1,1,2-Tris-(*p*-methoxyphenyl)-2-bromoethylene.—Treatment of 3.5 g. (0.01 mole) of tris-(*p*-methoxyphenyl)-ethylene[14] in 50 ml. of carbon tetrachloride with 1.8 g. (0.01 mole) of N-bromosuccinimide and 50 mg. of benzoyl peroxide in the manner described above gave 4.0 g. (93%) of 1,1,2-tris-(*p*-methoxyphenyl)-2-bromoethylene melting at 118–119°[15] after two recrystallizations from ethanol.

CHICAGO 37, ILLINOIS[16]

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[14] This compound, m.p. 97–98.5°, was prepared by a new method to be reported shortly.

[15] R. S. Shelton and M. G. Van Campen, Jr., U. S. Patent 2,430,-891 (Nov. 18, 1947); *C. A.*, **42**, 1968g (1948), reported a m.p. of 119–120.5°.

[16] After January, 1956, communications regarding this paper should be sent to Kyôto, Japan.

[CONTRIBUTION NO. 148 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Reduction of Gossypol with Lithium Aluminum Hydride[1]

BY DAVID A. SHIRLEY AND WILLIAM C. SHEEHAN

RECEIVED MARCH 11, 1955

The reduction of gossypol with lithium aluminum hydride followed by acetylation yields a product, designated as methylapogossypol hexaacetate (II), in which the aldehyde groups of gossypol have been reduced to methyl groups and all hydroxyl groups acetylated. Oxidation of methylapogossypol hexaacetate yields methylapogossypolone tetraacetate (IV). Reductive acetylation of this latter product leads to methylapohydrogossypolone octaacetate (V).

We have undertaken a study of new reactions and reaction products of gossypol (I), the principal pigment of cottonseed. Of initial interest was an examination of the reduction of gossypol with lithium aluminum hydride. Earlier work on reduction of gossypol and gossypol derivatives has been largely limited to catalytic hydrogenation.[2] The only report of the use of lithium aluminum hydride with gossypol or its derivatives is its use in determination of active hydrogen content.[2c] It was anticipated that a study of the reduction products would throw additional light on the problem of the structure of gossypol.[3]

A solution of gossypol in ether was treated with excess lithium aluminum hydride in ether. No substance could be isolated from the reaction mixture and the crude product was acetylated. Chromatographic separation on "Florisil" absorbent allowed isolation, in about 10% yield, of a white crystalline product, m.p. 277–280°. Analysis showed a molecular formula of $C_{42}H_{46}O_{12}$ containing six acetyl groups. Infrared and ultraviolet (see Table I and Fig. 1) absorption spectra showed the absence of the bands characteristic for the presence of aldehyde carbonyl groups in gossypol at 358 mμ and 6.19 μ.[4] The infrared spectrum of the new compound (Table I) resembled very closely that of gossypol hexaacetate[4b] (VI) in the range 2–9 μ. Gossypol hexaacetate (white form) is reported to melt at 276–279°.[5] That the new product is not gossypol hexaacetate is indicated by the following evidence: (1) a mixture melting point between the new product and gossypol hexaacetate shows a sharp depression; (2) the infrared spectra of the two materials are different in the fingerprint region above 9 μ; (3) solubilities of the two compounds in several solvents are significantly different; and (4) elementary analyses on the new material differ appreciably from the values for gossypol hexaacetate.

TABLE I

INFRARED ABSORPTION BANDS[a]

Compound	Bands, μ
Methylapogossypol hexaacetate[b]	3.39 (M),[c] 5.64 (VS), 6.14 (W), 6.23 (W), 6.95 (M), 7.27 (VS), 8.07 (W), 8.40 (VS), 8.73 (S), 8.95 (W), 9.60 (S), 9.85 (W), 10.6 (W), 11.0 (M), 11.25 (M)
Methylapogossypolone tetraacetate[d]	3.28 (W), 5.60 (S), 6.02 (S), 6.43 (W), 6.94 (W), 7.28 (M), 7.39 (W), 7.58 (S), 7.70 (M), 7.80 (W), 8.40 (VS), 8.88 (W), 9.18 (M), 9.50 (W), 9.82 (W), 10.38 (W), 10.80 (W), 11.13 (W), 11.38 (W)

[a] These spectra were determined by Mr. R. T. O'Connor and co-workers. For details on equipment and method used, see reference 4b. [b] Measured in chloroform solution at a concn. of 14.24 g. per l. in a 0.4 mm. cell. [c] The letters in parentheses represent the intensity of absorption in qualitative fashion (W = weak, M = medium, S = strong, VS = very strong). [d] Measured at 8.20 g. per l. of chloroform in a 0.4 mm. cell.

On the basis of analytical data, similarity of infrared spectrum below 9 μ to gossypol hexaacetate and the known properties of lithium aluminum hydride we propose that the new reduction product is 3,3′,8,8′-tetramethyl-5,5′-diisopropyl-1,1′,6,6′,7,-7′-hexaacetoxy-2-2′-binaphthyl as indicated by structure II. Continuing the common nomenclature used by Adams and by Clark in their extensive work on gossypol we designate this material as methylapogossypol hexaacetate. Formation of II depends on the reduction of the aldehyde group of the gossypol structure proposed by Adams[6] (I) to a

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[1] A report of work carried out under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act. The contract is being supervised by the Southern Regional Research Laboratory of the Agricultural Research Service.

[2] (a) R. Adams and W. R. Dial, THIS JOURNAL, **61**, 2077 (1939); (b) L. Schmid and S. Margulies, *Monatsh.*, **65**, 391 (1934); (c) V. L. Frampton, J. D. Edwards and H. R. Henze, paper presented before Combined Southeast and Southwest Regional Meeting of the American Chemical Society, New Orleans, December 12, 1953.

[3] C. H. Boatner in A. E. Bailey, editor, "Cottonseed and Cottonseed Products," Interscience Publishers, Inc., New York, N. Y., 1948.

[4] (a) W. A. Pons, M. D. Murray, R. T. O'Connor and J. D. Guthrie, *J. Am. Oil Chemists Soc.*, **25**, 308 (1948); (b) R. T. O'Connor, P. Von der Haar, E. F. DuPre, L. E. Brown and C. H. Pominski, THIS JOURNAL, **76**, 2368 (1954).

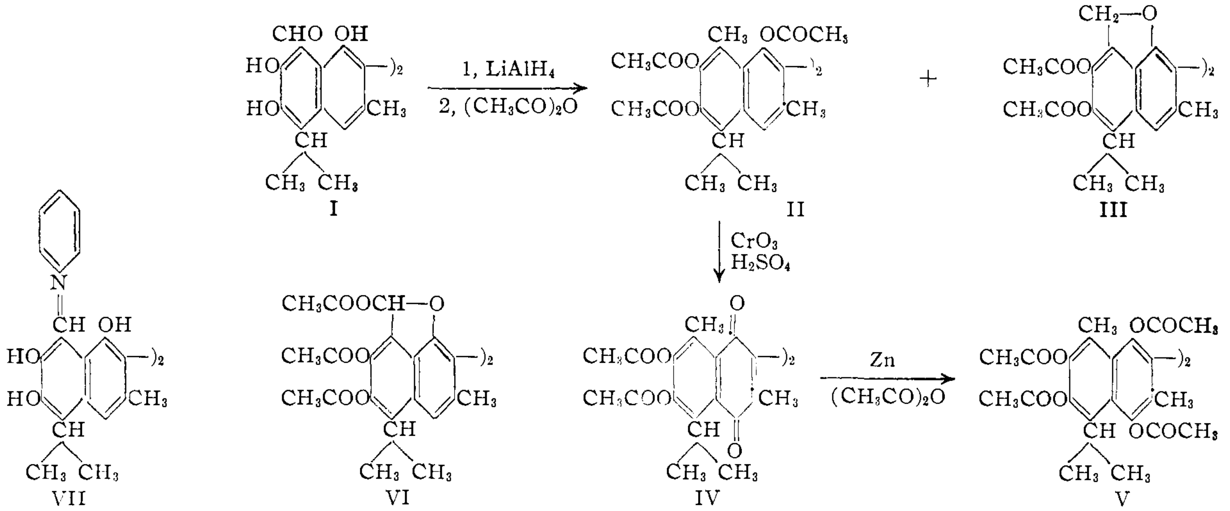
[5] R. F. Miller, D. J. Butterbaugh and R. Adams, *ibid.*, **59**, 1729 (1937).

[6] R. Adams, R. C. Morris, T. A. Geissman, D. J. Butterbaugh and E. C. Kirkpatrick, *ibid.*, **60**, 2193 (1938).

methyl group. Reduction of aldehydes by lithium aluminum hydride normally yields the corresponding carbinols but the reduction of the carbonyl groups to the methylene group can be rationalized on the basis of two observations. The carbonyl group in gossypol is a vinylog of the carbonyl group in a carboxylic acid which normally undergoes reduction to methylene; and secondly, Conover and Tarbell[7] have shown that 4,4′-dimethoxybenzophenone (vinylog of an ester) reduces to 4,4′-dimethoxydiphenylmethane. However, we were unable to demonstrate that the reduction by lithium aluminum hydride of 2-hydroxy-1-naphthaldehyde, under the conditions used on gossypol, produced an appreciable quantity of 1-methyl-2-hydroxynaphthalene.

The major portion of the reaction product from the lithium aluminum hydride reduction and acetylation of gossypol was a dark solid material which remained rather strongly absorbed on the "Florisil" after elution of the methylapogossypol hexaacetate. The use of elution solvents of gradually increasing polarity brought most of this material off the column in fractions but no pure product could be obtained.

In the work-up of at least two of the reduction and acetylation reactions, there was isolated a second crystalline product which was eluted from the "Florisil" column with solvent of lower polarity than the fraction in which the methylapogossypol hexaacetate normally appeared. This product had a constant melting point in the range 219–225°. Analytical data on the compound indicated that its structure is represented by III. This type of compound was isolated by Adams[2a] from the catalytic reduction of gossypol hexamethyl ether and using his nomenclature we designate III as desoxygossypol tetraacetate.



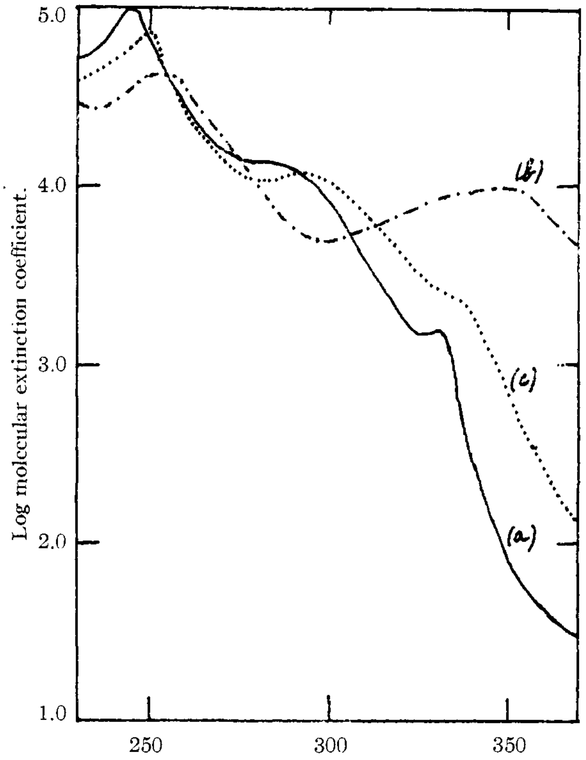


Fig. 1.—Ultraviolet absorption spectra in ethanol: (a) — methylapogossypol hexaacetate (II); (b) —·—·— methylapogossypolone tetraacetate (IV); (c) .... methylapohydrogossypolone octaacetate (V).

Methylapogossypol hexaacetate was oxidized with chromic anhydride and sulfuric acid[8] to IV designated as methylapogossypolone tetraacetate. The ultraviolet absorption spectrum of this compound (Fig. 1) shows a strong absorption at 345–350 mμ and a rather close resemblance to the curves for 1,4-naphthoquinone and 2-methyl-1,4-naphthoquinone given by Friedel and Orchin.[9] A strong absorption in the infrared (Table I) at 6.02 μ is also evidence for the quinone structure.

Reductive acetylation of methylapogossypolone tetraacetate with zinc and acetic anhydride[10] pro-

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(7) L. H. Conover and D. S. Tarbell, THIS JOURNAL, **72**, 3586 (1950).

(8) E. P. Clark, *ibid.*, **51**, 1475 (1929).

(9) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 254–255.

(10) R. Adams and D. J. Butterbaugh, THIS JOURNAL, **60**, 2174 (1938).

duced a new crystalline product which was indicated by analyses to be methylapohydrogossypolone octaacetate (V). This characteristic reaction of the naphthoquinone system lends support to the structures postulated earlier. The ultraviolet spectrum of this compound is given in Fig. 1. The absence of an absorption maximum in the 345–350 mμ region and the general similarity to the spectrum of methylapogossypol hexaacetate (II) is also evidence for the structure indicated (V).

Attempts to carry out the reduction of dianilinogossypol (VII) with lithium aluminum hydride were unsuccessful in producing a pure crystalline product.

The authors wish to acknowledge the help of Mr. R. T. O'Connor and his group at Southern Regional Research Laboratory with the infrared spectra and the advice and encouragement of Dr. F. H. Thurber and Dr. A. M. Altschul of the same laboratory.

Experimental[11]

Methylapogossypol Hexaacetate (II).—Four grams of powdered lithium aluminum hydride was stirred for 30 minutes under an atmosphere of dry nitrogen with 150 ml. of anhydrous ether and then a solution of 5.0 g. of gossypol[12] in 250 ml. of dry ether was added over a period of 30 minutes. The reaction mixture was stirred at room temperature for 18 hours, hydrolyzed by the cautious addition of ether saturated with water followed by methanol containing about 5% water, and then made acid by addition of a dilute solution of acetic and hydrochloric acid with cooling. The ether layer was separated, the aqueous layer extracted with ether and the combined ethereal extracts washed with several portions of water. The ethereal solution was dried over sodium sulfate and 50 ml. of acetic anhydride added. The ether was removed by distillation and to the residue was added 10 ml. of additional acetic anhydride and 4 g. of freshly fused sodium acetate. The mixture was heated under reflux for 1.5 hours in a bath maintained at 125°. The mixture was then poured into excess water and allowed to stand until the excess acetic anhydride was hydrolyzed. The resulting precipitate was removed by filtration, washed thoroughly with water and air-dried. The crude product was dissolved in petroleum ether (b.p. 80–120°) containing a small amount of benzene. The resulting solution was poured into a column 2 to 3 cm. in diameter containing 115 g. of 60–100 mesh "Florisil."[13] Approximately 100 ml. of the solvent used to dissolve the product was passed through the column. No banding or movement of the absorbed colored material was noted. The product was eluted from the column using pure benzene initially and followed by increasing amounts of ether in benzene. The ether content of the benzene was increased in increments of 5% by volume. All of the eluate up to and including the use of 20% ether–80% benzene had a volume of about 1700 ml. and was evaporated to dryness. The resulting solid was treated in the same fashion again on a column containing 25 g. of absorbent. The solid obtained from this treatment was recrystallized from benzene–petroleum ether (b.p. 80–120°) mixtures to yield 0.1 to 0.4 g. of white solid, m.p. 270–272°. Two additional recrystallizations with little loss were necessary to raise the m.p. to its maximum value of 277–279°. Material of this melting range was used for the analyses below, but some reactions were carried out on the lower melting samples. Analysis of the lower melting sample showed the carbon and hydrogen content to be well within the limits of acceptability.

Anal. Calcd. for $C_{42}H_{46}O_{12}$: C, 67.90; H, 6.24; acetyl, 34.75. Found: C, 67.86 and 67.86; H, 6.18 and 6.35; acetyl,[14] 34.90 and 35.05.

Continued elution of the original column with benzene containing still greater amounts of ether allowed separation of further fractions but no homogeneous product could be obtained.

It was found that the same amount of gossypol acetic acid complex could be substituted for gossypol in the above procedure and this offered two major advantages. Gossypol acetic acid can be purified by crystallization more quickly and with less loss than gossypol. The yield of methylapogossypol hexaacetate was more consistent from batch to batch and amounted to 0.3 to 0.4 g. per run.

Desoxygossypol Tetraacetate (III).—In two experiments of reduction and acetylation of 5.0 g. of gossypol as described above, no methylapogossypol hexaacetate was formed. In these cases there was isolated from the eluates with 95% benzene–5% ether and 90% benzene–10% ether 0.42 g. of a new white microcrystalline solid. This was recrystallized from a mixture of benzene and petroleum ether followed by a second recrystallization from isopropyl alcohol and petroleum ether to yield 3% of product melting in the range of 219–225°. The carbon and hydrogen content of the compound did not correspond to methylapogossypol hexaacetate, gossypol hexaacetate, or partially acetylated molecules of this type. A fair agreement was noted with structure III, desoxygossypol tetraacetate.[2a]

Anal. Calcd. for $C_{38}H_{38}O_{10}$: C, 69.71; H, 5.85. Found: C, 69.02 and 69.00; H, 5.87 and 5.76.

Methylapogossypolone Tetraacetate (IV).—A solution of 0.2 g. (0.00027 mole) of methylapogossypol hexaacetate in glacial acetic acid was oxidized with chromic anhydride and sulfuric acid to the corresponding quinone according to the procedure used by Clark[6] for the oxidation of apogossypol hexamethyl ether. The crude material resulting from this reaction was digested with hot methanol, and the residue after filtration was dried and recrystallized from a mixture of ethanol and ethyl acetate. A recrystallization from acetic acid and water followed by another from ethanol–ethyl acetate produced the bright yellow quinone, m.p. 262–264°. The yield was 0.04 g. (22%).

Anal. Calcd. for $C_{38}H_{38}O_{12}$: C, 66.48; H, 5.57. Found: C, 66.20 and 66.08; H, 5.80 and 5.87.

Methylapohydrogossypolone Octaacetate (V).—Methylapogossypolone tetraacetate (60 mg. or 0.000087 mole) was subjected to reductive acetylation according to the procedure of Adams and co-workers.[10] The crude product was recrystallized with considerable loss from a mixture of acetone and methanol and the resulting white crystalline solid (12 mg. or 19%) melted at 270–272° dec.

Anal. Calcd. for $C_{42}H_{46}O_{12}$: C, 64.33; H, 5.87. Found: C, 64.04 and 64.05; H, 6.19 and 5.94.

Reduction of 2-Hydroxy-1-naphthaldehyde with Lithium Aluminum Hydride.—2-Hydroxy-1-naphthaldehyde was prepared by the method of Duff and Bills[15] and 3.95 g. (0.023 mole) was reduced with 3.0 g. of lithium aluminum hydride using the same procedure as for gossypol. The crude product was crystallized from benzene–petroleum ether (b.p. 80–120°) and then from chloroform to give 1.9 g. of product melting at 189–191° dec. Melting points[16] of 188–189° dec. and 193° dec. are reported for 1-hydroxymethyl-2-naphthol. 1-Methyl-2-naphthol is reported to melt at 109–110°[17] and 109–111°.[18]

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(11) All melting points reported were obtained on a Kofler hot stage microscope and are uncorrected. All analyses, unless otherwise indicated, were by Galbraith Microanalytical Laboratories of Knoxville, Tennessee.

(12) The gossypol used was obtained from Dr. F. H. Thurber at Southern Regional Research Laboratory and purified by a procedure supplied by him.

(13) Obtained from the Floridin Co., Warren, Pa.

(14) Analysis by Clark Microanalytical Laboratory, Urbana, Ill.

(15) J. C. Duff and E. J. Bills, *J. Chem. Soc.*, 1305 (1934).

(16) (a) C. J. Clutterbuck, *ibid.*, **123**, 2510 (1923); (b) M. Betti and C. M. Mundici, *Gazz. chim. ital.*, **36II**, 655 (107); *Chem. Zentr.*, **78**, I, 966 (1907).

(17) R. Robinson and F. Weygand, *J. Chem. Soc.*, 386 (1941).

(18) J. W. Cornforth, R. Cornforth and R. Robinson, *ibid.*, 682 (1942).