SOME NEW CEDRANE DERIVATIVES FROM JUNIPERUS FOETIDISSIMA WILLD.

CONFIGURATION OF CEDROLIC ACID¹

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Abstract— The sesquiterpene oxide $C_{15}H_{24}O$ from Juniperus foetidissima Willd. has been characterized and shown to be a cedrane derivative, 8,14-cedranoxide (I). The new cedrane derivatives 8,14-cedranolide (II), 8S,14-cedranediol (III) and 8-cedren-13-ol (X) have been isolated from the same species. The configuration of cedrolic acid²,8S-hydroxycedrane-13-carboxylic acid (VIII),* has been determined.

IN A previous paper⁴ it was reported that the heartwood extracts of Juniperus foetidissima Willd. contained a sesquiterpene oxide $C_{15}H_{24}O$ together with appreciable quantities of several other unidentified compounds. We have now re-examined these extracts and established the structures and configurations of the oxide I and three other new cedrane derivatives II, III and X. Also during the course of this work the configuration of cedrolic acid² (VIII) has been determined.

The oxide, isolated as described previously, could not be reduced by LAH and was very stable to dehydrogenation.



* The R and S rotational rule for configurational definition has been used in this paper since the α - and β -system used previously³ is applicable only to parts of the cedrane skeleton.

The NMR spectrum (Fig. 1) shows bands corresponding to three Me groups at 9.15τ (3H, doublet, J = 7 c/s), 9.00τ (3H, singlet), 8.83τ (3H, singlet) indicating one secondary and two tertiary Me groups, one being situated on a C atom attached to an O atom. There is also a 13 proton signal between 8 and 8.8 and an AB quartet (J = 9.5 c/s) centered at 6.45τ . Neither the IR nor the NMR spectrum shows any indication of olefinic unsaturation. Treatment of the oxide I with BF₃-etherate in acetic anhydride yielded an acetate (IV), $C_{17}H_{26}O_2$ (IR, 1740 cm⁻¹). The NMR spectrum of this acetate showed that the Me groups at positions 2 and 6 had been retained (9.13 τ , 3H, doublet J = 7 c/s; 8.87 τ , 3H, singlet) and that it contained a trisubstituted double bond bearing a Me group as shown by bands at 8.32 τ (3H, singlet) and a broad singlet at 4.61 τ (1H), also bands characteristic of a tertiary acetoxymethylene group at 7.95 τ (3H, singlet) and an AB-quartet (J = 13 c/s) centered near 6 τ .

Reduction of this acetate with LAH yielded a crystalline alcohol $C_{15}H_{24}O$. This was shown to be 8-cedren-14-ol (V) by the following reactions. Oxidation of the alcohol by chromic acid gave the corresponding aldehyde, 8-cedren-14-al (VI), the tosylhydrazone of which yielded 8-cedrene (VII) on LAH reduction. Hence it follows



that the structure and configuration of the oxide must be as shown in I, i.e. 8,14-cedranoxide.

Having the compounds IV and V at hand made it possible to determine the orientation of the carboxylic acid group at C₆ in cedrolic acid (VIII) isolated by Runeberg⁵ from *J. utahensis* Lemm. The evidence for the structure of this compound was complete except for the configuration at C₆.²

The alcohol X and acetate XI were prepared from cedrolic acid (VIII), and were found to be different from V and IV, respectively. The "fingerprint" regions of the IR spectra were significantly different and the *p*-nitrobenzoates of the alcohols had different m.ps. In the NMR spectra of V and IV the C_{13} -Me group gave rise to singlets at 8.89 and 8.87 τ , whereas the signals from the proton of the C_{14} -Me group in X and XI appeared at slightly higher field, 8.93 and 8.90 τ , respectively. These shifts may be explained by the anisotropy of the neighbouring double bond. The signals due to the protons of the oxymethylene group show similar characteristic shifts.

Since the configurations at C_6 in IV and V are known it follows that cedrolic acid is 8S-hydroxycedrane-13-carboxylic acid (VIII).

From the neutral extracts of J. foetidissima three other cedrane derivatives were isolated.

An alcohol which was identical with X was found in the fraction boiling higher than the cedrane-oxide I.



FIG. 2 NMR spectrum of 8,14-cedranolide II (in CDCl₃; internal standard, TMS).

From the distillation residue a lactone (II) $C_{15}H_{22}O_2$ (IR, 1760 cm⁻¹, NMR see Fig. 2) and a diol (III) $C_{15}H_{26}O_2$, m.p. 146.5–147.5° (NMR see Fig. 3) were isolated by chromatography. LAH reduction of II gave III. In order to correlate the diol III with 8S-cedranol an attempt was made to prepare a suitable ester of the CH₂OH group which would permit a reduction to the corresponding Me group. However, treatment



FIG. 3 NMR spectrum of 8S,14-cedranediol III (in CDCl₃; internal standard, TMS).





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Common		Methyl g	sdnoz		Olefinic		
	C ₁₂	C ₁₃	C14	C13	protons		
-	9-15 (d)	906		8-83		$-CH_2 - O_{-}, AB(q) J = 9.5c/s$	A; 6-49 B: 6.40
II	9-13 (d)	8.79	I	8-62		1	0 °
III	J = 7 c/s 9-13 (d)	8-92	ł	8-72		$-CH_2OH, AB(q) \qquad J = 11 c/s$	A; 6-73
N	J = 7 c/s 9-13 (d) I = 7 c/s	8.87	ł	8-32	4-61		B; 6-01 A; 6-01 B: 6-04
۸	9-13 (d)	68.8	1	8-29	4-78	-COCH ₃ , 7.95 	A; 6-51 B: 5-40
IV	9-10 (d)	8-95	I	8-40	4-69		D, 049
ΠΛ	J = 7 c/s 9.13 (d)	8-97	9-04	8-29	4-68	I	
XI	J = 7 c/s 9-13 (d)	1	8-67	8-31	4-63		
×	J = 7 c/s 9-13 (d)	ŀ	8-93	8-33	4-80		A; 654
IX	J = 7 c/s 9-13 (d)	l	8-90	8.30	4.65	$-CH_2 - O_{}, AB(q) J = 12 c/s$	B; 640 A; 601
ШХ	J = 1 c/s 9·13 (d) J = 7 c/s	I	8-62	8-72		$-CH_2OH, AB(q) J = 11 c/s$	B; 644
8,(15)-codrene	9.13 (d) J = 7 c/s	9-03	[H9]				
 Internal stands 	ard, TMS; solvent,	CDCI ₃ . All p	caks are singl	ets except if s	ated otherwise	; (d) = doublet, (q) = quartet.	

of 8S,14-cedranediol (III) with methanesulphonyl chloride in pyridine gave a product which proved to be identical with 8,14-cedranoxide (I). From this reaction the configuration of 8S,14-cedranediol (III) can be immediately assigned to the diol and that of 8,14-cedranolide (II) follows for the lactone. Also the fact that the diol III differed from that obtained by LAH reduction of methyl 8S-hydroxycedrane-13-carboxylate (XII), is additional proof for the structure of cedrolic acid (VIII). The NMR spectra of the diols III and XII are worthy of comment. The signal due to the C_{13} -Me protons in the spectrum of III appears as a sharp singlet at 8.92 τ whereas in the epimeric diol XII the C_{14} -Me signal is strongly deshielded by the neighbouring C_8 -OH group and appears at 8.62 τ . The NMR spectra of all the compounds described above possessing C_{13} - or C_{14} -oxymethylene groups show AB-type patterns due to nonequivalent methylene protons. In the diol III where strong intramolecular hydrogen bonding is possible the non-equivalence of the two protons is very pronounced ($\Delta \tau$ 0.72) as compared with the difference between the corresponding protons in the epimeric diol XII ($\Delta \tau$ 0.21).

EXPERIMENTAL

M.ps were taken on a Kofler micro hot stage. NMR spectra were recorded on a Varian A-60 instrument operating at 60 Mc/s (solvent CDCl₃, internal standard TMS). Rotations were taken in CHCl₃. Light petroleum refers to the fraction b.p. 40–60°. In this work the fractions obtained by J. Runeberg⁴ from the wood of *Juniperus foetidissima* Willd. were used. They had been stored in glass stoppered bottles in the dark for 6 years. Column and thin layer chromatography was carried out using Merck silica gel.

Table 1 summarizes the NMR data for the compounds described in this paper together with those of 8,(15)-cedrene.

Treatment of the oxide I with boron trifluoride-etherate in acetic anhydride. BF₃-etherate (0.5 ml) was added dropwise at room temp to I (500 mg) in Ac₂O (20 ml). The reaction mixture immediately turned light brown. After stirring for 30 min the mixture was poured onto ice and extracted with ether; the organic phase was washed with NaHCO₃ aq, with water, and then dried (Na₂SO₄). Removal of the ether gave IV as a pale green oil which was purified by chromatography on silica gel followed by distillation: b.p. (bath) 90-95°/0.1 mm, n_{Dax}^{22} 1.4971; $v_{max}^{hinflim}$ 1740, 1250, 1040, 990, 920, 820, 810 cm⁻¹. (Found: C, 77.3; H, 10-0. C₁₇H₂₆O₂ requires: C, 77.8; H, 10-0%).

Conversion of 8-cedren-14-ol acetate (IV) to 8-cedrene (VII). Reduction of IV (1-05 g) with LAH (200 mg) in ether in the usual manner yielded, after work-up and purification by chromatography, the crystalline alcohol V as soft needles: m.p. $50-51^{\circ} [\alpha]_{D}^{21} - 100.6^{\circ} (c = 1.76); v_{max}^{melt} 3480, 1040, 930, 820, 810 cm^{-1}.$ (Found: C. 81.6; H, 11.0. C₁₅H₂₄O requires: C, 81.8; H, 110%). p-Nitrobenzoate (needles from light petroleum): m.p. 102-102.5°; $[\alpha]_{D}^{21} - 76.4^{\circ} (c = 0.97)$. (Found: C, 71.6; H, 7.3; N, 3.8. C₂₂H₂₇O₄N requires: C, 71.5; H, 7.4; N, 3.8%).

Oxidation of V (700 mg) in acetone (25 ml) with 8N chromic acid yielded a crude product (600 mg) which on chromatography gave unchanged alcohol V (200 mg) and VI (300 mg): $v_{max}^{\rm thinflim}$ 2720, 1730, 915, 910, 920 cm⁻¹. 2,4-Dinitrophenylhydrazone (needles from ethanol): m.p. 164–165.5°; $[\alpha]_D^{21} - 285.4^\circ$ (c = 0.67). (Found: N, 14.1. C₂₁H₂₆O₄N₄ requires: N, 14.1%).

A mixture of VI (150 mg) and tosylhydrazine (100 mg) was refluxed in MeOH (7 ml) for 2 hr. Removal of the solvent gave a gum (230 mg) which after chromatography yielded the tosylhydrazone as a viscous glass (210 mg): $v_{max}^{thinf1im}$ 3200, 1600, 1175 cm⁻¹.

The tosylhydrazone (150 mg) was refluxed in THF (20 ml) with LAH (100 mg) for 3 hr. The residual reagent was destroyed with a few drops EtOAc and the product worked up in the usual manner to yield, after chromatography, a material (150 mg) which was identical with VII (IR, NMR, GLC and argentative TLC).

Preparation of 8-cedren-13-ol (X) and the corresponding acetate (XI) from cedrolic acid (VIII). The methyl ester cedrolic acid (800 mg), prepared as described previously,⁵ in 99% formic acid (20 ml) was heated to 75-80° for 2 hr. The reaction mixture was poured into a large excess of water and extracted with ether, the combined ethereal extracts were washed thoroughly with water and NaCHO₃ aq and dried (Na₂SO₄). Removal of the solvent gave IX (800 mg), b.p. (bath) 85°/0·1 mm; $[\alpha]_D^{21} - 147 \cdot 5^\circ$, $c = 1\cdot3$; $n_D^{22} \cdot 15004$; $v_{max}^{thin film}$ 1730, 1230, 1125, 825, 805 cm⁻¹. (Found: C, 77·1; H, 9·7. C₁₆H₂₄O₂ requires: C, 77·4; H, 9·7%).

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Reduction of IX (650 mg) with LAH (100 mg) in ether yielded, after work-up and chromatography, X (430 mg) as a wax-like solid : v_{max}^{mett} 3480, 1080, 820, 810 cm⁻¹. *p*-Nitrobenzoate (needles from light petroleum): m.p. 93–95°; $[\alpha]_{2^{1}}^{2^{1}} - 77.7^{\circ}$ (c = 1.0). (Found : C, 71.7; H, 7.3; N, 3.9. C₂₂H₂₇O₄N requires: C, 71.5; H, 7.4; N, 3.8%). The acetate XI was obtained from 8-cedren-13-ol in the usual way (Ac₂O/Py): b.p. (bath) 90–95°/ 0.1 mm; $n_{2^{1}}^{2^{1}}$ 1.4970; $v_{max}^{thin film}$ 1745, 1250, 1040, 820, 810 cm⁻¹. (Found : C, 77.4; H, 9.9. C_{1.7}H₂₆O₂ requires: C, 77.8; H, 100%).

Isolation of 8-cedren-13-ol (X). Repeated column chromatography of fraction 1p (Ref. 4, p. 724) on silica gel using light petroleum-ether mixtures yielded an alcohol which was identical with X (IR; NMR, Fig. 4; m.p. and mixed m.p. of p-nitrobenzoates).

Isolation of 8,14-cedranolide (II) and 8S,14-cedranediol (III). These two compounds were isolated from the distillation residue M, (Ref. 4, p. 724) by repeated column chromatography on silica gel using light petroleum-ether mixtures. Compound II: b.p. (bath) $120^{\circ}/0.1 \text{ mm}$; n_{D}^{22} 1.5054; $[\alpha]_{D}^{21}$ -66.35 (c = 1.5); $\nu_{max}^{blichlim}$ 1760, 1290, 1243, 1120, 1070, 950 cm⁻¹. (Found: C, 77.1; H, 9.5. C₁₅H₂₂O₂ requires: C, 76.9; H, 9.5%).

Compound III had after final purification by vacuum sublimation (white needles) m.p. 148-5-149°; $[\alpha]_{D}^{21} + 0.6^{\circ} (c = 1.8); v_{max}^{EB}$ 3240, 1250, 1035, 970, 940 cm⁻¹. (Found: C, 75-3; H, 11-0. C₁₅H₂₆O₂ requires: C, 75-6; H, 11-0%). LAH reduction of II in ether gave a diol identical (m.p., mixed m.p., IR, NMR, TLC) with the natural III.

Treatment of 8S,14-cedranediol (III) with methanesulphonyl chloride in pyridine. To III (200 mg) in Py (1 ml) MeSO₂Cl (150 mg) was added dropwise; the mixture became warm and a white crystalline ppt was formed almost immediately. The mixture was allowed to stand at room temp for 2 days, then poured onto ice, extracted with water, very dil HCl, water and dried (Na₂SO₄). Removal of the solvent yielded an oil (80 mg) which was identical with I (TLC, GLC, IR and NMR).

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