Synthesis of Potential Metabolites of the Brain Imaging Agents Methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-Iodophenyl)-8-alkyl-8-azabicyclo[3.2.1]octane-2-carboxylate

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The synthesis of potential hydroxy metabolites of the brain imaging agents methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate and methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-(3-fluoropropyl)-8-azabicyclo[3.2.1]octane-2-carboxylate are reported. The nitration of iodophenyltropanes **1** or **2** with nitronium tetrafluoroborate afforded the nitro compounds **3** or **4** which were reduced with iron powder to the corresponding amino compounds **5** and **6**. The final hydroxylated products **7** and **8** were obtained *via* a modified Sandmeyer reaction.

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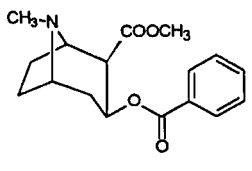
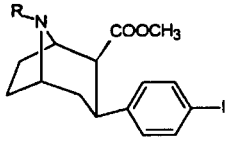
The cocaine congers methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**1**) [1] and its *N*-(3-fluoropropyl) analog **2** have been found to possess a high affinity for the cocaine binding site on the dopamine transporter. The ^{11}C, ^{18}F and ^{123}I analogs have been used for imaging the dopamine transporter with positron emission tomography and single photon emission computed tomography in the living human brain, respectively [2,3,4,5].



Cocaine

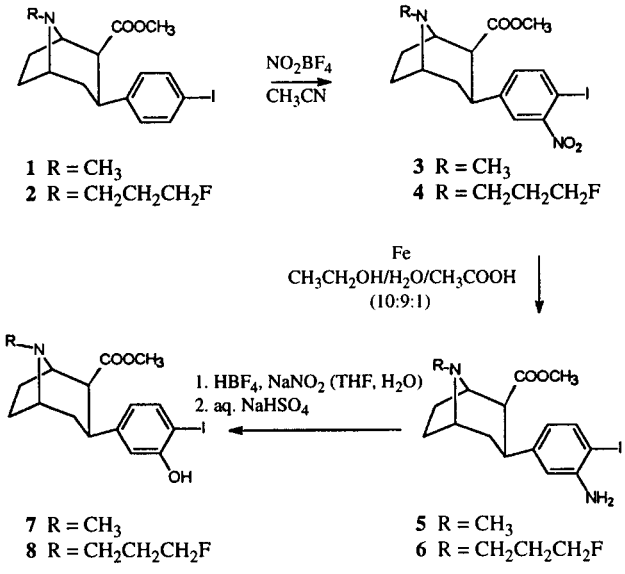


1 R = CH_3
2 R = $CH_2CH_2CH_2F$

Studies of the metabolism of cocaine has shown that one of the identified metabolites in urine is the *m*-hydroxylated cocaine analog [6] whose synthesis has recently been described [7]. This metabolic transformation could also be applied to compounds such as methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]-octane-2-carboxylate (**1**) and methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-(3-fluoropropyl)-8-azabicyclo[3.2.1]-octane-2-carboxylate (**2**). In order to positively identify the metabolites and to follow the metabolic breakdown of the phenyltropanes used for brain imaging studies, it is necessary to have available well characterized reference compounds [8]. Additionally, the synthesis of the potential hydroxy metabolites will make it possible to establish if they have retained affinity to the dopamine transporter or other pharmacological activity. The hydroxy metabolites would therefore be important tools for understanding the biochemistry of methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**1**) and methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-(3-fluoropropyl)-8-azabicyclo[3.2.1]octane-2-carboxylate (**2**).

The synthesis of the hydroxy compounds **7** and **8** are summarized in Scheme I. The published method for nitration of the aromatic ring in methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**1**) using 70% nitric acid and concentrated sulfuric acid [9] afforded very low yields (8%) of the *m*-nitro compound. None of the other possible *o*-nitro analogs were isolated. Nitration with nitronium tetrafluoroborate [10] under much milder conditions afforded **3** (54%) and a small amount of the crude *o*-nitro compound (about 4%). Nitration of methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-(3-fluoropropyl)-8-azabicyclo[3.2.1]octane-2-carboxylate (**2**) afforded only the desired *m*-nitro compound **4**, which was isolated in 56% yield after column chromatography. A number of reducing agents and conditions were used in an attempt to selectively reduce the nitro group without any deiodination. Sodium dithionite in different mixtures of methanol-water at either room temperature or 65° was attempted without a success. Reduction of the nitro group with 5% palladium on activated carbon at atmospheric pressure did not afford the corresponding amino analog. Reduction of the nitro group in compound **3** and **4** with iron powder under mild acid conditions [11] in a mixture of ethanol-water-acetic acid

Scheme I



afforded the desired amino compounds **5** (66%) and **6** (48%). A direct one-step amination of aromatic ring systems [12] with trimethylsilylazide and triflic acid was also tried for the synthesis of **6** from **2**. The hplc of the organic phase indicated that a number of different products were formed. An attempt to decompose the diazonium salt of **5** at room temperature by copper(II) oxide in an aqueous solution containing copper(II) nitrate [13] also did not afford the desired hydroxy compound. Hydroxydediazoniation of **5** and **6** *via* a modified Sandemeyer reaction gave the respective hydroxy metabolites **7** (52%) and **8** (44%). The reaction was carried out by preparing diazonium tetrafluoroborate *in situ* and decomposing the diazonium salt in aqueous sodium hydrogensulfate at 70°.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary tube apparatus and are reported uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Varian XL-300 spectrometer using tetramethylsilane as an internal reference. Mass spectra (FAB) were performed at Brown University Providence, RI, on a Kratos 80 spectrometer. High resolution FAB mass spectra was performed by M-Scan Inc., West Chester, PA on a VG Analytical ZAB 2SE high field mass spectrometer. All optical rotations were measured at the sodium D line using a Rudolph polarimeter (Model DP1A31, 10 cm cell). Elementary analyses, performed by Atlantic Microlabs, Atlanta, GA, were within ±0.4% of the theoretical values. Analytical thin layer chromatography was carried out on 0.2 mm thick Kiselgel $60F_{254}$ silica gel tlc plastic sheets (EM Science, Newark, NJ), and visualization was with 254 nm uv light. Flash chromatography on silica gel was used for routine purification of reaction products. The hplc instrument consisted of a Rainin gradient system with a multi-wavelength uv detector using Rainin microsorb C18, 5 μm (4.6 x 150 mm) column.

Methyl (1*R*,2*S*,3*S*,5*S*)-3-(3-Nitro-4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**3**).

To a solution of methyl (1*R*,2*S*,3*S*,5*S*)-3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**1**) (1.2 g, 3.13 mmoles) in dry acetonitrile at 0° under nitrogen was added solid nitronium tetrafluoroborate (1.5 g, 11.3 mmoles) in one portion. The stirred reaction mixture was kept between 0° and +2° for 6-7 hours and then left at -5° for 12 hours. The mixture was cooled in an ethanol-dry ice bath and ice (1.2 g) was added. The resulting mixture was filtered with suction. The filtrate was concentrated under vacuum and the orange-yellow residue was suspended in water, made alkaline (*p*H 8-9) with concentrated ammonium hydroxide and extracted with diethyl ether (4 x 50 ml). The combined organic phases were dried over magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography (hexane:diethyl ether 1:1 added 3% triethylamine) to give pure methyl (1*R*,2*S*,3*S*,5*S*)-3-(3-nitro-4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**3**) (720 mg, 54%) as a yellow-green gum and impure methyl (1*R*,2*S*,3*S*,5*S*)-3-(2-nitro-4-iodophenyl)-8-methyl-8-azabicyclo-[3.2.1]octane-2-carboxylate (48 mg) [14]. An analytical sample of **3** was crystallized from absolute ethanol and recrystallized from methanol-pentane to give yellow crystals, mp 100-101°; $[\alpha]^{20}_D$ -10.2° (free base, c 0.65, methanol); ^1H nmr (300 MHz, deuteriochloroform): of **3** δ 1.70 (m, 2H. H_{6ax}, H_{7ax}), 2.20 (m, 3H, H_{4eq}, H_{6eq}, H_{7eq}), 2.22 (s, 3H, N-CH_3), 2.54 (dt, 1H, H_{4ax}, J = 5.1 Hz, 12.8 Hz), 2.89 (t, 1H, H_2, J = 3.2 Hz), 3.00 (m, 1H, H_3), 3.38 (m, 1H. H_5), 3.54 (s, 3H, OCH_3), 3.62 (m, 1H, H_1); aromatic 7.20 (dd, 1H, J = 2.2 Hz, 7.7 Hz), 7.75 (d, 1H, J = 3.2 Hz), 7.90 (d, 1H, J = 7.7 Hz); ^{13}C nmr (75.4 MHz, deuteriochloroform): of **3** δ 25.4, 25.9 (C_6, C_7), 33.8, 34.0 (C_3, C_4), 42.0 (NCH_3), 51.5 (C_2), 52.6 (OCH_3), 62.2 (C_5), 65.4 (C_1), 171.8 (C=O); aromatic 82.9, 125.0, 133.0, 141.1, 146.0, 152.7; ms: (FAB, NBA) 443 (54, M+Na), 431 (100, $M+H^+$), 415 (8, M-CH_3), 399 (5, M-OCH_3), 371 (8, M-$COOCH_3$).

Anal. Calcd. for $C_{16}H_{19}IN_2O_4$: C, 44.67; H, 4.45; N, 6.51. Found: C, 44.77; H, 4.47; N, 6.45.

Methyl (1*R*,2*S*,3*S*,5*S*)-3-(3-Nitro-4-iodophenyl)-8-(3-fluoropropyl)-8-azabicyclo[3.2.1]octane-2-carboxylate (**4**).

The nitro compound was prepared from **2** (700 mg, 1.624 mmoles) as described for **3** using nitronium tetrafluoroborate (2.15 g, 16.2 mmoles). The crude product was purified twice by column chromatography (hexane:diethyl ether 6:1 added 3% triethylamine) to give **4** (430 mg, 56%) as a yellow foam. An analytical sample was crystallized from absolute ethanol to give a yellow crystalline powder, mp 68.5-70.0°; $[\alpha]^{20}_D$ -16.0 (free base, c 0.2, methanol); ^1H nmr (300 MHz, deuteriochloroform): δ 1.69 (m, 4H. H_{6ax}, H_{7ax}, CH_2), 2.09 (m, 2H, H_{6eq}, H_{7eq}), 2.38 (dt, 1H, H_{4eq}, J = 1.4 Hz, 6.3 Hz), 2.54 (dt, 1H, H_{4ax}, J = 1.9 Hz, 15.4 Hz), 2.91 (t, 1H, H_2, J = 3.8 Hz), 3.02 (m, 1H, H_3) 3.42 (bs, 1H, H_5), 3.52 (s, 3H, CH_3O), 3.72 (m, 1H, H_1), 4.42 (t, 1H, CH_2-F, J = 6.2 Hz), 4.59 (t, 1H, CH_2-F, J = 6.2 Hz); aromatic 7.20 (dd, 1H, J = 1.5 Hz, 8.5 Hz), 7.76 (d, 1H, J = 1.5 Hz), 7.90 (d, 1H, J = 8.5 Hz); ms: (FAB, NBA) 500 (11, M+Na), 477 (68, $M+H^+$).

Anal. Calcd. for $C_{18}H_{22}FIN_2O_4$: C, 45.39; H, 4.66; N, 5.58. Found: C, 45.45; H, 4.62; N, 5.78.

Methyl (1*R*,2*S*,3*S*,5*S*)-3-(3-Amino-4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**5**).

To a solution of **3** (408 mg, 0.95 mmole) in a mixture of ethanol:water:acetic acid (10:9:1) (40 ml), was added iron powder (400 mg). The suspension was refluxed for 20 minutes. The mixture was poured into 150 ml of water, made alkaline (*p*H 9) with concentrated ammonium hydroxide (28-30%) and extracted with ethyl acetate (4 x 100 ml). The combined organic layers were washed with water (2 x 100 ml), dried over magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography (hexane:diethyl ether 3:2 added 3% triethylamine) to give **5** as a yellow gum (250 mg, 66%); ^{1}H nmr (deuteriochloroform, 300 MHz): δ 1.64 (m, 2H. H_{6ax}, H_{7ax}), 2.10 (m, 3H, H_{4eq}, H_{6eq}, H_{7eq}), 2.20 (s, 3H, NCH_3), 2.49 (bt, 1H, H_{4ax}), 2.85 (m, 2H, H_2, H_3), 3.33 (bs, 1H, H_5), 3.52 (s, 3H, OCH_3), 3.54 (bs, 1H, H_1), 4.00 (bs, 2H, NH_2); aromatic 6.38 (dd, 1H, J = 3.2 Hz, 8.2 Hz), 6.65 (bs, 1H); 7.48 (d, 1H. J = 8.2 Hz); ^{13}C nmr (deuteriochloroform, 75.4 MHz): δ 25.2, 25.9 (C_6, C_7), 33.4, 34.0 (C_4, C_3), 42.0 (NCH_3), 51.2 (C_2), 52.6 (OCH_3), 62.3 (C_5), 65.3 (C_1), 172.0 (C=O); aromatic 81.1, 114.1, 119.4, 138.3, 145.0, 146.4. The hydrochloride salt of the amino compound was prepared by standard methods and recrystallized from methanol-diethyl ether to give a slightly yellow solid, mp 176° dec; $[\alpha]^{20}_D$ -98.0 (c 0.3, methanol); ms: (FAB, NBA) 423 (8, M+Na), 401 (100, M+H$^+$), 369 (2, M-OCH_3), 341 (3, M-$COOCH_3$).

Anal. Calcd. for $C_{16}H_{21}IN_2O_2$•2HCl•CH_3OH: C, 40.42; H, 5.39; N, 5.54. Found: C, 40.67; H, 5.35; N, 5.54.

Methyl (1*R*,2*S*,3*S*,5*S*)-3-(3-Amino-4-iodophenyl)-8-(3-fluoropropyl)-8-azabicyclo[3.2.1]octane-2-carboxylate (**6**).

The amino compound was prepared from **4** (527 mg, 1.106 mmoles) according to the method described for **5** using iron powder (200 mg). The reaction mixture was refluxed for 14 minutes. Purification of the crude product by column chromatography [step gradient with hexane:diethyl ether added 3% triethyl amine (4:1), (3:1), (2:1)] afforded **6** (238 mg, 48%) as a white foam. An analytical sample was converted to the mono hydrochloride salt by standard methods, mp 130°; $[\alpha]^{20}_D$ -115.8 (c 0.33, methanol); ^{1}H nmr (300 MHz, deuteriochloroform) (free base): δ 1.70 (m, 4H, H_{6ax}, H_{7ax}, CH_2), 2.03 (m, 2H, H_{6eq}, H_{7eq}), 2.35 (m, 2H, CH_2N), 2.49 (t, 1H, H_{4ax}, J = 13.6 Hz), 2.86 (m, 2H, H_2, H_3), 3.37 (m, 1H, H_5), 3.50 (s, 3H, CH_3O), 3.67 (m, 1H, H_1), 3.99 (bs, 2H, NH_2), 4.44 (t, 1H, CH_2F, J = 5.9 Hz), 4.60 (t, 1H, CH_2F, J = 5.9 Hz); aromatic 6.38 (dd, 1H, J = 2.1 Hz, 8.2 Hz), 6.67 (d, 1H, J = 2.1 Hz), 7.49 (d, 1H, J = 8.2 Hz); ms: (FAB, NBA) 469 (9, M+Na), 447 (100, M+H$^+$), 387 (3, M-$COOCH_3$).

Anal. Calcd. for $C_{18}H_{24}N_2O_2FI$•HCl•11/4 H_2O: C, 42.79; H, 5.49; N, 5.54. Found: C, 42.72; H, 5.39; N, 5.33.

Methyl (1*R*,2*S*,3*S*,5*S*)-3-(3-Hydroxy-4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**7**).

A solution of **5** (640 mg, 1.6 mmoles) in tetrahydrofuran was cooled in an ice bath. Water (4 ml) was added followed by 48% aqueous fluoboric acid (0.85 ml). A solution of sodium nitrite (153 mg, 2.2 mmoles) in water (4 ml) was added dropwise to the reaction mixture. The temperature was kept at 5-10° by the addition of crushed ice. The resulting mixture was stirred under nitrogen at 0° for 2.5 hours. The reaction mixture was added to a solution of 0.17 *M* aqueous sodium hydrogen sulfate (12 ml) at 70°. The mixture was stirred at 70° for 2 hours under nitrogen. The mixture was cooled, diluted with water (60 ml), made alkaline (*p*H 8) by addition of concentrated ammonium hydroxide and extracted with ethyl acetate (3 x 80 ml). The combined organic phases were washed with water (2 x 80 ml), dried over magnesium sulfate and evaporated to dryness under vacuum. Purification twice by column chromatography (first column eluted with dichloromethane:methanol 15:1 added 3% triethylamine. Second column eluted with ethyl acetate:toluene 10:1 added 3% triethylamine) afforded **7** (332 mg, 52%) as a white foam. An analytical sample was crystallized from hexane:ethyl acetate (49:1) to give a fine white microcrystalline powder, mp 107-109°; $[\alpha]^{20}_D$ -31.6 (c 0.25, methanol); ^{1}H nmr (deuteriochloroform, 300 MHz) δ 1.65 (m, 3H, H_{4eq}, H_{6eq}, H_{7eq}), 2.21 (m, 5H, H_{6eq}, H_{7eq}, NCH_3), 2.49 (m, 1H. H_{4ax}), 2.85 (m, 2H, H_2, H_3), 3.31 (m, 1H, H_5), 3.48 (s, 3H, OCH_3), 3.50 (m, 1H, H_1); aromatic 6.58 (dd, 1H, J = 2.0 Hz, 8.3 Hz), 6.91 (d, 1H, J = 2.0 Hz), 7.52 (d, 1H. J = 8.3 Hz); ^{13}C nmr (deuteriochloroform, 75.4 MHz): 25.3, 25.8, (C_6, C_7), 33.3, 34.1 (C_3,C_4), 42.1 (NCH_3), 51.3 (C_2), 52.7 (OCH_3), 62.4 (C_5), 65.4 (C_1), 172.2 (C=O); aromatic 82.5, 114.9, 120.5, 138.0, 145.7, 156.2; ms: (FAB, NBA) 424 (9, M+Na), 402 (100, M+H$^+$).

Anal Calcd. for $C_{16}H_{20}INO_3$: C, 47.9; H, 5.02; N, 3.49. Found: C, 48.03; H, 5.11; N, 3.38.

Methyl (1*R*,2*S*,3*S*,5*S*)-3-(3-Hydroxy-4-iodophenyl)-8-(3-fluoropropyl)-8-azabicyclo[3.2.1]octane-2-carboxylate (**8**).

The hydroxy compound was prepared from **6** (155 mg, 0.35 mmole) as described for **7** using aqueous fluoroboric acid 48% (0.2 ml) and sodium nitrite (33 mg, 0.48 mmole). Purification of the crude product by column chromatography [step gradient of diethyl ether:hexane added 3% triethylamine (2:1) and (5:1)] afforded **8** (69 mg, 44%) as a slightly beige powder, mp 62-64° dec; $[\alpha]^{20}_D$ -19.0 (c 0.21, methanol); ^{1}H nmr (deuteriochloroform, 300 MHz) (free base): δ 1.68 (m, 4H, H_{6ax}, H_{7ax}, CH_2), 2.02 (m, 2H, H_{6eq}, H_{7eq}), 2.36 (m, 3H. CH_2N, H_{4eq}), 2.48 (bt, 1H, H_{4ax}), 2.89 (m, 2H, H_2, H_3), 3.37 (m, 1H, H_5), 3.50 (s, 3H, CH_3O), 3.55 (bs, 1H, OH), 3.68 (m, 1H, H_1), 4.43 (t, 1H, CH_2F, J = 6.0 Hz), 4.59 (t, 1H, CH_2F, J = 6.0 Hz); aromatic 6.60 (dd, 1H, J = 3.0 Hz, 7.5 Hz), 6.86 (d, 1H, J = 3.0 Hz), 7.52 (d, 1H, J = 7.5 Hz); ms: (FAB, NBA) 470 (11, M+Na), 448 (100, M+H$^+$), 388 (3, M-$COOCH_3$).

Anal. Calcd. for $C_{18}H_{23}NO_3FI$•0.125 $(CH_3CH_2)_3N$: C,48.96; H, 5.45; N, 3.43. Found: C, 49.34; H, 5.47; N, 3.24. Repeated column chromatography followed by washing with brine and hexane did not afford a better elemental analysis; hrms (FAB+) of the product: Calcd. 448.0785. Found: 448.0746.

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