A new synthesis of 5,6-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid

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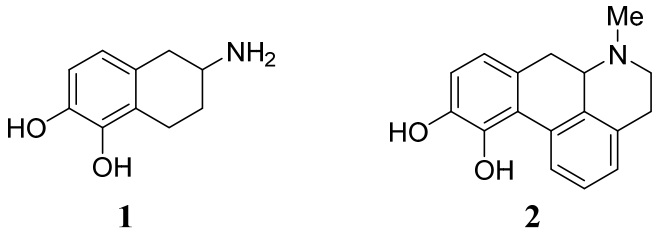
Abstract
The transformation of 6-methoxy-1-tetralone **3** into the title acid **9** has been accomplished. The overall yield of the acid is superior to that reported.

Keywords: 6-Methoxy-1-tetralone, diethyl carbonate, *N*-bromosuccinimide, cuprous bromide

Introduction

There are many chemical compounds that possess dopamine-like activities.[1] 2-Amino-1,2,3,4-tetrahydronaphthalene-5,6-diol (**1**) (5,6-ADTN) and some of its N- as well as O-alkyl derivatives (Me, Et, Bu etc) represent a fragment of apomorphine **2** (Figure 1) which is a potent dopamine agonist that has been used in acute and chronic studies of Parkinson's disease and other neuro-

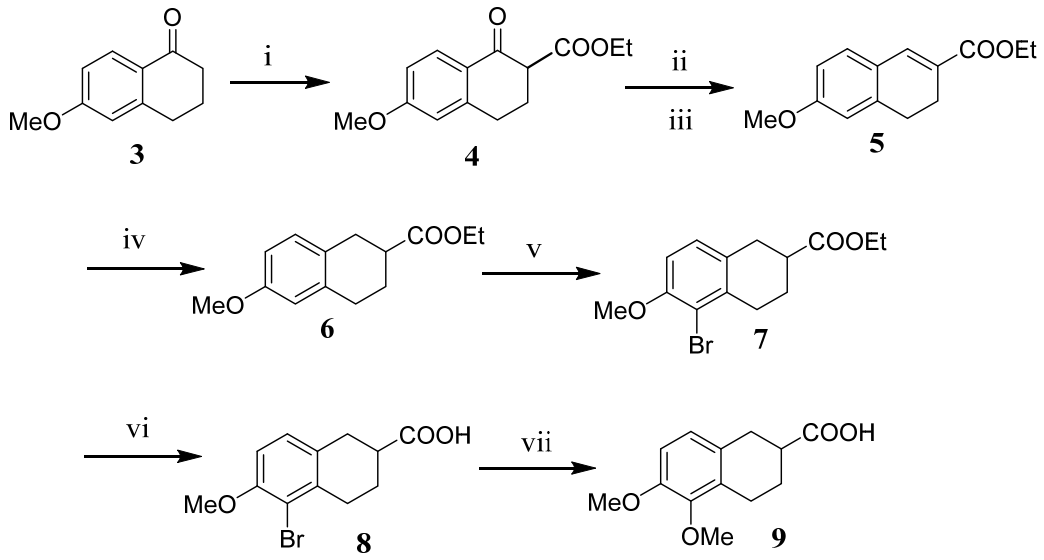


1 **2**

Figure 1

logical disorders.[2] Two racemic syntheses[3,4] and one enantioselective synthesis[5] of compound **1** have been reported. Gosku and collaborators reported[6] the transformation of 6-hydroxynaphthalene into 5,6-dimethoxynaphthalene-2-carboxylic acid (six steps) which on reduction with lithium in liquid ammonia afforded[7] the acid **9** (Scheme 1) with an overall yield 42% . The acid **9** failed to crystallize owing to the presence of some amount of starting material

(as evidenced by NMR spectroscopy) and thus it is very difficult to know its exact overall yield. The acid without purification was utilized for its conversion[7] (four steps) into the amine **1** as its hydrobromide salt. The importance of the amine **1** in medicine encouraged us to develop an alternative route for the acid **9**, which is described in Scheme 1.



Reagents: (i) $(C_2H_5O)_2CO$, THF, NaH; (ii) $NaBH_4$, EtOH: (iii) $MeC_6H_4SO_2OH$-H_2O; (iv) Pd/C (10%), EtOH, H_2; (v) NBS, DMF; (vi) NaOH, EtOH; (vii) NaOMe, DMF, Cu(I)Br.

Scheme 1

Results and Discussion

6-Methoxy-1-tetralone (**3**) in tetrahydrofuran on treatment with diethyl carbonate provided ketoester **4** which on reduction with sodium borohydride in ethanol followed by dehydration with p-toluenesulphonic acid monohydrate afforded the reported[8] unsaturated ester **5** in 96% yield. The reported procedure is very different from our approach and in addition the yield of the ester **5** has not been mentioned. The catalytic hydrogenation (H_2, Pd/C, 10%) of the ester **5** in ethanol under 200 psi afforded the ester **6** in 94% yield (overall yield 90%). The ester **6** was also prepared with an overall yield 66% by a different procedure by Perrone and collaborators.[9] Bromination of the ester **6** with NBS and dimethylformamide yielded the compound **7** in 67% yield as evidenced by ^{1}H NMR spectroscopy. The formation of the two doublets at δ 6.71 and δ 7.01 ppm (see experimental) for compound **7** corresponding to the protons at C-7 and C-8 corroborates the presence of bromine at the position C-5. The bromine at C-7 would have originated two singlets due to the protons of C-5 and C-8. The absence of these singlets provide strong support in favor of the structure of the compound **7**. The acid **8** obtained in 94% yield by

the alkaline hydrolysis of the compound **7,** was heated following the method of Alten[10] with a saturated solution of sodium methoxide, DMF and copper (I) bromide to afford the desired acid **9** in 93% yield which is superior (90%) to the published report.[7] The overall yield of the acid **9** was 52%. The spectral data support the assigned structure **9** for the acid.

Conclusions

A concise method for the synthesis of the acid **9** has been developed with a very satisfactory yield. The experimental procedures are very simple and can easily be reproduced. The already reported compounds **5** and **6** have been prepared by different procedures with a superior yield.

Experimental Section

General. Unless otherwise stated all melting points are uncorrected and were determined on an Electrothermal melting point apparatus. Infrared (IR) spectra were recorded on a Nicolet-Fourier Transform (FT) instrument and NMR (^{1}H and ^{13}C) spectra were determined on a Bruker AM-300 spectrometer in $CDCl_3$. Chemical shifts (δ) are expressed in ppm. Mass spectra (MS) were determined on a Dupont 21-492B. Column chromatography was carried out on silica gel 60 (Merck). Thin layer chromatography (TLC) plates were coated with silica gel and the spots were visualized using ultraviolet light. All organic solvents were dried over anhydrous $MgSO_4$ and solvents were evaporated *in vacuo.* Elemental analyses were performed on a Carlo-Erba 1108 Elemental Analyser**.**

2-Carboethoxy-6-methoxy-3,4-dihydronaphthalene (5). To a solution of the tetralone **3** (1g, 5.68 mmol) in THF (20 mL), diethyl carbonate (2.71 mL, 0.022 mmol) was added sodium hydride (200 mg, 7.39 mmol) and the mixture was heated in an oil bath at 85 ^{o}C for 2 h with stirring under nitrogen. Then the mixture was cooled to 0-5 ^{o}C, acidified with acetic acid, diluted with water and extracted with ether. The extracts were washed with water, dried and evaporated to afford a yellow oil which on chromatographic purification on alumina (activity II, eluent hexane) afforded ketoester **4** (1.72 g, 99%) as a pale yellow oil; ν_{max}(KBr) 1739 (ester CO) and 1687 (CO); *m/z*: 249 (M^+ +1).

Sodium borohydride (306 mg, 8.1 mmol) in ethanol (30 mL) was added to a solution of the ester **4** (1.70 g, 6.82 mmol) in ethanol (20 mL). The mixture was stirred for 2 h at room temperature, diluted with water and extracted with dichloromethane. The organic extracts were washed with dil. HCl (10%), brine, dried and evaporated to give an alcohol as deep yellow oil. To the resulting product in THF (20 mL) was added p-toluenesulfonic acid monohydrate (15 mg, 0.78 mmol) and heated under reflux for 12 h. The reaction was cooled, diluted with water and extracted with ether. The organic extracts were washed with brine, dried and evaporated to

afford a brown oil which was purified by chromatography (hexane: Et_2O 9:1) to yield the unsaturated ester **5** (1.52 g, 96%) (from ketoester **4**) as colorless viscous liquid, with an overall yield 90% (**3**→ **5**); ν_{max} 1702 (CO) cm^{-1}; ^1H NMR: (300 MHz $CDCl_3$) δ: 1.32 (t, 3H, *J* 7.1 Hz, Me), 2.55 (t, 2H, *J* 8.4 Hz), 2.81(t, 2H, *J* 8.1 Hz) (C-3, C-4), 3.77 (s, 3H, OMe), 4.23 (q, 2H, *J* 7.1 Hz, OCH_2), 6.68-6.71 (m, 2H, H-5, H-7), 7.10 (d, 1H, *J* 8.8 Hz, H-8), 7.47 (s, 1H, H-1) ppm; ^{13}C (300 MHz, $CDCl_3$) δ: 14.20 (Me), 21.90 (C-3), 28.23 (C-4), 55.19 (OMe), 60.20 (OCH_2), 111.17 (C-7), 113.88 (C-5), 125.84 (C-2), 126.58 (C-9), 129.63 (C-8), 135.91 (C-1), 138.97 (C-10), 160 (C-6), 167.52 (CO); MS: 232 (M^+), 187 (M^+ -OEt); Anal. Calc. for $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94 (Found: C, 72.63; H, 7.12).

2-Carboethoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (6). A solution of the ester **5** (0.41 g, 1.72 mmol) in ethanol (12 mL) was stirred for 2 h with (10%) Pd-C (35mg, 0.15 mmol) under hydrogen at 200 psi. Removal of the catalyst by filtration and evaporation of the solvent gave a residue which on chromatographic purification (hexane:ether 9:1) yielded the ester **6 (**379 mg, 94%) as viscous liquid; ν_{max} 1729 cm^{-1}(CO); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27 (t, 3H, *J* 7.1 Hz. Me), 1.80-1.88 (m, 1H, C3-H), 2.16-2.20 (m, 1H, C3-H), 2.67-2.71 (m, 1H, C2-H), 2.80-2.96 (m, 4H, C1-H, C4-H), 3.75 (s, 3H, OMe), 4.17 (q, 2H, OCH_2), 6.61 (d, 1H, *J* 2.4 Hz, C5-H), 6.67-6.70 (dd, 1H, *J* 2.6 Hz, *J* 8.4 Hz, C7-H), 7.01 (d, 1H, *J* 8.4 Hz, C8-H); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 14.13 (Me), 25.72 (C-3), 28.73 (C-4), 30.78 (C-1), 40.14 (C-2), 55.04 (OMe), 60.28 (OCH_2), 112.05 (C-7), 113.24 (C-5), 126.92 (C-), 126.6 (C-8), 136.65 (C-10), 157.62 (C-6), 175.33 (CO); MS: 235 (M^+1), 188.9 (M^{+1} – OCH_2CH_3); Anal. Calc. for $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74 (Found: C, 71.98; H, 7.91).

2-Carboethoxy-5-bromo-6-methoxy-1,2,3,4-tetrahydronaphthalene (7). To a solution of the compound **6** (201 mg, 0.85 mmol) in dimethylformamide (5 mL) was added NBS (151 mg, 0.85mmol). The solution was stirred for 10 h at room temperature under argon. To the resulting brown solution was added water and the mixture was extracted with ether. The organic extracts were washed with brine, dried and evaporated *in vacuo* to afford a viscous liquid which on chromatographic purification (hexane:ether 9:1) afforded the bromide **7** (181 mg, 67%) as white solid, mp. 75-77 °C (from hexane); ν_{max} 1732 cm^{-1}(CO); ^1H NMR (300 MHz $CDCl_3$) δ: 1.25 (t, 3H, *J* 7.1 Hz, Me), 1.74-1.87 (m, 1H, C3-H), 2.19-2.25 (m, 1H, C3-H), 2.59-2.73 (m, 2H, C4-H), 2.87-3.03 (m, 2H, C1-H), 3.84 (s, 3H, OMe), 4.13 (q, *J* 7.1 Hz, OCH_2), 6.71 (d, 1H, *J* 8.5 Hz, C7-H), 7.01 (d, 1H, *J* 8.5 Hz, C8-H); ^{13}C NMR (300 MHz $CDCl_3$) δ: 14.18 (Me), 25.87 (C-3), 29.89 (C-4), 31.56 (C-1), 39.57 (C-2), 56.32 (OMe), 60.46 (OCH_2), 109.65 (C-7), 114.36 (C-5), 128.33 (C-8), 129.19 (C-9), 136.68 (C-10), 154.18 (C-6), 175.07 (CO); MS:313(M^+); Anal. Calc. for $C_{14}H_{18}O_3$ requires C, 53.67; H, 5.43 (Found: C, 53.91; H, 5.62).

5-Bromo-6-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (8). To the ester **7** (201 mg, 0.63 mmol) in ethanol (15 mL) was added aqueous sodium hydroxide (3 mL, 1N). The solution was heated under reflux for 2 h, diluted with water, acidified with hydrochloric acid (2%) and extracted with dichloromethane. The organic extracts were washed, dried and evaporated to obtain a residue which on preparative thin layer chromatography (hexane: ether 7:3) afforded the acid **8** (172 mg, 94%), m.p 168-170 °C (ether); ν_{max} 3230 (OH), 1715 cm^{-1}

(CO); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.79-1.93 (m, 1H, C3 –H), 2.22-2.31 (m, 1H, C3-H), 2.66-2.77 (m, 1H, C2-H), 2.97-3.06 (m, C1-H, C4-H), 3.85 (s, 3H, OMe), 6.72 (d, 1H, *J* 8.4 Hz, C7-H), 7.02 (d, 1H, *J* 8.4 Hz, C8-H); ^{13}C NMR (300 MHz $CDCl_3$) δ: 2.67 (C-3), 29.76 (C-4), 31.29 (C-1), 39.21 (C-2), 56.38 (OMe), 109.68 (C-7), 114.39 (C-5), 128.43 (C-8), 128.81 (C-9), 136.59 (C-10), 154.30 (C-6), 180.34 (CO); MS: 284 (M^+-1), 238 (M^+-COOH). Anal. Calc. for $C_{12}H_{13}O_3Br$ requires C, 50.52; H, 4.56 (Found: C, 50.75; H, 4.74)

5,6-Dimethoxy-**1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (9).** To a saturated solution of sodium methoxide prepared by dissolving sodium (500 mg) in dry methanol (6 mL) was added dry dimethylformamide (3 mL). The solution was heated under reflux, copper (I) bromide (100 mg, 0.69 mmol) in dry dimethylformamide (2 mL) was added and heating was continued for an additional 30 min. To the suspension was added dropwise a solution of the compound **8** (100 mg, 0.35 mmol) in dry dimethylformamide under reflux for 24 h. The reaction was cooled, filtered, diluted with water and extracted with ether.The organic extracts were washed with dil HCl (4 mL, 5%), water, dried and evaporated to obtain a residue which on preparative chromatographic purification (hexane:ether 8:2) yielded the acid **9 (**65 mg, 93%) as white crystalline solid, m.p 133-135^{o} C (ether); ν_{max} 3230 (OH), 1715 cm^{-1} (CO); ^{1}H NMR (300 MHz $CDCl_3$) δ: 1.86-1.79 (m, 1H); 2.28-2.23 (m, 1H); 2.75-2.67 (m, 2H); 3.05-2.87 (m, 3H); 3.82 (s, 3H, OMe); 3.84 (s, 3H, OMe); 6.78 (d, 1H, *J* 8.4 Hz, C8-H); 6.87 (d, 1H, *J* 8.4 Hz, C7-H). ^{13}C NMR (300 MHz $CDCl_3$)δ: 22.5 (C3); 25.2 (C4); 30.9 (C1); 39.6 (C2); 55.8 (OMe); 59.9 (OMe); 110.5 (C7); 124.2 (C8); 127.7 (C9); 129.8 (C10); 146.5 (C6); 150.4 (C5); 181.6 (CO).MS 235 (M^+ -1); Anal . Calcd. for $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.83 (Found: C, 66.29; H, 6.96).

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