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PERYDISCOLIC ACID, A GERMACRANOLIDE FROM *PERYMENIUM* SPECIES*

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Key Word Index—*Perymenium discolor*; *P. mendezii* var. *mendezii*; Compositae; sesquiterpene lactones; melampolide; 14-acetoxydesacetyl laurenobiolide; kaurane derivatives.

Abstract The chemical investigation of two *Perymenium* species afforded, in addition to known kaurane derivatives and 14-acetoxydesacetyl laurenobiolide, a new sesquiterpene, perydiscolic acid. The structures were elucidated by spectroscopic methods and a few chemical transformations.

INTRODUCTION

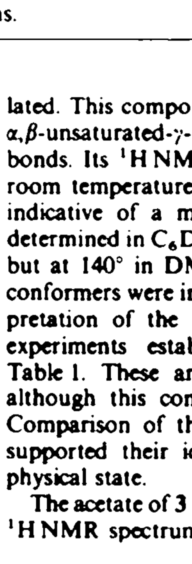
In a recent revision of the *Perymenium* genus from Mexico and Central America, a total of 33 species with 13 varieties have been recognized [1]. So far, from the three chemically analysed species *ent*-kaurane and eudesmane derivatives, together with a melampolide, have been isolated [2–4]. As a contribution towards the clarification of the chemotaxonomy of this genus, we have investigated two additional *Perymenium* species.

RESULTS AND DISCUSSION

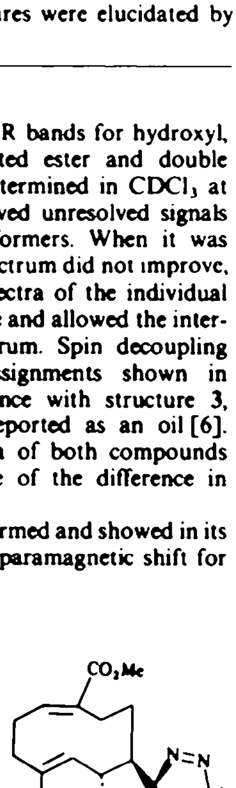
The aerial parts of *P. discolor* Schrader afforded *ent*-kaur-16-en-19-oic acid, *ent*-16α-hydroxykauran-19-oic acid, *ent*-16α-hydroxykauran-19-al [5] as well as the new melampolide **1**. The ^{1}H NMR spectrum of **1**, $C_{15}H_{18}O_4$ (EIMS), showed two doublets at δ6.13 (J = 3.5 Hz) and 5.9 (J = 3 Hz) corresponding to the exomethylene protons of an α,β-unsaturated-γ-lactone (IR 1762 cm^{-1}). The signal of the proton under the lactone closure appeared as a double doublet at δ4.55 (J = 10.5, 9.5 Hz) coupled with a double doublet at δ5.09 (J = 10.5, 1.5 Hz) assigned to a vinylic proton. This last proton was also coupled to a methyl group, which was responsible for a doublet at δ1.86 (J = 1.5 Hz). The above-mentioned data established the structural sequence from C-4 to C-7 shown in **1**. The remaining signals were a broad triplet at δ6.82 (J = 7 Hz) whose chemical shift together with the IR bands at 3300–2400 (br), 1687 and 1628 cm^{-1} revealed the presence of an *E*-double bond conjugated with a carboxyl group. Structure **1** with a melampolide skeleton was assigned to this compound, for which we propose the trivial name perydiscolic acid. The presence of the carboxyl group was proved by formation of the pyrazoline methyl ester **2**, in whose ^{1}H NMR spectrum the signals for the methoxyl group as well as those corresponding to the pyrazoline were clearly discernible.

From *P. mendezii* DC. var. *mendezii* only the germacrolide 14-acetoxydesacetyl laurenobiolide (**3**) was isolated. This compound exhibited IR bands for hydroxyl, α,β-unsaturated-γ-lactone, saturated ester and double bonds. Its ^{1}H NMR spectrum determined in $CDCl_3$ at room temperature (Table 1) showed unresolved signals indicative of a mixture of conformers. When it was determined in C_6D_6 at 72° the spectrum did not improve, but at 140° in DMSO-d_6 the spectra of the individual conformers were indistinguishable and allowed the interpretation of the resultant spectrum. Spin decoupling experiments established the assignments shown in Table 1. These are in concordance with structure **3**, although this compound was reported as an oil [6]. Comparison of the spectral data of both compounds supported their identity in spite of the difference in physical state.

The acetate of **3** (**4**) was easily formed and showed in its ^{1}H NMR spectrum the expected paramagnetic shift for



1



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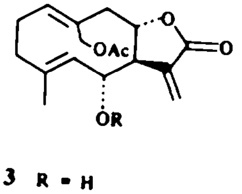

3 R = H
4 R = Ac
5 4α,5β-epoxide, R = H
6 4β,5α-epoxide, R = H

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Table 1. ^{1}H NMR spectral data of compounds 3–6 (80 MHz, $CDCl_3$, TMS as internal standard)

H	3	3*	3†	4†	5	6
1	5.25 (*br*)	4.75 *t* (*br*)‡	5.33 *t* (*br*) 8	5.32 *t* (*br*) 8	5.65 *t* (*br*) 8.5	5.54 *t* (*br*) 8.5
5	4.82 *d* (*br*) 9	4.54 *d* (*br*)‡	4.94 *d* (*br*) 8	4.97 *d* (*br*) 9	2.54 *d* 9	2.73 *d* 4
6	3.75–4.5 *br*‡	3.45–3.9 *br*‡	4.06 *dd*‡ 9.5, 8	5.18 *t* 9	3.43 *dd* 10, 9	4.09 *dd* 11, 4
7	2.7–3.2 *br*	2.72 *dd* (*br*) 13, 3.5	3.39 *dddd* 9.5, 5, 2.6, 2.2	3.18 *dddd* 9, 5, 3, 2.7	3.04 *dddd* 10, 5, 3.2, 2.9	3.05 *m*‡
8	3.75–4.5 *br*‡	3.45–3.9 *br*‡	4.15 *ddd*‡ 12, 5, 3.5	4.29 *ddd* 11, 5, 3.5	4.07 *ddd* 11, 5, 3.5	4.52 *ddd*‡ 11, 5, 3.5
13	6.35 (*dd*) 3.5, 1	6.36 *dd* 3, 1.5	6.13 *dd*‡ 2.6, 1.5	6.13 *dd* 3, 1	6.45 *dd* 3.2, 1.5	6.42 *dd* 3, 1.5
13′	6.12 *br* 6.03 *br*	5.90 *br*	6.11 *dd*‡ 2.2, 1.5	5.81 *dd* 2.7, 1	6.26 *dd* 2.9, 1.5	6.09 *dd* 2.5, 1.5
14	4.51 *s* (*br*)	4.34 *s* (*br*)	4.54 *s*	4.53 *s*	4.63 *s*	4.61 *s*
15	1.56 *br* 1.77 *br*	1.25 *s* (*br*)	1.63 *d* 1.3	1.64 *d* 1.5	1.30 *s*	1.52 *s*
OAc	2.06 *s*	1.71 *s*	2.03 *s*	2.01 *s* 2.03 *s*	2.10 *s*	2.05 *s*

*Run in C_6D_6 at 72°.

†Run in DMSO-d_6 at 140°.

‡Partially superimposed signal.

H-6, localizing the hydroxyl at C-6. Several attempts to oxidize this allylic alcohol (MnO_2, pyridinium dichromate) were unsuccessful. Nevertheless, more drastic conditions (Jones reagent) gave a mixture of the epoxy-alcohols **5** and **6**. This fact supports structure **3** since it is known that some allylic alcohols produce epoxyketones in a stereospecific process, which takes place *cis* to the hydroxyl group [7]. Although in this case the hydroxyl group could not be oxidized, the formation of two epoxides with different stereochemistries at C-4 and C-5 supports the existence of two principal conformers for **3**. The major epoxide (**5**) results from the conformation with the C-4 methyl group above the plane, while **6** comes from the conformer with the opposite orientation for this methyl group. The same mixture of epoxides **5** and **6** was obtained upon MCPBA oxidation of **3**.

EXPERIMENTAL

Ground, dried aerial parts (1.2 kg) of *P. discolor* Schrader, collected in Oaxaca, México (voucher deposited at the herbarium of the Instituto de Biologia, UNAM, MEXU 359549), afforded 29, 18.5 and 13.7 g of crude residues after extraction with hexane, hexane–EtOAc (3:2) and EtOAc–Me_2CO (1:1). The hexane residue gave, after successive CC (silica gel Merck G), *ent*-16α-hydroxykauran-19-oic acid (195.1 mg), kaur-16-en-19-oic acid (1.5 g) and *ent*-16α-hydroxykauran-19-al (25 mg). The remaining syrups (hexane–EtOAc and EtOAc–Me_2CO) were combined and percolated through bentonite ('Tonsil' [8]) with hexane, hexane–EtOAc (3:2) and EtOAc. Successive CC (silica gel Merck G; hexane–EtOAc, 7 : 3; with vacuum) afforded 217 mg **1**. Yellow gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300–2400, 1762, 1687, 1628, 979; ^{1}H NMR (80 MHz, $CDCl_3$): δ6.82 (1H, *t* (*br*), $J_{1,2} = J_{1,2'}$ = 6 Hz, H-1), 5.90 (H, *dd*, $J_{5,6}$ = 10.5, $J_{5,15}$ = 1.5 Hz, H-5), 4.55 (1H, *dd*, $J_{5,6}$ = 10.5, $J_{6,7}$ = 9.5 Hz, H-6), 6.13 (1H, *d*, $J_{7,13}$ = 3.5 Hz, H-13), 5.92 (1H, *d*, $J_{7,13'}$ = 3 Hz, H-13′), 1.86 (3H, *d*, $J_{5,15}$ = 1.5 Hz, H-15); EIMS *m/z* (rel. int.): 262 $[M]^+$ ($C_{15}H_{18}O_4$, 3.7), 248 $[M - Me]^+$, 244 $[M - H_2O]^+$, 206 $[M - HCO_2H]^+$, 91 (50.5), 84 (85.9), 81 (71.5), 53 (100).

Pyrazoline methyl ester **2**. An ethereal soln of CH_2N_2 was added dropwise to a cold soln of **1** (103 mg) in EtOH (10 ml) until the reaction was completed. The solvent was removed and the reaction mixture purified by CC (silica gel Merck G; hexane–EtOAc, 7:3; with vacuum) to give 26.8 mg **2**. Mp 155–157°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1773, 1705, 1631, 1602, 981; ^{1}H NMR (80 MHz, $CDCl_3$): δ6.73 (1H, *t* (*br*), $J_{1,2} = J_{1,2'}$ = 7 Hz, H-1), 5.03 (1H, *dq*, $J_{5,6}$ = 11, $J_{5,15}$ = 1.5 Hz, H-5), 5.59 (1H, *dd*, $J_{5,6}$ = 11, $J_{6,7}$ = 9.5 Hz, H-6), 1.93 (3H, *d*, $J_{5,15}$ = 1.5 Hz, H-15), 4.66 (1H, *t*, *J* = 8 Hz, H-A), 4.68 (1H, *dd*, *J* = 9.5, *J* = 7 Hz, H-A′), 3.70 (3H, *s*, OMe); CIMS *m/z* (rel. int.): 319 $[M + 1]^+$ ($C_{17}H_{22}N_2O_4$), 303 $[M + 1 - 16]^+$, 291 $[M + 1 - N_2]^+$, 275 $[M + 1 - CO_2]^+$ (100), 259 $[M + 1 - HOAc]^+$, 241 $[259 - H_2O]^+$, 231 $[291 - HOAc]$ (27.9), 213 $[231 - H_2O]^+$ (52.8), 185 $[213 - CO]$ (54.5).

14-*Acetoxydesacetyl laurenobiolide* (**3**). Ground, dried aerial parts (180 g) of *P. mendezii* DC. var. *mendezii*, collected in Oaxaca, México (voucher deposited at the herbarium of the Instituto de Biologia, UNAM, MEXU 410457), afforded, after extraction with hexane, $CHCl_3$ and Me_2CO, 2.5, 1.9 and 2.2 g of extracts, respectively. The $CHCl_3$ extract was percolated through bentonite ('Tonsil' [8]) eluting with $CHCl_3$ (fractions 1–3; 25 ml each), EtOAc (100 ml) and Me_2CO (100 ml). Fractions 2 and 3 gave, after crystallization ($CHCl_3$–hexane), 775 mg 14-acetoxy-desacetyl laurenobiolide (**3**). Mp 125–126°, $[\alpha]_D + 29.41°$ (*c* 0.153; $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 1753, 1732, 1650; EIMS *m/z* (rel. int.): 306 $[M]^+$ $C_{17}H_{22}O_5$ (0.6), 264 $[M - C_2H_2O]^+$ (0.6), 246 $[M - HOAc]^+$, 228 $[246 - H_2O]^+$, 84 (60.1), 43 (100).

Acetylation of **3**. A soln of **3** (99.6 mg) in C_5H_5N (1 ml) and Ac_2O (1 ml) was left to stand for 5 min and worked up as usual, affording 48 mg **4**. Colourless gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1758, 1733, 1655; CIMS *m/z* (rel. int.): 321 $[M + H - CO]^+$, 305 $[M + H - CO_2]^+$, 289 $[M + H - HOAc]^+$, 261 $[289 - CO]^+$ 245 $[289 - CO_2]^+$, 229 $[M + H - 2HOAc]^+$ (100), 201 $[229 - CO]^+$.

Oxidation of 3. Jones reagent was added dropwise to a cold (0°) soln of 3 (108 mg) in Me_2CO (10 ml). The mixture was kept at 0° for 30 min and worked up in the usual fashion. TLC of the crude product gave two spots, which were separated by silica gel CC (Merck G; hexane–EtOAc, 7:3; with vacuum). The first eluted fractions gave 9 mg **6**. Colourless gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 1765, 1739, 1658; EIMS *m/z* (rel. int.): 322 $[M]^+$ $C_{17}H_{22}O_6$ (0.6), 280 $[M - C_2H_2O]^+$ (0.6), 251 $[M - C_3H_3O_2]^+$, 43 (100). The more polar component (24 mg) could not be induced to crystallize. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3582, 1762, 1739, 1660; EIMS *m/z* (rel. int.): 322 $[M]^+$ $C_{17}H_{22}O_6$ (0.7), 306 $[M - O]^+$ (0.7), 280 $[M - C_2H_2O]^+$, 251 $[M - C_3H_3O_2]^+$, 43 (100).

Epoxidation of 3. MCPBA (31 mg) was added to a soln of 3 (48 mg) in $CHCl_3$ (10 ml). The soln was left to stand for 2 hr. TLC of the reaction mixture revealed the presence of epoxides **5** and **6**, which were separated as above to give 17 mg **5** and 7 mg **6**.

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