Crystal Structure of the Curcumin Derivative, Acetic Acid 4-[7-(4-Acetoxy-3-methoxyphenyl)-3,5-dioxoheptyl]-2-methoxyphenyl ester

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C₂₅H₂₈O₈ is monoclinic, $P2_1$. The unit-cell dimensions at 293 K are $a = 8.054(1)$, $b = 9.438(2)$, $c = 15.701(1)$ Å, $\beta = 98.875(2)^\circ$, $V = 1179.1(2)$ Å³, $D_x = 1.286$ g/cm³, and $Z = 2$. The R value is $R = 0.046$ for 4152 reflections. There is an intramolecular hydrogen bond with an O2...O1 distance of 2.496(1) Å. The molecules in the crystal are packed at the normal van der Waals distances.

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Curcumin **1** is a compound of natural origin, isolated from several curcuma species (*Curcuma longa*, *Curcuma zedoaria*, etc.). Curcumin enriched powder is extensively employed as a condiment and coloring agent in the culinary field. It is well known in the traditional medicine in several parts of Asia and it has extended its use to other continents. The antioxidative and antitumoral,¹⁻³ activities of curcumin have been reported, as well as its anticancer activity.

Curcumin exerts inhibitory effects in the formation of β -amyloids, which have been associated with Alzheimer disease.⁴ In addition, other studies have revealed enzyme that curcumin has some effect against integrase enzyme (IN) of HIV-1.⁵ As a part of our investigations about new semi synthetic derivatives of curcumin, we report the X-ray structure determination of a curcumin derivative, acetic acid 4-[7-(4-acetoxy-3-methoxyphenyl)-3,5-dioxoheptyl]-2-methoxyphenyl ester **3**. This compound was prepared by catalytic hydrogenation of **2**, this latter compound was obtained from the acetylating of curcumin **1** technical grade from Aldrich as depicted in Scheme 1.

X-ray data for crystals of the title compound were collected by graphite-monochromatized Mo K_α radiation at 293 K. No absorption correction was applied. The structure was solved by direct methods and refined by full-matrix least-squares with anisotropic temperature factors for the non-hydrogen atoms. C6 and C7 show two atomic positions with occupancy factors for C6, C6B, C7 and C7B of 0.50, respectively. The value of $(\Delta\rho)_{\max}$ is 0.386 quite high and may be due to molecular disorder present at C6 and C7. The positions of all H atoms were calculated geometrically and a riding model was used in their refinement, with C-H distances in the range of 0.85 – 0.98 Å and $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$. The software used to prepare the material for publication was PARST97.⁶ Table 1 summarizes the crystal and experimental data. The molecular structure is

shown in Fig. 1. The bond lengths for non-H atoms are listed in Table 2.

The molecule may be described as consisting of tri-substituted planar rings interconnected through the 3,5-dioxoheptyl moiety. The two terminal groups are identical but the inherent symmetry

Table 1 Crystal and experimental data

Formula: C ₂₅ H ₂₈ O ₈	
Formula weight = 456.47	
Crystal system: monoclinic	
Space group: $P2_1$	$Z = 2$
$a = 8.054(1)$ Å	
$b = 9.438(2)$ Å	
$c = 15.701(1)$ Å	
$\beta = 98.875(2)^\circ$	
$V = 1179.1(2)$ Å ³	
$D_x = 1.286$ g/cm ³	
μ (Mo K_α) = 0.096 mm ⁻¹	
$T = 293$ K	
Colorless	
$F(000) = 484$	
$0.21 \times 0.12 \times 0.06$ mm	
Radiation: Mo K_α	
ω scans with $\theta_{\max} = 25.0^\circ$	
$R = 0.046$ (on F^2)	
$wR = 0.059$ (on F^2)	
$(\Delta\rho)_{\max} = 0.386$	
$(\Delta\rho)_{\max} = 0.115$ e Å ⁻³	
$(\Delta\rho)_{\min} = -0.118$ e Å ⁻³	
No. of reflections measured = 9757	
No. of reflections used = 4152	
No. of parameters = 324	
Goodness-of-fit = 0.973	
Measurement: Bruker Smart Apex CCD diffractometer	
Program system: SMART V 5.625 and SAINT V 6.23C	
Structure determination: direct methods (SHELXS-97)	
Refinement: full matrix least-squares (SHELXL-97)	

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Table 2 Final atomic coordinates and equivalent isotropic temperature factors ($\text{\AA}^2$)

Atom	x	y	z	U_{eq}
O1	0.4096(4)	-0.0315(4)	0.8096(2)	0.1261(12)
O2	0.1237(3)	-0.0453(4)	0.72218(19)	0.0963(9)
O3	-0.5934(3)	-0.0785(3)	0.40498(16)	0.0844(8)
O4	-0.5570(3)	0.0952(2)	0.27382(14)	0.0710(7)
O5	-0.6721(4)	0.2413(3)	0.3597(2)	0.1310(13)
O6	1.3075(3)	0.4484(3)	0.91124(16)	0.0880(8)
O7	1.2297(3)	0.6729(3)	0.89387(19)	0.1010(10)
O8	1.0882(3)	0.4517(3)	1.02147(18)	0.0922(9)
C1	0.6397(5)	0.2495(4)	0.8071(3)	0.0939(14)
C2	0.6221(5)	0.1122(4)	0.7725(3)	0.140(2)
C3	0.4485(5)	0.0540(5)	0.7548(4)	0.0964(15)
C4	0.3353(6)	0.0905(4)	0.6838(3)	0.0938(14)
C5	0.1748(6)	0.0398(4)	0.6700(3)	0.0857(14)
C6	0.0291(18)	0.0825(10)	0.6011(8)	0.067(3)
C7	0.017(2)	-0.0152(16)	0.5237(8)	0.074(3)
C6B	0.101(4)	0.066(3)	0.5746(17)	0.081(7)
C7B	-0.043(3)	-0.029(4)	0.556(3)	0.091(10)
C8	-0.1447(5)	0.0141(4)	0.4621(3)	0.0770(12)
C9	-0.2998(5)	-0.0476(4)	0.4674(2)	0.0740(10)
C10	-0.4376(5)	-0.0213(3)	0.4059(2)	0.0616(10)
C11	-0.4211(4)	0.0695(4)	0.3398(2)	0.0582(9)
C12	-0.2709(5)	0.1279(4)	0.3320(2)	0.0792(12)
C13	-0.1323(5)	0.0997(4)	0.3927(3)	0.0835(12)
C14	-0.6121(4)	-0.1726(5)	0.4709(2)	0.1019(15)
C15	-0.6777(5)	0.1852(4)	0.2920(3)	0.0753(12)
C16	-0.8152(4)	0.2031(4)	0.2181(2)	0.0918(13)
C17	1.1403(5)	0.4034(4)	0.8842(3)	0.0693(11)
C18	1.0293(5)	0.4016(4)	0.9416(3)	0.0653(11)
C19	0.8688(4)	0.3530(3)	0.9166(2)	0.0707(11)
C20	0.8158(5)	0.3047(4)	0.8339(3)	0.0704(11)
C21	0.9302(5)	0.3111(4)	0.7756(3)	0.0821(13)
C22	1.0925(5)	0.3587(4)	0.8014(3)	0.0836(13)
C23	0.9698(4)	0.4825(4)	1.0762(2)	0.0985(14)
C24	1.3365(5)	0.5891(5)	0.9169(2)	0.0746(12)
C25	1.5098(4)	0.6204(4)	0.9547(2)	0.1014(15)

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} (a_i^* a_j^*) (a_i \cdot a_j)$$

Table 3 Bond distances ($\text{\AA}$)

O1 - C3	1.253(5)	O2 - C5	1.261(4)
O3 - C10	1.364(3)	O3 - C14	1.390(4)
O4 - C15	1.354(4)	O4 - C11	1.408(3)
O5 - C15	1.183(4)	O6 - C24	1.349(4)
O6 - C17	1.414(4)	O7 - C24	1.183(4)
O8 - C18	1.355(4)	O8 - C23	1.409(3)
C1 - C2	1.404(4)	C1 - C20	1.508(4)
C2 - C3	1.488(5)	C3 - C4	1.371(5)
C4 - C5	1.364(5)	C5 - C6	1.522(10)
C6 - C7	1.52(2)	C7 - C8	1.520(14)
C8 - C13	1.372(5)	C8 - C9	1.392(4)
C9 - C10	1.377(4)	C10 - C11	1.367(4)
C11 - C12	1.352(4)	C12 - C13	1.378(4)
C15 - C16	1.484(4)	C17 - C22	1.363(4)
C17 - C18	1.364(4)	C18 - C19	1.371(4)
C19 - C20	1.380(4)	C20 - C21	1.397(5)
C21 - C22	1.383(4)	C24 - C25	1.460(4)

of the molecule is distorted by a rotation of $-101.0(5)^\circ$ about the C2 - C3 bond. The dihedral angles between the 3,5-dioxoheptyl moiety and phenyl rings [C8 to C13 and C17 - C22] are $4.2(1)^\circ$ and $47.7(1)^\circ$, respectively.

The molecule is stabilized by the formation of an intramolecular hydrogen bond between the 2-hydroxyl group

Scheme 1

Fig. 1 Molecular structure of acetic acid 4-[7-(4-acetoxy-3-methoxyphenyl)-3,5-dioxoheptyl]-2-methoxyphenyl ester with atom labeling. Thermal ellipsoids are drawn at the 50% probability level.

and the carbonyl oxygen, O1. The H2...O1 distance is $1.57 \text{ \AA}$ and the O2-H2...O1 angle is 138° . Apart from the O...O intramolecular interactions, the molecules in the crystal are packed at normal van der Waals distances.

The detailed experimental conditions for the preparation of the tetrahydrogenated derivative will be published elsewhere.

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References

1. M. Y. Marion and F. Dunne, in "Food Phytochemicals for Cancer Prevention II; Teas, Spices, and Herbs," ed. C.T. Ho, T. Osawa, M.T. Huang, and R. T. Rosen, American Chemical Society, Washington, D. C., **1994**, 223.
2. D. L. Flynn, T. R. Belliotti, A. M. Boctor, D. T. Connor, C. R. Kostlon, D. E. Nies, D. F. Ortwine, D. J. Schirier, and J.C. Sircar, *J. Med. Chem.*, **1991**, 34, 518.
3. L. R. Barclay and M. R. Vinquist, *Org. Lett.*, **2000**, 18, 2841.
4. S. Y. Park and D. S. Kim, *J. Nat. Prod.*, **2002**, 65, 1227.
5. Mazumder, N. Neamati, S. Sunder, J. Schulz, H. Pertz, E. Eich, and Y. Pommier, *J. Med. Chem.*, **1997**, 40, 3057.
6. M. Nardelli, *J. Appl. Cryst.*, **1995**, 28, 659.