

## The Chemistry of the Natural Order Cupressales

## 46 \*. The Structure of Nootkatone

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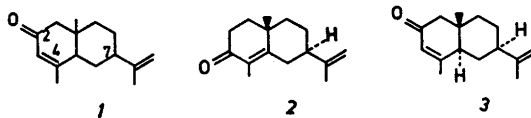
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A new eudalenoid sesquiterpene ketone, nootkatone, has been isolated from the heartwood of *Chamaecyparis nootkatensis*. It has been shown to possess the structure 1.

During our investigation of the acetone soluble heartwood constituents of Alaska yellow cedar (*Chamaecyparis nootkatensis* (Lamb.) Spach) several compounds have been isolated, e.g. the acidic compounds carvacrol, chamic and chaminic acid and nootkatin. The neutral part contains carvacrol methyl ether and various sesquiterpenes including the triply unsaturated, easily polymerisable, eudalenoid nootkatene. The presence of alcohols and ketones was also indicated<sup>1</sup>.

By treating the high boiling neutral fractions with semicarbazide or a Girard reagent a new sesquiterpene ketone, nootkatone, has now been isolated. Nootkatone has the composition  $C_{15}H_{22}O$ , melts at 36–37° and is dextrorotatory,  $[\alpha]_D + 195.5^\circ$ .

The infrared and ultraviolet spectra of nootkatone show that the compound is an  $\alpha,\beta$ -unsaturated ketone. Structure (1), which is proposed for this substance, is closely related to  $\alpha$ -cyperone (2).



Ozonisation of nootkatone gave formaldehyde but no acetone. Hydrogenation with palladium in ethanol furnished a viscous tetrahydro product from which crystalline tetrahydronootkatone semicarbazone was obtained. Similar hydrogenation with platinum oxide gave an alcoholic hexahydro product which on chromatographic purification gave, as the main product (70 %), tetrahydronootkatol, a solid melting at 76.5–77°,  $[\alpha]_D + 13.9^\circ$ ,

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together with a liquid which is presumably a mixture of isomers. On oxidation tetrahydronootkatol gave a ketone, the semicarbazone of which was identical with that of tetrahydronootkatone.

Reduction of nootkatone with potassium borohydride gave an oily alcohol which on dehydrogenation with selenium afforded eudalene.

In order to locate the carbonyl group, tetrahydronootkatone was treated with methyl magnesium iodide and the resulting alcohol dehydrogenated with selenium. A naphthalene derivative was obtained which was identified as 1,3-dimethyl-7-isopropyl naphthalene. These results clearly indicate that nootkatone possesses structure (1). There is no chemical proof of the position of the angular methyl group and an eremophilone-like structure would be an alternative.

Tetrahydronootkatone, prepared from pure, crystalline tetrahydronootkatol, was reduced by Clemmensen's method and the product which, according to its infrared spectrum contained some unsaturated contaminations, was subjected to ozonisation and purified by chromatography on alumina.

The resulting oil had  $[\alpha]_D + 19.2^\circ$ , closely similar to that of eudesmane from  $\beta$ -eudesmol and from elemol<sup>2</sup> ( $[\alpha]_D + 16.2^\circ$  and  $16.3^\circ$ , resp).

The essential features of the infrared absorption of eudesmane from the latter sources were identical with those of eudesmane from nootkatone. However, it does not appear safe to draw any definite conclusions about the configuration of nootkatone from this result only. The indications are, however, that nootkatone has the same configuration at the active centres as the eudesmols.

The proton magnetic resonance spectrum of nootkatone in carbon tetrachloride with benzene as internal standard showed a signal at 62 cps due to a single proton on a double bond. The low frequency is due to the proton being situated next to a carbonyl group. A signal at 103 cps is due to the two hydrogen atoms on the terminal methylene group of the isopropenyl group. Three sharp lines at 250, 223 and 207 cps correspond to three methyl groups, of which the latter is due to a methyl group in a system of the type  $-\text{CO}-\text{CH}=\text{C}(\text{CH}_3)-$ .

These results are in agreement with the proposed structure 1 as well as with the eremophilone-like alternative. The rotatory dispersion curves of tetrahydronootkatone and of nootkatone have been recorded by Professor Klyne to whom we express our gratitude. The R.D.-curve of nootkatone is very similar to that of  $5\alpha$ -cholest-3-en-2-one<sup>3</sup> kindly provided by Professor C. Djerassi. This indicates that nootkatone has the "ordinary" *trans*-fused ring system (10 $\beta$ ,5 $\alpha$ ).

The configuration at C<sub>7</sub> is not known with absolute certainty. In eudesmol it is  $\beta$ -oriented and the physical properties of the above eudesmane preparation indicate that it is similarly oriented in nootkatone. Assuming this to be correct then the methyl group at C<sub>4</sub> and the hydroxyl group at C<sub>2</sub> of tetrahydronootkatol should be  $\beta$ -oriented, hydrogenation occurring at the least sterically hindered side.

Further work is required to ascertain the absolute configuration of nootkatone and experiments in this direction are in progress. The most likely configuration is 3.

## EXPERIMENTAL

*Isolation of nootkatone.* (a) The neutral fraction from 28 kg of heartwood of *Chamaecyparis nootkatensis* (370 g) was distilled through an efficient column giving a series of fractions, of which those boiling between 156° and 158° at 5 mm pressure were redistilled through a spinning band column. Series of fractions boiling between 154° and 155° were obtained, the optical rotations of which varied between  $[\alpha]_D + 91^\circ$  and  $+ 148^\circ$ . These were dissolved in six times their volumes of ethanol and treated with sodium acetate and semicarbazide hydrochloride. Crystals separated (about 25 g) which were recrystallised from ethanol yielding pure nootkatone semicarbazone (15 g). The semicarbazone was mixed with phthalic anhydride (15 g) and water (45 ml) and the mixture steam distilled. The volatile organic material was extracted with ether and evaporation of the organic layer gave nootkatone as a pale yellow oil (5 g) which solidified when kept in the ice-box. Recrystallisation from light petroleum gave material, m.p. 36–37°,  $[\alpha]_D + 195.5^\circ$  ( $c = 1.5$  in  $\text{CHCl}_3$ ).  $\lambda_{\text{max}}$  238  $\mu$  ( $\epsilon$  15 000),  $\nu_{\text{max}}$  1680  $\text{cm}^{-1}$ . (Found: C 82.4; H 10.0. Calc. for  $\text{C}_{15}\text{H}_{22}\text{O}$ : C 82.5; H 10.2).

(b) The fraction of neutral oil boiling between 155 and 180°/5 mm (105 g) and Girard P reagent (16 g) were dissolved in ethanol (300 ml) containing acetic acid (30 g), and the resultant solution refluxed for 40 min. After cooling to room temperature, the solution was poured into ice-water (2 l), containing sodium carbonate (27 g), and the mixture extracted with ether. The aqueous phase was acidified with sulphuric acid and exhaustively extracted with ether. The latter ether solution was washed with water, dried and evaporated, leaving a brownish oil (10 g) which solidified on cooling. Recrystallisation from light petroleum gave pure nootkatone.

*Nootkatone semicarbazone.* The semicarbazone was prepared in the usual way and recrystallised from ethanol. It melted at 195–197° (decomp.),  $[\alpha]_D + 384^\circ$  ( $c = 0.51$  in  $\text{CHCl}_3$ ). (Found: C 69.8; H 9.1; N 15.6. Calc. for  $\text{C}_{16}\text{H}_{25}\text{ON}_3$ : C 69.9; H 9.15; N 15.3).

The 2,4-dinitrophenylhydrazone melted at 157.5–158.5°.  $\lambda_{\text{max}}$  384  $\mu$  ( $\epsilon$  26 000). (Found: C 62.9; H 6.6; N 14.0. Calc. for  $\text{C}_{21}\text{H}_{26}\text{O}_4\text{N}_4$ : C 63.3; H 6.6; N 14.1).

*Ozonolysis of nootkatone.* A solution of nootkatone (118 mg) in methylene chloride (20 ml) was treated with ozone for 1.5 h. Water (20 ml) was added and the mixture gently refluxed on a water bath for 2 h. After extraction with light petroleum the aqueous layer was mixed with a saturated solution of dimedone in water (20 ml). The precipitated dimedone derivative (45.3 mg, yield 28.6 %) was identified as the formaldehyde dimedone derivative, m.p. and mixed m.p. 189°.

The filtrate from the formaldehyde dimedone derivative was steam-distilled into 2,4-dinitrophenylhydrazine reagent solution, but no 2,4-dinitrophenylhydrazone was obtained.

*Tetrahydronootkatone semicarbazone.* Nootkatone (51.9 mg) was hydrogenated in ethanol in the presence of a palladium/charcoal catalyst. The hydrogenation was discontinued when 12.2 ml of hydrogen (2.1 moles) had been consumed. The product obtained was a viscous oil, b.p. 153–155°/7 mm. The semicarbazone was prepared and melted at 210–211° (decomp.)  $[\alpha]_D + 66.5^\circ$  ( $c = 0.9$  in  $\text{CHCl}_3$ ). (Found: 69.0; H 10.35; N 15.0. Calc. for  $\text{C}_{16}\text{H}_{25}\text{ON}_3$ : C 68.8; H 10.5; N 15.0).

*Tetrahydronootkatol (hexahydronootkatone).* Nootkatone (120 mg) was shaken with hydrogen in ethanol in the presence of Adams catalyst. Hydrogen (38.6 ml, 2.9 moles) was absorbed. The product was chromatographed on alumina yielding a liquid (30 %) and crystals (70 %). Recrystallisation of the latter from light petroleum gave material, m.p. 76.5–77°,  $[\alpha]_D + 13.9^\circ$  ( $c = 2.2$  in  $\text{CHCl}_3$ ). (Found: C 80.2; H 12.1. Calc. for  $\text{C}_{15}\text{H}_{28}\text{O}$ : C 80.3; H 12.6).

*Oxidation of tetrahydronootkatol to tetrahydronootkatone.* A solution of the above alcohol (320 mg) in pyridine (5 ml) was added to a solution of  $\text{CrO}_3$  (400 mg) in pyridine (5 ml). The mixture was kept overnight at room temperature and was then poured into water and the suspension extracted with ether. The product obtained had b.p. 152°/6 mm,  $n_D$  1.4886,  $[\alpha]_D + 54.1^\circ$  ( $c = 2.4$  in  $\text{CHCl}_3$ ). It was converted into the semicarbazone, m.p. and mixed m.p. with that of tetrahydronootkatone 210–211° (decomp.). The I.R. spectra were superimposable.

A sample of tetrahydronootkatone prepared in this way was reduced according to the Clemmensen method and the crude product dissolved in methylene chloride and ozonised at room temperature. The reaction product was heated under reflux with water and the organic material dissolved in light petroleum and the solution filtered through a short

alumina column. The filtrate was evaporated and the residue distilled. The product obtained had  $[\alpha]_D + 19.2^\circ$  (in  $\text{CHCl}_3$ ).

*Eudalene from nootkatone.* A solution of nootkatone (300 mg) in methanol (5 ml) was added to a solution of potassium borohydride (300 mg) in aqueous methanol and the mixture was kept overnight at room temperature. The reaction mixture was then treated with a cold solution of 5 % sodium hydroxide and shaken with ether. Evaporation of the organic extract gave a viscous oil (300 mg) that did not crystallise.

This oil (300 mg) was heated with selenium (300 mg) for 12 h. The light petroleum ether soluble product was passed through alumina to give a colourless liquid, which yielded a picrate, m.p.  $92-93^\circ$ . The melting point was not depressed by mixing with authentic eudalene picrate and their infrared spectra were superimposable.

*1,3-Dimethyl-7-isopropyl-naphthalene from tetrahydronootkatone.* A solution of tetrahydronootkatone (1.3 g) in dry ether (5 ml) was slowly added to a solution of a Grignard reagent, prepared from magnesium (0.2 g) and methyl iodide (1.5 g) in dry ether (5 ml). The mixture was kept overnight at room temperature. After treatment with a saturated solution of ammonium chloride, followed by extraction with ether, a pale yellow alcohol (0.9 g) was obtained. ( $\nu_{\text{max}}$   $3620 \text{ cm}^{-1}$ , no carbonyl band).

The above alcohol (0.9 g) was dehydrogenated with selenium (1.5 g) at  $330^\circ\text{C}$  for 30 h. The light petroleum soluble fraction of the product was chromatographed on alumina. Elution with light petroleum gave a colourless liquid (0.4 g), which afforded a picrate, m.p.  $104-106^\circ$  and a trinitrobenzene adduct, m.p.  $121-122^\circ$ . These melting points were not depressed when the derivatives were mixed with the appropriate authentic 1,3-dimethyl-7-isopropyl-naphthalene derivatives. The infrared spectra were also identical with those of the 1,3-dimethyl-7-isopropyl-naphthalene derivatives. Picrate: Found: C 59.05; H 5.2; N 10.0. Calc. for  $\text{C}_{21}\text{H}_{21}\text{O}_7\text{N}_3$ : C 59.0; H 4.95; N 9.8. Trinitrobenzene adduct: Found: C 61.3; H 5.1; N 10.2. Calc. for  $\text{C}_{21}\text{H}_{21}\text{O}_6\text{N}_3$ : C 61.3; H 5.15; N 10.2.

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