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HYPOCHAERIN: A NEW SESQUITERPENE LACTONE FROM *HYPOCHAERIS SETOSUS**

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Key Word Index—*Hypochaeris setosus*; Compositae; sesquiterpene lactones; hypochaerin; desacetoxymatricarin; achillin; 1-hydroxy-6β,7α,11β-H-eudesm-4-en-6,12 olide; jacquinelin.

Abstract—*Hypochaeris setosus* contains desacetoxymatricarin, achillin, 1-hydroxy-6β,7α,11β-H-eudesm-4-en-6,12 olide, jacquinelin and hypochaerin, a new guaianolide, established as 3-oxo-4β,5α,6β,7α,11β-H-guai-1(2)-en-6,12 olide.

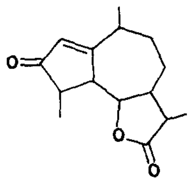
INTRODUCTION

Continuing our studies on sesquiterpene lactones of plants of the Compositae, we looked at the composition of *Hypochaeris setosus* Wedd, a Composite endemic to Venezuela. Five sesquiterpene lactones have been isolated from this plant, four of which were already known: desacetoxymatricarin [1], achillin [2], 1-hydroxy-6β,7α,11β-H-eudesm-4-en-6,12 olide [3] and jacquinelin [4]; the remaining lactone (minor component) is a new guaianolide which we have named hypochaerin.

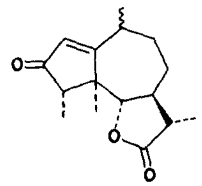
RESULTS AND DISCUSSION

Hypochaerin (**1**) mp 110–112° $C_{15}H_{20}O_3$ $[\alpha]_D$ $-64°$ has a UV spectrum characteristic of an enone (λ_{max} 229 nm, log ϵ 4.2) which is probably part of a cyclopentenone chromophore (IR band 1690 and 1590 cm^{-1}). The two remaining oxygen atoms of the empirical formula are contributed by the γ-lactone group (IR band at 1790 cm^{-1}). The PMR spectrum of hypochaerin exhibited a low field singlet (δ 6.1) assigned to the C_2 vinyl proton. The C-6 lactone proton appeared as a triplet at δ 3.8 (J 9 Hz). The coupling of this proton indicated its *trans*-diaxial disposition to the hydrogens at C-5 and C-7. In the Me region appear three superimposed doublets (9H) centred at δ 1.3 corresponding to three secondary methyls. The fore-going data lead to the assignment of structure (**1**) to hypochaerin.

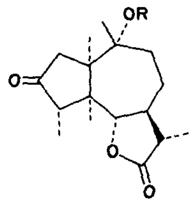
In the course of photochemical transformations of α-santonin [5], Barton and his collaborators reported the synthesis of anhydrodihydroisophoto-α-santonic lactone (**2**) mp 150–155° $[\alpha]_D$ 20°. The latter has the same gross structure as (**1**), although their physical constants are different.



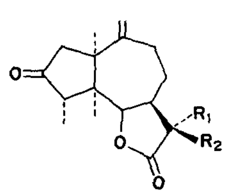
(**1**)



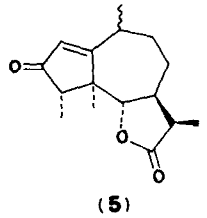
(**2**)



(**3a**) R = Ac
(**3b**) R = H



(**4a**) R_1 = H, R_2 = Me
(**4b**) R_1 = Me, R_2 = H



(**5**)

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* Part 30 in the series: "Constituents of Compositae". For Part 29, see: González, A. G., Bermejo, J., Cabrera, I., Galindo, A. and Massanet, G. M. (1976) *Anal. Quim.* (in press).

In order to establish the proposed formula, hypochaerin has been synthesized from dihydroisophoto-α-santonic lactone acetate (**3a**) treatment of the latter with 5% K_2CO_3 afforded four lactones: (**3b**), **1**, **2** and **4a**. Lactone **3b** was identified as dihydroisophoto-α-santonic lactone. Lactone **4a** mp 194–196° $C_{15}H_{20}O_3$ $[\alpha]_D$ −19° shows IR bands of saturated cyclopentanone (1735 cm^{-1}) and exocyclic double bond (1630 and 900 cm^{-1}). Its PMR spectrum has two singlets at δ 4.66 and 4.98 attributed to the hydrogens of the exocyclic methylene group attached to C-10. A pair of superimposed doublets centred at δ 1.25 is assigned to secondary Me groups. The structure and stereochemistry of **4a** was determined by correlation with dihydroestafiatone **4b** [6]. Epimerization at C-11 with 10% K_2CO_3 gave a crystalline compound mp 87–89° identified by direct comparison with an authentic sample of **4b** [7].

Compounds (**1**) and (**2**) are formed through the dehydration and further isomerization of the double bond to produce the α,β-unsaturated ketone. Hence, hypochaerin must have the structure of 3-oxo-guai-1(2)-en-6,12 olide.

The stereochemistry of hypochaerin (except at C-10) was determined as follows:

Stereochemistry at C-4. It was observed that the secondary β-methyl at C-4 with a keto group at C-3 readily isomerizes to a more stable α-configuration [8]. Very mild treatment with base of hypochaerin does not cause epimerization [9]. Hence, hypochaerin must have an α-configuration at C-4–Me.

Stereochemistry at C-11. Since hypochaerin could be the C-11 epimer of ketolactone **2**, we synthesized compound **5**. The usual photochemical rearrangement of α-santonin [10] and further hydrogenation gave **3b**. Treatment of **3b** with K_2CO_3 [9] afforded the C-11 epimer which was dehydrated with perchloric acid to give **5**. However, the IR and physical constants of the latter differed from those of hypochaerin.

Stereochemistry at C-10. Dehydration of C-10 OH and further isomerization of the double bond must involve change in the configuration of C-10–Me. Hence, hypochaerin and ketolactone **2** could be epimers at C-10. On the basis of this fact, a reinvestigation of the dehydration products of **3b** was undertaken. Treatment of the latter with perchloric acid in acetic acid yields dihydroestafiatone **4b**, ketolactone **2** and hypochaerin **1**. The formation of both **1** and **2** from **3b** is in accordance with the above suggestion and permits us to establish for hypochaerin the structure 3-oxo-4β,5α,6β,7α,11β-H-guai-1(2)-en-6,12 olide, epimeric at C-10 of the ketolactone **2**.

EXPERIMENTAL

Mp's recorded on a Koffler block are uncorrected. Optical activities were measured in $CHCl_3$, UV spectra in EtOH and PMR spectra on a 60-MHz instrument in $CDCl_3$ with TMS as internal reference. Column and dry column chromatography was performed on Si gel (0.2–0.5 and 0.063–0.20 mm respectively).

Extraction and separation. The dry plant (5 kg), collected near Merida (Venezuela) in the spring of 1974, was finely cut and exhaustively extracted with EtOH in a Soxhlet. The extract was filtered, concentrated to 500 ml and, after adding $Pb(OAc)_2$ (30 g) in hot H_2O (1 l.), was left for 24 hr. It was then filtered, concentrated until free of EtOH and the residue (17 g) was extracted with EtOAc and chromatographed on a column, yielding desacetoxymatricarin (C_6H_6–EtOAc 17:1), achillin (C_6H_6–EtOAc, 9:1), a mixture of 1-hydroxy-6β,7α,11β-H-eudesm-4-en-6,12 olide and hypochaerin (C_6H_6–EtOAc, 4:1) and, finally, jacquinelin (C_6H_6–EtOAc, 7:3).

Desacetoxymatricarin. (150 mg) mp 202–204° $[\alpha]_D$ 53° (*ca* 2.04). UV λ_{max} 255 nm (log ϵ 4.1). The physical and spectral data of this compound are identical to those cited [1].

Achillin. (50 mg) mp 142–144° $[\alpha]_D$ 160° (*ca* 1.20) UV λ_{max} 255 nm (log ϵ 4) was identified by direct comparison with an authentic sample (mmp, TLC, IR, PMR spectra superimposable [2].

1-*Hydroxy*-6β,7α,11β-H-*eudesm*-4-*en*-6,12 *olide*. (100 mg) mp 172–174° $[\alpha]_D$ 59° (*ca* 2.3) was separated from hypochaerin by dry column (C_6H_6–EtOAc 4:1). The identity of this compound was established by direct comparison (mp, IR, MS) with an authentic sample [3].

Hypochaerin. (100 mg) mp 110–112° $[\alpha]_D$ −64° (*ca* 4.1). (Found: C, 68.22; H, 8.40. $C_{15}H_{20}O_3$ H_2O requires: C, 67.65; H, 8.33%). IR ν_{max}^{KBr} 1760 (γ-lactone), 1690 (CO=C 5 membered ring), 1600 cm^{-1} (double bond). UV λ_{max} 229 nm (log ϵ 4.2). PMR ($CDCl_3$): 6.1 (1H *s* H–C-2), 3.85 (1H *t* *J* 8.5 Hz, H–C_6), 1.30 (9H complex Me–C-4 Me–C-10 Me–C-11).

Treatment of **3a** *with* K_2CO_3. To a soln of **3a** (400 mg) in MeOH (5 ml) was added a soln of 5% K_2CO_3 (20 ml). The soln was heated under reflux for 2 hr. The reaction mixture was acidified with 5% H_2SO_4, extracted with EtOAc and dried. Removal of solvent left a colourless gum which showed 4 spots on TLC. Dry column chromatography of this gum gave lactones **4a** (fractions 3–18), **2** (fractions 24–35), **1** (fractions 36–46) and **3b** (fractions 48–58).

Fractions 3–18: 1–13 *epidihydroestafiatone* **4a**. (50 mg) mp 194–196° $[\alpha]_D$ −19.1° (*ca* 1.34). (Found: C, 72.75; H, 8.01. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%). IR ν_{min}^{KBr} 1760 (γ-lactone), 1730 (cyclopentanone), 1630 and 900 cm^{-1} (double bond). PMR ($CDCl_3$): 4.99 [(1H *s*) and 4.68 (1H *s*), C-10=CH_2], 1.25 (3H *d* *J* 6 Hz, Me–C-4), 1.25 (3H *d* *J* 6 Hz, Me–C-11).

Epimerization of **4a** *to* **4b**. To a soln of **4a** (40 mg) in MeOH (2 ml) was added a soln of 10% K_2CO_3 (4 ml). The soln was heated under reflux for 2 hr. The reaction mixture was acidified with 5% HCl, extracted with $CHCl_3$ and evaporated to dryness. Dry column chromatography afforded **4a** (10 mg) and **4b** (20 mg) mp 87–90°, undepressed on admixture with the dihydroestafiatone. The IR spectra were superimposable.

Fractions 24–35: *ketolactone* **2**. (80 mg) mp 150–155° $[\alpha]_D$ 19.5° (*ca* 2.3). IR ν_{max}^{KBr} 1760 (γ--lactone), 1690 (·CO·C=C 5 membered ring), 1590 cm^{-1} (double bond). UV λ_{max} 228 nm (log ϵ 4.1). PMR ($CDCl_3$): δ 6.02 (1H *s* H–C-1), 3.85 (1H *t* *J* 10 Hz H–C-6), 1.30 (9H complex Me–C-4 Me–C-10 Me–C-11). The physical and spectral data of this compound are identical to those cited [5].

Fractions 36–46: *hypochaerin* **1**. Crystallization from Me_2CO–petrol gave prisms (50 mg) mp 108–110°, undepressed on admixture with an authentic specimen of natural hypochaerin. The IR spectra were superimposable.

Fractions 48–58: *dihydroisophoto-α-santonic lactone* **3b**. Crystallization from Me_2CO–petrol gave colourless needles (50 mg) mp 155–158° $[\alpha]_D$ 35° (*ca* 3.5). IR $\nu_{max}^{CHCl_3}$ 3410 (OH), 1760 (γ-lactone) and 1735 cm^{-1} (cyclopentanone). PMR ($CDCl_3$): δ 3.9 (1H *t* *J* 10 Hz H–C_6), 1.22 (3H *s* C-10–Me), 1.19 (3H *d* C-4–Me). A mixed mp with an authentic sample of **3b** obtained by saponification of **3a** showed no depression.

Stereochemistry at C_4. A soln of **1** (10 mg) in $CHCl_3$ (1 ml) was stirred with neutral Al_2O_3, grade I (60 mg) for 2 hr at room temp. The soln was filtered and evaporated to dryness. Crystallization from Me_2CO–petrol gave hypochaerin (8 mg) mp 108–110° identified with an authentic specimen by the standard methods.

Synthesis of **5**. (a) *Dihydroisophoto-α-santonic lactone* **3b**. Santonin (10 g) in 4:5 HOAc–H_2O (180 ml) was irradiated with a bare mercury-arc (Hanovia 100 W) lamp in a quartz flask under reflux for 14 hr. Removal of the solvent under red. pres. afforded a gum which was passed through a dry column (C_6H_6–EtOAc; 1 : 1). Elution gave 10-hydroxy-3-oxo-guai-4-en-6,12 olide (1.5 g) mp 169–171°. This compound (1.2 g) in EtOH (67 ml) was hydrogenated over 10% palladised charcoal (500 mg). The soln was filtered, evaporated to dryness and passed through a dry column (C_6H_6–EtOAc, 8:2). The eluted material (700 mg) after recrystallization from Me_2CO–petrol had mp 153–158°. Mixed mp with **3b** was undepressed and the IR spectra were superimposable.

(b) *Dihydroisophoto-β-santonic lactone* (C_{11} *epimer of* **3b**). To a soln of **3b** (140 mg) in MeOH (2 ml) was added a soln of 10% K_2CO_3 (10 ml). The soln was heated under reflux for 2 hr. The reaction mixture was acidified with 5% HCl, extracted with $CHCl_3$ and evaporated to dryness. Dry column chromatography afforded **3b** (40 mg) and its C–11 epimer mp 227–229° (80 mg). The physical and spectral data of the latter are identical to those cited.

(c) *Anhydrodihydroisophoto-β-santonic lactone* **5**. Dihydroisophoto-β-santonic lactone (60 mg) in 60% $HClO_4$–HOAc, (1:4 1 ml) was kept at room temp. for 24 hr. After dilution with H_2O and extraction with $CHCl_3$, the product was crystallized from Me_2CO–petrol to give **5** (30 mg) mp 68–70° $[\alpha]_D$ 30° (*ca* 1.04 $CHCl_3$). IR ν_{max}^{KBr} 1770 (γ-lactone), 1690 (·CO·C=C 5 membered ring), 1600 (double bond). UV λ_{max} 228 nm (log ε 4.2). PMR ($CDCl_3$): 3.90 (1H *s* H–C–2), 6.00 (1H *t* *J* 10 Hz H–C–6), 8.80 (9H complex Me–C–4 Me–C–10 Me–C–11).

Synthesis of hypochaerin from **3b**. A soln of **3b** (200 mg) in 60% $HClO_4$–HOAc (1:4) (10 ml) was kept at room temp. for 48 hr. After dilution with H_2O and extraction with $CHCl_3$, the soln was evaporated to dryness. Dry column chromatography gave **4b**, **2** and **1**.

Jacquinelin. (200 mg) mp 165–166° $[\alpha]_D$ 29° (*ca* 2.5). UV λ_{max} 255 nm (log ε 4.12). It was identified with an authentic sample by the standard methods.

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