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NEW PSEUDOGUAIANOLIDES FROM *PARTHENIUM CONFERTUM* GRAY (COMPOSITAE)

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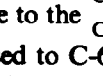
Abstract—Three pseudoguaianolides were isolated from various populations of *Parthenium confertum* located near the Conchos River south of Monterrey, N. L., Mexico. Two of the substances, conchosin-A (**1a**) and -B (**2**) are new C_{15}-oxygenated pseudoguaianolides while the third substance, hymenin (**13**) was previously isolated from *Hymenoclea salsola*, T. and G. The structure determinations of the new compounds are described.

INTRODUCTION

SEVERAL populations of a *Parthenium* taxon which occur in the Conchos River region south of Monterrey, N. L., Mexico, have many morphological characteristics of the *P. confertum* complex, but are nevertheless clearly distinct from any *P. confertum* types described by Rollins[1] in his monograph of the genus. Some of the floral characters are similar to those of *P. lyratum*; however, the distribution of this species is not known to include the Rio Conchos area. Therefore, we use the *P. confertum* designation for the populations presently under study until a more thorough re-interpretation of the entire genus has been accomplished.

Our first collection of *P. confertum*, which was made in the spring of 1968 near Linares, N. L., yielded only conchosin-A; thus, its structure was determined prior to the isolation of conchosin-B. One of the substances, compound **2**, derived in the course of the structure elucidation of conchosin-A was later found to be identical with a second new natural product which we then named conchosin-B. Hymenin (**13**) was isolated along with the conchosin compounds; however, since it was previously reported from *Hymenoclea salsola* T. and G.[2] no description of its chemistry is reported here.

Conchosin-A

$C_{15}H_{18}O_5$, m.p. 150–152°; $[\alpha]_D^{28}$ − 29·4° EtOH, is the third pseudoguaianolide isolated from *Parthenium* species (hysterin[3] and tetraneurin-A[4] are the two compounds previously described) which does not contain the C-10 Me group since the characteristic doublet is not shown in its NMR spectrum. Conchosin-A is the first pseudoguaianolide in which the C-10 substituent is involved in an ethereal bridge to a secondary C atom as indicated by the signals at 3·6 δ (dd) and 4·15 (dd) (—CH_2—O—) and the doublet of doublets at 4·1 δ due to the  group. Conchosin-A contains an α,β'-unsaturated γ-lactone closed to C-6, a structural feature common to all the pseudoguaianolides previously isolated from *Parthenium* species.[3–5] For example,

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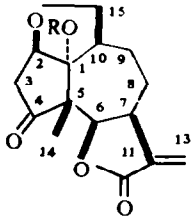

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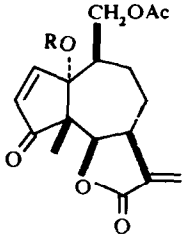
1b: R = Ac



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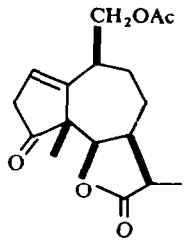

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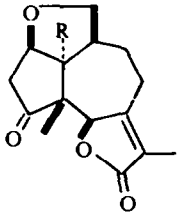

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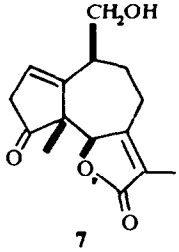
6: R = H



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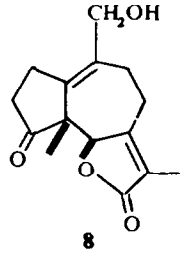

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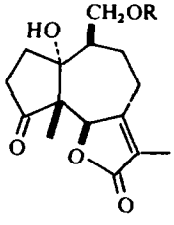
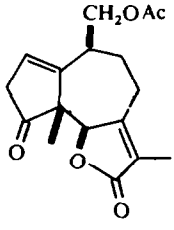


9: R = Ac
12: R = H



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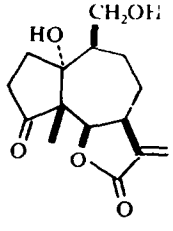

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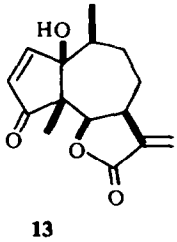

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this is shown in the NMR spectrum of conchosin-A by a doublet for the C-6 proton at 5·12 δ (J = 8 c/s) and two doublets for the exocyclic methylene group (Table 1). The two remaining O atoms of conchosin-A are involved in a tertiary OH group (IR: 3650 cm^{-1}) and a cyclopentanone ring (IR: 1740 cm^{-1}).

The presence of the cyclic ether group in conchosin-A and its position was proved in the following manner: When conchosin-A (**1a**) was treated with acetic anhydride in the presence of sodium acetate, 15-acetoxyparthenin (**2**) was produced; the NMR spectrum of **2** showed clearly the signals for an acetate group and for an AB coupling pattern (Table 1). Compound **2** was later found to be identical with conchosin-B, $C_{17}H_{20}O_6$, m.p. 143–144°. The position of the tertiary OH group in **2** was established as C-1 since the treatment of **3** (the acetate of **2**) with zinc dust in acetic acid eliminated the C-1 oxygen function and afforded **4**, which contains a double bond at the C_1—C_2 position as indicated by NMR signals at 6·09 δ (tr; J = 2·5 c/s) for the vinylic proton at C-2 and the two doublets at 2·88 δ (d; J = 2·5 c/s) and 3·05 δ (d; J = 2·5 c/s) due to the protons at C-3. That the exocyclic methylene group present in **2** was reduced in this reaction was evidenced by the absence of low field doublets for the C-13 protons and the presence of a new 3-proton doublet at 1·18 δ (J = 5 c/s) in the NMR spectrum of the product **4**.

All attempts to open the cyclic ether present in conchosin-A in acidic media failed due to a reversible addition reaction to the α,β-unsaturated ketone formed as intermediary. This was proved when compound **2** was hydrolyzed in the presence of hydrochloric acid; the tetrahydrofuran ring was regenerated giving conchosin-A in good yield. An attempt to open the cyclic ether of conchosin-A by treatment with acetic anhydride/*p*-toluenesulfonic acid leads only to acetoxyconchosin-A (**1b**) without opening of the ring. The above data clearly establishes, with the exception of the stereochemistry, formula **1a** for conchosin-A.

The stereochemistry of conchosin-A was provided by correlation with desacetyltetraneurin-A[4] (**11**). When the exocyclic double bond of **11** was isomerized to the endocyclic position, a compound identical in all respects with substance **12** of the conchosin series was formed. This correlation established that all the asymmetric centers of conchosin-A are the same as those in tetraneurin-A with the exception of the C-2 and C-7 positions; however, we assume that the side chain at C-7 is β-oriented as in all known sesquiterpene lactones. Since conchosin-A (**1a**) was easily reformed from conchosin-B (**2**) upon acidic treatment, the less strained isomer should represent **1a**; molecular models clearly indicate that a β-oriented C-2 cyclic ether is less strained. Therefore, the stereochemistry of conchosin-A should be as in **1a**. Other chemical transformations of conchosin-A and -B yielding **5**, **6**, **7**, **8**, **9**, and **10** are described in the experimental section. The stereochemistry shown at C-1 and C-2 for compound **6** is tentative.

EXPERIMENTAL*

Isolation of conchosin-A (**1a**). *Parthenium confertum* was collected near Linares, State of Nuevo León, along the Mexico City—Laredo highway in May, 1968. The whole plant (349 g) was extracted with EtOH and worked up in the usual manner, leaving an oil residue (21 g). The residue was dissolved in hot benzene and chromatographed over 500 g alumina Alcoa F-20 washed previously with EtOAc. The fractions eluted with benzene-EtOH (1 : 1) and EtOAc were combined and crystallized from acetone-$CHCl_3$ yielding 2·09 g

* All m.ps are uncorrected. IR were recorded in $CHCl_3$ and UV in 95% EtOH unless otherwise stated. Analyses were determined, in part, by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium Elbach über Engelskirchen, West Germany.

TABLE 1[a]. NMR SIGNALS FOR CONCHOSIN-A, -B AND DERIVATIVES

Compound	H-2	H-6	H-10	C_5-Me	C_{10}-CH_2OR	C_{11} = CH_2	C_{11}-Me	Miscellaneous
1a[b]	4·2dd	5.12d (J = 8)		1·22	4·3dd [J_{AB} = 4·5 3·6dd J_{AB} = 4·5 J_{AX} = 6]	5·58, d (J = 2) 6·12, d (J = 2)		
2	8·3d (J = 6)	4·9d (J = 8)		1·28	4·08d (J = 7·5)	5·6d (J = 2) 6·3d (J = 2)		2·05 H_3 -OAc 6·24d (J = 6)
3	8·18d (J = 6)	5·0d (J = 8)		1·25	4·12d (J = 7)	5·66d (J = 2·5) 6·33d (J = 3)		2·0; 2·08 H_3 -OAc 6·25d (J = 6)
4	6·09t (J = 2·5)	4·12d (J = 9)	2·43m	1·24	4·24d (J = 10)		1·18d (J = 5)	H_3 2·88d (J = 2·5) 3·05d (J = 2·5) 2·05; OAc
1b	4·95t (J = 4·5)	5·0d (J = 8)			3·58m	5·45d (J = 3·5) 6·24d (J = 3·5)		2·0 -OAc
5	3·58t (J = 9)	5·5d (J = 2)		1·08	4·41t (J = 9)		1·83d (J = 2)	
6[b]	4·83m	5·88d (J = 2)		0·99	4·09dd [J_{AB} = 4 3·4 dd J_{BX} = 5 J_{AX} = 3]		1·83t (J = 1·5)	H_3 [$J_{A'B'}$ = 11 2·3dd $J_{B'X'}$ = 4 2·82dd $J_{A'X'}$ = 2]
7	6·22t (J = 2·5)	4·51c (J = 2)		0·99	3·51d (J = 6)		1·85d (J = 1)	
8		4·69q (J = 1·5)		1·0	4·26q (J = 12)		1·83d (J = 1·5)	
9		5·41d (J = 2)	2·5t (J = 5)	0·73	4·16m (J = 5·5) 2dd		1·83d (J = 2)	2·05 -OAc
10	6·23t (J = 2·5)	4·53d (J = 2)		1·0	4·01d (J = 8)		1·85d (J = 2)	2·07 -OAc
12		5·25d (J = 1·5)		0·58	3·5m		1·7d (J = 1·5)	

[a] Spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer. Values are given in ppm (δ-scale) relative to TMS as an internal standard. Numbers in parentheses denote coupling constants in c/s; singlets are unmarked, multiplets are described as follows: d = doublet, t = triplet, q = quarter, m = complex signal whose center is given.

[b] Recorded on 100 Mc spectrometer

conchosin-A, m.p. 146–148°. Recrystallization from acetone-$CHCl_3$ raised the m.p. to 150–152°; $[\alpha]_D^{28}{}_{EtOH}$ −29·4°; λ_{max} 212 nm, ε 7550; ν_{max}: 3585, 1755, 1600, 1660 and 875 cm^{-1}; ν_{max} (Nujol): 3560, 3350, 1760, 1740, 1635 and 1660 cm^{-1}. (Found: C, 64·42; H, 6·57; O, 29·01. $C_{15}H_{18}O_5$: requires: C, 64·73; H, 6·52; O, 28·75%).

Isolation of conchosin-A (**1a**), *-B* (**2**), *-C, -D and hymenin* (**13**). *Parthenium confertum* collected 15·8 miles southeast of Linares, State of Tamaulipas, along Highway 85, May 27, 1969 (Voucher No. 277787),* yielded conchosin-A and -B and hymenin along with a mixture of two minor components† which were named conchosin-C and -D. When the air-dried and ground plant material (230 g) was extracted with $CHCl_3$ and worked up in the usual way, it yielded 5 g crude syrup. The syrup was dissolved in benzene-EtOAc (7:3) and chromatographed over silica gel (220 g) packed in benzene-EtOAc. The column was eluted with 78 fractions (50 ml each) of benzene-EtOAc (6:4). All the fractions were monitored by TLC. Fractions 19–20 yielded 0·5 g oil (designated a); fractions 31–35 yielded 0·5 g oil (designated b); and fractions 36–78 furnished 1 g crystals (designated c). Column chromatography of the oil (a) over silica gel (70 g) packed with EtOAc–n-hexane (1:1) and eluted with the same solvents yielded, after trituration with ether, 130 mg crystals. NMR analysis of the crystals indicated the presence of two new pseudoguaianolides in a 9:5 ratio; these substances were named conchosin-C and -D.† However, all attempts to separate the two compounds were unsuccessful.

Column chromatography of 0·5 g oil (b) over silica gel (70 g) packed with EtOAc–n-hexane (6:4) yielded 40 mg crystals, m.p. 173–174° (from EtOAc) [the crystals were identical with an authentic sample of **13**], 378 mg of **2**, m.p. 138–144° (from acetone-ether) and 193 mg of conchosin-A, m.p. 146–147·5° (from $CHCl_3$-EtOAc).

Recrystallization of crystals c (1 g) from $CHCl_3$-EtOAc yielded 0·5 g of **1a**.

Treatment of conchosin-A with Ac_2O *and* AcONa. Conchosin-A (10 g) was dissolved in Ac_2O (50 ml) containing NaOAc (10 g); the mixture was refluxed for 2½ h. The reaction mixture was poured into ice water and then the icy soln was extracted with $CHCl_3$; the organic layer was then washed with a $NaHCO_3$aq until the pH of the washings were neutral.

The soln was dried and concentrated and ,upon addition of ether, compound **2** crystallized (5·6 g). A pure sample was obtained after recrystallization from acetone–ether, m.p. 143–144°; λ_{max} 213 nm; ε 20900; ν_{max}: 3440, 1760, 1730, 1590, 1225 and 890 cm^{-1}. (Found: C, 63·54; H, 6·19; O, 30·03. $C_{17}H_{20}O_6$ requires: C, 63·74; H, 6·29; O, 29·97%).

Compound **2** was identical in all respects with natural conchosin-B.

Conchosin-B acetate (**3**). A soln of conchosin-A (1 g) in Ac_2O (10 ml) containing NaOAc (1 g) was refluxed for 5 hr; the reaction soln was worked up as in the preceding experiment and the oily residue thus obtained was chromatographed over alumina Alcoa F-20. Pure benzene eluted 160 mg of **3**, m.p. 144–145°: an analytical sample was obtained by recrystallization from acetone-$CHCl_3$, m.p. 144–145°; λ_{max}: 213 nm; ε 19300; ν_{max}: 1760, 1730, 1660 and 1230 cm^{-1}. (Found: C, 63·20; H, 6·08; O, 30·70. $C_{19}H_{22}O_7$ requires: C, 72·97; H, 6·12; O, 30·91%).

Treatment of **3** *with* Zn. A soln of **3** (50 mg) in AcOH (25 ml) was treated with Zn dust (3 g); the mixture was refluxed for 18 h. The mixture was filtered; the filtrate was diluted with water and extracted with $CHCl_3$; the organic layer was washed with a $NaHCO_3$aq and water and finally dried and concentrated. The elimination product **4** crystallized on addition of ether to the concentrate (260 mg, m.p. 167–170°); recrystallization from acetone-isopropyl ether raised the m.p. to 169–170°; ν_{max}: 1760, 1740, 1670 and 1240 cm^{-1}. (Found: C, 66·82; H, 7·25; O, 26·14. $C_{17}H_{22}O_5$ requires: C, 66·65; H, 7·24; O, 26·11%).

Conchosin-A acetate (**1b**). A soln of conchosin-A (500 mg) in Ac_2O (10 ml) was treated with *p*-toluenesulfonic acid (200 mg). The soln was kept at room temp for 24 h, poured in water and the resultant soln was extracted with $CHCl_3$; the organic layer was washed with $NaHCO_3$aq and then water. The $CHCl_3$ soln was dried and concentrated and, upon addition of isopropyl ether, 320 mg of **1b** crystallized, m.p. 180°. After several recrystallizations from acetone isopropyl-ether, the m.p. of the material was raised to 200–205°; ν_{max}: 1760 and 1210 cm^{-1}. (Found: C, 63·60; H, 6·30; O, 29·97. $C_{17}H_{20}O_6$ requires: C, 63·74; H, 6·29; O, 29·97%).

Isoconchosin-A (**5**). A soln of conchosin-A (1 g) in MeOH (40 ml) was treated under standard hydrogenation conditions using Pd-$CaCO_3$ (100 mg) as catalyst. After 4 h the soln was filtered and the filtrate was evaporated at reduced press and the residue, after crystallization from acetone-ether, afforded 850 mg of **5**,

* This voucher is deposited in the University of Texas Herbarium, Austin.

† These compounds will be the subject of a future communication.

m.p. 218–220°; recrystallization from acetone-ether raised the m.p. to 228–230°; λ_{max}: 220 nm; ε 14600; ν_{max}: 3580, 1750, 1730 and 1660 cm^{-1}. (Found: C, 64·64; H, 6·50; O, 28·92. Calc. for $C_{15}H_{18}O_5$ requires: C, 64·73; H, 6·52; O, 28·75%).

15-*Acetoxyisocoronopilin* (**9**). Conchosin-B **2** (1 g) dissolved in MeOH (50 ml) was hydrogenated in the presence of $Pd/CaCO_3$ (100 mg). When the absorption of H_2 ceased, the catalyst was removed and the filtrate was evaporated, yielding 850 mg of **9**, m.p. 190–193°; recrystallization from acetone-ether raised the m.p. to 200–202°; ν_{max}: 3600, 1760, 1680 and 1245 cm^{-1}. (Found: C, 63·21; H, 6·94; O, 29·84. $C_{17}H_{22}O_6$ requires: C, 63·34; H, 6·88; O, 29·78%).

15-*Acetoxyanhydroisocoronopilin* (**10**). A soln of 850 mg of **9** in 10 ml pyridine and 2 ml $SOCl_2$ was kept at 5° for 5 min and then mixed with ice water; the soln was extracted with $CHCl_3$, the organic layer was washed, dried and evaporated. The residue thus obtained crystallized from acetone-ether affording 425 mg of **10**, m.p. 155–157°; recrystallizations from the same solvents raised the m.p. to 174–176°; ν_{max}: 1765, 1680 and 1245 cm^{-1}. (Found: C, 67·27; H, 6·64; O, 26·24. $C_{17}H_{20}O_5$ requires: C, 67·09; H, 6·62; O, 26·29%).

Saponification of 15-*acetoxyanhydroisocoronopilin* (**10**). A MeOH soln (30 ml) of **10** (240 mg), $NaHCO_3$ (240 mg) and water (5 ml) was kept at room temp for 16 hr; the soln was diluted with water and then extracted with $CHCl_3$. The oily residue obtained on workup of the extract was chromatographed over alumina Alcoa F-20 affording **6**, **7** and **8**.

Compound **6** (40 mg) was recrystallized from acetone-ether, m.p. 155–156°; ν_{max}: 1760 and 1675 cm^{-1}. (Found: C, 68·43; H, 7·03; O, 24·33. $C_{15}H_{18}O_4$ requires: C, 68·68; H, 6·92; O, 24·40%).

Compound **7** (100 mg), m.p. 217–222°, was recrystallized from acetone-isopropyl ether; the m.p. was raised to 223–225°; ν_{max}: 3640, 1760 and 1680 cm^{-1}. (Found: C, 68·83; H, 6·84; O, 24·27. $C_{15}H_{18}O_4$ requires: C, 68·68; H, 6·92; O, 24·40%).

$CHCl_3$-MeOH (20:1) eluted the more polar **8** (15 mg); it is a yellow substance, m.p. 175–180°, which, after recrystallization from acetone-ether, showed a m.p. of 180–183°: ν_{max}: 3610, 1760, 1720 and 1680 cm^{-1}. (Found: C, 68·46; H, 6·87; O, 24·21. $C_{15}H_{18}O_4$ requires: C, 68·68; H, 6·92; O, 24·40%).

Hydrolysis of conchosin-B (**2**). A soln of conchosin-B (400 mg) in MeOH (20 ml) containing 2 ml of conc HCl was refluxed for 20 min, diluted with water, concentrated under reduced press, and then extracted with $CHCl_3$. The crystalline product obtained from the $CHCl_3$ extract, 175 mg, m.p. 142–143°, was identified as conchosin-A by direct comparison.

Correlation between conchosin-A and tetraneurin-A. Compound **9** (800 mg) was refluxed for 20 min in 40 ml of MeOH containing 4 ml conc HCl; workup afforded 410 mg of **12**, m.p. 210–212° (from acetone-ether); recrystallization from acetone ether raised the m.p. to 223–225°. (Found: C, 64·46; H, 7·25; O, 28·31. $C_{15}H_{20}O_5$ requires: C, 64·27; H, 7·19; O, 28·54%).

When desacetyltetraneurin-A[4] was hydrogenated with Pd/C as catalyst, material was obtained which was identical in all respects with an authentic sample of **12**.

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