A Synthesis of Diosphenols[1]

Masao Ōhashi†, Seiichi Inoue, and Kikumasa Sato*

Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Minami-ku, Yokohama 233

†*Chemical Laboratory, Seimi Chemical Co., Ltd., Chigasaki, Chigasaki-shi, Kanagawa 253*

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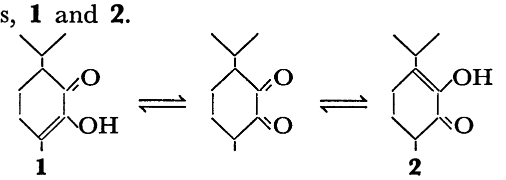
A new synthesis of diosphenols (**1** and **2**) is described. The oxidation of 2-isopropylcyclohexanone with copper(II) chloride gave the corresponding α-diketone (**8**), which was then methylated to afford diosphenol (**1**) together with a considerable amount of isodiosphenol (**2**). In particular, pure **2** has been isolated and the characteristics of **2** are also presented.

The monoterpenoid diosphenol (*buccocamphor*) (2-hydroxy-1-*p*-menthen-3-one) (**1**) has been found in the essential oil of various *Barosma* or *Mentha* species.[2] **1** has been synthesized from many terpenoid derivatives: 1-menthone,[3,4] carvomenthone,[4] piperitone,[4] and piperitone oxide [5]

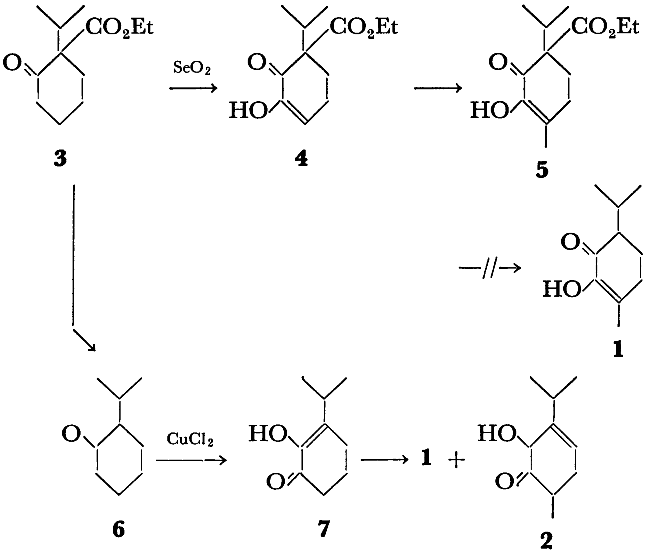
Diosphenol seems to exist as a mixture of two enolate forms, **1** and **2**.



Recently, Shibata *et al.*[6] reexamined the method of Macbeth and Robertson[3d] and isolated the reverse enol form; isodiosphenol (3-hydroxy-3-*p*-menthen-2-one) (**2**). But the details of **2** have not yet been reported.

Now we wish to report a convenient synthesis of **1** and **2** from ethyl 1-isopropyl-2-oxocyclohexanecarboxylate (**3**)[7] which is easily obtained by the condensation of ethyl cyclohexanecarboxylate with isopropyl iodide.

When **3** was refluxed with selenium dioxide in aqueous dioxane for 35 h, 6-ethoxycarbonyl-6-isopropyl-2-hydroxy-2-cyclohexen-1-one (**4**) was obtained. Compound **4** easily reacted with morpholine and formalin in dioxane at room temperature to afford a Mannich base, which was then hydrogenolyzed with zinc powder in acetic acid to give 6-ethoxycarbonyl-6-isopropyl-2-hydroxy-3-methyl-2-cyclohexen-1-one (**5**). In order to get **1**, we examined the deethoxycarbonylization of **5** with aqueous sulfuric acid, hydrochloric acid, or with lithium iodide dihydrate. However, in no case could **1** be obtained. The difficulty in hydrolysis of **5** is supposed to be due to the steric hindrance of the isopropyl group.[8] Then we examined the hydrolysis of **3**.



Although the attempted deethoxycarbonylization of **3** with sulfuric acid, barium hydroxide, or potassium hydroxide[9] was unfavorable, the refluxing of **3** with lithium iodide dihydrate in dimethylformamide gave 2-isopropylcyclohexanone (**6**) in excellent yield(91%).

Treatment of **6** with 4 molar amounts of copper(II) chloride in 50% acetic acid under reflux for 3 h afforded 2-hydroxy-3-isopropyl-2-cyclohexen-1-one (**7**) in moderate yield(61%). The structure of **7** was assigned on the basis of its IR, NMR, and UV spectra, and by elemental analysis. Then we examined the methylation[10] of **7** for the synthesis of **1** and **2**.

3-Alkyl-2-hydroxy-2-cycloalkenones easily reacted with morpholine and formalin in dioxane at room temperature to give corresponding bis-Mannich base.[11] Under the same conditions, compound **7** failed to react even when warmed at reflux, apparently because of the steric hindrance of the isopropyl group. However, **7** reacted with both morpholine hydrochloride and formalin in water under reflux to give the Mannich base, which was then hydrogenolyzed with zinc powder in acetic acid at 75—80 °C for 7 h, and gave a mixture of **1** and **2** in 31% yield. The ratio of the two components was **1**/**2**=62/38. Pure **1** and **2** can be isolated by crystallization or preparative GLC. The UV spectra of these two isomers in 95% ethanol slightly differ from each other: namely, **2** is bathochromic by *ca.* 1.0 nm. This result is parallel to the observations on 2-hydroxy-3-methyl-2-cyclohexen-1-one[11] and **7**. In the NMR spectra of **1** and **2**, the characteristic signals due to the methine proton in the isopropyl group and the methyl protons clearly differ from each other and are consistent with the assigned structures **1** and **2**, respectively. In mass spectra, a distinct difference between **1** and **2** is observed at *m*/*e* 125 (M^+—isopropyl) and 126 (association of the hydrogen shift with 125): the intensities of the two fragments are the reverse of each other. (see Experimental Section)

Finally, it should be noted that a fair amount of isodiosphenol (**2**) is formed along with **1** in the present reaction conditions and pure **2** is comparatively stable[12] at room temperature.

Experimental

All the points are uncorrected. The IR spectra were recorded with a Hitachi Model 215 spectrophotometer, and the UV spectra with a Hitachi Model EPS-3T spectro-

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* To whom all correspondence should be addressed.

photometer. The NMR spactra were obtained on a JEOL Model C-60H spectrometer, with tetramethylsilane as the internal reference. The mass spectra were determined on a Hitachi RMU-6E spectrometer.

Ethyl 1-Isopropyl-2-oxocyclohexanecarboxylate (**3**). This substance was prepared in 74% yield according to Ref. 7.

6-Ethoxycarbonyl-2-hydroxy-6-isopropyl-2-cyclohexen-1-one (**4**). A mixture of **3** (8.48 g, 40 mmol), selenium dioxide (8.8 g, 80 mmol), dioxane (100 ml), and water (30 ml) was stirred for 35 h under reflux. After cooling, the deposited selenium was filtered off, the solvent was distilled, and the residue was extracted with chloroform. After drying, the extract was concentrated and the residue was distilled to give the crude product **4** (3.1 g); bp 99—130 °C/0.4 mmHg. Redistillation afforded 1.60 g (17.7%) of pure **4**; bp 99—103 °C/0.3 mmHg. IR (neat) 3420 (O–H), 1730, w. 1710, 1675 (C=O), 1620 cm^{-1} (C=C). NMR (CCl_4) δ 0.78 (3H, d, $J=7.0$ Hz), 0.86 (3H, d, $J=7.0$ Hz), 1.26 (3H, t, $J=7.0$ Hz), 1.6—2.7 (5H, m), 4.16 (2H, q, $J=7.0$ Hz), 5.60 (1H, broad s), 6.95 (1H, m); mass *m/e*; 226 (M$^+$), 41 (100%).

6-Ethoxycarbonyl-2-hydroxy-6-isopropyl-3-methyl-2-cyclohexen-1-one (**5**). To a mixture of **4** (1.30 g, 5.75 mmol), dioxane (5 ml), and morpholine (0.50 g, 5.75 mmol), formalin (0.464 g, 5.75 mmol) in dioxane (1 ml) was added at 3—4 °C and the mixture was then stirred for 20 h at room temperature. After removal of the dioxane *in vacuo*, curde Mannich base (2.0 g) was obtained. To this Mannich base, acetic acid (18 ml) and zinc powder (1.9 g) were added, and the mixture was then stirred for 7 h at 72—74 °C. After the zinc had been filtered off and the acetic acid had been removed under reduced pressure, water (10 ml) was added. After extraction with chloroform and drying with magnesium sulfate, the solvent was evaporated and the residue was chromatographed on a silica gel column. Elution with benzene-ethyl acetate (10 : 1) yielded 0.345 g (Y=25%) of **5**; which was distilled at 100—110 °C/0.3 mmHg. IR (neat) 3370 (O–H), 1740, w. 1710, 1660 (C=O), 1643 cm^{-1} (C=C); NMR (CCl_4) δ 0.75 (3H, d, $J=7.0$ Hz), 0.88 (3H, d, $J=7.0$ Hz), 1.25 (3H, t, $J=7.0$ Hz), 2.02 (3H, s), 2.3—3.0 (5H, m), 4.13 (2H, q, $J=7.0$ Hz); mass *m/e*; 240 (M$^+$), 41 (100%).

2-Isopropylcyclohexanone (**6**). To a stirred, slightly boiling solution of lithium iodide dihydrate (16.7 g, 0.099 mol) in dimethylformamide (40 ml) was added ethyl 1-isopropyl-2-oxocyclohexanecarboxylate (7.0 g, 0.033 mol) dissolved in dimethylformamide (5 ml) over a period of 5 min under nitrogen atmosphere. The mixture was then refluxed for 45 h. The resulting mixture was diluted with aqueous hydrochloric acid and extracted with ether. The extract, after washing with water and drying over magnesium sulfate, was concentrated and the residual oil was distilled to give 4.2 g (Y=91%) of **6**; bp 81—85 °C/16 mmHg (lit,[8]) bp 80 °C/10 mmHg).

2-Hydroxy-3-isopropyl-2-cyclohexen-1-one (**7**). A mixture of **6** (1.95 g, 14 mmol), copper(II) chloride (7.53 g, 56 mmol), acetic acid (15.3 ml), and water (17.4 ml) was stirred for 3 h under reflux. After cooling, the mixture was saturated with ammonium chloride and extracted with ether. The extract was washed with aqueous ammonium chloride, dried over magnesium sulfate, and concentrated. The residual oil was distilled to give 1.30 g (Y=61%) of **7**; bp 71—73 °C/0.6 mmHg, $n_D^{25}=1.4994$. IR (neat) 3420 (O–H), 1665 (C=O), 1640 cm^{-1} (C=C); NMR (CCl_4) δ 1.06 (6H, d, $J=7.0$ Hz), 1.7—2.6 (6H, m), 3.16 (1H, heptet, $J=7.0$ Hz), 6.14 (1H, s); UV$_{max}$ (95% EtOH) 275.5 nm (ε 9500). Found: C, 70.57; H, 9.24%. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%. 2,4-Dinitrophenylhydrazone: mp 147—149 °C. Found: C, 54.14; H, 5.34; N, 16.77%. Calcd for $C_{15}H_{18}N_4O_5$: C, 53.89; H, 5.43; N, 16.76%.

Methylation of **7**: *2-Hydroxy-1-*p*-menthen-3-one* (**1**) *and 3-Hydroxy-3-*p*-menthen-2-one* (**2**). A mixture of **7** (0.924 g, 6 mmol), morpholine (1.04 g, 12 mmol), concentrated hydrochloric acid (1.25 g, 12 mmol), water (13.8 ml), and formalin (0.973 g, 12 mmol) was stirred for 8 h under reflux. Evaporation of water *in vacuo* gave the crude Mannich base. To this Mannich base, acetic acid (18 ml) and zinc powder (3.2 g) were added, and the mixture was then stirred for 7 h at 75—80 °C. After the zinc had been filtered off and the acetic acid had been removed under reduced pressure, a small amount of water was added. After extraction with ether, washing with saturated aqueous ammonium chloride, and drying with magnesium sulfate, the solvent was evaporated and the residue (647 mg) was chromatographed on a silica gel column (elution with benzene) to give a mixture of **1** and **2** (312 mg, Y=31%, **1** : **2**=62 : 38); these give rise to 6.4 and 5.7 min retention times. (DC-200 column 3 m, 150 °C, He, 1.5 kg/cm^2). When the mixture was allowed to stand in an ice box, **1** precipitated. After filtration and recrystallization from petroleum ether, pure diosphenol (**1**) (82 mg) was obtained. Mp 82—83 °C (lit,[3d)] mp 82 °C): IR (KBr) 3400 (O–H), 1665 (C=O), 1640 cm^{-1} (C=O); NMR (CCl_4) δ 0.86 (3H, d, $J=7.0$ Hz), 0.97 (3H, d, $J=7.0$ Hz), 1.80 (3H, broad s), 1.8—2.5 (6H, m), 5.99 (1H, s); UV$_{max}$ (95% EtOH) 274 nm (ε 9600); mass *m/e* (%) 168 (M$^+$, 14), 126 (42), 125 (32), 43 (74), and 41 (100). The filtrate was subjected to the preparative GLC (DC-200 column 1 cm × 2 m, 150 °C, He, 150 ml/min) and pure **2** (50 mg) was obtained as a colorless oil, which boiled at 67—70 °C/0.4 mmHg, $n_D^{25}=1.4925$. IR (neat) 3420 (O–H), 1665 (C=O), 1640 cm^{-1} (C=C); NMR (CCl_4) δ 1.05 (3H, d, $J=7.0$ Hz), 1.06 (3H, d, $J=7.0$ Hz), 1.15 (3H, d, $J=7.0$ Hz), 1.6—2.5 (5H, m), 3.15 (1H, heptet, $J=7.0$ Hz), 6.07 (1H, broad s); UV$_{max}$ (95% EtOH) 275 nm (ε 10000); mass *m/e* (%) 168 (M$^+$, 15), 126 (25), 125 (53), 43 (85), and 41 (100). Found: C, 71.80; H, 9.73%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%.

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10) Direct methylation of **7** with two equivalents of lithium diisopropylamide in tetrahydrofuran, followed by the addition of excess methyl iodide, gave a mixture of **1** and **2** in the ratio of 64 : 36 in a poor yield.

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12) **2** can be distilled under reduced pressure below 100 °C with no decomposition.