

## NEW DITERPENES FROM *SIDERITIS CANARIENSIS*\*

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**Key Word Index**—*Sideritis canariensis*; Labiatae; diterpenes; ribenol [3 $\alpha$ -hydroxy-(–)-13-epimanoyl oxide]; 7 $\beta$ -acetoxy-18-hydroxytrachylobane; (–)-13-epimanoyl oxide.

**Abstract**—Two new diterpenes ribenol [3 $\alpha$ -hydroxy-(–)-13-epimanoyl oxide] (I) and 7 $\beta$ -acetoxy-18-hydroxytrachylobane (IX) as well as the known (–)-13-epimanoyl oxide (IV) have been isolated from *Sideritis canariensis* Ait.

### INTRODUCTION

*Sideritis canariensis* Ait. is a good source of natural diterpenoids. In previous papers we reported the isolation of the known diterpenes (–)-kaurene, dehydroabietane and epican-dicandiol<sup>1</sup> as well as of the new natural products trachinol, trachinodiol, trachylobane,<sup>1</sup> tiganone,<sup>2</sup> vierol and powerol.<sup>3</sup> From the same plant we have also obtained the new cou-marin siderin and the lignan (+)-sesamin.<sup>4</sup> The present communication describes the isolation and structure elucidation of two further diterpenes: ribenol [3 $\alpha$ -hydroxyl-(–)-13-epimanoyl oxide] (I) and 7 $\beta$ -acetoxy-18-hydroxytrachylobane (IX).

### RESULTS AND DISCUSSION

Ribenol (I) has the molecular formula C<sub>20</sub>H<sub>34</sub>O<sub>2</sub> as determined by MS. Its IR spectrum shows the presence of a hydroxyl, a *gem*-dimethyl, and a vinyl group (3090, 1650, 990, 910 cm<sup>-1</sup>), suggesting also the possible existence of an ether bridge (strong bands between 1100 and 1000 cm<sup>-1</sup>). The NMR spectrum exhibits signals for a vinyl group, a proton geminal to a secondary equatorial hydroxyl, and five angular methyl groups. The spectro-scopic behaviour indicates that I has a labdane oxide structure. The Me-C<sub>8</sub> and Me-C<sub>13</sub> resonances at 8.78 and 8.88  $\tau$  prove the vinyl group to be axial.<sup>5</sup> Hence, ribenol must possess the skeleton of (–)-13-epimanoyl oxide or of its enantiomorph. I yielded the monoacetate II, of empirical formula C<sub>22</sub>H<sub>36</sub>O<sub>3</sub>, in the NMR spectrum of which the proton geminal to the acetoxy group appears as a triplet at 5.40 (W<sub>1/2</sub> 18 Hz), thus confirming that the OH in ribenol is equatorial. Oxidation of I with Jones reagent to the ketone III and subsequent

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<sup>1</sup> GONZÁLEZ, A. G., BRETÓN, J. L., FRAGA, B. M. and LUIS, J. G. (1971) *Tetrahedron Letters* 3097.

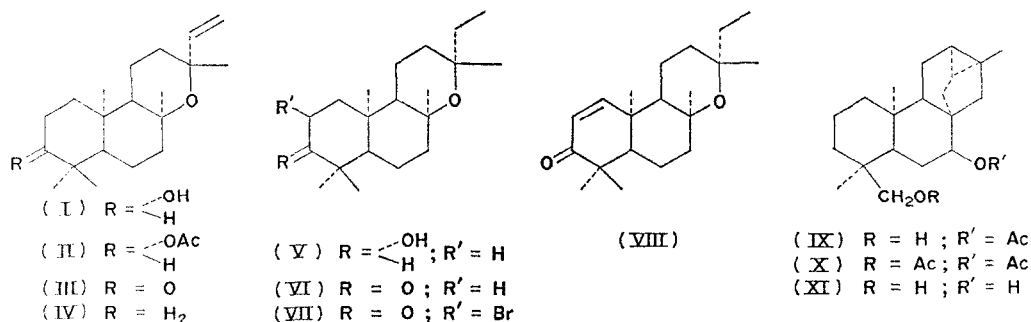
<sup>2</sup> GONZÁLEZ, A. G., BRETÓN, J. L., FRAGA, B. M. and LUIS, J. G. (1971) *Anal. Quím.* **67**, 1245.

<sup>3</sup> GONZÁLEZ, A. G., FRAGA, B. M., HERNÁNDEZ, M. G. and LUIS, J. G. (1973) *Tetrahedron* in press.

<sup>4</sup> GONZÁLEZ, A. G., FRAGA, B. M., HERNÁNDEZ, M. G. and LUIS, J. G. (1972) *Phytochem.* **11**, 2115.

<sup>5</sup> BOWER, C. L. and ROWE, J. W. (1967) *Phytochem.* **6**, 151.

Huang-Minlon reduction afforded (—)-13-epimanoyl oxide (IV),<sup>6</sup> identified through its physical constants and by comparison of the IR spectrum with that of an authentic sample. Compound IV was also isolated as natural product from this plant.



In order to determine the position of the hydroxyl in I it was hydrogenated to V followed by oxidation to VI. The ketone was then brominated with trimethylphenylammonium tribromide to give VII in which the configuration of the bromine is established as axial considering that the IR absorption of the carbonyl is the same as in VI.<sup>7</sup> Dehydrobromination of VII with LiBr–Li<sub>2</sub>CO<sub>3</sub> in dimethylformamide yielded the enone VIII which presents the characteristic bands of an  $\alpha,\beta$ -unsaturated ketone (1660 cm<sup>-1</sup> and 235 nm). Its NMR spectrum shows two vinyl proton doublets at 2.80 and 4.08 (*J* 10 Hz) which indicate that the keto group is situated at C<sub>1</sub> or C<sub>3</sub>. Position 1 can be discarded taking into account that between  $\tau$  7 and 8 the NMR spectra of the ketones III and VI do not exhibit signals for the equatorial proton at C<sub>11</sub>.<sup>8</sup> Further, the chemical shifts of the Me groups at C<sub>2</sub> in ribenol (I) and its acetate (II) are in agreement with those reported for triterpenes with equatorial OH at C<sub>3</sub>.<sup>9</sup>

7 $\beta$ -Acetoxy-18-hydroxytrachylobane (IX) has IR absorptions indicative of a hydroxyl, an ester and a cyclopropane ring. The NMR spectrum reveals the presence of a hydroxymethylene and an acetate group, a proton geminal to the acetate, and three angular Me groups. Acetylation of IX gave X, identical in all respects (m.m.p., TLC, IR, NMR) with the diacetate prepared from trachinodiol (XI).<sup>1</sup> On the other hand, partial hydrolysis of trachinodiol diacetate yielded a monoacetate which proved to be identical with the natural product IX. Hence, IX must be 7 $\beta$ -acetoxy-18-hydroxytrachylobane.

#### EXPERIMENTAL

The m.ps, determined on a Kofler block, are uncorrected. Solvent used for recrystallizing compounds was MeOH unless otherwise stated. The optical activities were measured in CHCl<sub>3</sub>, the NMR spectra on a 60-MHz instrument in CDCl<sub>3</sub> if not otherwise indicated, with TMS as internal reference. The acetates were prepared with Ac<sub>2</sub>O in pyridine at room temp. overnight. Column chromatography was performed on silica gel 0.2–0.5 mm and dry column chromatography on silica gel 0.05–0.2 mm; the spray reagent for TLC was H<sub>2</sub>SO<sub>4</sub>–H<sub>2</sub>AcOH–H<sub>2</sub>O (1:20:4).

<sup>6</sup> CROSS, B. E., GALT, R. H. B., HANSON, J. R., CURTIS, P. J., GROVE, J. F. and MORRISON, A. (1963) *J. Chem. Soc.* 2937.

<sup>7</sup> JONES, R. N., HUMPHRIES, P., HERLING, F. and DOBRINER, K. (1952) *J. Am. Chem. Soc.* **74**, 2820.

<sup>8</sup> BHACCA, N. S. and WILLIAMS, D. H. (1964) *Applications of NMR Spectroscopy in Organic Chemistry*, p. 66, Holden-Day, San Francisco.

<sup>9</sup> GONZÁLEZ, A. G., BRETÓN, J. L. and FRAGA, B. M. (1971) *Rev. Latinoam. Quím.* **2**, 167; and references therein.

**Isolation of the diterpenes.** The air-dried aerial part of the plant (4.5 kg), collected on the Monte de las Mercedes (Tenerife) was chopped and extracted several times with EtOH in a Soxhlet. The combined extracts were filtered in cold, concentrated *in vacuo* and chromatographed on a column using light petrol., light petrol.-C<sub>6</sub>H<sub>6</sub>, C<sub>6</sub>H<sub>6</sub>-EtOAc and EtOAc as eluents. The various fractions obtained were rechromatographed on dry columns obtaining the following substances, in order of elution: trachylobane; dehydroabietane and (–)-kaurene,<sup>1</sup> separated by dry column chromatography on silica gel with 20% AgNO<sub>3</sub>; (–)-13-epimanoyl oxide (IV); trachinol;<sup>1</sup> an unidentified pentacyclic triterpene; a mixture of sterols; (+)-sesamin;<sup>4</sup> ribenol (I); 7β-acetoxy-18-hydroxytrachylobane (IX); siderin;<sup>4</sup> vierol;<sup>3</sup> trachinodiol and epicandicandiol,<sup>1</sup> separated by dry column chromatography on silica gel with 20% AgNO<sub>3</sub>; powerol;<sup>3</sup> and finally a mixture of steroidal glycosides.

(–)-13-*Epimanoyl oxide* IV, m.p. 100–100.5°, [α]<sub>D</sub> –38° (c, 1.51) (lit.,<sup>6</sup> 98–99.5°, [α]<sub>D</sub> –37°). IR spectrum superimposable with that of an authentic sample.

*Ribenol* [3α-hydroxy-(–)-13-epimanoyl oxide] I, (1.9 g) m.p. 84–86°, [α]<sub>D</sub> –31° (c 0.21), ν<sub>max</sub><sup>CHCl<sub>3</sub></sup> 3610, 3090, 1650, 1395, 1385, 1100, 990, 910 cm<sup>–1</sup>. NMR: 3.90 (1H, *q*, *J* 10 and 18 Hz), 4.90 (1H, *dd*, *W*<sub>1/2</sub> 10 Hz), 5.10 (1H, *dd*, *W*<sub>1/2</sub> 4 Hz), 6.80 (1H, *t*, *W*<sub>1/2</sub> 18 Hz, CHOH), 8.78, 8.88 and 9.05 (each 3H, *s*; 3 Me), 9.29 (6H, *s*; 2 Me). MS: *m/e* 306 (2%, M<sup>+</sup>; C<sub>20</sub>H<sub>34</sub>O<sub>2</sub> requires: 306), 291 (100%), 273, 255, 208, 207, 190, 175, 135, 121. 3α-*Acetate* II, m.p. 132–134°, [α]<sub>D</sub> –49° (c 1.32). (Found: 75.59; H, 10.44. C<sub>22</sub>H<sub>36</sub>O<sub>3</sub> requires: 75.41; H, 10.25%). ν<sub>max</sub><sup>CHCl<sub>3</sub></sup> 3090, 1720, 1390, 1380, 1050, 990, 890 cm<sup>–1</sup>. NMR: 3.95 (1H, *q*, *J* 10 and 18 Hz), 4.85 (1H, *dd*, *W*<sub>1/2</sub> 10 Hz), 5.10 (1H, *dd*, *W*<sub>1/2</sub> 4 Hz), 5.40 (1H, *t*, *W*<sub>1/2</sub> 18 Hz, CH<sub>2</sub>OAc), 7.94 (3H, *s*, OAc), 8.78, 8.86, 9.11, 9.13 and 9.21 (each 3H, *s*; 5 Me). MS: *m/e* 348 (2%, M<sup>+</sup>), 333 (100%), 273, 255, 201, 190, 189, 175, 161, 159, 149, 147, 135, 121.

*Oxidation of ribenol.* I (290 mg) dissolved in acetone (minimum quantity) was treated dropwise with a slight excess of Jones reagent and left at room temp. for 15 min, when MeOH was added to destroy the excess reagent. The mixture was then poured into H<sub>2</sub>O and worked up, yielding the ketone III, m.p. 100–102° (acetone–MeOH), [α]<sub>D</sub> –80° (c 0.18). (Found: C, 79.14; H, 10.83. C<sub>20</sub>H<sub>32</sub>O<sub>2</sub> requires: C, 78.90; H, 10.59%). ν<sub>max</sub><sup>CHCl<sub>3</sub></sup> 3090, 1690, 1650, 1080, 990, 910, 840 cm<sup>–1</sup>. NMR (CCl<sub>4</sub>): 3.95 (1H, *q*, *J* 10 and 18 Hz), 4.85 (1H, *dd*, *W*<sub>1/2</sub> 10 Hz), 5.10 (1H, *dd*, *W*<sub>1/2</sub> 4 Hz), 7.65 (2H, complex), 8.75, 8.80, 8.94, 9.04 and 9.20 (each 3H, *s*; 5 Me).

*Huang–Minlon reduction of 3-oxo-(–)-13-epimanoyl oxide.* To a soln of III (200 mg) in diethylene glycol (17 ml) N<sub>2</sub>H<sub>4</sub>·H<sub>2</sub>O (1.6 ml) was added and the mixture refluxed for 90 min (temp. 130°). After the addition of KOH pellets (780 mg) refluxing was continued for 45 min. Then the temp. raised to 220° after which refluxing was continued again for 2 hr. The product was (–)-13-epimanoyl oxide (IV; 125 mg), m.p. 98–100°, [α]<sub>D</sub> –37° (c 0.23) (lit.,<sup>6</sup> m.p. 98–99.5°, [α]<sub>D</sub> –37°), (Found: C, 82.84; H, 10.83. Calc. for C<sub>20</sub>H<sub>34</sub>O: C, 82.69; H, 9.86%). IR spectrum superimposable with that of an authentic sample.

*Hydrogenation of ribenol.* I (1.5 g) was dissolved in EtOAc (70 ml) and hydrogenated for 12 hr over PtO<sub>2</sub> (470 mg) at room temp. and atm. press. This gave V, m.p. 82–83°, [α]<sub>D</sub> –13° (c 0.27). (Found: C, 78.00; H, 11.68. C<sub>20</sub>H<sub>36</sub>O<sub>2</sub> requires C, 77.87; H, 11.76%). ν<sub>max</sub><sup>Nujol</sup> 3350 (br), 1390, 1380, 1180, 1110, 970 cm<sup>–1</sup>. NMR: 6.71 (1H, *t*, *W*<sub>1/2</sub> 18 Hz, CHOH).

*Oxidation of 14,15-dihydro-3α-hydroxy-(–)-13-epimanoyl oxide.* V (1.35 g) was treated with Jones reagent, the reaction mixture being left at room temp. for only 5 min. This afforded the ketone VI, m.p. 90–93° (acetone–MeOH), [α]<sub>D</sub> –55° (c 0.21). (Found: C, 78.54; H, 11.45. C<sub>20</sub>H<sub>34</sub>O<sub>2</sub> requires: C, 78.38; H, 11.18%). ν<sub>max</sub><sup>Nujol</sup> 1700, 1390, 1380, 1130, 1090, 995, 965 cm<sup>–1</sup>.

*Bromination of 14,15-dihydro-3-oxo-(–)-13-epimanoyl oxide.* A soln of trimethylphenylammonium tribromide (300 mg) in dry THF (3 ml) was added dropwise and under stirring to a soln of VI (290 mg) in the same solvent till the yellow colour of the reagent persisted, upon which stirring at room temp. was continued for 30 min more. The reaction mixture was then poured into H<sub>2</sub>O, extracted with CH<sub>2</sub>Cl<sub>2</sub> and the solvent evaporated yielding VII (210 mg), which did not crystallize. ν<sub>max</sub><sup>film</sup> 1720, 1400, 1390, 1120, 1080, 1050, 960, 760 cm<sup>–1</sup>. NMR (CCl<sub>4</sub>): 5.10 (1H, *t*, *J* 14 Hz, CHBr).

*Dehydrobromination of 14,15-dihydro-2β-bromo-3-oxo-(–)-13-epimanoyl oxide.* A mixture of Li<sub>2</sub>CO<sub>3</sub> (300 mg), LiBr (150 mg), DMF (3 ml) and C<sub>6</sub>H<sub>6</sub> (2 ml) was heated until the H<sub>2</sub>O had been eliminated. Then a soln of VII (200 mg) in DMF (3 ml) was added and the reaction mixture refluxed for 1 hr under N<sub>2</sub>. The cooled soln was poured into H<sub>2</sub>O, extracted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 5% aq. HOAc, sat. aq. NaHCO<sub>3</sub> and H<sub>2</sub>O. After drying and evaporating the solvent, the residue afforded 14,15-dihydro-Δ<sup>1(2)</sup>-3-oxo-(–)-13-epimanoyl oxide (VIII), m.p. 96–100°. λ<sub>max</sub><sup>EtOH</sup> 235 nm. ν<sub>max</sub><sup>KBr</sup> 1660, 1380, 1365, 1100, 1075, 960, 825 cm<sup>–1</sup>. NMR (CCl<sub>4</sub>): 2.80 and 4.08 (each 1H, *d*, *J* 10 Hz). MS: *m/e* 289 (7%, M<sup>+</sup> – Me), 275 (65%, M<sup>+</sup> – C<sub>2</sub>H<sub>5</sub>), 257, 217, 201, 199, 175, 149, 135 (100%), 121, 107, 105.

7β-*Acetoxy-18-hydroxytrachylobane* IX, m.p. 156–160°, [α]<sub>D</sub> 8° (c, 1.19). ν<sub>max</sub><sup>KBr</sup> 3600, 3025, 1720, 1390, 1240, 1040 cm<sup>–1</sup>. NMR: 5.25 (1H, *t*, *W*<sub>1/2</sub> 6 Hz, CH<sub>2</sub>OAc), 6.65 and 7.00 (each 1H, *d*, *J* 12 Hz, CH<sub>2</sub>OH), 7.98 (3H, *s*, OAc), 8.88, 9.03 and 9.30 (each 3H, *s*; 3 Me).

7β,18-*Diacetoxytrachylobane* X, m.p. 134–136°. ν<sub>max</sub><sup>KBr</sup> 3025, 1750, 1250 cm<sup>–1</sup>. NMR: 5.27 (1H, *t*, *W*<sub>1/2</sub> 6 Hz, CH<sub>2</sub>OAc), 6.34 (2H, *s*, CH<sub>2</sub>OAc), 8.00 (6H, *s*, 2 OAc), 8.88, 9.03 and 9.21 (each 3H, *s*; 3 Me). Identical with the diacetate obtained from trachinodiol (XI).<sup>1</sup>

*Partial hydrolysis of trachinodiol diacetate.* A soln of X (365 mg) in 4% methanolic KOH (5 ml) was left at room temp. for 9 hr. This gave a mixture of trachinodiol (XI) and its 7 $\beta$ -monoacetate IX which were separated by dry column chromatography. IX, m.p. 157–160°,  $[\alpha]_D$  7.6° (c 1.71), identical with the natural product (m.m.p., TLC, IR, NMR).

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