Phytochemistry, Vol. 21, No. 4, pp. 895–897, 1982.
Printed in Great Britain.

0031-9422/82/040895-03$03.00/0

SUBEXPINNATIN, A NEW GUAIANOLIDE FROM *CENTAUREA CANARIENSIS**

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(*Received* 28 *April* 1981)

Key Word Index—*Centaurea canariensis*; Compositae; sesquiterpene lactones; subexpinnatin; aguerin B; guaianolides.

Abstract—Two sesquiterpene lactones, the new guaianolide subexpinnatin and aguerin B, were isolated from the aerial part of *Centaurea canariensis*.

INTRODUCTION

In a continuation of our investigations on the constituents of the genus *Centaurea* (Cynareae) [1], we have now isolated from the aerial parts of *Centaurea canariensis* Brouss (var. *subexpinnata* Burch), a plant endemic to the Canary Islands, a new sesquiterpene lactone, subexpinnatin (**1a**), together with the previously known aguerin B [2]. The structure of subexpinnatin was elucidated by spectroscopic methods and chemical transformations.

RESULTS AND DISCUSSION

Subexpinnatin (**1a**) was obtained from the medium polar fractions as an oil which appeared homogeneous on TLC. Its IR spectrum had bands at 3600 cm^{-1} (OH), 1760 cm^{-1} (α,β-unsaturated γ-lactone ring), 1710 (α,β unsaturated ester group) and 1650, 1635 (double bonds). MS peaks at m/z 228 $[M-102]^+$, 246 $[M-84]^+$, 85 $[C_4H_5O_2]^+$ and 57 $[C_3H_5O]^+$ coupled with an IR absorption band at 1710 cm^{-1} showed that subexpinnatin was an ester of α-hydroxymethylacrylic acid, a conclusion verified by the presence in the ^{1}H NMR spectrum of two broad singlets at δ 6.30 and 5.95 and a two-proton broad singlet at δ 4.32. In addition, the NMR spectrum showed signals typical of the α-methylene γ-lactone grouping ($d \times 2$, each 1 H, δ 6.15 and 5.60, $J = 3.5$ and 3 Hz), two terminal methylene double bonds [1 H, *s*(*br*), $\delta = 5.23$; 2 H, *s*(*br*), δ 5.03; and 1 H, *s*(*br*) δ 4.90] at C-4 and C-10, and a 1 H triplet at δ 4.03 ($J = 10$ Hz) for the lactonic proton at C-6. The nature of this signal shows the *trans*-diaxial disposition of the protons at C-5 (α), C-6 (β) and C-7 (α), a feature common to all the lactones of the genus. The signal of the C-8 proton was located at δ 5.14, almost overlapped with the signals of the terminal methylene protons.

On saponification of subexpinnatin a crystalline monohydroxylactone (**1b**) was obtained mp 106–108°, $[\alpha]_D + 61°$, $C_{15}H_{18}O_3$ (m/z 246). The structure **1b**, was in agreement with the IR, MS and NMR data. Characteristic absorptions in the ^{1}H NMR spectrum of **1b** were two lowfield doublets ($J = 3$ Hz) at δ 6.26 and 6.17 corresponding to the protons of the exocyclic methylene group conjugated with the lactone carbonyl, two pairs of broad singlets at δ 5.30 and 5.08, 5.05 and 4.97, attributed to C-4 and C-10 methylene groups, and a triplet ($J = 10$ Hz) at δ 3.95 for the proton attached to the carbon carrying the oxygen of the lactone. The H-8 signal was superimposed on the latter signal. The relative position of the secondary hydroxyl group of deacylsubexpinnatin (**1b**) was inferred from the results of chromium trioxide oxidation. Careful oxidation gave an unstable compound (**2**) (m/z 244), the NMR spectrum of which displayed two doublets at δ 6.55 and 6.10 ($J = 3$ Hz), characteristic of an oxomethylene grouping at C-11, a triplet at δ 4.15 ($J = 10$ Hz) for the lactonic proton at C-6 and a sharp signal at δ 3.35 (2 H, C-9 hydrogens). The latter signal was similar to that of the C-9 protons in dehydrodihydroligustrin [3]. Dry CC of **2** caused isomerization of the C-11 exomethylene double bond to form the endocyclic conjugated compound **3**, and isomerization of both C-11 and C-10 to form the cross-conjugated ketone **4**.

Compound **3** had an UV absorption maximum at 238 nm ($\epsilon = 10\,000$) and its IR spectrum had bands at 1690 and 1635 cm^{-1} due to the α,β-unsaturated cycloheptanone. Its ^{1}H NMR spectrum showed three broad singlets at δ 5.30, 5.18 and 5.10 (4 H) corresponding to C-4 and C-10 exomethylene groups. Decoupling experiments confirmed that the doublet ($J = 10$ Hz) at δ 5.00 assigned to the proton attached to the carbon carrying the oxygen of the lactone was split by homoallylic coupling ($J = 1$ Hz) with the C-11 vinylic Me group at δ 2.21. The protons at C-9 appeared as two doublets (1 H each) at δ 3.53 and 3.27 ($J = 13$ Hz). The ^{1}H NMR spectrum of **4** showed a quadruplet ($J = 1$ Hz) at δ 6.16 assigned to the C-9 proton. The lactonic proton appeared as a pair of quartets centred at δ 5.00 (J = 10 Hz, 1 Hz), one of which was superimposed on the broad singlet at δ 5.15 attributed to the C-4 exocyclic methylene group. A doublet at δ 2.22 ($J = 1$ Hz) was ascribed to the

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*Part 43 of the series "Constituents of the Compositae". For Part 42, see González, A. G., Bermejo, J., Toledo, F. and Daza, L. R. (1981) *Phytochemistry* **20**, 1895.

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vinylic Me group at C-11 and a sharp singlet at δ 2.18 corresponded to the other Me group at C-10.

Subexpinnatin is the first reported guaianolide of the genus *Centaurea* [1] which has no functional group at C-3. Indeed subexpinnatin and dehydrocostus lactone (**1d**) [4] are the only two guaianolides in the Cynareae tribe lacking a functional group at C-3. We attempted to correlate these two lactones by the following reaction sequence: treatment of **1b** with TsCl gave **1c** which was refluxed with NaI and Zn in glyme [5]. This procedure failed, because during the treatment with Zn–NaI, reduction of the C-11 methylene group took place and resulted in the formation of mixtures from which, due to the limited amount of material, no pure product could be separated. The next approach adopted was to functionalize the C-3 position in the subexpinnatin derivative **5** by selective isomerization of the C-4 exomethylene double bond. Compound **5** was obtained by saponification of **1a** and further reduction with aluminium amalgam [3]. Treatment of **5** with boron trifluoride etherate [6] gave **6** in high yield. Its ^{1}H NMR spectrum displayed a quadruplet at δ 5.55 ($J = 1$ Hz) and a 2 H singlet at δ 4.97 assigned to the C-3 proton and C-10 exomethylene group respectively. The proton at C-6 appeared as a triplet at δ 3.97 ($J = 10$ Hz) and the proton attached to C-8 was responsible for a multiplet centred at δ 3.75. A doublet ($J = 1$ Hz) at δ 1.80 was assigned to the C-4 Me group and a doublet at δ 1.40 ($J = 7$ Hz) corresponded to the C-11 Me group. Treatment of **6** with chromium trioxide yielded the ketone **7**. Its mp was identical with that of dehydrodihydroligustrin [3].

Definite proof of the structure and stereochemistry of **1a** was provided by the demonstration that treatment of **6** with *m*-chloroperbenzoic acid gave the epoxide viscidulin C (**8**) [7]. This correlation permitted us to establish that the configurations of all the asymmetric centres of subexpinnatin are as shown in formula **1a**.

EXPERIMENTAL

Mps are uncorr.

Extraction and purification. C. canariensis (var. *subexpinnata*) was collected in Sept. in Teno Bajo (Tenerife). The aerial part of the plant (20 kg) was extracted with hot EtOH. The EtOH extract was reduced in vol. to 0.5 l. (red. pres.), and after dilution with the same vol. of H_2O, was extracted with $CHCl_3$. The extract was evaporated to yield an oily residue (86 g) which was chromatographed on a column of Si gel (700 g).

Subexpinnatin (**1a**). Subexpinnatin was purified by $AgNO_3$ dry CC (C_6H_6–EtOAc, 7:3) to give 7 g oil which could not be crystallized: MS *m/z*: 228 $[M-102]^+$; $[\alpha]_D + 62$ ($CHCl_3$, *c* 3.0); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1760, 1710, 1650 and 1635; ^{1}H NMR (90 MHz, $CDCl_3$, TMS): δ 6.30 [1H, *s*(*br*), Hc], 5.95 [1H, *s*(*br*), Hd], 6.15 (1H, *d*, $J = 3.5$ Hz, Hb), 5.60 (1H, *d*, $J = 3$ Hz, Ha), 5.23, 5.03 [2H, each *s*(*br*), C-4=CH_2], 5.03, 4.90 [2H, each *s*(*br*), C-10=CH_2], 4.32 (2H, *s*, C-17 $\underline{H}_2$-OH), 4.03 (1H, *t*, $J = 10$ Hz, H-6).

Deacylsubexpinnatin (**1b**). Subexpinnatin (1.062 g) was mixed with aq. 5% K_2CO_3 (100 ml) and stirred for 5 days. After acidification with dil. HCl it was extracted with $CHCl_3$ and EtOAc. The organic soln was washed with H_2O, dried and evaporated to dryness. Crystallization of the residue from EtOAc–petrol yielded **1b** (0.9 g), mp 106–108°; MS *m/z* 246 $[M]^+$, 228, 166 $[\alpha]_D + 61°$; IR $\nu_{max}^{CHCl_3}$ 3600, 1760, 1655, 1640; ^{1}H NMR (90 MHz, $CDCl_3$, TMS): δ 6.26, 6.17 (2 H, each *d*, $J = 3$ Hz, Hb, Ha), 5.30, 5.08 [2H, each *s*(*br*), C-4=CH_2], 5.05, 4.97 [2H, each *s*(*br*), C-10=CH_2], 3.95 (1H, *t*, $J = 10$ Hz, H-6), 3.93 (1 H, *m*, H-8).

Dehydrodeacylsubexpinnatin (**2**). A soln of **1b** (248 mg) in Me_2CO (20 ml) was treated with 8 N CrO_3 at 5° until the orange colour persisted. The soln was diluted with EtOAc, washed with H_2O, dried and evaporated to dryness. This yielded **2** as an oil which decomposed very easily to give a mixture of **3** and **4**. ^{1}H NMR (immediately at end of work-up) (90 MHz, $CDCl_3$, THS): δ 6.55, 6.10 (2H, each *d*, $J = 3$ Hz, Hb, Ha), 5.32, 5.25 [2H, each *s*(*br*), C-4=CH_2], 5.25, 5.15 [2H, each *s*(*br*), C-10=CH_2], 4.15 (1H, *t*, $J = 10$ Hz, H-6), 3.35 (2H, *s*, H-9).

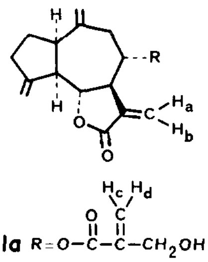
Ketolactones **3** *and* **4**. Compound **2** was chromatographed through a dry column and eluted with EtOAc–petrol (1:1). The first eluate (fractions 2–6) contained compound **3** which could not be crystallized. MS *m/z*: 244 $[M]^+$; UV λ_{max}^{EtOH} nm: 238 (ϵ 10.000); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1755, 1690, 1645; ^{1}H NMR (90 MHz, $CDCl_3$, TMS): δ 5.30, 4.94 (2 H, *s*(*br*), C-4 =CH_2), 5.25, 5.10 [2H, each *s*(*br*), C-10 =CH_2], 5.05, 4.94 (2H, pair of *q*, $J = 10$ Hz, 1 Hz, H-6). The subsequent fractions (7–10) contained mainly ketolactone (**4**). IR ν_{max}^{nujol} cm^{-1}: 1750, 1700, 1650, 1620, 1605; ^{1}H NMR (90 MHz, $CDCl_3$, TMS): δ 6.16 (1H, *q*, $J = 1$ Hz, H-9), 5.15 [2H, *s*(*br*), C-4 =CH_2], 5.00 (2H, pair of *q*, $J = 10$ Hz, 1 Hz, H-6), 2.22 (3 H, *d*, $J = 1$ Hz, Me-10), 2.18 (3 H, *s*, Me-11).

Dihydrodeacylsubexpinnatin (**5**). To a soln of **1b** (200 mg) in EtOH (50 ml) was added Al amalgam (1 g) and the mixture heated under reflux for 12 hr. The soln was filtered, evapd to dryness *in vacuo* and the residue crystallized from Et_2O–petrol to give **5** (160 mg) mp 135–138°, $[\alpha]_D + 36°$ IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3500, 1770, 1650; ^{1}H NMR (90 MHz, $CDCl_3$, TMS): δ 5.25, 5.10 [2H, each *s*(*br*), C-4=CH_2], 5.00, 4.95 [2H, each *s*(*br*), C-10=CH_2], 3.95 (1H, *t*, $J = 10$ Hz, H-6), 3.80 (1 H, *m*, H-8), 1.42 (3H, *d*, $J = 7$ Hz, Me-11).

8-*α*-*Hydroxy*-3(4),10(14)-*dien* 6,12-*olide* (**6**). A soln of **5** (150 mg) was dissolved in C_6H_6 (3 ml) and freshly distilled BF_3Et_2O (0.006 ml) was added. The mixture was stirred for 4 hr at room temp., diluted with EtOAc (10 ml), washed (×2) with aq. 5% $NaHCO_3$ (10 ml) and H_2O (20 ml), dried (Na_2SO_4) and concentrated. The residue (130 mg) was purified by dry CC (C_6H_6–EtOAc 8:2) to give **6** (110 mg), mp 109–111°, $[\alpha]_D$ 89°. MS *m/z* 248 $[M]^+$; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1770, 1650; ^{1}H NMR (90 MHz, $CDCl_3$, TMS): δ 5.55 (1H, *q*, $J = 1$ Hz, H-3), 4.97 (2 H, *s*, C-10 =CH_2), 3.97 (1H, *t*, $J = 10$ Hz, H-6), 3.75 (1H, *m*, H-8), 1.80 (3H, *d*, $J = 1$ Hz, Me-4), 1.40 (3H, *d*, $J = 7$ Hz, Me-11).

Dehydrodihydroligustrin (**7**). A soln of **6** (30 mg) in Me_2CO (1.5 ml) was treated with 8 N CrO_3 at 5° until the orange colour persisted. Chromatography on Si gel and crystallization from Me_2CO–hexane yielded **7** (5 mg), mp 115–118°.

Viscidulin C (**8**). A soln of **6** (60 mg) in $CHCl_3$ (16 ml) was cooled to 0° and treated with an ice-cold soln of *m*-chloroperbenzoic acid (60 mg) in $CHCl_3$ (1 ml) and the reaction mixture was kept in the refrigerator. Progress of the reaction was monitored by TLC for 24 hr until only traces of the starting material were left. The reaction mixture was then washed with $NaHCO_3$ soln and H_2O. Removal of $CHCl_3$ gave **8** (45 mg) which was crystallized from Et_2O–petrol, mp 145–147° either alone or in admixture with authentic viscidulin C. The IR and NMR spectra of these materials were also identical.

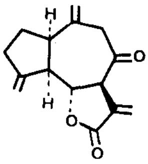


Ia $R{=}O{-}\overset{O}{\overset{\|}{C}}{-}\overset{CH_cH_d}{\overset{\|}{C}}{-}CH_2OH$

Ib R=OH

Ic R=OTs

Id R=H



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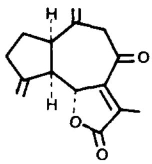

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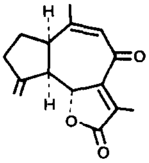

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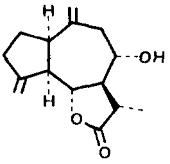

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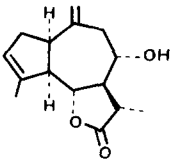

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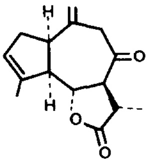

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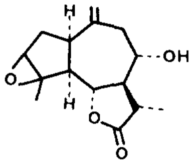

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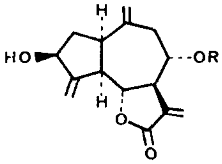

9 $R{=}\overset{O}{\overset{\|}{C}}{-}\overset{CH_2}{\overset{\|}{C}}{-}Me$

Aguerin B was obtained in the same medium polar fractions as subexpinnatin and purified by prep. TLC. The product was identified as aguerin B (**9**).

Acknowledgement—We thank Dr. R. C. Kelsey, University of Montana, for a sample of viscidulin C.

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