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INSECT REPELLENTS FROM VETIVER OIL: I. ZIZANAL AND EPIZIZANAL

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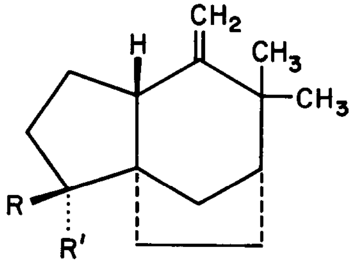
Abstract: On the basis of spectral data and partial syntheses, structures *1* and *2* are established for zizanal and epizizanal, two new insect-repelling aldehydes isolated from Javanese vetiver oil *(Vetiveria zizanoides).*

As part of our search for natural products of anti-insectan activity, we recently investigated vetiver oil, an extract of the roots of a grass *(Vetiveria zizanoides),* widely used in the perfume industry and purportedly repellent to insects.[1] Tests with a Javanese sample of the oil,[2] based on bioassays previously described,[3] showed the substance to have potent topical irritant activity on cockroaches and flies. Further testing showed this activity to be restricted largely to the carbonyl fraction (*ca.* 13%) of the oil, obtained using Girard reagent T.

Chromatography of this carbonyl fraction on silica gel, eluting with hexane and increasing amounts of methylene chloride, yielded seven fractions (A-G) of increasing polarity, all of which were found to be complex mixtures by GLC. Fractions A and G were inactive as insect repellents.



1 R = CHO, R' = H
2 R = H, R' = CHO
7 R = CO_2H, R' = H
8 R = CO_2CH_3, R' = H
9 R = CH_2OH, R' = H
10 R = H, R' = CO_2CH_3

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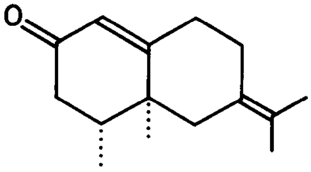
The most active fraction, B, which was eluted with 40:60 CH_2Cl_2/hexane, was twice chromatographed on 10% $AgNO_3$-silica gel to give a mixture of two new sesquiterpenes which we have named zizanal and epizizanal. These were separated and purified by GLC[4] and shown to have structures *1* and *2* as described below. Fractions D and F, eluted with 60:40 and 80:20 CH_2Cl_2/hexane respectively, contained the already well characterized ketones, α-vetivone[5] *(3)*, β-vetivone[6] *(4)*, khusimone[7] *(5)* and (+)-(1S,10R)-1,10-dimethylbicyclo[4.4.0]-dec-6-en-3-one[8] *(6)*. Compounds *1* through *6* all possess marked insect repellent properties.



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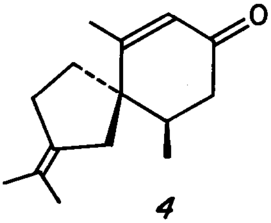

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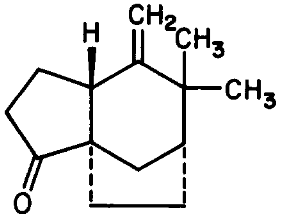

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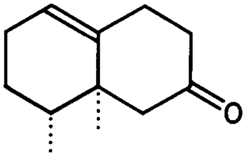

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Zizanal, a colorless oil, $[\alpha]_D^{20}$ + 69.5°(c 0.233 in $CHCl_3$), showed a parent peak corresponding to $C_{15}H_{22}O$ (*m/e* 218) in its mass spectrum. Its infrared spectrum indicated the presence of an aldehyde (1725, 2720 cm^{-1}) and an isolated exocyclic methylene group (3090, 1640, 892 cm^{-1}). These structural features were confirmed by its 300 MHz ^{1}H NMR spectrum in $CDCl_3$, which showed signals at δ 9.75 (1H,d,J=3 Hz) and at 4.59 (1H,t,J=1 Hz) and 4.74 (1H,t,J=1.5 Hz), corresponding to aldehydic and terminal methylene protons respectively. In addition, signals were observed for a *gem*-dimethyl group at δ 1.03 (6H,s), for two well separated methine protons at 2.35 (1H,m) and 2.57 (1H,m), and for a large group of alicyclic protons at 2.07 (1H,m), 1.94 (1H,d,J=11.4 Hz), 1.84 (1H,t,J=5.5 Hz), 1.32-1.81 (7H,m) and 1.05-1.17 (1H,m). Decoupling experiments revealed that the low field methine multiplet at δ 2.57 is due to a proton α to the aldehyde function, and that the multiplet at 2.35 corresponds to a proton allylic to the exocyclic methylene group.

The mass spectrum of zizanal[9] showed a base peak at *m/e* 91, and a fragmentation pattern which, when considered along with the ^{1}H NMR data, suggested that this compound is the aldehyde, *1*, corresponding to zizanoic acid *(7)*, previously isolated from oil of vetiver.[10] Comparison of the spectra of zizanal and zizanoic acid supported this hypothesis, which was confirmed by the synthesis of *1* *(vide infra)*.

Epizizanal, a colorless oil, $[\alpha]_D^{20}$ -5.9° (c 0.287 in $CHCl_3$), showed a mass spectra very similar to that of *1*. Other spectral data were as follows: IR ν max (film), 3090, 2715, 1720, 1638, 890 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 1.05 (3H, s), 1.09 (3H, s), 1.12-2.07 (11H,m), 2.47 (1H,m), 2.78 (1H,m), 4.58 (1H,bs), 4.78 (1H,m), 9.71 (1H,d,J=2.5 Hz). MS, *m/e* 218 (M^+,2), 189 (40), 148 (34), 133 (9), 119 (100), 105 (40), 93 (36), 91 (74), 79 (52), 77 (43), 67 (34), 55 (33), 41 (56), 39 (23).

These data indicated that epizizanal possesses a tricyclic sesquiterpene structure with the same skeleton and functionalities as *1*. The simplest hypothesis was that epizizanal is the aldehydic epimer, *2*, of zizanal.

The proposed structures for zizanal and epizizanal were confirmed by syntheses from zizanoic acid.[11] LAH reduction of methyl zizanoate *(8)*, followed by oxidation of the resulting alcohol *(9)* with PCC/CH_2Cl_2 gave *1*, whose spectra and biological properties were indistinguishable from those of the first-described vetiver aldehyde. The same reaction sequence, carried out on methyl epizizanoate *(10)*, gave the epimeric aldehyde *2*, again indistinguishable from our second aldehyde. Methyl epizizanoate *(10)* was obtained by refluxing *8* with $NaOCH_3$ in methanol to give a 1:1 equilibrium mixture of epimeric esters, from which *10* was separated by preparative GLC.[4]

The stereochemistry of zizanoic acid has been deduced by A. Yoshikoshi *et al.*[12] on the basis of a complex chemical degradation. We have verified the corresponding assignment for *1* itself by conducting difference NOE experiments on the synthetic aldehyde *1*.[13] Irradiation of the aldehydic proton in *1* produced enhancement of intensity of the two downfield methine absorptions at δ 2.35 and 2.57, while irradiation of either of these enhanced the intensity of the aldehydic proton along with other methylene protons. The interaction between the aldehydic proton and the bridgehead proton (δ 2.35) confirms the β-orientation of the aldehyde group in zizanal.[14]

Additional insect repelling activity is present in other carbonyl components from vetiver, and further examination of these substances is in progress. Data on the biological activity of the carbonyl compounds from vetiver oil, as well as a discussion of the possible bio-historial implications of the utilization of anti-insectan agents as human perfumes, will be given elsewhere.

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References and Notes:

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13. We thank Mr. Braden Roach for carrying out these experiments.
14. These studies on the chemistry of vetiver oil were presented at the American Chemical Society R. B. Woodward Memorial Symposium in New York, N.Y., August, 1981.

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