The first synthesis of dopamine and rotigotin analogue 2-amino-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene

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SUPPORTING INFORMATION

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. IR spectra were obtained from solutions in 0.1 mm cells with a *Perkin-Elmer* spectrophotometer. The ^1H - and ^{13}C - NMR spectra were recorded on 400 (100)-MHz *Varian and Bruker spectrometers*; δ in ppm, Me_4Si as the internal standard. Elemental analyses were performed on a Leco CHNS-932 apparatus. 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.

Acid **8**,¹ alkyl halide **10**² and tetralone **13**³ were synthesized according to the literature procedure.

3-(3,5-Dimethoxyphenyl)propanoic acid (**8**)

Mp. 58-60 °C (lit¹ Mp. 60.5-61.5 °C). ^{13}C -NMR (100 MHz, CDCl_3) δ 179.2 (CO), 161.2 (2C), 142.8 (C), 106.6 (2CH), 98.6 (CH), 55.5 (2OCH₃), 35.6 (CH₂), 31.1 (CH₂).

^1H -NMR data of **8** is in agreement with data given in the lit.¹

3-(3,5-Dimethoxyphenyl)propan-1-ol (**9**)

To a stirred solution of acid **8** (2.00 g, 9.5 mmol) in THF (50 ml) at 0 °C was added LiAlH_4 (0.36 g, 9.5 mmol) carefully. The reaction mixture was stirred at the same tem. for 30 min and then at room temp. for 24 h. The mixture was cooled to 0 °C and a solution of THF- H_2O (1:1, 20 ml) was added to the reaction mixture dropwise. After the most of THF was evaporated, EtOAc (40 ml) and H_2O (20 ml) were added to the residue. Organic layer was separated and

H₂O layer was extracted with EtOAc (2x20 ml). Drying of combined organic layers over Na₂SO₄ and evaporation of the solvent afforded colorless oily alcohol **9** (1.65 g, 88% yield). ¹³C-NMR (100 MHz, CDCl₃) δ 161.0 (2C), 144.5 (C), 106.8 (2CH), 98.1 (CH), 62.4 (CH₂OH), 55.5 (2OCH₃), 34.2 (CH₂), 32.6 (CH₂).

¹H-NMR data of **9** is in agreement with data given in the lit.⁴

4-(3,5-Dimethoxyphenyl)butanenitrile (11)

NaCN (1.08 g, 22.02 mmol) was added to a solution of alkyl bromide **10** (1.90 g, 7.34 mmol) in DMF (25 ml) at 50 °C. The reaction mixture was stirred at the same temperature for 24 h. After the mixture was cooled to room temperature, EtOAc (80 ml) and H₂O (20 ml) was added to this mixture. Organic layer was separated and extracted with H₂O (3x20 ml). Organic phase was dried over Na₂SO₄ and the solvent was evaporated. Chromatography of the residue on silica gel column (30 g) with 30% EtOAc-hexane gave colorless liquid nitrile **11** (1.28 g, 85%). ¹H-NMR (400 MHz, CDCl₃) δ 6.33 (s, 3H, Ar-H), 3.77 (s, 6H, 2OCH₃), 2.71 (t, 2H, CH₂, J=7.4 Hz), 2.31 (t, 2H, CH₂, J=7.4 Hz), 1.96 (quintet, 2H, CH₂, J=7.4 Hz). ¹³C-NMR (100 MHz, CDCl₃) δ 161.22 (2C), 142.30 (C), 119.80 (CN), 106.41 (2CH), 98.50 (CH), 55.52 (2OCH₃), 34.84 (CH₂), 26.94 (CH₂), 16.59 (CH₂). IR (CH₂Cl₂ cm⁻¹) 3001, 2939, 2840, 2246, 1732, 1597, 1463, 1430, 1349, 1325, 1294, 1255, 1205, 1154, 1071, 940. Anal. Calcd for C₁₂H₁₅NO₂: C 70.22, H 7.37, N 6.82; found: C 70.18, H 7.39, N 6.80.

4-(3,5-Dimethoxyphenyl)butanoic acid (12)

6 M aqueous solution of NaOH (5 ml) was added to a solution of nitrile **11** (1.20 g, 5.85 mmol) in EtOH (50 ml) at room temp. The reaction mixture was heated to 78 °C. After the mixture was refluxed for 24 h at the same temp., it was cooled to rt and the most of EtOH was evaporated. Ice (30 g) was added to the residue and the mixture was acidified with 37% aq. HCl to pH 2. To this mixture was added EtOAc (40 ml) and organic layer was separated. H₂O layer was extracted with EtOAc (2x30 ml). The Combined organic layers were dried over Na₂SO₄. Evaporation of solvent and crystallization of the residue with CH₂Cl₂-hexane yielded acid **12** as white crystals (1.25 g, 90% yield). Mp. 60-62 °C (lit⁵ Mp. 58-60 °C). ¹H-NMR (400 MHz, CDCl₃) δ 11.10 (bs, 1H, OH), 6.34 (s, 2H, 2Ar-H), 6.32 (s, 1H, Ar-H) 3.78 (s, 6H, 2xOCH₃), 2.62 (t, 2H, CH₂, J=7.7 Hz), 2.38 (t, 2H, CH₂, J=7.7 Hz), 1.96 (quintet, 2H, CH₂, J=7.4 Hz). ¹³C-NMR (100 MHz, CDCl₃) δ 180.00 (CO₂H), 161.00 (2C), 143.8 0 (C), 106.80 (2CH), 98.20 (CH), 55.50 (2xOCH₃), 35.48 (CH₂), 33.50 (CH₂), 26.20 (CH₂).

Methyl 6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (16)

To a stirred solution of ketone **13** (1.20 g, 5.83 mmol) in dry THF (30 ml) were added NaH (0.35 g, 14.6 mmol) and a solution of Me₂CO₃ (1.31 g, 14.6 mmol) in dry THF (10 ml) under N₂(g) at rt. The mixture was refluxed for 24 h under N₂(g). After AcOH (2 ml) was added to the cooled reaction mixture, most of THF was evaporated. CH₂Cl₂ (60 ml) and a solution of Na₂CO₃ (50 ml) were added to the residue. Organic layer was separated, washed with Na₂CO₄ (2x30 ml) and H₂O (30 ml). After drying over Na₂SO₄ and evaporation of CH₂Cl₂, column chromatography of the residue on silica gel (30 g) with 30% EtOAc-hexane afforded an inseparable mixture of **14** and **15** which were directly converted to **16** without further characterization. CF₃CO₂H (10 ml) and Et₃SiH (1.43 g, 12.31 mmol) were added to a mixture of **14** and **15** (1.30 g, 4.92 mmol). The reaction mixture was refluxed for 2.5 h under N₂(g). The reaction mixture was cooled to rt and CF₃CO₂H was evaporated. Conc. NaHCO₃ solution in H₂O (40 ml) and EtOAc (40 ml) were added to the residue and organic layer was separated. H₂O phase was extracted with EtOAc (2x40 ml) and combined organic layers were washed with H₂O (30 ml). Organic phase was dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. Oily compound **16** was obtained by eluting of the residue on silica gel column with 5%, 10% and 30% EtOAc-hexane (1.16 g, 80% yield). ¹H-NMR (400 MHz, CDCl₃) δ 6.29 (d, 1H, Ar-H, J=2.0 Hz), 6.2 (d, 1H, Ar-H, J=2.0 Hz), 3.79 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.08-2.96 (m, 1H), 2.82-2.78 (m, 2H), 2.70-2.64 (m, 2H), 2.20-2.13 (m, 1H), 1.80 (dddd, 1H, ³J=6.9, ³J=10.8, ³J=12.4, ²J=17.7 Hz). ¹³C-NMR (100 MHz, CDCl₃) δ 176.4 (CO), 158.7 (C), 158.5 (C), 137.7 (C), 116.5 (C), 104.2 (CH), 96.2 (CH), 55.4 (2C, OCH₃), 51.9 (OCH₃), 40.1 (CH), 29.4 (CH₂), 25.8 (CH₂), 25.5 (CH₂). IR (CH₂Cl₂, cm⁻¹): 3006, 2996, 2949, 2839, 1735, 1609, 1596, 1492, 1458, 1436, 1360, 1342, 1301, 1273, 1256, 1236, 1196, 1170, 1148, 1105, 1052, 1027, 1027, 962, 937. Anal. Calcd for C₁₄H₁₈O₄: C 67.18, H 7.25; found: C 67.12, H 7.28.

6,8-Dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (17)

10% aqueous solution of NaOH (20 ml) was added to a solution of carboxylate **16** (1.10 g, 4.40 mmol) in MeOH (40 ml). The reaction mixture was stirred at rt for 24 h. After MeOH was evaporated, ice (40 g) was added to the residue and the mixture was acidified with 37% aq. HCl to pH 2. CH₂Cl₂ (50 ml) was added to the mixture and organic layer was separated. H₂O layer was extracted with CH₂Cl₂ (3x50 ml). After drying of the combined organic layers over Na₂SO₄, CH₂Cl₂ was evaporated. Crystallization of the residue with CH₂Cl₂-hexane gave acid **17**⁶ (0.90 g, %87 yield). Mp. 134-136 °C. ¹H-NMR (400 MHz, CDCl₃): δ 11.56 (bs, 1H,

OH), 6.31 (d, 1H, Ar-H, J=2.1 Hz), 6.25 (d, 1H, Ar-H, J=2.1 Hz), 3.80 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.11-3.05 (m, 1H), 2.85-2.82 (m, 2H), 2.76-2.64 (m, 2H), 2.25-2.17 (m, 1H), 1.85 (dddd, 1H, ³J=6.4, ³J=10.7, ³J=12.46, ²J=17.0 Hz). ¹³C-NMR (100 MHz, CDCl₃): δ 182.6 (CO), 158.8 (C), 158.5 (C), 137.6 (C), 116.3 (C), 104.2 (CH), 96.3 (CH), 55.5 (2x OCH₃), 40.0 (CH), 29.3 (CH₂), 25.6 (CH₂), 25.2 (CH₂). Anal. Calcd for C₁₃H₁₆O₄: C 66.09, H 6.83; found: C 66.16, H 6.78.

Benzyl 6,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-ylcarbamate (18)

To a stirred solution of acid **17** (2.00 g, 8.47 mmol) in anhydrous benzene (40 ml) were added diphenylphosphoryl azide (2.80 g, 10.16 mmol) and Et₃N (1.03 g, 10.16 mmol) at rt. The mixture was heated at reflux temp for 6 h. Benzyl alcohol (2.75 g, 25.41 mmol) was added to the reaction mixture, and it was refluxed for 30 h. After the mixture was cooled to rt, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (40 g) with 20% EtOAc-hexane. The latest solid was crystallized with EtOAc-hexane and carbamate **18** was obtained as white crystals (2.46 g, 85% yield). Mp. 129-131 °C. ¹H-NMR (400 MHz, CDCl₃): δ 7.37-7.30 (m, 5H, Ar-H, (Ph)), 6.28 (d, 1H, Ar-H, J=2.2 Hz), 6.23 (d, 1H, Ar-H, J=2.2 Hz), 5.11 (s, 2H, OCH₂), 4.84 (d, 1H, NH, J=7.1 Hz), 4.05-3.96 (m, 1H, CH) 3.78 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 3.00 (A part of AB, dd, 1H, ²J=16.7, ³J=5.2 Hz), 2.85-2.81 (m, 2H), 2.38 (B part of AB, dd, 1H, ²J=16.7, ³J=8.2 Hz), 2.06-2.00 (m, 1H), 1.82-1.68 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ 160.0 (CO), 158.7 (C), 156.0 (C), 137.5 (C), 136.9 (CH (Ph)), 128.8 (3CH (Ph)), 128.3 (2CH (Ph)), 115.6 (C), 104.2 (CH), 96.3 (CH), 66.8 (OCH₂), 55.53 (OCH₃), 55.47 (OCH₃), 47.0 (CH), 29.7 (CH₂), 28.9 (CH₂), 28.0 (CH₂). IR (CH₂Cl₂, cm⁻¹): 3684, 3317, 2943, 2880, 2838, 1692, 1595, 1519, 1493, 1455, 1424, 1342, 1306, 1271, 1212, 1194, 1147, 1097, 1050, 934. Anal. Calcd for C₂₀H₂₃NO₄: C 70.36, H 6.79, N 4.10; found: C 70.35, H 6.80, N 4.13.

2-Amino-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene hydrogen chloride (19)

Pd/C (80 mg) and carbamate **18** (2.00 g, 5.87 mmol) in MeOH (60 ml) and CHCl₃ (4 ml, for producing HCl) were placed in a 100-mL flask. A balloon filled with H₂ gas (3 L) was fitted to the flask. The mixture was deoxygenated by flushing with H₂. The mixture was hydrogenated for 24 h at rt. After the catalyst was removed by filtration, evaporation of the solvent and recrystallization of the residue from MeOH-Et₂O afforded amine hydrochloride salt **19** (1.86, 94% yield). Colorless solid. Mp. 280-282 °C. ¹H-NMR (400 MHz, D₂O): δ 6.30 (s, 1H, Ar-H), 6.27 (s, 1H, Ar-H), 4.65 (bs, 3H of NH₃ and H₂O of D₂O), 3.66 (s, 3H, OCH₃),

3.64 (s, 3H, OCH₃), 3.45-3.37 (m 1H, CH), 2.93 (dd, 1H, ²J=16.4 Hz, ²J=5.5 Hz), 2.73-2.69 (m, 2H), 2.36 (dd, 1H, ²J=16.4, ³J=9.6 Hz), 2.06-1.98 (m, 1H), 1.66 (dddd, 1H, ³J=7.5, ³J=10.3, ³J=12.2, ²J=17.3 Hz). ¹³C-NMR (100 MHz, D₂O): δ 158.5 (C), 158.1 (C), 137.3 (C), 113.9 (C), 105.0 (CH), 96.6 (CH), 55.7 (OCH₃), 55.5 (OCH₃), 47.6 (CH), 27.0 (CH₂), 26.8 (CH₂), 26.4 (CH₂). Anal. Calcd for C₁₂H₁₈ClNO₂: C 59.14, H 7.44, N 5.75; found: C 59.10, H 7.47, N 5.74.

¹H and ¹³C-NMR spectra of synthesized compounds 8-13 and 16-19

¹H-NMR spectra of compound 8.

¹³C-NMR spectra of compound 8.

¹H-NMR spectra of compound 9.

^{13}C -NMR spectra of compound 9.

¹H-NMR spectra of compound 10.

¹³C-NMR spectra of compound 10.

¹H-NMR spectra of compound 11.

¹³C-NMR spectra of compound 11.

¹H-NMR spectra of compound 12.

^{13}C -NMR spectra of compound 12.

^1H -NMR spectra of compound 13.

¹³C-NMR spectra of compound 13.

¹H-NMR spectra of compound 16.

¹³C-NMR spectra of compound 16.

¹H-NMR spectra of compound 17.

¹³C-NMR spectra of compound 17.

¹H-NMR spectra of compound 18.

¹³C-NMR spectra of compound 18.

¹H-NMR spectra of compound 19.

¹³C-NMR spectra of compound 19.

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