Rapid Paper

2(£)-(4-Methyl-3-pentenyl)-butenedial, \( \alpha \)-Acariadiol, a Novel Monoterpene from the Acarid Mite Tyrophagus perniciosus (Acarina, Acaridae)\(^1\)

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A novel monoterpene, 2(£)-(4-methyl-3-pentenyl)-butenedial (\( \alpha \)-acaridial (1) for the trivial name), was isolated from the secretion of the acarid mite Tyrophagus perniciosus. The structure was clarified in the light of spectral data, and the geometry of the double bond in the butenedial moiety was assigned based on the \( \gamma \)-deshielding effect on a methylene and on an aldehyde group. Coupling the Grignard reagent \((\text{CH}_3)_2\text{C}=\text{CHCH}_2\text{CH}_2\text{MgBr}\) to \(\text{THP-OCH}_2\text{(C = O)}\text{CH}_2\text{CH}_2\text{O-THP}\), and dehydration and deprotection of the \(\text{OH}\) groups gave \(\alpha-(£)\)- and \(\alpha-(Z)\)-acaridiol, which were fully assigned by MS and NMR. Matching the spectral data of the synthetic alcohols with those of the alcohol derived from the natural product, or of natural acaridial with those of synthetic \(\alpha-(E)\)- and \(\alpha-(Z)\)-acaridial, corroborated beyond all doubt the structure of this new monoterpene dial.

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Tyrophagus perniciosus Zachvatkin, 1941, an acarid mite closely related to the mold mite \(T. \) putrescentiae (Schranks, 1781), has been recently recorded in Japan as an economically important agricultural pest.\(^1\) The opisthonotal glands exudates of these mites differ both qualitatively and quantitatively as highlighted by their alarm pheromones\(^2,3\) and the occurrence of 2,3-epoxyneral\(^4\) and \( \beta \)-acaridial.\(^5\) Furthermore, \(T. \) perniciosus possesses a new monoterpene dial containing a butenedial moiety, whose structural characterization and synthesis is presented here; the possible biological significance will be discussed elsewhere.

TLC with hexane-ether (1:1) showed that the polarity of the isolated compound \((R_f 0.38)\) was between that of neral \((R_f 0.41)\) and \( \beta \)-acaridial \((R_f 0.28)\). The compound gave \(t_R\) 5.96 min and 38.88 min on CP-Sil and FFAP columns, respectively.

Low-resolution MS (Fig. 1A) displayed the molecular peak, which was found to be \(m/z\)

Fig. 1. MS Data.
The MS of the natural product (A) was identical to that of \(\alpha-(E)\)-acaridial (B) and differed from the one of \(\alpha-(Z)\)-acaridial (C).

\(^1\) Pheromone Study on Acarid Mites. Part XX. See ref. 4 for the previous paper.

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166.0983 by high-resolution, indicating the molecular formula \( \text{C}_{10}\text{H}_{14}\text{O}_{2} \) (requires \( m/z \) 166.0992).

NMR (500 MHz) showed two aldehydic protons at \( \delta \) 9.67 (s) and 10.17 (d, \( J = 7.54 \text{ Hz} \)). The other signals were a vinyl proton coupled to one of the aldehydes at 6.51 (d, \( J = 7.54 \text{ Hz} \)), a vinyl proton at 5.07 (apparent triple quintet, \( J = 7.74, 7.64 \) and 1.5 ppm), two methylenes at 2.71 (t, \( J = 7.14 \text{ Hz} \)) and 2.19 (q, \( J = 7.4 \text{ Hz} \)), and two methyls at 1.65 and 1.50 ppm.

That both aldehyde groups were conjugated was based on GC-FTIR (Fig. 2A), which exhibited one single carbonyl absorption band at 1712 ± 4 cm\(^{-1} \) (1690 cm\(^{-1} \) in 
\( \text{CCl}_4 \)). UV (hexane), \( \lambda_{\text{max}} \) 240 nm, \( \varepsilon = 23,500 \) confirmed this assignment.

These data suggested the structure 1 for this novel monoterpene, which we gave the trivial name \( \alpha \)-acaridial. The assignment of the \( E \)-geography was achieved by examining the CMR (Scheme 1). First, the methylene closer to the butenedial moiety appeared at 33.75 ppm (for comparison, that methylene of neral appeared at 32.5 ppm, and that of geranial — with no deshielding effect — did at 40.5 ppm). Secondly, one aldehyde at 191.15 ppm (the other at 195.02 ppm) confirmed the \( \gamma \)-effect of the methylene at 33.75 ppm (for comparison with neral and geranial, this signal appeared at ca. 190 ppm, while in \( \text{trans-2-hexenal} \) — without the \( \gamma \)-effect — it appeared at 194.15 ppm).

\( \alpha \)-Acaridial was synthesized by coupling the Grignard reagent \( (\text{CH}_3)_2\text{C}=\text{CHCH}_2\text{CH}_2\text{-MgBr} \) to 1,4-ditetrahydropyranoxy-2-oxobutane (Scheme 2). Dehydration of 1 and deprotection of the hydroxy groups gave a mixture of alcohols, which was separated by LC to give (\( E \))-II and (\( Z \))-II. Oxidation of (\( E \))-II with pyridinium chlorochromate adsorbed on alumina\(^6 \) gave \( \alpha \)-acaridial with the same NMR, MS (Fig. 1B), GC-FTIR (Fig. 2B), \( t_R \) on the two capillary columns and the same \( R_f \). The (\( E \))- and (\( Z \))-structures of the alcohols
a-Acaridial from *Tyrophagus perniciosus*

Fig. 3. MS Data.
Although the MS of \(\alpha-(E)\)-acaridiol (A) and \(\alpha-(Z)\)-acaridiol (B) showed the same peaks, they differed in the intensity of the peaks at \(m/z\) 41 and 69. The MS of the alcohol derived from the natural product (C) and that of \(\alpha-(E)\)-acaridial matched each other.

were assigned in three different ways. First, as in the case of nerol/geraniol, the (Z)-geometry favored the fragment at \(m/z\) 69 giving rise to a higher intense peak (Figs. 3A and 3B). Secondly, the (E)-isomer gave the shorter \(t_R\) (for comparison: nerol \(t_R\) 4.40 min and geraniol \(t_R\) 4.74 min) on the CP-Sil column. Finally, CMR showed the signal of the methylene closer to the butenediol at 28.24 ppm for (E)-II (nerol, 32.21 ppm) and at 35.82 ppm for (Z)-II (geraniol, 39.66 ppm). In addition, (E)-II exhibited the two alcohols at 66.38 ppm (reflecting no \(\gamma\)-effect) and 58.88 ppm (compressing the methylene at 28.24 ppm), whereas (Z)-II showed the signals at 61.05 and 58.83, which is evidence for a deshielding effect not on the methylene, but on each other.

In order to corroborate the assignment of the \(2(E)\)-geometry of the natural product, this was reduced with LiAlH\(_3\)OEt as before\(^5\) to give one single peak with the same retention time and MS as those of \(\alpha-(E)\)-acaridiol (Figs. 3A and 3C). Moreover, oxidation of \(\alpha-(Z)\)-acaridiol gave \(\alpha-(Z)\)-acaridial, which differed from the natural product in MS (Fig. 1C), \(t_R\) and \(R_f\).

In the light of these results, this novel—both synthetically and in nature—compound was fully assigned as \(2(E)-(4\text{-}methyl\text{-}3\text{-}pentenyl\text{-})\text{-butenedial}\).

\(\alpha\)-Acaridial was also identified in the bulb mite *Rhizoglyphus robini* Claparède, but not in other related mites, even of the same genus *Tyrophagus*.

**Experimental**

*Materials and Methods.* GLC was done on a Hitachi model 263-30 instrument with a CP-Sil capillary column (0.22 mm x 25 m, Chrompack) operated at a temperature programmed from 135 to 250°C at 4°C/min, and on a Yanaco model G 180 FTP, either with a 2% OV-1 packed column (3 mm x 0.75 m) operated at a temperature programmed from 100 to 250°C at 5°C/min or with an FFAP chemically bonded capillary column (0.25 mm x 25 m, Quadrex) operated at 110°C. Wako-gel C-200 was used for LC, and silica gel 60 HF\(_{254}\) (E. Merck, 5 cm x 20 cm, 0.25 mm in thickness) for TLC. MS was measured by a Hitachi M-80 B high-resolution mass spectrometer operated at 70 eV. IR were obtained with a JASCO IRA-1 instrument and by a Shimadzu GC-FTIR with an OV-1 bonded wide-bore column (0.53 mm x 25 m, df = 5 \(\mu\)m, Gasukuro Kogyo). NMR was done on a JEOL FX-100 instrument and on a Bruker 500 MHz with CDCl\(_3\) solutions. UV was obtained with a Shimadzu UV-240 UV-visible recording spectrometer. *Tyrophagus perniciosus* was reared as already reported,\(^2\) separated from the foodstuff and extracted with hexane as previously described.\(^4\) Two hundred and ten milligrams of hexane-extractable material (from 53 g of mites) was chromatographed on a silicic acid column by successively eluting with a stepwise hexane−ether mixture. The unknown compound, which was eluted in the hexane−ether (95:5) and (90:10) fractions (6 mg total), was further purified until it gave one single peak on CP-Sil and FFAP capillary columns, and one single spot on TLC.

**Synthesis**

7-Methyl-1-tetrahydropyranoxy-3-tetrahydropyranoxy-methyl-6-hexen-3-ol (I). To an ethereal solution (20 ml) of
the Grignard reagent, obtained from Mg (0.3 g, 12.5 mmol) and 1-bromo-4-methyl-3-pentene (2.27 g, 14 mmol) that was prepared by the Julia \textit{et al.} method,\textsuperscript{7} an ethereal solution (30 ml) of 1,4-dietathydropyranoxy-2-oxobutane (2.72 g, 10 mmol) was slowly added. The mixture was stirred for 0.5 hr and hydrolyzed by pouring into an ice-cooled saturated solution of NH$_4$Cl (150 ml). The aqueous phase was extracted four times, and the combined ethereal solution was washed with brine and dried over anhydrous sodium carbonate. After filtration, evaporation of the solvent and purification on an SiO$_2$ column, I was obtained (3.1 g, 87\%). IR $\nu$$_{max}$ 1030 cm$^{-1}$ (also 3500). MS (M$^+$-73) at m/z 283 (1.6\%) and base peak at m/z 85. Other peaks were: 41 (16), 55 (8), 69 (10), 101 (2), 152 (2), 157 (6), 170 (5), 188 (8), 241 (10), 254 (7) and 272 (5). NMR (100 MHz) $\delta$: 5.1 (1H, t, $\nu$=6.8 and 6.4 Hz), 4.6 (2H, br. s), 3.2~4.2 (9H, m), 2.0~2.3 (2H, m), 1.9 (2H, t, $\nu$=6.8 and 6.4 Hz), 1.3~1.68 (20H, m). CMR (25.1 MHz) $\delta$: 131.17, 124.65, 99.63, 98.87, 73.24, 64.14, 62.19, 35.86, 30.66, 30.77, 25.68, 25.41, 19.56, 19.39 and 17.66.

\textit{$\alpha$-($\text{E}$)-Acaridiol. A 50 ml flask, charged with dry pyridine (5 ml) and I (0.85 mg, 2.4 mmol), was flushed with nitrogen and then fitted with a serum cap. Phosphorus oxychloride (3.5 ml) was added via a syringe while stirring in an ice-cooling bath. After 20 min., the cooling bath was removed and the mixture was stirred for 2 hr more. Pyridine (1 ml) and hexane (50 ml) were added, and the mixture was washed with water and dried over anhydrous sodium sulfate. At this point, the reaction yield (88\%) was measured by GLC-OV-1, by comparing the ratio of the product (t$_R$ 20.94 min) to the starting material (t$_R$ 23.38 min) peaks. Attempts to dehydrate I at higher temperatures (70$^\circ$C or 50$^\circ$C), by adding smaller amounts of POCl$_3$ (1.5 ml or 2 ml) or by omitting additional stirring, all gave lower yields (<40\%). The hydroxy groups were deprotected with $\beta$-toluenesulfonic acid in methanol as before.\textsuperscript{5} Chromatography on silica gel afforded $\alpha$-($\text{E}$)-acaridiol (188 mg, 46\%) and $\alpha$-($\text{Z}$)-acaridiol (74 mg, 18\%) along with $\beta$-acaridiol. $\alpha$-($\text{E}$)-Acaridiol gave t$_R$ 11.32 min (CP-Sil) and MS as shown (Fig. 3A). NMR (500 MHz) $\delta$: 5.69 (1H, t, $\nu$=6.85 Hz), 5.11 (1H, m), 4.21 (2H, d, $\nu$=6.85 Hz), 4.09 (2H, s), 2.05~2.20 (4H, m), 1.69 and 1.61 (3H each, s). CMR $\delta$: 142.34, 132.76, 124.72, 123.57, 66.38, 58.88, 28.24, 27.19, 25.68 and 17.75. $\alpha$-($\text{Z}$)-Acaridiol gave t$_R$ 11.46 min (CP-Sil) and MS as shown (Fig. 3B). NMR $\delta$: 5.64 (1H, t, $\nu$=6.87), 5.11 (1H, m), 4.21 (2H, d, $\nu$=6.87), 4.18 (2H, s), 2.02~2.20 (4H, m), 1.69 and 1.61 (3H each, s). CMR $\delta$: 143.71, 132.22, 126.75, 123.68, 61.05, 58.83, 35.82, 26.71, 25.68 and 17.75. $\alpha$-($\text{E}$)-Acaridial (1). To a solution of $\alpha$-($\text{E}$)-acaridiol (170 mg, 1 mmol) in hexane (20 ml), pyridinium chlorochromate adsorbed on alumina (2.2 g), which was prepared by the method of Cheng \textit{et al.},\textsuperscript{6} was added. After stirring for 1.5 hr, the solid was filtered, washed with hexane and the solvent distilled off. The resulting oily material was chromatographed on silica gel to yield I (42 mg, 25\%). Its spectral data were identical to those of the natural product.

\textbf{References}