

The Chemistry of the Natural Order Cupressales

44*. The Synthesis of DL-Hinokione Methyl Ether**

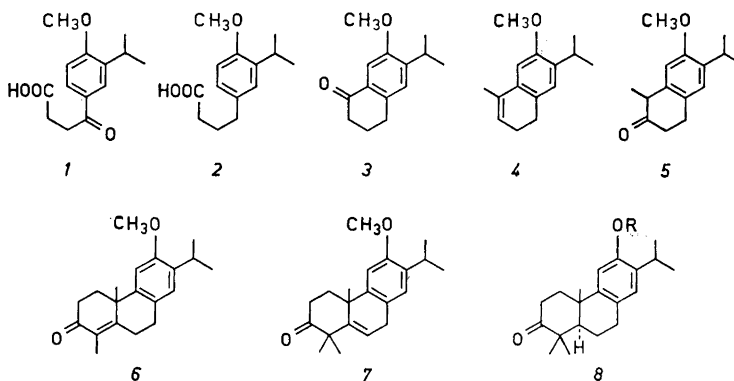
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A synthesis of DL-hinokione methyl ether from 2-isopropylphenol is described.

The phenolic diterpene ketone hinokione which has now been isolated from several conifer species¹ has recently been shown to possess structure 8 (R = H)². A synthesis of DL-hinokione methyl ether (8; R = CH₃) has now been carried out following the general lines of Howell and Taylor's perhydrophenanthrene synthesis³.

6-Isopropyl-7-methoxy- α -tetralone (3) was prepared from 2-isopropylanisole and succinic acid anhydride via the intermediates 1 and 2. The tetralone reacted smoothly with methyl magnesium iodide giving a tertiary alcohol which was dehydrated directly to 1-methyl-6-isopropyl-7-methoxy-3,4-dihydronaphthalene (4) with potassium hydrogen sulphate. Epoxidation of 4



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and subsequent treatment with dilute sulphuric acid³ gave liquid 1-methyl-6-isopropyl-7-methoxy- β -tetralone (5). Condensation of the β -tetralone with β -chloropentan-3-one in the presence of sodium hydride³ gave the crystalline α,β -unsaturated ketone 6 which was methylated with methyl iodide and potassium *t*-butoxide⁴ to give a non-crystalline resin which on chromatography yielded DL-*A*⁵-hinokione methyl ether (7) and an isomer (compound A). The methyl ether (7) was smoothly hydrogenated in ethanol solution in the presence of a palladium catalyst and a little acetic acid to give DL-hinokione methyl ether. The I.R. spectra of synthetic and natural hinokione methyl ether were superimposable.

EXPERIMENTAL

U.V. spectra were taken in 95 % ethanol solution and I.R. spectra in potassium bromide discs unless otherwise stated. Melting points were taken on a Kofler block.

2-Isopropyl-4-succinoylanisole (1). A solution of succinic anhydride (65 g) and 2-isopropylanisole (80 g) in nitrobenzene (50 ml) was added during one hour to a cold, mechanically stirred solution of aluminium chloride (170 g) in nitrobenzene (400 ml). The mixture was left at room temperature for 10 h and then poured into ice-water (1.5 l) containing hydrochloric acid (100 ml). The nitrobenzene was removed by steam distillation and the resulting organic residue cooled to give a solid. The product was dissolved in hot 10 % sodium carbonate solution (1 l). On cooling the sodium salt precipitated. The salt was collected and washed with cold water and ether. Acidification of the hot aqueous solution gave the keto-acid 1 (115 g). Crystals from ethanol, m.p. 133–135°. (Found: C 66.8; H 7.1. $C_{14}H_{18}O_4$ requires: C 67.2; H 7.25.)

2,4-Dinitrophenylhydrazone, deep red crystals from ethanol, m.p. 85–88°. (Found: C 55.6; H 5.4; N 12.9. $C_{20}H_{22}O_7N_4$ requires: C 55.8; H 5.15; N 13.0.)

4-(3-Carboxypropyl)-2-isopropylanisole (2). A mixture of crude keto-acid 1, amalgamated mossy zinc (220 g), water (150 ml), concentrated hydrochloric acid (350 ml), and toluene (200 ml) was boiled under reflux for 36 h with constant stirring. Concentrated hydrochloric acid (25 ml) was added every 6 h. The toluene phase was separated and the aqueous phase extracted with ether. The combined organic phases were extracted with 3 N sodium hydroxide solution. The acid products were remethylated with dimethyl sulphate and alkali. The acid was distilled, b.p. 142–145°/0.4 mm. (Yield 95 g or 75 % calculated on 2-isopropyl anisole.) The acid crystallised on cooling. Crystals from ethanol, m.p. 31–34°. (Found: C 71.4; H 8.6. $C_{14}H_{20}O_3$ requires: C 71.2, H 8.5 %.)

5-Isopropyl-6-methoxy- α -tetralone (3). The acid 2 (80 g) and thionyl chloride (160 g) were boiled under reflux for one hour and the excess thionyl chloride was then removed by distillation under reduced pressure. Tetrachloroethane (350 ml) was added to the cold solution, followed by aluminium chloride (75 g) in one lot. When the vigorous evolution of hydrogen chloride had subsided, the mixture was stirred and cooled in an ice bath for one hour. The mixture was left at room temperature for 10 h and then poured into dilute hydrochloric acid. The organic layer was distilled with steam and the residue extracted with ether. After evaporation of the ether, the product was distilled under vacuum giving a main fraction, b.p. 136–138°/1 mm; λ_{\max} 210 μ (ϵ 13 800), 225 (19 700) and 263 (12 700); ν_{\max}^{film} 1675 and 1260 cm^{-1} .

The red 2,4-dinitrophenylhydrazone (from ethyl acetate-ethanol) had m.p. 198–200°. (Found: C 60.2; H 5.5; N 13.8. $C_{20}H_{22}O_7N_4$ requires: C 60.3; H 5.6; N 14.1 %).

1-Methyl-6-isopropyl-7-methoxy-3,4-dihydronaphthalene (4). The α -tetralone (55 g) in ether (200 ml) was added to a Grignard reagent made from magnesium (12.5 g) and methyl iodide (36 ml) in ether (450 ml) and the mixture was boiled under reflux for 5 h. The product was isolated in the usual manner. A mixture of the dry product and fused potassium hydrogen sulphate (70 g) was heated at 120–150° for 2.5 h. The organic material was dissolved in light petroleum and washed with water. After evaporation of the solvent the product was distilled in vacuum. A main fraction, b.p. 101–104°/0.3 mm, was obtained (42 g). ν_{\max} 835, 1613 and 1630 cm^{-1} .

1-Methyl-6-isopropyl-7-methoxy- β -tetralone (5). Solutions of compound 4 (40.7 g) in chloroform (250 ml) and perbenzoic acid (27.2 g) in chloroform (350 ml) were mixed at -5° and the mixture kept at 0° for 10 h. The solution was washed with cold 1 N sodium hydroxide and water and the solvent removed by distillation. To the residue a mixture of ethanol (450 ml), water (200 ml), and concentrated sulphuric acid (50 ml) was added and the solution boiled under reflux for 4 h. The reaction product was extracted with ether and distilled giving a main fraction (17 g), b.p. $120-140^{\circ}/0.4$ mm, which was redistilled, b.p. $111-116^{\circ}/0.1$ mm. ν_{\max} 1690 and 1718 cm^{-1} (shoulder).

The semicarbazone, crystals from ethanol, melted at $184-187^{\circ}$. (Found: C 66.2; H 8.2; N 14.5. $\text{C}_{16}\text{H}_{23}\text{O}_2\text{N}_3$ requires: C 66.4; H 8.0; N 14.5 %).

α,β -Unsaturated ketone 6. β -Chloropent-3-one (1.92 g) was added rapidly with vigorous stirring to a mixture of the β -tetralone (5) (3.72 g), a 50 % suspension of sodium hydride (870 mg) and light petroleum (80 ml) kept under a nitrogen atmosphere. The mixture was boiled under reflux for 15 min and then cooled. More sodium hydride suspension was added (870 mg) and the heating continued for another 45 min. 2 N hydrochloric acid (90 ml) was added to the cold mixture and the organic layer separated. The aqueous layer was extracted with ether. The combined organic phases were evaporated and the residue distilled to give a fraction, b.p. $136-148^{\circ}/0.05$ mm (2.8 g), which was chromatographed on alumina (90 g). The fraction eluted with benzene-light petroleum (3:1) gave a crystalline compound which was recrystallised from methanol, m.p. $92-94^{\circ}$; ν_{\max} 1615, 1623, 1665 cm^{-1} ; λ_{\max} 287 $\text{m}\mu$ (ϵ 4160), 279 (4720), 247 (17100), 230 (16000). (Found: C 80.2; H 8.7. $\text{C}_{20}\text{H}_{28}\text{O}_2$ requires: C 80.5; H 8.8 %).

2,4-Dinitrophenylhydrazone: red crystals from ethanol, m.p. $225-228^{\circ}$.

Methylation of 6. A solution made from potassium (900 mg) and *t*-butanol (20 ml) was added to a solution of 6 (800 mg) in *t*-butanol (30 ml) and the mixture heated under nitrogen. Methyl iodide (6 ml) was added dropwise and the mixture boiled under reflux for one hour. The solvent was removed under vacuum and the residue dissolved in light petroleum and chromatographed on alumina (30 g). Elution with light petroleum-benzene (5:1, 50 ml) gave a compound (A) (200 mg); m.p. $96-97.5^{\circ}$ (from methanol). The I.R. absorption of this compound (ν_{\max} 1615, 1673, 1712 cm^{-1}) was very similar to that of 7. (Found: C 80.8; H 9.2. $\text{C}_{21}\text{H}_{28}\text{O}_2$ requires: C 80.7; H 9.0 %.) Continued elution with the same solvent (150 ml) gave a mixture of A and 7 (175 mg). Elution with light petroleum-benzene (4:1) gave 7 (250 mg) which was recrystallised from methanol and sublimed, m.p. $92-94^{\circ}$, ν_{\max} 1614, 1668, 1712 cm^{-1} . (Found: C 80.0; H 8.9. $\text{C}_{21}\text{H}_{28}\text{O}_2$ requires: C 80.7; H 9.0 %.)

The 2,4-dinitrophenylhydrazone, yellow crystals (from methanol), had m.p. $212-214^{\circ}$. A mixture of compound A and 7 melted at $65-85^{\circ}$. Compound A has not been subjected to further investigation but is obviously closely related to 7. On hydrogenation A gave an amorphous product.

DL-Hinokione methyl ether (8). A mixture of 7 (100 mg), prehydrogenated 20 % palladised charcoal (30 mg), ethanol (30 ml), and acetic acid (0.5 ml) was shaken with hydrogen at room temperature for 6 h. Filtration and evaporation gave a resinous product which was recrystallised three times from methanol, m.p. $119-121^{\circ}$. The I.R. spectrum was superimposable with that of natural hinokione methyl ether. (Found: C 80.0; H 9.3. $\text{C}_{21}\text{H}_{30}\text{O}_2$ requires: C 80.2; H 9.6 %.) The 2,4-dinitrophenylhydrazone formed yellow crystals (from ethanol-ethyl acetate) melting at $215-218^{\circ}$.

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