

An Alternative Synthesis of the Dopaminergic Drug 2-Amino-1,2,3,4-tetrahydronaphthalene-5,6-diol (5,6-ADTN)

by Süleyman Göksu*, Hasan Seçen, and Yaşar Sütbeyaz

Department of Chemistry, Faculty of Arts and Sciences, Atatürk University, TR-25240 Erzurum, Turkey

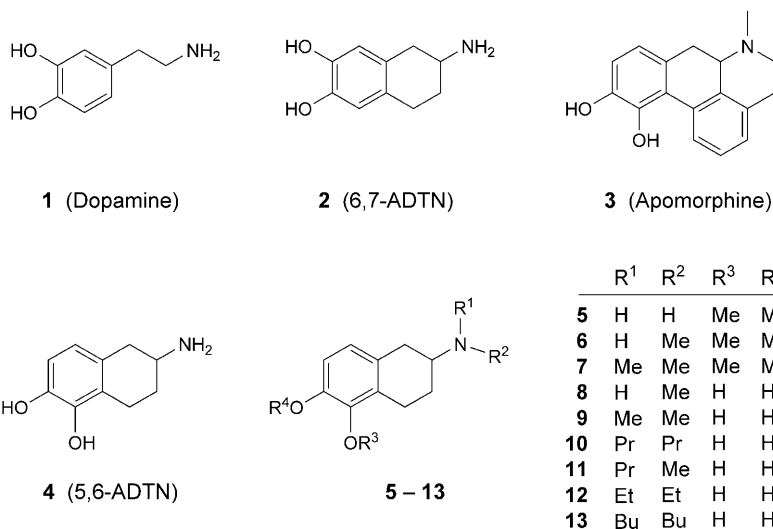
Racemic 2-amino-1,2,3,4-tetrahydronaphthalene-5,6-diol (5,6-ADTN; **4**) was synthesized from 5,6-dimethoxynaphthalene-2-carboxylic acid (**14**) in four steps (60% overall yield; *Scheme*). The crucial steps of the synthesis are *Birch* reduction of **14** to the valuable synthon **15**, *Curtius* reaction and carbamate formation (**16**), hydrogenolysis (**17**), and demethylation to the biologically active hydrobromide salt **18** of **4**.

Introduction. – The neurotransmitter dopamine (**1**) plays a central role in central nervous system (CNS)-related disorders such as schizophrenia and *Parkinson's* disease [1]. In recent years, many chemical compounds have been found to possess dopamine-like actions [2]. It has been suggested that 2-amino-1,2,3,4-tetrahydronaphthalene-1,2-diol (6,7-ADTN; **2**)¹⁾, a dopamine-like compound, acts as a potential agonist at the dopamine receptors [3], and interacts with the dopamine receptors with slightly greater affinity than dopamine proper [4]. Apomorphine (**3**), a potent dopamine agonist, has been used in acute and chronic studies of *Parkinson's* disease and other neurological disorders [5].

The title compound **4** (5,6-ADTN) and some of its derivatives (**5–13**) represent a fragment of apomorphine (**3**). Compounds **5–7** and the hydrobromide salts of **4**, **8**, and **9** have been reported to have emetic activities in pigeons and dogs [6]. Also, *McDermid* and co-workers have corroborated the dopaminergic activities of 5,6-ADTN (**4**) and of its *N*-alkylated derivatives **10–13**. They have demonstrated that the hydrochloride salts of all these compounds are in the potency range of apomorphine (**3**), the hydrochloride salt of **10**, *e.g.*, being 50-times more potent than **3** [7]. The cerebral dopamine agonist properties [8], the potent inhibitory effect of [³H]-DA [9], the cardiac inotropic/chronotropic and blood-pressure activity [10] of 5,6-ADTN (**4**) and of its derivatives are well-described.

The known procedures for the synthesis of *racemic* 5,6-ADTN (**4**), described by *Cannon* and co-workers [6a,b], and by *Horn et al.* [9], are based on reductive amination of tetralones. The first enantioselective synthesis of (*R*)- and (*S*)-**4** was reported by *Baxter et al.* [11], who used D- or L-serine as chiral auxiliaries [11]. Starting from 2,3-dimethoxybenzaldehyde, another method for the preparation of (*S*)-2-amino-5,6-dime-

¹⁾ In the literature, the acronym ADTN refers to the '2-amino-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene' moiety. For systematic names, see *Exper. Part*.



thoxy-1,2,3,4-tetrahydronaphthalene-L-mandelic acid, a precursor of (*S*)-**4**, was described by *Fantucci et al.* [12].

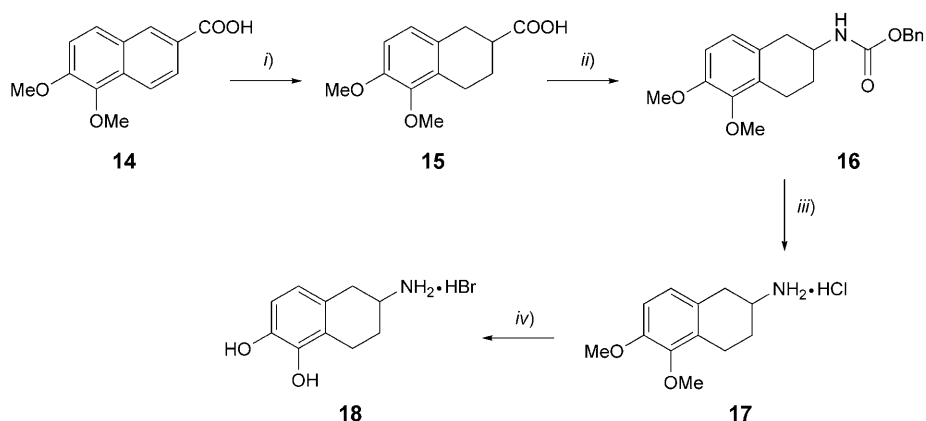
In our ongoing project on the synthesis of dopamine-like compounds, we already reported a concise synthesis of 6,7-ADTN (**2**) [13] and of 2-aminoindans [14]. In the present study, we describe an alternative, straight-forward synthesis of 5,6-ADTN (**4**) from 5,6-dimethoxynaphthalene-2-carboxylic acid (**14**) in four steps (*Scheme*).

Results and Discussion. – In our synthetic methodology, 5,6-dimethoxynaphthalene-2-carboxylic acid (**14**) was used as a key compound. Two synthetic procedures have been described for the preparation of **14**. *Burke et al.* [15] prepared **14** from 6-bromo-2-naphthol in an overall yield of 34%. Recently, we have described an alternative method for the preparation of **14** from 2-naphthol in an overall yield of 46% [16].

In the synthesis of 5,6-ADTN (**4**), *Birch* reduction of **14** was the crucial step. As expected, the reaction with Na in liquid NH₃ took place on the electron-deficient ring of **14**, giving rise to the carboxylic acid **15** in high yield (90%; *Scheme*). Next, **15** was transformed into the carbamate **16** by applying a literature procedure described for the synthesis of 6,7-ADTN [13][17]: reaction of **15** with diphenylphosphoryl azide in the presence of Et₃N *via Curtius* rearrangement, followed by treatment with benzyl alcohol, afforded **16** in high yield (88%). Hydrogenolysis of **16** in MeOH in the presence of CHCl₃ then afforded pure **17**, which was finally demethylated to the hydrobromide **18** with 48% HBr, as previously described for the synthesis of 5,6-ADTN [8].

In summary, we have achieved a concise synthesis of 5,6-ADTN (**4**) in the form of its hydrobromide salt **18** starting from 5,6-dimethoxynaphthalene-2-carboxylic acid (**14**). Further, the intermediary 1,2,3,4-tetrahydronaphthalene-2-carboxylic acid **15** should be a useful synthon for the preparation of biologically active tetralin derivatives.

Scheme



i) 1. Na, liq. NH₃; 2. 37% aq. HCl; 90%. ii) 1. (PhO)₂P(O)N₃, Et₃N, C₆H₆, reflux; 2. PhCH₂OH, reflux; 88%. iii) H₂, Pd·C, MeOH/CHCl₃; 95%. iv) 48% HBr, reflux; 80%.

Experimental Part

General. Column chromatography (CC): *silica gel 60* (70–230 mesh). TLC: aluminum-backed *silica gel 60 F₂₅₄* plates (Merck). Solvents were purified and dried by standard procedures before use. M.p.: Büchi-539 cap. melting-point apparatus; uncorrected. IR Spectra (KBr or film): Mattson-1000 FT-IR spectrophotometer; in cm⁻¹. ¹H- and ¹³C-NMR Spectra: at 400 or 100, or at 200 or 50 MHz, resp., on Varian spectrometers; δ in ppm, J in Hz. EI-MS: Thermo-Finnigan mass analyzer; in m/z (rel. int. in %). Elemental analyses were carried out with a Leco CHNS-932 instrument.

1,2,3,4-Tetrahydro-5,6-dimethoxynaphthalene-2-carboxylic Acid (15). To a stirred soln. of **14** (13.00 g, 56.0 mmol) in liq. NH₃ (300 ml) at –70° were added small pieces of elemental Na (5.2 g, 226.1 mmol) over 1.5 h under N₂ atmosphere. When the addition of Na was complete, the mixture was stirred at this temp. for 1 h. Then, H₂O (25 ml) in EtOH (40 ml) was added dropwise over 1 h under N₂ fume. The NH₃ and EtOH were evaporated, and ice (150 g) was added to the mixture, which was acidified with 37% aq. HCl to pH 3. The solidified material was suction-filtered and dried at 35° to afford 12.00 g (90%) of **15**. NMR analysis of the crude product showed the presence of 5–10% of unreacted starting material. Since recrystallization and CC failed to give pure **15**, the crude product was used without further purification in the next step. ¹H-NMR (400 MHz, CDCl₃): 10.90 (br. s, COOH); 6.84, 6.76 (2 AB-type d, J(7,8)=8.4 each, H–C(7), H–C(8)); 3.85, 3.81 (2s, 2 MeO); 3.07–2.91 (m, 3 H); 2.77–2.68 (m, 2 H); 2.30–2.25 (m, 1 H); 1.87–1.80 (m, 1 H). ¹³C-NMR (50 MHz, CDCl₃): 181.6; 150.6; 146.6; 129.9; 127.8; 124.1; 110.6; 59.9; 55.9; 39.7; 30.9; 25.2; 22.7.

Phenylmethyl (1,2,3,4-Tetrahydro-5,6-dimethoxynaphthalen-2-yl)carbamate (16). To a stirred soln. **15** (2.00 g, 8.5 mmol) in anh. benzene (60 ml) was added diphenylphosphoryl azide (2.81 g, 10.2 mmol) and Et₃N (1.00 g, 10.2 mmol). The mixture was heated at reflux for 6 h. Then, benzyl alcohol (2.75 g, 25.5 mmol) was added, and reflux was continued for 30 h. The mixture was cooled to r.t., the solvent was evaporated, and the resulting residue was purified by CC (SiO₂, 15 g; hexane/AcOEt 80:20) to afford 2.54 g (88%) of **16**. Colorless solid. M.p. 118–120° (CH₂Cl₂/hexane). IR (KBr): 3336, 3055, 2953, 2851, 1702, 1625, 1574, 1523, 1446, 1319, 1268, 1217. ¹H-NMR (400 MHz, CDCl₃): 7.41–7.29 (m, 5 arom. H); 6.78, 6.74 (2 AB-type d, J(7,8)=8.4 each, H–C(7), H–C(8)); 5.10 (s, PhCH₂); 4.83 (d, J=7.3, NH); 4.02–3.94 (m, H–C(2)); 3.83, 3.80 (2s, 2 MeO); 3.06 (AB-type dd, J(1a,1b)=16.0, J(1a,2)=4.6, H_a–C(1)); 2.92 (AB-type dt, ²J=18.0, ³J=6.1, H_a–C(4) or H_b–C(4)); 2.80 (AB-type dt, ²J=18.0, ³J=7.3, H_b–C(4) or H_a–C(4)); 2.60 (AB-type dd, J(1a,1b)=16.0, J(1b,2)=7.9, H_b–C(1)); 2.07–2.03 (m, H_a–C(3) or H_b–C(3)); 1.79–1.70 (m, H_b–C(3) or H_a–C(3)). ¹³C-NMR (100 MHz, CDCl₃): 156.0 (NHCOO); 151.0; 146.7; 136.7; 130.0; 128.8; 128.4 (2C); 127.4; 124.8; 110.8; 66.9 (PhCH₂); 60.2, 56.1

(2 MeO); 46.8 (C(2)); 35.6; 28.6; 21.6. Anal. calc. for $C_{20}H_{23}NO_4$ (341.4): C 70.36, H 6.79, N 4.10; found: C 70.62, H 6.58, N 4.27. EI-MS: 340.8 (15, M^+), 286.7 (4), 265.8 (3), 249.7 (7), 232.7 (17), 217.7 (5), 191.9 (8), 190.9 (30), 189.4 (100), 174.8 (23), 158.9 (25), 157.7 (13), 148.8 (11), 142.7 (9), 114.8 (11), 90.8 (33).

1,2,3,4-Tetrahydro-5,6-dimethoxynaphthalene-2-amine Hydrochloride (17). In a 100-ml flask were placed Pd·C (80 mg) and **16** (1.00 g, 2.94 mmol) in MeOH (50 ml) and $CHCl_3$ (3 ml), and 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 to afford 0.68 g (95%) of **17**. Colorless solid. M.p. 275–277° (dec.; MeOH/Et₂O) [lit. m.p. 270–272° (dec. EtOH/Et₂O) [6a]]. ¹H-NMR (400 MHz, D₂O): 6.77, 6.74 (2 AB-type *d*, $J(7,8)=8.8$ each, H–C(7), H–C(8)); 4.65 (br. s, NH_3^+ , overlapping with solvent signals); 3.64, 3.56 (2s, 2 MeO); 3.42–3.36 (*m*, H–C(2)); 2.93 (AB-type *dd*, $J(1a,1b)=16.1$, $J(1a,2)=5.0$, $H_a-C(1)$); 2.79 (AB-type *dt*, $^2J=17.4$, $^3J=5.0$, $H_a-C(4)$); 2.65–2.54 (AB-type *m*, $H_b-C(1)$, $H_b-C(4)$); 2.07–2.00 (*m*, $H_a-C(3)$); 1.67–1.57 (*m*, $H_b-C(3)$). ¹³C-NMR (100 MHz, D₂O): 150.4; 145.3; 129.3; 125.9; 125.4; 111.4; 60.2, 55.9 (2 MeO); 47.3 (C(2)); 32.3; 26.1; 21.0.

2-Amino-1,2,3,4-tetrahydronaphthalene-5,6-diol Hydrobromide (18). Prepared from **17** according to [8] in 80% yield. Colorless solid. M.p. >290° (MeOH/Et₂O) (lit m.p. >300° [6b]). ¹H-NMR (400 MHz, D₂O): 6.58, 6.45 (2 AB-type *d*, $J(7,8)=8.1$ each, H–C(7), H–C(8)); 4.64 (br. s, NH_3^+ , overlapping with solvent and phenolic OH signals); 3.40–3.33 (*m*, H–C(2)); 2.88 (AB-type *dd*, $J(1a,1b)=15.7$, $J(1a,2)=4.2$, $H_a-C(1)$); 2.69 (AB-type *dt*, $^2J=17.8$, $^3J=5.3$, $H_a-C(4)$); 2.58 (AB-type *dd*, $J(1a,1b)=15.7$, $J(1b,2)=9.5$, $H_b-C(1)$); 2.47 (AB-type *ddd*, $^2J=17.8$, $^3J=9.9$, 6.6, $H_b-C(4)$); 2.06–1.99 (*m*, $H_a-C(3)$); 1.67–1.57 (*m*, $H_b-C(3)$). ¹³C-NMR (100 MHz, D₂O): 142.0; 141.3; 125.0; 123.2; 121.1; 114.1; 47.4; 32.5; 26.1; 21.1.

We thank the *State Planning Organization* (Grade No. DPT 2004K/02) and the Atatürk University for financial support of this work.

REFERENCES

- [1] S. R. Haadsma-Svensson, K. A. Svensson, *CNS Drug Rev.* **1998**, 4, 42.
- [2] J. G. Cannon, *Prog. Drug Res.* **1985**, 29, 303.
- [3] G. N. Woodruff, *Comp. Gen. Pharmacol.* **1971**, 2, 439.
- [4] M. S. Abel, Y. Clement-Cormier, *Pharmacologist* **1978**, 20, 141.
- [5] S. T. Ganchar, W. R. Woodward, B. Boucher, J. G. Nutt, *Ann. Neurol.* **1989**, 26, 232.
- [6] a) W. K. Sprenger, J. G. Cannon, B. K. Barman, A. M. Burkman, *J. Med. Chem.* **1969**, 12, 487; b) J. G. Cannon, J. C. Kim, M. A. Aleem, J. P. Long, *J. Med. Chem.* **1972**, 15, 348.
- [7] J. D. McDermed, G. M. McKenzie, A. P. Phillips, *J. Med. Chem.* **1975**, 18, 362.
- [8] J. G. Cannon, T. Lee, H. D. Goldman, B. Costal, R. J. Naylor, *J. Med. Chem.* **1977**, 20, 1111.
- [9] A. S. Horn, C. J. Grol, D. Dijkstra, A. H. Mulder, *J. Med. Chem.* **1978**, 21, 825.
- [10] R. J. Gorczynski, W. G. Anderson, D. M. Stout, *J. Med. Chem.* **1981**, 24, 835.
- [11] A. D. Baxter, P. J. Murray, R. J. K. Taylor, *Tetrahedron Lett.* **1992**, 33, 2331.
- [12] M. Fantucci, S. Montanari, F. Santangelo, S. Ianelli, M. Nardelli, *Acta Crystallogr., Sect. C* **1996**, 52, 3147.
- [13] S. Göksu, C. Kazaz, Y. Sütbeyaz, H. Seçen, *Helv. Chim. Acta* **2003**, 86, 3310.
- [14] S. Göksu, H. Seçen, *Tetrahedron* **2005**, 61, 6801.
- [15] T. R. Burke, B. Lim, V. E. Marquez, Z. H. Li, J. B. Bolen, I. Stefanova, I. D. Horak, *J. Med. Chem.* **1993**, 36, 425.
- [16] S. Göksu, M. T. Uğuz, H. Özdemir, H. Seçen, *Turk. J. Chem.* **2005**, 29, 199.
- [17] J. L. Charlton, K. Koh, G. L. Plourde, *Can. J. Chem.* **1990**, 68, 2028.

Received October 28, 2005