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THE STEREOCHEMISTRY OF OCCIDENTALOL AND ITS HYDROGENATION PRODUCTS*

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Abstract—The hydrogenation of occidentalol using palladium-on-charcoal gave mainly dihydro-occidentalol, and hydrogenation of the latter over platinum catalyst gave tetrahydro-occidentalol, m.p. 84°. In polar solvents occidentalol was reduced to a mixture containing a second fully saturated compound, epitetrahydro-occidentalol, m.p. 117°. Dihydro-occidentalol was not identical with α-eudesmol, nor was either of the tetrahydro derivatives identical with dihydroeudesmol. Hydrogenation of eudesmol over palladium-on-charcoal gave an equimolar mixture of dihydroeudesmol and a new isomer, epidihydroeudesmol, isolated by means of gas liquid chromatography and found to differ from the tetrahydro-occidentalols. From these data it is deduced that occidentalol and its derivatives have a *cis*-fused decalene ring system. This was supported by oxidation studies on the fully hydrogenated derivatives.

OCCIDENTALOL, a eudalene-type sesquiterpene alcohol, was isolated by Nakatsuka and Hirose[1] from the wood of Eastern white cedar (*Thuja occidentalis* L.) and on the basis of degradative experiments was assigned structure I. More recently, Hirose and Nakatsuka[2] confirmed this structure by preparation and pyrolysis of a diene adduct. The position of the conjugated double bonds was also confirmed[3] when glyoxal was obtained as an ozonolysis product from occidentalol (see Experimental). By hydrogenation of occidentalol over palladium-on-charcoal the Japanese workers obtained dihydro-occidentalol (II), but failed to obtain a well-defined tetrahydro-derivative in the reaction with platinum catalyst.[1]

If occidentalol is a member of the eudesmane (selinane, III) group of sesquiterpenes,[4] then dihydrooccidentalol (II) should be identical with α-eudesmol (IV), and also, it should be possible to obtain a tetrahydro-derivative equivalent to dihydroeudesmol (V). McQuillin and Parrack[5] prepared pure α-eudesmol and reported m.p. 81–82°, $[\alpha]_D$ +30·5°. Klyne[6] refers to a synthetic α-eudesmol having $[\alpha]_D$ +84° and a dihydro derivative $[\alpha]_D$ +37°. This compares with m.p. 87·5–88·5° $[\alpha]_D$ +59·2° for dihydro-occidentalol.[1] Since it is difficult to obtain the pure sesquiterpene alcohols of this group by conventional means, and since α- and β-eudesmol do not depress each other's melting point,[5] it is possible that II and IV are identical. Gas-liquid chromatography (GLC) appeared to be a suitable technique to determine not only the purity of these compounds, but also to analyze the hydrogenation products obtained from occidentalol.

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[1] T. Nakatsuka and Y. Hirose, *Bull. Agric. Chem. Soc. Japan* **20**, 215 (1956).

[2] Y. Hirose and T. Nakatsuka, *Bull. Agric. Chem. Soc. Japan* **23**, 140 (1959).

[3] H. Erdtman and E. von Rudloff, unpublished results (1958).

[4] W. Cocker and T. B. H. McMurry, *Tetrahedron* **8**, 181 (1960).

[5] F. J. McQuillin and J. D. Parrack, *J. Chem. Soc.* 2973 (1956).

[6] W. Klyne, *J. Chem. Soc.* 3072 (1953).

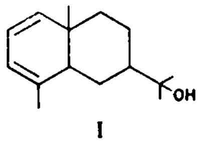
Previously it was shown[7] that occidentalol and eudesmol can be chromatographed on polyester and polyphenyl ether GLC columns without apparent decomposition and the degree of separation obtained on these columns was such as to make a detailed study feasible. Small amounts of occidentalol, dihydro-occidentalol, and eudesmol were hydrogenated under a variety of conditions and the products were analyzed by GLC. The most suitable conditions were then chosen for the preparation of the various hydro-derivatives.

Pure occidentalol (GLC analysis 99·5 ± 0·5%) was hydrogenated using palladium-on-charcoal catalyst to give mainly dihydro-occidentalol and two minor products with relative retention times (RRT) on an adipate polyester column (see Table 1) of 0·90 and 1·16 respectively. Nearly pure dihydro-occidentalol (96%) was isolated from this mixture and this was found to have m.p. 86–87° $[\alpha]_D$ +65·5°, i.e., practically the same constants as reported by Nakatsuka and Hirose.[1] Its RRT was 1·06, whereas that of eudesmol under the same conditions was 1·46. The non-identity of these two compounds was apparent also from a strongly depressed melting point and different IR spectra. Hydrogenation of dihydro-occidentalol over platinum catalyst in methanol–acetic acid (4:1) proceeded slowly and gave mainly a tetrahydro-derivative, $C_{15}H_{28}O$, m.p. 82·5–84° [α]D +42·5°. This compound had RRT of 1·16 and was identical with the second minor component obtained in the hydrogenation of occidentalol over palladium-on-charcoal (see above), but was not identical with dihydroeudesmol (RRT 1·24, m.p. 85·5–86°, $[\alpha]_D$ +18·1°) as deduced from the depressed melting point, different IR spectra and GLC retention data. When occidentalol was hydrogenated

TABLE 1. PHYSICAL CONSTANTS OF OCCIDENTALOL, EUDESMOL AND THEIR HYDRO-DERIVATIVES

Compound	M.p.	$[\alpha]_D$	RRT*
Occidentalol	97·5–98·0	+363·2°	0·92
Dihydro-occidentalol	86·0–87·0	+65·5°	1·06
Tetrahydro-occidentalol	82·5–84·0	+42·5°	1·15
Epitetrahydro-occidentalol	116·0–117·0	+9·3°	0·90
Eudesmol	81·0–82·0	+35·0°	1·46
Dihydroeudesmol	85·5–86·0	+18·1°	1·24
Epidihydroeudesmol	73·0–75·5	−12·8°	0·96

* Relative retention time with respect to cedrol (1·00) on a 6′ × 1/4″ O.D. adipate polyester column at 160° and 60 ml helium/min.



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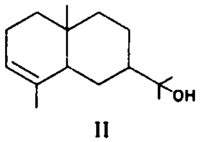

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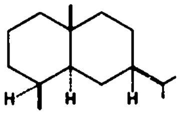

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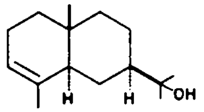

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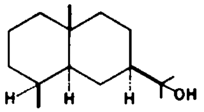

V

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[7] E. von Rudloff, *Canad. J. Chem.* **38**, 631 (1960).

directly with platinum catalyst in acetic acid as solvent, a mixture of dihydro-occidentalol (2–3%), tetrahydro-occidentalol (55%) and the compound RRT 0·90 (40%) (VI) was obtained. That VI was not unreacted occidentalol (RRT 0·92)* was demonstrated by removing any unsaturated compound by exhaustive oxidation with permanganate. The neutral material consisted of VI and tetrahydro-occidentalol, m.p. 84°. The unknown compound VI was obtained pratically pure and was found to be a fully saturated alcohol, $C_{15}H_{28}O$, m.p. 116–117°, $[\alpha]_D$ +9·3, which will be referred to as epitetrahydro-occidentalol. When occidentalol was hydrogenated in dry benzene the yield of this tetrahydro-isomer dropped to 3–5%. This suggests that 1:4 addition may be involved and that VI is the C-4 epimer of the lower melting tetrahydro-occidentalol.

If the isopropyl alcohol group in occidentalol and its hydrogenation products is equatorial(4,8), then these compounds can differ from eudesmol and its dihydro-derivative only at the ring juncture, i.e., occidentalol must have *cis*-fused rings. However, since the hydro-derivatives of occidentalol have been obtained after initial hydrogenation over palladium catalyst, it can be argued that epimerization at C-5 has occurred. Siegel and Smith[9] as well as Sauvage *et al.*[10] have shown recently that this catalyst can cause extensive isomerization to the more stable isomer during hydrogenation of cyclohexene derivatives. Gardner *et al.*[11] have encountered epimerization at C-5 when the *cis*-fused bicyclic sesquiterpene alcohol verbesinol and its *p*-hydroxycinnamate ester were subjected to hydrogenolysis over palladium catalyst. These epimerizations from a *cis*-fused system to the *trans*-isomer indicate that the latter is the more stable system and therefore, the production of two tetrahydro-occidentalol isomers different from dihydroeudesmol cannot be explained by epimerization at C_5. This conclusion was further strengthened, when the hydrogenation of eudesmol with palladium catalyst gave two dihydro-derivatives in about equal amounts. One of these (RRT 1·24) was the normal dihydroeudesmol, the other, epidihydroeudesmol (RRT 0·96), had m.p. 73–75·5°, $[\alpha]_D$ −12·8°, and differed from the two tetrahydro-occidentalol isomers. Also, when the fully saturated compounds were treated with hydrogen and palladium-on-charcoal at room temperature for 24 hours no epimerization could be detected. If the assumption that the isopropyl alcohol group is equatorially oriented at all times is correct (see below), then epidihydroeudesmol must be the C_4 epimer (VII), and the two tetrahydro-occidentalol isomers are the C-4 epimers of VIII. The assignment of structure V to the "normal" dihydroeudesmol was based on Barton's assumption[8] that the α-side of eudesmol is less hindered and that hydrogen would be added from that side to give the C-4 β-methyl isomer, and this has been shown to be correct.[4] In the *cis*-decalin system the β-face appears to be more open to attack[12] and the "normal" tetrahydro-occidentalol, m.p. 84°, should therefore be the α-methyl isomer and epitetrahydro-occidentalol the β-methyl isomer.

The above assignment of the *cis*-fused ring system to occidentalol and its derivatives is based on the reasonable assumption that the isopropyl alcohol group is equatorial

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* On other columns the difference in RRT for these two compounds was larger, e.g., 0·84 and 1·10 on a 6′ SE-30 silicone polymer column for occidentalol and VI respectively.

[8] D. H. R. Barton, *Chem. & Ind.* 664 (1953).

[9] S. Siegel and G. V. Smith, *J. Amer. Chem. Soc.* **82**, 6087 (1960).

[10] J. F. Sauvage, R. H. Baker and A. S. Hussey, *J. Amer. Chem. Soc.* **83**, 3874 (1961).

[11] P. D. Gardner, G. J. Park and C. C. Albers, *J. Amer. Chem. Soc.* **83**, 1511 (1961).

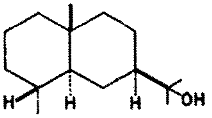
[12] W. Klyne, *The Chemical Society, Annual Reports* **52**, 212 (1955).

at all times (see below)*. Models of the *cis*-fused system show that this is indeed the only possible configuration when both rings are in the chair form. However, with the rings in a boat form, or with the *trans-fused* chair configuration, an axial isopropyl alcohol group is sterically possible. To eliminate the possibility that the occidentalol compounds are, after all, C-7 α-epimers of eudesmol, the isopropyl alcohol group was removed by oxidation with chromic acid. Ruzicka *et al.*[14] had oxidized dihydroeudesmol with chromic acid in aqueous acetic acid to give 5,9-dimethyl decalone-3 (IX) and a dicarboxylic acid. When this reaction was repeated in the present study the major neutral oxidation product was found to be IX (RRT = 0·90, see Table 2),

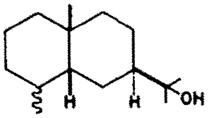
TABLE 2. RELATIVE RETENTION TIMES (CEDROL = 1·00) AND PERCENTAGE COMPOSITIONS OF NEUTRAL PRODUCTS FROM CHROMIC ACID OXIDATION

Dihydroeudesmol		Tetrahydro-occidentalol		Epitetrahydro-occidentalol	
RRT	%	RRT	%	RRT	%
0·90	36	0·63	12·5	0·91*	77
1·08	8	0·79	9·5	1·17	23
1·24*	47	1·16*	76		

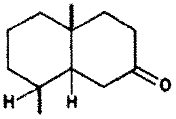
* Recovered starting material.



VII



VIII



IX

with smaller amounts of another ketone (RRT 1·08) and two hydrocarbons (GLC analysis) being present. However, oxidation of the two tetrahydro-occidentalol isomers in the same manner yielded distinctly different products. Tetrahydro-occidentalol gave two ketones, RRT 0·63 and 0·79 in low yield, and epitetrahydro-occidentalol gave a ketone, RRT 1·17. Since neither of the tetrahydro-occidentalols gave IX, it follows that they must differ from dihydroeudesmol at the ring juncture, thus confirming the above conclusions.

EXPERIMENTAL

M.ps. were determined on a Leitz hot-stage microscope and are uncorrected. The gas-liquid chromatographic data were obtained by means of a modified Beckman GC-2 Chromatograph equipped with a thermal conductivity cell. Columns of 6′ × 1/4″ O.D. (183 × 0·6 cm) coiled copper tubing containing adipate polyethylene glycol (APEG) polyester, *m*-bis (*m*-phenoxyphenoxy)-benzene (polyphenyl ether PPE), and SE-30 silicone polymer on Chromosorb W (60/80 mesh) in the ratio of 1:6 were made up as described previously.[7] Preparative runs were also carried out with 3′ × 1/4″ O.D. columns containing SE-30 silicone polymer or polyphenyl ether on Chromosorb W (30/60 mesh) in the ratio of 1:4. Fractions were collected in traps containing glass wool moistened with chloroform and externally cooled in acetone-dry ice mixture. In analytical runs each column was standardized by injecting 2 μl cedrol solution (50%, in chloroform) and all retention times are reported relative to this compound (see Tables 1 and 2). Retention times were measured at the initial point of emergence

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* *This assumption is strengthened by the recent report by* Nakazaki[13] *that in* occidol, *the second major* sesquiterpene alcohol isolated from Eastern white cedar[1], this group is indeed equatorial.

[13] M. Nakazaki, *Chem. & Ind.* 413 (1962).

[14] L. Ruzicka, A. L. Wind and D. R. Koolhaas, *Helv. Chim. Acta* **14**, 1132 (1931).

of each peak.[7] The exit of the columns was at atm. press. and the flow rates were measured by means of a moving soap bubble. Samples were introduced as solutions (approx. 50% in chloroform) by means of a hypodermic syringe.

Micro-hydrogenation. The sesquiterpene alcohol (10 mg) was added to reduced catalyst (5 mg) in the desired solvent (3 ml) and the hydrogenation was continued until no more hydrogen was consumed The solution was filtered, neutralized when acetic acid was present, and the product extracted with ether. After drying (Na_2SO_4) the solution was evaporated to dryness and the residual product was analysed by GLC.

In the attempts to isomerize the fully saturated alcohols, the compound (10 mg) and reduced palladium-on-charcoal (10 mg) in methanol (3 ml) were stirred in the presence of hydrogen for 24 hr. The filtered solution was evaporated to dryness and the product was analyzed by GLC. In each instance, a single peak corresponding to the starting material was obtained.

Occidentalol (I). The milled heartwood of a mature Eastern white cedar tree (*Thuja occidentalis* L.) from the Winnipeg district, Manitoba, was extracted with acetone. The extract was evaporated to a small volume and the dark, viscous residue was poured into ether. The ether solution was decanted from the insoluble residue and was extracted with 3 portions aqueous potassium hydroxide (10%) to remove acidic and phenolic material. The ether solution was washed with water, dried (Na_2SO_4) and evaporated to dryness. A full description of the yields and composition of the various fractions obtained from the wood extract will be reported elsewhere.

The neutral residue was fractionally distilled through a spinning band column at 18 mm press. The fraction b.p. 148–149° solidified and was crystallized from pet ether (b.p. 60–80°); m.p. 94–96·5°. The material was sublimed and twice crystallized from pet ether to give occidentalol, m.p. 97·5–98°, $[\alpha]_D^{25}$ +363·2° (*c*, 1·6, $CHCl_3$), which was undepressed in admixture with an authentic sample of occidentalol, m.p. 95·2–95·6°, $[\alpha]_D$ +361° (Found: C, 81·63; H, 10·92. Calc. for $C_{15}H_{24}O$: C, 81·76; H, 10·98%). GLC analysis showed this product to be better than 99·5% pure. The relative retention time with respect to cedrol is shown in Table 1.

Ozonolysis of occidentalol. Occidentalol (0·5 g) was dissolved in methylene dichloride and ozone was led through this solution at −70° until it acquired a distinctly blue colour. The solution was extracted with water and excess phenylhydrazine hydrochloride was added to the water extract. The resulting phenylhydrazones were filtered off, dissolved in a little benzene, and chromatographed on a column of silica gel (Kieselgel, Gebr. Hermann, Cologne, Germany). Development with benzene gave two distinct zones of which one was eluted readily and from which crude glyoxal bis(phenylhydrazone) (0·15 g) of m.p. 169–172° was obtained on evaporation. Recrystallization from benzene-pet ether raised the m.p. to 173–175°. The mixed m.p. with an authentic sample of glyoxal bis(phenylhydrazone) (m.p. 176–178°) was 174–178°.

Dihydro-occidentalol (II). Occidentalol (5·0 g) was dissolved in ethanol (20 ml) and hydrogenated in the usual manner with reduced palladium-on-charcoal (0·5 g). When the rapid uptake of hydrogen had ceased, the product was filtered and water was added (3–5 ml). On standing at 2 to 5° crude dihydro-occidentalol, m.p. 81–86°, crystallized. It was recrystallized, sublimed, and once again crystallized to constant m.p. 86–87·8°, $[\alpha]_D^{25}$ +65·5° (*c*, 2·3, $CHCl_3$). GLC analysis showed less than 2–3% each of *tetrahydro-* and *epitetrahydro-occidentalol* (RRT 1·15 and 0·90 respectively) to be present. (Found: C, 81·01; H, 11·79. Calc. for $C_{15}H_{26}O$: C, 81·02; H, 11·92%). The mixed m.p. with eudesmol was 72–84°.

Tetrahydro-occidentalol. Dihydro-occidentalol (1·0 g) in methanol (8 ml) and acetic acid (2 ml) was hydrogenated with reduced platinum oxide catalyst (0·1 g) until no more hydrogen was consumed. The mixture was filtered, poured slowly into saturated aqueous sodium bicarbonate solution and the product was extracted with ether. GLC analysis showed two peaks of RRT 1·15 (91%) and RRT 0·90 (9%). The mixture was crystallized from methanol–pet ether (b.p. 40–60°), sublimed, and recrystallized to give practically pure tetrahydro-occidentalol, m.p. 82·5–84°, $[\alpha]_D^{25}$ +42·5° (*c*, 3·4, $CHCl_3$). Mixed m.p. with dihydroeudesmol 60–82°. (Found: C, 80·29; H, 12·62. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%).

Epitetrahydro-occidentalol (VI). Occidentalol (3·0 g) was hydrogenated in aqueous ethanol (90%) using palladium-on-charcoal (0·3 g) as catalyst. When the reaction was complete the mixture was filtered, water was added and the product was extracted with ether. The crude mixture (3·0 g) was dissolved in t-butanol (50 ml) and to this was added in small aliquots with intermittant stirring potassium permanganate (10 g) and potassium hydroxide (0·5 g) in water (200 ml). After stirring for an additional 3 hr the mixture was left overnight and the excess permanganate was destroyed by addition of sodium metabisulphite. The precipitated manganese dioxide was filtered off, washed with aqueous t-butanol (90%) and the filtrate and washings were reduced to a small volume on a rotary evaporator. Fine crystals (0·3 g) separated out and these were filtered off and recrystallized from aqueous methanol to give epitetrahydro-occidentalol, m.p. 114·5–116°, which gave a negative reaction with tetranitromethane in ethanol. It was purified further by sublimation and recrystallization, m.p. 116–117°, $[\alpha]_D^{25}$ +9·3° (*c*, 1·6, $CHCl_3$). (Found: C, 80·38; H, 12·52. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%). Mixed m.p. with dihydroeudesmol 73–88°.

Eudesmol (IV). Crude eudesmol (Plaimar Ltd., Perth, Western Australia) was fractionally distilled and the fraction, b.p. 140–142° at 10 mm press. was recrystallized several times from pet ether (b.p. 40–60°) or methanol. Sublimation and recrystallization gave practically pure eudesmol (mixture of α- and β-isomers,[5] m.p. 81–82°, $[\alpha]_D$ +35·0° (*c*, 2·2, $CHCl_3$). (Found: C, 81·14; H, 11·74. Calc. for $C_{15}H_{26}O$: C, 81·02; H, 11·92%).

Dihydroeudesmol (V). Eudesmol (5·0 g) was dissolved in methanol (20 ml) and hydrogenated in the usual manner with red. platinum oxide catalyst (0·25 g). The product was filtered, water (3–5 ml) added and allowed to crystallize at 2–5° to give dihydroeudesmol, m.p. 81–85·5°. Recrystallization from aqueous methanol and sublimation raised the m.p. to 85·5–86°, $[\alpha]_D^{25}$ +18·1° (*c*, 2·16, $CHCl_3$). (Found: C, 80·39; H, 12·67. Calc. for $C_{15}H_{28}O$: C, 80·29; H, 12·58%).

Epidihydroeudesmol (VII). Eudesmol (2·0 g) was dissolved in methanol (16 ml) and acetic acid (4 ml) and was hydrogenated at 45–55° in the presence of palladium-on-charcoal (0·2 g). The uptake of hydrogen ceased after 5–6 hr. The product was worked up in the usual manner and analyzed by GLC when two peaks with RRT 0·98 and 1·27 in 53% and 47% amount respectively were recorded. The mixture was separated by preparative GLC (10 mg aliquots) to give crude *epidihydroeudesmol*, m.p. 75–82·5°, and crude dihydroeudesmol, m.p. 85–87·5°, $[\alpha]_D$ +15°. The impure epidihydroeudesmol was purified by sublimation and recrystallization to constant m.p. 73–75·5°, $[\alpha]_D$ −12·8° (*c*, 1·9, $CHCl_3$). (Found: C, 80·38; H, 12·52. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%).

Chromium oxide oxidation. The dihydroeudesmol (1·4 g) was dissolved in acetic acid (8 ml) to which a few drops of dil. sulphuric acid had been added. The mixture was heated to about 80° on a steam bath and then chromium trioxide (1·25 g) in water (8 ml) and acetic acid (16 ml) was added dropwise with stirring during 1 hr. The solution was left at 80–85° for 2 hr and methanol (1 ml) was added to reduce the excess chromic acid. The solution was cooled, neutralized with sodium bicarbonate and ether extracted. The ether solution was dried (Na_2SO_4) and then evaporated to dryness and gave the crude neutral product (0·95 g). The crude product was analyzed by GLC (see Table 2) and it was then fractionated on a silicic acid column. Elution with pet ether eluted first the hydrocarbons (0·05 g) and then a ketonic fraction (0·30 g), which formed a semicarbazone, m.p. 219–221°, in low yield. Reported for 5,9-dimethyl decalone-3 semicarbazone m.p. 222°, $[\alpha]_D$ +26°.[18] Elution of the silicic acid column with ether or chlofororm gave unreacted dihydroeudesmol (0·35 g).

Tetrahydro-occidentalol (0·2 g) and epitetrahydro-occidentalol (0·05 g) were degraded in the same manner and the neutral products were analyzed by GLC (see Table 2). Column chromatography gave liquid ketone fractions and crystalline starting material in each instance. However, GLC analysis of the ketone fractions did not show a peak of RRT 0·90, nor was a crystalline semicarbazone of m.p. 222° obtained.

Acknowledgments—We wish to thank Dr. Y. Hirose for a sample of occidentalol and Mr. M. Kaye, Extension Forester, Winnipeg, for having procured the wood of Eastern white cedar. Microanalyses were carried out by Mr. M. Mazurek and IR spectra were recorded by Mr. W. C. Haid.