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Phenolic Compounds and Terpenoids from *Hypericum lanceolatum*

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Abstract: A benzophenone, 2,2',5,6'-tetrahydroxybenzophenone (**1**), and one xanthone, 5-hydroxy-3-methoxyxanthone (**2**), were newly described as natural products from the leaves and the stem barks of *Hypericum lanceolatum*, along with the known compounds friedelin (**3**), betulinic acid (**4**), allanxanthone A (**5**), 1,3,6-trihydroxyxanthone (**6**), isogarcinol (**7**), sitosterol 3-*O*-β-D-glucopyranoside (**8**), 1-hydroxy-6-methoxyxanthone (**9**), 6,7-dihydroxy-1,3-dimethoxyxanthone (**10**), 3-hydroxy-5-methoxyxanthone (**11**), 1,7-dihydroxy-3,6-dimethoxyxanthone (**12**) and calophyllumin A (**13**). Their structures were elucidated by spectroscopic means and comparison with published data.

Keywords: *Hypericum lanceolatum*; Guttiferae; xanthones; benzophenones; terpenoids.

1. Introduction

Hypericum lanceolatum Lam. (Guttiferae), is a small tree or shrub occurring in mountainous region of West Cameroon [1]. In Cameroonian traditional medicine, the leaves of the plant are extracted with palm wine and used for the treatment of skin infections, epilepsies and tumours, while the roots are boiled in water and used to treat venereal diseases, gastrointestinal disorders and infertility. Phytochemical reports on the genus *Hypericum* have revealed the presence of xanthones [2-4], benzophenones [5-8], terpenoids [9,10] and xanthonolignoids [11]. Previous chemical investigations of *H. lanceolatum* have revealed qualitative and quantitative contents of both

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anthraquinone derivatives and flavonoids [12]; the composition of essential oils from this plant was also studied [13]. As part of our continuing studies on Cameroonian plants from the Guttiferae family [14,15], we have examined the leaves and the stem barks of the title plant and report herein on the isolation and structure elucidation of one benzophenone, 2,2',5,6'-tetrahydroxybenzophenone (**1**) and one xanthone, 5-hydroxy-3-methoxyxanthone (**2**) for the first time from a natural source.

2. Materials and Methods

2.1. Plant Material

The leaves and the stem barks of *H. lanceolatum* were collected at Mount Bamboutos, West Region of Cameroon in May 2009 and identified by Mr. Nana Victor of the National Herbarium of Cameroon, Yaounde (Cameroon), where a voucher specimen (No. 32356 HNC) is deposited.

2.2. Extraction and isolation

The air-dried and powdered leaves (2 kg) of *H. lanceolatum* were exhaustively and sequentially extracted with EtOAc and MeOH. Each extract was concentrated *in vacuo* to obtain EtOAc- and MeOH-soluble fractions. A portion of the MeOH extract (55 g) was subjected to silica gel column chromatography, eluted with gradients of *n*-hexane-EtOAc and EtOAc-MeOH. Thirty eight fractions of 600 ml each were collected and combined on the basis of TLC analysis to afford five main fractions (A–E). Fraction A contained mostly fatty material and was not further investigated. Fraction B was further separated by silica gel column chromatography eluting with *n*-hexane-EtOAc to give white needles of friedelin (**3**, 14 mg). Betulinic acid (**4**, 1.2 g) was purified from fraction C by recrystallization in MeOH. Fraction D was submitted to a silica gel column chromatography eluted with *n*-hexane-EtOAc to afford three sub-fractions (D_1-D_3). Sub-fraction D_1 was further purified by Sephadex LH-20 using CH_2Cl_2-MeOH (1:1) to give 2,2',5,6'-tetrahydroxybenzophenone (**1**, 30 mg). Repeated column chromatography of sub-fraction D_2 on silica gel using *n*-hexane-EtOAc yielded allanxanthone A (**5**, 16 mg) and 1,3,6-trihydroxyxanthone (**6**, 7 mg). Isogarcinol (**7**, 18 mg) was purified from sub-fraction D_3 by recrystallization in *n*-hexane. Sitosterol 3-*O*-β-D-glucopyranoside (**8**, 15 mg) crystallized from fraction E.

The air-dried and powdered stem barks (1.5 kg) of *H. lanceolatum* was extracted by maceration with MeOH at room temperature, to afford a crude extract after evaporation under vacuum. A portion of this extract was dissolved in H_2O and sequentially partitioned with *n*-hexane, EtOAc, and *n*-BuOH to give respective extracts. Part of the EtOAc extract (45 g) was subjected to a silica gel column chromatography eluting with gradients of *n*-hexane-EtOAc and EtOAc-MeOH. Twenty seven fractions of 500 ml each were collected and combined on the basis of their TLC profiles into five major fractions (F1-F5). Fraction F1 contained mostly mixture of sterols. Fraction F2 was purified on a silica gel column chromatography, eluted with a gradient of *n*-hexane-EtOAc to give betulinic acid (**4**, 90 mg) and 2,2',5,6'-tetrahydroxybenzophenone (**1**, 150 mg). Fraction F3 was submitted to a silica gel column chromatography eluted with gradients of CH_2Cl_2-EtOAc and EtOAc-MeOH to yield 5-hydroxy-3-methoxyxanthone (**2**, 9 mg), and 1-hydroxy-6-methoxyxanthone (**9**, 5 mg). Fraction F4 was chromatographed on a silica gel column with increasing mixtures of *n*-hexane-EtOAc. Sub-fractions eluted by *n*-hexane-EtOAc (8:2) were further purified on Sephadex LH-20 using CH_2Cl_2-MeOH (1:1) to give 6,7-dihydroxy-1,3-dimethoxyxanthone (**10**, 8.5 mg) and 3-hydroxy-5-methoxyxanthone (**11**, 15 mg). Sub-fractions eluted by *n*-hexane-EtOAc (1:1) were rechromatographed on silica gel with CH_2Cl_2-EtOAc (7:3) as solvent system to yield 1,7-dihydroxy-3,6-dimethoxyxanthone (**12**, 2.5 mg) and calophyllumin A (**13**, 4 mg).

3. Results and Discussion

The MeOH extract of the leaves and the EtOAc-soluble fraction of the stem barks of *H. lanceolatum* were subjected to silica gel and gel permeation through Sephadex LH-20 to afford one benzophenone, 2,2',5,6'-tetrahydroxybenzophenone (**1**) and one xanthone, 5-hydroxy-3-methoxyxanthone (**2**) for the first time, along with the known compounds friedelin (**3**) [16], betulinic acid (**4**) [17], allanxanthone A (**5**) [18], 1,3,6-trihydroxyxanthone (**6**) [19], isogarcinol (**7**) [20], sitosterol 3-*O*-β-D-glucopyranoside (**8**) [21], 1-hydroxy-6-methoxyxanthone (**9**, 5 mg) [22], 6,7-dihydroxy-1,3-dimethoxyxanthone (**10**) [11], 3-hydroxy-5-methoxyxanthone (**11**) [23], 1,7-dihydroxy-3,6-dimethoxyxanthone (**12**) [24] and calophyllumin A (**13**) [25]. Their structures (Fig. 2) were established conclusively by UV, IR, MS and extensive ^{1}H- and ^{13}C NMR spectral analysis and comparison with literature data.

Compound **1** was obtained as yellow needles from *n*-hexane-EtOAc, mp 201-202 °C. It reacted positively to $FeCl_3$ reagent, suggesting the presence of phenolic hydroxyl group in the molecule. Its molecular formula $C_{13}H_{10}O_5$, corresponding to 9 degrees of unsaturation was determined from the HREIMS (*m/z* = 228.0413 $[M - H_2O]^+$) in conjunction with the NMR spectra. The IR spectrum exhibited vibration bands due to free hydroxyl groups (ν_{max} 3367 cm^{-1}), chelated hydroxyl groups (ν_{max} 3265 cm^{-1}), conjugated carbonyl (ν_{max} 1637 cm^{-1}) and aromatic ring (ν_{max} 1527 and 1479 cm^{-1}). The UV spectrum showed absorption bands at λ_{max} 385, 287, 259, 234 and 204 nm characteristic of a benzophenone system [26]. In the ^{13}C NMR spectrum, the signal at δ_C 182.9 for the carbonyl group and 12 other signals of aromatic carbons at δ_C 162.7 (C-2'), 157.3 (C-6'), 154.9 (C-2), 151.0 (C-5), 137.7 (C-4'), 126.1 (C-4), 121.8 (C-1), 120.1 (C-3), 110.5 (C-3'), 109.1 (C-6/C-1') and 107.0 (C-5') were characteristic of a benzophenone structure [5]. In the ^{1}H NMR spectrum, two chelated hydroxyl groups were observed at δ_H 12.70 (1H, s, 2'-OH) and 9.00 (1H, s, 2-OH). This spectrum also showed the presence of two ABX-spin systems at δ_H 7.58 (1H, d, *J* = 3.0 Hz, H-6), 7.50 (1H, d, *J* = 9.0 Hz, H-3) and 7.41 (1H, dd, *J* = 3.0, 9. 0 Hz, H-4) and at δ_H 7.68 (1H, t, *J* = 8.3 Hz, H-4'), 6.97 (1H, dd, *J* = 1.0, 8.2 Hz, H-5') and 6.75 (1H, dd, *J* = 1.0, 8.2 Hz, H-3') assignable to two 1,2,5- and 1,2,6-trisubstituted benzene rings respectively. In the HMBC spectrum (Fig. 1), pertinent correlations were observed between H-3 and C-1 and C-5, between H-4 and C-2 and between H-6 and C-2, C-5 and the carbonyl group. Further correlations were observed between H-3' and C-1' and C-5', between H-4' and C-2' and C-6', between H-5' and C-3', as well as between the chelated proton δ_H 12.70 (2'-OH) and C-2' and C-3'. Therefore, the structure of compound **1** was established as 2,2',5,6'-tetrahydroxybenzophenone (Fig. 2). It is new as a natural product and fully characterized here for the first time. It has been previously reported as a synthetic compound in a Japanese patent, providing a magnetic recording medium having an oxygen-containing thin ferromagnetic metal layer, having an enhanced corrosion resistance and at the same time having an improved travel performance and durability [27].

Compound **2** was obtained as yellow powder from *n*-hexane-EtOAc, mp 166-168 °C. It reacted positively to $FeCl_3$ reagent, suggesting the presence of phenolic hydroxyl group in the molecule. The molecular formula was determined as $C_{14}H_{10}O_4$ by the HRESIMS (*m/z* = 242.0583 $[M]^+$) in conjunction with the NMR spectra. This formula accounted for 10 degrees of unsaturation. Its EIMS spectrum showed a fragment at *m/z* = 227 due to the loss of a methyl group. Absorptions of hydroxyl group (ν_{max} 3326 cm^{-1}), conjugated carbonyl (ν_{max} 1641 cm^{-1}), and aromatic ring (ν_{max} 1579 and 864 cm^{-1}) were observed in the IR spectrum. The UV spectrum showed absorption bands of a xanthone chromophore at λ_{max} 368, 257 and 202 nm [2]. The ^{13}C NMR spectrum revealed 14 carbon signals that were sorted by APT and HSQC experiments into one CH_3, six CH and seven quaternary carbon atoms including one conjugated carbonyl group at δ_C 175.3 (C-9) and four oxygenated aromatic carbons at δ_C 155.5 (C-3), 150.0 (C-4a), 146.5 (C-5) and 145.1 (C-10a). The ^{1}H NMR spectrum showed the presence of one methoxyl group at δ_H 3.95. It also showed signals of aromatic

protons at δ_H 7.60 (1H, dd, *J* = 1.5, 9.2 Hz, H-8), 7.32 (1H, dd, *J* = 1.5, 9.2 Hz, H-6) and 7.25 (1H, t, *J* = 8.7 Hz, H-7), characteristic of a 1,2,3-trisubstituted benzene ring. The HMBC correlation (Fig. 1) observed between the proton at δ_H 7.60 and the carbonyl group indicated the *peri* position of this proton (H-8). These data clearly indicated that the free hydroxyl group was located at C-5. The ^{1}H NMR spectrum also displayed resonances typical of an ABX system at δ_H 7.65 (1H, d, *J* = 9.2 Hz, H-1), 7.55 (1H, d, *J* = 3.0 Hz, H-4) and 7.46 (1H, dd, *J* = 3.0, 9.2 Hz, H-2). Further analysis of the HMBC spectrum revealed a correlation between the proton at δ_H 3.95 and the carbon at δ_C 155.5 (C-3), indicating the C-3 position of the methoxyl group. Pertinent correlations were also observed between H-1 and C-3, C-4a and C-9a, between H-6 and C-10a as well as between H-7 and C-5 and C-8a. Thus, compound **2** was established as 5-hydroxy-3-methoxyxanthone (Fig. 2). It is also fully characterized here for the first time as a natural product, but was previously reported as a synthetic compound [28].

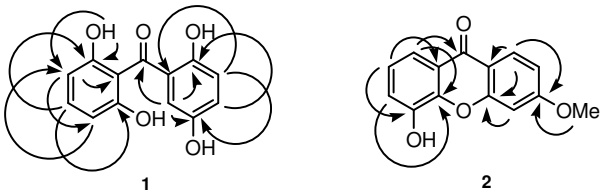

Figure 1. Key HMBC correlations for compounds **1** and **2**

3-hydroxy-5-methoxyxanthone (**11**) was also isolated here for the first time from a natural source; it has been previously reported as a synthetic derivative [23]. Our data were in agreement with those reported [23].

Preliminary biological studies showed that 2,2',5,6'-tetrahydroxybenzophenone (**1**) was weakly active against *Pseudomonas aeruginosa*. 3-hydroxy-5-methoxyxanthone (**11**) did not show any activity against *Pseudomonas aeruginosa*, *Shigella flexneri*, *Klebsiella pneumonia*, *Candida lusitaniae*, *Cryptococcus neoformans*, *Candida krusei* and *Candida albicans*, while 5-hydroxy-3-methoxyxanthone (**2**) was very active against *Shigella flexneri*.

Benzophenones, xanthones and terpenoids are widely distributed in the Guttiferae family. The present study reports the isolation of two benzophenones (**1** and **7**), seven xanthones (**2**, **5**, **6**, **9**-**12**), two triterpenes (**3** and **4**), one steroid (**8**) for the first time from the leaves and the stem barks of *H. lanceolatum*. Allanxanthone A (**5**), 1-hydroxy-6-methoxyxanthone (**9**) and 6,7-dihydroxy-1,3-dimethoxyxanthone (**10**) were previously and respectively reported from *Allanblakia floribunda* [18], *Garcinia buchananii* [22] and *Hypericum geminiflorum* [11] from the same family. This could indicate that the genera *Allanblakia*, *Garcinia* and *Hypericum* are closely related. Several oxygenated xanthones have been isolated from *Hypericum scabrum*, *Hypericum chinense*, *Hypericum roeperanum*, *Hypericum japonicum* and *Hypericum henryi* [2,4,8,29]. Several benzophenones, structurally related to isogarcinol (**7**) have been isolated from other species within the Guttiferae family [15,30,31]. Simple benzophenones containing phloroglucinol and resorcinol rings structurally related to 2,2',5,6'-tetrahydroxybenzophenone (**1**) were isolated from *Hypericum thasium* and *Hypericum annulatum* [5,6,32]. There are six species of *Hypericum* found in Cameroon, namely *H. lanceolatum*, *H. riparium*, *H. peplidifolium*, *H. aethiopicum*, *H. lalandii* and *H. leucoptychodes*. The, isolation of compounds **1**, **2**, **5**-**7** and **9**-**13** in the present investigation could be a useful contribution to the chemotaxonomic studies of the *Hypericum* species from Cameroon.

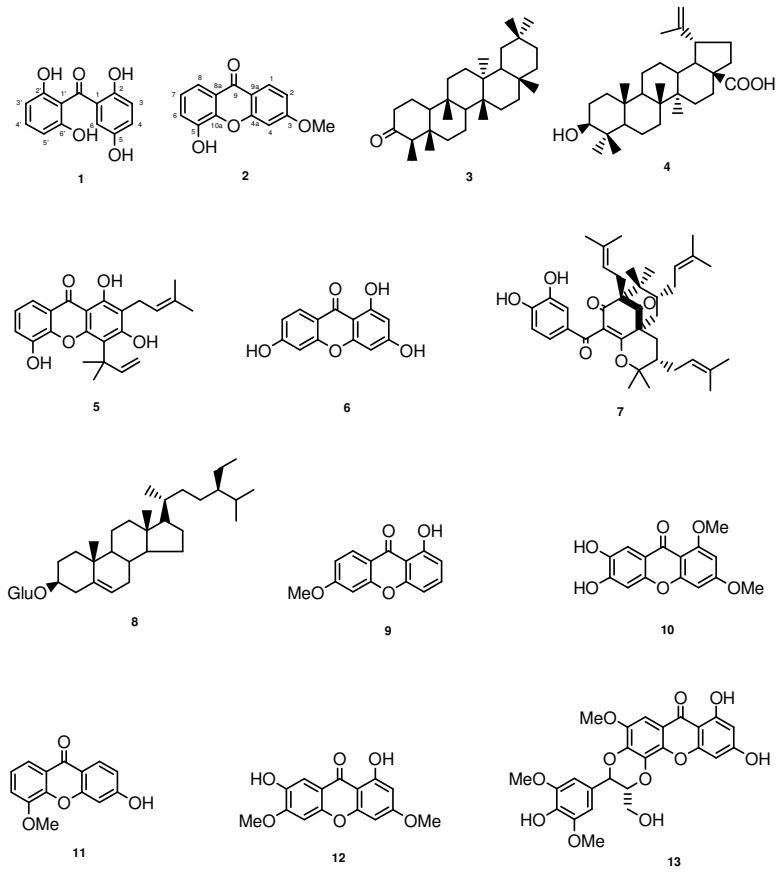

Figure 2. Structures of compounds **1**-**13**.

*2,2',5,6'-tetrahydroxybenzophenone (**1**):* Yellow needles; mp 201-202 °C; UV (MeOH): λ_{max} nm (log ε): 385 (4.70), 287 (4.84), 259 (5.41), 234 (5.44), 204 (5.32); IR (KBr): ν_{max} cm^{-1}: 3367, 3265, 1637, 1527, 1479; ^{1}H NMR (600 MHz, acetone-d_6): δ = 12.70 (1H, s, 2'-OH), 9.00 (1H, s, 2-OH), 7.68 (1H, t, *J* = 8.3 Hz, H-4'), 7.58 (1H, d, *J* = 3.0 Hz, H-6), 7.50 (1H, d, *J* = 9.0 Hz, H-3), 7.41 (1H, dd, *J* = 3.0, 9.0 Hz, H-4), 6.97 (1H, dd, *J* = 1.0, 8.2 Hz, H-5'), 6.75 (1H, dd, *J* = 1.0, 8.2 Hz, H-3'); ^{13}C NMR (150 MHz, acetone-d_6): δ = 182.9 (C=O), 162.7 (C-2'), 157.3 (C-6'), 154.9 (C-2), 151.0 (C-5), 137.7 (C-4'), 126.1 (C-4), 121.8 (C-1), 120.1 (C-3), 110.5 (C-3'), 109.1 (C-6/C-1'), 107.0 (C-5'); HREIMS: *m/z* = 228.0413 $[M - H_2O]^+$ (Calcd. for $C_{13}H_8O_4$: 228.0423); EIMS: *m/z* = 228 ($[M - H_2O]^+$, 100), 200 (10), 144 (4).

*5-hydroxy-3-methoxyxanthone (**2**):* Yellow powder; mp 166-168 °C; UV (MeOH): λ_{max} nm (log ε): 368 (3.40), 257 (4.63), 202 (4.30); IR (KBr): ν_{max} cm^{-1}: 3326, 1641, 1579, 1120, 864; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.65 (1H, d, *J* = 9.2 Hz, H-1), 7.60 (1H, dd, *J* = 1.5, 9.2 Hz, H-8), 7.55 (1H, d, *J* = 3.0 Hz, H-4), 7.46 (1H, dd, *J* = 3.0, 9.2 Hz, H-2), 7.32 (1H, dd, *J* = 1.5, 9.2 Hz, H-6), 7.25 (1H, t, *J* = 8.7 Hz, H-7), 3.95 (3H, s, OMe); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 175.3 (C-9), 155.5 (C-3), 150.0 (C-4a), 146.5 (C-5), 145.1 (C-10a), 124.4 (C-2), 123.7 (C-7), 121.5 (C-8a), 121.2 (C-9a), 119.8 (C-1), 119.7 (C-6), 115.0 (C-8), 105.6 (C-4), 55.6 (3-OMe); HREIMS: *m/z* = 242.0583 $[M]^+$ (Calcd. for $C_{14}H_{10}O_4$: 242.0579); EIMS: *m/z* = 242 (100), 241 (61), 227 (52), 228 (15), 213 (30), 212 (34), 199 (20), 171 (42), 115 (28).

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/RNP

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