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Article

16,17-*Seco*- and 2,3:16,17-di-*Seco*-pregnanes from *Guarea guidonia*

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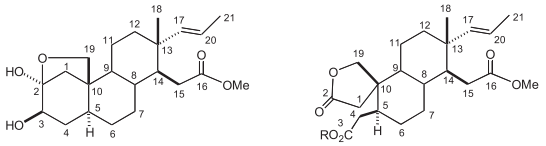
Dois novos *seco*- e di-*seco*-pregnanos, 2α,3β-diidróxi-2β,19-hemicetal-16,17-*seco*-pregn-17-en-16-oato de metila (**1**) e ácido 2,3:16,17-di-*seco*-pregn-17-en-3-óico-16-oato de metila-19-hidróxi-2-carboxílico-2,19-lactona (**2**), foram isolados da casca do caule de *Guarea guidonia*. Suas estruturas foram determinadas com base em dados espectrais, particularmente RMN uni- e bidimensionais e massas. Os esqueletos pregnânicos incomuns *seco*- e di-*seco* destes compostos estão sendo relatados pela primeira vez em Meliaceae, assim como a ocorrência de pregnanos no gênero *Guarea*.

Two new *seco*- and di-*seco*-pregnanes, 2α,3β-dihydroxy-16,17-*seco*-pregn-17-ene-16-oic acid methyl ester 2β,19-hemiketal (**1**) and 2,3:16,17-di-*seco*-pregn-17-ene-3-oic acid-16-oic acid methyl ester-19-hydroxy-2-carboxylic acid-2,19-lactone (**2**), have been obtained from the trunk bark of *Guarea guidonia*. Their structures have been established by a combination of 1D- and 2D-NMR spectroscopic techniques and MS data. The unique *seco*- and di-*seco*-pregnane carbocyclic skeletal types as found in compounds **1** and **2** are being reported in the Meliaceae for the first time as well as the occurrence of pregnanes in the genus *Guarea*.

Keywords: *Guarea guidonia*, Meliaceae, *seco*-pregnane, di-*seco*-pregnane

Introduction

Species of *Guarea* (Meliaceae) are found throughout tropical America and also in Africa.[1] This genus has been the subject of a number of investigations and is known as a rich source of secondary metabolites, including limonoids, sesqui-, di- and triterpenes and steroids.[2-5] *Guarea guidonia* L. Sleumer is a tree widely distributed in Brazil and the wood bark of this plant is employed in traditional medicine as an abortive and febrifugal agent and the seeds are used to treat rheumatism while the leaves and fruits are reported to be toxic to cattle.[6,7] Moreover, seed extracts of *G. guidonia* were shown to have anti-inflammatory activity in rats while antiviral properties against pseudo-rabies virus were reported for crude extracts of leaves and fruits.[7,8] In previous works sesquiterpenes were isolated from the stem bark of a specimen of *G. guidonia* occurring in south-eastern Brazil[3] while a specimen of *G. guidonia* collected in the central-western region of Brazil afforded a number of constituents, including di-, tri- and sesquiterpenes and steroids from the leaves[4] and compounds of the sesquiterpene, limonoid and coumarin types from the trunk bark.[5] In the course of the investigation of the trunk bark of the latter specimen,[5] the $CHCl_3$-soluble fraction of the ethanol extract was shown to contain two minor steroidal derivatives which, nevertheless, were not further isolated. The present study of the trunk bark of this same specimen has now allowed the isolation of these constituents which were characterized as two novel *seco*- and di-*seco*-pregnane derivatives (**1** and **2**). Their structural elucidation was mainly based on 1D and 2D NMR spectroscopic techniques.



1 **2:** R = H **2a:** R = Me

Figure 1. *Seco*- and di-*seco*-pregnanes from *G. guidonia.*

Results and Discussion

Compound **1** was obtained as an oil. Its molecular formula was established as $C_{22}H_{34}O_5$ by NMR spectroscopic data and HREIMS, which showed a molecular ion peak at *m/z* 378.2410, indicating six degrees of unsaturation. The IR absorptions at 3402 and 1734 cm^{-1} were consistent with

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the presence of hydroxyl and ester carbonyl groups. The ^{1}H NMR spectrum of **1** (Table 1) showed signals attributable to a propenyl moiety [δ 5.36 (dq, J = 16.6, 6.0 Hz), 5.23 (brd, J = 16.6 Hz), 1.61 (brd, J = 6.0 Hz)], a methoxyl group [δ 3.60 (*s*)], a carbinolic hydrogen [δ 3.60 (*m*)] and two AB doublets at δ 3.92 (J = 8.1 Hz) and 3.67 (J = 8.1 Hz) ascribed to an oxymethylene group. The ^{13}C NMR spectrum (Table 1) displayed signals for 22 carbon atoms, seven of which, with the aid of information afforded by the DEPT spectrum, confirmed the presence of propenyl (δ 142.0, 122.4, 18.2), carbomethoxy (δ 175.0, 51.6), oxymethylene (δ 67.4) and oxymethine (δ 73.6) groups. The remaining signals were attributed to a methyl, seven methylenes, four methines and three quaternary carbons, one of which could be assigned to a hemiketal carbon (δ 104.5). Comparison of ^{1}H and ^{13}C NMR data of **1** and 2α,3β-dihydroxypregnan-16-one 2β,19-hemiketal (**3**), a pregnane previously isolated from *Trichilia claussenii*[9] and *Melia volkensii*,[10] revealed that they have identical rings A, B and C, with the same cyclic hemiketal funcionality with an oxy linkage between C-2 and C-19 and with a β-hydroxyl substituent at C-3, bearing a *trans* di-equatorial relationship with the hydroxyl group at C-2. The presence of the aforementioned propenyl and carbomethoxy groups in **1**, in addition to the long-range connectivities observed in the HMBC spectrum between the methylene hydrogens at δ 2.27 and 1.88 assigned to H_2-15 and the carbonyl ester carbon and between H_3-18 (δ 0.79) and the olefinic carbon at δ 142.0 of the propenyl moiety were in accordance with a 16,17-*seco*-pregnane skeleton. The location of the 1-propenyl and the carbomethoxy groups at C-13 and C-14, respectively, was then established. Accordingly, two-bond proton-carbon correlations were observed between H_2-15 and C-14 (δ 46.5) and the olefinic hydrogen H-17 (δ 5.23) and C-13 (δ 39.5). The *cis*-orientation of C-18 methyl and the C-14 CH_2CO_2Me substituents was revealed by the correlations observed in the NOESY spectrum between H-18 and H-15. Hence, considering that the carbon backbones of **1** and **3** are likely to be formed by the same biosynthetic route accepted for all pregnane structural types, the orientation of both C-18 methyl group and H-14 of these compounds are assumed to be the same. The structure of this 16,17-*seco*-pregnane was then characterized as **1**.

Table 1. ^{1}H and ^{13}C NMR spectral data of **1** ($CDCl_3$) and **2** (pyridine-d_5)

No.	**1**			**2**		
	δ_C	δ_H (J in Hz)[a]	HMBC (H→C)	δ_C	δ_H (J in Hz)[a]	HMBC (H→C)
1	42.1	1.16 d (12.0) 2.32 brd (12.0)	C-2, C-3, C-5, C-10, C-19	37.3	2.90 d (18.6) H-1a 2.51 d (18.6) H-1b	C-2, C-9, C-10, C-19
2	104.5	-		175.3	-	C-1, C-19
3	73.6	3.60 m		177.2	-	
4	37.7	2.05 ddd (13.2, 11.8, 4.6) H-4a 1.11 m H-4b	C-2, C-3, C-5, C-10	36.9	2.92 dd (15.1, 1.9) H-4a 2.39 dd (15.1, 9.5) H-4b	C-5 C-3, C-5
5	42.3	1.42 m		41.3	1.13 m	
6	30.7	1.56 m		29.5		
7	29.3	1.58 m		30.4		
8	39.5	1.40 m		38.6	1.35 m	
9	45.3	1.20 m		50.5	1.34 m	
10	47.6	-		45.5	-	
11	20.8	1.37 m		21.8	1.03 m	
12	39.4	1.38 m		39.6		
13	39.5	-		39.6	-	
14	46.5	1.54 m		46.3	1.33 m	
15	35.2	2.27 dd (15.0, 3.0) H-15a 1.88 dd (15.0, 7.9) H-15b	C-8, C-12, C-13, C-14, C-16	35.3	2.38 dd (17.0, 1.6) H-15a 2.01 dd (17.0, 7.8) H-15b	C-8, C-14, C-16 C-8, C-14
16	175.0	-		174.6	-	
17	142.0	5.23 brd (16.6)	C-8, C-12, C-13, C-14, C-18, C-20, C-21	142.5	5.37 m	C-13, C-18, C-20, C-21
18	16.3	0.79 s	C-8, C-13, C-14, C-17	16.6	0.81 s	C-12, C-13, C-14, C-17
19	67.4	3.92 d (8.1) H-19a 3.67 d (8.1) H-19b	C-1, C-2, C-5, C-10	69.5	4.28 d (10.3) H-19a 4.20 d (10.3) H-19b	C-5, C-9
20	122.4	5.36 dq (16.6, 6.0)	C-12, C-17, C-18, C-21	122.5	5.37 m	C-12, C-13, C-18, C-21
21	18.2	1.61 brd (6.0)	C-17, C-20	18.2	1.56 d (4.3)	C-17, C-20
OCH_3-16	51.6	3.60 s		51.4	3.60 s	C-16

[a]The assignments were obtained by ^{1}H-^{1}H and ^{13}C-^{1}H correlations.

Compound **2** was isolated as an oil. The HRESITOFMS ([MH$^+$], *m/z* 393.2328) and NMR spectroscopic data of **2** suggested a molecular formula of $C_{22}H_{32}O_6$. Its IR spectrum showed absorption bands at 3451 (broad), 1774 and 1732 (broad) cm^{-1} indicating the presence of lactone and ester carbonyl and carboxyl groups. The ^{1}H and ^{13}C NMR spectra of **2** (Table 1) were similar in many respects to those of **1**. The proton and carbon shifts of the rings B and C corresponded to each other as well as the signals relative to the propenyl and methylene carbomethoxy groups. The ^{13}C NMR spectrum of **2**, however, lacked the hemiketal and carbinolic carbon resonances at δ 104.5 and 73.6 assigned to C-2 and C-3, respectively, in **1** and instead displayed signals ascribed to a carboxyl group (δ 177.2) and a lactone moiety (δ 175.3). Likewise, the multiplet at δ 3.60 attributed to the carbinolic hydrogen at C-3 in **1** was absent in the ^{1}H NMR spectrum of **2**. When **2** was methylated with diazomethane, a methyl ester derivative (**2a**) was obtained. Its ^{1}H NMR spectrum showed, in addition to a singlet at δ 3.69 assignable to a second carbomethoxy group and besides the one located at C-15, an AB pattern of two doublets at δ 4.03 and 4.20 (J = 10.7 Hz), suggestive of methylene hydrogens linked to an oxygen ester group. This pair of doublets showed a connectivity in the HMQC spectrum with the carbon signal at δ 69.1, and three-bond correlations in the HMBC spectrum with the carbon signals attributable to C-5 (δ 41.2) and C-9 (δ 50.3). These information, along with the long-range correlations discernible between the two-proton singlet at δ 2.48 (H-1) and the carbon signals at δ 69.1 (C-19), 176.7 (lactone carbonyl) and 45.3 (C-10), and between H_2-4 and the carbonyl group at δ 172.6 attributable to C-3, supported the presence of a 2,3-*seco*-A ring in **2a**, and also, in compound **2**. Accordingly, the location of a carboxyl moiety at C-3 as well as the formation of a γ-lactone ring between C-19 and C-2, with the latter bearing the carbonyl group, were established. As in the case of **1**, the β-configurations suggested for C-19 and C-4 are based on biogenetic grounds. The above-mentioned data could be satisfactorily assembled to give structure **2** for this 2,3:16,17-di-*seco*-pregnane steroid, whose unusual skeleton could have been originated from **1** through an oxidative cleavage of the C-2/C-3 bond. In order to allow a better comparison between the spectral data of **1** and **2**, ^{1}H and ^{13}C NMR spectra of **1** were also obtained in pyridine-d_5 (Table 2) whose results further supported the proposed structures for these compounds.

The finding of pregnane steroids in the *Guarea* genus is noteworthy, since this class of compounds has so far been described in only seven among the almost fifty genera comprising the Meliaceae, namely *Trichilia*,[9] *Melia*,[10] *Aglaia*,[11] *Dysoxylum*,[12] *Munronia*,[13] *Toona*[14] and *Turraea*.[15] In addition, *seco*-pregnane steroid derivatives are not of widespread occurrence in plant taxa. The great majority of these compounds has been described in members of the Asclepiadaceae, namely 14,15-, 15,16- and 8,14-*seco*- and 13,14:14,15-di-*seco*-pregnanes and their glycosides isolated from *Cynanchum* species[16] and from *Adelostemma gracillimum*,[17] *Biondia insignis*,[18] *Sarcostemma viminal*e,[19] *Solenostemma argel*[20] and *Tylophora tanakae*.[21] However, no records are available for the occurrence in the family Meliaceae of the unique 16,17-*seco*- and 2,3:16,17-di-*seco*-pregnane carbocyclic skeletal types displayed by compounds **1** and **2**.

Table 2. ^{1}H and ^{13}C NMR spectral data of **1** in pyridine-d_5

No.	δ_C	δ_H (J in Hz)[a]	HMBC (H→C)
1	43.9	1.34, overlapped H-1a 2.52 d (11.2) H-1b	C-3, C-5, C-10, C-19 C-2, C-3, C-5, C-9, C-10
2	105.6	-	
3	74.2	4.06 dd (10.2, 6.1)	C-4, C-5, C-10
4	38.4	2.14 m 1.66 m	C-3
5	42.6	1.36 m	
6	31.2	0.95 m 1.64 m	
7	29.9	1.50 m 1.99 m	
8	39.6	0.78 m	
9	45.6	1.08 m	
10	47.8	-	
11	20.9	1.27 m 1.56 m	
12	39.9	1.33 m	
13	39.7	-	
14	46.8	1.74 m	
15	35.5	2.37 dd (16.3, 2.0) H-15a 2.02 dd (16.3, 7.9) H-15b	C-3, C-8, C-14
16	174.8	-	
17	142.9	5.38 m	C-13, C-18, C-20, C-21
18	16.5	0.76 s	C-13, C-14, C-17
19	67.1	4.05 d (8.1) H-19a 3.83 d (8.1) H-19b	C-5 C-1, C-2, C-3, C-5, C-10
20	122.2	5.38 m	C-17, C-21
21	18.2	1.57 m	C-17, C-20
OCH_3-16	51.4	3.61 s	C-16

[a]The assignments were obtained by ^{1}H-^{1}H and ^{13}C-^{1}H correlations.

Experimental

General experimental procedures

Optical rotations were determined on a Perkin-Elmer 341 polarimeter (Na filter, λ=589 nm). IR spectra were recorded as films on a Bomem-Hartmann & Braun FT IR

spectrometer. 1D- and 2D-NMR experiments were run on a Bruker DPX-300 spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C), using TMS as an internal standard. HREIMS data was obtained at 70 eV on a VG Autospec spectrometer (Instituto de Química, UNICAMP, SP, Brazil), and HRQTOFESIMS spectrum (positive mode) was performed with an UltrOTOF mass spectrometer (Fiocruz/Farmanguinhos, RJ, Brazil). Silica gel 70-230 mesh and Sephadex LH-20 were used for column chromatography. Preparative TLC was performed on silica gel 60 PF_{254} and compounds were visualized by exposure of the edges of the plate to iodine vapors.

Plant material

The trunk bark of *Guarea guidonia* L. Sleumer was collected in Campo Grande, MS, Brazil, in June, 2002. The plant material was identified by Dr. Humberto Barreiros, Jardim Botânico do Rio de Janeiro, RJ, Brazil, where a voucher specimen (No. 1870) is deposited.

Extraction and isolation of chemical constituents

Air-dried and powdered trunk bark of *G. guidonia* (2.2 kg) was extracted successively at room temperature with hexane and then with EtOH. After evaporation of the solvent under reduced pressure, the residue obtained from the EtOH extract (145.3 g) was subsequently partitioned between MeOH-H_2O 1:1 and hexane, $CHCl_3$ and EtOAc. The dried $CHCl_3$ partition (29.5 g) was applied to a silica gel column and eluted with hexane-$CHCl_3$, $CHCl_3$-EtOAc and EtOAc-MeOH gradient systems to give 9 fractions. Gel filtration chromatography over Sephadex LH-20 of fraction 5 ($CHCl_3$-EtOAc 1:1, 315.3 mg) using $CHCl_3$-MeOH 7:3 as eluent gave 80 fractions. Fractions 47-52 from this column (18.0 mg) afforded **1** (7.8 mg) and **2** (4.9 mg) after prep. TLC on silica gel (CH_2Cl_2-EtOAc-MeOH-AcOH 10:4:0.15:0.1), R_f values 0.4 (**1**) and 0.5 (**2**).

*2α,3β-dihydroxy-16,17-seco-pregn-17-ene-16-oic acid methyl ester 2β,19-hemiketal (**1**)*

Yellowish oil; $[\alpha]_D^{23}$ - 4.5° (*c* 0.88, $CHCl_3$); IR (film) ν_{max}/cm^{-1}: 3402, 2930, 2856, 1734; ^{1}H and ^{13}C NMR data: see Table 1; HREIMS: *m/z* 378.2410 $[M]^+$ (calcd for $C_{22}H_{34}O_5$, 378.2407).

*2,3:16,17-di-seco-pregn-17-ene-3-oic acid-16-oic acid methyl ester-19-hydroxy-2-carboxylic acid-2,19-lactone (**2**)*

Yellowish oil; $[\alpha]_D^{23}$ - 7.8° (*c* 0.25, $CHCl_3$); IR (film) ν_{max}/cm^{-1}: 3451, 2962, 2927, 1774, 1732; ^{1}H and ^{13}C NMR data: see Table 1; HRESIMS: *m/z* 393.2328 $[M+H]^+$ (calcd for $C_{22}H_{33}O_6$, 393.2278). Compound **2** was treated with an ethereal solution of diazomethane to yield the corresponding dimethyl ester **2a**. ^{1}H NMR spectral data ($CDCl_3$): δ 0.88 (3H, s, H-18), 1.26 (1H, m, H-9), 1.56 (2H, m, H-11), 1.58 (2H, m, H-7), 1.66 (3H, dd, *J* 6.8, 0.9 Hz, H-21), 1.70 (1H, m, H-14), 1.96 (1H, dd, *J* 16.8, 8.4 Hz, H-15b), 1.98 (1H, m, H-5), 2.11 (1H, dd, *J* 16.0, 10.1 Hz, H-4b), 2.37 (1H, dd, *J* 16.8, 2.4 Hz, H-15a), 2.48 (2H, s, H-1), 2.48 (1H, dd, *J* 16.0, 2.8 Hz, H-4a), 3.64 (3H, s, OCH_3-16), 3.69 (3H, s, OCH_3-3), 4.03 (1H, d, *J* 10.7 Hz, H-19b), 4.20 (1H, d, *J* 10.7 Hz, H-19a), 5.27 (1H, dq, *J* 16.8, 6.8 Hz, H-20), 5.42 (1H, dd, *J* 16.8, 0.9 Hz, H-17). ^{13}C NMR spectral data ($CDCl_3$): δ 16.5 (q, C-18), 18.2 (q, C-21), 21.6 (t, C-11), 29.2 (t, C-6), 29.9 (t, C-7), 35.1 (t, C-15), 36.2 (t, C-4), 37.1 (t, C-1), 38.8 (d, C-8), 39.1 (s, C-13), 39.1 (t, C-12), 41.2 (d, C-5), 45.3 (s, C-10), 46.1 (d, C-14), 50.3 (d, C-9), 51.7 (q, OCH_3-3), 52.0 (q, OCH_3-16), 69.1 (t, C-19), 122.8 (d, C-20), 141.6 (d, C-17), 172.6 (s, C-3), 174.8 (s, C-16), 176.7 (s, C-2).

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Supplementary Information

^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}1H COSY, HMQC and HMBC NMR spectra of compounds **1**, **2** and **2a** are available free of charge at http://jbcs.org.br, as PDF file.

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