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CONSTITUTION OF THE SESQUITERPENOID, CENTDAROL*

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Key Word Index—*Cedrus deodara*; Pinaceae; centdarol; isocentdarol; sesquiterpene diol; structural analysis

Abstract—Various chemical and spectroscopic methods have been employed to elucidate the structure of centdarol as 2β,7β-dihydroxyhimachal-3-ene.

INTRODUCTION

In our earlier communications [1,2] the isolation of himachalol [3], allohimachalol [4] and three new sesquiterpene alcohols, himadarol, centdarol and isocentdarol from the wood of *Cedrus deodara* Loud. along with their pharmacological evaluation as spasmolytic agents have been described. The present communication describes the structural elucidation of centdarol.

RESULTS AND DISCUSSION

Centdarol $C_{15}H_{26}O_2$ (M^+ 238) showed the presence of OH, a *gem* di Me group and a trisubstituted double bond in the IR spectrum. Its PMR spectrum indicated the presence of three *tert* C-Me and a vinylic Me, two OHs, one methine proton on a carbon bearing oxygen function and a vinylic proton on the trisubstituted double bond. It formed a monoacetate, $C_{17}H_{28}O_3$ (M^+ 280) whose PMR showed the acetoxyl Me at 2·08 ppm and a mono *p*-nitrobenzoate. $C_{22}H_{29}NO_5$, showing a 4H aromatic singlet at 8·2 ppm and a strong ion at *m/e* 220 due to $M-NO_2C_6H_4COOH$ in the MS. In the PMR spectrum of both the esters the carbonol proton signal had shifted downfield by more than 1 ppm indicating the presence of a *sec* OH group in the molecule.

When the PMR spectrum of centdarol was recorded in presence of trichloroacetylisocyanate (TAI) [5] the protons of the OH (3·12 ppm) were replaced by two broad multiplets of carbamate protons at 8·33 and 8·6 ppm with a concurrent shift of the carbinol proton (3·91) to 5·2 ppm confirming the presence of one secondary and one tertiary OH group in centdarol. Further, a downfield shift of the vinylic proton signal by 17 Hz was observed which indicated the allylic nature of one of the OHs. However, the PMR spectrum of centdarol monoacetate in the presence of TAI showed only 1H carbamate signal at 8·41 ppm without any shift of the vinylic H multiplet but a shift of one of the *tert* C-Me singlets from 1·25 to 1·70 ppm. This indicated the placement of the sec OH allylic to the double bond and a Me group on the carbon carrying the *tert* OH group.

The chromic acid oxidation of centdarol furnished a monoketo derivative centdarone, II, $C_{15}H_{24}O_2$ (M^+ 236), which showed an enone absorption both by IR (1660, 1618 cm^{-1}) and UV (240 nm) confirming the allylic nature of the *sec*-OH group. The inertness of centdarol towards sodium periodate proved that the OHs did not constitute a 1,2 glycol grouping in the molecule.

Centdarol acetate formed a monoepoxy derivative $C_{17}H_{28}O_4$ ($M-42$ *m/e* 254), whose PMR spectrum showed a 1H narrow multiplet at 3·1 and a 3H singlet at 1·4 ppm which were assignable to the proton and a methyl on the carbons constituting the epoxy ring. Therefore, the presence of a H–C=C–Me grouping in the molecule was established.

* Part 3 in the series, "Chemical Examination of *Cedrus deodara* Loud." Please refer to Ref. 2 for Part 2. CDRI Communication No. 2023.

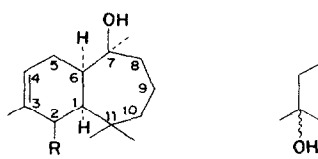
Hydrogenation of centdarol in presence of Adam's catalyst gave three products designated as A, B and C in the decreasing order of R_f values on TLC, with a relative ratio of *ca* 1:1·5:7·5 which were separated by Si gel chromatography. Product C, $C_{15}H_{28}O_2$ (M^+ 240) was characterized as the normal dihydro derivative of centdarol resulting from the saturation of the trisubstituted double bond. Product B, $C_{15}H_{28}O$ ($M - 18$ *m/e* 206) did not show vinylic H, vinylic Me and the carbinol proton signals in PMR spectrum and was the dihydrodesoxycentdarol obtained by the hydrogenolysis of the allylic OH group along with the saturation of the double bond. It was identified as dihydrohimachalol by direct comparison of its physical data with those of the authentic sample. Thus, the basic skeleton of centdarol was firmly established along with the position of the *tert* OH group.

In view of the above data, the double bond in centdarol could be assigned Δ^2 or Δ^3 positions. The former position could be eliminated on comparison of the vinylic H signal with that of himachalol which appeared at 5·5 ppm as a doublet of multiplets (*J* 5 Hz) due to its coupling with the adjacent C_1 proton and allylic coupling with methyl and methylene protons at C_3 and C_4. In contrast, the vinylic H signal in centdarol appeared as a narrow multiplet at 5·66 ppm with a *W* 1/2 of 7 Hz. Consequently with the placement of Δ^3 and the *sec* OH on the α-carbon to the vinylic H, the structure of centdarol could be extended to **1a**. This was supported by a large lowfield shift (67 Hz) of the vinylic H in the PMR spectrum of centdaron **1b**, the presence of the C_1 proton as a doublet (*J* 3 Hz) at 2·87 ppm and a 2H multiplet at 2·31 ppm assignable to C_5 methylene protons. These assignments were confirmed by its hydrogenation to dihydrocentdarone when the methylene multiplet moved upfield but the C_1 methine doublet at 2·7 ppm maintained its position in the PMR spectrum.

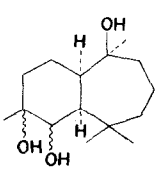
Further, the solvent-induced shifts in benzene d_6 and pyridine-d_5 observed in the PMR spectra for the protons of ring A in centdarone, as shown in Table 1, were also consistent with the position of the carboxyl group at C_2 according to the geometry of the solvent-carbonyl group complex postulated by Wilson *et al* [6].

The final proof of the structure of centdarone was obtained by $LiAlH_4$ reduction of epoxycentdarol acetate which led to the formation of a product ($C_{15}H_{28}O_3$) of lower R_f value, having no carbonyl absorption in its IR spectrum. Its PMR spectrum exhibited signals for two *tert* Me on carbons bearing oxygen functions at 1·27 and 1·28 ppm and one carbinol proton as doublet at 3·65 ppm. This product could, therefore, be formulated as **2**.

The triol (**2**) was oxidized with $NaIO_4$ to yield a *seco*-product which was found to be unstable. It was purified by filtration through Si gel to a viscous liquid, $C_{16}H_{26}O_3$. Its IR spectrum showed OH (3400 cm^{-1}), –CHO (2710, 1727 cm^{-1}) and –C=O groups (1706 cm^{-1}). The PMR spectrum displayed a MeCO singlet at 2·17 ppm and a 1H doublet at 9·95 ppm assignable to the aldehyde proton. The *seco*-product would, therefore, have the structure **3***, which was also supported by its MS which did not show M^+ but a $M-H_2O$ peak at *m/e* 236 followed by loss



(1a) R = H, OH
(1b) R = O



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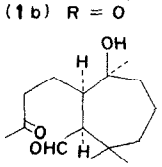

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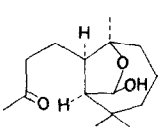
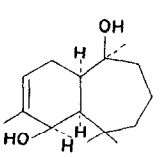


(4)



(5)

* Same product was obtained [3] from himachalol by oxidation with O_5O_4 followed by HIO_4. It (**3**) slowly cyclises to (**4**).

Table 1. Displacement of protons in centdarone relative to $CDCl_3$

	C_4–H (Hz)	C_5–H_2 (Hz)	C_1–H (Hz)
Benzene d_6	+35	+26	0
Pyridine-d_5	+16	+8	−21

of Me and MeCO radicals to give ions at *m/e* 221 and 193 respectively.

A Dreiding model of centdarol having both 6 and 7-membered rings in chair conformation, showed that an α-carbinol H and β-OH at C_2 would make an angle of 60° and 180° respectively with the C_1-H. The carbinol H would, therefore, be expected to couple with C_1-H with a *J* value of *ca* 1·5–2 Hz. Conversely, a β-carbinol H forming an angle of 180° with C_1-H would display splitting of *ca* 9 Hz. The observed *J* value for this proton in centdarol was 2 Hz and consequently the secondary hydroxyl must have a β-configuration. The stereochemical structure of centdarol would be **5**.

EXPERIMENTAL

All the mps are uncorrected. The NMR spectra were recorded at 60 MHz in $CDCl_3$ with TMS as internal standard. *Centdarol.* Mp 140°. $(\alpha)_D$ −97·34° (c 1% EtOH). ν_{max}^{KBr}: 3300, 1375, 830 cm^{-1}. PMR (ppm): 0·702, 1·02, 1·25 (3H each, *s*, 3 × Me), 1·82 (3H, *d*, *J* 1 Hz, C=C–Me), 3·12 (2H, broad *s*, 2 × OH, disappeared with D_2O), 3·91 (1H, *d*, *J* 2 Hz, –CH–O), 5·66 (1H, *m*, *W* 1/2 7 Hz, C=C–H). PMR with TAI: 0·833, 1·13, 1·68 (3H each, *s*, 3 × Me). 1·82 (3H, *d*, *J* 1 Hz, C=C–Me), 5·2 (1H, *d*, *J* 2 Hz, CH–O). 5·91 (1H, *m* C=C–H), 8·33, 8·6 (1H each, *m*, CONH–CO). *MS*: *m/e* 238 (M^+), 220 (M − 18), 205 (M^+ − 18 − 15), 177, 137, 135, 127, 121, 112, 109, 95, 93, 84, 71, 69, 55, 43. (Found: C, 74·9; H, 11·14. $C_{15}H_{26}O_2$ requires C, 75·57; H, 11·00%).

Centdarol acetate. Centdarol (100 mg) in C_5H_5N (1 ml) was allowed to stand 18 hr with Ac_2O (1 ml) and worked up as usual. The derivative (120 mg) was a viscous liquid. ν_{max}^{neat}: 3400, 1727, 1250, 863 cm^{-1}. PMR (ppm): 0·80, 1·11, 1·28 (3H, *s*, 3 × Me), 2·08 (3H, *s*, –OCOMe), 5·3 (1H, *d*, *J* 2 Hz, CH–OCO–), 5·88 (1H, *m*, C=C–H). PMR with TAI: 0·80, 1·11, 1·70 (3H each, *s*, 3 × Me), 2·08 (3H, *s*, OCOMe), 5·21 (1H, *d*, *J* 2 Hz, CH–O), 5·88 (1H, *m*, C=C–H), 8·41 (1H, *m*, CONH–CO). *MS*: *m/e* 280 (M^+), 262 (M − 18), 220 (M − 60), 202, 187, 159, 145, 132, 127, 119, 93, 77, 71, 69.

Centdarol-p-nitrobenzoate. Centdarol (50 mg) was treated with *p*-nitrobenzoyl chloride (75 mg) in C_5H_5N (3 ml) for 16 hr. The product (80 mg) crystallized from EtOH as colourless needles mp 164°. ν_{max}^{KBr}: 3484 (OH), 1712, 1267 (ester), 1604, 1524, 1106, 923, 791, 723 cm^{-1}. *MS*: *m/e* 220 (M − 167) Found: C, 67·8; H, 7·92; N, 3·28. $C_{22}H_{29}O_5N$ requires, C, 68·2; H, 7·54; N, 3·613%).

Centdarone: Centdarol (100 mg) and CrO_3–C_5H_5N complex (containing *ca* 100 mg CrO_3) were kept in C_5H_5N soln for 45 min. The product (85 mg) was crystallized from $CHCl_3$–C_6H_{14} as colourless needles mp 167°. λ_{max}^{EtOH} 240 (9660). ν_{max}^{KBr}: 3344 (OH), 1660, 1618 cm^{-1} (enone). PMR (ppm): 0·775. 1·033, 1·275 (3H each, *s*, 3 × Me), 1·8 (3H, *s*, C=C–Me), 2·31 (2H, *m*, $-CH_2$), 2·87 (1H, *d*, *J* 3 Hz, –CH–), 6·78 (1H, *m*, C=C–H). PMR (pyridine d_5): 0·701, 1·06, 1·23 (3H each, *s*, 3 × Me), 1·725 (3H, *d*, *J* 1·5 Hz, C=C–Me), 2·18 (2H, *m*, $-CH_2$), 3·225 (1H, *d*, *J* 2 Hz, –CH–), 6·51 (1H, *m*, C=C–H). PMR (C_6D_6): 0·65, 0·901, 1·05 (3H, *s*, 3 × Me), 1·7 (3H, *d*, *J* 3 Hz, C=C–Me), 1·83 (2H, *m*, $-CH_2$–), 2·86 (1H, *d*, *J* 2 Hz, –CH–), 6·2 (1H, *m*, C=C–H). *MS*: *m/e* 236 (M^+), 218 (M − 18), 203, 175, 161, 151, 135, 109, 95, 82, 71, 69. (Found: C, 76·25; H, 10·40, $C_{15}H_{24}O_2$ requires, C, 76·6; H, 10·0%).

Epoxycentdarol acetate. Centdarol acetate (100 mg) was treated with *m*-chloroperbenzoic acid (100 mg) in $CHCl_3$ (5 ml) at 20° for 44 hr and worked up as usual. The product (90 mg) was a viscous liquid. ν_{max}^{neat}: 3400, 1712, 1244, 1037, 914, 845, 814. PMR (ppm): 0·933, 1·033, 1·21, 1·4 (3H, *s*, 4 × Me), 2·1 (3H, *s*, OCOMe), 3·1 (1H, *t*, *J* 1·5 Hz, –C=O=C–H), 5·21 (1H, *d*, *J* 1·5 Hz, CH–OCO–). *MS*: *m/e* 254 (M − 42), 236 (M − 60), 221, 203, 193, 175, 161, 151, 135, 109, 95.

Hydrogenation of centdarol. Centdarol (250 mg) was dissolved in EtOAc (10 mg) and hydrogenated in the presence of PtO_2 (25 mg) for 6 hr. The reaction product (240 mg) showed 3 spots on TLC designated as A, B and C (R_f 0·66, 0·53 and 0·16 respectively in C_6H_6 − MeOH 96:4). The mixture was chromatographed on Si gel furnishing product B (20 mg) on elution with C_6H_6–$CHCl_3$. Product C (180 mg) was obtained from the $CHCl_3$ eluate. Product A could not be isolated in pure form. Product B was a colourless viscous liquid. ν_{max}^{neat} 3300, 2857, 1441, 1362, 1157, 1106, 1016, 914, 859, 831 cm^{-1}. PMR (ppm): 0·933, 1·08, 1·35 (3H each, *s*, 3 × Me). *MS*: *m/e* 206 (M^+ −18), 191, 163, 149, 137, 129, 121, 109, 95, 81, 71, 55. Product *C* crystallized as colourless needles, mp 115° from C_6H_6–C_6H_{14}. ν_{max}^{KBr}: 3350, 1130, 1004, 900, 860 cm^{-1}. PMR (ppm): 0·983, 1·03, 1·25 (3H, *s*, 3 × Me), 2·11 (2H, *s*, OH, D_2O exchangeable). 3·46 (1H, *dm*, *J* 7 Hz, CH–O). *MS*: *m/e* 240 (M^+). 222, 207, 189, 179, 161, 137, 122, 109, 95, 82.

Dihydrocentdarone. Centdarone (240 mg) was hydrogenated in the presence of Adams catalyst (25 mg), in EtOH for 4 hr. The dihydro derivative (235 mg) crystallized from C_6H_{14}, as colourless needles, mp 73–75°, ν_{max}^{KBr}: 3400 (OH), 1700 (C=O). PMR (ppm): 0·925, 1·1, 1·18 (3H each, *s*, 3 × Me), 1·01 (3H, *d*, *J* 7 Hz, *sec* Me), 2·703 (1H, *d*, *J* 4 Hz, CO–CH). *MS*: *m/e* 238 (M^+), 223, 195, 181, 163, 153, 139, 111, 109, 95, 81.

$LiAlH_4$ reduction of epoxycentdarol acetate. Epoxycentdarol acetate (290 mg) was heated with $LiAlH_4$ (1·5 ml, 1 M soln in diglyme) at 110° for 6 hr. The reaction product (230 mg) showing 1 major spot and 3 minor spots (TLC), was chromatographed on Si gel and the $CHCl_3$ eluate furnished a triol derivative (90 mg) as a viscous liquid. ν_{max}^{neat}: 3380, 1144, 1021, 910, 859 cm^{-1}. PMR (ppm): 1·083 (6H, *s*, 2 × Me), 1·27, 1·28 (3H each, *s*, 2 × Me), 3·65 (1H, *d*, *J* 6·5 Hz, CH–O). *MS*: *m/e* 238 (M − 18), 220, 205, 177, 162, 153, 137, 123, 109, 95.

The triol (80 mg) was dissolved in a mixture of EtOH (1 ml) and EtOAc (0·25 ml) and a soln of $NaIO_4$ (120 mg in 1 ml H_2O) was added. The reaction mixture was allowed to stand for 4 hr, diluted with H_2O and then extracted with EtOAc. The residue from EtOAc layer was chromatographed through Si gel and obtained as a colourless viscous liquid (25 mg) which showed a single spot on TLC. ν_{max}^{neat}: 3400 (OH), 2710, 1727 (CHO), 1706 cm^{-1} (C=O). PMR (ppm): 1·01, 1·1, 1·16 (3H each, *s*, 3 × Me), 2·166 (3H, *s*, COMe), 9·95 (1H, *d*, *J* 3 Hz, –CHO). *MS*: *m/e* 236 (M − 18), 221, 193, 175, 149, 127, 109, 95.

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