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Research Article

Synthesis of deuterium labeled standards of 5-methoxy-*N*,*N*-dimethyltryptamine (5-Meo-DMT)

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Summary

The Batcho-Leimgruber strategy was employed to synthesize 5-[$^{2}H_3$]-methoxy-1*H*-indole **4** from commercially available 5-hydroxy-2-nitrotoluene **1** and CD_3I. Compound **4** was treated with oxalyl chloride, dimethylamine and lithium aluminum hydride to yield 5-[$^{2}H_3$]-methoxy-*N*,*N*-dimethyltryptamine **6**. Copyright © 2006 John Wiley & Sons, Ltd.

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Key Words: 5-methoxy-*N*,*N*-dimethyltryptamine; phenylethylamine; deuterium labeled; internal standard

Introduction

Unknown drugs of abuse are typically detected and identified by GC-MS because of the high sensitivity of this method and its ability to separate complex mixtures of organic compounds. Based on electron impact (EI), this technique commonly does not suffice to discriminate among structurally closely related phenylethylamine drug variants, because of their often almost identical mass spectra and extremely few molecular and fragment ions,[1–4] which adversely influence the ability of the method to detect novel amphetamine controlled-substance analogs.[5,6]

The abuse of psychoactive phenylethylamines and phenylisopropylamines has become a very serious social problem in Taiwan over the last decade.[7,8]

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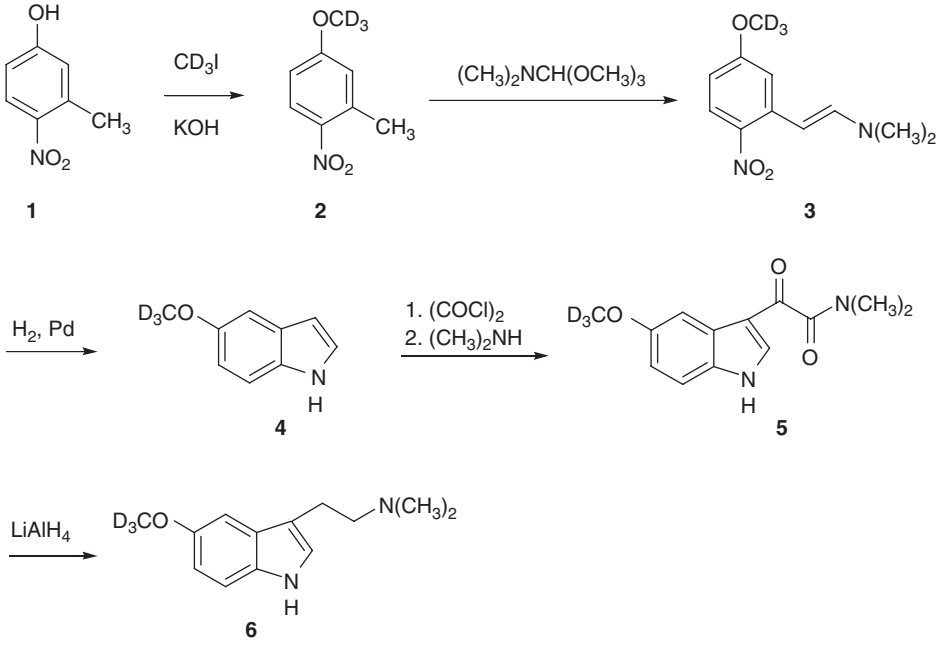
Standard samples for analyzing controlled drugs in Taiwan are very difficult to obtain. This work describes synthetic routes to 5-Meo-DMT-d_3, and presents related characteristic analytical data. To the authors' knowledge, no report has addressed these compounds.

Results and discussion

Scheme 1 presents the preparation of the 5-[$^2H_3$]-methoxy-*N*,*N*-dimethyltryptamine **6**. 5-Hydroxy-2-nitrotoluene **1** was treated with CD_3I in the presence of potassium hydroxide and tetrabutylammonium bromide,[9–11] to give 4-[$^2H_3$]-methoxy-2-methyl-1-nitro-benzene **2** in 81% yield. As in the Batcho-Leimgruber synthesis of indole,[12–17] compound **2** was condensed with *N*,*N*-dimethylformamide dimethyl acetal to yield [2-(5-[$^2H_3$]-methoxy-2-nitro-phenyl)-vinyl]-dimethyl-amine **3**. Reductive cyclization of compound **3** with hydrogen (50 psi) and Pd/C (10%) gave 5-[$^2H_3$]-methoxy-1*H*-indole **4** in 70% yield. A reaction between oxalyl chloride and dimethyl amine formed 2-(5-[$^2H_3$]-methoxy-1*H*-indol-3-yl)-*N*,*N*-dimethyl-2-oxo-acetamide **5** in 55% yield. The reduction of compound **5** with lithium aluminum hydride produced 5-[$^2H_3$]-methoxy-*N*,*N*-dimethyltryptamine **6** in 97% yield.



Scheme 1.

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Experimental

General

^{1}H NMR spectra were obtained at 300 or 500 MHz (indicated in each case), and ^{13}C NMR spectra were obtained at 75.5 MHz using a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) were obtained using a Micromass Platform II mass spectrometer at 70 eV. High-resolution mass spectra (HRMS) were obtained using a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded using an ATI Mattson spectrometer. All reactions were performed in anhydrous solvents. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone in argon. Benzene and *N*,*N*-dimethylformamide were distilled from calcium hydride. All air-sensitive reactions were performed in dry glassware under nitrogen using a standard glovebox. Flash column chromatography was performed using MN silica gel 60 (70–230 mesh) which was purchased from Macherey-Nagel.

The following reactions were performed without deuterium-labeled compounds as starting materials to elucidate the reaction conditions.

*Synthesis of 4-[$^{2}H_3$]-methoxy-2-methyl-1-nitro-benzene (**2**)*: Adequate amounts of potassium hydroxide in pellet form (2.53 g, 45.0 mmol) were ground to powder; tetrbutylammonium bromide (207 mg, 0.6 mmol) and 5-hydroxy-2-nitrotoluene **1** (6.30 g, 41.0 mmol) were then added, and blended in a nitrogen atmosphere. CD_3I (2.70 ml, 42.5 mmol) was then added and the mixture was heated in an oil bath for 3 days at 40–45°C. The crude mixture was then transferred to a separating funnel with water, and extracted using dichloromethane. The extract was dried over anhydrous magnesium sulfate. Filtration and concentration yielded a residue, which was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane (1:19) as the mobile phase, to generate compound **2** (6.14 g, 36.0 mmol). Yield: 81%. m.p.: 54–55°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.10 (d, $J = 8.8$ Hz, 1H), 6.81-6.76 (m, 2H), 2.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 163.0, 142.1, 137.1, 127.5, 117.4, 111.8, 21.7. IR (KBr, thin film): 3120, 3054, 2985, 2931, 2075, 1608, 1581, 1496, 1334, 1292, 1265 cm^{-1}. MS-FAB (*m*/*z*): 170 (M^+, 6), 167 (10), 75 (100). HRMS-FAB (*m*/*z*): [M^+] calculated for $C_8H_6D_3NO_3$, 170.0767; found 170.0765.

*Synthesis of [2-(5-[$^{2}H_3$]-methoxy-2-nitro-phenyl)-vinyl]-dimethyl-amine (**3**)*: A solution of 5-[$^{2}H_3$]-methoxy-2-nitrotoluene **2** (6.07 g, 35.7 mmol) in *N*,*N*-dimethylforamide dimethyl acetal (14.2 ml, 107.1 mmol) and *N*,*N*-dimethylforamide (36.0 ml) was heated at 130°C using a reflux condenser for 7 h.[12–17] The condenser was replaced with a distillation apparatus to remove the remaining *N*,*N*-dimethylforamide and *N*,*N*-dimethylforamide dimethyl

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acetal. The dark brown residue was used in the subsequent reaction without further purification.

*Synthesis of 5-[$^2H_3$]-methoxy-1H-indole (**4**)*: A solution of crude compound **3** in benzene (125 ml) and 10% Pd/C (0.80 g) was hydrogenated in an atmosphere of hydrogen (50 psi) at room temperature using a Parr apparatus. After being shaken for 1.5 h, the catalyst was removed by filtration through a bed of celite, and thoroughly extracted using benzene. Concentration left a residue, which was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate-hexane (1:19) as the mobile phase, to produce compound **4** (3.75 g, 25.0 mmol). Yield: 70%. m.p.: 58–59°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.04 (br, 1H), 7.30 (d, $J = 8.6$ Hz, 1H), 7.19 (t, $J = 2.8$ Hz, 1H), 7.11 (d, $J = 2.4$ Hz, 1H), 6.88 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.49-6.48 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 154.2, 131.0, 128.5, 125.0, 112.3, 111.8, 102.3, 55.9-54.8 (m). IR (KBr, thin film): 3401, 3100, 2221, 2063, 1612, 1577, 1477, 1322, 1284, 1230, 1164 cm^{-1}. MS-FAB (*m*/*z*): 151 ($M^+ + 1$, 100), 150 (74), 132 (35), 117 (9), 116 (3). HRMS-FAB (*m*/*z*): [M^+] calculated for $C_9H_6D_3NO$, 150.0869; found 150.0865.

*Synthesis of 2-(5-[$^2H_3$]-methoxy-1H-indol-3-yl)-N,N-dimethyl-2-oxo-acetamide (**5**)*: To a cooled and well-stirred solution of oxalyl chloride (2.28 ml, 26.1 mmol) in anhydrous diethyl ether (35 ml) was added 5-methoxyindole-d_3 (1.95 g, 13.0 mmol) in portions. Stirring was continued for an additional 30 min, and the red solids thus formed were washed lightly with diethyl ether. To a solution of dimethylamine hydrochloride (45.8 g, 561.6 mmol) and sodium hydroxide (22.4 g, 560 mmol) in water (54 ml) was added compound **4** in a little anhydrous diethyl ether. Stirring was continued for a further 30 min, and the red solid was collected and washed with diethyl ether. The red solid was dissolved in hot tetrahydrofuran. It was then cooled to room temperature and diethyl ether was added to precipitate a white solid, 2-(5-[$^2H_3$]-methoxy-1*H*-indol-3-yl)-*N*,*N*-dimethyl-2-oxo-acetamide **5** (1.76 g, 7.1 mmol). Yield: 55%. m.p.: 226–227°C. ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD, δ): 7.68 (d, $J = 3.3$ Hz, 1H), 7.61 (s, 1H), 7.20 (d, $J = 8.9$ Hz, 1H), 6.78-6.74 (dd, $J = 8.8$, 2.5 Hz, 1H), 2.96 (s, 3H), 2.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD, δ): 186.0, 168.2, 156.4, 136.5, 131.8, 126.0, 114.1, 113.5, 112.8, 103.0, 37.3, 34.0. IR (KBr, thin film): 3131, 3100, 3046, 2896, 2248, 2217, 2071, 1631, 1469, 1442, 1276 cm^{-1}. MS-FAB (*m*/*z*): 250 ($M^+ + 1$, 34), 207 (42), 149 (37), 75 (100). HRMS-FAB (*m*/*z*): [$M^+ + H$] calculated for $C_{13}H_{12}D_3N_2O_3$, 250.1267; found 250.1272.

*Synthesis of [2-(5-[$^2H_3$]-methoxy-1H-indol-3-yl)-ethyl]-dimethyl-amine (**6**)*: To a well-stirred suspension of lithium aluminum hydride (0.89 g, 2.3 mmol) in anhydrous tetrahydrofuran (30 ml) was added, in small portions, a suspension of 2-(5-[$^2H_3$]-methoxy-1*H*-indol-3-yl)-*N*,*N*-dimethyl-2-oxo-acetamide **5** (1.46 g, 5.9 mmol) in tetrahydrofuran (20 ml); the mixture was refluxed

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for 1.5 h. Following cooling in an external ice bath, the reaction complex and excess hydride were decomposed by the cautious addition of 2 M aqueous NaOH. The inorganic solid was removed by filtration; the filter cake was washed using additional diethyl ether. The filtrate and washes were combined and dried over anhydrous magnesium sulfate, and the solvents were removed in vacuo, yielding 5-[$^2H_3$]-methoxy-*N*,*N*-dimethyltryptamine **6** (1.26 g, 5.7 mmol). Yield: 97%. ^{1}H NMR(300 MHz, $CDCl_3$, δ): 7.94 (br, 1H), 7.25 (d, $J = 8.8$ Hz, 1H), 7.04 (d, $J = 2.4$ Hz, 1H), 7.01 (d, $J = 2.3$ Hz, 1H), 6.86 (dd, $J = 8.8$, 2.4 Hz, 1H), 2.93 (t, $J = 2.7$ Hz, 2H), 2.65 (t, $J = 2.3$ Hz, 2H), 2.34 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 153.8, 131.5, 127.8, 122.4, 113.9, 112.0, 111.9, 100.6, 60.2, 45.4, 23.8. IR (KBr, thin film): 3131, 3104, 3035, 2946, 2857, 2819, 2784, 2240, 2210, 2059, 1473 cm^{-1}. MS-FAB (*m*/*z*): 222 ($M^+ + 1$, 100), 220 (18), 177 (64), 132 (19), 130 (8), 75 (4). HRMS-FAB (*m*/*z*): [$M^+ + H$] calculated for $C_{13}H_{16}D_3N_2O$, 222.1682; found 222.1687.

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