A New Benzophenone from *Lindera fruticosa*

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Lindera fruticosa is a perennial shrub widely distributed in China, Nepal, India and Ethiopia. The root is a traditional anti-inflammatory medicine folk remedy, but few studies on its active components has been reported.[1] The potential therefore exists for new and valuable compounds to be discovered from *L. fruticosa*. This paper describes the isolation and structural determination of a new benzophenone from the *L. fruticosa*. Although this compound was reported by Kang *et al*.[2] as a new compound from *Securidaca inappendiculata*, the authors of this paper suggest that the identification of the compound carried out by Kang *et al*. was incorrect.

Experimental Section

Instruments. HREIMS was recorded on a JEOL JMS 700 (JEOL, Tokyo, Japan). IR spectrum was run on a Perkin Elmer Spectrum One FT-IR spectrometer (Perkin Elmer, Norwalk, USA). ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were collected on a Varian Unity Inova AS 400 FT-NMR spectrometer (Varian, California, USA).[3]

Plant Materials. *L. fruticosa* roots were collected from a rural forest in Addis Ababa province, Ethiopia, by Prof. Fikru Nigussie and identified by Prof. Dae-Keun Kim, Woosuk University, Jeonju, Korea. A voucher specimen (KHU02031) was deposited in the Laboratory of Natural Products Chemistry, Kyung Hee University, Suwon, Korea.

Isolation of 2,3-Dimethoxy-4-hydroxybenzophenone. The dried powdered roots (1 kg) were extracted with 80% aqueous methanol (20 L × 3) and concentrated *in vacuo*. The extracts were partitioned with H_2O (2 L) and EtOAc (2 L × 3). The concentrated EtOAc fraction (LFE, 14 g) was subjected to silica gel column chromatography (CC) (150 g, Φ 5 × 12 cm) and eluted with a gradient of $CHCl_3$-MeOH (10:1 → 7:1, v/v, 1 L of each), resulting in 12 fractions (LFE1~ LFE12). Fraction LFE3 [1.4 g, Ve/Vt (elution volume/total volume) 0.10-0.15] was separated by RP-18 CC (150 g, Φ 4 × 6 cm) and eluted with MeOH-H_2O (1:1 → 2:1, 1 L of each), resulting in 11 fractions (LFE3-1~LFE3-11). Fraction LFE3-4 (648 mg, Ve/Vt 0.13-0.22) was subjected to silica gel CC (75 g, Φ 3.5 × 9 cm) and eluted with *n*-hexane-EtOAc (2:1, v/v, 1.5 L) yielding compound 1 [230 mg, Ve/Vt 0.13-0.26; TLC (Silica gel 60 F_{254}) R_f 0.6, *n*-hexane-EtOAc = 1:1].

2,3-Dimethoxy-4-hydroxybenzophenone (1): Colorless oil: IR (CaF_2 window in $CHCl_3$) ν_{max} 3624, 2924, 1468, 1225, 1065 cm^{-1}; EIMS *m/z* 258 [M]$^+$ (100), 241 (100), 225 (30), 209 (58), 181 (100), 167 (70), 151 (16), 137 (47), 105 (74); HREIMS *m/z* 258.0865 [M] $^+$ (calcd. for $C_{15}H_{14}O_4$ = 258.0892); ^{1}H NMR (400 MHz, $CDCl_3$, δ) and ^{13}C NMR (100 MHz, $CDCl_3$, δ). see Table 1.

Results and Discussion

The roots of *L. fruticosa* were extracted with 80% aqueous MeOH, and the concentrated extract was partitioned with EtOAc and H_2O. From the EtOAc fraction, a benzophenone was isolated through repeated SiO_2 and ODS column chromatography.

The compound was obtained as a colorless oil. The IR spectrum showed an absorption characteristic of phenolic alcohol (3624 cm^{-1}), phenyl (2924, 1468 cm^{-1}) and ether (1225, 1065 cm^{-1}). A molecular formula of $C_{15}H_{14}O_4$ was determined by HREIMS ([M] $^+$, *m/z* 258.0865, calcd 258.0892 for $C_{15}H_{14}O_4$). The ^{1}H NMR spectrum revealed an AB aromatic system at δ_H 7.78 (2H, dd, *J* = 8.4, 2.0 Hz, H-2',6'), δ_H 7.53 (1H, dd, *J* = 8.4, 2.0 Hz, H-4'), and δ_H 7.41 (2H, dd, *J* = 8.4, 8.4 Hz, H-3',5') as a 1-substituted benzene ring and δ_H 7.06 (1H, d, *J* = 8.4 Hz, H-6) and δ_H 6.74 (1H, d, *J* = 8.4 Hz, H-5) as a 1,2,3,4-tetrasubstituted benzene ring with 2 methoxy at δ_H 3.92 (3H, H-OCH_3 at C-3) and δ_H 3.71 (3H, H-OCH_3 at C-2). The ^{13}C NMR spectrum showed a characteristic non-chelated ketone carbon at δ_C 195.2 (C-7), 5 quaternary sp^2 carbons at δ_C 152.4 (C-4), δ_C 151.9 (C-2), δ_C 139.5 (C-3), δ_C 138.2 (C-1'), δ_C 125.4 (C-1), 5 methine sp^2 carbons at δ_C 132.6 (C-4'), δ_C 125.8 (C-6), δ_C 110.1 (C-5) including 2 overlapping signals at δ_C 129.7 (C-2',6'), δ_C 128.1 (C-3',5'), and 2 methoxy signals at δ_C 61.5 and δ_C

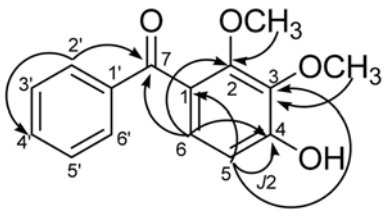

Figure 1. Chemical structure of 2,3-dimethoxy-4-hydroxybenzophenone from *Lindera fruticosa*. The arrows indicate correlations between proton and carbon signals in the HMBC spectrum.

Table 1. ^{1}H (400 MHz, $CDCl_3$) & ^{13}C NMR (100 MHz, $CDCl_3$) spectroscopic data of 2,3-dimethoxy-4-hydroxybenzophenone from *Lindera fruticosa* and *Securidaca inappendiculata*[2]

Carbon Number	From *Lindera fruticosa*		From *Securidaca inappendiculata*[2]	
	δ_H	δ_C	δ_H	δ_C
1		125.4		124.0
2		151.9		152.5
3		139.5		140.4
4		152.4		154.4
5	6.74 (1H, d, *J* = 8.4 Hz)	110.1	6.72 (1H, d, *J* = 8.4 Hz)	111.5
6	7.06 (1H, d, *J* = 8.4 Hz)	125.8	6.97 (1H, d, *J* = 8.4 Hz)	124.8
7		195.2		194.7
1'		138.2		138.2
2'/6'	7.78 (1H, dd, *J* = 8.4, 2.0 Hz)	129.7	7.67 (1H, d, *J* = 8..0 Hz)	129.7
3'/5'	7.41 (1H, dd, *J* = 8.4, 8.4 Hz)	128.1	7.49 (1H, t, *J* = 7.7 Hz)	128.2
4'	7.53 (1H, dd, *J* = 8.4, 2.0 Hz)	132.6	7.61 (1H, d, *J* = 7.5 Hz)	132.6
OCH_3(C2)	3.71 (3H, s)	61.5	3.78 (3H, s)	61.1
OCH_3(C3)	3.92 (3H, s)	61.1	3.60 (3H, s)	60.2
OH	–	–	10.01 (1H, s)	–

61.1. This spectroscopic data implied that the compound was a trioxygenated benzophenone with a 1-substituted benzene ring and a 1,2,3,4-tetrasubstituted benzene ring. In the gHMBC spectrum, every signal showed cross peaks by *J*3 correlation. An olefin methine signal at δ_H 7.06 (H-6) showed cross peaks with a non-chelated ketone signal at δ_C 195.2 (C-7) and 2 olefin quaternary carbon signals at δ_C 151.9 (C-2) and δ_C 152.4 (C-4). Another olefin methine signal at δ_H 6.74 (H-5) showed cross peaks with 2 olefin quaternary carbon signals at δ_C 125.4 (C-1) and δ_C 139.5 (C-3). Two methoxy protons at δ_H 3.92 and δ_H 3.71 showed correlations with 2 olefin quaternary carbons at δ_C 139.5 and δ_C 151.9, respectively. The former correlation indicated 1 methoxy was at C-3 and the latter correlation indicated another methoxy was at C-2 or C-4. *J*2 correlation was observed only between H-5 and an olefin quaternary carbon at δ_C 152.4 (C-4), which showed no correlation with any methoxy proton, leading to the conclusion that another methoxy was at C-2. Thus, the compound was identified as 2,3-dimethoxy-4-hydroxybenzophenone.

The 2,3-dimethoxy-4-hydroxybenzophenone was reported to have been previously isolated from *Securidaca inappendiculata* by Kang *et al*.[2] The ^{1}H- and ^{13}C-NMR data suggested by Kang *et al*. showed many differences from the data proposed in this study (Table 1). The ^{1}H-NMR data proposed by Kang *et al*. showed many the relative upfield shifts of H-5 (–0.02 ppm), H-6 (–0.09 ppm), H-2'/6' (–0.11 ppm) and C3-methoxy (–0.32 ppm), and the downfield shifts of H-3'/5' (+0.08 ppm), H-4' (+0.08 ppm) and C2-methoxy (+0.07 ppm). The ^{13}C-NMR showed the variations mainly on the 1,2,3,4-tetrasubstituted benzene ring such as upfield shifts of C-1 (–1.4 ppm) and C-6 (–1.0 ppm), and the downfield shifts of C-2 (+0.6 ppm), C-3 (+0.9 ppm), C-4 (+2.0 ppm), and C-5 (+1.4 ppm). However, the proton signal of a hydroxy at δ_H 10.01 was observed, which indicates that there should be a H-bond between a hydrogen of the hydroxy and an oxygen of a ketone (C-7).[4-6] Accordingly, the benzophenone isolated by Kang *et al*. should have a hydroxyl at C-2, indicating the chemical structure of the compound could be a 3,4-dimethoxy-2-hydroxybenzophenone. This evidence led to the conclusion that the 2,3-dimethoxy-4-hydroxybenzophenone isolated from *L. fruticosa* was a new compound.

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