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Curcumin and derivatives

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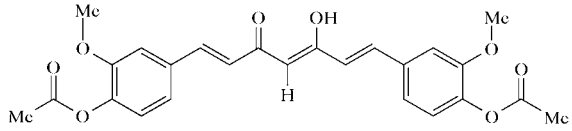
The title compound, 4-[7-(4-acetoxy-3-methoxyphenyl)-5-hydroxy-3-oxohepta-1,4,6-trienyl]-2-methoxyphenyl acetate [or bis(acetoxy)curcumin, $C_{25}H_{24}O_8$], is shown unequivocally to exist in the keto–enol form, with only intramolecular hydrogen bonding. A redetermination of the structure of curcumin itself confirms the results of a previous report that it also exists in the keto–enol form.

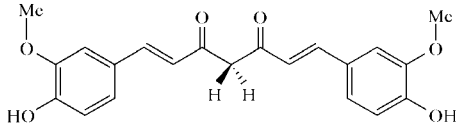
Comment

The active yellow pigment in turmeric, a popular spice and coloring agent for cosmetics and pharmaceuticals, is curcumin [often named diferuloylmethane or sometimes 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, (II*a*)]. Recently, curcumin has attracted considerable interest because of its demonstrated ability to act as a cancer chemopreventive agent (Leu & Maa, 2002; Surh, 2003; Conney, 2003). It has also been found to inhibit the cytochrome P450-dependent activation of aflatoxin B_1 (Lee *et al.*, 2001), to be an irreversible inhibitor of aminopeptidase N (CD13) (Shim *et al.*, 2003), to inhibit the MRP1 and MRP2 efflux transporters (Wortelboer *et al.*, 2003) and to correct cystic fibrosis defects in a mouse model (Egan *et al.*, 2004). We have been investigating derivatives of curcumin as cancer chemoprotective agents and report here the structure of the bis(acetoxy) derivative (I).

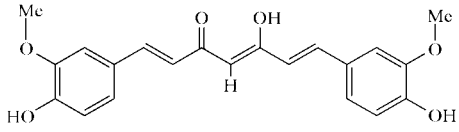
A perspective view of (I) is given in Fig. 1, which, together with the data in Table 1, clearly indicates that (I) exists in the keto–enol form in the crystal structure. Difference maps calculated in the latter stages of refinement show the two largest peaks to be in appropriate positions to correspond to one H atom on atom C13 and a H atom on atom O5. A smaller peak near O4 suggests that the enol H atom is disordered between O4 and O5 as has also been found for curcumin itself (*vide infra*). Although these are included as riding contributions in the subsequent refinement, it is abundantly clear that there is only one H atom attached to atom C13 and that there is also clearly an adjacent hydroxy group. Further evidence for the formulation of (I) in the keto–enol form comes from the facts (Table 1) that the C12—O4 distance is significantly shorter than the C14—O5 distance ($\Delta/\sigma = 8.8$) and the C12—C13 distance is significantly longer than the C13—C14 distance ($\Delta/\sigma = 8$). The aliphatic chain (C10–C16) is largely untwisted, as indicated by the relevant torsion angles (Table 1), while the benzene rings are inclined to a modest extent with respect to the mean plane of this unit. The conformation of the aliphatic chain is determined in part by the existence of a strong intramolecular hydrogen bond between the hydroxy and keto groups [H5O and O4 (major component) or H4O and O5 (minor component); Table 2]. The acetoxy groups are significantly twisted with respect to the mean planes of the benzene rings.



(I)



(II*a*)



(II*b*)

In a review of molecular mechanisms for the antitumorigenic effect of curcumin (Leu & Maa, 2002), its structure is explicitly described in terms of the β-diketone, (II*a*), and keto–enol, (II*b*), tautomers; these authors recognized that, with curcumin as well as with (I), the keto–enol form is of potential importance to the solution reactivity of curcumin. Indeed, a determination of the structure of curcumin (Tonnesen *et al.*, 1982) found it to be (II*b*), although the keto and enol groups were disordered. We have redetermined the structure of curcumin using a sample of commercial material (Fluka 28260) recrystallized from ethanol (Mague *et al.*, 2004) and find, apart from that fact that our crystals are bright yellow while those used by Tonnesen *et al.* (1982) were reported to be dark red, an identical structure. As with (I), a difference map calculated with all atoms except the two H

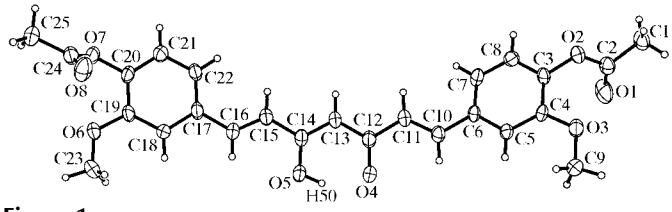


Figure 1
A perspective view of (I). Only one location of the disordered hydroxy H atom is shown. Displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn arbitrarily small.

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atoms associated with the keto–enol unit included showed unequivocally that there is only one H atom attached to the central C atom and that the other is disordered between the two O atoms. It thus seems clear that, at least in the solid state, curcumin and its bis(acetoxy) derivative exist wholly in the keto–enol form. Despite structural evidence dating from 1982 that the keto–enol tautomer is of importance and two papers explicitly describing curcumin and derivatives in this form (Leu & Maa, 2002; Ireson *et al.*, 2002), many current discussions of curcumin (Surh, 2003; Conney, 2003; Lee *et al.*, 2001), as well as the drawings provided by the Cambridge Structural Database [Allen (2002); refcode BINMEQ for the Tonnesen *et al.* (1982) structure and refcode BINMEQ01 for a subsequent redetermination (Ishigami *et al.*, 1999)], have shown it solely as the β-diketone tautomer. This extends to two highlight news stories on useful biological activities of curcumin (Dalton, 2003; Halford, 2004). We consider it particularly important to emphasize that, as illustrated by the structures of (I) and (II), curcumin tends to exist in the tautomeric keto–enol form. Thus, investigators studying molecular mechanisms responsible for the varied biological effects of curcumin and its derivatives or those modeling their interactions with proteins should be aware of this property, since this structural feature may be involved in the action of curcumin as an inhibitor of the Zn-dependent aminopeptidase N (CD13) (Shim *et al.*, 2003) and/or its ability to correct cyctic fibrosis defects, perhaps by reducing the effective concentration of calcium ion in the lumen of the endoplastic reticulum (Egan *et al.*, 2004).

Experimental

Compound (I) was prepared according to a literature method (Gomes & Vilela, 2002) and recrystallized from chloroform/hexane. The product was characterized by comparison of its ^{1}H NMR and IR spectra with those in the literature.

Crystal data

$C_{25}H_{24}O_8$
M_r = 452.44
Monoclinic, $P2_1$
a = 8.841 (2) Å
b = 7.746 (1) Å
c = 16.326 (3) Å
β = 98.092 (2)°
V = 1106.9 (4) Å^3
Z = 2
D_x = 1.357 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4191 reflections
θ = 2.3–28.3°
μ = 0.10 mm^{-1}
T = 100 (2) K
Plate, yellow
0.22 × 0.19 × 0.05 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002)
T_{min} = 0.948, T_{max} = 0.995
9606 measured reflections
2794 independent reflections
2222 reflections with $I > 2\sigma(I)$
R_{int} = 0.051
θ_{max} = 27.9°
$h = -11 \rightarrow 11$
$k = -10 \rightarrow 9$
$l = -21 \rightarrow 21$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.113
S = 1.03
2794 reflections
304 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0576P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O4—C12	1.274 (4)	C12—C13	1.412 (4)
O5—C14	1.306 (3)	C13—C14	1.384 (4)
C10—C11	1.330 (4)	C14—C15	1.457 (4)
C11—C12	1.469 (4)	C15—C16	1.327 (4)
O4—C12—C13	121.4 (3)	O5—C14—C13	121.5 (3)
O4—C12—C11	120.1 (2)	O5—C14—C15	118.0 (2)
C13—C12—C11	118.6 (3)	C13—C14—C15	120.5 (3)
C14—C13—C12	121.6 (3)		
C2—O2—C3—C4	70.1 (4)	C13—C14—C15—C16	176.2 (3)
C7—C6—C10—C11	−21.5 (5)	C14—C15—C16—C17	−179.5 (3)
C6—C10—C11—C12	179.0 (3)	C15—C16—C17—C22	16.0 (6)
C10—C11—C12—C13	165.7 (3)	C24—O7—C20—C19	73.3 (4)
C12—C13—C14—C15	−177.7 (3)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O4—H4O···O5	0.82	1.80	2.541 (3)	149
O5—H5O···O4	0.84	1.81	2.541 (3)	145

H atoms were placed in calculated positions (C—H = 0.95–0.99 Å), except for the disordered hydroxy H atom (H4O/H5O), whose alternate locations were those derived from a difference map. All H atoms were included as riding atoms, with isotropic displacement parameters of 1.2–1.5 times those of the attached atoms. The absolute structure could not be determined reliably and Friedel pairs were averaged.

Data collection: *SMART* (Bruker, 2000); cell refinement: *SMART*; data reduction: *SAINT-Plus* (Bruker, 2004); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2000); software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1497). Services for accessing these data are described at the back of the journal.

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