

The structure of hafellic acid, a new diphenyl ether from the lichen *Cratiria subtropica*

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Abstract

Hafellic acid has been isolated from the lichen *Cratiria subtropica*, and its structure established by mass spectrometry and NMR spectroscopy.

Introduction

Hafellic acid was first detected in the lichen *Cratiria subtropica* (Elix) Elix (Elix & McCarthy 2008), and subsequently found in *Lecanora hafelliana* Lu *et al.* (Lu *et al.* 2011). Although hafellic acid could readily be characterized by thin-layer chromatography (Elix & McCarthy 2008; Elix 2014), its structure remained unknown. This paper describes the structural elucidation of hafellic acid. Methods are as described in Elix *et al.* (2019).

Extraction of *Hafellia subtropica* (Elix) Elix

The lichen *Cratiria subtropica* was collected in the Queens Head area, Limeburners Creek Nature Reserve, 15 km south of Crescent Head, 31°19'09"S, 152°58'05"E, 5 m alt., New South Wales, *J.A. Elix 43588*, 7.viii.2008 (CANB). The dried lichen thallus (0.3 g) was extracted in a Soxhlet extractor with anhydrous diethyl ether (320 mL) and anhydrous acetone (320 mL) for 48 h, respectively. The corresponding extracts were concentrated to dryness to yield 23.6 mg and 12.5 mg of a white solid, respectively. The white solids were combined and then purified by flash column chromatography over silica gel using 50% ethyl acetate/light petroleum as eluent. Four major bands developed, and the third band eluting had strong blue fluorescence under UV light (254 nm). This blue fluorescent band was collected from the chromatographic column and concentrated to afford hafellic acid (1) (1.6 mg) as a colourless solid, $[\alpha]_D^{25} -12.5$ (c = 0.08, (CH₃)₂CO).

Structural elucidation of hafellic acid (1)

The hafellic acid (1) exhibited m/z [M+Na]⁺ 523.1942 on high-resolution ESIMS with a sodiated adduct ion corresponding to C₂₇H₃₂O₉Na⁺, thus establishing the molecular formula of hafellic acid as C₂₇H₃₂O₉. UV (MeOH) λ_{max} 225 (ε10,450), 263 (8030), 302 (2920) nm.

NMR spectroscopic evidence showed that hafellic acid (1) possessed a novel structure, which is similar to the lichen metabolite epiphorellin acid 1 (2) (Fiedler *et al.* 1986; Elix & Jenie 1989) and the artefact 8''-O-ethyl-β-alectoronic acid (3) (Gollapudi *et al.* 1994) [Figure 1].

Assignments in the ¹H-NMR spectrum of compound (1) are summarized in Table 1. The ¹³C-NMR spectrum of hafellic acid (1) (Table 2) exhibited twenty six carbon signals with one overlapping carbonyl resonance [d 170.5], the integral of which was almost twice that

of the carbonyl resonance [d 167.4]. In the HSQC spectrum of (1), two carbon signals (d 14.06 and 14.13) were strongly associated with two triplet CH₃ proton signals (d 0.89 and 0.97) respectively, indicating that two methyl groups are bonded to methylene groups in (1). A carbon signal (δ 21.0) was associated with a singlet proton signal (δ 1.93, 3H) indicating this methyl is bonded to a carbonyl group. A carbon signal (δ 52.2) was associated with a singlet proton signal (δ 3.69, 3H), as expected for a methoxy group in (1). Two tertiary carbon signals (δ 74.6, 79.9) were associated with two methine proton signals (δ 5.07–5.10 and 4.63–4.66) respectively, indicating that these carbon atoms were bonded to oxygen. Four carbon signals (d 103.5, 107.9, 108.2 and 115.9) were associated with four proton signals (δ 6.26, 6.48, 6.36 and 6.75) respectively, with proton signals (δ 6.26, 6.36 having $J = 2.4$ Hz) and proton signals (δ 6.48, 6.75 with $J = 2.3$ Hz), consistent with two *meta*-substituted aromatic rings. No carbon signals were found to be associated with proton signals (d 9.16, 11.30), indicating the presence of two hydroxy groups, the latter forming an intramolecular hydrogen bond.

Correlations in the gHMBC spectrum of hafellic acid (1) are illustrated in Figure 2.

In the NOESY spectrum (Figure 3), H1''-a (δ 2.91-2.94), H1''-b (δ 3.02) and H1 (δ 6.36) are correlated with one another. However, only H1''-a and H4'' (δ 1.48-1.60) are correlated with one another, while there is no correlation between H1''-b and H4''.

Both compound 1 and 2 have a methoxycarbonyl group (COOMe) bonded directly to an aromatic ring, so the close similarity of ¹H and ¹³C NMR data for these respective groups is as expected (Table 1, 2). Further, both compounds 1 and 3 possess carbon side chains substituted by oxygen atoms at C2'' position and a saturated lactone ring. The similarity of ¹H and ¹³C NMR data for the respective C1'' methylene groups can be observed in Table 1 and 2. More particularly, the chemical shift of the lactone carbonyl in 3 (d 169.1), is very close to that observed in hafellic acid (1) (d 170.5), with the latter being weakly associated with adjacent protons in gHMBC spectrum and overlapping in ¹³C-NMR spectrum. All these data are consistent with structure (1) for hafellic acid.

Acknowledgement

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Table 1. ¹H-NMR data of compounds 1–3

Position	δ_{H} mult (<i>J</i> in Hz)		
	1 ((CD ₃) ₂ CO)	2 ((CD ₃) ₂ CO)*	3 (CDCl ₃)#
1-H	6.36, m	-	-
3-H	6.26, d (2.4)	5.83, d (2.5)	6.32, br s
5-H	-	6.40, d (2.5)	6.46, d (1.5)
8-H	-	3.90, s	-
3'-H	6.48, d (2.3)	6.50, s	6.40, s
5'-H	6.75, d (2.3)	-	-
8'-H	3.69, s	3.70, s	-
1''-H	a 2.91-2.94, m b 3.02, dd (16.6, 3.2)	2.57, t (7.0)	6.13, s
2''-H	4.63-4.66, m	1.37, m	-
3''-H	a 1.70-1.74, m b 1.80-1.84, m	1.37, m	2.44, t, (7.5)
4''-H	1.48-1.60, m	1.37, m	1.24-1.64, m
5''-H	0.97, t (7.4)	0.90, m	1.24-1.64, m
6''-H	-	-	1.24-1.64, m
7''-H	-	-	0.84, t (5.9)*
1'''-H	2.93, d (6.6)	2.90, t (7.0)	2.90, br d (15.8) 3.10, br d (15.8)
2'''-H	5.07-5.10, m	1.37, m	-
3'''-H	1.54-1.57, m	1.37, m	1.90, m
4'''-H	1.31-1.40, m	1.37, m	1.24-1.64, m
5'''-H	0.89, t (7.4)	0.90, m	1.24-1.64, m
6'''-H	-	-	1.24-1.64, m
7'''-H	1.93, s	-	0.89, t (6.9)*
8'''-H	-	-	3.57, m 3.63, m
9'''-H	-	-	1.07, t (6.9)
4-OH	11.30, s	-	8.98, br s
2'-OH	-	-	11.0, br s
4'-OH	9.16, s	-	8.98, br s

* Fiedler *et al.* (1986), Elix & Jenie (1989)
Gollapudi *et al.* (1994)

Table 2. ¹³C-NMR data of compounds 1–3

Position	δ_{C}		
	1 ((CD ₃) ₂ CO)	2 ((CD ₃) ₂ CO)*	3 (CDCl ₃)#
1-C	108.2	115.1	102.5
2-C	165.2	163.8	161.8
3-C	103.5	99.3	103.4
4-C	164.8	158.5	162.8
5-C	104.3	109.6	105.6
6-C	143.4	143.7	142.2
7-C	170.5	168.7	160.8
8-C	-	51.7	-
1'-C	119.9	104.5	99.9
2'-C	154.4	159.4	163.8
3'-C	107.9	98.5	103.4
4'-C	160.5	157.8	156.9
5'-C	115.9	140.6	133.3
6'-C	141.4	134.4	131.7
7'-C	167.4	173.6	169.1
8'-C	52.2	56.0	-
1''-C	33.4	30.3	103.2
2''-C	79.9	29.6	159.1
3''-C	37.5	32.0	33.1
4''-C	18.8	22.7	26.4
5''-C	14.1	14.0	31.1
6''-C	-	-	22.3
7''-C	-	-	13.9
1'''-C	38.8	31.3	35.5
2'''-C	74.6	28.8	107.7
3'''-C	37.2	32.5	31.6
4'''-C	19.2	22.7	23.1
5'''-C	14.1	14.0	31.2
6'''-C	170.5	-	22.4
7'''-C	21.0	-	13.9
8'''-C	-	-	58.1
9'''-C	-	-	15.2

* Fiedler *et al.* (1986), Elix & Jenie (1989)
Gollapudi *et al.* (1994)

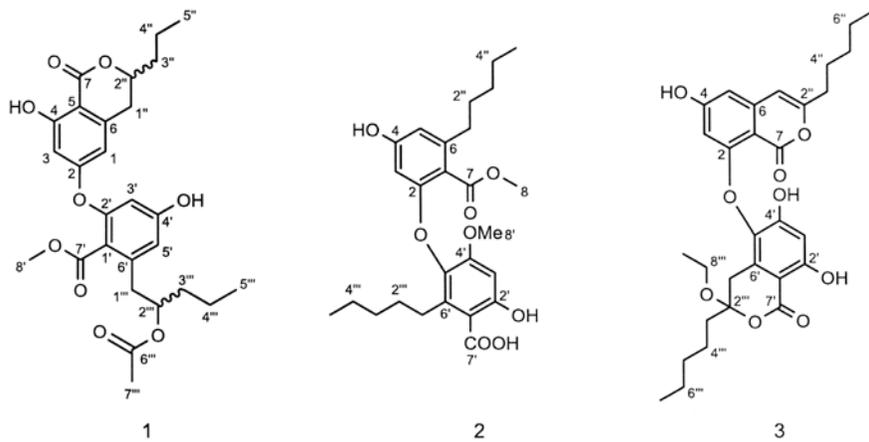


Figure 1. Structures of compounds (1), (2), and (3)

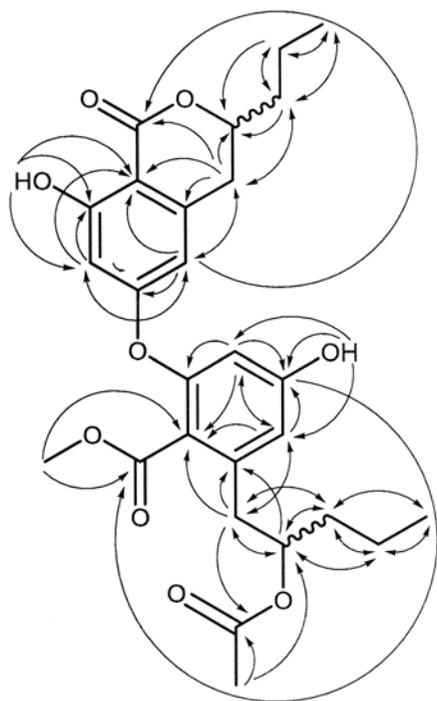


Figure 2. gHMBC correlations of hafellic acid (1)

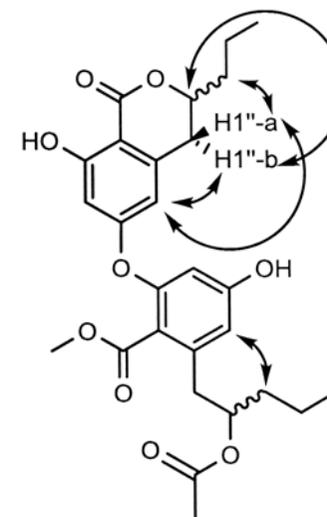


Figure 3. NOESY associations of hafellic acid (1)