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ORIGINAL PAPER

Syntheses and Crystal Structures of Two Apigenin Alkylation Derivatives

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Abstract Two apigenin alkylation derivatives, 4′,7-dimethoxyl-5-hydroxyflavone (I) and 4′,7-diethoxyl-5-hydroxyflavone (II), have been synthesized and their crystal structures were determined by ^{1}H NMR and single crystal X-ray diffraction study. (I) is triclinic, space group P–1 with a = 7.120(5) Å, b = 7.297(5) Å, c = 13.559(10) Å, α = 89.313(12)°, β = 86.298(12)°, γ = 83.999(13)° and Z = 2. (II) is monoclinic, space group $P\,2_1/c$ with a = 16.309(4) Å, b = 7.303(2) Å, c = 15.185(4) Å, α = 90.00°, β = 115.70(2)°, γ = 90.00° and Z = 4. They have the same flavone skeleton which is composed of a benzopyranone moiety and a phenyl moiety. Molecules of (I) are linked into a two-dimensional network by a combination of C–H···O hydrogen bond and π–π stacking interactions. (II) shows some discrepancies with (I) and the molecules are linked into a column by π–π stacking interaction.

Keywords Apigenin · Crystal structure · 4′,7-Dimethoxyl-5-hydroxyflavone · 4′,7-Diethoxyl-5-hydroxyflavone · π–π Stacking

Introduction

Flavonoids are diphenyl propanoids that occur far and wide in plant foods and form important constituents of human diet. Apigenin (4′,5,7,-trihydroxyflavone), one of the most common flavonoids, is widely distributed in many fruits and vegetables including parsley, onions, orange, tea, chamomile, wheat sprouts and in some seasonings [1]. Apigenin has been shown to possess anti-inflammatory, anti-carcinogenic effects for skin and free radical scavenging properties [2]. In some cells, apigenin has been shown to display a variety of anti-tumor effects including stimulation of gap junctional and intracellular communication [3], inhibition of mutagenesis [4], transformation [5], angiogenesis [6] and tumorigenesis [7]. In this paper, the derivatives, 4′,7-dimethoxyl-5-hydroxyflavone (I) and 4′,7-diethoxyl-5-hydroxyflavone (II), resulting from alkylation of apigenin, at the 4′ and 7 positions are obtained. Both I and II are of interest due to their potential medical applications. Here, we report the crystal structures of (I) and (II) (Scheme 1).

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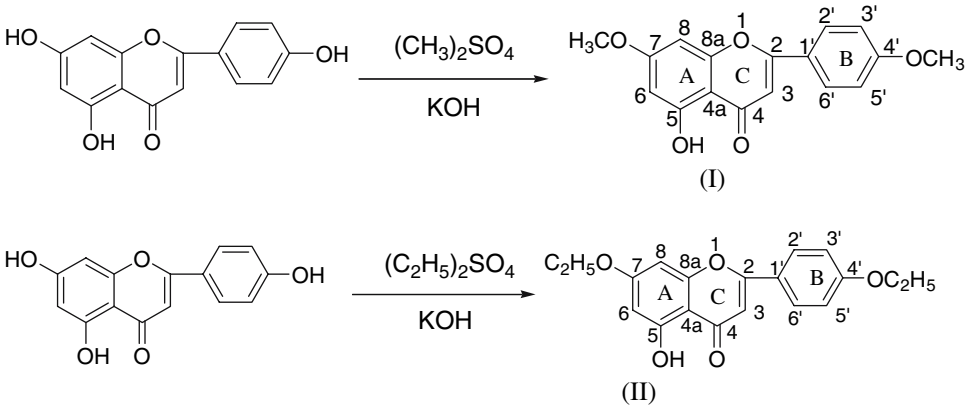
Experimental

Reagent grade chemicals were used directly without further purification. The ^{1}H NMR spectra were recorded on a Bruker-1000 CCD spectrometer with TMS as internal reference and DMSO-d_6 as solvent. The crystal structure of (I) was determined using Bruker Smart-1000 CCD Diffractometer instrument, the crystal structure of (II) was determined using Siemens P4 four-circle diffractometer instrument. Melting points were obtained with an X4 melting point apparatus and uncorrected.

Synthesis of Derivatives (I) and (II)

For the preparation of (I), apigenin (1.0 g) was dissolved into acetone (30 mL) and KOH (1 mL, 0.3%). Dimethyl sulfate

Scheme 1 Routes of synthesis (I) and (II)



(1 mL) was added dropwise to the solution with strong stirring. The mixture was stirred at room temperature for 4 h and then poured into 50 mL water, resulting in appearance of yellow precipitation. After settlement for 2 h, the precipitate was filtered and dissolved in 50 mL NaOH (3 mol/L). The insoluble matter in NaOH (3 mol/L) was filtered and washed with water until the pH was 7, the title compound (I), 4′,7-dimethoxyl-5-hydroxyflavone was obtained, which was recrystallized from benzene to give colorless needle crystal after 5 days at room temperature. The yield is 80%, m.p: 446 K. ^{1}H NMR (DMSO-d_6, ppm) δ: 12.92(s, 1H, HO–C_5), 8.06(d, 2H, J = 8.8 Hz, H–$C_{2'}$,$C_{6'}$), 7.12 (d, 2H, J = 8.8 Hz, H–$C_{3'}$,$C_{5'}$), 6.94(s, 1H, H–C_3), 6.79(s, 1H, H–C_8), 6.38 (s, 1H, H–C_6), 3.87(s, 3H, CH_3O–C_7), 3.86(s, 3H, CH_3O–$C_{4'}$). The process of preparing (II) is similar to that of (I), except that dimethyl sulfate is substituted by diethyl sulfate. Crystals of (II) suitable for X-ray diffraction analysis were obtained by slow evaporation from 95% ethanol solution after 3 days at room temperature. The yield is 60%, m.p: 452 K. ^{1}H NMR (DMSO-d_6, ppm) δ: 13.10(s, 1H, HO–C_5), 8.33 (d, 2H, J = 8.8 Hz, H–$C_{2'}$,$C_{6'}$), 7.02 (d, 2H, J = 8.8 Hz, H–$C_{3'}$,$C_{5'}$), 6.98(s, 1H, H–C_3), 6.81(s, 1H, H–C_8), 6.39(s, 1H, H–C_6), 4.12(m, 4H, –OCH_2–), 1.34(m, 6H, –OC–OCH_3).

X-ray Crystal Structure Determinations

The data of (I) and (II) were collected with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) using ω-2θ scan technique. The structures were solved using direct methods and refined by full-matrix least-squares techniques. All non-hydrogen atoms were assigned anisotropic displacement parameters in the refinement. All hydrogen atoms were added at calculated positions and refined using a riding model. Four C–H bond lengths for (I) were restrained. The structures were refined on F^2 using SHELXTL-97 [8]. The crystal used for the diffraction study showed no decomposition during data collection. The crystal data and refinement data are list in Table 1.

Table 1 Crystal data and structure refinement for (I) and (II)

Compound	(I)	(II)
CCDC deposit No.	291112	291113
Empirical formula	$C_{17}H_{14}O_5$	$C_{19}H_{18}O_5$
Formula weight	298.28	326.33
Temperature	298(2) K	296(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Monoclinic
Space group	*P*-1	*P* 2_1/c
Unit cell dimensions	a = 7.120(5) Å	a = 16.309(4) Å
	b = 7.297(5) Å	b = 7.303(2) Å
	c = 13.559(10) Å	c = 15.185(4) Å
	α = 89.313(12)°	α = 90.00°
	β = 86.298(12)°	β = 115.70(2)°
	γ = 83.999(13)°	γ = 90.00°
Volume	699.1(9) Å^{-3}	1629.7(7) Å^{-3}
Z	2	4
Density (calculated)	1.417 mg m^{-3}	1.330 mg m^{-3}
Absorption coefficient	0.105 mm^{-1}	0.096 mm^{-1}
F(000)	312	688
θ range for data collection	2.81–25.01°	3.07–14.60°
Limiting indices	$-8 \le h \le 8$	$-20 \le h \le 18$
	$-8 \le k \le 6$	$-9 \le k \le 0$
	$-16 \le l \le 16$	$0 \le l \le 18$
Independent reflections	3720/2448 [*R*(int) = 0.0497]	3713/3194 [*R*(int) = 0.0224]
Absorption correction	Semi-empirical from equivalents	Multi-scan
Data/restraints/parameters	2448/4/256	3194/0/224
Goodness-of-fit on F^2	1.002	0.935
Final R indices [$I > 2$sigma(I)]	R_1 = 0.0573, wR_2 = 0.0857	R_1 = 0.0472, wR_2 = 0.0924
R indices (all data)	R_1 = 0.1893, wR_2 = 0.1146	R_1 = 0.1217, wR_2 = 0.1049
Extinction coefficient	0.007(3)	0.0098(7)
Largest diff. peak and hole	0.338 and –0.226 e. Å^{-3}	0.244 and –0.127 e. Å^{-3}

Table 2 Selected bond lengths (Å) and angles (°) for (I) and (II)

	(I)	(II)
Bond lengths (Å)		
O1–C9	1.362(4)	1.367(2)
O1–C1	1.389(4)	1.379(2)
O2–C3	1.357(5)	1.356(2)
O2–C16	1.440(6)	1.437(3)
O3–C5	1.369(5)	1.362(3)
O4–C7	1.252(5)	1.264(2)
O5–C13	1.376(5)	1.364(2)
C1–C6	1.381(5)	1.381(3)
C1–C2	1.377(6)	1.388(3)
C3–C4	1.384(6)	1.397(3)
C4–C5	1.349(6)	1.363(3)
C5–C6	1.415(6)	1.413(3)
C6–C7	1.426(6)	1.438(3)
C7–C8	1.434(5)	1.422(3)
C8–C9	1.343(5)	1.336(3)
C9–C10	1.465(5)	1.466(3)
C10–C11	1.391(5)	1.375(3)
C11–C12	1.388(5)	1.391(3)
C12–C13	1.369(6)	1.365(3)
C14–C15	1.374(6)	1.368(3)
Bond angles (°)		
C9–O1–C1	119.6(3)	119.52(17)
C3–O2–C16	117.8(4)	118.44(18)
O1–C1–C6	120.2(4)	121.1(2)
O1–C1–C2	115.0(4)	115.59(19)
C6–C1–C2	124.8(4)	123.3(2)
C1–C2–C3	116.7(5)	117.5(2)
O2–C3–C2	123.3(5)	123.8(2)
O2–C3–C4	114.7(4)	115.1(2)
C2–C3–C4	122.0(5)	121.1(2)
C5–C4–C3	118.9(5)	119.8(2)
O3–C5–C6	117.8(5)	118.6(2)
C4–C5–C6	122.8(5)	121.2(2)
C1–C6–C7	121.2(4)	119.9(2)
C5–C6–C7	124.0(5)	123.0(2)
O4–C7–C6	121.5(4)	121.1(2)
C8–C7–C6	115.2(4)	115.8(2)
C9–C8–C7	122.0(5)	122.3(2)
O1–C9–C10	127.5(4)	126.5(2)
C11–C10–C15	119.0(4)	117.2(2)
C15–C10–C9	119.8(4)	120.6(2)
C10–C11–C12	118.1(4)	122.0(2)
C13–C12–C11	122.0(4)	119.5(2)
O5–C13–C14	115.3(4)	115.3(2)
C12–C13–C14	120.3(4)	119.3(2)
C14–C15–C10	122.1(5)	121.1(2)

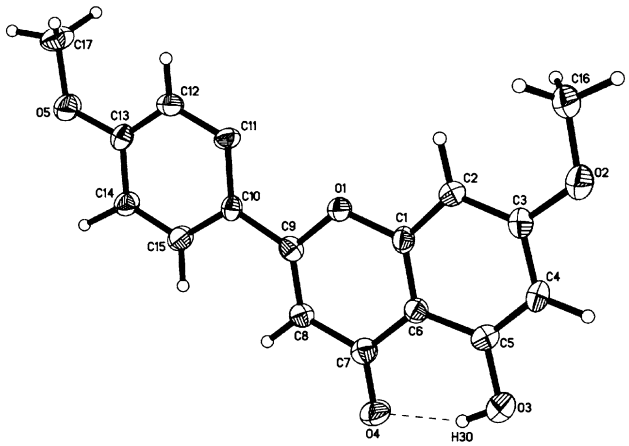
Table 3 Typical hydrogen bond lengths (Å) and bond angles (°) for (I) and (II)

	D–H···A	D–H(Å)	H···A(Å)	D···A(Å)	D–H···A(°)
(I)	O3–H3O···O4	0.83(4)	1.80(4)	2.582(5)	156(4)
	C8–H8···O4[a]	0.97(3)	2.60(3)	3.543(6)	165(3)
	C15–H15···O4[a]	0.97(4)	2.44(4)	3.390(6)	166(3)
	C16–H16A···O5[b]	0.97(4)	2.41(4)	3.375(8)	171(4)
(II)	O3–H3O···O4	0.92(3)	1.70(3)	2.566(3)	156(3)

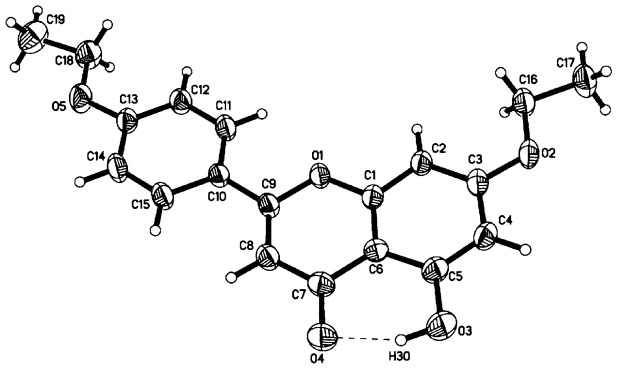
Symmetry code: [a] (1 – x, 3 – y, –z); [b] (x, y, 1 + z).

Selected bond lengths and bond angles are given in Table 2 for (I) and (II).

CCDC-291112 and CCDC-291113 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; email: deposit@ccdc.cam.ac.uk].



(I)



(II)

Fig. 1 A view of the molecules of (I) and (II), showing the atom-labelling schemes. Displacement ellipsoids are drawn at the 30% probability level

Results and Discussion

In the crystal structures of (I) and (II) (Fig. 1), the atoms of benzopyranone moiety containing rings A(C1–C6) and C(O1/C1/C6–C9), display an almost coplanar configuration with the dihedral angles being 178.6(2)° of (I) and 178.8(6) of (II). The phenyl ring B(C10–C15) and benzopyranone moiety are also almost coplanar with the dihedral angles being 179.3° of (I) and 173.3° of (II), respectively. In the crystal structure of (I), methoxyl groups bonded to C3 and C13 are nearly coplanar with their attached rings, A and B, as indicated by the torsion angles separately being C16–O2–C3–C4 = 178.3(5)° and C17–O5–C13–C14 = 179.2(5)°. In the crystal structure of (II), the ethoxy groups bonded to C3 and C13 are nearly coplanar with their attached rings, A and B, as indicated by the torsion angles being C16–O2–C3–C2 = 179.0(4)° and C18–O5–C13–C12 = 175.8(4)°, respectively. Each of the molecule (I) and (II) has an independent O3–H3O···O4 intramolecular hydrogen bond, which generates a characteristic intramolecular *S*(6) motif.

In the crystal structure of (I), hydrogen bonding and offset face-to-face aromatic π–π stacking interactions lead

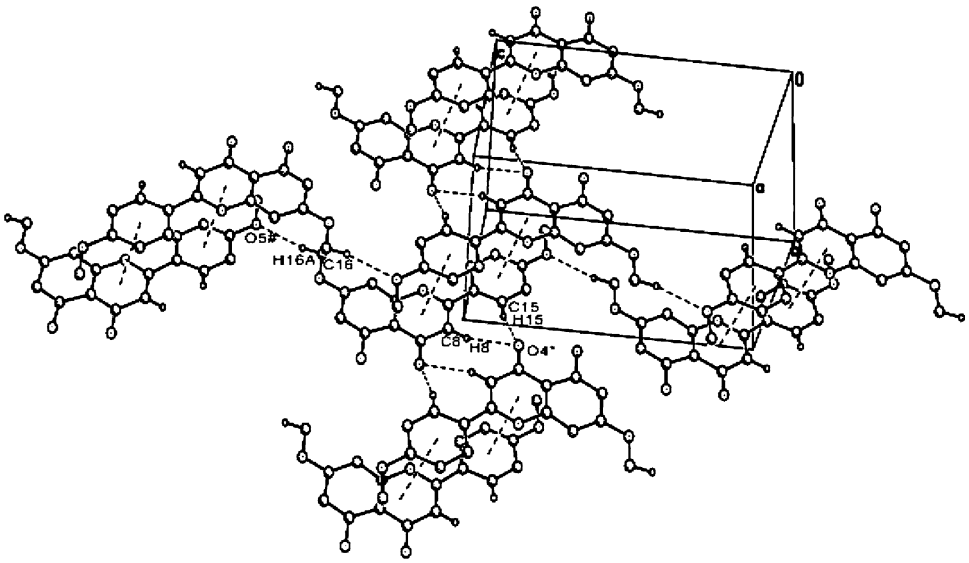


Fig. 2 Part of the crystal structure of (I), showing the formation of bi-chains and sheet via hydrogen bonds and π–π stacking interactions. For clarity, some hydrogen atoms are omitted. Symmetry code: * (1 – x, 3 – y, –z); # (x, y, 1 + z)

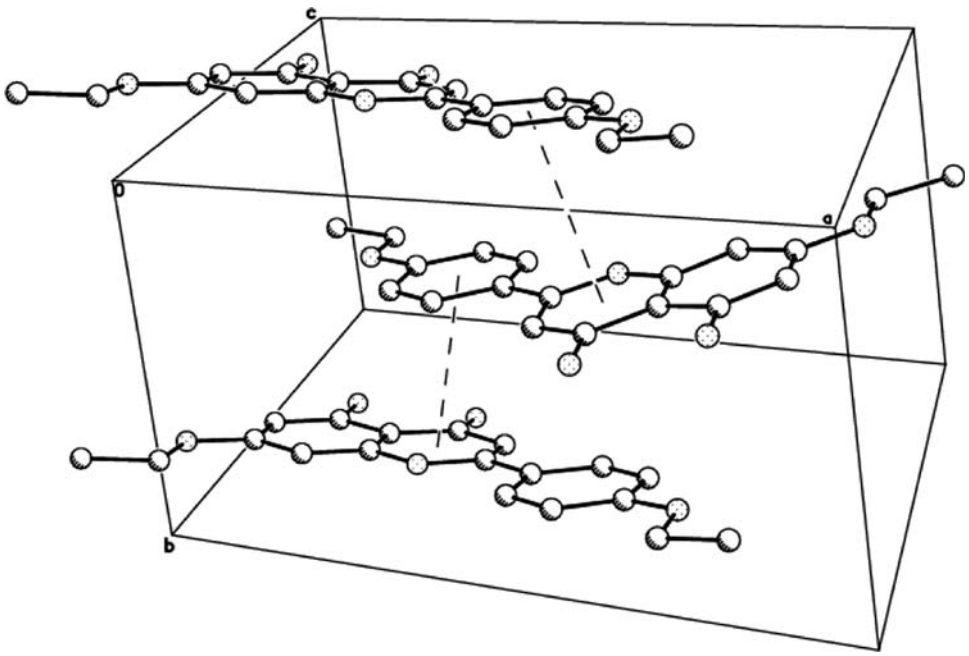


Fig. 3 Part of the crystal structure of (II), showing the formation of column by π–π stacking interactions. For clarity, all hydrogen atoms are omitted

to the formation of a (200) sheet (Fig. 2). The flavone skeletons are arranged in an anti-parallel fashion; ring B (C10–C15) [symmetry code: (x, y, z)] of one molecular stacks with ring C (O1/C1/C6–C9) [symmetry code: (x + 1, y, z)] of a neighbouring molecule with the interplanar distance of 3.347 Å and the intercentroid of 3.546 Å, the displacement of the two rings is 1.171 Å. A dimer is formed by the π–π stacking between two flavone moieties. Paired hydrogen bonds C16–H16A···O5# (Table 3) exit between dimers, which lead to the formation of an infinite zig-zag bi-chains along *c*-axis. One molecule carbonyl O4 accepts protons from the other molecule to form trifurcated hydrogen bonds by C15–H15···O4* and C8–H8···O4*. Paired hydrogen bonds C15–H15···O4* and paired hydrogen bonds C8–H8···O4* separately generate the supramolecular $R_2^2(14)$ and $R_2^2(8)$ synthons [9], which link the bi-chains into a (200) sheet. Hydrogen bonding and π–π stacking interactions assemble (I) into a two-dimensional network.

As is shown in Fig. 3, in the crystal structure of (II), the ring B (C10–C15) [symmetry code: (x, y, z)] of one molecule is nearly parallel to the ring C (O1/C1/C6–C9) [symmetry code: (x, 0.5 + y, z)] of a molecule with the dihedral angle being 13°. They stack with each other and its centriod–centriod distance is 3.756 Å, which is in the normal range of 3.3–3.8 Å [10]. Propagation of the π–π stacking interaction of (II) results in the formation of a column along b-axis.

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