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STUDIES IN SESQUITERPENES—LI

β-HIMACHALENE EPOXIDE—STEREOCHEMISTRY AND SOLVOLYSIS†

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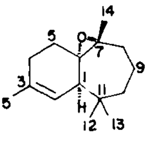
Abstract—Stereochemistry of β-himachalene oxide has been established by its correlation with himachalol. Products of solvolysis of this oxide are dependent on conditions and reagents used. Homoallylic participation becomes the dominant mode with perchloric acid in aqueous dioxane.

Rearrangement of β-himachalene oxide[1] (**1/2**) can conceivably lead to diverse carbon skeletons, some of which (e.g. **3**[2a], **4**[2b], **5**[2a]) represent carbon frame-work of naturally occurring sesquiterpenes, and hence, such transformations have biomimetic significance.[2] Homoallylic participation[3] during cleavage of oxirane ring leading to structures of type **6** is another pathway of possible biogenetic significance (cf, e.g. cubebol,[4] **7**). These considerations prompted us to investigate rearrangement of β-himachalene mono-oxide (**1/2**).

β-Himachalene (**8**) on epoxidation is known[1] to give a monoepoxide,§ for which stereochemistry **1** has been suggested on the premise that the peracid will approach the hydrocarbon molecule from the α-face, which appears to be less hindered for the preferred[7] conformation **9**. However, a careful analysis of the various low-energy conformations possible for β-himachalene, does not lead to a unique answer and this reopens the question of the stereochemistry of the oxide. Since for any meaningful discussion of the results of solvolysis of this oxide, one must know its stereochemistry, this problem has been tackled first.

Stereochemistry of β-himachalene monoepoxide

An answer to the question of stereochemistry of β-himachalene monoepoxide, could conceivably be obtained by studying the product(s) of hydride cleavage of this epoxide. In principle, the two oxides (**1, 2**) can generate four alcohols each, taking into consideration both *cis* and *trans* modes of oxirane ring cleavage. An analysis of the possible products will show that in each case, a unique alcohol of known stereo-structure results: **1** leading to epi-himachalol (**10**),[8] while **2** resulting in himachalol (**11**).[9]



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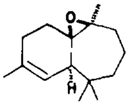

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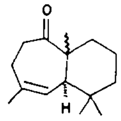

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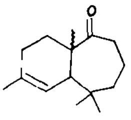

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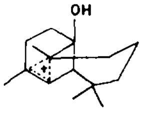

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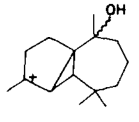

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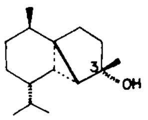

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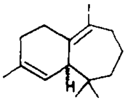

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In actual practice, exposure of β-himachalene monoepoxide to lithium–ethylenediamine,[10] resulted in a complex product consisting of hydrocarbons (25%, 7 components, two major) and alcohols (75%, 4 components, three major). Of the latter, himachalol (**11**), identified by reference to an authentic sample (mixed GLC, IR, PMR), constitutes ~27% and, this correlation defines the stereochemistry of the oxide as shown in **2**.

The other major products of reaction are considered from their spectral characteristics, to be **12–15**, and their formation is readily rationalised.

Solvolysis of β-himachalene oxide (2)

Products of solvolysis of β-himachalene oxide were found to depend on the reagent used. Thus, sulphuric acid (0.16%) in aq. acetone at ~29° (24 hr, N_2) gave essentially a mixture of hydrocarbons, which was not investigated further. Perchloric acid (0.7%) in methyl ethyl ketone (~29°, 5 min, N_2) furnished chiefly a mixture of ketones

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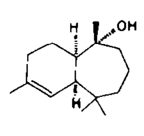
§Both epoxides (**1, 2**) have been isolated recently[5] from the essential oil of wood of *Cedrus atlantica* Manet, without of course identifying which is which. The two epoxides differ only in their GLC retention times and, show identical IR, PMR and mass spectra. In this connection it may be mentioned here that β-himachalene mono-oxide (**1/2**) is one of the auto-oxidation products of β-himachalene.[6]



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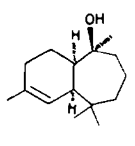

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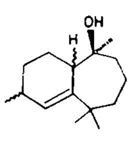

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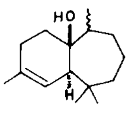

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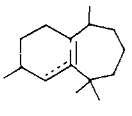
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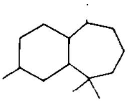
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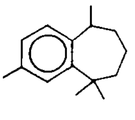
(TLC, 2,4-dinitrophenylhydrazine reagent spray), in which, isohimachalone (4)† could be identified (GLC, TLC, PMR). Perchloric acid (2.8%) in aq. dioxane (25–33°, 34 hr, N_2), on the other hand, yielded a mixture containing hydrocarbons (~20%) and alcohols (~60%), which has been investigated in detail.

Suitable chromatography of the above product yielded two pure hydrocarbons and four alcohols. The two hydrocarbons, and one alcohol (*RRf* 0.73) were recognised from their spectral characteristics to be the known *ar*-himachalene (**16**),[11] himachala-2,5,7-triene (**17**)[1] and the allylic tertiary alcohol **18**.[1] The remaining three alcohols (*RRf*, 0.64, 0.29 and 0.09) have been assigned structures **19**, **20** and **22** respectively, on the basis of their spectral properties (Table 1) and mechanistic considerations. Structure **19** is further supported by the UV absorption of the compound, which shows the expected[12] cyclopropane-olefine conjugation: λ_{max}^{EtOH} 223 nm (ϵ, 2480). The two diols (**20**, **22**), as expected,[13] give a distinct, though a faint, yellow color with tetranitromethane.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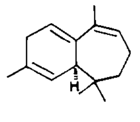

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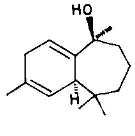

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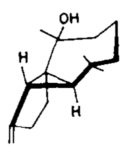

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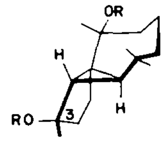

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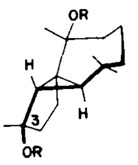
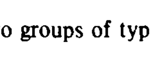
21 R = HCO



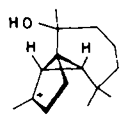
22 R = H

23 R = HCO



The presence of two groups of type Me–$\overset{\overset{\displaystyle C}{|}}{\underset{\underset{\displaystyle C}{|}}{C}}$–OH in **20**, **22** is fully supported by the expected desheilding of the two Me groups, which occurs (cf. Table 1) on formylation.[14] The mass spectral fragmentations of **20** and **22** are essentially identical, as expected on the basis that epimeric compounds generally generate similar spectra.[15] The assignment of configuration at C_3 in **20**, **22** is based on analogy to the chemical shifts for a very similar situation in epimeric cubebols (see **7**), configurations of which are well-secured:[4] cubebol (**7**), which has C_3–Me on the side opposite to that containing cyclopropane ring displays its C_3–Me upfield (1.27 ppm) in contrast to that in epicubebol (1.33 ppm).

It is rather surprising that in the above solvolytic reaction, homoallylic participation occurs with facility leading to, what may be termed, *cyclohimachalene* system (e.g. **19**). Effective homoallylic participation requires proper orientation of the leaving group for backside overlap of the π-electrons with the developing vacant p-orbital,[3] leading, in the present case to the geometrically prohibitive structure **24**.‡ It is suggested that epoxide **2** first suffers solvolytic *trans*-scission to the protonated glycol,§ which *via* conformer **25**, is all set for a back-side participation, generating products **19–20** and **22**.



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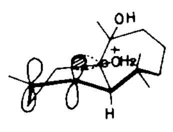

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It is quite conceivable that cubebols arise in nature by a similar process from a suitable cadinenic precursor.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Light petroleum refers to the fraction b.p. 40–60°. All solvent extracts were dried over Na_2SO_4. Optical rotations were measured at room temp. (26 ± 3°) in $CHCl_3$ on a Perkin-Elmer Polarimeter, model 141.

UV spectra were taken on a Perkin-Elmer spectrophotometer, model 350, in 95% EtOH. IR spectra were recorded as smears (liquids) or Nujol mulls (solids), on a Perkin-Elmer Infracord, model 137E. PMR spectra were taken in 10–20%, soln in CCl_4, unless stated to the contrary, on a Varian T-60 spectrometer; signals are recorded in (ppm) relative to TMS as zero; multiplicity abbreviations: s (singlet), d (doublet), t (triplet), m (multiplet), b (broad). Mass spectra were determined on a CEC Mass spectrometer, model 21-110B using an ionizing voltage of 70 eV and a direct inlet system; besides the molecular ion, ten most abundant ions are given with their relative intensities.

Silica gel for column chromatography (−100, +200 mesh) was activated at 125–130°/6–8 hr and standardised.[18] SiO_2–$AgNO_3$ was prepared and activated at 100–110°, as reported earlier.[19] TLC was carried out on 0.3 mm layers of SiO_2-gel or 15% $AgNO_3$–SiO_2-gel

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†This is one of the constituents of the essential oil of *Cedrus deodara* Loud., and is described elsewhere.[2b]

‡Structure **24** has *trans*-locked cyclopropane and cycloheptane rings, which is highly strained. Smallest ring to which cyclopropane can be fused in *trans*-fashion is cyclo-octane.[16] The observed coupling constant (J = 4.5 Hz) of the cyclopropane ring protons is consistent only with structure **19**; *cis*-hydrogens on cyclopropane as in **24** usually have J = 7.0–12.6 Hz.[17]

§Under the conditions of reaction, we have failed to get any evidence for the formation of the glycol. Apparently, free glycol is not an intermediate, its rate of formation being slower than the rate of its further transformation.

Table 1. Spectral characteristics of some tricyclo-[6,3,0,0^{1,7}]-undecane derivatives

Compd.	RRf*	PMR				IR
		Chemical shift in ppm				(cm^{-1})
		(Solv.)	Me-C- (3H,s)	Me-C-OR (3H,s)	other relevant signals.	
19	0.64	(CCl_4)	0.95 1.02	1.23	$\triangleright C\underline{H}$,$^{+}$ 1H,d,0.53,J=4.5Hz $-C=C\underline{H}_2$, 2H, s, 4.75	OH: 3350,1106 $-C=C\underline{H}_2$:1625,880
20	0.29	($CDCl_3$)	0.81 0.95	1.06 1.36		OH: 3390, 1047
21	-	(CCl_4)	0.81 0.93	1.26 1.58	$\underline{H}$COO: 1H, s, 7.71 $\underline{H}$COO: 1H, s, 7.78	HCOO: 1731,1158
22	0.09	($CDCl_3$)	0.81 0.90	1.06 1.23		OH: 3400, 1047
23	-	(CCl_4)	0.88 0.91	1.25 1.50	$\underline{H}$COO: 1H, s, 7.73 $\underline{H}$COO: 1H, s, 7.81	$\underline{H}$COO: 1733, 1716, 1160

* TLC (solvent: 15% EtOAc in C_6H_6; temp. ~30°; relative to Rf of ar-himachalene as 1.0.)

$^{+}$ Coupling is with the other cyclopropane H. This signal is not observed with the other compounds of this series, and hence, must be occurring relatively down-field.

containing 15% gypsum. GLC was carried out on Aerograph model A-350-B using 300 × 0.6 cm Al column packed with 20% diethyleneglycol polysuccinate on chromosorb W (60–80 mesh) with H_2 as carrier gas.

β-Himachalene mono-epoxide (**2**). This was prepared as reported elsewhere.[2b] The product is completely identical (IR, PMR and GLC) with the product prepared earlier[1] by a different method.

Action of lithium-ethylenediamine on β-himachalene oxide. To a mixture of the above oxide (5.5 g; 0.025 mole) and dry ethylenediamine (30 ml), maintained at 50–55° (N_2), Li (4.0 g, 0.576 g atoms; small pieces) was, portionwise, introduced with stirring during 2 hr. At the end, the blue mixture was cooled (ice), crushed ice (~300 g) added and the product taken up in ether (100 ml × 4) after saturating aqueous phase with NaCl. The ether phase was washed with water (20 ml × 5), brine (25 ml × 2) dried and freed of solvent. Programmed GLC (temp. 150–220°; 6°/min) of the product (5.5 g), revealed the presence of at least 11 components in which 5 predominated: RRT 1.0 (10.2%), 1.12 (12.7%), 5.60 (14.8%), 6.56 (27.8%) and 7.62 (27.3%).

The above product (5.5 g) was chromatographed over Al_2O_3/III (100 × 2.5 cm) with TLC (solvent: 15% EtOAc in C_6H_6) and GLC monitoring of fractions obtained with light petroleum and light petroleum containing increasing quantities of C_6H_6 (15–50%) and, finally with C_6H_6. Different fractions were further processed as follows.

Hydrocarbons **14**, **15**. The material eluted with light petroleum (200 ml) × 3) was essentially a mixture of two components (GLC: RRT 1.0, 1.12). In the mass spectrum the mixture showed *m/e* 206 and 208 (relative intensity ratio 2 : 1) assigned to hydrocarbons **14** ($C_{15}H_{26}$) and **15** ($C_{15}H_{28}$) respectively. Mixed GLC with an authentic sample of himachalane[11] identified compound with RRT of 1.12 as himachalane (**15**). From the PMR spectrum of the mixture, the other compound is tentatively considered to be **14**.

6β-Hydroxy-1α-himachal-2-ene (**13**; *RRT*, 6.56). The material (2.45 g) eluted with 15% C_6H_6 in light petroleum (200 ml × 10) was rechromatographed on Al_2O_3/III (110 × 2.0 cm) as before and the fractions eluted with 10% C_6H_6 in light petroleum gave pure **13** (0.65 g); b.p. 130° (bath)/0.5 mm, $[\alpha]_D + 52.01°$ (*c* 2.48%). IR: OH 3400, 1020 cm^{-1}. PMR: two tertiary Me (3 H singlets at 0.87 and 0.97 ppm), $\underline{Me}$–CH (3 H, d, 1.05 ppm, J = 6 Hz), $\underline{Me}$–C=CH (3 H, d, 1.72 ppm, J = 2 Hz), –C=C$\underline{H}$–CH (1 H, bs, 5.37 ppm); in the PMR spectrum, there is clear evidence in the Me region for the presence of its epimer (at C_7). Mass: *m/e* 222 (M^+, 47%), 204 (47%), 137 (39%), 121 (48%), 119 (100%), 111 (47%), 109 (62%), 95 (49%), 82 (73%), 69 (58%) and 55 (69%). (Found: C, 80.71; H, 12.27. $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%).

Himachalol (**11**; *RRT*, 7.62). The product (2.30 g) eluted with 20–40% C_6H_6 in light petroleum (200 ml × 13) was rechromatographed over Al_2O_3/III (100 × 2.0 cm); 20% C_6H_6 in light petroleum eluted a solid, m.p. 67–68° (CH_3CN), which was identified as himachalol[9] (**11**). 50% C_6H_6 in light petroleum (100 ml × 9) eluted material (0.994 g) which was processed for **12** (*vide infra*).

7β-Hydroxy-himachal-1-ene (**12**; *RRT*, 5.60). The above material (0.994 g) was purified by inverted-dry-column-chromatography (IDCC)[20] using SiO_2–gel/II (25 × 4 cm) as adsorbent and 10% EtOAc in C_6H_6 as solvent, to give a product, b.p. 140°

Table 2.

Fraction 1	light petroleum	600 ml × 4	3.25 g, *RRf* 1.00
Fraction 2	light petroleum	600 ml × 13	0.85 g, mixture
Fraction 3	25% C_6H_6 in light petroleum	600 ml × 5	0.154 g, unreacted oxide
Fraction 4	50% C_6H_6 in light petroleum	600 ml × 7	0.371 g, *RRf* 0.73
Fraction 5	50% C_6H_6 in light petroleum 75% C_6H_6 in light petroleum	600 ml × 6 600 ml × 2	0.537 g, mixture.
Fraction 6	75% C_6H_6 in light petroleum	600 ml × 13	0.743 g, *RRf* 0.64
Fraction 7	C_6H_6 5–15% EtOAc in C_6H_6	600 ml × 2 600 ml × 10	3.855 g, *RRf* 0.29
Fraction 8	20–25% EtOAc in C_6H_6	600 ml × 10	0.896 g, mixture
Fraction 9	50% MeOH–25% EtOAc	600 ml × 5	3.115 g, *RRf* 0.09
Fraction 10	MeOH	600 ml × 2	1.60 g, mixture, polymeric.

(bath)/0.7 mm, $[\alpha]_D + 8.17°$ (*c* 2.57%). IR: OH 3300, 1017 cm^{-1}. PMR: two tertiary Me (3 H singlets at 0.97 and 1.10 ppm), $\underline{\text{Me}}\text{–}\overset{|}{\text{C}}\text{H}$ (3 H, d, 0.97 ppn, J = 7 Hz), $\text{Me –}\underset{|}{\overset{|}{\text{C}}}\text{–OH}$ (3 H, s, 1.13 ppm), $\text{–}\underset{|}{\text{C}}\text{=C}\underline{\text{H}}\text{–CH–}$ (1 H, t?, 5.50 ppm). Mass: *m/e* 222 (M^+, 10%), 204 (29%), 137 (93%), 127 (75%), 109 (84%), 95 (100%), 84 (48%), 81 (48%), 71 (40%), 69 (49%) and 55 (54%). (Found: C, 80.60; H, 11.99. $C_{15}H_{26}O$ requires: C 81.02; H, 11.79%).

Action of perchloric acid in aqueous dioxane on β-himachalene oxide. To a soln of perchloric acid (60%, 0.47 g) in dioxane (53.5 ml) and water (12 ml), maintained at 0°, β-himachalene oxide (16.0 g, 0.078 mole) was added with swirling. It was then allowed to attain room temp. (33°) with occasional swirling, during 3 hr, when it was left aside at this temp. for 34 hr. The mixture had become homogeneous after 34 hr. The light yellow mixture was diluted with ice-water (300 ml) and the product taken up in ether (100 ml × 4). The ether extract was washed with water (50 ml × 4), 10% Na_2CO_3 aq. (15 ml × 2), water, brine and dried. Solvent removal gave a product (16.0 g), showing by TLC (solvent: 15% EtOAc in C_6H_6) five new compounds having *RRf* of 1.00, 0.73, 0.64, 0.29 and 0.09, besides some unchanged epoxide (*RRf*, 0.89). The product (16.0 g) was chromatographed on Al_2O_3/III (164 cm × 4.7 cm) with TLC monitoring(Table 2).

ar-*Himachalene* (**16**) *and himachala*-2,5,7-*triene* (**17**). Fraction 1 was separated by IDCC (15% $AgNO_3$–SiO_2-gel/IIA, 25 × 6.6 cm; solvent: 1:1 C_6H_6-light petroleum) into **16** (0.377 g, *RRf* 1.0) and **17** (0.647 g, *RRf* 0.71) and identified as such by standard comparison (IR, PMR, Mass) with authentic samples.[1,11]

7β-*Hydroxy*-1α-*himachal*-2,5-*diene* (**18**). Fraction 4 distilled at 130–140°(bath)/0.8 mm and was characterised as **18** by comparison (IR, PMR) with the previously published data.[1]

7β-*Hydroxy*-3(15)-*dehydro*-1α-2,6-*cyclohimachalane* (**19**). Fraction 6 was distilled to give pure **19**, b.p. 135°(bath)/0.7 mm, $[\alpha]_D + 110.3°$ (*c* 1.43%). Mass: *m/e* 220 (M^+, 44%), 206 (100%), 178 (68%), 163 (44%), 148 (22%), 124 (71%), 122 (39%), 106 (37%), 92 (55%), 83 (58%) and 55 (32%). (Found: C, 81.53; H, 10.76. $C_{15}H_{24}O$ requires: C, 81.76; H, 10.98%).

7β-3β-*Dihydroxy*-1α-2,6-*cylohimachalane* (**20**). Crystallisation of Fraction 7 from light petroleum yielded colorless flakes, m.p. 106–107°, $[\alpha]_D + 8.3°$ (*c* 0.74%). Mass: *m/e* 238 (M^+, 1%), 124 (26%), 110 (9%), 109 (100%), 99 (33%), 97 (44%), 95 (5%), 81 (7%), 69 (5%), 67 (7%) and 55 (10%). (Found: C, 75.63; H, 11.39. $C_{15}H_{26}O_2$ requires: C, 75.58; H, 11.00%).

This compound (0.143 g) on treatment with acetic-formic anhydride[14] (1.8 ml) at 30° for 16 hr yielded the *diformate* (**21**), b.p. 130–140°(bath)/0.2 mm. (Found: C, 69.00; H, 9.50. $C_{17}H_{26}O_4$ requires: C, 69.36; H, 8.90%).

7β,3α-*Dihydroxy*-1α-2,6-*cyclohimachalane* (**22**). Fraction 9 was crystallised from CH_3CN to give crystals, m.p. 78–80°, $[\alpha]_D + 102.7°$ (*c* 0.85%). Mass: *m/e* 238 (M^+, 0.13%), 124 (33%), 110 (9%), 109 (100%), 99 (28%), 97 (46%), 95 (3%), 81 (5%), 69 (5%), 67 (5%) and 55 (9%). (Found: C, 74.82; H, 11.03. $C_{15}H_{26}O_2$ requires: C, 75.58; H, 11.00%).

Diformate (**23**) was prepared as above, m.p. 79–81° (light petroleum). (Found: C, 69.05; H, 9.05. $C_{17}H_{26}O_4$ requires: C, 69.36; H, 8.90%).

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