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Chemical constituents of *Ficus nota*

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ABSTRACT

*Chemical investigation of the dichloromethane extract of the unripe fruits of Ficus nota afforded 4-(2-hydroxyethyl)-2-methoxyphenol (**1**), a mixture of meso-2,3-butanediol (**2a**), (2R,3R)-2,3-butanediol (**2b**) and (2S,3S)-2,3-butanediol (**2c**) and β-sitosterol (**3**). The structure of **1** was elucidated by extensive 1D and 2D NMR spectroscopy.*

Keywords: *Ficus nota*, Moraceae, 4-(2-hydroxyethyl)-2-methoxyphenol, meso-2,3-butanediol, (2R,3R)-2,3-butanediol, (2S,3S)-2,3-butanediol, meso-2,3-butanediol, β-sitosterol

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INTRODUCTION

Ficus nota (Blancoi) Merr., locally known as tibig is a small tree endemic to the Philippines. The fruit can be eaten raw when ripe, while the young leaves are cooked as a vegetable [1]. The water extracted from the tree is used for the treatment of fever and to relieve muscle pain. A decoction of the roots and bark is used for urinary tract infections, hypertension and diabetes [2]. There is no reported study on the chemical constituents of *F. nota*.

This study was conducted as part of our research on the chemical constituents of *Ficus* species found in the Philippines. Nine *Ficus* species, five of which are endemic to the Philippines have been studied [3-9]. We earlier reported the isolation of a new neohopane triterpene [3], furanocoumarin derivatives, bergapten and oxypeucedanin hydrate [4] which exhibited antimicrobial properties from *F. pumila*. In another study, we reported the isolation of squalene, polyprenol, β-amyrin fatty acid ester, α-amyrin acetate, β-amyrin acetate, lupeol fatty acid ester, lupenone, oleanone, and ursenone from the leaves of *F. pseudopalma* and lutein, lupeol acetate, β-carotene, phytol, α-amyrin fatty acid ester, squalene, polyprenol, β-amyrin fatty acid ester, α-amyrin acetate, β-amyrin acetate, β-sitosterol and stigmasterol from the leaves of *F. ulmifolia* [5]. Chemical investigation of the dichloromethane extracts of the leaves of two *Ficus species* led to the isolation of 11α,12α-epoxyurs-14-en-3β-yl acetate, β-amyrin, α-amyrin, squalene, β-sitosterol, stigmasterol, polyprenol, linoleic acid and lutein from *F. linearifolia*; and ergosta-6,22-dien-3,5,8-triol, ergosterol, taraxerol, hop-22(29)-ene, squalene, β-sitosterol, stigmasterol, polyprenol, linoleic acid and lutein from *F. triangularis* [6]. *F. odorata* afforded β-sitosteryl-3β-glucopyranoside-6'-*O*-palmitate, squalene, lutein, α-amyrin acetate, lupeol acetate, and β-carotene. β-Sitosteryl-3β-glucopyranoside-6'-*O*-palmitate exhibited cytotoxicity against AGS cell line with 60.28% growth inhibition [7]. Recently, the isolation of lupenone, β-friedelinol, squalene, β-sitosterol, cycloeucalenol, lupeol, α-amyrin, and β-amyrin from *F. nervosa* [8] and ursolic acid, oleanolic acid, butyrospermol cinnamate and lutein from *F. ampelas* [9] have been reported.

We report herein the isolation of 4-(2-hydroxyethyl)-2-methoxyphenol (**1**), a mixture of meso-2,3-butanediol (**2a**)**:**[(2R,3R)-2,3-butanediol (**2b**) and (2S,3S)-2,3-butanediol (**2c**)] in a 2:3 ratio and β-sitosterol (**3**) from the unripe fruits of *Ficus nota*. To the best of our knowledge this is the first report on the isolation of **1-3** from *F. nota* (Fig 1).

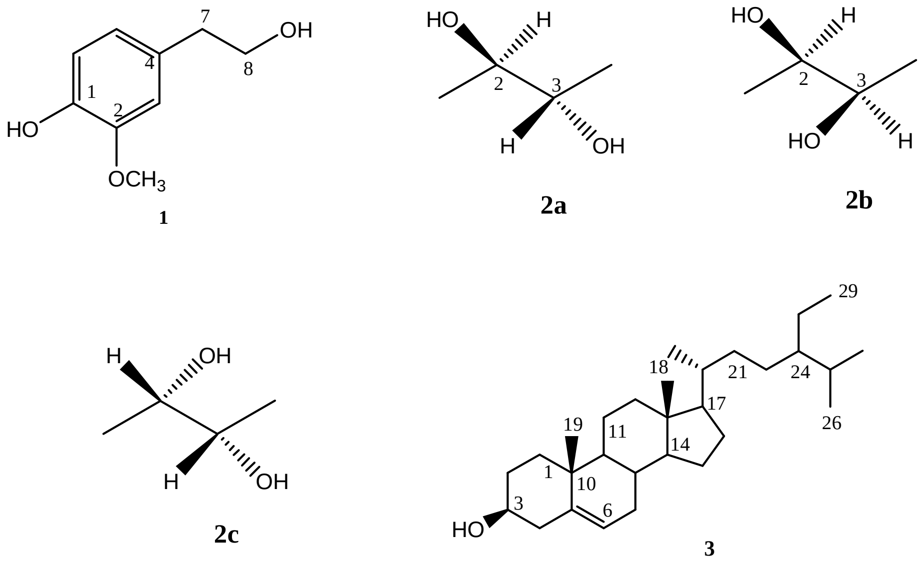

Fig. 1. Chemical constituents of *F. nota*: 4-(2-hydroxyethyl)-2-methoxyphenol (1), meso-2,3-butanediol (2a), (2R,3R)-2,3-butanediol (2b), (2S,3S)-2,3-butanediol (2c), and β-sitosterol (3)

MATERIALS AND METHODS

General Experimental Procedures

NMR spectra were recorded on a Varian VNMRS spectrometer in $CDCl_3$ at 600 MHz for ^1H NMR and 150 MHz for ^{13}C NMR spectra. 2D NMR (COSY, HSQC, HMBC) spectra were recorded on a Varian VNMRS spectrometer. Column chromatography was performed with silica gel 60 (70-230 mesh); TLC was performed with plastic backed plates coated with silica gel F_{254}; plates were visualized by spraying with vanillin sulfuric acid, followed by warming.

Sample Collection

Unripe fruits of tibig were collected from Tanay, Rizal, Philippines in June 2008. The sample was identified as *Ficus nota* (Blancoi) Merr. at the Philippine National Herbarium, National Museum of the Philippines, Manila.

General Isolation Procedure

A glass column 20 inches in height and 2.0 inches internal diameter was packed with silica gel. The crude extract from the fruits were fractionated by silica gel chromatography using increasing proportions of acetone in dichloromethane (10% increment) as eluents. One hundred milliliter fractions were collected. All fractions were monitored by thin layer chromatography. Fractions with spots of the same *Rf* values were combined and rechromatographed in appropriate solvent systems until TLC pure isolates were obtained. A glass column 18 inches in height and 1.0 inch internal diameter was used for the crude extracts from the fruits and seeds. Ten milliliter fractions were collected. A glass column 12 inches in height and 0.5 inch internal diameter was used for the rechromatography. Two milliliter fractions were collected. Final purifications were conducted using Pasteur pipettes as columns.

Isolation of Chemical Constituents

The unripe fruit of *F. nota* was cut into small pieces, ground in a blender and then freeze-dried. The freeze-dried fruit (786.5 g) was soaked in CH_2Cl_2 for three days and then filtered. The filtrate was concentrated under vacuum to afford a crude extract (23.5 g) which was chromatographed in increasing proportions of acetone in CH_2Cl_2 at 10% increment. The 30% acetone in CH_2Cl_2 fraction was rechromatographed (3 ×) in 15% EtOAc in petroleum ether to afford **3** (8 mg) after washing with petroleum ether. The 50% acetone in CH_2Cl_2 fraction was rechromatographed (5

×) in $CH_3CN:Et_2O:CH_2Cl_2$ (1.5:1.5:7 by volume ratio) to afford **1** (5 mg) after washing with petroleum ether. The 60% acetone in CH_2Cl_2 fraction was rechromatographed (4 ×) in $CH_3CN:Et_2O:CH_2Cl_2$ (2:2:6 by volume ratio) to afford a mixture of **2a**, **2b** and **2c** (12 mg).

4-(2-Hydroxyethyl)-2-methoxyphenol (**1**): ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.71 (H-3, d, *J*=1.8 Hz), 6.69 (H-5, dd, *J*=9, 1.8 Hz), 6.84 (d, *J* = 9 Hz), δ 2.78 (H_2-7, t, *J*=7.8 Hz), 3.81 (H_2-8, t, *J*=7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.26 (C-1), 146.55 (C-2), 111.51 (C-3), 130.21 (C-4), 121.60 (C-5), 114.46 (C-6), 38.81 (C-7), 63.80 (C-8).

RESULTS AND DISCUSSION

Silica gel chromatography of the dichloromethane extract of the freeze-dried unripe fruits of *Ficus nota* afforded **1-3**. The structure of **1** was elucidated by extensive 1D and 2D NMR spectroscopy as follows. The ^{1}H NMR spectrum of **1** indicated resonances for aromatic proton at δ 6.71 (dd, *J* = 9, 1.8 Hz) ortho coupled to the proton at δ 6.84 (d, *J* = 9 Hz) and meta coupled to the proton at δ 6.69 (d, *J* = 1.8 Hz). These resonances suggested a 1,2,4-trisubstituted benzene. Benzylic methylene protons were deduced from the resonance at δ 2.78 (t, *J* = 7.8 Hz) which were coupled to oxymethylene protons at δ 3.81 (t, *J* = 7.8 Hz). The coupled protons were confirmed by the COSY spectrum (Fig. 2). A broad singlet at δ 5.53 suggested an aromatic hydroxyl. The presence of a methoxy in **1** was deduced from the resonance at δ 3.87 (3H, s). Thus, **1** contains a 2-hydroxyethyl, a hydroxyl and a methoxy substituents.

Protons attached to carbons were assigned from HSQC 2D NMR data. The positions of the 2-hydroxyethyl, hydroxyl and methoxy substituents were deduced from analysis of the HMBC 2D NMR data: key HMBC correlations are shown in Fig. 2. Thus, the benzylic protons were attached to C-4 based on long-range correlations between these protons and C-3, C-4, C-5 and the hydroxyethyl carbon. The methoxy was attached to C-2 due to long-range correlations between these protons and C-2. The hydroxyl was attached to C-1 since long-range correlation was observed between H-5 and this carbon and no correlation was observed between H-5 and the methoxy bearing carbon (C-2). All long-range correlations observed are consistent with the structure of **1**. Literature search revealed that **1** is 4-(2-hydroxyethyl)-2-methoxyphenol as confirmed by similar ^{1}H NMR data [10].

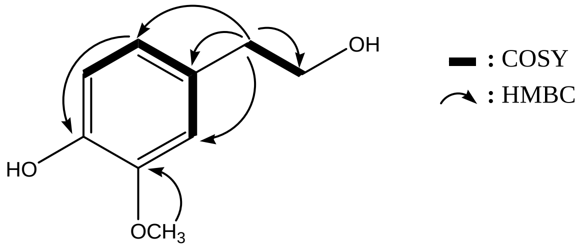

Fig. 2. ^{1}H-^{1}H COSY and Key HMBC correlations of 1

The mixture of **2a:**(**2b** and **2c**) in a 2:3 ratio was deduced from the corresponding ^{13}C NMR resonance intensities. The ^{1}H NMR spectrum indicated resonances for methyl doublet at δ 1.14 (6H, d, *J* = 6.6 Hz), and oxymethine protons at δ 3.76 (m) and 3.48 (m) for **2a**. The ^{13}C NMR spectrum gave resonances for **2a** at δ 16.86 and 70.83 for methyl and oxymethine carbons, respectively. This compound was identified by comparison of its ^{1}H and ^{13}C NMR data with those reported in the literature for a meso compound, (2R,3S)-2,3-butanediol [11]. The ^{1}H NMR spectrum indicated resonances for methyl doublet at δ 1.10 (6H, d, *J* = 7.8 Hz), and oxymethine protons at δ 3.76 (m) and 3.48 (m) for the mixture of **2b** and **2c**. The ^{13}C NMR spectrum gave resonances for methyl carbons at δ 19.26 and oxymethine carbons at δ 72.50 for the mixture of **2b** and **2c**. Compounds **2b** and **2c** were identified by comparison of their ^{1}H and ^{13}C NMR data with those reported in the literature for (2R,3R)-2,3-butanediol [11-13] and (2S,3S)-2,3-butanediol [11,14]. The structure of **3** was identified by comparison of its ^{1}H and ^{13}C NMR data with those reported in the literature for β-sitosterol [15].

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