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Article

Synthesis of 6α,7β-Di-Hydroxyvouacapan-17β-Oic Acid Derivatives Part III: Synthesis, ^{1}H- and ^{13}C-NMR of Amide Derivatives[1]

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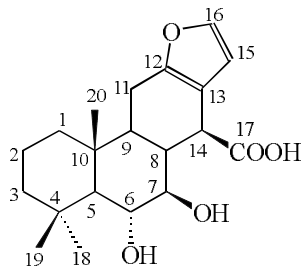
Sete novas amidas (**III-IX**) derivadas do ácido 6α,7β-di-hidroxivouacapan-17β-óico **I** (ADV) foram sintetizadas. Suas estruturas foram determinadas através da análise de dados espectrométricos, destacando-se os resultados fornecidos pelas experiências de RMN bidimensionais de correlação de deslocamentos químicos homonuclear (^{1}H x ^{1}H-COSY) e heteronuclear (^{1}H x ^{13}C-COSY).

Seven new amide (**III-IX**) derivatives of 6α,7β-di-hydroxyvouacapan-17β-oic acid **I** (ADV) have been synthesized. Their structures were established by spectroscopic data, including 2D-NMR methods.

Keywords: *6α,7β-di-hydroxyvouacapan-17β-oic acid, furane-diterpene, amide, ^{1}H- and ^{13}C-NMR*

Introduction

The genus *Pterodon* is widely distributed in the Brazilian savannah, and includes different species among which *P. apparicioi* Pedersoli and *P. polygalaeflorus* Benth are commonly know as "Sucupira-Branca"[2]. Alcoholic infusions from the fruit are employed in Brazilian folk medicine for rheumatic affection and throat infections[3]. Since it was verified that the furane-diterpene 6α,7β-di-hydroxyvoua capan-17β-oic acid **I** (ADV), isolated from the hexane extract from the fruit of *Pterodon polygalaeflorus* Benth, presents anti-inflammatory and analgesic activity[3,4], a variety of derivatives of ADV has been synthesized in order to obtain more information about the structure-activity relationship of this series of compounds[4,5].



I ADV

Here we now report the synthesis of seven new amide derivatives of **I**, according to Scheme 1, and the complete assignment of their ^{1}H- and ^{13}C-NMR data. The main purpose of this paper is the structural characterization of these compounds employing mainly one-and two-dimensional NMR.

Experimental

All reactions were followed by analytical thin-layer chromatography (TLC, Merck Sílica Gel 60G, 3:2:1 hexane:dichloromethane:ethanol). Melting points were observed on a Mettler FP 82 HT and are not corrected. Elemental analyses were obtained on a Perkin Elmer 2400 apparatus. Infrared spectra were taken on a Shimadzu IR 408 spectrophotometer on KBr disks. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL EX 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz), Bruker AC 200 (^{1}H: 200 MHz; ^{13}C: 50 MHz), or Bruker AC 80 (^{1}H: 80 MHz; ^{13}C: 20 MHz) spectrometer. The NOE difference spectrum was recorded on a Bruker DRX 400 spec-

trometer. Tetramethylsilane was utilized as the internal standard (δ = 0). The ^{13}C signals due to $\underline{C}H/\underline{C}H_3$ and $\underline{C}H_2$ were assigned according to the DEPT 135 ^{13}C-NMR spectra. Multiplicities are indicated by s (singlet), d (doublet),dd (double doublet), t (triplet), q (quartet), m (multiplet), and b (broad). Low resolution mass spectra were obtained on a Varian Mat 311 A instrument operating at 70 eV. ADV derivatives were prepared as indicated in Scheme 1, according to the methods described below[1].

General experimental procedure

(X) mmol of lactone **II** and (Y) mmol of the respective amine were added to 20.0 mL of THF. The reaction mixture was stirred for (Z) hr under reflux or at room temperature, and monitored by TLC and infrared spectroscopy. After completion of the reaction, the mixture was poured over crushed ice. The resulting white solid was filtered off, washed with water, air dried and recrystallized (see Table 1). In the case of the preparation of amide **VII**, a very fine white solid was formed. Therefore the reaction mixture was extracted with dichloromethane. The dichloromethane solution was dried over anhydrous magnesium sulfate, the solvent was removed under reduced pressure, and the residue was recrystallized to yield **VII** (see Table 1).

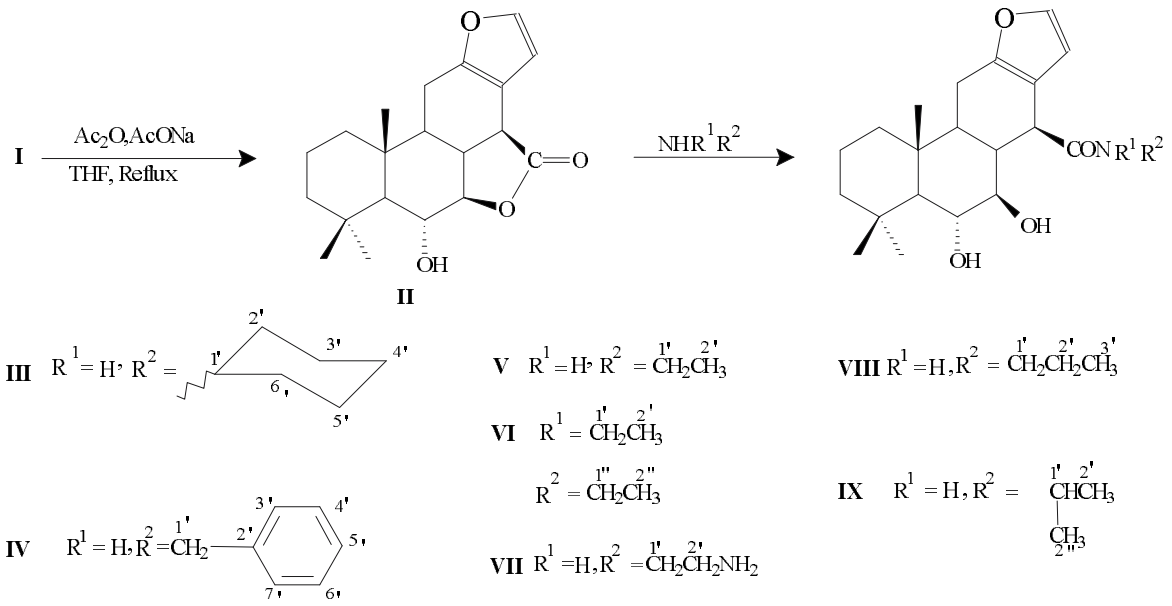
*6α,7β-di-hydroxy-N-cyclohexylvouacapan-17β-amide (**III**)*

M.p. 194.5-196.1 °C. Anal. Calcd. for $C_{26}H_{39}NO_4$: C:72.79%, H: 9.15%, N:3.26%. Found: C: 72.86%, H: 9.29%, N: 3.28%. IR ν (cm^{-1}): 3600-3100, 1680-1610, 1570-1500; MS: M^+= (m/z)= 429 (22%); ^1H-NMR ($CDCl_3$, 80 MHz) δ= 0.98 (s, 3H: CH_3), 1.06 (s, 3H: CH_3), 1.18 (s, 3H: CH_3), 0.8-2.0 (m, 19H: 2H1, 2H2, 2H3, H5, H9, H1', 2H2', 2H3', 2H4', 2H5', 2H6'), 2.1-3.0 (m, 4H: H8, 2H11, OH*), 3.2-3.5 (m, 2H: H7, H14), 3.6-3.9 (m, 1H: H6), 4.5-4.7 (b, 1H: OH*), 5.6-5.8 (b, 1H: NH*), 6.14

Table 1. Summary of the data for the preparation of the amide derivatives of ADV.

Amide	mmol **II** X	mmol/amine Y	Time (h) Z	Temperature	Recrystallized from	Yield (mmol, %)
III	0.91	50.0/$C_6H_{11}NH_2$	6.0	Reflux	EtOAc*	0.54, 60
IV	0.91	50.0/ $(CH_2NH_2$	7.0	Reflux	DCM**:EtOAc 1:2	0.54, 60
V	1.5	4.5/$C_2H_5NH_2$	1.5	RT#	EtOAc	0.72, 48
VI	0.75	39.0/ $(C_2H_5)_2NH$	15.0	Reflux	DCM:Hexane 2:1	0.24, 33
VII	0.91	3.45/H_2N $(CH_2)_2NH_2$	3.5	Reflux	EtOAc:Ethanol 1:1	0.14, 15
VIII	0.91	3.6/CH_3 $(CH_2)_2NH_2$	1.5	Reflux	DCM:Hexane 2:1	0.74, 82
IX	0.91	3.5/ $(CH_3)_2CHNH_2$	14.0	Reflux	EtOAc:Hexane 2:1	0.48, 53

*Ethyl Acetate **Dichloromethane #Room Temperature.



Scheme 1. Synthesis of amide derivatives **III** to **IX**.

(d, 1H: 3H: CH_3), 0.8-2.0 (m, 19H: 2H1, 2H2, 2H3, H5, H9, H1', 2H2', 2H3', 2H4', 2H5', 2H6'), 2.1-3.0 (m, 4H: H8, 2H11, OH*), 3.2-3.5 (m, 2H: H7, H14), 3.6-3.9 (m, 1H: H6), 4.5-4.7 (b, 1H: OH*), 5.6-5.8 (b, 1H: NH*), 6.14 (d, 1H: H15, J = 1.8Hz), 7.26 (d, 1H: H16, J = 1.8Hz); ^{13}C-NMR ($CDCl_3$, 20 MHz): see Table 3.

*D_2O exchangeable

*6α,7β-di-hydroxy-N-benzylvouacapan-17β-amide (**IV**)*

M.p. 188-190.1 °C. Anal. Calcd. for $C_{27}H_{35}NO_4$: C:74.21%, H: 8.06%, N: 3.20%. Found: C: 73.96%, H: 8.04%, N: 3.33%. IR ν (cm^{-1}): 3600-3150, 1680-1620, 1580-1500; MS: M^+ = (m/z) = 437 (9%); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ=0.93 (s, 3H: CH_3),1.03 (s, 3H: CH_3), 1.16 (s, 3H: CH_3), 0.8-1.17 (m, 8H: 2H1, 2H2, 2H3, H5, H9), 2.1-2.4 (m, 2H: H8, H11ax, J_{gem} = 15.9 Hz, J_{11ax-9} = 11.0Hz), 2.61 (dd, 1H: $H11_{eq}$, J_{gem} = 15.9Hz, J_{11eq-9} =4.9Hz), 3.2-3.4 (m, 3H: H7, H14, OH*), 3.6-3.8 (m, 1H: H6), 4.2-4.6 (m, 3H: 2H1', OH*), 6.07 (d, 1H: H15, J = 1.8Hz), 6.44 (t, 1H: NH*), 7.19 (d, 1H: H16, J = 1.8Hz), 7.2-7.4 (m, 5H: H3', H4', H5', H6', H7'); ^{13}C-NMR ($CDCl_3$, 50 MHz): see Table 3.

*D_2O exchangeable

*6α,7β-di-hydroxy-N-ethylvouacapan-17β-amide (**V**)*

M.p. 219.8-221.3 °C. Anal. Calcd. for $C_{22}H_{33}NO_4$: C:70.46%, H: 8.86%, N:3.73%. Found: C: 70.15%, H: 9.15%, N: 3.59%. IR ν (cm^{-1}): 3600-3150, 1660-1620, 1560, 1530; ^{1}H-NMR ($CDCl_3$, 80 MHz) δ = 0.98 (s, 3H: CH_3), 1.06 (s, 3H: CH_3), 1.18 (s, 3H: CH_3), 0.9-1.18 (m, 11H: 2H1, 2H2, 2H3, H5, H9, 3H2'), 2.0-3.0 (m, 3H: H8, 2H11), 3.1-3.6 (m, 5H: H7, H14, 2H1', OH*), 3.6-3.9 (m, 1H: H6), 4.5-4.7 (b, 1H: OH*), 5.7-6.0 (b, 1H: NH*), 6.14 (d, 1H: H15, J = 1.8Hz), 7.26 (d, 1H: H16, J = 1.8Hz); ^{13}C-NMR ($CDCl_3$, 20 MHz): see Table 3.

*D_2O exchangeable

*6α,7β-di-hydroxy-N,N-diethylvouacapan-17β-amide (**VI**)*

M.p. 187.9-190.1 °C. Anal. Calcd. for $C_{24}H_{37}NO_4$: C:71.53%, H: 9.24%, N:3.49%. Found: C: 70.78%, H: 9.26%, N: 3.69%. IR ν (cm^{-1}): 3600-3100, 1650-1600, MS: M^+ = (m/z)= 403 (78%); ^{1}H-NMR ($CDCl_3$, 80 MHz) δ = 0.93 (s, 3H: CH_3), 1.04 (s, 3H: CH_3), 1.17 (s, 3H: CH_3), 0.8-1.8 (m, 14H: 2H1, 2H2, 2H3, H5, H9, 3H2', 3H2"), 2.3-2.8 (m, 5H: H8, 2H11, 2H1"), 2.8-3.3 (m, 5H: H7, H14, 2H1', OH*), 3.3-3.9 (m, 2H: H6, OH*), 6.0 (d, 1H: H15, J = 1.8Hz), 7.20 (d, 1H: H16, J = 1.8Hz); ^{13}C-NMR ($CDCl_3$, 20 MHz): see Table 3.

*D_2O exchangeable

*N- (2-aminoethyl)-6α,7β-di-hydroxyvouacapan-17β-amide (**VII**)*

M.p. 199.6-201.1 °C. Anal. Calcd. for $C_{22}H_{34}N_2O_4$: C: 67.75%, H: 8.78%, N: 7.18%. Found: C: 67.49%, H: 8.58%, N: 6.99%. IR ν (cm^{-1}): 3550-3050, 1680-1610, 1580-1510; MS: M^+= (m/z)= 390 (8%); ^{1}H-NMR (DMSO-D_6, 400 MHz) δ= 0.93 (s, 3H: CH_3), 1.0 (s, 3H: CH_3), 1.13 (s, 3H: CH_3), 0.9-1.65 (m, 8H: 2H1, 2H2, 2H3, H5, H9), 2.1-2.2 (m, 1H: H8), 2.2-2.35 (m, 1H: H11ax), 2.42-2.52 (m, 3H: H11eq, NH_2*), 3.0-3.60 (m, 7H: H6, H7, H14, 2H1', 2H2'), 4.2 (d, 1H: OH*), 4.55 (d, 1H: OH*), 6.13 (d, 1H: H15, J = 1.8Hz), 7.40 (d, 1H: H16, J = 1.8Hz), 7.65-7.75 (b, 1H: NH*); ^{13}C-NMR (DMSO-D_6, 100 MHz): see Table 3.

*D_2O exchangeable

*6α,7β-di-hydroxy-N-propylvouacapan-17β-amide (**VIII**)*

M.p. 168.9-170.3 °C. Anal. Calcd. for $C_{23}H_{35}NO_4$: C: 71.00%, H: 9.06%, N: 3.60%. Found: C: 70.25%, H: 9.40%, N: 4.40%. IR ν (cm^{-1}): 3600-3100, 1670- 1610, 1570-1510; MS: M^+ = (m/z) = 389 (35%); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ= 0.97 (s, 3H: CH_3), 1.05 (s, 3H: CH_3), 1.17 (s, 3H: CH_3), 0.90 (t, 3H: 3H3', J = 7.4Hz), 0.8-1.8 (m, 8H: 2H1, 2H2, 2H3, H5, H9), 1.3-1.6 (m, 2H: 2H2'), 2.0-2.20 (m, 1H: H8), 2.3-2.5 (m, 1H: H11ax, J_{gem} = 16.0Hz, J_{11ax-9} = 11.5Hz), 2.70 (dd, 1H: H11eq, J_{gem}=16.0Hz, J_{11eq-9}=5.0Hz), 3.10-3.40 (m, 5H: H7, H14, 2H1',OH*), 3.75 (dd, 1H: H6), 6.10 (t, 1H: NH*), 6.14 (d, 1H: H15, J = 1.8Hz), 7.25 (d, 1H: H16, J = 1.8Hz); ^{13}C-NMR ($CDCl_3$, 50 MHz): see Table 3.

*D_2O exchangeable

*6α,7β-di-hydroxy-N-isopropylvouacapan-17β-amide (**IX**)*

M.p. 184.6-186.2 °C. Anal. Calcd. for $C_{23}H_{35}NO_4$: C:71.00%, H: 9.06%, N:3.60%. Found: C: 70.50%, H: 9.22%, N: 3.67%. IR ν (cm^{-1}): 3550-3100, 1670-1610, 1560-1510; MS: M^+ = (m/z)= 389 (100%); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ= 0.99 (s, 3H: CH_3), 1.06 (s, 3H: CH_3), 1.14 (d, 3H: CH_3 (i-pr), J = 8.0Hz), 1.15 (d, 3H: CH_3 (i-pr), J = 8.0Hz), 1.17 (s, 3H: CH_3), 0.8-1.7 (m, 8H: 2H1, 2H2, 2H3, H5, H9), 2.0-2.10 (m, 1H: H8, J_{8-14} = 8.6Hz), 2.3-2.4 (m,1H: H11ax, J_{gem} = 16.0Hz, J_{11ax-9} = 11.5Hz, $J_{11ax-14}$ = 2.2Hz), 2.2 (s, 1H: OH*), 2.68 (dd, 1H: H11eq, J_{gem} = 16.0Hz, J_{11eq-9} = 5.0Hz), 3.28 (dd, 1H: H14, J_{14-8} = 8.4Hz), 3.37 (dd, 1H: H7, J_{7-6} = 8.7Hz, J_{7-8} = 9.3Hz), 3.74 (dd, 1H: H6, J_{6-7} = 8.4Hz, J_{6-5} = 11.3Hz), 4.0-4.2 (m, 2H: H1', $J_{1'-NH}$ = 8.0Hz, $J_{1'-2'}$ = $J_{1'-2"}$ = 6.0Hz, and OH*), 5.62 (d, 1H: NH*, $J_{1'-NH}$ = 8.0Hz), 6.14 (d, 1H: H15, J = 1.8Hz), 7.27 (d, 1H: H16, J = 1.8Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz): see Table 3.

*D_2O exchangeable

Results and Discussion

A general preparation procedure for the amide derivatives of ADV is described. The most efficient synthetic route for this preparation utilized 6α-hydroxyvouacapan-7β,17β-lactone **II** (Scheme 1), since the opening of the

lactone group is entropically favored. The lactone **II** was obtained by reacting ADV with acetic anhydride in the presence of anhydrous sodium acetate, in THF, as previously reported[4].

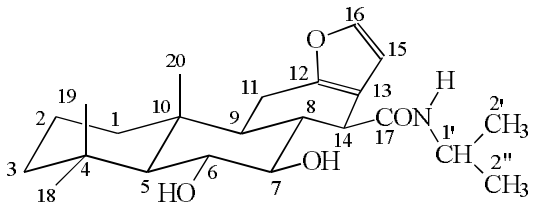
The reactions were monitored by TLC, the disappearance of the IR band of the carbonyl lactone at ν 1770 cm^{-1}, and the appearance and intensification of bands I and II at 1680-1630 and 1570-1515 cm^{-1}, respectively, which are characteristic of amide groups[6].

Some additional comments may be made regarding the reactivity of the amines employed (Table 1). The relative reactivities in the cases of propyl and isopropylamine used for the preparation of **VIII** and **IX**, respectively, were influenced by steric factors. In the synthesis of **VIII** the reaction time was approximately 1/10 of that necessary when isopropylamine was employed. The use of ethylenediamine could suggest a very favorable reaction due to the presence of two NH_2 groups. However, the reaction time and the low yield of **VII** revealed a low reactivity of ethylenediamine as compared to propylamine. This reaction difficulty may be due to the existence of intramolecular hydrogen bonding in ethylenediamine. On the other hand, the steric effect should be the principal factor determining the facility of these reactions, since despite their higher basicity, disubstituted amines show a lower nucleophilic ability due to steric hindrance. This consideration is supported by the fact that the synthesis of **VI** took longer than all the others, as shown in Table 1.

The structures of all compounds were determined by spectral properties (see the experimental part). The assignment of the ^1H and ^{13}C-NMR signals was based on the observed signal multiplicities and empirical shift rules, along with the ^1H x ^{13}C-COSY shift correlations (Tables 2 and 3, respectively)[7,8].

The assignments of the ^1H-NMR signals of the diterpene skeleton atoms for all amides shown in Table 2 may be better understood by a more detailed analysis of amide **IX**, taken as a reference, whose ^1H x ^{13}C COSY and ^1H x ^1H COSY spectra are depicted in Figs. 1 and 2, respectively.

The higher shielding region (δ 0.8-1.7) of the ^1H-NMR spectrum of the ADV derivatives is very complex due to the overlapping of the methyl, methylene, and methyne signals of the diterpene moiety. The ^1H x ^{13}C-COSY



IX

Table 2. ^1H chemical shifts (δ) of the amide derivatives of ADV *

H	III[a]	IV[b]	V[a]	VI[a]	VII [d]	VIII[b]	IX[c]
1,2,3,5,9	0.8-2.0	0.8-1.17	0.9-1.18	0.8-1.8	0.9-1.65	0.8-1.8	0.8-1.7
6**	3.6-3.9	3.6-3.8	3.6-3.9	3.3-3.9	3.0-3.6	3.75	3.74
7**	3.2-3.5	3.2-3.4	3.1-3.6	2.8-3.3	3.0-3.6	3.1-3.4	3.37
8**	2.1-3.0	2.1-2.4	2.0-3.0	2.3-2.8	2.1-2.2	2.0-2.2	2.0-2.1
11**	2.1-3.0	2.1-2.4 ax 2.61 eq	2.0-3.0	2.3-2.8	2.2-2.35 ax 2.42-2.52 eq	2.3-2.5 ax 2.7 eq	2.3-2.4ax 2.68 eq
14**	3.2-3.5	3.2-3.4	3.1-3.6	2.8-3.3	3.0-3.6	3.1-3.4	3.28
15	6.14 (1.8)	6.07 (1.8)	6.14 (1.8)	6.0 (1.8)	6.13 (1.8)	6.14 (1.8)	6.14 (1.8)
16	7.26 (1.8)	7.19 (1.8)	7.26 (1.8)	7.20 (1.8)	7.40 (1.8)	7.25 (1.8)	7.27 (1.8)
18	1.18	1.16	1.18	1.17	1.13	1.17	1.17
19	1.06	1.03	1.06	1.04	1.0	1.05	1.06
20	0.98	0.93	0.98	0.93	0.93	0.97	0.99
NH #	5.6-5.8	6.44	5.7-6.0	-	7.65-7.75	6.1	5.62
OH #	2.1-3.0 4.5-4.7	3.2-3.4 4.2-4.6	3.1-3.6 4.5-4.7	2.8-3.3 3.3-3.9	4.2 4.55	3.1-3.4	2.2[a] 4.0-4.2[a]

Spectra recorded in $CDCl_3$ at (a) 80 MHz, (b) 200 MHz, (c) 400 MHz, and (d) in DMSO-D_6 at 400 MHz.
*Some coupling constants J in Hz are in parentheses. The chemical shifts and coupling constants for compounds **III**, **V**, **VI** and **VII** were deduced from the 1D NMR spectra. ^1H x ^1H-COSY and ^1H x ^{13}C-COSY were also used to confirm the chemical shift assignments, mainly those of compounds **IV**, **VIII**, and **IX**. For assignments of the N-substituent hydrogen groups, see the Experimental part.
** Coupling constant values in the Experimental part.
# D_2O exchangeable.

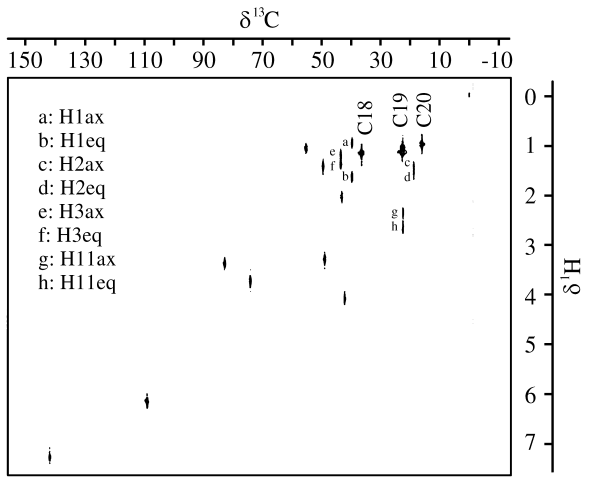


Figure 1. The ^{1}H x ^{13}C 2D shift correlated spectrum of **IX**.

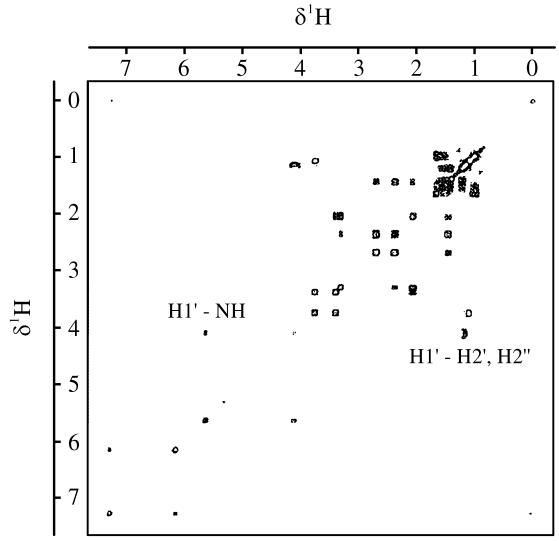


Figure 2. The ^{1}H x ^{1}H 2D shift correlated spectrum of **IX**.

spectrum of **IX** (Fig.1) confirmed the assignment for hydrogens attached to C18, C19, and C20, observed at δ 1.17, 1.06 and 0.99, respectively. The axial and equatorial hydrogens belonging to the methylene at positions 1, 2, and 3 (H1, H2, and H3) showed resolved signals in the ^{1}H x ^{13}C-COSY spectrum (Fig.1). The multiplicities, chemical shifts, and coupling constant values for the H11 methylene were used for the stereochemistry assignment of both H11ax and H11eq. The multiplet in the δ 2.3-2.4 range was assigned to hydrogen at the axial position (J_{gem} = 16.0 Hz, J_{11ax-9} = 11.5 Hz). The latter value confirms the axial-axial relationship between H9 and H11ax. Besides these two coupling constant values, another of 2.2 Hz was observed, corresponding to the long range coupling ^{5}J between H11ax and H14. The ^{1}H x ^{1}H-COSY spectrum confirmed this assignment (Fig.2). The hydrogen H11 in the equatorial position showed a double doublet at δ 2.68 (J_{gem} = 16.0 Hz, J_{11eq-9} = 5.0Hz). The latter value confirms the axial-equatorial stereochemistry between hydrogen H9 and H11.

Hydrogen H8 showed a multiplet due to its coupling with H7, H9, and H14. In the case of **IX**, this signal is observed at δ 2.0-2.1 (J_{8-9} = 11.9Hz, J_{8-7} = 9.7 Hz, J_{8-14} = 8.6Hz). Hydrogens H7 (J_{7-6} = 8.7 Hz, J_{7-8} = 9.3 Hz) and H14 (J_{14-8} = 8.4 Hz) showed two double doublets at δ 3.37 and 3.28, respectively. These signals were very well resolved by ^{1}H x ^{13}C-COSY and ^{1}H x ^{1}H-COSY spectra (Figs. 1 and 2, respectively). Hydrogen H6 showed a double doublet at δ 3.74. The J_{6-5} = 11.3 Hz and J_{6-7} = 8.4 Hz confirm the axial-axial stereochemistry between hydrogen H6 with both H5 and H7, respectively. The signals at δ 6.14 (J = 1.8 Hz) and 7.27 (J = 1.8 Hz) of **IX** were assigned to H15 and H16, respectively.

For all amides (**III** to **IX**) the ^{1}H-NMR spectral data due to the N-alkyl substituent are presented in the Experimental part. In the case of amide **IX**, two doublets of equal intensity at δ 1.14 and δ 1.15 characterize the methyl hydrogens of the isopropyl group. A multiplet between δ 4.04 and

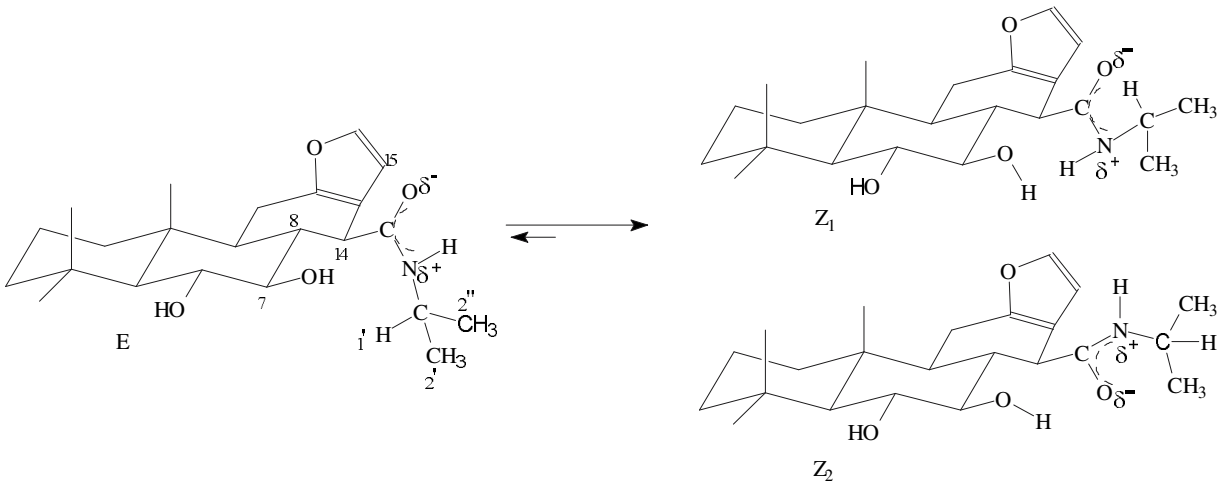


Figure 3. Configuration isomers (E/Z) and conformers (Z1/Z2) possible for **IX**.

4.14, is also observed which is due to the coupling of the isopropyl group methyne hydrogen (H1' in Scheme 1) with both NH and the CH_3 groups (H2' and H2" in Scheme 1). The ^1H x ^{13}C-COSY spectrum showed cross coupling between H1'and the NH hydrogen at δ 5.62 (see Fig. 2). This multiplet was simplified after the addition of D_2O, and showed two overlapping heptets, with an intensity ratio of 3:1. This fact may indicate the configurational isomerism existing in amides (E and Z isomers), as illustrated in Fig. 3.

According to the stereochemical analysis of **IX** with Drieding models, the environment of the isopropyl group varies from isomers E to Z both configurationally and conformationally, being much less crowded in the Z isomer. On the other hand, conformers Z_1 and Z_2, presented in Fig. 3, could form hydrogen bonds between either HO-HN$^{\delta}$+ or OH-$^{-}$δO-C. However, these hydrogen bonds do not occur because the chemical shift for the OH7 group in $CDCl_3$ is at δ 2.0 or δ 4.0-4.2 (Table 2). If hydrogen bonds were present, the hydrogen of the OH7 group would be much more deshielded[9]. Moreover, because of the slower intermolecular proton exchange in DMSO-d_6, the spectrum of **IX** in this solvent shows duplets at δ 4.04 ($J_{H7\text{-}OH}$ = 4.3Hz) and δ 4.13

Table 3. ^{13}C chemical shifts (δ) of the amide derivatives of ADV.

Carbon	**III** [a]	**IV** [b]	**V** [a]	**VI** [a]	**VII** [d]	**VIII** [b]	**IX**[c]
1	39.64	39.39	39.66	39.65	39.14	39.46	39.55
2	18.59	18.45	18.31	18.63	18.04	18.47	18.52
3	43.51	43.79	43.51	43.13	43.73	43.37	43.37
4	33.51	33.41	33.55	33.58	33.41	33.42	33.46
5	55.40	55.35	55.40	55.83	55.41	55.26	55.15
6	73.96	73.94	74.08	74.29	73.92	73.92	73.88
7	82.66	82.61	82.70	83.69	82.11	82.54	82.55
8	42.79	42.20	43.00	42.71	40.89	42.66	42.95
9	49.47	48.94	49.63	48.55	48.40	49.31	49.37
10	38.26	38.19	38.32	38.58	38.91	38.18	38.20
11	22.21	21.99	22.32	22.26	21.88	22.08	22.14
12	151.90	151.80	152.13	151.17	150.32	151.91	152.08
13	113.84	113.72	113.62	114.46	115.93	113.59	113.44
14	48.66	48.36	48.62	48.55	47.81	48.47	48.71
15	108.84	108.65	108.97	107.96	109.23	108.82	108.83
16	141.52	141.39	141.67	141.31	141.15	141.52	141.65
17	175.33	176.10	176.41	174.20	174.23	176.44	175.71
18	36.41	36.48	36.39	36.51	36.81	36.33	36.32
19	22.33	22.28	22.36	22.52	22.50	22.25	22.27
20	15.80	15.62	15.85	15.57	15.49	15.69	15.78
1'	48.66	43.38	34.89	43.65	40.61*	41.63	41.89
2'	32.71#	138.41	14.63	12.85#	37.96*	22.57	22.38#
3'	25.53	127.36	-	-	-	11.33	-
4'	24.77	127.67*	-	-	-	-	-
5'	25.53	128.58*	-	-	-	-	-
6'	32.91#	127.67*	-	-	-	-	-
7'	-	127.36	-	-	-	-	-
1"	-	-	-	41.31	-	-	-
2"	-	-	-	14.59#	-	-	22.51#

Spectra recorded in $CDCl_3$ at (a) 20 MHz, (b) 50 MHz, (c) 100 MHz, and (d) in DMSO-D_6 at 100 MHz.
*^1H x ^{13}C-COSY 2D NMR spectra were also used for the assignments.
#May be interchangeable, they are different due to the chiral neighborhood.

Table 4. Interpretation of NOE difference spectrum[a].

δ Irradiation (H)	Observed Nuclear Overhauser enhancements (δ/H)
5.62 (NH)	7.0 (3.28 / H14)
	3.5 (6.14 / H15)
	2.4 (4.0-4.2 / H1')
	1.2 (1.14; 1.15 / H2'; H2")
	1.2 (2.0-2.1 / H8; OH7)

a - At 400 MHz in $CDCl_3$.

($J_{H6\text{-}OH}$ = 4.0 Hz) for OH7 and OH6, respectively. These chemical shifts are also characteristic of OH groups without hydrogen bonding[6,9]. Therefore, the two heptets observed for the isopropyl methyne hydrogen in the ^{1}H-NMR spectrum of **IX** may indicate either an equilibrium between E and Z isomers or between Z_1 and Z_2 conformers.

Further information about these stereoisomers was derived from the NOE difference spectrum with the decoupling of NH hydrogen.

NOE enhancement observed for H14 (Table 4) reflects a syn relationship between this hydrogen and the NH, indicating the presence of the Z conformer. The higher NOE value for H14 (7.0), as compared to that for H15 (3.5), shows a Z_1 preponderance over Z_2. The weak NOE effect observed for H8 and OH7 shows some spatial proximity of NH. This proximity is possible only in the Z_1 form.

The ^{13}C-NMR (DEPT 90, 135, BB decoupled spectrum, and ^{1}H x ^{13}C-COSY spectra) confirmed the assignments for the carbon atoms of the isopropyl group. Its methyl groups are magnetically nonequivalent due to the chiral neighborhood, independent of the conformational problem discussed above.

The reaction of the furane-diterpene lactone **II** with a wide variety of amines was shown to be a convenient and versatile method for amide derivatives preparation. The structural characterization of these compounds employing one and two-dimensional ^{1}H and ^{13}C-NMR may be quite interesting for researchers, in the fields of natural products and synthetic chemistry.

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References

1. This work is part of C.R.A. Maltha's Ph.D. Thesis, *Estudo da Síntese de Aminas e Amidas Derivadas do Ácido 6α,7β-di-hidroxivouacapan-17β-óico*; Departamento de Química - ICEx - Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, 1994.
2. Correa, M.P. In *Dicionário de Plantas Úteis do Brasil e das Exóticas Cultivadas*; M.A. IBDF, Rio de Janeiro, 1978; *6*, p. 153.
3. Nunan, E.A.; Piló-Veloso, D.; Turchetti, R.M.M.; Alves, D.L.F. *J. Med. Exp. Sc.* **1982**, *50* (6), 450.
4. Rubinger, M.M.M.; Piló-Veloso, D.; Stefani, G.M., Alves, D.L.F. *J. Braz. Chem. Soc.* **1991**, *2* (3), 124.
5. Maltha, C.R.A.; Stefani, G.M.; Piló-Veloso, D. *J. Braz. Chem. Soc*. **1995**, *6* (4), 357.
6. Silverstein, R.M.; Bassler, G.C., Morril, T.C. In *Spectrometric Identification of Organic Compounds;* John Wiley & Sons; New York, 1991.
7. Breitmaier, E.; Voelter, W. In *Carbon-13 Spectroscopy: High-Resolution Methods and Applications in Organic Chemistry and Biochemistry;* VCH; Weinhein, 1987.
8. Sanders, J.K.M.; Hunter, B.K. In *Modern Spectroscopy: A Guide for Chemists;* Oxford University Press; Oxford, 1988.
9. Bovey, F.A. In *Nuclear Magnetic Resonance Spectroscopy*; Academic Press; San Diego, 1987.