REVIEW

Reaction Chemistry of Gossypol and Its Derivatives

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ABSTRACT: Gossypol, a complex polyphenolic compound, is a naturally occurring highly colored yellow pigment found in the small intercellular pigment glands in the leaves, stems, roots, and seed of cotton plants. In cottonseed, gossypol contributes to its toxicity and therefore it is regarded as an unwanted processing component. It was not until its antitumor and male infertility activities were discovered that gossypol was considered as a value-added natural product from cottonseed with useful physiological and chemical properties. These serendipitous discoveries created much excitement, and an enormous amount of research on gossypol has ensued. Since then, much research has focused on the preparation of suitable gossypol derivatives for medicinal applications. This review summarizes current knowledge about gossypol, its stereochemistry, tautomerism, and the many varied reactions the gossypol molecule can undergo.

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KEY WORDS: Apogossypol, gossypol, gossypol derivatives, gossypol reactions, male contraceptive, oxidation, reduction, review, Schiff bases.

Gossypol, [1,1′6,6′,7,7′-hexahydroxy-5,5′-di-isopropyl-3,3′-dimethyl-(2,2′-binaphthalene)-8,8′-dicarboxaldehyde] **1** (Fig. 1), is a naturally occurring, highly colored yellow pigment found in the small intercellular pigment glands of cotton plants. Gossypol, a complex polyphenolic compound proposed to be part of a plant's defense system against pathogenic fungi and insects (1), was discovered at the end of the 19th century by Longmore (2) and Marchlewski (3). These investigators sought to use gossypol as dyestuffs but found the pigment to be unstable in light, which prevented its use.

As early as 1915, gossypol was suggested as a substance contributing to the toxicity of raw cottonseed meal (4,5). By 1923, the evidence correlating gossypol content in cottonseed meal to toxicity in nonruminant animals was growing (6), and today, it is well established that gossypol can be toxic to monogastric animals such as swine, poultry, fish, and rodents. The gossypol in cottonseed requires that the meal be cooked to bind the gossypol to other meal components and that the oil be miscella-refined (refined in the extraction solvent) to reduce the tendency of the oil to discolor.

The complex polyphenolic structure of gossypol, in conjunction with its assorted enantiomeric and tautomeric forms (Figs. 1 and 2), made much of the earlier work directed toward identifying gossypol's structure quite challenging, especially when one remembers that the spectroscopic instrumentation routinely used today was not available. Adams classical studies on gossypol's reactions, properties, and degradation products were used to determine gossypol's structure and helped to elucidate a great deal of gossypol's unusual reaction chemistry (7–32). This work, in addition to the work of other researchers such as Clark and Carruth, is well documented in reviews by Adams *et al.* (33), Boatner (34), and Markman and Rzhekhin (35).

Almost two decades passed after Adams' initial studies before the structure postulated by Adams for gossypol was confirmed through gossypol's total synthesis, completed by Edwards and colleague (36–38). With gossypol's structure now firmly established, researchers turned to improving cottonseed's meal and oil quality by developing methods to remove gossypol and other gossypol-like pigments.

It was not until the early 1960s, when the antitumor activity of gossypol was first demonstrated (39), that a fundamental shift in the scientist's perception of gossypol occurred. Gossypol was no longer viewed as a detrimental compound contained in cottonseed, but as a potentially valuable natural product with useful physiological and chemical properties to be exploited. Then in 1978, Chinese scientists announced gossypol's capacity to act as a reversible male infertility agent when orally administered (40). This serendipitous discovery created much excitement, and an enormous research effort has ensued to understand gossypol's mechanism of action (41–45).

Because gossypol itself was found to have serious side effects when used directly for contraceptive applications, efforts focused on modifying gossypol's structure to enhance its therapeutic effects while minimizing its toxicity (46). As a result, a large number of gossypol derivatives (e.g., Schiff's bases, esters, and ethers) have been prepared and characterized. Many of these derivatives and analogs possess a diverse array of unusual disease-inhibiting activities as antimalarial (47,48), anticancer (49,50), HIV (human immunodeficiency virus) (51–54), and antiparasitic (55) agents.

Much of the varied reaction chemistry in which gossypol has been studied has been used in research efforts to obtain suitable gossypol derivatives for medical applications. This review summarizes the large and rapidly growing body of literature pertaining to the diverse reactions available to the gossypol molecule.

THE GOSSYPOL MOLECULE: STRUCTURE, STEREOCHEMISTRY, TAUTOMERISM, AND HYDROGEN BONDING

Structure. To understand gossypol's reaction chemistry, one needs to understand the structure, stereochemistry, tautomerism,

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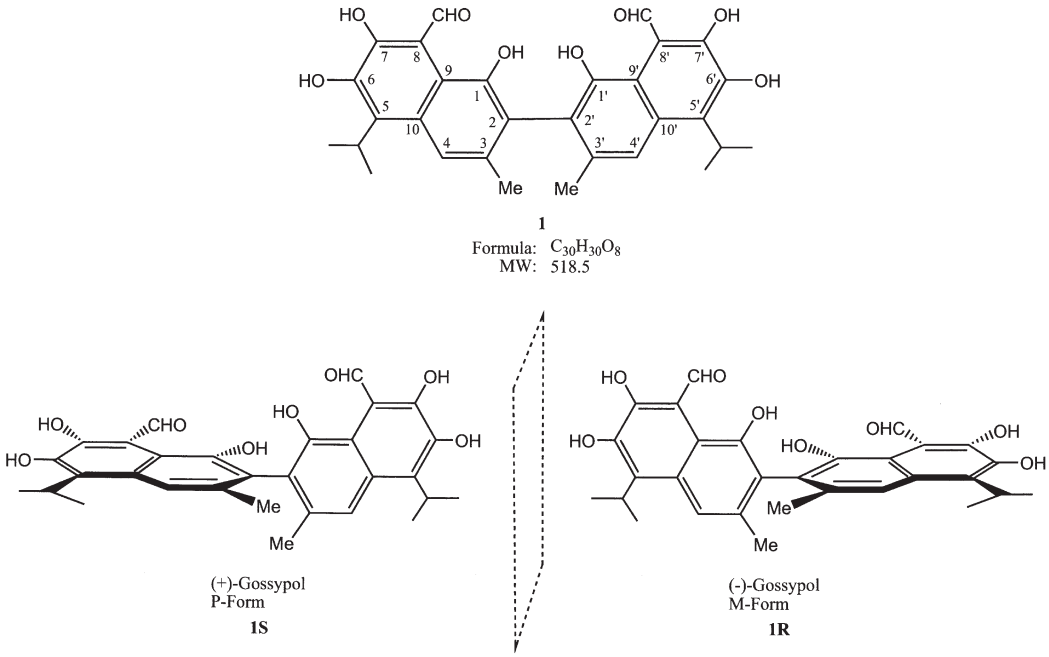


FIG. 1. The chemical (**1**) and enantiomeric (+ and -) structures of gossypol. **1S**, (P)-form or (*S*)-gossypol enantiomer. **1R**, (M)-form or (*R*)-gossypol enantiomer. The (P) and (M) designations correspond to the (+) and (-) atropomeric stereocenter according to the helicity rule.

and hydrogen bonding. As depicted in Figure 1, gossypol's structure consists of two naphthalene rings joined by a single internaphthyl bond between the 2- and 2′-carbon atoms. Attached to this dimeric naphthalenic framework are six hydroxyl groups, two of which reside in the 1- and 1′-positions (these positions are also commonly designated as the *peri* positions). These two 1- and 1′-hydroxyl groups are more reactive than the remaining four hydroxyl groups at the 6,6′- and 7,7′-positions, and in conjunction with their proximity to the aldehyde groups located at the 8- and 8′-positions give rise to some of the rich chemistry

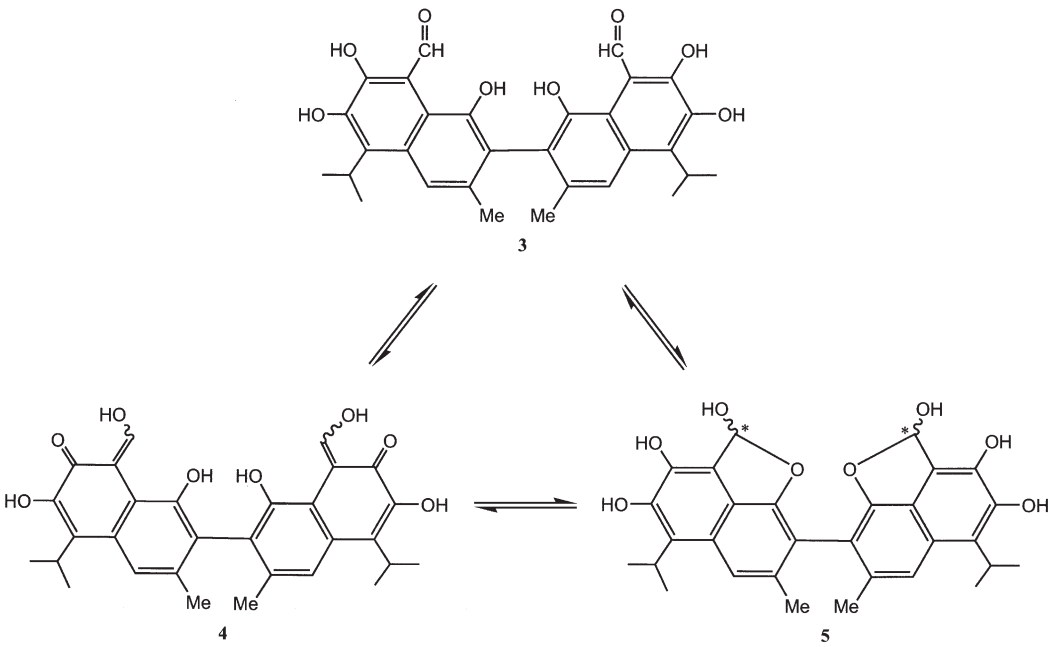
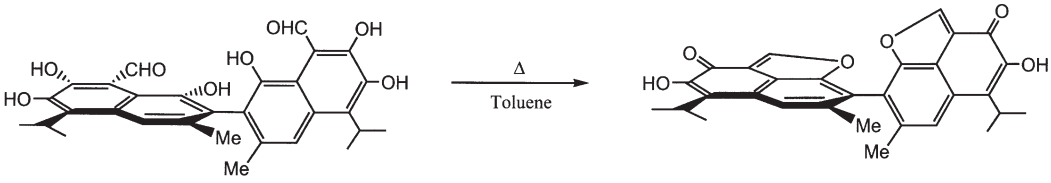


FIG. 2. Symmetrical tautomeric forms of gossypol. Dialdehyde **3**, diketone **4**, and dilactol **5** (* indicates a new asymmetric center in the molecule).



(+)-Gossypol
1S

(+)-Anhydrogossypol
2

FIG. 3. Preparation of (+)-anhydrogossypol **2** from (*S*)-gossypol used in thermal racemization experiments (66).

and hydrogen bonding inherent to the gossypol molecule. The two aldehyde groups also lend themselves to a great deal of interesting chemistry, play a role in gossypol's tautomeric forms (Fig. 2), and are suggested to be the main contributor to gossypol's toxicity (56).

Finally, the four alkyl moieties, two methyl and two isopropyl groups at the 3,3′- and 5,5′-positions, respectively, reside on the same side of the planar naphthalene rings and define gossypol's lipophilic region, whereas the hydroxyl and aldehyde groups, on the other side of the naphthalene ring, characterize the lipophobic region of the molecule.

Stereochemistry. Interaction between gossypol's 3,3′-methyl and 1,1′-hydroxyl substituents results in steric congestion around the 2,2′-internaphthyl bond and effectively restricts rotation around this bond. This hindered rotation results in atropisomerism of the C_2 symmetric gossypol enantiomers shown in Figure 1. X-ray crystallographic studies on crystalline gossypol show that the dihedral angle between the dimeric naphthalene rings in crystalline gossypol lies within approximately 20° of perpendicular (57).

The (+)- and the (−)-enantiomers (**1S** and **1R**, respectively) correspond to the (*S*)-gossypol (P-form) and (*R*)-gossypol (M-form) enantiomers commonly designated in the literature. Vibrational circular dichroism measurements and density functional theory calculations were used to assign the absolute configuration of gossypol enantiomers (58,59). More recently, crystallographic support for these assignments has been made (60). Both enantiomers are abundantly available from cottonseed, although the relative proportions vary with the species and cotton variety. For example, in Pima varieties (*Gossypium barbadense*), (−)-gossypol generally predominates, whereas in Upland cotton (*G. hirsutum*) the (+)-enantiomer prevails (61). Several research groups reported that the tropical tree *Thespesia populnea* is a source of enantiomerically pure (+)-gossypol (62–64).

Because the (−)- and (+)-gossypol enantiomers differ in pharmacological activity (65), the optical stability of these enantiomers is of central importance to pharmacological studies involving gossypol. Computational studies on gossypol racemization carried out by Jaroszewski and coworkers (66) suggest the energy barrier for rotational inversion around the 2-,2′-internaphthyl bond is above 50 kcal/mol for ground state gossypol. Thermal racemization experiments on optically active (+)-gossypol, using a water/dioxane (1:3) solvent system to avoid the facile dehydration of gossypol's aldehyde groups, showed no racemization occurred after prolonged heating (15 h) at 90°C (66). Because gossypol readily dehydrates to form anhydrogossypol **2** (Fig. 3), which is expected to racemize easier than gossypol since the newly formed ring acts to ease the steric congestion around the 2-,2′-internaphthyl bond, the thermal racemization of (+)-anhydrogossypol, **2**, was also examined by Jaraszewski *et al.* (66). Optically active (+)-anhydrogossypol, **2**, synthesized by dehydrating (+)-gossypol (**1S**) in refluxing toluene, was found to racemize at 149°C with a half-life of 22 h, whereas at 190°C racemization was rapid with a half-life below 30 min, but concomitant thermal degradation was also observed.

Fish *et al*. (67,68) reported an interesting photoisomerization method to resolve (+)- and (−)-gossypol enantiomers and recycle the undesired enantiomer (67,68). They found that any of the gossypol Schiff's bases derived from D- or L-phenylalanine methyl ester can be equilibrated using sunlight in approximately 9 h to a 50:50 equilibrium mixture of diastereoisomers that can then be separated chromatographically.

Because the (−)-gossypol enantiomer is not directly isolable from plant sources in optically pure form, methods to resolve racemic gossypol mixtures through crystallization or chromatography have been developed based on diastereoisomeric gossypol derivatives, typically Schiff's bases. Tyson (69) found the (+)-phenylalanine methyl ester Schiff's base prepared from racemic gossypol and phenylalanine methyl ester (Fig. 4) is separated into its diastereomers by preparative TLC or, for larger scales (approximately 70 g), silica gel column chromatography (70). Subsequent hydrolysis of the separated Schiff's bases regenerates multi-gram quantities of optically pure (+)- and (−)-gossypol.

Normal and reversed-phase HPLC is also routinely used to separate and quantify diastereoisomeric gossypol Schiff's base mixtures prepared from various chiral amines and racemic gossypol (71–74). Recently, Cass and coworkers (75) described the first direct resolution of racemic gossypol without the need for derivatization on a chiral amine reversed-phase HPLC column prepared from cellulose *tris*-(3,5-dimethyl carbamate) supported on 5 µm microporous aminopropylated silica.

Dowd (76) recently reported a potentially promising method to obtain large enantiomorphic crystals of gossypol-acetone (1:3) from acetone solutions of *rac*-gossypol-acetic acid (1:1) at 4°C; the method competes favorably with preparative-scale chromatographic procedures (76).

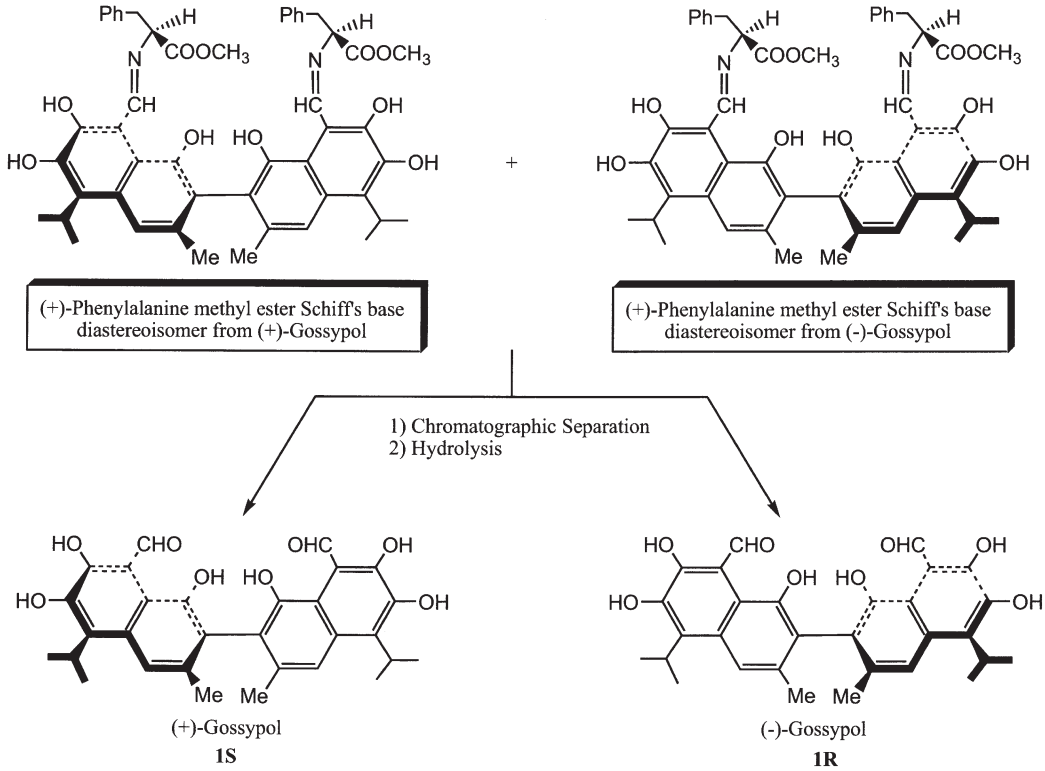


FIG. 4. Chromatographic resolution of diastereomeric gossypol (+)-phenylalanine methyl ester Schiff's bases into enantiomerically pure (+)- and (–)-gossypol (69).

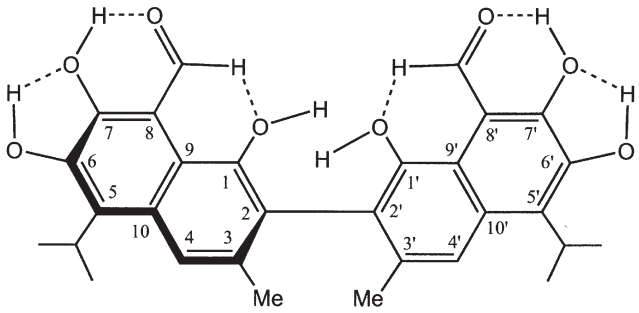
Tautomerism. The complicated reaction chemistry observed for gossypol is attributable, in part, to its various tautomeric forms (Fig. 2). Adams *et al*. (33) proposed three tautomeric forms to explain many of gossypol's reactions, properties, and degradation products encountered during their work. These three forms can be categorized as the aldehyde tautomer **3**, the ketone (quinoid) tautomer **4**, and the lactol (hemiacetal) tautomer **5**. To complicate matters, gossypol's dimeric structure can also give rise to mixed tautomeric forms within the same molecule, in addition to tautomer **5**'s newly formed asymmetric centers (indicated by an asterisk in tautomer **5**), and the possible *E*- and *Z*-geometrical isomers derived from the enol in the ketone tautomer **4** (77).

Extensive ^{1}H NMR, ^{13}C NMR (78), and IR (79) spectroscopic studies in various solvents have examined the equilibrium that exists between these gossypol tautomers. In solvents such as $CHCl_3$, benzene, acetone, or dioxane, gossypol's ^{1}H NMR spectrum shows the aldehydic **3** to be the only tautomeric form present in solution (80–82). The dialdehyde tautomer is also the predominant form found in the solid state (76,83). In contrast, the ^{1}H NMR spectrum of gossypol in DMSO solutions shows mixtures of gossypol tautomers **3**, **4**, and **5**. Tautomer **5** (dilactol form) predominates in the mixture, accompanied by lesser amounts of **4** (diketone form) and approximately 15% of tautomer **3** (dialdehyde form). Interestingly, crystalline gossypol-DMSO clathrate compounds exist only as **3**, the dialdehydic tautomeric structure (84). In CH_2Cl_2 solution, IR spectroscopy showed gossypol exists predominantly as the aldehyde tautomer whereas in DMSO solution an equilibrium exists between the aldehyde and lactol tautomers in which the lactol tautomers predominate (79).

Bronislaw and coworkers (85) examined the ^{1}H NMR spectra of gossypol in deuterated ethanol solutions and found gossypol to exist as a mixture of **3** (dialdehyde form) and **5** (dilactol form), in which the dialdehyde form predominates. Acidification of this solution with DCl to a pH ≤ 1 shifts the equilibrium so that only tautomer **5** is observable. UV-vis spectroscopy experiments performed in conjunction with ^{1}H NMR studies led Bronislaw to propose that the rate-determining step for the tautomerization of **3** to **5** involves the simultaneous protonation of the aldehydic oxygen and lactol cyclization (85).

From these extensive studies, it can be seen that the equilibria between the various tautomeric gossypol forms in nonaqueous solutions are quite complex and sensitive to solvent effects. Tautomers **5** (dilactol form) and **4** (diketone form) appear to be stabilized in solvents such as DMSO that have high hydrogen bond acceptor basicity, whereas solvents able to form hydrogen bonds with gossypol's aldehydic group, such as ethanol, stabilize tautomer **3** (dialdehyde form).

Hydrogen bonding. As previously mentioned, the hydroxyl and aldehyde groups, located on the same side of the gossypol molecule, create a lipophobic region. This arrangement, typically shown for the aldehydic tautomeric form **3** when hydrogen bonding is considered, allows the formation of an extensive



3

FIG. 5. The intramolecular hydrogen bonding interactions in dialdehyde gossypol tautomer **3**.

intramolecularly hydrogen bonded system, shown in Figure 5. The hydrogen bonding interactions in gossypol have been extensively studied by NMR (77), UV, and IR (86).

A strong hydrogen-bonded interaction is formed between the carbonyl oxygen of the C-8 aldehyde and the C-7 hydroxyl hydrogen to give a pseudo six-membered ring that is held nearly coplanar with the naphthalene framework (57). The energy of this hydrogen bond is estimated to be approximately 10.7 kcal/mol (78), which is roughly 4 kcal/mol stronger than the similar intramolecular hydrogen bonding interactions observed in salicylaldehyde's *o*-hydroxybenzaldehyde system (87,88). The aforementioned planarity arising from H-bonding forces a close contact between the aldehydic hydrogen and the oxygen atom of the 1-hydroxyl group to give what is generally looked on as a C-H···O hydrogen bond. Additionally, weak H-bonding between the C-6 hydroxyl hydrogen and the C-7 hydroxyl oxygen forms a pseudo five-membered ring. As expected, the hydrogen bonding interactions for the other half of the gossypol molecule are identical to those just described.

GOSSYPOL REACTIONS

In 1918, Carruth described the following three procedures for the isolation and purification of gossypol from ethereal extracts of cottonseed (89): (i) adding acetic acid to diethyl ether extracts of defatted seed to precipitate gossypol as gossypol-acetic acid (1:1), (ii) precipitating gossypol-acetic acid (1:1) by first adding sodium hydroxide to solvent extracts, separating the soap phase, then treating the separated soap with hot acetic acid, and (iii) adding aniline to the diethyl ether extract to form dianilinolgossypol that was subsequently hydrolyzed with base, steam-stripped to remove the aniline, and acidified to precipitate the gossypol. Almost all currently used gossypol isolation methods use some elements of these early procedures.

Gossypol ethers. Gossypol is quite sensitive to oxidation and has a tendency to react or degrade in the presence of numerous reagents; therefore, gossypol's hydroxyl groups are typically first protected by converting them into ether or ester derivatives. These gossypol ethers and esters routinely serve as starting materials to further derivatize the gossypol structure. Etherification of gossypol's hydroxyl groups has been extensively studied, and a number of mixed gossypol methyl and ethyl ethers have been characterized (9,13,28,64,90–92).

These seemingly simple reactions have proven challenging because the product mixtures derived from alkylation or esterification are quite complex owing to gossypol's various tautomeric forms (Fig. 2) and to the reaction conditions that influence the equilibrium between gossypol's tautomeric forms. Typical alkali-mediated methylation procedures are not practical because of gossypol's instability toward alkali, and over the years several procedures that use diazomethane, methyl iodide, and dimethyl sulfate have been developed (33,93–95). Adams and coworkers used dimethyl sulfate to methylate gossypol (9), and, depending on the reaction conditions, gossypol can be methylated to provide a tetramethyl ether product **6**, or two distinct isomeric hexamethyl ethers **7a** (red form) and **7b** (white form) (Fig. 6). As shown in Figure 6, Adams and colleagues found an interrelationship between **6**, **7a**, and **7b**, and even though **7a** and **7b** appear to be different based on their reported m.p., they react similarly to give identical reaction products.

These stable tetramethyl (**6**) and hexamethyl ethers (**7a** and **7b**) were of particular importance in early studies of gossypol's structure. Using these ethers, especially the hexamethyl gossypol ethers, Adams and coworkers performed a series of oxidation, reduction, and derivatization reactions (alkylation, esterification, and Schiff's base formation) allowing them to postulate gossypol's structure (9,13,14,15,22,28,33). These seminal papers also outlined the fundamental reaction chemistry surrounding the gossypol molecule. From these studies Adams concluded that two of the –OMe groups in gossypol hexamethyl ether are different from the other four methoxyl groups and, based on their reactivity in acidic media, postulated isomeric structures **7** (dilactol hexamethyl ether) and **8** (dialdehyde hexamethyl ether), shown in Figure 7.

Seshadri and coworkers showed the existence of a third mixed gossypol hexamethyl ether **9** (monoaldehyde-monolactol) (91,96,97). Abdugabbrarov and coworkers (98) prepared a gossypol hexamethyl ether mixture composed of **7**, **8**, and **9**, using dimethyl sulfide in basic solutions, and studied the product mixture using Direct Analysis of Daughter Ions MS (98). They reported the ratio between **7**, **8**, and **9** to be 27.1:20.8:52.1, respectively.

Recently, Nguyen and coworkers (99) used solid-liquid phase transfer catalysis without solvent to synthesize the monoaldehyde-monolactol hexamethyl ether **9** in high yield.

Raju and Cater (100) silylated gossypol's hydroxyl groups using bis-(trimethylsilyl) acetamide in an attempt to obtain the corresponding hexatrimethylsilyl gossypol ether **10** (Fig. 8). The trimethylsilyl (TMS) ether groups in **10** render gossypol volatile, and subsequent GC analyses showed three peaks in the chromatogram that they attributed to gossypol's various tautomeric forms trapped during silylation. Later, work by McClure (101) showed that some of the peaks observed in the work by Raju and Cater were due to incomplete gossypol silylation and not to trapping of gossypol's various tautomeric forms. During this time period Abou-Donia *et al.* (102) also reported the mass spectra of hexatrimethylsilyl gossypol ether **10**.

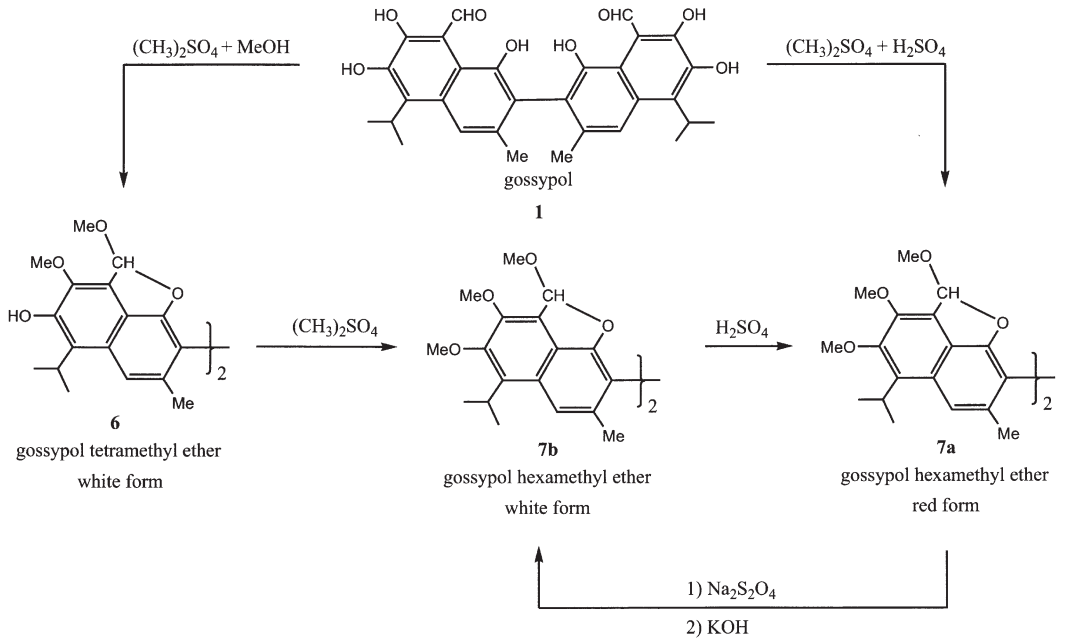


FIG. 6. The conversion of gossypol into its tetramethyl and hexamethyl protected ethers and their interdependencies.

While preparing gossypol dimethyl ether **11**, Xue and coworkers (103) isolated monomethyl ether **12** as its $Na_2B_4O_7$ complex, its structure was confirmed using NMR and mass spectral data (Fig. 8). Stipanovic *et al.* (104) identified compounds **11** and **12** as natural products of *G. barbadense* cottonseed.

The asymmetric carbons in dilactol hexamethyl ether **7** (designated by asterisks in Fig. 7) give rise to several optically active diastereomeric forms of this compound. Ibragimov and coworkers (105) separated methyl ether stereoisomers **13**, **14,** and **15** (Fig. 9) by fractional crystallization and determined their configuration by X-ray analysis. In their review article, Jaroszewski and coworkers (77) described some of their efforts to separate individual hexamethyl diastereomeric products derived from the methylation of gossypol using dimethyl sulfate.

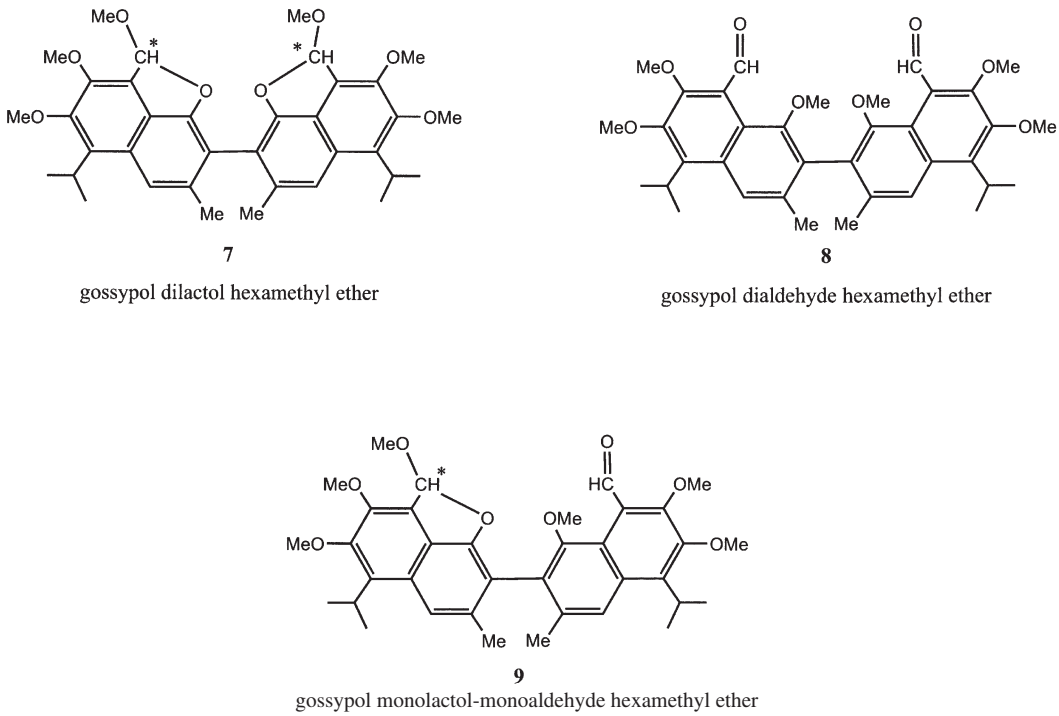
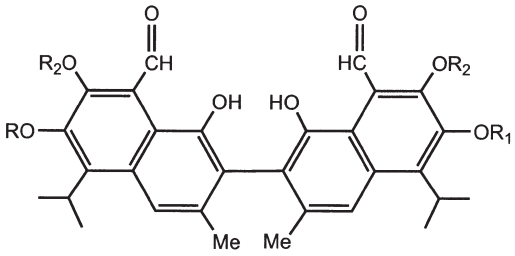


FIG. 7. Isomeric gossypolhexamethyl ether isomeric forms. The asterisks in **7** and **9** designate asymmetric carbons.



10 R, R_1, R_2 = $Si(CH_3)_3$
11 R, R_1 = Me; R_2 = H
12 R = Me; R_1 = H; R_2 = H

FIG. 8. Various gossypol ethers prepared by researchers.

Baram and coworkers (106) reported the synthesis of gossypol ethers in which some of the ether moieties contain the epoxide functionality (Fig. 10). Accordingly, the reaction between gossypol tetramethyl ether **6** and epichlorohydrin gave mixed ether **16**, which can be viewed as a difunctional epoxy monomer.

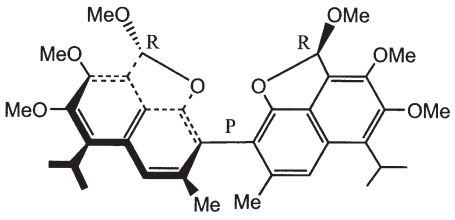
Wichmann and coworkers (107) examined the ability of gossypol tetramethyl and hexamethyl ethers to inhibit spermatozoal metabolism and found these ethers to be much less active than gossypol. Baram and Ismailov (108) reviewed the biological activity of gossypol and its derivatives and suggested that gossypol ether and ester compounds show no interesting biological activity because, to have any physiological activity, a free hydroxyl must be present in the gossypol molecule.

Gossypol esters. The reactions used to prepare gossypol esters exhibit many of the same difficulties observed for the preparation of gossypol ethers, namely, complications arising from an equilibrium mixture between the various gossypol tautomeric structures. Carruth (89) was the first to acetylate gossypol, but since gossypol hexaacetate degrades along several pathways it was not a useful starting point for their early studies. Gossypol acetate esters appear to be the most commonly reported and used ester, although the hexabenzoate (109,110) and hexapalmitate (111) esters have also been reported. In 1966, Correa *et al*. (112) reported the synthesis of gossypol hexaesters prepared from propionic through decanoic FA.

Jaroszewski and coworkers (77) separated the products obtained from gossypol acetylation by preparative HPLC. They isolated and characterized the five racemic hexaacetates shown in Figure 11. Interestingly, the hexaacetate esters of the dialdehyde **3** and enol **4** tautomers (Fig. 2) were not observed.

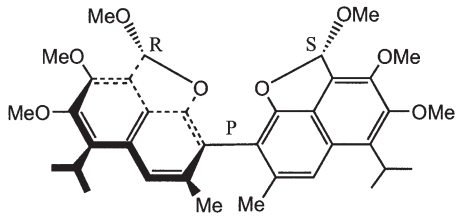
Apogossypol and apogossypol derivatives. In 1918, Carruth (89) first reported the formation of the unstable compound **19**, formed by treating gossypol with hot aqueous alkali (Fig. 12).

Later, Clark repeated Carruth's experiments, better characterized the isolated compound, **19**, and named it apogossypol (113). Clark showed that gossypol's two aldehyde groups are lost during the reaction and that methylation or acetylation of **19** (114) affords the corresponding stable hexasubstituted derivatives **20a** (R = Me) from methylation and **20b** (R = $-C(=O)CH_3$) from acetylation. Apogossypol derivatives **20** undergo several transformations as shown in Figure 12. Oxidation of **20a** or **20b** with



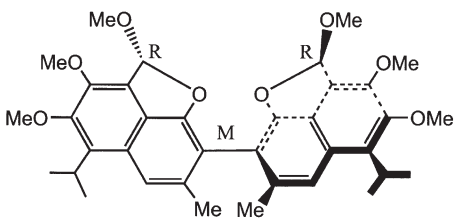
(RPR)-dilactol hexamethyl gossypol

13



(RPS)-dilactol hexamethyl gossypol

14



(RMR)-dilactol hexamethyl gossypol

15

FIG. 9. The diastereoisomeric dilactol hexamethyl gossypol ethers isolated by Ibragimov and coworkers (105). **13** is the RPR stereoisomer, **14** is the RPS stereoisomer, and **15** is the RMR stereoisomer. The (P) and (M) designations correspond to the (+) and (–) atropomeric stereocenters, respectively, according to the helicity rule.

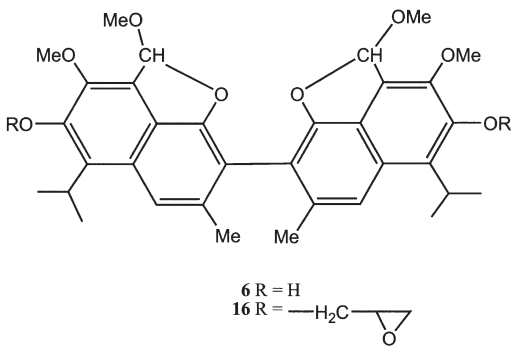


FIG. 10. Preparation of gossypol tetramethyl ether **16** containing epoxy ether functionality from gossypol tetramethyl ether **6**.

chromic acid gives the corresponding tetramethoxy and tetraacetoxy quinones **21a** and **21b**, respectively, known generally as apogossypolones (16,114).

Adams and Butterbaugh (16) also reported that hexamethoxy apogossypol **20a** (R = Me) reacts in concentrated H_2SO_4 to give desapogossypol **22** in which the two isopropyl groups are lost. Subsequent oxidation of **22** with chromic or periodic acid gives quinone desapogossypolone **23** (16).

Gossypol oxidation. Gossypol is highly sensitive to oxidation and this reaction is undesirable for cottonseed oil processors, since oxidation often gives products more highly colored than gossypol. Clark (115) reported that mild oxidizing agents degrade gossypol into unrecognizable components. Because of gossypol's sensitivity to oxidation, experiments on gossypol are typically performed with protected gossypol derivatives. Treatment of alkyl ether (**7**)- or acetyl ester (**18**)-protected gossypol derivatives with chromic acid or similar oxidizing agents gives the corresponding protected gossypol quinones **24a** and **24b**, respectively, known as gossypolone (Fig. 13) (15,114,115).

Haas and Shirley (116) obtained 50–70% yields in the direct oxidation of gossypol to gossypolone **24c** by using ferric chloride in acetic acid/acetone mixtures (Fig. 13). Recently, Dao and coworkers (117) reported the preparation of interesting dithiane and dithiolane derivatives of gossypol and gossypolone by reacting their aldehyde moieties with dithiolethane or dithiolpropane in the presence of BF_3/Et_2O. Scheiffele and Shirley (118) also reported the rapid uptake of oxygen by gossypol in alkaline solutions at low temperatures to give tetrone **24d** through an unusual Dakin-type reaction.

Talipov and coworkers (119,120) isolated gossindane **25** by treating gossypol with pure oxygen in an alkaline solution (Fig. 14). Gossindane's structure was confirmed by IR, NMR, MS, and X-ray. Like gossypol, gossindane has two optically active atropisomers in addition to four asymmetric carbon atoms (designated by asterisks in Fig. 14).

Anhydrogossypol. Anhydrogossypol **26**, another gossypol reaction product identified in early gossypol studies, is prepared by heating crystalline gossypol to 190–200°C or by treating gossypol above its m.p. with pyridinium chloride in a toluene solution (Fig. 15) (10,17,89,109). Anhydrogossypol undergoes a Diels–Alder reaction with 2,3-dimethylbutadiene to give the Diels–Alder adduct **27** (12).

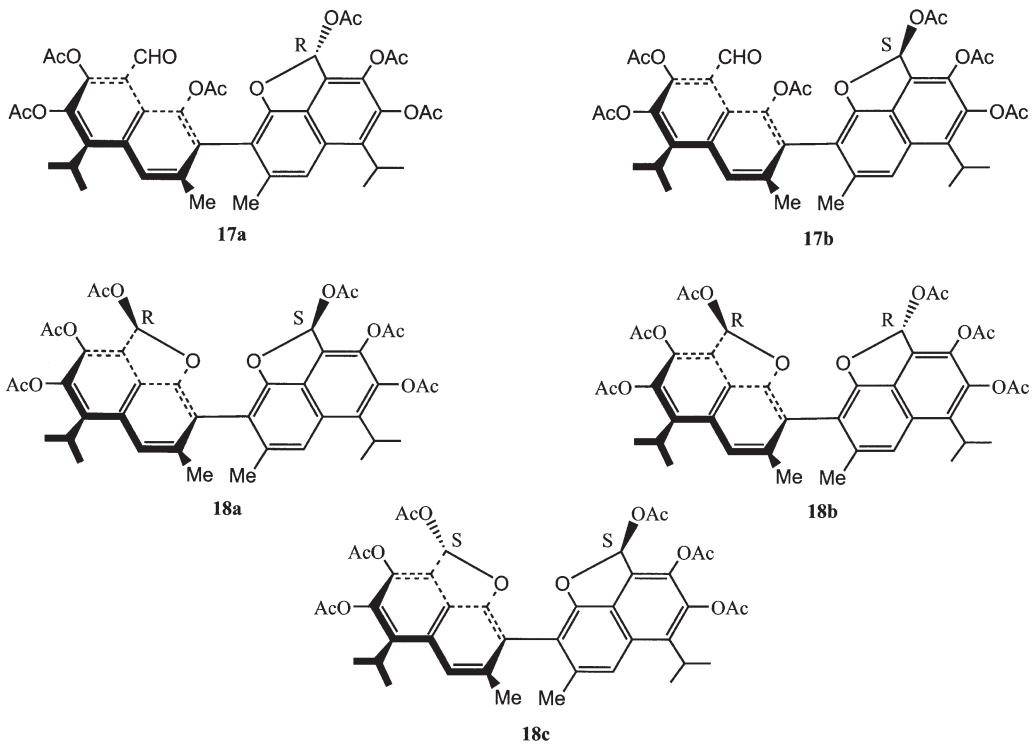


FIG. 11. Five racemic gossypol hexaacetates isolated by HPLC from acetylation of gossypol (figure adapted from Ref. 77).

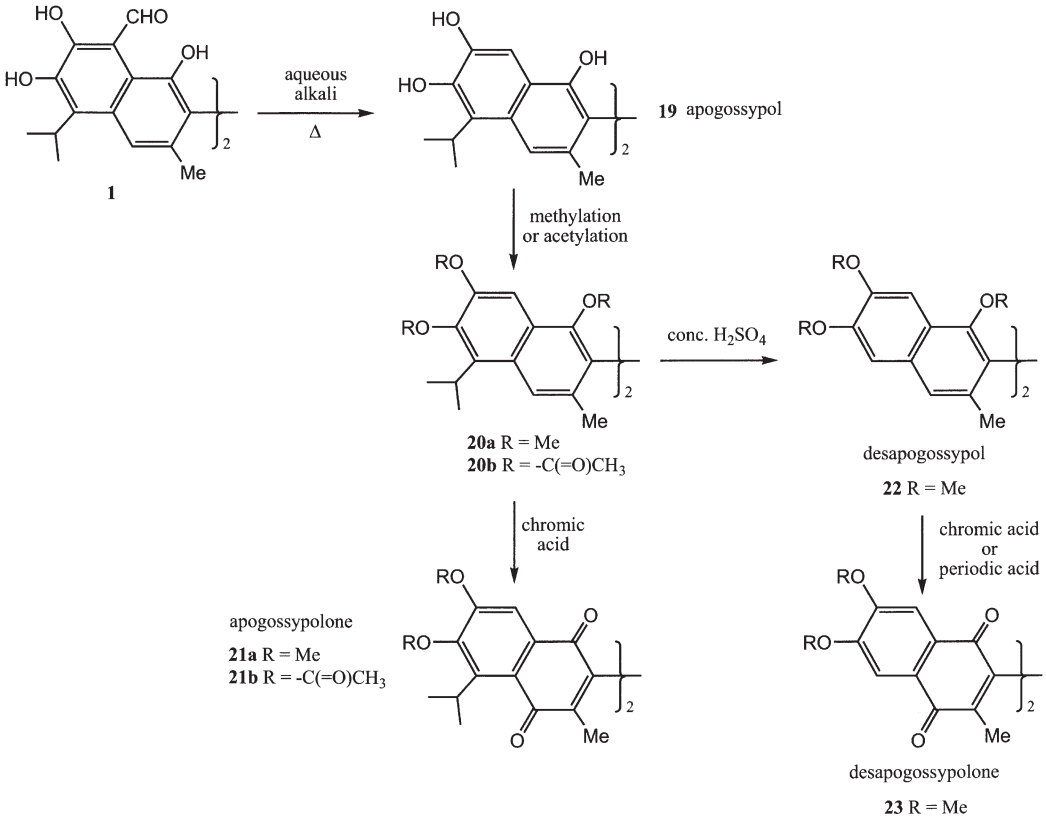


FIG. 12. Preparation and transformations of apogossypol **19**.

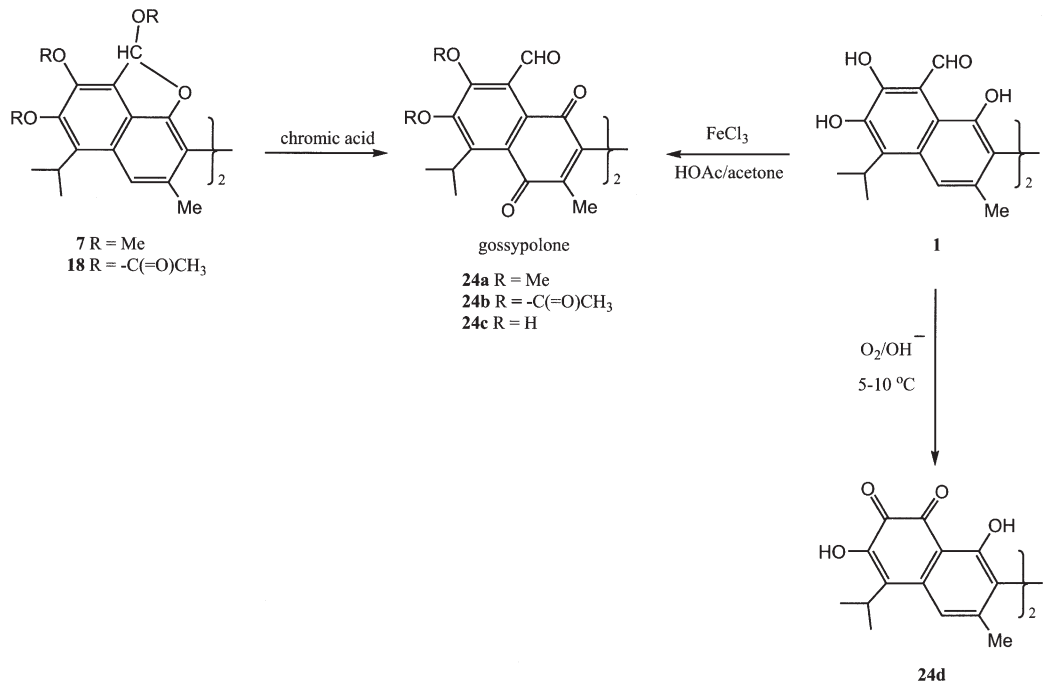
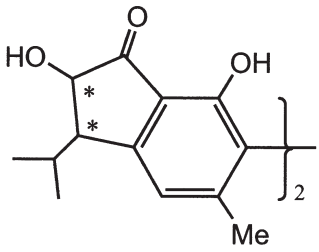


FIG. 13. Oxidation of gossypol and gossypol derivatives to give gossypolone derivatives **24**.



25

FIG. 14. Gossindane **25** produced by the oxidation of gossypol using pure oxygen in alkaline solution. Asterisks (*) represent chiral centers.

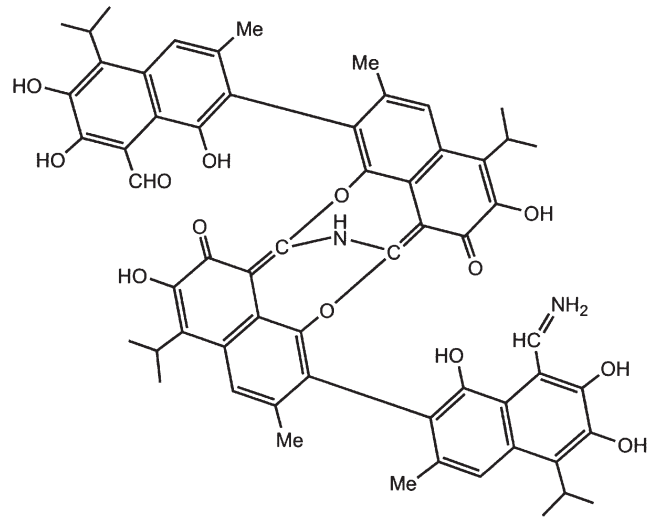
Glushenkova and coworkers (121) have shown that gossypurpurin **28** (Fig. 16), a naturally occurring nitrogen-containing purple pigment also found in cottonseed, is derived from the reaction between monoanhydrogossypol and diaminoanhydrogossypol and not from gossypol and diaminogossypol as previously believed (122).

Reduction of gossypol. Gossypol's aldehyde groups are susceptible to reduction, and treatment of gossypol with $LiAlH_4$ gives **29** (R = H, Fig. 17) in which the aldehyde moieties are reduced to methyl groups (123,124). Subsequent methylation or acetylation of **29** gives the corresponding compounds **30** and **31**, respectively.

Recently, Dao and colleagues (125) reduced gossypol's aldehyde groups directly with $NaBH_3CN$ to give **32** in 15% yield (Fig. 17) (125).

Adams and Dial (28) were able to obtain gossypol tetramethoxy derivative **33** by reducing hexamethoxy gossypol derivative **7** with H_2 in the presence of Pt and acetic acid (Fig. 17).

Electrochemistry of gossypol. Several reports examined the electrochemical properties of gossypol in solution (126–131). Although many of theses studies deal primarily with analytical aspects, insight into gossypol's reaction chemistry and pharmacological activities, some of which are dependent on electron transfer, can also be gained. Typically, the electrochemical reactions are performed such that gossypol's two aldehydic moieties are irreversibly reduced with mercury or graphite electrodes. In aqueous acidic media, Tonholo *et al.* (128) found gossypol's dialdehyde tautomer (structure **3**, Fig. 2) to be reasonably stable to the acidic reaction conditions used for their studies and suggested gossypol's aldehyde groups are initially protonated by the acidic media to give **34** as shown in Figure 18. When a negative potential is applied to a solution containing **34**, one electron is transferred per aldehyde group to give intermediate radical **35**. Radical **35** then undergoes radical-radical dimerization to give **36** along with unidentified oligomeric materials. If a more negative potential is applied to the solution containing **34**, an electron is transferred to the aldehyde groups of **34**, as before, to generate radical **35**. Because of the more negative applied potential, another electron is immediately transferred to radical **35** to give anion **37** that is subsequently protonated by the acidic media to give alcohol **38**.



28

FIG. 16. Structure of gossypurpurin **28** proposed by Glushenkova *et al.* (121).

Reaction of gossypol with ammonia and primary amines (Schiff's bases). In 1917, Carruth noted that aniline, a primary aromatic amine, reacts with gossypol to give an insoluble condensation product (89,132). Later, Clark (109,133) determined the chemistry and stoichiometry of the reaction in which two aniline molecules react with one molecule of gossypol to produce a stable crystalline compound and two water molecules.

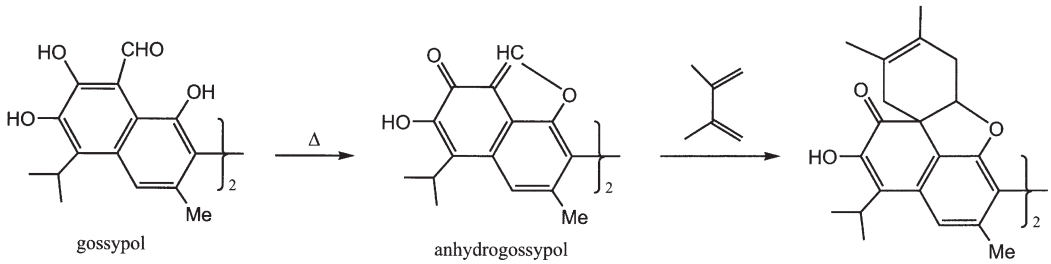


FIG. 15. Preparation of anhydrogossypol **26** from gossypol. Also shown is the Diels–Alder reaction between anhydrogossypol and 2,3-dimethylbutadiene to give **27**.

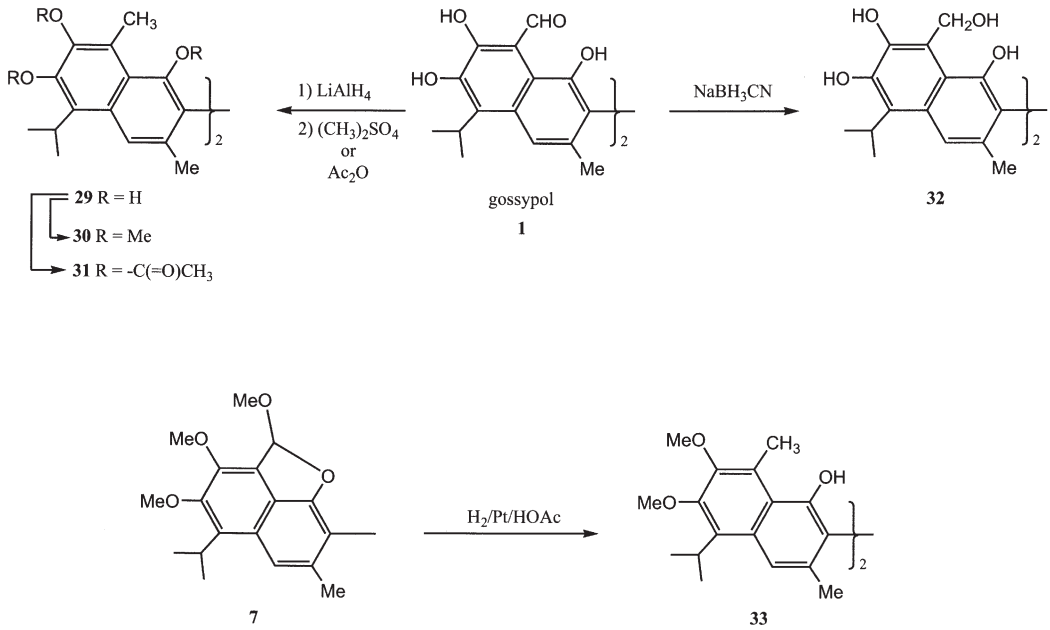


FIG. 17. Reduction of gossypol **1** with $LiAlH_4$ and with $NaBH_3CN$ and of gossypol hexamethyl ether **7** with H_2.

The name coined for the new compound, dianilinogossyol, was adopted by later investigators, and this reaction has been used to remove and quantify gossypol contained in cottonseed meal. Importantly, this reaction is general for ammonia, other primary amines, and also the free amino groups contained in proteins (134). In fact, cottonseed processors use the reaction between gossypol and the free lysine amino groups contained in cottonseed protein to bind gossypol to the protein, thereby retaining it in the cottonseed meal during oil processing (135,136). Available lysine, which accounts for the majority of free amino groups in cottonseed protein, is reduced from 83 to 49% following reaction with gossypol (137–139).

Numerous studies suggest that gossypol's toxicity is reduced while its therapeutic effects are retained by modification of gossypol's reactive aldehyde groups (140,141). Therefore, many different primary amines have been reacted with gossypol's aldehydes to give gossypol Schiff's bases (also termed gossypol imine derivatives), and this condensation reaction is

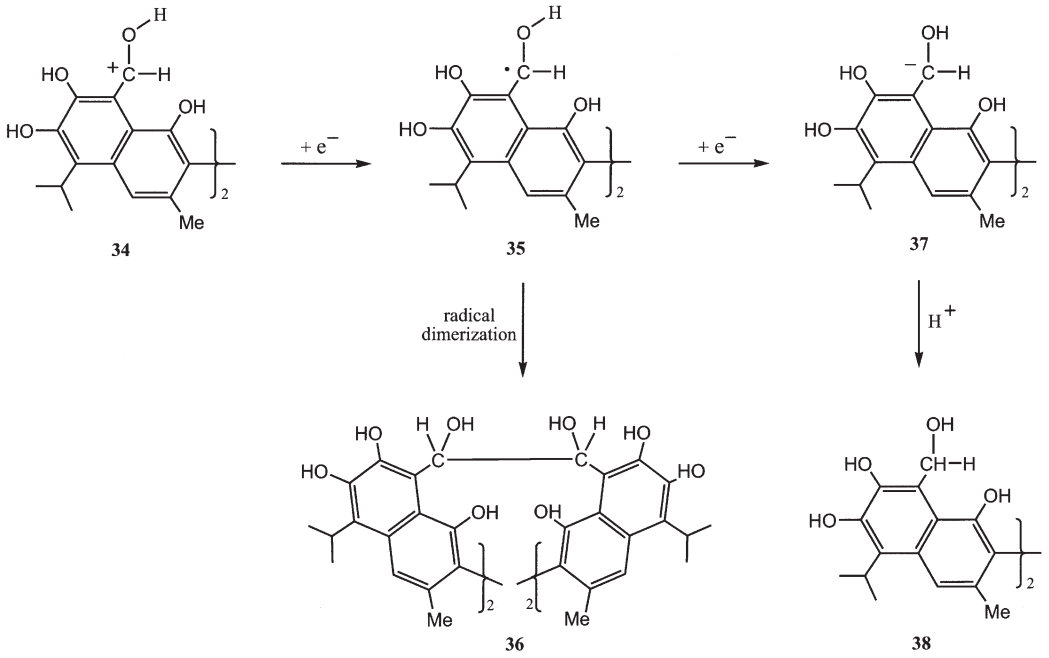
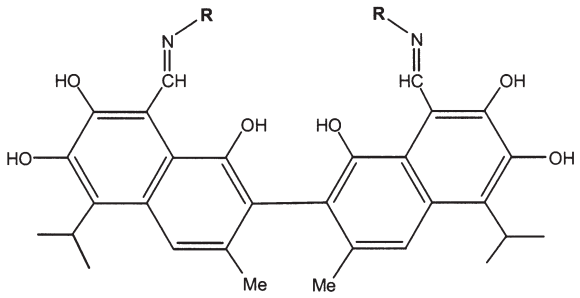


FIG. 18. Electrochemical reduction of protonated gossypol **34** in acidic media.

TABLE 1
Aliphatic Gossypol Schiff's Base Derivatives

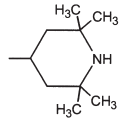
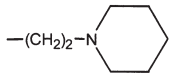
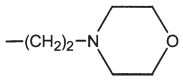
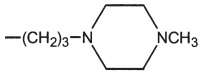
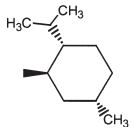
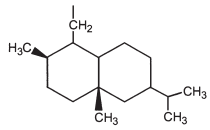
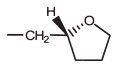


Gossypol Schiff's Bases

Entry	R =	Molecular formula	Yields[a]	mp[a] (°C)	Reference
1	–OH	$C_{30}H_{32}N_2O_8$			
2	$-CH_3$	$C_{32}H_{36}N_2O_6$	95[125]	—	125, 198
3	$-CH_2CH_3$	$C_{34}H_{40}N_2O_6$	72[200] 96[125]	251–255[200]	125, 198, 199, 200, 201
4	$-CH_2CH_2CH_3$	$C_{36}H_{44}N_2O_6$	100[112] 92[74]	255–256[112] 235[74]	125, 198, 199,112, 74
5	$-(CH_2)_3CH_3$	$C_{38}H_{48}N_2O_6$	96[112] 90[125]	223[112]	125, 198, 199, 112
6	$-(CH_2)_4CH_3$	$C_{40}H_{52}N_2O_6$	69[200] 83[125]	218–221[200]	125, 198, 200
7	$-(CH_2)_5CH_3$	$C_{42}H_{56}N_2O_6$	63[112] 86[125]	201[112]	125, 198, 112
8	$-(CH_2)_6CH_3$	$C_{44}H_{60}N_2O_6$	71[125]		125, 198
9	$-(CH_2)_9CH_3$	$C_{50}H_{72}N_2O_6$	64[200]	164.5–165.5[200]	200, 202
10	$-(CH_2)_{11}CH_3$	$C_{54}H_{80}N_2O_6$	91[125]	—	125, 198
11	$-(CH_2)_{13}CH_3$	$C_{58}H_{88}N_2O_6$	75	126.5–127	200
12	$-(CH_2)_{15}CH_3$	$C_{62}H_{96}N_2O_6$	50	116–116.5	200
13	$-(CH_2)_{17}CH_3$	$C_{66}H_{104}N_2O_6$	60	112.5–113	200
14	$-CH(CH_3)_2$	$C_{36}H_{44}N_2O_6$	82[112] 96[125]	195[112] —	125, 198, 199, 112
15	$-C(CH_3)_3$	$C_{38}H_{48}N_2O_6$	89[112] 87[125]	270[112] —	125, 198, 112
16	$-CH_2CH(CH_3)_2$	$C_{38}H_{48}N_2O_6$	90	—	125
17	$-CH_2CH(CH_3)CH_3$	$C_{38}H_{48}N_2O_6$	—	—	198
18	–2-Ethylhexyl	$C_{46}H_{64}N_2O_6$	78	200–201	201
19	$-CH_2CH{=}CH_2$	$C_{36}H_{40}N_2O_6$	97[201]	>200 (dec.)[201]	201, 214
20	–Cyclohexyl	$C_{42}H_{52}N_2O_6$	89	319	112
21	$-(CH_2)_4$–1:1 with gossypol	$C_{34}H_{38}N_2O_6$	—	—	203
22	$-(CH_2)_5$–1:1 with gossypol	$C_{35}H_{40}N_2O_6$	—	—	203
23	$-(CH_2)_3NH(CH_2)_4$–1:1 with gossypol	$C_{37}H_{45}N_3O_6$	—	—	203
24	$-(CH_2)_{10}$–1:1 with gossypol	$C_{40}H_{50}N_2O_6$	—	—	202
25	$-CH_2(CH_2)_2Br$	$C_{36}H_{42}N_2O_6Br_2$	80.0	183–185	142
26	$-CH_2CN$	$C_{34}H_{34}N_4O_6$	57.9	>360	142
27	$-CH_2CH_2Cl$	$C_{34}H_{38}N_2O_6Cl_2$	64	>300	204
28	$-CH_2CH_2SH$	$C_{34}H_{40}N_2O_6S_2$	93	256	112
29	$-CH_2CH_2OH$	$C_{34}H_{40}N_2O_8$	90[112]	276[112]	112, 204, 205
30	$-CH(OH)CH_2CH_3$	$C_{36}H_{44}N_2O_8$	79.4	243–245	142
31	$-C(CH_2OH)(CH_3)_2$	$C_{38}H_{48}N_2O_8$	45.5	280–282	142
32	$-CH(CH_2OH)CH_2CH_3$	$C_{38}H_{48}N_2O_8$	68.3	255–257	142
33	$-C(CH_2OH)_3$	$C_{38}H_{44}N_2O_{12}$	32.4	295–297	142
34	$-CH_2CH(OH)CH_3$	$C_{36}H_{44}N_2O_8$	—	—	202
35	$-CH(CH_2OH)CH_3$	$C_{36}H_{44}N_2O_8$	—	—	71, 206
36	$-CH_2CH_2CH_2OMe$	$C_{38}H_{48}N_2O_8$	90	230	69, 112
37	$-CH_2CH(OCH_2CH_3)_2$	$C_{42}H_{56}N_2O_{10}$	77	207 (dec.)	201
38	$-(CH_2)_2O(CH_2)_2O(CH_2)_2OCH_3$	$C_{44}H_{60}N_2O_{12}$		—	147
39	$-(CH_2)_2O(CH_2)_2OH$	$C_{38}H_{48}N_2O_{12}$	—	—	158
40	$-CH_2CH_2CO_2H$	$C_{36}H_{40}N_2O_{10}$	49.6	197–199	207
41	$-CH_2CO_2CH_3$	$C_{36}H_{40}N_2O_{10}$	9	205–210 (dec.)	201

(continued)

TABLE 1 (continued)
Aliphatic Gossypol Schiff's Base Derivatives

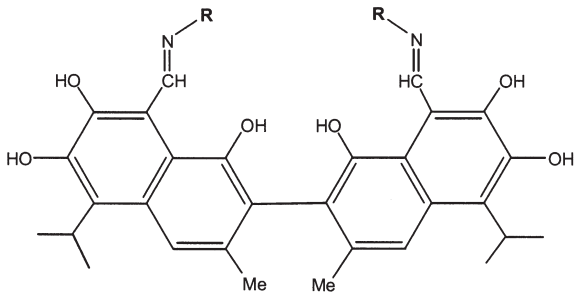
Entry	R =	Molecular formula	Yields[a]	mp[a] (°C)	Reference
42	$-CH(CO_2R')CH_2CH(CH_3)_2$	(R′ = CH_3) $C_{44}H_{56}N_2O_{10}$ (R′ = $CH(CH_3)_2$) $C_{48}H_{54}N_2O_{10}$	—	—	69
43	$-(CH_2)_4CH(NH_2)CO_2H$	$C_{42}H_{54}N_4O_{10}$	43.3	247–248	207
44	$-(CH_2)_4CH(NH_2)COOCH_3$ (Mono derivative)	$C_{37}H_{44}N_2O_9$	53	—	201
45	$-CH_2CH_2SO_3R'$ Megosin	(R′ = H) $C_{34}H_{40}N_2O_{12}S_2$ (R′ = Na) $C_{34}H_{40}N_2O_{12}S_2Na$	58.6[142] 41.2[204]	312–314[142] 300[204]	142, 205 204, 208
46	$-(CH_2)_4NH_2$		—	—	203
47	$-(CH_2)_7NH_2$	$C_{44}H_{62}N_4O_6$	98.7	>350	207
48	$-(CH_2)_2N(CH_2CH_3)_2$	$C_{42}H_{58}N_4O_6$	72[201]	>200 (dec.)[201] 229–230[35]	201, 209, 35
49	$-(CH_2)_2N(CH_3)_2$	$C_{38}H_{50}N_4O_6$	—	—	209, 210
50	$-(CH_2)_3N(CH_3)_2$	$C_{40}H_{54}N_4O_6$	88	200 (dec.)	201
51	$-(CH_2)_3N(CH_2CH_3)_2$	$C_{44}H_{62}N_4O_6$	—	—	209, 211
52		$C_{46}H_{66}N_4O_6$	59.5	242–244	142
53		$C_{44}H_{58}N_4O_6$	55	181–182	212
54		$C_{42}H_{54}N_4O_8$	40[212]	178–180[212] dec	212, 213
55		$C_{46}H_{64}N_6O_6$	84.8	288–290	142
56	$-(CH_2)_2N(CH_3)_2 \cdot HCl$	$C_{38}H_{52}N_4O_6Cl$	—	—	210
57	$-(CH_2)_2N(CH_2CH_3)_2 \cdot HCl \cdot 3H_2O$	$C_{42}H_{72}N_4O_9Cl$	—	—	210
58	$-(CH_2)_3N(CH_2CH_3)_2 \cdot HCl \cdot 3H_2O$	$C_{44}H_{76}N_4O_6Cl$	—	—	210
59		$C_{50}H_{68}N_2O_6$	—	—	69
60		$C_{62}H_{88}N_2O_6$	82.2	188–190	142
61		$C_{40}H_{48}N_2O_8$	—	—	151
62	$-CH_2$(15 crown 5 ether)	$C_{52}H_{72}N_2O_{16}$	76	148–151	146
63	$-CH_2$(18 crown 6 ether)	$C_{56}H_{80}N_2O_{18}$	79	95–101	146

[a]Superscripts refer to the reference from which the data were taken.

undoubtedly the reaction most often applied to the gossypol molecule. An enormous number of gossypol Schiff's base derivatives have been prepared for physiological studies, and it is challenging to locate and identify all the information regarding their preparation and characterization. Tables 1–3 compile many of the numerous gossypol Schiff's base derivatives reported in the literature. These tables contain information, when available, regarding molecular formulae, yields, and m.p. for over 170 different aliphatic, aromatic, and heterocyclic gossypol Schiff's base derivatives, shown as their imine tautomer (**40a**, Fig. 19) for convenience, although the enamine (**40b** or **40c**, Fig. 19) tautomers may predominate. The list is by no means complete and the author apologizes to researchers whose results may have been inadvertently omitted. In some cases, the yields and m.p. for a reported derivative vary widely, likely because of the formation of different solvates; whereas some entries may contain no yield or m.p. data information owing to the difficulty in finding the desired information.

The mechanism typically invoked for this transformation is outlined in Figure 19 (125). The reaction between the primary amine's nitrogen and gossypol's aldehyde groups gives intermediate carbinol **39**. Subsequent dehydration leads directly to Schiff's base **40** that exists mainly as a tautomeric mixture between the imine and enamine forms **40a** and **40b**, respectively, although tautomer **40c** also has been suggested to exist for specific gossypol Schiff's bases made

TABLE 2
Aromatic Gossypol Schiff's Base Derivatives

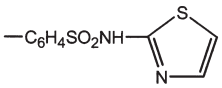
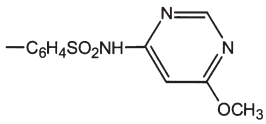
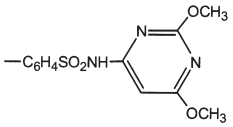
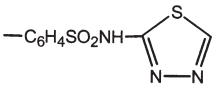
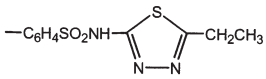
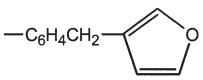
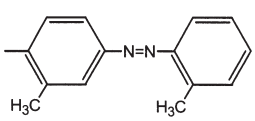


Gossypol Schiff's Bases

Entry	R =	Molecular formula	Yields[a]	mp[a] (°C)	Reference
1	$-C_6H_5$	$C_{42}H_{40}N_2O_6$	80.0	258–260[204] 228–231[74]	74, 204
2	$-C_6H_4(CH_2CH_3)$ *para* isomer	$C_{46}H_{48}N_2O_6$	95.9	235–237	142
3	$-C_6H_4CN$ *para* isomer	$C_{44}H_{38}N_4O_6$	87.5	293–295	142
4	$-C_6H_4SH$ *ortho* isomer	$C_{42}H_{40}N_2O_6S_2$	100	227–228	215
5	$-C_6H_4OH$	$C_{42}H_{40}N_2O_8$			215,
	ortho isomer		91[215]	268–269[215]	143
	meta isomer		94[215]	287[215]	
	para isomer		97[215]	291[215]	
6	$-C_6H_4OR'$	(R′ = CH_3) $C_{44}H_{44}N_2O_8$	94	287–289	214,
	para isomer	(R′ = CH_2CH_3) $C_{46}H_{48}N_2O_8$	100	246	112,
		(R′ = $(CH_2)_4CH_3$) $C_{52}H_{60}N_2O_8$	63	211–213	216
7	$-C_6H_4CO_2H$	$C_{44}H_{40}N_2O_{10}$			215, 143,
	ortho		87[215]	>360[215]	216
	meta		91[215], 78[216]	>360[215], 269–271[216]	
	para		93[215]	>360[215]	
8	$-C_6H_4CO_2R'$	(R′ = CH_3) $C_{44}H_{44}N_2O_{10}$	79	292	112
	para isomers	(R′ = CH_2CH_3) $C_{48}H_{48}N_2O_{10}$	70[143]	292–294[143] 305–307[35]	143, 35
		(R′ = $(CH_2)_3CH_3$) $C_{52}H_{56}N_2O_{10}$	100	200–210	201
9	$-C_6H_4F$ *para* isomer	$C_{42}H_{38}FN_2O_6$	90	—	217, 218
10	$-C_6H_4Cl$	$C_{42}H_{38}N_2O_6Cl_2$			
	meta		93	286	112
	para		88	302	215
11	$-C_6H_4Br$ *para* isomer	$C_{42}H_{38}N_2O_6Br_2$	87[112]	283[112] 213–215[74]	112, 74
12	$-C_6H_4I$ *para* isomer	$C_{42}H_{38}N_2O_6I_2$	91	280	112
13	$-C_6H_4CF_3$ *meta* isomer	$C_{44}H_{38}F_6N_2O_6$	—	—	217
14	$-C_6H_4(CF_2)_4Cl$ *para* isomer	$C_{50}H_{38}Cl_2F_{16}N_2O_6$	—	—	217
15	$-C_6H_4NO_2$ *ortho* isomer mono derivative	$C_{36}H_{34}N_2O_9$	94	202	215
16	$-C_6H_4NO_2$	$C_{42}H_{38}N_4O_{10}$			
	ortho		97	234.5–235.5	215
	meta		90	280–282	
	para		75	305–306	
17	$-C_6H_4NH_2$ *ortho* (mono derivative)	$C_{36}H_{34}N_2O_6$	—	251–258	219
18	$-C_6H_4NH_2$ *ortho*	$C_{42}H_{42}N_4O_6$	—	246	11

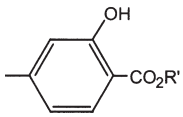
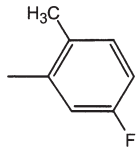
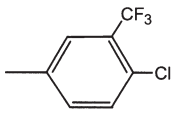
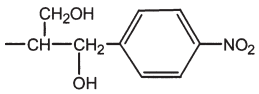
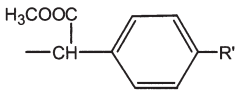
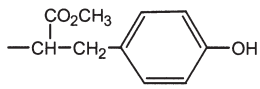
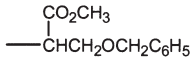
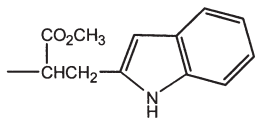
(continued)

TABLE 2 (continued)
Aromatic Gossypol Schiff's Base Derivatives

Entry	R =	Molecular formula	Yields[a]	mp[a] (°C)	Reference
19	$-C_6H_4N(C_2H_5)_2$	$C_{50}H_{58}N_4O_6$			220
	meta isomer		52	182 dec	
	para isomer		56	186–187	
20	$-C_6H_4N(CH_2CH_2OH)_2$	$C_{50}H_{58}N_4O_{10}$	51.8	205–207	204
21	$-C_6H_4SO_2NH_2$	$C_{42}H_{42}N_4O_{10}S_2$	77	>200 (dec.)	201
	para isomer				
22	$-C_6H_4SO_2NHCONH_2$	$C_{44}H_{44}N_6O_{12}S_2$	48.0[143]	238–240[143]	143,35
				234–235[35]	
23	$-C_6H_4SO_2NHC(=NH)NH_2$	$C_{44}H_{46}N_8O_{10}S_2$	83.7[143]	254–256[143]	143,35
				245–247[35]	
24	$-C_6H_4SO_2NHCN$	$C_{44}H_{40}N_6O_{10}S_2$	—	225–227	35
25		$C_{48}H_{44}N_6O_{10}S_4$	—	253–254	35
	para isomer				
26		$C_{52}H_{50}N_8O_{12}S_2$	—	—	143
	para isomer				
27		$C_{54}H_{54}N_8O_{14}S_2$	—	—	143
	para isomer				
28		$C_{46}H_{42}N_8O_{10}S_4$	89.3	254–256	143
29		$C_{50}H_{50}N_8O_{10}S_4$	56.6	232–234	143
30	$-SO_2C_6H_4NH_2$	$C_{42}H_{42}N_4O_{10}S_2$	80.6[143]	262–265[143]	143, 35
				274–276[35]	
31		$C_{52}H_{48}N_2O_8$	78.6	170–172	142
32	$-C_6H_4CONHCH_2CO_2H$	$C_{48}H_{46}N_4O_{12}$	80	>200 (dec.)	201
	para isomer				
33	$-C_6H_4(O)CHNCH_2CO_2H$	$C_{48}H_{46}N_4O_{12}$	68.1	>300	142
34	$-C_6H_4CONHCH_2CO_2H$	$C_{48}H_{46}N_4O_{12}$	92.3	>350	220
35	$-C_6H_4-C_6H_5$	$C_{54}H_{48}N_2O_6$	88	327–328	200
	para isomer				
36	$-C_6H_4-CH_2-C_6H_4-$	$C_{56}H_{50}N_2O_6$	98	322–323	200
	p,p'-isomer				
	1:1 with gossypol				
37	$-C_6H_4N{=}NC_6H_5$	$C_{54}H_{48}N_6O_6$	81[143]	280 (dec.)[143]	201
	para isomer		84.9[143]	288–290[143]	143
38		$C_{58}H_{56}N_6O_6$	87[143]	270–273[143]	201
			89.7[143]	260–262[143]	143

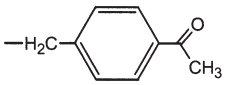
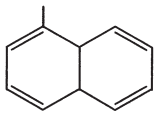
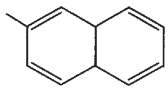
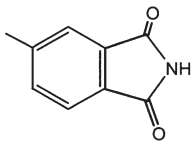
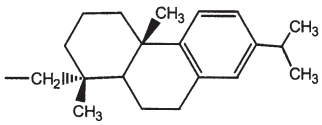
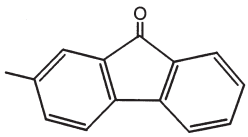
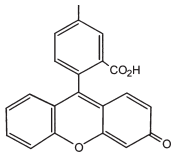
(continued)

TABLE 2 (continued)
Aromatic Gossypol Schiff's Base Derivatives

Entry	R =	Molecular formula	Yields[a]	mp[a] (°C)	Reference
39	$-C_6H_4-N=N-COOCH_2CH(C_2H_5)_2$ *para* isomer	$C_{56}H_{64}N_6O_{10}$	59.4	190–192	143
40		(R′ = OH) $C_{44}H_{40}N_2O_{12}$ (R′ = CH_3) $C_{46}H_{44}N_2O_{12}$	77 81	230 280	112
41	$-C_6H_3(C(CH_3)_3)(OH)$ isomer not designated	$C_{50}H_{56}N_2O_8$	62.6	292–295	142
42		$C_{44}H_{42}F_2N_2O_6$	—	—	217
43		$C_{44}H_{36}Cl_2F_6N_2O_6$	—	—	217
44	$-CH_2C_6H_5$	$C_{44}H_{44}N_2O_6$	72[200]	241.5[200]	200, 202
45	$-CH_2CH_2C_6H_5$	$C_{46}H_{48}N_2O_6$	91	>225 (dec.)	201
46	$-CH(CH_3)C_6H_5$	$C_{46}H_{48}N_2O_6$	80.5[143]	234-236[143]	143, 202
47	$-CH(CH_3)CH_2C_6H_5$	$C_{48}H_{52}N_4O_6$	—	—	221, 222, 72
48	$-CH_2CH(CH_3)C_6H_5$	$C_{48}H_{52}N_2O_6$	92[125]	—	125, 198
49	$-CH(CH_2OH)CH_2C_6H_5$	$C_{48}H_{42}N_2O_8$	—	—	73, 223
50		$C_{48}H_{52}N_4O_{14}$	—	—	224
51		(R′ = H) $C_{48}H_{48}N_2O_{10}$ (R′ = OH) $C_{48}H_{48}N_2O_{12}$	—	—	69
52	$-CH(CO_2CH_3)CH_2C_6H_5$ both enantiomers	$C_{50}H_{52}N_2O_{10}$	84[125]	—	125, 198, 225
53		$C_{50}H_{52}N_2O_{12}$	—	—	69
54		$C_{52}H_{56}N_2O_{12}$	—	—	69
55		$C_{54}H_{54}N_4O_{10}$	—	—	69, 226

(continued)

TABLE 2 (continued)
Aromatic Gossypol Schiff's Base Derivatives

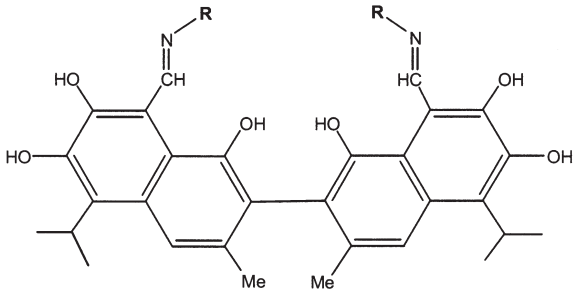
Entry	R =	Molecular formula	Yields[a]	mp[a] (°C)	Reference
56	$-CH_2C_6H_4Br$ *para* isomer	$C_{44}H_{42}Br_2N_2O_6$	100	251–254 (dec.)	201
57	$-CH_2C_6H_4Cl$ *para* isomer	$C_{44}H_{42}Cl_2N_2O_6$	94	236.5–237.5 (dec.)	201
58	$-CH_2C_6H_4NO_2$ *para* isomer	$C_{44}H_{42}N_4O_{10}$	97	234 (dec.)	201
59		$C_{48}H_{48}N_2O_8$	100	>200 (dec.)	201
60	 α-naphthyl	$C_{50}H_{44}N_2O_6$	82	283–285.5	215
61	 β-naphthyl	$C_{50}H_{44}N_2O_6$	91	302–303	215
62		$C_{46}H_{38}N_4O_{10}$	90.2	259–262	216
63		$C_{70}H_{88}N_2O_6$	—	—	69
64		$C_{56}H_{44}N_2O_8$	65	>320	144
65		$C_{70}H_{52}N_2O_{14}$	84	>320	144

[a]Superscripts refer to the reference from which the data were taken.

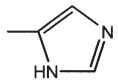
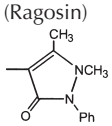
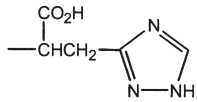
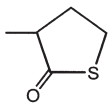
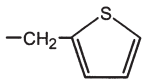
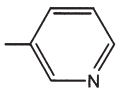
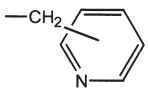
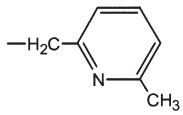
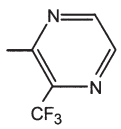
from phenylhydrazine or ammonia (R = $-NHC_6H_5$ or H, respectively; Fig. 19) (35).

The equilibrium between the various tautomeric Schiff's base structures (**40a–c**) has been extensively investigated by IR, NMR, and molecular modeling (125,142–153). For example, NMR experiments by Matlin and colleagues (144) on dianilinogossypol (R = $-C_6H_5$, Fig. 19) showed this compound exists as the enamine tautomer **40b** based on the signal observed at 174 ppm in the ^{13}C NMR spectrum, which is characteristic of a carbonyl carbon (144). The molecular crystal structures for dianilinogossypol crystals grown from ethyl acetate and dichloromethane indicate that dianilinogossypol exists as the enamine tautomer, **40b** (R = $-C_6H_5$, Fig. 19) regardless of the solvent used to grow the crystals (143,154). Dao and

TABLE 3
Heterocyclic and Hydrazine-Based Gossypol Schiff's Base Derivatives

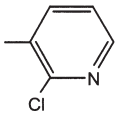
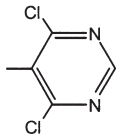
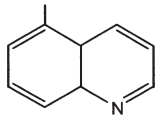
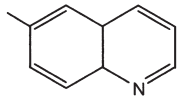
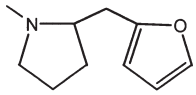
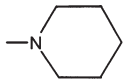
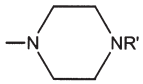
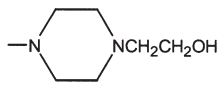
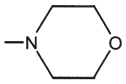
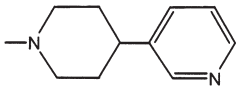
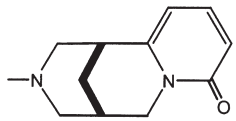


Gossypol Schiff's Bases

Entry	R =	Molecular formula	Yields[a]	mp[a] (°C)	Reference
	Heterocyclic				
1		$C_{36}H_{36}N_4O_6$	73.4	248–250	142
2	(Ragosin) 	$C_{50}H_{52}N_6O_8$	—	—	208
3		$C_{40}H_{42}N_8O_{10}$	39.2	271–272	207
4		$C_{38}H_{40}N_2O_8S_2$	63.4	201–203	142
5		$C_{40}H_{40}N_2O_6S$	—	—	69
6		$C_{40}H_{38}N_4O_6$	89.6	>300	142
7		$C_{42}H_{42}N_4O_6$			142, 112
	ortho (α-picolyl) *meta* (β-picolyl) *para* (γ-picolyl)		91[112], 97.4[142] 91[112], 96.0[142] 99[112]	251[112], 245–247[142] 248[112], 225–227[142] 234[112]	
8		$C_{44}H_{46}N_4O_6$	92	282	112
9		$C_{40}H_{34}N_6O_6F_2$	83.4	275–278	13, 14

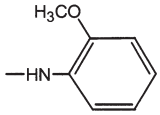
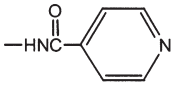
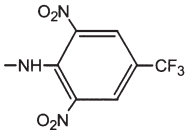
(continued)

TABLE 3 (continued)
Heterocyclic and Hydrazine-Based Gossypol Schiff's Base Derivatives

Entry	R =	Molecular formula	Yields[a]	mp[a] (°C)	Reference
10		$C_{40}H_{363}N_4O_6Cl_2$	74.3	246–248	142
11		$C_{36}H_{32}N_6O_6Cl_4$	80.2	214–216	142
12		$C_{48}H_{42}N_4O_6$	89.6	257–258	142
13		$C_{48}H_{42}N_4O_6$	—	—	144
	Hydrazine-based				
14	–NHC(=S)NH_2	$C_{32}H_{36}N_6O_6S_2$		215	35
15		$C_{48}H_{54}N_4O_8$	91.3	265–268	142
16		$C_{40}H_{50}N_4O_6$	—	—	227
17		(R′ = CH_3) $C_{40}H_{52}N_6O_6$ (R′ = H) $C_{38}H_{48}N_6O_6$	— —	— —	213 228
18		$C_{42}H_{54}N_6O_8$	—	—	213, 228
19		$C_{38}H_{46}N_4O_8$	—	—	213
20		$C_{50}H_{56}N_6O_6$	—	—	227
21		$C_{52}H_{52}N_6O_8$	—	—	227
22	–NHC_6H_5	$C_{42}H_{42}N_4O_6$	—	—	13, 14
23	–NH—$CH_2C_6H_5$	$C_{44}H_{46}N_4O_6$	68.4	172–175	142
24	–$NH(CH_2)_2OCH_3$	$C_{36}H_{46}N_4O_8$	50.8	—	145

(continued)

TABLE 3 (continued)
Heterocyclic and Hydrazine-Based Gossypol Schiff's Base Derivatives

Entry	R =	Molecular formula	Yields[a]	mp[a] (°C)	Reference
25		$C_{44}H_{46}N_4O_8$	52.6[142]	256 (dec) [142]	142, 216
26	—NHC_6F_5	$C_{42}H_{32}F_{10}N_4O_6$	91.9	250–252	142, 207
27		$C_{42}H_{40}N_6O_8$	—	245–247	35
28		$C_{44}H_{36}N_8F_6O_{14}$	—	—	229
29	–$NHCH_2CH(OCH_2CH_3)_2$	$C_{42}H_{58}N_4O_{10}$	55.6	153–156	230

[a]Superscripts refer to the reference from which the data were taken.

coworkers (125) reported that only some of the Schiff's bases they prepared (R = $–C_2H_5$, $–C_4H_9$, $–C(CH_3)_3$, and $–CH(COOCH_3)CH_2C_6H_5$, Fig. 19) exist as the enamine tautomer **40b** when examined by NMR in deuteriochloroform solutions (125). Brzezinski and coworkers (155–159) have examined the equilibrium of some unique gossypol Schiff's bases and studied how complexed metals influence the gossypol Schiff's base equilibrium distribution.

Ziyaev *et al*. (142) examined gossypol Schiff's bases prepared from hydrazines (R = $–NHCH_2C_6H_5$, $–NHC_6H_4(OCH_3)$, and $–NHC_6F_5$ in Fig. 19). For these derivatives the tautomeric equilibrium shifted from the enamine structure **40b**, observed for Schiff's bases in solution, to the imine structure **40a**. No reason for the equilibrium shift was given, although presumably the additional nitrogen atom reduces the nucleophilicity of the corresponding imine nitrogen, making it less likely to

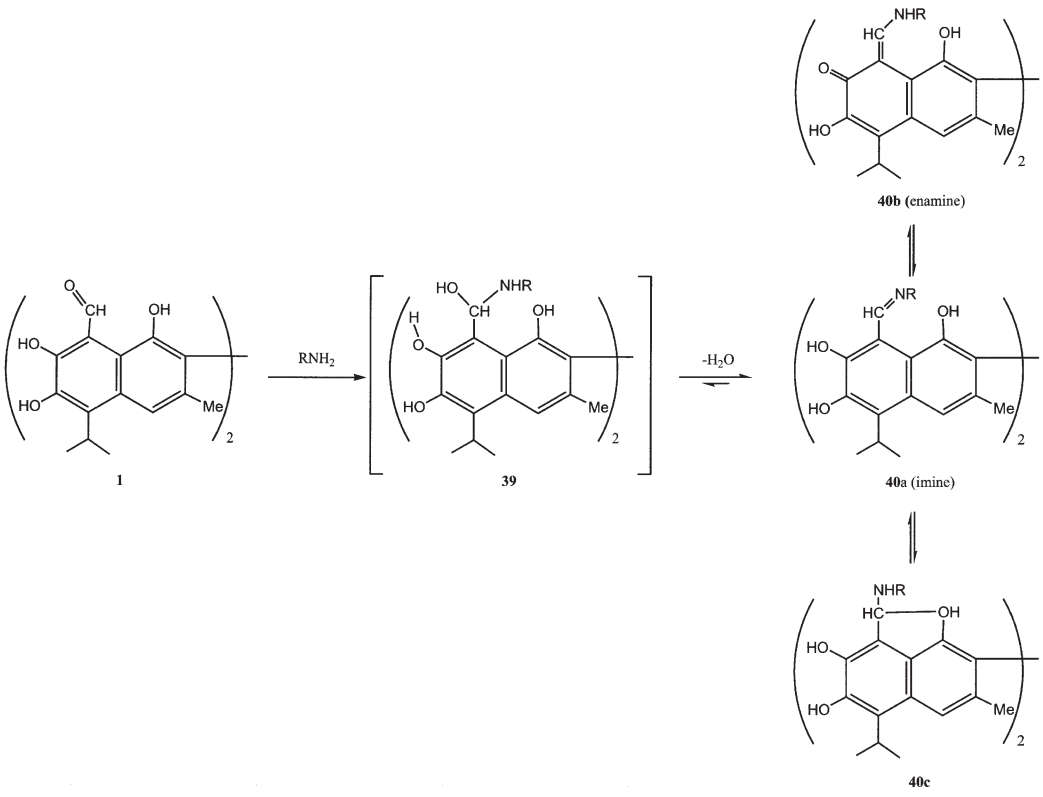


FIG. 19. Mechanism for the formation of gossypol Schiff's bases by reacting an amine with gossypol.

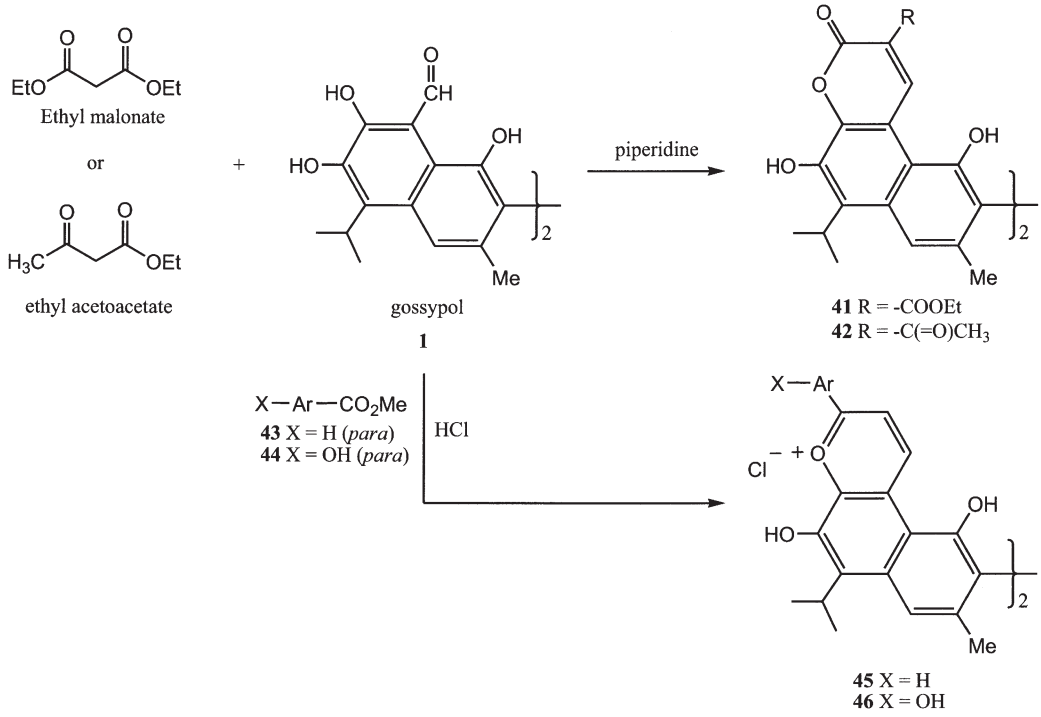


FIG. 20. Condensation reactions of gossypol.

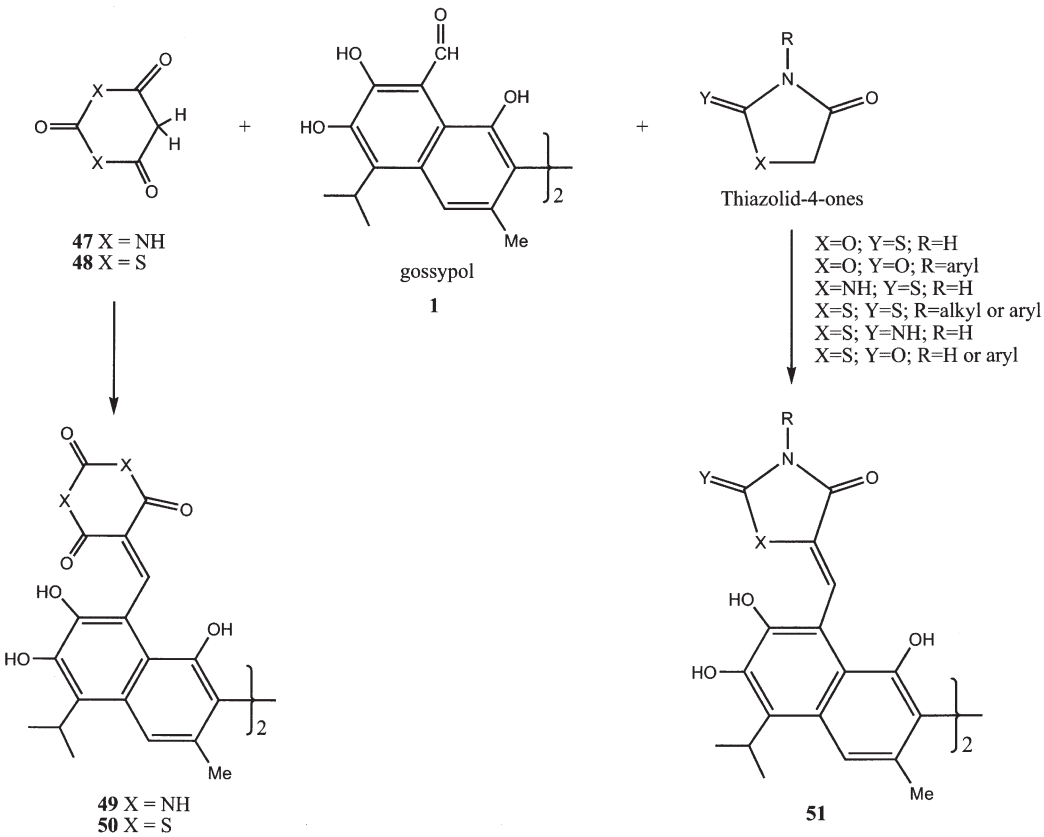


FIG. 21. Condensation reaction between gossypol and barbituric acids **47** and **48** to give condensation products **49** and **50**, respectively.

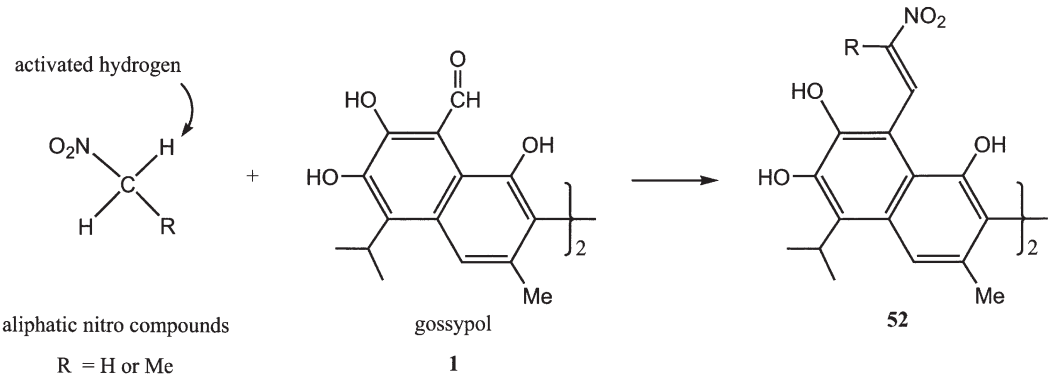


FIG. 22. Possible condensation reaction between gossypol and nitromethane or nitroethane to give new gossypol derivatives, **52**.

accept a proton needed to tautomerize into the enamine form.

Gossypol Schiff's bases also have been prepared by reacting apogossypol **19** with *N,N*-dimethylformamidine. This method is routinely used to label gossypol at gossypol's aldehyde carbon with ^{14}C radioisotopes useful for kinetic studies (160). More recently, Sumin and coworkers (161,162) have improved this methodology by reacting apogossypol with appropriately labeled ^{14}C-*N,N*-diphenylformamide under reduced pressure at 170°C to obtain 60.4% yields of ^{14}C-labeled dianilinogossypol, Subsequent hydrolysis of the Schiff's base and purification by recrystallization in acetic acid gave high-purity ^{14}C-gossypol-acetic acid labeled at gossypol's aldehyde carbons.

Talipov and coworkers (163) used solid-state reaction conditions and a gossypol polymorph to prepare unsymmetrical Schiff's bases in which only one aldehyde was derivatized. This unsolvated crystal form has a wide empty channel that strongly absorbs linear amines, and because one of gossypol's two aldehyde groups is located near the channel wall, they were able to selectively react this aldehyde group with ammonia or methylamine in the solid state and prepare the corresponding unsymmetrical Schiff's base derivatives in high yields.

Reaction of gossypol with activated hydrogen-containing compounds. In contrast to the vast amount of literature pertaining to the condensation reaction between amines and gossypol to obtain the corresponding Schiff's bases, only a few reports have been published describing the condensation reactions between gossypol and compounds possessing activated hydrogen. This is somewhat surprising, because the condensation between gossypol and compounds containing activated hydrogen was first reported in 1944 (164) and represents a research area that has provided organic chemists with many useful reactions such as the Stobbe condensation, Knovenagel condensation, Henry condensation, and Perkin reaction.

As shown in Figure 20, Krishnaswamy and coworkers (164) condensed gossypol with esters of malonic or acetoacetic acids in the presence of piperidine to obtain a-pyrone gossypol derivatives **41** and **42**, respectively.They also reported the condensation of gossypol with acetophenone **43** (X = H) and hydroxyacetophenone **44** (X = OH) in the presence of HCl to give their corresponding flavylium salts **45** and **46**, respectively (Fig. 20).

Other work reported in this area includes the condensation reaction between gossypol and barbituric or thiobarbituric acids, **47** and **48**, respectively (108). Removal of an activated hydrogen located between the 1,3-diketone moiety in barbituric acid (or thiobarbituric acid) gives its corresponding anion, which subsequently reacts with gossypol's aldehyde groups to

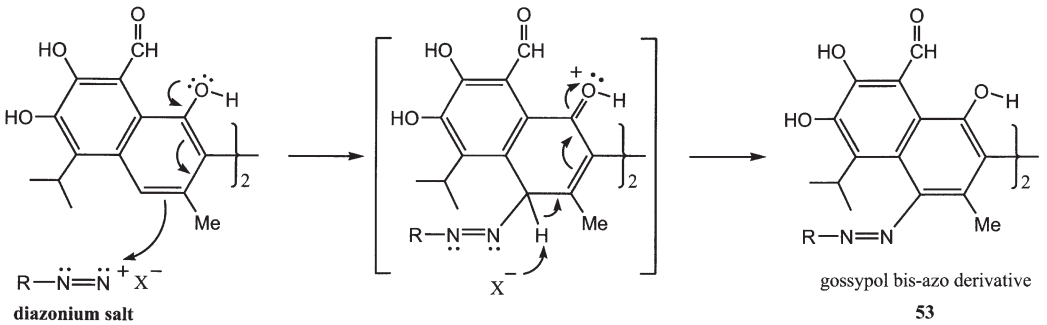
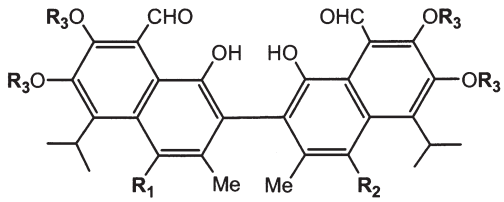


FIG. 23. Electrophilic aromatic substitution reaction between gossypol and diazonium salts to give gossypol bis-azo derivatives. R = alkyl or aromatic. Monosubstituted gossypol azo derivatives also can be prepared using one equivalent of diazonium salt.

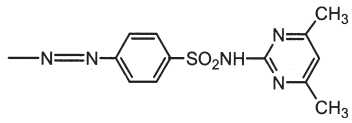
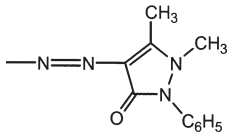
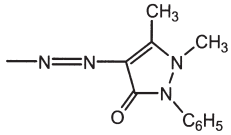
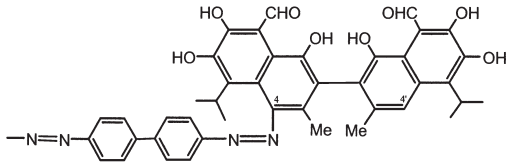
TABLE 4
Mono- and Bis-gossypol Azo Derivatives Prepared from Gossypol and Diazonium Salts



Entry[a]	R_1	R_2	R_3	mp (°C)	Molecular formula
1[168]	—N=N—C_6H_5	H	H	150	$C_{36}H_{34}O_6N_2$
2[35]	—N=N—C_6H_5	$R_2 = R_1$	H	152–154	$C_{42}H_{38}O_8N_4$
3[168]	—N=N—C_6H_4—NO_2	H	H	215	$C_{38}H_{33}O_{10}N_3$
4[168]	—N=N—C_6H_4—SO_3	H	H	N/A[b]	$C_{36}H_{34}O_9SN_2$
5[168]	—N=N—C_6H_3(HOOC)	H	H	151	$C_{37}H_{34}O_8N_2$
6[168]	—N=N—naphthyl	H	H	180	$C_{40}H_{35}O_8N_2$
7[168]	—N=N—C_6H_4—NO_2	$R_2 = R_1$	H	200	$C_{42}H_{36}O_{12}N_6$
8[35]	—N=N—CH_2CH_2OH	$R_2 = R_1$	H	205–207	$C_{34}H_{38}N_4O_{10}$
9[35]	—N=N—CH_2SO_3ONa	$R_2 = R_1$	H	315–317	$C_{34}H_{36}N_4O_{16}S_2Na_2$
10[35]	—N=N—C_6H_4—N=N—C_6H_5	$R_2 = R_1$	H	254–256	$C_{54}H_{46}N_8O_8$
11[35]	—N=N—($C_6H_3CH_3$)—N=N—($C_6H_3CH_3$)	$R_2 = R_1$	H	283–285	$C_{58}H_{54}N_8O_8$
12[35]	—N=N—C_6H_4—SO_2NH_2	$R_2 = R_1$	H	248–250	$C_{42}H_{40}N_6O_{12}S_2$
13[35]	—N=N—C_6H_4—SO_2NH—thiazole	$R_2 = R_1$	H	275–277	$C_{44}H_{48}N_8O_{12}S_4$
14[35]	—N=N—C_6H_4—SO_2NH—thiadiazole—C_2H_5	$R_2 = R_1$	H	248–250	$C_{48}H_{48}N_{10}O_{12}S_2$
15[35]	—N=N—C_6H_4—SO_2NH—pyrimidine	$R_2 = R_1$	H	277–278	$C_{50}H_{44}N_{10}O_{12}S_2$
16[35]	—N=N—C_6H_4—SO_2NH—pyridazine—OCH_3	$R_2 = R_1$	H	298–300	$C_{52}H_{48}N_{10}O_{14}S_2$
17[35]	—N=N—C_6H_4—SO_2NH—(H_3CO)pyrimidine	$R_2 = R_1$	H	235–237	$C_{52}H_{48}N_{10}O_{14}S_2$
18[35]	—N=N—C_6H_4—SO_2NH—pyrimidine—OCH_3	$R_2 = R_1$	H	224–226	$C_{52}H_{48}N_{10}O_{14}S_2$

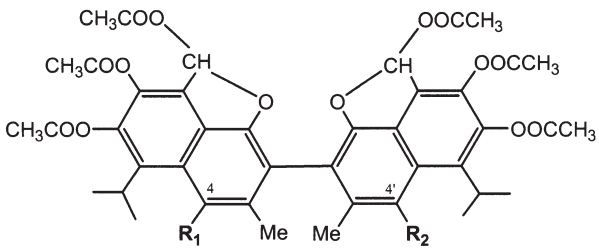
(continued)

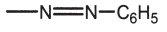
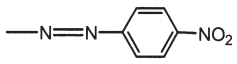
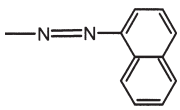
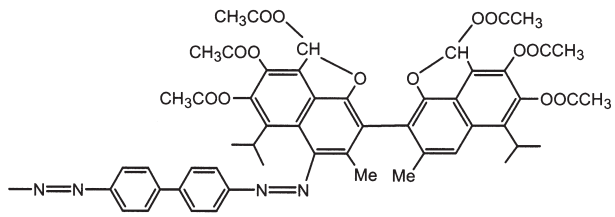
TABLE 4 (continued)
Mono- and Bis-gossypol Azo Derivatives Prepared from Gossypol and Diazonium Salts

Entry[a]	R_1	R_2	R_3	mp (°C)	Molecular formula
19[35]		$R_2 = R_1$	H	215–218	$C_{54}H_{52}N_{10}O_{12}S_2$
20[35]		$R_2 = R_1$	H	279–281	$C_{52}H_{50}N_8O_{10}$
21[35]		$R_2 = R_1$	OMe	192–194	$C_{56}H_{59}N_8O_{10}$
22[c,35]		H	H	145	$C_{72}H_{66}O_{16}N_4$

[a]Superscripts refer to the reference from which the data were taken.
[b]N/A, not available.
[c]Prepared by reacting two equivalents of gossypol with one equivalent of benzidine diazonium salt.

TABLE 5
Gossypol Hexaacetate Azo Derivatives Prepared from Gossypol Hexaacetate and Diazonium Salts[a]



Entry	R_1	R_2	mp (°C)	Molecular formula
1		H	148	$C_{48}H_{46}O_{14}N_2$
2		H	185	$C_{48}H_{45}O_{16}N_3$
3		H	150	$C_{52}H_{48}O_{14}N_2$
4[b]		H	150	$C_{96}H_{90}O_{28}N_4$

[a]From Reference 35.
[b]Prepared by reacting two equivalents of gossypol hexaacetate with one equivalent of benzidine diazonium salt.

provide the condensation products **49** (known as Batridene) and **50,** as shown in Figure 21.

Baram and Ismailov (108) prepared a series of gossypol derivatives **51** based on variously substituted thiazolid-4-ones containing activated hydrogen (Fig. 21). They suggested that some of these compounds had high antitumor activities.

Interestingly, no reports concerning the condensation reaction between gossypol and nitro compounds containing activated hydrogen such as nitromethane, nitroethane, or trinitrotoluene have appeared. The condensation between a nitronate anion and aldehyde or ketone (Henry reaction) is expected to give nitroalkene gossypol condensation product **52** in the case of nitromethane or nitroethane as shown in Figure 22. Syntheses of these derivatives may be interesting because the nitro group is a versatile synthetic intermediate. Additionally, the nitro functionality, specifically nitrate esters, has known vasodilating properties (165), and in conjunction with gossypol's unique characteristics may make attractive synthetic intermediates or drug candidates.

Other potentially interesting active compounds of the form Z–CH_2–Z′ or Z–CHR–Z′, where Z and Z′ may be CHO, COR, COOH, COOR, CN, SOR, SO_2R, SO_2OR, may also be useful to make new gossypol condensation derivatives.

Azo derivatives of gossypol. Diazonium ions are weak electrophiles and react with reactive phenolic compounds such as gossypol as shown in Figure 23. As can be seen, aliphatic and aromatic diazonium salts react with gossypol at the 4- and 4′-positions *via* electrophilic aromatic substitution to give highly colored gossypol azo derivatives **53.**

Zalesov and Markman (166) were the first to report this reaction in 1960, and by controlling the stoichiometric ratio between diazonium salt and gossypol, either the mono- or disubstituted azo compounds of gossypol or its hexaacetate derivative could be prepared. Since then, only three reports describing the preparation of gossypol azo compounds have been published (35,167,168). Tables 4 and 5 tabulate the gossypol and gossypol hexaacetate azo derivatives, respectively, and depict them in their azo tautomeric form for simplicity. These azo compounds are soluble in organic solvents but nearly insoluble in aqueous media. To confer water solubility on these azo compound, –SO_3H and –COOH groups are introduced onto the azo compound and subsequently converted into their corresponding salts. Some of these compounds have been shown useful as azo dyes (entry 21, Table 4; entry 4, Table 5) on cotton, although early work reported dyed cotton acquired a brown shade on standing in air. The formation of the gossypol azo derivative containing the –SO_3H group (entry 4, Table 4) using *p*-sulfobenzene diazonium chloride was used by Zalesov and Markman as a means to determine total gossypol in cottonseed oil (166).

Aryl azo compounds are well known to exist as tautomers between the hydroxyazo and quinonhydrazo forms, and this equilibrium has been well studied by IR and NMR methods (169–171). Baram and coworkers (168,172) examined some new gossypol azo compounds they had synthesized by using IR and UV spectroscopy as well as molecular modeling (168,172). Their experimental results suggest that an equilibrium exists in solution between hydroxyazo tautomer **54** and quinonhydrazo tautomer **55**, shown in Figure 24 although the relative amounts of each tautomer were not reported. Interestingly, molecular modeling calculations (PCMODE MMX) on the bis-phenyl azo derivative (R = –C_6H_5, Fig. 24) suggest the quinonhydrazo tautomer **55** is more stable and predominates in the solid state. No insight was offered as to how the tautomeric structures for gossypol's aldehyde, i.e., structures **3**, **4**, and **5** in Figure 2, might complicate their interpretations regarding the hydroxyazo and quinonhydrazo equilibrium reported. These gossypol azo compounds were said to possess interferon-inducing activity of 320–640 units/mL at a dose of 100 mg/kg (168).

Halogenation. Because halogen-containing compounds, particularly fluoro compounds, are known to display biological activities, several halogenated derivatives of apogossypol hexamethyl ether have been prepared from a number of halogenating agents. Zhu and coworkers (173) brominated apogossypol hexamethyl ether (**20a**) under a variety of conditions as shown in Figure 25. Depending on the conditions used, gossypol was brominated at various locations on the molecule and in some cases formed a five-membered cyclic ether linkage between the 1- and 1′-methyl ethers of apogossypol (compounds **57** and **58**, Fig. 25). Presumably, the acidic conditions resulting from the bromination are the impetus for the ether formation in compounds **57** and **58**.

Zhang and Matlin (174) also have examined the free radical halogenation of apogossypol hexamethyl ether (**20a**) using *N*-bromosuccinimide (NBS). In opposition to brominated compound **56** reported by Zhu and coworkers (173), they obtained compound **60** in which only the 4-, 8′-ring positions were brominated. They isolated and characterized **60** (Fig. 25) by NMR and MS. The reasons for the different brominated products (**56** vs. **60**) resulting from using NBS in these two reports is not clear.

Zhu and coworkers (173) also examined the fluorination of apogossypol hexamethyl ether (**20a**). In contrast to the bromination of **20a** by these researchers, attempts to directly fluorinate **20a** using F_2, $CsSO_4F$, or CH_3COOF under a variety of conditions were unsuccessful. Treatment of the tetrabrominated compound **57**, obtained from ultrasonic bromination, with potassium fluoride in the presence of crown ether, 18-crown-6, provided difluoro compound **61** in which the benzylic bromine atoms were replaced by fluorine atoms.

These researchers also attempted the fluorination of **57** by using silver fluoride or a CuI/CF_3COONa mixture (173) (Fig. 26). Curiously, compounds **62**, **63,** and **64** resulted from these reactions, and their formation suggests the ease by which **57** is hydrolyzed.

Preparation of gossylic nitrile derivatives. Royer and coworkers (47), interested in the biological reactivity of gossypol, have extensively studied the synthesis and reactivity of novel gossypol derivatives that do not contain the aldehyde functionality. Their recent review details much of their work on converting gossypol's aldehyde groups into nitriles, and

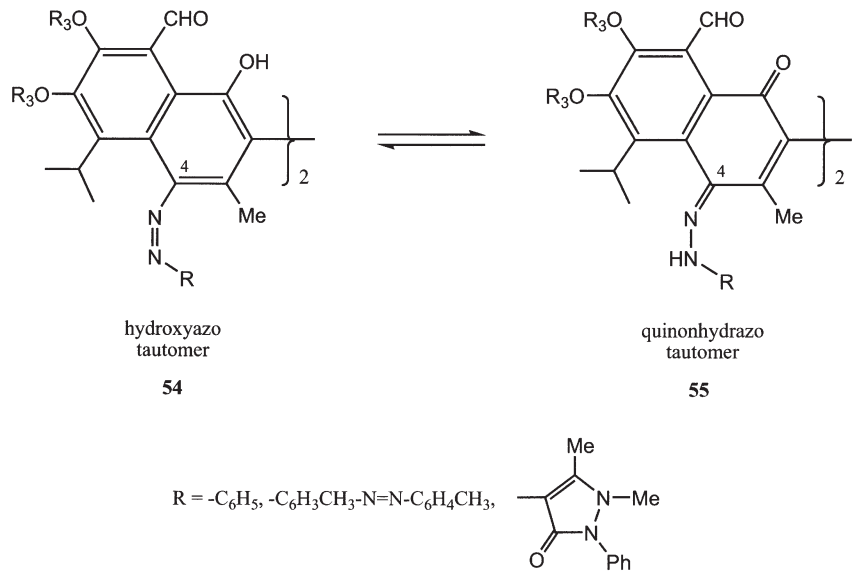


FIG. 24. Hydroxyazo **54** and quinonazo **55** tautomeric forms of gossypol azo derivatives.

they have found the nitrile groups are stable only if the 1- and 1′-hydroxyl groups are derivatized (56). To prepare these gossylic nitrile compounds, they treat known gossypol dioxime **65** with a series of different acyl anhydrides to obtain bis(anhydro oxime) intermediates **66**. Intermediate **66** is gently heated with a carboxylic acid sodium salt identical to the anhydride used in the previous step, to give gossylic nitrile hexaacetate **67** (Fig. 27). Refluxing **67** in aqueous methanol with sodium bicarbonate gives the desired acylated gossylic nitrile compound **68**. They have also prepared the analogous 1,1′- and 6,6′-dimethyl gossylic nitrile compounds using similar approaches (56).

These researchers subsequently used gossylic nitrile **68** as a starting point to prepare other gossylic compounds (56,175).

Gossypol metal complexes. Gossypol's two distinctly acidic hydroxyl groups at C-1 and C-1′ and the aldehydic oxygens can interact with various metal cations and form gossypol metal

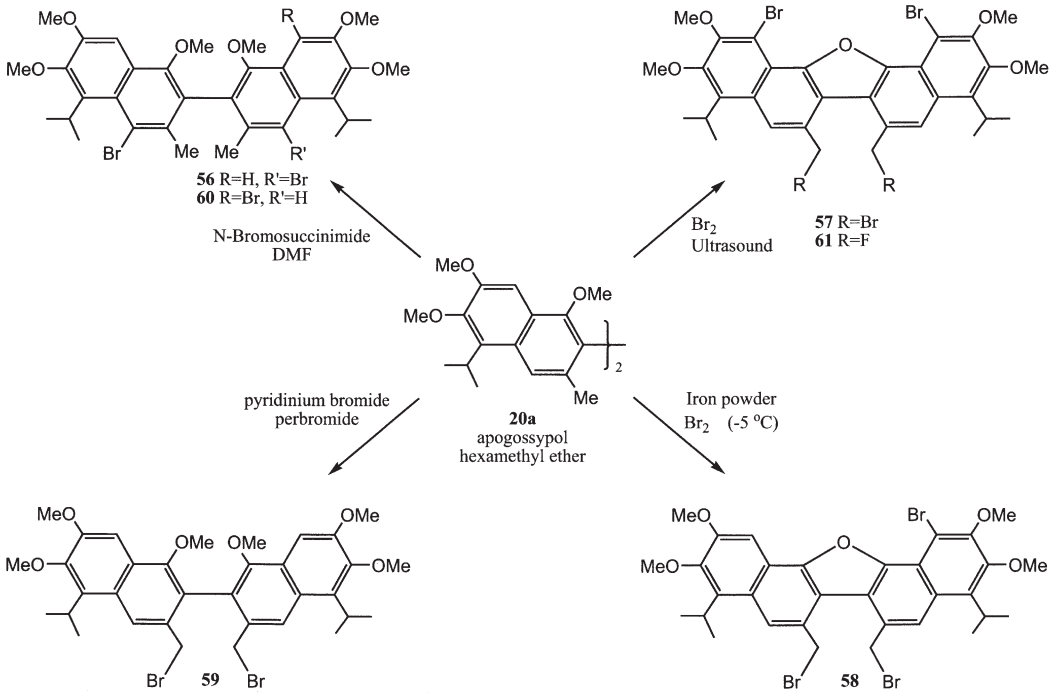


FIG. 25. Bromination products derived from appogossypol hexamethyl ether (**20a**) under various bromination conditions. DMF, dimethylformamide.

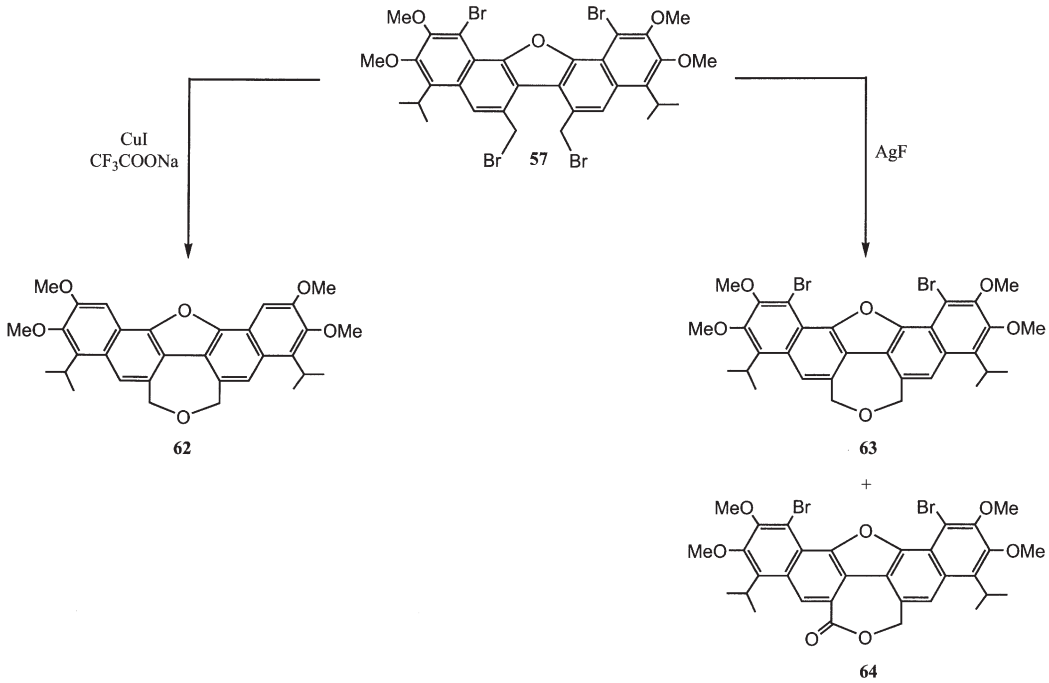


FIG. 26. Attempted fluorination of compound **57**.

complexes (33,34,35,176–178). Gossypol metal complexes have been prepared using metal ions from metals such as: Na, Mg, Al, K, Ca, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Sr, Nb, Mo, Ag, Cd, Sn, Sb, Ba, W, Hg, Pb, lanthanide group (III) cations (Dy, Gd, Tb, Eu), and U (155–159,176–178).

Brzezinski and coworkers (155–159,179–181) have performed extensive NMR, IR, and semiempirical molecular modeling studies to examine how the tautomeric equilibrium is affected when various metal ions are complexed with gossypol and its derivatives.

Two papers by Zaidi and Hadi (182,183) demonstrate the potential to use gossypol metal complexes to mediate reactions. In the presence of Cu^{2+}, gossypol mediates DNA cleavage by reducing Cu^{2+} to Cu^{1+}. They showed that Cu^{1+} is required for DNA cleavage to take place and found that up to eight Cu^{2+} ions could be reduced by a single gossypol molecule. Importantly,

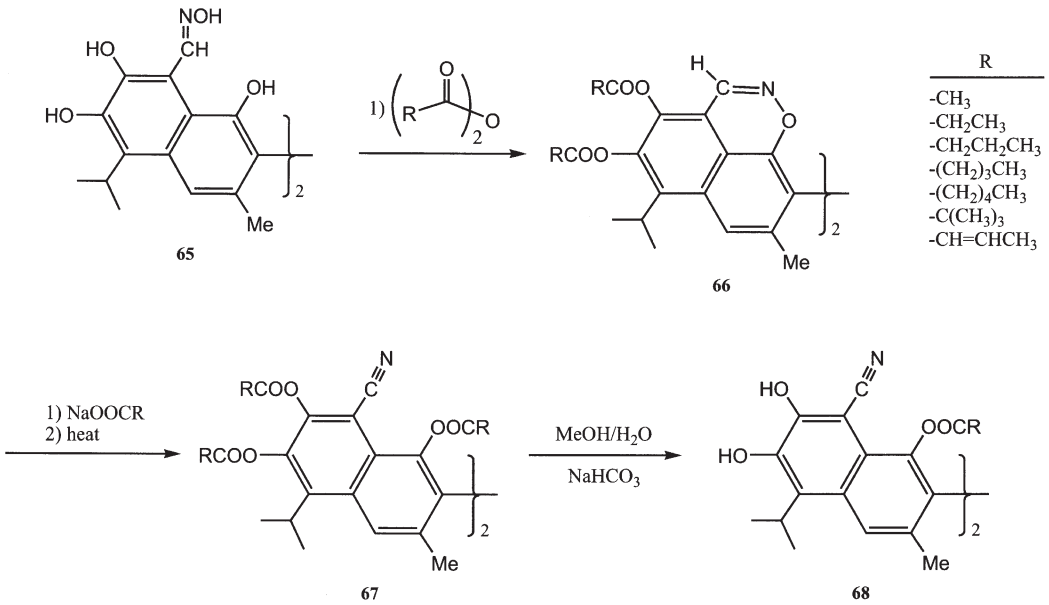


FIG. 27. Preparation of peri-acylated nitriles derivatives **68** starting from gossypol dioxime **65**.

this work suggests the potential for gossypol metal complexes to act in a catalytic fashion.

Total syntheses of gossypol and its derivatives. Initial efforts to synthesize the gossypol molecule were carried out solely for the purposes of structure proof. Of paramount importance to this endeavor is the synthesis of apogossypol (**19**, Fig. 12) in 5% overall yield by Edwards and Cashaw (36–38). From this pioneering work, much research (47,54,56,175,184–193) has followed to devise new, higher-yielding methodologies to prepare gossypol's basic naphthalene framework. This work is beyond the scope of this review. Of recent interest is the work by Meyers and Willemsen (194–196) to complete the first asymmetric synthesis of (*S*)-apogossypol hexamethyl ether (18–19% overall yield) and (*S*)-gossypol (8–9% overall yield) (194–196).

SUMMARY, FUTURE DIRECTIONS

Gossypol has been known for well over a hundred years and the dichotomy between its toxicity to man and nonruminant animals and its unique biological activities as antifertility, anticancer, and plant defense agent places gossypol in an unusual position. On one hand, researchers are currently working diligently to produce glandless strains of cottonseed devoid of gossypol to provide high-quality cottonseed products without gossypol's associated toxicity (197). On the other hand, researchers are using gossypol's binaphthyl structure, functionality, and unique biological activities to make gossypol a potentially important value-added natural product.

A great deal of gossypol's basic reaction chemistry, discovered while elucidating its structure during work in the early part of the 20th century, in conjunction with reports on gossypol's antifertility and anticancer properties in the later part of the 20th century, have sustained and fueled research to understand gossypol's reaction chemistry and mechanism of action and has led to the development of many new biologically active gossypol derivatives. The synergy of these research efforts has opened future opportunities for gossypol research pertaining to its reaction chemistry and also its utilization.

Of particular importance to gossypol's future use is the development of new reaction chemistry and new derivatives to provide novel drug candidates. One potential growth area that warrants further exploration is based on the condensation chemistry between reagents containing activated hydrogen and gossypol's reactive aldehydes. There appear to be many possible unique gossypol derivatives yet to be made using this chemistry.

Gossypol's ability to complex metal ions may also represent an interesting research area useful for chemical reactions. Gossypol metal complexes are known to control the equilibrium between the various gossypol tautomers. Can metal ions complexed to gossypol during a reaction sequence be used to allow chemical reagents to react with a specific gossypol tautomer instead of a tautomeric mixture? Additionally, can optically pure gossypol enantiomers be used to complex metal ions and form chiral metal complexes that may serve as potentially useful chiral catalysts for organic syntheses? These are appealing ideas, and to date, their merit remains relatively unexplored.

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