Synthesis of Deuterium Labeled Standards of 1-Benzylpiperazine, Fenetylline, Nicocodeine and Nicomorphine

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Increasingly abused, 1-benzylpiperazine (BZP), fenetylline, nicocodeine and nicomorphine are central nervous system stimulants with neurotoxic properties. In recent years, many controlled substance analogs (designer drugs) with a large variety of structures have reached illegal markets, making their identification difficult. This work studies the synthesis of BZP-d_7, fenetylline-d_4, nicocodeine-d_4 and nicomorphine-d_8, as internal standards for use in gas chromatography-mass spectrometry (GC-MS) analysis for identification of these controlled substances.

Keywords: BZP; Fenetylline; Nicocodeine; Nicomorphine; GC-MS.

INTRODUCTION

Unknown drugs are generally detected and identified by gas chromatography-mass spectrometry because of the high sensitivity and capability of this method to separate organic compounds from complex mixtures. Some abused drugs, such as 1-benzylpiperazine,[1-2] fenetylline,[3] nicocodeine[4] and nicomorphine[5] are increasingly abused psychoactive drugs and have been well documented in the literature. Widespread consumption of designer drugs has led to an increased number of reports of abuse and intoxication.

The abuse of psychoactive drugs in the phenethylamine and morphine groups has become an extremely serious problem in Taiwan in the most recent decade.[6-18] Amphetamine, its *N*-methyl homologue methylamphetamine, and 4-methylenedioxmethylamphetamine (MDMA), are among those most widely abused by young people. Although 1-benzylpiperazine[19] was originally synthesized by Wellcome Research Laboratories as a potential antihelminthic agent, research indicated that 1-benzylpiperazine caused a reversal of the effects of tetrabenazine (a dopamine-depleting drug) in rats and mice, indicating a potential antidepressant activity. Notably, 1-benzylpiperazine caused hyperactivity, involuntary head movements and a reduction in reaction time in shock-avoidance studies, properties also found in amphetamines.[20] Baumann et al.[21] reported that 3,4-methylenedioxymethamphetamine is an illicit drug that stimulates release of serotonin and dopamine from neurons. Recent evidence in rats reveals that drug users are ingesting piperazine analogs, such as 1-benzylpiperazine and 1-(*m*-trifluoromethylphenyl) piperazine (TFMPP), that mimic the psychoactive effects of 4-methylenedioxmethylamphetamine. Baumann's results showed that BZP/TFMPP and MDMA can evoke monoamine release; however, a dangerous drug-drug synergism may occur when piperazines are coadministered at high doses. Fenetylline[3] is on a list of compounds that were considered by a World Health Organization (WHO) expert committee in April 1985 for possible international scheduling under the Convention on Psychotropic Substances. For over 23 years, fenetylline has been administered therapeutically to hyperkinetic children and in other indications in place of amphetamines and other central stimulants with high risk levels. Nicocodeine,[22] an opiate derivative developed as a cough suppressant and analgesic is metabolized in the liver by demethylation to produce 6-nicotinoylmorphine and then further metabolized to morphine. Side effects are similar to those of other opiates, including itching, nausea and respiratory depression. Nicomorphine,[22] the 3,6-dinicotinate ester of morphine is a strong opioid agonist analgesic two to three times as potent as morphine with a side effect profile similar to that of dihydromorphine, hydromorphone, and diamorphine. Nicomorphine is commonly used in patient-controlled analgesia units. Nicomorphine, the nicocodeine parent chemical is a cough suppressant. Nicomorphine's side effects are similar to those of other opiates and include itching, nausea and respiratory depression.[23]

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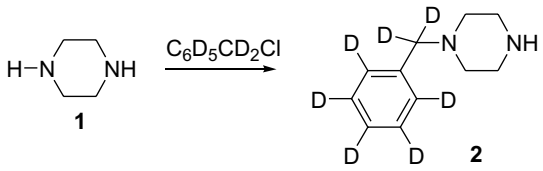
Standard samples for controlled drug analysis in Taiwan are very difficult to obtain. Many researchers are interested in the preparation of deuterium-labeled controlled drugs as internal standards for GC-MS analysis.[24-30] This study describes the synthetic routes to BZP-d_7, fenetylline-d_4, nicocodeine-d_4 and nicomorphine-d_8, and presents relevant characteristic analytical data. The synthetic approach described herein is potentially applicable to the synthesis of a wide variety of other drugs. No reports exist for the compounds investigated in this study.

RESULTS AND DISCUSSION

1-Benzylpiperazine,[31-36] fenetylline,[37-39] nicocodeine[40-41] and nicomorphine[42] were readily prepared using various synthetic routes. Preparation of BZP-d_7, fenetylline-d_4, nicocodeine-d_4 and nicomorphine-d_8 has not been described previously. Scheme I presents the general synthetic scheme for preparing 1-benzylpiperazine-d_7 (**2**).[32] The reaction between piperazine (**1**) and benzyl chloride-d_7 gave 1-benzylpiperazine-d_7 (**2**) in a 99% yield.

Scheme II presents the preparation of fenetylline-d_4 (**7**).[37] The reaction of 5,6-diamino-1,3-dimethyl-1*H*-pyrimidine-2,4-dione (**3**) and formic acid produced trophylline (**4**) in a 51% yield. Trophylline (**4**) and 1,2-dichloroethane-d_4 were refluxed in 2-propanol to give 7-(2-chloroethyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione-d_4 (**5**) in a 33% yield. Fenetylline-d_4 (**7**) was prepared by heating compound **5** with 1-methyl-2-phenyl-ethylamine (**6**).

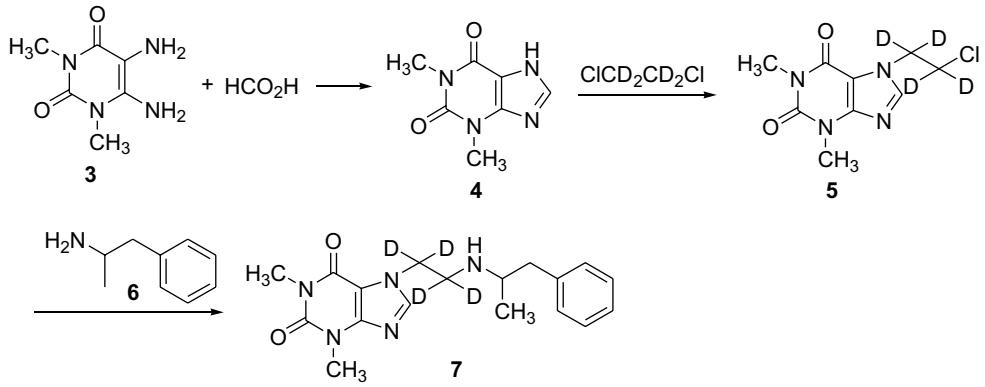
Scheme I



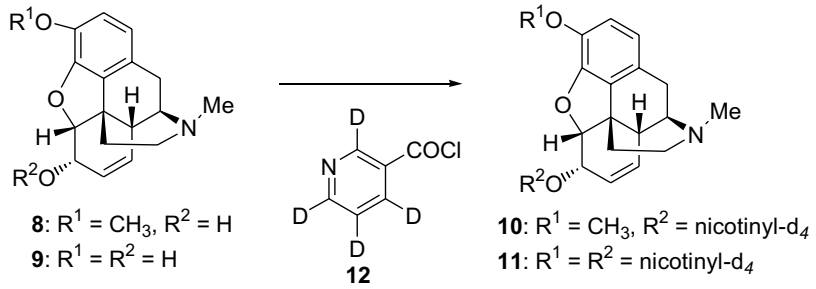
Scheme III presents the preparation of nicocodeine-d_4 (**10**) and nicomorphine-d_8 (**11**).[41] Codeine **8** and morphine **9** were treated with nicotinoyl-d_4 chloride (**12**) to give the corresponding nicocodeine-d_4 (**10**) and nicomorphine-d_8 (**11**).

In conclusion, this study demonstrates the syntheses of BZP-d_7, fenetylline-d_4, nicocodeine-d_4 and nicomorphine-d_8. 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 per-

Scheme II



Scheme III



formance 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 acquired at 300 and 400 MHz (indicated in each case), and ^{13}C NMR were acquired at 75.5 and 100 MHz on a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) and high resolution mass spectra (HRMS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded using a JASCO FT/IR 410 spectrometer. Dichloromethane and pyridine were distilled from calcium hydride. Flash column chromatography was performed using MN silica gel 60 (70-230 mesh) or basic Al_2O_3 which were purchased from Macherey-Nagel.

All reactions were initially optimized using unlabeled compounds.

1-Benzylpiperazine-d_7.HCl (2)

A solution of piperazine hexahydrate (1.46 g, 7.5 mmol) in absolute ethanol (3.0 mL) was warmed at 65 °C, and piperazine dihydrochloride monohydrate (1.33 g, 7.5 mmol) was added. After warming in a bath to 65 °C, benzyl chloride-d_7 (1.00 g, 7.5 mmol, isotope purity, D7, 98%, Cambridge Isotope Laboratories) was added during 5 min of vigorous stirring. The separation of white needles was almost immediate. The solution was stirred for an additional 25 min at 65 °C and then cooled in an ice bath without stirring for about 30 min. The crystals of piperazine dihydrochloride monohydrate were collected by filtration and then washed with ice-cold absolute ethanol. The combined filtrate and washings from the piperazine dihydrochloride were cooled in an ice bath and treated with 25 mL absolute ethanol saturated at 0 °C with dry hydrogen chloride. After the solution was well mixed, it was cooled for 10-15 min in an ice bath. The precipitated white plates of 1-benzylpiperazine dihydrochloride were collected by filtration, washed with dry benzene, and dried to give the product **2** (1.90 g, 7.4 mmol). Yield: 99%. mp: 277-280 °C. ^{1}H NMR (300 MHz, D_2O, δ): 3.47 (s, 8H). ^{13}C NMR (75 MHz, D_2O, δ): 131.2-130.1 (m), 129.3-128.6 (m), 127.1, 60.4-60.0 (m), 47.8, 40.7. IR (thin film): 3448, 2896, 2768, 2520, 1630, 1559, 1420, 1301, 1192, 1082, 941, 578, 540 cm^{-1}. MS-EI (*m/z*): 183 (M^+, 27), 152 (3), 141 (71), 127 (4), 98 (100), 85 (13), 70 (10), 56 (20). HRMS-EI (*m/z*): [M^+] calcd for $C_{11}H_9D_7N_2$ 183.1746; found 183.1756.

Throphylline (4)

Throphylline **4** was obtained by heating a mixture of dimethyldiaminouracil **3** (4.25 g, 25.0 mmol) and HCOOH (4.8 mL, 0.13 mol) in an open round flask at 110-140 °C for 2 h. Excess formic acid was removed by boiling at atmospheric pressure, and the red-brown residue was converted to throphylline **4** by heating at 275-300 °C for 20 min. The crude product was triturated with ethanol and filtrated to give a brown solid **4** (2.30 g, 12.8 mmol). Yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.86 (s, 1H), 3.66 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 156.2, 151.5, 149.1, 140.4, 106.9, 30.3, 28.5. IR (thin film): 3447, 3120, 3066, 2916, 2853, 1717, 1668 cm^{-1}. MS-EI (*m/z*): 180 (M^+, 100), 151 (7), 95 (44), 68 (33). HRMS-EI (*m/z*): [M^+] calcd for $C_7H_8O_2N_4$, 180.0647, found, 180.0642.

7-(2-Chloro-ethyl)-1,3-dimethyl-3,7-dihydro-purine-2,6-dione-d_4 (5)

To a solution of theophylline **4** (0.55 g, 3.1 mmol) and sodium hydroxide (0.12 g) in water (4 mL) was added a solution of 1,2-dichloroethane-d_4 (2.50 g, 24.3 mmol, isotope purity, D4, 99%, Cambridge Isotope Laboratories) in 2-propanol (6.0 mL). After refluxing at 80-90 ºC for 18 h, the solvent was evaporated under reduced pressure, and the solid was filtered out and discarded. The aqueous layer was extracted 3 times with chloroform, and combined organic layers were dried over anhydrous sodium 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 (1:1) as the mobile phase to produce compound **5** (0.24 g, 1.0 mmol). Yield: 33%. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.63 (s, 1H), 3.59 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 160.7, 155.3, 151.6, 149.4, 142.1, 106.4, 29.8, 28.0. IR (thin film): 3105, 2953, 2359, 2284, 1704, 1660, 1602, 1546, 1471, 1453, 1428, 1348, 1287, 1241, 1197, 1086 cm^{-1}. MS-EI (*m/z*): 248 (M+2, 27), 246 (M^+, 100), 211 (47), 181 (53), 96 (42), 67 (27). HRMS-EI (*m/z*): [M^+] calcd for $C_9H_7D_4ClO_2N_4$, 246.0818, found, 246.0829.

Fenetylline-d_4 (7)

A mixture of 7-(3-chloroethyl)-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione-d_4 **5** (0.22 mg, 0.9 mmol) and 1-methyl-2-phenyl-ethylamine **6** (0.49 g, 3.6 mmol) was heated at 100 °C for 17 h. After cooling to room temperature, the saturated aqueous solution of sodium bicarbonate was added to basify the reaction mixture to a pH of 8. The aqueous phase was extracted with dichloromethane, and

the organic phase was dried over anhydrous sodium sulfate. Filtration and concentration yielded a residue, which was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate as the mobile phase to produce compound **7** (0.15 g, 0.4 mmol). Yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.45 (s, 1H), 7.25-7.17 (m, 3H), 7.09-7.07 (m, 2H), 3.58 (s, 3H), 3.39 (s, 3H), 2.89-2.84 (m, 2H), 2.61-2.57 (m, 1H), 1.04-1.03 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 155.2, 151.7, 148.9, 141.7, 139.0, 129.1, 128.3, 126.2, 106.7, 54.3, 43.5, 29.7, 28.0, 20.4. IR (thin film): 3420, 2963, 1704, 1659, 1546, 1453, 1349, 1290, 1235, 1184, 1020 cm^{-1}. MS-FAB (*m/z*): 347 (M^+ + 2, 55), 345 (M^+, 18), 254 (39), 228 (17), 211 (25), 181 (22), 166 (24), 119 (38), 105 (37), 91 (60), 77 (32), 69 (87), 58 (98), 56 (100). HRMS-EI (*m/z*): [M^+] calcd for $C_{18}H_{19}D_4N_5O_2$, 345.2099; found 345.2098.

Nicocodeine-*d*$_4$ (10)

A solution of nicotinic acid-d_4 (1.10 g, 8.0 mmol, prepared from nicotinic acid ethyl ester, isotope purity, 2,4,5,6-D4, 98%, Cambridge Isotope Laboratories) in thionyl chloride (5.0 mL) was refluxed for 2 h, and excess thionyl chloride was removed by distillation to yield nicotinoyl chloride-d_4. A solution of nicotinoyl chloride-d_4 in dichloromethane (15.0 mL) was added to a solution of codeine (1.20 g, 4.0 mmol) and pyridine (1.2 mL) in dichloromethane (10.0 mL). After stirring at room temperature for 15 h, the reaction solution was basified by adding a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted with dichloromethane, and the combined organic solution was dried over anhydrous magnesium sulfate. Filtration and concentration yielded a residue, which was purified by flash column chromatography using Al_2O_3 as the stationary phase and ethyl acetate-hexane (1:4, 2:3) as the mobile phase to produce compound **10** (1.65 g, 3.9 mmol). Yield: 97%. mp: 134.7-135.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.67 (d, J = 8.2 Hz, 1H), 6.58 (d, J = 8.2 Hz, 1H), 5.78 (d, J = 9.8 Hz, 1H), 5.54 (d, J = 7.4 Hz, 1H), 5.47 (d, J = 6.7 Hz, 1H), 5.20 (d, J = 6.8 Hz, 1H), 3.70 (s, 3H), 3.39 (s, 1H), 3.08 (d, J = 18.5 Hz, 1H), 2.81 (s, 1H), 2.60 (d, J = 20.0 Hz, 1H), 2.45 (s, 3H), 2.38-2.34 (m, 2H), 2.08-2.06 (m, 1H), 1.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 164.8, 146.6, 142.2, 130.6, 130.0, 128.0, 126.9, 125.8, 119.4, 114.1, 87.6, 68.7, 59.2, 56.6, 46.8, 43.0, 42.6, 40.6, 35.3, 20.4. IR (KBr): 2918, 2839, 2284, 2260, 1969, 1820, 1723, 1557, 1504, 938, 788, 701 cm^{-1}. MS *m/z*: 408 (M^+, 100), 282 (66), 271 (20), 229 (18), 110 (34), 82 (23). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{24}H_{20}D_4N_2O_4$, 408.1983; found, 408.1983.

Nicomorphine-*d*$_8$ (11)

A solution of nicotinic acid-d_4 (1.02 g, 8.0 mmol, prepared from nicotinic acid ethyl ester, isotope purity, 2,4,5,6-D4, 98%, Cambridge Isotope Laboratories) in thionyl chloride (5.0 mL) was refluxed for 2 h, and excess thionyl chloride was removed by distillation to yield nicotinoyl chloride-d_4. To a solution of morphine (1.10 g, 3.8 mmol) and pyridine (1.2 mL) in dichloromethane (10.0 mL) was added a solution of nicotinoyl chloride-d_4 (8.0 mmol) in dichloromethane (15.0 mL). After stirring at room temperature for 15 h, an additional solution of nicotinoyl chloride-d_4 (8.0 mmol) in dichloromethane (15.0 mL) was added. After stirring at room temperature for 15 h, the reaction solution was basified by adding a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted with dichloromethane, and the combined organic solution 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 dichloromethane-ethyl acetate (1:9, 1:4) as the mobile phase producing compound **11** (0.60 g, 1.1 mmol). Yield: 30%. mp: 174.3-175.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.90 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 5.79 (d, J = 9.8 Hz, 1H), 5.57 (d, J = 7.4 Hz, 1H), 5.28 (d, J = 6.8 Hz, 1H), 3.44 (s, 1H), 3.13 (d, J = 18.8 Hz, 1H), 2.86 (s, 1H), 2.73 (d, J = 20.0 Hz, 1H), 2.46 (s, 3H), 2.42-2.37 (m, 2H), 2.18-2.09 (m, 1H), 1.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 164.5, 162.7, 150.6, 132.4, 131.5, 129.5, 128.2, 125.3, 124.7, 121.9, 119.7, 88.4, 67.1, 60.0, 46.6, 42.9, 42.5, 40.2, 34.8, 29.7, 20.9. IR (KBr): 2923, 2893,2290, 2260, 1736, 1718, 1560, 1447, 1250, 1060, 776, 557 cm^{-1}. MS *m/z*: 503 (M^+, 91), 393 (56), 377 (84), 324 (23), 271 (50), 214 (21), 110 (100), 82 (70). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{29}H_{17}D_8N_3O_5$, 503.2288; found, 503.2288.

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