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### Synthesis of 1-*p*-Methoxyphenyl and 1-*p*-Methoxyphenyl-4-methylbicyclo-[2.2.1]heptan-7-one. The Oxidation of 7-Hydroxy-1-*p*-methoxyphenyl-4-methylbicyclo[2.2.1]heptan-7-carboxylic Acid with Lead Tetraacetate

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SYNTHESIS OF 1-p-METHOXYPHENYL AND 1-p-METHOXYPHENYL-4-METHYLBICYCLO-[2.2.1]HEPTAN-7-ONE. THE OXIDATION OF 7-HYDROXY-1-p-METHOXYPHENYL-4-METHYLBICYCLO[2.2.1]HEPTAN-7-CARBOXYLIC ACID WITH LEAD TETRAACETATE

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**Abstract :** A simple synthetic route to 1-p-methoxyphenyl and 1-p-methoxyphenyl-4-methylbicyclo[2.2.1]heptan-7-one **6b,a** has been developed through benzilic acid rearrangement of the bicyclo[2.2.1]octandiones **2b,a**. The oxidation of 7-hydroxy-1-p-methoxyphenyl-4-methylbicyclo[2.2.1]heptan-7-carboxylic acid **3a** with lead tetraacetate gives the carbolactone **7a** which is also formed by the reaction of the ketone **6a** with m-chloroperbenzoic acid.

Although a number of synthetic methods for 7-oxygenated norbornanes are known<sup>1-3</sup> these are not applicable to the respective bridgehead substituted derivatives. The only recorded synthesis of 1-methyl- and 1,4-dimethyl-7-oxonorbornanes was achieved through a bicyclo[3.2.0]heptane to bicyclo[2.2.1]heptane rearrangement<sup>4</sup>. We report here a synthesis of the novel-1-p-methoxyphenyl- and 1-p-

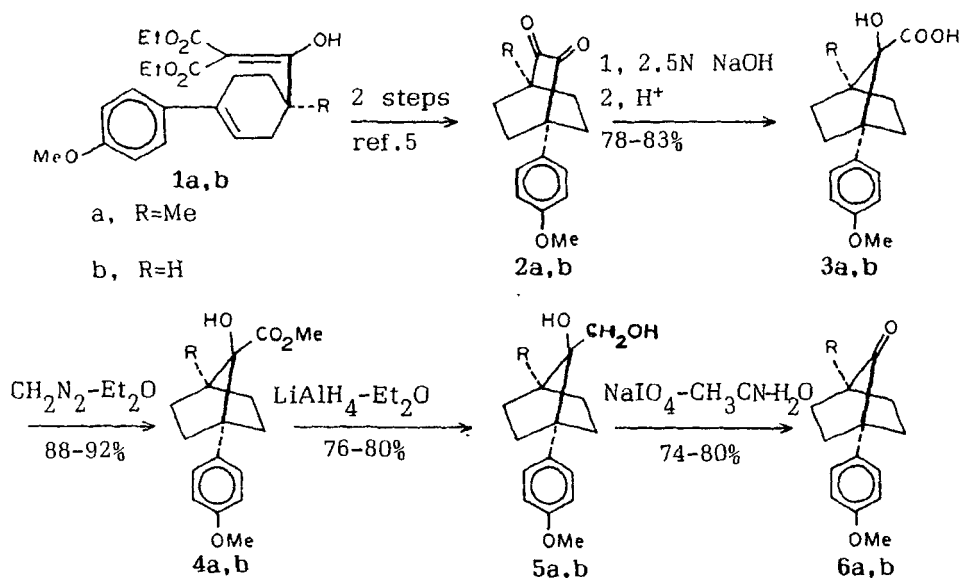
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methoxyphenyl-4-methyl-7-oxonorbornanes **6b,a** involving benzoic acid rearrangement of the bicyclo[2.2.2]octanones **2b,a** to the bicyclo[2.2.1]heptane acids **3b,a** followed by oxidative cleavage of the respective diols **5b,a** (Scheme-1).

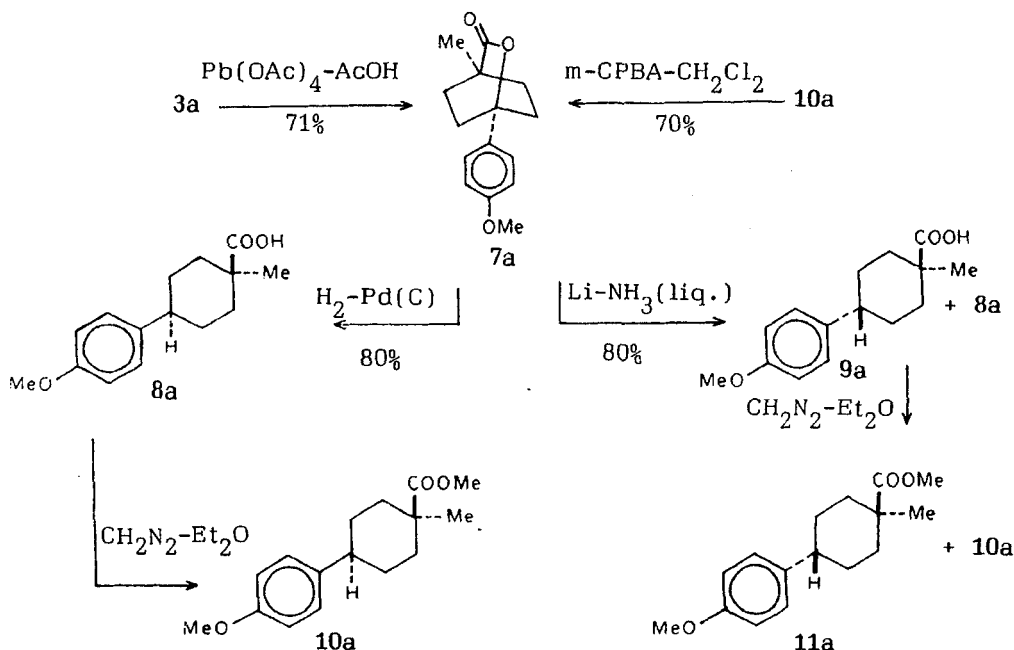
The readily accessible diones **2a,b** were prepared by an intramolecular acid-catalyzed cyclization and decarboxylation of the enolized  $\beta$ -keto diesters **1a,b** followed by oxidation as described earlier<sup>5</sup>. Benzoic acid rearrangement<sup>6</sup> **2a,b** with aqueous sodium hydroxide afforded the respective  $\alpha$ -hydroxy acids **3a,b**. The methyl esters **4a,b**, obtained by esterification of the acids **3a,b** with diazomethane, were reduced with lithium aluminium hydride and the resulting diols **5a,b** were smoothly transformed to the ketones **6a,b** by oxidation with sodium metaperiodate<sup>7</sup>.

Scheme - 1



The oxidative decarboxylation of the  $\alpha$ -hydroxy acid 3a with lead tetraacetate<sup>8</sup> in acetic acid produced the lactone 7a (Scheme-2), which was also obtained by Bayer-Villiger oxidation of the ketone 6a with *m*-chloroperbenzoic acid<sup>9</sup>. To our knowledge the formation of Bayer-Villiger product in the oxidation of  $\alpha$ -hydroxy acid with lead tetraacetate has not been observed earlier<sup>10</sup>. The structure of the benzylic lactone 7a was established by its reductive cleavage on catalytic hydrogenolysis in the presence of palladium-charcoal in ethanol to a single epimeric acid, assigned as 8a, involving inversion at the benzylic chiral centre by analogy with earlier observations<sup>11</sup> in similar systems.

Scheme - 2



The  $^1\text{H}$  NMR and GLC analyses of the methyl ester 10a, of the acid 8a, established its homogeneity. In contrast the reductive cleavage of the benzylic bond in 7a with lithium-liquid ammonia<sup>11</sup> produced a mixture of the diastereoisomeric acids 8a and 9a, characterized through the respective methyl esters 10a and 11a, evidently involving inversion and retention of configuration at the benzylic centre<sup>11</sup>.

### EXPERIMENTAL

The compounds described are all racemates. Melting points taken in open capillary, are uncorrected. IR spectra were recorded on a Perkin-Elmer model 298 spectrometer.  $^1\text{H}$  NMR spectra (unless otherwise stated) were taken in  $\text{CDCl}_3$  on a Varian Associates XL-200 spectrometer with TMS acting as internal standard. Elemental analysis were performed by Mr. P.P. Bhattacharya and Mr. S.K. Sarkar of this laboratory. Column chromatography was performed on 'Brockman' neutral alumina (BDH, India), petroleum and light petroleum refer to the fraction with b.p.  $60-80^\circ\text{C}$  and  $40-60^\circ\text{C}$  respectively. GLC were performed on a Shimadzu GC-9A model with flame ionization detector employing a 1.5% OV-17 column. Mass spectra were recorded on a Finnegan 4000 spectrometer.

7-Hydroxy-1-p-methoxyphenyl-4-methylbicyclo[2.2.1]heptane-7-carboxylic Acid (3a) : The diketone  $2\text{a}^5$  (450 mg, 1.74 mmol) in aqueous sodium hydroxide solution (2.5 N; 90 ml) was

heated under reflux for 3 h. The cooled solution was acidified with hydrochloric acid (6N) and extracted with ether (3 x 50 ml). The ether extract was repeatedly washed with 5% sodium hydroxide solution (3 x 25 ml) and washed with brine. The alkaline extract was acidified in cold with hydrochloric acid (6N) and extracted with ether (3 x 50 ml), washed with brine and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of solvent afforded the solid acid 3a (390 mg, 83%); m.p.  $130^\circ\text{C}$  (ether/petroleum). IR(KBr) : 3600, 3540(OH); 1670(C=O); 1610(Ar)  $\text{cm}^{-1}$ . Anal calcd for  $\text{C}_{16}\text{H}_{20}\text{O}_4$ : C, 69.54; H, 7.30. Found C, 69.78; H, 7.36.

The acid 3a (340 mg) was esterified with an excess of ethereal diazomethane. Excess diazomethane was decomposed with dilute acetic acid and extracted with ether (3 x 30 ml). The ether extract was washed with 5% sodium bicarbonate solution, brine and dried ( $\text{Na}_2\text{SO}_4$ ). Evaporation of the solvent gave a liquid, which was purified by filtration through a wide short column of alumina. Elution with ether-petroleum (1:3) afforded the hydroxyester 4a, as an oil (330 mg, 92%). IR (film) : 3600, 3540(OH), 1700(C=O), 1610(Ar)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.98 (s, 3H,  $\text{CH}_3$ ), 1.37-2.04 (m, 6H,  $\text{CH}_2$ ), 2.31-2.54 (m, 2H,  $\text{CH}_2$ ), 3.34 (s, 1H, OH), 3.70 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 3.80 (s, 3H,  $\text{OCH}_3$ ), 6.86 (d, 2H arom,  $J = 8$  Hz), 7.32 (d, 2H arom,  $J = 8$  Hz).

**Methyl-7-Hydroxy-1-p-methoxyphenyl bicyclo[2.2.1]heptane-7-carboxylate (4b)** : The diketone **2b**<sup>5</sup> (360 mg, 1.47 mmol) in aqueous sodium hydroxide (2.5 N, 72 ml) was heated under reflux for 3 h. The cooled reaction mixture on usual work-up afforded the acid **3b** (300 mg, 78%), m.p. 152-154°C. IR (KBr) : 3410(OH) 1675(C=O), 1610(Ar)  $\text{cm}^{-1}$ .

The acid **3b** (270 mg) was esterified with excess ethereal diazomethane and worked up in the usual way. Evaporation of the solvent afforded the solid ester **4b** (250 mg, 88%), m.p. 74°C (ether/petroleum). IR (KBr) : 3400(OH), 1700(CO<sub>2</sub>CH<sub>3</sub>), 1610(Ar)  $\text{cm}^{-1}$ . <sup>1</sup>H NMR (CDCl<sub>3</sub>) :  $\delta$  1.36-1.84 (m, 4H, CH<sub>2</sub>), 2.00-2.58 (m, 5H, CH<sub>2</sub>+CH), 3.12 (br s, 1H, OH), 3.68 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 6.86 (d, 2H arom, J = 8 Hz), 7.32 (d, 2H arom, J = 8 Hz). Anal calcd for C<sub>10</sub>H<sub>20</sub>O<sub>4</sub> : C, 69.54; H, 7.30. Found : C, 69.31; H, 7.40.

**7-Hydroxymethyl-1-p-methoxyphenyl-4-methylbicyclo[2.2.1]heptan-7-ol (5a)** : A solution of the hydroxy ester **4a** (250 mg, 0.90 mmol) in dry ether (5 ml) was added dropwise to a suspension of lithium aluminium hydride (60 mg, 1.58 mmol) in ether (15 ml). The mixture was then refluxed for 4 h, cooled, decomposed with saturated aqueous sodium sulphate solution, and filtered through anhydrous sodium sulphate. Removal of the solvent afforded a solid. Recrystallisation from ether-petroleum gave pure **5a** (180 mg, 80%), m.p. 96-97°C. IR

(KBr) : 3500, 3470(OH), 1615(Ar)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.98 (s, 3H,  $\text{CH}_3$ ), 1.16-2.52 (m, 8H,  $\text{CH}_2$ ), 2.90 (br s, 1H, OH), 3.60 (m, 2H,  $\text{OCH}_2$ ), 3.76 (s, 3H,  $\text{OCH}_3$ ), 6.88 (d, 2H arom,  $J = 8$  Hz), 7.49 (d, 2H arom,  $J = 8$  Hz). Anal. calcd. for  $\text{C}_{16}\text{H}_{22}\text{O}_3$  : C, 73.25; H, 8.45. Found : C, 73.41; H, 8.39.

**7-Hydroxymethyl-1-p-methoxyphenyl bicyclo[2.2.1]heptan-7-ol (5d).** The hydroxyester 5a (220 mg, 0.79 mmol) in dry ether (5 ml) was reduced with lithium aluminium hydride (60 mg, 1.5 mmol) in ether (15 ml) to afford the diol 5b (150 mg, 76%), m.p.  $88^\circ\text{C}$  (ether petroleum). IR (KBr) : 3350(OH), 1615(Ar)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.08-2.48 (m, 9H,  $\text{CH}_2+\text{CH}$ ), 1.58 (br s, 1H, OH), 3.64 (m, 2H,  $\text{OCH}_2$ ), 3.76 (s, 3H,  $\text{OCH}_3$ ), 6.91 (d, 2H arom,  $J = 8$  Hz), 7.45 (d, 2H arom,  $J = 8$  Hz). Anal. calcd. for  $\text{C}_{15}\text{H}_{20}\text{O}_3$ ; C, 72.55; H, 8.12. Found : C, 72.56; H, 8.15.

**1-p-Methoxyphenyl-4-methylbicyclo[2.2.1]heptan-7-one (6a) :** The diol 5a (100 mg, 0.38 mmol) in acetonitrile (3 ml) and water (3 ml) was stirred at room temperature with sodium metaperiodate (244 mg, 11.5 mmol) for 4 h. The reaction mixture was diluted with water and extracted with ether (3 x 25 ml). The combined ether extract was washed with brine and dried (sodium sulphate). Removal of the solvent afforded 6a (70 mg, 80%), m.p.  $58^\circ\text{C}$  (ether-light petroleum). IR (KBr) 1760( $\text{C}=\text{O}$ ), 1605(Ar)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ );  $\delta$  1.10 (s, 3H,



CH<sub>3</sub>), 1.70-2.30 (m, 8H, CH<sub>2</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 6.94 (d, 2H arom, J = 8 Hz), 7.26 (d, 2H arom, J = 8 Hz); MS : m/z 230 (M<sup>+</sup>); Anal. calcd. for C<sub>15</sub>H<sub>18</sub>O<sub>2</sub> : C, 78.06; H, 8.17. Found : C, 78.23; H, 7.88.

**1-p-Methoxyphenyl bicyclo[2.2.1]heptan-7-one (6b)** : A solution of the diol 5b (125 mg, 0.5 mmol) in acetonitrile (3 ml) and water (3 ml) was oxidized with sodium metaperiodate (320 mg, 1.5 mmol) to afford the ketone 6b (80 mg, 74%), m.p. 80-81°C (ether-light petroleum). IR (KBr) : 1760(C=O), 1605(Ar) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.36-2.40 (m, 9H, CH<sub>2</sub>+CH), 3.78 (s, 3H, OCH<sub>3</sub>), 3.91 (d, 2H arom, J = 8 Hz), 7.23 (d, 2H arom, J = 8 Hz); MS : 217 (M+1). Anal. calcd. for C<sub>14</sub>H<sub>16</sub>O<sub>2</sub> : C, 77.75; H, 7.76. Found : C, 77.93; H, 7.76.

**c-4-Hydroxy-1-methyl-t-4-p-methoxyphenyl-r-1,4-carbolactone (7a) - (A)** : A mixture of the hydroxy acid 4a (75 mg, 0.27 mmol) and lead tetraacetate (123 mg, 1.1 eq.) in acetic acid (8 ml) was heated at 65-70°C for 1 h. The cooled solution was diluted with water (25 ml) and extracted with ether (3 x 25 ml). The ether extract was washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent gave an oil which on chromatography on neutral alumina and elution with ether-petroleum (1:3) afforded the lactone 11a as a crystalline solid (45 mg, 71%), m.p. 112°C (ether-petroleum). IR (KBr) : 1740 (lactone C=O), 1610 (Ar) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) : δ 1.28 (s, 3H, CH<sub>3</sub>), 1.86 (t, 4H, J = 8 Hz, CH<sub>2</sub>), 1.96-2.26 (m, 4H, CH<sub>2</sub>)

3.84 (s, 3H, OCH<sub>3</sub>), 6.94 (d, 2H arom, J = 8 Hz), 7.42 (d, 2H arom, J = 8 Hz); MS : 247 (M+1). Anal. calcd. for C<sub>15</sub>H<sub>18</sub>O<sub>3</sub> : C, 72.93; H, 7.57; Found : C, 73.14; H, 7.37.

(B) : The ketone 6a (50 mg, 0.28 mmol) in methylene chloride (10 ml) was stirred with *m*-chloroperbenzoic acid (50 mg, 0.28 mmol) and sodium bicarbonate (110 mg) at room temperature for 48 h. Usual work-up afforded a mixture of lactone 7a and the unreacted ketone 6a (by IR). Chromatography on silica gel with 5 to 15% of ether-petroleum afforded the recovered pure ketone 6a (10 mg). Further elution with 20 to 30% ether-petroleum gave the pure lactone 7a (30 mg, 70%), m.p. and m.m.p. 112°C, identical in all respect (IR, NMR, GLC) with the sample obtained by Method A.

Catalytic Reduction of lactone (7a). 1-Methyl-4-*t-p*-methoxy-phenylcyclohexane-*r*-1-carboxylic Acid (8a) : The lactone 7a (25 mg, 0.1 mmol) was hydrogenated in ethanol (5 ml) in the presence of 10% palladium-charcoal (10 mg) at room temperature and pressure. After complete uptake of hydrogen, the catalyst was filtered and removal of the solvent afforded a solid (25 mg) which on recrystallisation from ether-petroleum gave the pure acid 8a (20 mg, 80%), m.p. 110°C. IR (KBr) : 1690(C=O), 1605(Ar) cm<sup>-1</sup>. Anal. calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>3</sub> : C, 72.59; H, 8.15. Found : C, 72.55; H, 8.12.

The acid 8a was esterified with excess of ethereal diazomethane to afford the ester 10a. IR (KBr) : 1730(C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) :  $\delta$  1.21 (s, 3H,  $\text{CH}_3$ ), 1.26-1.88 (m, 6H,  $\text{CH}_2$ ), 2.24-2.52 (m, 3H,  $\text{CH}_2+\text{CH}$ ), 3.76 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 3.82 (s, 3H,  $\text{OCH}_3$ ), 6.88 (d, 2H arom,  $J = 8$  Hz), 7.16 (d, 2H arom,  $J = 8$  Hz). GLC :  $R_t = 2.73$  min at column temperature  $210^\circ\text{C}$  by coinjection with the authentic sample.

**Lithium-Ammonia Reduction of (7a) to the Acids (8a) and (9a) :**  
To a well-stirred solution of 7a (25 mg, 0.1 mmol) in dry tetrahydrofuran (5 ml) and dry liquid ammonia (ca. 30 ml) distilled from sodium, was added freshly scrapped lithium metal (20 mg, 3 mg atom) in small portions during 5 min. After another 5 min, the blue colour was discharged by cautious addition of solid ammonium chloride. After evaporation of ammonia, the residue was diluted with water (15 ml) and extracted with ether (3 x 20 ml). The combined ether extract was washed with 2% potassium hydroxide solution. The aqueous extract was acidified with (6N) hydrochloric acid solution. Usual work-up afforded a mixture of the acids 8a and 9a (20 mg, 80%). IR (KBr) : 1690(C=O)  $\text{cm}^{-1}$ .

The above acid mixture on esterification with an excess of ethereal diazomethane gave the corresponding ester mixture 10a and 11a. GLC and  $^1\text{H}$  NMR showed the ester to be a mixture of diastereomers, 10a and 11a in a ratio of 35:65. IR:

1730(CO<sub>2</sub>CH<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCL<sub>3</sub>) : δ 1.21, 1.29 (s, CH<sub>3</sub>, minor and major respectively), 1.32-1.90 (m, CH<sub>2</sub>), 3.70, 3.72 (s, each CO<sub>2</sub>CH<sub>3</sub>, major and minor respectively), 3.78, 3.80 (s, each OCH<sub>3</sub>, minor and major respectively), 6.82 - 7.00 (m, 2H arom), 7.08-7.26 (m, 2H arom). GLC : R<sub>t</sub> = 2.74 min (35%), 3.34 min (65%) at column temperature 210°C, by coinjection with the authentic sample.

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