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ORIGINAL PAPER

Synthesis and Crystal Structure of 1,7-Bis(4-methoxyphenyl)-4-(1,3-dithiolan-2-ylidene)-1,6-heptadiene-3,5-dione

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Abstract The synthesis and crystal structure of 1,7-bis(4-methoxyphenyl)-4-(1,3-dithiolan-2-ylidene)-1,6-heptadiene-3,5-dione is described. This compound crystallizes in the space group $P2_1$ with unit cell parameters $a = 14.207$ Å, $b = 7.752(1)$ Å, $c = 19.473(1)$ Å, $\beta = 91.00(3)°$, with two molecules in the asymmetric unit. The ketenedithioacetal functionality present between the carbonyl groups prevents the possibility of keto-enol tautomerization in this compound. The cinnamoyl groups are organized parallel to each other due to the push–pull nature of the ketenedithioacetal functionality.

Keywords Crystal structure · 1,6-Heptadiene-3,5-dione · Curcumin analogue · Ketenedithioacetal · X-ray diffraction

Introduction

The title compound 1,7-bis(4-methoxyphenyl)-4-(1,3-dithiolan-2-ylidene)-1,6-heptadiene-3,5-dione is a derivative of curcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, the main yellow bioactive component of turmeric, which is widely used as a spice in traditional cooking in Asia. Curcuminoids (1,7-diaryl-1,6-heptadiene-3,5-diones) constitute the most important active chemical components in the herbaceous medicinal plant Curcuma longa Linn (turmeric). Extensive work has been done to establish the biological activities and pharmacological actions of turmeric and its extracts. Curcumin (diferuloylmethane) has been shown to have anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, antibacterial, antifungal properties, etc. [1–7]. Natural and synthetic curcuminoid analogues are reported to possess antitumour, antioxidant, antimutagenic and anti-inflammatory activities [8–13]. The synthetic curcuminoid analogue 1,7-bis(4-methoxyphenyl)-1,6-heptadiene-3,5-dione which also shows antitumour activity is closely related to the title compound except for the cyclic ketenedithioacetal substitution at the C(4) position [14]. The structure investigation of the title compound gains considerable attention in this context (Fig. 1).

Curcumin and its analogues usually have a linear structure and they exist in the completely enolized form, with the substituted cinnamoyl groups far apart (5.015 Å in curcumin), as shown by their crystal structures [15, 16]. The crystal studies on 1,6-hexadiene-3,5-dione and 1,6-heptadiene-3,5-dione, having unsubstituted methylene groups show linear structures as should be expected due to the keto-enol tautomerisation [15–19]. The extended conjugation resulting from the enolization contributes to the stability of their linear structure. Crystal structures of 3-aryl-substituted 2,4-pentanedione derivatives are found to exist in enol forms [20, 21] whereas cyclic ketenedithioacetal substitution prevents enolization in 3-(1,3-dithiolan-2-ylidene) pentane-2, 4-dione [22]. In bis (cinnamoyl) ketenedithioacetal, the ketenedithioacetal functionality present between the carbonyl groups prevents the possibility of keto-enol tautomerization observed in enolizable 1,3-carbonyl compounds [23–26]. The crystal structure of the title compound shows

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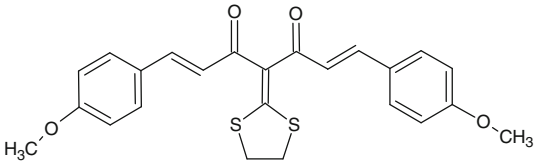

Fig. 1 Structure of the title compound

that the conformational change induced by the simple introduction of the cyclic ketenedithioacetal group brings the double bonds spatially close enough for an effective intramolecular photochemical [2 + 2] cycloaddition. Irradiation of bis(alkenoyl)-ketenedithioacetals in solution leads to facile and stereospecific intramolecular [2 + 2] photocycloadditions resulting in the formation of substituted bicyclo[3.2.0]heptane-2,4-diones, the observed conformational rigidity of which is attributed to the push–pull character of the ketenedithioacetal group [27].

Experimental

Synthesis

Sodium metal (0.45 g, 20 mmol) was dissolved in ethanol (20 ml) to which cyclic ketenedithioacetal (1.01 g, 5 mmol) was added followed by para-methoxy benzaldehyde (10 mmol). The reaction mixture was stirred at 0–5 °C for 4 h. The solid obtained was filtered, washed in ethanol and recrystallized from a mixture of hexane and ethyl acetate to give the title compound.

X-ray Crystallography

Light brown prismatic crystals of the title compound were obtained from acetone–ethyl acetate solution by slow evaporation. The dimension of the crystal used for data collection was 0.18 mm × 0.18 mm × 0.12 mm. The crystals of the compound belong to the monoclinic space group $P2_1$ with unit cell parameters $a = 14.207$ Å, $b = 7.752(1)$ Å, $c = 19.473(1)$ Å, $\beta = 91.00(3)°$. The intensity data were collected up to 2θmax of 69.89° by an Enraf-Nonius CAD-4 diffractometer using crystal monochromated CuKα ($\lambda = 1.5418$ Å) radiation. The $\omega - 2\theta$ scan mode was used. The usual precaution of checking the consistency of the intensities of three strong reflections periodically (every 1 h) for monitoring the stability of the crystal during X-ray exposure was observed. The intensities were corrected for Lorentz and polarization.

The structure was solved by direct methods using SHELXS-97 [28] and all the non-hydrogen atoms were located from the E-map. The structure was refined using SHELXL-97 [28]. The ideal hydrogen atom coordinates

Table 1 Crystal data, intensity collection conditions and refinement parameters for 1,7-bis(4-methoxyphenyl)-4-(1,3-dithiolan-2-ylidene)-1,6-heptadiene-3,5-dione

CCDC no.	763042
Empirical formula	$C_{24}H_{22}O_4S_2$
Formula weight	438.54
Temperature (K)	293(2)
Wavelength (Å)	1.54180
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions (Å, °)	$a = 14.207$, $b = 7.752(1)$, $c = 19.473(1)$, $\beta = 91.00(3)$
Volume (Å^3)	2144.3(3)
Z, calculated density (mg/m^3)	4, 1.358
Absorption coefficient (mm^{-1})	2.486
Absorption correction	Psi-scan [29]
Crystal size (mm)	0.18 × 0.18 × 0.12
F(000)	920
θ Range for data collection (°)	2.27 to 69.89
Index ranges	$0 \le h \le 14$, $0 \le k \le 9$, $-23 \le l \le 23$
Reflections collected/unique	4330/4146 [R(int) = 0.0198]
Completeness to $2\theta = 69.89°$	94.3%
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.098
Data/restraints/parameters	4146/1/666
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0332$, $wR_2 = 0.0815$
R indices (all data)	$R_1 = 0.0396$, $wR_2 = 0.0887$
Extinction coefficient	0.0014(2)
Largest diff. peak and hole (eÅ^{-3})	0.267, −0.198

Table 2 Selected bond lengths (Å) for 1,7-bis(4-methoxyphenyl)-4-(1, 3-dithiolan-2-ylidene)-1, 6-heptadiene-3,5-dione

S(1)–C(20)	1.735(3)	S(1′)–C(20′)	1.741(3)
S(1)–C(21)	1.809(5)	S(1′)–C(21′)	1.809(4)
S(2)–C(20)	1.733(3)	S(2′)–C(20′)	1.742(3)
S(2)–C(22)	1.824(5)	S(2′)–C(22′)	1.813(4)
O(1)–C(3)	1.226(4)	O(1′)-C(3′)	1.224(4)
O(2)–C(5)	1.222(4)	O(2′)–C(5′)	1.225(4)
O(3)–C(17)	1.372(4)	O(3′)–C(17′)	1.368(4)
O(3)–C(23)	1.418(5)	O(3′)–C(23′)	1.432(6)
O(4)–C(11)	1.361(4)	O(4′)–C(11′)	1.371(4)
O(4)–C(24)	1.434(5)	O(4′)–C(24′)	1.435(5)
C(21)–C(22)	1.466(7)	C(21′)–C(22′)	1.499(7)
C(2)–C(3)	1.471(5)	C(2′)–C(3′)	1.484(4)
C(3)–C(4)	1.477(4)	C(3′)–C(4′)	1.473(4)
C(4)–C(20)	1.386(5)	C(4′)–C(20′)	1.385(4)
C(4)–C(5)	1.481(4)	C(4′)–C(5′)	1.476(4)
C(5)–C(6)	1.474(5)	C(5′)–C(6′)	1.473(5)

Table 3 Selected bond angles (°) of 1,7-bis(4-methoxyphenyl)-4-(1,3-dithiolan-2-ylidene)-1,6-heptadiene-3,5-dione

C(20)–S(1)–C(21)	96.2(2)	C(20′)–S(1′)–C(21′)	96.1(2)
C(20)–S(2)–C(22)	95.7(2)	C(20′)–S(2′)–C(22′)	96.5(2)
C(2)–C(1)–C(14)	127.7(3)	C(2′)–C(1′)–C(14′)	126.0(3)
C(1)–C(2)–C(3)	120.3(3)	C(1′)–C(2′)–C(3′)	120.2(3)
C(2)–C(3)–C(4)	120.7(3)	C(2′)–C(3′)–C(4′)	119.5(3)
C(20)–C(4)–C(3)	118.2(3)	C(20′)–C(4′)–C(3′)	118.0(3)
C(20)–C(4)–C(5)	118.2(3)	C(20′)–C(4′)–C(5′)	118.5(3)
C(3)–C(4)–C(5)	123.5(3)	C(3′)–C(4′)–C(5′)	123.5(3)
C(6)–C(5)–C(4)	120.1(3)	C(6′)–C(5′)–C(4′)	121.5(3)
C(7)–C(6)–C(5)	120.1(3)	C(7′)–C(6′)–C(5′)	119.8(3)
C(6)–C(7)–C(8)	127.8(3)	C(6′)–C(7′)–C(8′)	129.6(3)
O(4)–C(11)–C(10)	115.1(3)	O(4′)–C(11′)–C(10′)	124.5(3)
O(3)–C(17)–C(18)	115.2(4)	O(3′)–C(17′)–C(18′)	124.1(3)
S(1)–C(20)–S(2)	114.3(2)	S(1′)–C(20′)–S(2′)	113.9(2)
C(22)–C(21)–S(1)	108.0(4)	C(22′)–C(21′)–S(1′)	107.5(3)
C(21)–C(22)–S(2)	108.2(3)	C(21′)–C(22′)–S(2′)	107.2(3)

were calculated by the program and were made to ride on the coordinates and temperature factors of the respective carbon atoms. The refinement was continued until the maximum shift/e.s.d was 0.000. The final difference map was featureless with maximum and minimum electron densities at 0.267 and -0.198 eÅ^{-3}, respectively. The crystal data, intensity collection conditions and refinement parameters are presented in Table 1. Selected bond lengths and bond angles are given in Tables 2 and 3, respectively.

Results and Discussion

The substituted cinnamoyl groups are arranged parallel to each other in the title compound. The carbon atoms C(2) and C(6), α to the carbonyl groups, are separated by 2.903(4) Å in molecule 1 and 2.862(4) Å in molecule 2 (Fig. 2). The parallel alignment of the cinnamoyl groups apparently results from the push–pull nature of the ketene dithioacetal moiety. Due to the electron releasing nature of the ketene dithioacetal functionality, the oxygen atoms of the carbonyl groups develop partial negative charges while the sulphur atoms develop partial positive charges. This would bring the ketene dithioacetal group and the carbonyl groups into the same plane, forming a relatively more stable conformation. The sulphur atoms S(1) & S(2) are close to the oxygen atoms O(1) & O(2), respectively. The non-bonded distances between these atoms are O(1)–S(1) = 2.591(3) Å, O(2)–S(2) = 2.575(2) Å, O(1)′–S(1)′ = 2.613(2) Å, O(2)′–S(2)′ = 2.565(2) Å. Thus the ketene dithioacetal functionality organizes the cinnamoyl groups parallel and close to each other. Bond lengths and angles in this compound are comparable with those reported for other curcumin analogues [19, 23, 27, 30–32]. The *push–pull* character of polarized ketenedithioacetal group can bring about favorable spatial relationships between the double bonds of bis(cinnamoyl)ketenedithioacetals to effect efficient and stereospecific intramolecular photochemical [2 + 2] cycloadditions in solution [27].

The two phenyl rings [C(8)–C(15)–C(16)–C(17)–C(18)–C(19) and C(9)–C(10)–C(11)–C(12)–C(13)–C(14)] are inclined at an angle of 35.06° and 32.83° with the dithiolan ring [S(2)–C(20)–S(1)–C(21)–C(22)] in molecule 1 and 24.83° and 33.06° in molecule 2. The methoxy substitutions in both the molecules lie close to the plane of the ring to which they substitute as seen from the torsion angles C24–O4–C11–C12 and C23–O3–C17–C16 in molecule 1 and C24′–O4′–C11′–C10′and C23′–O3′–C17′–C18′ in molecule 2 (Table 4). The five member rings, S(2)–C(20)–S(1)–C(21)–C(22) in molecule 1 and S(2)′–C(20)′–S(1)′–C(21)′–C(22)′ in molecule 2, have the distorted half chair conformation which are twisted on C(21)–C(22) and C(21)′–C(22)′ bonds respectively. A similar conformation is also observed for other compounds with a dithiolane ring substitution [30, 32].

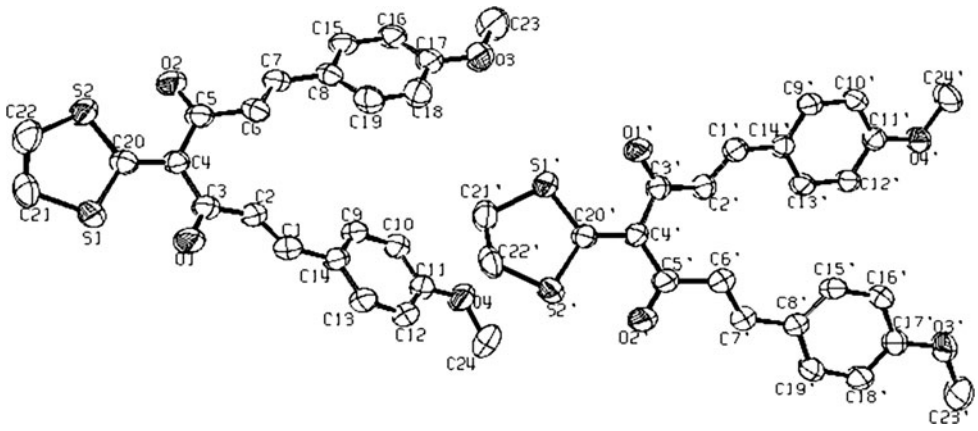

Fig. 2 ORTEP drawing of 1, 7-bis(4-methoxyphenyl)-4-(1, 3-dithiolan-2-ylidene)-1, 6-heptadiene-3,5-dione

Table 4 Selected torsion angles (°)

O1–C3–C4–C20	19.7(6)	O1′–C3′–C4′–C20′	−22.4(6)
C20–C4–C5–O2	15.2(6)	C20′–C4′–C5′–O2′	−9.2(6)
C24–O4–C11–C12	−4.3(6)	C24′–O4′–C11′–C12′	177.6(4)
C24–O4–C11–C10	174.8(4)	C24′–O4′–C11′–C10′	−2.1(6)
C23–O3–C17–C16	−2.2(8)	C23′–O3′–C17′–C16′	−177.2(5)
C23–O3–C17–C18	178.1(5)	C23′–O3′–C17′–C18′	2.4(7)
C5–C4–C20–S2	−2.7(5)	C5′–C4′–C20′–S2′	3.2(5)
C3–C4–C20–S1	−2.5(5)	C3′–C4′–C20′–S1′	3.7(5)

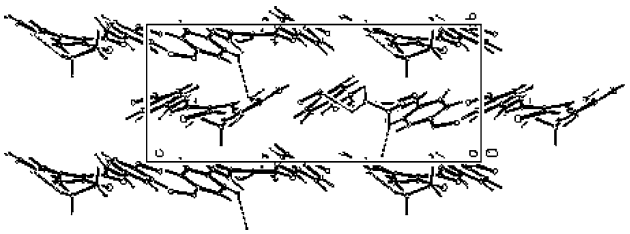

Fig. 3 Packing of molecules down *a*-axis

Table 5 Hydrogen bonding parameters

Donor–H···acceptor	Symm	H···A (Å)	D···A (Å)	D–H···A (°)
C(2)′–H(2)′···O(1)	*x*, *y*, *z*	2.5852	3.4165	142.26
C(21)′–H(21D)···O(4)′	1 + *x*, *y*, *z*	2.3782	3.3332	153.68

The title compound, though symmetric in solution, is asymmetric in the crystal with two molecules in the asymmetric unit. The absence of symmetry in the molecule in the crystal form may be attributed to the crystal packing forces. The packing of the molecules of the compound is shown in Fig. 3. The two phenyl planes make an angle of 30.75° between them in molecule 1 and 13.73° in molecule 2. There is probable hydrogen bonding between carbon atom C(2) in molecule 1 and carbonyl oxygen O(1)′ in molecule 2 and also between carbon atom of the dithiolan ring C(21)′ and the oxygen atom O(4)′ of the methoxy group at the symmetry position 1 + *x*, *y*, *z*. The hydrogen bonding parameters are given in Table 5. An increased number of short contacts may be a reason for its asymmetry observed in the crystal structure.

Conclusion

The title compound crystallized in the space group $P2_1$ with two molecules in the asymmetric unit. The ketene dithioacetal functionality present in the compound prevents the possibility of keto-enol tautomerization. The push–pull nature of polarized ketenedithioacetal group organizes the cinnamoyl groups close and parallel to each other. The five member rings, S(2)–C(20)–S(1)–C(21)–C(22) in molecule 1 and S(2)′–C(20)′–S(1)′–C(21)′–C(22)′ in molecule 2, are in a distorted half chair conformation.

Supplementary material

All crystallographic data for this paper are deposited with the Cambridge Crystallographic Data Centre (CCDC No. 763042). The data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from 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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