Improved Fischer Indole Reaction for the Preparation of *N,N*-Dimethyltryptamines: Synthesis of L-695,894, a Potent 5-HT_{1D} Receptor Agonist

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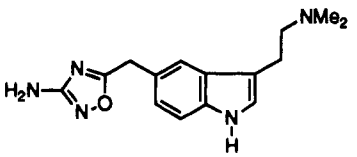
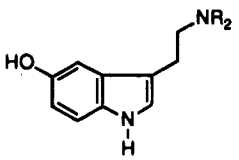
Among biologically active indoles, tryptamines show tremendous central nervous system activity. For example, the neurotransmitter serotonin (**2**) [5-hydroxytryptamine (5-HT)] is involved in the regulation of various physiological functions, such as appetite, sleep, body temperature, blood pressure, and sexual behavior;[1] its *N,N*-dimethyl analogue bufotenine (**3**) is a hallucinogen. The *N,N*-dimethyltryptamines also act as 5-HT_{1D} agonists and possess great potential for the treatment of migraine. Sumatriptan (4) is the first of this class of drugs to be approved for this use.[2] L-695,894 (**1**), which contains the 3-amino-1,2,4-oxadiazole heterocycle instead of a sulfonamide, is also a potent 5-HT_{1D} agonist that is a potential agent for migraine therapy.[3] We now wish to disclose a highly efficient method for the preparation of *N,N*-dimethyltryptamines with application to the synthesis of L-695,894 (**1**).

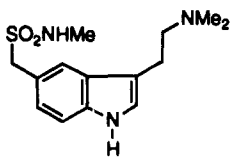


1, L-695,894



2, Serotonin: R = H

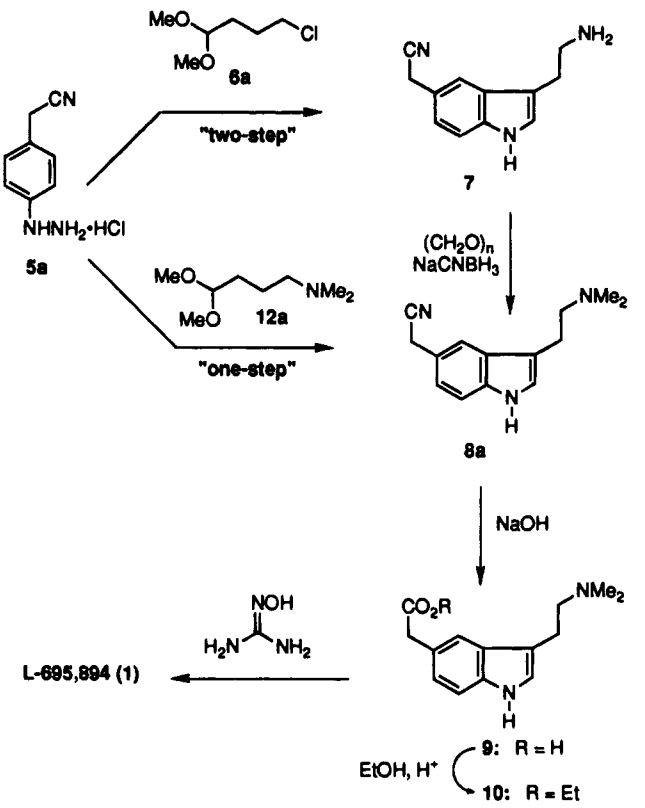
3, Bufotenine: R = Me

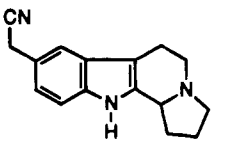


4, Sumatriptan

Traditional syntheses of *N,N*-dimethyltryptamines use a two-step procedure: a Fischer indole reaction[4] between a hydrazine[5] and the acetal **6**[6] to construct the heterocycle, followed by a reductive alkylation of the resultant primary amine. There are major shortcomings with this sequence for the synthesis of L-695,894 (Scheme 1): First, the side chain precursor 4-chlorobutane dimethyl acetal (**6**) necessitates displacement of the chloride by the hydrazine to afford the tryptamine. Although yields as high as 80% have been reported with this reaction,[7] we only achieved a 40% yield in the conversion of **5a** to **7**. Second, during indolization, the tryptamine product **7** underwent an alkylation/Pictet–Spengler reaction with unreacted **6** to form the β-carboline **11**.[8] Finally, the two-step procedure for incorporating the dimethylamino group further lowered the overall yield to 34%. Dimethylamino side chain precursor **12** overcame these drawbacks: No nitrogen transfer was required, the Pictet–Spengler side reaction was not a concern with the tertiary amine, and the reductive amination was obviated.

Scheme 1





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The requisite side chain **12**[9] was prepared via a three-step process: (1) Rosenmund reduction,[10] (2) acetalization of the resultant unisolated aldehyde **14**, and (3) dimethylamine displacement of the alkyl chloride (Scheme 2). 4-(*N,N*-Dimethylamino)butanal dimethyl acetal (**12a**)[9a] was obtained in 66% overall yield from **13**. Commercially available (*N,N*-dimethylamino)butanal diethyl acetal (**12b**)[9b] can be prepared in the same fashion.

(1) Castro, J. L.; Matassa, V. G. *Tetrahedron Lett.* **1993**, *22*, 4705 and references cited therein.
(2) Hopkins, S. J. *Drugs Today* **1992**, *28*, 155.
(3) Street, L. J.; Baker, R.; Castro, J. L.; Chambers, M. S.; Guiblin, A. R.; Hobbs, S. C.; Matassa, V. G.; Reeve, A. J.; Beer, M. S.; Middlemiss, D. N.; Noble, A. J.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J. *J. Med. Chem.* **1993**, *36*, 1529.
(4) Robinson, B. *The Fischer Indole Synthesis*; John Wiley and Sons: New York, 1982; pp 487–495.
(5) Winchester, M. J.; Popp, F. D. *J. Heterocycl. Chem.* **1975**, *12*, 547.
(6) Fleming, I.; Pearce, A. *J. Chem. Soc., Perkin Trans 1* **1981**, 251.
(7) Grandberg, I. I. *J. Org. Chem. USSR* **1984**, 2135.
(8) Matassa, V. Personal communication.
(9) (a) Takahara, M.; Yoshida, R. *Chem. Abstr.* **1969**, *25*, 107070z. (b) Kelevic, D. *Croat. Chem. Acta* **1964**, *36*, 103. **12b** was purchased from Orchimie, France.
(10) For a review, see: Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; pp 398–404.

0022-3263/94/1959-3738$04.50/0

Scheme 2

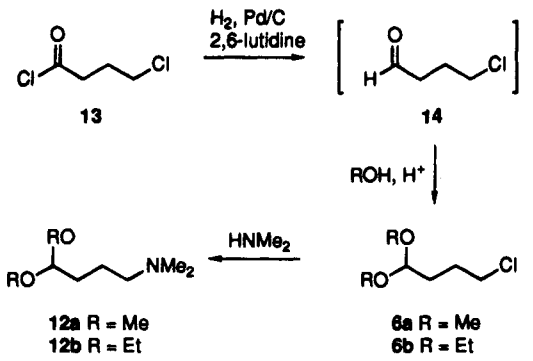
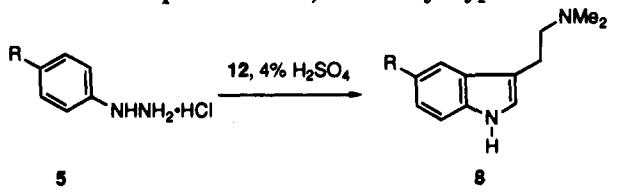


Table 1. Preparation of *N,N*-Dimethyltryptamines 8

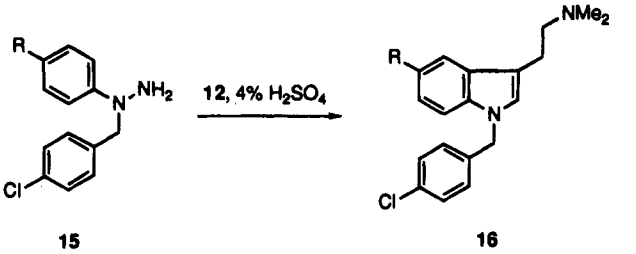


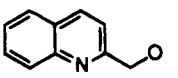
entry	*R*	yield (%)
b	H	86
c	Me	89
d	*i*-Pr	91
e	F	100
f	Cl	82
g	Br	93
h	OMe	85

Conditions suitable for effecting the indolization with the side chain **6a** failed to provide any reaction of **5a** with **12a** or **12b**. No hydrolysis of **12** to its aldehyde form was observed. Apparently, the dimethylamine interferes with activation of the acetal toward hydrazone formation (*vide infra*). The choice of acid that would provide protonation of the amine as well as aldehyde formation was critical to the success of the reaction. Direct condensation of 4-substituted phenylhydrazines with 4-(*N,N*-disubstituted amino)butanal acetals using 25% acetic acid at 80 °C has been reported to give tryptamines in variable yields (8–80%).[11] Using the same conditions, the reaction of hydrazine **5a**[4] and **12a** proceeded sluggishly with the eventual decomposition of the product. Use of the stronger acid H_2SO_4 as a 4% solution at reflux for 2 h proved successful in providing **8a** in 72–81% yield.[12] The generality and scope of the reaction were demonstrated: a variety of 4-substituted hydrazines **5b–h** were converted to the 5-substituted-*N,N*-dimethyltryptamines **8b–h** (Table 1). In addition, *N*1-substituted indoles **16** can be prepared in high yields from substituted hydrazines **15** (Table 2).

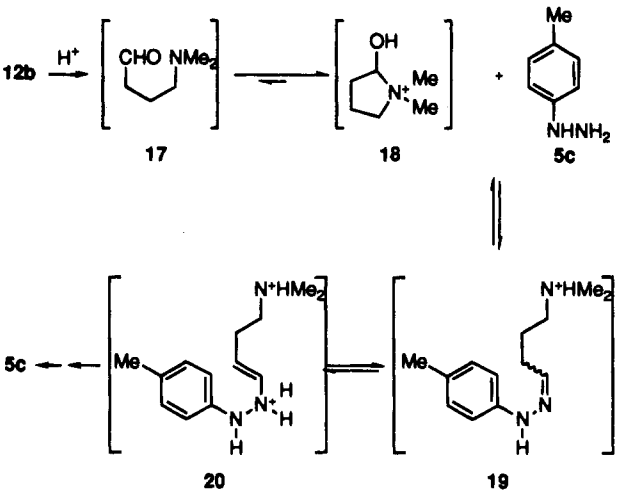
The Fischer indolization probably involves (1) hydrolysis of dimethylamino acetal **12**, (2) formation of hydrazone, (3) isomerization of hydrazone to ene–hydrazine, and (4)

Table 2. Preparation of N1-Substituted Tryptamines 16



entry	*R*	yield (%)
a	*i*-Pr	91
b		88

Scheme 3



[3,3] sigmatropic rearrangement followed by ring closure to give indole (Scheme 3).[17] Acetal **12** is stable in 8% acetic acid at room temperature, but it can be readily hydrolyzed to aldehyde **17** at 100 °C, which cyclizes to hemiaminal **18**. Hemiaminal **18** is formed quantitatively under acidic conditions such as 8% hydrochloric acid, 4% sulfuric acid, and 8% trifluoroacetic acid at room temperature. A mixture of **17** and **18** in a ratio of 5:95 (by ^{1}H NMR) was obtained. We then chose *p*-methylphenylhydrazine **5c** as a model compound to study the catalytic efficiency of acids in the Fischer indolization. Since the formation of hydrazone **19** occurs readily for all these acids, the successful indolization has to rely on step 3: the isomerization of hydrazone **19** to ene–hydrazine **20**. Indolization of hydrazine free base **5c** in 8% acetic acid proceeds slowly to give product **8c** but is still incomplete after 24 h. The intermediate hydrazone **19** is seen by ^{1}H NMR. The reaction in 8% hydrochloric acid leads to **8c** and other impurities such as aniline presumably due to the N–N bond cleavage. Finally, the reaction proceeds cleanly in 4% sulfuric acid or 8% TFA in 2 h to give indole **8c** in 89% and 80% yield, respectively. These results indicate that sulfuric acid is superior to other protic acids like hydrochloric acid and acetic acid because it effectively catalyzed the isomerization of hydrazone to ene–hydrazine. Although TFA works equally well for hydrazine **5c**, the generality of the TFA-catalyzed indolization is yet to be investigated.

(11) Desaty, D.; Keglevic, D. *Croat. Chem. Acta* **1964**, *36*, 103. Desaty, D.; Keglevic, D. *Croat. Chem. Acta* **1965**, *37*, 25.
(12) Similar conditions were also used in the synthesis of the *Aristotelia* alkaloid penduncularine, see: Klaver, W. H.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588.
(13) Pachter, I.; Zacharias, D. E.; Riberio, S. *J. Org. Chem.* **1959**, *24*, 1285.
(14) Benington, F.; Morin, R. D.; Clark, L. C. *J. Org. Chem.* **1960**, *25*, 1542.
(15) Pelchowicz, Z.; Kaluszyner, A.; Bentov, M. *J. Chem. Soc.* **1961**, 5418.
(16) Djura, P.; Stierle, B.; Sullivan, B.; Faulkner, D. J.; Arnold, E.; J. Clardy, J. *J. Org. Chem.* **1980**, *45*, 1435.
(17) For a leading reference on the Fischer indolization mechanism, see: Hughes, D. L.; Zhao, D. *J. Org. Chem.* **1993**, *58*, 228.

Application of the Fisher indole reaction to the synthesis of L-695,894 gave a highly efficient preparation of the key intermediate **8a** doubling the overall yield as compared to the original method (75% versus 34%). To complete the synthesis the cyano group was converted to the aminooxadiazole. First, hydrolysis of the cyano group to the corresponding sodium salt of acid **9** was carried out in refluxing 2 N NaOH in ethanol. After concentration of the reaction mixture, the crude product was azeotropically dried with ethanol and toluene. Concentrated sulfuric acid was added to the crude sodium carboxylate in ethanol, and this mixture was heated at reflux to afford the ethyl ester **10** in 83% overall yield from **8a**.

The oxadiazole ring of L-695,894 (**1**) was constructed with 1.5 equiv of dried hydroxyguanidine sulfate and freshly prepared sodium ethoxide. Under rigorous drying conditions, condensation of ester **10** with hydroxyguanidine leads to L-695,894 (**1**) in 75% yield and the acid **9** in 23–25% yield. Apparently, water in the ethanol or hydroxyguanidine leads to saponification of the ester, the resultant carboxylate being unreactive toward hydroxyguanidine. The acid **9**, however, could be extracted from the oxadiazole and recycled. On a large scale, L-695,894 (**1**) was obtained in 51% overall yield from nitrile **8a**.

In summary, we have developed an effective Fisher indole reaction for the direct conversion of 4-substituted hydrazines to the important class of compounds, the 5-substituted *N,N*-dimethyltryptamines, that does not require a separate reductive amination step. A high-yielding synthesis of the 5-HT_{1D} agonist L-695,894 (**1**) was possible with this methodology.

Experimental Section

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 250 MHz for ^1H and 62.5 MHz for ^{13}C. Flash column chromatography was performed on silica gel 60 (230–400 mesh, Merck).

4-(*N,N*-Dimethylamino)butanal dimethyl Acetal (12a).[9a] In a 7-L steel hydrogenation vessel was dissolved 4-chlorobutyryl chloride **13** (300 mL, 2.68 mol) in dry methyl acetate (3 L). 2,6-Lutidine (360 mL, 3.09 mol) and 10% Pd/C (44.1 g) were added sequentially to the mixture. This mixture was shaken under a hydrogen atmosphere (40 psi) at 23 °C for 3.5 h. The product mixture was filtered through Solka Floc (100 g), and the cake was washed with dry methyl acetate (0.8 L). Methanol (0.6 L) was added directly to the filtrate, and the mixture was stirred for 15 min. Concentrated sulfuric acid (36 mL) was added dropwise over 30 min at 25–30 °C with vigorous stirring. This solution was then stirred for 1 h, and the solid was filtered. The filtrate was washed with aqueous $NaHCO_3$ (125 g diluted to 1.7 L) and 10% aqueous NaCl (0.55 L). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was distilled to afford 310 g (76%) of pure 4-chlorobutanal dimethyl acetal (**6a**): bp 50 °C/8.5 mmHg; ^1H NMR ($CDCl_3$) δ 1.67–1.90 (m, 4H), 3.30 (s, 6H), 3.60 (t, J = 7.0 Hz, 2H), 4.38 (t, J = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.5, 30.0, 45.0, 52.8, 103.8. This material was directly used in the next step.

4-Chlorobutanal dimethyl acetal (**6a**) (1605 g, 10.5 mol) was dissolved in 40% aqueous dimethylamine (8 L), and the solution was stirred at room temperature for 15 min. The reaction mixture was then warmed to 62 °C and stirred for 1 h. After the mixture was cooled to rt, the product was extracted with CH_2Cl_2 (1 × 7.5 L; 1 × 5.5 L). The combined organic layers were washed with 5% aqueous $NaHCO_3$ (2 L) and brine (100 g diluted to 1.5 L). The organic layer was evaporated, and the residue was distilled to afford 1476.4 g (87%) of 4-(*N,N*-dimethylamino)butanal dimethyl acetal (**12a**) as a colorless liquid: bp 40 °C/1 mmHg (lit.[9a] bp 53.5 °C/5 mmHg); ^1H NMR ($CDCl_3$) δ 1.47–1.63 (m, 4H), 2.21 (s, 6H), 2.24 (t, J = 7.0 Hz, 2H), 3.31 (s, 6H), 4.37 (t, J = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.6, 30.2, 45.3, 52.4, 59.3, 104.2.

***N,N*-Dimethyl-2-[5-(cyanomethyl)-1*H*-indol-3-yl]ethylamine (8a).** A solution of 4% aqueous sulfuric acid (30 L) was heated to 50 °C over 30–60 min. Nitrogen was bubbled through the solution as it was heated to displace dissolved air. The hydrazine **5a** (1080 g, 4.77 mol) was added to the heated mixture, and the solid was allowed to dissolve. The acetal **12a** (965 g, 5.98 mol, 1.2 equiv) was then added as a stream over 30 min, and this mixture was heated at reflux for 2 h. The reaction mixture was cooled to rt, and 30% aqueous ammonium hydroxide (2 L) was added portionwise over 0.5 h maintaining the temperature at 25–30 °C. The product was extracted with isopropyl acetate (3 × 10 L). Concentration of the combined organic layers under vacuum (10 mm, 20–25 °C) to 3 L crystallized the product. The indole **8a** was obtained as a pale yellow solid after filtration, washing with cold (0–5 °C) isopropyl acetate (500 mL) and suction drying under nitrogen (827.4 g, 76% yield): mp 106–107 °C; IR (CH_2Cl_2) 3450, 2200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 6H), 2.65 (m, 2H), 2.95 (m, 2H), 3.84 (s, 2H), 7.06 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 2.0, 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.53 (s, 1H), 8.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.5, 23.7, 45.3, 60.2, 112.0, 113.7, 118.1, 119.2, 120.2, 121.5, 123.2, 127.8, 135.9. Anal. Calcd for $C_{14}H_{17}N_3$: C, 73.97; H, 7.53; N, 18.48. Found: C, 73.82; H, 7.73; N, 18.45.

***N,N*-Dimethyl-2-[5-(carbethoxymethyl)-1*H*-indol-3-yl]ethylamine (10).** *N,N*-Dimethyl-2-[5-(cyanomethyl)-1*H*-indol-3-yl]ethylamine (**8a**) (700 g, 3.08 mol) was dissolved in a mixture of ethanol (1.4 L) and 2 N NaOH (2.8 L). This solution was heated at reflux for 12 h and then cooled to rt. The volatiles were removed under vacuum to provide a thick slurry. To this material was added ethanol (10.5 L) and concentrated sulfuric acid (1.2 L) sequentially. The mixture was heated at reflux for 6 h. To the cooled mixture (−10 °C) was added 5 N NaOH dropwise to pH = 6.5. The solvent was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 (8 L) and water (12 L). The aqueous layer was extracted with CH_2Cl_2 (2 × 4 L). The combined organic layers were washed with 12% aqueous K_2CO_3 (1.7 L), dried ($MgSO_4$), and concentrated *in vacuo* to afford ester **10** as a crude solid: mp 45–46 °C; (99 A% by HPLC); ^1H NMR ($CDCl_3$) δ 1.24 (t, J =7 Hz, 3H), 2.34 (s, 6H), 2.64 (t, J = 7.5 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H), 3.71 (s, 2H), 4.15 (q, J = 7.0 Hz, 2H), 7.00 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 2.2, 4.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.49 (s, 1H); 8.0 (s, 1H). This material was used directly in the next step.

***N,N*-Dimethyl-2-[5-[[5-(3-amino-1,2,4-oxadiazolyl)]methyl]-1*H*-indol-3-yl]ethylamine; L-695,894 (1).** To ethanol (36.2 L) was added sodium (28.3 g dry weight, 12.3 mol) over 4 h under a nitrogen atmosphere at 25–30 °C. The solution was stirred at rt for 4 h. In a separate flask hydroxyguanidine sulfate hemihydrate (1.054 kg, 3.96 mol) was dried by azeotropic distillation with ethanol (3 × 2L) followed with toluene (2 × 2L). The mixture was concentrated to dryness each time. The dried hydroxyguanidine sulfate was added to the stirred solution of sodium ethoxide at rt, and this mixture was aged for 45 min. The ester **10** (724 g, 2.64 mol) in ethanol (3 L) was added to the reagent mixture at rt. The reaction mixture was refluxed for 5 h and then cooled to rt. The volatiles were removed under vacuum. The resultant thick solid was partitioned between isopropyl acetate (18.1 L) and an aqueous phase composed of a 1:1 mixture of 5% aqueous K_2CO_3 (9.06 L) and 5% aqueous NaCl (9.06 L). The organic layer was concentrated in vacuo to provide 496 g of L-695,-894 (1) as a solid in 66% yield. In order to remove 1.8% of the *N*-monomethyl byproduct of L-695,894 the crude solid was chromatographed over silica gel (isopropyl acetate–ethanol–30% aqueous NH_4OH, 10:0.25:0.1) to provide 387 g of L-695,894 free base as a white solid (51% overall yield, >99.6 A%): mp 122–124 °C; ^1H NMR (DMSO-d_6) δ 2.49 (s, 6H), 2.48 (m, 2H), 2.75 (m, 2H), 4.14 (s, 2H), 6.17 (s, 2H), 7.00 (dd, J = 0.2, 8.3 Hz, 1H), 7.14 (d, J = 0.2 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 7.43 (s, 1H), 10.79 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.0, 32.4, 45.0, 59.9, 111.4, 112.5, 118.5, 121.9, 123.1, 123.9, 127.4, 135.2, 168.4, 177.3. Anal. Calcd for $C_{15}H_{19}N_5O$: C, 63.14; H, 6.71; N, 24.54. Found: C, 63.02; H, 6.69; N, 24.43.

General Procedure for the Preparation of Tryptamines 8b-h and 16a,b. Under a nitrogen atmosphere, a mixture of hydrazine hydrochloride **5b–h** and **15a** or hydrazine **15b** (20 mmol) and (*N,N*-dimethylamino)butanal dimethyl acetal (**12a**) (24 mmol) in 120 mL of 4% aqueous sulfuric acid was heated at reflux for 2 h. The product mixture was cooled to rt and treated with 15 mL of 30% aqueous NH_4OH. The tryptamine was

extracted into isopropyl acetate or CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The residue was either chromatographed or recrystallized to give the tryptamine **8b–h** or **16a,b**.

***N,N*-Dimethyl-*1H*-indole-3-ethanamine (8b)**: mp 44–47 °C (lit.[13] mp 48–49 °C).

***N,N*-Dimethyl-5-methyl-*1H*-indole-3-ethanamine (8c)**: mp 90–92 °C (lit.[14] mp 94–95 °C).

***N,N*-dimethyl-5-isopropyl-*1H*-indole-3-ethanamine (8d)**: mp 84–85 °C; IR (CCl_4) 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (d, J = 6.9 Hz, 6H), 2.36 (s, 6H), 2.65 (m, 2H), 2.96 (m, 3H), 7.00 (d, J = 1.6 Hz, 1H), 7.10 (dd, J = 1.6, 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.7, 24.8, 34.3, 45.5, 60.4, 111.0, 113.8, 115.6, 121.0, 121.8, 127.5, 135.0, 139.8. Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.62; N, 12.16. Found: C, 78.24; H, 9.83; N, 11.88.

***N,N*-Dimethyl-5-fluoro-*1H*-indole-3-ethanamine (8e)**. As the hydrochloride salt: mp 172–174 °C (lit.[15] mp 175–176 °C).

5-Chloro-*N,N*-dimethyl-*1H*-indole-3-ethanamine (8f). As the hydrochloride salt: mp 197–198 °C (lit.[14] mp 197–198 °C).

5-Bromo-*N,N*-dimethyl-*1H*-indole-3-ethanamine (8g): mp 96–98 °C (lit.[16] mp 98–99 °C).

***N,N*-dimethyl-5-methoxy-*1H*-indole-3-ethanamine (8h)**: mp 65–67 °C (lit.[13] mp 67.5–68.5 °C).

1-(4′-Chlorobenzyl)-*N,N*-dimethyl-5-isopropyl-*1H*-indole-3-ethanamine (16a): IR (neat) 2700–3000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (d, J = 6.9 Hz, 6H), 2.45 (s, 6H), 2.75 (m, 2H), 3.02 (m, 3H), 5.20 (s, 2H), 6.94 (s, 1H), 7.06 (m, 4H), 7.26 (m, 2H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.3, 24.8, 34.2, 45.2, 49.3, 60.2, 109.5, 113.0, 116.0, 121.12, 125.7, 128.2, 128.2, 128.9, 133.3, 135.2, 136.4, 139.9.

1-(4′-Chlorobenzyl)-*N,N*-dimethyl-5-(2′-quinolylmethoxy)-*1H*-indole-3-ethanamine (16b): mp 89–90 °C; IR (CCl_4) 2750–2850, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 6H), 2.55 (m, 2H), 2.86 (m, 2H), 5.19 (s, 2H), 5.45 (s, 2H), 6.91 (s, 1H), 6.94–7.03 (m, 4H), 7.10 (d, J = 8.9 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 7.53 (m, 1H), 7.70 (m, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H). Anal. Calcd for $C_{29}H_{28}ClN_3O$: C, 73.92; H, 6.00; N, 8.94. Found: C, 73.92; H, 6.19; N, 8.79.

Chracterization of hemiacetal 18: ^1H NMR (DMSO-d_6) δ 1.90 (m, 3H), 2.25 (m, 1H), 2.75 (s, 3H), 2.92 (s, 3H), 3.43 (m, 2H), 5.11 (t, J = 6.8 Hz, 1H), 7.45 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 17.1, 27.0, 41.7, 47.7, 49.4, 97.4.