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MOLECULAR AND CRYSTAL STRUCTURES OF HEMIGOSSYPOLONE AND GOSSYPOLONE

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The results are given of an x-ray structural investigation of hemigossypolone isolated from the stems of a wilt-infected cotton plant and of gossypolone obtained by oxidizing gossypol.

The hemigossypolone isolated from the stems of a wilt-infected cotton plant [1] and the gossypolone obtained by oxidizing gossypol [2] have been subjected to an x-ray structural investigation. The corresponding numberings and conformations of the hemigossypolone and gossypolone molecules (**1**) and (**2**) are given in Fig. 1.

The naphthoquinone nuclei in the molecules both of hemigossypolone and of gossypolone are not strictly planar: the deviations of the C4 atoms from the mean square plane of *AB* amount to 0.37 Å (**1**) and 0.28 Å (**2**) (Table 1). No such deviations from coplanarity are observed in the molecules of other naphthoquinone derivatives [3-8]. It arises because of the mutual repulsion in each case of the O5 atom and the isopropyl group, the C13···O5 distances being 2.86 Å (**1**) and 2.85 Å (**2**). In the gossypolone molecule the dihedral angle between the mean square planes of the naphthoquinone nuclei amounts to 84.6°.

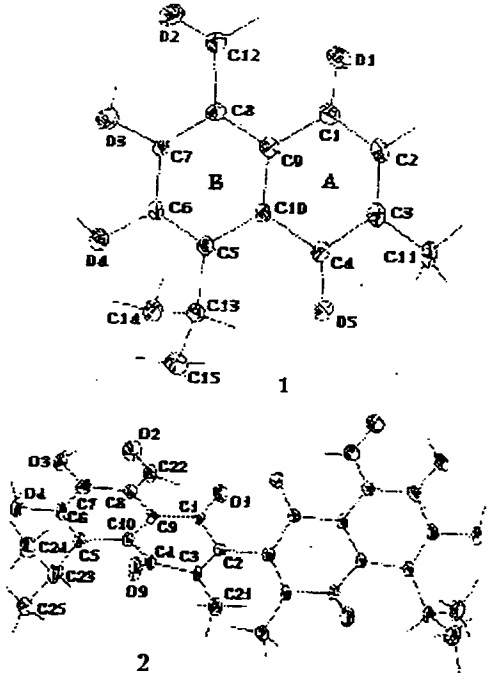

Fig. 1. Conformations and numberings of the hemigossypolone (**1**) and gossypolone (**2**) molecules.

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TABLE 1. Deviations (Å) of the δ Atoms from the Corresponding Planes in the Molecules of Hemigossypolone (1) and Gossypolone (2)

Atoms	Plane *B*		Plane *A*		Plane *AB*	
	1	2	1	2	1	2
C1	−0.112	0.101	0.034*	0.047*	0.008*	0.068*
C2	−0.255	−0.005	−0.054*	−0.029*	−0.099*	−0.032*
C3	−0.103	0.001	0.036*	0.005*	0.037*	−0.008*
C4	0.286	0.276	0.297	0.281	0.371	0.281
C5	−0.031*	−0.056*	−0.211	−0.076	−0.040*	−0.041*
C6	0.000*	0.015*	−0.234	−0.033	−0.044*	0.024*
C7	0.023*	0.039*	−0.145	−0.038	−0.004*	0.029*
C8	−0.016*	−0.051*	−0.060	−0.131	0.010*	−0.075*
C9	−0.015*	0.008*	−0.001*	−0.044*	0.048*	−0.010*
C10	0.038*	0.044*	−0.016*	−0.021*	0.083*	0.044*
C11	−0.192	−0.104	0.001	−0.070	−0.016	−0.106
C12	−0.069	−0.366	−0.053	−0.477	−0.030	−0.409
C13	−0.207	−0.325	−0.461	−0.316	−0.236	−0.290
O1	−0.066	0.247	0.146	0.169	0.073	0.198
O2	−0.020	−0.385	−0.057	−0.520	−0.013	−0.432
O3	0.021	0.071	−0.214	−0.031	−0.045	0.058
O4	0.000	0.031	−0.355	−0.017	−0.096	0.053
O5	0.862	0.757	0.823	0.785	0.935	0.777

*Denotes the atoms through which the corresponding planes pass.

TABLE 2. Geometries of the Intra- and Intermolecular Hydrogen Bonds

Atoms	Symmetry	O...O, Å	O–H, Å	H...O, Å	Angle, deg
	In hemigossypolone				
O3–H..O2		2.55	0.73	1.89	150.4
O4–H...O3		2.60	0.71	2.19	118.4
O4–H...O5	1.5-*x*;*y*–0.5;0.5–*z*	2.90	0.71	2.26	150.5
	In gossypolone				
O3–H..O2		2.54	1.03	1.71	134.7
O4–H...O3		2.62	0.98	2.01	118.8
O4–H...O1	0.5+*x*;1.5–*y*;0.5+*z*	3.14	0.98	2.47	113.8

TABLE 3. Crystallographic Parameters of Gossypol Complexes

Parameters	Guest	
	methylene chloride	chloroform
a(Å)	10.920(4)	11.014(5)
b(Å)	11.990(8)	11.801(9)
c(Å)	13.468(6)	13.554(7)
α, deg	68.44(4)	68.73(5)
β, deg	84.41(3)	82.88(4)
γ, deg	64.77(4)	66.01(6)
V, Å^3	1480(1)	1499(1)
Sp. gr.	$P\bar{1}$	$P\bar{1}$
*Z**	4	4
ρ, g/cm^3	1.42	1.48

*Z is the number of gossypolone molecules in the cell.

In each of the (1) and (2) molecules there are two systems of intramolecular H-bonds, analogous to those observed in gossypol [10, 11]. The carbonyl O2 atom forms an H-bond with the hydroxy group O3-H, closing the six-membered ring C7–C8–C12–O2···H–O3. The O3···H–O4 H-bond closes the five-membered ring C6–C7–O4–H···O3 (Table 2).

In crystals, the molecules of (1) are linked in chains parallel to the *y* axis through O4–H···O5 H-bonds with a length of 2.90 Å (Fig. 2). The packing of these chains of molecules forms dense-packed columns (~3.34 Å).

TABLE 4. Coordinates ($\times 10^4$, or $\times 10^3$ for H atoms) and Temperature Factors ($Å^2 \times 10^3$) of the Atoms in the Structures of Hemigossypolone and Gossypolone

Atoms	Hemigossypolone				Gossypolone			
	x	*y*	*z*	*U**	*x*	*y*	*z*	*U**
O1	4058(4)	6579(3	875(4)	46(2)	695(2)	7950(2)	2059(3)	54(1)
O2	4042(4)	7551(4)	711(5)	51(2)	2747(2)	6801(3)	2134(4)	81(2)
O3	4880(4)	8050(3)	999(4)	45(2)	3819(2)	7365(3)	4176(3)	69(2)
O4	5872(4)	7609(3)	1554(4)	38(2)	4336(2)	8745(3)	5922(3)	66(1)
O5	6924(3)	6197(3)	1643(4)	35(2)	1681(2)	10355(3)	5838(3)	71(2)
C1	6958(3)	5263(3)	1725(4)	39(2)	983(2)	8636(3)	2813(4)	40(2)
C2	6076(4)	4753(3)	1559(4)	40(2)	431(2)	9446(3)	2957(4)	38(2)
C3	5117(4)	5147(3)	1279(4)	38(2)	702(2)	10140(3)	3874(4)	43(2)
C4	5056(3)	6101(3)	1213(4)	37(2)	1547(2)	10006(3)	4837(4)	46(2)
C5	5958(3)	6608(3)	1442(4)	32(2)	3017(2)	9496(3)	5326(4)	45(2)
C6	4891(6)	9057(4)	880(8)	70(3)	3528(2)	8750(4)	5165(4)	48(2)
C7	4232(4)	4536(4)	1060(4)	50(2)	3245(3)	8021(4)	4237(4)	50(2)
C8	7882(4)	6720(3)	1711(4)	45(2)	2436(2)	8016(3)	3386(4)	43(2)
C9	8315(5)	6431(4)	854(6)	57(3)	1877(2)	8695(3)	3586(4)	40(2)
C10	8675(5)	6677(5)	2839(5)	62(3)	2157(2)	9396(3)	4553(4)	41(2)
C11	3250(3)	6187(3)	738(4)	84(2)	189(3)	10972(4)	4076(5)	61(2)
C12	4320(3)	3722(3)	1163(3)	66(2)	2256(3)	7406(4)	2281(5)	61(2)
C13	6244(3)	3857(3)	1646(4)	58(2)	3366(3)	10384(4)	6188(5)	59(2)
C14	7868(3)	4834(3)	1966(4)	58(2)	3693(3)	10043(5)	7508(5)	70(2)
C15	6583(3)	8050(2)	2136(3)	54(1)	4000(3)	10990(4)	5882(6)	82(3)
H3o	576(3)	366(3)	162(4)	3(2)	365(3)	698(4)	336(4)	10(1)
H4o	780(4)	437(4)	206(5)	8(2)	454(3)	810(4)	570(4)	10(1)
H2	337(4)	781(3)	47(4)	6(2)				
H11a	537(5)	927(4)	46(5)	10(2)	−37(3)	1088(3)	352(4)	9(1)
H11b	419(5)	926(4)	54(5)	10(2)	38(3)	1111(4)	501(5)	7(1)
H11c	505(6)	934(5)	151(6)	12(3)	38(3)	1161(4)	391(4)	9(1)
H12	353(4)	482(4)	92(5)	8(2)	175(3)	755(3)	152(4)	9(1)
H13	769(4)	735(3)	156(4)	5(1)	292(3)	1072(3)	623(4)	6(1)
H14a	780(4)	645(4)	11(5)	8(2)	392(3)	1059(4)	792(4)	7(1)
H14b	889(5)	688(5)	77(6)	11(3)	323(3)	973(4)	773(4)	7(1)
H14c	858(4)	585(4)	91(5)	8(2)	412(3)	939(3)	749(4)	10(1)
H15a	833(4)	688(4)	340(5)	9(2)	410(3)	1166(4)	634(4)	8(1)
H15b	926(5)	708(4)	283(5)	10(2)	443(3)	1054(4)	588(4)	10(1)
H15c	898(5)	611(5)	300(5)	11(2)	375(3)	1115(4)	505(5)	11(2)

*$U = (1/3)\sum_{i}\sum_{j} Uija_i^* a_j^* ai \cdot aj.$

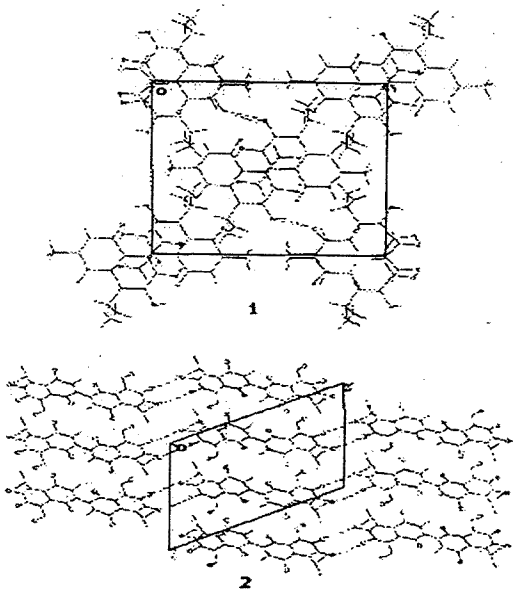

Fig. 2. Crystal structures of hemigossypolone (**1**) and gossypolone (**2**).

TABLE 5. Bond Lengths (Å) in the Hemigossypolone (1) and Gossypolone (2) Molecules

C1–C2	1.457(7)	1.488(6)	C1–C9	1.489(7)	1.490(5)
C1–O1	1.226(7)	1.221(5)	C2–C3	1.325(7)	1.349(6)
C3–C4	1.480(7)	1.498(5)	C3–C11	1.503(8)	1.488(7)
C4–C10	1.502(6)	1.483(7)	C4–O5	1.220(5)	1.214(6)
C5–C6	1.389(6)	1.387(7)	C5–C10	1.419(6)	1.445(5)
C5–C13	1.522(7)	1.500(6)	C6–C7	1.396(7)	1.389(6)
C6–O4	1.357(6)	1.361(4)	C7–C8	1.390(7)	1.395(5)
C7–O3	1.349(6)	1.348(6)	C8–C9	1.418(6)	1.412(6)
C8–C12	1.478(8)	1.463(7)	C9–C10	1.408(6)	1.396(6)
C12–O2	1.217(7)	1.232(7)	C13–C14	1.52(1)	1.518(7)
C13–C15	1.534(8)	1.529(9)	C2–C2a	–	1.489(6)

TABLE 6. Valence Angles (degrees) in the Hemigossypolone (1) and Gossypolone (2) Molecules

Atoms	1	2	Atoms	1	2
C2–C1–C9	118.8(5)	118.8(3)	C2–C1–O1	118.7(5)	119.4(3)
C9–C1–O1	122.5(5)	121.9(4)	C1–C2–C3	122.8(5)	121.3(3)
C1–C2–C2a		116.6(3)	C2a–C2–C3		122.0(4)
C2–C3–C4	118.8(4)	118.5(4)	C2–C3–C11	124.3(5)	124.5(3)
C4–C3–C11	116.7(5)	116.7(4)	C3–C4–C10	118.7(4)	119.0(4)
C3–C4–O5	120.1(4)	117.6(4)	C10–C4–O5	121.2(4)	123.3(3)
C6–C5–C10	116.7(4)	115.6(4)	C6–C5–C13	119.8(4)	120.6(3)
C10–C5–C13	123.4(4)	123.6(4)	C5–C6–C7	121.5(4)	122.1(3)
C5–C6–O4	119.4(4)	119.1(4)	C7–C6–O4	119.1(4)	118.8(4)
C6–C7–C8	122.1(4)	122.0(4)	C6–C7–O3	113.7(4)	115.2(3)
C8–C7–O3	124.1(4)	122.7(4)	C7–C8–C9	117.9(4)	117.6(4)
C7–C8–C12	117.2(4)	117.1(4)	C9–C8–C12	124.8(4)	124.8(3)
C1–C9–C8	121.6(4)	120.7(4)	C1–C9–C10	119.0(4)	119.4(4)
C8–C9–C10	119.3(4)	119.8(3)	C4–C10–C5	120.7(4)	119.2(4)
C4–C10–C9	117.0(4)	118.7(3)	C5–C10–C9	122.1(4)	122.0(4)
C8–C12–O2	122.7(5)	123.8(4)	C5–C13–C14	112.2(4)	112.4(4)
C5–C13–C15	111.2(5)	111.5(5)	C14–C13–C15	112.6(5)	112.5(4)

The method of packing the molecules in the (2) crystals differs from the method of forming the crystal structure of gossypol [10-13]. The reason for this is the replacement of the proton-donating O1–H group of gossypol by an acceptor carbonyl group in (2). The presence of the O1 atom in (2) prevents the formation of the centrosymmetric dimers that are characteristic for the crystal structures of gossypol and some of its derivatives [10-15]. In the crystal structure of (2) not all the groups active in the sense of H-bond formation actually participate in hydrogen bonds. Only through weak O4–H···O1 intermolecular H-bonds 3.14 Å long are the (2) molecules linked into columns parallel to the *xz* axis (Fig. 2). The interaction between the columns is purely of the van der Waals type.

The solvate-free crystalline modification of (2) is formed from acetone and acetonitrile and from weakly polar solvents (methylene chloride, chloroform) under certain precipitation conditions. Thus, the solvent-free form of (2) was obtained from the above-mentioned solvents when the temperature of precipitation was no lower than 32°C. Otherwise, clathrates of (2) with the solvent used were formed, with the crystallographic parameters given in Table 3.

EXPERIMENTAL

After the purification and chromatographic separation of a chloroform extract of the stems of a wilt-infected cotton plant on a column of silica gel, the fractions containing hemigossypolone (R_f 0.74 in the benzene–methanol (9:1) system) was evaporated in a current of nitrogen, and the residue was dissolved in a small volume of diethyl ether. When the ether solution was allowed to evaporate in the cold (in the dark), the supersaturated solution deposited dark yellow crystals with mp 160-162°C.

Gossypolone was obtained by a known procedure [2], and its solvate-free form by crystallization from acetone solution.

The crystallographic parameters of single crystals were determined and refined from 15 reflections on a Syntex-$P2_1$ automatic four-circle diffractometer:

hemigossypolone (1): a = 13.953 (2) Å, b = 14.834 (2) Å, c = 13.327 (2) Å, β = 109.96 (2)°, Z = 8, V = 2592.7 (1.4) Å^3, D_{calc} = 1.41 g/cm^3, space gr. C2/c;

gossypolone (**2**): a = 17.764 (2) Å, b = 12.880 (3) Å, c = 11.984 (4) Å, β = 113.32(2)°, Z = 4, V = 2517.9 (2.1) Å^3, D_{calc} = 1.44 g/cm^3, space gr. C2/c.

Integral intensities (1808 reflection for (**1**), and 2043 for (**2**)) were measured by the $\theta/2\theta$ scanning method using CuK_α radiation monochromatized by reflection from a graphite crystal. After allowing for Lorentz and polarization factors and eliminating weak reflections with $I < 2\sigma$, the working groups consisted of 1288 (**1**) and 1624 (**2**) reflections. The structures were interpreted by the direct method using the SHELX program package adapted for an IBM-386 PC [16].

The structures were refined with the aid of the SHELXS-86 program package [17] set up on the same PC. The hydrogen atoms were localized in the molecules with the aid of Fourier difference syntheses. The divergence factors after the final stage of refining the positions and anisotropic temperature factors were R = 0.058 (**1**) and 0.072 (**2**). The coordinates of the atoms are given in Table 4, and bond lengths and valence angles in Tables 5 and 6.

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