Synthesis of 3,4,5-Trimethoxy-4'-hydroxystilbene Derivatives and Crystal Structure of Ethyl {4-[(*E*)-2-(3,4,5-trimethoxyphenyl)vinyl]phenoxy}acetate

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Several new 4'-O-substituted derivatives of 3,4,5-trimethoxy-4'-hydroxystilbene were synthesized and characterized by their IR and NMR spectra. The crystal structure of ethyl {4-[(*E*)-2-(3,4,5-trimethoxyphenyl)vinyl]phenoxy}acetate, one of these stilbene derivatives, has been solved by single-crystal X-ray structure analysis. The results show that all carbon and oxygen atoms in the molecule are nearly coplanar except C(16), and molecules stack to a column arrangement owing to C–H$\cdots\pi$ interactions. Pairs of these columns are linked by other molecules, and these linker molecules themselves also produce a column along the other direction. A puckered cyclic tetramer $R_4^4(46)$ is formed and the tetramer propagates itself *via* intermolecular hydrogen bonds and C–H$\cdots\pi$ interactions. In this way, molecules are interrelated and assembled to a two-dimensional layer structure.

Key words: 3,4,5-Trimethoxy-4'-hydroxystilbene Derivatives, Crystal Structure, Hydrogen Bond

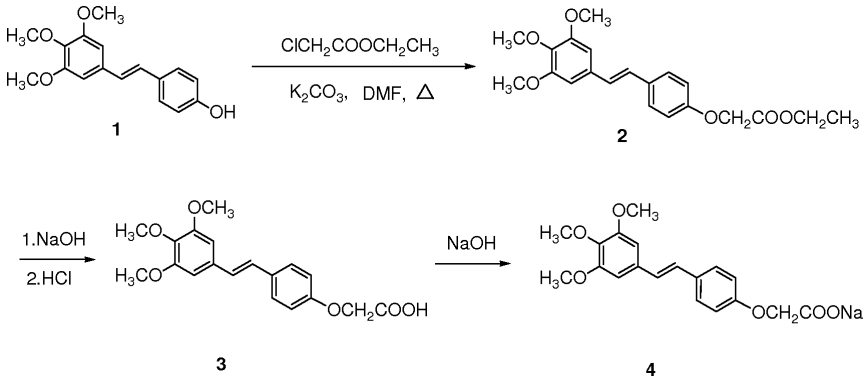
Introduction

The stilbene scaffold is a basic element for a number of biologically active natural and synthetic compounds. One of the most relevant and studied stilbenes is resveratrol (3,4',5-trihydroxy-*trans*-stilbene), a natural phytoalexin which occurs in grapes and other food products [1 – 3], endowed with several different biological properties and able to act and bind at different cellular targets [4, 5]. Therefore, the past several years have witnessed intense research devoted to its biological activities [3, 6, 7]. Resveratrol has been reported to play a role in the prevention of heart diseases associated with red wine consumption because it inhibits platelet aggregation [8], alters eicosanoid synthesis [8, 9], and modulates lipid and lipoprotein metabolism [10, 11]. In contrast to the extensive research devoted to resveratrol analogues which were synthesized and evaluated for their anticancer and antioxidant activities [12 – 17], fewer analogues have been synthesized and evaluated for prevention of platelet aggregation and modulating lipid and lipoprotein metabolism. Recently, some carbonylmethyl derivatives of resveratrol have been reported as thrombolytic agents and were found to have good effects [18]. In order to obtain relevant information on their analogues, we synthesized some new 4'-O-substituted derivatives of 3,4,5-trimethoxy-4'-hydroxystilbene. Furthermore, stilbene and its derivatives have attracted recent interest because of their unique structures [19, 20]. We were able to obtain single crystals of ethyl {4-[(*E*)-2-(3,4,5-trimethoxyphenyl)vinyl]phenoxy}acetate suitable for X-ray structure determination. In this paper we report on our results.

Results and Discussion

Chemistry

The starting material, 3,4,5-trimethoxy-4'-hydroxystilbene (**1**), was prepared according to literature procedures [21]. Ethyl {4-[(*E*)-2-(3,4,5-trimethoxyphenyl)vinyl]phenoxy}acetate (**2**) was synthesized by a nucleophilic substitution reaction of **1** and ethyl chloroacetate in dry DMF in good yield (86 %) (Scheme 1). Hydrolysis of **2** gave {4-[(E)-2-(3,4,5-trimethoxyphenyl)vinyl]phenoxy}acetic acid (**3**) in 95 % yield, which after acidification with HCl was filtered off as a white solid. Sodium salt **4** was prepared from **3** with NaOH solution. In order to get pure **4**, **3** was used in excess and the excess of **3** was filtered off from the solution. In this way we finally obtained a pale-yellow soluble solid **4** (Scheme 1). All of the final compounds had IR and ^{1}H NMR spectra which were in accordance with the proposed structures.



Scheme 1. Synthesis of 4'-O-substituted derivatives **2**–**4** of 3,4,5-trimethoxy-4'-hydroxystilbene.

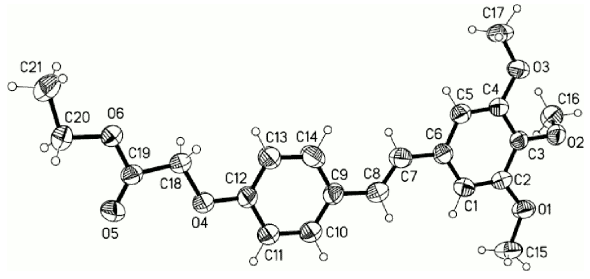


Fig. 1. Molecular structure of **2**.

Table 1. Crystal data and structure refinement for **2**.

	2
Empirical formula	$C_{21}H_{24}O_6$
Formula weight	372.40
Crystal size, mm^3	$0.40 \times 0.28 \times 0.21$
Temperature, K	296(2)
Wavelength, Å	0.71073
Crystal system	monoclinic
Space group	*C*2/*c*
a, Å	39.999(8)
b, Å	7.5712(12)
c, Å	13.889(2)
β, deg	108.225(5)
Volume, Å^3	3995.1(12)
Z	8
Calculated density, mg m^{-3}	1.238
Absorption coefficient, mm^{-1}	0.090
F(000), e	1584
θ range for data collection, deg	2.14 – 25.10
hkl range	$-47 \le h \le 47$, $-9 \le k \le 8$, $-16 \le l \le 14$
Reflections collected/unique	9688/3548 (R_{int} = 0.0272)
T_{max}/T_{min}	0.9809/0.9650
Refinement method	Full-matrix least-squares on F^2
Data/parameters	3548/249
Goodness-of-fit (F^2)	1.042
Final *R* indices [$I \ge 2\sigma(I)$]	$R1 = 0.0486$, $wR2 = 0.1348$
R indices (all data)	$R1 = 0.0934$, $wR2 = 0.1599$
Extinction coefficient	0.0006(3)
Largest diff. peak and hole, e Å^{-3}	0.271, −0.139

Crystal structure of ***2***

The structure of the parent compound, stilbene, was first studied using X-ray structure analysis by Robertson and Woodward [22] and has been the subject of many studies because the molecules having the *trans* stilbene skeleton seem to have an anomalously short ethylene bond. A view of the molecule **2** is shown in Fig. 1. Compound **2** also has an anomalously short olefinic bond: C(7)–C(8) = 1.293(3) Å. Especially for unsubstituted *trans* stilbene this fact has been attributed to dynamical disorder due to torsional vibration of the C-phenyl bonds in a direction perpendicular to the molecular plane [19, 20].

Characteristic of stilbene structures is the coplanarity of the molecular skeleton. The structure analysis of **2** shows the bond lengths C(6)–C(7) = 1.488(4) and C(8)–C(9) = 1.486(4) Å which are relatively short as compared with a normal C(sp^3)–C(sp^3) single bond of 1.54 Å. In addition to the known bond shortening due to the different hybridization of the carbon atoms (sp^2 *vs.* sp^3) this may indicate a partial double bond character of C(6)–C(7) and C(8)–C(9). As a consequence, the stilbene scaffold in molecule **2** is almost planar, with torsion angles of C(1)–C(6)–C(7)–C(8) = 2.2° and C(7)–C(8)–C(9)–C(14) = −2.0°. This shows that the coplanarity of the stilbene skeleton of **2** is better than of many other known stilbene analogues. Moreover, virtually all other carbon and oxygen atoms in the molecule **2** are also nearly coplanar with the stilbene scaffold except C(16) (torsion angle C(16)–O(2)–C(3)–C(2) = 104.6°) which is bent out of the plane to avoid steric hindrance with the nearby methoxy groups at C(2) and C(4) (Table 2).

In the crystal of **2** there are two different C–H$\cdots\pi$ interactions. Molecules are arranged in an *anti-*

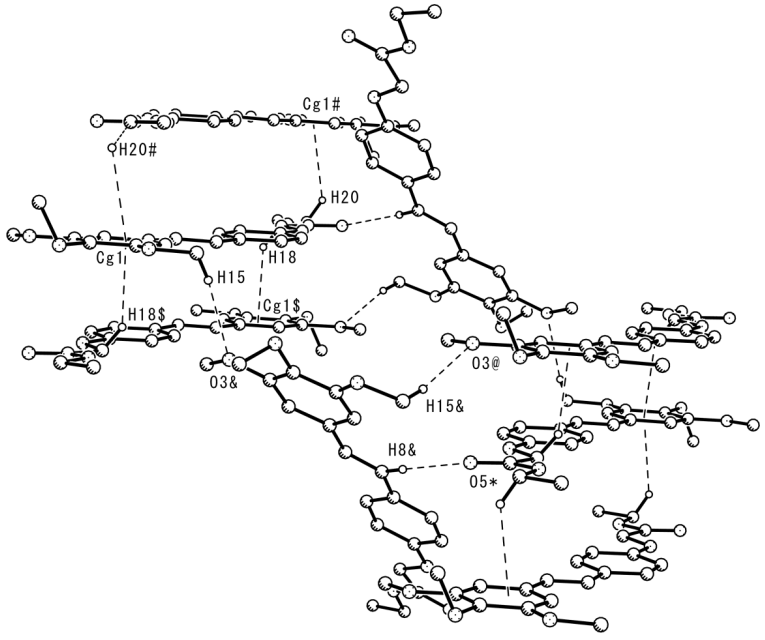


Fig. 2. The formation and propagation of the columns in the crystal of **2**. Hydrogen bonds are indicated by dashed lines. Some hydrogen atoms have been omitted for clarity. Symmetry codes: (&) x, $3-y$, $z-1/2$; (#) $1/2-x$, $3/2-y$, $2-z$; ($) $1/2-x$, $5/2-y$, $2-z$; (*) $1/2-x$, $5/2-y$, $z-1/2$; (@) x, y, $z-1$.

Table 2. Selected bond lengths (Å) and torsion angles (deg) for **2**.

O(1)–C(2)	1.368(3)	O(2)–C(3)	1.378(3)
O(3)–C(4)	1.364(3)	O(4)–C(12)	1.376(3)
O(4)–C(18)	1.408(3)	O(5)–C(19)	1.187(3)
O(6)–C(19)	1.325(2)	O(6)–C(20)	1.442(3)
C(6)–C(7)	1.488(3)	C(7)–C(8)	1.293(3)
C(8)–C(9)	1.486(3)	C(18)–C(19)	1.493(3)
C(20)–C(21)	1.508(3)		
C(1)–C(6)–C(7)–C(8)		2.2(5)	
C(7)–C(8)–C(9)–C(14)		–2.0(5)	
C(16)–O(2)–C(3)–C(2)		104.6(3)	
C(15)–O(1)–C(2)–C(1)		–1.5(4)	
C(17)–O(3)–C(4)–C(5)		4.2(4)	
C(18)–O(4)–C(12)–C(13)		0.3(4)	
C(20)–O(6)–C(19)–O(5)		–0.9(4)	
O(4)–C(18)–C(19)–O(6)		175.4(2)	
C(19)–O(6)–C(20)–C(21)		–179.7(2)	

parallel fashion and pairs of them are connected by two C–H$\cdots\pi$ bonds, C(20#)–H(20#)$\cdots$Cg(1) and C(20)–H(20)$\cdots$Cg(1#) (Fig. 2). Adjacent pairs of stilbenes are tied together by another two intermolecular C–H$\cdots\pi$ bonds, C(18$)–H(18$)$\cdots$Cg(1) and C(18)–H(18)$\cdots$Cg(1$), where Cg(1) is the centre of the ring formed by C(1)–C(6). In this way the molecules are stacked to columns. Two of these columns are linked to other molecules *via* three weak C–H$\cdots$O hydrogen bonds, (C(8&)–H(8&)$\cdots$O(5*), C(15&)–H(15&)$\cdots$O(3@) and C(15)–H(15)$\cdots$O(3&)) in which the oxygen atoms belong to methoxy and carbonyl groups, and the hydrogen atoms belong to vinyl and methoxy groups, respectively. These linker molecules themselves also produce a column along a different direction. It should be noted that a puckered cyclic tetramer $R_4^4(46)$ is formed owing to these hydrogen bonds (Fig. 3). The tetramer formed by intermolecular C–H$\cdots$O hydrogen bonds is seldom found in the crystal structure of stilbenes, probably because there are fewer oxygen atoms that can act as hydrogen-bond acceptors than in molecule **2**. Interestingly, the tetramer propagates itself *via* another intermolecular hydrogen bonds C(15)–H(15)$\cdots$O(3) and also *via* the weak intermolecular C–H$\cdots\pi$ interactions discussed above. In this way, molecules assemble to a two-dimensional layer structure.

Experimental Section

Reagents and techniques

3,4,5-Trimethoxy-4'-hydroxystilbene was synthesized according to literature [21]. Other chemicals were of analytical grade and were used without purification. The NMR spectra were recorded with a Bruker AVANCE300 spectrometer, using TMS as internal standard. The IR spectra were recorded with a Nicolet 170SX FT-IR spectrometer using KBr pellets. The melting points were determined using a WRS-113 digital melting point instrument (the thermometer was not corrected).

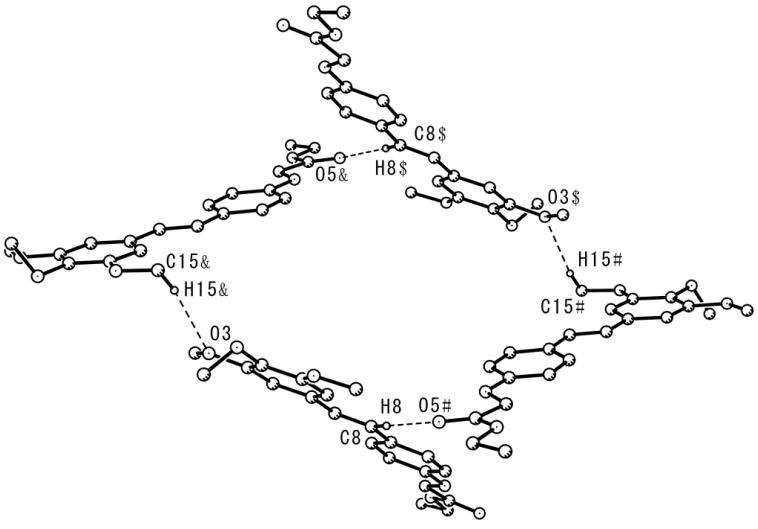


Fig. 3. The puckered cyclic tetramer $R_4^4(46)$ in the crystal of **2** (most hydrogen atoms omitted for clarity). Hydrogen bonds are indicated by dashed lines. Symmetry codes: (\$) $1/2-x, 2-y, 1-z$; (#) $1/2-x, 2-y, 3/2-z$; (&) $x, 2-y, z-1/2$.

*Ethyl {4-[(E)-2-(3,4,5-trimethoxyphenyl)vinyl]phenoxy} acetate (**2**)*

3,4,5-Trimethoxy-4'-hydroxystilbene (0.57 g, 2.0 mmol) and anhydrous K_2CO_3 (0.55 g, 4.0 mmol) were dissolved in dry DMF (12 mL) in a 25 mL round flask. The ethyl chloroacetate (0.43 mL, 4.0 mmol) was added to the solution with strong stirring. The mixture was heated at 100 °C for half an hour. After cooling to r. t., the mixture was poured into water (15 mL) and extracted with dichloromethane (3×10 mL). Then the dichloromethane solution was washed with water (3×10 mL) and dried over anhydrous Na_2SO_4. The drying agent was filtered off, the solvent was removed and from the residual oil yellow single crystal suitable for X-ray diffraction grew within a week. The residual oil was recrystallized from ethanol-water (1 : 1) to afford the target compound **2** (0.61 g, 86 %). M. p. 98 – 100 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, 3H, $-CH_3$), 3.87 (s, 3H, $-OCH_3$), 3.91 (s, 6H, $-OCH_3$), 4.27 (q, 2H, $-CH_2-$), 4.64 (s, 2H, $-CH_2-$), 6.71 (s, 2H, Ar–H), 6.89 (d, 1H, J = 16.2 Hz, –CH=CH–), 6.93 (d, 2H, Ar–H), 6.94 (d, 1H, J = 16.2 Hz, –CH=CH–), 7.42 (d, 2H, Ar–H). – IR (KBr): ν = 2930, 2834 (C–H), 1759 (C=O), 1216 (Ar–O), 1581, 1510 and 1458 (Ar–H), 975 (*trans*, –CH=CH–) cm^{-1}. – $C_{21}H_{24}O_6$ (372.41): calcd. C 67.73, H 6.50, O 25.78; found C 67.63, H 6.32, O 26.05.

*{4-[(E)-2-(3,4,5-Trimethoxyphenyl)vinyl]phenoxy}acetic acid (**3**)*

2 (0.39 g, 1.0 mmol) and sodium hydroxide (0.20 g, 5 mmol) were dissolved in a mixture of ethanol (20 mL) and water (15 mL), and heated at 50 °C for 10 min. Then the solvent was removed and water (25 mL) was added to dissolve the solid. The solution was washed with dichloromethane (15 mL) and ethyl acetate (15 mL). After acidification with HCl the white precipitate was filtered off (yield: 0.33 g, 91.7 %). M. p. 138 – 140 °C. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.66 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3), 4.56 (s, 2H, CH_2), 6.88 (s, 2H, ArH), 6.90 (d, 2H, ArH), 7.04 (d, 1H, J = 16.2 Hz, CH=CH), 7.14 (d, 1H, J = 16.2 Hz, CH=CH), 7.48 (d, 2H, ArH). – IR (KBr): ν = 3601, 3435 (OH), 2936, 2836 (CH), 1761 (C=O), 1588, 1511 and 1462 (ArH), 1231 (ArO), 957 (*trans*, CH=CH) cm^{-1}. – $C_{19}H_{20}O_6$ (344.13): calcd. C 66.27, H 5.85, O 27.88; found C 64.00, H 5.89, O 26.99.

*Sodium {4-[(E)-2-(3,4,5-trimethoxyphenyl)vinyl]phenoxy} acetate (**4**)*

3 (0.13 g, 0.35 mmol) and sodium hydroxide (0.01 g, 0.25 mmol) were dissolved in water (15 mL) with strong stirring. The residual solid was filtered off and the water solution was concentrated to leave a pale-yellow solid **4** (yield: 0.088 g, 95.7 %. M. p. 263 – 265 °C. – IR (KBr): ν = 2935, 2834 (CH), 1610 (COO^-), 1509 and 1457 (ArH), 1235 (ArO), 953 (*trans*, CH=CH) cm^{-1}.

*Crystal structure determination of **2***

X-Ray diffraction data were collected on a Bruker Smart-1000 CCD diffractometer with graphite-monochromated Mo K_α radiation (λ = 0.71073 Å) by using φ and ω scan techniques. The structure was solved by Direct Methods with SHELXS-97 [23] and refined on F^2 by full-matrix least-squares techniques using SHELXL-97 [24]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were added in calculated positions and refined using a riding model. The crystal used for the diffraction study

showed no decomposition during data collection. The crystal data, experimental details, and refinement results are summarized in Table 1.

CCDC 208115 (**2**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk/data_request/cif.

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