,7-DHT,[6] 4,6-difluoro-5,7-DHT does not appear to undergo any detectable autoxidation at pH 7.4. It is also surprising that 5,7-DHT reacts readily with O_2 when substituted individually at either position 4 or 6 with a fluoro group, but not when substituted jointly at both the 4 and 6 positions. Two likely reasons for the lack of reaction with O_2 may be as follows: (1) the presence of two fluoro groups in **30c** reduces the basicity of either phenolate derivable from **30c** to the extent that electron transfer from these phenolates to O_2 became highly unfavorable, and (2) the carbanions derived from the keto tautomers of **30c** may be unreactive toward O_2 because of lack of sufficient basicity and/or the presence of four contiguous and highly electronegative groups may prevent approach of highly electronegative O_2 near the carbanionic reaction centers.

Concluding Remarks Efficient methods for the synthesis of 4-fluoro-, 6-fluoro-, and 4,6-difluoro-5,7-DHT's were devised. All the fluorine-substituted analogs, like 5,7-DHT, underwent electrochemical oxidation by a variety of mechanisms, one of which was identified as an ECE process. The chemical mechanism of this ECE process for 6-fluoro-5,7-DHT was identical to that for 5,7-DHT and involved addition of H_2O, while those for 4-fluoro-, and 4,6-difluoro-5,7-DHTs involved addition of H_2O followed by loss of F from position 4. The nature of the interaction of dissolved O_2 with the fluorine-substituted analogs at pH 7.4 appears to be strikingly different from that of 5,7-DHT, which undergoes autoxidation at pH 7.4 *via* the corresponding 4-hydroperoxy derivative **4** to the quinone **6**. Thus, 4-fluoro-5,7-DHT appears to undergo autoxidation *via* the *p*-quinoneimine derivative **31a**, 6-fluoro-5,7-DHT reacts with O_2 rapidly at pH 7.4 apparently without involving position 4 and without producing the expected colored products, and 4,6-difluoro-5,7-DHT does not react with O_2 to any detectable extent. The fundamental reasons behind the observed effects of fluorine substitution on the nature of the interaction of 5,7-DHT with dissolved O_2 are not clear.

Experimental

Melting points (mp) were taken on a Thomas-Hoover melting point apparatus and are uncorrected. IR data were collected on a Perkin-Elmer 700 spectrophotometer. The ^{1}H-NMR spectra were recorded on Varian T-60, FT-80A and XL-300 spectrometers with Me_4Si as the internal standard. For compounds whose spectra were recorded in D_2O, chemical shifts were measured with *p*-dioxane (δ 3.56) as the internal standard. The MS were obtained on a Varian MAT CH-5 and exact masses were determined using a VG ZAB mass spectrometer. UV-visible spectra were recorded on a Shimadzu UV-260. Elemental analyses were performed at Desert Analytics, Inc., Tucson, AZ or the Department of Medicinal Chemistry, University of Kansas. Column chromatography was performed on Merck silica gel 60 (70—230 mesh) Anhydrous tetrahydrofuran (THF), Et_2O, and Me_2NCHO (DMF), all from Fisher Scientific Co., were stored for 24 h over 3Å molecular sieves prior to use.

1-(*tert*-Butyldimethylsilyloxy)-4-fluorobenzene (8a) *tert*-Butyldimethylsilyl chloride (16.58 g, 0.11 mol) and imidazole (7.5 g, 0.11 mol) were added to a stirred solution of **7a** (11.2 g, 0.10 mol) in dry DMF (50 ml) at 0 °C under an Ar atmosphere, and the mixture was stirred at 25 °C for 12 h, then diluted with H_2O (80 ml) and extracted with pertroleum ether (3 × 80 ml). The combined extracts were washed successively with H_2O (80 ml), 10% Na_2CO_3 (3 × 50 ml) and H_2O (2 × 80 ml), and dried over Na_2SO_4. Evaporation of the solvent gave chromatographically pure **8a** (7.4 g, 98%) which was used in the next step without further purification. An analytical sample was prepared by distillation: bp 71—72 °C (0.4 mmHg).^{1}H-NMR ($CDCl_3$) δ: 0.18 (s, 6H, Me), 1.00 (s, 9H, Me), 6.58—6.92 (m, 4H). MS *m/z*: 226 (M^+). Exact mass Calcd for $C_{12}H_{19}FOS$: 226.1188. Found: 226.1179.

1-(*tert*-Butyldimethylsilyloxy)-2,4-difluorobenzene (8b) Compound **8b** was obtained in 100% yield from **7b** by the same procedure as described for **7a** and was utilized in the next step without further purification: ^{1}H-NMR ($CDCl_3$) δ: 0.16 (s, 6H, Me), 1.00 (s, 9H, Me), 6.53—6.95 (m, 3H).

4-(*tert*-Butyldimethylsilyloxy)-1-fluoro-2-hydroxybenzene (9a) A 1.4 M solution of *sec*-BuLi in hexane (20 ml, 28.0 mmol) was added dropwise over 15 min to a stirred solution of **8a** (5.65 g, 25 mmol) in dry THF (25 ml) below −65 °C under an Ar atmosphere. The mixture was stirred for 0.5 h, then a solution of $(MeO)_3B$ (2.9 ml, 25.5 mmol) in dry THF (5 ml) was added over 0.5 h and stirring was continued for 0.5 h; the cooling bath was removed and the solution was allowed to warm to 0 °C. HOAc (2.3 ml, 37.5 mmol) was added all at once and then 30% H_2O_2 (2.8 ml, 27.5 mmol) was added dropwise over 0.5 h. The mixture was stirred at 25 °C for 12 h, diluted with H_2O (60 ml) and then extracted with Et_2O (2 × 100 ml). The combined Et_2O extracts were washed successively with H_2O (80 ml), 10% Fe (II) $(NH_4)_2(SO_4)_2 \cdot 7H_2O$ (2 × 50 ml) and H_2O (80 ml), then extracted with 10% NaOH (2 × 10 ml). The combined NaOH extracts were acidified with concentrated HCl to pH *ca.* 1 and the acidic solution was extracted with CH_2Cl_2 (2 × 80 ml). The combined CH_2Cl_2 extracts were washed with H_2O (50 ml) and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* followed by distillation of the residue gave 4.42 g (73%) of **9a**: bp 102—104 °C (0.23 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.17 (s, 6H, Me), 0.96 (s, 9H, Me), 4.95 (d, 1H, J = 4.5 Hz, OH), 6.15—6.55 (m, 2H, H-3, H-5), 6.90 (dd, 1H, J = 10.0, 10.5 Hz, H-6). IR (neat): 3375 cm^{-1}. MS *m/z*: 242 (M^+). Exact mass Calcd for $C_{12}H_{19}FO_2S$: 242.1137, Found: 242.1147.

1-(*tert*-Butyldimethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9b) Compound **9b** was obtained in 87% yield from **8b** by the same procedure as described for **9a**: bp 99—102 °C (0.1 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.16 (s, 3H, Me), 0.17 (s, 3H, Me), 0.98 (s, 9H, Me), 4.85—5.30 (br, 1H, OH), 6.25—6.90 (m, 2H). IR (neat) 3450 cm^{-1}. MS *m/z*: 260 (M^+). Exact mass Calcd for $C_{12}H_{18}F_2O_2Si$: 260.1043. Found: 260.1050.

2,4-Bis(*tert*-butyldimethylsilyloxy)-1-fluorobenzene (10a) Compound **10a** was obtained in 99% yield from **9a** by the same procedure as described for **8a** and was utilized in the next step without further purification. An analytical sample was prepared by distillation: bp 116—118°C (0.15 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.17 (s, 6H, Me), 0.18 (s, 6H, Me), 0.96 (s, 9H, Me), 0.99 (s, 9H, Me), 6.33—6.45 (m, 2H), 6.74—6.99 (m, 1H). MS *m/z*: 356 (M^+). Exact mass Calcd for $C_{18}H_{33}FO_2Si_2$: 356.2001. Found: 356.2016.

1,3-Bis(*tert*-butyldimethylsilyloxy)-2,4-difluorobenzene (10b) Compound **10b** was obtained in 98% yield from **9b** by the same procedure as described for **8a** and was utilized in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 0.18 (br s, 12H, Me), 1.00 (br s, 18H, Me), 6.18—6.68 (m, 2H).

3,5-Bis(*tert*-butyldimethylsilyloxy)-2-fluorobenzaldehyde (11a) A 1.4 M solution of *sec*-BuLi in hexane (79 ml, 0.11 mol) was added dropwise over 1 h to a stirred solution of **10a** (35.6 g, 0.10 mol) in dry THF (100 ml) at −78 °C under an Ar atmosphere. The mixture was stirred for 1 h, then a solution of DMF (8.5 ml, 0.11 mol) in dry THF (15 ml) was added over 0.5 h and stirring was continued for 1 h at −78 °C and then at 25 °C for 2 h. The mixture was diluted with H_2O (150 ml) and extracted with Et_2O (2 × 200 ml). The combined Et_2O extracts were washed with H_2O (3 × 150 ml) and dried over Na_2SO_4. Evaporation of the solvent gave essentially pure **11a** (37 g, 96%), which was used in the next step without further purification. The pure aldehyde **11a** was isolated by chromatography on a column of silica gel (CH_2Cl_2–hexane, 1 : 4): mp 46—48 °C, ^{1}H-NMR ($CDCl_3$) δ: 0.19 (s, 6H, Me), 0.21 (s, 3H, Me), 0.22 (s, 3H, Me), 0.97 (s, 9H, Me), 1.01 (s, 9H, Me), 6.58—6.90 (m, 2H), 10.27 (s, 1H, CHO). IR (Nujol): 1705 cm^{-1}. MS *m/z*: 384 (M^+). Exact mass Calcd for $C_{19}H_{33}FO_3Si_2$: 384.1951. Found: 384.1946.

3,5-Bis(*tert*-butyldimethylsilyloxy)-2,4-difluorobenzaldehyde (11b) Compound **11b** was obtained in 96% yield from **10b** by the same procedure as described for **11a** and was utilized in the next step without further purification. The pure aldehyde **11b** was isolated by chromatography on a column of silica gel (CH_2Cl_2–hexane, 1 : 1): mp 57—59 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.19 (s, 6H, Me), 0.20 (s, 6H, Me), 1.00 (s, 9H, Me). 1.03 (s, 9H, Me), 6.99 (dd, 1H, J=6.2 Hz, 8.7 Hz, H-6), 10.23 (s, 1H, CHO). IR (Nujol): 1700 cm^{-1}. MS *m/z*: 402 (M^+). Exact mass Calcd for $C_{19}H_{32}F_2O_3Si_2$: 402.1856. Found: 402.1843.

1-(*tert*-Butyldimethylsilyloxymethyl)-4-fluorobenzene (13) Compound **13** was obtained in 100% yield from **12** by the same procedure as described for **8a** and was utilized in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (s, 6H, Me), 0.93 (s, 9H, Me), 4.67 (s, 2H, CH_2), 6.73—7.37 (m, 4H).

1-(*tert*-Butyldimethylsilyloxymethyl)-4-fluoro-3-hydroxybenzene (14) Compound **14** was obtained in 87% yield from **13** by the same procedure as described for **9a**: bp 109—110 °C (0.2 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.17 (s, 6H, Me), 1.01 (s, 9H, Me), 4.72 (s, 2H, CH_2), 5.09 (br s, 1H, J=4.5 Hz, OH), 6.63—7.07 (m, 3H). IR (neat): 3440 cm^{-1}. MS *m/z*: 256 (M^+). Exact mass Calcd for $C_{13}H_{21}FO_2Si$: 256.1294. Found: 256.1284.

3-(*tert*-Butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)-4-fluoro-5-hydroxybenzene (16) The phenol **14** was silylated, as described for the synthesis of **8a**, to give **15** in 100% yield. The phenol **16** was obtained in 94% yield from **15** following the hydroxylation procedure described for **9a** with the following modification: the step involving extraction with 10% NaOH was omitted because of the poor solubility of **16** in NaOH solution: bp 153—156 °C (0.1 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.18 (s, 6H, Me), 0.19 (s, 6H, Me), 0.92 (s, 9H, Me), 0.98 (s, 9H, Me), 4.57 (s, 2H, CH_2), 5.01 (d, 1H, J=4.5 Hz, OH), 6.48—6.50 (m, 2H). IR (neat); 3450 cm^{-1}. MS *m/z*: 371 ($M^+ - 15$).

3,5-Bis(*tert*-butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)-4-fluorobenzene (17) Compound **17** was obtained in 100% yield from **16** by the same procedure as described for **8a** and was utilized in the next step without further purification. Pure **17** was obtained by distillation: bp 161—164 °C (0.2 mmHg). ^{1}H-NMR ($CDCl_3$): 0.14 (s, 6H, Me), 0.23 (s, 6H, Me), 0.25 (s, 6H, Me), 0.99 (s, 9H, Me), 1.06 (s, 18H, Me), 4.63 (s, 2H, CH_2), 6.56 (d, 2H, J=7.1 Hz, H-4, H-6). MS *m/z*: 485 ($M^+ - 15$).

3,5-Bis(*tert*-butyldimethylsilyloxy)-1-hydroxymethyl-4-fluorobenzene (18) A solution of **17** (25 g, 0.05 mol) in dry MeOH (150 ml) was stirred with Dowex 50W-X8 resin (H^+ form, 4.5 g) at 25 °C for 5 h. The mixture was filtered and the filtrate was evaporated to give crude **18** (19.3 g, 100%) which was used in the next step without further purification. An analytical sample was prepared by distillation: bp 158—161 °C(0.3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.18 (s, 6H, Me), 0.19 (s, 6H, Me), 0.99 (s, 18H, Me), 1.54 (s, 1H, OH), 4.49 (d, 2H, J=6.2 Hz, CH_2) 6.49 (d, 2H, J=7.1 Hz, H-4, H-6). IR (neat): 3375 cm^{-1}. MS *m/z*: 386 (M^+). Exact mass Calcd for $C_{19}H_{35}FO_3S$: 386.2107. Found: 386.2107.

3,5-Bis(*tert*-butyldimethylsilyloxy)-4-fluorobenzaldehyde (19) A mixture of pyridinium chlorochromate (21.5 g, 0.10 mol) and NaOAc (16.4 g, 0.20 mol) in dry CH_2Cl_2 (100 ml) was added all at once to a stirred solution of crude **18** (19.3 g, 0.05 mol) in dry CH_2Cl_2 (100 ml) at 0 °C under an Ar atmosphere. The mixture was stirred for 1.2 h at 25 °C and then filtered through a Celite pad. The filtrate was passed through a column of silica gel in CH_2Cl_2. Further elution with CH_2Cl_2 and subsequent evaporation of the solvent gave a pale yellow oil, which was chromatographed on a column of silica gel using CH_2Cl_2–hexane (1 : 1) as the eluent to give 14.0 g (73%) of **19**: ^{1}H-NMR ($CDCl_3$) δ: 0.21 (s, 6H, Me), 0.22 (s, 6H, Me), 1.01 (s, 18H, Me), 7.05 (d, 2H, J=7.2 Hz, H-2, H-6), 9.79 (s, 1H, CHO). IR (neat); 1705 cm^{-1}. MS *m/z*: 384 (M^+). Exact mass Calcd for $C_{19}H_{33}FO_3Si_2$: 384.1951. Found: 384.1949.

Synthesis of Bis(benzyloxy)benzaldehydes 20a—c. General Procedure A mixture of **11a**, **b** or **19** (0.1 mol), dry KF (23.3 , 0.4 mol) and $PhCH_2Br$ (14.2 ml, 0.12 mol) in dry DMF (120 ml) was stirred under an Ar atmosphere at 25 °C for 3h. The mixture was diluted with H_2O (500 ml) and extracted with Et_2O (2 × 250 ml). The combined Et_2O extracts were washed with H_2O (2 × 200 ml) and dried over Na_2SO_4. The solvent was evaporated off *in vacuo* and the resulting solid was washed with hexane (3 × 20 ml), and dried under vacuum for 24 h at 25 °C to yield the corresponding product **20a—c**, which was used in the next step without further purification. Analytical samples were prepared by recrystallization.

The aldehyde **20a** was recrystallized from PhH–hexane to yield 31.2 g (93%); mp 77—78 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.02 (s, 2H, CH_2) 5.12 (s, 2H, CH_2), 6.82—6.95 (m, 2H), 7.38 (s, 10H, Ph), 10.36 (s, 1H, CHO). IR (Nujol): 1695 cm^{-1}. MS *m/z*: 336 (M^+). *Anal.* Calcd for $C_{21}H_{17}FO_3$. C, 74.99; H, 5.09. Found: C, 74.78; H, 4.95.

The aldehyde **20b** was recrystallized from PhH–hexane to yield 31.6 g (94%); mp 123—124.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.20 (s, 4H, CH_2), 7.20 (d, 2H, J=6.9 Hz, H-2, H-6), 7.36—7.41 (m, 10H, Ph), 9.79 (s, 1H, CHO). IR (Nujol): 1695 cm^{-1}. MS *m/z*: 336 (M^+). *Anal.* Calcd for $C_{21}H_{17}FO_3$: C, 74.99; H, 5.09. Found: C, 74.70; H, 4.97.

The aldehyde **20c** was recrystallized from cyclohexane–hexane to yield 33.9 g (96%). mp 58—59°C. ^{1}H-NMR ($CDCl_3$) δ: 5.11 (s, 2H, CH_2), 5.22 (s, 2H, CH_2), 7.09—7.27 (m, 1H, H-6), 7.39 (s, 10H, Ph), 10.23 (s, 1H, CHO). IR (Nujol): 1695 cm^{-1}. MS *m/z*: 354 (M^+). *Anal.* Calcd for $C_{21}H_{16}F_2O_3$: C, 71.18; H, 4.55. Found: C, 70.90; H, 4.55.

Synthesis of Indole-1-carboxylates 22a—c. General Procedure A solution of **20** (30 mmol) and methyl azidoacetate (10.4 ml, *ca.* 90 mmol) in dry THF (60 ml) was added to a stirred solution of sodium (2.07 g, 90 mg-atm) in dry MeOH (40 ml) at −10 °C over 1 h under an Ar atmosphere. The mixture was stirred for a further 3h at −10 °C, allowed to warm to 25°C, and the poured onto crushed ice (500 g). The mixture was kept at 0 °C for 1 h and the precipitated solid was collected by filtration. The solid was washed with H_2O and dried (over P_2O_5). The crude product **21a—c** was used in the next step without further purification.

Yield of azide **21a** was 5.72 g (44%). mp 103—106 °C. ^{1}H-NMR ($CDCl_3$) δ:3.91 (s, 3H, Me), 5.03 (2, 2H, CH_2), 5.09 (s, 2H, CH_2), 6.59—6.71 (m, 2H), 7.13 (s, 1H, vinyl), 7.38 (s, 10H). IR (Nujol): 1715, 2130 cm^{-1}.

Yield of azide **21b** was 9.61 g (74%). mp 111 °C (dec.), ^{1}H-NMR ($CDCl_3$) δ: 3.88 (s, 3H, Me), 5.16 (s, 4H, CH_2), 6.70 (s, 1H, vinyl), 7.14 (d, 2H, J=7.1 Hz), 7.39 (br s, 10H). IR (Nujol): 1700, 2125 cm^{-1}.

Yield of azide **21c** was 7.05 g (52%). mp 72 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 3.88 (s, 3H, Me), 5.12 (s, 4H, CH_2), 6.92 (s, 1H, vinyl), 7.11—7.61 (m, 11H). IR (Nujol): 1710, 2160 cm^{-1}.

Crude **21** (20 mmol) in dry xylene (350 ml) was heated under reflux for 3 h. Evaporation of the solvent and recrystallization of the residue gave the pure **22**.

The carboxylate **22a** was recrystallized from PhH–hexane to yield 7.61 g (94%). mp 125—126 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.92 (s, 3H, Me), 5.07 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 6.55 (d, 1H, J=5.9 Hz, H-6), 7.23 (d, 1H, J=3.0 Hz, H-2), 7.28—7.40 (m, 10H, Ph), 9.00 (br s, 1H, NH). IR (Nujol): 1700, 3375 cm^{-1}. MS *m/z*: 405 (M^+). *Anal.* Calcd for $C_{24}H_{20}FNO_4$: C, 71.10; H, 4.97; N, 3.45. Found; C, 71.39; H, 4.98; N, 3.33.

The carboxylate **22b** was recrystallized from PhH–hexane to yield 7.60 g (94%). mp 134—136 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.88 (s, 3H, Me), 5.30 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 6.90 (d, 1H, J=7.0 Hz, H-4), 7.04 (d, 1H,

$J=2.2$ Hz, H-3), 7.39 (br s, 10H, Ph), 8.77 (br, 1H, NH). IR (Nujol): 1695, 3400 cm^{-1}. MS *m/z*: 405 (M^+). *Anal.* Calcd for $C_{24}H_{20}FNO_4$: C, 71.10; H, 4.97; N, 3.45. Found: C, 71.06; H, 4.96; N, 3.40.

The carboxylate **22c** was recrystallized from hexane to yield 8.29 g (98%). mp 74—74.5 °C. 1H-NMR ($CDCl_3$) δ: 3.88 (s, 3H, Me), 5.10 (s, 2H, CH_2), 5.16 (s, 2H, CH_2), 7.17 (d, 1H, $J=2.5$ Hz, H-3), 7.33 (br s, 10H, Ph), 8.72 (br, 1H, NH). IR (Nujol): 1700, 3350 cm^{-1}. MS *m/z*: 424 ($M^+ + 1$). *Anal.* Calcd for $C_{24}H_{19}F_2NO_4$: C, 68.21; H, 4.69; N, 3.21. Found: C, 68.08; H, 4.52; N, 3.31.

Synthesis of Indole-2-carboxaldehydes 24a—c. General Procedure A solution of **22** (10 mmol) in dry THF (30 ml) was added gradually to a stirred suspension of $LiAlH_4$ (570 mg, 15 mmol) in dry THF (15 ml) at 0 °C under an Ar atmosphere. The mixture was stirred for 1 h at 25°C and then excess $LiAlH_4$ was decomposed at 0 °C by the sequential addition of H_2O (0.8 ml), 15% NaOH (0.8 ml) and H_2O (2.0 ml). The mixture was filtered through a Celite pad and the filter pad was washed with CH_2Cl_2 (3 × 30 ml). The filtrate was dried over Na_2SO_4 and evaporated to yield the crude alcohol **23**. The alcohol **23** was dissolved in dry CH_2Cl_2 (60 ml), and activated MnO_2 (8.7 g, 100 mmol) was added. The mixture was stirred rapidly at 25°C for 1.5 h and then filtered. The filter cake was washed with CH_2Cl_2 (3 × 30 ml) and the combined filtrates were concentrated under reduced pressure. The residue was recrystallized from PhH–hexane to give the pure carboxaldehyde **24**.

The carboxaldehyde **24a** was obtained in 85% yield (3.2 g). mp 128—129 °C. 1H-NMR ($CDCl_3$) δ: 5.12 (s, 2H, CH_2), 5.29 (d, 2H, $J=1.4$ Hz, CH_2), 6.90 (d, 1H, $J=7.0$ Hz, H-6), 7.04 (d, 1H, $J=2.3$ Hz, H-3), 7.25—7.49 (m, 10H, Ph), 8.70 (br s, 1H, NH), 9.64 (s, 1H, CHO). IR (Nujol): 1680, 3375 cm^{-1}. MS *m/z*: 375 (M^+). *Anal.* Calcd for $C_{23}H_{18}FNO_3$: C, 73.59; H, 4.83; N, 3.73. Found; C, 73.87; H, 4.81; N, 3.67.

The carboxaldehyde **24b** was obtained in 85% yield (3.2 g). mp 113—114 °C. 1H-NMR ($CDCl_3$) δ: 5.05 (s, 2H, CH_2), 5.11 (s, 2H, CH_2), 6.57 (d, 1H, $J=5.9$ Hz, H-4), 7.21 (d, 1H, $J=2.3$ Hz, H-3), 7.36 (s, 10H, Ph), 9.02 (br s, 1H, NH), 9.74 (s, 1H, CHO). IR (Nujol): 1660, 3325 cm^{-1}. MS *m/z*: 375 (M^+). *Anal.* Calcd for $C_{23}H_{18}FNO_3$: C, 73.59; H, 4.83; N, 3.73. Found: C, 73.65; H, 4.79; N, 3.65.

The carboxaldehyde **24c** was obtained in 77% yield (3.03 g). mp 138—139 °C. 1H-NMR ($CDCl_3$) δ: 5.13 (s, 2H, CH_2), 5.14 (s, 2H, CH_2), 7.12—7.52 (m, 11H, H-3, Ph), 9.65 (s, 1H, CHO). IR (Nujol): 1690, 3360 cm^{-1}. MS *m/z* 393 (M^+). *Anal.* Calcd for $C_{23}H_{17}F_2NO_3$: C, 70.21; H, 4.35; N, 3.56. Found: C, 70.32; H, 4.38; N, 3.43.

Synthesis of Indoles 25a—c. General Procedure A mixture of $(Ph_3P)_2Rh(I)(CO)_2Cl$ (1.04 g, 1.5 mmol), $Ph_2P(CH_2)_3PPh_2$ (1.24 g, 3.0 mmol) and dry mesitylene (50 ml) was stirred at 100°C for 1 h under an Ar atmosphere, then a solution of **24** (5 mmol) in dry mesitylene (50 ml) was added, and the mixture was refluxed under an Ar atmosphere for 20 h. The cooled mixture was passed through a column of silica gel in CH_2Cl_2–hexane (2:1). Further elution with the same solvent mixture and subsequent evaporation of the solvent gave the corresponding **25a—c** as a solid, which was utilized in the next step without further purification. Analytical samples were prepared by recrystallization from PhH–hexane. The indole **25a** was obtained in 72% yield (1.25 g). mp 68—69 °C. 1H-NMR ($CDCl_3$) δ: 5.04 (s, 2H, CH_2), 5.09 (s, 2H, CH_2), 6.43 (d, 1H, $J=5.9$ Hz, H-6), 6.55 (t, 1H, $J=2.7$ Hz, H-3), 7.07 (t, 1H, $J=2.7$ Hz, H-2), 7.34 (s, 10H, Ph), 8.13 (br, 1H, NH). IR (Nujol): 3475 cm^{-1}. MS *m/z*: 347 (M^+). Anal. Calcd for $C_{22}H_{18}FNO_2$: C, 76.07; H, 5.22; N, 4.03. Found; C, 76.17; H, 5.25; N, 4.00.

The indole **25b** was obtained in 66% yield (1.15 g). mp 88—89 °C. 1H-NMR ($CDCl_3$) δ: 5.11 (s, 2H, CH_2), 5.26 (d, 2H, $J=1.1$ Hz, CH_2), 6.35 (t, 1H, $J=2.5$ Hz, H-3), 6.89 (d, 1H, $J=7.0$ Hz, H-4), 7.00 (t, 1H, $J=2.5$ Hz, H-2), 7.15—7.55 (m, 10H, Ph), 7.80 (br, 1H, NH). IR (Nujol): 3475 cm^{-1}. MS *m/z*: 347 (M^+). *Anal.* Calcd for $C_{22}H_{18}FNO_2$: C, 76.07; H, 5.22, N, 4.03. Found: C, 76.00; H, 5.12; N, 4.04.

The indole **25c** was obtained in 51% yield (0.93 g). mp 76—77 °C. 1H-NMR ($CDCl_3$) δ: 5.11 (s, 2H, CH_2), 5.14 (s, 2H, CH_2), 6.48 (t, 1H, $J=2.8$ Hz, H-3), 6.97 (t, 1H, $J=2.8$ Hz, H-2), 7.10—7.54 (m, 10H, Ph), 7.85 (br, 1H, NH). IR (Nujol): 3425 cm^{-1}. MS *m/z*: 365 (M^+). *Anal.* Calcd for $C_{22}H_{17}F_2NO_2$: C, 72.32; H, 4.69; N, 3.83. Found: C, 72.19; H, 4.66; N, 3.74.

Synthesis of Indole-3-acetonitriles 28a—c. General Procedure A solution of **25** (2 mmol) in HOAc–EtOH (1 : 1, 5 ml) was added to a stirred solution of 37% aqueous CH_2O (400 mg, 5 mmol) and 40% aqueous Me_2NH (600 mg, 5 mmol) in EtOAc–EtOH (1 : 1, 16 ml) at 0—5 °C. After being stirred at 0—5 °C for 2 h and then at 25°C for 20 h, the mixture was diluted with H_2O (100 ml) and made strongly basic (pH > 10) with 4 N NaOH under cooling in an ice bath. The mixture was extracted with CH_2Cl_2 (3 × 20 ml). The combined extracts were washed with saturated NaCl (30 ml) and dried over K_2CO_3. The solvent was evaporated off to give the corresponding gramine **26a—c** as a gum, which was used in the next step without further purification.

A solution of the crude gramine **26** (2 mmol) in EtOAc (20 ml) was added dropwise to a stirred solution of MeI (14.5 g, 100 mmol) in EtOH (20 ml) at 0—5 °C under an Ar atmosphere. The mixture was refrigerated for 24 h and then evaporated *in vacuo* at 30 °C to dryness to give the corresponding methiodide **27a—c** as a gum that was used in the next step without further purification.

A solution of KCN (520 mg, 8 mmol) in H_2O (6 ml) was added quickly to a stirred solution of the gramine methiodide **27** (2 mmol) in DMF (10 ml) at 75 °C. The mixture was then heated with stirring at 75 °C for 1.5 h, cooled to 25 °C, and diluted with H_2O (150 ml). The mixture was kept at 0°C for 1 h and the precipitated gum was collected by decantation. The residue was washed with H_2O (2 × 30 ml) and dissolved in CH_2Cl_2 (100 ml) and the CH_2Cl_2 solution was washed with saturated NaCl (50 ml), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel using CH_2Cl_2 as the eluent to give the corresponding product **28a—c**. Analytical samples were prepared by recrystallization from PhH.

The nitrile **28a** was obtained in 75% yield (579 mg). mp 98—99 °C. 1H-NMR ($CDCl_3$) δ: 3.92 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 5.08 (s, 2H, CH_2), 6.44 (d, 1H, $J=6.7$ Hz, H-6), 7.11 (br s, 1H, H-2), 7.34 (s, 10H, Ph), 8.30 (br, 1H, NH). IR (Nujol): 2275, 3400 cm^{-1}. MS *m/z*: 386 (M^+). *Anal.* Calcd for $C_{24}H_{19}FN_2O_2$: C, 74.60; H, 4.96; N, 7.25. Found: C, 74.96; H, 4.95; N, 7.33.

The nitrile **28b** was obtained in 81% yield (652 mg). mp 89—90 °C. 1H-NMR ($CDCl_3$) δ: 3.68 (d, 2H, $J=1.0$ Hz, CH_2), 5.12 (s, 2H, CH_2), 5.26 (d, 2H, $J=1.2$ Hz, CH_2), 6.80 (d, 1H, $J=6.2$ Hz, H-4), 7.01 (d, 1H, $J=2.4$ Hz, H-2), 7.17—7.51 (m, 10H, Ph), 7.85 (br, 1H, NH). IR (Nujol): 2400, 3425 cm^{-1}. MS *m/z*: 386 (M^+). *Anal.* Calcd for $C_{24}H_{19}FN_2O_2$: C, 74.60; H, 4.96; N, 7.25. Found: C, 74.45; H, 4.89; N, 7.27.

The nitrile **28c** was obtained in 78% yield (630 mg), mp 91—92°C. 1H-NMR ($CDCl_3$) δ: 3.84 (s, 2H, CH_2), 5.11 (s, 2H, CH_2), 5.14 (s, 2H, CH_2), 7.08 (br s, 1H, H-2), 7.31 (br s, 10H, Ph), 8.00 (br, 1H, NH). IR (Nujol): 2275, 3400 cm^{-1}. MS *m/z*: 404 (M^+). *Anal.* Calcd for $C_{24}H_{18}F_2N_2O_2$: C, 71.28; H, 4.49; N, 6.93. Found: C, 71.17; H, 4.62; N, 6.55.

Synthesis of Dihydroxytryptamines 30a—c. General Procedure A solution of **28** (1 mmol) in dry PhH (30 ml) was added gradually to a stirred suspension of $LiAlH_4$ (570 mg, 15 mmol) in dry Et_2O (30 ml) under an Ar atmosphere, and the mixture was then refluxed for 5 h. After the reaction mixture had been cooled in an ice bath, excess $LiAlH_4$ was decomposed by carefully adding H_2O. The organic solution was collected by filtration of the mixture and then washed with H_2O (2 × 50 ml), dried over K_2CO_3 and evaporated *in vacuo* to dryness to give the corresponding tryptamine **29a—c** in greater than 90% yield in each case. These tryptamines (pure by 1H-NMR) were utilized in the next step without further purification: **29a**: 1H-NMR ($CDCl_3$) δ: 1.29 (br s, 2H, NH_2), 2.94 (br s, 4H, CH_2CH_2), 5.13 (s, 2H, CH_2), 5.19 (s, 2H, CH_2), 6.42 (d, 1H, $J=5.9$ Hz, H-6), 6.80 (s, 1H, H-2), 7.34 (br s 10H, Ph), 8.25 (br, 1H, NH). **29b**: 1H-NMR ($CDCl_3$) δ: 1.29 (s, 2H, NH_2), 2.60—3.04 (m, 4H, CH_2CH_2), 5.11 (s, 2H, CH_2), 5.25 (d, 2H, $J=1.1$ Hz, CH_2), 6.83 (d, 1H, $J=6.6$ Hz, H-4), 6.86 (d, 1H, $J=2.7$ Hz, H-2), 7.16—7.56 (m, 10H, Ph), 7.80 (br, 1H, NH). **29c**: 1H-NMR ($CDCl_3$) δ: 1.43 (s, 2H, NH_2), 2.90 (br s, 4H, CH_2CH_2), 5.09 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 6.78 (s, 1H, H-2), 7.15—7.49 (m, 10H, Ph), 7.70 (br, 1H, NH).

A 1 M H_2SO_4 solution (0.98 ml, 0.98 mmol) and 10% Pd/C (200 mg) were added to a solution of **29** (1 mmol) in deoxygenated 95% EtOH (50 ml). The mixture was shaken in a Parr shaker at 40 psi of H_2 for 5h at 25 °C. [All the operations described below were conducted, as far as practicable, in an Ar atmosphere.] The mixture was then filtered under gravity, and a solution of creatinine (108.5 mg, 0.96 mmol) in deoxygenated H_2O (1 ml) was added to the filtrate. The resulting cloudy mixture was stored at −20°C overnight. The precipitate was collected by filtration and dried under vacuum.

5,7-Dihydroxy-4-fluorotryptamine Creatinine Sulfate (30a) Compound **30a** was obtained in 61% yield (279 mg); mp 228 °C (dec.). 1H-NMR (D_2O) δ: 2.74—3.18 (m, 7H, CH_2CH_2, NMe), 4.03 (s, 2H, CH_2 of creatinine), 6.25 (br, 1H, H-6), 6.94 (s, 1H, H-2); partial 1H-NMR (Me_2SO-d_6) δ: 6.24 (m, 1H, H-6), 6.95 (d, 1H, $J=2.2$ Hz, 2-H). MS (FAB) *m/z*: 211 (tryptammonium moiety). Exact mass Calcd for $C_{10}H_{12}FN_2O_2$ (tryptammonium moiety): 211.0883 Found: 211.0860.

5,7-Dihydroxy-6-fluorotryptamine Creatinine Sulfate (30b) Compound

30b was obtained in 71% yield (324 mg); mp 201 °C (dec.). ^{1}H-NMR (D_2O) δ: 2.71—3.15 (m, 7H, CH_2CH_2, NMe), 4.03 (s, 2H, CH_2 of creatinine). 6.42 (d, 1H, J=7.2 Hz, H-4), 6.91 (s, 1H, H-2); partial ^{1}H-NMR (Me_2SO-d_6)δ: 6.43 (d, 1H, J=7.4 Hz, H-4), 6.99 (d, 1H, J=1.9 Hz, H-2). MS (FAB) m/z: 211 (tryptammonium moiety). Exact mass Calcd for $C_{10}H_{12}FN_2O_2$ (tryptammonium moiety): 211.0883. Found: 211.0845.

4,6-Difluoro-5,7-dihydroxytryptamine Creatinine Sulfate (30c) Compound **30c** was obtained in 73% yield (347 mg); mp 191 °C (dec.). ^{1}H-NMR (D_2O) δ: 2.70—3.18 (m, 7H, CH_2CH_2, NMe), 4.06 (s, 2H, CH_2 of creatinine), 6.79 (s, 1H, H-2); partial ^{1}H-NMR (Me_2SO-d_6) δ: 7.01 (d, 1H, J=2.2 Hz, H-2). MS (FAB) m/z: 229 (tryptammonium moiety). Exact mass Calcd for $C_{10}H_{12}F_2N_2O_2$ (tryptammonium moiety): 229.0789. Found: 229.0776.

Cyclic Voltammetry An electrochemical cell with a carbon paste working electrode, a saturated calomel reference electrode (SCE), and a Pt foil auxiliary electrode was used.[12] The C paste was prepared by mixing ultracarbon (Ultra F purity) and hexadecane in a ratio of 2:1 by weight. Each voltammogram was generated by using a freshly prepared electrode surface with an area of approximately 1.5 mm^2. The solvent/electrolyte was 1 M H_2SO_4 which was freed of dissolved O_2 by purging with Ar for at least 1 h. The cyclic voltammograms were recorded while maintaining the test solutions quiet in an Ar atmosphere by using an IBM EC 225 voltammetric analyzer.

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References and Notes

1) Presented in Part: M. Kawase, A. K. Sinhababu and R. T. Borchardt, Abstracts of Papers, 195th National Meeting of the American Chemical Society and the 3rd Chemical Congress of North America, Toronto, June 1988; American Chemical Society, Washington, DC, 1988, ORGN 314.
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3) H. G. Baumgarten and L. Lachenmayer, *Z. Zell forsch.*, **135**, 399 (1972); H. G. Baumgarten, A. Bjorklund, L. Lachenmayer and A. Nobin, *Acta Physiol. Scand.*, Suppl., **391**, 1 (1973).
4) For reviews see: J. H. Jacoby and L. D. Lytle, *Ann. N. Y. Acad. Sci.*, **305**, 1 (1979); H, G. Baumgarten, S. Jenner, A. Bjorklund, H. P. Klemm and H. G. Schlossberger, "Biology of Serotonergic Transmission," ed. by N. N. Osborne, Wiley, New York, 1982, pp. 249—277; G. Jonsson, "Handbook of Chemical Neuroanatomy, Vol. 1: Methods in Chemical Neuroanatomy," ed. by A. Bjorklund and T. Hokfelt, Elsevier, Amsterdam, 1983, pp. 463—507; T. Schallert and R. E. Wilcox, "Neuromethods, Vol. 1. General Neurochemical Techniques," ed. by A. A. Boulton and G. B. Baker, Humana Press, Clifton, NJ, 1985, pp. 343—387; A. K. Sinhababu and R. T. Borchardt, *Neurochem. Internatl.*, **12**, 273 (1988).
5) H. G. Baumgarten, A. Bjorklund, A. Nobim, E. Rosengren and H. G. Schlossberger, *Acta Physiol. Scand.*, Suppl., **429**, 1 (1975).
6) A. K. Sinhababu and R. T. Borchardt, *J. Am. Chem. Soc.*, **107**, 7618 (1985).
7) M. Z. Wrona, D. Lemordant, L. Lin, C. L. Blank and G. Dryhurst, *J. Med. Chem.*, **29**, 499 (1986).
8) A. K. Sinhababu and R. T. Borchardt, *J. Heterocycl. Chem.*, **25**, 1155 (1988).
9) A. K. Sinhababu and R. T. Borchardt, *J. Am. Chem. Soc.*, **111**, 2230 (1989).
10) A. K. Sinhababu, M. Kawase and R. T. Borchardt, *Tetrahedron Lett.*, **28**, 4139 (1987).
11) H. G. Schlossberger and H. Kuch, *Chem. Ber.*, **93**, 1318 (1960); *idem.*, *Justus Liebigs Ann. Chem.*, **662**, 132 (1963).
12) *a)* R. N. Adams, "Electrochemistry at Solid Electrodes," Marcel Dekker, New York, 1969; *b)* L. R. Faulkner in "Physical Methods in Modern Chemical Analysis," Vol. 3, ed. by T. Kuwana, Academic Press, New York, 1983, pp. 137—248.