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STRUCTURE OF GOSSYPOL ARYLIMINES

N. I. Baram, F. G. Kamaev,
Kh. L. Ziyaev, L. Biktimirov,
A. I. Ismailov, G. B. Nazarov, and
B. T. Ibragimov

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A number of new Schiff's bases of gossypol with aromatic amines and sulfanilamide compounds has been obtained. It has been shown by UV and PMR spectroscopy and x-ray structural analysis that in some solvents they exist predominantly in the quinoid form. For dianilinegossypol (in the solid state) the quinoid structure has been demonstrated and two polymorphic modifications have been revealed by x-ray structural analysis.

The possibility of the existence of gossypol in three tautomeric forms — dialdehyde, dilactol, and diquinoid — has been discussed in the literature [1], although the last-mentioned has been shown only in the case of its derivatives [2], including imino compounds [3]. Continuing a study of azomethines of gossypol with the aim of obtaining physiologically active compounds, we have synthesized a number of its derivatives with aromatic amines and sulfanilamide compounds (Fig. 1). In spite of the fact that compounds (I—VII) had been described previously [4], it was desirable to perform a spectral study of them in order to determine their structures more accurately.

The phenomenon of tautomerism, in which the sigmatropic transfer of a proton leads to a benzoid-quinoid equilibrium shifted in one direction or the other is characteristic for aromatic aldimines [5]. It can be seen from Table 1, which gives the parameters of the electronic spectra of Schiff's bases obtained from gossypol that absorption in the 440-480 nm region is most characteristic for them. The position and the intensity of the absorption maximum does not depend on the polarity of the solvent, which indicates their existence in practically a single tautomeric form [6]. Comparison with the spectra of 2-hydroxy-1-naphthaldimines [7] permits the absorption in the 440-480 nm region to be assigned to the quinoid form (II). This assignment was confirmed by the presence in the PMR spectra of the gossypol arylimines in CCl_4 of a doublet with a coupling constant J = 10-12 Hz in the 9.63-10.12 ppm region appearing as the result of the spin-spin coupling of the methine and amine protons, which is characteristic for compounds existing in the quinoid form [8].

Unfortunately, the majority of the gossypol derivatives obtained were sparingly soluble in organic solvents and it was possible to record the PMR of some of them only in DMSO. In the PMR spectra in DMSO-d_6, a signal in the 10.18-10.62 ppm region represented a superposition

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A. S. Sadykov Institute of Bioorganic Chemistry, Uzbek SSR Academy of Sciences, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 650-654, September-October, 1988. Original article submitted December 22, 1987.

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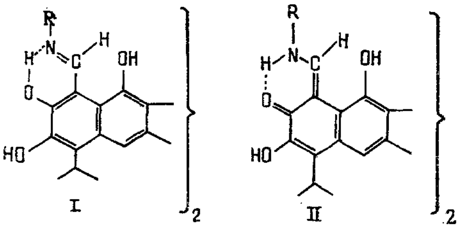


I

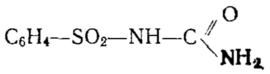
II

R

I. C_6H_5
II. o-C_6H_4OH
III. m-C_6H_4OH
IV. p-C_6H_4OH
V. o-C_6H_4COOH
VI. m-C_6H_4COOH
VII. p-C_6H_4COOH
VIII. p-$C_6H_4COOC_2H_5$
IX. $C_6H_4COOCH_2CH_2(C_2H_5)_2$
X. *$CH-(CH_3)-C_6H_5$
XI. $C_6H_4-N=N-C_6H_5$
XII. $C_6H_3(CH_3)-N=N-C_6H_4CH_3$
XIII. $C_6H_4SO_2NH_2$

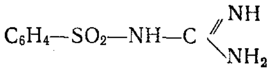
R

XIV.



$C_6H_4-SO_2-NH-C(=O)NH_2$

XV.



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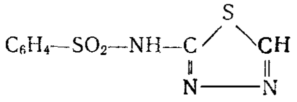
XVI.



XVII.

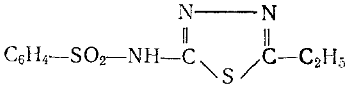


Fig. 1

TABLE 1. Spectral Characteristics of Gossypol Arylimines

Compound	UV spectrum		PMR spectrum	
	solvent	λ_{max}, nm (lg ε)	solvent	δ, ppm (J, Hz)
I	CCl_4	310 (4,3), 445–455 (4,60)	CCl_4	10,00–10,12 (d, 12) 14,94–15,10 (d, 12)
	Dioxane	310 (4,18), 440 (4,34)		
	C_3H_7OH	300–320 (4,43), 440 (4,13)		
IV	Dioxane	440 (4 54)	Acetone-d_6	10,32–10,40 (d, 12); 15,24–15,50 (br.)
	DMSO	455 (1,85)	DMSO-d_6	10,20–10,40 (br.); 14 6–14,78 (br.)
	CH_3OH	250 (2,0) 275–290 (sh) 455 (3,82)	CD_3OD	10,52 (s)
VII	Dioxane	320 (4,14) 450 (4,15)	Dioxane-d_8	10,12–10,26 (d, 12); 14,86–15,05 (d, 12)
	DMSO	460 (4,50)	DMSO-d_6	10,28–10,62 (br.) 14,6–14,9 (br.)
	CH_3OH	250 (1,8) 450 (3,82)		
VIII	CCl_4	320 (4,61); 450 (4,73)	CCl_4	9,63–9,88 (d, 12), 14,56–14,82 (d, 12)
	DMSO	455 (4,26)	DMSO-d_6	10,20–10,40 (br.), 14,62–14,80 (br.)
	CH_3OH	270–290 (sh), 310 (infl.) 440–450 (3,93)		

TABLE 2. Some Physicochemical Characteristics of the New Gossypol Arylimines

Compound	T.mp., °C	R_f	Empirical formula	Yield, %
VIII	292–294	0,85	$C_{48}H_{48}N_2O_{12}$	70,00
IX	190–192	0,80	$C_{56}H_{66}N_4O_{10}$	59,43
X	234–236	0,52	$C_{46}H_{48}N_2O_6$	80,49
XI	288–290	0,18	$C_{54}H_{48}N_6O_6$	84,93
XII	260–262	0,37	$C_{58}H_{56}N_6O_6$	89,69
XIII	262–265	0,71	$C_{42}H_{44}N_4O_{10}S_2$	80,63
XIV	238–240	0,74	$C_{44}H_{44}N_6O_{12}S_2$	47,95
XV	254–256	0,51	$C_{44}H_{46}N_8O_{10}S_2$	83,67
XVI	254–256	0,65	$C_{48}H_{44}N_6O_{10}S_4$	89,32
XVII	232–234	0,74	$C_{50}H_{50}N_8O_{10}S_4$	56,60

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*The N and S analyses of compound (VIII)-(XVII) corresponded to the calculated figures.

of a doublet and a singlet with different intensities, and to a first approximation this can be interpreted as the presence of the signals of the protons of two forms — benzoid and quinoid — as was confirmed, moreover, by a considerable complication of the spectrum in the region of the aromatic protons of the amine component at 7-8 ppm. The appearance of a singlet in the place of a doublet can be explained in two ways: both by the presence of the benzoid form (—CH=N—) and by the transformation of the doublet signal of the methine proton through rapid vibrations of the acidic proton in the quinoid form [9]. Furthermore, in all the spectra, both in CCl_4 and in DMSO-d_6, a doublet or a broadened unresolved signal was observed in the 13.80-15.80 ppm region due to the presence of a NH proton bound by a strong hydrogen bond [8]. On deuteration (compound (IV)), the doublet from the methine proton was converted into a singlet, and the signal of the acidic proton disappeared as the result of deuterium exchange. All that has been said above confirms a rule established previously [10]: an increase in the volume of the annealed π-electron system leads to an enhancement of the aromaticity of the quinoid tautomer and increases its stability.

Attention must be drawn to a spectral characteristic of compound (X), consisting of the product of the condensation of gossypol with an alkylaryl substituent containing an asymmetric carbon atom. In the PMR spectrum of this compound in CCl_4 a double set of signals of the functional groups of the molecule is observed, which shows the presence of two optical isomers [11].

The question of the form of existence of aryl derivatives of gossypol in the solid state was solved by performing a complete x-ray structural analysis of a single crystal of compound (I). Ethyl acetate and dichloroethane were used as the solvents for crystallization in order simultaneously to show the influence of the polarity of the medium on the tautomeric state of the substance. The determination of the crystallographic parameters of the single crystals that had been grown showed that compound (I), like gossypol itself [12], tends to pseudopolymorphism and crystallizes in two different forms from the solvents mentioned:

Ethyl acetate	Dichloroethane
$a = 18.025$ (3): $b = 10.840$ (2);	$a = 11.996$ (3); $b = 13.647$ (3)
$c = 25.021$ (3) Å; $\beta = 126.36$ (1)°;	$c = 16.793$ (5) Å; $d = 119.76$ (2)°
$V = 3937.55$ (0.95) Å^3	$\beta = 91.07$ (2)°; $\gamma = 71.74$ (2)°
	$V = 2234.98$ (1.06) Å^3
Space group	**Space group**
$P2_1/c$	$P1$

Both crystalline forms were monosolvates of dianilinegossypol with the corresponding solvents. The results of the interpretation and refinement of the figures obtained with the aid of the direct methods of the XTLSM group of programs to R = 0.055 (ethyl acetate) and R = 0.068 (dichloroethane) indicated that in the crystals grown both from ethyl acetate and from dichloroethane the dianilinegossypol existed in the quinoid form, i.e., the tautomeric state in the solid samples did not depend on the polarity of the medium.

EXPERIMENTAL

The arylimines were obtained by the method of [4]. PMR spectra were recorded on a Varian XL-200 spectrophotometer with a working frequency of 200 MHz in CCl_4, $CDCl_3$, CD_3OD, DMSO-d_6, acetone-d_6, and dioxane-d_8. UV spectra were taken on a SF-26 spectrophotometer at a concentration of 0.002% with a cell thickness of 1 cm (for solvents, see Table 1). The compounds obtained were pulverulent or crystalline brightly colored substances with high melting points readily soluble in the usual organic solvents (Table 2).

TLC was performed on Silufol UV-254 plates using the acetone—toluene (4:6) system. Single crystals of (I) were obtained from the corresponding solvent medium during the condensation of gossypol with aniline. The experimental results were acquired on a Syntex-P2 diffractometer.

SUMMARY

A number of new Schiff's basis of gossypol with aromatic amines and sulfanilamide compounds have been obtained, and their existence in solvents predominantly in the quinoid form has been shown by UV spectroscopy and PMR. An x-ray structural investigation of one of the compounds — dianilinegossypol — has shown its quinoid form in the solid state. In addition, two polymorphic modifications have been found for dianilinegossypol.

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INTERACTION WITH CHOLINESTERASES AND CONFORMATIONAL ANALYSIS OF ANALOGS OF ACETYLCHOLINE CONTAINING THE ALKALOIDS EPHEDRINE AND PSEUDOEPHEDRINE

A. G. Dobren'kov, V. B. Leont'ev,
Z. Tilyabaev, D. N. Dalimov, and
A. A. Abduvakhabov

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Acetyl-β-methylcholine analogs of ephedrine and pseudoephedrine have been synthesized. The kinetics of their interaction with cholinesterases have been studied. To explain the differences in the sensitivity of the enzymes to conformers, a conformational analysis of the compounds synthesized has been made by the NMR method.

Continuing work in the field of the synthesis of alkaloid derivatives containing the structural elements of acetylcholine, we have performed the synthesis of diacetyl-N-(β-hydroxypropylephedrine and of diacetyl-N-β-hydroxypropylpseudoephedrine. Using these compounds as examples, it appeared of interest to elucidate the influence of conformational states on the catalytic activity of cholinesterases. As has been shown previously [1], substances with analogous structures may be present in solution in structurally fluctuating states, thanks to which they are capable of forming complexes with the acetylcholine receptor and with cholinesterases [2-4].

TABLE 1. Anticholinesterase Efficacy of O-Diacetyl-N-(β-acetoxypropyl)ephedrine (I, II), -pseudoephedrine (III, IV), and Their Methiodides

Compound	K_i (M)		K_i BuCE/K_i ACE
	ACE	BuCE	
I	$7{,}4\cdot10^{-4}$	$2{,}0\cdot10^{-3}$	2,7
II	$5{,}5\cdot10^{-5}$	$3{,}6\cdot10^{-4}$	6,5
III	$2.3\cdot10^{-4}$	$1{,}6\cdot10^{-3}$	7 0
IV	$8{,}5\cdot10^{-4}$	$4{,}9\cdot10^{-3}$	5,7

A. S. Sadykov Institute of Bioorganic Chemistry, Uzbek SSR Academy of Sciences, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 654-658, September-October, 1988. Original article submitted July 21, 1987; revision submitted May 7, 1988.

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