

6,6'-Dimethoxygossypolone

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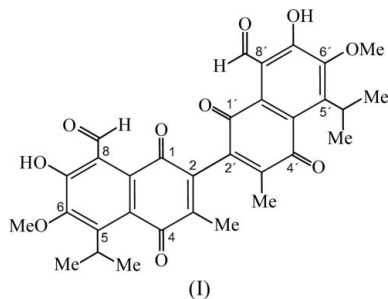
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6,6'-Dimethoxygossypolone (systematic name: 7,7'-dihydroxy-5,5'-diisopropyl-6,6'-dimethoxy-3,3'-dimethyl-1,1',4,4'-tetraoxo-2,2'-binaphthalene-8,8'-dicarbaldehyde), C₃₂H₃₀O₁₀, is a dimeric molecule formed by oxidation of 6,6'-dimethoxygossypol. When crystallized from acetone, 6,6'-dimethoxygossypolone has monoclinic (*P*2₁/*c*) symmetry, and there are two molecules within the asymmetric unit. Of the four independent quinoid rings, three display flattened boat conformations and one displays a flattened chair/half-chair conformation. The angles between the planes of the two bridged naphthoquinone structures are fairly acute, with values of about 68 and 69°. The structure has several intramolecular O—H···O and C—H···O hydrogen bonds and several weak intermolecular C—H···O hydrogen bonds, but no intermolecular O—H···O hydrogen bonds.

Comment

Gossypol is a disesquiterpene of the cotton plant that is of research interest because of its wide sphere of bioactivity (Wang *et al.*, 2009). Gossypolone is prepared from gossypol by mild oxidation with ferric chloride (Haas & Shirley, 1965). Like its parent compound, gossypolone exhibits anticancer and antifungal effects (Paizieva *et al.*, 1977; Dao *et al.*, 2000).



As part of an effort to generate related compounds of this family, 6,6'-dimethoxygossypol was isolated from cotton roots (Dowd & Pelitire, 2006) and oxidized to prepare 6,6'-dimethoxygossypolone, (I), which was then crystallized and studied by X-ray diffraction (Fig. 1).

Like gossypol and gossypolone, (I) exists in the aldehyde tautomeric form. The aldehyde groups are oriented coplanar with the extended naphthalene ring planes, which allows for the formation of O—H···O hydrogen bonds between the O3 and O8 hydroxy H atoms and the carbonyl O atoms (Table 1), and the formation of C—H···O hydrogen bonds between the formyl H atoms and quinoid ring atoms O1 and O6. This tautomerization, orientation and basic pattern of hydrogen bonding are also observed in related gossypol and gossypolone crystal structures (Talipov *et al.*, 1995; Gdaniec *et al.*, 1996). The isopropyl groups of (I) are oriented with the single H atoms of the ternary C atoms lying close to the extended naphthalene ring planes, and such that the methyl groups are directed outward and away from the center of the molecule. This orientation gives torsion angles involving the H atoms of the ternary C atoms close to either 0 or 180°, depending on the naphthalene ring atom used to define the angle (Table 2). This orientation is supported by intramolecular C—H···O hydrogen bonds formed between the H atoms of the ternary C atoms and quinoid ring atoms O5 and O10, as well as by several C—H···O interactions formed between the H atoms of the isopropyl methyl groups and the methoxy O atoms at the 6- and 6'-positions. A similar orientation of the isopropyl groups is observed in the crystal structures of hemigossypolone and gossypolone. It is also observed in most, but not all, gossypol crystal forms (Talipov *et al.*, 1995; Gdaniec *et al.*, 1996).

Compound (I) also exhibits structural differences with gossypol, gossypolone and other substituted 1,4-naphtho-

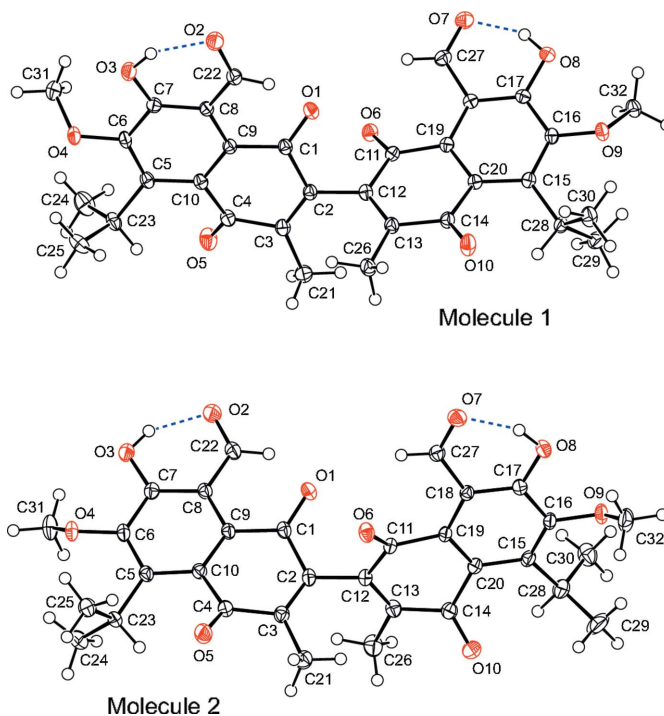
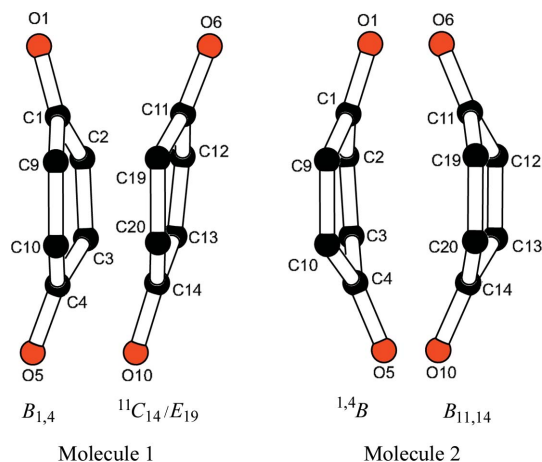


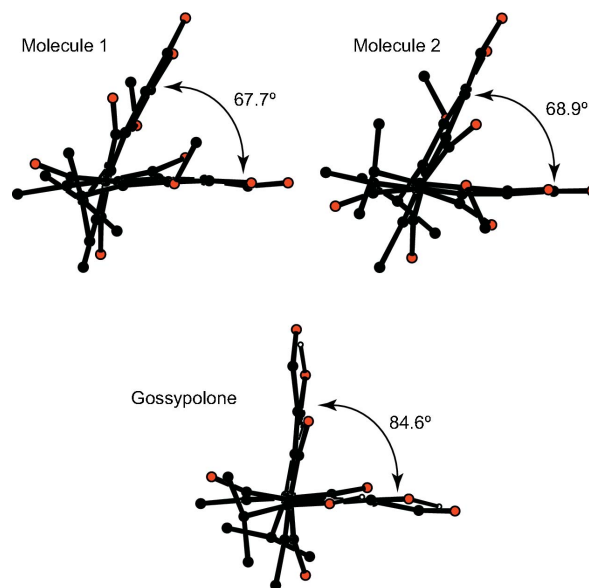
Figure 1
The molecular structure and atom numbering of the two independent molecules of (I). Displacement ellipsoids are drawn at the 50% probability level. Intramolecular O—H···O hydrogen bonds are shown as dashed lines.

**Figure 2**

The puckering of the four independent quinoid rings in the crystal structure of (I).

quinones. All gossypol and most 1,4-naphthoquinone structures, including the bridged 2,2'-binaphtho-1,4-quinone (Ammon *et al.*, 1969), have their naphthalene or naphthoquinone rings in close to planar conformations. In contrast, the quinoid rings in gossypolone-type structures exhibit a modest degree of puckering. In hemigossypolone, the quinoid ring has a flattened boat conformation, with a Cremer–Pople (Cremer & Pople, 1975) puckering amplitude (Q) of 0.222 (6) Å and orientation angles θ and φ of 109 (1) and 15 (2)°, respectively. In gossypolone, the quinoid rings also have flattened boat conformations, with $Q = 0.213$ (4) Å and θ and φ angles of 104 (1) and 356 (1)°, respectively. In the Cremer–Pople system for describing six-atom ring puckering, Q is a measure of the average displacement of the ring atoms away from a best-fit plane, φ describes where the puckering occurs around the ring and θ is an inversion angle that accounts for the possibility of inverted ring forms. In this system, boat conformers have θ angles near 90°, with φ angles near 0, 60, 120, 180, 240 or 300°. In (I), three of the four quinoid rings are found in a flattened boat conformation (Fig. 2), with Q values between 0.25 and 0.31 Å, θ angles between 83 and 92°, and φ angles near either 0 or 180° (Table 3). The fourth ring, however, has a different conformation. This ring has an angle of 35.0 (6)°, which is between that of an ideal chair form with $\theta = 0^\circ$ and an ideal half-chair form with $\theta = 40.8^\circ$ (Cremer & Szabo, 1995). The observed ring puckering appears to occur because of 1,3-steric interactions between the O atoms of the quinoid rings and the formyl and isopropyl groups at the naphthalene 5- and 8-positions.

In related 1,4-naphthoquinone structures, specific substitutions at both the 5- and 8-positions appear to be necessary to observe puckering within the quinoid ring. A single C-, N- or Cl-atom substituent at either of these positions, *e.g.* as found in 5-chloro-1,4-naphthoquinone (Scheringer, 1973), 5-acetamido-2,3-dimethyl-1,4-naphthoquinone (Feldman *et al.*, 2007) or dimethyl 7-hydroxy-1,4-naphthoquinone-6,8-dicarboxylate (Furuichi *et al.*, 1992), results in little quinoid ring puckering. O-atom substituents at both the 5- and 8-positions result in variable puckering. If one or both O-atom substituents are

**Figure 3**

Views along the bridge bond, showing the relative orientations of the naphthoquinoid rings of (I) and gossypolone (Talipov *et al.*, 1995).

part of hydroxy groups, intramolecular hydrogen bonds form with the quinoid O atoms at the 1- or 4-positions. This added stabilization appears to negate the steric effects and minimal ring puckering is observed, *e.g.* as found in 2,5-dihydroxy-3,8-dimethoxy-7-methyl-1,4-naphthoquinone (Cannon *et al.*, 1980). Derivatized hydroxy groups, however, lose this additional stabilization and some puckering is observed, as in 2,5,8-triacetoxy-3-methoxy-6-methyl-1,4-naphthoquinone (Cannon *et al.*, 1987), which has a flattened-boat conformation with a puckering amplitude of 0.113 (3) Å. Structures with two C- or larger atom substituents at the 5- and 8-positions generally exhibit puckering of the quinoid rings. Examples include 5,8-di-2-thienyl-1,4-naphthoquinone (Jones, 2004), with a puckering amplitude of 0.309 (3) Å, and 5-(*p*-methoxyphenyl)-8-(*p*-cyanophenyl)-1,4-naphthoquinone (Jones & Dix, 2004), with a puckering amplitude of 0.104 (3) Å. When puckering occurs, a flattened-boat conformation is usually observed. The exception to this appears to be the chair/half-chair ring form found in (I).

Additionally, the naphthoquinoid rings of (I) are oriented less close to perpendicular than they are in gossypolone and most related structures. From the best-fit planes of the ten atoms of each naphthoquinoid ring, the dihedral angles for the two bridged ring systems in the asymmetric unit are 67.69 (4) and 68.87 (4)° (Fig. 3). The same angle is 84.6° (Fig. 3) in the gossypolone structure (Talipov *et al.*, 1995), and the range reported for gossypol structures is 70–110° (Gdaniec *et al.*, 1996). Because of the shorter C=O bonds of gossypolone compared with the longer C—OH bonds of gossypol, rotation about the inter-naphthalene bridge bond should be less restricted in 2,2'-binaphthoquinone-based structures than for comparable 2,2'-binaphthalene-based structures. Hence, these compounds should be more likely to exhibit smaller angles between the bridged rings. The effect has, in essence, been observed both experimentally, in that gossypolone Schiff bases

are more prone to isomerize at room temperature than are gossypol Schiff bases (Dao *et al.*, 2004), and computationally from *MM3* modeling studies, which indicate that the binaphthyl rotational barrier is lower for gossypolone than it is for gossypol (Beisel *et al.*, 2005).

In gossypol and gossypolone crystal structures, the 6-position hydroxy groups donate to the O atoms of the hydroxy groups at the 5-position. However, these intramolecular interactions are weak, and these hydroxy groups often also donate into intermolecular hydrogen bonds (Gdaniec *et al.*, 1996). For both hemigossypolone and gossypolone, these intermolecular interactions result in column-like assemblies (Talipov *et al.*, 1995). Because methylation of the 6-position hydroxy groups in (I) eliminates these donating groups, no intermolecular O—H...O hydrogen bonding is possible. However, several weak intermolecular C—H...O interactions are present.

An intramolecular C—H...O hydrogen bond exists between the aldehyde H27_1 atom and the carbonyl O6_2 atom of a neighbouring molecule at ($x + 1, -y + 1, -z + 1$) (supplementary figure S1A). This interaction ties together pairs of molecules of (I) into dimeric units that are also supported by hydrophobic stacking interactions between both pairs of naphthoquinone rings. This dimer is tied to an adjacent dimer (formed from a pair of molecules of the opposite chirality) through an additional pair of C—H...O interactions between atom H32A_1 and the carbonyl O6_1 atom of the molecule at ($-x + 2, -y + 1, -z + 1$) (supplementary figure S1B). These four-molecule assemblies then pack into layers that are supported by three additional weak C—H...O interactions. The alignment of these groups is slightly offset, such that the layers formed are skewed relative to the long axis of the individual molecules and the assemblies (supplementary figure S2). Adjacent layers are held together only by hydrophobic interactions between molecules from opposing layers.

Experimental

A mixture of gossypol, 6-methoxygossypol and 6,6'-dimethoxygossypol was isolated from the root bark of *Gossypium barbadense* St Vincent Sea Island cotton, as described previously by Dowd & Pelitire (2006). The mixture was oxidized to form the equivalent gossypolone compounds according to the method of Haas & Shirley (1965). Compound (I) was separated by preparative reverse-phase high-performance liquid chromatography, with a mobile phase of acetonitrile and aqueous phosphate buffer. A single crystal was prepared by dissolving a few milligrams of (I) in acetone and allowing petroleum ether to diffuse into the solution over a period of several weeks.

Crystal data

$C_{32}H_{30}O_{10}$	$V = 5424.7$ (5) Å ³
$M_r = 574.56$	$Z = 8$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 17.8278$ (10) Å	$\mu = 0.11$ mm ⁻¹
$b = 26.2103$ (16) Å	$T = 100$ K
$c = 12.2116$ (7) Å	$0.60 \times 0.40 \times 0.10$ mm
$\beta = 108.069$ (1)°	

Table 1
Hydrogen-bond geometry (Å, °).

Numbers following underscores denote molecule 1 or 2.

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
O3_1—H3_1...O2_1	0.88 (2)	1.78 (2)	2.5622 (14)	148 (2)
O8_1—H8_1...O7_1	0.87 (2)	1.70 (2)	2.5044 (15)	153 (2)
O3_2—H3_2...O2_2	0.85 (2)	1.76 (2)	2.5405 (15)	151 (2)
O8_2—H8_2...O7_2	0.91 (2)	1.69 (2)	2.5203 (14)	149.6 (18)

Table 2
Selected torsion angles (°).

	Molecule 1	Molecule 2
C6—C5—C23—H23	−171.3	165.7
C10—C5—C23—H23	5.1	−1.5
C16—C15—C28—H28	−170.7	−175.0
C20—C15—C28—H28	5.1	2.7

Table 3
Cremer–Pople ring-puckering parameters for gossypolone structures (Å, °).

Parameters calculated using *PLATON* (Spek, 2009).

Structure	Molecule	Quinoid ring shape	Q	θ	φ
(I)	1	$B_{1,4}$	0.246 (2)	83.6 (3)	173.7 (3)
(I)	1	$^{11}C_{14}/E_{19}$	0.145 (1)	35.1 (6)	296.1 (10)
(I)	2	$^{1,4}B$	0.271 (2)	92.1 (3)	8.9 (3)
(I)	2	$B_{11,14}$	0.312 (2)	88.9 (3)	180.1 (3)
Gossypolone†		$^{1,4}B$	0.213 (4)	104.4 (11)	356.1 (12)
Hemigossypolone†		$^{1,4}B$	0.222 (6)	109.4 (16)	15.2 (15)

† Data from Talipov *et al.* (1995).

Data collection

Bruker APEXII CCD diffractometer	88778 measured reflections
Absorption correction: empirical (using intensity measurements) (<i>SADABS</i> ; Bruker, 2005)	13486 independent reflections
$T_{\min} = 0.940, T_{\max} = 0.990$	11234 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.032$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.045$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.127$	$\Delta\rho_{\text{max}} = 0.47$ e Å ⁻³
$S = 1.09$	$\Delta\rho_{\text{min}} = -0.22$ e Å ⁻³
13486 reflections	
785 parameters	

Hydroxy H-atom positions were refined, but their isotropic displacement parameters were constrained to $1.5U_{\text{eq}}(\text{O})$. The remaining H atoms were placed in idealized positions, with C—H = 0.95 (aldehyde), 0.98 (methyl) or 1.00 Å (methine), and allowed to ride on their parent C atoms, with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ for methyl H atoms or $1.2U_{\text{eq}}(\text{C})$ for methine and aldehyde H atoms.

Data collection: *APEX2* (Bruker, 2005); cell refinement: *SAINT* (Bruker, 2005); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXTL* (Sheldrick, 2008).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: KU3027). Services for accessing these data are described at the back of the journal.

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