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

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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. Regioselective hydroxylation and formylation ortho to fluoro groups, both via aryllithium intermediates, were made possible by the blocking effect of tert-butylidimethylsilyloxy functions and allowed the conversion of the starting materials to the key intermediates, namely, 3,5-bis(tert-butylidimethylsilyloxy)-2-fluoro-, 4-fluoro- and 2,4-difluorobenzaldehyde (11a, b and 19, respectively). The latter were converted in one step to the corresponding benzylxylbenzaldehydes, from which indole-2-carboxylates 22a–c were synthesized via azidostyrenes 21a–c, respectively. Decarboxylation 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 H₂SO₄ 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-hydroxytryptamin-4,7-dione (6) derivatives 33a–c. The nature of the interaction of dissolved O₂ 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-hydroxypropanol 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-butylidimethylsilyl ether; silyl ether O-alkylation; hydroxyindole; decarboxylation, 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.³⁴ 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 ¹⁸O-labeling studies.⁹

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 O₂ 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-butylidimethylsilyl (TBDMS)
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.

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 siloxybenzaldehydes were first converted to benzaldehydes 20 in near quantitative yields using a procedure developed in our laboratory which involved treatment of the silyl ethers with PhCH2Br in the presence of KF in Me2NCHO (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 carbonylate to the alcohol 23, oxidation of the alcohol to the aldehyde 24, and, finally, decarboxylation of the aldehyde catalyzed by (Ph3P)3RhCl in the presence of Ph2P(CH2)3PPh2. 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 Et3O:PhH with a 15-fold excess of LiAlH4.6,11 Catalytic debenzyla-
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.59 The cyclic voltammometric 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$_2$SO$_4$ (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-DHT59), 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 to a classic electrochemical-electrochemical-electrochemical (ECE) process (31 → 32 → 33 → 34) 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

![Diagram](attachment:diagram.png)

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.
structure 6) from the electrochemical oxidation of 5,7-DHT at acidic pH.9 Surprisingly, all the fluorine-substituted analogs also displayed similar cathodic peaks. The corresponding peak potentials (labeled 1c in Fig. 1b—d) for 30a—e, were 5, 10 and 5 mV, respectively. In analogy to 5,7-DHT and 6-methyl-5,7-DHT,90 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—32b. The occurrence of the cathodic peaks labeled 1c for 4-fluoro-5,7-DHT (30a) and 4,6-difluoro-5,7-DHT (30e) 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.90 The similarity of the cyclic voltammograms in Figs. 1b and 1d to those in Figs. 1a and 1c clearly indicate that both 30a and 30e undergo ECE processes and that the products of such processes have structures analogous to 32b and 32d. Formation of 32a, c from 30a, e, respectively, requires the loss of fluorine from C-4 and the most likely mechanism, involving intermediacy of 34, 35 and 33 in that order, is indicated in Chart 5.

On the first anodic follow-up scan a peak labeled 1a is observed for each of 1 and 30a—e with peak potentials of 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 autooxidation 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 4,90 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 autooxidation 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 autooxidation (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.90 Based on the results with 5,7-DHT and 4-fluoro-5,7-DHT, it was expected that 4-fluoro-5,7-DHT would undergo autooxidation to produce colorless products such as those resulting from the degradation of 4-fluoro analogs of the free radical-O_2 complex 3 and hydroperoxide 4. Formation of the quinone 6 from the autooxidation 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 autooxidation to proceed via the p-quinonemine 31a. The analogous p-quinonemine 31d from 5,7-DHT is not formed to any significant extent during the autooxidation of
5,7-DHT, as has been demonstrated by conducting autoxidation of 5,7-DHT in the presence of either 18O or H2 18O.

6-Fluoro-5,7-DHT (30b) displays a prominent absorption band at 361 nm at pH 7.4 in the absence of O2 or in the presence of O2 at zero time (Fig. 2c). In the presence of O2 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. Lack of formation of a colored, quinoidal product(s) from 30b indicates that neither the p-quinonemine 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 O2 via stabilized carbocations 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.

The UV absorption bands of 4,6-difluoro-5,7-DHT (30c) remain virtually unchanged even after prolonged exposure to O2 at pH 7.4 and these bands are identical to those observed in the absence of dissolved O2 (Fig. 2d). Thus, in contrast to 4,6-dimethyl-5,7-DHT, which reacts with dissolved O2 at least fifteen times faster than 5,7-DHT, 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 O2 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 O2 may be as follows: (1) the presence of two fluoro groups in 30c reduces the basicity of either phenolate derivative from 30c to the extent that electron transfer from these phenolates to O2 became highly unfavorable, and (2) the carbanions derived from the keto tautomers of 30c may be unreactive toward O2 because of lack of sufficient basicity and/or the presence of four contiguous and highly electronnegative groups may prevent approach of highly electronegative O2 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 fluoro-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 H2O, while those for 4-fluoro- and 4,6-difluoro-5,7-DHTS involved addition of H2O followed by loss of F from position 4. The nature of the interaction of dissolved O2 with the fluoro-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-quinonemine derivative 31a, 6-fluoro-5,7-DHT reacts with O2 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 O2 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 O2 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 1H-NMR spectra were recorded on a Varian EM-360 instrument. The spectra were referenced to TMS and the chemical shifts were measured in ppm from TMS as the internal standard. For compounds whose spectra were recorded in CD3OD, chemical shifts were measured with p-dioxane (δ 3.50) 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-2450. 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), Et2O, and Me2NCHO (DMF), all from Fisher Scientific Co., were stored for 24 h over 3 Å molecular sieves prior to use.

1-(Butylmethylsilyl)oxy)-4-fluorobenzene (8a) tert-Butylmethylsilyl 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 H2O (80 ml) and extracted with petroleum ether (3 x 80 ml). The combined extracts were washed successively with H2O (80 ml), 0.05 Na2CO3 (3 x 50 ml) and H2O (2 x 50 ml), and dried over Na2SO4. 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).1H-NMR (CDCl3): δ 0.18 (s, 6H, Me), 1.00 (s, 9H, Me), 6.59—6.92 (m, 4H). MS: m/z 226 (M+). Exact mass Calcd for C13H18O: 226.1188. Found: 226.1179.

1-(Butylmethylsilyl)-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: 1H-NMR (CDCl3): δ 0.16 (s, 6H, Me), 1.00 (s, 9H, Me), 6.53—6.95 (m, 3H).

1-(Butylmethylsilyl)-1-fluoro-2-hydroxybenzene (9a) A 1.4M solution of sec-ButLi 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 Me2S (2.9 ml, 25.5 mmol) in dry THF (3 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% H2O2 (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 H2O (60 ml) and then extracted with Et2O (2 x 100 ml). The combined Et2O extracts were washed successively with H2O (80 ml), 0.1% FeCl3 (10 ml), (NH4)2SO4 (10 ml), H2O (2 x 50 ml) and H2O (80 ml), then extracted with 10% NaOH (2 x 10 ml). The combined NaOH extracts were acidified with concentrated HCl to pH ca. 1 and the acidic solution was extracted with CH2Cl2 (2 x 80 ml). The combined CH2Cl2 extracts were washed with H2O (50 ml) and dried over Na2SO4. Evaporation of the solvent in vacuo followed by distillation of the residue gave 4.42 (73%) of 9a: bp 102—104°C (0.23 mmHg).1H-NMR (CDCl3): 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, 6.5 Hz, H-6). IR (neat): 3375 cm−1. MS m/z: 242 (M+). Exact mass Calcd for C13H14FO3S: 242.1137. Found: 242.1147.
1-(tert-Butylmethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9a) Compound 9a was obtained in 100% yield from 8b by the same procedure as described for 8a and was used in the next step without further purification.

1-(tert-Butylmethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9b) Compound 9b was obtained in 98% yield from 9a by the same procedure as described for 8a and was utilized in the next step without further purification.

1-(tert-Butylmethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9c) Compound 9c 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.

1-(tert-Butylmethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9d) Compound 9d was obtained in 98% yield from 9a by the same procedure as described for 8a and was utilized in the next step without further purification.

1-(tert-Butylmethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9e) Compound 9e was obtained in 98% yield from 9a by the same procedure as described for 8a and was utilized in the next step without further purification.

1-(tert-Butylmethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9f) Compound 9f was obtained in 98% yield from 9a by the same procedure as described for 8a and was utilized in the next step without further purification.

1-(tert-Butylmethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9g) Compound 9g was obtained in 98% yield from 9a by the same procedure as described for 8a and was utilized in the next step without further purification.

1-(tert-Butylmethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9h) Compound 9h was obtained in 98% yield from 9a by the same procedure as described for 8a and was utilized in the next step without further purification.

1-(tert-Butylmethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9i) Compound 9i was obtained in 98% yield from 9a by the same procedure as described for 8a and was utilized in the next step without further purification.

1-(tert-Butylmethylsilyloxy)-2,4-difluoro-3-hydroxybenzene (9j) Compound 9j was obtained in 98% yield from 9a by the same procedure as described for 8a and was utilized in the next step without further purification.
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\[ J = 2.2 \, \text{Hz}, \, H(1) \text{-} 3.79, \, (\text{brs}, \, 10H, \, Ph), \, 8.77, \, (1H, \, NH), \, IR \,(Nujol): \, 1695, \, 3400\text{cm}^{-1}; \, MS \, m/z: \, 405 \,(M^+) \, \text{Anal. Caled for} \, C_{24}H_{38}F(NO_3)C_3: \, 71.10; \, H, \, 4.97; \, N, \, 3.45. \, \text{Found:} \, C, \, 71.06; \, H, \, 4.96; \, N, \, 3.40. \]

The carbazole 220 was recrystallized from hexane to yield 8.28 g (98%), mp 74–75°C. 1H-NMR (CDCl3): δ = 3.88 (s, 3H, Me), 5.10 (s, 2H, CH2), 7.17 (d, J = 2.2 Hz, H-3), 7.33 (s, 10H, Ph), 8.72 (br, 1H, NH). IR (Nujol): 1730 (Nυ(C=O) cm⁻¹), MS m/z: 424 (M+ 1). Anal. Caled for C_{24}H_{38}F(NO_3)C_3: 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 0–5°C under an Ar atmosphere. The mixture was then heated with stirring at 75°C for 1.5 h, cooled to 25°C, and diluted with H_2O (450 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 x 30 ml) and dissolved in CHCl_3 (100 ml) and the CHCl_3 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 25a–c. Analytical samples were prepared by recrystallization from PhH.

The nitrite 28a was obtained in 75% yield (579 mg), mp 98–99°C. 1H-NMR (CDCl3): δ = 3.92 (s, 2H, CH2), 5.03 (s, 2H, CH2), 5.08 (s, 2H, CH2), 6.44 (d, J = 6.7 Hz, H-6), 7.11 (brs, 1H, H-2), 7.34 (s, 10H, Ph), 7.59 (br, 1H, NH). IR (Nujol): 2275, 3400 cm⁻¹. MS m/z: 386 (M^+). Anal. Caled for C_{24}H_{38}F(NO_3)C_3: 74.60; H, 4.96; N, 7.25. Found: C, 74.76; H, 4.95; N, 7.33.

The nitrite 28b was obtained in 81% yield (652 mg), mp 89–90°C. 1H-NMR (CDCl3): δ = 3.68 (d, J = 1.0 Hz, CH2), 5.12 (s, 2H, CH2), 5.26 (d, J = 1.2 Hz, CH2), 6.80 (d, J = 6.2 Hz, H-4), 7.01 (d, J = 2.4 Hz, H-2), 7.17–7.31 (m, 10H, Ph), 7.85 (br, 1H, NH). IR (Nujol): 2400, 3425 cm⁻¹. MS m/z: 393 (M^+). Anal. Caled for C_{24}H_{38}F(NO_3)C_3: 74.60; H, 4.96, N, 7.25. Found: C, 74.45; H, 4.89; N, 7.27.

The nitrite 28c was obtained in 78% yield (630 mg), mp 91–92°C. 1H-NMR (CDCl3): δ = 3.84 (s, 2H, CH2), 5.11 (s, 2H, CH2), 7.08 (brs, 1H, H-2), 7.31 (brs, 10H, Ph), 8.00 (br, 1H, NH). IR (Nujol): 2275, 3400 cm⁻¹. MS m/z: 404 (M^+). Anal. Caled for C_{24}H_{38}F(NO_3)C_3: 71.28; H, 4.49; N, 6.93. Found: C, 71.17; H, 4.62; N, 6.55.

**Synthesis of Dihydroxytropolitamine 29a–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 EtOAc (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 x 50 ml), dried over K_2CO_3 and evaporated in vacuo to dryness to give the corresponding product 29a–c in greater than 90% yield in each case. These tropolitamines were characterized by 1H-NMR and 13C-NMR, and recrystallized in the next step without further purification. 29a: 1H-NMR (CDCl3): δ = 1.29 (2H, 2H), 2.88 (4H, CH_2CH_2), 5.13 (s, 2H, CH2), 5.19 (s, 2H, CH2), 6.42 (d, J = 5.9 Hz, H-6), 6.80 (s, 1H, H-2), 7.34 (brs, 10H, Ph), 8.25 (br, 1H, NH). 29b: 1H-NMR (CDCl3): δ = 1.29 (2H, 2H), 2.60–3.04 (m, 4H, CH_2CH_2), 5.11 (s, 2H, CH2), 5.25 (d, J = 1.1 Hz, H-6), 6.83 (s, 1H, H-2), 7.16–7.56 (m, 10H, Ph), 7.80 (br, 1H, NH). 29c: 1H-NMR (CDCl3): δ = 1.43 (2H, 2H), 2.95 (4H, CH_2CH_2), 5.09 (2H, 2H), 5.13 (s, 2H, CH2), 6.78 (s, 1H, H-2), 7.15–7.49 (m, 10H, Ph), 7.70 (br, 1H, NH).

A 1m H_2SO_4 solution (0.98 ml, 9.96 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 5 min at 5°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 then poured into ice-water and kept at 20°C overnight. The precipitate was collected by filtration and dried under vacuum.

5,7-Dihydroxy-4-fluorophenylalanine 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(CH_2)_2NMe), 4.03 (s, 2H, CH_2 of creatinine), 6.58 (br, 1H, H-6), 6.94 (s, 1H, H-2); partial 1H-NMR (MeSO_4-d_3): δ = 6.24 (s, 1H, H-6), 6.95 (d, 1H, J = 2.2 Hz, 2H). MS (FAB) m/z: 211 (tryptophanmoiety). Exact mass Caled for C_{17}H_{19}FNO_4 (tryptamino moiety): 211.0883. Found: 211.0860.

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


30h was obtained in 71% yield (324 mg); mp 201 °C (dec.). 1H-NMR (D2O) δ: 2.71—3.15 (m, 7H, CH2CH2, NMe), 4.03 (s, 2H, CH2 of creatinine). 6.42 (d, 1H, J = 7.2 Hz, H-4), 6.91 (s, 1H, H-2); partial 1H-NMR (Me2SO-d6) 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 (triptammonium moiety). Exact mass Calc'd for C10H12F2N2O2 (triptammonium moiety): 211.0883. Found: 211.0845.

4,6-Difluoro-5,7-dihydroxytriptamine Creatinine Sulfate (30c) Compound 30c was obtained in 73% yield (247 mg); mp 191 °C (dec.). 1H-NMR (D2O) δ: 2.70—3.18 (m, 7H, CH2CH2, NMe), 4.06 (s, 2H, CH2 of creatinine), 6.79 (s, 1H, H-2); partial 1H-NMR (Me2SO-d6) δ: 7.01 (d, 1H, J = 2.2 Hz, H-2). MS (FAB) m/z: 229 (triptammonium moiety). Exact mass Calc'd for C10H12F2N2O3 (triptammonium 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. The 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 mm². The solvent/electrolyte was 1 m H2SO4 which was freed of dissolved O2 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

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