Terpenoids. Part V.
The Synthesis of Occidol

By Yoshiyuki Hirose and Tomoichiro Nakatsuka
Department of Forest Products, Faculty of Agriculture, University of Tokyo
Received September 3, 1958

The structure (I) of occidol, a new sesquiterpene alcohol isolated from the essential oil of Thuja occidentalis L. has been proposed in a recent paper. The structure is confirmed by (a) comparison of the infrared spectrum of the synthesized racemate with that of occidol, and (b), by the mixed m.p. of picrate of the synthesized 6-isopropyl-1,4-dimethylnaphthalene with that of a dehydrogenated product of occidol.

Occidol, m.p. 69-70°C, is a tertiary sesquiterpene alcohol found in the essential oil of Thuja occidentalis L. The structure (I) has been proposed in the preceding paper1). In that report, an alkyl naphthalene obtained by the dehydrogenation of occidol has been supposed to be 6-isopropyl-1,4-dimethylnaphthalene by the melting points of its picrate and the trinitrobenzene adduct but has not been identified with an authentic sample. This paper deals with the syntheses of the racemate of occidol and 6-isopropyl-1,4-dimethylnaphthalene.

In Scheme A, syntheses of compounds (IV), (V) and (VI) are carried out following the procedures of Barnett and Sanders.2) 5,8-Dimethyl-1-tetralone (VI) is identified in the following way: catalytic reduction of (VI) with palladium charcoal, followed by dehydrogenation with palladium charcoal yields 1,4-dimethylnaphthalene (picrate, m.p. 140°C; trinitrobenzene adduct, m.p. 160°C).

Preparations of compounds (VII) and (VIII) are carried out according to Bachmann, Cole and Wilds3). Methyl 5,8-dimethyl-1-tetralone-2-glyoxalate (VII) is obtained as yellow crystals, m.p. 69-70°C, soluble in an alkaline solution and gives an intense red-brown color with ferric chloride in ethanol. It may exist in the enol form as formulated in (VIII). Pyrolysis of (VII) with glass powder gives the keto ester (VIII), which slowly develops a deep blue-green color with ferric chloride in ethanol.

On reduction of (VIII) to the alcohol (IX) with sodium borohydride, followed by dehydration with phosphorus pentoxide in benzene and catalytic hydrogenation, methyl 1,2,3,4-tetrahydro-5,8-dimethylnaphthalene-2-carboxylate (XI) is obtained in a good yield. The compound (XI) is reacted with methyl magnesium iodide in the usual manner. The product (I) is obtained as colorless crystals, m.p. 101-102°C, having an infrared absorption spectrum identical with that of natural occidol (Figs. 1 and 2).

Furthermore, the dehydrogenation of the compound (I) with 5% palladium charcoal gives 6-isopropyl-1,4-dimethylnaphthalene, the picrate of which melts at 102-103°C, undepressed by that prepared from natural occidol. The structure of occidol has thus been definitely established. It is of interest to note that an alcohol, containing an aromatic nucleus in the molecule which is closely related to cudalene, has been isolated for the first time.
Scheme A

Fig. 1. Natural d-Ociddol (in CCl₄, 0.1 mm)
We have already isolated occidentalol (II) of eudalene type from the same essential oil. The fact that occidol is accompanied by occidentalol seems to suggest that the latter would be biogenetically transformed to the former by rearrangement involving the migration of an angular methyl group.

**EXPERIMENTAL**

3-(2,5-Dimethylbenzoyl)-propionic acid (IV) Powdered aluminium chloride (300 g) was slowly added to a mixture of p-xylene, b.p. 135.5-136.0°C (120 g), succinic anhydride (100 g) and tetrachloroethane (350 cc). The reaction mixture was kept overnight and treated with ice and hydrochloric acid. The product, b.p. 186-189°C/2 mm, m.p. 80°C (110 g; 47%) was obtained, (lit2). m.P. 86°C).

4-(2,5-Dimethylphenyl)-butyric acid (V). A solution of the above acid (IV) (67 g) in toluene (300 cc) was mixed with amalgamated zinc (120 g), concentrated hydrochloric acid (200 cc) and water (75 cc) and the mixture was refluxed on a sand bath for 30 hr. Evaporation of toluene under reduced pressure gave a crystalline mass, recrystallized from petroleum ether, (50 g; 81%). It did not show a sharp melting point, ca. 60°C, (lit2). 70°C).

5,8-Dimethyl-1-tetralone (VI). The acid (V) (75 g) was heated with 80% sulfuric acid (400 cc) on a water bath for 5 hr. The ether-soluble product was distilled to give a fraction, b.p. 134-135°C/6 mm, (41 g; 60%).

Infrared maximum at 1678 (Ph-CO CO) cm⁻¹.

1, 4-Dimethylnaphtalene. 5,8-Dimethyl-1-tetralone (500 mg), palladium charcoal (50 mg) and glacial acetic acid (30 cc) were shaken together in hydrogen until absorption was ceased (30 hr.). Filtration and evaporation in vacuo gave an oil (500 mg). This liquid was heated with 5% palladium charcoal (100 mg) under reflux for 5 hr. The petrolatum-ether-soluble product gave a picrate, m.p. 139-140°C and a trinitrobenzene adduct, m.p. 159-160°C. Anal. of picrate. Found; N, 11.07. Calcd. for C₁₆H₁₅O₇N₃: N, 10.91%.

Methyl 5,8-dimethyl-1-tetralone-2-glyoxalate (VII). According to the procedure of Bachmann, Cole and Wilds3), to a solution of the sodium derivative of dimethyl oxalate in dry benzene (500 cc), which was prepared from sodium (2.0 g), absolute methanol (30 cc) and dimethyl oxalate (11 g), was added a solution of 5,8-dimethyl-1-tetralone (V1) (9 g) in dry benzene (60 cc) in an atmosphere of dry nitrogen. After the mixture was swirled at room temperature for 5 hr., the benzene solution was extracted with 2% sodium hydroxide solution. Acidification of the alkaline solution gave yellow crystalline glyoxalate, m.p. 69-70°C (from acetone), (12.5 g; 93%). Anal. Found: C, 70.08; H, 6.42. Calcd. for C₁₅H₁₆O₉: C, 70.21; H, 6.20%.

Methyl 5,8-dimethyl-1-tetralone-2-carboxylate (VIII). The above-glyoxalate (12 g) was heated with powdered soft glass (6 g) at 180°C. After a vigorous evolution of carbon monoxide, the ether-soluble product was distilled to give a fraction, b.p. 148-152°C/4 mm, (8.5 g; 79%). The fraction was crystallized from ethanol, m.p. 75-76°C. The infrared spectrum (Nujol) showed bands at 1733 (ester), 1672 (Ph-CO-) and 1650 cm⁻¹.
(enol form of β-keto ester) cm$^{-1}$. Anal. Found: C, 72.69; H, 6.92. Calcd. for C$_{14}$H$_{16}$O$_3$: C, 72.39; H, 6.94%.

**Methyl 1, 2, 3 4-tetrahydro-1-hydroxy-5, 8-dimethyl-naphthalene-2-carboxylate (IX).** The keto ester (VIII) (7 g) in ethanol (30 cc) was reduced with sodium borohydride (1.5 g) in ethanol (50 cc) at room temperature for 5 hr. After treatment with cold dilute hydrochloric acid, the mixture was poured into water. The ether-soluble product was distilled to give a fraction, b.p. 170–174°C/4 mm, (6 g; 85%). The infrared spectrum showed bands at 3425 (OH), 1718 (ester), 806 (1,2,3,4-tetrasubstituted benzene) cm$^{-1}$. The result of analysis did not agree with the calculated value for C$_{14}$H$_{16}$O$_3$.

**Methyl 1, 2-dihydro-5, 8-dimethylnaphthalene-3-carboxylate (X).** The alcohol (IX) (6 g) in dry benzene (30 cc) was added to a suspension of phosphorus pentoxide (2.6 g) in dry benzene (10 cc) with stirring in the cold. The mixture was poured into water and extracted with ether. The ether-soluble product was distilled to give a fraction, b.p. 145–150°C/4 mm, (3.5 g; 64%). The infrared spectrum showed bands at 1698 (αβ-unsaturated ester), 1629 (C=C conjugated with benzene) and 806 (1,2,3,4-tetrasubstituted benzene) cm$^{-1}$. Anal. Found: C, 77.22; H, 8.29. Calcd. for C$_{14}$H$_{16}$O$_2$: C, 77.03; H, 8.31%.

**Methyl 1, 2, 3, 4-tetrahydro-5, 8-dimethylnaphthalene-2-carboxylate (XI).** The above unsaturated ester (X) (3.5 g) in ethanolic acetic acid (2: 1) was hydrogenated using Adams’ catalyst until absorption was ceased (17 hr.). After working up the reaction mixture in the usual manner, the product (3.1 g; 90%), b.p. 142–145°C/2 mm, was obtained. The infrared spectrum showed bands at 1739 (ester) and 806 (1, 2, 3, 4-tetra-substituted benzene) cm$^{-1}$. Anal. Found: C, 79.10; H, 8.79. Calcd. for C$_{14}$H$_{18}$O$_2$: C, 77.03; H, 8.31%.

**The racemate of occidol (I).** To a Grignard solution prepared from magnesium (1.2 g) and methyl iodide (9.0 g) in dry ether (30 cc) was added the compound (XI) (3.0 g) in dry ether (15 cc) at room temperature. After being left for 24 hr. at room temperature, the mixture was treated with a saturated ammonium chloride solution in the cold. Evaporation of ether gave a brown residue (ca. 3 g), which was solidified, recrystallized from petroleum ether, m.p. 101–102°C, (1 g; 33%). The infrared spectrum (CCl$_4$) (Fig. 2) was identical with that of occidol (Fig. 1). Anal. Found: C, 82.54; H, 10.61. Calcd. for C$_{15}$H$_{22}$O: C, 82.51; H, 10.16%.

**6-Isopropyl-1, 4-dimethylnaphthalene (XII).** The racemate of occidol (100 mg) was dehydrogenated with 5% palladium charcoal (100 mg) for 2 hr. The product was passed through a column of alumina and eluted with petroleum ether to afford a liquid, which gave picrate, m.p. 102–103°C, undepressed by that prepared from natural occidol. Anal. Found: N, 9.87. Calcd. For C$_{21}$H$_{21}$O$_7$N$_3$: N, 9.8%.

**Acknowledgements.** The authors are indebted to Mr. K. Aizawa, the Faculty of Agriculture, University of Tokyo, for infrared analyses. Thanks are due to the Faculty of Agriculture, University of Tokyo for performing the micro-analyses. This experiment was supported in part by a grant from the Ministry of Education.