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

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Interesting pharmacological results obtained with C7- and C7-methylated derivatives of 5-hydroxy-2-(di-n-propylamino)-tetralin1,2 provide impetus for preparation and subsequent pharmacological evaluation of C7-methylated analogues. Access to 5-methoxy-3-methyl-2-tetralone (I) 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 I, using 1,6-dihydroxynaphthalene as starting material (Scheme 1). Pure 1,6-dimethoxynaphthalene (2)3 is readily obtained by methylation of commercially available 1,6-dihydroxynaphthalene (Me2SO4, K2CO3, acetone, reflux 4 h; 94%). Sodium reduction of 2 in ethanol was already reported in the late forties4 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,5 and Kocor and Kotlarek6 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/tetrahedrofuran with methanol, ethanol, or 2-propanol as proton donors. However, the 1H NMR spectroscopic data reported in the latter article indicate that the product isolated was the isomeric enol ether 4; 1H 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 C7- and C7-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 from the absorption due to the vinylic C7-H of 4. These differences were utilized to calculate relative amounts of 3 and 4 from 1H 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 literature4-5 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)6 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).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Equivalents of Na&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Reaction time&lt;sup&gt;a&lt;/sup&gt; (min)</th>
<th>Yield of 3 and 4&lt;sup&gt;e&lt;/sup&gt; (%)</th>
<th>Isomeric ratio&lt;sup&gt;e&lt;/sup&gt; (3:4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIOH</td>
<td>23&lt;sup&gt;d&lt;/sup&gt;</td>
<td>35</td>
<td>85</td>
<td>3.2:1</td>
</tr>
<tr>
<td>EIOH</td>
<td>7</td>
<td>5</td>
<td>50</td>
<td>25:1</td>
</tr>
<tr>
<td>EIOH/H&lt;sub&gt;2&lt;/sub&gt;O (50:4)</td>
<td>20</td>
<td>20</td>
<td>55</td>
<td>12:1</td>
</tr>
<tr>
<td>2-PrOH</td>
<td>23</td>
<td>35</td>
<td>95</td>
<td>18:1</td>
</tr>
<tr>
<td>NH&lt;sub&gt;4&lt;/sub&gt;/THF/EIOH (2:2:1.5)</td>
<td>3</td>
<td>4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>70&lt;sup&gt;f&lt;/sup&gt;</td>
<td>9&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<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<sup>7,11</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 δ 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 δ 14.80. Thus, the possibility that 5 would have rearranged into a benzocycloheptene 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.

<sup>1,4</sup>-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>): δ 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
column eluted with light petroleum. $^1$H NMR (89.55 MHz, CDCl$_3$): δ 7.22–6.55 (m, 3H), 5.50 (broad s, C$_6$H$_5$), 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 (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. $^1$H NMR (89.55 MHz, CDCl$_3$): δ 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. C$_{13}$H$_{12}$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 and diiodomethane in ether according to the literature. 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. $^1$H NMR (89.55 MHz, CDCl$_3$): δ 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. C$_{13}$H$_{16}$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 nitrogen. After 10 h, the methanol was evaporated and the residue was extracted with ether. The ether layer was dried (MgSO$_4$) and evaporated to give 950 mg of slightly yellow crystals. Trituration with pentane gave 785 mg of I (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) (cm$^{-1}$): 1710 (vC=O). $^1$H NMR (89.55 MHz, CDCl$_3$): δ 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, 6.2 Hz, C$_3$-Me). MS [m/e (% rel. int.)]: 190 (62, M), 134 (100). Anal. C$_{10}$H$_{12}$O$_2$: C, H.

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

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References
SHORT COMMUNICATION


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