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Short Report

Three New Natural Cyclopentenedione Derivatives from *Piper carniconnectivum*

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Três novos derivados ciclopentenodiônicos e a conhecida cumarina xantiletina foram isoladas das raízes de *Piper carniconnectivum*. As estruturas foram estabelecidas por RMN 1D e 2D e por espectrometria de massas.

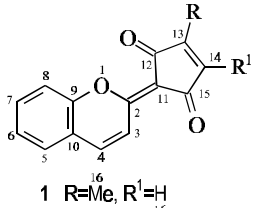
Three new natural cyclopentenedione derivatives (**1**-**3**) and the known coumarin xanthyletin (**4**) were isolated from the roots of *Piper carniconnectivum*. The structures were established by spectroscopic data, mainly 1D and 2D NMR and EIMS.

Keywords: *Piper carniconnectivum*, Piperaceae, cyclopentenedione derivatives, xanthyletin

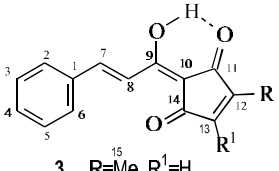
Introduction

Piperaceae is a tropical family that comprises many pharmaceutically important plants, useful in folk medicine and as bioproducer of essential oils. *Piper carniconnectivum* is a species found in the Amazon in the northern part of Brazil.[1]

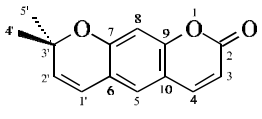
Results of an investigation of a specimen of *Piper carniconnectivum* collected in Porto Velho, Rondônia, Brazil, are reported in this paper. Three new natural cyclopentenediones (**1**-**3**) and the known coumarin xanthyletin (**4**) were isolated from the ethanol extract from roots.



1 R=Me, R^1=H
2 R=H, R^1=Me



3 R=Me, R^1=H
3a R=H, R^1=Me



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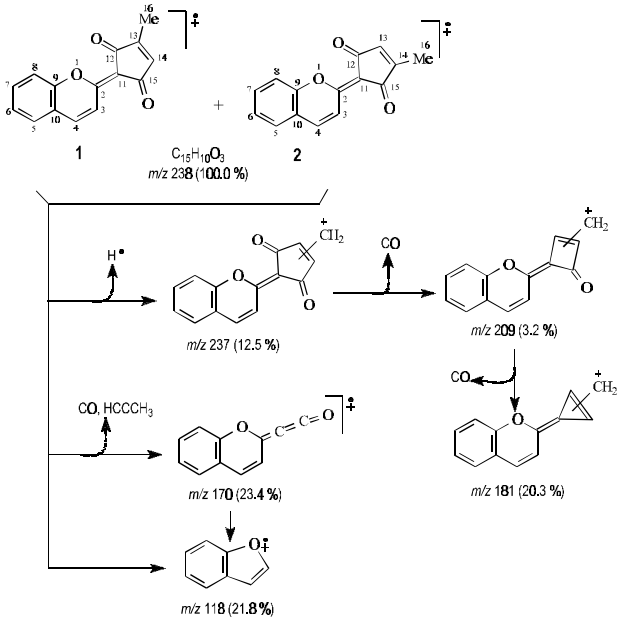
Results and Discussion

The known coumarin xanthyletin (**4**) was identified by spectral data, involving mainly ^{1}H and ^{13}C NMR spectra and comparison with literature values.[2]

The EIMS (Scheme 1) of **1** and **2** showed molecular peaks at *m/z* 238 daltons ($[M]^{\bullet+}$). The ^{1}H and ^{13}C (HBBD



Scheme 1. Proposed fragmentation mechanisms of **1** and **2** (only peaks classified as principals).

Table 1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectral data for **1** and **2**, including heteronuclear 2D shift-correlated obtained by ^{1}H-^{13}C-COSY-$^nJ_{CH}$ (n=1, HNQC; n=2 and 3, HMBC) experiments, in $CDCl_3$ as solvent, chemical shifts (δ, ppm) and coupling constants (J, Hz, in parenthesis)[a]

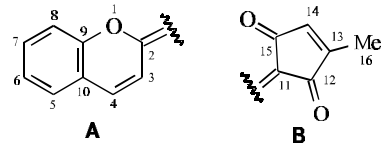
	1		**2**		**1** and/or **2**	
		^{1}H-^{13}C-COSY-$^1J_{CH}$			^{1}H-^{13}C-COSY-$^nJ_{CH}$	
	δ_C	δ_H	δ_C	δ_H	$^2J_{CH}$	$^3J_{CH}$
C						
2	159.39	-	159.66	-	H-3	H-4
9	152.22	-	152.22	-		H-4; H-5; H-7
10	120.23	-	120.20	-		H-3; H-6
11	102.23	-	102.22	-		H-13 (**2**); H-14 (**1**)
12	192.34	-	192.90	-	H-13 (**2**)	H-14 (**1**); 3H-16 (**1**)
13	155.57	-	-	-	H-14; 3H-16	
14	-	-	155.73	-	H-13; 3H-16	
15	194.04	-	194.78	-		3H-16 (**2**)
CH						
3	117.59	8.11 (d, 9.5)	117.82	8.13 (d, 9.5)		
4	137.72	7.54 (d, 9.5)	137.64	7.54 (d, 9.5)		H-5
5	127.57	7.41 (br d, 7.7)	127.54	7.42 (br d, 7.7)		H-4; H-7
6	125.15	7.32-7.20	125.15	7.32-7.20		
7	132.20	7.60-7.50	132.20	7.60-7.50		H-5
8	117.25	7.60-7.50	117.39	7.60-7.50		H-6
13	-	-	139.37	6.63 (q, 1.4)		
14	139.23	6.62 (q, 1.5)	-	-		
CH_3						
16	10.95	2.09 (d, 1.5)	11.05	2.08 (d, 1.4)		H-13 (**2**); H-14 (**1**)

[a]Number of hydrogens bound to carbon atoms deduced by comparative analysis of HBBD- and DEPT-^{13}C NMR spectra. Chemical shifts and coupling constants (J) obtained from 1D ^{1}H NMR spectrum. Superimposed ^{1}H signals are described without multiplicity and chemical shifts deduced by HMQC, HMBC and ^{1}H-^{1}H-COSY spectra.

and DEPT) NMR data (Table 1) coupled with the [$M^{+\cdot}$] allowed us to deduce the molecular formula, $C_{15}H_{10}O_3$ for **1** and **2** (eleven degrees of unsaturation). This formula suggests the presence of a modified coumarin skeleton (C_9H_6O, chromenylidene-) linked to a $C_6H_4O_2$ moiety.

Comparative analysis of HBBD- and DEPT-^{13}C NMR spectra was used to identify signals attributed to quaternary [$(C)_{14}$, all sp^2, $(C)_7$ attributed to each component, including two ketone C=O (**1**: δ_C 194.04 and 192.34; **2**: δ_C 194.78 and 192.90], two involved in an ether function (**1**: δ_C 159.39 and 152.22; **2**: δ_C 159.66 and 152.22] and one conjugated with a carbonyl group (**1**: δ_C 155.57; **2**: δ_C 155.73], methine [$(CH)_{14}$, all sp^2, $(CH)_7$ representing each compound] and methyl [$(CH_3)_2$, one for each component] carbon atoms (Table 1). The ^{1}H (1D and 2D ^{1}H-^{1}H-COSY) and ^{1}H-^{13}C-COSY-$^nJ_{CH}$ (n=1, HMQC; n=2 and 3, HMBC) spectra are in agreement with these deductions (Table 1 and 2).

The ^{1}H NMR spectra (1D and 2D ^{1}H-^{1}H-COSY) of **1** + **2** (Table 1) displayed signals of an AB system (J 9.5 Hz) attributed to *cis*-related H-3 [δ_H 8.11 (**1**) and 8.13 (**2**)] and H-4 [δ_H 7.54 (**1** and **2**)], correlated via one bond ($^1J_{CH}$) with the corresponding carbon atoms by cross-peaks observed in the HMQC spectrum (Table 1), which in combination with the ^{1}H and ^{13}C signals due to four aromatic methines (CH-5 to CH-8) and three non-hydrogenated (C-2, C-9 and C-10), suggested the presence of a chromenylidene moiety **A** (C_9H_6O, coumarin type). The peaks at *m/z* 170 (23.4 %) and 118 (21.8 %) observed in the EIMS are in agreement with the presence of this moiety (Scheme 1). The remaining signals observed in the ^{1}H [singlet signals at δ_H 6.62(H-14)/6.63 (H-13) and 2.09/2.08 (3H-16 linked to sp^2 carbon atom)] and ^{13}C [four sp^2 quaternary: δ_C 194.04/194.78 (conjugated ketone carbonyl group), 192.34/192.90 (conjugated ketone carbonyl group), 155.57/155.73 (non-hydrogenated olefinic carbon conjugated with carbonyl group); and one sp^2 methine: δ_C 139.23/139.37] NMR spectra were used to establish the partial structure **B**, which was also confirmed by homonuclear 2D ^{1}H-^{1}H-COSY (long-range spin-spin interaction of the H-14 and 3H-16 and H-13 and 3H-16) and heteronuclear 2D shift-correlated ^{1}H-^{13}C-COSY-$^nJ_{CH}$ (n=1, HMQC; n=2 and 3, HMBC)[3] summarized in Table 1.



The junction of two **A** and **B** moieties was confirmed by a heteronuclear long-range coupling ($^3J_{CH}$) of C-11 [δ_C 102.23 (**1**) and 102.22 (**2**)] and H-14 (δ_H 6.62) and H-13

(δ_H 6.63), respectively, allowing to postulate the isomeric structures **1** ($[M]^{\cdot+}$ 238) and **2** ($[M]^{\cdot+}$ 238).

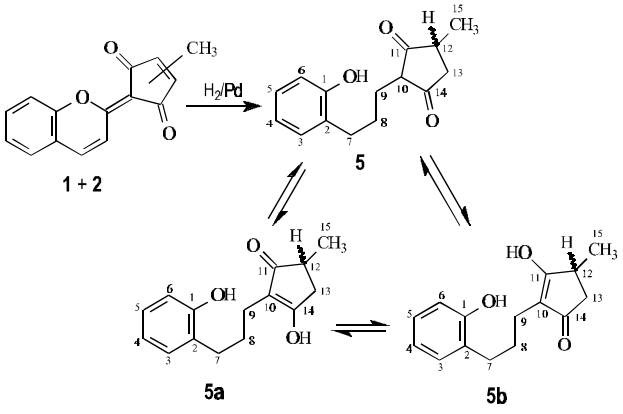
The presence of **1** and **2** in the mixture was additionally confirmed by 1D and 2D ^{1}H and ^{13}C NMR spectra recorded in benzene-d_6, which revealed best resolution induced by aromatic solvent effect (Table 2).

The results of the extensive application of 1D and 2D NMR spectral techniques in $CDCl_3$ and benzene-d_6 were also used to confirm the structures and to establish the ^{1}H and ^{13}C resonance assignments of **1** and **2** (Tables 1 and 2).

Catalytic reduction (H_2/10 % Pd-C, MeOH, 50 psi, 6 h) of the mixture of **1** and **2** yielded 1,3-diketooctahydro-derivative **5** {2-[3-(2-hydroxyphenyl)propyl]-4-methylcyclopentan-1,3-dione}, which appears in a keto-enol tautomerism represented by enols **5a** {3-hydroxy-2-[3-(2-hydroxyphenyl)propyl]-5-methyl-2-cyclopenten-1-one} and **5b** {3-hydroxy-2-[3-(2-hydroxyphenyl)propyl]-4-methyl-2-cyclopenten-1-one}, as shown in Scheme 2. These enols were characterized on the basis of EIMS (Scheme 2) and 1D and 2D NMR (Table 3). At room temperature, a relatively rapid interconversion between the enol forms probably occurs and consequently average ^{1}H and ^{13}C NMR spectra are observed (Table 3).

Therefore, the structures of the new natural products isolated from *Piper carniconnectivum* were postulated as 2-(2*H*-2-chromenyliden)-4-methyl-4-cyclopenten-1,3-dione (**1**) and 2-(2*H*-2-chromenyliden)-5-methyl-4-cyclopenten-1,3-dione (**2**).

The isomeric structures **1** and **2** are very similar and are clearly in agreement with the ^{1}H and ^{13}C NMR spectral data, revealing ^{1}H and ^{13}C chemical shifts with slight differences. The attribution of ^{1}H and ^{13}C chemical shifts of **1**, present in the mixture (about 50% of each component) was based in a major γ effect (shielding) of the heterocyclic oxygen atom on the carbonyl carbon C-12, justifying the its minor ^{13}C chemical shift, as observed (e. g.) in the



Scheme 2. Products obtained by catalytic reduction (H_2/Pd/C) of the mixture of **1** and **2**.

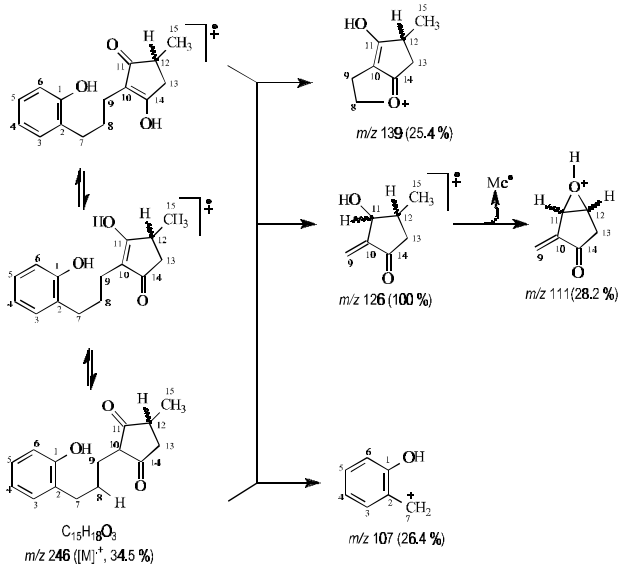
Table 2. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectral data for **1** and **2**, including heteronuclear 2D shift-correlated obtained by ^{1}H-^{13}C-COSY-$^nJ_{CH}$ (n=1, HNQC; n=2 and 3, HMBC) experiments, in benzene-d_6 as solvent, chemical shifts (δ, ppm) and coupling constants (J, Hz, in parenthesis)[a]

	1		**2**		**1** and/or **2** ^{1}H-^{13}C-COSY-$^nJ_{CH}$	
		^{1}H-^{13}C-COSY-$^1J_{CH}$				
	δ_C	δ_H	δ_C	δ_H	$^2J_{CH}$	$^3J_{CH}$
C						
2	158.96	-	159.24	-	H-3	H-4
9	152.53	-	152.53	-	H-8	H-4; H-5; H-7
10	120.82	-	120.78	-	H-4	H-3; H-6; H-8
11	103.03	-	104.64	-		H-13 (**2**); H-14 (**1**)
12	191.89	-	191.15	-	H-13 (**2**)	H-14 (**1**); 3H-16 (**1**)
13	155.96	-	-	-	H-14; 3H-16	-
14	-	-	155.53	-	H-13; 3H-16	
15	193.54	-	194.48	-	H-14 (**1**)	H-13 (**2**); 3H-16 (**2**)
CH						
3	118.15	8.17 (d, 9.5)	117.94	8.13 (d, 9.5)		
4	136.80	6.49 (d, 9.5)	136.88	6.49 (d, 9.5)		H-5
5	127.44	6.55 (br d, 7.7)	127.44	6.55 (br d, 8.4)		H-4; H-7
6	124.61	6.62 (br dd, 7.7, 8.4)	124.61	6.62 (br dd, 7.7, 8.4)		H-8
7	131.86	6.81 (br t, 8.4)	131.94	6.81 (br t, 8.4)		H-5
8	117.36	7.16 (br d, 8.4)	117.44	7.19 (br d, 8.4)		H-6
13	-	-	139.86	6.26 (q, 1.8)		3H-16
14	139.59	6.25 (q, 1.8)	-	-		3H-16
CH_3						
16	10.76	1.68 (d, 1.8)	10.76	1.66 (d, 1.8)		H-13 (**2**); H-14 (**1**)

[a]Number of hydrogens bound to carbon atoms deduced by comparative analysis of HBBD- and DEPT-^{13}C NMR spectra. Chemical shifts and coupling constants (J) obtained from 1D ^{1}H NMR spectrum. ^{1}H-^{1}H-COSY spectrum was also used in these assignments.

comparative analysis of the ^{13}C chemical shifts of the methylene carbon atoms CH_2-3 of cyclohexane (δ_C 27.6), methylcyclohexane (δ_C 26.6, Δ_C = -1.0 ppm) and cyclohexanol (δ_C 24.4, Δ_C = - 2.2 ppm).

Comparative analysis of HBBD- and DEPT-^{13}C NMR of **3** was used to recognize signals corresponding to quaternary [$(C)_6$, all sp^2, including two ketone C=O (δ_C 192.64 and 201.08), one oxygenated (δ_C 168.11) and one conjugated with carbonyl group (δ_C 158.46)], methine [$(CH)_6$ representing eight carbons, all sp^2] and one methyl (CH_3). The ^1H (1D and 2D ^1H-^1H-COSY) and ^1H-^{13}C-COSY-$^nJ_{CH}$ (n=1, HMQC; n=2 and 3, HMBC) spectra are in agreement with these deductions (Table 1). The *E*-configuration of the double bond between the carbon atoms CH-7 (δ_H/δ_C 7.79/143.56) and CH-8 (δ_H/δ_C 7.75/117.90) was defined by a coupling constant *J* 16.0 Hz observed in the 1D ^1H NMR spectrum. The 2D ^1H-^1H-COSY spectrum was used to confirm the spin-spin interaction ($^3J_{H,H}$) of these hydrogen atoms. The chemical shift of the olefinic quaternary carbon C-9 (δ_C 168.11) was assigned on the basis of its heteronuclear long-range coupling with both hydrogens H-7 (δ_H 7.79, $^2J_{CH}$) and H-8 (δ_H 7.75, $^3J_{CH}$) and, consequently, the two ketone carbonyl groups (δ_C 192.64, C-11, and 201.08, C-14) were located at a methyl-cyclopentene ring, which was confirmed by heteronuclear long-range of these carbons with H-13 and 3H-15 (Table 4). The NMR spectra only showed the presence enol tautomer **3** and/or **3a** when the experiments were done in $CDCl_3$, allowing to postulate the absence of the tautomers **3b**, **3c** and **3d** (Scheme 4) based in the ^1H and ^{13}C chemical shifts of the signals observed in the ^1H and ^{13}C NMR spectra (Table 4). At room temperature, a relatively rapid interconversion between the tautomer forms probably

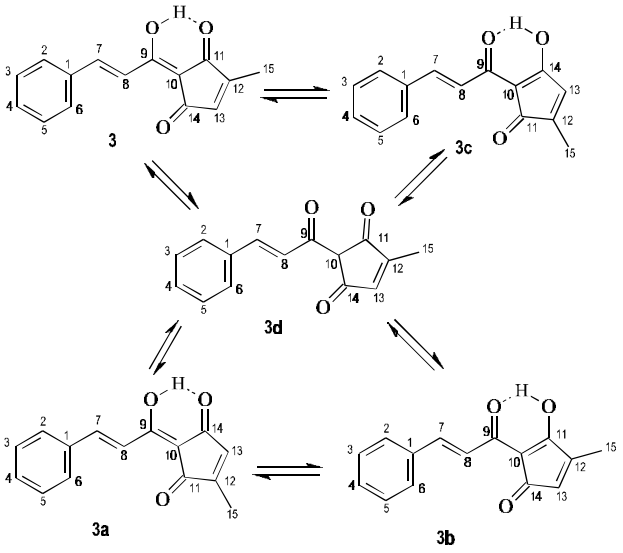


Scheme 3. Proposed fragmentation mechanisms of **5** (only peaks classified as principals).

Table 3. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectral data for octahydroderivative **5**, including heteronuclear 2D shift-correlated obtained by ^1H-^{13}C-COSY-$^nJ_{CH}$ (n=1, HNQC; n=2 and 3, HMBC) experiments, in $CDCl_3$ as solvent. Chemical shifts (δ, ppm) and coupling constants (*J*, Hz, in parenthesis)[a]

	^1H-^{13}C-COSY-$^1J_{CH}$		^1H-^{13}C-COSY-$^nJ_{CH}$	
	δ_C	δ_H	$^2J_{CH}$	$^3J_{CH}$
C				
1	156.34	-		H-3; H-5; 2H-7
2	129.84	-	2H-7	H-4; H-6; 2H-8
10	115.74	-	2H-9	2H-8
11	202.14	-	H-12	2H-9; H-13a; 3H-15
14	193.12	-	2H-13	2H-9; H-12
CH				
3	131.00	7.03 (dd, 7.3, 1.5)		H-5; 2H-7
4	120.05	6.69 (dt, 7.3, 1.4)		H-6
5	127.41	6.95 (ddd, 7.3, 8.1, 1.5)		H-5
6	116.30	6.77 (dd, 8.1, 1.4)		H-4
12	37.93	2.45 (qdd, 7.3, 7.3, 2.2)	3H-15	2H-13
CH_2				
7	30.66	2.59 (t, 7.7)	2H-8	2H-9
8	30.39	1.70 (tt, 7.7, 7.3)	2H-7; 2H-9	
9	21.58	2.15 (t, 7.3)	2H-8	2H-7
13	39.62	2.65 (dd, 17.6, 7.3) 1.99 (dd, 17.6, 2.2)		3H-15
CH_3				
15	18.23	1.12 (d, 7.3)	H-12	2H-13

[a]Number of hydrogens bound to carbon atoms deduced by comparative analysis of HBBD- and DEPT-^{13}C NMR spectra. Chemical shifts and coupling constants (*J*) obtained from 1D ^1H NMR spectrum. ^1H-^1H-COSY spectrum was also used in these assignments.



Scheme 4. Tautomer forms of **3**.

occurs and consequently average ^{1}H and ^{13}C NMR spectra of **3** and/or **3a** are observed (Table 4).

Therefore, the structure of this unknown natural product was established as 2-[1-hydroxy-3-phenyl-(*Z*,2*E*)-2-propenylidene]-4-methyl-4-cyclopentene-1,3-dione (**3** and/or **3a**).

The results of the extensive application of 1D and 2D NMR spectral techniques were also used to confirm the structure and to establish the ^{1}H and ^{13}C resonance assignments of the natural products**1**, **2** (Tables 1 and 2) and **3** (Table 4), and of the derivative **5** (Table 3) obtained by catalytic reduction of the mixture of **1** and **2**.

The biosynthesis of these new compounds has not yet been investigated. Structural examination of the compounds **1**, **2** and **3** in view of biosynthetic arguments and application of a biosynthetic retroanalysis led us to suggest a biogenetic route. Cyclopentenoids are metabolites of varied biogenetic routes.[4] Thus, the methylcyclopentene-1,3-dione ring present in the compounds **1**, **2** and **3** can be postulated as a bioproduct of mevalonic acid, as summarized speculatively in Scheme 5. The C_6-C_3 moiety (cinnamoyl type) is in accordance with the shikimate (shikimic pathway) route,[4] similar to the route of the bioformation of coumarins (e. g. xanthyletin, a prenylated coumarin, **4**, which was also isolated of this plant) and other compounds isolated from *Piper* genus.[5]

The compound **3** may be postulated as precursor of **1** and **2** after it appropriated *ortho*-hydroxylation to produce the intermediary 2-hydroxy derivative.

Experimental

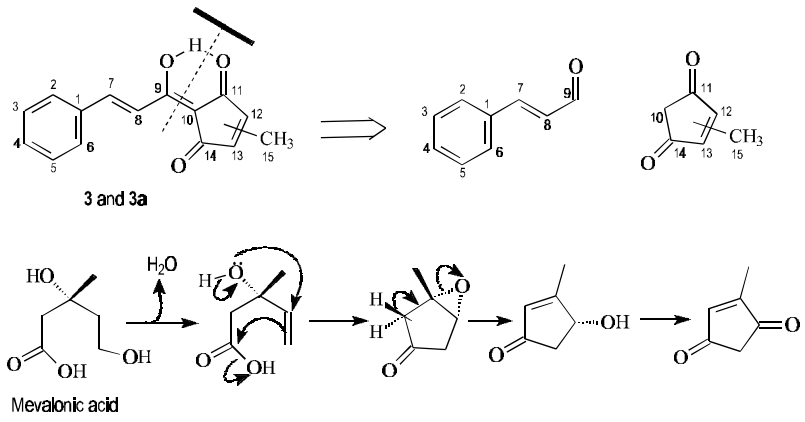
General experimental procedures

Mps are uncorr. NMR spectra were run on Bruker - Advance 500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) and Jeol – 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometers in $CDCl_3$ (**1**-**4**) or benzene-d_6 (**1** and **2**) using TMS as internal standard

Table 4. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectral data for **3** including heteronuclear 2D shift-correlated obtained by ^{1}H-^{13}C-COSY-$^{n}J_{CH}$ (n=1, HNQC; n=2 and 3, HMBC) experiments, in $CDCl_3$ as solvent, chemical shifts (δ, ppm) and coupling constants (*J*, Hz, in parenthesis)[a]

	^{1}H-^{13}C-COSY-$^{1}J_{CH}$		^{1}H-^{13}C-COSY-$^{n}J_{CH}$		
	δ_C	δ_H	$^{2}J_{CH}$	$^{3}J_{CH}$	$^{4}J_{CH}$
C					
1	135.24	-		H-3/H-5; H-8	
9	168.11	-	H-8	H-7	
10	103.55	-			
11	201.08	-		H-13; 3H-15	
12	158.46	-	3H-15		
14	192.64	-	H-13		3H-15
CH					
2,6	129.05	7.67-7.65 (m)		H-4; H-7	
3,5	129.39	7.44-7.42			
4	131.11	7.44-7.42		H-2/H-6	
7	143.56	7.79 (d, 16.0)	H-8	H-2/H-6	
8	117.90	7.75 (d, 16.0)	H-7		
13	137.39	6.70 (q, 1.6)		3H-15	
CH_3					
15	11.79	2.12 (d, 1.6)			
HO	-	12.12 (sl)			

[a]Number of hydrogens bound to carbon atoms deduced by comparative analysis of HBBD- and DEPT-^{13}C NMR spectra. Chemical shifts and coupling constants (*J*) obtained from 1D ^{1}H NMR spectrum. Superimposed ^{1}H signals are described without multiplicity and chemical shifts deduced by HMQC, HMBC and ^{1}H-^{1}H-COSY spectra.



Scheme 5. Biosynthetic retroanalysis of **3**/**3a** and possible biogenetic pathway of methylcyclopentene-1,3-dione from mevalonic acid.

or by reference to the solvent signal ($CHCl_3$ at δ_H 7.24 or C_6D_5H at δ_H 7.26 and $CDCl_3$ at δ_C 77.00 or C_6D_6 at δ_C 128.00). EIMS were obtained at 70 eV on a Shimadzu QP-2000 spectrometer. The IR spectra were recorded on a Perkin-Elmer FT-1500 spectrometer. Column chromatography was carried out with silica gel 0.063-0.2 mm and TLC was done employing silica gel Kieselgel 60 from Merck and spots were visualized by UV (λ_{max} 259 and 360 nm) and exposure to I_2 vapour.

Plant material

Roots of *Piper* c*arniconnectivum* were collected from the same specimen, in Porto Velho, Rondônia, Brazil. The botanical identification (exsiccate number 211718) was confirmed by Instituto Nacional de Pesquisas da Amazônia (INPA), Manaus, Brazil.

Isolation of the compounds

A mixture of chromenylidene- (**1** and **2**), a hydroxyphenylpropenylidenecyclopentenedione (**3**) and xanthyletin (**4**) were isolated by the use of column chromatography, after partition of the EtOH extract with hexane, $CHCl_3$, EtOAc and MeOH. The residue obtained from the $CHCl_3$ solution was submitted to a silica gel column chromatography and fractions 5 and 6 eluted with hexane-$CHCl_3$ yielded a mixture of **1** + **2** (yellow crystals, m. p. 128-136° C) and **3** (yellow crystals, m. p. 122-124° C), whereas the fraction 7 afforded **4** and additional quantity of the mixture of **1** + **2**.

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