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

Cheng-yi Chen,* Chris H. Senanayake, Timothy J. Bill, Robert D. Larsen, Thomas R. Verhoeven, and Paul J. Reider

Department of Process Research, Merck Research Laboratories, Division of Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065

Received March 4, 1994

Among biologically active indoles, tryptamines show tremendous central nervous system activity. For example, the neurotransmitter serotonin (2β-(5-hydroxytryptamine (5-HT)) is involved in the regulation of various physiological functions, such as appetite, sleep, body temperature, blood pressure, and sexual behavior; 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 migraines. Sumatriptan (11) is one of this class of drugs to be approved for this use. 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. 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).

Traditional syntheses of N,N-dimethyltryptamines use a two-step procedure: a Fischer indole reaction between a hydrazine and the acetal 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, 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. Finally, the two-step procedure for incorporating the dimethylamino group further lowered the overall yield to 34%. Dimethylamino side chain precursor 12b 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.

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

(8) Matassa, V. Personal communication.
(b) Kelevic, D. Croat. Chem. Acta 1964, 36, 103. 12b was purchased from Orchimie, France.
Table 2. Preparation of N1-Substituted Tryptamines 16

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>i-Pr</td>
<td>91</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>90</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>86</td>
</tr>
<tr>
<td>d</td>
<td>i-Pr</td>
<td>91</td>
</tr>
<tr>
<td>e</td>
<td>F</td>
<td>82</td>
</tr>
<tr>
<td>f</td>
<td>Br</td>
<td>93</td>
</tr>
<tr>
<td>g</td>
<td>OMe</td>
<td>85</td>
</tr>
</tbody>
</table>

Conditions suitable for effecting the indolization with the side chain 6a failed to provide any reaction of 6a with 12a or 12b. No hydrolysis of 12 to its aldehyde form was observed. Apparently, the dimethylamine interferes with activation of the acetol 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-fluorodisubstituted aminolbutanal 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 and 12a proceeded sluggishly with the eventual decomposition of the product. Use of the stronger acid H2SO4 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, N1-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-hydrazone, and (4) [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 '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 to ene-hydrazone. 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 '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-hydrazone. Although TFA works equally well for hydrazine 5c, the generality of the TFA-catalyzed indolization is yet to be investigated.

12) Similar conditions were also used in the synthesis of the Aristotelis alkaoid penduncularine, see: Klaver, W. H.; Hiemstra, H.; Speckamp, W. N. J. Am. Chem. Soc. 1969, 111, 2588.
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 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 carboxylic acid 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 Tryptamine to L-695,894. A 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 carboxylic acid 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.

Experimental Section

General. Melting points are uncorrected. 1H and 13C NMR spectra were recorded at 250 MHz for 1H and 62.5 MHz for 13C. Column chromatography was performed on silica gel 60 (230–400 mesh, Merck). The solvent was removed under vacuum (10 mm, 20–25 °C) to 3 L crystallized the product. The oxadiazole ring of L-695,894 was constructed as a colorless liquid: bp 40 °C/1 mmHg; 1H NMR (CDCl3) 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). 13C NMR (CDCl3) δ 22.6, 30.2, 45.3, 52.4, 59.3, 104.2. This material was used directly in the next step. The oxadiazole ring of L-695,894 was constructed as a colorless liquid: bp 40 °C/1 mmHg; 1H NMR (CDCl3) 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). 13C NMR (CDCl3) δ 22.6, 30.2, 45.3, 52.4, 59.3, 104.2.

N,N-Dimethyl-2-[5-(carbethoxymethyl)-1H-indol-3-yl]ethy lamine (8a). A solution of 4% aqueous sulfuric acid (30 L) was heated to reflux for 15 min. Concentrated sulfuric acid (36 mL) was added to the heated mixture, and the mixture was heated at reflux to afford the ethyl ester 10 in 76% yield from 8a. This mixture was shaken under a nitrogen atmosphere at 25–30 °C. The solvent was removed under vacuum (10 mm, 20–25 °C) to 3 L crystallized the product. The oxadiazole ring of L-695,894 was constructed as a colorless liquid: bp 40 °C/1 mmHg; 1H NMR (CDCl3) 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). 13C NMR (CDCl3) δ 22.6, 30.2, 45.3, 52.4, 59.3, 104.2.

N,N-Dimethyl-2-[5-(aminophenyl)-1H-indol-3-yl]ethy lamine (8a). A solution of 4% aqueous sulfuric acid (30 L) was heated to reflux for 15 min. Concentrated sulfuric acid (36 mL) was added to the heated mixture, and the mixture was heated at reflux to afford the ethyl ester 10 in 76% yield from 8a. This mixture was shaken under a nitrogen atmosphere at 25–30 °C. The solvent was removed under vacuum (10 mm, 20–25 °C) to 3 L crystallized the product. The oxadiazole ring of L-695,894 was constructed as a colorless liquid: bp 40 °C/1 mmHg; 1H NMR (CDCl3) 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). 13C NMR (CDCl3) δ 22.6, 30.2, 45.3, 52.4, 59.3, 104.2.

N,N-Dimethyl-2-[5-(aminophenyl)-1H-indol-3-yl]ethy lamine (8a). A solution of 4% aqueous sulfuric acid (30 L) was heated to reflux for 15 min. Concentrated sulfuric acid (36 mL) was added to the heated mixture, and the mixture was heated at reflux to afford the ethyl ester 10 in 76% yield from 8a. This mixture was shaken under a nitrogen atmosphere at 25–30 °C. The solvent was removed under vacuum (10 mm, 20–25 °C) to 3 L crystallized the product. The oxadiazole ring of L-695,894 was constructed as a colorless liquid: bp 40 °C/1 mmHg; 1H NMR (CDCl3) 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). 13C NMR (CDCl3) δ 22.6, 30.2, 45.3, 52.4, 59.3, 104.2.
extracted into isopropyl acetate or CH₂Cl₂. The organic layer was dried (Na₂SO₄) 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. mp 48–49 °C).

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

**N,N-Dimethyl-1H-indole-3-ethanamine** (8d): mp 84–88 °C; IR (CCl₄) 3500 cm⁻¹; ¹H NMR (CDCl₃) δ 7.10 (d, J = 1.6 Hz, 1H), 7.15 (d, J = 1.6, 8.0 Hz, 1H), 7.28 (d, J = 1.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.96 (s, 1H); ¹³C NMR (CDCl₃) 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 C₁₆H₁₉N₂: 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. mp 175–176 °C). 5-Chloro-N,N-dimethyl-1H-indole-3-ethanamine (8f). As the hydrochloride salt: mp 197–198 °C (lit. mp 175–176 °C).

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

1-(4'-Chlorobenzyl)-N,N-dimethyl-1H-indole-3-ethanamine (16a): IR (neat) 2700–3000 cm⁻¹; ¹H NMR (CDCl₃) δ 1.32 (d, J = 6.9 Hz, 6H), 2.26 (s, 6H), 2.65 (m, 2H), 3.02 (m, 3H), 5.20 (s, 2H), 6.25 (s, 1H), 7.06 (m, 4H), 7.26 (m, 2H), 7.46 (s, 1H); ¹³C NMR (CDCl₃) δ 23.2, 24.8, 34.2, 45.2, 49.3, 60.2, 109.5, 113.0, 116.0, 121.12, 125.7, 128.2, 128.9, 133.3, 135.2, 136.4, 139.9.

**N,N-Dimethyl-5-methoxy-1H-indole-3-ethanamine** (16b): mp 89–90 °C; IR (CCl₄) 2750–2850, 1480 cm⁻¹; ¹H NMR (CDCl₃) 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 C₂₅H₂₂ClN₂O: C, 73.92; H, 6.00; N, 8.94. Found: C, 73.92; H, 6.19; N, 8.78.

**Characterization of hemiacetal 18**: ¹H NMR (DMSO-d₆) 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); ¹³C NMR (DMSO-d₆) δ 17.1, 27.0, 41.7, 47.7, 49.4, 97.4.