IMINES OF GOSSYPOL ETHERS

N. I. Baram, L. Biktimirov, S. B. Dzhurabekova, F. G. Kamaev, and A. I. Ismailov

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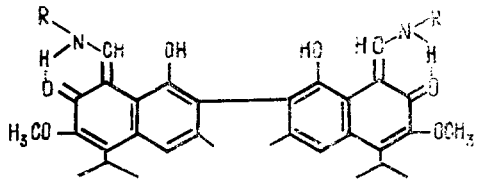
Imines of methyl ethers of gossypol have been synthesized for the first time, their structures have been shown, and their immunomodulating activities have been determined. The quinoid form of existence of the imines of the dimethyl ether and the benzoid form of the imine of the mexamethyl ether of gossypol have been shown.

It is known that the specific pigment of the cotton plant gossypol (I) and some of its derivatives possess a broad spectrum of biological activity [1]. The results of a structural-functional analysis of a number of derivatives of (I) showing the dependence of the antiviral and immunosuppressive activity on the presence of particular functional groups in its molecule have been published previously [2, 3]. Thus, it has been established in the methyl ethers possess activities lower than that of (I), while in the case, for example, of imines of (I) the type and magnitude of the immunomodulating [2] and interferon-inducing activity [4] depend on the nature of the amine component at the aldehyde groups.

Continuing investigations to establish the structure–property relationships in a number of gossypol derivatives, we have synthesized imines of methyl ethers of (I). As the initial substances we used the dimethyl ether (II) and the hexamethyl ether (IX) with free aldehyde groups. Although (II) itself was described a comparatively long time ago [5], no derivatives of it have been obtained. As the amine components we used aliphatic, aromatic, and tetracyclic amines (Table 1). The compounds obtained were colored pulverulent substances insoluble in water and sparingly soluble in other solvents.

As can be seen from Table 1, the nature of the electronic absorption spectra and the intensities of the main maxima of the absorption of the imines of (II) do not depend on the nature of the solvent, which indicates their existence in solution predominantly in a single tautomeric form [6], while the position of the long-wave absorption maximum in the 400-450 nm region permits the quinoid form to be assumed [6]. A proof of this assumption is the presence in the PMR spectra of solutions of the imines of (II) of a doublet in the 9.68-11.40 ppm region with J(CH–NH) ~ 11 Hz, which is characteristic for azomethines existing in the quinoid form, and of a doublet or an unresolved broad signal in the 13.8-17.0 ppm region the appearance of which is due to the presence of a NH proton bound by a strong intramolecular hydrogen bond. By analogy with the imines of (I), for the imines of (II), as for the Schiff's bases synthesized from o-hydroxyaldehydes, the quinoid structure may be assumed to be the most probable [7]



where R represents alkyl, aryl, or heteryl.

If the hexamethyl ether of gossypol with free aldehyde groups (IX) is used as the initial aldehyde component for obtaining a Schiff's base, the imine (X) obtained can be regarded as a typical Schiff's base of an o-methoxyaldehyde with a fixed structure, and the benzoid form of existence may be proposed for it [8]. And, in actual fact, in the UV spectrum of

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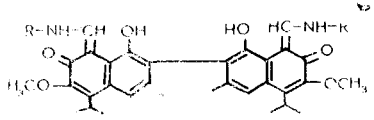
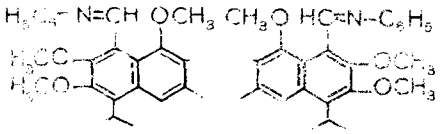
TABLE 1. Some Physicochemical Properties of Imines of Gossypol Dimethyl Ethers



R	mp, °C	UV spectrum: Solvent	UV spectrum: λ_{max}, nm ($lg\varepsilon$)	Empirical formula	N, %: Calculated	N, %: found	Yield, %
(II). Gossypol dimethyl ether		CCl_4	345(4,23)	$C_{32}H_{34}O_8$	—	—	63,4
III.—CH_2CH_2OH	>300	CCl_4	375(1,28); 415(1,28)	$C_{36}H_{44}N_2O_8$	4,43	4,55	64,0
		Dioxane	350(1,23); 410—430(4,30)				
		CH_3OH	355(1,19); 410—430(4,32)				
IV.—CH_2CH_2Cl	300	Dioxane	345(1,11); 410—435(4,20)	$C_{36}H_{42}N_2O_6Cl_2$	4,20	4,11	67,1
		CH_3OH	355(1,12); 415—435(4,20)				
V.—$CH_2CH_2SO_3ONa$	300	Acetone—water (3:1)	375(1,20); 445—485(1,32)	$C_{36}H_{42}N_2O_{14}S_2Na_2$	3,31	3,48	41,2
VI.—C_6H_5	258—260	CCl_4	440—445(1,33)	$C_{44}H_{41}N_2O_6$	4,02	4,26	80,0
		Dioxane	445(4,50)				
		CH_3OH	450(4,11)				
VII.—$C_6H_4CH_2N(CH_2CH_2OH)_2$	205—207	CH_3OH	455(4,56)	$C_{54}H_{66}N_4O_{10}$	6,03	6,15	51,8
VIII.	>350	CCl_4	405—410(4,56)	$C_{54}H_{58}N_6O_8$	9,16	9,22	65,2
		Acetone	350(4,33); 405—410(4,53)				

5,5'-diisopropyl-1,1',6,6',7,7'-hexamethoxy-3,3'-dimethyl-8,8'-di(phenyliminomethyl)-2,2'-binaphthalene (X) in chloroform the main absorption maximum was observed in the 290-300 nm region and the long-wave absorption at 390-450 nm that is characteristic for the imines of (I) and (II), for which the quinoid structure has been shown, was absent. In addition, in the PMR spectrum of compound (X) in $CDCl_3$ a singlet was observed in the 9.04 ppm region the appearance of which is characteristic for the proton of a CH=N group and there were no signals in the weak-field part of the spectrum, which, according to [6], indicates the benzoid structure of the substance obtained.

What has been said above permits the following structure to be proposed for compound (X):



In view of the low solubility of the imines of (II), it was possible to determine the immunosuppressive activity of only some of them. A study of the influence of the imines of (II) on the primary immune response in ram erythrocytes was carried out by G. A. Ismailova. It was shown that some of the compounds studied possess a stimulating effect (compounds (II) and (VI) in a dose of 50 mg/kg), while others (VIII) exhibited an inhibiting action. The results of a study of the biological activities of the imines of (II) permit the conclusion that an immunomodulating activity that bears a well-defined dose-dependent nature, is characteristic for them, as for the imines of (I).

EXPERIMENTAL

The TLC of the dimethyl ether and its iminoderivatives was carried out on Silufol UV-254 plates. The TLC of the hexamethyl ethers was carried out on Al_2O_3 (Brockmann activity grade II, neutral) and on an Alufol plate (Kavalier) in the chloroform–methanol–tridecane (12:1:4) system with concentrated H_2SO_4 as the revealing agent. UV spectra were taken on a SF-26 spectrophotometer (c = 0.002%). PMR spectra were recorded on a Varian XL-200 instrument in $CDCl_3$, DMSO-d_6, and CCl_4.

8,8'-Diformyl-1,1',7,7'-tetrahydroxy-5,5'-diisopropyl-6,6'-dimethoxy-3,3'-dimethyl-2,2'-binaphthalene (II). The hexamethyl ether of gossypol (dilactol form) was obtained as described by Adams et al. [5]. With heating in the boiling water bath, a solution of 3.5 ml of concentrated H_2SO_4 in 100 ml of acetic acid was carefully added to a solution of 10.5 g (0.017 mole) of gossypol hexamethyl ether in 40 ml of acetic acid, and heating was continued for another 30 min. After cooling, 300 ml of distilled water was added to the reaction mixture. The precipitate that deposited was filtered off and was washed with acetic acid and with water and dried.

After recrystallization from benzene, a light yellow microcrystalline substance with a green tinge was obtained. The yield was 6.03 g (63.4%). PMR spectrum (200 MHz, $CDCl_3$); 1.52 (12 SH, d, J = 6.8 Hz; isopropyl groups at C-5 and C-5'); 2.16 (6 H, s, CH_3 groups at C-3 and C-3'); 3.96 (2 H, m, isopropyl groups at C-5 and C-5'); 4.00 (6H, s, OCH_3 groups at C-6 and C-6'); 6.00 (2 H, s, OH groups at C-1 and C-1'); 7.84 (2 H, s, H atoms at C-4 and C-4'); 11.16 (2 H, s, CHO groups at C-8 and C-8'); 14.56 (2 H, s, OH groups at C-7 and C-7').

1,1',7,7'-Tetrahydroxy-8,8'-(β-hydroxyethyliminomethyl)-5,5'-diisopropyl-6,6'-dimethoxy-3,3'-dimethyl-2,2'-binaphthalene (III). A solution of 0.55 g (0.001 mole) of (II) in 45 ml of absolute ethanol was treated with 0.12 ml (0.002 mole) of monoethanolamine, and the mixture was heated in the water bath for 3 h. The yellow precipitate that deposited after cooling was filtered off and was washed with ethanol. Some physicochemical properties of compound (III) are given in Table 1. PMR spectrum (200 MHz, DMSO-d_6): 1.39 (12 H, d, J = 6.8 Hz, isopropyl groups at C-5 and C-5'); 1.90 (6 H, s, CH_3 groups at C-3 and C-3'); 3.52 (2 H, m, isopropyl groups at C-5 and C-5'); 3.4-3.7 (8 H, m, CH_2CH_2 groups); 3.84 (6 H, s, OCH_3 groups at C-6 and C-6'); 7.48 (2 H, s, H atoms at C-4 and C-4'); 9.74 (2 H, d, J = 11.3 Hz, H atoms at C-8 and C-8'); 13.92 (2 H, m, NH groups).

The other imines of (II) were obtained in the same way.

8,8'-Diformyl-5,5'-diisopropyl-1,1',6,6',7,7'-hexamethoxy-3,3'-dimethyl-2,2'-binaphthalene (IX). The separation of the isomeric mixture of hexamethyl ethers of gossypol obtained

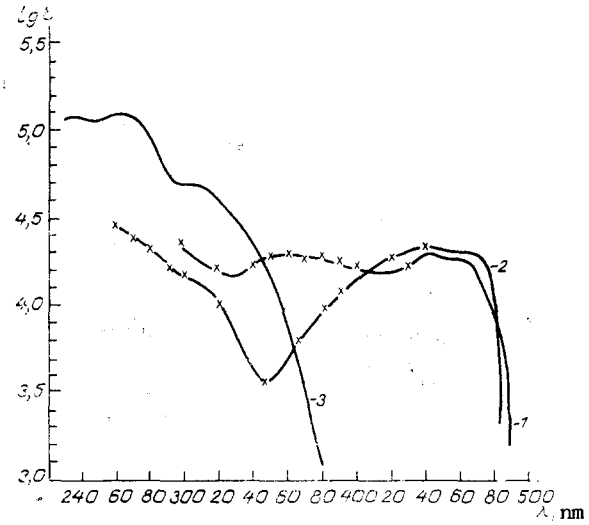


Fig. 1. Absorption spectra of dianilinogossypol (1) in $CHCl_3$ and of compounds (VI) (2) and (X) (3) in CCl_4.

by the method of Adams et al. [5] was achieved with the aid of a column of Al_2O_3 (Brockmann activity grade II, neutral) and elution by benzene–petroleum ether (3:1). The fractions showing, in TLC on Al_2O_3, a bright yellow spot on treatment with concentrated H_2SO_4 were combined and concentrated. The residue (a white pulverulent substance) corresponded in its parameters to compound (X) described in [9].

5,5'-Diisopropyl-1,1',6,6',7,7'-hexamethoxy-3,3'-diemthyl-8,8'-di(phenyliminomethyl)-2,2'-binapthalene (X). A mixture of 0.16 g (0.00027 mole) of (IX) and 0.05 g (0.00054 mole) of aniline in 50 ml of ethanol was boiled on the water bath for 3 h. After the elimiantion of part of the solvent and cooling, a precipitate deposited. It was filtered off and was washed with cold ethanol and dried.

A white pulverulent substance with a slight yellowish tinge was obtained; mp 203-205°C, R_f 0.87. UV spectrum: $\lambda_{max}^{CHCl_3}$ nm: 250, 270, 290-300 ($\log \varepsilon$ 5.08, 5.10, 4.65). PMR spectrum (200 MHz, $CDCl_3$): 1.52 (12 H, d, J = 6.8 Hz, isopropyl groups at C-5 and C-5'); 2.00 (6 H, s, CH_3 at C-3 and C-3'); 3.22 (6 H, s, OCH_3 groups at C-6 and C-6'); 3.92 and 4.00 (each 6 H, s, CH_3 groups at C-1 and C-1' and at C-7 and C-7'); 3.96 (2 H, m, isopropyl groups at C-5 and C-5'); 7.2-7.5 (10 H, m, C_6H_5 groups); 7.90 (2 H, s, H atoms at C-4 and C-4'); 9.04 (2 H, s, CH=N groups at C-8 and C-8').

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