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The Synthesis of 6α,7β-Dihydroxyvouacapan-17β-oic Acid Derivatives. Part II: Carbamate and Amine Derivatives[1]

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O ácido 6α,7β-diidroxivouacapan-17β-óico **I** (ADV), isolado dos frutos de *Pterodon polygalaeflorus* Benth apresenta atividade antiinflamatória e analgésica *in vivo*. Modificações químicas em sua estrutura têm sido efetuadas para que possa ser estabelecida a relação estrutura química – atividade biológica. Este trabalho relata a síntese de derivados obtidos através dos rearranjos de Hofmann e de Lossen. As estruturas foram determinadas pela análise de espectros no IV, RMN de ^{1}H e de ^{13}C, e de Massas.

The furane-diterpene 6α,7β-dihydroxyvouacapan-17β-oic acid **I** (ADV), isolated from *Pterodon polygalaeflorus* Benth fruits presents both anti-inflammatory and analgesic activities. In order to gather data for pharmacological studies, new derivatives of ADV were obtained: urethane **V** and amine **VI**. Their structures were determined on the basis of IV, ^{1}H-NMR, ^{13}C-NMR and Mass spectrometric data.

Keywords: *6α,7β-dihydroxyvouacapan-17β-oic acid, furane-diterpene, carbamate, molecular rearrangement*

Introduction

The employment of alcoholic infusions from the fruits of the 'sucupira branca' (*Pterodon*), Leguminosae family, in Brazilian folk medicine for the treatment of rheumatic affections and throat infections is well known[2].

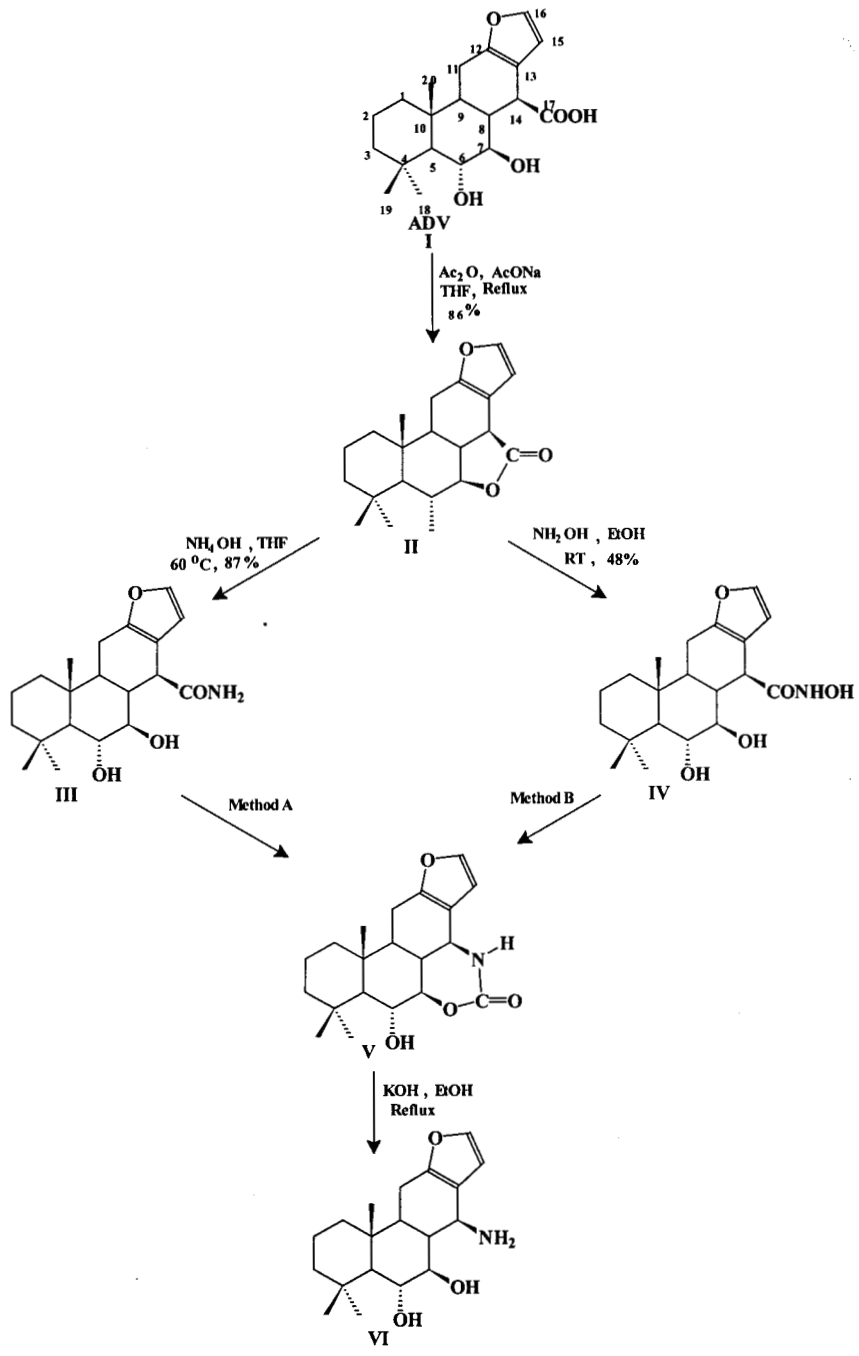
From the hexanic extract of the fruits of *Pterodon polygalaeflorus* Benth three linear diterpenes and four furane-diterpenes were isolated and identified, one of which was 6α,7β-dihydroxyvouacapan-17β-oic acid **I** (ADV)[3-5]. The latter presents anti-inflammatory and analgesic activities[6]. The vouacapan anti-inflammatory activity does not seem to be related to fatty acid cyclo-oxigenase inhibition.

New derivatives of ADV have been obtained in order to elucidate the mechanism of vouacapan action. Glycosyl derivatives were obtained, but the yields were very low[7,8]. Nitrogenated derivatives were previously obtained, but did not present improvement in the anti-inflammatory activity of orally taken ADV. However, they did present higher analgesic activity[6].

In this paper we report the Hofmann (Method A) and Lossen (Method B) rearrangements which were carried out on the amide **III** and hydroxamic acid **IV** (Scheme 1). The product in both cases was the cyclic urethane **V**, the hydrolysis of which produced the amine **VI**.

Experimental

Routine experimental procedures and instruments for physical measurements were used[1]: ^{1}H and ^{13}C-NMR spectra were recorded on both a JEOL EX 400 operating at 400 and 100 MHz respectively, and on a Bruker AC 80, operating at 80 and 20 MHz, respectively. The signals (+) or (-) indicate whether the signal was in the positive or in the negative phase in the DEPT 135 ^{13}C-NMR spectra. Mass spectra were obtained using electron ionization at 70 eV on a Varian Mat 311 A. Infrared spectra were recorded using KBr disks on a Shimadzu IR 408. Melting points were measured on a Mettler FP 82 HT and are not corrected.



Scheme 1.

ADV derivatives were prepared as indicated in Scheme 1, according to the methods described below[1].

The Preparation of 6α-hydroxy-17β-azavouacapane-17,7β-carbolactone (V)

Method A (Hofmann rearrangement)[9]: To 10.0 mL of methanol was added 0.20 g (0.57 mmol) of amide **III** and 0.05 g (2.2 mmol) of metallic sodium dissolved in 5.0 mL of methanol. The mixture was vigorously stirred for 15 min at room temperature, and 2.0 mL (1.14 mmol) of a solution (0.58 M) of bromine in methanol was added. Then, the mixture was heated at 60 °C, with stirred for 1 h and monitored by TLC. The reaction mixture was allowed to cool to room temperature and then neutralized with acetic acid, and poured onto crushed ice. The resulting white solid was filtered off, washed with water and air dried. The product thus obtained was pure on TLC (3:1 chloroform/ethanol). Recrystallization from dichloromethane/petroleum ether (1:2) gave 0.08g (0.22 mmol, 38% yield) of white crystals, m. p. 339.8-341.7 °C.

Method B (Lossen rearrangement)[10]: To a solution of 2.5g (23.6 mmol) of sodium carbonate in 25.0 mL of water was added 0.20 g (0.55 mmol) of hydroxamic acid **IV**. The reaction mixture was stirred at room temperature for 20 min. After this time 0.07 mL (0.55 mmol) of benzenesulfonyl chloride was added with stirring, and the reaction was monitored by TLC. After 4 h the reaction was complete and the solution was poured onto crushed ice. The resulting white solid was filtered off, washed with water until it reached a neutral pH, and then dried. The product thus obtained was pure on TLC (3:1 chloroform/ethanol). Recrystallization from methanol gave 0.18 g (0.52 mmol, 95% yield) of white crystals, m. p. 339.8-341.7 °C. Anal. Calcd. for $C_{20}H_{27}NO_4$: C:69.62, H:7.88, N:4.05. Found: C:69.16, H:7.74, N:4.01. IR ν (cm^{-1}): 3600-3100, 1725, 1630; MS: M^+ (m/z) = 345 (100%); ^{1}H-NMR (Py-d_5)δ = 0.85 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 0.80-1.60 (m, 8H, H1,2,3,5,9), 1.70-1.85 (m,1H, H8, $J_{8\text{-}14}$ = 9.1 Hz), 2.30-2.50 (m,1H, H11a), 2.55 (dd, H11e, $J_{11a\text{-}11e}$ = 16.6 Hz, $J_{11e\text{-}9}$ = 6.6 Hz), 4.18-4.20 (dd, 1H, H6, $J_{6\text{-}7}$ = 9.0 Hz, $J_{6\text{-}5}$ = 10.8 Hz), 4.30-4.50 (m, 2H, H7, H14), 4.80-5.40 (bb,1H*,OH), 6.90 (d,1H, H15, J = 1.8Hz), 7.60 (d, 1H, H16, J = 1.8 Hz), 8.90 (s, 1H*, NH); ^{13}C-NMR (Py-d_5) δ = 15.45(+), 18.56(-), 22.56(-), 22.82(+), 33.96, 37.39(+), 38.42, 39.17(-), 40.32(+), 44.27(-), 45.28(+), 51.93(+), 55.61(+), 70.66(+), 86.53(+), 108.22(+), 117.51, 142.22(+), 150.76, 154.58.

* D_2O exchangeable.

*The Preparation of 6α,7β-dihydroxy-17-norvouacapan-14β-amine (**VI**)*

To a solution of 2.5 g (44 mmol) of potassium hydroxide in 25.0 mL of ethanol was added 0.20 g (0.58 mmol) of **V**. The reaction mixture was stirred for 2 h at the reflux temperature and, monitored by TLC (chloroform/ethanol 3:1). After this time the mixture was allowed to cool to room temperature and then poured onto crushed ice. The resulting white solid was filtered off, washed with water, dried and recrystallized from dichloromethane/n-hexane (1:2). Thus, 0.08 g (0.25 mmol, 44% yield) of white crystals were obtained, m. p. 179.6-180.4 °C. Anal. Calcd. for $C_{19}H_{29}NO_3$: C:71.50, H:9.15, N:4.39. Found: C:70.5, H:9.08, N:4.28. IR ν (cm^{-1}): 3500-3100, 1650-1560; MS: M^+ (m/z) = 319 (15%); ^{1}H-NMR ($CDCl_3$) δ = 0.98 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 0.80-1.70 (m, 9H, H1,2,3,5,8,9), 2.30-2.40 (m, 1H, H11a), 2.60 (dd, 1H, H11e, $J_{11a\text{-}11e}$ = 13.2Hz, $J_{11e\text{-}9}$ = 5.0 Hz), 3.00-3.50 (bb, 2H*, NH_2), 3.50-3.70 (m, 1H, H7), 3.70-3.90 (m, 2H, H6, H14), 6.26 (d, 1H, H15, J = 1.8 Hz), 7.26(d, 1H, H16, J = 1.8 Hz); ^{13}C-NMR ($CDCl_3$) δ = 15.68(+), 18.42(-), 22.15(-), 22.37(+), 33.34, 36.40(+), 38.01, 39.43(-), 43.46(-), 45.41(+), 47.97(+), 53.64(+), 54.74(+), 73.70(+), 83.05(+), 107.21(+), 120.90, 141.53(+), 149.96.

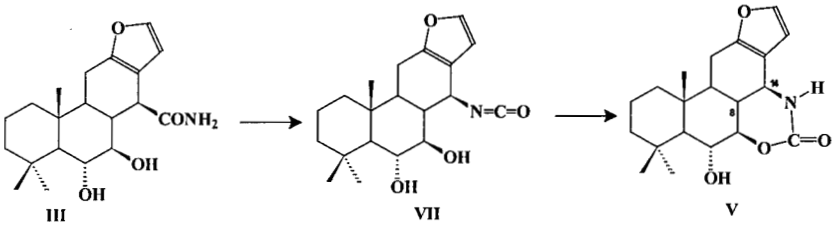
* D_2O exchangeable.

Results and Conclusion

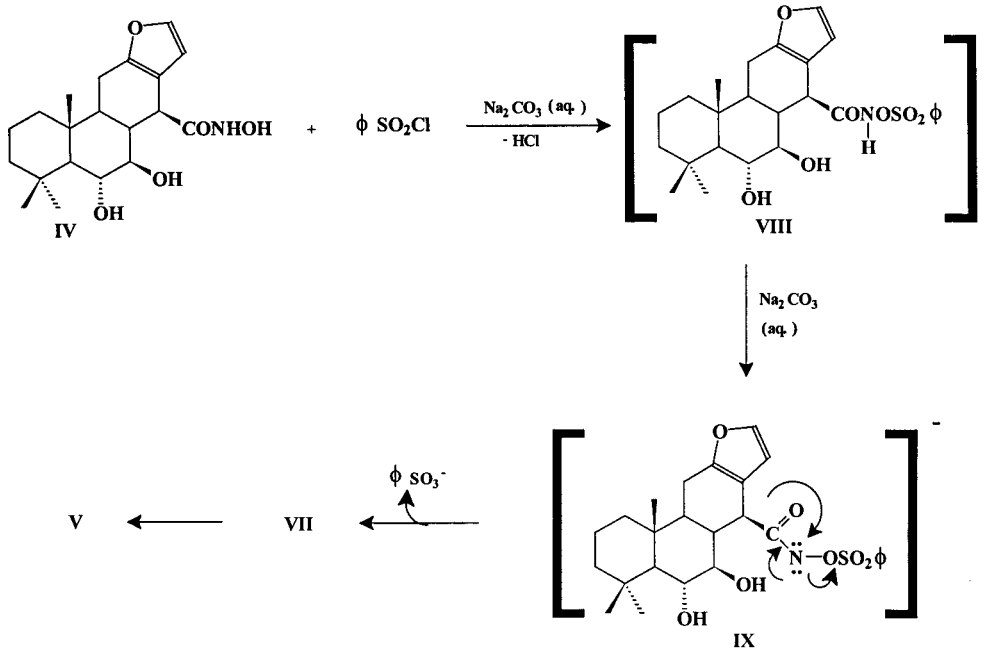
Compounds V and **VI** (Scheme 1) are new derivatives of ADV. The former was obtained throught two different molecular rearrangements: the Hofmann (Method A) and the Lossen procedures (Method B). Although amines may be obtained by several methods[11], the Lossen procedure offered advantages in terms of both convenience and yield when compared to the Hofmann method. The latter, when carried out under standard conditions[12], dissolving the amide in a very slight excess of cold aqueous hypobromite solution, followed by warming, results in a complex mixture, containing a basic product identified by TLC (a blue spot detected by the blue of bromothymol). In the Hofmann procedure special conditions for higher aliphatic amides, described in the experimental part (Method A)[13], compound **V** was obtained in only a 38% yield. In contrast, the Lossen rearrangement provides a 95% yield of compound **V**.

Urethane **V** was obtained by the Hofmann reaction (special conditions) of the amide **III**, probably involving the intramolecular nucleophilic attack of the C-7 hydroxyl on the isocyanate carbonyl group of intermediate **VII**, as shown in Scheme 2. On the other hand, the methyl carbamate derivative that would be obtained by the intermolecular attack of methanol on the carbonyl group of **VII** was not formed. By ^{1}H-NMR analysis of the reaction solution, the methoxyl resonance signal was not observed. The signal at δ 8.90 was attributable to the proton of the NH group in urethane **V**. These facts confirm the preferability of the intramolecular reaction over the intermolecular one (Scheme 2).

The ^{1}H-NMR of urethane **V** showed a multiplet from δ 1.70 to δ 1.85 due to proton H-8. The analysis of this signal



Scheme 2.



Scheme 3.

provides $J_{8\text{-}14}$ = 9.1 Hz indicating the axial-axial stereochemistry between H-8 and H-14. This confirms the retention of the configuration in the referred rearrangements.

When urethane **V** was obtained by the Lossen procedure, the compound **VIII** shown in Scheme 3 was not isolated. Probably, sodium carbonate was capable of promoting an intramolecular rearrangement through the intermediate **IX**.

The amine **VI** was obtained by alkaline hydrolysis of urethane **V** in a 44% yield. Finally, besides the better yield of the intermediate urethane **V**, Method B in Scheme 1 was more convenient because of the simplicity of the reagents employed.

Acknowledgments

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