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FIVE NEW LABDANE DITERPENE OXIDES FROM *EUPATORIUM JHANII**

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Key Word Index—*Eupatorium jhanii*; Compositae; labdane diterpene oxides; jhanol; jhanidiol; jhanol acetate jhnidiol-18-monoacetate; jhanidiol diacetate.

Abstract—Five new labdane diterpene oxides jhanol, jhanidiol, jhanol acetate, jhanidiol-18-monoacetate and jhanidiol diacetate were isolated from the aerial parts of *Eupatorium jhanii*.

INTRODUCTION

From species of *Eupatorium*, several sesquiterpene lactones with cytotoxic activity [1–67] and a number of interesting flavonoid compounds [7–11] have been isolated. However, there is not much information about the presence of diterpenoid compounds in this genus [12,13].

In the present communication, we report the isolation and structural determination of five hydroxylated derivatives of 8,13-epoxylabd-14-ene (manoyl oxide) from *Eupatorium jhanii*.

RESULTS

The first free alcohol isolated was jhanol, $C_{20}H_{34}O_2$, (**1a**). Spectral and chemical data showed it to be a primary alcohol: IR 3480 cm^{-1}, ^1H NMR two doublets, J 11 Hz at 3.14 and 3.45; it gave an acetate and was oxidized to the aldehyde **1c**.

The presence of a vinyl group, suggested by the IR spectrum (bands at 3080, 1640, 980 cm^{-1}), was confirmed by the ^1H NMR spectrum which exhibited the signals characteristic of this group: a set of three quartets at 4.95, 5.15 and 5.92 ppm [14].

The remaining oxygen atom must be part of an ether bridge connecting two fully substituted carbon atoms; the IR spectrum showed strong absorption at 1120 cm^{-1} while there was no ^1H NMR signal for a hydrogen geminal to the oxygen. This spectrum also showed two methyl singlets at 1.31 and 1.35 ppm (Me—C(0)) and two more at 0.80 and 0.88 ppm. Consequently jhanol is probably a compound belonging to the 8,13-epoxylabdene series.

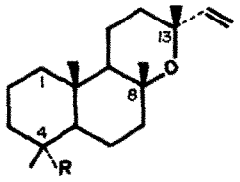
This was proved by Huang-Minlon reduction of the aldehyde **1c**, affording two substances identified as 8,13-epoxylabdane (**2a**) [15,16] and 8,13-epoxylabd-14-ene (**1d**) [17,18]. Comparison of the methyl carbon-13 NMR signals of the jhanol acetate with those of manoyl oxide (**2a**), Table 1, showed that **1b** is an 18-hydroxyditerpene. The C-18, C-19 and C-20 methyls of manoyl oxide [19,20] and also of other tri and tetracyclic diterpenes resonate at different field positions, near to 33, 20 and 15 ppm [21–23]. On the other hand, the ^{13}C-NMF (SFORD) spectrum of **1b** showed only two quartets, at 17.80 and 15.23 ppm, and a new triplet at 72.5 ppm. The stereochemistry at C-4, depicted in **1b**, was corroborated by the ^1H-NMR spectrum because both the methyl and oxymethylene signals occupy different field positions in the two possible structures [24,25]. The position of the aldehyde signal for **1c** is typical of equatorial substituents [26].

Table 1. ^{13}C-NMR spectra of manoyl oxide (**1d**) jhanol acetate (**1b**) and jhanidiol-18-monoacetate (**3b**)

Carbon No	1d	1b	3b
1	39.12	38.61	79.14
2	18.62	17.20	28.89
3	42.23	35.93	34.04
4	33.32	36.56	36.22
5	56.55	50.64	49.26
6	20.03	19.95	19.73
7	43.40	43.01	42.77
8	75.09	74.89	74.80
9	55.60	56.05	55.86
10	37.11	37.02	42.91
11	51.41	15.42	18.49
12	35.73	35.93	35.30
13	73.25	73.28	73.28
14	148.07	148.04	147.96
15	110.21	110.23	110.28
16	28.71	78.52	28.81
17	25.58	25.43	25.69
18	33.40	72.99	72.49
19	21.39	17.80	16.91
20	15.41	15.83	11.71

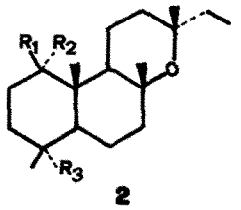
* Part 33 in the series "Chemistry of the Compositae". For Part 32 see: A. G. González, J. Bermejo, J. L. Bretón, G. Martínez, B. Domínguez, J. M. Amaro, *J. Chem. Soc. Perkin I* 1976, 1663.

The most polar diterpene of this series, jhanidiol (**3a**), had the empirical formula $C_{20}H_{34}O_3$; its polarity and the ^{1}H-NMR spectrum, which showed signals for protons under the hydroxyls at 3.14*d*, 3.45*d* and 3.41*t* ppm, suggested the presence of a primary and a secondary alcohol; according to the conditions, this compound gave the monoacetate **3b** or the diacetate **3c**. Comparison of the ^{1}H-NMR resonances of **1a** and **3a** made it obvious that the only difference between these compounds was the existence of an additional OH group in **3a**. Oxidation of monoacetate **3b** to the ketone **3d** and Huang–Minlon reduction yielded an alcohol identical with jhanol (**1a**).



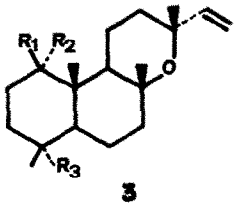
1

a R=CH_2OH
b R=CH_2OAC
c R=CHO
d R=Me



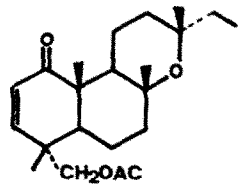
2

a R_1=R_2=H R_3=CH_3
b R_1=R_2=H R_3=CH_2OAC
c R_1 R_2=O R_3=CH_2OAC



3

a R_1=OH R_2=H R_3=CH_2OH
b R_1=OH R_2=H R_3=CH_2OAC
c R_1=OAC R_2=H R_3=CH_2OAC
d R_1 R_2=O R_3=CH_2OAC
e R_1 R_2=O R_3=CHO
f R_1 R_2=O R_3=COOH



4

Analyses of the ^{13}C-NMR spectrum of **3b** indicated the position and stereochemistry of oxymethine hydrogens. In the expoylabdane [19,20] and also in other series of diterpenes, C-2, C-6 and C-11 triplets were found near 20 ppm; the resonance signals of C-1, C-3, C-7 and C-12 appeared much lower in the field [21–23]. Comparison of the secondary carbon resonances of **1b** and **3b** suggested that one of the latter's carbons must be substituted The paramagnetic shift undergone by C-2 (11.7) and C-10 (5.9), together with the diamagnetic one experienced by C-3 (11.9) and C-20 (4.12 ppm) clearly point to C-1 as the locus of the hydroxyl group with an equatorial orientation [27]. The ^{1}H-NMR spectrum of **3c** corroborated this conclusion, showing the oxymethine resonance as a clear quartet at 4.53 ppm. Moreover, the spectra of all the oxidation products of **3a** had signals for the equatorial proton at C-11 [28].

Jhanidiol did not form an acetonide nor did the ketoacid **3f** show β-ketoacid properties. Bromination and dehydrobromination of ketodihydroacetate **2c** afforded the enone 4 which presented the characteristic ^{1}H-NMR signals for a Δ^2-1-one [29], in full accord with structure **3a**. Jhanol acetate (**1b**), jhanidiol-18-monoacetate (**3b**) and jhanidiol diacetate (**3c**) were also found as natural products in the plant.

EXPERIMENTAL

Mp's are uncorr. Optical activities were taken in $CHCl_3$, ^{1}H-NMR spectra on a 90 MHz and ^{13}C-NMR on a 20 MHz instrument in $CDCl_3$ with TMS as internal reference. Column and dry column chromatography was performed on Si gel.

Isolation of the diterpenes. Air-dried aerial part of the plant *Eupatorium jhanii* Robinson (4 kg) collected at El Delgadito (Mérida, Venezuela) in June, was finely cut and Soxhlet extracted several times with EtOH. Combined filtered ethanolic extracts were concentrated *in vacuo* and chromatographed on a Si gel column. Petrol, petrol–EtOAc and EtOAc eluted a mixture of diterpenes, triterpenes and flavones which was rechromatographed on dry column, yielding the following diterpenes, in the order of elution: jhanol acetate (**1b**), jhanidiol diacetate (**3c**), jhanidiol-18-monoacetate (**3b**), jhanol (**1a**), jhanidiol (**3a**).

Jhanol acetate (**1b**). **1b** (400 mg) was isolated as a liquid; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3080, 1720, 1640, 1120, 990, 920; NMR δ 0.88 (6H, *s*, $C_{10}C_{20}$), 1.31 and 1.35 (each 3H, *s*, C-14 and C-17), 2.10 (3H, *s*), 3.68, 3.90 (each 1H, *d*, *J* 11 Hz, C-18), 4.97 (1H, *q*, J 11 Hz, *J* 2 Hz), 5.17 (1H, *q*, *J* 17 Hz, *J* 2 Hz), 5.94 (1H, *q*, *J* 11 Hz, *J* 17 Hz); MS: *m/e* (%) 348 (1) (M^+), 333, 273, 255, 191, 149 (100), 135. Identical to that obtained from jhanol by standard acetylation.

Jhanidiol acetate (**3c**). **3c** (500 mg was isolated as a liquid; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3080, 1720, 1110, 980, 920; NMR. δ 0.80 (3H, *s*), 0.96 (3H, *s*), 1.20 (3H, *s*), 1.26 (3H, *s*), 1.96 (3H, *s*), 2.02 (3H, *s*), 3.67, 3.84 (each 1H, *d*, *J* 11 Hz), 4.53 (1H, *q*, *J* 9 and 5 Hz), 4.94 (1H, *q*, *J* 11 and 2 Hz), 5.12 (1H, *q*, *J* 17 and 2 Hz), 5.86 (1H, *q*, *J* 17 and 11 Hz). Identical to the product obtained by acetylation of jhanidiol. MS: *m/e* (%) 391 (M^+-15), 331, 271, 253, 223, 201, 189, 176, 174, 149 (100), 133.

Jhanidiol-18-*monoacetate* (**3b**). **3b** (1200 mg) was isolated as a liquid; IR ν_{max}^{KBr} cm^{-1}: 3330, 3080, 1740, 1640, 1240, 1120, 980, 920; NMR: δ 0.82, 0.88, 1.24, 1.29, 2.06 (all 3H, *s*), 3.38 (1H, *q*, $W_{1/2}$ 14 Hz), 3.62, 3.84 (each 1H, *d*, *J* 11 Hz), 4.92 (1H, *q*, *J* 11 and 2 Hz), 5.14 (1H, *q*, *J* 17 and 2 Hz), 5.80 (1H, *q*, *J* 17 and 11 Hz); MS: *m/e* (%) 364 (1) (M^+), 349 (100), 331, 313, 271, 253, 223, 201, 188, 149.

Jhanol (**1a**). **1a** (2.3 g) was isolated as a solid; mp 139–141° $[\alpha]_D$ + 27° (*c* 0.65); IR ν_{max}^{KBr} cm^{-1}: 3480, 3080, 1640, 1120, 980, 930; NMR: δ 0.80, 0.88, 1.31, 1.35 (each 3H, *s*), 3.15, 3.47 (each 1H, *d*, *J* 11 Hz), 4.95 (1H, *q*, *J* 11 and 2 Hz), 5.15 (1H, *q*, *J* 17 and 2 Hz), 5.92 (1H, *q*, *J* 17 and 11 Hz); MS: *m/e* (%) 306 (1) (M^+), 291, (98), 273, 261, 255, 243, 208, 177 (100), 151, 149, 147, 135, 133, 123, 121. (Found: C 78.30; H 10.89. $C_{20}H_{34}O_2$ requires: C 78.38; H 11.18%).

Jhanidiol (**3a**). **3a** (4.0 g) was isolated as a solid; mp 189° $[\alpha]_D$ +90° (*c* 0.8); IR ν_{max}^{KBr} cm^{-1} 3460, 3080, 1640, 1120, 990, 920; NMR: δ 0.78, 0.92, 1.28, 1.34 (each 3H, *s*), 3.14, 3.45 (each 1H, *d*, *J* 11 Hz), 3.41 (1H, *t*, $W_{1/2}$ 14 Hz), 4.95 (1H, *q*, *J* 11 and 2 Hz), 5.15 (1H, *q*, *J* 17 and 2 Hz), 5.92 (1H, *q*, *J* 17 and 11 Hz); MS: *m/e* (%) 322 (0.5), (M^+), 307 (100), 289, 271, 259, 231, 224, 206, 193, 189, 175, 173, 161, 159, 149, 137. (Found: C 74.18; H 10.71. $C_{20}H_{34}O_3$ requires: C 74.49: H 10.63%).

Oxidation of jhanol. Pyridinium chlorochromate (1.5 g) was suspended in dry CH_2Cl_2 (20 ml) and jhanol (290 mg) in CH_2Cl_2 (15 ml) was added once to the stirred sol. After 1 hr, dry Et_2O (20 ml) was added and the supernatant decanted from the black gum formed. The insoluble residue was washed 3 × with 30 ml portions dry Et_2O. Combined CH_2Cl_2–ether sol was passed through a short column of Celite and solvent removed by distillation, giving 8,13-epoxylabd-14-en-al (210 mg) (**1c**); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3080, 2700, 1720; NMR: δ 0.85, 1.04, 1.28, 1.31 (each 3H, *s*), 4.94 (1H, *q*, *J* 11 and 2 Hz), 5.12 (1H, *q*, *J* 17 and 2 Hz), 5.89 (1 H, *q*, *J* 17 and 11 Hz) and 9.18 (1 H, *s*).

Huang–Minlon reduction of 8,13-*epoxylabdan*-18-*al.* $N_2H_4.H_2O$ was added to a soln of **1c** (210 mg) in diethylene glycol (14 ml) and the mixture refluxed for 90 min (temp. 130°). After the addition of KOH pellets (300 mg), refluxing continued for a further 45 min. Then the temp was raised to 210° by distillation of the excess water–hydrazine and the refluxing continued for another 3 hr. The usual work-up afforded a mixture of 2 products which were separated by dry column chromatography, using petrol–C_6H_6 (4:1) as eluent. 8,13-*Epoxylabdane* (dihydromanoyl oxide) (2a) (65 mg); isolated as a liquid $[\alpha]_D$ + 3° (*c* 1.1) Lit + 5.9; NMR: δ 0.78, 0.80, 0.85 (*t*), 0.86, 1.18, 1.29 (each 3H, *s*) 8, 13-*Epoxylabd*-14-*ene* (manoyl oxide) (**1d**). **1d** (95 mg) was isolated as a solid; mp 26–28° $[\alpha]_D$ + 11 (*c* 2.0) Lit 22.5–26.5 $[\alpha]_D$ + 19 ; NMR; δ 0.83 (6H, *a*), 0.90, 1.31, 1.33 (each 3H, *s*), 4.94 (1H, *q*, *J* 11 and 2 Hz), 5.16 (1H, *q*, *J* 17 and 2 Hz), 5.92 (1H, *q*, *J* 17 and 11 Hz); MS: *m/e* (%) 290 (1) (M^+), 275 (100), 257, 245, 192, 177, 149, 137.

Partial acetylation of jhanidiol. To a soln of **3a** (700 mg) in C_5H_5N (2 ml), cold Ac_2O (3 ml) was added and the mixture was left for 10 min. The usual work-up gave a mixture of diacetate (70 mg), monoacetate (410 mg) and unaltered starting material, which was separated by dry column chromatography, using C_6H_6–EtOAc (9:1) as eluent. The diacetate and 18-monoacetate of jhanidiol were identical to the natural products obtained.

Oxidation of jhanidiol monoacetate (**3b**). **3b** (410 mg) was oxidized as described above for **1a**. 18-acetate-1-keto-8,13-epoxylabd-14-ene (400 mg) was obtained; mp 87–89°; $[\alpha]_D$ +70°; IR ν_{max}^{KBr} cm^{-1}: 3090, 1735, 1700, 1240, 1120, 990, 920, 910; NMR: δ 1.05, 1.21, 1.30, 1.35 (each 3H, *s*), 2.06 (3H, *s*), 2.8 (1H, *m*), 3.74, 3.98 (each 1H, *d*), 4.93 (1H, *q*), 5.13 (1H, *q*), 5.93 (1H, *q*); NMR: δ (benzene-d_6) 0.72, 0.92, 1.20, 1.36 (each 3H, *s*), 3.58, 3.76 (each 1H, *d*), 4.93 (1H, *q*), 5.26 (1H, *q*), 5.97 (1H, *q*); MS: *m/e* (%) 362 (1) (M^+), 347, 269, 224, 200, 191, 173, 167, (100).

Jhanol from jhanidiol. The above substance **3d** (300 mg) was reduced under Huang–Minlon conditions. Work up gave jhanol: mp, mixed mp and IR superimposable.

Hydrogenation of **3d**. **3d** (400 mg) was dissolved in EtOAc (20 ml) and hydrogenated for 1 hr over Pd/C(5%) at room temp and atm press. This gave **2c** (350 mg); NMR: δ 0.85 (3H, *t*, *J* 6 Hz), 1.04 (3H, *s*), 1.21 (6H, *s*) and 1.32 (3H, *s*).

Bromination of keto-18-*acetoxy*-8,13-*epoxy-labdane.* A soln of trimethylphenylammonium tribromide (400 mg) in dry THF (6.ml) was added in drops while stirring a soln of **2c** (350 mg) in the same solvent until the mixture turned yellow and it was then stirred at room temp for a further 30 min. The reaction mixture was poured into H_2O, extracted with CH_2Cl_2 and the solvent was evaporated, yielding a Br derivative (300 mg) which did not crystallize; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1700, 1120, 960; NMR: δ 0.82 (3H, *t*, 6 Hz), 1.02 (3H, *s*), 1.18 (6H, *s*), 1.30 (3H, *s*), 2.03 (3H, *s*), 2.8 (1H, *m*), 3.64, 3.72 (each 1H, *d*), 4.12 (1H, *m* $W_{1/2}$ 27 Hz).

Dehydrobromination of 1-*keto*-2β-*bromo*-18-*acetoxy*-18,13-*epoxylabdane.* A mixture of Li_2CO_3 (400 mg), LiBr (250 mg), DMF (15 ml) and C_6H_6 (6 ml) was heated until the H_2O and C_6H_6 had been eliminated. Then a soln of bromide (300 mg) in DMF (15 ml) was added and the reaction mixture refluxed for 1 hr under N_2. The cooled soln was poured into H_2O, extracted with CH_2Cl_2 and washed with 10% aq HOAc, sat aq $NaHCO_3$ and H_2O. After the solvent was evaporated, the residue afforded 1-keto-18-acetoxy-8,13-epoxy-labd-2-ene (**4**); mp 84–88°; $[\alpha]_D$ +46°; UV λ_{max}^{EtOH} nm: 223 (*c* 22000); IR $\nu_{max}^{CHCl_3}$ cm^{-1}; 1730, 1700, 1680, 1120, 950; NMR; δ 0.84 (3H, *t* *J*6 Hz), 1.02 (3H, *s*), 1.20 (6H, *s*), 1.32 (3H, *s*), 2.03 (3H, *s*), 2.75 (1H, *m*, $W_{1/2}$ 27 Hz), 3.71, 3.50 (each 1H, *d*, *J* 11 Hz), 5.82 and 6.32 (each 1H, *d*, *J* 11 Hz).

8,13-*Epoxy-labd*-14-*en*-1-*keto*-18-*al* (**3e**). **3a** (100 mg) was oxidized as described above for **1a**, giving **3e** (80 mg); mp 88–93°; $[\alpha]_D$ +62; M^+ 318; IR ν_{max}^{KBr} cm^{-1}. 3080, 2700, 1720, 1700, 1640, 1260, 1130, 990, 960, 920, 895; NMR: δ 1.23, 1.27, 1.30, 1.35 (each 3H, *s*), 2.78 (1H, *m*), 4.92 (1H, *q*), 5.11 (1H, *q*), 5.86 (1H, *q*).

Oxidation of keto-aldehyde (**3f**). **3e** (100 mg) dissolved in Me_2CO (min quantity) was treated dropwise with Jones' reagent and left at room temp for 3 hr, upon which MeOH was added to destroy any excess reagent. The mixture was poured into water and extracted as usual, giving **3f**; mp 206–209°; $[\alpha]_D$ +33° (*c* 0.57); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500–2500 (br) 1700, 1640, 1110; NMR: δ 1.17, 1.29 (each 3H, *s*), 4.90 (1H, *q*), 5.12 (1H, *q*), 5.88 (1H, *q*); MS: *m/e* (%) 319 (100) (M^+-15), 256, 186, 173, 149.

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