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STEREOSTRUCTURE OF VETIDIOL, A NEW ANTIPODAL SESQUITERPENE DIOL FROM VETIVER OIL; A NOVEL ROLE OF BIOLOGICAL ACTIVITY TO PREDICT THE POSITION AND STEREOCHEMISTRY OF ONE OF THE HYDROXYL GROUP

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Abstract - Several hithertounknown terpenoids have been isolated from North Indian Vetiver oil (Vetiveria zizanioides). The most interesting of these is a diol in which the position & stereochemistry of one of the hydroxyl groups could be correctly predicted from its biological activity. This prediction as well as the stereostructure of the diol has been confirmed from spectral data and chemical correlation with khusinol of known absolute configuration.

Recent work from our laboratory reports on the plant growth activity of terpenoids in general and terpenoid lactones in particular.[1] Extensive structure biological activity relationships have also been established.[2-4] The most important of these from a structure elucidation point of view is the observation[5,6] that in a cadinane the occurrence of a C-5 hydroxyl, C-6 ring junction hydrogen and C-7, 14 epoxy group with relative cis- β stereochemistry leads to biological activity in terms of root initiation in the hypoxotyl cuttings of Phaseolus aureus. Thus khusinoloxide 1, is biologically active and from the biological activity displayed by a recently isolated C_{14} antipodal terpenoid[6] 13 it was predicted that these stereochemical features must be present in the new compound and this prediction was proved to be so on the basis of chemical degradation & spectra data.

We have now isolated another new diol 2, $C_{15}H_{14}O_2$, m.p. 170° $[\alpha]_D^{30}$ -140° from North Indian Vetiver oil (Vetiveria zizanioides) which we propose to name vetidiol. In vetidiol the position & stereochemistry of one of the hydroxyl groups (β -oriented at C-5) was again predicted on the basis of biological activity & this was proved to be so on the basis of the correlation of vetidiol with khusinol of known absolute configuration.

Vetidiol in its IR spectrum displayed bands due to hydroxyl group (3500 cm^{-1}), exomethylene group (1642 & 895 cm^{-1}) and a trisubstituted double bond (840 cm^{-1}). The ^1H NMR spectrum displayed signals at δ (ppm) 0.78 and 0.90 (3H, each, d, J = 7 Hz Me_2 CH-),

1.8 (3H, s, $-\underset{|}{C}=\underset{|}{C}-CH_3$), 4.15 (1H, bm, $W_{\frac{1}{2}}$ 20 Hz, $-C\underline{H}OH$) 4.5 (1H,s, $W_{\frac{1}{2}}$ 6Hz $-C\underline{H}OH$) 5.05 and 5.2 (1H, each s, $C=CH_2$) and 5.6 (1H, bs, $-\underset{|}{C}=\underset{|}{C}-H$). On acetylation vetidiol afforded a liquid diacetate 3, $C_{19}H_{28}O_4$. These data, coupled with the formation of cadalene on dehydrogenation, showed that one hydroxyl group in vetidiol is axial while the other is equatorial. On epoxidation, vetidiol afforded a monoepoxide 4, $C_{15}H_{24}O_3$, m.p. 116° which was distinctly more active in generating root formation in the stem cuttings of Phaseolus aureus when compared with vetidiol. This, along with the results of dehydrogenation, led us to predict a cadinane skeleton for vetidiol & that one of the secondary hydroxyl groups may be located at C-5 and may be β -equatorial. This observation further suggested that the relative stereochemistry of the C-6 ring juncture hydrogen and the epoxy group is β . In keeping with these predictions the ditosylate derivative 5 on reduction with lithium aluminium hydride afforded (+)-α-cadinol[7] 6, which could be converted to (-)- γ -cadinene[8] 7 and then to the characteristic (+) - cadinenedihydrochloride 8.

The allylic nature and location of the β -axial hydroxyl group at C-8 was proved by the manganese dioxide oxidation of vetidiol to the hydroxy ketone 9 in which the exocyclic double bond is in conjugation with the keto group [(^{1}H NMR, δ 5.8 and 6.2, 1H each br S) and the presence of a broadened multiplet at 4.15 (1H, $W_{\frac{1}{2}}$ 20 Hz, - $C\underline{H}OH$)] . The location (C-5) and stereochemistry (β equatorial of the second hydroxyl group as inferred from biological activity was confirmed by a correlation with khusinol 11. On Wolff-Kishner reduction the hydroxy ketone 9 afforded an alcohol 10 with the expected double bond shift[9]. The alcohol 10 was found to be identical in all respects with isokhusinol prepared earlier[10] from khusinol. Modified Wolff-Kishner reduction[11] on the semicarbazone of 9 did not lead to the double bond shift and afforded a compound identical in all respects with khusinol. These data, therefore, show that vetidiol has absolute configuration 2. The results indicate that biological activity can indeed be used to predict some stereochemical features in a new compound which belongs to a series already evaluated biologically.

Experimental - Mps are uncorr. IR spectra were measured in $CDCl_3$ with TMS as internal standard.

Isolation of Vetidiol - Vetiver oil (10 kg) was chromatographed over $SiO_2/AgNO_3$ (15 kg) and was eluted with hexane, benzene, and then followed by ether. From the benzene fraction (250 g), carbonyl compounds were eliminated as their semicarbazones. The residual fraction (125 g) was chromatographed on $SiO_2/AgNO_3$ (10% 6.0 kg). Four fractions were collected by eluting the column with benzene-ether (19:1); (9:1); (8:2) followed by ether. Each fraction was further subjected to extensive chromatography followed by preparative TLC for the isolation of different compounds. Known terpenoids were identified from their mmp and comparison of IR spectra with authentic samples.

Fraction 1 (90 g, biologically inactive) afforded mainly khusinol 11.
Fraction 2 (50 g, biologically inactive) afforded khusol and other new epoxy alcohols.
Fraction 3 (35 g, biologically active) afforded khusinoloxide 1, isokhusinol-oxide 12, norkhusinoloxide 13 alongwith other new epoxy alcohols.
Fraction 4 (50 g, biologically inactive) afforded khusinoldiol 14, Cadina-4α, 10 β -diol 15, and vetidiol 2, $C_{15}H_{24}O_2$ (Found : C, 76.00; H, 10.14 $C_{15}H_{24}O_2$ requires : C, 76.22, H, 10.24%), m.p. 170°, $[\alpha]_D^{25}$ -140°.

Dehydrogenation of vetidiol - 150 mg of vetidiol (2) was sealed under vacuum in a glass tube with 150 mg of Pd/C (5%) and heated at 200° for 12 hr. PLC of the product afforded 100 mg cadalene whose TNB derivative, mp 113° was undepressed on admixture with an authentic specimen.

Acetylation of 2 - Acetylation of 250 mg of 2 with Ac_2O/Py at room temperature gave a diacetate 3, 255 mg. IR (cm^{-1}) 1738, 1650, 890 & 830. ^{1}H NMR (δ, ppm) 0.78 and 0.95 to d, J = 8Hz $(CH_3)_2$-CH-), 1.6 (bs, 3H-$\underset{|}{C}=\underset{|}{C}-CH_3$), 1.9 and 2.0 (bs,3H each -O-CO-CH_3), 4.6 and 5.0 (bs 1H each $>C=CH_2$), 5.1 (bm, 1H $W_{\frac{1}{2}}$ 20 Hz $C\underline{H}$-OAc),

5.3 (bs, 1H, CH-OAc) and 5.5 (bs, 1H - C=C-H). (Found: C, 71.20; H, 8.77. $C_{19}H_{28}O_4$ requires: C, 71.22; H, 8.81%).

Epoxidation of 2 - Epoxidation of 100 mg of 2 in $CHCl_3$ with excess PBA at 0° for 24 hr gave the epoxide 4, m.p. 124°, 125mg with usual IR & ^1H NMR features (absence of >C=CH$_2$ and presence of epoxy protons 2.30 d, 1H, J = 4Hz and 2.90 dd 1H J = 2 & 4 Hz) (Found: C, 71.40; H, 9.60. $C_{15}H_{24}O_3$ requires: C, 71.39; H, 9.59%).

(+)- α -Cadinol 6 from Vetidiol 2 - Dihydroxy epoxide 4 (0.2 g) in pyridine (5 ml) was reacted with TsCl (0.4 g) in pyridine (5 ml.). The crude tosylate (IR) was reduced with LAH under reflux for 20 hr. Chromatography of the product over SiO_2 gave (+)- α -cadinol m.p. 78° ,$[\alpha]_D^{25}$ + 52° (Lit.[7] m.p. 75°,$[\alpha]_D$ + 49°).

(-)- γ -cadinene 7 from vetidiol 2 - (+)- α -Cadinol (made above) (200 mg) was dissolved in a mixture of pyridine: benzene (2:1 , 5 ml). To this a solution of $POCl_3$ (1 ml) in benzene (3 ml) was added dropwise at room temp. After 2 hr. the product was isolated by usual work up, distilled and identified as (-)- γ -cadinene 7, by superimposable IR spectra with an authentic sample and conversion to crystalline dihydrochloride m.p. 118°$[\alpha]_D$ + 39°. Mixed m.p. with an authentic sample of (+)-cadinene dihydrochloride, (m.p.118°, $[\alpha]_D$ + 36°) remained undepressed.

Isokhusinol 10 from vetidiol 2 - Vetidiol 2, (450 mg) in hexane 20 ml was stirred with active MnO_2. After 24 hr the product was chromatographed over SiO_2 to afford 9 (400 mg) as a viscous liquid IR bands (cm^{-1}) at : 3450, 1640, 1610, 1700, 890 and 810. (Found: C, 76.78; H, 9.52. $C_{15}H_{22}O_2$ requires: C, 76.88; H, 9.46%), semicarbazone m.p. 188°.

A mixture of semicarbazone (0.4 g) diethylene glycol (10 ml) & KOH pellets (1.0 g) was heated for 2 hr (N_2 atmosphere) initially at 100° & then to 200°. Usual work up followed by chromatography afforded isokhusinol (300 mg), m.p.90° mixed m.p. with an authentic sample 90°.

Khusinol 11 from vetidiol 2 - A mixture of semicarbazone of hydroxyketone 9 (0.2 g) in toluene (20 ml) & potassium tertiary butoxide (1 g) was heated under reflux for 20 hr. The mixture was decomposed with water and the toluene layer was separated & made neutral & dried. Evaporation afforded a crystalline material identified as khusinol m.p. and mmp with an authentic sample 87°.

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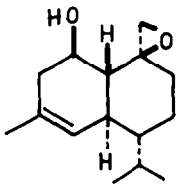

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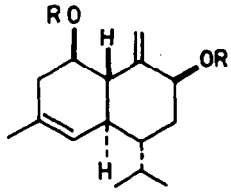

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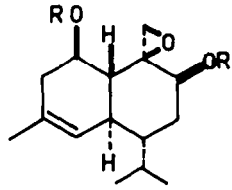

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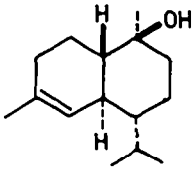

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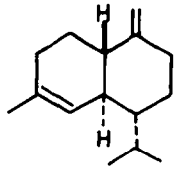

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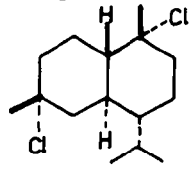

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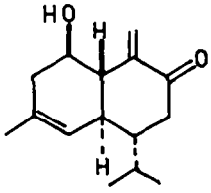

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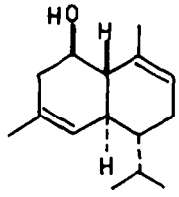

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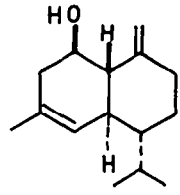

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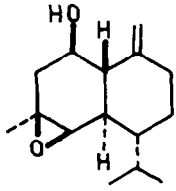

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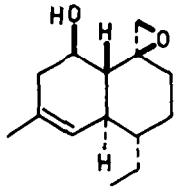

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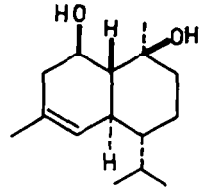

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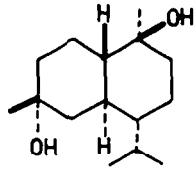

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