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X-RAY STRUCTURAL INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES. XXVII. STRUCTURE OF THE CONDENSATION PRODUCT OF GOSSYPOL AND (−)-α-PHENYLETHYLAMINE

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The structure of the product of condensation of gossypol with (−)-α-phenylethylamine has been determined. It has been shown that a possible cause of the difficulty in separating racemic gossypol into optically active components is not a racemization of (−)-α-phenylethylamine on its condensation with gossypol but the high tendency of gossypol and its derivatives to form dimers.

Gossypol can possess optical activity as a result of atropoisomerism. Optically active (+)-gossypol has been isolated from the tree *Thespesia populnea* [1, 2] in very low yield, and, as has recently been shown, the usual source of gossypol — the cotton plant — synthesizes it with a slight predominance of one of the atropoisomers over the other [3].

In order to study the physiological action of optically active gossypol, researchers have endeavored to obtain it by separating ordinary racemic gossypol. However, attempts at separation using both ordinary and chiral supports have not been successful [4]. Only comparatively recently have the enantiomers of gossypol been obtained by the chromatography of optically active gossypol derivatives, using chiral supports [5-7]. The toxicity of the (−)-gossypol obtained in this way proved to be one half that of the racemate. However, the cost of obtaining gossypol is very high and the method itself is complicated, which prevents the wide use of enantiomeric gossypol.

The classical method of separation by the fractional crystallization of diastereoisomers obtained from a racemate by the addition of optically active substituents to the molecule is cheap and simple. Deshary and Padel [4] state that gossypol is not separated via the product of its condensation with (−)-α-phenylethylamine (DPEAG). Sampath and Balaram [7] explain this by the assumption that racemization of the initial phenylethylamine may take place during the condensation reaction.

In many of the crystalline forms of gossypol, the dextrorotatory and levorotatory gossypol molecules are united in the form of centrosymmetric dimers with the aid of two strong H-bonds [8-10]. The same thing is observed in derivatives — for example, in dianilinegossypol [11]. If this also applies to di(phenylethylamine)gossypol (DPEAG), it is just this that may prevent the isolation of chiral gossypol via this derivative. To answer these questions, we have synthesized DPEAG and have determined its molecular and crystal structures.

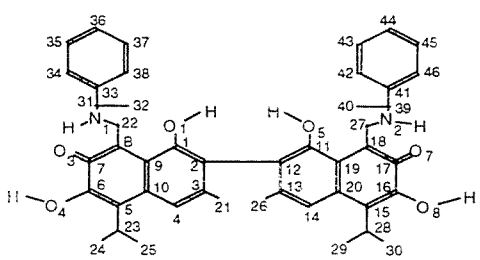

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TABLE 1. Geometry of the Intermolecular H-Bonds in the Structure of DPEAG

Bond	Distance, Å			O–H···O angle, degrees
	O...O	O–H	H...O	
O(5A)–H...O(3B)	2.711	1.25	1.57	148
O(5B)–H...O(3A)	2.708	1.19	1.63	147
O(8A)–H...O(7B)^{i}	2.759	0.78	2.47	103
O(8B)–H...O(7A)^{ii}	2.875	1.15	2.30	108

Symmetry codes: (i) x + 2; y; z — 1; (ii) x — 2; y; z + 1

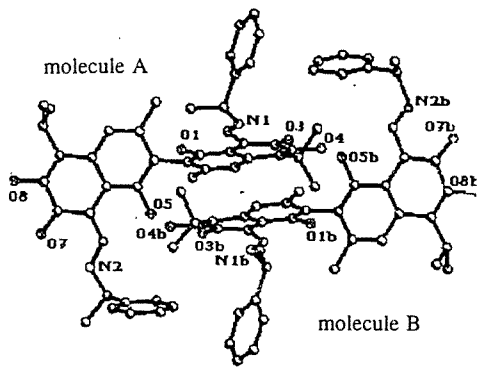

Fig. 1. Conformations of molecules A and B in DPEAG.

From solution in alcohol, DPEAG crystallizes in space group P1 with two molecules (A and B) in the independent part of the unit cell. Analysis of the structures of molecules A and B has shown that no racemization takes place in the condensation of (−)-α-phenylethylamine with gossypol — the substituent has the same (−)-configuration as the initial reactant (Fig. 1). Pairs of H-bonds of the O5−H···O3 type occur between molecules A and B, forming dimers as is observed in crystals of gossypol [8-10] and of dianilinegossypol [11]. However, in the structure under consideration the dimers are not centrosymmetric, since the enantiotopicity between the individual molecules of the dimer is disturbed because of the presence in them of substituents having the same configuration. Because of this, the crystals of DPEAG are not centrosymmetric but pseudocentrosymmetric. The latter hypothesis is supported by the fact that it is possible to refine the structure to a fairly low R factor in the centrosymmetric space group $\bar{P}1$.

The diastereoisomeric molecules A and B, having the quinoid tautomeric form, differ from one another in conformation (see Fig. 1). Thus, the dihedral angle between the naphthyl nuclei of molecule A is 71°, while in molecule B the same angle is 78°. The conformation of the four phenylethylamine groupings also differ somewhat: the benzene rings of the substituents have different inclinations relative to their naphthyl nuclei (102±6°).

In the C1-C10 naphthyl nuclei of molecules A and B, the isopropyl groups are turned in the direction of the closest hydroxy groups, and in the other halves of the molecules they have the opposite orientations. The molecules are characterized by intramolecular H-bonds of the O4−H···O3 and N1−H···O3 types for the C1-C10 naphthyl nuclei and of the O8−H···O7 and N2−H···O7 types for the C11-C20 naphthyl nuclei. The parameters of these H-bonds are very close to those that are observed in the dianilinegossypol molecule [11]. The naphthyl nuclei of molecules A and B are nearly planar, the maximum deviations of the atoms from the mean square planes of the corresponding ten carbon atoms not exceeding 0.06 Å.

The geometric parameters of the intermolecular H-bonds are given in Table 1. The lengths and angles of the dimer-forming H-bonds scarcely differ from one another. Pairs of Molecules A and B (Figure 1) that are related by pseudo inversion center and linked by hydrogen bonds (O5A···O3B and O5B···O3A) are linked by an additional pair of inversion related hydrogen bonds (O8A-H···O7B and O7B-H···O8A) to form columns parallel to the [201] direction (Figure 2). The O1−H and O4−H hydroxy groups do not participate in intermolecular H-bonds, which is rarely observed for gossypol and its derivatives. Van der Waals forces act between the columns. In the structure, the principle of the separation of hydrophilic and hydrophobic intermolecular contacts that is characteristic for the majority of crystal structures of gossypol [8-10] is not adhered to.

TABLE 2. Coordinates ($\times 10^4$; for H atoms, $\times 10^3$) and Temperature Factors ($Å^2 \times 10^3$) of the Atoms of DPEAG

Atom	x	y	z	U^*
C(1)A	2383(7)	6425(6)	7835(5)	38(3)
C(2)A	2643(7)	6330(6)	6943(5)	32(3)
C(3)A	1624(8)	6375(7)	6566(5)	41(3)
C(4)A	344(8)	6439(7)	7054(5)	38(3)
C(5)A	−1383(7)	6451(7)	8380(5)	42(4)
C(6)A	−1645(7)	6601(8)	9247(6)	47(4)
C(7)A	−645(7)	6671(7)	9722(5)	42(3)
C(8)A	745(7)	6505(6)	9258(5)	34(3)
C(9)A	1068(7)	6464(6)	8351(5)	36(3)
C(10)A	−5(7)	6459(6)	7933(5)	34(3)
C(11)A	4767(7)	7000(6)	6141(5)	36(3)
C(12)A	4079(7)	6147(7)	6434(5)	38(3)
C(13)A	4703(8)	5070(7)	6168(5)	41(3)
C(14)A	6009(8)	4912(6)	5660(5)	36(3)
C(15)A	8080(7)	5565(6)	4829(5)	32(3)
C(16)A	8729(8)	6401(6)	4541(5)	37(3)
C(17)A	8100(8)	7477(6)	4704(5)	38(3)
C(18)A	6733(8)	7674(6)	5200(5)	36(3)
C(19)A	6057(7)	6839(6)	5567(4)	32(3)
C(20)A	6713(8)	5766(6)	5366(5)	36(3)
C(21)A	1885(12)	6307(11)	5606(7)	69(6)
C(22)A	1701(9)	6305(7)	9668(5)	43(4)
C(23)A	−2486(9)	6269(9)	7902(7)	60(4)
C(24)A	−3361(15)	5263(12)	8026(12)	110(9)
C(25)A	−3247(13)	7321(12)	8064(11)	99(8)
C(26)A	4026(10)	4101(8)	6472(7)	49(4)
C(27)A	6094(9)	8663(7)	5263(5)	44(4)
C(28)A	8789(9)	4422(7)	4513(6)	48(4)
C(29)A	8222(10)	3511(8)	3829(6)	56(4)
C(30)A	9040(12)	4005(9)	5242(7)	62(5)
C(31)A	2347(9)	5969(8)	10906(6)	58(4)
C(32)A	3803(11)	5892(13)	10408(10)	82(7)
C(33)A	1837(8)	4819(7)	11004(5)	48(4)
C(34)A	1404(9)	4737(9)	11817(7)	68(5)
C(35)A	1007(12)	3738(13)	11945(10)	90(7)
C(36)A	1007(12)	2740(14)	11242(12)	106(9)
C(37)A	1404(15)	2818(10)	10403(11)	122(8)
C(38)A	1804(11)	3882(9)	10281(7)	81(5)
C(39)A	5782(10)	10459(7)	5081(6)	61(4)
C(40)A	6681(15)	11261(10)	4658(9)	94(7)
C(41)A	5252(10)	11058(7)	6045(7)	60(4)
C(42)A	6087(13)	11529(10)	6601(8)	88(6)
C(43)A	5566(19)	12035(13)	7499(10)	126(9)
C(44)A	4198(21)	12020(12)	7774(9)	126(9)
C(45)A	3385(12)	11573(11)	7250(10)	94(7)
C(46)A	3855(11)	11057(8)	6376(8)	74(5)
O(1)A	3404(6)	6454(5)	8226(4)	48(3)
N(1)A	1433(7)	6345(6)	10484(4)	48(3)
O(3)A	−1002(5)	6795(5)	10533(3)	51(2)
O(4)A	−2933(6)	6668(7)	9732(5)	68(4)
O(5)A	4189(6)	8050(5)	6415(4)	51(3)
N(2)A	6588(8)	9458(6)	4936(5)	53(3)
O(7)A	8775(5)	8191(4)	4383(4)	50(2)
O(8)A	9983(5)	6228(5)	4047(4)	50(3)
C(1)B	−1264(7)	9533(6)	10486(5)	33(3)
C(2)B	−1590(7)	9573(6)	11353(5)	36(3)
C(3)B	−483(7)	9539(7)	11752(5)	43(3)
C(4)B	825(8)	9540(7)	11276(5)	48(4)
C(5)B	2500(8)	9640(7)	9964(5)	44(3)
C(6)B	2793(8)	9416(6)	9086(6)	48(4)
C(7)B	1740(8)	9313(6)	8608(5)	41(3)
C(8)B	405(7)	9477(6)	9072(4)	33(3)
C(9)B	63(6)	9529(6)	9989(4)	30(3)
C(10)B	1101(7)	9583(6)	10424(5)	40(3)
C(11)B	−3700(7)	8875(6)	12103(4)	38(3)
C(12)B	−3001(7)	9747(6)	11872(4)	35(3)
C(13)B	−3595(7)	10825(6)	12132(5)	33(3)
C(14)B	−4882(8)	10980(7)	12633(5)	42(3)
C(15)B	−6977(7)	10393(6)	13462(5)	42(3)
C(16)B	−7690(7)	9529(6)	13666(5)	40(3)
C(17)B	−7170(7)	8367(6)	13396(5)	44(3)
C(18)B	−5844(7)	8119(6)	12900(5)	39(3)
C(19)B	−5037(7)	9027(6)	12637(5)	36(3)
C(20)B	−5613(7)	10112(6)	12910(4)	36(3)

TABLE 2 (continued)

Atom	x	y	z	U^*
C(21)B	−763(10)	9480(12)	12654(6)	80(6)
C(22)B	−518(8)	9672(6)	8641(5)	41(3)
C(23)B	3577(8)	9973(8)	10500(6)	51(4)
C(24)B	4247(12)	8884(10)	10455(9)	86(6)
C(25)B	4555(10)	10795(9)	10299(8)	90(6)
C(26)B	−2837(11)	11794(8)	11888(7)	57(4)
C(27)B	−5346(8)	7008(7)	12713(5)	43(3)
C(28)B	−7636(8)	11566(7)	13804(5)	46(3)
C(29)B	−7929(9)	12031(8)	13142(6)	60(4)
C(30)B	−6906(11)	12440(8)	14439(7)	61(4)
C(31)B	−1145(9)	10027(7)	7413(6)	55(4)
C(32)B	−1156(19)	9095(11)	6526(9)	121(9)
C(33)B	−674(8)	11168(7)	7317(6)	54(4)
C(34)B	−789(11)	12131(9)	8052(7)	80(5)
C(35)B	−346(13)	13175(10)	7989(10)	104(7)
C(36)B	174(14)	13275(11)	7218(12)	109(8)
C(37)B	298(12)	12419(12)	6502(11)	95(7)
C(38)B	−126(9)	11320(8)	6511(6)	73(5)
C(39)B	−5459(9)	5076(7)	12819(6)	57(4)
C(40)B	−5048(12)	5076(10)	13655(7)	110(7)
C(41)B	−4343(8)	4676(7)	12015(6)	50(4)
C(42)B	−3045(10)	4970(9)	12060(8)	86(6)
C(43)B	−1915(12)	4582(12)	11271(12)	116(9)
C(44)B	−2427(18)	3967(14)	10570(12)	127(10)
C(45)B	−3659(22)	3641(12)	10479(10)	147(10)
C(46)B	−4637(13)	4023(9)	11255(7)	90(6)
O(1)B	−2298(5)	9492(5)	10082(4)	47(2)
N(1)B	−251(8)	9628(6)	7809(5)	50(3)
O(3)B	2171(5)	9160(4)	7773(3)	51(2)
O(4)B	4067(5)	9357(6)	8596(4)	64(3)
O(5)B	−3149(5)	7800(4)	11817(3)	47(2)
N(2)B	−6012(6)	6229(5)	12963(4)	48(3)
O(7)B	−7952(5)	7626(5)	13622(4)	65(3)
O(8)B	−8975(5)	9691(5)	14178(4)	49(2)

$U^* = 1/3 \sum_i \sum_j u_{ij} a_i^* a_j^* a_i \cdot a_j$.

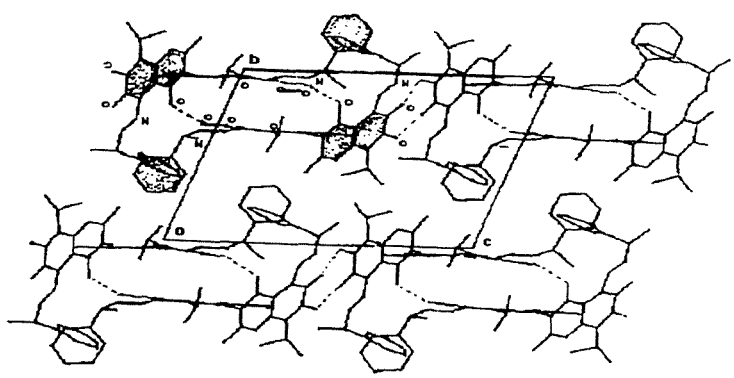

Fig. 2. Crystal structure of DPEAG.

It is known that gossypol and dianilinegossypol have a strong tendency to dimerize through H-bonds. Even with a disturbance of the enantiotopic ratios between the atropoisomeric gossypol molecules through the addition of optically active substituents, the tendency of the dextrorotatory and the levorotatory molecules to undergo dimerization is retained. This prevents the separation of racemic gossypol by the expedients of classical stereochemistry, i.e., by the stepwise crystallization of diastereoisomers obtained from the initial racemate.

The dimerization of gossypol and its derivatives apparently takes place even in solution, which prevents the separation of the racemates by column chromatography. Success may probably be achieved by the fractional crystallization of derivatives in which the possibility of dimerization has been eliminated — for example, because of the absence of *peri*-hydroxyls.

Thus, the structure of the product of the condensation of gossypol with (−)-α-phenylethylamine has been determined. It has been shown that a possible reason for the difficulty in separating racemic gossypol into its optically active components is not the racemization of (−)-α-phenylethylamine but the strong tendency of gossypol and its derivatives to form dimers.

EXPERIMENTAL

Single crystals were grown from a solution of gossypol in ethyl alcohol during condensation with (−)-α-phenylethylamine at room temperature. The crystallographic parameters of a single crystal were determined and refined from 15 reflections in a Syntex-$P2_1$ automatic four-circle diffractometer: a = 10.297(1) Å, b = 12.465(2) Å, c = 16.698(2) Å, α = 109.87(2)°, β = 76.06(1)°, γ = 93.95(1)°, V = 1959.5(1.4) Å^3, Z = 2, d_{calc} = 1.23 g/cm^3, space gr. P1.

Integral intensities were measured by the method of $\theta 2/\theta$ scanning 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 group consisted of 3618 reflections. The structure was determined by direct method using SHELXS-86 adapted for an IBM AT-386 PC [12].

The structure was refined with SHELX-76 [13] on the same PC. The hydrogen atoms in the molecules were located with the aid of difference Fourier syntheses. The divergence factor after the final stage of refinement of the position and anisotropic temperature factors was R = 0.043. The coordinates of the atoms are given in Table 2.

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