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TETRANEURIN-B, -C AND -D, NEW C_{14}-OXYGENATED PSEUDOGUAIANOLIDES FROM *PARTHENIUM* (COMPOSITAE)

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Abstract—The structures of two new pseudoguaianolides, tetraneurin-B (2) and -C (3), first isolated from *Parthenium alpinum* var. *tetraneuris*, have been established. The isolation and structure determination of tetraneurin-D (4), a new pseudoguaianolide from *P. lozanianum* and *P. fruticosum*, are reported; the latter two species also contained tetraneurin-B and -C.

INTRODUCTION

IN CONNECTION with our previous investigation of the pseudoguaianolide tetraneurin-A (1),[1] we also reported the isolation from *Parthenium alpinum* var. *tetraneuris* (Barneby) Rollins (collected near Portland, Colorado in 1966) of two other new sesquiterpene lactones, which we named tetraneurin-B, $C_{17}H_{22}O_6$, m.p. 194–195°, $[\alpha]_D^{23}$ -44·7° and tetraneurin-C, $C_{19}H_{26}O_7$, m.p. 145°, $[\alpha]_D^{25}$ -109°. A 1969 collection of *P. lozanianum* Bartlett obtained from near Cerro de la Silla, Monterrey, N. L., Mexico yielded tetraneurin-B and -C and a third substance which we named tetraneurin-D, $C_{17}H_{24}O_6$, m.p. 203·5–205·5°, $[\alpha]_D^{25}$ −72·8°. Finally, a 1969 collection of *P. fruticosum* Less. var. *trilobatum* Rollins from near Linares, N. L., Mexico, yielded tetraneurin-B, -C and -D and still another new, as yet uninvestigated, sesquiterpene lactone which we named fruticosin. We describe here the structure determinations of tetraneurin-B, -C and -D.

Structure of tetraneurin-B(2)

The UV, IR and NMR spectral data for tetraneurin-B indicated that it had structural features similar to those previously encountered in tetraneurin-A (1): For example, the presence of an α,β′-unsaturated γ-lactone ring and a non-conjugated cyclopentanone function in tetraneurin-B were evident from the following data: λ_{max1} 211 nm (ε 9630), λ_{max2} 290 nm (ε 39); IR bands at 1725 and 1760 cm^{-1}. An IR band at 3500 cm^{-1} is typical for a tertiary OH group. Although the NMR spectrum of tetraneurin-B displayed a 3-proton doublet at 1·15 δ for a C_{10}-secondary Me group, a singlet for the C_5-tertiary Me group was missing. Instead, the spectrum exhibited a 2-proton signal at 4·36 δ which could be attributed to the presence of a —CH_2OAc group attached to the C_5-tertiary C-atom. Since the NMR spectrum of tetraneurin-D (**4**) also displayed a 2-proton singlet at 4·35 and tetraneurin-C (**3**) exhibited a pair of AB doublets centered at 4·15 and 4·31 δ ($J = 12$, each), all the three natural products, tetraneurin-B, -C and -D, appeared to have similar methylene-oxy groups at C-5. Although a C_{14}-oxygenated pseudoguaianolide, mexicanin-H (**5**), has been described from *Helenium* species,[2] this is the first report of this type of compound from *Parthenium*.

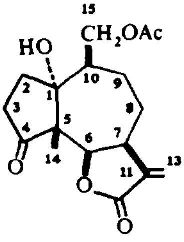
A peracetic acid Baeyer–Villiger oxidation of tetraneurin-B provided in a low yield a crystalline product, $C_{17}H_{22}O_7$, m.p. 187–189°, whose structure appeared from NMR data to correspond to structure **6**. Oxidative cleavages of C_4-oxypseudoguaianolides by Baeyer–Villiger oxidation yielding similar products are well known: For example, coronopilin (**8**) afforded psilostachyin[3] (**7**); damsin (**9**) yielded psilostachyin C (**10**).[4]

The Baeyer–Villiger product **6** was converted with $NaBH_4$ to the dihydrodesacetyl derivative **11** whose NMR spectrum displayed a doublet at 1·17 δ for a new C_{11}-secondary Me group. The absence of the acetate group in **11** was indicated by the lack of a signal for an acetyl Me group. When **11** was oxidized with periodic acid, the vicinal glycol function was cleaved yielding a crystalline product, identical in all respects with noranhydrodihydropsilostachyin[3] (**12**). The correlation of tetraneurin-B with **12** provided structure **2** for tetraneurin-B with the exception of the stereochemistry at C-5. The configuration at C-5 was assigned on the basis of comparative CD studies of tetraneurin-B with coronopilin (**8**): Coronopilin exhibited a single positive Cotton effect at 294 nm; $[\theta]$ +4930° (MeOH) and tetraneurin-B also displayed a similar Cotton effect at 292 nm, $[\theta]$ +7030° (MeOH). Thus, this result indicates a β-orientation for the C_5 CH_2OAc group in tetraneurin-B and establishes structure **2** for this compound.

Structures of tetraneurin-C (3) *and -D* (4)

Tetraneurin-D was converted with acetic anhydride and pyridine to an acetate which was identical in all respects with tetraneurin-C; therefore, -D is the desacetyl analog of -C. Tetraneurin-D was also converted after oxidation with CrO_3-H_2SO_4 to a ketone which was identical in all respects with tetraneurin-B (**2**); this result established that -D is the C_4-OH analog of -B. On the basis of these conversions, tetraneurin-C and -D could be assigned structures **3** and **4**, respectively, with the exception of their stereochemistry at C-4. The absolute configuration at C-4 in -D (and thus also in -C) was determined by the Horeau method:[5] Following the asymmetric esterification[6] of -D with excess racemic α-phenylbutyric acid anhydride, (−)-α-phenylbutyric acid was recovered in an optical yield of 38%. This result indicated that the orientation of C-4 OH group in -D is β and, accordingly, that the C_4 acetoxyl function in -C is β. The assigned stereochemistry at C-4 in -C and -D was also in accord with the observation that for tetraneurin-C (**3**), NOE irradiation at the NMR frequency of the H_{14} protons showed no response on the H_4 proton.

Therefore, all the available evidence indicates that tetraneurin-B, -C and -D correspond to structures **2**, **3**, and **4**, respectively.



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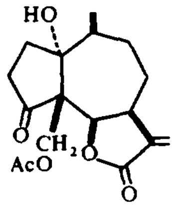

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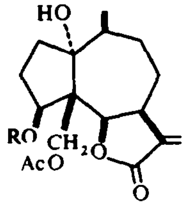

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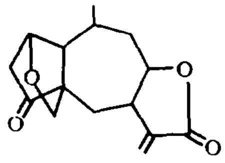
4: R = H



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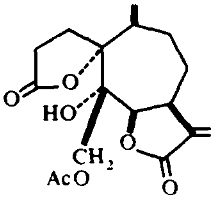

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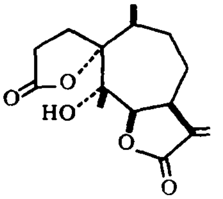

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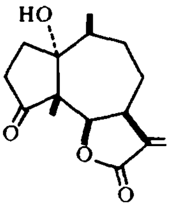

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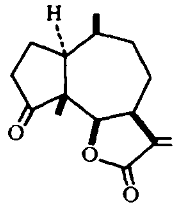

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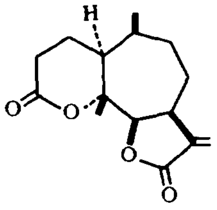

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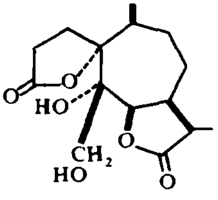

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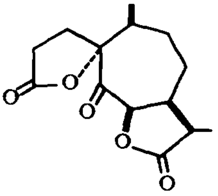

12

TABLE 1. NMR DATA OF TETRANEURIN-B, -C, AND -D AND DERIVATIVES[a]

Compd.	H_4	H_6	H_7	$C_{11}=CH_2$	H_{14}	C_{10}-Me	Acetyl-Me	Other
2		5·02d (J = 8)	3·40m	5·64d (J = 2·5) 6·26d (J = 3·0)	4·36	1·15d (J = 7·5)	2·01	
3[b]	5·71dd (J = 6 and 9)	5·23d (J = 10)	3·38m[d]	5·48d (J = 3·0) 6·16d (J = 3·3)	4·15d 4·31d (J = 12 ea)	1·10d (J = 7·5)	2·02 2·06	
4	4·95dd (J = 7 and 9)	5·50d (J = 10)	3·43m	5·65d (J = 3·0) 6·32d (J = 3·3)	4·35	1·12d (J = 7·5)	2·03	
4[c]	4·57m	5·13d (J = 9·5)	3·40m	5·65d (J = 3·0) 6·06d (J = 3·3)	4·08	0·97d (J = 7·5)	1·94	3·33 (C_1-OH) 4·40 (C_4-OH)
6		5·10d (J = 10)	3·53m	5·63d (J = 3·0) 6·34d (J = 3·0)	4·11d 4·42d (J = 12 ea)	1·00d (J = 7·0)	2·12	
11	4·95	4·95 brd. d (J = 6)				0·93d (J = 7·0)		1·17 (C_{11}-Me)*d* (J = 6)

[a] Spectra were recorded in $CDCl_3$ on a Varian A-60 spectrometer unless otherwise noted. Values are given in ppm (δ-scale) relative to TMS as an internal standard

[b] Recorded on a Varian HA-100 spectrometer

[c] Recorded in DMSO-d_6

[d] Confirmed by spin decoupling experiments

EXPERIMENTAL*

The isolation tetraneurin-B (**2**) and -C (**3**) from *Parthenium alpinum* var. *tetraneuris* (Barneby) Rollins was previously described.[1]

Tetraneurin-B (**2**), *-C* (**3**) *and -D* (**4**) *from* Parthenium lozanianum *Bartlett*. air dried and ground material of *Parthenium lozanianum* (Voucher No. 272653†) collected in the Summer of 1969 on the hillside of Cerro de la Silla, Monterrey, N.L., Mexico, was extracted 3 times with $CHCl_3$ and worked up in the usual way;[3] yield: 38·5 g of crude syrup from 1 kg of plant material. About 200 ml of ether were added to the crude syrup and the resultant amorphous deposits were removed by filtration. After evaporation of the ether, 40 ml of $CHCl_3$ were added to the syrup. The soln was allowed to stand in a refrigerator for a few hr; yield of crude crystals: 1·55 g. The crude crystals were recrystallized from 20 ml acetone; yield: 550 mg pure **4**, m.p. 203·5–205·5°. When the mother liquor from the first crop was concentrated to half of the original volume, an additional 410 mg of slightly impure tetraneurin-D, m.p. 197–199°, were obtained. The $CHCl_3$ filtrate from the crude crystals was chromatographed over a column of silica gel (650 g packed in ether–$CHCl_3$: 1:1). The column was successively eluted in 60 ml portions with 29 fractions of ether–$CHCl_3$ (1:1), then eluted in 250 ml portions with 8 fractions of ether–$CHCl_3$ (4:1) and finally eluted with 1 l. ether.

All fractions were monitored by TLC. Fractions 12–19 yielded 5 g of oil which was a mixture of tetraneurin-B (**2**) and -C (**3**) by NMR analysis. Fractions 22–29 yielded 2·4 g of oil which afforded, after trituration with ether, 303 mg of crystals. The crystals were a mixture of tetraneurin-B (**2**) and -D (**4**) in a 3:2 ratio by NMR analysis. Fractions 30–38 yielded 2·0 g of oil which furnished, after trituration with ether, 1·1 g of crude tetraneurin-D as crystals. Recrystallisation from acetone yielded 500 mg of pure tetraneurin-D (**4**), (0·01% overall yield): m.p. 203·5–205·5° (from acetone): $[\alpha]_D^{25}$ $-72·8°$ (MeOH: C, 0·54): λ_{max} (MeOH): 212 nm (ε 10500); IR bands (nujol): 3500, 1750 and 1720 cm^{-1}. (Found: C, 62·83; H, 7·51; O, 29·49. Calc. for $C_{17}H_{24}O_6$ requires: C, 62·98; H, 7·42; O, 29·61%).

Tetraneurin-B (**2**), *-C* (**3**), *-D* (**4**) *and fruticosin from* Parthenium fruticosum *Less. var.* trilobatum *Rollins*. Air-dried and ground material of *P. fruticosum* (Voucher No. 277721) collected July 6, 1969 near Linares, N.L., Mexico, was extracted with $CHCl_3$ and worked up in the usual way; yield: 1·3 g of crude syrup from 75 g of plant material. The syrup was chromatographed over silica gel (75 g packed with benzene): elution with benzene gave 65 mg (0·01% yield) of a new substance which we named fruticosin: m.p. 127–129°; NMR ($CDCl_3$); 1·1, d (J=7), 3H; 2·12 and 2·17, s, 3H each; 4·85, m, 1H; 5·15–5·50, m, 2H; 5·56, d (J=2·5) 1H; 6·28, d (J=3·3) 1H. Elution of the column with benzene-acetone (8:1) afforded -B **2**, -C (**3**) and -D (**4**): yield of tetraneurin-D; 0·2 g (0·03%).

Formation of tetraneurin-B(**2**) *from tetraneurin-D* (**4**). A soln of 30 mg of tetraneurin-D in 2 ml of acetone was cooled with ice–water and then treated with 10 drops of CrO_3-H_2SO_4 reagent.[7] After 1 min, 5 ml water was added to the reaction soln. The soln was then extracted with 3 (2 ml) portions $CHCl_3$. The combined $CHCl_3$ extract was washed with sat $NaHCO_3$ aq, dried over Na_2SO_4 and then evaporated. The resultant residue was chromatographed on silica gel G TLC plates (developed twice with benzene–EtOAc; 1:1). A major band (R_f 0·6) afforded 20 mg crude crystals; recrystallization from $CHCl_3$–light petroleum furnished pure -B (**2**): m.p. 194–195° (from $CHCl_3$–light petroleum); $[\alpha]_D^{25}$ $-44·7°$ (MeOH: c, 0·62); λ_{max1} (MeOH): 211 nm (ε 9630); λ_{max2} 290 (ε 39); IR bands (nujol): 3500, 1760 and 1725 cm^{-1}. (Found: C, 63·34; H, 7·10; O, 30·41. $C_{17}H_{22}O_6$ requires C, 63·34; H, 7·10; O, 30·55. CD of **2** (c, 0·55; MeOH): $[\theta]_{335}$ 0; $[\theta]_{292}$ +7030°; $[\theta]_{245}$ 0; Γ/2 22 nm; CD of coronopilin (c, 0·50; MeOH): $[\theta]_{330}$ 0; $[\theta]_{294}$ + 4930°; $[\theta]_{237}$ 0. Γ/2 22 nm. The material was identical in all respects with the natural product.

Tetraneurin-C (**3**) *from -D* (**4**). A soln of 30 mg of **4** in 2 ml dry pyridine was mixed with 1 ml Ac_2O. The soln was kept standing at room temp overnight. After working up the reaction soln in the usual way, 30 mg crude crystals were obtained. The NMR spectrum of the crude crystals was identical with that of the naturally occurring -C (**3**). Recrystallization of the crude crystals from $CHCl_3$–light petroleum afforded a pure specimen of -C (**3**): m.p. 145° (from $CHCl_3$–light petroleum); $[\alpha]_D^{25}$ $-109·0°$ (MeOH: c, 0·05); λ_{max} (MeOH): 212 nm (ε 11000); IR bands (nujol): 3500 and 1730 cm^{-1} (Found: C, 62·57; H, 7·10; O, 30·41. $C_{19}H_{26}O_7$ requires: C, 62·40; H, 7·10; O, 30·59%).

Baeyer–Villiger product **6** *from tetraneurin-B* (**2**). Tetraneurin-B (1·1 g) was mixed with 8·2 ml of 40% peracetic acid in AcOH which contained 1 g of NaOAc–$3H_2O$; the mixture was then diluted with 21 ml

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* M.ps are uncorrected. Analyses were determined by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium, Elbach über Engelskirchen, West Germany.

† All voucher specimens are deposited in the University of Texas at Austin Herbarium.

AcOH and placed at room temp in the dark for a week. It was then discharged into 100 ml water. The aqueous soln was extracted 4 times with 40 ml portions $CHCl_3$; the combined $CHCl_3$ extracts were mixed with 100 ml water and $NaHCO_3$ powder was added to the $CHCl_3$–water mixture until the aqueous layer was slightly alkaline. The $CHCl_3$ layer was taken up and dried over Na_2SO_4. Evaporation of the $CHCl_3$ *in vacuo* gave a residue (0·3 g) which was preparatively chromatographed on silica gel G TLC plates with ether. A major band (R_f 0·45) yielded 180 mg oil which crystallized after standing in a minimum amount of EtOAc. Recrystallization from EtOAc afforded 50 mg of an analytically pure specimen of **6**. m.p. 187–189°; IR bands (nujol): 3450 and 1750 cm^{-1}. (Found: C, 60·26; H, 6·62; O, 33·15. $C_{17}H_{22}O_7$ requires: C, 60·38; H, 6·50; O, 33·10%).

Noranhydrodihydropsilostachyin (**12**) *from the Baeyer–Villiger product* **6** *via the dihydrodesacetyl derivative* (**11**). Ten mg of $NaBH_4$ were added portion-wise to a soln of 15 mg of **6** in 2 ml MeOH. After a few min, the MeOH was evaporated *in vacuo* and the resultant residue was mixed with 1 ml water and then 10 drops 10% H_2SO_4 were added. The acidified soln was extracted with 3 (2 ml) portions $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and then evaporated *in vacuo* to leave 15 mg of **11** as a colorless oil. A 1 ml $CHCl_3$ soln of the oil (**11**) was mixed with 50 mg periodic acid dihydrate in 1 ml water. The mixture was then vigorously shaken for 5 min and the $CHCl_3$ layer was removed from the aqueous layer and dried over Na_2SO_4. The $CHCl_3$ afforded, after evaporation, a crystalline residue. When the residue was triturated with a few drops ether, it furnished 7 mg crude **12**. Recrystallization from EtOAc gave 4 mg **12** (m.p. 181–183°),* which was identical in all respects with an authentic specimen of **12** prepared from **7**.

Determination of absolute configuration of C_4 *in tetraneurin-D* (**4**) *by the Horeau method.* A soln of 52·2 mg tetraneurin-D in 203·5 mg α-phenylbutyric acid anhydride was mixed with 1·5 ml dry pyridine. The soln was allowed to stand overnight at room temp and was then worked up in the standard manner;[6] yield: 160 mg of crystalline α-phenylbutyric acid, $[\alpha]_D^{24}$ −5·1° (*c*, 1·6, benzene). Fully stereospecific esterification should yield $[\alpha]_D^{24}$ −95·6°/[2(4·06)−1]=−13·1°; therefore, the optical yield is 38%.

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* Although the m.p. of **12** had been reported to be 170–172°,[3] a pure specimen of **12** from **7** melted at 180–182°.