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.

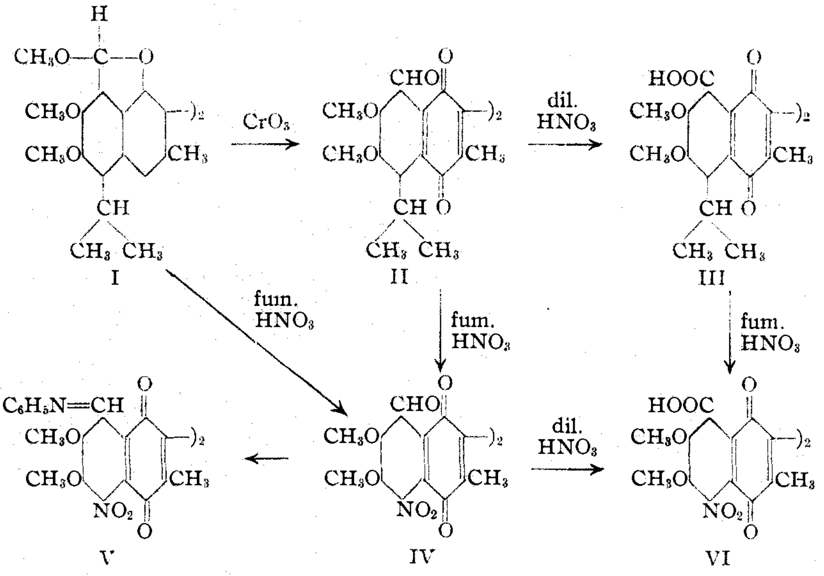
URBANA, ILLINOIS RECEIVED OCTOBER 17, 1938

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

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).

The replacement of an isopropyl group by a nitro group during nitration has been observed in other, although not strictly analogous, cases. The nitration of *p*-cymene has been found to yield nitrated toluenes along with simple nitration products,[5] while dinitrothymol yields trinitro-*m*-cresol upon further nitration.[6] A similar elimination of the isopropyl group from a gossypol derivative has been observed in the formation of desapogossypol hexamethyl ether from apogossypol hexamethyl ether by the action of concentrated sulfuric acid,[7] although the elimination by means of sulfuric acid may follow a different course from that in the replacement by a nitro group during nitration.

Experimental

Nitration of Gossypol Hexamethyl Ether; Compound IV.—To 15 cc. of fuming nitric acid (sp. gr. 1.50) cooled to −5° was added 1 g. of gossypol hexamethyl ether. The compound dissolved instantly to give a deep red-brown solution which was immediately poured onto ice. The product from five such runs was collected, dried and dissolved in a small amount of boiling methanol. A yellow crystalline material separated and after cooling was filtered; weight 0.5 g. It was purified from acetone–methanol, forming bright yellow prisms. The product has no sharp melting point but when placed in a preheated bath darkens at about 220° and decomposes at 257–262° (corr.).

Anal. Calcd. for $C_{28}H_{20}O_{14}N_2$: C, 55.26; H, 3.29; N, 4.60. Found: C, 54.91, 54.90, 55.28; H, 3.41, 3.33, 3.22; N, 4.47, 4.64, 4.86.

The compound gives a clear brownish-red color with concentrated sulfuric acid and reduces Tollens' reagent quickly in pyridine solution in the cold. It is insoluble in alcoholic alkali, although it decomposes slowly on standing in contact with the reagent.

Nitration of Gossypolone Tetramethyl Ether; Compound IV.—To 5 cc. of fuming nitric acid (sp. gr. 1.50) cooled in ice-salt was added in small portions 0.25 g. of gossypolone tetramethyl ether. As soon as solution had taken place, the red-brown reaction mixture was poured onto ice. The insoluble material was collected and dissolved in a small amount of methanol, from which 0.1 g. of yellow crystalline material separated. After recrystallization from acetone–methanol bright yellow, flat prisms were obtained.

The compound gave the same type of decomposition as the product previously described, alone or when mixed with the product made by the other procedure. It also gave the same analytical results and the same color in sulfuric acid.

Anilino Derivative of Compound IV; Compound V.—An excess of aniline was added to a suspension of compound IV in boiling benzene. A red solution formed. After a few minutes ligroin (b. p. 90–110°) was added and the mixture concentrated and cooled. The product which separated was recrystallized from benzene–ligroin. It forms tiny, brownish-orange prisms which do not melt, but darken at about 210° and become charred at about 260°.

Anal. Calcd. for $C_{40}H_{30}O_{12}N_4$: C, 63.32; H, 3.96; N, 7.39. Found: C, 63.92; H, 4.17; N, 7.63.

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

Nitration of Gossypolonic Acid Tetramethyl Ether; Compound VI.—To 2.5 cc. of yellow fuming nitric acid (sp. gr. 1.5) at 0° was added in portions with stirring 0.1 g. of gossypolonic acid tetramethyl ether. Solution took place rapidly and, as soon as complete, the reaction mixture was poured onto ice. The precipitate was washed, dried and recrystallized from methanol. It forms light yellow crystals which become brown at about 220° and darken at 260–270°; yield 0.04 g.

Anal. Calcd. for $C_{28}H_{20}O_{16}N_2$: C, 52.50; H, 3.12; N, 4.38. Found: C, 52.18; H, 3.43; N, 4.43.

The product gives no color with cold concentrated sulfuric acid and a green-violet color upon heating.

Oxidation of Compound IV to Compound VI by Means of Dilute Nitric Acid.—Two procedures for this oxidation were used:

(a).—To a solution of 0.20 g. of compound IV in 5 cc. of acetic anhydride was added gradually 20 cc. of a mixture of equal parts of acetic acid, concentrated nitric acid and water. The acetic anhydride decomposed vigorously at the beginning and when complete the remainder of the 20 cc. was added all at once. A small amount of compound V crystallized and was filtered. The filtrate was treated with 10 cc. of concentrated nitric acid and the solution refluxed for two hours. Upon cooling, the product V separated. It was purified by dissolving in acetic anhydride, decomposing the anhydride with water and diluting. About 0.05 g. of shining buff leaflets was obtained. The compound does not melt up to 320° (bloc Maquenne).

Anal. Calcd. for $C_{28}H_{20}O_{16}N_2$: C, 52.50; H, 3.12. Found: C, 52.42; H, 3.32.

The product is soluble in sodium bicarbonate solution; it gives no color with concentrated sulfuric acid in the cold but a green color upon warming.

(b).—A solution of the compound IV in hot, concentrated nitric acid was diluted with a few drops of water. A small amount of material separated. The mixture was heated for an hour on the steam-bath. Enough concentrated nitric acid was then added to bring all the solid into solution at the boiling point, the solution boiled a short time, diluted with water and cooled. The solid was recrystallized as in (a), and was identical in solubility in sodium bicarbonate solution, color in sulfuric acid and melting point behavior with VI as prepared above.

Anal. Calcd. for $C_{28}H_{20}O_{16}N_2$: C, 52.50; H, 3.12. Found: C, 52.69; H, 3.71.

Summary

1. Gossypol hexamethyl ether by the action of fuming nitric acid is converted into a derivative of gossypolone tetramethyl ether in which the iso-

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[5] Alfthan, *Ber.*, **53**, 78 (1920).

[6] Armstrong and Rennie, *Chem. News*, **47**, 115 (1883).

[7] Adams and Butterbaugh, THIS JOURNAL, **60**, 2174 (1938).

propyl groups are replaced by nitro groups. The same compound also may be produced directly by nitration of gossypolone tetramethyl ether.

2. Gossypolonic acid tetramethyl ether by a similar procedure is converted into a derivative with the isopropyl groups replaced by nitro groups.

3. Just as gossypolone tetramethyl ether can be oxidized to the corresponding carboxylic acid by means of dilute nitric acid, so can the nitration product of gossypol hexamethyl ether or gossypolone tetramethyl ether be converted into the corresponding nitration product of gossypolonic acid tetramethyl ether.

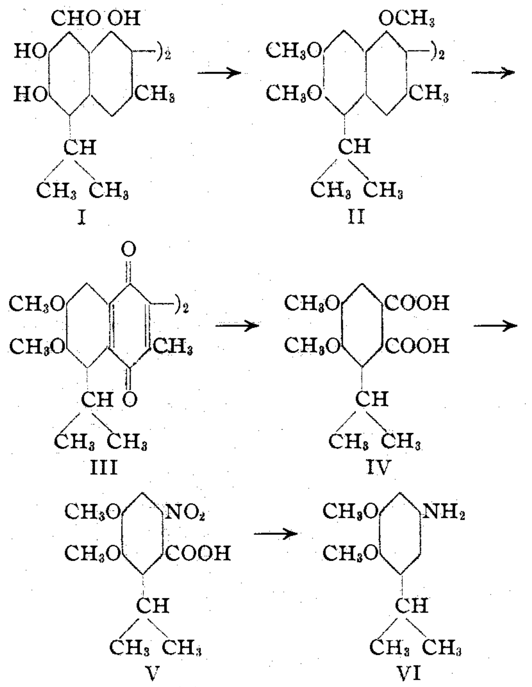
URBANA, ILLINOIS RECEIVED OCTOBER 17, 1938

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

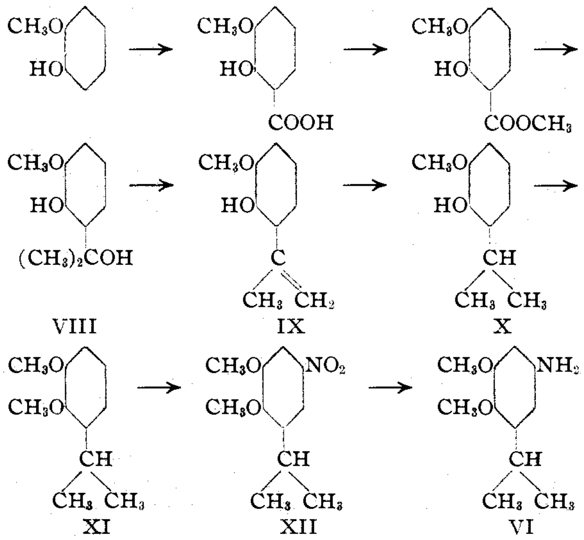
Structure of Gossypol. XVIII. Synthesis of 1,2-Dimethoxy-3-isopropyl-5-aminobenzene, a Degradation Product of Gossypol[1]

BY ROGER ADAMS, MADISON HUNT AND R. C. MORRIS

Structure I has been assigned to gossypol.[2] By the action of concentrated alkali, gossypol loses two aldehyde groups and is converted into the unstable apogossypol. The latter product is stabilized by the formation of the hexamethyl ether. Apogossypol hexamethyl ether (II) upon oxidation with chromic acid gives apogossypolone tetramethyl ether (III) which is further oxidized with potassium permanganate to apogossypolic acid (IV). Nitration of this last product results in a mononitro monocarboxylic acid (V) which upon reduction and sublimation of the product gives a decarboxylated amine (VI).[3] The amine is converted to a diacetyl derivative by the action of acetic anhydride and sodium acetate. Whether the 5-carboxyl or the 4-carboxyl in apogossypolic acid (IV) is replaced by a nitro group was not certain so that the amine which was assigned structure VI might have an isomeric formula, with the amino group in the 4-position.



The compound 1,2-dimethoxy-3-isopropyl-5-aminobenzene has now been synthesized by methods leaving little doubt as to its complete structure and no doubt as to the relative positions of the two dimethoxy and the isopropyl groups. It proved to be identical with the compound VI obtained by degradation of gossypol as shown by melting point and mixed melting points of the two amines and their acetyl derivatives. The synthesis employed is shown by the following series of reactions



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[1] For previous paper see Adams, Geissman and Morris, THIS JOURNAL, **60**, 2970 (1938).

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

[3] Adams, Morris, Butterbaugh and Kirkpatrick, *ibid.*, **60**, 2191 (1938).