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Von Rudloff, E.; Nair, G. V.

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THE SESQUITERPENE ALCOHOLS OF THE HEARTWOOD OF THUJA OCCIDENTALIS L.[1]

E. VON RUDLOFF AND G. V. NAIR[2]
National Research Council of Canada, Prairie Regional Laboratory, Saskatoon, Saskatchewan
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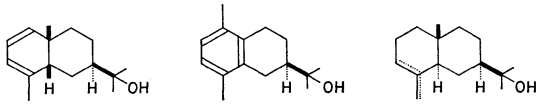
ABSTRACT

γ-Eudesmol, a mixture of α- and β-eudesmol, and a new sesquiterpene diol, occidiol, were found to be minor components of the neutral extract of eastern white cedar heartwood. A tentative structure for occidiol is proposed. The biogenetic relationship between these compounds is discussed and a common precursor for the eudesmol and occidentalol series is suggested.

Nakatsuka and Hirose (1, 2) have isolated from the heartwood of eastern white cedar (*Thuja occidentalis* L.) the two sesquiterpene alcohols occidentalol (I) and occidol (II).



I II III

Nakazaki (3) has reported that in (+)-occidol the isopropanol group has the R-configuration (as shown). By conversion to the dihydro and tetrahydro derivatives and comparison with eudesmol (III) and its dihydro derivatives, occidentalol has been shown by von Rudloff and Erdtman (4) to have cis-fused rings. This was based on the reasonable assumption that the isopropanol group is in the equatorial position, i.e., as in the trans-fused eudesmane-type of compound (5). Recently, Mislow and Moscowitz (6) have presented arguments which indicate that the isopropanol group of occidentalol at C-7 has the R-configuration. This lends support to Nakazaki's view (3, 7) that occidentalol and occidol are biogenetically closely related.

In view of the unusual cis-fused ring system found in occidentalol and a possible biogenetic relationship with the eudesmols, it was of interest to determine the nature of the minor sesquiterpenoid constituents of the wood of eastern white cedar. Gas–liquid chromatography (G.L.C.; cf. also Refs. 4 and 8) showed that the wood extract from a mature tree from the Winnipeg district, Manitoba, contained mainly occidentalol (peak 1) and occidol (peak 6), three minor, and two trace constituents (see Table I). The three minor constituents (peaks 2, 3, and 5) were isolated in milligram amounts and were shown to be a mixture of γ-eudesmol and an unidentified compound, a mixture of α- and β-eudesmol, and a new sesquiterpene diol respectively.

Peak 2 had the retention time of α-cadinol and γ-eudesmol. Its infrared spectrum was similar in all respects to that of α-cadinol, when these were recorded as liquid films (8). The weak, but distinct, absorption bands near 1650 and 815 cm^{-1} are indicative of the trisubstituted double bond found in α-cadinol. However, the fraction of the oil of araucaria identified as α-cadinol by one of us (8) mainly on this basis was shown to be essentially γ-eudesmol by Bates and Hendrickson, who employed nuclear magnetic resonance (n.m.r.) spectroscopy and obtained dihydroeudesmol by hydrogenation of the material.

[1]*Issued as N.R.C. No. 7691.*
[2]*National Research Council of Canada Postdoctoral Fellow, 1958–1960.*

TABLE I

Sesquiterpenoid components of the wood of *Thuja occidentalis* L.

Peak	Compound	R.R.T.*	%
1	Occidentalol	0.92	36
2	γ-Eudesmol and unidentified	1.02	3
3	α- + β-Eudesmol	1.46	10
4	Unidentified	2.08	0.5
5	Diol	2.20	3
6	Occidol	6.0	46–47
7	Unidentified	6.5	0.5–1.0

*R.R.T. = relative retention time (cedrol = 1.00) on a 6 ft × 1/4 in. O.D. adipate polyester column.

Since insufficient amounts of peak 2 were isolated in this study to permit the recording of an n.m.r. spectrum, the component was hydrogenated over platinum catalyst. The product crystallized on standing and was found to be mainly dihydroeudesmol. Therefore, peak 2 must contain γ-eudesmol. However, rechromatography of peak 2 showed that it contained a second component, but this could not be isolated.

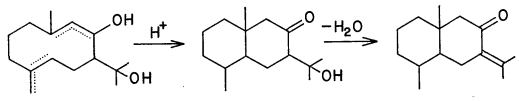
Peak 3 was obtained crystalline and a mixed melting point and comparison of infrared spectra and G.L.C. retention data confirmed that this was identical with the mixture of α- and β-eudesmol, which is the major constituent of the oil of araucaria (8). G.L.C. analysis also showed that the ratio of α- to β-isomer was nearly the same as that in oil, i.e., about 1 to 3.

Peak 5 was a viscous liquid, which appeared to decompose gradually under atmospheric conditions. The infrared spectrum of the freshly isolated material indicated it to be an unsaturated alcohol (strong bands at 3440, 2920, 1650, with a shoulder at 1670, 1382, and 1370 cm^{-1}, weaker ones at 3080, 3040, 1035, 915, 875, 850–825, and 750 cm^{-1}) which may have a terminal methylene and an isopropyl or isopropanol group and possibly a trisubstituted double bond. The molecular weight (236), obtained by mass spectroscopy,* and the elementary analysis agreed fairly well with $C_{15}H_{24}O_2$. The unsaturated character was confirmed by a strongly positive tetranitromethane test, as may also be deduced from the relatively high optical rotation ($[\alpha]_D^{23}$ $-125.5°$) and refractive index (n_D^{23} 1.5129). No characteristic ultraviolet spectrum was recorded. Thus, the compound appears to be a diol with at least two isolated double bonds. Hydrogenation over palladium catalyst gave a liquid dihydro product, the infrared spectrum of which no longer showed the peaks at 3080 and 875 cm^{-1}. Hydrogenation over platinum catalyst gave inconclusive results, possibly because hydrogenolysis took place. Dehydrogenation over palladium-on-charcoal at 250° C gave a high yield of guaiazulene, which was also obtained in very low yield when the total mixture of terpenes was distilled at temperatures above 150 to 160° C.

Most remarkable was the behavior of peak 5 towards dilute acids. Treatment with aqueous oxalic or methanolic sulphuric acid resulted in the formation of a ketol (strong I.R. bands at 3420 and 1710 cm^{-1}, weaker ones at 1643, 910, and 825 cm^{-1}). When this ketol was dehydrogenated over either selenium or palladium no guaiazulene was obtained, but a low yield of an aromatic hydrocarbon with the same retention time as eudalene was recorded by G.L.C. Dehydration of the ketol with pyridine-modified alumina reagent (10) gave mainly an unsaturated ketone (strong I.R. bands at 1740, 1693, 1633, and 1377 cm^{-1}). The ultraviolet absorption at 290 and 228 mμ confirmed α,β-conjugation.

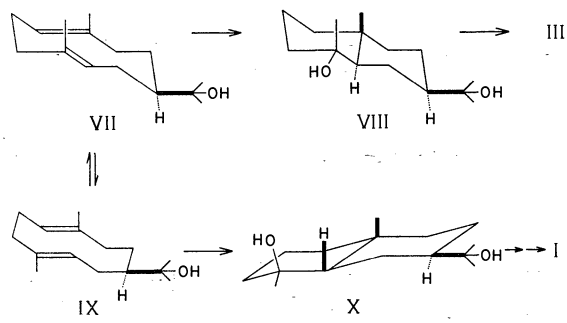
The formation of guaiazulene from the parent diol and its acid-catalyzed rearrangement to a eudalene precursor are reminiscent of the behavior of germacrone (11). Further,

Kindly obtained by Prof. H. Erdtman, Royal Institute of Technology, Stockholm.



the above data can be reconciled with the properties of a diol having a 10-membered ring of type IV, which isomerizes to the ketol V under acidic conditions. Dehydration would produce the α,β-unsaturated ketone VI. The n.m.r. spectrum confirms the presence of an isopropanol group (singlet equivalent to 6 protons at 8.75), a trisubstituted double bond (triplet equivalent to 1 proton near 4.00) and two C-methyl groups. However, a complete interpretation of this spectrum was not possible. This may be due to some unusual properties of protons found in 10-membered rings. Also, the material isolated may be a mixture of double bond isomers. Further work to establish the structure more definitely will be carried out when the isolation of larger amounts of pure material has been achieved. The name "occidiol" is proposed for this component of the wood of *Thuja occidentalis* L.

Hendrickson (12) has discussed the stereochemical implications in sesquiterpene biogenesis and has shown that eudesmol may be formed from *trans*-farnesol via the 10-



membered intermediate VII, which would form the precursor VIII by a concerted cyclization. This would then lead to α-, β-, and γ-eudesmol as described by Bates and Hendrickson (9). If the two methyl groups are aligned on opposite sides of the 10-membered ring (IX), then by the same mechanism the cis-fused precursor X would obtain, which would then lead to occidentalol, and further to occidol (3, 7). Such a scheme would result in the R-configuration of the isopropanol group at C-7 in both cases, and would predict the absolute configuration of occidentalol to be I.* Furthermore, a single oxidative step with perhaps a double bond isomerization would account for the formation of the diol in *Thuja occidentalis*.

EXPERIMENTAL

Melting points were determined on a Leitz hot-stage microscope. Infrared spectra were recorded with a Perkin–Elmer model 21 double beam spectrophotometer, liquids being mounted as films between sodium chloride plates and solids as KBr disks, unless otherwise indicated. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer, using tetramethyl silane as internal standard. The G.L.C. columns and apparatus have been described previously (4, 8). Known compounds were identified by comparison of infrared spectra, G.L.C. retention data, and mixed melting point. All retention times (R.T.) were measured relative to cedrol (= 1.00).

Isolation of Sesquiterpenes

The milled heartwood (5.5 kg) of eastern white cedar (part of a mature tree from the Winnipeg district, Manitoba (4)) was extracted with acetone in a Soxhlet extractor for 36 hours. The solvent was removed under reduced pressure from the extract in a rotary evaporator at 40–50° C. The dark brown, viscous residue

See also H. Ziffer, I. T. Batterham, U. Weiss, and E. von Rudloff. Tetrahedron. In press (1963).

(313 g, 6.3%) was poured with stirring into ether (3 liters) and the insoluble precipitate was filtered off. The ethereal solution was shaken with several aliquots of aqueous potassium hydroxide solution (10%) to remove all acidic and phenolic components. After it was washed with water and dried over anhydrous sodium sulphate, the ether was moved by evaporation. The residue (195 g, 3.5%) was composed mainly of sesquiterpenoid compounds and G.L.C. analysis gave the composition shown in Table I.

Aliquots (20 mg) of the total neutral material were injected repeatedly onto the 6 ft × 1/4 in. adipate polyester column (160° C, flow rate 120 ml He/minute) and components 1, 2, 3, 5, and 6 were isolated practically pure. Components 1 and 5 were obtained crystalline (m.p. 94–96° and 66–69° C. respectively) and were found to be occidentalol and occidol.

γ-Eudesmol

Component 2, $[\alpha]_D$ −34.3° (*c*, 2.0, $CHCl_3$) was reinjected (0.5 μl) onto a 6 ft × 1/4 in. polyethylene glycol (Carbowax 20 M at 160° C) column, when two partially resolved peaks were recorded. In runs using more than 1–2 mg aliquots these merged into one single peak.

Component 2 (8.7 mg) was hydrogenated over reduced Adams catalyst with acetic acid as solvent; consumed: 0.70 ml H_2 at N.T.P.; required for 1 mole H_2 per mole: 0.85 ml. The product, after filtration, crystallized on standing; m.p. 78–82° C. G.L.C. analysis of this product gave, besides starting material, a peak corresponding in R.T. to dihydroeudesmol.

Eudesmol

Component 3 was also obtained crystalline; m.p. 81–84° C, $[\alpha]_D$ +33° ($CHCl_3$). Hydrogenation gave dihydroeudesmol, m.p. 81–83° C. G.L.C. analysis gave two partially resolved peaks (area ratio approximately 1:3) with the same R.T. of the mixture of α- and β-eudesmol, m.p. 82.0–83.5° C, isolated from the oil of araucaria (8).

Occidiol

Component 5 was obtained as a viscous liquid, b.p. (at 11 mm) 135–140° C (air bath); n_D^{23} 1.5129; $[\alpha_D]$ −125.5 (*c*, 2.3, $CHCl_3$). It did not form a crystalline nitrobenzoate or phenylurethane. Treatment with tetranitromethane in ethanol gave a strong yellow-brown color immediately. Found (for the freshly isolated material); C, 76.97; H, 9.93%; mol. wt. (by mass spectroscopy) 236. Caculated for $C_{15}H_{24}O_2$: C, 76.88; H, 9.46%; mol. wt. 236.34. Infrared spectrum: 3420(s), 3080(w), 3040(w), 2930(s), 1668(m), 1650(s), 1452(s), 1377(broad, s), 1197(s), 1125 (s), 1100 (s), 918(m), 878(m), 750(m) cm^{-1}. In chloroform solution there was also a strong band at 3620 cm^{-1}, and that at 886 was strong. The n.m.r. spectrum was recorded in $CDCl_3$ solution.

Dihydrooccidiol

Occidiol (7.4 mg) in ethanol (1 ml) was hydrogenated in a microhydrogenation apparatus over palladium-on-charcoal catalyst (2 mg). Hydrogen was absorbed rapidly during 10 minutes and much more slowly thereafter. Hydrogen consumed: 0.74 ml at N.T.P.; required for 1 mole H_2 per mole of diol: 0.71 ml. The solution was filtered and the solvent evaporated to give the sirupy dihydro diol. Infrared spectrum: 3440, 2940–2860, 1465, 1377, 1265(m), 1120, 950(m), 915(m), and 815(m) cm^{-1}.

Guaiazulene

Occidiol (15 mg) was mixed with palladium-on-charcoal catalyst (15 mg) and heated at 250° C for 30 minutes. The blue-black product was taken up in petrol (b.p. 60–66° C) and filtered, and the derived azulene was extracted with phosphoric acid (85%). Dilution with water liberated the azulene; trinitrobenzene adduct m.p. 162° C, picrate m.p. 120° C (lit. 121–122° C (13)). G.L.C. analysis gave a single peak having the same R.T. as guaiazulene.

Ketol

Occidiol (20 mg) in methanol (10 ml) and a few drops of dilute sulphuric acid (10%) were heated on a steam bath for 5 minutes, when a pink color developed. The product was extracted into ether and worked up to give a viscous residue. Infrared spectrum: 3420, 2930, 2700(w), 1710, 1643(w), 1463, 1378–1363, 1110, 1020(m), 910(m), 825(w) cm^{-1}. The same product was obtained when the diol was heated with aqueous oxalic acid.

The ketol (3 mg) was dehydrogenated as above and the colorless product was analyzed by G.L.C.; major peak with the same R.T. as eudalene, several smaller peaks in the eudesmene–eudesmane (selinane) range.

The ketol (10 mg) was heated with twice its weight pyridine-modified alumina (10) at 230° C for 15 minutes. A viscous product was obtained after extraction, filtration, and evaporation of solvent; infrared spectrum: 2960–2920, 1740, 1693, 1633, 1455, 1377, 1110(m), 877(w); λ_{max}^{EtOH} 290 mμ and inflexion near 228 mμ.

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