ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2010, Vol. 36, No. 3, pp. 390–395. © Pleiades Publishing, Ltd., 2010.
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# Synthesis, Structures, and Acute Toxicity of Gossypol Nonsymmetrical Aldehyde Derivatives

**K. Z. Tilyabaev[1], F. G. Kamaev, N. L. Vypova, A. M. Yuldashev, B. T. Ibragimov, and S. A. Talipov**

*Sadykov Institute of Bioorganic Chemistry, Uzbek Academy of Sciences, Mirzo Ulugbek str. 83, Tashkent, 100125 Uzbekistan*

Received June 21, 2009; in final form, September 8, 2009

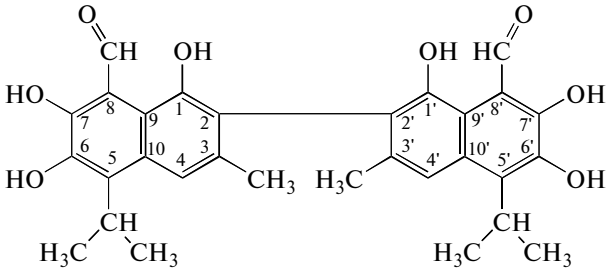
**Abstract**—Nonsymmetrical aldehyde derivatives of gossypol, a yellow polyphenolic pigment of cottonseed, were synthesized by reactions with ammonia, aniline, 4-aminoantipyrine, and barbituric acid. Their structures were determined by UV spectrophotometry and IR and $^1$H NMR spectroscopy methods. Their acute toxicities in white mice were compared with those of gossypol and the corresponding symmetrical analogues. It was demonstrated that in general, the fewer free aldehyde groups available in the gossypol derivative, the lower its acute toxicity. Only in the case of a nonsymmetrical gossypol derivative bearing a 4-aminoantipyrine residue did we observe a deviation from the above correlation: its symmetrical counterpart was even more toxic, but still less toxic than gossypol.

*Key words: acute toxicity, gossypol, gossypol symmetrical and nonsymmetrical aldehyde derivatives, synthesis*

**DOI:** 10.1134/S1068162010030167

## INTRODUCTION

Gossypol, 2,2'-bis(8-formyl,1,6,7-trihydroxyl,5-isopropyl,3-methylnaphtaline) (**I**), is a specific cottonseed pigment.



Gossypol (**I**)

The poisoning of nonruminant farm animals and birds observed over the course of long-term feeding with cotton cake and cottonseed meal is the basis for numerous studies of the physiological activities of gossypol [1–4]. It was shown that gossypol can bind to iron and give a low soluble and poorly absorbed complex compound, which may result in disorder in the iron circulation in the organism followed by an imbalance in the functioning of iron-dependent enzymatic systems [5–8].

It was found in vivo and in vitro that gossypol inhibited the activity of Na and K-ATPase [9, 10] and decreased the activity of the metabolic system in an organism, especially during long-term administration [11]. At high doses, gossypol also reduces the activity of enzymatic systems of mitochondrial electron transport chains and disconnects the processes of respiration and oxidative phosphorylation [12–14]. Thus, the toxic effects of gossypol can be partially explained by the inhibition of gossypol-mediated enzymatic systems.

Antitumor and antiviral properties displayed by gossypol [15] allow for its consideration as a potential drug. However, pharmacological studies have shown some disadvantages preventing its use as an effective drug, in particular, marked toxicity at optimal therapeutic doses, cumulating properties, insolubility in water, and pain at the injection sites [16–18]. The preparation of gossypol derivatives could reduce the side effects. Therefore, many efforts were taken to modify its structure and study the structural specific features and physiological activities of the synthesized compounds.

Gossypol derivatives were obtained by coupling with the corresponding aliphatic, aromatic, and heterocyclic amines; sulfanyl amide agents; and some compounds containing reactive methylene groups [19–24]. In addition, gossypol esters and ethers were synthesized [25, 26].

For derivatives of compound (**I**), the structure–activity relationship was most reliably found for immunomodulating activity [27]. The comparative analysis of gossypol derivatives differing in the substitution degree of the hydroxyl groups demonstrated that gossypol methyl ethers were less active than gossypol. The substitution of hydroxyl groups decreased the activity nearly proportionally to the substitution degree. The absence of aldehyde groups also supported

[1] Corresponding author; phone: (99871) 260-3758; e-mail: tilyabaevzaid@mail.ru.

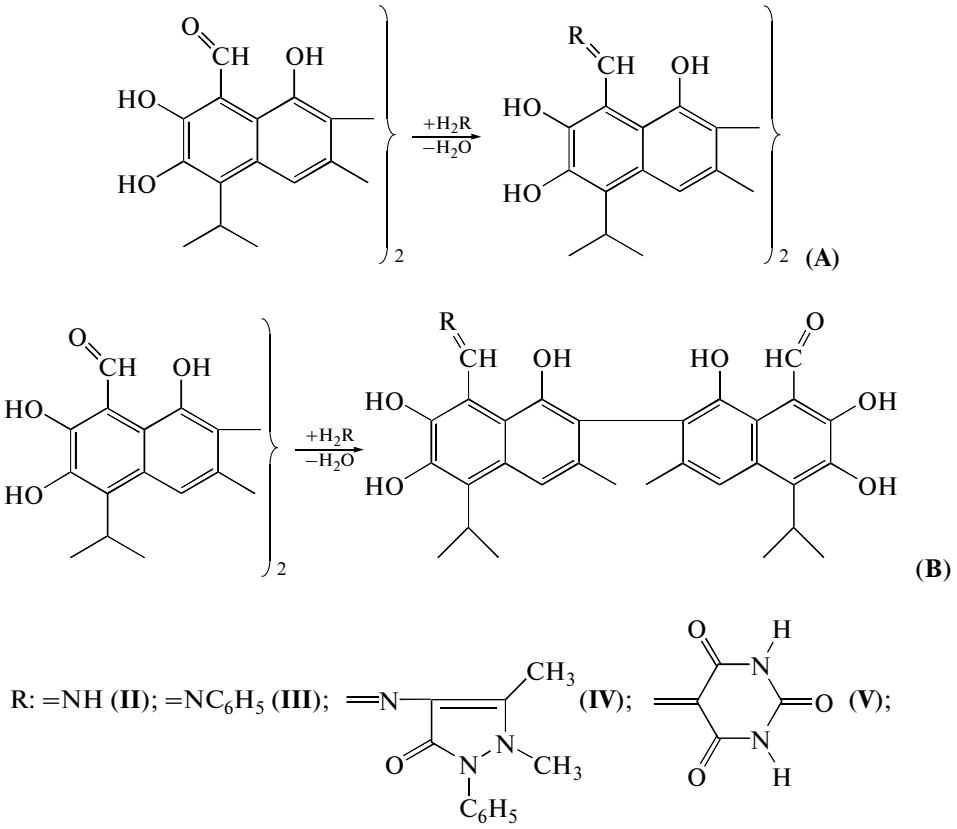



**Fig. 1.** General scheme of the formation of gossypol amino derivatives.

a decrease in activity, whereas the transformation of gossypol into quinone resulted in low activity and considerably increased toxicity. It is noteworthy that the presence of unsubstituted hydroxyl groups and the nature of the substituents at the aldehyde groups were also essential [28].

Due to the symmetry of the starting compound, for a long time only symmetrical derivatives were available. However, at present there are a lot of data on the higher activity of nonsymmetrical gossypol derivatives as compared with the symmetrical counterparts [29–31].

The goal of the present work was the synthesis of nonsymmetrical gossypol derivatives modified at the aldehyde groups and prepared by reactions with ammonia, aniline, 4-aminoantipirine, and barbituric acid and the study of the acute toxicities in white mice with gossypol and the corresponding symmetrical bisanalogues as reference compounds.

## RESULTS AND DISCUSSION

The general scheme of the preparation of gossypol amino derivatives **(IIA)**–**(VA)** and **(IIB)**–**(VB)** is given in Fig. 1.

The optimal conditions for the formation of gossypol monoderivatives were found using high-dilution technologies: a cooled amine solution was added to a preliminary cooled diluted solution of starting **(I)**. When selecting the reaction conditions, we took into consideration that the formation of Schiff bases is known to be highly exothermic [32]. The relatively low solubility of the target products in chloroform at low temperatures enabled their isolation by precipitation followed by filtration and recrystallization.

This method resulted in the preparation of monoderivatives of gossypol **(I)** from amino compounds of various types.

A spectral criterion of the completeness of the monoderivative formation was the presence in the $^1$H NMR spectra of resonances of aldehyde protons at 11–11.3 ppm and ketimine protons at 9.4–10.4 ppm at a 1 : 1 ratio.

The quinoid structure of the synthesized nonsymmetrical monoimines of compound **(I)** (or more exactly, of their amino-substituted fragment) was corroborated by NMR spectroscopy data (see the Experimental section) based on the appearing doublet at 10.1–10.9 ppm (Fig. 2) resulting from the spin–spin interaction of methine and amine protons inherent for quinoid-like forms [28]. Absorption peaks at 460–470 nm in the UV spectra of compounds **(IIIB)** and **(IVB)** (see the Experimental section) also supported the quinoid structure of compounds **(IIIB)** and **(IVB)** [28].

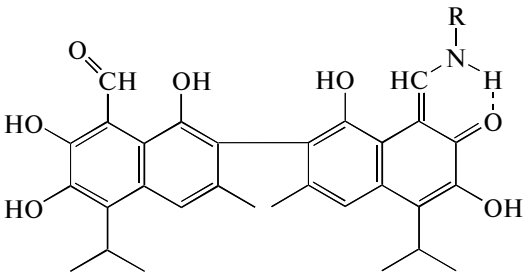


**Fig. 2.** Quinoid structure of nonsymmetrical gossypol amino derivatives.

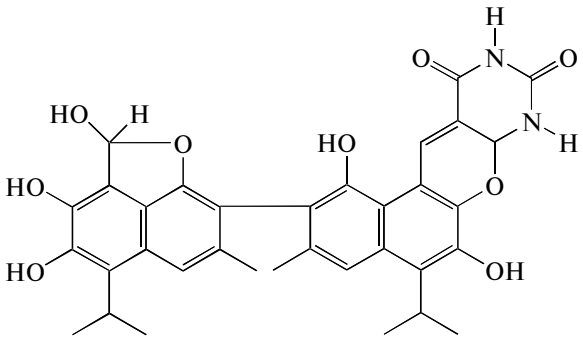


**Fig. 3.** The lactol structure of the nonsymmetrical product of the gossypol reaction with barbituric acid.

It is noteworthy that the aldehyde form remained intact in all of the synthesized nonsymmetrical gossypol derivatives bearing unsubstituted aldehyde groups, except the compounds that could only be dissolved in deuterated DMSO. In these cases, we observed the formation of lactol tautomeric forms, as was found for gossypol [33]. In the UV spectrum of product **(VB)** obtained by the reaction of gossypol with barbituric acid in ethanol, in which the gossypol aldehyde group was transformed into a lactol one [34] as it was observed in DMSO, the absorption maximum at 376–378 nm inherent for aldehyde groups [35] was absent. At the same time, there was a maximum at 261 nm, which is characteristic of a gossypol lactol tautomer [35, 36]. The analysis of the $^1$H NMR spectrum of compound **(VB)** provided the assumption that the intramolecular dehydration accompanying the reaction resulted in a heterocycle joining the gossypol backbone with the substituent (the absence of the C7'–OH resonance upfield (14.5–16.0 ppm) and the absence of one of the substituent NH protons (Fig. 3)). The presence in the IR spectrum of an absorption band at 1670 cm$^{-1}$ characteristic of C=C bonds whose π electrons were conjugated with free oxygen electron pairs [37] also supported the assumed structure for derivative **(VB)**.

Acute toxicity of gossypol and its derivatives

| Tested compound | $LD_{50}$, mg/kg* |
|---|---|
| **(I)** | 154 (130–180) |
| **(IIA)** | 1620 (1400–1800) |
| **(IIIA)** | 4400 (3400–5800) |
| **(IVA)** | 1500 (1200–2000) |
| **(VA)** | 2240 (1000–2500) |
| **(IIB)** | 1200 (900–1600) |
| **(IIIB)** | 3860 (3200–4600) |
| **(IVB)** | 3160 (2000–5100) |
| **(VB)** | 257 (230–290) |

* The dose range at which the death of the minimal ($LD_{10}$) and maximal ($LD_{95}$) number of white mice was observed.

The data on the acute toxicities of the synthesized gossypol derivatives are shown in the table.

Five to ten minutes after the introduction in white mice, the suppression and weakness of the pelvic limbs were observed for 4–5 h. Autopsy studies demonstrated a lack of obvious disorders (flatulence and diarrhea), peritoneal hemorrhage, and peritoneal liquid. In dead animals with high doses of the tested compounds, their traces were found 1–4 days after dosing, and most often in the liver, seminal glands, mesenteries, and stomach. In the surviving animals, the tested compounds in capsulated forms were found in the liver, seminal glands, mesenteries, and sites of the injection 14 days after the administration.

Based on the data obtained, we can conclude that, in general, gossypol monoderivatives **(IIB)**–**(VB)** displayed higher acute toxicity than the corresponding bisderivatives **(IIA)**–**(VA)**, which can probably be explained by the presence of free aldehyde groups. Due to the presence of two aldehyde groups, gossypol **(I)** displayed the highest acute toxicity.

It is interesting that compound **(IVB)** was less toxic than **(IVA)**.

For the understanding of the mechanism of physiological activity, as well as for an explanation of the side effects, data on the distribution of the compound in organelles and organ macromolecules are essential. The increased gossypol affinity to microsome membranes resulted in an adaptive increase in the activity of oxidative enzymes, which in turn stimulated the microsomal system of xenobiotic detoxication [38]. It was also shown that gossypol oxidation (decarbonylation) is one of the principal ways of detoxication upon its elimination from the animal's body.

As follows from the above data, the detoxication of gossypol-like compounds in organisms of warm-blooded animals occurs via their oxidation.

Based on the theory of hard and soft bases and acids [39], we can regard derivative (**IVC**) as a softer acid and, therefore, it must be oxidized under more drastic conditions than a harder acid (**IVA**). This fact may explain the lower toxicity of (**IVB**) than that of the corresponding bisderivative.

With the analysis of the data shown in the table, we can also evaluate the effect of the substituent nature on the acute toxicity. Aliphatic and heterocyclic substituents (compounds (**IIC**), (**IVB**), and (**VB**)) supported its augmentation, whereas aromatic substituents (compounds (**IIIB**)) exhibited the opposite effect.

## EXPERIMENTAL

Gossypol (**I**) was prepared at an experimental plant of the Institute of Bioorganic Chemistry, Uzbek Academy of Sciences, from side products of cotton-oil production. Chemical reagents and solvents were obtained from Aldrich. Compounds (**IIA**)–(**VA**) and (**IIB**) were synthesized as described in [32, 40–42].

The melting points were measured in a glass capillary. TLC was carried out on Silufol UV-254 plates with the development in an iodine chamber.

The UV spectra were registered on a Specord spectrophotometer.

The IR spectra were recorded on an IR-10 spectrophotometer in the region of 3700–750 $cm^{-1}$ in KBr tablets.

The $^1H$ NMR spectra ($CDCl_3$ and DMSO-$d_6$) were registered on a Tesla BS 567-A spectrometer with a working frequency of 100 MHz and tetramethylsilane as an internal standard.

**8-Formyl-1,1,6,6',7-pentahydroxyl-3,3'-dimethyl-8'-methyniminobenzene-7'-oxo-5,5'-diisopropyl-2,2'-binaphthalene (IIIB).** Solutions of compound (**I**) (104 mg, 0.2 mmol) in chloroform (3 ml) and aniline (20 μl, 0.2 mmol) in chloroform (1 ml) were kept for 1 day at −15°C and then mixed and kept for several days at the same temperature. The reaction was monitored by TLC (elution with chloroform, $R_f$ 0.3 for compound (**IIIB**). The precipitate was filtered and recrystallized from acetone to give 65% (**IIIB**); mp 238–240°C. Found, %: C 72.71; H 5.82; N 2.28. $C_{36}H_{35}N_1O_7$. Calc., %: C 72.85; H 5.90; N 2.36. After concentrating followed by separation by column chromatography on silica gel (100/160 μm, elution with chloroform), the filtrate contained 10 and 25% of compounds (**I**) and (**IIIA**), respectively. UV ($CCl_4$), $\lambda_{max}$, nm, (ε): 242 (11570), 280 (5340), 411 (3850), 470 (2970). IR (KBr), $cm^{-1}$: 3560, 2350, 1620, 1540, 1240, 840. $^1H$ NMR: (100 MHz, $CDCl_3$): 15.28 (1 H, s, C7–OH), 11.18 (1 H, s, –CHO), 10.13 (1 H, d, =CH–N), 7.79 (1H, 1, H4), 7.63* (1 H, s, H4'), 7.83–7.88* (5 H, m, substituent's Ph), 3.5–3.96 (2 H, m, C5–CH<), 2.18 (3 H, s, C3–$CH_3$), 2.12* (3H, s, C3'–$CH_3$), 1.59 (6 H, d, isopropyl $CH_3$), 1.52* (6 H, d, isopropyl $CH_3$'). The C1–OH and –C1'–OH, as well as the C6–OH and –C6'–OH protons could not be identified separately because of proton exchange. Herein and below, the resonances of the substituted fragments are marked with an asterisk.

**8-Formyl-1,1',6,6',7-pentahydroxyl-3,3'-dimethyl-8'-methyn-[4"-imino-(1"-phenyl-2",3"-dimethylpyrazol-5"-one]7'-oxo-5,5'-diisopropyl-2,2'-binaphthalene (IVB).** A solution of gossypol (104 mg, 0.2 mmol) and 4-aminoantipyrine (39 mg, 0.2 mmol) in chloroform (5 ml) was kept for 3 days at −15°C. The reaction course was monitored by TLC (9 : 1 chloroform–ethyl acetate, $R_f$ of product (**IVB**) 0.5). The precipitate was filtered off and recrystallized from acetone (mp 200–202°C) to give 43% of compound (**IVB**). Found, %: C 69.89; H 5.72; N 5.83. $C_{41}H_{41}N_3O_8$. Calc., %: C 69.99; H 5.83; N 5.97. After the filtrate was concentrated and purified by column chromatography on silica gel (100/160 μm) in 9 : 1 (v/v) chloroform–ethyl acetate, it contained 30 and 27% of (**I**) and (**IVA**), respectively. UV ($CCl_4$), $\lambda_{max}$, nm, (ε): 243 (13640), 280 (6160), 414 (3430), 462 (3520). IR (KBr), $cm^{-1}$: 3550, 2360, 1630, 1590, 1170, 840. $^1H$ NMR: (100 MHz, $CDC1_3$): 16.24* (1 H, br s, –NH), 15.25 (1 H, s, C7–OH), 11.12 (1 H, s, –CHO), 10.98* (1 H, br s, =CH–N), 7.73–7.75* (5 H, m, substituent Ph), 7.71 (1 H, s, H4), 7.62* (1 H, s, H4'), 3.84(1 H, m, –C5-isopropyl CH), 3.11* (3 H, s, N–$CH_3$ substituent), 2.45* (3 H, s, C-$CH_3$ substituent), 2.16 (3 H, s, $C_3$–$CH_3$), 2.11* (3 H, s, C3–$CH_3$'), 1.59 (6 H, d, isopropyl $CH_3$), 1.52* (6 H, d, isopropyl $CH_3$'). The OH-1, OH-1' and OH-6, OH-6' protons could not be identified separately because of the proton exchange.

**8-Formyl-1,1',6,6',7-pentahydroxyl-3,3'-dimethyl-8'-methyn-[pyrimidine-1",3",5"-trione]7'-oxo-5,5'-diisopropyl-2,2'-binaphthalene (VB).** Dry gossypol (**I**) (104 mg, 0.2 mmol) was added to a solution of barbituric acid (26 mg, 0.2 mmol) in ethanol (50 ml) and the mixture was kept at room temperature for 1 h. The reaction course was monitored by TLC (ethyl acetate, $R_f$ of product (**VA**) 0.89). In 1 h, the mixture containing 35% (**I**) and 35% (**V**) was evaporated and chromatographed on a silica gel column (100/160 μm) in ethyl acetate to give 30% (**VB**). Found, %: C 66.84; H 4.85; N 4.47. $C_{34}H_{30}N_2O_9$. Calc, %: C 66.89; H 4.92; N 4.59. Melting point 220–223°C (ethyl acetate). UV ($C_2H_5OH$), $\lambda_{max}$, nm, (ε): 229 (14370), 261 (13740), 485 (2780). IR (KBr), $cm^{-1}$: 3680, 2870, 1670, 1610, 1525, 1220, 860. $^1H$ NMR (100 MHz, DMSO-$d_6$): 11.31* (1 H, br s, NH), 10.58* (1 H, br s, >C15=CH–), 7.89 (1 H, s, H4), 7.45* (1 H, s, H4'), 7.12 (1 H, br s, >CH–O-lactol). The individual attribution of hydroxyl groups with resonances at 10.3, 9.2, 8.6, 7.8, and 7.0 ppm (broad singlets) was difficult. The singlets of

methyl groups from the two molecule halves only insignificantly differed and were located at the standard spectral regions [33, 43].

**Acute toxicity** was determined in white mice with $20 \pm 1$ g of body weight using the Prozorovskii method [44]. The tested compounds were administered intraperitoneally at doses of 150–5000 mg/kg. The experiments were observed for 14 days.

## ACKNOWLEDGMENTS

The work was supported by the Foundation for Support of Fundamental Research, Academy of Sciences of the Uzbekistan Republic, project no. FA-F3-T-141.

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