Synthesis of Deuterium Labeled Tryptamine Derivatives

Yu-Yun Wang (王雨筠) and Chinpiao Chen* (陳清漂)
Department of Chemistry, National Dong Hwa University, Soufeng, Hualien 974, Taiwan, R.O.C.

The synthesis of deuterium labeled tryptamine derivatives, [2-(1*H*-indol-3-yl)-[$^2H_4$]-ethyl]-dimethyl-amine (DMT), [$^2H_{10}$]-diethyl-[2-(1*H*-indol-3-yl)-ethyl]-amine (DET), [2-(1*H*-indol-3-yl)-ethyl]-[$^2H_6$]-dipropyl-amine (DPT) and [$^2H_2$]-alpha-methyltryptamine (AMT) is described. The isotopically labeled compounds are used as internal standards in gas chromatography-mass spectrometry (GC-MS) assays.

Keywords: DMT; DET; DPT; AMT; Deuterium labeled; Internal standard.

INTRODUCTION

Alpha-methyltryptamine (AMT), which is an indole analogue of amphetamine, was investigated in the 1960s as an antidepressant, stimulant, and monoamine oxidase inhibitor. Today, AMT is recognized as a powerful psychedelic drug used by high school and college-aged men and women.[1-2] *N*,*N*-Dimethyltryptamine (DMT) is a hallucinogenic indole alkaloid that occurs naturally in a variety of plants and preparations used by ancient and modern South American cultures when performing shamanistic divination rituals.[3-6] Notably, DMT occurs naturally in the mammalian brain as a neurotransmitter.[7-12] Diethyl-tryptamine (DET) is an orally active hallucinogenic drug and psychedelic compound with effects that last for a moderate duration. The DET is a substituted for diethyl groups and structurally similar to DMT and dipropyltryptamine (DPT).[13] Dipropyltryptamine, a psychedelic drug belonging to the tryptamine family, is found either as a crystalline hydrochloride salt or as an oily or crystalline base. When smoked, the effects of DPT onset is in minutes and lasts for less than one hour.

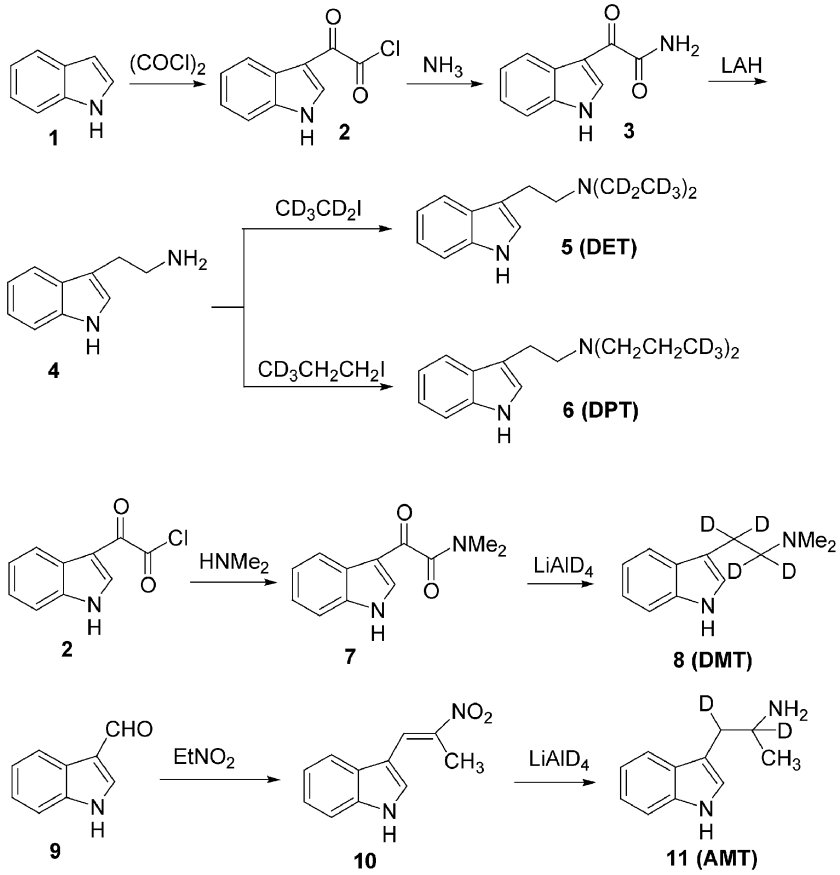
Unknown drugs that are abused are typically detected and identified by gas chromatography-mass spectrometry (GC-MS) due to the high sensitivity of GC-MS and its ability to separate complex mixtures of organic compounds. The abuse of psychoactive tryptamine derivatives has become a very serious social problem. Standard samples for analyzing controlled drugs in Taiwan are very difficult to obtain. Many researchers are interested in the preparation of deuterium-labeled control drugs as internal standards for GC-MS analysis.[14–24] This work describes synthetic routes to [$^2H_4$]-DMT, [$^2H_{10}$]-DET, [$^2H_6$]-DPT and [$^2H_2$]-AMT and presents related characteristic analytical data. No report has addressed these compounds.

RESULTS AND DISCUSSION

Although tryptamine derivatives DMT,[25-30] DET,[32] DPT[32] and AMT[33-35] have been readily prepared via several synthetic routes, preparation of [$^2H_4$]-DMT, [$^2H_{10}$]-DET, [$^2H_6$]-DPT and [$^2H_2$]-AMT has not been described. Scheme I presents the general synthetic scheme for preparing [$^2H_4$]-DMT (**8**), [$^2H_{10}$]-DET (**5**), [$^2H_6$]-DPT (**6**) and [$^2H_2$]-AMT (**11**). Compound **4** was prepared by reacting indole **1** and oxalyl chloride to yield (1*H*-indol-3-yl)-oxo-acetyl chloride (**2**); compound **2** was then treated with ammonium hydroxide to form 2-(1*H*-indol-3-yl)-2-oxo-acetamide (**3**) in an 89% yield. Reduction of compound **3** with lithium aluminum hydride produced 2-(1*H*-indol-3-yl)-ethylamine (**4**) in a 70% yield. Compound **5** was prepared by reacting compound **4** and [$^2H_5$]-iodoethane in the presence of potassium carbonate in a 20% yield. Compound **6** was synthesized using the same conditions as that for preparing compound **5** in the presence of [$^2H_3$]-iodopropane ($ICH_2CH_2C[^2H_3]$) in a 68% yield. Synthesis of compound **8** followed the same conditions as those for preparing compound **5** in the presence of [$^2H_3$]-iodomethane; however, compound **8** was not obtained. Instead of compound **8**, qua-

* Corresponding author. Tel: +886-3-8633597; Fax: +886-3-8630475; E-mail: chinpiao@mail.ndhu.edu.tw

Scheme I



ternary ammonium salt was obtained. Quaternary ammonium salt was applied to convert to compound **8** via treatment with *n*-butyllithium or superhydride, but we did not obtain the desired product **8**. Alternatively, the following pathway successfully yielded compound **8**. A reaction of compound **2** and dimethylamine formed 2-(1*H*-indol-3-yl)-*N,N*-dimethyl-2-oxo-acetamide (**7**) in a 92% yield. The reduction of compound **7** with lithium aluminum [$^2H_4$]-hydride produced [2-(1*H*-indol-3-yl)-[$^2H_4$]-ethyl]-dimethylamine (**8**) in an 85% yield. A reaction of indole-3-carboxaldehyde (**9**) and nitroethane formed 3-(2-nitro-propenyl)-1*H*-indole (**10**) in a 63% yield. The reduction of compound **10** with lithium aluminum [$^2H_4$]-hydride produced 2-(1*H*-indol-3-yl)-1-methyl-[$^2H_2$]-ethylamine (**11**) in a 95% yield.

In conclusion, this study demonstrates the syntheses of DMT-d_4, DET-d_{10}, DPT-d_6 and AMT-d_2. Although the retention times of gas chromatography (GC) of labeled and unlabeled compounds vary very little, quantification by mass spectrometry (MS) with the selected ion monitoring (SIM) technique enhances the performance of quantitative analysis. Therefore, deuterium-labeled compounds possess the potential for use as an internal standard in GC-MS analysis.

EXPERIMENTAL SECTION

General Chemical Procedures

^{1}H NMR spectra were obtained at 300 or 400 MHz (indicated in each case), and ^{13}C NMR spectra were obtained at 75.5 or 100.6 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. Deuterium labeled compounds were purchased from Cambridge Isotope Laboratories, Inc.

All reactions were initially optimized using unlabelled compounds.

2-(1*H*-Indol-3-yl)-ethylamine (4)

Oxalyl chloride (17.3 mL, 198.0 mmol) was added to a cooled and well-stirred solution of indole (20.20 g, 171.0 mmol) in anhydrous diethyl ether (340 mL). Stirring was continued at 0 °C for an additional 3 h, and at room temperature for 1 h, generating yellow solids. The yellow solids were collected by filtration and washed with diethyl ether to give compound **2** (33.47 g, 162.0 mmol) in a 94% yield. A suspension solution of compound **2** (5.07 g, 24.5 mmol) in dichloromethane (120 mL) was saturated with ammonia gas and stirred for 30 min. The solvent was removed, and water (240 mL) was added. The resulting aqueous solution was extracted with ethyl acetate. The combined extracts were washed with brine, and then dried over anhydrous magnesium sulfate. Following filtration and concentration, a yellowish solid of **3** (4.08 g, 21.7 mmol) was formed in an 89% yield. To a suspension solution of lithium aluminum hydride (3.03 g, 79.8 mmol) in dioxane (109 mL), compound **3** (1.50 g, 8.0 mmol) was added through a Soxhlet extraction apparatus by refluxing for 34 h. Following cooling in an external ice bath, the reaction complex and excess hydride were decomposed by cautiously adding 2 M aqueous NaOH. The inorganic solid was removed by filtration; the filter cake was washed using additional tetrahydrofuran. The filtrates and washes were combined and concentrated to yield an aqueous solution. Diethyl ether was then added, and the aqueous solution was acidified by 1 M hydrochloric acid. The aqueous solution was extracted with diethyl ether, and the aqueous phase was basified utilizing 2 M aqueous NaOH. The basic aqueous solution was extracted with diethyl ether, and the combined extracts were dried over anhydrous sodium sulfate. The solvents were removed in vacuo, yielding 2-(1*H*-indol-3-yl)-ethylamine (**4**) (0.90 g, 5.6 mmol). Yield: 70%. mp: 112-113 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.02 (s, br, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.05 (s, 1H), 3.04 (t, J = 6.5 Hz, 2H), 2.92 (t, J = 6.5 Hz, 2H). IR (KBr, thin film): 3343, 3280, 3029, 2868, 1591, 1453, 1345, 1232, 1109, 1007, 934, 804, 743 cm^{-1}.

***N,N*-[^{2}H$_{10}$]-diethyltryptamine (5)**

A mixture of 2-(1*H*-indol-3-yl)-ethylamine **4** (1.60 g, 10.0 mmol), [$^2H_5$]-iodoethane (5.00 g, 31.1 mmol) and anhydrous potassium carbonate (5.53 g, 40.0 mmol) in anhydrous methanol (10 mL) was stirred at 45-50 °C for 5 days. After cooling to room temperature, the solid was removed by filtration and washed with methanol. The combined filtrate and methanol solution was concentrated, the remained solid was suspended in dichloromethane solution, and the non-dissolving salt was removed by filtration. The filtrate was concentrated, and the residue was purified by flash column chromatography using silica gel (deactivated by ammonia) as the stationary phase and ethyl acetate-hexane (1:9) as the mobile phase, producing a brown syrupy compound **5** (0.45 g, 2.0 mmol). Yield: 20%. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.28 (s, br, 1H), 7.61(d, J = 7.1 Hz, 1H), 7.36 (d, J = 7.2 Hz, 1H), 7.20-7.07 (m, 2H), 7.07 (s, 1H), 3.09-3.02 (m, 2H), 2.98-2.90 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 142.5, 133.5, 128.4, 128.0, 125.3, 124.7, 118.7, 117.7, 59.2, 52.6-51.6 (m), 28.1, 16.9-15.2 (m). IR (KBr, thin film): 3237, 3054, 2924, 2823, 2713, 2223, 2073, 1454, 1113, 738 cm^{-1}. MS-EI (*m/z*): 226 (M^+, 2), 144 (2.6), 130 (7.6), 96 (100), 64 (2.5). HRMS-EI (*m/z*): [M^+] calcd for $C_{14}H_{10}D_{10}N_2$, 226.2244; found 226.2260.

[2-(1*H*-Indol-3-yl)-ethyl]-[^{2}H$_6$]-dipropylamine (DPT) (6)

A mixture of 2-(1*H*-indol-3-yl)-ethylamine **4** (1.60 g, 10.0 mmol), 1,1,1-[$^2H_3$]-3-bromopropane (5.00 g, 39.7 mmol) and anhydrous potassium carbonate (5.53 g, 40.0 mmol) in anhydrous methanol (10 mL) was stirred at 55 °C for 5 days. After cooling to room temperature, the solid was removed by filtration and washed with methanol. The combined filtrate and methanol solution was concentrated, the remaining solid was suspended in dichloromethane solution and the non-dissolving salt was removed by filtration. The filtrate was concentrated, and the residue was purified

by flash column chromatography using silica gel (deactivated by ammonia) as the stationary phase and ethyl acetate-hexane (1:4) as the mobile phase, producing a brown syrupy compound **6** (1.71 g, 6.8 mmol). Yield: 68%. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.97 (s, br, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 7.0 Hz, 1H), 7.21-7.12 (m, 2H), 7.02 (s, 1H), 2.94-2.89 (m, 2H), 2.84-2.80 (m, 2H), 2.52 (t, J = 2.4 Hz, 4H), 1.51 (t, J = 7.3 Hz, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 136.4, 127.7, 121.9, 121.7, 119.3, 119.1, 114.6, 111.3, 56.1, 54.9, 22.9, 20.1, 11.8-10.6 (m). IR (KBr, thin film): 3421, 3055, 2939, 2875, 2803, 2218, 2075, 1654, 1457, 1053, 739 cm^{-1}. MS-EI (*m/z*): 250 (M^+, 10), 164 (17), 130 (91), 120 (100), 115 (17), 103 (11), 90 (21), 75 (32), 46 (43). HRMS-EI (*m/z*): [M^+] calcd for $C_{16}H_{18}D_6N_2$, 250.2310; found 250.2312.

2-(5-Benzyloxy-1*H*-indol-3-yl)-*N,N*-dimethyl-2-oxo-acetamide (7)

Compound **2** (1.0 g, 4.8 mmol) in a small amount of anhydrous diethyl ether was added to a solution of dimethylamine hydrochloride (13.05 g, 160.0 mmol) and sodium hydroxide (6.37 g, 159.3 mmol) in water (15.4 mL). The mixture was stirred for a further 30 min, and the white solid was obtained via filtration and washed with water and dichloromethane. The aqueous phase was extracted with dichloromethane, and the combined organic phase was concentrated. The residue was purified by flash column chromatography using silica gel as the stationary phase and methanol-ethyl acetate (1:9) as the mobile phase, producing a brown syrupy compound **7** (0.96 g, 4.5 mmol). Yield: 92%. mp: 173-175 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.25 (s, br, 1H), 8.37-8.38 (m, 1H), 7.93 (d, J = 4.3 Hz, 1H), 7.44-7.40 (m, 1H), 7.34-7.30 (m, 2H), 3.10 (s, 1H), 3.07 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 186.1, 168.3, 136.9, 136.0, 125.2, 124.1, 123.1, 121.7, 114.0, 112.3, 37.5, 34.4. IR (thin film): 3103, 2925, 1630, 1523, 1447, 1245, 1127, 747 cm^{-1}.

3-(2-Dimethylamino-[$^2H_4$]-ethyl)-1*H*-indol-5-ol (8)

To a well-stirred suspension of lithium aluminum [$^2H_4$]-hydride (0.71 g, 16.9 mmol) in anhydrous tetrahydrofuran (20 mL), a suspension of 2-(5-benzyloxy-1*H*-indol-3-yl)-*N,N*-dimethyl-2-oxo-acetamide **7** (0.94 g, 4.35 mmol) in tetrahydrofuran (15 mL) was added in small portions; the mixture was refluxed for 4 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 via filtration; the filter cake was washed using additional diethyl ether. The filtrate and washes were combined and dried over anhydrous magnesium sulfate. The solvents were removed in vacuo, yielding 3-(2-dimethylamino-[$^2H_4$]-ethyl)-1*H*-indol-5-ol (**8**) (0.74 g, 3.85 mmol). Yield: 89%. mp: 43-44 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.96 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.19-7.09 (m, 2H), 7.04 (d, J = 2.3 Hz, 1H), 2.39 (s, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 136.8, 127.7, 122.3, 121.8, 119.1, 118.9, 113.5, 111.6, 60.0-59.2 (m), 45.4, 23.1-22.7 (t). IR (thin film): 3424, 2823, 2183, 2057, 1452, 1245, 988, 796, 742, 425 cm^{-1}. MS-EI (*m/z*): 192 (M^+, 46), 148 (7), 132 (23), 118 (6), 104 (6), 78 (6), 60 (100). HRMS-EI (*m/z*): [M^+] calcd for $C_{12}H_{12}D_4N_2$, 192.1560; found 192.1567.

3-(2-Nitro-propenyl)-1*H*-indole (10)

A solution of indole-3-carboxaldehyde (**9**) (2.17 g, 15.0 mmol) in nitroethane (8.6 mL, 119.7 mmol) was treated with anhydrous ammonium acetate (0.39 g, 5.0 mmol) and heated at 100 °C for 2.5 h until the starting material was completely consumed by thin layer chromatography (TLC) monitoring. The solvent was removed under vacuum, yielding a solid that was then washed with water. The remaining solid was recrystallized from ethanol to give 3-(2-nitro-propenyl)-1*H*-indole (**10**) (1.90 g, 9.4 mmol) as a yellow crystal. Yield: 63%. mp: 190-192 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.70 (br, 1H), 8.52 (s, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.57 (d, J = 2.8 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.36-7.27 (m, 2H), 2.55 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 142.9, 135.8, 127.6, 126.2, 124.0, 121.8, 118.9, 111.7, 110.3, 14.9. IR (KBr, thin film): 3428, 3136, 1623, 1527, 1471, 1420, 1268, 1223, 1103, 967, 748 cm^{-1}. MS-EI (*m/z*): 202 (M^+, 100), 154 (80), 145 (48), 128 (56), 117 (23), 104 (14), 77 (24), 65 (10), 51 (7). HRMS-EI (*m/z*): [M^+] calcd for $C_{11}H_{10}N_2O_2$, 202.0742; found 202.0744.

2-(1*H*-Indol-3-yl)-1-methyl-[$^2H_2$]-ethylamine (11)

A suspension of 3-(2-nitro-propenyl)-1*H*-indole (**10**) (1.80 g, 8.9 mmol) in tetrahydrofuran (40 mL) was added in small portions to a well-stirred suspension of lithium alu-

minum [$^2H_4$]-hydride (2.20 g, 53.4 mmol) in anhydrous tetrahydrofuran (40 mL); the mixture was refluxed for 2 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. The solvents were removed in vacuo, yielding 2-(1*H*-indol-3-yl)-1-methyl-[$^2H_2$]-ethylamine **11** (1.46 g, 8.3 mmol). Yield: 94%. mp: 91-92 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.14 (s, br, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.20-7.04 (m, 2H), 7.04 (s, 1H), 2.88 (s, 1H), 2.64 (s, 1H), 1.24 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 136.4, 127.8, 122.5, 121.8, 119.3, 119.1, 113.8, 111.2, 47.1-46.5 (t), 35.8-35.3 (t), 24.7. IR (KBr, thin film): 3415, 3357, 3299, 2863, 2129, 1573, 1455, 1353, 1005, 742, 422 cm^{-1}. MS-EI (*m/z*): 176 (M^+, 19), 160 (1), 148 (1), 132 (100), 117 (2), 104 (8), 78 (6), 46 (1). HRMS-EI (*m/z*): [M^+] calcd for $C_{11}H_{12}D_2N_2$, 176.1280; found 176.1274.

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