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Novel Hopanoic Acid and Depside from the Lichen *Dirinaria applanata*

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Abstract: From the extract of lichen *Dirinaria applanata*, two hopane derivatives including 1*β*-acetoxy-3*β*-hydroxy-21*α*-hopan-29-oic acid (**1**), hopane-3*β*, 6*β*, 21*α*-triol (**2**) and a depside namely 2-*O*′-methylnordivaricatic acid (**3**) were isolated and identified by extensive analyzing 1D-NMR, 2D-NMR, HRESI-MS, and FT-IR. Notably, compound **1** and **3** were novel compounds while compound **2** was isolated from this lichen species for the first time.

Keywords: *Dirinaria applanata*; lichen; hopan-29-oic acid; depside.

1. Introduction

Lichens are symbiotic organisms which usually include fungi and photosynthesis organisms (alga or cyanobacteria) [1]. Previous studies on lichens composition unfolded the existence of diverse secondary metabolites including monocyclic phenols, depsides, depsidones, xanthones and terpenoids [2]. Moreover, the investigation of biological activities indicated that lichens and its composition exhibited a wide range of biological activities such as antioxidant, anticancer, antibacterial, and antifungal, antiviral and enzyme inhibitory [3-5]. *Dirinaria applanata* is a foliose lichen, which widely distributes in tropical areas. Previous chemical investigation showed that *D. applanata* contained antranorin, divaricatinic acid and its ester derivatives, methyl haematommate, methyl *β*-orcinolcarboxylate, ramalinic acid, lichenxanthones, tannins, and terpenes [6-8]. In continuing to explore the chemical composition of *D. applanata*, we herein reported the structural elucidation of two hopane derivatives and a depside.

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2. Materials and Methods

2.1. General Experimental Procedures

NMR spectra were acquired on Bruker Advance 500 MHz and Bruker Advance 600 MHz using TMS as an internal standard. FT-IR was conducted using KBr pellet method on Thermo Nicolet 6700. HRESI-MS observation was performed on a Bruker MicrOTOF-Q mass spectrometer and on a SCIEX X500R-QTOF. The melting point was recorded using glass capillaries without calibration on Stuart Scientific SMP3. Optical rotation instrument was SEPA-200 (Horiba, Japan) with cell length: 50 mm. Silica gel 60 (Merck, 230-400 mesh ASTM) and RP-18 (Sigma-Aldrich) were packed for column chromatography (CC). Precoated silica gel 60 F254 plates (Merck) were used for analytical TLC.

2.2. Lichen Sample

The lichen thallus was collected in Can Tho University campus II, Can Tho city, Vietnam from January to April 2018 by observing thallus morphology and comparing with the literature [9]. The identification was conducted by Dr. Ngo Thanh Phong, Department of Biology, College of Natural Sciences, Dr. Dang Minh Quan, Department of Biology Education, Can Tho University, and Dr. Vo Thi Phi Giao, Faculty of Biology, HCM University of Science. A voucher specimen was deposited in Laboratory of Plant Biology Department of Biology, Can Tho University, Vietnam under number (Li012018-CT001) and in Herbarium of University of Science, Ho Chi Minh City, Vietnam National University (PHH) with the voucher specimen number PHH0011078. Lichen thallus was kept in paper bags and was naturally dried at room temperature.

2.3. Extraction and Isolation

Lichen material was finely powdered (1.28 kg) and extracted with methanol (3 × 5 L) at room temperature. The solvent was evaporated using rotary evaporator to obtain methanol extract (210 g). The methanol extract was well-mixed with water followed by shaking with hexane and ethyl acetate to give a hexane extract (88 g) and ethyl acetate extract (76 g), respectively. The remaining water layer was condensed to afford water extract (32 g).

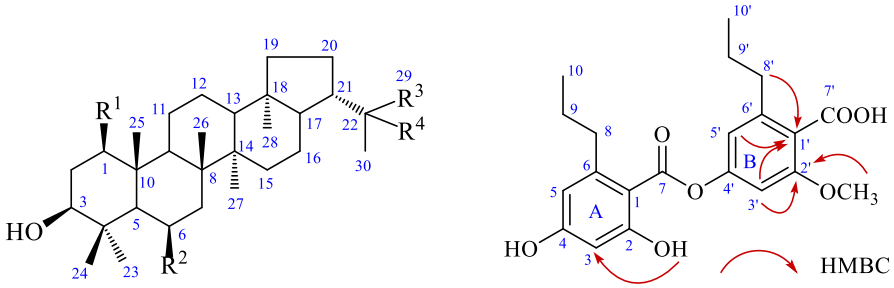
The ethyl acetate (30 g) was separated to 10 fractions (**EA1-10**) by flash column chromatography eluted with hexane:EtOAc (5:1 to 0:10) and EtOAc:MeOH (10:1 to 2:1). Fraction **EA3** was applied to column chromatography and was washed with CH_2Cl_2:MeOH (0:10 to 10:0) to afford 8 fractions (**EA3.1-3.8**). Compound **1** (79 mg) was obtained after purifying fraction **EA.3.4** by hexane:CH_2Cl_2 (2:8 to 0:10) and recrystallizing in CH_2Cl_2. Solid residue in fraction **EA.3.3** was washed and repeatedly recrystallized in CH_2Cl_2 to give a white solid named as compound **2** (10.5 mg). The water residue (10 g) was subjected to RP-18 column chromatography and washed with H_2O:MeOH (10:0 to 0:10) to give four fractions (**W1-4**). Repeated purifying fraction **W-3** (0.67 g) by using H_2O:MeOH (3:7) on RP-18 afforded compound **3** (13.5 mg) as a solid.

1β-Acetoxy-3β-hydroxy-21α-hopan-29-oic acid (***1***). White needles, MP. 270-272°C. $[\alpha]_D^{25}$ +12.0 (c = 0.267, $CHCl_3$). HR-ESI-MS *m/z*: $[M–H]^-$ = 515.3734 (calcd. for $C_{32}H_{53}O_5^-$, 515.3736). IR (KBr) ν_{max} (cm^{-1}): = 3418, 2949, 1732, 1716, 1467, 1376, 1248, 1184, 1043, 1019. ^{1}H-NMR and ^{13}C-NMR (see Table 1).

21α-Hopane-3β, 6β, 22-triol (***2***). White solid, MP. 287-289°C. $[\alpha]_D^{25}$ +6.0 (c = 0.2, $CHCl_3$). IR ν_{max} (cm^{-1}): = 3414, 2944, 2851, 1472, 1387, 669. ^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.69 (1H, *m*, H-5), 0.77 (3H, *s*, C-28), 0.91 (3H, *s*, C-27), 0.93 (1H, *m*, H-19α), 0.97 (1H, *m*, H-19β), 1.06 (3H, *s*, H-23), 1.16 (3H, *s*, H-24), 1.18 (3H, *s*, H-29), 1.19 (3H, *s*, H-25), 1.21 (3H, *s*, H-30), 1.24 (1H, *m*, H-15α), 1.26 (1H, *m*, H-9), 1.30 (3H, *s*, H-26), 1.44 (1H, *m*, H-15β), 1.45 (2H, *m*, H-11), 1.46 (1H, *m*, H-12α), 1.46 (1H, *m*, H-17), 1.47 (1H, *m*, H-7β), 1.47 (1H, *m*, H-13), 1.50 (1H, *m*, H-20α), 1.57 (1H, *m*, H-2α), 1.57 (1H, *m*, H-12β), 1.55 (1H, *m*, H-19α), 1.58 (1H, *m*, H-16α), 1.64 (1H, *m*, H-2β), 1.67 (1H, *m*, H-1β), 1.72 (1H, *m*, H-7α), 1.76 (1H, *m*, H-20β), 1.94 (1H, *m*, H-16β), 2.23 (1H, *dt*, 10.8 &

9.0 Hz, H-21), 3.14 (1H, *m*, H-3), 4.55 (1H, *s*, H-6). ^{13}C-NMR (150 MHz, $CDCl_3$): δ (ppm) = 16.3 (C-28), 16.9 (C-24), 17.0 (C-27), 17.3 (C-26), 17.6 (C-25), 21.1 (C-12), 21.9 (C-16), 24.2 (C-11), 26.6 (C-20), 27.6 (C-2) 27.7 (C-23), 28.8 (C-29), 30.9 (C-30), 34.5 (C-15), 36.7 (C-10), 39.6 (C-4), 40.7 (C-14), 40.8 (C-1), 41.0 (C-7), 41.3 (C-19), 42.0 (C-8), 44.0 (C-18), 48.8 (C-13), 50.9 (C-9), 51.1 (C-21), 54.0 (C-17), 55.6 (C-5), 69.0 (C-6), 73.9 (C-22), 79.1 (C-3). HR-ESI-MS *m/z*: $[M-H]^-$ = 459.3840 (calcd. for $C_{30}H_{51}O_3^-$, 459.3843).

2′-O-Methylnordivaricatic acid (***3***). Brownish orange solid, MP. 149-151°C. HR-ESI-MS *m/z*: $[M-H]^-$ = 387.1449 (calcd. for $C_{21}H_{23}O_7^-$, 387.1449). IR ν_{max} (cm^{-1}): = 3408, 2962, 2933, 2873, 1651, 1615, 1586, 1432, 1249, 1206, 1160, 1140, 1043, 956, 826. ^{1}H-NMR and ^{13}C-NMR (see Table 2).



1: R^1 = OAc, R^2 = H, R^3 = COOH, R^4 = H
2: R^1 = H, R^2 = OH, R^3 = CH_3, R^4 = OH

3

Figure 1. The structure of compound (**1-3**) and the selected key HMBC correlations of compound **3**

3. Results and Discussion

*3.1. Structure Elucidation of Compound **1***

Compound **1** appeared as a white solid. Mass spectra exhibited a pseudo-molecular ion at 515.3734 (calcd. for $C_{32}H_{53}O_5^-$, 515.3736), which corresponded with $C_{32}H_{52}O_5$. The FT-IR spectrum displayed the existence of a hydroxy moiety at 3418 cm^{-1} together with two carbonyl groups at 1732 and 1716 cm^{-1}. The ^{1}H-NMR indicated that there were 7 methyl groups attached to quaternary carbon and one methyl group at δ_H 1.13 (3H, *d*) attached to methine carbon. Furthermore, two peaks at δ_H 4.59 (1H, *dd*) and 3.31 (1H, *dd*) were deduced for two oxygenated methine carbons. The ^{13}C-NMR and DEPT revealed 32 signals, two of which were oxygenated methine carbons at δC 80.9 (C-1) and 75.2 (C-3). Further analysis carbon spectrum showed resonance signals of two carbonyl groups at δ_C 170.5 (C-1′) and 183.6 (C-29) which were well-matched to FT-IR. For these initial analysis, it is proved that compound **1** shared some similarities with 3*β*-hydroxyhopan-29-oic acid [10, 11] except for the presence of an additional acetoxy group.

In HMBC spectrum, proton H-2 exhibited correlations with both oxygenated methine carbons at δ_C 80.9 (C-1) and 75.2 (C-3). Moreover, methine proton at δ_H 4.59 (H-1) interacted with the other oxygenated methine carbon at δ_C 75.2 (C-3) together with C-9,10. Besides, the proton at δ_H 3.31 (H-3) gave cross-signals with two methyl groups C-23 and C-24. These above data evidenced that two oxygenated methine carbons were located at C-1 and C-3. The position of the acetoxy group was confirmed at C-1 as indicated by a cross-peak between H-1 at 4.59 (1H, *dd*) and carbonyl carbon at δ_C 170.5 (C-1′). Further analyzing HMBC indicated that both protons at δ_H 1.13 (H-30) and 2.36 (H-22) showed cross-signals with a carboxyl group at δ_C 183.6 (C-29); therefore, the position of carboxylic acid moiety was logically deduced for attaching to C-22 (Figure 2a).

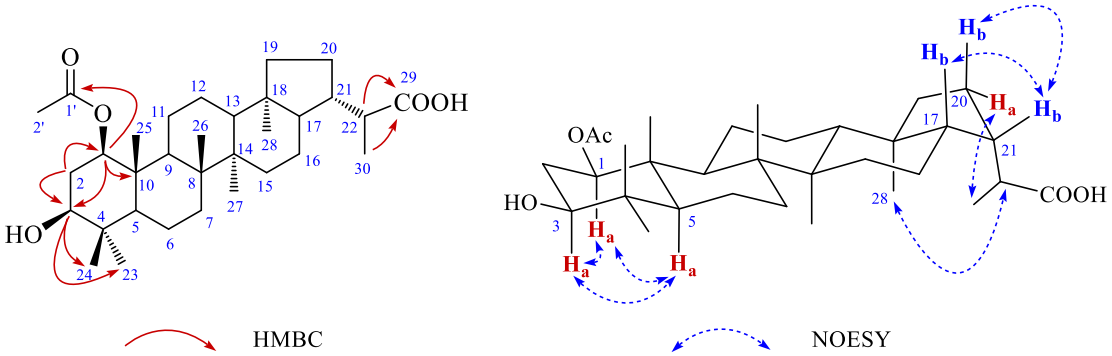


Figure 2. The selected key HMBC (*a*) and NOESY (*b*) correlations of compound **1**

The relative stereochemistry of C-1, C-3 was unambiguously identified by NOESY spectrum (Figure 2b). Three protons including H-1, H-3, H-5 exhibited pair-to-pair interactions, which can be firmly concluded that these protons were oriented on the same side. In addition, due to the rigidity of pentacyclic skeleton, the H-5 must be downward, and as a result, the conformation of C-1 and C-3 were both *beta*. From all the above data, compound **1** was readily interpreted as 1β-acetoxy-3β-hydroxy-21α-hopan-29-oic acid and this was a new compound.

3.2. Structure Elucidation of Compound **3**

Compound **3** was a brownish orange solid. The negative HRESI-MS exhibited a signal at 387.1449 $[M-H]^-$ (calcd. for $C_{21}H_{23}O_7^-$, 387.1449) which was deduced for chemical formula $C_{21}H_{24}O_7$. The ^{1}H-NMR spectrum indicated the presence of two pairs of *meta* coupling at δ_H 6.39 (1H, *d*, 2.5 Hz, C-3); 6.45 (1H, *d*, 2.5 Hz, C-5) and 6.57 (1H, *d*, 2.5Hz, C-3′); 6.50 (1H, *d*, 2.5 Hz, C-5′), suggested for two tetrasubstituted benzene rings. In the upfield region, there were proton signals of two *n*-propyl side chains at δ_H 2.95 (2H, H-8); 1.70 (2H, *m*, H-9); 0.95 (3H, *t*, H-10) and 3.12 (2H, *t*, H-8′); 1.63 (2H, *m*, H-9′); 0.90 (3H, *t*, H-10′). Furthermore, a singlet signal at 3.86 (*s*, 2′–OCH_3) was proposed for a methoxy group. In the downfield of spectra, there were two signals of hydroxy groups, one of which at δ_H 11.17 (1H, *s*, 2-OH) was a chelated hydroxy group, the remaining at δ_H 14.22 (1H, *brs*, -CO<u>OH</u>) was assigned for carboxylic acid moiety. Independently, the ^{13}C-NMR and DEPT spectra were also evidenced for two *n*-propyl side chains at δ_C 39.3 (C-8); 25.9 (C-9); 14.4 (C-10) and 38.0 (C-8′); 25.5 (C-9′); 14.4 (C-10′); four unsubstituted aromatic carbon at δ_C 99.8 (C-3), 111.3 (C-5), 114.5 (C-3′), 108.2 (C-5′); and one methoxy carbon at δ_C 55.9 (2′-OCH_3). The other characteristics derived from these spectra were two carbonyl signals at δ_C 170.2 (C-7) and 176.7 (C-7′). In brief, these spectroscopic data indicated key similarity with divaricatic acid, yet compared with published data of divaricatic acid in different solvents, its spectra data showed some minor distinction [Table S3] [12, 13]. From the above evidence, the structure of compound **3** was initially interpreted as an isomer of divaricatic acid.

The structure of this compound was not divaricatic acid **3a** as the above discussion. It meant that the methoxy group did not locate at C-4. Thus, two possible isomers were that the methoxy group resided at C-2 in 2-*O*-methylnordivaricatic acid **3b** (Figure S2) or at C-2′ in 2′-*O*-methylnordivaricatic acid **3 (**Figure 1). In this case, the position of methoxy group could be literally determined by HMBC correlation. Firstly, for a typical depside derivative, the aromatic carbon-bearing ester group C-1 generally shifted to upfield region compared to carboxylic acid moiety at C-1′ as in case of divaricatic acid **3a** (Table S3) [12]. The HMBC analysis revealed that three protons including H-3′, 5′, 8′ gave correlated peaks with nearby C-1′. In addition, both proton of methoxy group and H-3′ correlated with C-2′ (Table 2). As a result, the methoxy group must reside in B-ring at C-2′. Secondly, the deeper analysis HMBC revealed that the 2-OH proton of compound **3** also showed a three-bond correlation with C-3 but not with C-3’. This result confirmed that the 2-OH was located in A ring, and the methoxy group must be bound to C-2′. In brief, the above analysis from HMBC supported the

methoxy group located in B-ring and it can be deduced that compound **3** was 2′-*O*-methylnordivaricatic acid, which was a novel compound.

Table 1. The spectroscopic data of compound **1** ($CDCl_3$, δ in ppm, J in Hz)

Position	^{13}C-NMR (150 MHz)	^{1}H-NMR (600 MHz)	HMBC (^{1}H → ^{13}C)	NOESY (^{1}H → ^{1}H)
1	80.9	4.59 (1H, *dd*, 11.34 & 4.62 Hz)	C-2, 3, 9, 10, 25, 1’	2α, 2β, 3, 5, 9, 23
2	33.4	1.91 (1H, *m*, H$_\alpha$)	C-1, 3, 4, 10	1, 2β, 3
		1.62 (1H, *m*, H$_\beta$)	C-1, 3, 4, 10	1, 2α, 24, 32
3	75.2	3.31 (1H, *dd*, 12.24 & 4.26 Hz)	C-1, 2, 4, 5, 23, 24	1, 2α, 5, 23
4	38.8	-		
5	53.0	0.65 (1H, *dd*, 11.58 & 2.04 Hz)	C-1, 3, 4, 6, 7, 9, 10, 23, 24, 25	1, 3, 6α, 9, 23
6	17.9	1.57 (1H, *m*, H$_\alpha$)		5, 23
		1.49 (1H, *m*, H$_\beta$)	C-26	24
7	33.1	1.40 (1H, *m*, H$_\alpha$)	C-26	7β
		1.21 (1H, *m*, H$_\beta$)	C-5, 6, 8, 9, 26	7α, 26
8	42.2	-		
9	50.7	1.45 (1H, *m*)	C-9	1, 5, 23, 27
10	42.2	-		
11	23.0	1.46 (2H, m)		32
12	23.8	1.46 (1H, *m*)	C-13	
		1.32 (1H, *m*)	C-9, 13	
13	48.6	1.32 (1H, *m*)		
14	41.9	-		
15	33.5	1.16 (1H, *m*, H$_\alpha$)	C-13, 16, 17, 27	15β, 27,16β
		1.32 (1H, *m*, H$_\beta$)	C-16	15α, 26
16	19.8	1.28 (1H, *m*, H$_\alpha$)		
		1.48 (1H, *m*, H$_\beta$)	C-14, 15, 17, 18	15α, 21
17	53.6	1.25 (1H, *m*)	C-16, 18, 20, 21, 28	21
18	44.3	-		
19	40.9	1.51 (1H, *m*, H$_\alpha$)	C-17, 18, 20, 21, 28	28
		0.90 (1H, *m*, H$_\beta$)	C-18	17, 19α, 20β
20	26.6	1.43 (1H, *m*, H$_\alpha$)		22, 20β, 30
		1.87 (1H, *m*, H$_\beta$)	C-17, 18, 19	21, 20α, 19α, 30
21	42.0	2.34 (1H, *m*)	C-17, 18, 20, 22	16β, 17, 20β, 30
22	42.8	2.36 (1H, *m*)	C-21, 29, 30	20α, 28, 30
23	27.9	0.97 (3H, *s*)	C-3, 4, 5, 24	1, 3, 5, 6α, 9, 24
24	15.0	0.77 (3H, *s*)	C-3, 4, 5, 23	2β, 6β, 23
25	12.8	0.98 (3H, *s*)	C-1, 5, 9, 10	
26	16.9	0.94 (3H, *s*)	C-7, 8, 9	7β, 15β
27	16.6	0.91 (3H, *s*)	C-8, 13, 15	9, 15α, 28
28	15.7	0.70 (3H, *s*)	C-13, 17, 18, 19	22, 27, 19α
29	183.6	-		
30	17.6	1.13 (3H, *d*, 6.48 Hz)	C-21, 22, 29	20α, 20β, 21, 22
1′	170.5	-	C-1, 2′	
2′	21.9	1.99 (3H, *s*)	C-1′	2β, 11

Table 2. The spectroscopic data of compound **3** (Acetone-*d6*, δ in ppm, J in Hz)

Position	^{13}C-NMR (125 MHz)	^{1}H-NMR (500 MHz)	HMBC (^{1}H → ^{13}C)
1	105.7	-	
2	166.1	-	
3	99.8	6.39 (1H, *d*, 2.5 Hz)	C-1, 2, 5
4	165.3*	-	
5	111.3	6.45 (1H, *d*, 2.5 Hz)	C-1, 3, 4, 8
6	148.4	-	
7	170.2	-	
8	39.3	2.95 (2H)#	C-1, 5, 6, 9, 10
9	25.9	1.70 (2H, *m*)	C-6, 8, 10
10	14.4	0.95 (3H, *t*, 7.0 Hz)	C-8, 9
1′	116.2	-	
2′	165.3*	-	
3′	114.5	6.57 (1H, *d*, 2.5 Hz)	C-1′, 2′, 4′, 5′
4′	152.8	-	
5′	108.2	6.50 (1H, *d*, 2.5 Hz)	C-1′, 3′, 4′, 8′
6′	149.3	-	
7′	176.7	-	
8′	38.0	3.12 (2H, *t*, 7.5 Hz)	C-1′, 5′, 6′, 9′, 10′
9′	25.5	1.63 (2H, *sextet*, 7.5 Hz)	C-6′, 8′, 10′
10′	14.4	0.90 (3H, *t*, 7.0 Hz)	C-8′, 9′
2−OH	-	11.17 (1H, *s*)	C-3
2′−OCH$_3$	55.9	3.86 (3H, *s*)	C-2′
−COOH	-	14.22 (1H, *brs*)	

* These signals were interchangeable.

This signal was overlapped with acetone-*d6* solvent and was determined by HSQC.

Although the structure of compound **2** has been recorded, the referenced spectroscopic data were not available for comparison. In this study, we fully reported the spectroscopic assignment for this compound (see Table S2). In addition, this compound was firstly isolated from *D. applanata*.

In combination with the previous report [8], we have isolated six phenolic compounds, one depside, two lichenxanthones, and three hopane triterpenoids. They complement to phytochemical database of *D. applanata*. Hopane triterpenoid, especially 3*β*-acetoxyhopane-1*β*,22-diol, was recorded in *Dirinaria* genus [9]. Our results in chemical composition of *D. applanata* have identified three hopane triterpenoids which are hydroxylated at C-3 position whereas the hydroxylation of those hopanes in other lichen genus occurred at C-6 [14, 15]; C-6, 7 [16]; C-6, 15 [17]; C-6, 16 [18]; C-6, 7, 15 [19] or C-6, 7, 16 [20]. This means that 3-hydroxyhopane derivatives could be recognized as a fingerprint for *D. applanata*. In addition, divaricatic acid **3a,** a depside, is recorded in *Dirinaria* genus [9]. A new 2′-*O*-methylnordivaricatic acid **3**, an isomer of **3a**, could be generated from the late-stage functionalization in biosynthesis pathway of *Dirinaria* species. These findings might contribute to chemotaxonomy for determining *D. applanata* among a pool of lichen species.

In conclusion, from the extract of the lichen *Dirinaria applanata*, three compounds were isolated and fully characterized by both 1D and 2D-NMR. Notably, compound **1** was a new hopanoic acid while compound **3** was a new depside. Moreover, compound **2** was firstly isolated from *D.applanata*.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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