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ORIGINAL PAPER

Synthesis and Crystal Structure of Heptyl 3-(3,4-dihydroxyphenyl)-2-propenoate

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Abstract The title compound, $C_{16}H_{22}O_4$, synthesized by modified Knoevenagel condensation of protocatechualdehyde with monoheptyl-malonate and recrystallized from benzene, was confirmed by single-crystal X-ray diffraction (CCDC 272827). The compound crystallizes in triclinic space group $P\bar{1}$ with cell parameters a = 5.296(3) Å, b = 10.711 (13) Å, c = 13.870(4) Å, $\alpha = 98.84(7)°$, $\beta = 90.97(4)°$, $\gamma = 96.77(7)°$ and Z = 2. The structure is the *E* isomer and its packing is stabilized by intermolecular O–H···O and C–H···O hydrogen bonds.

Keywords Caffeic acid ester · Synthesis · Crystal structure · Knoevenagel condensation · X-ray diffraction

Introduction

Some naturally occurring caffeic acid esters are widely distributed in plant kingdom [1, 2]. Most of them have bioactivities such as antibacterial [3], antiviral [4], anti-inflammatory [5], antiatherosclerotic [6], anti-HIV [4, 7], antitumor [8] and so on. Epidemiological studies indicate that a rich diet in fruits and vegetables reduces cancer risk in humans, suggesting that certain dietary constituents may be effective in preventing cancer [9]. Especially, caffeic acid phenethyl ester (CAPE) have been identified as the major biologically active compounds [10]. Caffeic acid esters have been synthesized previously by methods such as: acid-catalyzed esterification [7a, 11]. alkylation of caffeic acid with halohydrocarbons [2, 12], esterification via acyl chlorides [8a, 13], coupling reaction with DCC as coupling agent [14], transesterification [1, 15] and Wittig reaction [7a, 11b, 16]. Comparing with the reported methods, a more convenient synthetic route was found as outlined in Scheme 1. The properties of caffeic acid esters are affected by the length of ester moiety [17], so the knowledge of the structural characteristic of these analogues is of the utmost importance of the understanding of the quantitative structure–activity relationships (QSARs) underlying their biological activity. Encouraged by the aforementioned information, it was considered valuable to synthesize compound **3** characterized by X-ray studies.

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Experimental

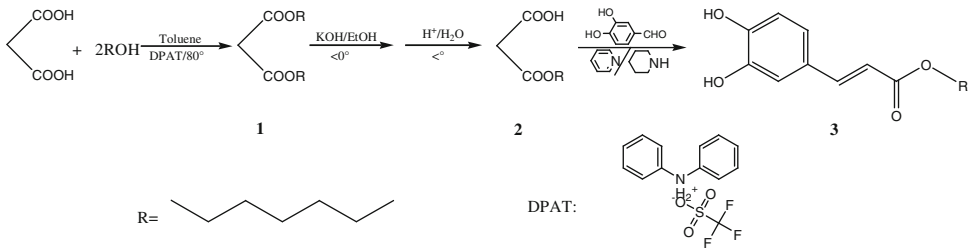
Diheptyl-malonate (**1**)

Malonic acid (10.4 g, 0.1 mol), heptyl alcohol (23.2 g, 0.2 mol) and DPAT (Diphenyammonium triflate) [18] (0.64 g, 0.002 mol) were heated to 80 °C in toluene monitoring by TLC (about 6 h). After evaporation of toluene in vacuum, the crude material was washed with diluted HCl solution, saturated $NaHCO_3$ solution and water respectively to afford diheptyl-malonate 29.5 g (98.3%).

Monoheptyl-malonate (**2**)

KOH (5.6 g, 0.1 mol) in ethanol (64 mL) was added into a solution of diheptyl-malonate (0.1 mol) and absolute ethanol (64 mL) at the temperature below 0 °C in 0.5 h, and

Scheme 1 The synthesis route of caffeic acid heptyl ester



stirred an additional 0.5 h. The white precipitate of monopotassium malonate was collected by suction filtration. The potassium salt was dissolved in 20 mL water cooled to 0 °C, concentrated HCl was added till pH to 2 then was extracted by diethyl ether. After removal of the ether, the monoheptyl-malonate (15.6 g, 77.2%) was obtained.

Heptyl 3-(3,4-dihydroxyphenyl)-2-propenoate (**3**)

3,4-Dihydroxybenzaldehyde (1.4 g, 10 mmol) and monoheptyl malonate (5.1 g, 25 mmol) were dissolved in a mixture of pyridine (5 mL) and piperidine (0.2 mL). The solution was stirred at room temperature for 16.5 h and concentrated in vacuo to give a dark-brown mixture. The mixture was dissolved in diethyl ether (30 mL), washed with saturated $NaHCO_3$ solution, diluted HCl solution and distilled water respectively; then dried with anhydrous $MgSO_4$. The solution was filtered and concentrated to yield a light yellow crystalline product (1.9 g, 68.3%). Recrystallization from a mixture of benzene and diethyl ether (1:1) gave colorless crystalline prisms (m.p. 381–382 K). Single crystals of **3** suitable for X-ray analysis were obtained by slow evaporation from benzene.

IR (KBr)/cm^{-1}: 3489, 3317, 1682, 1604, 1441, 1282; ^{1}H NMR(DMSO-d_6): δ9.57(s, 1H, OH),9.11(s, 1H, OH),7.46(d, 1H, J = 15.9 Hz, α-H), 7.04 (d, 1H, J = 1.9Hz, Ph-H), 7.00 (dd, 1H, J = 1.9, 8.4 Hz, Ph-H), 6.78 (d, 1H, J = 8.1 Hz, Ph-H), 6.25 (d, 1H, J = 15.9 Hz, β-H), 4.10 (t, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.13 (m, 8H, $4CH_2$), 0.86 (t, 3H, CH_3). MS: *m/z* 278(M^+, 67%) 180(100), 163(76), 136(38), 134(47), 89(59), 55(44), 41(59). Anal. Cal. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.43; H, 7.97%.

Crystal Structure Determination of **3**

A single crystal of 3 of dimensions 0.40 × 0.30 × 0.20 mm was chosen for X-ray diffraction studies. The measurements were made on an Enraf-Nonius CAD-4 diffractometer [19] with graphite MoKα monochromated radiation (λ = 0.71073 Å). Intensity data were collected up to a θ_{max} of 25.2° by the $\omega/2\theta$ scan. A total of 3258 reflections were collected, resulting in 2769 independent reflections of which 1145 had $I > 2\sigma(I)$ and these are considered as observed. During data collection three standard reflections were monitored at intervals of 60 min. The ranges of *h, k, l* are $-6 \le h \le 6$, $-1 \le k \le 12$, $-16 \le l \le 16$. The intensities were corrected for Lorentz and polarization effects but not for absorption correction. The details of crystal data and refinement are given in Table 1.

Table 1 Crystal data and experimental crystallographic details

Empirical formula	$C_{16}H_{22}O_4$
Formula weight	278.34
Temperature (K)	293(2)
Wavelength	λ = 0.71073 Å
Crystal system	Triclinic
Space group	P$\bar{1}$
Cell dimensions	
a(Å)	5.296(3)
b(Å)	10.711(13)
c(Å)	13.870(4)
α(°)	98.84(7)
β(°)	90.97(4)
γ(°)	96.77(7)
Volume(Å^3)	771.5(11)
Z	2
Density(calculated) (Mg/m^3)	1.198
Absorption coefficient (mm^{-1})	0.085
F000	300
Crystal size	0.40 × 0.30 × 0.20 mm
θ range for data collection	1.49 to 25.17°
Index ranges	$-6 \le h \le 6$
	$-1 \le k \le 12$
	$-16 \le l \le 16$
Reflections collected	3258/2769 [R(int) = 0.0312]
Independent reflections	2769
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2769/0/182
Goodness-of-fit on F^2	1.020
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0749, wR2 = 0.1937
R indices (all data)	R1 = 0.1785, wR2 = 0.2730
Largest diff. peak and hole (e Å^{-3})	0.464 and −0.336
CCDC deposit no.	272827

Table 2 Bond lengths (Å) and bond angles (°)

Bond length			
O(1)–C(3)	1.372(4)	C(4)–C(5)	1.377(6)
O(2)–C(4)	1.361(5)	C(5)–C(6)	1.369(6)
O(3)–C(9)	1.202(5)	C(7)–C(8)	1.326(6)
O(4)–C(9)	1.335(5)	C(8)–C(9)	1.432(6)
O(4)–C(10)	1.448(5)	C(10)–C(11)	1.518(5)
C(1)–C(6)	1.397(5)	C(11)–C(12)	1.501(5)
C(1)–C(2)	1.400(5)	C(12)–C(13)	1.523(5)
C(1)–C(7)	1.449(5)	C(13)–C(14)	1.497(5)
C(2)–C(3)	1.358(5)	C(14)–C(15)	1.552(6)
C(3)–C(4)	1.395(5)	C(15)–C(16)	1.425(6)
Bond angle			
C(9)–O(4)–C(10)	118.5(3)	C(5)–C(6)–C(7)	123.5(4)
C(2)–C(1)–C(6)	122.4(3)	C(1)–C(6)–C(7)	119.6(3)
C(1)–C(2)–O(1)	124.3(3)	C(8)–C(7)–C(6)	128.2(4)
C(1)–C(2)–C(3)	119.7(4)	C(7)–C(8)–C(9)	122.8(4)
O(1)–C(2)–C(3)	116.0(3)	O(3)–C(9)–O(4)	121.6(4)
O(2)–C(3)–C(4)	119.0(3)	O(3)–C(9)–C(8)	126.6(4)
O(2)–C(3)–C(2)	122.1(4)	O(4)–C(9)–C(8)	111.8(3)
C(4)–C(3)–C(2)	119.0(3)	O(4)–C(10)–C(11)	105.7(3)
C(5)–C(4)–C(3)	121.2(4)	C(14)–C(13)–C(12)	115.3(4)
lC(4)–C(5)–C(6)	120.8(4)	C(13)–C(14)–C(15)	112.3(5)
C(5)–C(6)–C(1)	116.9(3)	C(16)–C(15)–C(14)	116.4(6)

Results and Discussion

The structure was solved by direct methods procedures as implemented in SHELXS97 program [20]. The positions of all the non-hydrogen atoms were included in the full-matrix least-squares refinement using SHELXL97 program [21]. Table 2 gives the bond distances and angles of non-hydrogen atoms respectively. The C15–C16 bond is too short (at 1.425 Å) for a C–C single bond. Maybe it is short because of too much motion at the end of the alkyl chain. Figure 1 represents the ORTEP diagram [22] of the molecule **3** with thermal ellipsoids at 30% probability. H atoms were included at calculated positions and refined using a riding model. H atoms were given isotropic displacement parameters equal to 1.2 times (1.5 times for methyl) the equivalent isotropic displacement parameters of their parent atoms, and C–H distances were set to 0.97 Å for the methylene H atoms, 0.96 Å for the methyl H atoms and 0.93 Å for the remainder. O–H banded to the benzene distances were fixed at 0.83 Å. After refinement, the hydrogen atoms were placed at chemically acceptable positions.

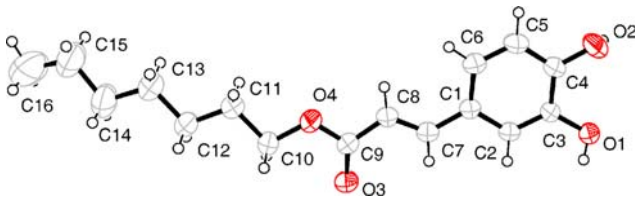


Fig. 1 ORTEP of the molecule at 30% probability

Benzene ring is planar within experimental observation and it makes an angle of 0.6(8)° to the linker (C7–C8–C9–O3). In the case of caffeic esters, the presence of an ethylenic spacer allows the formation of a conjugated system, strongly stabilized through π-electron delocalization. The

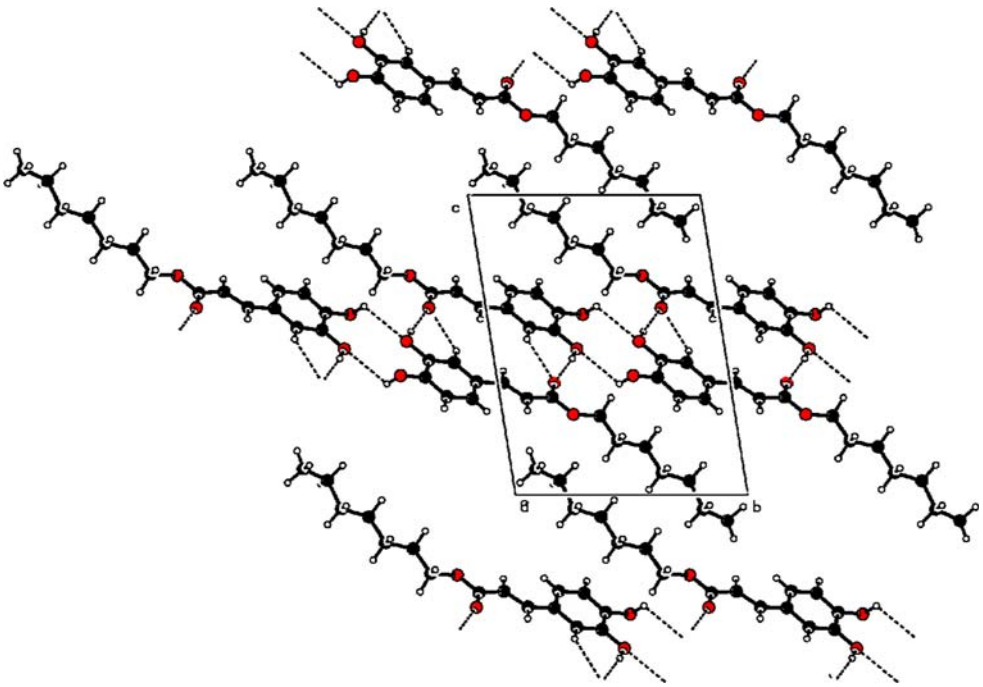


Fig. 2 Packing of the molecules down a axis. Dashed lines represent the hydrogen bonds

Table 3 Hydrogen-bonding geometry (Å, °)

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
O1–H1···O3^{ii}	0.83	1.97	2.790(4)	169.4
O2–H2···O1^{i}	0.83	2.53	2.862(5)	105.2
C2–H2A···O3^{ii}	0.93	2.52	3.227(5)	133.5

Symmetry codes: (i) 1 − x; −1 − y; 1 − z; (ii) −x, −y, 1 − z

bond C7=C8 is a *trans*-double bond (*E* form) which seem to be essential for the cytotoxic activity [12, 23]. The crystal packing (Fig. 2) is stabilized by intermolecular O–H···O and C–H···O hydrogen bonds (Table 3). The molecules of the caffeic acid ester form stacks along the a axis in a head-to head manner to form dimeric structure [24] One dimmer interacts another dimmer with C2–H2A···O3 and O1–H1···O3 hydrogen bonds to form network. The electrostatic factors, molecular hydrogen bonds, *E* conformation, dimeric structure and ester groups in the structure are important determinants for some potent biological activities which are worth to research further.

Supplementary Material

CCDC-272827 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at 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; e-mail: deposit@ccdc.cam.ac.uk.

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