

## Facile Synthesis of 5-Methoxy-3-methyl-2-tetralone

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Interesting pharmacological results obtained with C<sub>1</sub>- and C<sub>2</sub>-methylated derivatives of 5-hydroxy-2-(di-*n*-propylamino)-tetralin<sup>1,2</sup> provide impetus for preparation and subsequent pharmacological evaluation of C<sub>3</sub>-methylated analogues. Access to 5-methoxy-3-methyl-2-tetralone (*1*) would enable the preparation of such compounds since 2-aminotetralins are readily synthesized from the corresponding 2-tetralones (*cf.* Ref. 3). In this report we describe a facile, four-step synthesis of *1*, using 1,6-dihydroxynaphthalene as starting material (Scheme 1). Pure 1,6-dimethoxynaphthalene (*2*)<sup>4</sup> is readily obtained by methylation of commercially available 1,6-dihydroxynaphthalene (Me<sub>2</sub>SO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, acetone, reflux 4 h; 94%). Sodium reduction of *2* in ethanol was already reported in the late forties<sup>5</sup> but the primary product(s) was neither characterized nor isolated. More recently, the conversion of *2* to 1,2-dihydro-3,8-dimethoxy-naphthalene (*4*) by use of sodium in ethanol has been described in a patent,<sup>6</sup> and Kocor and Kotlarek<sup>7</sup> have reported the isolation of 1,4-dihydro-2,5-dimethoxynaphthalene (*3*) in 90% yield from sodium or lithium reduction of *2* in liquid ammonia/tetrahydrofuran with methanol, ethanol, or 2-propanol as proton donors. However, the <sup>1</sup>H NMR spectroscopic data reported in the latter article indicate that the product isolated was the isomeric enol ether *4*; <sup>1</sup>H NMR spectra of regioisomers *3* and *4* differ considerably when recorded in deuterio chloroform. The

four benzylic hydrogens of *3* form a narrow multiplet at δ 3.39 whereas the four C<sub>1</sub>- and C<sub>2</sub>-hydrogens of *4* form two apparent triplets centered at δ 2.38 and δ 2.92, respectively. In addition, the vinylic proton of *3* absorbs 0.72 ppm upfield of the absorption due to the vinylic C<sub>4</sub>-H of *4*. These differences were utilized to calculate relative amounts of *3* and *4* from <sup>1</sup>H NMR spectra of crude product mixtures. In our preparation, the reduction of *2* using a large excess of sodium in ethanol proved unpredictable; isomeric ratios of *3* to *4* ranged from 17:1 to 3:1. Most likely, the discrepancy between our results and those in the literature<sup>6,7</sup> was due to the marked tendency of *3* to isomerize to *4* in the presence of base. The sensitivity of *3* to base-catalyzed isomerization was demonstrated by conversion of a 3:1 mixture of *3* and *4* into isomerically pure *4* by use of potassium hydride in tetrahydrofuran. In order to improve the regioselectivity of the reduction, other reaction conditions were explored (Table 1). The best results were obtained by using 2-propanol as solvent instead of ethanol. This modification gave, reproducibly, high yields of *3* and high isomeric ratios of *3* to *4*.

Cyclopropanation of *3* by use of a homogeneous modification of the Simmons-Smith reaction (diiodomethane and diethylzinc in benzene)<sup>8</sup> followed by chromatography provided the cyclopropane *5* in 78% yield. Enol ether *4* was converted to the cyclopropane *6* in 30% yield by use of a zinc-copper couple and diiodomethane in ether. Reaction of *3*, using this latter procedure, re-

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Table 1. Isomeric ratios and yields in sodium reductions of 1,6-dimethoxynaphthalene (2).

Solvent	Equivalents of Na <sup>a</sup>	Reaction time <sup>b</sup> (min)	Yield of 3 and 4 <sup>c</sup> (%)	Isomeric ratio <sup>c</sup> (3:4)
EtOH	23 <sup>d</sup>	35	85	3.2:1
EtOH	7	5	50	25:1
EtOH/H <sub>2</sub> O (50:4)	20	20	55	12:1
2-PrOH	23	35	95	18:1
NH <sub>3</sub> /THF/EtOH (2:2:1.5)	3	4 <sup>e</sup>	70 <sup>f</sup>	<sup>g</sup>

<sup>a</sup>Granulated sodium. <sup>b</sup>Reaction mixtures were heated to gentle reflux and quenched with water and ammonium chloride. <sup>c</sup>Numbers represent the average of at least two experiments and are based on relative peak areas in <sup>1</sup>H NMR spectra of crude reaction products. <sup>d</sup>Pea size lumps of sodium. <sup>e</sup>Reaction performed at -78°C. <sup>f</sup>In addition, overreduced products (30%) were formed. <sup>g</sup>No formation of 4 was observed.

sulted in partial isomerization of 3 to 4; compound 5 was isolated in 34% yield. The availability of both isomer 5 and 6 allowed unambiguous assignments of their structures. Acid-catalyzed ring opening<sup>9,10</sup> of 5 furnished target compound 1. The conversion of 5 to 1 appeared to be quantitative (GC, TLC) but decomposition of 1 during work-up lowered the yield of isolated 1 (85%). Similarly, compound 6 was solvolyzed to 5-methoxy-1-methyl-2-tetralone (7)<sup>5,11</sup> in 81% yield. The structure of 1 was supported by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data as well as by its IR spectrum, mass spectrum and combustion analysis. Especially informative in the <sup>1</sup>H NMR spectrum of 1 was the doublet at  $\delta$  1.21 ( $J = 6.2$  Hz), which is due to the C<sub>3</sub>-methyl substituent. The presence of the C<sub>3</sub>-methyl was apparent also in the <sup>13</sup>C NMR spectrum of 1 as an absorption at  $\delta$  14.80. Thus, the possibility that 5 would have rearranged into a benzocycloheptenone derivative could be ruled out.

## Experimental

Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. IR spectra were recorded on a Perkin-Elmer 157G spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a JEOL FX 90Q spectrometer. Mass spectra were obtained at 70 eV on a LKB 9000 spectrometer. Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden.

*1,4-Dihydro-2,5-dimethoxynaphthalene (3).* To a vigorously stirred solution of 1,6-dimethoxynaphthalene (2)<sup>4</sup> (2.50 g, 13.3 mmol) in 250 ml of dry 2-propanol kept at gentle reflux under nitrogen was rapidly added 7.9 g (304 mmol) of granulated sodium. After 35 min, heating was interrupted and 25 ml of water were added. Ammonium chloride (35 g, 608 mmol) was added 15 min later and 2-propanol was evaporated. To the semisolid residue were added water (200 ml) and ether (200 ml). The ether layer was separated, dried (MgSO<sub>4</sub>), filtered, and evaporated to give 2.36 g of a mixture of unreacted 2 (7%), 4 (4%), and 3 (89%) which was used in further reactions without any purification. <sup>1</sup>H NMR (89.55 MHz, CDCl<sub>3</sub>):  $\delta$  7.25–6.55 (m, 3H), 4.78 (narrow m, C<sub>3</sub>-H), 3.75 (s, 3H), 3.56 (s, 3H), 3.39 (narrow m, 4H).

*Isomerization of 3. Preparation of 1,2-dihydro-3,8-dimethoxy-naphthalene (4).*<sup>6</sup> To a suspension of potassium hydride (0.5 g, 10 mmol) in 250 ml of dry THF, kept under nitrogen, was carefully added a solution of 5.0 g of a mixture of 2 (10%, 2.7 mmol), 3 (68%, 17.9 mmol) and 4 (22%, 5.8 mmol) in 50 ml of dry ether. The reaction mixture was stirred at room temperature overnight and then quenched by dropwise addition of 50 ml of a saturated ammonium chloride solution. The volatiles were evaporated and the residue was partitioned between water and ether. The ether layer was dried (MgSO<sub>4</sub>) and evaporated to give 4.07 g of a mixture of 2 and 4 with no contamination of 3. Pure 4 (2.09 g) was obtained by chromatography of the mixture on an alumina

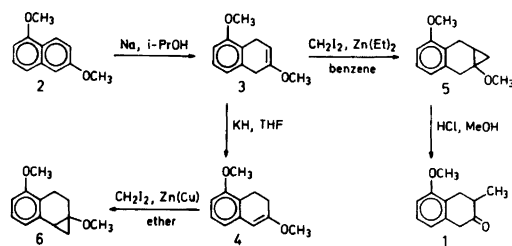
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column eluted with light petroleum.  $^1\text{H}$  NMR (89.55 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.22–6.55 (m, 3H), 5.50 (broad s,  $\text{C}_4\text{-H}$ ), 3.81 (s, 3H), 3.69 (s, 3H), 3.05–2.78 (m, 2H), 2.50–2.25 (m, 2H).

*1,2,3,4-Tetrahydro-2,3-methano-2,5-dimethoxy-naphthalene* (5). To a solution of crude 3 [8.10 g; consisting of 77% of 3 (32.8 mmol), 17% of 2 (7.3 mmol) and 6% of 4 (2.6 mmol)] in dry benzene (80 ml), kept under nitrogen, were carefully added 35.4 ml (35.4 mmol) of a 1.0 M solution of diethylzinc in toluene. After five min, a solution of 4.3 ml (53.1 mmol) of diiodomethane in 20 ml of dry benzene was added dropwise to the rapidly stirred reaction mixture. After addition of four more 4 ml portions of diiodomethane during the next eight h, the reaction flask was heated (50 °C for two h) then left at room temperature overnight. A precooled saturated ammonium chloride solution (125 ml) was carefully added and the resulting solution was diluted with ether. The organic layer was washed several times with water, dried ( $\text{MgSO}_4$ ), filtered, and evaporated. Flash chromatography of the residue using ether/light petroleum (1:19) gave 0.5 g of recovered 2, several impure fractions, and 5.22 g (78%) of pure 5, b.p. 94 °C/0.05 mmHg.  $^1\text{H}$  NMR (89.55 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.25–6.63 (m, 3H), 3.77 (s, 3H), 3.37 (s, 3H), 3.30–2.66 (m, 4H), 1.63–1.40 (m, 1H), 0.79–0.61 (m, 1H), 0.48–0.31 (m, 1H). MS [*m/e* (% rel. int.)]: 204 (99, M), 203 (14), 189 (100). Anal.  $\text{C}_{13}\text{H}_{16}\text{O}_2$ : C, H.

*1,2,3,4-Tetrahydro-1,2-methano-2,5-dimethoxy-naphthalene* (6) was prepared from 4 by use of a zinc-copper couple<sup>12</sup> and diiodomethane in ether according to the literature.<sup>13</sup> The crude reaction product was purified using flash chromatography with ether/light petroleum (1.5:10) as eluent. Partially purified fractions were pooled and rechromatographed using dichloromethane as eluent yielding 0.76 g of 6. Distillation gave 0.66 g (30%) of analytically pure 6, b.p. 78–86 °C/0.1 mmHg.  $^1\text{H}$  NMR (89.55 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.24–6.59 (m, 3H), 3.77 (s, 3H), 3.37 (s, 3H), 3.28–2.90 (m, 1H), 2.45–1.85 (m, 4H), 1.29–1.09 (m, 2H); MS [*m/e* (% rel. int.)]: 204 (37, M), 203 (15), 189 (14). Anal.  $\text{C}_{13}\text{H}_{16}\text{O}_2$ : C, H.

*5-Methoxy-3-methyl-2-tetralone* (1). A solution of 5 (1.010 g, 5.3 mmol) in 27 ml of 3M HCl and 35 ml of methanol was heated to reflux under nitro-



Scheme 1. Facile synthesis of 5-methoxy-3-methyl-2-tetralone.

gen. After 10 h, the methanol was evaporated and the residue was extracted with ether. The ether layer was dried ( $\text{MgSO}_4$ ) and evaporated to give 950 mg of slightly yellow crystals. Trituration with pentane gave 785 mg of 1 (85%), m.p. 89–90 °C. An analytical sample was prepared by recrystallization from ether-hexane (10:1), m.p. 89.5–90.5 °C. IR (KBr) ( $\text{cm}^{-1}$ ): 1710 ( $\nu\text{C}=\text{O}$ ).  $^1\text{H}$  NMR (89.55 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.26–6.66 (m, 3H), 3.85 (s, OMe), 3.59 (narrow m, 2H), 3.45–3.20 (m, 1H), 2.70–2.35 (m, 2H), 1.21 (d, *J* 6.2 Hz,  $\text{C}_3\text{-Me}$ ). MS [*m/e* (% rel. int.)]: 190 (62, M), 134 (100). Anal.  $\text{C}_{12}\text{H}_{14}\text{O}_2$ : C, H.

*5-Methoxy-1-methyl-2-tetralone* (7)<sup>5,11</sup> was prepared from 6 (600 mg, 3.2 mmol) according to the procedure described for the preparation of 1. The product, which was obtained in 81% yield, was identical (IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy) to that previously obtained<sup>11</sup> by methylation of the pyrrolidine enamine of 5-methoxy-2-tetralone.

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