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Article

Two Dibenzylbutyrolactol Derivatives and Other Chemical Constituents from *Aristolochia peltato-deltoidea*

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Do extrato hexânico das partes aéreas de *Aristolochia peltato-deltoidea* Hoehne (Aristolochiaceae) foram isolados duas novas lignanas epiméricas do tipo dibenzilbutirolactol, *rel*-(8*R*, 8'*S*, 9*S*)-3,4-dimetoxi-3',4'-metilenodioxi-9β-etoxi- e *rel*-(8*R*, 8'*S*, 9*R*)-3,4-dimetoxi-3',4'-metilenodioxi-9α-etoxi-lignanas-8.8',9.O.9', além da neolignana benzofurânica eupomatenóide-7, α-tocoferilquinona, β-sitosterol e estigmasterol. Do extrato clorofórmico foram isoladas duas lignanas dibenzilbutirolactonas diasteroisoméricas: *rel*-(8*R*, 8'*R*)- e *rel*-(8*R*, 8'*S*)-3,4-dimetoxi-3',4'-metilenodioxi-9-oxo-lignanas-8.8',9.O.9'. A composição química das frações apolares do extrato hexânico também foi analisada por CG/EM. Dentre os componentes detectados, dez foram identificados. As estruturas dos compostos isolados foram elucidadas utilizando-se métodos espectrométricos.

The hexane extract from the aerial parts of *Aristolochia peltato-deltoidea* Hoehne (Aristolochiaceae) afforded two new epimeric lignans dibenzylbutyrolactol type, *rel*-(8*R*, 8'*S*, 9*S*)-3,4-dimethoxy-3',4'-methylenodioxy-9β-ethoxy- and *rel*-(8*R*, 8'*S*, 9*R*)-3,4-dimethoxy-3',4'-methylenodioxy-9α-ethoxy-lignans-8.8',9.O.9', besides a benzofuran neolignan, known as eupomatenoid-7, α-tocopherylquinone, β-sitosterol and stigmasterol. From chloroform extract were isolated two diastereomeric dibenzylbutyrolactone lignans: *rel*-(8*R*, 8'*R*)- and *rel*-(8*R*, 8'*S*)-3,4-dimethoxy-3',4'-methylenodioxy-9-oxo-lignans-8.8',9.O.9'. Chemical composition analysis by GC/MS of the non polar fractions from hexane extract also was carried out and ten components were identified. The structures of the isolated compounds were elucidated utilizing spectrometric methods.

Keywords: Aristolochia peltato-deltoidea, *Aristolochiaceae, benzofuran neolignan, dibenzylbutyrolactol lignans, α-tocopherylquinone*

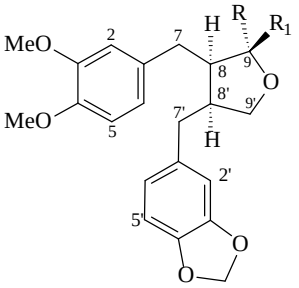
Introduction

The genus *Aristolochia* (Aristolochiaceae) is found in wide areas from the tropics to temperate zones and consists of about 300 species[1]. In Brazil, their genetic diversity has been about 90 species[2]. Some species from this genus has been known to possess some medicinal properties[3-4]. The specie *Aristolochia peltato-deltoidea* Hoehne, known as "jarrinha", is originated from South America[5] and no chemical or biological studies on this plant have been reported. Hexane and chloroform extracts of the dried aerial parts of a specimen of this plant after chromatographic fractionations afforded two epimeric dibenzylbutyrolactol lignans (**1** and **2**), two diastereomeric dibenzylbutyrolactone lignans (**3** and **4**), a benzofuran neolignan (**5**), previously isolated from *A. taliscana*[6], along with α-tocopherylquinone (**6**), not reported from any *Aristolochia* species so far, β-sitosterol and stigmasterol. Analysis by GC/MS of the non polar fractions from hexane extract resulted in the identification of phytol, farnesol, sphatulenol, hedycaryol, α-eudesmol, δ-selinene, 9-aristolen-1α-ol, caryophyllene oxide, and methyl and ethyl esters of hexadecanoic and nonanoic acids, respectively.

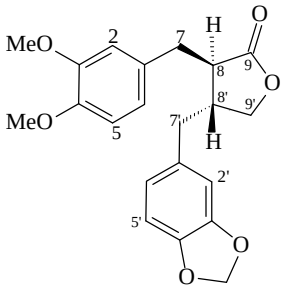
Results and Discussion

Compounds **1** (major component) and **2** were isolated as a mixture whose separation was not achieved by silica gel chromatography. Low resolution mass spectra, [M] at *m/z* 400, and comparative analysis of the ^{13}C-NMR proton noise-decoupled and DEPT spectra suggested for both compounds molecular formula of $C_{23}H_{28}O_6$, revealing that the two compounds were isomerics. The IR spectrum indicated the presence of absorption for aromatic ring, ether linkage and methylenedioxy groups and no absorption was observed for carbonyl or hydroxyl functions.

The NMR spectra of **1** and **2** (Table 1) showed signals for methoxyl [**1**: δ_H 3.75 and 3.78 (s each); δ_C 55.83 and 55.67 (CH_3 each); **2**: δ_H 3.76; 3.79 (s each); δ_C 55.83 and 55.67 (CH_3 each)] and methylenedioxy groups [**1**: δ_H 5.85 (s); δ_C 100.82 (CH_2); **2**: δ_H 5.84 (s) δ_C 100.71 (CH_2)] and also provided evidence of the existence of two dibenzylbutyrolactol lignans by the presence of multiplets signals for benzylic hydrogens and methine groups (δ_H 1.96-2.62), oxymethylene of the tetrahydrofuran system (δ_H 3.24-3.90) and aromatic hydrogens (δ_H 6.39-6.69). Moreover, the NMR spectra showed characteristic signals for acetalic hydrogens [**1**: δ_H 4.74 (d, J = 1.6 Hz), δ_C 109.17 (CH); **2**:



1 R = H; R_1 = OEt
2 R = OEt; R_1 = H



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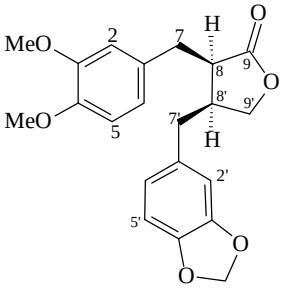

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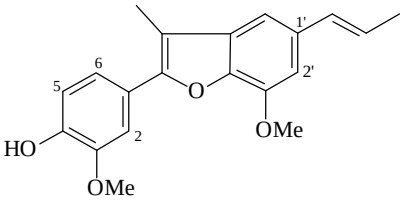

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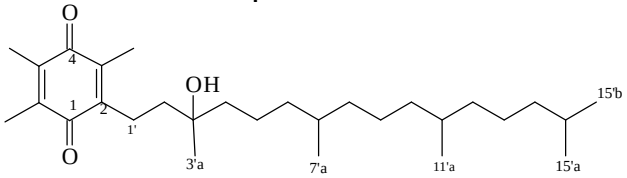

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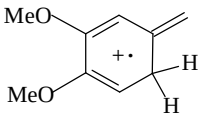
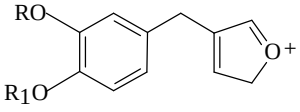
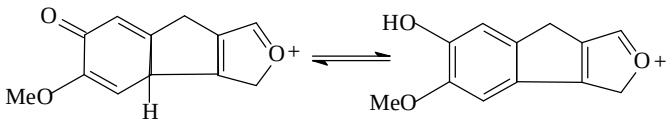


3a



1a R = R_1 = Me
1b R = R_1 = CH_2



2a

δ_H 4.70 (d, J = 4 Hz); δ_C 110.97 (CH)] and for ethoxy groups by the presence of signals for methyl hydrogens [δ_H 1.13 (t, J = 6.6 Hz); δ_C 15.26 (CH_3) and oxymethylene hydrogens probably submerged in the signals for methoxyl groups and methylene in the tetrahydrofuran system [**1**: δ_C 62.83 (CH_2); **2**: δ_C 62.69 (CH_2)] as well as the appearance of peaks at *m/z* 354 in their MS spectra corresponding to the loss of ethanol from molecular ions. Analysis using Dreiding models and observed couplings between H-8 and H-9 [**1** (J = 1.6 Hz); **2** (J = 4 Hz)] suggested the relative configurations depicted in formula **1** and **2** for ethoxy groups at C-9 since their couplings were consistent with the *cis*- (a dihedral angle of nearly 90°) and *trans*-configurations (a dihedral angle of nearly 120°), respectively.

The presence of two lignans was also discernable from the ^{13}C-NMR spectra (Table 1) which showed the doubling of the signals. Since these spectra furnished different intensities signals for both compounds [ratio 2:1 (**1**):(**2**)], assignments of the chemical shifts for individually lignan were inferred. Noteworthy is the fact that corresponding carbon chemical shifts for lignans **1** and **2** are very similar, the only significative difference being the chemical shifts of C-8'[**1** (δ_C 45.81); **2** (δ_C 43.29, γ-effect by the oxygen atom of the ethoxy group on C-8')], reflecting the different configuration at the C-9 chiral centre. Considering that **1** and **2** have a *cis*- and *trans*-relationship between H-8 and H-9, and *trans*- and *cis*-relationship between H-8' and the ethoxy groups at C-9, respectively, is consistent deduced that the relative configurations between H-8 and H-8' for both lignans are *cis*. By analogy of the chemical shifts of H-9' of other 8,8'-*trans*-dibenzylbutyrolactol lignans containing ethoxy group at C-9 (δ_H 3.22-4.20)[7-8], **1** as well as **2**, must be *cis*-oriented since its chemical shifts of H-9' (δ_H 3.24-3.90) revealed at upfield (anisotropic effect by the π-sistem aromatic ring). This fact, suggest that **1** and **2** are epimers.

Of additional interest were also the mass spectra which exhibited strong tropilium ions at *m/z* 135 [**1** (100); **2** (71)] and *m/z* 151 [**1** (85); **2** (100)] assignable to methylenedioxy- and dimethoxybenzyl units, respectively. Besides from the base peaks, the MS spectra also showed peaks with different intensities at *m/z* 219 [**1** (9); **2** (3)], *m/z* 203 [**1** (4); **2** (20)] and *m/z* 152 [**1** (32); **2** (43)] corresponding to the fragments **1a**, **1b**, **2a** and **3a**, respectively. Thus, the structures of two epimers were elucidated as *rel*-(*8R, 8'S, 9S*)-3,4-dimethoxy-3',4'-methylenodioxy-9β-ethoxy- (**1**) and *rel*-(*8R, 8'S, 9R*)-3,4-dimethoxy-3',4'-methylenodioxy-9α-ethoxy-lignans-8.8',9.O.9' (**2**).

The possibility that the lignans **1** and **2** are artifacts is discarded due to the fact that its presence have been confirmed by comparison with the original hexane extract on co-TLC. Lignans containing β- and α-ethoxy groups at C-9 have been isolated previously from some *Piper*[7-10] and *Dacrydium*[11-12] species.

The structures of two diastereomeric lignans (**3** and **4**)[13-17], neolignan eupomatenoid-7 (**5**)[6] and α-tocopherylquinone (**6**)[18-21] were established on the basis of their spectral data and comparison with those of the analogous compounds recorded in previous reports.

Experimental

General experimental procedures

Mp are uncorrected. IR spectrum was obtained as film on a FT-IR/1600 Perkin Elmer spectrofotometer. NMR spectra were measured in a Bruker AC-200 spectrometer at 200 and 50.3 MHz for ^{1}H- and ^{13}C-NMR, respectively. Proton and carbon shifts are reported in δ units (ppm) relative to TMS as the internal standard. Mass spectra were recorded in a Hewlett Packard instrument using electron impact (EI) at 70 eV. Qualitative GC/MS analysis was carried out on GC-5890 (Hewlett Packard) coupled to a Mass Selective Detector (Hewlett Packard MSD-5970) controled by a computer ChemStation 50070 C, utilizing a glass capillary column coated with dimethylsiloxane immobilized (12 m x 0.32 mm x 0.25 μm). The column temperature was programmed from 100 to 150 °C at a rate of 5°/min. and Helium was the carrier gas (1mL/min.).

Plant material

Aerial parts of *A. peltato-deltoidea* Hoehne were collected in Ilha de Maçaranduba, Pará State, Brazil, and identified by a specialist from the Museu Paraense Emílio Goeldi (Belém/PA), where a voucher specimen (MG-0147607) was deposited.

Extraction and isolation of the constituents

850 g of dried aerial parts were successively extracted in a Soxhlet apparatus with *n*-hexane and 90% ethanol. After removal solvents under vacuum, the residues were suspended in 90% and 60% MeOH/H_2O solutions and extracted with *n*-C_6H_{14} and *n*-C_6H_{14}, $CHCl_3$ and EtOAc, respectively.

The hexane residues were combined (35.5 g) and chromatographed on a silica gel column with *n*-hexane containing gradually increased amounts of ethyl acetate. Eleven fractions of 150 mL each were collected. Fractions 3-6 (7.8 g) were submitted on qualitative analysis by GC/MS in the conditions described previously. This procedure, after comparison of their mass spectra with those in the data system library and/or retention time and/or co-injection with authentic sample, resulted in the identification of phytol, farnesol, sphatulenol, hedycaryol, α-eudesmol, δ-selinene, 9-aristolen-1α-ol, caryophyllene oxide, and methyl and ethyl esters of hexadecanoic and nonanoic acids, respectively. Fraction 8 (2.3 g) was rechromatogra-

Table 1. NMR data for compounds **1** and **2**. ^{1}H (200 MHz, $CDCl_3$); ^{13}C (50.3 MHz, $CDCl_3$). Chemical shifts (δ) expressed in ppm from internal TMS or residual undeuterated solvent, coupling constants (J) in Hz.

Proton	**1**	**2**	Carbon	**1**	**2**	DEPT
7,7', 8,8'	1.96-2.62 m		1	133.15	132.73	C
			2	111.65	111.79	CH
			3	148.74	148.74	C
9	4.74 d, 1.6	4.70 d, 4.0	4	147.58	147.58	C
			5	111.06	111.16	CH
9'	3.24-3.90 m		6	120.45	120.85	CH
			7	38.57	39.30	CH_2
			8	52.29	52.16	CH
Ar-H	6.39-6.69 m		9	109.17	110.97	CH
			1'	133.47	132.25	C
OEt	1.13 t, 6.6		2'	107.88	107.95	CH
			3'	147.48	147.26	C
	3.71-3.79 m		4'	147.27	145.81	C
			5'	109.17	108.03	CH
OMe	3.75; 3.78 s	3.76; 3.79 s	6'	121.74	121.34	CH
			7'	38.99	39.12	CH_2
OCH_2O	5.85 s	5.84 s	8'	45.81	43.29	CH
			9'	72.03	72.19	CH_2
			OEt	15.26	15.26	CH_3
				62.83	62.69	CH_2
			OMe	55.83	55.83	CH_3
				55.67	55.67	CH_3
			OCH_2O	100.82	100.71	CH_2

phed as described above for furnished a mixture, mp 138-138.8 °C, containing β-sitosterol and stigmasterol (168 mg) after crystalization from MeOH. Fraction 9 (2.6 g) was rechromatographed as described previously and the fractions were combined. Some of them were further purified by gel filtration on Sephadex LH-20 with MeOH to yield eupomatenoid-7 (**5**, 7.9 mg) and α-tocopherylquinone (**6**, 13 mg) after preparative TLC [silica gel PF-254, *n*-C_6H_{14}-EtOAc (9:1)] in three consecutives elutions. Finally, fraction 10 (3.1 g) was dissolved in MeOH and submitted to centrifugation (1 h/7000 rpm). The portion soluble in MeOH (1.3 g) was permeated on Sephadex LH-20 with MeOH. After chromatographic fractionation on silica gel 60 H [*n*-C_6H_{14}-EtOAc (9:1)] and preparative TLC [silica gel PF-254, *n*-C_6H_{14}-EtOAc (9:1)] in four successives developments afforded a mixture containing lignans **1** and **2** (19.7 mg).

The $CHCl_3$ residue (8.2 g) was suspended in aqueous 5 % $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was taken to dryness (1.1 g) and fractioned on silica gel column using *n*-C_6H_{14} with increasing proportions of $CHCl_3$. This procedure resulted in the isolation of a mixture constituted lignans **3** and **4** (38 mg).

*Rel-(8R, 8'S, 9S)-3,4-dimethoxy-3',4'-methylenodioxy-9β-ethoxy- (**1**) and rel-(8R, 8'S, 9R)- 3,4-dimethoxy-3',4'-methylenodioxy-9α-ethoxy-lignans-8.8',9.O.9' (**2**)*

Yellow oil, IR ν_{max} (cm^{-1}, Film): 2925, 1609, 1511, 1460, 1445, 1367, 1267, 1147, 1058, 932. ^{1}H-NMR (200 MHz, $CDCl_3$, δ): Table 1. ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): Table 1. EIMS *m/z* (rel. int.): 400 (**1**, 3; **2**, 9), 354 (**1** and **2**, 7), 219 (**1**, 9; **2**, 3), 203 (**1**, 4; **2**, 20), 178 (**1**, 12; **2**, 16), 177 (**1**, 69; **2**, 10), 152 (**1**, 32; **2**, 43), 151 (**1**, 85; **2**,100), 135 (**1**, 100; **2**, 71), 113 (**1**, 44; **2**, 5), 91 (**1**, 9; **2**, 12).

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