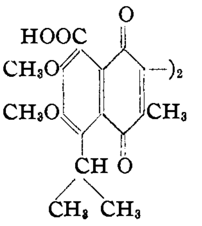
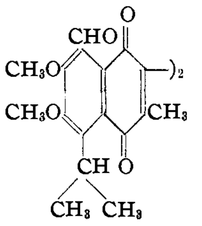
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. XVI. Reduction Products of Gossypolone Tetramethyl Ether and Gossypolonic Acid Tetramethyl Ether[1]

BY ROGER ADAMS, T. A. GEISSMAN AND R. C. MORRIS

Gossypolonic acid tetramethyl ether, obtained by the oxidation of gossypol hexamethyl ether with dilute nitric acid,[2] was assigned the structure I, and gossypolone tetramethyl ether, derived from gossypol hexamethyl ether by chromic acid oxidation,[2] was assigned the structure II.[1]


I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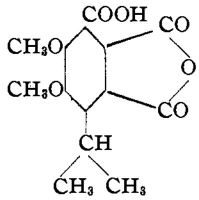
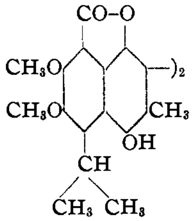
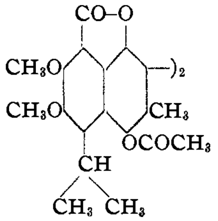
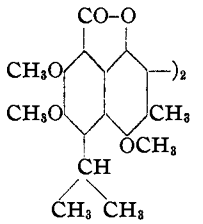

III

These structures were assumed largely on the basis of the analytical figures, coupled with the facts that I was easily soluble in sodium bicarbonate solution, II formed an anilino derivative, mild oxidation converted II into I and that both I and II yielded gossic acid (III) on oxidation with potassium permanganate. No direct evidence was presented to show that the compounds were quinones, though by a comparison of these and their degradation products with apogossypolone tetramethyl ether, desapogossypolone tetramethyl ether and their degradation products,[3] quinone structures appeared likely. The results described in this paper offer more direct evidence for the correctness of the structures I and II for these compounds.

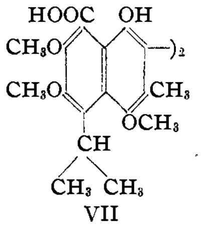
Gossypolonic acid tetramethyl ether can be reduced with zinc and acetic acid to a compound having the properties of the hydroxy lactone (IV) and reductively acetylated with zinc and acetic anhydride to the acetoxy lactone (V). It is also possible to obtain V by acetylation of IV with acetic anhydride in pyridine.


IV


V


VI

Methylation of the hydroxy compound (IV) yielded the methoxy lactone (VI). This compound was insoluble in cold alcoholic alkali but dissolved on warming. When the alkaline solution was acidified, the hydroxy acid (VII) was obtained as a colorless crystalline compound, soluble in cold, dilute aqueous alkali. This establishes the presence of the lactone grouping in VI and by analogy in IV and V.


VII

The free hydroxy compound (IV) is readily soluble in cold, dilute alcoholic alkali to a deep wine-red solution which on warming becomes first brown, then a deep blue-green identical in appearance with that obtained by dissolving gossypolonic acid tetramethyl ether (I) in alcoholic alkali of the same strength. This points to an opening of the lactone linkage followed by air oxidation. The blue-green solution contains decomposition products of gossypolonic acid tetramethyl ether since none of this compound could

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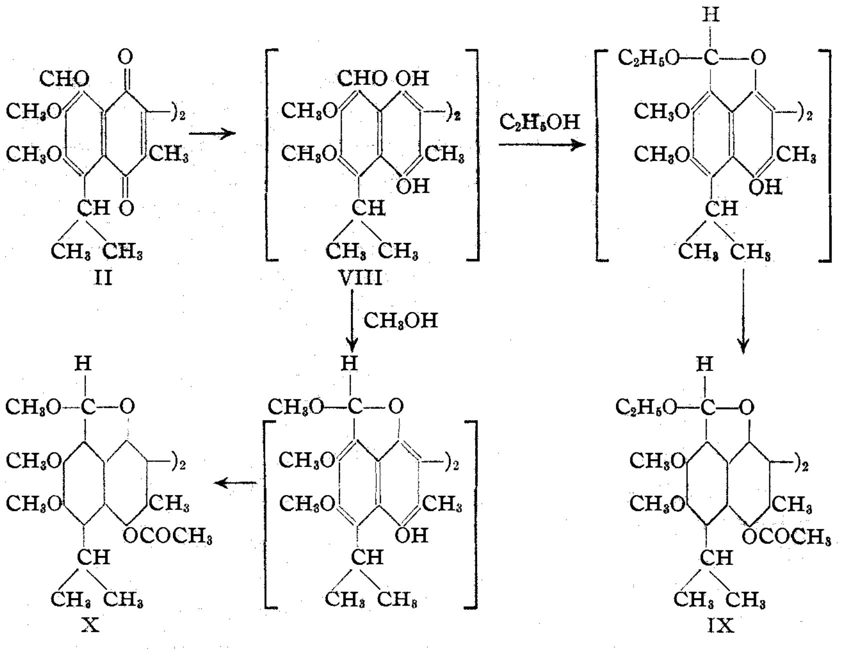
[1] For previous paper see Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, THIS JOURNAL, **60**, 2193 (1938).

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

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

be obtained from it on acidification. The free hydrogossypolonic acid tetramethyl ether (hydroquinone of I) could not be obtained crystalline.

The reduction of gossypolone tetramethyl ether (II) was much more difficult because of the extreme sensitivity of the compound. It was finally accomplished by adding an aqueous solution of sodium hydrosulfite to its ethanolic solution; reduction took place smoothly, the solution, deep yellow at first, becoming deep brown and then changing to a pale yellow. Rapid isolation of the unstable reduction product by means of ether extraction followed by treatment with pyridine and acetic anhydride in the cold led to the isolation of a colorless crystalline compound. This compound, however, did not give analytical figures consistent with a simple reduction and acetylation of the quinone linkage, but it was readily reconverted into the original quinone (II) by oxidation with chromic acid, indicating that no deep-seated change had taken place. By carrying out the reduction in methanol solution, following the same procedure as outlined above, a different compound was obtained, lending support to the assumption that acetal formation had occurred in the primary reduction product (VIII). The compound obtained, therefore, when the reduction was carried out in ethanol was diacetoxy gossypol tetramethyl diethyl ether (IX), and in methanol was diacetoxy gossypol hexamethyl ether (X)



Experimental

Improved Procedure for the Preparation of Gossypol Hexamethyl Ether.—Gossypol hexamethyl ether has been one of the important derivatives of gossypol used in degradation studies. An improved method of preparation has been found which deserves detailed description.

A solution of 25 g. of once recrystallized gossypol-acetic acid is prepared by gentle warming in a mixture of 80 cc. of methanol and 80 cc. of redistilled dimethyl sulfate. The solution is cooled under the tap and 110 cc. of 10% methanolic potassium hydroxide is added in 10-cc. portions with continued cooling. After all of the alkali is added the mixture is allowed to stand at room temperature, with occasional shaking, for two days. The solid which precipitates is collected on a filter and washed with methanol, then thoroughly with water. There remains undissolved 21–23 g. of yellowish, crystalline tetramethyl ether melting around 165° and giving a scarlet color with concentrated sulfuric acid.

This crude material is methylated further by dissolving it in a mixture of 100 cc. of benzene and 60 g. of dimethyl sulfate and adding to the warm solution a 20% solution of potassium hydroxide in methanol until the solution is alkaline. An additional 40 g. of dimethyl sulfate is then added, followed by 20% methanolic potassium hydroxide until the solution is again alkaline. The mixture is then evaporated to a sludge on the steam-bath (with stirring), methanol being added frequently and the evaporation continued until most of the benzene has been removed. The final sludge is cooled and filtered. The solid is washed with methanol until the filtrates are colorless and then washed thoroughly with water to remove potassium salts. The product remaining on the filter is white, crystalline hexamethyl ether. The yield in this step is nearly quantitative. The product is pure enough for most purposes. It gives a yellow-orange color with concentrated sulfuric acid and melts, depending upon the purity of the gossypolacetic acid used, at from 195–210°. It can be recrystallized most conveniently from ligroin (b. p. 90–110°), from which it is obtained in clusters of long white needles, m. p. 175°.

Hydroxygossylic Acid Lactone Tetramethyl Ether (IV).—To a solution of 0.50 g. of gossypolonic acid tetramethyl ether[1] in 10 cc. of boiling glacial acetic acid, zinc dust was added in small portions. The solution first turned a reddish-yellow color and on continued addition of zinc dust became a clear pale yellow. Yellow crystals separated from the hot solution. The zinc dust was removed by filtration and boiled several times with small portions of acetic acid to remove admixed reduction product, and the combined filtrates diluted to incipient cloudiness and cooled. The product (0.38 g.) was purified from glacial acetic acid and formed tiny canary-yellow prisms melting at 320° (bloc Maquenne).

Anal. Calcd. for $C_{34}H_{34}O_{10}$: C, 67.77; H, 5.65. Found: C, 67.60; H, 5.64.

The compound gives a deep yellow color with concentrated sulfuric acid and a deep wine-red solution in methanolic potassium hydroxide.

Acetoxygossylic Acid Lactone Tetramethyl Ether (V). (a).—To a mixture of 0.5 g. of gossypolonic acid tetramethyl ether, 0.5 g. of fused sodium acetate and 5 cc. of boiling acetic anhydride, zinc dust was added in small portions until the color of the solution had become a pale yellow. The solution was filtered onto ice and allowed to stand until the acetic anhydride had decomposed, the product collected and triturated with boiling methanol. The pale yellow prisms obtained weighed 0.40 g. After two recrystallizations from acetone–methanol the product formed tiny rosets of colorless prisms, m. p. 231–233° (corr.).

Anal. Calcd. for $C_{38}H_{38}O_{12}$: C, 66.47; H, 5.54. Found: C, 66.32; H, 5.50.

The product gives a deep yellow color in concentrated sulfuric acid. It is insoluble in cold methanolic alkali, but dissolves on heating with the formation of a deep wine-red solution.

(b).—The same compound is formed when the hydroxy lactone (IV) is acetylated with acetic anhydride in pyridine.

Methoxygossylic Acid Lactone Tetramethyl Ether (VI).—To a suspension of 0.5 g. of hydroxygossylic acid lactone tetramethyl ether in a cooled mixture of 5 cc. of dimethyl sulfate and 5 cc. of methanol was added 7 cc. of 10% methanolic potassium hydroxide. The solution, originally deep red, gradually turned yellow. The addition of further 1-cc. portions of alcoholic alkali was continued until a further addition no longer produced the red color. The mixture was concentrated under reduced pressure to a mush, filtered, the solid washed with methanol and the salt removed by washing with water. There remained on the filter 0.30 g. of yellow crystalline product. After several recrystallizations from dilute acetic acid and from acetone–methanol, the compound formed pale yellow needles, m. p. 273–274° (corr.).

Anal. Calcd. for $C_{36}H_{38}O_{10}$: C, 68.57; H, 6.03. Found: C, 68.46; H, 6.01.

The compound gives a clear yellow color with concentrated sulfuric acid and is insoluble in cold alcoholic alkali.

Methoxygossylic Acid Tetramethyl Ether (VII).—A solution of 0.20 g. of methoxygossylic acid lactone tetramethyl ether (VI) in 10 cc. of 10% methanolic potassium hydroxide was boiled with a pinch of zinc dust and a few cubic centimeters of water until the originally red-brown color had faded to yellow. The solution was filtered into dilute sulfuric acid and extracted with ether. The ether solution was dried, concentrated and diluted with petroleum ether (b. p. 30–60°). The hydroxy acid separated as tiny white needles, weighing 0.1 g. After recrystallization from ether–petroleum ether it formed tiny, soft white needles which sintered over a broad range and melted at 270–272° (corr.). When a sample was plunged into a bath preheated to 250° it melted instantly with vigorous decomposition, crystallized on cooling, then remelted at 273–274° (corr.).

Anal. Calcd. for $C_{36}H_{42}O_{12}$: C, 64.83; H, 6.36. Found: C, 64.70; H, 6.36.

The compound is readily soluble in cold, dilute sodium hydroxide solution. It gives no color with ferric chloride and a pale yellow color with concentrated sulfuric acid. The methoxy lactone (VI) is regenerated on warming the hydroxy acid in acetic anhydride.

Reduction and Acetylation of Gossypolone Tetramethyl Ether in Ethanol (Compound **IX**).—An aqueous solution of sodium hydrosulfite was added in portions to a hot solution of 1.0 g. of gossypolone tetramethyl ether in 25 cc. of absolute ethanol. The solution first became deep brown in color and upon continued addition of the reducing agent changed to a pale yellow color. At this point, it was poured into iced water, quickly extracted with ether, the ether solution washed with a solution of sodium hydrosulfite and dried by shaking it with anhydrous sodium sulfate. The ether was removed quickly, at first on the hot-plate, then under reduced pressure, and to the residual dark red oil was added a mixture of 15 cc. of pyridine and 7 cc. of acetic anhydride. The bright red solution was allowed to stand at room temperature for two hours, poured into water and the pink solid collected. The product was dissolved in warm methanol, from which it crystallized quickly as short white needles, weighing 0.18 g. After recrystallization from acetone–methanol the compound formed soft white needles, m. p. 264–265° (corr.).

Anal. Calcd. for $C_{42}H_{50}O_{12}$: C, 67.52; H, 6.75. Found: C, 67.18, 67.37; H, 6.91, 6.50.

Reduction by means of zinc dust and acetic acid in presence of sodium acetate, zinc dust in acetic anhydride with sodium acetate, zinc dust in pyridine and acetic anhydride and zinc dust in ethanolic calcium chloride was unsuccessful. Acid reducing agents were excluded, as gossypolone tetramethyl ether is converted to uncrystallizable tars in acid solution.

Oxidation of this compound with 10% aqueous chromic acid in acetic acid gave a yellow crystalline compound which was proved by melting point, mixed melting point, preparation of the anilino derivative and color in sulfuric acid to be identical with II.

Reduction and Acetylation of Gossypolone Tetramethyl Ether in Methanol (Compound **X**).—The reduction was run in exactly the same manner as given above when ethanol was used as the solvent. The crude crystalline material obtained from methanol formed tiny pink nodules and weighed 0.23 g. Recrystallized from acetone–methanol it formed tiny, soft white needles, m. p. 266–267° (corr.).

Anal. Calcd. for $C_{40}H_{46}O_{12}$: C, 66.85; H, 6.41. Found: C, 66.65; H, 6.34.

A mixture of the ethyl acetal (IX), m. p. 264–265°, and of the methyl acetal (X), m. p. 266–267°, melted at 245–253°.

The compound gives a yellow-orange color in concentrated sulfuric acid.

Oxidized with chromic acid it yielded gossypolone tetramethyl ether (II).

Summary

1. Support for the previously proposed structures of gossypolonic acid tetramethyl ether and of gossypolone tetramethyl ether as quinones has now been furnished. These products have been converted to reduction products.

2. Gossypolonic acid tetramethyl ether gives hydroxy gossylic acid lactone tetramethyl ether which may be acetylated to the corresponding acetyl derivative or methylated to the methyl ether. The latter can be transformed by the action of alkali into the corresponding gossylic acid derivative; thus the presence of the lactone linkage is demonstrated.

3. Gossypolone tetramethyl ether is a much more sensitive compound and most alkaline and acid reducing agents cause decomposition. However, a solution of sodium hydrosulfite in ethanol and methanol gives successful results. Diacetoxygossypol tetramethyl diethyl ether forms when ethanol is used as a solvent, and diacetoxygossypol hexamethyl ether when methanol is employed.

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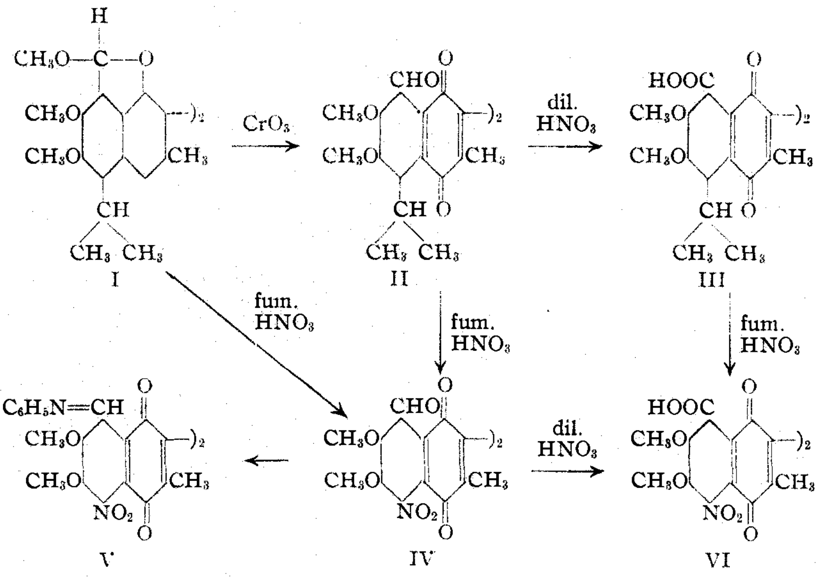
Structure of Gossypol. XVII. Nitration Products of Gossypol Hexamethyl Ether, Gossypolone Tetramethyl Ether and Gossypolonic Acid Tetramethyl Ether[1]

BY ROGER ADAMS, T. A. GEISSMAN AND R. C. MORRIS

The structural relationship between gossypol hexamethyl ether (I), gossypolone tetramethyl ether (II) and gossypolonic acid (III) has been substantiated in part by studies of oxidation[2] and other degradation reactions[3] of gossypol derivatives and by the coördination of these structures in a consistent picture of the properties and reactions of gossypol.[1,4]



Further confirmation has been found in a study of the action of fuming nitric acid on these compounds, products being obtained whose analyses and properties allow their formulation in accord with the above structures.

By the action of fuming nitric acid on gossypol hexamethyl ether (I), there is obtained a crystalline compound to which has been assigned the structure IV, since it forms an anilino derivative formulated as V. Compound IV also results from the action of fuming nitric acid on gossypolone tetramethyl ether (II). Treatment of gossypolonic acid tetramethyl ether (III) with fuming nitric acid under similar conditions results in the formation of an acidic compound (VI) which is assumed to be the carboxylic acid corresponding to the aldehyde (IV). This assumption is substantiated by the fact that oxidation of IV with dilute nitric acid results in the formation of the acid (VI). This is exactly analogous to the oxidation of gossypolone tetramethyl ether (II) to gossypolonic acid tetramethyl ether (III) by means of dilute nitric acid.

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[1] For previous paper, see Adams, Geissman and Morris, THIS JOURNAL, **60**, 2967 (1938).

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

[3] Adams and Geissman, *ibid.*, **60**, 2184 (1938).

[4] Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, *ibid.*, **60**, 2193 (1938).