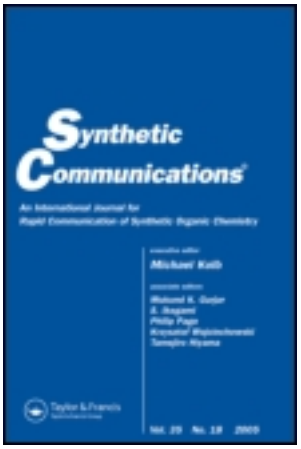

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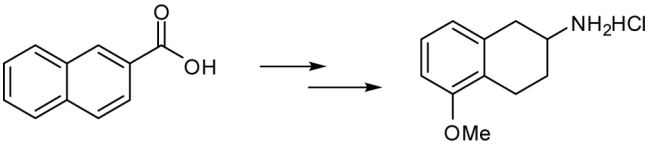
ALTERNATIVE AND STRAIGHTFORWARD SYNTHESIS OF DOPAMINERGIC 5-METHOXY-1,2,3,4-TETRAHYDRONAPHTHALEN-2-AMINE

Necla Öztaşkın, Süleyman Göksu, and Hasan Seçen
Department of Chemistry, Faculty of Science, Ataturk University, Erzurum, Turkey

GRAPHICAL ABSTRACT



Abstract *5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-amine was synthesized from 2-naphthoic acid in six steps with an overall yield of 27%. Following the reaction sequence, bromination, esterification, substitution with NaOMe in the presence of CuI, the Birch reduction, Curtius rearrangement, and hydrogenolysis afforded biologically active title compound 5-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine as hydrogen chloride salt.*

Keywords Aminotetralin; Birch reduction; Curtius rearrangement; dopamine; neurotransmitter; synthesis

Dopamine (**1**), a hormone-like neurotransmitter compound, plays an important role in central nervous system (CNS)–related disorders such as schizophrenia and Parkinson's disease.[1] Many chemical compounds have dopamine-like actions.[2] 2-Amino-1,2,3,4-tetrahydronaphthalene-6,7-diol (6,7-ADTN; **2**)[3] and 2-amino-1,2,3,4-tetrahydronaphthalene-5,6-diol (5,6-ADTN; **3**),[4] dopamine-like compounds, are potential agonists at dopamine receptors. Apomorphine (APM **4**), a potent dopamine agonist drug, has been tried for a variety of uses including psychiatric treatment and the treatment of neurological disorders, Parkinson's disease, and erectile dysfunction.[5]

McDermed and coworkers have reported that hydrogen iodide salt of levo enantiomer of aminotetralin **5** has the same dopaminergic activity as that of APM.[6] Hacksell et al. investigated the central dopamine-receptor stimulating activity of **6**, **7**, and some N-ethyl, methyl, and propyl derivatives of these compounds. They experimentally demonstrated that especially N-alkylated derivatives have important stimulating activities.[7] Binding assays of compounds **5**–**7** and their

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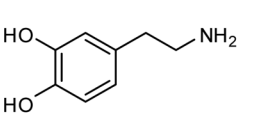
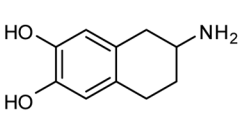
N-arylalkyl substituents for human dopamine D_2, D_3, and D_4 receptors have been evaluated by van Vliet et al. According to their experimental results, (S)-5-OH-DPAT **5** is more active at D_2 and D_3 receptors than **7**.[8] N,N-Dipropyl substituent of (R)-**6** has important agonist activity at the dopamine D_{2A} receptor.[9] α-Adrenergic activity of **6** has been investigated by DeMarinis et al.[10] Compound **6** and its N-alkyl substituents are potent monoamine oxidase inhibitors. N-Methylated substituent of this compound is an analgesic.[11] The title compound, 5-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (**6**), and some of its N-alkylated derivatives have been studied for 5-hydroxytryptaminergic (5-HT) actions in 5-HT receptors[12a,12b] and for their binding affinities at α_1-, α_2-, β-adrenergic; muscarinic; dopamine D_1, D_2, and D_3; and serotonin $5HT_{1A}$ and $5\text{-}HT_2$ receptors.[12c] Compounds **6**, **7**, and their N-alkylated compounds are also important antifungal agents.[13] Aminotetralin **7** has been defined as a tyramine analog and acts as an inhibitor of phenylethanolamine N-methyltransferase.[14]

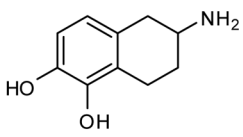
To the best of our knowledge, the known procedures for the synthesis of **6** and its N-alkyl derivatives are based on the preparation of 1-tetralone or 2-tetralone, which involves a number of steps. In the previous studies, the title compound has been synthesized by α-amination or carboxylation of 1-tetralone and by reductive amination of 2-tetralone.[7,8,10,13–15]



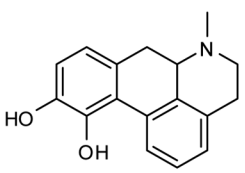
1 Dopamine



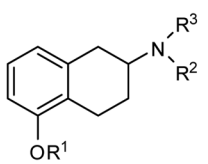
2 6,7-ADTN



3 5,6-ADTN



4 Apomorphine (APM)



5 R^1=H, R^2=R^3=n-propyl (5-OH-DPAT)
6 R^1=Me, R^2=R^3=H
7 R^1=R^2=R^3=H

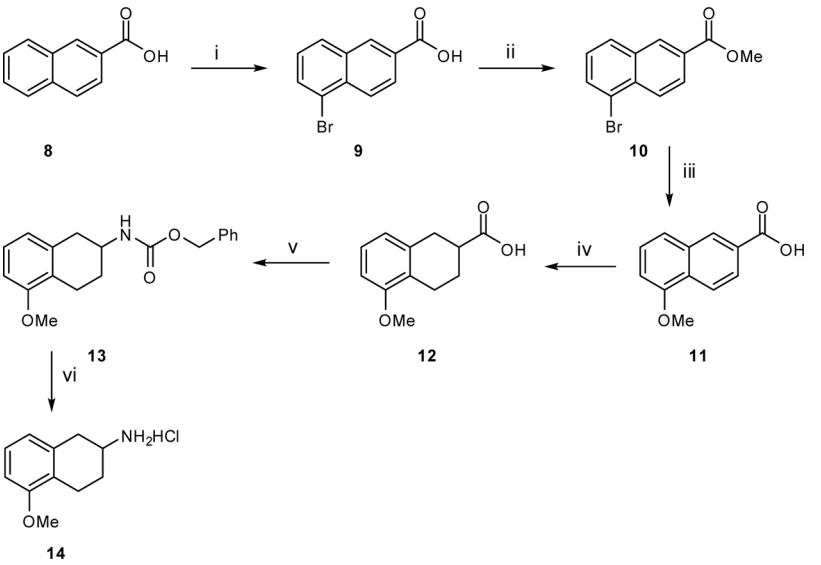
In our ongoing project on the synthesis of dopaminergic aminotetralines and aminoindanes, we have already reported[16] concise syntheses of 6,7-ADTN (**2**), 5,6-ADTN (**3**), and 2-aminoindanes. In the present study, we describe an alternative and straightforward synthesis of 5-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (**6**) as a hydrochloride salt starting with 2-naphthoic acid (**8**) in six steps.

Synthesis is started with 2-naphthoic acid (**8**). I_2-catalyzed bromination of **8** with molecular bromine in AcOH at 118 °C gave 5-bromo-2-naphthoic acid (**9**) with a yield of 46%.[17] Esterification of **9** in MeOH in the presence of TsOH (p-toluenesulfonic acid) gave the corresponding methyl ester **10** in good yield

(95%).[17] One of the critical steps of our synthesis was the substitution of bromine in compound **10** with NaOMe. Copper-assisted nucleophilic substitutions of similar aryl halides have been reported in our previous studies.[16c,18] By a similar approach, the reaction of bromoester **10** with NaOMe in the presence of CuI followed by NaOH-assisted hydrolysis of the residue in MeOH-H_2O and subsequent acidification of the residue afforded corresponding carboxylic acid **11**.[19]

The second crucial step in the synthesis of **6** was the Birch reduction of 5-methoxy-2-naphthoic acid (**11**). Fortunately, the reaction of **11** with 4 mol. equiv. of Na in liquid NH_3 proceeded from the electron-deficient ring of **11**, and acidification of the residue provided 5-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**12**) in excellent yield (90%). In the next step, carboxylic acid **12** was converted to carbamate **13** by applying the procedure described in the literature for the synthesis of 6,7-ADTN and 5,6-ADTN.[16a,16b,20] The Curtius reaction of **12** with diphenylphosphoryl azide in the presence of Et_3N in benzene at 80 °C for 6 h, followed by treatment with benzyl alcohol at the same temperature for 30 h, afforded **13** with a yield of 90%. Hydrogenolysis of **13** in MeOH in the presence of $CHCl_3$ (for producing HCl) gave **14**, a hydrochloride salt of **6**, as a pure and sole product in good yield (94%; Scheme 1).

In summary, we have achieved an alternative and convenient straightforward synthesis of biologically important 5-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (**6**) as a hydrochloride salt starting with 2-naphthoic acid (**8**) in six steps with an overall yield of 27%. In addition, we synthesized 5-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**12**), by an alternative method, and



Scheme 1. Synthesis of 2-aminotetralin **14**. Reagents and conditions: (i) Br_2 (I_2, catalytic), AcOH, 118 °C, 46%; (ii) MeOH/TsOH, 64 °C, 95%; (iii) (1) NaOMe/MeOH, DMF, CuI, reflux; (2) NaOH/MeOH-H_2O, 0–25 °C then HCl, 80%; (iv) (1) Na, liq. NH_3/THF; −70 °C; (2) 37% aq. HCl; 90%; (v) (1) $(PhO)_2P(O)N_3$, Et_3N, C_6H_6, reflux; (2) $PhCH_2OH$, reflux; 90%; and (vi) H_2, Pd-C, MeOH/$CHCl_3$, 25 °C, 94%.

carbamate **13** for the first time, which can be important synthons for further biological and synthetic purposes.

EXPERIMENTAL

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Melting points were determined on a capillary melting apparatus (Buchi 530) and are uncorrected. Infrared (IR) spectra were obtained from solutions in 0.1-mm cells with a Perkin-Elmer spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on Varian spectrometers at 200 (50) and 400 (100) MHz with Me_4Si as the internal standard. Coupling constants are reported in hertz (Hz). Multiplicity is defined as s (singlet), d (doublet), t (triplet), br (broad), or m (multiplet). Elemental analyses were performed on a Leco CHNS-932 apparatus. Electrospray ionization–mass spectra (ESI-MS) were performed on a Bruker MicroTOF-Q. All column chromatography was performed on silica gel (60 mesh, Merck). PLC is preparative thick-layer chromatography: 1 mm of silica gel 60 PF (Merck) on glass plates.

5-Bromo-2-naphthoic Acid (9)

A solution of Br_2 (10.00 g, 62.50 mmol) and I_2 (0.3 g, catalytic) in AcOH (10 mL) was added dropwise to a stirred solution of 2-naphthoic acid (**8**) (10.00 g, 58.12 mmol) in AcOH (40 mL) at 118 °C over a period of 20 min. The reaction mixture was stirred at the same temperature for 1 h. After the reaction mixture was cooled down to 60 °C (note: If the mixture is cooled to rt, further brominated products are also precipitated), solidified **9** was filtered and washed with hot H_2O (2×30 mL). Drying of the residue at 60 °C and recrystallization from MeOH afforded 5-bromo-2-naphthoic acid (**9**) (6.7 g, 46%). White crystals. Mp 266–268 °C (lit.[21] 267–269 °C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.69 (bs, 1H, H-1), 8.23 (AB, d, $J_{(3,4)} = 8.8$ Hz, 1H, H-4), 8.21 (ABX, d, $J_{(7,8)} = 7.7$ Hz, 1H, H-8), 8.15 (AB, dd, $J_{(3,4)} = 8.8$ Hz, $J_{(1,3)} = 1.6$ Hz, 1H, H-3), 8.03 (ABX, d, $J_{(6,7)} = 7.4$ Hz, 1H, H-6), 7.54 (ABX, quasi t, $J = 7.8$ Hz, 1H, H-7), 3.40 (bs, OH). ^{13}C NMR (50 MHz, DMSO-d_6): δ 168.7, 135.4, 134.8, 134.0, 132.9, 131.5, 131.0, 129.3, 128.8, 128.6, 123.3.

Methyl 5-Bromo-2-naphthoate (10)

5-Bromo-2-naphthoic acid (**9**) (6.00 g, 24 mmol) was dissolved in MeOH (60 mL). A catalytic amount of TsOH (90 mg) was added to this solution, and the reaction mixture was refluxed for 24 h. After MeOH was evaporated, $CHCl_3$ (80 mL) and H_2O (60 mL) were added to this residue. The organic layer was separated and washed with a saturated solution of Na_2CO_3 (3×10 mL). Drying of the organic layer over Na_2SO_4, and evaporation of the solvent and crystallization from AcOEt/hexane gave methyl 5-bromo-2-naphthoate (**10**) (6.00 g, 95%). White crystals. Mp 70–72 °C (lit.[17] 72–73 °C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.56 (bs, 1H, H-1), 8.12–8.02 (m, 4H, H-3, H-4, H-6, and H-8), 7.46 (quasi t, $J = 7.8$ Hz, 1H, H-2), 3.92 (s, methoxide, 3H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 167.5, 135.2, 134.8, 134.1, 132.8, 131.4, 129.6, 129.3, 128.6, 128.2, 123.3, 54.1.

5-Methoxy-2-naphthoic Acid (11)

Na (1.56 g, 67.83 mmol) was added to refluxed MeOH (90 mL) in small pieces for 1 h under N_2. To this solution was added a solution of **10** (6.00 g, 22.65 mmol) in freshly distilled DMF (50 mL) over CaH_2. While the reaction mixture was being refluxed, CuI (100 mg) was added. After refluxing for 3 days, the reaction mixture was cooled to room temperature and MeOH was evaporated. Then 150 mL of $CHCl_3$ and 60 mL of H_2O were added, and the organic phase was separated. The organic phase was washed with H_2O (5×50 mL). After evaporation of the solvent, the residue was hydrolyzed with 2 M NaOH in MeOH/H_2O (80 mL, 4:1) at room temperature for 12 h. Then MeOH was evaporated. H_2O (70 mL) and CH_2Cl_2 (70 mL) were added to the residue. The organic phase was dispatched, and the aqueous phase was acidified with 37% HCl (pH 2). AcOEt (100 mL) was added to the aqueous phase, and the organic phase was separated. The aqueous phase was again extracted with AcOEt (2×60 mL), and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent yielded **11** (3.66 g, 80%). White crystals. Mp 213–215 °C (solidified, lit.[21] 214–216 °C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.57 (d, $J_{(1,3)} = 1.7$ Hz, 1H, H-1), 8.24 (AB, d, $J_{(3,4)} = 8.8$ Hz, 1H, H-4), 7.98 (AB, dd, $J_{(3,4)} = 8.8$ Hz, and $J_{(1,3)} = 1.7$ Hz, 1H, H-3), 7.67 (ABX, d, $J_{(7,8)} = 8.3$ Hz, 1H, H-8), 7.53 (ABX, quasi t, $J = 8.0$ Hz, 1H, H-7), 7.12 (ABX, d, $J_{(6,7)} = 6.8$ Hz, 1H, H-6), 4.00 (s, methoxide, 3H); 3.38 (bs, OH). ^{13}C NMR (50 MHz, DMSO-d_6): δ 169.2, 156.5, 135.0, 131.8, 130.4, 128.9, 128.5, 126.3, 123.7, 123.0, 108.4, 57.5.

5-Methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid (12)

Small pieces of Na (2.27 g, 98.7 mmol) were added to a stirred solution of **11** (5.00 g, 24.75 mmol) in liquid NH_3 (200 mL) and THF (50 mL) at −70 °C for 1.5 h under an N_2 atmosphere. When the addition of Na was complete, the mixture was stirred at the same temperature for 1 h. H_2O (25 mL) in EtOH (40 mL) was added to the reaction mixture dropwise for 1 h at the same temperature under N_2 fumes. After NH_3 and EtOH were evaporated from the reaction mixture, ice (150 g) was added to the mixture. The cold mixture was acidified with 37% aq. HCl (pH 3). The aqueous layer was extracted with AcOEt (3×50 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated, and the residue was crystallized from $CHCl_3$/hexane to afford 4.60 g (90%) of **12**. White crystals. Mp 147–149 °C (lit.[22] 150–151 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.60 (bs, 1H, OH); 7.11 (quasi t, $J = 7.8$ Hz, 1H, H-7), 6.74 (d, $J_{(7,8)} = 7.8$ Hz, 1H, H-8), 6.68 (d, $J_{(6,7)} = 8.2$ Hz, 1H, H-6), 3.82 (s, methoxide, 3H), 3.08–2.90 (m, 3H), 2.79–2.71 (m, 1H), 2.60 (ddd, $J = 17.2$ Hz, $J = 10.9$ Hz, and $J = 6.2$ Hz, 1H, H-2), 2.32–2.25 (m, 1H), 1.85 (dddd, $J = 17.2$ Hz, $J = 13.2$ Hz, $J = 11.3$ Hz, and $J = 5.9$ Hz, 1H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.5, 157.5, 136.2, 126.5, 124.8, 121.4, 107.5, 55.4, 39.7, 31.7, 25.6, 22.6.

Benzyl 5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-ylcarbamate (13)

Diphenylphosphoryl azide (1.50 g, 5.4 mmol) and Et_3N (0.60 g, 5.94 mmol) were added to a stirred solution of **12** (1.00 g, 4.86 mmol) in anhydrous benzene

(40 mL). After the mixture was heated at reflux for 6 h, benzyl alcohol (1.57 g, 14.54 mmol) was added to the reaction mixture, and the solution was refluxed for 30 h. After the mixture was cooled to room temperature, the solvent was evaporated. The residue was purified by column chromatograhy (SiO_2, 20 g; hexane/AcOEt, 4:1) to give 1.36 g (90%) of **13**. Colorless solid. Mp 84–86 °C ($CHCl_3$/hexane). IR (KBr, cm^{-1}): 3326, 3064, 3034, 2937, 2837, 1699, 1586, 1470, 1456, 1439, 1344, 1306, 1257, 1220, 1092, 1077, 913. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44–7.32 (m, aromatic, 5H); 7.12 (quasi t, $J = 7.8$ Hz, 1H, H-7), 6.70 (br d, $J = 8.0$ Hz, 2H, H-6, and H-8), 5.13 (s, 2H, OCH_2), 4.88 (bs, 1H, NH), 4.06 (m, 1H, H-2), 3.84 (s, methoxide, 3H), 3.13 (dd, $^2J = 15.6$ Hz, and $^3J = 4.7$ Hz, 1H, H-1), 2.95–2.60 (m, 3H), 2.17–2.00 (m, 1H), 1.89–1.64 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.2 (CO), 155.8 (C-5), 136.6, 135.3, 128.5, 128.1 (2C), 126.5, 124.4, 121.6, 107.4, 66.6, 55.2, 46.4, 36.0, 28.4, 21.0. Elemental analysis calculated for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.24; H, 6.86; N, 4.40. EI-MS: 311.1 (M^+, 1), 219.8 (28), 173.8 (20), 160.9 (25), 159.9 (75), 158.7 (100), 143.7 (28), 90.8 (65).

5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-amine Hydrochloride (14)

Pd/C (60 mg) and **13** (0.50 g, 1.6 mmol) in MeOH (30 mL) and $CHCl_3$ (1 mL, for producing HCl) were placed in a 100-mL flask. A balloon filled with H_2 gas (3 L) was fitted to the flask. The mixture was deoxygenated by flushing with H_2 and then hydrogenated for 24 h at room temperature. The catalyst was removed by filtration. The evaporation of the solvent and recrystallization of the residue from MeOH/Et_2O resulted in 0.32 g (94%) of **14**. Colorless solid. Mp 264–266 °C (lit.[13a] 265–267 °C). ^{1}H NMR (400 MHz, D_2O): δ 7.03 (t, $J = 7.9$ Hz, 1H, H-7), 6.68 (d, $J_{(7,8)} = 8.1$ Hz, 1H, H-8), 6.64 (d, $J_{(6,7)} = 7.8$ Hz, 1H, H-6), 4.65 (bs, NH_3^+), 3.64 (s, methoxide, 3H), 3.37 (m, 1H, H-2), 2.97 (dd, $^2J = 16.1$ Hz, and $^3J = 4.4$ Hz, 1H, H-1), 2.73–2.65 (m, 2H), 2.43 (ddd, $J = 14.3$ Hz, $J = 10.3$ Hz, and $J = 6.2$ Hz, 1H), 2.04 (m, 1H), 1.64 (dddd, $J = 16.5$ Hz, $J = 12.8$ Hz, $J = 10.3$ Hz, and $J = 5.9$ Hz, 1H). ^{13}C NMR (100 MHz, D_2O): δ 156.8, 133.8, 127.3, 123.6, 121.9, 109.0, 55.7, 47.2, 32.9, 22.2, 20.8.

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