# New Gossypol Derivatives

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## Abstract

Twenty new gossypol imines and eight new gossypol hexaesters have been prepared. Preparations of the compounds and selected physical properties are reported. The imines were easily crystallizable solids, generally insoluble in ethanol, and yellow to orange in color. The hexaesters were solids or waxes.

## Introduction

Gossypol 1,1′,6,6′,7,7′-hexahydroxy-5,5′-diisopropyl-3,3′-dimethyl-[2,2′-binaphthyl 8,8′-dicarboxaldehyde] (I in Fig. 1) is the main pigment in glanded cottonseed. Its physical properties, chemical characteristics, and a considerable number of derivatives have been described (1). Although several investigators (2–9,11–12,15–17) have reported the preparation and properties of various gossypol imino-derivatives and gossypol hexaesters, we undertook the preparation of new gossypol imines and hexaesters of probable biological or industrial interest. Imines prepared included those in which R (II in Fig. 1) is n-propyl, i-propyl, n-butyl, t-butyl, n-hexyl, hydroxyethyl, thioethyl, 3-methoxypropyl, m-chlorophenyl, p-bromophenyl, p-iodophenyl, p-ethoxyphenyl, p-carbomethoxyphenyl, p-carboxy-m-hydroxyphenyl, p-carbomethoxy-m-hydroxyphenyl, cyclohexyl, α-, β-, and γ-picolyl, and 6-methyl-α-picolyl. The hexaesters prepared included the normal propanoyl, butanoyl, pentanoyl, hexanoyl, heptanoyl, octanoyl nonanoyl, and decanoyl. The hexaacetate, hexabenzoate, and hexapalmitate have been reported previously (5,9,12,16).

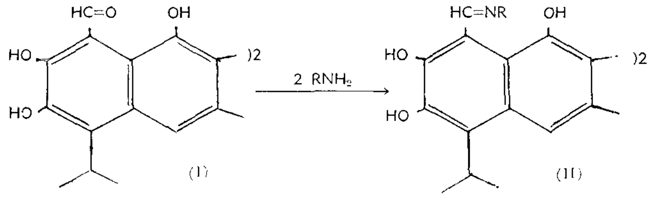

FIG. 1. Reaction of gossypol with amines: I, gossypol; II, Schiff base.

## Experimental

### Materials

Yellow microcrystalline pure gossypol, mp 178C, was obtained from gossypolacetic acid prepared by water washing of cottonseed oil gums according to the procedure of Pons et al. (14) and recrystallization from aqueous acetone.

*Anal.* Calcd. for $C_{30}H_{30}O_8$: C, 69.48; H, 5.83 Found: C, 69.30; H, 5.93.

Available commercial-grade solvents and reactants were purified by either distillation or crystallization. Cysteamine (mp 96C) was prepared starting with ethanolamine (10), via ethyleneimine (13). p-carbomethoxyphenylamine (mp 111C), and p-carbomethoxy-m-hydroxyphenylamine (mp 120C) were prepared by direct esterification of their corresponding acids. The following acid chlorides were prepared by accepted procedures: pentanoyl (bp 126C), hexanoyl (bp 151C), heptanoyl (bp 172C), octanoyl (bp 195C), nonanoyl (bp 215C), and decanoyl (bp 230C).

### Imino Derivatives

For preparation of imino derivatives from the solid and some liquid amines the following procedure was used. The amine (0.002 M) dissolved in

TABLE I

Preparative Data of Imino Gossypol Derivatives

| Gossypol imino derivative | Yield,[a] % | mp, C | Recrystallization solvent | Molecular formula | Elemental composition (%) Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| n-Propyl | 100 | 255/6 | PhCH₂OH/EtOH | $C_{36}H_{44}O_6N_2$ | 72.01 | 7.38 | 4.66 | 71.40 | 7.17 | 4.53 |
| i-Propyl | 82 | 195 | Benzene | $C_{36}H_{44}O_6N_2$ | 72.01 | 7.38 | 4.66 | 71.9 | 7.59 | 4.70 |
| n-Butyl | 96 | 223 | Acetone/water | $C_{38}H_{48}O_6N_2$ | 72.58 | 7.69 | 4.45 | 72.45 | 7.80 | 4.34 |
| t-Butyl | 89 | 270 | Toluene | $C_{38}H_{48}O_6N_2$ | 72.58 | 7.69 | 4.45 | 72.50 | 7.45 | 4.47 |
| n-Hexyl | 63 | 201 | Benzene/Ligroin [b] | $C_{42}H_{56}O_6N_2$ | 73.65 | 8.24 | 4.09 | 73.48 | 8.13 | 4.07 |
| Hydroxyethyl | 90 | 276 | Acetone/water | $C_{34}H_{40}O_8N_2$ | 67.30 | 7.00 | 4.60 | 67.50 | 7.19 | 4.68 |
| Thioethyl | 93 | 256 | PhCH₂OH/EtOH | $C_{34}H_{40}O_6N_2S_2$ | 64.14 | 6.33 | 4.40 | 64.25 | 6.50 | 4.58 |
| 3-Methoxypropyl | 90 | 230 | Pyridine/EtOH | $C_{38}H_{48}O_8N_2$ | 69.06 | 7.32 | 4.24 | 69.10 | 7.42 | 4.30 |
| m-Chlorophenyl | 93 | 286 | DMF [c] | $C_{42}H_{38}O_6N_2Cl_2$ | 68.38 | 5.19 | 3.80 [d] | 68.40 | 5.34 | 4.64 |
| p-Bromophenyl | 87 | 283 | PhCH₂OH/EtOH | $C_{42}H_{38}O_6N_2Br_2$ | 61.03 | 4.63 | 3.40 [e] | 61.15 | ...... | 3.36 |
| p-Iodophenyl | 91 | 280 | PhCH₂OH/EtOH | $C_{42}H_{38}O_6N_2I_2$ | 54.80 | 4.16 | 3.05 [f] | 54.60 | 4.25 | 2.90 |
| p-Ethoxyphenyl | 100 | 246 | DMF/water | $C_{46}H_{48}O_8N_2$ | 72.99 | 6.40 | 3.71 | 73.0 | 6.50 | 3.65 |
| p-Carbomethoxy-phenyl | 79 | 292 | DMF | $C_{46}H_{44}O_{10}N_2$ | 70.40 | 5.65 | 3.57 | 70.32 | 5.50 | 3.46 |
| p-Carboxy-m-hydroxyphenyl | 77 | 230 | DMF | $C_{44}H_{40}O_{12}N_2$ | 66.99 | 5.11 | 3.55 | 66.76 | 5.28 | 3.50 |
| p-Carbomethoxy-m-hydroxyphenyl | 81 | 280 | DMF | $C_{46}H_{44}O_{12}N_2$ | 67.63 | 5.42 | 3.43 | 67.60 | 5.40 | 3.40 |
| Cyclohexyl | 89 | 319 | Benzene | $C_{42}H_{52}O_6N_2$ | 74.08 | 7.70 | 4.11 | 74.50 | 7.76 | 3.90 |
| α-Picolyl | 91 | 251 | Pyridine/EtOH | $C_{42}H_{42}O_6N_4$ | 72.18 | 6.06 | 8.01 | 72.30 | 6.12 | 7.95 |
| β-Picolyl | 91 | 248 | PhCH₂OH/EtOH | $C_{42}H_{42}O_6N_4$ | 72.18 | 6.06 | 8.01 | 72.25 | 6.10 | 7.90 |
| γ-Picolyl | 99 | 234 | Pyridine/EtOH | $C_{42}H_{42}O_6N_4$ | 72.18 | 6.06 | 8.01 | 72.32 | 6.15 | 8.14 |
| 6-Methyl-α-Picolyl | 92 | 282 | Pyridine/EtOH | $C_{44}H_{46}O_6N_4$ | 72.70 | 6.38 | 7.71 | 72.35 | 6.50 | 7.93 |

[a] Yield based on crude product; other data given for recrystallized product.
[b] Ligroin, bp 55–65C.
[c] Dimethylformamide.
[d] Calcd. % Cl, 9.61; found 9.74.
[e] Calcd. % Br, 19.34; found 19.10.
[f] Calcd. % I, 27.59; found 26.90.

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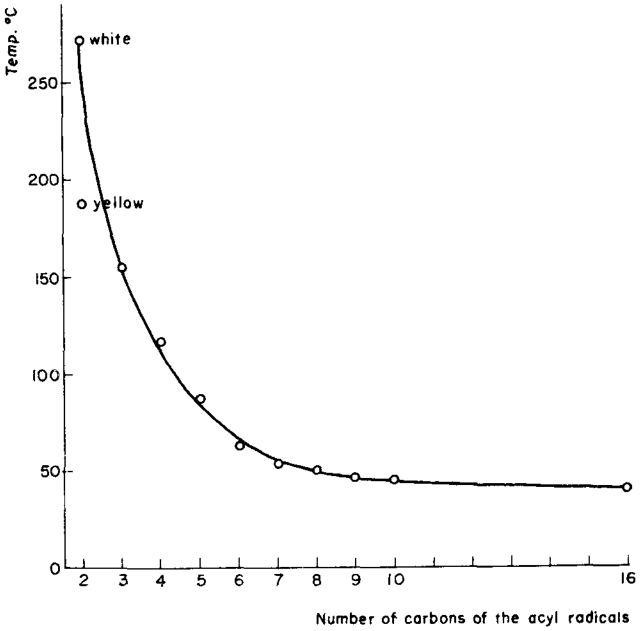

FIG. 2. Relation between melting temperature and number of carbon atoms in acyl radical of gossypol hexaesters.

an excess of absolute ethanol (50 ml) was refluxed with 0.001 M gossypol or gossypol acetic acid for 1.5 hr. The solid, crystalline imino-gossypol derivative was recovered by filtration and purified by recrystallization from suitable solvents as shown in Table I. With liquid amines, 0.001 M gossypol or gossypol acetic acid was refluxed for 0.5 hr in the amine that also acted as a solvent. The imino derivative was recovered by cooling the solution and filtering. The precipitate was washed with water acidulated with HCl and further purified by recrystallization.

### Esters

To a solution of gossypol or gossypol acetic acid (0.1 M) in 20 times its weight of anhydrous pyridine, cooled in an ice bath, was added dropwise and with constant stirring 0.6 M acyl chloride. The mixtures were allowed to stand for 6 to 48 hr at ambient conditions and then poured slowly over a mixture of 20 ml 10% $H_2SO_4$ and 200 g chopped ice. The mixtures were acidulated with dilute sulfuric acid, when necessary, and stored in a refrigerator for 2–3 hr. If a solid mass formed, it was recovered by filtration and then recrystallized. If a semisolid or viscous liquid formed, the hexaester was extracted with diethyl ether and purified by successive washes with dilute HCl and finally water. The preferred solvent for recrystallization of the recovered hexaester was aqueous or absolute ethanol (Table I).

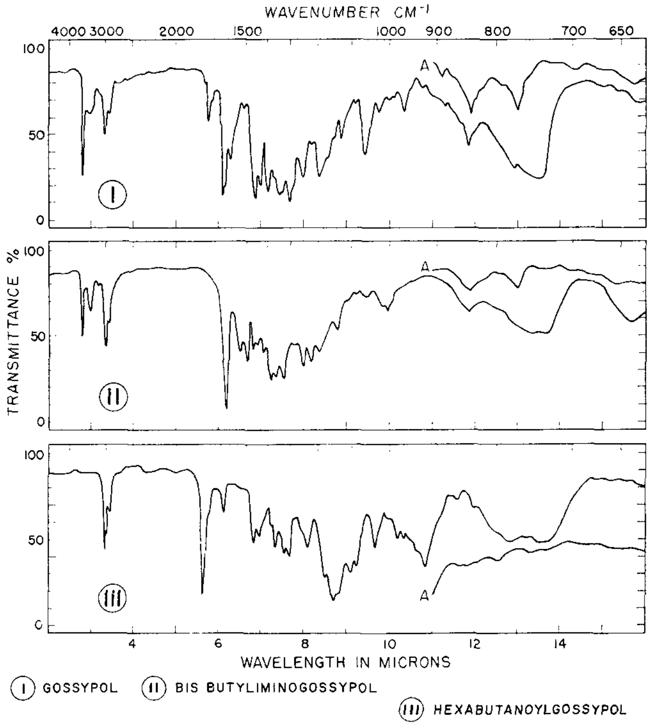

FIG. 3. Infrared spectra of gossypol (I), bisbutylimino gossypol (II), and hexabutanoyl gossypol (III). "A" curves from KBr pellets.

Infrared absorption spectra of the recovered gossypol imines and esters were determined in $CCl_4$ solution and, for the 12–15 $\mu$ region, in KBr pellets using a Beckman model IR 5A spectrophotometer. Melting points of the recrystallized, dry gossypol derivatives were determined with an E. Leitz microscope heating stage model 350.

## Results and Discussion

In Table I are listed the amino-gossypol derivatives, their yield, melting points, solvents employed for recrystallization, and elemental composition.

As shown in Figure 1, one mole of gossypol reacts with two moles of amine. Although the Schiff base form is indicated in Figure 1, Adams (1) has postulated the existence also of an aminoethylene structure analogous to the hydroxymethylene tautomeric form of an o-hydroxyaldehyde. These new imino derivatives were easily crystallizable, ranged from yellow to orange in color, and were generally insoluble in ethanol. For some, dimethylformamide (DMF) was an especially suitable recrystallization solvent.

In Table II are listed the new gossypol hexaesters prepared, together with their yield, melting points,

TABLE II

Preparative Data of Gossypol Hexaesters

| Gossypol hexaesters | Yield,[a] % | MP, °C | | Recrystallization solvent | Molecular formula | Elemental composition (%) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Exptd. | Calcd. | | | Calcd. | | Found | |
| | | | | | | C | H | C | H |
| Propanoyl | 100 | 115 | | EtOH/water | $C_{48}H_{54}O_{14}$ | 67.42 | 6.37 | 66.96 | 6.42 |
| n-Butanoyl | 99 | 117 | | EtOH/water | $C_{54}H_{66}O_{14}$ | 69.07 | 7.08 | 69.28 | 7.13 |
| n-Pentanoyl | 100 | 87 | | EtOH/water | $C_{60}H_{78}O_{14}$ | 70.44 | 7.68 | 70.80 | 7.80 |
| n-Hexanoyl | 88 | 63 | | EtOH/water | $C_{66}H_{90}O_{14}$ | 71.58 | 8.19 | 72.50 | 7.75 |
| n-Heptanoyl | 91 | 55 | 55.3 | EtOH | $C_{72}H_{102}O_{14}$ | 72.57 | 8.62 | 73.15 | 8.48 |
| n-Octanoyl | 90 | 50 | 50.3 | EtOH | $C_{78}H_{114}O_{14}$ | 73.44 | 9.01 | 73.20 | 8.96 |
| n-Nonanoyl | 92 | 47 | 47.0 | EtOH | $C_{84}E_{126}O_{14}$ | 74.18 | 9.34 | 74.00 | 9.26 |
| n-Decanoyl | 100 | 45 | 44.7 | EtOH | $C_{90}H_{138}O_{14}$ | 74.85 | 9.62 | 74.70 | 9.61 |

[a] Yield based on crude product; other data given for recrystallized product.

solvents employed for recrystallization, and elemental composition. The propanoyl, butanoyl, and pentanoyl esters were white microcrystalline solids, the hexanoyl ester was a yellowish white solid, and the octanoyl, nonanoyl, and decanoyl esters were red, waxy products. It was noted that the melting points of the gossypol hexaester decreased, with increasing chain length of the acyl radicals, as shown in Figure 2. This variation in melting points of the gossypol hexaesters, from heptanoyl to palmitoyl, may be expressed by the empirical equation:

$$\log\ (t - 39.7) = 2.3467 - 0.1650\ n$$

where *t* is the melting point in degrees Centigrade and *n* the number of carbons in the acyl group. The melting points thus calculated for the hexaesters, heptanoyl through decanoyl, shown in Table II, are in good agreement with those obtained experimentally, as is the calculated value for the hexapalmitoyl ester (40.2C) with the value (40 − 2C) previously reported (9). Also, we were able to confirm the existence of two gossypol hexaacetates, one yellow melting at 188C and the other white melting at 272C, although their melting points differed slightly from those reported by others (12,16).

Infrared absorption spectra were determined for all compounds prepared, and the characteristic absorption maxima noted. In Figure 3 are shown infrared spectra of gossypol, bisbutylimino gossypol and hexabutanoyl gossypol. Examination of the spectral curves discloses the characteristic absorption maxima for certain specific groups of each compound as,

Gossypol:

$cm^{-1}$ 3550 (OH), 3000 (CH), 1625 (C:O), 1440 ($-CH_3$), and 1245 ($\equiv C-O-$).

Bisbutylimino gossypol:

$cm^{-1}$ 3580 (OH), 3330 (imino), 3000 (CH), 1625 ($=C=N-$), 1245 ($\equiv C-O-$).

Gossypol hexabutanoyl ester:

$cm^{-1}$ 3000 (CH), 1777 (C:O), 1240 ($\equiv C-O-$), 1140 (arylester), and 925 ($CH_2$).

ACKNOWLEDGMENTS

This work was supported by a Public Law 480 grant (Fg. UR-100-61) from the USDA, sponsored by the Southern Regional Research Laboratory (SRRL), New Orleans, Louisiana. SRRL supplied pure gossypol and technical assistance in this work; Mrs. Leah C. Berardi of SRRL revised the manuscript, J. R. Reguli and R. Sosa, Facultad de Quimica (Montevideo), provided mathematical calculations; S. Dittrich and W. Cerveñansky, Facultad de Quimica (Montevideo), performed the microanalyses.

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[Received June 21, 1965]