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THE STRUCTURE OF ZIZANOIC ACID, A NOVEL SESQUITERPENE IN VETIVER OIL[1]

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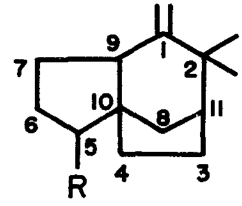
Isolation of acidic constituents from the essential oil of vetiver (*Vetiveria zizanoides* Stapf) has been reported by several investigators.[2-4] We have also isolated a sesquiterpene carboxylic acid from the essential oil of the vetiver cultivated in Japan. We propose the name zizanoic acid for this carboxylic acid[5] and wish to report evidence for its proposed structure I.

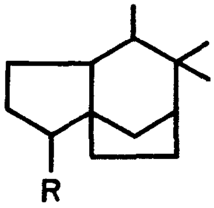
The acidic portion was extracted from the essential oil with aqueous alkali and purified, after conversion into methyl ester with diazomethane, by fractional distillation and chromatography on silica gel. Pure zizanoic acid,[6] $C_{15}H_{22}O_2$, was obtained, after alkaline hydrolysis of the methyl ester, in approximately 0.4% yield from the essential oil and showed the following properties: ν_{max}^{liq} 2600, 1700 (-COOH), 1640, 892 ($>C=CH_2$) cm^{-1}; δ^{CCl_4}[7] 1.05, 1.08 (s., 3H, each), 2.62 (q., 1H; $>C\underline{H}$-COOH), 4.53, 4.70 (t., 1H, each; $>C=CH_2$), 11.08 (s., 1H; -COOH); cyclohexylamine salt, m.p. 146° The methyl ester (II), $C_{16}H_{24}O_2$, b.p. 120-121°/1.8 mm, showed: $[\alpha]_D^{20}$ + 39.7° (c=1.2, MeOH); ν_{max}^{liq} 3056, 1732, 1639, 1385, 1356, 890 cm^{-1}; δ^{CCl_4} 1.03, 1.06 (s., 3H, each), 4.55, 4.70 (t., 1H, each), 3.60 (s., 3H); M^+=248.

Catalytic hydrogenation of methyl zizanoate (II) resulted in the uptake of one mole of hydrogen to give a saturated compound, methyl dihydrozizanoate (V), $C_{16}H_{26}O_2$, b.p. 125°/2.8 mm; ν_{max}^{liq} 1733 cm^{-1}; δ^{CCl_4} 0.78 (s., 3H), 0.78 (d., 3H, J=5), 0.84 (s., 3H), 2.46 (q., 1H), 3.54 (s., 3H); M^+=250. Consequently, zizanoic acid should be tricyclic.

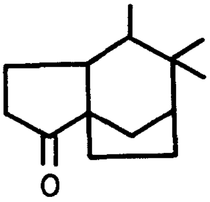
After methyl dihydrozizanoate (V) was reduced to an alcohol by LAH reduction, tosylation followed by LAH reduction of the latter gave a saturated hydrocarbon, zizane (VI), $C_{15}H_{26}$; ν_{max}^{liq} 1388, 1370, 1318, 1240, 1062, 962, 870 cm^{-1}; δ^{CCl_4} 0.75 (d., 3H, J=5), 0.78, 0.83 (s., 3H, each), 0.87 (d., 3H, J=7). Comparison of



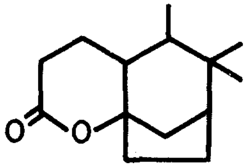
I; R=COOH
II; R=$COOCH_3$
III; R=CH_2OH
IV; R=CH_3



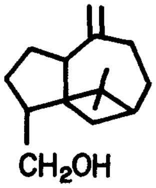
V; R=$COOCH_3$
VI; R=CH_3
VII; R=COOH
VIII; R=$COCH_3$
IX; R=OH



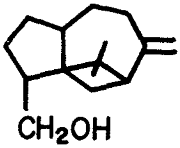
X



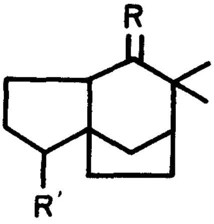
XI



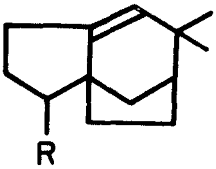
XIIa



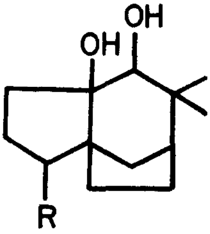
XIIb



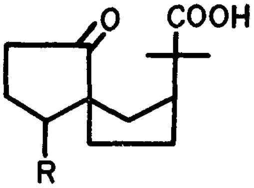
XIII; R=O, R'=$COOCH_3$
XIV; R=H,OH, R'=$COOCH_3$
XV; R=O, R'=CH_3
XVI; R=H,OH, R'=CH_3



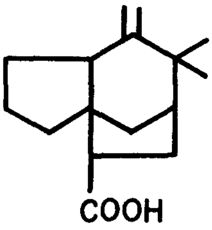
XVII; R=$COOCH_3$
XVIII; R=CH_3



XIX; R=CH_3
XX; R=$COOCH_3$



XXI; R=CH_3
XXII; R=COOH



XXIII

the IR spectrum of zizane (VI) with those of the known tricyclic, saturated sesquiterpene hydrocarbons[8)] showed that zizane has a new carbon skeleton.

Methyl zizanoate (II) was reduced to the unsaturated alcohol (III), $C_{15}H_{24}O$; $[\alpha]_D^{20}$+26.6° (c=1.0, MeOH); ν_{max}^{liq} 3325, 3056, 1640, 889 cm^{-1}; δ^{CDCl_3} 1.08, 1.10 (s., 3H, each), 3.61 (m., 2H), 4.63 (t., 1H), 4.75 (t., 1H); 3,5-dinitrobenzoate, m.p. 111.5-113°, and LAH reduction of the tosylate of the alcohol (III) yielded the parent hydrocarbon of zizanoic acid, zizaene (IV), $C_{15}H_{24}$; ν_{max}^{liq} 3060, 1642, 1378, 1363, 890 cm^{-1}; δ^{CCl_4} 0.95 (d., 3H, J=7), 1.04, 1.06 (s., 3H, each), 4.53 (t., 1H), 4.68 (t., 1H).

Neither zizanoic acid (I), methyl zizanoate (II) nor zizaene (IV) afforded any aromatic compound by dehydrogenation on selenium or palladium-carbon.

Dihydrozizanoic acid (VII) obtained by alkaline hydrolysis of the ester (V) was treated with methyl lithium to yield an epimeric mixture of the methyl ketones (VIII), and the latter gave a mixture of the epimeric alcohols (IX) by peracid oxidation followed by hydrolysis. One of the epimers (IX), $C_{14}H_{24}O$, m.p. 136°; ν_{max}^{KBr} 3300 cm^{-1}; δ^{CDCl_3} 0.77 (d., 3H, J=5), 0.82, 0.86 (s., 3H, each), 1.41 (s., 1H), 3.86 (d., 1H, J=4.6), crystallized from the mixture. The above mixture of alcohols was oxidized with Jones' reagent to give the ketone (X), $C_{14}H_{22}O$; ν_{max}^{liq} 1735, 1408 cm^{-1}; δ^{CCl_4} 0.82, 0.88 (s., 3H, each), 0.83 (d., 3H, J=5), thus indicating that the ring to which the carboxyl group of zizanoic acid is attached is five-membered. Peracid oxidation of the ketone (X) gave the crystalline δ-lactone (XI), $C_{14}H_{22}O_2$, m.p. 104.5-105.5°; ν_{max}^{KBr} 1732, 1412 cm^{-1}, whose NMR spectrum showed neither signal at field lower than 3 ppm nor methyl signal attributable to the $-O-\overset{|}{\underset{|}{C}}-CH_3$ grouping. This fact indicates that zizanoic acid bears neither hydrogen nor methyl group on C_{10}[9)]

The characteristics mentioned above are very similar to those reported for khusimol[10)], which has also been isolated from South Indian vetiver oil and assigned the provisional structures XIIa or XIIb.

The IR and NMR spectra of the unsaturated alcohol (III) were identical with those of khusimol. The methyl ester of the unsaturated acid[10)] obtained from khusimol by Jones' oxidation was also found to be identical with methyl zizanoate (II) by comparison of their spectra.

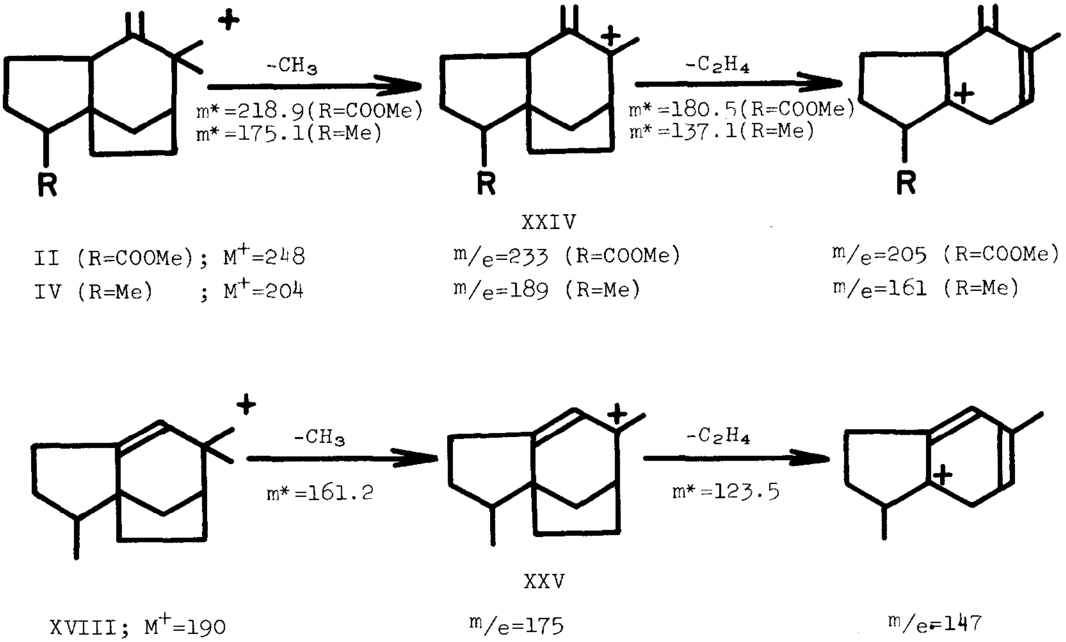
In order to explore the other rings, methyl zizanoate (II) was subjected to ozonolysis to yield the ketoester (XIII), $C_{15}H_{22}O_3$, m.p. 103.5°; $[\alpha]_D^{20}$ + 129.8° (c=1.0, dioxane); $\nu_{max}^{CHCl_3}$ 1723, 1705 cm^{-1}; δ^{CCl_4} 0.97, 1.17 (s., 3H, each), 3.60 (s., 3H), 3.02 (m., 1H), 2.56 (q., 1H), whose IR spectrum shows that the ring containing the keto group is strainless and no absorption of α-methylene adjacent to the keto group. The keto group of XIII appears to be hindered since it resisted peracid oxidation, however the ketoester (XIII) could be reduced to the hydroxy-ester (XIV). XIV was dehydrated with phosphorus oxychloride in pyridine to afford the unsaturated ester (XVII), $C_{15}H_{22}O_2$, m.p. 66°; ν_{max}^{KBr} 1728, 840 cm^{-1}; δ^{CCl_4} 0.97 (s., 6H), 4.84 (q., 1H), as almost the sole product. The nature of the double bond of XVII is trisubstituted ethylene as shown on IR and NMR spectra.

In order to eliminate ambiguity arising from probable skeletal rearrangement during the dehydration of XIV, the following transformations were examined. The unsaturated ester (XVII) was converted into the olefin (XVIII), $C_{14}H_{22}$; ν_{max}^{liq} 842 cm^{-1}; δ^{CCl_4} 0.87 (d., 3H, J=7), 0.95 (s., 6H), 4.81 (q., 1H), by the reaction sequence $-COOCH_3 \longrightarrow -CH_2OH \longrightarrow -CH_2OTs \longrightarrow -CH_3$. A mixture of epimeric ketones (XV), $C_{14}H_{22}O$; ν_{max}^{liq} 1708 cm^{-1}; M^+=206, was derived from XVIII by hydroboration-Jones' oxidation. On the other hand, the same mixture of the ketones (XV) resulted from Jones' oxidation of the alcohol (XVI) which was obtained from the hydroxy ester (XIV) by the same transformation sequence as mentioned above.

Deuteration introduced one deuterium atom into the ketone (XV) (deuterated XV: M^+=207), supporting the situations at C_2 and C_9 of zizanoic acid; one of the groups adjacent to the keto group in XV is methine and another is tertiary or bridge-head methine (non-enolizable).

The olefin (XVIII) was oxidized with osmium tetroxide to give the glycol (XIX), $C_{14}H_{24}O_2$, m.p. 94°; ν_{max}^{KBr} 3400, 3352 cm^{-1}, and the latter afforded the keto acid (XXI), $C_{14}H_{22}O_3$, m.p. 72-73°; $\nu_{max}^{CHCl_3}$ 1732, 1701, 1410 cm^{-1}, by oxidation with lead tetraacetate followed by Jones' oxidation. Similarly, the unsaturated ester (XVII) gave the diol ester (XX), $C_{15}H_{24}O_4$, m.p. 90°; ν_{max}^{KBr} 3480, 3400, 1727 cm^{-1}; δ^{CDCl_3} 1.03 (s., 6H), 3.66 (s., 3H), 2.68 (d., 1H, J=4.6), 3.16 (s., 1H), 3.32 (d., 1H, J=4.6), and the keto diacid (XXII), $C_{14}H_{20}O_5$, m.p. 153-153.5°; $\nu_{max}^{CHCl_3}$ 1740, 1709, 1407 cm^{-1}.

The methyl esters of these acids (XXI and XXII) showed the peak of m/e 102 $\left(\begin{smallmatrix}CH_3\\ CH_3\end{smallmatrix}\!>C=C<\!\begin{smallmatrix}OH^+\\ OCH_3\end{smallmatrix}\right)$ as base peak on their mass spectra, thus indicating that zizanoic



II (R=COOMe); M^+=248
IV (R=Me) ; M^+=204

XXIV
m/e=233 (R=COOMe)
m/e=189 (R=Me)

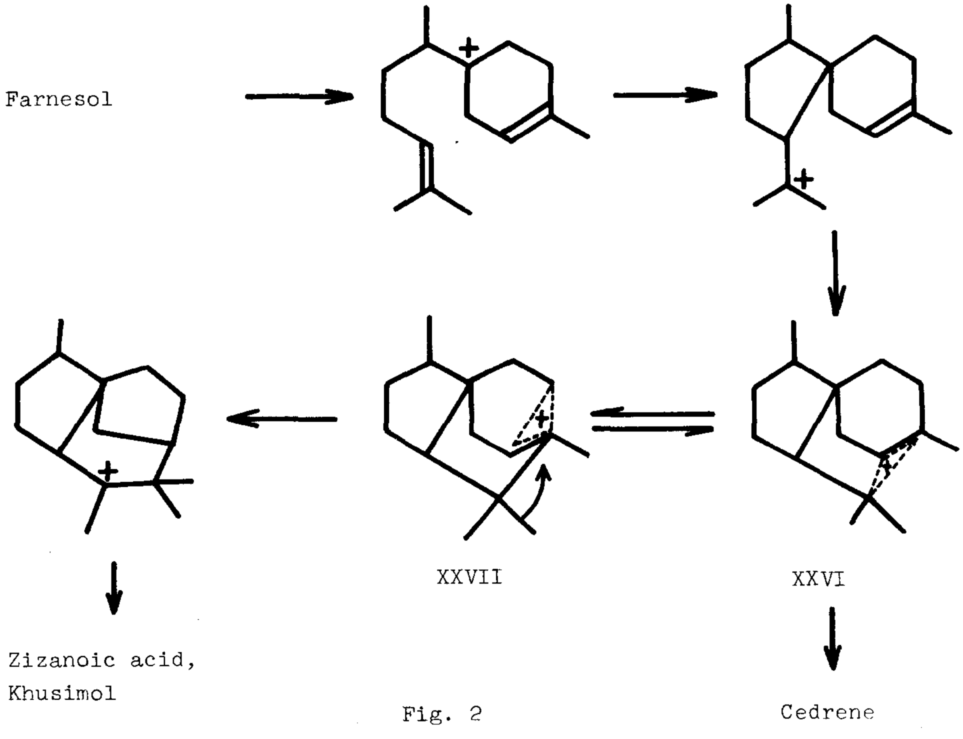
m/e=205 (R=COOMe)
m/e=161 (R=Me)

XVIII; M^+=190

XXV
m/e=175

m/e=147

Fig. 1



XXVII

XXVI

Fig. 2

acid bears a gem-dimethyl group on C_2. However, since the mass spectra do not show any prominent peak of m/e 115 (CH_2-CMe_2-$COOCH_3^+$), C_{11} of zizanoic acid appears to belong to the methine which constitutes the junction with the third ring rather than to the methylene group.

The mass spectra of zizaene (IV), methyl zizanoate (II), and the olefin (XVIII) were measured to distinguish the structure I from another structure XXIII possible for zizanoic acid. Fragmentations as shown in Fig. 1 are notably observed, but the peaks which correspond to ions formed by eliminations of substituted ethylenes from the allylic ions XXIV, XXV are negligible. Thus, the structure I and III are preferable for zizanoic acid and khusimol, respectively.

Further confirmation of the structure I and elucidation of the stereochemistry are in progress.

Fig. 2 shows a probable biogenetic pathway of zizanoic acid through the cations XXVI and XXVII or equivalent bicyclobutonium ions.

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