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SESQUITERPENE LACTONES FROM *CENTAUREA ARBUTIFOLIA**

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Key Word Index—*Centaurea arbutifolia*; Compositae; germacranolides; elemanolides; sesquiterpene lactones; partial synthesis.

Abstract—The investigation of the aerial parts of *Centaurea arbutifolia* afforded four new sesquiterpene lactones; two germacranolides and two elemanolides, plus aguerin A. Their structures were elucidated by spectroscopic methods and by partial synthesis.

INTRODUCTION

In the course of our research on Compositae metabolites we studied the composition of *Centaurea arbutifolia*, a plant endemic to the Canary Islands. Five sesquiterpene lactones were isolated from this plant, one of which, aguerin A, was already known [1]. The other four were new germacranolides and elemanolides and were named arbutifolin (**1a**), 11,13-dihydroarbutifolin (**2a**), isoarbutifolin (**3a**) and 11,13-dihydroisoarbutifolin (**4a**).

RESULTS AND DISCUSSION

Arbutifolin (**1a**) is a colourless oil: $C_{20}H_{28}O_5$; MS *m/z* 348 (M^+); IR bands at 3500 (hydroxyl), 1760 (α-methylene-γ-lactone), 1730 (ester) and 1650 cm^{-1} (double bonds). The ^1H NMR displays two doublets at δ 6.36 and 5.86 (2 H, $J = 3.5$ Hz) characteristic of a $=CH_2$ group conjugated with the lactone CO, and a pair of doublets at 4.20 (2 H, $J = 12$ Hz) corresponding to C-4—CH_2OH. Between δ 5.20 and 4.60 a group of signals appear, corresponding to four protons assigned to C-1, C-5, C-6 and C-8. A singlet at δ 1.50 is assigned to the methyl of C-10, another at δ 2.20 is assigned to the protons of C-17 and a doublet characteristic of the methyls of an isopropyl group appears at δ 0.96. The presence of this last group in the ester is confirmed by MS: *m/z* 246 ($M - C_5H_{10}O_2$). Compound **1a** was treated with Ac_2O–pyridine to give the monoacetate (**1b**) in the form of an oil: $C_{22}H_{30}O_6$; (no M^+) *m/z* 228 ($M^+ - 162$) ($M^+ - C_5H_{10}O_2 - C_2H_4O_2$). Arbutifolin was subjected to $NaBH_4$ [2] reduction yielding **2a**, of which the ^1H NMR spectrum is analogous to that of arbutifolin except for a doublet at δ 1.42 in the region of the methyls, typical of a methyl α to the lactone carbonyl group.

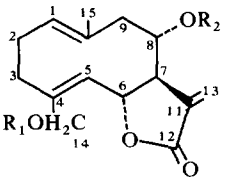
11,13-Dihydroarbutifolin (**2a**), $C_{20}H_{30}O_5$, MS *m/z* 350 (M^+) displayed IR bands at 3500 (hydroxyl). 1770 (γ-lactone), 1730 (ester) and 1640 cm^{-1} (double bond). Its ^1H NMR spectrum showed a doublet at δ 0.98 which suggested the presence of an isopropyl group; a doublet at δ 1.42 was assigned to the methyl lactone and two singlets at δ 1.49 and δ 2.12 were assigned to the methyl at C-10 and to the protons at C-17, respectively. A monoacetate **2b**, $C_{22}H_{32}O_6$ MS *m/z* 392 (M^+) was formed with the spectral properties which are identical to those of the acetate of **2a** obtained as described above by reduction of arbutifolin.

Isoarbutifolin **3a** was obtained as a colourless oil: $C_{20}H_{28}O_5$; MS *m/z* 348 (M^+); IR bands at 3535 (hydroxyl), 1770 and 1725 (γ-lactone + ester) and 1635 cm^{-1} (double bonds). The ^1H NMR displays a doublet at δ 0.97 assigned to the methyls of an isopropyl group; a singlet at 1.15 is assigned to an angular allylic methyl at C-10, a broad singlet at δ 4.05 typical of a primary hydroxyl was confirmed by acetylation which resulted in a displacement of approx. δ −0.5 in the spectrum of acetate **3b**. A triplet is present centred at δ 4.23 which is characteristic of the lactone oxygen geminal proton; between δ 5.95 and δ 4.88 a series of signals appear which are typical of an ABX system and characteristic of terminal vinyl groups with two doublets at δ 6.16 and 5.58 (1 proton each assigned to a lactonic methylene). The ^1H NMR and MS spectrum, with a fragment at *m/z* 246 ($M^+ - C_5H_{10}O_2$), clearly showed that substance **3a** is an isovaleryl ester.

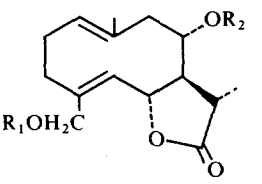
11,13-Dihydroisarbutifolin (**4a**) was obtained as an oil: $C_{20}H_{30}O_5$; MS *m/z* 350 (M^+); IR bands at 3560 (hydroxyl), 1770 and 1725 (γ-lactone + ester) and 1635 cm^{-1} double bonds. Its ^1H NMR spectrum is analogous to that of isoarbutifolin (**3a**) except for a doublet at δ 1.25 in the region of the methyls (three protons, $J = 7$ Hz) typical of a methyl group α to the lactone carbonyl group.

The structures of substances **1b**, **2b** and **3b** were confirmed by the following sequence of reactions: hydrolysis of the cnicin (**5**) with K_2CO_3 in dioxane [3] gave **6** whose IR and ^1H NMR spectra are superimposable with those of salonitenolide. Partial acetylation of the latter gave a monoacetyl derivative **7** which when treated later with the chloride of isovaleric acid led to a product whose IR and ^1H NMR spectra are identical to those of substance **1b**. $NaBH_4$ reduction gave **2b** (IR and ^1H NMR

*Part 42 of the series "Constituents of the Compositae". For Part 41 see González, A. G., Bretón, J. L., Cabrera, I. and Galindo, A. (1980) *Anal. Quim. C* **76**, 152.



1a $R_1 = H$
1b $R_1 = Ac$



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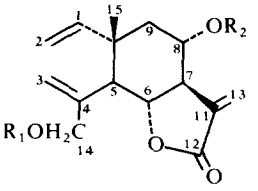
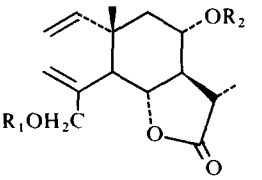
2b $R_1 = Ac$

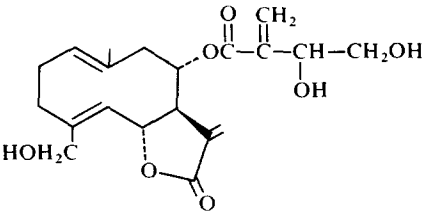


3a $R_1 = H$
3b $R_1 = Ac$

$R_2 = C(=O)-CH_2-CH(Me)_2$



4a $R_1 = H$
4b $R_1 = Ac$



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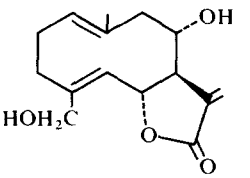

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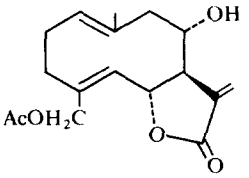

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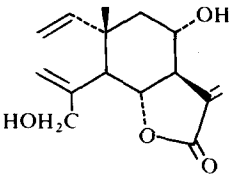

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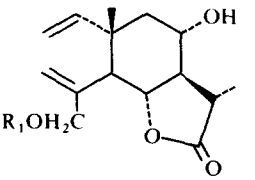

9a $R_1 = H$
9b $R_1 = Ac$

spectra superimposable). Cope rearrangement [4] of **1b** gave an elemanolide identical to **3b** (IR and ^{1}H NMR spectra superimposable). The elemanolide **4b** was synthesized by Cope rearrangement of the salonitenolide **6** giving a dehydromelitensin **8** [5]. $NaBH_4$ treatment led to melitensin **9a** [6] which when added to Ac_2O–pyridine led to the monoacetate **9b**. This was acylated with the chloride of isovaleric acid yielding **4b** (IR and ^{1}H NMR spectra superimposable).

EXPERIMENTAL

Optical activities were measured in $CHCl_3$, ^{1}H NMR spectra at 90 and 60 MHz in $CDCl_3$ with TMS as internal standard.

Extraction and separation of substances. The aerial part of *Centaurea arbutifolia* Svent (4 kg), grown in the Botanic Gardens at Las Palmas in Grand Canary and collected in August 1979, was triturated and extracted with EtOH in a Soxhlet. The resulting alcoholic extract was concd *in vacuo* to approx. 200 ml and dissolved with hot EtOH (1 l.), boiling H_2O being added (2 l.) with $Pb(OAc)_2$ (60 g) and the mixture was left for 12 hr. The greater part of the EtOH was eliminated and the residue extracted with EtOAc. Evaporation of the solvent resulted in an intensely bitter residue (14 g), later chromatographed on a column of Si gel (500 g) eluted with petrol and mixtures of petrol–EtOAc, with the latter in increasing quantities. Rechromatography of the fractions where there was a mixture of substances, using C_6H_6–EtOAc in different proportions, led to no further purification. By repeated prep. TLC using C_6H_6–EtOAc (1:1), 70 mg **1a**, 30 mg **2a**, 20 mg **3a** and 35 mg **4a** were obtained.

Arbutifolin (**1a**). A colourless oil: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1760, 1730 and 1650; ^{1}H NMR: δ 0.96 (6 H, *d*, J = 7 Hz, $-CH(Me)_2$), 1.50 (3 H, *s*, C-10 Me), 2.20 (2 H, *s*, C-17), 3.00 (1 H, *m*, C-7), 4.20 (2 H, *dd*, J = 12 Hz, $HOCH_2-$C-4), 4.60–5.20 (4 H, *m*, C-1, C-5, C-6 and C-8), 5.86 and 6.36 (1 H each, *d*, J = 3.5 Hz, C-11=CH_2). MS *m/z*: 348 (M^+).

Monoacetylarbutifolin (**1b**). A mixture of arbutifolin (40 mg), C_5H_5N (1 ml) and Ac_2O (0.5 ml) was left for 24 hr and the monoacetate recovered as an oil: MS *m/z* (no M^+). 228 (M^+

$-C_5H_{10}O_2-C_2H_4O_2$); $[\alpha]_D$ +84.8° (*c* 0.5); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1740 and 1660; ^1H NMR: δ 0.98 (6H, *d*, *J* = 7 Hz, $-CH(Me)_2$), 1.52 (3H, *s*, C-10 Me), 2.10 (3H, *s*, OAc), 2.20 (2H, *s*, C-17), 3.04 (1H, *m*, C-7), 4.62 (2H, *s*, CH_2OAc), 5.25–4.89 (4H, *m*, C-1, C-5, C-6 and C-8); 6.35 and 5.85 (1H each, *d*, *J* = 3.5 Hz, C-11 = CH_2).

$NaBH_4$ *reduction.* About 24 mg of arbutifolin was dissolved in MeOH (5 ml), $NaBH_4$ (24 mg) being added and the mixture was stirred at 0° for 15 min. The MeOH was eliminated and the residue acidified with 0.1 N HCl and extracted with EtOAc. Purification of the residue by dry column chromatography (C_6H_6–EtOAc, 8:2) gave an oil (**2a**): MS *m/z*: 350 (M^+); 248 ($M^+ - C_5H_{10}O_2$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1770, 1730 and 1640; ^1H NMR; δ 0.98 (6H, *d*, *J* = 7 Hz, $-CH(Me)_2$; 1.49 (3H, *s*, C-10 Me); 1.42 (3H, *d*, *J* = 7 Hz, C-11 Me); 4.18 (2H, *dd*, *J* = 12 Hz, $-CH_2OH$).

11,13-*Dihydroarbutifolin* (**2a**). The IR and ^1H NMR spectra of this substance were superimposable on those of the product obtained by the $NaBH_4$ reduction of arbutifolin. Compound **2a** was treated with Ac_2O–pyridine to give the monoacetate (**2b**): $[\alpha]_D$ 95° (*c* 5.2).

Isoarbutifolin (**3a**). This was obtained as an oily substance which could not be crystallized: MS *m/z*: 348 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1770, 1725 and 1635; ^1H NMR: δ 0.97 (6H, *d*, *J* = 7 Hz, $-CH(Me)_2$); 1.15 (3H, *s*, C-10 Me); 2.22 (2H, *s*, C-17); 4.05 (2H, *s*, $-CH_2OH$); 4.23 (1H, *t*, *J* = 11 Hz, C-6); 5.42–4.98 (1H each, *s*, C-3=CH_2); 5.95–4.88 (3H, complex signal, $-CH=CH_2$). Acetylation in the usual way gave the monoacetate (**3b**); $[\alpha]_D$ 42.2° (*c* 3.9); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1740 and 1640; MS *m/z* (no M^+); 228 ($M^+ - C_5H_{10}O_2 - C_2H_4O_2$).

11,13-*Dihydroisoarbutifolin* (**4a**). This product looked identical to the others. It could not be crystallized but TLC resulted in a pure compound. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560, 1770, 1725 and 1635; ^1H NMR: δ 0.96 (6H, *d*, *J* = 7 Hz, $-CH(Me)_2$); 1.25 (3H, *d*, *J* = 7 Hz, C-11 Me); 1.14 (3H, *s*, C-10 Me); 2.18 (2H, *s*, C-17); 4.02 (2H, *s*, $-CH_2OH$); 4.24 (1H, *t*, *J* = 10 Hz, C-6); 5.04–4.95 (1H each, *d*, C-3=CH_2) and 5.92–4.88 (3H, complex signal, $-CH=CH_2$): MS *m/z* 350 (M^+); 248 ($M^+ - C_5H_{10}O_2$). Compound **4a** was treated with Ac_2O–pyridine to give the monoacetate (**4b**): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1735 and 1650; MS *m/z*: 392 (M^+), 230 ($M^+ - C_5H_{10}O_2 - C_2H_4O_2$).

Hydrolysis of **5**. Compound **5** (3.8 g) was dissolved in dioxane (20 ml), a 5% aq. soln of K_2CO_3 (30 ml) was added and the mixture continually stirred over 7 hr at room temp. It was recovered in the usual way as a colourless oil (2.17 g). The IR and ^1H NMR spectra of the product were superimposable on those of the salonitenolide **6**.

C_{15}-*Acetylsalonitenolide* (**7**). Compound **6** (1 g) was dissolved in pyridine (1 ml), Ac_2O (0.2 ml) was added and the mixture stirred at −20°. The reaction was followed by TLC and when no initial substance remained, the mixture was poured into ice-water, and the product recovered in the usual way. Compound **7** was obtained by dry-column chromatography (C_6H_6–EtOAc, 8:2): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1735, 1640; ^1H NMR: δ 1.36 (3H, *s*, C-10 Me), 2.07 (3H, *s*, OAc), 4.59 (2H, *s*, $-CH_2OAc$), 6.47–6.28 (2H, *m*, C-11=CH_2).

C_{15}-*Acetyl-8α-isovaleryl salonitenolide* (**1b**). Compound **7** (400 mg) was dissolved in pyridine (2 ml), cooled to 0°, and isovaleryl chloride (1.5 ml) added. It was recovered in the usual way to yield **1b** (380 mg): $[\alpha]_D$ 84.7° (*c* 3.0).

$NaBH_4$ *reduction.* Compound **1b** (120 mg) was dissolved in MeOH (1.5 ml) and the mixture stirred at 10° for 20 min. Recovery in the usual way gave 40 mg of 11,13-dihydroacetylarbutifolin (**2b**). Its IR, ^1H NMR and mass spectra were superimposable with those of the acetate of the natural product.

Cope rearrangement of acetylarbutifolin (**1b**). Compound **1b** (260 mg) was heated *in vacuo* in a closed tube at 220° for 10 min. After cooling, it was extracted with MeOH and concd to give 30 mg of acetylarbutifolin (**3b**), $[\alpha]_D$ 43.2° (*c* 2.0). Its IR, ^1H NMR and MS were identical with those of the acetate of the natural product.

Cope rearrangement of salonitenolide (**6**). Compound **6** (350 g) was treated in the same way as above, yielding 40 mg of a substance with IR, ^1H NMR and MS superimposable with those of dehydromelitensin (**8**).

$NaBH_4$ *reduction.* Salonitenolide (200 mg) was treated with $NaBH_4$ in the usual way. A non-crystalline product **9a** (100 mg) was obtained with IR and ^1H NMR spectra superimposable with those of melitensin.

C_{15}-*Acetyl melitensin* (**9b**). About 100 mg of **9a** was dissolved in pyridine (2 ml) and Ac_2O (0.5 ml) as for salonitenolide **6**. A non-crystalline product **9b** was obtained. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560, 1775, 1650. ^1H NMR: δ 1.08 (3H, *s*, C-10 Me), 1.32 (3H, *d*, *J* = 6.5 Hz, C-11 Me), 2.05 (3H, *s*, OAc), 4.50 (2H, *s*, CH_2OAc) and 5.70–4.70 (3H, complex signal $-CH=CH_2$).

C_{15}-*Acetyl-8-isovaleryl melitensin* (**4b**). Compound **9b** (40 mg) was treated as for compound **7** yielding an oily product (**4b**), identical with the acetyl derivative of the natural **4a**.

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