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New quinolizidine and diaza-adamantane alkaloids from *Acosmium dasycarpum* (Vog.) Yakovlev—Fabaceae

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ABSTRACT

The phytochemical investigation of the methanol crude extract obtained from *Acosmium dasycarpum* (Vog.) Yakovlev root bark led to the isolation of the quinolizidine alkaloids lupanine, acosmine, acosminine and lupanacosmine, as well as the diaza-adamantane alkaloids panacosmine and dasycarpumine. Lupanacosmine (**4**) and dasycarpumine (**6**) have been described for the first time herein.

Acosmium dasycarpum (Vog.)Yakovlev,[1–3] occurs predominantly at the Brazilian savannahs (the 'Cerrados'),[3,4] being locally known as perobinha, chapada, pau paratudo, or unha d'anta.[4–6] The tea prepared from the root bark of this species has been described in the first edition of the Brazilian Pharmacopoeia as a sedative. In folk medicine, the stem and root tea preparation have been used to treat inflammation, skin diseases, and disturbances from central nervous and cardio-vascular systems.[7–10] Quinolizidine alkaloids (QAs) are secondary compounds found in seeds of many species of plants, possibly protecting them against pathogens and seed predators. Structural, spectroscopic and computational studies on both natural and synthetic quinolizidines are also reported regularly and have shown to be an important class of alkaloid with biological significance.[11] Studies on the biological activity of compounds containing azabicyclic building blocks (e.g., rigid bicyclic peptidomimetics) are gaining momentum because this class is attractive as nematicidal and has shown to be especially active at the muscarinic receptor, enhancing insulin secretion and also presenting diuretic properties.[12] On the other hand, diaza-adamantane skeleton was firstly encountered in a natural product, isolated from the seeds of *Acosmium panamense*.[1] This class of compounds is uncommon, but due to the high pharmacological activities it has recently drawn great attention in folk medicine research.[13]

Aiming the isolation and identification of bioactive substances, we have isolated several alkaloids during the conventional chromatographic fractioning of the methanol crude extract from the root bark of *A. dasycarpum*. The alkaloids lupanine **1**, acosmine **2**, acosminine **3**, and panacosmine **5** have been previously reported in *Acosmium*.[1,14] However, the alkaloids lupanacosmine **4** and dasycarpumine **6** have been described for the first time herein. *Acosmium dasycarpum* aerial roots were collected at Chapada dos Guimarães, state of Mato Grosso, Brazil and identified by Dr. M. Macedo (Universidade Federal de Mato Grosso—UFMT). Voucher specimens numbered 24079 (01/02/2000) were deposited at UFMT Central Herbarium. The dried root barks (3.3 kg) were sequentially extracted with hexane (3 L) and methanol (5 L). A portion (55.0 g) of the crude methanol extract (EBMeOH) dissolved in methanol (200 mL) was acidified with 10% acetic acid (pH 2.5–3.0), extracted with $CHCl_3$ (3 × 50 mL) and alkalinized with NH_4OH (pH 8.9–9.0), affording the alkaloids fraction FA-I (5.5 g; 9.98%). FA-I was submitted to column chromatography, affording compound **6** (11.5 mg; 0.02%). Compound **1** (3.3 mg; 0.006%) was obtained after HPLC purification.[15] Another EBMeOH portion (150.0 g) was acidified with 5% HCl (pH 2.5–3.0), extracted with ethyl ether (4 × 50 mL) and alkalinized with 28% NH_4OH (pH 8.5–9.0), affording the alkaloids fraction FA-II (3.8 g; 2.53%). Preparative thin-layer chromatography carried out on FA-II led to the isolation of **2** (15.3 mg; 0.01%),[1] **3** (21.2 mg; 0.14%),[1] **4** (56.4 mg; 0.04%),[16] and **5** (8.1 mg; 0.01%).[1,17] Compound **1** has shown, in its IR spectrum, typical amide absorption at 1620 cm^{-1}. This absorption is coherent with the ^{13}C NMR signal at δ 172.0. These and the other spectral

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data obtained for compound **1** were fully consistent with the literature description for the quinolizidine alkaloid lupanine.[12,14,18] Mass spectra for compound **2** has shown an odd molecular ion [M^+] at 357, pointing out to the presence of an odd number of nitrogen atoms in its structure. The DEPT experiment has presented a methinic signal at δ 70.9. Therefore in comparison with compound **1**, compound **2** must have a substituent at C-10. The absence of an amide carbonyl group at C-2, as well as the evidences for the presence of the substituent at C-10, could be demonstrated from the HMBC data, correlating H-10 (δ 2.36) to C-2 (δ 52.9) C-8 (δ 27.9), C-9 (δ 37.3), C-11 (δ 60.8), C-18 (δ 117.4), C-19 (δ 24.7), and C-23 (δ 123.0) (Fig. 1A; Table 2). In the same experiment, the correlation of H-23 (δ 6.67/7.27) to C-10 (δ 70.9), C-19 (δ 24.7) and C-21 (δ 40.4) (Fig. 1B; Table 2) and the correlation of H-25 (δ 2.20/2.15) to C-23 (δ 123.0/122.0) and C-24 (δ 168.0) (Table 2) has also been observed. The coupling of H-23 (δ 6.67/ 2.15) to C-23 (δ 123.0/122.0) has been shown by the COSY and HSQC experiments. HMBC experiments has shown that the methylic H-25 (δ 2.20/7.27) correlates to C-24 (δ 168.0) and C-23 (δ 123.0/122.0), confirming the presence of an acetylamide portion at the substituent (Fig. 1B). Restricted rotation around C–N bond at the acetylamide moiety has caused the doubling of ^{13}C NMR signals at C-23 and C-25 (Table 2). The same has been observed in ^{1}H NMR spectra, at positions H-23 and H-25, as previously observed in the literature.[1,14] The stereochemistry of the substituent at C-10 in compound **2** has been demonstrated to be equatorial, as it could be seen by the coupling of H-8_{ax} with H-10_{ax} in the COSY experiment (Table 2). These data are fully supportive of structure **2**, previously reported by the literature.[14] However, literature ^{13}C NMR spectral data have shown the following attribution to C-6 (δ 57.9), C-7 (δ 37.1), C-9 (δ 44.8), C-11 (δ 67.6), C-19 (δ 33.3), and C-20 (δ 25.7).[14] These data are not consistent with the ones we have

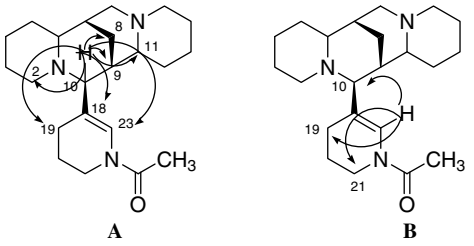

Figure 1. Main ^{1}H–^{13}C long-range correlation signal in the HMBC spectrum of **2**.

Table 1
^{13}C NMR spectral data of compounds **1**–**4**

C	1	2	3	4
2	172.0	52.9	53.2	54.6
3	33.1	26.1	26.0	26.2
4	19.5	25.1	24.9	25.6
5	27.5	30.1	30.0	30.3
6	60.8	67.5	67.3	67.0
7	31.7	33.0	36.8	33.6
8	26.4	27.9	27.8	27.8
9	34.3	37.3	33.1	34.3
10	46.5	70.9	70.7	70.7
11	64.6	60.8	57.8	59.3
12	32.1	34.3	42.9	31.7/30.7
13	23.8	25.1	68.6	136.1
14	24.1	25.7	34.2	116.3
15	55.6	56.0	52.2	42.4/42.3
17	52.1	53.3	52.8	50.9
18		117.4	117.5	118.0
19		24.7	25.5/34.2	25.4
20		21.6	21.5/22.2	21.6/22.2
21		40.4	40.2/44.5	40.4
23		123.0/122.0	122.8/123.5	123.4/121.8
24		168.0	167.9	168.2/167.5
25		21.6/22.6	21.2/22.2	22.0/23.0

Table 2
^{1}H and ^{13}C NMR attributions and nuclear correlations of **2**

H Position	δ_H	COSY	HMBC	δ_C
H_2a	1.48	n.o	n.o.	
H_2b	3.33	n.o.	C_2, C_{10}	52.9
H_3ax, equiv	1.56	H_2	n.o.	26.1
H_4ax	1.74	H_5 ax,equiv	n.o	
$H_{4'}$equiv	1.60	n.o.	n.o.	25.1
H_5ax	1.31	H_4ax	n.o.	
$H_{5'}$equiv	1.31	H_4ax,equiv, H6ax	C_4	30.1
$H_{6'}$	1.95	H_4ax, H_7, H_{17}ax	n.o.	67.5
$H_{7'}$	1.95	H_6, H_9, H_{17}	C_{17}	33.0
H_{8ax}	2.24	H_8 , H_9, H_{10ax}	n.o.	
H_{8equiv}	1.15	H_8	C_{11}	27.9
H_9	1.53	H_8, H_{10}, H_7	C_7	37.3
H_{10}ax	2.36	H_9, H_{11}	C_2, C_8, C_9, C_{11}, C_{18}, C_{19}, C_{23}	70.9
$H_{11'}$	1.97	H_9, H_{10}, H_{15}ax, H_{17}ax	C_{17}	60.8
H_{12}ax	1.12	H_{11}, H_{12}ax, H_{13}ax	C_{13}, C_{11}	
$H_{12'}$equiv	1.41	H_{11}, H_{12}ax, H_{13}ax	n.o	34.3
H_{13}ax	1.60	H_{13}equiv	n.o.	
H_{13}equiv		n.o.	n.o.	25.1
H_{14}ax,equiv	1.89	H_{15}	n.o	
		n.o.	n.o	25.7
H_{15}ax,equiv	2.94	H_{14}	n.o.	56.0
		n.o.		
H_{17}ax	2.83	H_6, H_{11}, H_{17}equiv	C_{11}	53.3
H_{17}equiv	2.36	H_{17}ax	n.o.	
C_{18}	n.a.	n.a.	n.a.	117.4
H_{19}a	1.75	H_{20}b, H_{19}b	n.o.	24.7
H_{19}b	1.24	H_{19}a	n.o.	
H_{20}a	1.75	H_{21}b	n.o.	
H_{20}b		H_{21}a	n.o.	21.6
H_{21}a	3.77	H_{20}b	n.o.	40.4
H_{21}b	3.53	H_{20}a	n.o.	
$H_{23'}$	6.67/7.27	—	C_{10}, C_{19}, C_{21}	123.0/122.0
C_{24}	n.a.	n.a.	n.a.	168.0
$H_{25'}$	2.20/2.15	—	C_{23}, C_{24}	21.6/22.6

a;b: Stereochemistry not observed.; n.o.: not observed.; n.a.: not apply.

Table 3
Homo (^{1}H–^{1}H) and heteronuclear (^{1}H–^{13}C) correlations of **4**

H	δ_H	COSY/HSQC	HMBC	C
H_2	H_{2x} = 1.59	H_{2y}, H_6	n.o	54.6
	H_{2y} = 3.32	H_{2x}	J^3 C_4, J^3 C_6	
H_3	1.53	n.o.	n.o.	26.2
H_4	1.79	H_{5ax}	J^2 C_5, J^3 C_2, J^3 C_6	25.6
H_5	H_{5ax} = 1.37	H_4	J^3 C_3	30.3
	H_{5equiv} = 1.60	H_6	n.o.	
H_6	2.04	H_2	J^5 C_{15}, J^3 C_{17}	67.0
H_7	1.83	H_{17}, H_{8x}, H_{8y}	n.o.	33.6
H_8	H_{8x} = 1.33	H_{8y}, H_7	J^3 C_6, J^3 C_{10}, J^3 C_{11}, J^3 C_{17}	27.8
	H_{8y} = 1.97	H_{8x},H_9, H_7	J^3 C_6, J^3 C_{10}	
H_9	1.66	H_{8x}, H_{8y}, H_{10}, H_{11}	n.o.	34.3
H_{10}	2.57	H_9	J^2 C_{18}, J^3 C_{23}, J^3 C_{11}	70.7
H_{11}	2.59	H_{12}, H_9	n.o.	59.3
H_{12}	2.16	H_{11}, H_{12}, H_{13}	J^3 C_9, J^2 C_{11}, J^2 C_{13}, J^3 C_{14}	31.7/30.7
H_{13}	5.56	H_{14}, H_{12}	n.o.	136.1
$H_{14a,b}$	5.02	$H_{14x,y}$, H_{13}	J^3 C_{12}	116.3
H_{15}	2.24	n.o.	J^3 C_{11}, J^3 C_{17}	42.4/42.3
$H_{17a,b}$	2.65	$H_{17x,y}$	n.o.	50.9
C_{18}	n.a.	n.a.	n.a.	118.0
H_{19}	1.85	n.o.	n.o.	25.4
H_{20}	1.79	H_{20}	n.o.	21.5
H_{21}	H_{21x}= 3.55	H_{21y}, H_{20}	n.o.	40.4
	H_{21y} = 3.59	H_{21x}	n.o.	
H_{23}	6.89/7.24	n.o.	J^3 C_{10}, J^3 C_{21}, J^4 C_{19}	123.4/121.8
C=O	n.a.	n.a.	n.a.	168.2/167.5
H_{25}	2.18	H_{11}	J^2 C_{24}, J^4 C_{23}	22.0/23.0

x and *y*: Stereochemistry not defined.; n.a.: not apply; n.o.: not observed.