A Concise Synthesis of 2-Amino-1,2,3,4-tetrahydronaphthalene-6,7-diol ('6,7-ADTN') from Naphthalene-2,3-diol

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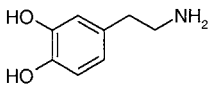
2-Amino-1,2,3,4-tetrahydronaphthalene-6,7-diol (**2**; 6,7-ADTN) was synthesized starting from naphthalene-2,3-diol in seven steps and with an overall yield of 44%. Methylation of naphthalene-2,3-diol with dimethyl sulfate, followed by *Friedel–Crafts* acylation with AcCl, gave 2-acetyl-6,7-dimethoxynaphthalene. 2-Acetyl-6,7-dimethoxynaphthalene was converted to 6,7-dimethoxynaphthalene-2-carboxylic acid by a haloform reaction. *Birch* reduction of the carboxylic acid with 4 mol-equiv. of Na in liquid ammonia afforded 1,2,3,4-tetrahydro-6,7-dimethoxynaphthalene-2-carboxylic acid, from which **2** was obtained by a *Curtius* reaction, followed by hydrogenolysis and demethylation.

Introduction. – Dopamine (**1**) [1], a hormone-like substance, is an important neurotransmitter. When present in normal quantities, it facilitates critical brain functions. 2-Amino-1,2,3,4-tetrahydronaphthalene-6,7-diol (='2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene', 6,7-ADTN; **2**) is a compound suggested to act as a potential agonist at the dopamine receptors [2] and to stimulate helix dopamine receptors [3]. It also has a strong central stimulant action [4] and is as active as dopamine in producing adenylate cyclase activity [5][6]. It has been suggested that 6,7-ADTN (**2**) interacts with the dopamine receptor with slightly greater affinity than dopamine itself [7].



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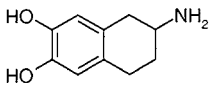

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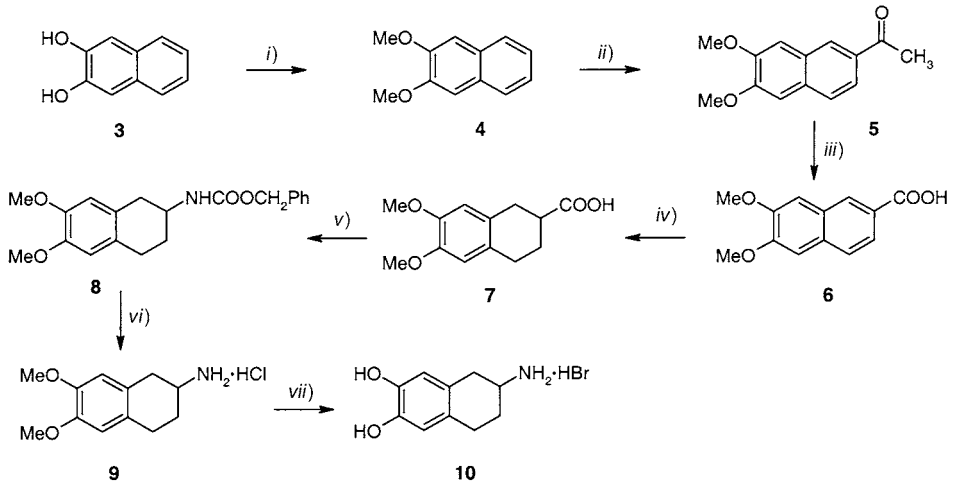
Thrift [8a], starting from veratrol, performed the first synthesis of 6,7-ADTN (**2**)[1]). *Cannon et al.* [9] described the second method for the preparation of **2** starting from ethyl 3-(3,4-dimethoxyphenyl)propanoate. *Horn et al.* [10] developed a procedure for the synthesis of **2** starting from (3,4-dimethoxyphenyl)acetic acid. *Narula* and *Schuster* [11] synthesized **2** from 2-(3,4-dimethoxyphenyl)ethanol *via* functionalized aryllithium reagents. *Nordlander et al.* [12] developed the first asymmetric synthesis of (*R*)-6,7-ADTN by using veratrol and D-aspartic acid. (*R*)-1,2,3,4-tetrahydro-6,7-dimethoxynaphthalene-2-amine, *O*-methylated 6,7-ADTN, was synthesized by *Charlton et al.* [13] starting from 2-amino-4,5-dimethoxybenzoic acid. These syntheses of **2** were performed in 5–9 steps with overall yields ranging from 12 to 52%. In this paper, we report a convenient synthesis of 6,7-ADTN (**2**) with a moderate overall yield (44%) starting

[1]) For a modified synthesis, see [8b].

from naphthalene-2,3-diol (**3**), a commercially available naphthalene derivative, which was used in the synthesis of **2** for the first time (*Scheme*).

Scheme



i) Me_2SO_4, K_2CO_3, acetone, reflux; 94%. *ii*) AcCl, $AlCl_3$, 1,2-dichloroethane, 0°; 88%. *iii*) Br_2, NaOH, then 6M HCl, 90%. *iv*) Na, liq. NH_3, then 37% HCl; 90%. *v*) $(PhO)_2P(O)N_3$, Et_3N, C_6H_6, reflux; then $PhCH_2OH$, reflux; 86%. *vi*) H_2, Pd-C, EtOH, $CHCl_3$; 96%. *vii*) 48% HBr, reflux; 80%.

Results and Discussion. – The synthesis started with naphthalene-2,3-diol (**3**). Methylation of **3** with Me_2SO_4 in the presence of K_2CO_3 gave 2,3-dimethoxynaphthalane (**4**). Our literature search showed that the *Friedel–Craft* acetylation of **4** has been performed by reacting with AcCl in $PhNO_2$ to give 1-(6,7-dimethoxynaphthalen-2-yl)ethanone (**5**) [14][15]. Despite moderate yields, these procedures involve some difficulties related to the removal of solvent and a series of workup procedures. Another procedure [16], again performed in $PhNO_2$ with Ac_2O, gave **5** in low yield. Our method for the preparation of **5** was to react **4** with AcCl in 1,2-dichloroethane. Thus, this simple method gave **5** in high yield. Acetyl compound **5** was converted to carboxylic acid **6** by a haloform reaction (Br_2/NaOH). The most critical step of our synthesis was the *Birch* reduction of 6,7-dimethoxynaphthalene-2-carboxylic acid (**6**). We assume that the *Birch* reaction of **6** proceeded by the reduction of the electron-deficient ring of **6**. Indeed, the reaction of **6** with 4 mol.-equiv. of Na in liquid NH_3 afforded tetrahydronaphthalene derivative **7** in high yield (90%). The conversion of the carboxylic acid **7** to carbamate **8** was performed by a known procedure *via Curtius* rearrangement, followed by treatment with $PhCH_2OH$. Hydrogenolysis of **8** in MeOH in the presence of $CHCl_3$ gave a pure dimethoxy derivative of 6,7-ADTN hydrochloride **9** as the sole product. The demethylation of **9** to hydrobromide of 6,7-ADTN, **10**, was performed as described in the literature.

In summary, with relatively little synthetic effort, we have achieved a concise synthesis of 6,7-ADTN (**2**) in seven steps starting from commercially available naphthalane-2,3-diol (**3**) (overall yield of 44%).

Experimental Part

General. Column chromatography (CC): silica gel (60 mesh, *Merck*). Prep. thick-layer chromatography (PLC): 1-mm of silica gel *60 PF* (*Merck*) on glass plates. M.p.: *Thomas-Hoover* cap. melting-point apparatus; uncorrected. IR Spectra: from solns., 0.1-mm cells, with a *Perkin-Elmer* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: 200 (50)-MHz *Varian* spectrometer; δ in ppm.

2,3-Dimethoxynaphthalene (**4**). A 500-ml, three-necked flask fitted with a condenser and a 50-ml dropping funnel was charged with anh. K_2CO_3 (38 g, 275 mmol), 300 ml of acetone, and naphthalene-2,3-diol (**3**; 20 g, 125 mmol). Me_2SO_4 (34.6 g, 26.6 ml, 275 mmol) was added under stirring from the dropping funnel to the mixture over a period of 2 min. The mixture warmed appreciably and began to reflux after an additional 5 min. When the spontaneous boiling subsided (15–20 min after the addition of the Me_2SO_4), the stirred mixture was heated gently under reflux for 15 h. The precipitate was filtered off, and the acetone was evaporated. The residue was dissolved in CH_2Cl_2, and the soln. was washed with H_2O (2×40 ml) and dried (Na_2SO_4). Removing the solvent under reduced pressure gave **4** (22.2 g, 94%). White solid. M.p. 110–112° (CH_2Cl_2/hexane; [15]: 113–116°). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.70 (*AA′* of *AA′BB′*, 2 H); 7.34 (*BB′* of *AA′BB′*, 2 H); 7.13 (*s*, 2 H); 4.00 (*s*, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 151.5; 131.2; 128.3; 126.2; 108.3; 57.8.

1-(6,7-Dimethoxynaphthalene-2-yl)ethanone (**5**). To a stirred soln. of **4** (22 g, 117.0 mmol) in 350 ml of dry 1,2-dichloroethane was added freshly distillated AcCl (11.0 g, 140.1 mmol) in one portion and $AlCl_3$ (42.0 g, 315 mmol) in small portions over 1 h at 0°. The mixture was stirred for 12 h at 0°, and then 300 g of ice and 100 ml of conc. HCl were added. The org. phase was separated, and the aq. phase was extracted with CH_2Cl_2 ($2 \times$ 150 ml). The org. phases were combined and dried (Na_2SO_4). Evaporation of the solvents and chromatography of the residue through a short silica-gel column (10 g; CH_2Cl_2) gave **5** (23.7 g, 88%). White crystals. M.p.104–106° (EtOH; [15]: 104–106°). ^{1}H-NMR (200 MHz, $CDCl_3$): 8.20 (br. *s*, 1 H); 7.76 (*A* of *AB*, *dd*, $J = 8.5, 1.3$, 1 H); 7.59 (*B* of *AB*, br. *d*, $J = 8.5$, 1 H); 7.08 (*s*, 1 H); 7.00 (*s*, 1 H); 3.91 (*s*, 6 H); 2.59 (*s*, 3 H). ^{1}H-NMR: in agreement with the data given in [16]. ^{13}C-NMR (50 MHz, $CDCl_3$): 199.8; 153.5; 152.0; 135.0; 133.9; 130.3; 128.5; 124.6; 109.5; 108.0; 57.8 (2 C); 28.2.

6,7-Dimethoxynaphthalene-2-carboxylic Acid (**6**). To a stirred soln. of NaOH (34.89 g, 870 mmol) in 120 ml of H_2O was added Br_2 (42.6 g, 266.2 mmol) over 30 min at 0°. To this mixture was added a soln. of **5** (20.00 g, 87.0 mmol) in 60 ml of THF slowly over 30 min at 0°. The mixture was warmed to r.t. and stirred for 8 h. The org. phase was separated in a separatory funnel and dispatched. To the aq. soln. were added ice (200 g) and 20% $NaHSO_3$ soln. (100 ml). After acidification of the aq. soln. with 37% HCl ($pH \leq 3$), the solidified acid **6** was filtered with suction and dried at 60° (18.2 g, 90%). White crystals, solidified. M.p. 238–240° ([15]: 240–243°). ^{1}H-NMR (200 MHz, (D_6)DMSO): 12.65 (br. *s*, 1 H); 8.42 (br. *s*, 1 H); 7.79 (*m*, 2 H); 7.48 (*s*, 1 H); 7.36 (*s*, 1 H); 3.90 (*s*, 3 H); 3.89 (*s*, 3 H). ^{13}C-NMR (50 MHz, (D_6)DMSO): 169.5; 152.9; 151.6; 133.2; 130.6; 129.8; 128.1; 127.8; 125.3, 109.5; 108.1; 57.4 (2 C).

1,2,3,4-Tetrahydro-6,7-dimethoxynaphthalene-2-carboxylic Acid (**7**). To a stirred soln. of **6** (10 g, 43.1 mmol) in 300 ml of liq. NH_3 at -70° were added small thinly cut pieces of Na (4.0 g, 174.0 mmol) over 1 h under N_2 atmosphere. The mixture was additionally stirred for 1 h at the same temp. Then, 20 ml of H_2O in 30 ml of EtOH was added dropwise over 1 h under N_2. After the NH_3 and EtOH were evaporated, ice (100 g) was added. After acidification of the aq. soln. with 37% HCl ($pH \leq 3$), the solidified acid **7** was filtered with suction and dried at 40° (9.2 g, 90%). White crystals. M.p. 135–137° (CH_2Cl_2/hexane; [17]: 136.5–137.5°). ^{1}H-NMR (200 MHz, $CDCl_3$): 11.76 (br. *s*, 1 H); 6.58 (*s*, 1 H); 6.57 (*s*, 1 H); 3.83 (*s*, 6 H); 3.01–2.93 (*m*, 2 H); 2.89–2.68 (*m*, 3 H); 2.26–2.18 (*m*, 1 H); 1.95–1.75 (*m*, 1 H). ^{1}H-NMR: in agreement with the data given in [13]. ^{13}C-NMR (50 MHz, $CDCl_3$): 183.8; 149.4; 149.3; 129.4; 128.4; 114.0; 113.8; 57.9 (2C); 41.9, 32.9; 30.0; 27.7.

Benzyl N-*(1,2,3,4-Tetrahydro-6,7-dimethoxynaphthalene-2-yl)carbamate* (**8**). Carbamate **8** was prepared from **7** according to the procedure described by *Charlton et al.* [13] in a yield of 86%. M.p. 123–125° ([13]: 130–131.5°). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.34 (*m*, 5 H); 6.56 (*s*, 1 H); 6.51 (*s*, 1 H); 5.09 (br. *s*, 2 H); 5.02 (*d*, $J = 8$, 1 H); 4.00 (*m*, 1 H); 3.82 (*s*, 6 H); 3.01 (*dd*, $J = 16.2, 4.5$, 1 H); 2.81–2.76 (*m*, 2 H); 2.56 (*dd*, $J = 16.2, 8.0$, 1 H); 2.05–1.99 (*m*, 1 H); 1.79–1.69 (*m*, 1 H). ^{1}H-NMR: in agreement with the data given in [13]. ^{13}C-NMR (50 MHz, $CDCl_3$): 157.8; 149.6; 149.4; 138.6; 130.5; 130.1, 129.3; 128.9; 127.8; 114.3; 113.7; 68.6; 57.9 (2 C); 48.9; 37.5; 30.9; 28.7.

2-Amino-1,2,3,4-tetrahydro-6,7-dimethoxynaphthalene Hydrochloride (**9**). By a little modification, the procedure described in [18] for the reduction of 4-azido-3-hydroxybutanenitrile was applied to **8** to give **9**. Into a 100-ml flask were placed Pd/C (50 mg) and **8** (0.50 g, 1.47 mmol) in MeOH (30 ml) and $CHCl_3$ (1 ml). 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 r.t. The catalyst was removed by filtration. Concentration gave **9** (0.34 g, 95%). Beige

solid. M.p. 217–219° (MeOH/Et_2O; [8]: 220–221°). ^{1}H-NMR (200 MHz, D_2O): 6.62 (*s*, 2 H); 3.67 (*s*, 3 H); 3.66 (*s*, 3 H); 3.64–3.40 (*m*, 1 H); 2.96 (*dd*, *J* = 16.1, 4.8, 1 H); 2.73–2.60 (*m*, 3 H); 2.12–2.02 (*m*, 1 H); 1.81–1.66 (*m*, 1 H). ^{1}H-NMR: in agreement with the data given in [13]. ^{13}C-NMR (50 MHz, D_2O): 151.4; 151.1; 132.0; 129.0; 116.8; 116.4; 60.3 (2 C); 52.1; 36.8; 31.1; 30.3.

2-Amino-1,2,3,4-tetrahydronaphthalene-6,7-diol Hydrobromide (**10**). This compound was prepared from **9** by the procedure described by *Cannon et al.* [9] in a yield of 80%. M.p. 267–269° (MeOH/Et_2O; [8]: 270–271°). ^{1}H-NMR (200 MHz, D_2O): 6.48 (*s*, 2 H); 3.45–3.31 (*m*, 1 H); 2.85 (*dd*, *J* = 16.1, 4.8, 1 H); 2.62–2.49 (*m*, 3 H); 2.06–1.97 (*m*, 1 H); 1.74–1.58 (*m*, 1 H). ^{13}C-NMR (50 MHz, D_2O): 146.8; 146.5; 131.3; 128.4; 120.3, 119.9; 51.9; 36.4; 31.0; 30.0.

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Received May 31, 2003