purified by sublimation followed by crystallization from benzene; colorless plates, m. p. 167–169°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.4; H, 7.15. Found: C, 64.85; H, 7.42.

Action of Dilute Nitric Acid on Apogossypolic Acid.—A mixture of 0.15 g. of apogossypolic acid, 3 cc. of concentrated nitric acid and 9 cc. of water was refluxed for two hours. Upon cooling, fine white crystals separated. These were purified by crystallization from cyclohexane, m. p. 155–158°; yield 0.105 g.

Anal. Calcd. for $C_{12}H_{15}O_6N$: C, 53.55; H, 5.58; N, 5.21; neut. equiv., 269. Found: C, 53.79; H, 5.75; N, 5.19; neut. equiv., 268.

Reduction of the Nitric Acid Product of Apogossypolic Acid.—The product just described was reduced with Raney nickel and hydrogen under 2.5 atm. pressure in ethanol solution. The product was purified by twice subliming at 25 mm.; white crystals, m. p. 74–76°, that turn dark after standing a few hours in air.

Anal. Calcd. for $C_{11}H_{17}O_2N$: C, 67.7; H, 8.72; N, 7.18. Found: C, 67.84; H, 8.62; N, 6.96.

This material was insoluble in dilute aqueous sodium hydroxide but soluble in 5% aqueous hydrochloric acid. It diazotized with nitrous acid and the solution gave a red color on treatment with a solution of β-naphthol.

Acetylation of the Amine.—A mixture of 30 mg. of the amine just described, 2 cc. of acetic anhydride and 50 mg. of fused sodium acetate was refluxed gently for thirty minutes. After cooling, the excess acetic anhydride was decomposed by the addition of three to four volumes of water. The solution was evaporated to dryness under a stream of air and the amine acetate extracted from the sodium acetate by means of ether. From this extract a colorless oil was obtained which crystallized after standing for two to three hours. Purification of this crystalline material was accomplished by two sublimations at a bath temperature of 100–125° (18 mm.). This was followed by a dilute acid wash and by a third sublimation; white crystals, m. p. 85–86°.

Anal. Calcd. for diacetate, $C_{15}H_{21}O_4N$: C, 64.52; H, 7.53; N, 5.02. Found: C, 64.73; H, 7.49; N, 5.11.

Summary

Apogossypolic acid is decarboxylated and demethylated by the action of hydrobromic acid. The product, upon methylation with diazomethane and subsequent saponification gives a monobasic acid, decarboxylated apogossypolic acid. A discussion of the structure of this latter product is given.

Apogossypolic acid is converted to a mononitro monocarboxylic acid by the action of nitric acid. The nitro compound upon reduction followed by sublimation gives an aromatic amine containing no carboxyl group. This must be a dimethoxy *n*- or isopropyl aminobenzene. Its structure and the analogous compounds from gossypol are discussed.

The absorption spectrum of decarboxylated apogossypolic acid is similar to that of veratric and dissimilar to homoveratric acid.

URBANA, ILLINOIS RECEIVED JUNE 27, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. XV.[1] An Interpretation of its Reactions

BY ROGER ADAMS, R. C. MORRIS, T. A. GEISSMAN, D. J. BUTTERBAUGH AND E. C. KIRKPATRICK

A large number of reactions of gossypol and of its degradation products have been studied. As the result of this accumulation of experimental evidence, it is now possible to formulate deductively a reasonable structure for the gossypol molecule. The purpose of this communication is to correlate and interpret the physical and chemical properties of gossypol in terms of this structure.

The absorption spectra of gossypol[2] and its derivatives and the formation of many of its degradation products are indicative of a molecule containing two naphthalene nuclei connected either directly or through an alkylene chain. The formula for gossypol must be essentially symmetrical and probably completely so, for an even number of moles of reagent reacts in every instance. The diverse and unusual reactions of gossypol as well as the absorption spectra show every indication that the molecule is tautomeric.

The postulated structure of gossypol is represented by Ia with Ib and Ic representing two possible tautomeric forms.

The structural configuration of gossypol will be discussed and formulas will be assigned for all the significant derivatives and degradation products.

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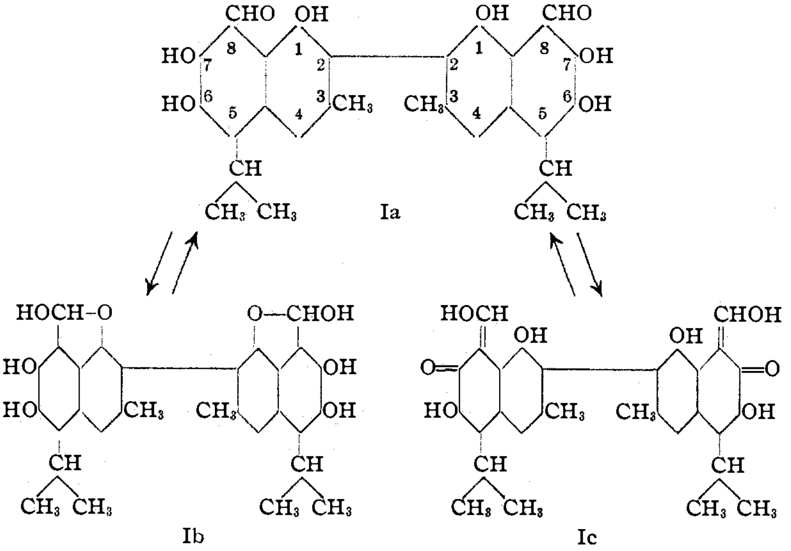
[1] For previous paper in this series, see Adams, Morris, Butterbaugh and Kirkpatrick, THIS JOURNAL, **60**, 2191 (1938).

[2] Adams and Kirkpatrick, *ibid.*, **60**, 2180 (1938); Marchlewski, *J. prakt. Chem.*, **60**, 84 (1899); Grünbaumowna and Marchlewski, *Biochem. Z.*, **286**, 295 (1936); Zamyshlyaeva and Krivich, *J. Gen. Chem.*, (U. S. S. R.), **7**, 1969 (1937).



Ia

Ib

Ic

Wherever structural formulas are used, only half the molecule will be written in order to conserve space. It must be remembered, however, that in all cases double the number of moles of reagents react than is indicated by the half molecules and double the number of groups are introduced.

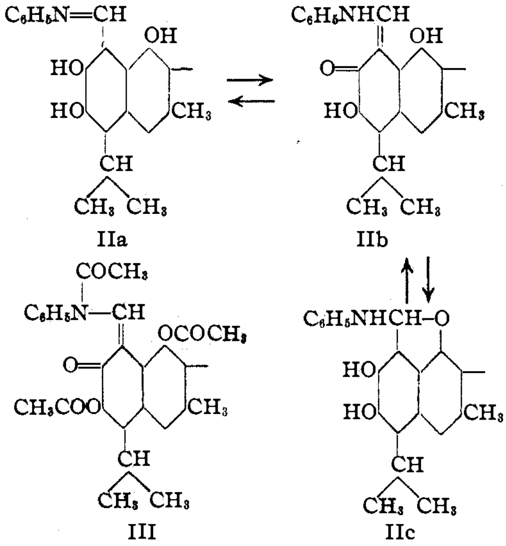
Color Reactions and Salts.[3]—Gossypol gives (1) a green color with ferric chloride, (2) a deep red with pyroboroacetate and (3) a purple red with stannic chloride. These colors have been shown previously to be rather characteristic, particularly in the naphthalene series, (1) of two phenolic hydroxyls ortho to each other, (2) and (3) of a hydroxyl peri or ortho to a carbonyl. These colors may be expected of a molecule with formula Ia. Gossypol forms a stable compound with stannic chloride which was isolated and analyzed. It has a Sn:Cl ratio of 1:2. Naphthalene molecules with two peri hydroxyls and a ketone or aldehyde group form similar compounds. It is not unreasonable to believe that an arrangement of hydroxyls and aldehyde groups as shown in formula Ia would give the same result though no simple naphthalene derivatives with hydroxyls and aldehyde thus placed have been tested.

Gossypol titrates dibasic and forms a dipyridyl salt. Many hydroxyaldehydes show a similar acidity for the phenol group possibly due to the vinylogous relationship of an *o*- or *p*-hydroxyaldehyde to a carboxylic acid.

Aniline and Ammonia Derivatives.[4]—Gossypol condenses readily with two moles of aniline with the elimination of two moles of water. Several substituted anilines, including *o*-phenylenediamine, also condense in the same ratio; others give products which do not analyze for simple derivatives. All these products, however, are readily hydrolyzed by acid to gossypol.

Liquid ammonia reacts similarly to give an easily hydrolyzed diaminogossypol.

Of importance from the structural standpoint are the methylation and acetylation of the yellow dianilinogossypol.[4] Under proper conditions a red dimethylated compound is isolated which has the methyl groups attached to nitrogens since they cannot be removed by hydriodic acid; the methylated compound cannot be hydrolyzed to gossypol. The hexaacetyldianilinogossypol has two acetyls attached to nitrogens since acetanilide is obtained by pyrolysis. These experiments establish the probability of the dianilino compound existing not as a simple Schiff base but as a tautomeric structure such as might be formed from an hydroxymethylene compound, the tautomeric form of an *o*-hydroxy aldehyde. The anilino compound of gossypol therefore is formulated as IIa, IIb, IIc and the hexaacetate possibly as III though it could be based on structure IIc.



IIa

IIb

III

IIc

The amino derivatives produced by the action

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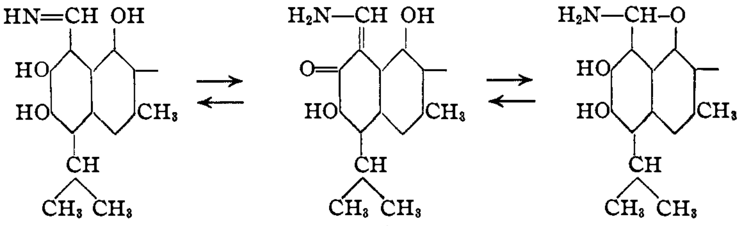
[3] Campbell, Morris and Adams, This Journal, **59**, 1723 (1937).

[4] Adams, Price and Dial, *ibid.*, **60**, 2158 (1938).

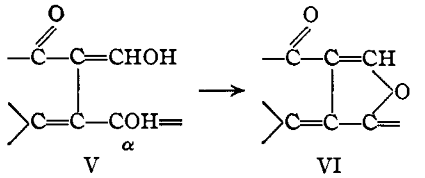
of liquid ammonia probably have analogous formulas, IVa, IVb, IVc.



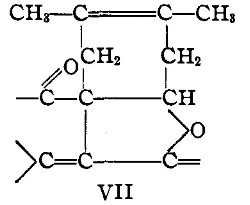
IVa IVb IVc

Anhydrogossypol.[5]—Anhydrogossypol is produced by heating gossypol above its melting point or by the use of a mild dehydrating agent in an inert solvent. It is very sensitive to hydrolysis, regenerating gossypol. The reactions which were attempted such as methylation, acetylation or treatment with liquid ammonia or amines even under strictly anhydrous conditions result not in anhydrogossypol derivatives but in derivatives of gossypol. In the case of anhydrogossypol, the reactions always involve simple addition; in the case of gossypol, the same derivatives are obtained by elimination of water, acetic acid or analogous molecules but never by simple addition. A very easily opened oxygen-containing ring must therefore be present in anhydrogossypol.

The anhydro compound reacts with both butadiene and dimethylbutadiene[6] to give addition products. This indicates the probability of the presence of an α,β-unsaturated carbonyl grouping. The stability of the diene addition compounds to hydrolysis leads to the conclusion that the unstable oxygen-containing ring of anhydrogossypol has been modified and stabilized. It is probable, therefore, that the carbon–carbon double bond of the α,β-unsaturated carbonyl grouping is part of the oxygen-containing ring of anhydrogossypol. Nuclei postulated to account for these transformations are shown in V (gossypol), VI (anhydrogossypol), and VII (diene addition product).



V VI

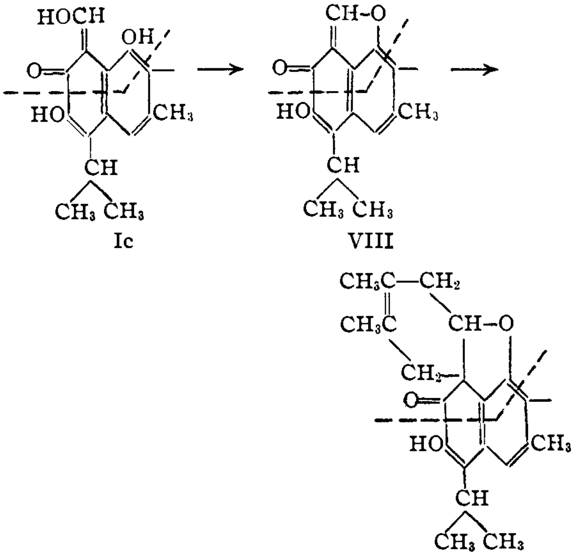


VII

Gossypol also adds dienes but with the simultaneous loss of water to give the same compound obtained from anhydrogossypol.

The α-hydroxyl in formula V must be phenolic since otherwise a nitrogen-containing ring[4] analogous to VI should be produced upon treatment with anhydrous ammonia.

The tautomeric formula of gossypol (Ic) contains just such a nucleus as is shown in V and the formula of anhydrogossypol may thus be VIII and the dimethylbutadiene addition product IX. The portions of the molecules above the dotted lines in Ic, VIII and IX are identical with the corresponding nuclei V, VI and VII.



Ic VIII IX

The oxygen-containing ring structure in VIII probably would hydrolyze readily and that in IX would undoubtedly be stable.

The diene addition products also contain two phenolic hydroxyls which are readily methylated or acetylated. These are shown in IX. The red color which the addition products give with pyroboroacetate is found in molecules with an hydroxyl ortho or peri to a carbonyl.

From a survey of the literature of hydroxy aldehydes of the benzene and naphthalene series, it was impossible to find any record of a derivative

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(5) Miller and Adams, THIS JOURNAL, **59**, 1736 (1937).

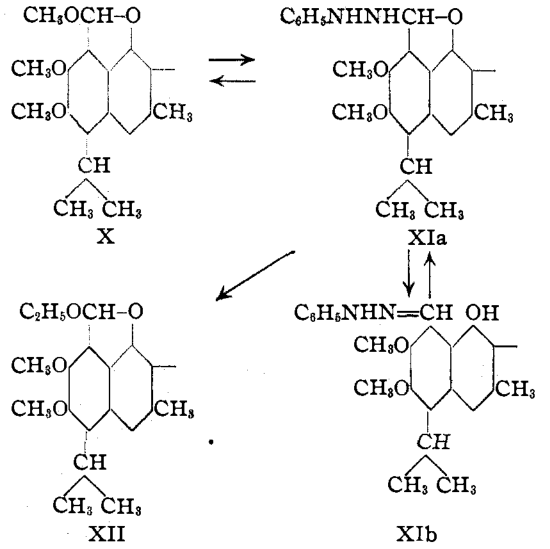
(6) Adams, Friedman, Price, Morris and Kirkpatrick, *ibid.*, **60**, 2160 (1938).

of the tautomeric forms of the hydroxymethylene type. On the other hand, it seems likely they should exist, especially in certain types of polyhydroxy naphthaldehydes and an attempt is now being made to prepare such derivatives. It is worthy of note that Windaus[7] on the basis of sound experimental evidence postulated the hydroxymethylene form of an aromatic hydroxy aldehyde for the structure of colchicine.

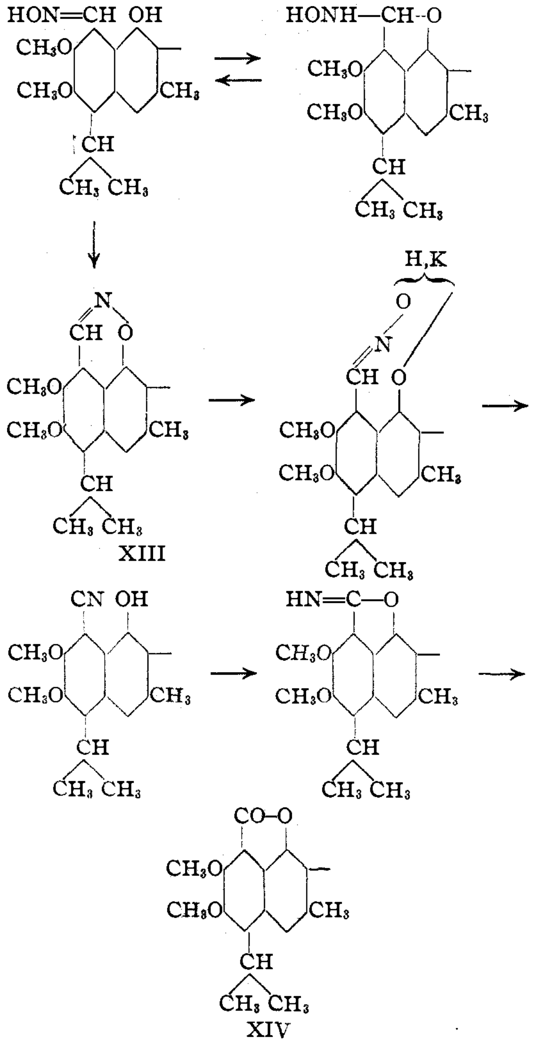
Ethers of Gossypol.[8]—A white tetramethyl ether of gossypol is obtained by the action of dimethyl sulfate on gossypol under conditions which exclude degradation due to the presence of *alkali. Further methylation of this compound* gives a white or a red hexamethyl ether, depending on the experimental conditions. Moreover, it acetylates to a gossypol tetramethyl ether diacetate.

The tetramethyl ether and the white hexamethyl ether are very stable to alkali or alkaline oxidizing agents in contrast to gossypol. They do not react with aldehyde reagents in neutral solvents. In the presence of acetic acid, however, condensation reactions with aldehyde reagents take place.[9] The substances produced no longer contain six methoxyls. Two apparently are hydrolyzed to hydroxyls and then two moles of reagent react in the normal way with the aldehyde groups. The phenylhydrazine derivative of gossypol hexamethyl ether is a diphenylhydrazone of a gossypol tetramethyl ether; of gossypol tetramethyl ether a diphenylhydrazone of a gossypol dimethyl ether. By means of methanolic hydrochloric acid, the diphenylhydrazone of gossypol tetramethyl ether is reconverted to gossypol hexamethyl ether or by ethanolic hydrochloric acid to gossypol tetramethyl diethyl ether.

It is thus obvious that two of the methoxyls in gossypol hexamethyl ether differ from the other four and their reactivity suggests they are of an acetal type. A lactol structure of a *peri*-hydroxynaphthaldehyde is written to account for these results. Gossypol hexamethyl ether (X) is thus based on structure Ib. The phenylhydrazine derivative is represented by XIa and XIb and the gossypol tetramethyl diethyl ether by XII.


X XIa XII XIb

The reaction of hydroxylamine[9] in acetic acid solution with gossypol tetramethyl and hexamethyl ethers also involves the hydrolysis of two methoxyl groups. Two moles of reagent then condense in the usual way, followed however by loss of two more molecules of water. These


XIII XIV

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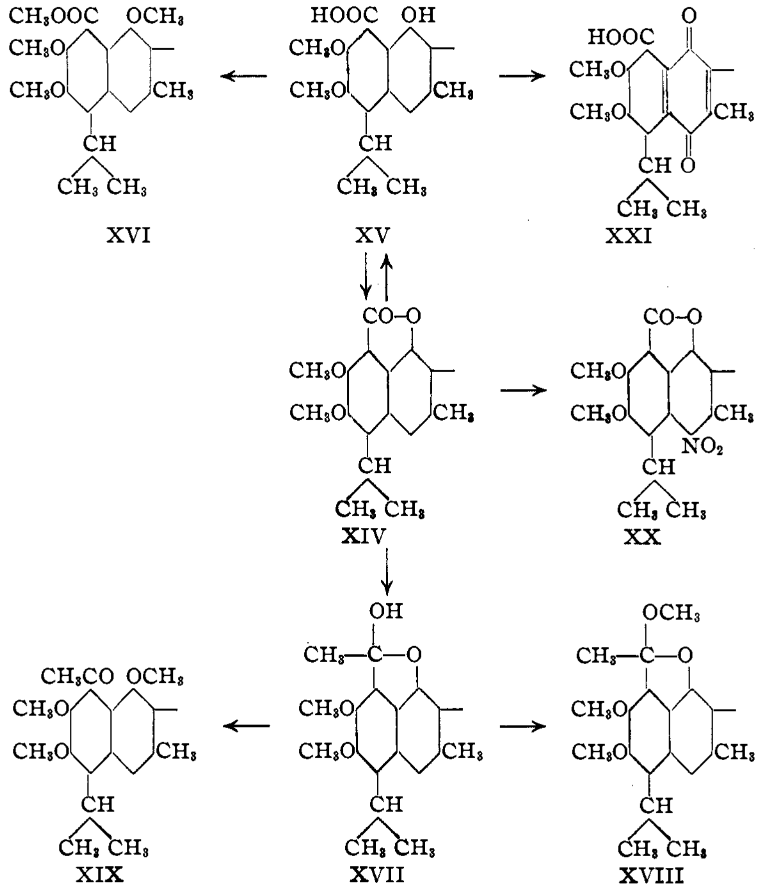
(7) Windaus, *Ann.*, **439**, 59 (1924).

(8) Morris and Adams, This Journal, **59**, 1931 (1937).

(9) Adams and Geissman, *ibid.*, **60**, 2166 (1938).

reactions may best be interpreted by the assumption that orthoxazine rings have formed XIII.

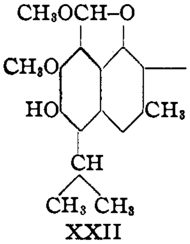


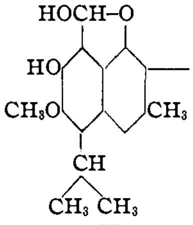
Hydrolysis of the orthoxazine (XIII) followed by treatment with acetic acid results in a lactone, gossylic acid lactone tetramethyl ether (XIV). The hypothetical intermediates in this transformation, the structures of which are given but not numbered, were not isolated.

The lactone[10] (XIV) is hydrolyzed to the hydroxy acid (XV), which can be methylated by treatment either with diazomethane, thus indicating that a phenolic hydroxyl is involved in the lactone, or by dimethyl sulfate and alkali, to give dimethyl gossylate hexamethyl ether (XVI). The fact that XVI could not be hydrolyzed under any usual conditions constitutes evidence for the presence of orthosubstituted groups.

Additional reactions of the lactone (XIV) were also carried out. It reacts with one molecule of methylmagnesium iodide instead of two, as is common to ordinary lactones which are not hindered, and gives homogossypol tetramethyl ether (XVII). Upon methylation with methanolic sulfuric acid, this yields the ether (XVIII) whereas dimethyl sulfate and alkali gives the isomeric ether (XIX). Nitration of the lactone (XIV) results in a dinitro compound (XX). The action of dilute nitric acid upon the hydroxy acid (XV), however, oxidizes it to the quinone, gossypolonic acid tetramethyl ether, shown in XXI.

Gossypol hexamethyl ether[11] can be demethylated partially by means of a drop of sulfuric acid in acetic acid. A dimethyl ether is formed which, unlike the tetra- and hexamethyl ethers, shows many of the characteristic reactions of gossypol. It condenses readily with aniline in neutral solution and undergoes loss of two carbons and two oxygen atoms by treatment with concentrated aqueous sodium hydroxide. Gossypol tetramethyl ether, when demethylated in a similar way, is converted to gossypol. This shows conclusively that the two hydroxyls in gossypol tetramethyl ether are those which are methylated in gossypol dimethyl ether. In view of these facts the formula for the tetramethyl ether is XXII and of the dimethyl ether XXIII.


XXII


XXIII

It becomes obvious why the phenylhydrazine derivatives of gossypol tetramethyl ether (XXIV) and of the dimethyl ether (XXV) are isomeric and not identical.[9]

The structure assigned the hexamethyl ether (X) accounts satisfactorily for the existence of two stereoisomeric forms.[11] The two lactol carbon atoms are asymmetric and, therefore, allow two stereoisomers. Stereoisomers could

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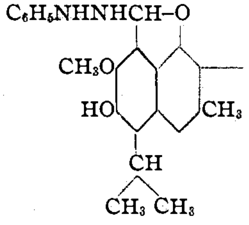
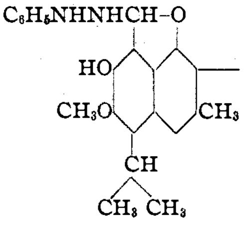
[10] Adams and Geissman, THIS JOURNAL, 60, 2184 (1938).

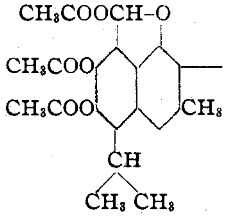
[11] Adams and Geissman, *ibid.*, 60, 2163 (1938).

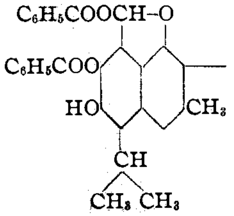

XXIV


XXV

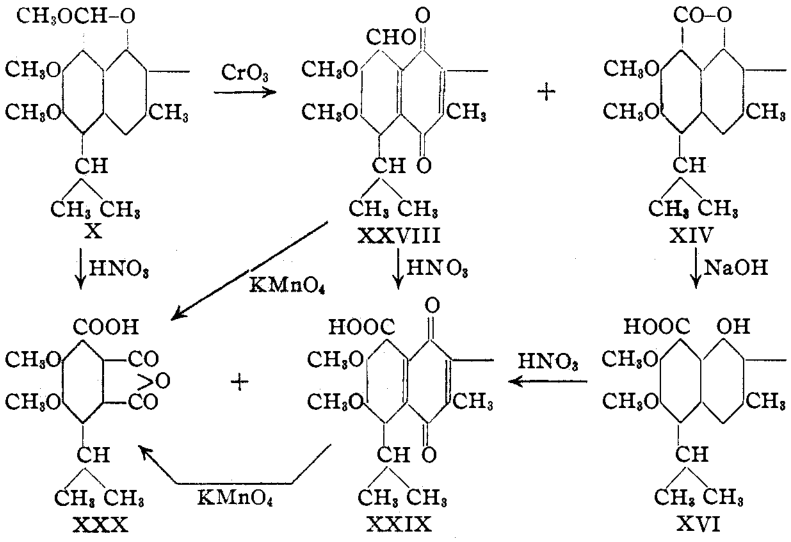
also be explained on the basis of formula Ia due to restricted rotation between the naphthalene nuclei. Since, however, stereoisomers were isolated only in the case of gossypol hexamethyl ether, the first explanation seems preferable. The formula (X) also explains why its absorption spectra[2] and that of the tetramethyl ether (XXII) differ from those of gossypol and the dimethyl ether (XXIII). The third peak in the spectra of the latter two compounds is missing in the first two. This peak is presumably due to the tautomeric *o*-hydroxyaldehyde nucleus and confirms the structures written for those molecules.

Esters of Gossypol.—Gossypol hexaacetate[12] is formed from gossypol, acetic anhydride and sodium acetate under very mild conditions. In addition to the white hexaacetate, a yellow product is obtained. This latter product is also formed upon heating the white hexaacetate with acetic anhydride. The yellow substance has not been obtained in an analytically pure state so that its character is undetermined. It is natural to assume that the white gossypol hexaacetate has a structure analogous to the hexamethyl ether and is, therefore, XXVI, though other formulas may be written based on the other tautomeric forms of gossypol. Benzoylation of gossypol[13] results merely in a tetrabenzoate and is represented by XXVII.


XXVI


XXVII

Oxidation Reactions of Gossypol Hexamethyl Ether.[14]—Gossypol hexamethyl ether (X) upon oxidation with chromic acid yields primarily a compound, gossypolone tetramethyl ether (XXVIII), in which two methoxyls have been hydrolyzed and two hydrogens have been replaced by an oxygen. As a minor by-product the lactone (XIV) is formed. Oxidation of X by dilute nitric acid yields two products in about equal amounts, the first, the water-insoluble gossypolonic acid tetramethyl ether (XXIX) of molecular size about that of the starting material, the second the water-soluble gossic acid (XXX) of about half the molecular size. Gossypolonic acid tetramethyl ether (XXIX) by the action of permanganate gives gossic acid (XXX). Moreover, gossypolone tetramethyl ether (XXVIII) is oxidized by nitric acid to gossypolonic acid tetramethyl ether (XXIX) and by permanganate to gossic acid (XXX). The lactone (XIV) is stable to nitric acid but the corresponding acid (XVI) is oxidized with nitric acid to gossypolonic acid tetramethyl ether (XXIX).



It is obvious how gossic acid (XXX) is produced. The quinone rings of gossypolonic acid tetramethyl ether (XXIX) are oxidized to two *o*-carboxyls which form the anhydride linkage. On the other hand, it is not so clear why gossypolonic acid tetramethyl ether (XXIX) cannot be oxidized with nitric acid to gossic acid (XXX) and still gossic acid is formed directly and simultaneously along with (XXIX) by the nitric acid oxidation of gossypol hexamethyl ether (X). An oxidation with degradation of the naphthalene

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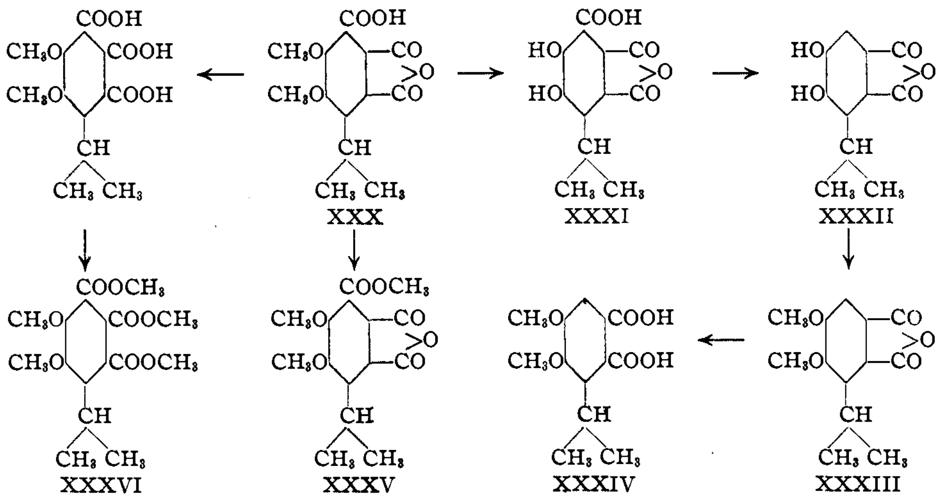
[12] Miller, Butterbaugh and Adams, THIS JOURNAL, **59**, 1729 (1937).

[13] Adams and Butterbaugh, *ibid.*, **60**, 2174 (1938).

[14] Adams, Morris and Kirkpatrick, *ibid.*, **60**, 2170 (1938).

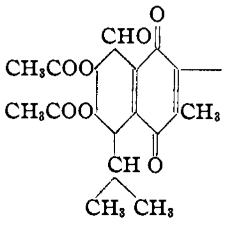


nucleus can take place apparently without quinone formation as an intermediate.

An extended study of the reactions of gossypolone tetramethyl ether (XXVIII) or of gossypolonic acid tetramethyl ether (XXIX) has not yet been completed. It has been shown, however, that the former contains no carboxyl groups while the latter contains two. Evidence yet unpublished is that they are quinones. Gossic acid (XXX), on the other hand, by degradation studies has been shown to be a benzene derivative with two methoxyls, a carboxyl, a dibasic acid anhydride and an isopropyl group. The evidence for this last group will be discussed under the heading "Desapogossypol."

Gossic acid[15] (XXX) is converted to apogossypolic acid (XXXIV) through the following intermediates, all of which can be isolated in a pure state, (1) demethylated gossic acid (XXXI), (2) demethylated decarboxylated gossic acid (XXXII), (3) decarboxylated gossic acid or apogossypolic acid anhydride (XXXIII), (4) apogossypolic acid (XXXIV). Other derivatives of gossic acid are also shown, methyl gossate (XXXV) by the action of diazomethane on gossic acid and the trimethyl ester (XXXVI) of hydrolyzed gossic acid by treatment of gossic acid with alkali, followed by acidification and methylation.

Gossypol hexaacetate[16] acts similarly to gossypol hexamethyl ether and undergoes oxidation with chromic acid to gossypolone tetraacetate (XXXVII). Further degradations of this molecule are not feasible because of the tendency for the acetyls to hydrolyze and thus to give products which are unstable and which rapidly decompose.



XXXVII

Apogossypol and its Derivatives.—Gossypol (Ia or Ic) loses two carbons and two oxygens by the action of concentrated aqueous sodium hydroxide.[5,13] The unstable compound produced, apogossypol (XXXVIII), is undoubtedly formed by the loss of the two aldehyde groups. Such a reaction is common to many hydroxyaldehydes of the benzene and naphthalene series. The instability of the product is explicable if compared with many polyhydroxynaphthalenes. The hexaacetate (XXXIX) and hexamethyl ether (XLII) of apogossypol, however, are stable compounds. Both of these derivatives oxidize, the first to apogossypolone tetraacetate (XL) and the second to apogossypolone tetramethyl ether (XLIII). Two methoxyls or two acetoxyls are lost during these reactions and the products are quinones as shown by reductive acetylation to hydroapogossypolone octaacetate (XLI) and hydroapogossypolone tetramethyl ether tetraacetate (XLIV). In the case of the hydroapogossypolone octaacetate (XLI) reoxidation to the quinone takes place readily. It is important to note that parallel series of derivatives are formed from the hexaacetate and hexamethyl ether.

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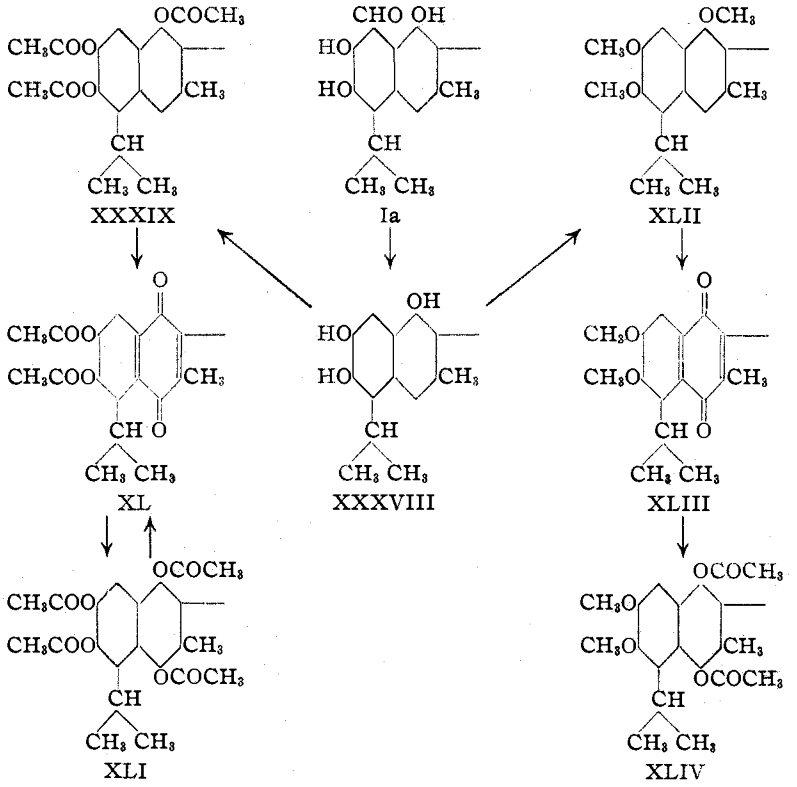
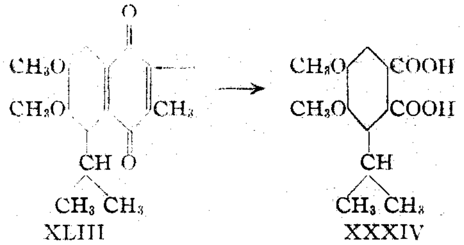
[15] Adams and Morris, THIS JOURNAL, **60**, 2188 (1938).

[16] Clark, *ibid.*, **51**, 1475 (1929).



The quinone,[13,17] apogossypolone tetramethyl ether (XLIII), upon oxidation with permanganate gives the water-soluble apogossypolic acid (XXXIV) described in connection with the degradation reactions of gossic acid (XXX). This transformation is shown below, the quinone ring oxidizing to two carboxyl groups.



It is significant that apogossypol (XXXVIII), apogossypol hexamethyl ether (XLII) and apogossypolone tetramethyl ether (XLIII) correspond exactly to gossypol Ia, gossypol hexamethyl ether (X), and gossypolone tetramethyl ether (XXVIII). There are two aldehyde groups less in each of the members of the former series, and consequently no condensation with aniline occurs. With the latter series aniline derivatives are formed. Apogossypolic acid (XXXIV) from the first series and gossic acid (XXX) from the second series differ merely by a carboxyl group[18] which presumably has formed from the aldehyde group by oxidation. Observation of this parallelism in the gossypol and apogossypol series leads to the conclusion that gossypolone tetramethyl ether and apogossypolone tetramethyl ether must have analogous structures. Since the latter has been shown unquestionably to be a quinone, the former is almost certain to be one also. This is confirmed by comparison of their absorption spectra.

Apogossypolic acid (XXXIV) has been degraded in a number of ways.[1] Methylation gives a dimethyl ester (XLV), and sublimation, the anhydride (XXXIII). Hydrobromic acid hydrolyzes the methoxyl groups and at the same time a carboxyl group is eliminated as carbon dioxide giving compound (XLVI). Methylation of (XLVI) gives the dimethoxy ester (XLVII) and saponification of the latter the acid (XLVIII).

Apogossypolic acid upon treatment with nitric acid is converted to a compound in which one carboxyl has been replaced by a nitro group, postulated as XLIX. Reduction of this substance gives the amino acid (L) which was not isolated as such, for attempted purification by sublimation results in the loss of carbon dioxide with the formation of the amine (LI). This series of reactions has eliminated both of the carboxyl groups in apogossypolic acid and has thus demonstrated that they must be directly attached to the benzene nucleus.

The structures of these substances are assigned on the basis of indirect evidence or by analogies and not upon experimental data. Further study may necessitate changes in them. Thus, the nitro derivative (XLIX) of apogossypolic acid may have the nitro group in place of one or the other of the two carboxyls. Moreover, by hydrobromic acid treatment of apogossypolic acid,

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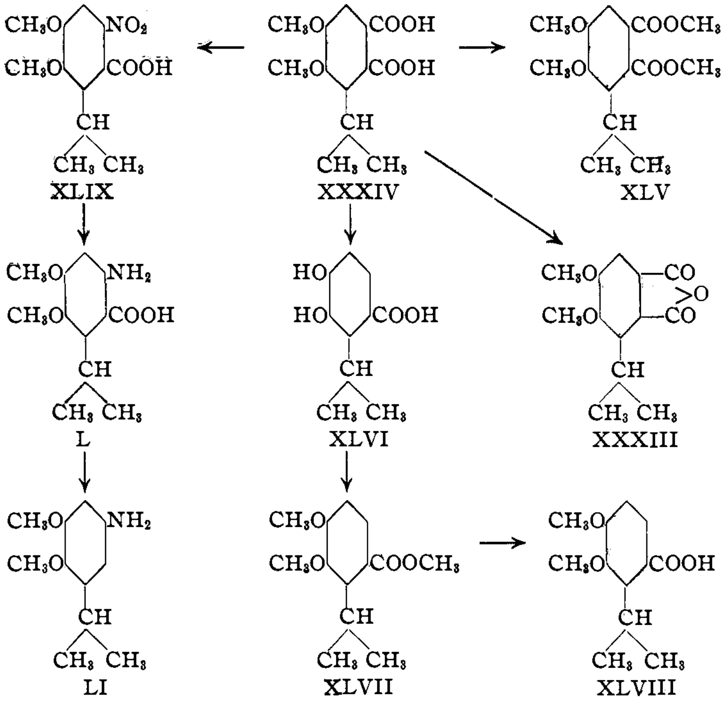
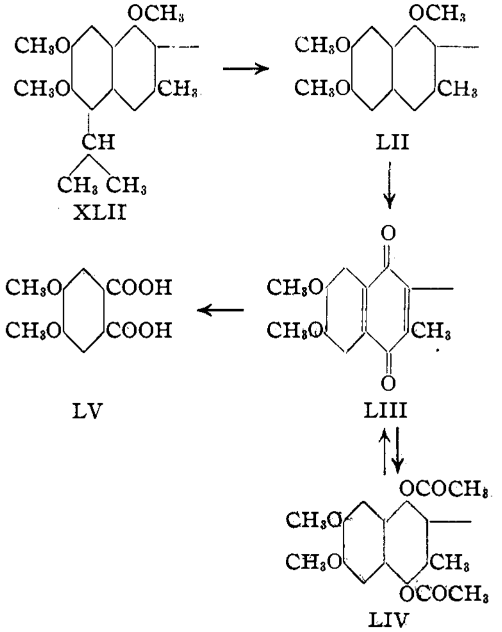
[17] Clark, *Oil & Fat Industries*, **6**, 7, 15 (1929).

[18] The fact that two carboxyls stabilize themselves as an anhydride linkage in gossic acid is of secondary importance.



the resulting molecule will be different depending upon which carboxyl is lost. The relative positions of the methoxyls and isopropyl group from indirect evidence appear indisputable and are the important factor in these molecules. The position of the other groups is less significant.

Desapogossypol and its Derivatives.[13]—Apogossypol hexamethyl ether (XLII) reacts with cold concentrated sulfuric acid and a loss of C_6H_{12} occurs. The product, which still contains six methoxyl groups, is desapogossypol hexamethyl ether (LII). It is not unlike the corresponding apo compound in its reactions for it oxidizes to a quinone, desapogossypolone tetramethyl ether (LIII), with loss of two methoxyls. Moreover, the quinone is reductively acetylated to hydrodesapogossypolone tetramethyl ether tetraacetate (LIV) which in turn can be reoxidized to the quinone (LIII).



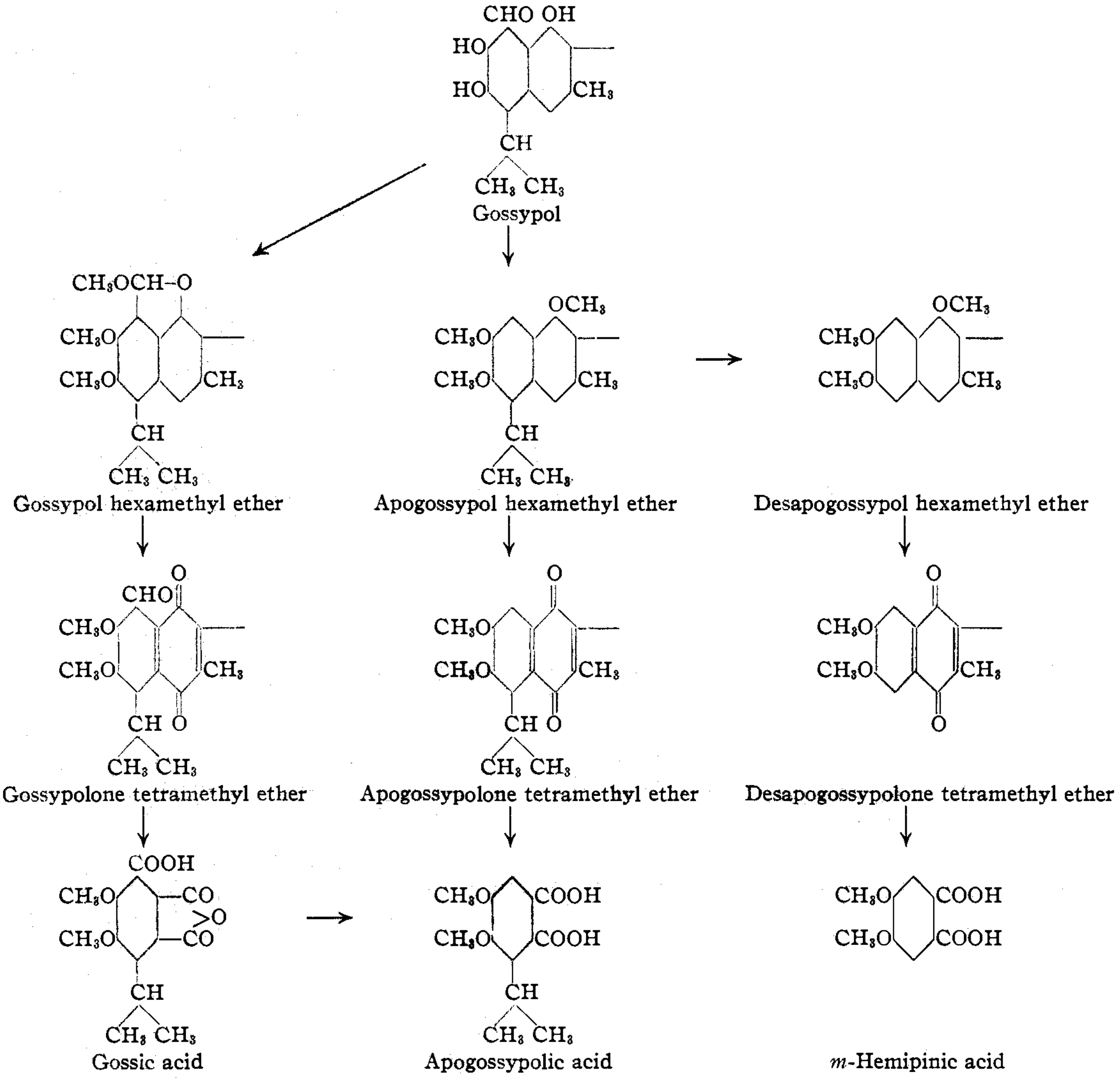
Desapogossypolone tetramethyl ether oxidizes with permanganate to *m*-hemipinic acid (LV), the only known product from gossypol which has yet been isolated. The difference between the molecular formula of *m*-hemipinic acid and apogossypolic acid (XXXIV) is a C_3H_6 residue. Between the corresponding but less degraded compounds of the desapogossypol and the apogossypol series, there is a difference of C_6H_{12} and between those of the desapogossypol and gossypol series C_6H_{12} and 2CO. It is, therefore, reasonably certain that the C_6H_{12} residue merely corresponds to two C_3H_7 groups, one in each naphthalene nucleus. By distilling the dilute sulfuric acid filtrate from the preparation of desapogossypol, a distillate is obtained which on oxidation gives a test for acetone. This demonstrates that the groups are isopropyls and are being removed directly from the naphthalene nuclei by hydrolysis.

The deductive evidence that has just been submitted for assuming gossypol to contain two naphthalene nuclei and that the functional groups present are of the kind and in the location shown in Ia, can best be summarized by a table of formulas (Table I) in which the relationships between the most important derivatives of gossypol are clearly apparent. All intermediates are omitted.

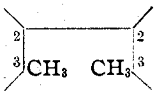
The experimental facts discussed in this communication have established without much question the functional groups in the 1, 5, 6, 7 and 8-positions of the two naphthalene nuclei. There is reasonable certainty of a hydrogen in the 4-position as deduced by the yellow color of the quinones; the possibility that the hydrogen may be in the 2-position is not absolutely excluded. No direct evidence is yet in hand from which the linkages and groups in the 2,3-positions may be

TABLE I

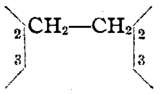
CORRELATION OF GOSSYPOL, APOGOSSYPOL AND DESAPOGOSSYPOL DERIVATIVES



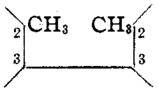
assigned. Alternative isomeric structures for that portion of the molecule associated with the linkage of the two naphthalene rings are shown in LVIa, LVIb, LVIc, LVId.



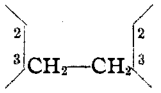
LVIa



LVIb



LVIc



LVId

All four of these structures could be formed from isoprene units of which so many natural products appear to be built. Thus, two examples are given in formulas LVII and LVIII.

Numerous naturally-occurring compounds contain methyl and isopropyl groups in the relative positions 3,5 in naphthalene skeletons. Only formula LVIa has such a structure though LVId might result from the oxidation of a methyl group in the 3-position. A most important fact is that a substantial quantity of acetic acid can be isolated along with formic and isobutyric acids, by the limited permanganate oxidation of gossypol.[19] The aldehyde group may be the source of the formic acid and the isopropyl group with a carbon atom from the ring the source of the isobutyric acid. The formation of the acetic acid can be explained only on the basis of LVIa and LVIc. Attempted isolation of suc-

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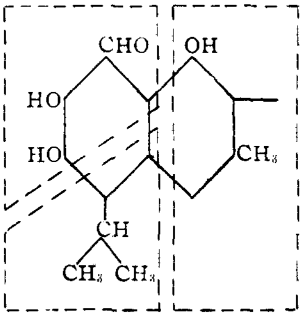
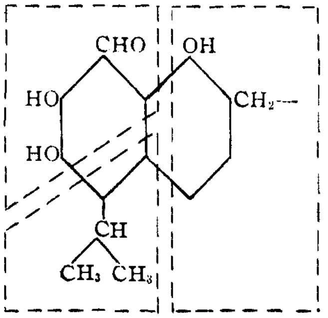
(19) Clark, *J. Biol. Chem.*, **77**, 81 (1928).



LVII (Ia)



LVIII

cinic acid which should result from LVIb and LVId by a similar oxidation was unsuccessful. Since LVIc is less likely because it does not have the 3-methyl-5-isopropyl arrangement, LVIa is considered as the most acceptable. It is obvious that other combinations in the 2,3-positions may be written but none other than those mentioned would result in a completely symmetrical molecule.

In view of these facts, formula Ia has been tentatively adopted for gossypol and is 2,2-bi-1,6,7-trihydroxy-5-isopropyl-8-aldehydonaphthyl.

The structure of gossypol (Ia) accounts for the anomalous results found by Clark[20] in carrying out a Zeisel determination. Gossypol gave a value of 5.7% though it contains no methoxyls. In the investigations from this Laboratory, methoxyl values of most of the gossypol derivatives were very frequently high. These can be accounted for by the fact that hydriodic acid removes, partially at least, the isopropyl groups as isopropyl iodide. The removal of an isopropyl group from a naphthalene by means of hydriodic acid is not entirely to be unexpected for it is reported in the literature that α-isopropylnaphthalene can be converted by means of hydriodic acid into naphthalene and isopropyl iodide.[21]

The definite establishment of structure Ia for gossypol must await (1) the synthesis of one or more of the benzene derivative degradation products, (2) a further study of gossypolone tetramethyl ether and gossypolonic acid tetramethyl ether, (3) knowledge concerning the arrangement of linkages and groups at the 2,3-positions.

Two oxidation products of gossypol dimethyl ether which have not been discussed are (1) that obtained by passing air through an alkaline solution, and (2) that resulting from treatment with ferric chloride.[11] These are of less significance in connection with the gossypol structure and consequently their further investigation is of secondary importance. The same is true of the oxidation product of demethylated apogossypolic acid in alkaline solution by means of air.[15]

The red gossypol hexamethyl ether requires further study.[3] This substance is not easily isolated in a pure state and consequently there is some doubt as to its exact empirical formula. The yellow product formed along with gossypol hexaacetate or from the latter by the action of acetic anhydride falls into the same category.[12] The complex compounds[4] from gossypol and certain substituted anilines need clarification. The character of the nitration products of gossypol hexamethyl ether and gossypolonic acid tetramethyl ether has not yet been determined. The structure of red gossypol may be Ic though no evidence for this is available.[22]

No simple naphthalene compounds have ever been isolated by degradation of gossypol except that reported by Schmid[23] as β-isoamylnaphthalene, obtained by exhaustive hydrogenation of gossypol and distillation of the reaction mixture with excess zinc dust. The identification of the product mentioned was not convincing and the formula for gossypol proposed would not give β-isoamylnaphthalene by the procedure used. Schmid also reported the isolation of *n*-butyric acid, a compound which could not be obtained from formula Ia.

The character of gossypolic acid reported by Karrer and Tobler[24] cannot be determined until a satisfactory method is found for its preparation.

The authors desire to express their sincere thanks to the Proctor and Gamble Company for furnishing through their subsidiary, the Buckeye Cotton Oil Company, the cottonseed meats from which the gossypol is being extracted for use in these investigations.

Summary

1. The correlation of the results of the study of gossypol has been made. The deductions from (1) the color reactions and salts, (2) the anilino

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[20] Clark, THIS JOURNAL, **51**, 1479 (1929).

[21] Meyer and Bernhauer, *Monatsh.*, **54**, 721 (1929).

[22] Podolskaja, *Biochem. Z.*, **284**, 401 (1936); *Fettchemische Umschau*, **42**, 96 (1935).

[23] Schmid and Margulies, *Monatsh.*, **65**, 391 (1934).

[24] Karrer and Tobler, *Helv. Chim. Acta*, **15**, 1204 (1932).

and amino derivatives, (3) anhydrogossypol and its derivatives, (4) the esters, (5) the ethers and their degradation products, (6) apogossypol and its degradation products, (7) desapogossypol and its degradation products lead to the postulation that gossypol is 2,2-bi-1,6,7-trihydroxy-3-methyl-5-isopropyl-8-aldehydonaphthyl.

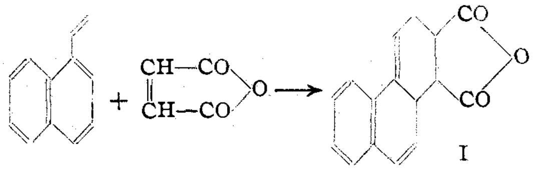
Urbana, Illinois Received June 27, 1938

[Contribution from the Chemistry Laboratory of the University of Michigan]

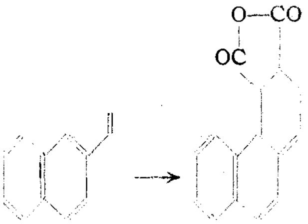
The Diels–Alder Reaction between Naphthylcyclopentenes and Maleic Anhydride

By W. E. Bachmann and M. C. Kloetzel[1]

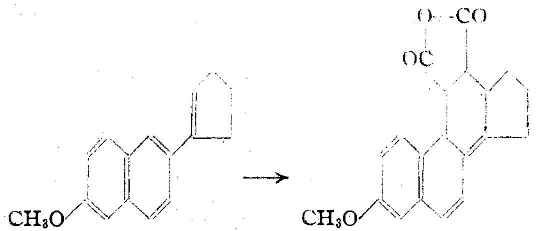
Cohen and Warren[2] have shown recently that 1-vinylnaphthalene and 2-vinylnaphthalene undergo the Diels–Alder reaction with maleic anhydride to give 1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid anhydride (I) and 2,3,4,4a-tetrahydrophenanthrene-3,4-dicarboxylic acid anhydride (II), respectively. A similar addition of maleic anhydride to 1-(6′-methoxy-2′-naphthyl)-cyclopentene-1 (III) would be expected to form a compound (IV) having the sterol skeleton, but it has been reported by Bergmann and Bergmann[3] that maleic anhydride reacts neither with 1-(α-naphthyl)-cyclopentene-1 (V) nor with (III). We have now found that (III) and (V) can be made to react practically quantitatively with maleic anhydride. Similarly, 1-(β-naphthyl)-cyclopentene-1 (VI) can be made to react with maleic anhydride to the extent of 92%.



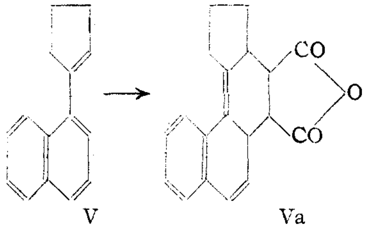
I



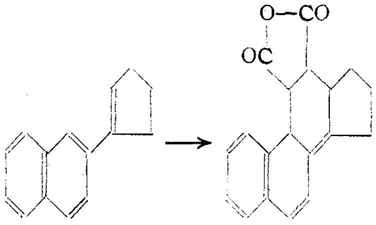
II



III IV



V Va



VI VIa

When a xylene solution of equimolecular proportions of (V) and maleic anhydride was refluxed for two hours and allowed to cool, a mixture of 3,4-cyclopentano-1,2,3,10a-tetrahydrophenanthrene-1,2-dicarboxylic acid and the corresponding acid anhydride (Va) was deposited. Under these conditions, reaction was found to have gone to the extent of 63%. A quantitative yield of the adduct could be obtained by fusing (V) with ten mole equivalents of maleic anhydride for twenty hours on a steam-bath.

When 1-(β-naphthyl)-cyclopentene-1 (VI) was refluxed for two hours in xylene solution with maleic anhydride and the solution was allowed to cool, 1,2-cyclopentano-2,3,4,4a-tetrahydrophenanthrene-3,4-dicarboxylic acid anhydride (VIa) was deposited as a resin, but (VIa) and (IV) were best prepared by fusing (VI) or (III), respectively, with ten mole equivalents of maleic anhydride on a steam-bath for twenty hours, dissolving the adduct in aqueous potassium hydroxide and precipitating by acidification with hydrochloric acid.

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(1) Du Pont Post-Doctorate Fellow.

(2) Cohen and Warren, *J. Chem. Soc.*, 1318 (1937).

(3) Bergmann and Bergmann, This Journal, **59**, 1443 (1937).