Independent Synthesis of 5-Hydroxytryptamine-4,7-dione - The Neurocytotoxic Product of Autoxidation of 5,7-Dihydroxytryptamine

Achintya K. Sinhababu and Ronald T. Borchardt*

Departments of Medicinal Chemistry and Pharmaceutical Chemistry,
School of Pharmacy, University of Kansas,
Lawrence, KS 66045

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Synthesis of 5-hydroxytryptamine-4,7-dione hydrochloride (**20**) is described starting from 3-bromo-4,5-dimethoxybenzaldehyde (**6**). Compound **6** was converted to 2,3,5-tris(benzyloxy)benzaldehyde (**10**) in 4 steps. Nitromethylenation of **10** followed by nitration and subsequent reductive cyclization gave 4,5,7-tris(benzyloxy)indole (**13**). Introduction of the aminoethyl (hydrochloride) side chain on C-3 of **13**, *via* the corresponding indole-3-acetonitrile, and subsequent debenzylation generated *in situ*, 4,5,7-trihydroxytryptamine hydrochloride (**19**) which underwent rapid autoxidation in ethanol to give **20**. 4,5,7-Trihydroxyindole (**21**) and 3-[2-(ethoxycarbonylamino)ethyl]-4,5,7-trihydroxyindole (**24**), both generated *in situ*, were also found to undergo rapid autoxidation to the corresponding 5-hydroxyindole-4,7-diones.

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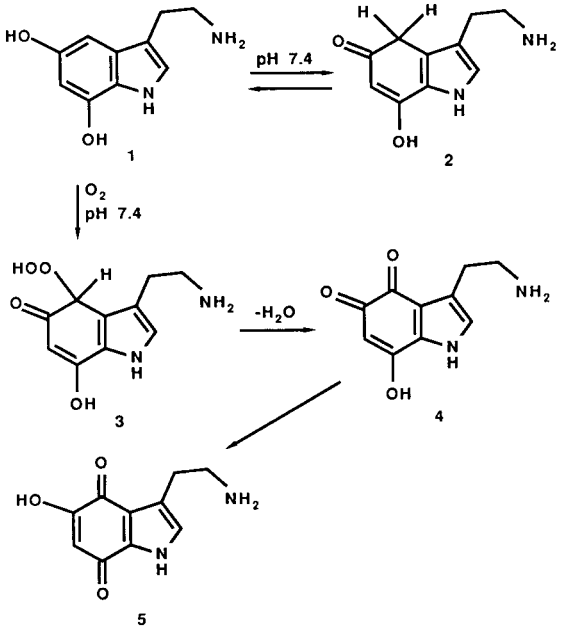
Introduction.

5,7-Dihydroxytryptamine (5,7-DHT, **1**) is a general pharmacological tool used to produce selective chemical denervation of 5-hydroxytryptamine neurons [1,2]. There is strong evidence that the neurodegeneration is brought about not by 5,7-DHT itself, but by the products of its autoxidation [3]. 5,7-DHT, which exhibits pronounced phenol-keto tautomerism at *p*H 7.4, with **2** (Scheme 1) being the predominant keto tautomer, undergoes rapid autoxidation at the same *p*H [4]. The initial product of autoxidation, which appears to be the unstable hydroperoxide **3**, breaks down in a time-dependent manner to eventually produce quinone **5** [4].

Scheme 1



The molecular mechanism by which 5,7-DHT induces neurodegeneration is not clear. However, it has been found that quinone **5** is a more potent neurocytotoxin than 5,7-DHT itself [5] and it may be the major 5,7-DHT-derived cytotoxin generated intraneuronally from 5,7-DHT [6]. It has been proposed that quinone **5**, when formed intraneuronally by the autoxidation of **1**, may undergo enzyme catalyzed redox cycling leading to the formation of cytotoxic reduced oxygen species such as superoxide, hydrogen peroxide and hydroxyl radical [6].

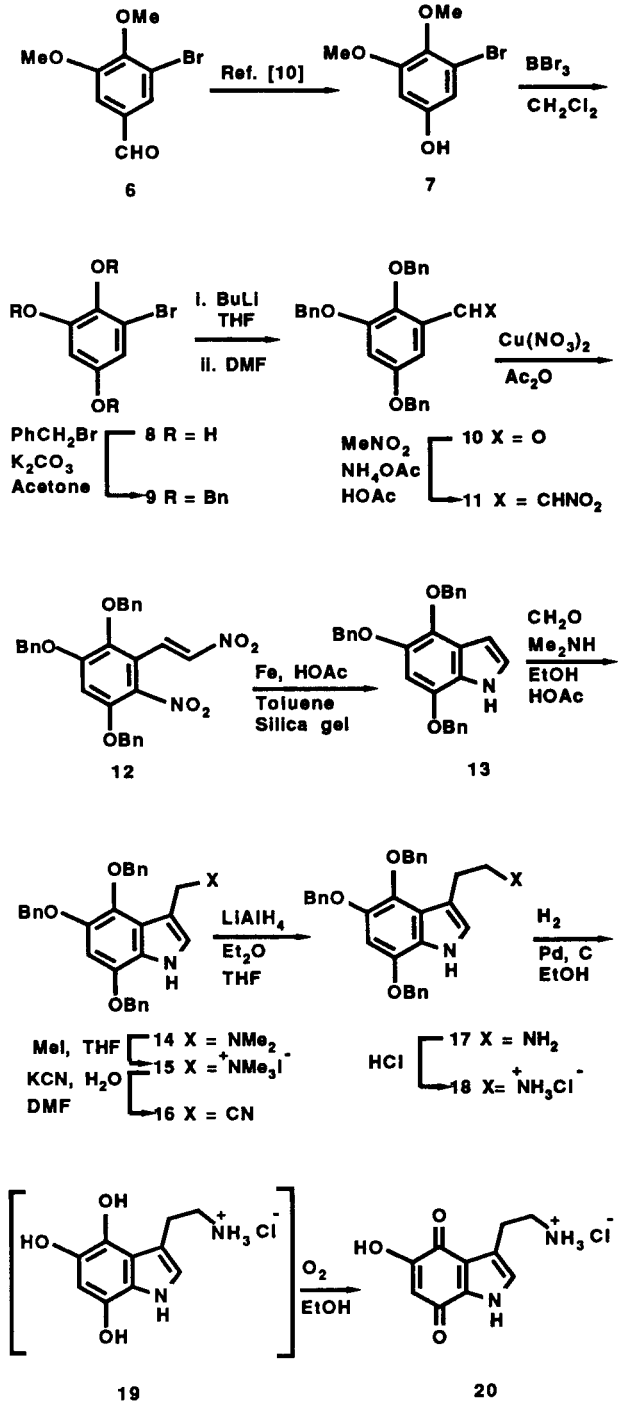
In this paper we describe the first independent and unambiguous synthesis of quinone **5** (isolated as its hydrochloride salt **20**). In addition to confirming the structure of **5**, this synthesis provides ready access to quantities of quinone **5** required for further biochemical and biological studies.

Results and Discussion.

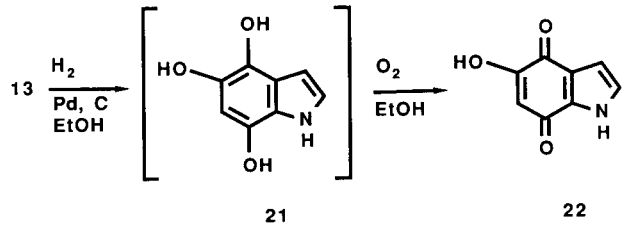
The propensity of dihydroxyindole derivatives such as 5,7-DHT and 5,6-dihydroxytryptamine to undergo rapid autoxidation [7] suggested that 4,5,7-trihydroxytryptamine (4,5,7-THT) should undergo even more facile autoxidation to give the target quinone **5**. Consequently, our penultimate target was a suitable salt of 4,5,7-THT. Although numerous methods are available for the synthesis of indoles and tryptamines [8], the specific arrangement of the functional groups and the presence of the 7-hydroxy function in the target tryptamine precluded the application of many of these methods. The synthetic route adopted here is similar to that applied successfully to the synthesis of highly substituted hydroxytryptamines described previously [4,9]. Thus, the strategy involved transformation of an appropriately substituted benzaldehyde to 2,3-unsubstituted indole *via* 2,β-dinitrostyrene followed by introduction of the aminoethyl side chain.

The synthesis started with commercially available **6** (Scheme 2), which was converted to phenol **7** [10] by the modified Baeyer-Villiger rearrangement [11] followed by the hydrolysis of the intermediate formate. *O*-Demethylation of **7** followed by *O*-benzylation gave tris(benzyloxy)-bromobenzene **9**. Bromine-lithium exchange of **9** followed by treatment of the *in situ* generated aryllithium with *N,N*-dimethylformamide (DMF) gave aldehyde **10**. Nitromethylenation of **10** and subsequent nitration gave a single product which was assigned the structure **12** based on its successful conversion to indole **13** and the pmr data. In the pmr spectra, the H-4 and H-6 signals of nitrotoluene **11** occurred at δ 6.55 and 6.82 ppm downfield from tetramethylsilane while the H-4 signal of dinitrostyrene **12** occurred at 6.67 ppm. Reductive cyclization [12] of dinitrostyrene **12** gave indole **13** in 92% yield.

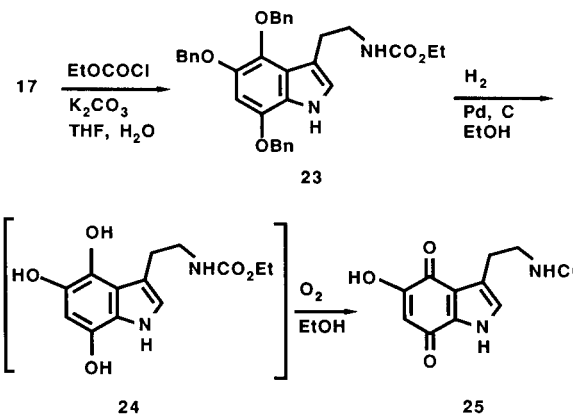
For the introduction of the aminoethyl side chain on C-3, indole **13** was first converted to gramine **14**. Quaternization of **14** and subsequent displacement of the ammonium moiety with cyanide gave nitrile **16** in 68% overall yields (based on indole **13**). Initial attempts to reduce nitrile **16** to tryptamine **17** with lithium aluminum hydride (LAH) in THF under reflux was not successful and the product was mostly a tar-like material. However, it was possible to reduce **16** to **17** in near quantitative yields using a 15-20 fold excess of LAH in 10:1 ether-THF at 0-5 °C. The tryptamine **17**, which turned dark when exposed to air, especially in solution, was isolated as its hydrochloride salt and then subjected to hydrogenolysis. The intermediate trihydroxytryptamine **19** underwent rapid autoxidation in ethanol when exposed to air (complete in less than 2 minutes) without requiring any added base to give target quinone **20** in 87% yield. The pmr and uv-visible spectra of **20** were essentially identical to those described previously. Further confirmation of the structure of **20** was obtained through elemental analyses and cmr spectral data.



Scheme 3



Scheme 4



To determine the scope of the present method for the synthesis of quinones containing the 5-hydroxyindole-4,7-dione moiety, we synthesized 5-hydroxyindole-4,7-dione (**22**, Scheme 3) and quinone **25** (Scheme 4), the ethoxycarbonyl derivative of **5**. Thus, the trihydroxyindoles **21** and **24**, generated *in situ*, underwent rapid autoxidation in ethanol to give quinones **22** and **25**, respectively in high yields. A general characteristic shared by the quinones **20**, **22** and **25** was that H-6 in each compound underwent rapid exchange with deuterium in deuterium oxide (as determined by pmr). Not surprisingly, the uv-visible spectra of the quinones displayed *p*H dependency. Thus, the absorption maximum of **20** at 522 nm (ε 1370) observed at *p*H 7.4 shifted to 463 nm (ε 850) at *p*H 2.0. Esssentially identical *p*H-dependent shifts in the higher wavelength absorption maxima were observed for quinones **22** and **25**.

EXPERIMENTAL

Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (pmr) spectra were recorded on a Varian FT-80A and carbon nuclear magnetic resonance (cmr) spectra were recorded on a Varian XL-300 and chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane (0.00 ppm). The assignment of ^{13}C chemical shifts were based on the comparison of the spectra obtained for quinone **20**, **22** and **25** with each other and with those described in the literature for hydroxyindole derivatives [13] and carbocyclic quinones [14]. Infrared spectra (ir) were recorded on a Perkin Elmer 1420. Mass spectra (ms) were recorded on a Nermag R10-10 and high-resolution mass spectra (hrms) were recorded on a VG ZAB. Ultraviolet-visible (UV-visible) spectra were recorded on a Shimadzu UV-260. Chromatography was performed on a 60-200 mesh silica gel. Anhydrous tetrahydrofuran (THF), ether and *N,N*-dimethylformamide (DMF), all from Fisher Scientific Co. were stored for 24 hours over 3A molecular sieves prior to use.

2,3,5-Tris(benzyloxy)bromobenzene (**9**).

To a stirred solution of phenol **7** (27.5 g, 118 mmoles), (prepared from commercially available benzaldehyde **6** following the procedure of Sanchez *et al.* [10]) in dichloromethane (100 ml) at -78° under an argon atmosphere was added a solution of boron tribromide (62.5 g, 250 mmoles) in dichloromethane (50 ml). The mixture was stirred at -78° for 2 hours and then at 25° for 2 hours. Methanol (65 ml) was added with cooling (ice bath) and the mixture was diluted with saturated sodium chloride (100 ml) and ethyl acetate (300 ml). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (4 x 60 ml). The combined organic layers were washed with saturated sodium chloride (4 x 50 ml) and dried (magnesium sulfate). Evaporation of the solvent *in vacuo* gave 23.5 g (97%) of **8** as an amorphous powder which was used in the next step without further purification, mp 137-139°; pmr (deuterioacetone): δ 6.40 (d, J = 2.7 Hz, 1H), 6.49 (d, J = 2.8 Hz, 1H), 7.25 (s, 1H, OH), 8.00 (s, 1H, OH), 8.37 (d, J = 1.8 Hz, 1H, OH).

Anal. Calcd. for $C_6H_5BrO_3$: C, 35.15; H, 2.46. Found: C, 35.17; H, 2.42.

Phenol **8** was benzylated by heating under reflux a mixture of **8** (22 g, 107 mmoles), benzyl bromide (60.4 g, 353 mmoles), powdered, anhydrous potassium carbonate (55 g, 400 mmoles), sodium iodide (2.4 g, 16 mmoles) and dry acetone (500 ml) for 24 hours with efficient stirring under an argon atmosphere. The mixture was filtered and the filtrate was concentrated *in vacuo* to a syrup. A solution of the syrup in dichloromethane (200 ml) was washed with water, dried (sodium sulfate) and evaporated *in vacuo*. The residue was recrystallized from cyclohexane-hexane to give 33 g (65%) of **9**, mp 112-113°; pmr (deuteriochloroform): δ 4.95 (s, 2H, OCH_2), 4.96 (s, 2H, OCH_2), 5.04 (s, 2H, OCH_2), 6.58 (d, J = 2.8 Hz, 1H, H-4), 6.77 (d, J = 2.8 Hz, 1H, H-6), 7.24-7.41 (m, 15H, Ph).

Anal. Calcd. for $C_{27}H_{25}BrO_3$: C, 68.22; H, 4.88. Found: C, 68.41; H, 4.91.

2,3,5-Tris(benzyloxy)benzaldehyde (**10**).

To a stirred solution of **9** (9.5 g, 20 mmoles) in anhydrous THF (60 ml) at -78° under an argon atmosphere was added 2.5 *M* *n*-butyllithium in hexane (16 ml, 40 mmoles). After the addition was over the mixture was stirred at -78° for 10 minutes and then a solution of DMF (7.3 g, 100 mmoles) in THF (10 ml) was added keeping the temperature at -78°. The mixture was stirred at -78° for a further 2 hours and then warmed to 25°. After acidification to *p*H 1 with 2*N* hydrochloric acid, the mixture was diluted with water and ether. The organic layer was collected and washed, in order, with water, sodium bicarbonate solution and saturated sodium chloride. After drying (sodium sulfate), the solvent was evaporated *in vacuo*. The residue was recrystallized from toluene-cyclohexane to give 5.5 g (65%) of **10** as colorless plates, mp 135°; pmr (deuteriochloroform): δ 5.01 (s, 2H, OCH_2), 5.11 (s, 4H, OCH_2), 6.92 (s, 2H, H-4, H-6), 7.30 (s, 5H, Ph), 7.38 (s, 10H, Ph), 10.18 (s, 1H, CHO).

Anal. Calcd. for $C_{28}H_{24}O_4$: C, 79.23; H, 5.70. Found: C, 79.10; H, 5.89.

2,3,5-Tris(benzyloxy)-β-nitrostyrene (**11**).

A mixture of aldehyde **10** (7 g, 16.5 mmoles), nitromethane (2 g, 33 mmoles) ammonium acetate (freshly dried under vacuum, 2.54 g, 33 mmoles) and acetic acid (50 ml) was refluxed protected from moisture for 1.25 hours. After cooling, the mixture was poured into water and the solid was collected by filtration. A solution of the solid in dichloromethane was washed with saturated sodium bicarbonate, dried (sodium sulfate) and then applied on a column of silica gel (20 g) in dichloromethane. Elution with dichloromethane and evaporation of solvent *in vacuo* gave a yellow residue which was recrystallized from toluene-cyclohexane to give 5.5 g (72%) of **11** as bright yellow plates, mp 155-156°; pmr (deuteriochloroform): δ 5.03 (s, 4H, OCH_2), 5.13 (s, 2H, OCH_2), 6.55 (d, J = 2.2 Hz, 1H, H-4), 6.82 (d, J = 2.2 Hz, 1H, H-6), 7.32 (s, 5H, Ph), 7.40 (s, 10H, Ph), 7.50 (d, J = 14 Hz, 1H, C*H*=$CHNO_2$), 8.05 (d, J = 14 Hz, 1H, CH=C*H*NO_2).

Anal. Calcd. for $C_{29}H_{25}NO_5$: C, 74.50; H, 5.39; N, 3.00. Found: C, 74.60; H, 5.33; N, 2.93.

2,3,5-Tris(benzyloxy)-6,β-dinitrostyrene (**12**).

To a stirred solution of **11** (6.8 g, 14.56 mmoles) in acetic anhydride (distilled from phosphorus pentoxide, 90 ml) protected from moisture was added cupric nitrate trihydrate (7.2 g, 30 mmoles) over a period of 20 minutes keeping the temperature at 65°. Heating at 65° was continued for a further 1.5 hours and the mixture was then poured into ice-water (1 ∝) with vigorous stirring. The precipitated solid was collected by filtration and dried over phosphorus pentoxide. Recrystallization from toluene-cyclohexane gave 6.6 g (89%) of **12** as a yellow solid, mp 115.5-116.5°; pmr (deuteriochloroform): δ 4.93 (s, 2H, OCH_2), 5.05 (s, 4H, OCH_2), 6.67 (s, 1H, H-4), 7.20-7.55 (m, 17H, Ph and CH=$CHNO_2$).

Anal. Calcd. for $C_{29}H_{24}N_2O_7$: C, 67.96; H, 4.72; N, 5.47. Found: C, 67.65; H, 4.59; N, 5.57.

4,5,7-Tris(benzyloxy)indole (**13**).

A mixture of **12** (1.03 g, 2 mmoles), reduced iron powder (N.F. IX, Electrolytic, Mallinckrodt, 2.57 g, 45 mmoles), silica gel (60-200 mesh, 7 g), acetic acid (20 ml) and toluene (40 ml) was refluxed for 1 hour under an argon atmosphere. The mixture was filtered and the filter cake was thoroughly washed with dichloromethane. The combined filtrates were washed, in order, with sodium metabisulfite solution (7 g in 50 ml water), water, saturated sodium chloride. After drying (sodium sulfate), the solvent was evaporated *in vacuo* to give a light brown residue which was chromatographed on a column of silica gel (15 g) with 9:1 dichloromethane-hexane as eluent. Evaporation of solvent *in vacuo* gave an off-white residue which was recrystallized from toluene-cyclohexane to give 804 mg (92%) of **13** as white solid, mp 87-89°; pmr (deuteriochloroform): δ 4.95 (s, 2H, OCH_2), 5.05 (s, 2H, OCH_2), 5.13 (s, 2H, OCH_2), 6.42-6.53 (m,

2H, H-3, H-6), 6.80 (t, J = 2.5 Hz, 1H, H-2), 7.12-7.46 (m, 15H, Ph), 8.10 (br, s, 1H, H-1).

Anal. Calcd. for $C_{29}H_{25}NO_3$: C, 79.98; H, 5.79; N, 3.22. Found: C, 79.92; H, 5.67; N, 3.09.

[4,5,7-Tris(benzyloxy)indole-3]acetonitrile (**16**).

To a stirred mixture of 37% aqueous formaldehyde (800 mg, 10 mmoles), 40% aqueous dimethylamine (1.2 g, 10 mmoles), ethanol (5 ml) and acetic acid (15 ml) at 0-5° was added a solution of indole **13** (1.43 g, 3.3 mmoles) in ethanol (15 ml). The stoppered reaction mixture was stirred at 0-5° for 2 hours and then at 25° for 15 hours. After dilution with water (100 ml), the mixture was made strongly basic (*p*H > 11) with 4*N* sodium hydroxide with cooling (ice-water). The mixture was extracted with ethyl acetate (3 x 30 ml) and the combined organic layers were washed with saturated sodium chloride. After drying over potassium carbonate, the solvent was evaporated *in vacuo* to give 1.61 g of a solid (or occasionally a gum), a portion of which was recrystallized from ethyl acetate-cyclohexane to give gramine **14** as white needles, mp 147-149°; pmr (deuteriochloroform): δ 2.16 (s, 6H, NMe_2), 3.65 (s, 2H, CH_2N), 5.01 (s, 2H, OCH_2), 5.05 (s, 2H, OCH_2), 5.13 (s, 2H, OCH_2), 6.46 (s, 1H, H-6), 6.87 (br s, 2H, H-2), 7.37 (s, 15H, Ph), 8.67 (br s, 1H, H-1).

Anal. Calcd. for $C_{32}H_{32}N_2O_3$: C, 78.02; H, 6.55; N, 5.69. Found: C, 77.94; H, 6.57; N, 5.64.

A solution of crude gramine **14** (1.61 g), in THF (20 ml) was added dropwise to a stirred solution of iodomethane (14.2 g, 100 mmoles) in THF (10 ml) at 0-5° protected from moisture. The stoppered reaction mixture was then stored at 0-5° for 16 hours. The volatiles were removed by evaporation *in vacuo* in a well ventilated hood to give methiodide **15** as a grey solid (mp 198° dec).

A solution of crude methiodide **15** in DMF (20 ml) was placed in a water bath at 75° and a solution of potassium cyanide (650 mg, 10 mmoles) in water (6 ml) was added dropwise with stirring. The solution was stirred at 75° for a further 1.5 hours and then diluted with water (100 ml). The mixture was cooled to 0-5° and the precipitated solid was collected by filtration. A solution of the solid in dichloromethane was washed with saturated sodium chloride and dried (sodium sulfate). Evaporation of dichloromethane gave a solid which was first chromatographed on a column of silica gel (30 g) with 95:5 dichloromethane-hexane as the eluent and then recrystallized from toluene-cyclohexane to give 1.06 g (68%, based on indole **13**) of nitrile **16** as white flakes, mp 129-130.5°; ir (nujol): ν 2230 (CN) cm^{-1}; pmr (deuteriochloroform): δ 3.72 (s, 2H, CH_2CN), 5.03 (s, 2H, OCH_2), 5.07 (s, 2H, OCH_2), 5.25 (s, 2H, OCH_2), 6.49 (s, 1H, H-6), 6.95 (d, J = 2.5 Hz, 1H, H-2), 7.32 (s, 15H, Ph), 8.13 (br s, 1H, H-1).

Anal. Calcd. for $C_{31}H_{26}N_2O_3$: C, 78.46; H, 5.52; N, 5.90. Found: C, 78.40; H, 5.52; N, 5.61.

4,5,7-Tris(benzyloxy)tryptamine Hydrochloride (**18**).

To a stirred mixture of lithium aluminum hydride (760 mg, 20 mmoles) in anhydrous ether (70 ml) as 0° under an argon atmosphere was added dropwise a solution of nitrile **16** (474 mg, 1 mmoles) in anhydrous THF (7 ml). The mixture was stirred at 0° for further 4.5 hours and then at 25° for 0.5 hour. Excess water (10-15 ml) was added carefully to destroy excess lithium aluminum hydride and to cause precipitation of the inorganics as a gel. The clear supernatant was collected and the residue was extracted with ether (4 x 30 ml). The combined organic layers were washed with saturated sodium chloride and dried (potassium carbonate). Evaporation of solvent gave 4,5,7-tris(benzyloxy)tryptamine (**17**) as a colorless syrup (which darkened when exposed to air and solidified upon refrigeration); pmr (deuteriochloroform): δ 1.15 (br s, 2H, NH_2), 2.65-2.95 (m, 4H, CH_2CH_2N), 5.04 (s, 2H, OCH_2), 5.07 (s, 2H, OCH_2), 5.11 (s, 2H, OCH_2), 6.48 (s, 1H, H-6), 6.81 (s, 1H, H-2), 7.19-7.49 (m, 15H, Ph), 8.25 (br s, 1H, H-1); hrms: m/e for $C_{31}H_{30}N_2O_3$, Calcd. 478.2255. Found: 478.2259.

To a solution of the crude tryptamine in absolute ethanol (20 ml) at 0-5° was added 6*N* hydrochloric acid (0.25 ml, 1.5 mmoles). The volatiles were removed by evaporation *in vacuo* to give a light grey solid which was recrystallized from ethyl acetate-cyclohexane to give 422 mg (82%) of tryptamine hydrochloride **18**, mp 103-104°; pmr (deuterioacetone): δ 3.24 (br s, 4H, CH_2CH_2N), 5.10 (s, 2H, OCH_2), 5.12 (s, 2H, OCH_2), 5.17 (s, 2H, OCH_2), 6.73 (s, 1H, H-6), 7.22-7.56 (m, 19H, Ph, H-2, $^+NH_3$), 8.54 (br s, 1H, H-1); (deuterioacetone + deuterium oxide): δ 3.03-3.40 (m, 4H, CH_2CH_2N), 5.15 (s, 4H, OCH_2), 5.24 (s, 2H, OCH_2), 6.78 (s, 1H, H-6), 7.23 (s, 1H, H-2), 7.30-7.58 (m, 15H, Ph); hrms: m/e for free base, $C_{31}H_{30}N_2O_3$, Calcd. 478.2255. Found: 478.2259.

Anal. Calcd. for $C_{31}H_{31}ClN_2O_3$: C, 72.29; H, 6.07; N, 5.44. Found: C, 72.22; H, 6.00; N, 5.25.

5-Hydroxytryptamine-4,7-dione Hydrochloride (**20**).

To a mixture of 5% palladium on charcoal (100 mg) and ethanol (10 ml) was added a solution of **18** (515 mg) in ethanol (25 ml). The mixture was shaken in a Parr shaker at 40 psi of hydrogen for 5 hours at 25°. The mixture was filtered under gravity and the orange filtrate was again filtered under gravity to remove the remaining traces of charcoal. To ensure complete autoxidation of intermediate **19**, the orange filtrate was stirred for 5 minutes exposed to air. Evaporation of ethanol *in vacuo* gave an orange solid, which was recrystallized from ethanol-ethyl acetate to give 210 mg (87%) of **20**, mp 245° dec; uv-visible: λ max (*p*H 7.4, phosphate buffer) 522 (ε 1370), 299 (ε 12,000), 231 (ε 12,000) nm; λ max (*p*H 2.0, hydrochloric acid-potassium chloride buffer) 463 (ε 850), 337 (ε 3600), 285 (ε 14,600), 226 (ε 14,400); lit [5] λ max (*p*H 2) 458, 332, 277, 220 nm; pmr (deuteriodimethyl sulfoxide): δ 2.99 (br s, 4H, CH_2CH_2N), 5.73 (s, 1H, H-6), 7.03 (d, J = 2.2 Hz, 1H, H-2), 8.04 (br s, 3H, NH^+_3), 11.15 (br s, 1H, OH), 12.47 (br s, 1H, H-1); deuteriodimethyl sulfoxide + deuterium oxide): δ 3.02 (unresolved t, 4H, CH_2CH_2N), 7.02 (s, 1H, H-2); cmr (deuteriodimethyl sulfoxide): δ 23.45 (CH_2CH_2N), 38.15 (CH_2N), 106.45 (C-6), 119.42 (C-3), 120.01 (C-2), 123.68 (C-3a), 132.26 (C-7a), 159.60 (C-5), 178.41 (C-7), 178.88 (C-4); hrms: m/e for free base, $C_{10}H_{10}N_2O_3$: Calcd. 206.0691. Found: 206.0697.

Anal. Calcd. for $C_{10}H_{11}ClN_2O_3$: C, 49.50; H, 4.56; N, 11.54. Found: C, 49.46; H, 4.44; N, 11.19.

5-Hydroxyindole-4,7-dione (**22**).

This compound was obtained from indole **13** (0.5 mmoles) by the debenzylation and subsequent air oxidation during work up as described above for the synthesis of **20** from **18**. The crude product (80 mg) was first chromatographed on a column of silica gel (4 g) with 4:1 ether-methanol as the eluent and then recrystallized from ethyl acetate-cyclohexane to give 71 mg (87%) of **22** as a purple solid, mp 195° dec; uv-visible: λ max (*p*H 7.4) 527 (ε 1800), 287 (ε 13,000), 212 (ε 13,000) nm; pmr (deuteriodimethyl sulfoxide): δ 5.68 (s, 1H, H-6), 6.51 (t, J = 2.1, 2.3 Hz, 1H, H-3), 7.11 (t, J = 2.7 Hz, 1H, H-2), 12.00 (br s, 1H, OH), 12.59 (br s, 1H, H-1); (deuteriodimethyl sulfoxide + deuterium oxide): δ 6.54 (d, J = 2.7 Hz, 1H, H-3), 7.11 (d, J = 2.7 Hz, 1H, H-2); cmr (deuteriodimethyl sulfoxide): δ 106.53 (C-6), 107.24 (C-3), 122.05 (C-2), 125.03 (C-3a), 132.33 (C-7a), 160.28 (C-5), 178.47 (C-7), 178.67 (C-4); hrms: m/e for $C_8H_5NO_3$, Calcd. 163.0269. Found: 163.0275.

3-[2-(Ethoxycarbonylamino)ethyl]-4,5,7-tris(benzyloxy)indole (**23**).

To a stirred solution of crude 4,5,7-tris(benzyloxy)tryptamine (**17**, 460 mg, 0.96 mmole; obtained by the reduction of 1 mmole of nitrile **16** as described above) in THF (5 ml) were added at 20-25° a solution of potassium carbonate (238 mg, 1 mmole) in water (3 ml) followed by ethoxycarbonyl chloride (217 mg, 2 mmoles). The mixture was stirred at 25° for an additional 1.5 hours. After evaporation of THF *in vacuo*, the mixture was diluted with water (10 ml) and dichloromethane (25 ml). The organic layer was collected, dried (sodium sulfate) and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel (12 g) with 90:10 dichloromethane-ether as the eluent. Recrystallization of the chromatographed product from ethyl acetate-cyclohexane gave 475 mg (90%) of **23** as white solid, mp 124°; pmr (deuteriochloroform): δ 1.18 (t, J = 7.1 Hz, 3H, CH_3), 2.88 (t, 2H, CH_2CH_2N), 3.37 (q, 2H, CH_2CH_2NH), 4.04 (q, J = 7.1 Hz, 2H, CH_2CH_3), 4.65 (br s, 1H, NHCO), 5.10 (s, 4H, OCH_2), 5.15 (s, 2H, OCH_2), 6.52 (s, 1H, H-6), 6.88 (d, J = 2.3 Hz, 1H, H-2), 7.25-7.47 (m, 15H, Ph), 8.15 (br s, 1H, H-1).

Anal. Calcd. for $C_{34}H_{34}N_2O_5$: C, 74.16; H, 6.22; N, 5.09. Found: C, 74.24; H, 6.09; N, 4.93.

3-[2-(Ethoxycarbonylamino)ethyl]-5-hydroxyindole-4,7-dione (**25**).

This compound was prepared from the tryptamine derivative **23** (0.5 mmoles) by the debenzylation and subsequent air oxidation as described above for the synthesis of **20** from **18**. The crude product was recrystallized from ethyl acetate-cyclohexane to give 112 mg (81%) of **25** as a reddish-brown solid, mp 180° dec; uv-visible: λ max (*p*H 7.4) 527 (ε 1100), 302 (ε 11,000), 235 (ε 12,000), 205 (ε 9500) nm; λ max (*p*H 2.0) 466, 339, 286, 226 nm; pmr (deuteriodimethyl sulfoxide): δ 1.12 (t, J = 7.1 Hz, 3H, CH_3), 2.77 (t, J = 6.8 Hz, 2H, CH_2CH_2NH), 3.06-3.40 (m, 2H, CH_2CH_2N), 3.95 (q, J = 7.1 Hz, 2H, CH_2CH_3), 5.64 (s, 1H, H-6), 6.90 (d, J = 1.9 Hz, 1H, H-2), 7.04 (br s, 1H, NHCO), 11.49 (br s, 1H, OH), 12.35 (br s, 1H, H-1); (deuteriodimethyl sulfoxide + deuterium oxide): δ 1.13 (t, J = 7.1 Hz, 3H, CH_3), 2.80 (t, 2H, CH_2CH_2N), 3.25 (t, 2H, CH_2CH_2N), 3.95 (q, J = 7.1 Hz, 2H, CH_2CH_3), 6.92 (s, 1H, H-2); cmr (deuteriodimethyl sulfoxide): δ 14.60 (CH_3), 25.73 (CH_2CH_2N), 38.35 (CH_2N), 59.37 (OCH_2), 106.31 (C-6), 119.43 (C-3), 122.65 (C-2), 123.15 (C-3a), 132.05 (C-7a), 156.11 ($NHCO_2$), 159.47 (C-5), 178.50 (C-7), 178.75 (C-4); hrms: m/e for $C_{13}H_{14}N_2O_5$, Calcd. 278.0902. Found: 278.0913.

Anal. Calcd. for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.28; H, 5.28; N, 9.66.

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