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Alkaloids from *Oriciopsis glaberrima* Engl. (Rutaceae) ☆

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Abstract

Two alkaloid derivative, oriciacridone A and B, were isolated from the stem bark of *Oriciopsis glaberrima* (Rutaceae). The structures were elucidated by a detailed spectroscopic analysis. The extract exhibited in vitro significant antimicrobial activity against a range of micro-organisms.

Keywords: *Oriciopsis glaberrima*; Rutaceae; Oriciacridone A and B; Antimicrobial activity

1. Introduction

Oriciopsis glaberrima Engl. (Rutaceae) is a monotypic genus endemic to the humid rain forests of Cameroon (Letouzey, 1963). It is used as medicinal plant against infections, hypotension, mycoses, dermatitis and many other diseases (Bouquet, 1969). Previous phytochemical studies of *O. glaberrima* resulted in the isolation of one tretranortriterpenoid namely oriciopsin, and the furoquinoline alkaloid (Ayafor et al., 1982).

This paper describes the isolation and structural elucidation of two new alkaloids; only the antimicrobial activities of the isolates and the extract were examined.

2. Results and discussion

Ground, air-dried, stem bark of *O. glaberrima* was extracted with CH_2Cl_2/MeOH (1:1) at room temperature. The extract was concentrated under reduced pressure and its anti-microbial activities against a range of micro-organisms were evaluated in vitro, using the agar diffusion test. Following bioassay-directed chromatographic fractionation, two new alkaloid, oriciacridone A (**1**) and oriciacridone B (**2**), were isolated, together with the known lichexanthone (**3**).

Oriciacridone A (**1**), m.p. 294 °C, $[\alpha]_D^{25} - 45.7°$, was obtained as yellow crystals and reacted positively with $FeCl_3$, thereby indicating the presence of a phenolic hydroxyl group. Alkaloid **1** was shown to have the molecular formula of $C_{36}H_{32}N_2O_9$ by HR-EIMS ($[M]^+$; $m/z = 636.2108$; calc. 636.21024). The IR ($\nu = 3360$, 2972, 1649, 1620, 1563 cm^{-1}) and UV ($\lambda_{max} = 401$, 352, 323, 285, 272, 269 nm) spectra suggested the presence of a 9-acridone moiety (Takemura et al., 1998) and a xanthone skeleton (Peres and Nagem, 1997; Peres et al., 2000). The characteristic signals of two chelated hydroxyl protons at δ 14.40 and δ 13.15 (*s*, each 1H) in the ^1H NMR spectrum, coupled with its molecular ion, suggested a dimeric structure. Similarly, the resonances at δ 11.32 (*s br*, 1H) and δ 10.70 (*s br*, 1H) indicated the presence of two further D_2O exchangeable protons. The ^1H NMR spectrum also showed signals of five aromatic protons at δ 8.14 (*dd*, $J = 7.8$, 1.8 Hz,

☆ Part 1 in the series *Oriciopsis* studies (Pygmee's plant).
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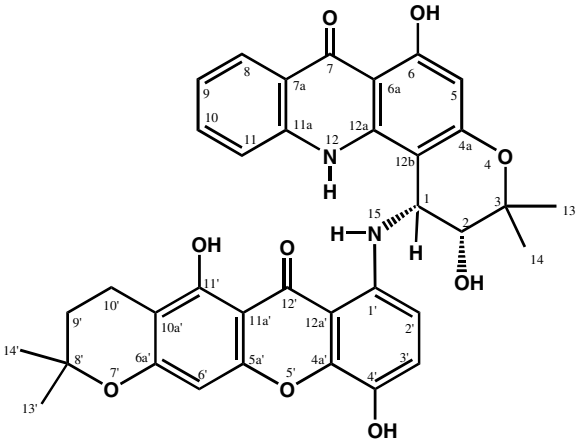
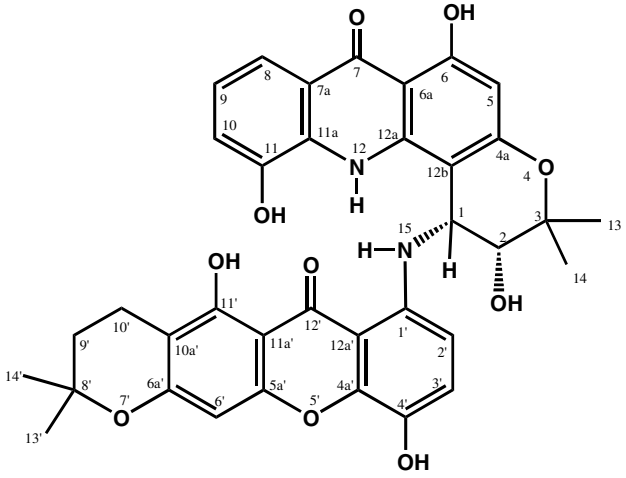
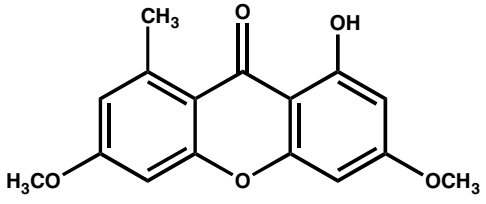
Structures of compounds **1**, **2** and **3**



Oriciacridone A(**1**)



Oriciacridone B (**2**)



Lichexanthone (**3**)

1H), 7.80 (*s br*, 1H), 7.78 (*s br*, 1H), 7.30 (*m*, 1H), and 5.98 (*s*, 1H), the signals of a substituted pyran ring at δ 1.62 (*s*, 3H), 1.42 (*s*, 3H), 5.29 (*dd*, $J = 3.7$, 3.8 Hz, 1H), 4.30 (*d*, $J = 3.8$ Hz, 1H), and a doublet at δ 9.56 (*d*, $J = 5.2$ Hz, 1H). The aromatic lowfield signal at δ 8.14 was deshielded by a carbonyl group (Takemura et al., 1998). The presence of a pyran ring was further confirmed by the ^{13}C NMR spectrum, which showed characteristic signals at δ 22.2 (C-13), 23.7 (C-14), 42.5 (C-1), 70.9 (C-2), and 76.9 (C-3) (Magiatis et al., 1999). 2D NMR techniques (HSQC and HMBC) indicated a hydroxydimethylchroman ring. In the HMBC spectrum (Fig. 1), the proton at δ 5.29 showed cross-peaks with carbon signals at C-12a (δ 141.5), C-12b (δ 96.7), and C-4a (δ 158.8). This finding clearly indicated that the hydroxydimethylchroman ring was fused in an angular fashion. All this information is in agreement with the acridone skeleton (Bahar et al., 1982; Magiatis et al., 2001). The presence of an acridone skeleton was also confirmed by the EI MS mass spectrum, which showed a peak at m/z 311 ($C_{18}H_{16}NO_4$). Furthermore, the ^{1}H NMR spectrum showed signals corresponding *ortho*-coupled aromatic protons at δ 7.13 and 6.50 (*d*, $J = 8.8$ Hz, 1H each), an aromatic proton singlet at δ 6.28 (*s*, 1H) and a dimethylchroman ring [δ 1.14 (*s*, 6H), 1.48 (*m*, 2H), 2.54 (*m*, 2H)] indicating the presence of a dihydro-6-desoxyjacareulin skeleton (Locksley et al., 1971). The latter was confirmed by ^{13}C NMR, DEPT, and 2D NMR techniques (HMBC, HSQC and COSY). The HMBC spectrum showed cross-peaks of the chelated hydroxyl signal at δ 13.15 with the carbon signals at C-11a′ (δ 100.9) and C-10a (δ 110.9), and between the aromatic proton singlet at δ 6.28 (H-6′) and C-11a′ (δ 100.9), C-10a′ (δ 110.9). Further correlations were observed between the aromatic proton at δ 6.50 (H-2′) and carbon signals at C-4′ (δ 150.6) and C-12a′ (δ 105.2), and between the proton at δ 7.13 (H-3′) and carbons C-1′ (δ 136.3), and C-4a′ (δ 133.3). Thus, **1** has a dihydro-6-desoxyjacareulin group linked to an acronycine skeleton.

To confirm the linkage of the two skeletons, 2D NMR (HMBC and NOESY) experiments were used. In the HMBC spectrum, cross-peaks between the proton signal at δ 9.56 (H-15) and carbons C-2′ (δ 105.2) and C-2 (δ 70.9), and between the proton at δ 5.29 (H-1) and carbon signals at C-1′ (δ 136.3), C-12a (δ 141.5), and C-4a

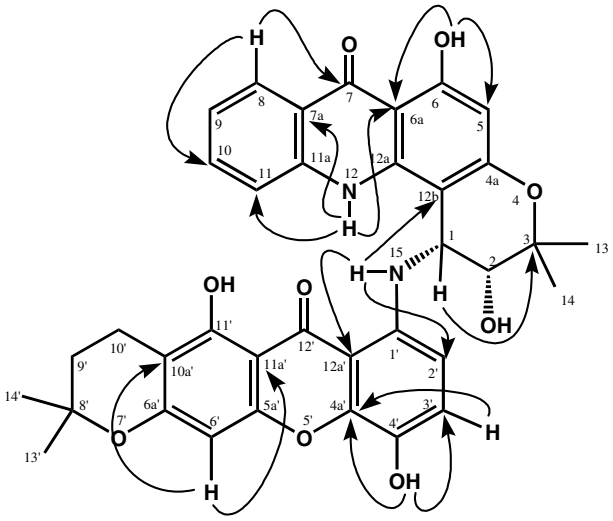


Fig. 1. Significant long-range correlations observed in ^{1}H–^{13}C HMBC for compound **1** in DMSO-d_6.

(δ 158.8), suggested that the two substructures were linked by nitrogen, furthermore, in the NOESY spectrum, there were cross-peaks between the proton H-15 (δ 9.56) and the aromatic proton H-2′ (δ 6.50), and between the same proton H-15 (δ 9.56) and protons at δ 5.29 (H-1) and δ 4.30 (H-2), indicating clearly the linkage position of the two fragments. The coupling constant of $J = 3.7$ Hz between protons H-1 and H-2 showed that they are in a *cis* relationship (Magiatis et al., 1999). From the above spectroscopic studies, compound **1** was characterized as (−)-*cis*-2-hydroxy-1-(3,4-dihydro-6-desoxyjacareulin)amino-1,2-dihydroacronycine named oriciacridone A.

Alkaloid **2**, m.p. 309 °C, $[\alpha]_D^{25} - 85.3°$, isolated as a yellow solid, had the molecular formula $C_{36}H_{32}N_2O_{10}$ (HR-EIMS, *m/z* found 652.2061; calc. 652.20515) and thus one oxygen more than oriciacridone A (**1**). The ^{13}C NMR spectrum revealed 36 carbon signals, which were sorted by DEPT and APT experiments into four methyl, two methylene, eight sp^2 methine, two sp^3 methine, and 20 quaternary carbons; among the latter, two were

Table 1
^1H (300 MHz) and ^{13}C (75.5 MHz) assignments for oriciacridone A (**1**) and oriciacridone B (**2**) in DMSO-d_6

Attribution	**1**		**2**	
	^{13}C	^1H [*m*, *J* (Hz)]	^{13}C	^1H [*m*, *J* (Hz)]
1	42.5	5.29 (*dd*, 3.7, 3.8)	42.8	5.72 (*m*)
2	70.9	4.30 (*d*, 3.7)	71.5	4.13 (*d*, 3.9)
3	76.9	–	76.2	–
4	–	–	–	–
4a	158.8	–	159.0	–
5	95.7	5.98 (*s*)	94.9	5.99 (*s*)
6	162.7	–	163.9	–
6a	104.6	–	105.2	–
7	180.2	–	181.6	–
7a	118.8	–	119.5	–
8	124.7	8.14 (*br d*, 7.8)	115.5	7.57 (*dd*, 9.0, 3.0)
9	121.9	7.30 (*ddd*, 6.8, 5.6, 2.3)	123.3	7.22 (*d*, 9.0)
10	133.3	7.78 (*br d*, 5.7)	119.9	7.17 (*d*, 9.0)
11	117.5	7.82 (*td*, 8.7, 1.5)	148.8	–
11a	140.4	–	141.5	–
12	–	–	–	–
12a	141.5	–	142.8	–
12b	96.7	–	96.7	–
13	22.2	1.42 (*s*)	22.9	1.39 (*s*)
14	23.7	1.62 (*s*)	24.9	1.62 (*s*)
1′	136.3	–	136.3	–
2′	105.2	6.50 (*d*, 8.8)	105.7	6.58 (*d*, 11.4)
3′	121.9	7.13 (*d*, 8.8)	122.0	7.18 (*d*, 11.4)
4′	150.6	–	151.2	–
4a′	133.3	–	134.3	–
5′	–	–	–	–
5a′	154.5	–	155.4	–
6′	92.6	6.28 (*s*)	93.2	6.30 (*s*)
6a′	163.2	–	163.2	–
7′	–	–	–	–
8′	68.9	–	68.9	–
9′	42.3	1.48 (*m*)	43.2	1.45 (*m*)
10′	17.0	2.54 (*m*)	15.2	2.57 (*m*)
10a′	110.9	–	110.9	–
11′	159.3	–	159.2	–
11a′	100.9	–	100.6	–
12′	182.6	–	183.8	–
12a′	101.9	–	101.9	
13′	29.1	1.14 (*s*)	25.4	1.18 (*s*)
14′	29.0	1.14 (*s*)	27.4	1.18 (*s*)
2-OH		4.14 (*br s*)		10.72 (*br s*)
6-OH		14.40 (*s*)		14.60 (*s*)
4′-OH		11.32 (*br s*)		10.84 (*br s*)
11′-OH		13.15 (*s*)		13.12 (*s*)
11-OH		–		10.59 (*br s*)
12-NH		10.70 (*br s*)		10.42 (*br s*)
15-NH	–	9.56 (*d*, 5.2)	–	9.28 (*m*)

carbonyls. The IR spectrum showed vibration bands at 3428, 3250, and 1664 cm^{-1}, due to hydroxyl groups, a methine, and a chelated carbonyl group, respectively. These data, together with those obtained from UV (λ_{max} 257, 275, 278, 295, 312, 372, 404 nm), ^1H NMR (two singlets, 1H each at δ 14.60 and 13.12 due to chelated OH) and ^{13}C NMR data (Table 1), suggested that alkaloid **2** has the same skeleton as oriciacridone A (**1**). Furthermore, in the ^1H NMR spectrum, an ABM spin system corresponding to a 1,2,3-trisubstituted benzene ring [δ 7.57 (*dd*, $J = 9.0$, 3.0 Hz, 1H), 7.22 (*d*, $J = 9.0$ Hz, 1H), 7.17 (*d*, $J = 9.0$ Hz, 1H)], three hydroxyl signals [δ 10.84, 10.59, 10.72 (*s br*, each 1H)], and signals corresponding to hydroxyldimethylchroman and dimethylchroman units were also observed. These data suggested that the additional oxygen atom in **2** is attached as a hydroxy group in the acronycine moiety. Since the lowfield signal at δ 7.57 of the ABM-type aromatic protons was deshielded by a carbonyl group and the presence of H-8, H-9 and H-10 of acridone skeleton was revealed, this indicated that the free phenolic hydroxyl group was attached to C-11 (Basa, 1975). This location was confirmed by the NOESY spectrum in which a cross-peak was observed between the hydroxyl proton H-11 (δ 10.59) and the proton at H-12 (δ 10.42) and by HMBC experiments. Therefore, the structure of alkaloid **2** was concluded to be (−)-*cis*-2,11-dihydroxy-1-(3,4-dihydro-6-desoxyjacareulin)amino-1,2-dihydroacronycine, named oriciacridone B.

Compounds **1**–**3** were tested for their antimicrobial potential against four bacteria (*Bacillus subtilis*, *Streptomyces viridochromogenes*, *Staphylococcus aureus*, and *Escherichia coli*), two fungi (*Mucor miehei* and *Candida albicans*), and three microalgae (*Chlorella vulgaris*, *Chlorella sorokiniana*, and *Scenedesmus subspicatus*) in the agar diffusion test, as shown in Table 2.

The extract exhibited in vitro significant antimicrobial activity against *C. albicans*, *M. miehei* and *S. aureus*. Oriciacridone B (**2**) also exhibited in vitro significant antimicrobial activity against *M. miehei* compared to the Nystatin as reference.

3. Experimental section

3.1. General

Melting points are uncorrected; optical rotations: Perkin–Elmer model 241 polarimeter. ^1H (300 and 600 MHz) and ^{13}C NMR spectra (75.5 and 125.7 MHz) were measured on a Bruker AMX 300 and on a Varian Inova 600 (599.740 MHz) spectrometer, respectively. ESI mass spectra were recorded on a Quattro Triple Quadrupole Mass Spectrometer, Finnigen TSQ 7000 with nano-ESI-API-ion source. ESI HRMS was measured on a Micromass LCT mass spectrometer coupled with a HP 1100 HPLC with a Diode Array Detector. Reserpin (MW = 608) and Leucin–Enkephalin (MW = 555) were used as standards in positive and negative modes. EI-MS was recorded on Varian MAT 95 Finnigan (70 eV), high resolution with perfluorokerosine as standard. IR spectra were recorded on a Perkin–Elmer 1600 Series FT-IR spectrometer as KBr pellets. UV–VIS spectra were recorded on a Perkin–Elmer Lambda 15 UV/VIS spectrometer. Flash chromatography was carried out on silica gel (230–400 mesh, Merck) and silica gel (70–230 mesh, Merck) was used for column chromatography. Thin layer chromatography (TLC) was performed on Polygram SIL G/UV_{254} (Macherey-Nagel & Co.).

3.2. Plant material

Stem bark of *O. glaberrima* was collected in January 2002, at Bertoua, Cameroon. The plant was identified by Nana Victor of National Herbarium. A voucher specimen (1888/HNC) documenting the collection is deposited in the National Herbarium, Yaoundé, Cameroon.

Table 2
Diameter of inhibition zones of compounds **1**–**3** from *Oriciopsis glaberrima* in the agar diffusion test with 20 μg/disk (∅ in mm, paper disk ∅ 9 mm)

Sample	Micro-organism tested								
	BS[a]	SV[b]	SA[c]	EC[d]	MM[e]	CA[f]	CV[g]	CS[h]	SS[i]
CH_2Cl_2–MeOH (1/1)	10	13	12	11	17	18	15	11	13
Oriciacridone A (**1**)	10	11	9	10	11	14	12	9	9
Oriciacridone B (**2**)	12	11	11	9	15	12	10	9	10
Lichexanthone (**3**)	9	10	11	9	12	11	12	10	9
Nystatin	16	14	12	14	15	18	–	–	–

[a] *Bacillus subtilis*.
[b] *Streptomyces viridochromogenes*.
[c] *Staphylococcus aureus*.
[d] *Escherichia coli*.
[e] *Mucor miehei*.
[f] *Candida albicans*.
[g] *Chlorella vulgaris*.
[h] *Chlorella sorokiniana*.
[i] *Scenedesmus subspicatus*.

4. Extraction and isolation

Air-dried; powdered stem bark of *O. glaberrima* (10 kg) was extracted with a mixture of CH_2Cl_2/MeOH (1/1) at room temperature during 48 h. The extract was concentrated under reduced pressure to yield a brown viscous extract (99 g). This extract was evaluated for its antimicrobial activity and then subjected to flash column chromatography on silica gel (500 g) (70–230 mesh, Merck) with a hexane–EtOAc–MeOH mixture of increasing polarity. A total of 90 sub-fractions (ca. 250 ml each) were collected and combined on the basis of TLC analysis leading to four main fractions A–D. Sub-fractions 1–20, eluting with a mixture of hexane–EtOAc (17:3) gave main fraction A (15 g). Fraction B (20 g) was constituted of sub-fractions 21–40 eluted with a mixture of hexane–EtOAc (1:1), main fraction C (10 g) was constituted of sub-fractions 41–66 eluted with hexane–EtOAc (1:4), and fraction D (4 g) was constituted of sub-fractions 67–90 eluted with EtOAc–MeOH (19:1). Main fraction A was chromatographed on a silica gel column (250 g) with a hexane–EtOAc gradient. A total of 20 fractions of ca. 100 ml each were collected and combined on the basis of TLC. Fractions 1–10 eluted with a mixture of hexane–EtOAc (9:1) yielded lichexanthone (**3**) (10 mg).

Main fraction C was column chromatographed over silica gel with hexane–EtOAc (2:1). A total of 30 fractions of ca. 100 ml each were collected and combined on the basis of TLC. Fractions 1–10, eluted with a mixture of hexane–EtOAc (1:9), yielded oriciacridone A (**1**) (30 mg). Fractions 20–30 eluted with EtOAc yielded oriciacridone B (**2**) (5 mg).

4.1. Oriciacridone A (*1*)

Yellow crystals; m.p. 249 °C; $[\alpha]_D^{25} - 45.7°$ (DMSO, *c* 0.070); UV (DMSO) λ_{max} nm (log ε) 269 (4.84), 272 (4.85), 285 (4.62), 323 (4.28), 352 (4.15), 401 (4.14); IR (KBr) ν_{max} cm^{-1}: 3360, 2972, 2362, 1920, 1731, 1649, 1619,1558, 1489, 1394, 1289, 1156, 1025; ^1H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75.5 MHz, DMSO-d_6) see Table 1; HR-EIMS *m/z* 636.2108 (calc. for $C_{36}H_{32}N_2O_9$, 636.21024); EI MS (70 eV) *m/z* (%): 636 $[M]^+$ (15), 619 (40), 580 (18), 410 (45), 363 (5), 346 (60), 311 (100), 298 (80), 245 (20), 191 (30), 149 (35), 119 (28), 101 (50).

4.2. Oriciacridone B (*2*)

Yellow crystals, m.p. 309 °C; $[\alpha]_D^{25} - 85.3°$ (DMSO, *c* 0.075); UV (DMSO) λ_{max} nm (log ε) 239 (4.48), 257 (4.60), 275 (4.40), 278 (4.40), 295 (4.12), 312 (4.13), 372 (3.80), 404 (3.88); IR (KBr) ν_{max} cm^{-1}: 3425, 2923, 2853, 2376, 2246, 1650, 1620,1558, 1502, 1471, 1380, 1360, 1279, 1171, 1025, 819; ^1H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75.5 MHz, DMSO-d_6) see Table 1; HR EIMS *m/z* 652.2061 (calc. for $C_{36}H_{32}N_2O_{10}$, 652.20515); EI MS (70 eV) *m/z* (%): 652 $[M]^+$ (20), 635 (10), 620 (30), 537 (40), 394 (25), 345 (15), 317 (100), 294 (80), 150 (45), 97 (18).

4.3. Lichexanthone (*3*)

M.p. 187–188 °C; IR (KBr), ^1H NMR and EI MS data were identical with those reported by Garcia et al. (1976).

5. Antimicrobial assay

Agar diffusion tests were performed in the usual manner (Maskey et al., 2002) with *B. subtilis* and *E. coli* (on peptone agar), *S. aureus* (Bacto nutrient broth), *S. viridochromogenes* (M_2 agar), the fungi *M. miehei* and *C. albicans* (Sabouraud agar), and three microalgae (*C. vulgaris*, *C. sorokiniana* and *S. subspicatus*).

Compounds **1**, **2**, **3** and Nystatin were dissolved in MeOH/chloroform (87:18) at a concentration of 500 μg/ml. Paper disks (∅ 9 mm) were impregnated with 40 μl each using a HPLC syringe, dried for 1 h under sterile conditions and placed on the pre-made agar test plates.

Bacteria and fungi plates were kept in an incubator at 37 °C to 12 h, micro algae plates for three days at room temperature in a day light incubator. The diameter of inhibition zones was measured.

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