X-RAY STRUCTURAL INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES.

VII. MOLECULAR AND CRYSTAL STRUCTURE OF DIANILINEGOSSYPOL

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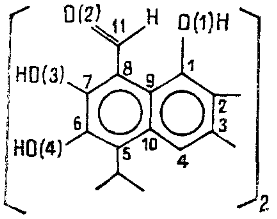
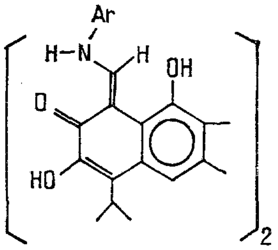
A complete x-ray structural investigation of the complex of dianilinegossypol with ethyl acetate has been made and it has been shown that in these crystals the dianilinegossypol has predominantly the quinoid tautomeric form.

Recently, a series of derivatives of gossypol (I) possessing a broad spectrum of physiological activity has been obtained [1, 2]. Among them, a special place is occupied by derivatives of the type of Schiff's bases [3]. Aromatic amines (aniline, phenylethylamine) readily react with (I) under the usual conditions, while the addition of alkylamines to (I) requires activation energy.



I



II

The reaction product may exist in both the quinoid and the benzene tautomeric forms, depending on the nature of the amine component and the solvent used, as has been confirmed by the results of a NMR investigation of various derivatives of (I) [4]. To determine the tautomeric state of the product of the reaction of aniline with (I) — dianilinegossypol (II) — in the solid phase and to establish the details of its geometric structure we have performed an x-ray structural analysis of this compound.

The result showed that from a solution of (II) in ethyl acetate its monosolvate with this solvent crystallizes. In the crystal structure, the ethyl acetate molecule is bound to a molecule of (II) with the aid of a O1—H...O1E hydrogen bond having a length of 2.79 Å. For the molecule of (I) present in the aldehydic tautomeric form in all the crystalline modifications investigated, intramolecular H-bonds of two types are characteristic: O2...H—O3 completes a hexacycle of the C7, C8, C11, O2, and H—O3 atoms, and the O3...H—O4 H-bond, completing a 5-membered ring of the atoms C6, C7, O3, and H—O4 [5-7]. Two systems of intramolecular H-bonds likewise exist in the molecule of (II), but with a somewhat different nature. The C7—C8—C22—N1—H...O2 hexacycle is closed through the O2...H—N1 H-bond, and the 5-membered ring of C7—C6—O3—H...O2 through the O2...H—O3 H-bond (Fig. 1). It must be mentioned that for both types of intramolecular hydrogen bonds the O2 oxygen atom acts as a proton acceptor. Analogous bonds are formed in the other half of the (II) molecule, as well. Below we give the geometries of the intramolecular H-bonds in the crystal structure of (II) (A represents an acceptor and D a donor):

Bond	A...D Å	A...H Å	Angle D-H...A, degrees
O2...N1	2,57	1,69	138,9
O5...N2	2,48	1,61	138,9
O2...O3	2,61	2,11	119,8
O5...O6	2,58	2,08	115,2

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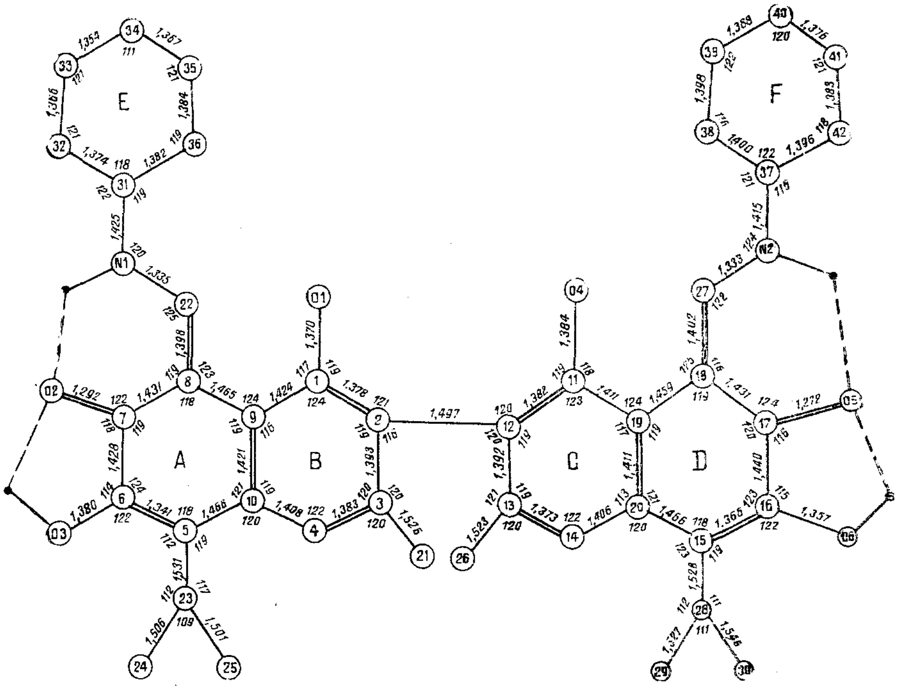

Fig. 1. Bond lengths and valence angles of the molecule of (II).

The N1 and N2 nitrogen atoms have plane-trigonal coordination, which indicates the existence of conjugation of the bonds along the chains of atoms C8, C22, N1, and C31, and C18, C27, N2, and C37. However, the delocalization of electron density along these chains is incomplete, since the lanes of the corresponding naphthalene and aniline rings are not parallel. The dihedral angles between the A + B and E rings and between the C + D and F rings amount to 38.3 and 26.6°, respectively. This noncoplanarity of the rings is the result of repulsion between the C22 and C36 atoms in the first half of the molecule and the C27 and C28 atoms in the second half. Even then, the nonvalent distances between these atoms amount to 2.91 and 2.98 Å, while the Van der Waals length should be 3.42 Å [8].

The distriution of the bond lengths and valence angles in the naphthalene nuclei agree with those found in other naphthalene systems, with the exception of the region of the C7—C9 and C17—C19 atoms where an increase in the length of the bonds is observed. The O2—C7 and O5—C17 bonds are also lengthened (see Fig. 1). The bond lengths and valence angles of the aromatic rings E and F are close to the "standard" values [9].

All this shows that in these regions of the molecule the electron density is distributed differently from that in the molecule of (I). In addition to the fact of the displacement of the hydrogen atom from the O2 atom to the N1 atoms (in the other half, from the O5 atom to the N2 atom), this indicates that the molecule of (II) in the crystals under consideration is present predominantly in the quinoid tautomeric form. The dihedral angle between the naphthyl nuclei of the molecule amounts to 88.4°.

The centrosymmetric dimers exiting in various crystalline modifications and complexes of (I) [5-7] have also been detected in the crystals under consideration, since the aniline molecules attached to the aldehyde groups create no steric hindrance to the formation of dimers. In the centrosymmetric dimer, one molecule of (II) is united with another through a O2...O4 H-bond. The length of the hydrogen bond is 2.77 Å, and the corresponding angle 139.2°. The dimers are linked with one another likewise with the aid of centrosymmetric O6—H...O5 H-bonds with a length of 2.80 Å and an angle of 147.1° (Fig. 2). As a result, infinite chains parallel to the [111] direction are formed. Van der Waals contact exists between the chains, and no shortened intermolecular distances are observed in the structure.

EXPERIMENTAL

Single crystals of (II) were grown during the reaction of (I) with aniline in ethyl acetate. The crystallographic parameters of a single crystal were determined and were refined from 15 reflections on a Syntex $P2_1$ automatic four-circle diffractometer: a = 18.025 (3)

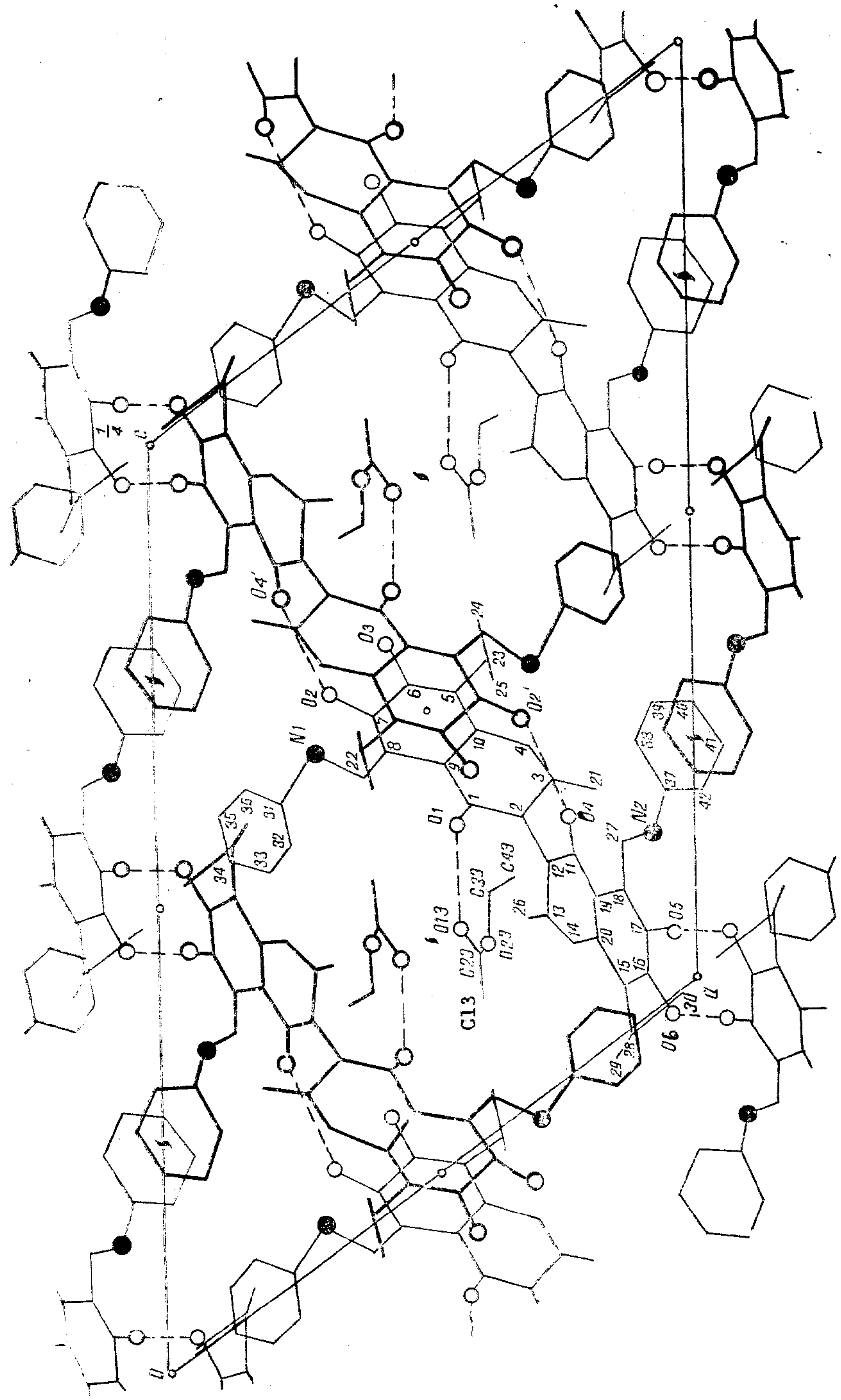

Fig. 2. Crystal structure of (II).

TABLE 1. Coordinates of the Atoms (×10⁴; for hydrogen atoms, ×10³) in the Crystal Structure of (II)

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
C1	4145 (4)	—0476 (5)	3562 (2)	C2	3226 (4)	—0678 (5)	3044 (2)
C3	2680 (4)	—1374 (5)	3126 (3)	C4	3068 (4)	—1995 (5)	3718 (3)
C5	4376 (4)	—2526 (5)	4876 (3)	C6	5272 (4)	—2387 (5)	5373 (3)
C7	5882 (4)	—1598 (5)	5344 (2)	C8	5545 (4)	—0949 (5)	4743 (2)
C9	4577 (4)	—1087 (5)	4184 (2)	C10	4004 (4)	—1860 (5)	4255 (2)
C11	2568 (3)	1159 (5)	2273 (2)	C12	2812 (4)	0042 (5)	2397 (2)
C13	2835 (4)	—0494 (5)	1902 (3)	C14	2380 (4)	0072 (5)	1293 (2)
C15	1422 (4)	1734 (5)	0488 (2)	C16	1040 (4)	2877 (6)	038[illegible] (2)
C17	1056 (4)	3536 (6)	0892 (3)	C18	1454 (3)	2969 (5)	1524 (2)
C19	1908 (3)	1776 (5)	1658 (2)	C20	1901 (3)	1189 (5)	1151 (2)
C21	1654 (4)	—1562 (7)	2559 (3)	C22	6172 (4)	—0255 (5)	4707 (3)
C23	3737 (4)	—3359 (7)	4930 (3)	C24	3722 (6)	—4656 (8)	4709 (4)
C25	3883 (5)	—3397 (7)	5586 (3)	C26	3366 (5)	—1684 (6)	2029 (3)
C27	1326 (4)	3582 (5)	1957 (2)	C28	1303 (4)	1053 (6)	—0093 (3)
C29	1748 (4)	1742 (8)	—0368 (3)	C30	0276 (5)	0776 (7)	—0644 (3)
C31	7044 (4)	0610 (6)	5117 (3)	C32	7536 (4)	0625 (7)	4525 (3)
C33	8079 (5)	1344 (7)	4438 (2)	C34	8731 (5)	2085 (8)	4937 (4)
C35	8869 (4)	2061 (7)	5531 (3)	C36	8332 (4)	1329 (7)	5631 (3)
C37	0618 (4)	5226 (5)	2176 (3)	C38	1145 (4)	5096 (7)	2866 (3)
C39	0811 (5)	5700 (7)	3177 (3)	C40	0019 (5)	6386 (7)	2834 (3)
C41	-0474 (5)	6506 (7)	2156 (3)	C42	-0174 (4)	5954 (6)	1816 (3)
O1	4694 (3)	0258 (4)	3485 (2)	O2	6723 (2)	—0015 (4)	5867 (2)
O3	5687 (3)	—3019 (4)	5964 (2)	O4	2383 (2)	1718 (3)	2776 (2)
O5	0669 (3)	4588 (4)	0729 (2)	O6	0589 (3)	3452 (4)	—0211 (2)
N1	7059 (5)	—0091 (5)	5208 (2)	N2	0879 (5)	4653 (4)	1803 (3)
C.1E	4154 (7)	2002 (9)	1401 (4)	C.2E	4213 (5)	2253 (9)	1995 (4)
C.3E	3979 (6)	3750 (9)	2583 (4)	C.4E	3607 (7)	4994 (10)	2505 (5)
O.1E	4507 (3)	1554 (5)	2449 (3)	O.2E	3907 (4)	3382 (6)	1986 (2)
H4	269	—266	377	H14	241	—033	0928
H21.1	161	—195	213	H21.2	133	—213	2669
H21.3	135	—085	254	H22	591	021	4259
H23	301	—312	455	H24.1	374	—478	4379
H24.2	441	—503	508	H24.3	312	—520	4623
H25.1	408	—269	579	H25.2	434	—384	5829
H25.3	323	—374	550	H26.1	415	—147	2388
H26.2	308	—233	212	H26.3	328	—208	1609
H27	167	323	243	H28	169	032	0091
H29.1	235	183	—006	H29.2	177	131	—0725
H28.1	130	260	—056	H30.1	027	026	—0995
H30.2	-003	155	—079	H30.3	-003	036	—0416
H32	698	019	415	H33	802	116	4003
H34	911	259	478	H35	939	246	5903
H36	834	133	601	H38	180	454	3116
H39	115	571	370	H40	-020	670	3099
H41	-115	700	191	H42	-054	600	130
H.N1	722	—052	564	H.N2	061	495	133
H.O1	431	053	320	H.O3	623	—293	616
H.O4	270	125	318	H.O6	028	432	—023
H1.C1E	399	123	126	H2.C1E *	483	218	151
H3.C1E *	364	263	100	H1.C3E	470	389	295
H2.C3E.	363	303	268	H1.C4E	314	505	216
H2.C4E*	409	568	255	H3.C4E *	351	517	298

Å, b = 10.841 (2) Å, c = 25.021 (3) Å, β = 126.36(1)°, V = 3937.04(0.95) Å³, z = 4, space group $P2_1/c$; ρ_{calc} = 1.27 g/cm³.

A group of integral intensities was obtained on the diffractometer mentioned by the θ/2θ-scanning method using a graphite monochromator in CuK_α radiation. After allowing for the Lorentz and polarization factors and eliminating weak reflections with $F \leq 2\sigma$, the working group amounted to 2941 reflections. The structure was interpreted by the direct method with the aid of the XTL group of programs realized on a SM-4 computer [10]. The best E-synthesis enabled about 60% of the atoms in the molecule to be linked with electron-density peaks. Further F-syntheses revealed the positions of all the nonhydrogen atoms of the molecules of (II) and the solvent on the electron-density maps.

The structure was refined with the aid of the SHELX group of programs [11] on a ES-1030 computer. With the aid of difference Fourier syntheses it was possible to determine the positions of all the hydrogen atoms except for the four belonging to the methyl groups of the ethylacetate molecules. The coordinates of these hydrogen atoms were calculated geometrically (they are marked with asterisks in Table 1). The divergence factor after the final stage of refining the position and anisotropic thermal parameters, taking all the hydrogen atoms into account, had a value of 0.055. The coordinates of the atoms are given in Table 1.

SUMMARY

A complete x-ray structural study of the complex of dianilinegossypol with ethyl acetate has been made, and it has been shown that in these crystals the dianilinegossypol has predominantly the quinoid tautomeric form.

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