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IRIDOID GLUCOSIDES FROM *ANGELONIA INTEGERRIMA*

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Key Word Index—*Angelonia integerrima*; Scrophulariaceae; iridoid glucosides; angeloside.

Abstract—*Angelonia integerrima* gave the known iridoid glucosides galiridoside, harpagide, ajugol, 6-hydroxy-antirrhide, antirrhide, daunoside, aucubin and stegioside II, together with a new compound, named angeloside. © 1997 Elsevier Science Ltd

INTRODUCTION

The genus *Angelonia* comprises 25 species from tropical South America reaching to Mexico and the West Indies; many species are cultivated [1] as ornamentals. Iridoids have been reported only for one species (*A. grandiflora*), where aucubin was detected by paper chromatography [2]. In the present work we have investigated *A. integerrima* Spreng.

RESULTS AND DISCUSSION

Reverse phase chromatography of the water-soluble part of an ethanolic extract of *A. integerrima* gave eight known iridoid glucosides, namely galiridoside (**1**), harpagide (**2**), ajugol (**3**), 6-hydroxy-antirrhide (**4**), antirrhide (**5**), daunoside (**6**), aucubin (**7**), and stegioside II (**8**) in addition to a new compound (**9**) which we have named angeloside. The new compound was isolated in admixture with **5**. However, acetylation allowed separation of **5a** and angeloside hexaacetate (**9a**) by preparative TLC, and pure angeloside was obtained from the latter by deacetylation.

The ^{13}C NMR spectrum of angeloside (Table 1) showed 15 carbon signals of which six could be assigned to a β-glucopyranosyl moiety. The remaining nine signals fitted well with an iridoid aglucone structure. Two signals appearing at δ 77.4 and 80.0 showed the presence of two hydroxymethine groups in the iridoid skeleton, consistent with the overall structure **9**. Assuming the usual stereochemistry at C-1, C-5 and C-9, the configuration at C-6, C-7 and C-8 remained to be determined. To our knowledge, no decarboxylated iridoids with this overall structure have been reported. However, some related compounds are known either as plant constituents [3–6] or from synthesis [7]. The compounds for which ^{13}C data have been reported are the 8α-isomer 5-deoxypulchelloside (**10**) [4, 5], and the two 8β-isomers 6β-hydroxyloganin (**11**) [3] and 6β-hydroxy-7-*epi*-loganin (**12**) [6] (the spectrum of the latter in Table 1 was re-recorded in deuterium oxide for better comparison). It was conspicuous that the signals from C-5 through C-9 were very similar in the spectra of **9** and **10** and this suggested the same stereochemistry in the two compounds. In particular,

Table 1. ^{13}C NMR spectral data (glucosides in D_2O; **9a** in $CDCl_3$)

C	9	9a	10*	11†	12
1	95.0	92.6	96.2	97.3	96.1
3	140.3	140.4	153.7	153.0	152.7
4	105.7	103.4	113.1	111.2	110.8
5	36.7	34.7	37.4	38.3	37.8
6	80.0	79.0	79.0	79.4	84.6
7	77.4	76.2	76.8	75.0	83.4
8	37.3	34.8	37.7	37.8	40.0
9	38.7	37.6	39.4	44.6	43.3
10	13.9	13.5	13.4	13.3	16.2
11			170.0	170.7	52.8
OMe			52.6	52.7	52.8
1′	98.8	95.2	99.0	99.2	99.4
2′	73.5	70.6	73.3	73.6	73.5
3′	76.4	72.0	77.0	76.4	76.4
4′	70.4	68.3	70.3	70.3	70.4
5′	77.0	72.5	76.3	77.1	77.2
6′	61.5	61.7	61.5	61.5	61.5

* Data from [5]—the signals for C-5 and C-9 were interchanged.
† Data from [3].

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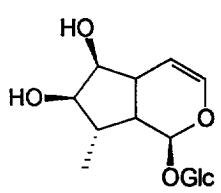

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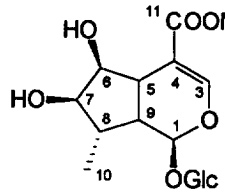

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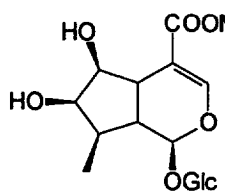

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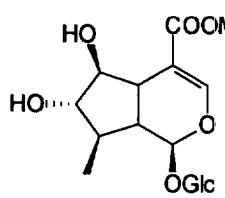

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the signal from C-9 is 4–5 ppm more high field in the 8α-series than in the 8β-series, as has been shown earlier for model compounds [8]. Furthermore, the 6β-hydroxy-stereochemistry in **9** was indicated by the smaller difference (34.6 ppm) in the chemical shifts of C-3 and C-4 compared to the larger value (*ca* 40 ppm) usually found in the 6α-hydroxy-substituted analogues [8, 9]. Finally, the *cis* configuration for the C-6 and C-7 substituents in **9** was shown by the low δ-values (77–80 ppm) for these carbon atoms compared to those (83–84 ppm) seen in **12**. This analysis was confirmed by the ^{1}H NMR spectrum (see Experimental) of angeloside. Thus, the small value for $J_{5,6}$ (1.9 Hz) showed the *trans*-orientation of these protons. Additionally, the large coupling between H-8 and H-9 (11.1 Hz) indicated a *trans*-diaxial relationship between these protons although this is hardly a proof since couplings as large as 10 Hz has been seen for *cis*-oriented protons in these positions [8]. However, the orientation of the 8-methyl group could conveniently be determined by comparison of the spectrum with those of loganin [10] and 8-*epi*-loganin [11]. The chemical shift of H-9 was especially informative, namely at δ 2.13 and 2.71, respectively, for loganin and 8-*epi*-loganin, while in **9** this signal occurs at δ 2.69, further indicating the α-orientation for the methyl group of angeloside.

Iridoid glucosides are very common in Scrophulariaceae and its related families in Scrophulariales/Lamiales with aucubin (**7**) and catalpol being those most commonly found [12]. However, aucubin has to our knowledge not yet been reported from Lamiaceae even if catalpol is common in that family. The garniture of iridoids found in *Angelonia integerrima* in the present work is not surprising, however, and the actual compounds found are to some degree the same as those reported from *Physostegia virginiana* (Lamiaceae) of which several chemotypes exist [13, 14]. Thus, galiridoside (**1**) is the main constituent in both plants while harpagide (**2**), ajugol (**3**), daunoside (**6**) and stegioside II (**8**) have been reported from one or more of the chemotypes of *P. virginiana*—in fact **8** has so far only been reported from this source.

EXPERIMENTAL

General procedures. Mp: uncorr.; ^{13}C NMR: 125 MHz (C-6′ was set to 61.5 ppm as a standard [8] in spectra recorded in D_2O); Prep. TLC: 20 × 40 cm plates coated with 1 mm layers of silica gel PF_{254} (Merck); RP-MPLC; Merck Lobar C-18 columns size B and C. H_2O–MeOH mixt were used as eluents and peaks were detected by UV at 206 and 240 nm. *Angelonia integerrima* was collected in Guaiba, Rio Grande do Sul, Brazil and identified by M. Sobral (Curso de Pós-Graduação em Ciências Farmacêuticas, UFRGS). The voucher specimen (M. Sobral, 8078) is deposited in the herbarium of the Federal University of Rio grande do Sul (ICN).

Isolation of glucosides. Dry leaves (57 g) were extracted with EtOH for 4 days and the concd extract partitioned in Et_2O–H_2O. The aq. phase was concd (8.2 g). Chromatography of an aliquot (4 g) using a C-size column and eluting with H_2O–MeOH (25:1 to 1:1) gave first a polar fr. mainly consisting of carbohydrates which was discarded. The next frs A (0.28 g) and B (0.31 g) were mixts. Fr. C (1.3 g, 4.6%) consisted of galiridoside (**1**).

Rechromatography of fr. A on a B-size column eluting with H_2O–MeOH (25:1) provided daunoside (**6**, 10 mg); a mixt. (20 mg) of 6-hydroxyantirride (**4**) and daunoside in the proportion *ca* 2:1; aucubin (**7**, 60 mg) and a mixt. (40 mg) of antirrhide (**5**) and angeloside (**9**) in the proportion *ca* 2:1.

Rechromatography of fr. B on a B-column eluting with H_2O–MeOH (15:1) gave **7** (7 mg) followed by a mixt. (63 mg) of **5** and **9** in the same proportion as above; **5** (10 mg); a mixt. (90 mg) of harpagide (**2**) and stegioside II (**8**) in the proportion of 2:1 and finally a mixt. (60 mg) of harpagide and ajugol (**3**) in the proportion of 3:2.

Angeloside hexaacetate (**9a**). The two frs containing **9** were combined and acetylated with pyridine–Ac_2O (2:1), 2 h at room temp. Prep. TLC EtOAc–toluene (1:1) gave antirrhide pentaacetate (**5a**) (84 mg) and (**9a**) (50 mg). Crystals from EtOH mp 151–152°; $[a]_D^{21}$ −138° ($CHCl_3$; *c* 0.4); ^{1}H NMR (500 MHz); δ 6.18 (*dd*, *J* = 2 and 6.5 Hz, H-3), 5.28 (*d*, *J* = 1.7 Hz, H-1), 5.21 (*t*, *J* = 9.5 Hz, H-3′), 5.09 (*dd*, *J* = 1.5 and 4 Hz, H-6); 5.07 (*t*, *J* = 9.6 Hz, H-4′), 4.97 (*dd*, *J* = 8 and 9.5 Hz, H-2′), 4.92 (*dd*, *J* = 4 and 9 Hz, H-7), 4.83 (*d*, *J* = 8 Hz, H-1′), 4.80 (*br dd*, *J* = 2.5 and 6.5 Hz, H-4), 4.27 (*dd*, *J* = 4.5 and 12.5 Hz, H-6′), 4.13 (*dd*, *J* = 2.5 and 12.5 Hz, H-6′), 3.71 (*ddd*, *J* = 2.5, 4.5 and 10 Hz, H-5′), 2.78 (*br dd*, *J* = 8.5 and 11.5 Hz, H-9), 2.61 (*dq*-like, *J* = *ca* 2.2 and 8.5 Hz, H-5) 3.71 (*qdd*, *J* = 7.5, 9 and 11.5 Hz, H-8), *ca* 2.0 (6 × OAc), 1.07 (*d*, *J* = 7.5 Hz, 10-CH_3); ^{13}C NMR: Table 1. (Found: C, 53,7; H, 6.0. $C_{27}H_{36}O_{15}$ requires: C, 54.0; H, 6.0%).

Angeloside (**9**) was prepd by deacetylation of **9a** in (NaOMe in MeOH). Amorphous form; $[\alpha]_D^{20}$ −206° (MeOH; *c* 0.3); ^{1}H NMR (500 MHz, CD_3OD): 6.18

(*dd*, J = 6.2 and 1.9 Hz, H-3), 5.39 (*d*, J = 2.3 Hz, H-1), 4.77 (*dd*, J = 6.2 and 2.9 Hz, H-4), 4.61 (*d*, J = 8.1 Hz, H-1′); 3.88 (*dd*, J = 11.9 and 1.6 Hz. H-6′), 3.75 (*dd*, J = 3.9 and 1.9 Hz, H-6), 3.71 (*dd*, J = 8.4 and 3.9 Hz, H-7), 3.67 (*ddd*, J = 11.9, 4.1 and 1.6 Hz, H-6′), 3.37 (*dd*, J = 9.2 and 9.2 Hz, H-3′), 3.30 (H-4′) and 3.29 (H-5′) both obscured by the solvent peak, 3.19 (*dd*, J = 9.2 and 8.1 Hz, H-2′), 2.69 (*ddd*, J = 11.1, 8.5 and 2.3 Hz, H-9), 2.62 (*dddd*, J = 8.5, 2.9, 1.9 and 1.9 Hz, H-5), 2.19 (*ddq*, J = 11.1, 8.4 and 7.3 Hz, H-8) 1.12 (*d*, J = 7.3; H-10); ^{13}C NMR: Table 1. (Found: C, 49.0; H, 7.1. $C_{15}H_{24}O_9 \cdot H_2O$ requires: C, 49.2; H, 7.2%).

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