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THE STRUCTURES OF ZIZANOL AND VETISELINENOL[*,1]

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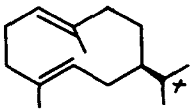
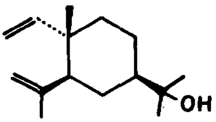
Our earlier studies[2,3] of vetiver oils from various producing regions indicate that all varieties except the wild North Indian Khus variety are chemically similar. The Khus variety, which contains no vetivone-related compounds, is characterized by the presence of antipodal cadalenes and eusdesmanes. In contrast, the biogenetic origin (normal or antipodal germacrenes) of the known constituents of typical vetiver oils could not be ascertained since all components known at that time had an sp^2-center at the point of attachment of the isopropyl group .[2] Our general interest in purportedly antipodal sesquiterpenes[3] led us to a study of vetiver oils. The present communication deals with preliminary studies of the owygenated sesquiterpenes of the Haiti and Reunion varieties and reports the isolation of α- and β-vetivone, khusimol (all previously obtained from this oil), together with khusimyl acetate,[**] elemol[+], and β-eudesmol.[‡] The rotation data for derivatives of elemol and β-eudesmol clearly indicate that typical vetiver sesquiterpenes are derived from the normal (not antipodal) H^+-germacrene-A ion[4] shown.

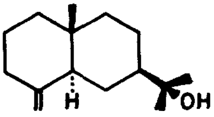
In addition more than a dozen new sesquiterpene alcohols have been isolated.



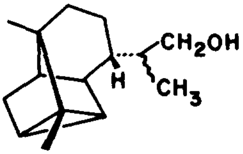
H^+-germacrene-A



elemol



β-eudesmol



cyclocopacamphenols

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[*] Paper II in the series, "Vetiver Oil Constituents." Presented in part at the Symposium on The Chemistry of Essential Oils at the 158th Meeting, ACS, New York (Sept., 1969).

[**] Identified by NMR and IR. Saponification afforded khusimol identical to an authentic sample.

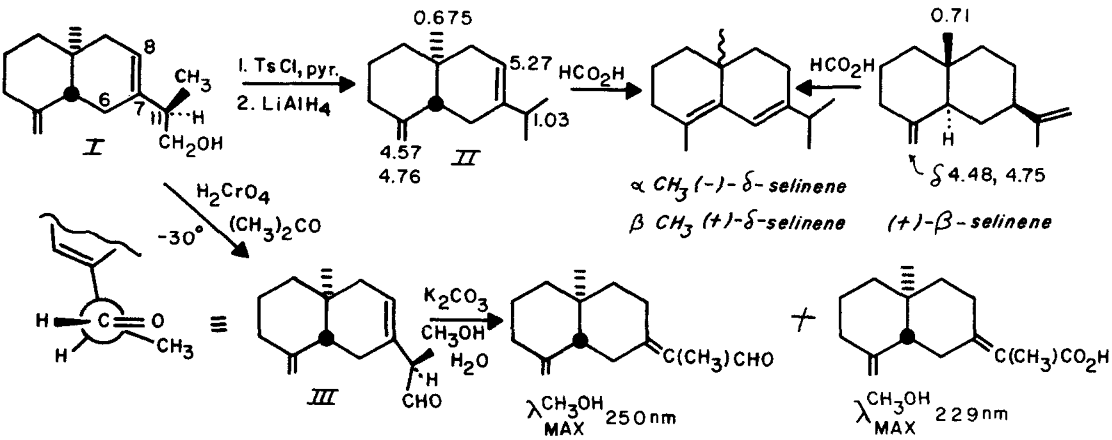
[+] Elemol, obtained as a waxy solid, was identified from the published IR[5] and NMR[6] spectra. The p-nitrobenzoate - mp 73-74.5° $[\alpha]_D$ = -7° (c = 0.95, CHCl$_3$) - proved identical (tlc, UV, ORD, mixed mp) with that from elemol derived from citronella.

[‡] β-Eudesmol, $[\alpha]_D$ = +61°, obtained as a waxy solid, showed the expected NMR[6] and IR[5] spectra. Formic acid treatment afforded (+)-δ-selinene.

These include two epimeric cyclocopacamphenols (vetiverol-d[2]),* zizanol (vetiverol-g[2], IV), and vetiselinenol (vetiverol-c[2], I). The data which led to the structure assignments is presented below.

Vetiselinenol, isolated as a colorless oil, was a bis-unsaturated bicyclic primary alcohol displaying a plain negative RD curve[8]: $[\alpha]_D$ = -22°; ms: 220 (P), 205, 189 (base), 161, 133; ν_{max}^{film} 3380, 1030-1040 (C-O-H); 3083, 1780, 1643, 890 (C=CH$_2$); ∼3055, 1658, 812 (-CH=C<); 1191, and 859 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 0.69 (CH$_3$, s), 1.01 (CH$_3$, d, 6.8 Hz), 1.94 (6H, W_h∼2.5 Hz), 2.0 - 2.5 (2H, m), 3.52 ($C\underline{H}_2OH$, apparent d, 6.2 Hz), 4.545 and 4.78 (C=CH$_2$), and 5.43 ppm (=CH-, W_h ∼ 8 Hz). In 1:1 CDCl$_3$-C$_5$D$_5$N the hydroxymethyl signal appeared as an AB of ABX pattern ($\Delta\nu_{AB}$ = 8.1, J_{AB} = 10.2, J_{AX} ∼ J_{BX} = 6.5 Hz). Irradiation at δ 1.94 (=C-C$\underline{H}_3$) transformed the =CH- signal to a sharp singlet and the C=CH$_2$ signals became a pair of doublets (J, 1.6 Hz). A -CH(CH$_3$)CH$_2$OH grouping was suggested by the significant m/e 161 fragment in the mass spectrum. Furthermore, irradiation at δ 2.25 produced a simple AB pattern for the -CH$_2$OH grouping and also collapsed the CH$_3$ doublet at δ 1.01. The downfield position of this methine signal (H-11) suggested its allylic position.

The 10-<u>epi</u>-eudesmane skeleton was demonstrated by conversion to (-)-δ-selinene (see chart) which was identical (in all respects but RD) to (+)-δ-selinene prepared from authentic (+)-β-selinene (from celery oil). The intermediate tosylate and diene (vetiselinene, II) showed the expected spectra. Chemical studies (given below) indicated a 6(7) or 7(8) double bond. The extreme upfield position of the angular methyl in vetiselinene suggests a <u>trans</u> ring fusion and suggests the 7(8)-position for the trisubstituted double bond. Hydrogenation of vetiselinene produced the antipode of 4,5αH-eudesmane confirming the <u>trans</u>-fusion.



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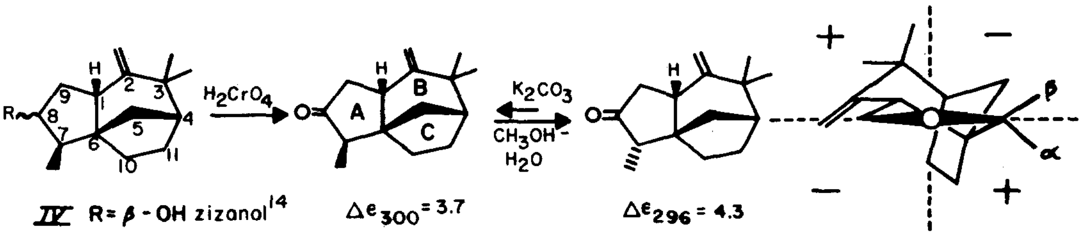
* The two epimeric cyclocopacamphenols were obtained as a mixture and identified by nmr and ir comparison with the reduction products of the corresponding esters.[7]

Gentle oxidation with insufficient Jones' reagent in acetone (at -30°) afforded a mixture from which unrearranged aldehyde III (ν 2700, 1728 cm.$^{-1}$-CHO) was isolated by column chromatography on neutral silica. A -CH(CH_3)CHO grouping was clearly indicated by the NMR spectrum (and confirmed by decoupling) $\delta_{TMS}^{CDCl_3}$: 0.70 (CH_3, s), 1.21 (CH_3, d, 6.8 Hz), 1.97 (b.s.), 2.98 (1H,-C<u>H</u>(CH_3)CHO, quartet of doublet, Jq = 7, $J_d \sim$ 1.6 Hz), 4.53 and 4.78 (C=CH_2, 2 b singlets), 5.50 (-CH=C$<$, b.s.), and 9.51 ppm (-C<u>H</u>O, d, J $\sim$ 1.7 Hz). The aldehyde shows a weak negative cotton effect ($\lambda_c \sim$ 293 nm) superimposed on the usual plain negative curve of the diene and its non-conjugated derivatives. The negative cotton effect observed for this β,γ-unsaturated aldehyde suggests the C-11 configuration shown (tentative only), assuming partial eclipsing of the carbonyl oxygen and the methyl group.[9]

Finally aldehyde III was treated under basic conditions affording a mixture of products. The -CH=C signals had completely disappeared from both the IR and NMR spectra of the product. The methyl doublet also vanished. The IR (C=C-C=O, 1668, and 1622 cm^{-1}) and UV spectrum (see chart) indicated a mixture of conjugated aldehyde and acid. NMR studies indicated that the exomethylene grouping was unaffected by the equalibration.

Zizanol (IV), isolated as a colorless oil, was a mono unsaturated tricyclic secondary alcohol displaying a positive RD curve: $[\alpha]_D$ = +28°; m.s.: 220 (P), 205, 202, 189, 159; 150 (base peak), 145, 133, 131[10]; ν_{max}^{film} 3360, 1047 (COH); 3086, 1783, 1639, 892 (C=CH_2); 1170, 1097, 1010, and 980 cm.$^{-1}$; $\delta_{TMS}^{CDCl_3} \sim$ 1.04 (CH_3, d), 1.06 (2 CH_3, s), 2.52 (H-1, m) 3.83 (1H,$>$C<u>H</u>OH, doublet of triplets; J_d = 3.1, J_t = 7.1 Hz), 4.56 and 4.73 ppm (C=CH_2, 2 triplets, 1.7 Hz). In C_6D_6 the CH_3 region of the NMR was clearer - both lines of the doublet CH_3 (δ 0.93) appearing upfield from the six proton singlet due to the gem-dimethyl (δ 1.045). The zizaene skelton, suggested by the $>$CH-C=CH_2 grouping and its behavior in NMDR experiments,[11] was confirmed via reduction ($LiAlH_4$/THF) of the tosylate which afforded a single hydrocarbon identified as zizaene (VI) by glc comparison (4 columns).[12] The coupling pattern of the $>$C<u>H</u>OH was consistent with either a C-8 or a C-11 hydroxyl.[13]

Oxidation afforded the corresponding cyclopentanone (VII): m.p. 51°, ν_{max}^{film} 1742, 1410 cm^{-1} (-CH_2CO-); $\delta_{TMS}^{CDCl_3}$ 1.086 (CH_3, s), 1.105 (CH_3 d 7.4 Hz), 1.131 (CH_3 s), 4.59 and 4.87 ppm (C=CH_2, 2 doublets).



IV R= β-OH zizanol[14]
V R= α-OH
VI R= H zizaene

$\Delta\epsilon_{300}$ = 3.7
VII

$\Delta\epsilon_{296}$ = 4.3
VIII

The proximity of the carbonyl and doublet-CH_3 was shown by a 0.2 ppm upfield shift in deuterobenzene. Reduction ($LiAlH_4/Et_2O$) afforded zizanol and epizizanol (IV:V = 72:28). Basic equilibration of ketone VII afforded a mixture (4:1) of ketones VIII and VII. The positive cotton effect of the original ketone and its epimer confirm the A/B trans-fusion and absolute stereochemistry. The greater amplitude for ketone VIII indicates the CH_3 group has moved to a positive octant on epimerization. Finally equilibration in deuterated solvents led products incorporating three deuterium atoms (M^+ 218 → 221) and the methyl doublet (of VIII) at δ 0.95 is replaced by a broad singlet. Our data does not allow a final decision between structures IV and V for zizanol and we choose to use that structure suggested by Yoshikoshi et al.[14]

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1. Acceptable combustion analyses or exact mass determinations confirm the molecular formula of all new substances. Rotation data, unless otherwise specified, was obtained in methanol solutions ($c \leq 0.1$).
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4. K. Morikawa and Y. Hirose, Tetrahedron Letters, 1799 (1969).
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6. NMR Collection of R. B. Bates (Univ. of Arizona).
7. F. Kido, R. Sakuma, H. Uda, and A. Yoshikoshi, Tetrahedron Letters, 3169 (1969).
8. Vetiselinenol samples of equal purity (as judged by glc, and NMR) had $[\alpha]_D$-values as high as +10°, but all showed the characteristic negative trend, $[\alpha]_{300} \sim -170°$.
9. The negative cotton effect is predicted either on the basis of an unperturbed carbonyl or by considering the β γ-unsaturated system as an inherently disymmetric chromophore. We did not pursue a chemical proof of stereochemistry at C-11 since we were informed of Professor Yoshikoshi's work on this compound that confirmed our tentative conclusions.
10. Mass spectrum similar to that of khusimol.
11. See "Vetiver Oil Constituents - IV" which follows.
12. Our glc methods have been published: N. H. Andersen, M. S. Falcone, J. Chromatog., 44, 52 (1969).
13. The numbering of Nigam et al. See G. A. Neville and I. C. Nigam, Tetrahedron Letters, 837 (1969) and references therein.
14. A. Homma, M. Kato, M-D. Wu, and A. Yoshikoshi, ibid, in press.