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PSEUDOGUAIANOLIDES FROM *PARTHENIUM FRUTICOSUM**

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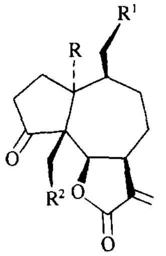
Key Word Index—*Parthenium fruticosum*; Compositae; sesquiterpene lactones; pseudoguaianolides, tetraneurines B–D; chiapine A, isochiapine B; parthoxetine.

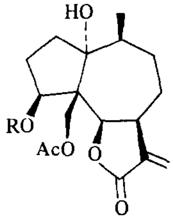
Abstract—In addition to the known tetraneurines B–D and chiapine A, two new pseudoguaianolides, parthoxetine and isochiapine B were isolated from *P. fruticosum* Less var. *fruticosum*. The structure of parthoxetine, which contains an oxetane ring was confirmed by X-ray analysis.

INTRODUCTION

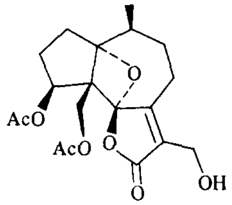
The two varieties of *P. fruticosum* Less, have been examined [1, 2]. A close structural relationship exists between the metabolites isolated from both varieties. The pseudoguaianolides tetraneurines B, C and D and the xanthanolide fruticosine were isolated from *P. fruticosum* Less var. *trilobatum* Rollins [1], while in the var. *fruticosum* only the pseudoguaianolides chiapine A, B and tetraneurine A were found [2]. In this paper we report the examination of *P. fruticosum* var. *fruticosum* collected in Chiapas, México. This study has resulted in the isolation of six pseudoguaianolides, two of which, isochiapine B (**2**) and parthoxetine (**6**), are new.



1 R = H, R^1 = Oibu, R^2 = H
2 R = OH, R^1 = H, R^2 = Oibu
3 R = OH, R^1 = H, R^2 = OAc



4 R = Ac
5 R = H



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RESULTS AND DISCUSSION

Aerial parts of *P. fruticosum* var. *fruticosum* afforded the new pseudoguaianolides isochiapine B (**2**) and parthoxetine (**6**), in addition to the previously reported chiapine A (**1**) [2], and tetraneurines B (**3**), C (**4**) and D (**5**) [1]. Spectroscopic data of isochiapine B (**2**) closely resembled those of tetraneurine B (**3**), the only dissimilarity being the signals corresponding to the ester residue bonded to C-15 which was that of an isobutyrate.

The novel lactone parthoxetine (**6**) contains two acetate groups as shown by the IR absorption at 1741 cm^{-1} and the ^1H NMR spectrum which showed two singlets (3H each) at δ 1.88 and 2.02 (Table 1). This was confirmed by the corresponding signals in the ^{13}C NMR spectrum (Table 2) and the fragments at *m/z* 321 [M + 1 − HOAc] and 261 $[M + 1 - 2HOAc]^+$ in the CIMS. The presence of a secondary methyl group ($\delta_{^1H}$ 1.05 *d*, $\delta_{^{13}C}$ 36.21 *d*) together with an oxygenated methylene carrying one of the acetates bonded to a tertiary carbon (AB system at $\delta_{^1H}$ 4.56 *d*, $\delta_{^1H}$ 4.22 *d*, $\delta_{^{13}C}$ 59.63 *t*) suggested the presence of a pseudoguaiane skeleton, which was supported by the presence of structurally related metabolites in the same plant. The other acetate was located at C-4 ($\delta_{^1H}$ 5.94 *d*, $\delta_{^{13}C}$ 77.46 *d*). The IR spectrum also exhibited adsorptions for hydroxyl (3536 cm^{-1}) and α,β-unsaturated-γ-lactone (1775, 1677 cm^{-1}). The typical lowfield signals of the C-13 vinylic protons in the ^1H NMR spectra of **1**–**5** were substituted by an A_2 system at δ 4.37 which is shifted downfield (δ 4.93) after addition of TAI.

The ^{13}C NMR spectrum contained a carbonyl carbon at δ 169.66 (*s*) and two vinylic carbons at δ 161.64 and 127.13 assigned to a conjugated endocyclic double bond. All these facts revealed the presence of the fragment A in the molecule. The remaining oxygen atom must be forming an ether bridge. This is supported by the presence of two lowfield singlets in the ^{13}C NMR spectrum at δ 105.67 (ketalic carbon) and 94.33 (tertiary carbon bearing oxygen). These signals were assigned to C-6 and C-1,

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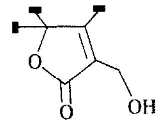

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Table 1. ^{1}H NMR spectral data of compounds **2** and **6** (80 MHz, $CDCl_3$, TMS as internal standard)

	2	**6**	**6** + TAI
H-4	—	5.94 *d* 5	5.93 *d* 5
H-6	4.95 *d* 8	—	—
H-7	3.37 *m*	—	—
H-8	—	2.99 *t* 6	3.06 *t* 6
H-13	6.22 *d* 3	4.37 (2H)	4.93 (2H)
H-13′	5.58 *d* 2.5		
H-14	1.13 *d** 7	1.05 *d* 7	1.05 *d* 7
H-15	4.36 *s* (2H)	4.56 *d* 11	4.55 *d* 11
H-15		4.22 *d* 11	4.14 *d* 11
$OCOCHMe_2$	1.13 *d** 7	—	—
	2.70 7	—	—
OAC		2.04 *s* (3H) 1.93 *s* (3H)	2.02 *s* (3H) 1.88 *s* (3H)

*Superimposed signal.

Table 2. ^{13}C NMR spectral data of parthoxetine (**6**) (20 MHz, $CDCl_3$, TMS as internal standard)

C		C	
1	94.33 *s*	11	127.13 *s*
2	34.94 *t**	12	169.66 *s*
3	31.55 *t**	13	54.66 *t*
4	77.46 *d*	14	15.68 *q*
5	61.01 *s*	15	59.63 *t*
6	105.67 *s*	O$\underline{C}$OMe	170.64 *s*
7	161.64 *s*		169.09 *s*
8	23.30 *t*†	OCO$\underline{Me}$	21.00 *q*
9	29.07 *t**		20.44 *q*
10	36.21 *d*		

*Assignments possibly interchangeable.
†Assigned by selective proton decoupling.

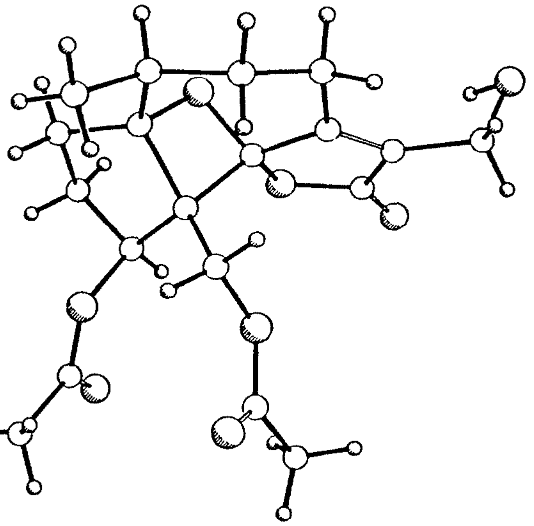

Fig. 1. Perspective drawing of parthoxetine (**6**).

respectively, taking into account the exitence in the same plant of pseudoguaianolides **1**–**5** which could be possible precursors of the oxetane. The structure of parthoxetine proposed as depicted in **6** was corroborated by X-ray analysis. Figure 1 shows a perspective molecular drawing which represents the absolute configuration if C-14 and C-15 are β as in all the pseudoguaianolides isolated from *Parthenium* species.

EXPERIMENTAL

Air dried aerial parts of *Parthenium fruticosum* var. *fruticosum* (1.4 kg) collected in Chiapas, México (voucher deposited in the Herbarium of the Instituto de Biología, UNAM, MEXU 321974) were extracted with $CHCl_3$. The solvent-free extract (126 g) was percolated through bentonithic earth [SiO_2 (72.5%), Al_2CO_3 (13.0%), Fe_2O_3 (5.0%), MgO (1.5%), CaO (0.8%), humidity (8.5%)] with hexane, $CHCl_3$ and EtOAc. The $CHCl_3$ fraction (67.4 g) was separated by CC (silica gel) affording 182 mg of chiapine A (**1**), 626 mg of isochiapine B (**2**), 247 mg of tetraneurine B (**3**), 7.71 g of tetraneurine C (**4**), 133 mg of tetraneurine D (**5**) and 96 mg parthoxetine (**6**). Known compounds were identified by comparison of their physical and spectroscopic constants with those reported in the literature.

Isochiapine B (**2**). Mp 154–156° (Me_2CO–hexane); $[\alpha]_D = -47.7°$ (c 0.195; $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1760, 1660; CIMS (CH_4, probe) 220 eV, m/z (rel. int.): 351 $[M+H]^+$ (100%); 333 $[M+H-H_2O]^+$; 263 $[M+H-C_4H_8O_2]^+$; 245 $[M+H-H_2O-C_4H_8O_2]^+$.

Parthoxetine (**6**). Mp 53–55° ($CHCl_3$–hexane); $[\alpha]_D = +78.4°$ (c 0.153; $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3536, 1775, 1741, 1677; CIMS (CH_4, probe) 220 eV, m/z (rel. int.): 381 $[M+H]^+$ (27.9), 363 $[M+H-H_2O]^+$ (51.1), 321 $[M+H-HOAc]^+$ (17), 303 $[M+H-H_2O-HOAc]^+$ (18), 261 $[M+H-2HOAc]^+$ (100), 243 $[M+H-2HOAc-H_2O]$ (32.1).

X-ray analysis of parthoxetine (**6**). Single crystals of **6** were obtained by slow crystallization from Me_2CO–hexane. They were monoclinic, space group P_{2_1} with $a = 9.1328$ (4), $b = 12.5114$ (6), $c = 9.3169$ (4) A, $F(000) = 423.96$, $\mu = 0.99$ cm^{-1},

$Z = 2$. Intensity data were measured on a Nicolet R3m four circle diffractometer operated in the ω scan mode using CuK_α monochromatic radiation. 1402 reflections collected up to $2\theta < 45$, yielded 1073 observed independent reflections with $I > 1.73\sigma(I)$. The structure was solved by direct methods [3] and refined by a matrix cascade procedure with anisotropic temperature factors for H-atoms to converge until a final R of 0.0613. The final difference map had no peaks greater than ± 0.26 eA^{-3}. The data on the bond lengths and angles, anisotropic temperature factors, hydrogen coordinates and temperature factors have been deposited at the Cambridge Crystallographic Data Centre.

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