An efficient approach for the synthesis of 6,7-dimethoxy-2-tetralone and 5,6-dimethoxy-1-tetralone

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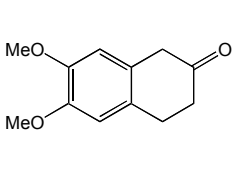
Abstract
Transformation of 6-methoxy tetralin into 6,7-Dimethoxy-2-tetralone and 5,6-Dimethoxy-1-tetralone is described.

Keywords: 6-Methoxytetralin, bromination, methoxylation, oxidation

Introduction

6,7-Dimethoxy-2-tetralone **1** is a starting material for many dopaminergic compounds[1]. Its utility has been recorded in the synthesis of natural alkaloids[2], cyclic amino acids[3] and as novel antagonists[4] of human TRPVI. 5,6-Dimethoxy-1-tetralone **2** is a key intermediate in the synthesis of novel antidepresants[5] which are the α-2-antagonists and norepinephrine uptake inhibitors eg. ABT-200. It can also be a synthon for certain 2-substituted octobenzo(f) quinoline which are dopamine agonists[6].



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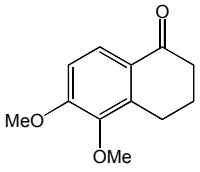

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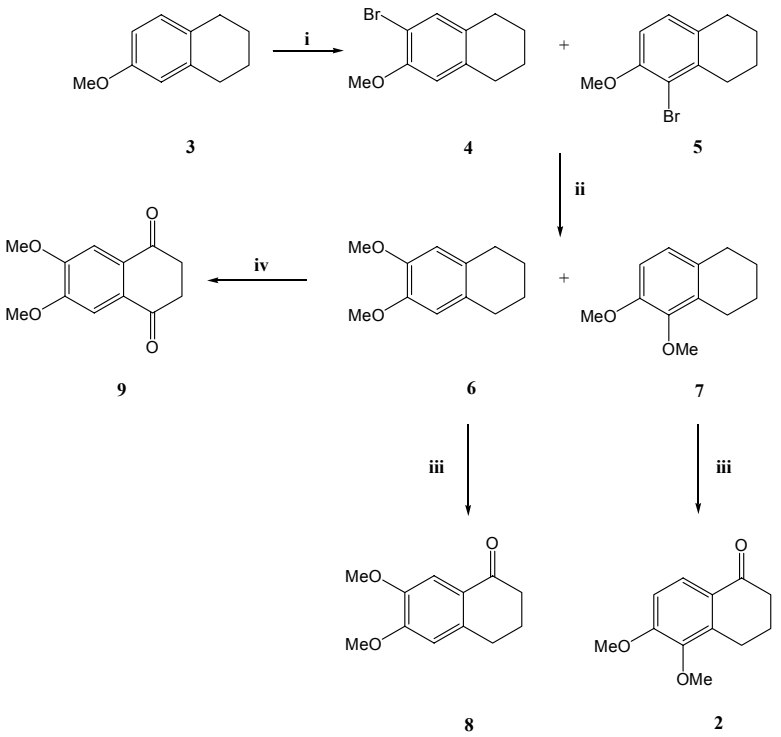
An efficient, short step and high yielding approach of these tetralones will be of great utility for large scale synthesis of several bioactive compounds for their complete preclinical and clinical evaluations. Several approaches have been developed for the synthesis of tetralone[7,8] **1** and tetralone[9,10] **2**. In some of these methods we have observed (i) long reaction sequences affording low to moderate yield, (ii) difficult experimental procedures which require skilled experimentalists to reproduce the results, (iii).the use of expensive reagents (rhodium, triphenylphosphonium chloride, ionic liquids etc) and (iv) the use of reagents (diazoketone,ethylene gas, βketosulfoxide etc) which are injurious for health. Analysing some of

these draw backs and considering our interest on the synthesis of α and β-substituted tetralones[11] we believe that still a more efficient and facile synthesis can be developed for tetralones **1** and **2** which have proved to be potential intermediate for the synthesis of several bioactive compounds. We have sought a facile synthesis of the tetralones **1** and **2** by a single route instead of independent approach for each of these tetralones. To the best of our knowledge this is the first example of the synthesis of the tetralones **1** and **2** by a single route and the present paper documents our results.

Results and Discussion

The commercially available 6-methoxy-1,2,3,4-tetrahydronaphthalene **3** on aromatic bromination[12] with *N*-bromo succinimide provided a mixture of the bromo compounds **4** and **5** in a ratio 1.3:1 as evidenced by ^{1}H NMR spectroscopy. As their separation could not be effected by column chromatography their transformation to the tetralins **6** and **7** were effected by treatment of the mixture with CuI and dimethylformamide in a solution of sodium methoxide.[13] The resuting material on chromatographic purification afforded tetralines **6** and **7** in an overall yield 31.1% and 30.7% respectively for the two steps. Their structures were confirmed by spectroscopic evidences (Scheme 1).

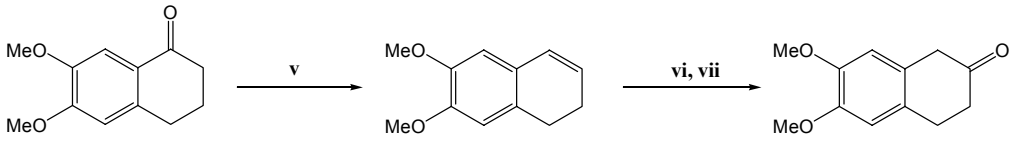


Reagents: (i) CH2Cl2 , Toluene, NBS, -78ºC. (ii) Na, MeOH, CuI, DMF, reflux 24h. (iii) KMnO4, CH3CN, 25ºC. (iv) CrO3, AcOH, 15-20ºC, 3h.

Scheme 1

As the oxidation is the only reaction which can provide the desired tetralones , suitable oxidizing reagents were sought to obtain the tetralones in satisfactory yield. A series of oxidizing reagents were tried to achieve the oxidation but among these $KMnO_4$ in acetonitrile[14] proved to be satisfactory. Oxidation of the tetralins **6** and **7** with this reagent afforded tetralones **8** and **2** in 44% and 39% respectively. The m.p. and the spectroscopic data perfectly matched with the data reported (see experimental). In one occasion the oxidation of the tetralin **6** was tried with chromium trioxide and acetic acid and the product obtained in major amount was identified as quinone **9** by spectroscopic analysis.

Heating the tetralone **8** with 2,4-pentanediol and p-toluenesulphonic acid in toluene [15] furnished the dihydronaphthalene **10 (**Scheme 2**)** which on epoxidation with m-chloroperbenzoic acid in dichloromethane followed by hydrolysis of the resulting epoxide with dilute sulphuric acid furnished the tetralone **1** in 41% yield.



8 **10** **1**

Reagents: (v) 2,4-PD, toluene, reflux Dean-Stark, 24h. (vi) m-CPBA, CH_2Cl_2. (vii) H_2SO_4, EtOH, reflux 3h.

Scheme 2

Conclusions

In conclusion a three step synthesis of tetralone **2** and a five step synthesis of tetralone **1** have been accomplished by a single route. The present approach for the synthesis of tetralone **1** and tetralone **2** is very practical, has the merit of relative brevity and offers advantages in ease of manipulation.. The starting material is inexpensive and commercially available. Most of the intermediates were found to stable to permit its isolation even by repeated chromatographic purification..The present method can be utilized for the synthesis of tetralones **1** and **2** in quantities sufficient to accomplish their transformations to bioactive compounds in acceptable yield to investigate their broad biological and medicinal properties.

Experimental Section

General Procedures. Unless otherwise stated, IR spectra were taken on Nicolet FT and NMR spectra recorded on a Bruker AM-300 spectrometer were taken in $CDCl_3$. Mass spectra were carried on Dupont 21-492B. Column chromatograhy was carried out on silica gel 60 (Merck),

TLC plates were coated with silica gel and the spots were located by exposing to UV light. Microanalyses were carried out in the Chemistry Deparment, IVIC, Caracas.

5-Bromo-6-methoxytetralin (5) and 7-bromo-6-methoxytetralin (**4).** To a suspension of *N*-bromosuccinimide (11,21 g, 62.9 mmol) and benzoylperoxide (1.51 g, 6.2 mmol) in dry toluene (370 ml) cooled at -78^{o}C was added dropwise under inert atmosphere a solution of 6-methoxy-1,2,3,4-tetrahydronaphthalene (10g, 61.7 mmol) in dichloromethane (100 ml) and stirred at -78^{o} C for 7 hr and then at room temperature for 10 hr. The reaction mixture was filtered, concentrated at reduced pressure, added hexane to precipitate succinimide and finally the filtrate was washed successively with hydrochloric acid (5%), saturated sodium chloride solution and concentrated to obtain a mixture of **4** and **5** as a yellow liquid (13.67 g) in proportion 1.3 :1 as evidenced by ^{1}H NMR spectroscopy and they could not be separated by column chromatography: MS (m/z) 242 [M+2] (91%), 240 [M] (100%), 212 [M-C_2H_4] (28%), 161 [M-Br] (91%).^{1}H $\delta_{(ppm)}$ 7.22 (s, 1H, 8′-H), 6.98 (d, 1H, 8-H, J=8Hz), 6.69 (d,1H, 7-H, J=8 Hz), 6.59 (s, 1H, 5′-H), 3.85 (s, 3H, OMe), 3.82 (s, 3H, OMe),2.78-2.54 (m, 8H, 4 x CH_2), 1.85-1.65 (m, 8H, 4 x CH_2); ^{13}C $\delta_{(ppm)}$ 153.8, 153.4 (C-6, C-6′), 137.8, 137.4 (C-10, C-10′), 133.3, 131.4 (C-9, C-9′), 130.7,128.3 (C-8, C-8′), 114.6, 112.4 , 109.2, 108.3 (C-5, C-5′, C-7,C-7′), 56.3, 56.2 (MeO), 30.6, 29.4, 28.3 (C4, C4', C-1, C-1′), 23.3, 23.1, 22.9, 22.8 (C2, C2', C-3, C-3′).

6,7-Dimethoxy-1,2,3,4-tetrahydronaphthalene 6 and 5,6-dimethoxy1,2,3,4 tetrahydro-naphthalene (7). A solution of sodium (13.8 g, 0.6 mol) in methanol (176 mL), was diluted with dry dimethylformamide (250 mL) and then added copper(I) iodide (24.8g, 0.13mol) and bromotetrahydronaphthalenes **4** and **5** (7.54 g, 0.03 mol). The reaction mixture was stirred under reflux for 24 hr, cooled, filtered, concentrated, and acidified with hydrochloric acid (5%). The reaction product was isolated with chloroform and the chloroform extract was washed with water, brine, dried and concentrated to obtain a liquid which on chromatographic purification (eluant hexane) yielded in an overall yield 31% of the compound **6** (2.03 g) for the two steps, m.p. 49-51^{o} C (lit.[16] m.p. 52-54.5^{o}C); MS(m/z) 193 [M + 1] (24%), 161 (M-MeO) (8%), 151 [M + 1]-C_3H_6 (100%),^{1}H $\delta_{(ppm)}$ 6.54 (s, 2H, 8-H, 5-H), 3.81 (s, 6H, 2 x OMe), 2.60-2.70 (m, 4H, 2 x CH_2), 1.70-1.76 (m, 4H, 2 x CH_2); ^{13}C $\delta_{(ppm)}$ 146.9 (C-6, C-7), 128.8 (C-9, C-10), 111.9 (C-5, C-8), 55.9 (MeO), 28.9 (C-1, C-4), , 23.3 (C-2, C-3). (Found: C, 75.19; H, 8.55. C_{12} H_{16} O_2 requires C, 74.97; H, 8.39).

Further elution with hexane yielded in an overall yield 30.7% of the oily compound **7(**1.98 g) for the two steps; MS (m/z) 193 [M+1] (54%), 161 [M – MeO] (61%), 151 [M + 1] – C_3H_6 (100%); ^{1}H $\delta_{(ppm)}$ 6.79-6.71 ($q_{AB,}$ 2H, 7-H, 8-H, J=8 Hz), 3.83 (s, 3H, MeO), 3.79 (s, 3H, MeO), 2.76-2.69 (m, 4H, 2 x CH_2), 1.77-1.74 (m, 4H, 2 x CH_2); ^{13}C $\delta_{(ppm)}$ 150.3 (C-5), 146 .7 (C-6), 131.4 (C-9), 130.5 (C-10), 124.2 (C-8), 110 (C-7), 59.8 (C-5 OMe), 55.9 (C-6 OMe), 28.9 (C-1), 23.4, 23.1 (C-2, C-3), 22.8 (C-4). (Found: C, 75.23; H, 8.57. C_{12} H_{16} O_2 requires C, 74.97; H, 8.39).

5,6-Dimethoxy-α-tetralone (2). To a solution of the compound **7** (510 mg, 2.6 mmol) in acetonitrile (67 ml) was added potassium permanganate (2.59 g, 16.4 mmol) in portion and

stirred for 24 hr at room temperature. The reaction mixture was filtered and the residue washed with chloroform. To the combined filtrate was added hydrazine hydrochloride, water and extracted with chloroform. The extract was washed, dried and concentrated to obtain a solid which on crystallization afforded the tetralone **2** (211 mg, 39%) m.p. 97-98°C (lit[9]. 101-102°C); IR υ_{max} (cm^{-1}): 1666 (CO); MS (m/z): 207 [M + 1] (100%), 189 [M + 1] - H_2O (68%), 179 [M + 1] - CO (26%), 174 [M + 1] -H_2O - Me (32%); ^1H $\delta_{(ppm)}$ 7.84 (d, 1H, J=8.7 Hz), 6.85 (d, 1H, J=8.7 Hz) (7-H, 8-H), 3.90 (s, 3H, MeO), 3.80 (s, 3H, MeO), 2.94 (t, 2H, J= 6 Hz), 2.57 (t, 2H, J=6 Hz), 2.07 (q, 2H, J=6 Hz).
^{13}C $\delta_{(ppm)}$ 197.5 (C-1), 156.8 (C-6), 145.2 (C-5), 138.6 (C-10), 126.6 (C-9), 124.4 (C-8), 109.9 (C-7), 60.2 (MeO), 55.7 (MeO), 38.7 (C-2), 23.2, 22.8 (C-3, C-4). (Found: C, 70.09; H, 6.98. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84).

6,7-Dimethoxy-α-tetralone (8). To a solution of the dimethoxytetrahydronaphthalene **6** (4g, 20.8 mmol) in acetonitrile (520 ml) was added potassium permanganate (20 .7 g, 131 mmol) portionwise during a period of 15 min and stirred vigorously at room temperature for 24 hr. The reaction mixture was filtered and the residue was washed with chloroform. To the combined extract was added hydrazine hydrochloride, diluted with water and extracted with chloroform. The organic extract was washed, dried and evaporated to obtain a solid which on crystallization with ether-hexane afforded the tetralone **8** (1.89 g, 44%), m.p. 92-95°C (lit.[16] 93.5-95.5° C); IR υ_{max} (cm^{-1}): 1670 (CO); Ms (m/z): 207 [M + 1] (100%), 189 [M +1] - H_2O (54%), 179 [M + 1] – CO (81%), 174 [189 – Me] (18%); ^1H $\delta_{(ppm)}$ 7.40 (s,1H, 8-H), 6.57 (s, 1H, 5-H), 3.83 (s, 3H, MeO), 3.81 (s, 3H,MeO), 2.79 (t, 2H, J= 6 Hz), 2.49 (t, 2H, J= 6 Hz), 2.01 (q, 2H, J= 6 Hz) ^{13}C $\delta_{(ppm)}$ 196.6 (C-1), 153.2 (C-6), 147.6 (C-7), 139 .1 (C-10), 126.2 (C-9), 109.9 , 108.1 (C-5, C-8), 55.7 , 55.6 (OMe), 38.2 (C-2), 29.1 (C-4), 23.4 (C3). (Found: C, 70.04; H, 6.96. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84).

6,7-Dimethoxy-3,4-dihydronaphthalene (10). To a solution of the tetralone **8** (670 mg, 3.3 mmol) in toluene (66 ml) was added p-toluenesulphonic acid (240 mg, 0.12 mmol) and 2,4-pentanediol (1.45 ml, 13.4 mmol) and then heated under reflux for 24 hr using a Dean-Stark apparatus. The reaction mixture was cooled, diluted with sodium bicarbonate solution (5%) and extracted wih ether. The extract was washed, dried, evaporated and chromatographed over silica (eluent hexane-ether 8:2) to obtain the dihydronaphthalene **10 (**580 mg, 92%); MS: (m/z) 191 [M + 1] (100%), 176 [M + 1] – Me (24%), 160 [M + 1] - Me (24%), 160 [M + 1] - OMe (82%); ^1H $\delta_{(ppm)}$ 6.64 (s, 1H), 6.57 (s, 1H) (5-H, 8-H), 6.35 (dt, 1H, J= 1.70 Hz, J= 9.57 Hz), 5.91 (dt, 1H, J= 4.38 Hz, J= 9.54 Hz) (1-H, 2-H), 3.84 (s, 3H, MeO), 3.83 (s, 3H, MeO), 2.70 (t, 2H, J= 8.3 Hz), 2.29-2.18(m, 2H), (3-H, 4-H); ^{13}C $\delta_{(ppm)}$ 147.6, 147.3 (C-7, C-6), 127.8 (C-10), 127.2 (C-2),126.8 (C-9), 126.4 (C-1), 111.4 (C-8),109.8 (C-5), 55.9 (MeO), 27.1(C-4), 23.2 (C-3). (Found: C, 76.02; H, 7.58. $C_{12}H_{14}O_2$ reqires C, 75.76; H, 7.42).

6,7- Dimethoxy-2-tetralone (1). To a suspension of m-chloroperbenzoic acid 77% (920 mg, 4.1 mmol) in dry dichloromethane (10 mL), cooled in ice, was added dihydronaphthalene **10** (350mg, 1.8 mmol) dissolved in dichloromethane (2 mL). The reaction mixture was stirred overnight, filtered, diluted with dichloromethane, washed with a solution of sodium bicarbonate

(5%), brine, dried and evaporated to obtain an oil (268 mg) which was dissolved in ethanol (2 mL) and sulphuric acid (2 mL, 10%) and heated under reflux for 3 hr. The reaction mixture was cooled, diluted with water and extracted with chlororm. The organic extract was washed, dried and evaporated to obtain an oil which on purification (eluent hexane-ether 7:3) afforded tetralone **1 (**110 mg, 41%), m.p. 83-86°C (lit.[7] 84-86°C); IR υ_{max} (cm^{-1}) 1705 (CO); MS (m/z): 207 [M + 1] (14%), 189 [M + 1] - H_2O (100%), 179 [M + 1] – CO (22%). ^1H $\delta_{(ppm)}$ 6.71 (s, 1H, 8-H), 6.59 (s, 1H, 5-H), 3.85 (s, 3H, MeO), 3.83 (s, 3H, MeO), 3.48 (s, 2H), 2.97 (t, 2H, J= 6 Hz), 2.52 (t, 2H, J= 6 Hz); ^{13} C $\delta_{(ppm)}$ 210.8 (C-2), 147.9, 147.7 (C-6, C-7), 128.4 (C-10), 124.9 (C-9), 111.3, 111,1 (C-8, C-5), 55.9 (MeO), 44.1 (C-1), 38.5 (C-3), 28.1 (C-4). (Found: C, 70.11; H, 6.99; $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84).

6,7-Dimethoxy-1,4-naphthoquinone (9). To a solution of the tetrahydronaphthalene **6** (601 mg, 3.13 mmol) in glacial acetic acid (80 mL), cooled in ice, was added dropwise an aqueous solution of chromic acid (15 mL, 10%) (prepared by dissolving 5.25 g of CrO_3 in 47.5 mL of acetic acid and 2.5 mL of water).The reaction mixture was stirred for 3 hr at a temperature between 15-20^{o}C with an ice bath. The progress of the reaction was monitored by tlc. It was then diluted with water and extracted with ether. The ether extract was washed with water, sodium bicarbonate solution, brine, dried ($MgSO_4$) and concentrated to obtain the naphthaquinone **9** (590 mg, 92%), m.p. 194-196^{o}C (decompose); MS (m/z) 221 [M+1] (48%), 193 [M+1] – CO (100%), 175 [193 - H_2O] (24%), 165 [193 – CO] (48%); δ $_{(ppm)}$ 7.44 (s, 2H), 3.98 (s, 6H, MeO), 3.02 (s, 4H); ^{13}C $\delta_{(ppm)}$ 195.3 (C-1, C-4), 153.8 (C-6, C-7), 130.1 (C-9, C-10), 107.5 (C-5, C-8), 56.4 (OMe), 37.3 (C-2, C-3). (Found: C, 65.71; H, 5.68. C_{12} H_{12} O_4 requires C, 65.44; H, 5.49).

Acknowledgements

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