

The acid gave a dimethyl ester,¹² m. p. 161–162°.

Anal. Calcd. for $C_{29}H_{44}O_7$: C, 69.0; H, 8.79. Calcd. for $C_{29}H_{46}O_7$: C, 68.73; H, 9.15. Found: C, 68.63, 68.58; H, 9.20, 9.21.

Treatment of the dimethyl ester with boiling acetic anhydride for twenty minutes gave a product which was crystallized from ether–pentane to give long white needles of the dimethyl ester acetate, m. p. 158–160°.

Anal. Calcd. for $C_{31}H_{46}O_8$: C, 68.10; H, 8.47. Calcd. for $C_{31}H_{48}O_8$: C, 67.85; H, 9.01. Found: C, 67.74, 67.93; H, 8.93, 8.91.

C₂₇ Neutral Oxidation Product from Sarsasapogenin.—The neutral fraction obtained in the chromic anhydride oxidation of sarsasapogenin acetate was crystallized from acetone to give white needles, m. p. 162–164°, of a neutral acetate.¹²

Anal. Calcd. for $C_{29}H_{44}O_8$: C, 73.65; H, 9.4. Calcd. for $C_{29}H_{46}O_8$: C, 73.4; H, 9.8. Found: C, 73.2; H, 9.7.

Hydrolysis of this product with an excess of ethanolic potassium hydroxide gave the 3-hydroxy compound¹² which crystallized from acetone as small white plates, m. p. 215–217°.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.3; H, 9.85. Calcd. for $C_{27}H_{44}O_4$: C, 74.9; H, 10.2. Found: C, 75.6, 75.7; H, 10.0, 10.1.

The neutral acetate when treated with semicarbazide hydrochloride under the usual conditions gave a semicarbazone which crystallized from acetone as small white needles, m. p. 249–251° dec.

Anal. Calcd. for $C_{30}H_{47}O_5N_3$: C, 68.0; H, 9.0; N, 7.9. Calcd. for $C_{30}H_{49}O_5N_3$: C, 67.75; H, 9.3; N, 7.9. Found: C, 67.5, 67.5; H, 8.9, 8.7; N, 7.6.

Reduction of C₂₇ Neutral Oxidation Product. (a) **By Catalytic Hydrogenation.**—A mixture of 1.5 g. of the neutral acetate, 1 g. of Adams catalyst, 100 cc. of glacial

acetic acid and 30 cc. of 99% ethanol was shaken with hydrogen at 3 atmospheres pressure at 25° for fourteen hours. The mixture was filtered and the filtrate diluted with water, the precipitated solid was extracted with ether and the ethereal extract washed with sodium carbonate solution. The ether was evaporated and the residue refluxed for twenty minutes with an excess of ethanolic potassium hydroxide. The product was crystallized from methanol–ethanol as white plates, m. p. 215–217°.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.9; H, 10.3. Calcd. for $C_{27}H_{46}O_4$: C, 74.6; H, 10.7. Calcd. for $C_{27}H_{48}O_4$: C, 74.26; H, 11.1. Found: C, 74.6, 74.4; H, 10.7, 10.9.

The neutral acetate was recovered unchanged after shaking with Adams catalyst and hydrogen at 3 atmospheres pressure for six hours at 28° in ethanol solution.

(b) **By Clemmensen Reduction.**—To a boiling solution of 300 mg. of the neutral acetate in 100 cc. of 95% ethanol with 20 g. of amalgamated 20-mesh zinc was added 16 cc. of concentrated hydrochloric acid over a period of nine hours. The solution was decanted into water and the precipitated solid extracted with ether. The ether was evaporated and the residue crystallized from acetone–ethyl acetate to give 200 mg. of compact white crystals, m. p. 191–193°. This gave no depression with a sample of tetrahydrosarsasapogenin.

Anal. Calcd. for $C_{27}H_{48}O_3$: C, 77.1; H, 11.5. Found: C, 76.8; H, 11.5.

Summary

The structure of sarsasapogenic acid and its transformation products is discussed in terms of the ketone spiro acetal structure for the saponin side chain.

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

Structure of Gossypol. XXII. Gossypol Ethers and their Reduction Products¹

BY ROGER ADAMS AND W. R. DIAL²

Gossypol hexamethyl ether³ was one of the most important gossypol derivatives since it served as the compound from which many significant degradation products were obtained.⁴ It was assigned the structure I on the basis of its reactions with a drop of sulfuric acid in acetic acid to give gossypol dimethyl ether (II), with phenylhydrazine in glacial acetic acid to give a phenylhydrazone of a gossypol tetramethyl ether (III), which on treatment with methanolic or

ethanolic hydrogen chloride reverted to gossypol hexamethyl ether (I) or gossypol tetramethyl diethyl ether (IV).⁵

The study of gossypol ethers has now been extended to a variety of others. Gossypol tetramethyl ether (V)³ has been ethylated to gossypol diethyl tetramethyl ether (VI), isomeric with IV. This same ether (VI) was also prepared by methylation of gossypol diethyl ether (VII).⁵

The new ether (VI) formed a phenylhydrazone of gossypol dimethyl diethyl ether which with methanolic hydrogen chloride gave back VI or

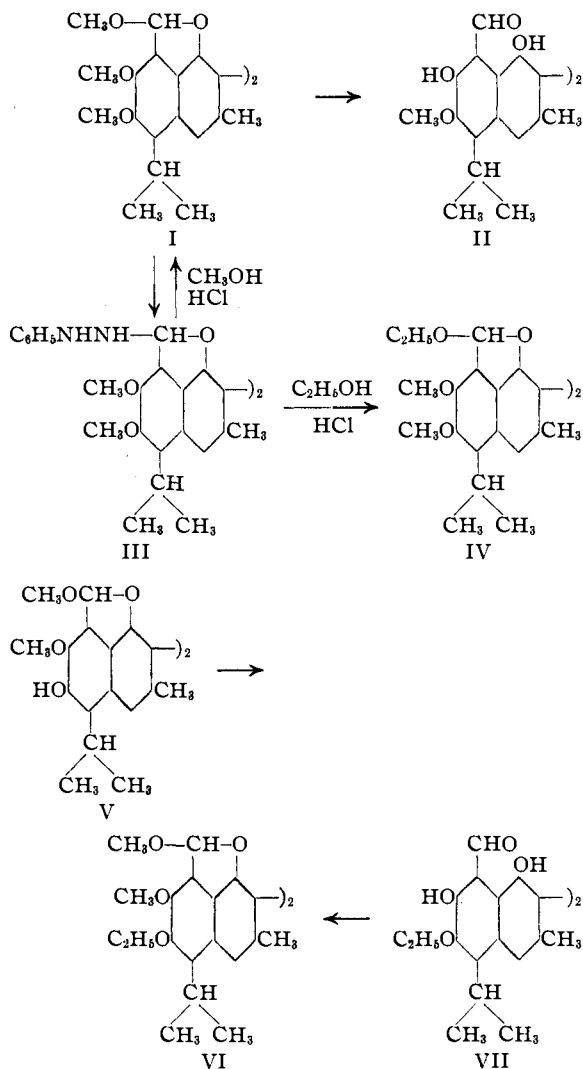
(1) For previous paper see Adams and Baker, *THIS JOURNAL*, **61**, 1138 (1939).

(2) Dow Chemical Company Fellow, 1936–1939.

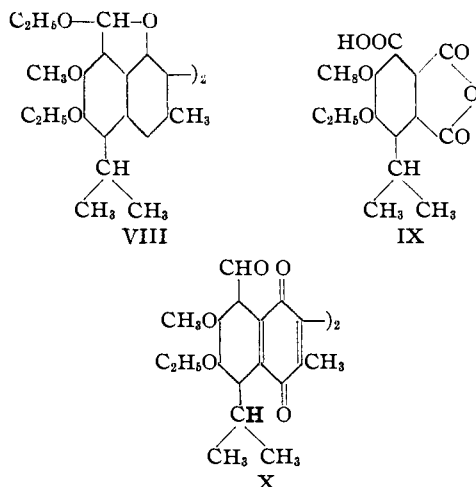
(3) Adams, Geissman and Morris, *THIS JOURNAL*, **60**, 2967 (1938).

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

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

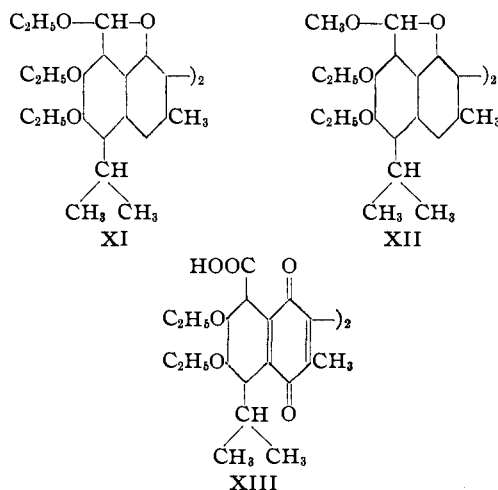


with ethanolic hydrogen chloride gave gossypol tetraethyl dimethyl ether (VIII).

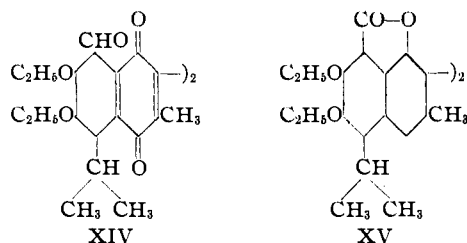


The ether (VI) undergoes reactions similar to gossypol hexamethyl ether. It was dealkylated with a drop of sulfuric in acetic acid⁶ to gossypol diethyl ether (VII), and was oxidized with dilute nitric acid to a gossic acid analog (IX)⁶ or by chromic acid to a gossypolone derivative (X).

Gossypol hexaethyl ether (XI)⁷ was also converted into a phenylhydrazine derivative which on treatment with methanolic hydrogen chloride gave gossypol tetraethyl dimethyl ether (XII) and with ethanolic hydrogen chloride the original ether (XI)



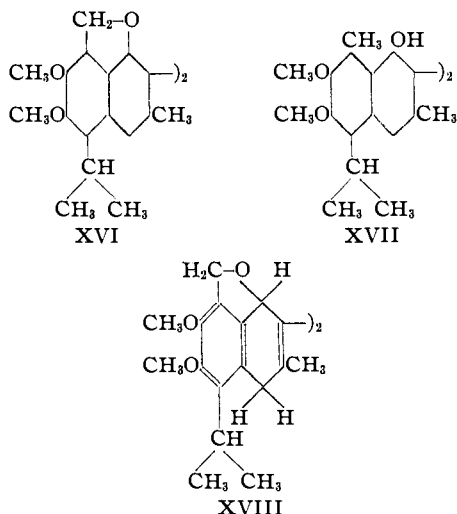
By action of dilute nitric acid on XI, a gossypolonic acid derivative (XIII) resulted⁶; by action of chromic acid XI was converted to gossypolone tetraethyl ether (XIV) and gossylic acid lactone tetraethyl ether (XV).⁶



Gossypol hexamethyl ether was unaffected by hydrogen in the presence of platinum catalyst if ethanol or ethyl acetate was used as a solvent, but in acetic acid it was reduced to a new derivative which has been called desoxygossypol tetramethyl ether and has been assigned formula XVI. Formation of such a derivative may be by direct hydrogenolysis of the two acetal methoxyls in gossypol hexamethyl ether or more likely by hy-

(6) Adams, Morris and Kirkpatrick, *THIS JOURNAL*, **60**, 2170 (1938).

(7) Morris and Adams, *ibid.*, **59**, 1731 (1937).



drolisis of the acetal methoxyls, reduction of the two aldehyde groups and subsequent loss of water.

The analyses for this reduction product were more consistent with formula XVII or XVIII but the chemical reactions excluded the latter two possibilities. This substance may be of the nature of gossypol itself for which consistent analyses for its molecular formula, $C_{30}H_{30}O_8$, were practically impossible to obtain.

The evidence for structure XVI and against XVII is as follows. The compound gave no color with ferric chloride; it was insoluble in methanolic alkali; it could not be methylated or acetylated; it gave no phenylhydrazine derivative; bromination, nitration, Friedel and Crafts reactions and dealkylation with a drop of sulfuric acid in acetic acid gave no definite products. Neither this product nor gossypol hexamethyl ether with diazotized aniline gave a color; on the other hand, gossylic acid tetramethyl ether which has a free hydroxyl in the same position as is shown in compound XVII did give a color. Diazotized 2,4-dinitroaniline gave a color with all three products. Meyer⁸ has shown that diazotized aniline will couple only with phenols and not with phenol ethers whereas diazotized dinitroaniline will couple with both phenols and their ethers. This is evidence for an ether linkage (XVI) in desoxygossypol tetramethyl ether and makes formulas XVII or XVIII unlikely. The infrared absorption spectra⁹ of XVI in carbon tetrachloride indicated that no phenolic or alcoholic hydroxyl was present.

(8) Meyer, Isschick and Schlosser, *Ber.*, **47**, 1741 (1914).

(9) The infrared absorption spectra were determined by G. W. McMillan of this Laboratory, to whom we are indebted.

Desoxygossypol tetramethyl ether gave on oxidation with dilute nitric acid gossic acid⁶ and with chromic anhydride gossypolone tetramethyl ether. These are the same products as are obtained from gossypol tetramethyl ether with the same reagents.

The gossypol diethyl tetramethyl ether (VI) was reduced under similar conditions with formation of desoxygossypol diethyl dimethyl ether (XIX).

Gossypol tetramethyl ether (V) was reduced also but no crystalline product was isolated. The crude product must have been the expected desoxy compound for on methylation, crystalline desoxygossypol tetramethyl ether (XVI), and on ethylation, crystalline desoxygossypol diethyl dimethyl ether (XVIII), resulted.

Compounds with this type of ether linkage across the *peri* positions in naphthalene are rare and no very simple compounds of this type have been described with which to compare properties.

Experimental

Gossypol Diethyl Tetramethyl Ether

(a) **Ethylation of Gossypol Tetramethyl Ether.**—A solution of 5.0 g. of recrystallized gossypol tetramethyl ether in a warm mixture of 13 cc. of diethyl sulfate and 22 cc. of benzene was treated with 33 cc. of 20% ethanolic potassium hydroxide added in small portions. The solution was heated for fifteen minutes on the steam-bath and then treated with an additional 13 cc. of diethyl sulfate and 20% ethanolic potassium hydroxide was added until the reaction mixture was alkaline. This was then evaporated to a sludge on the steam-bath with stirring, ethanol being added from time to time until most of the benzene had been removed. The sludge was then cooled and filtered. The solid was washed with ethanol until the filtrates were colorless and then thoroughly with water to remove inorganic salts. The residue (4.0 g.) of gossypol diethyl tetramethyl ether was purified by recrystallizing several times from acetone-methanol mixture and then from benzene-methanol mixture; white microcrystalline powder, m. p. 271–272° (corr.).

Anal. Calcd. for $C_{38}H_{46}O_8$: C, 72.36; H, 7.35. Found: C, 71.99; H, 7.31.

The compound gave an orange color in concentrated sulfuric acid and no color with ferric chloride.

When recrystallized from acetone-methanol mixture alone, the melting point could not be raised above 228–

229° (corr.). The white prisms thus obtained gave no melting point depression when mixed in various proportions with the 271–272° form.

Anal. Calcd. for $C_{38}H_{46}O_8$: C, 72.36; H, 7.35. Found: C, 72.47; H, 7.55.

(b) **Methylation of Gossypol Diethyl Ether.**—To a solution of 0.15 g. of gossypol diethyl ether in a mixture of 2 cc. of methanol and 2 cc. of dimethyl sulfate, 3 cc. of 10% methanolic potassium hydroxide was added slowly. The mixture was allowed to stand at room temperature for thirty-six hours and then filtered. The precipitate was filtered and washed with methanol, then with water. The product (0.14 g.) was purified as previously described and gave a crystalline powder, m. p. 271–272° (corr.).

Gossypol Diethyl Ether: Demethylation of Gossypol Diethyl Tetramethyl Ether.—To a solution of 1.0 g. of gossypol diethyl tetramethyl ether (272° form) in 40 cc. of hot glacial acetic acid was added 10 cc. of acetic acid containing ten drops of concentrated sulfuric acid. The solution turned dark red and after heating for fifteen minutes on a steam-bath, it was diluted with 20 cc. of water and cooled. The crude yellow product weighed 0.9 g. It was purified by recrystallization from benzene; yellow needles, m. p. 195–196° (corr.). This product proved to be identical with the diethyl ether of gossypol prepared previously by deethylation of gossypol hexaethyl ether.⁷

Phenylhydrazine from Gossypol Diethyl Ether.—This was prepared by adding 0.5 cc. of phenylhydrazine to a hot solution of 0.1 g. of gossypol diethyl ether in 3 cc. of glacial acetic acid. After warming for thirty minutes on the steam cone, slender yellow needles of phenylhydrazine separated. These were filtered and washed with methanol; yield, 0.1 g., m. p. 260–261° (corr.). No satisfactory method could be found for the recrystallization of this material.

Anal. Calcd. for $C_{48}H_{50}O_6N_4$: C, 73.22; H, 6.68; N, 7.43. Found: C, 73.07; H, 6.64; N, 7.59.

The same product was obtained from the gossypol diethyl ether formed from gossypol hexaethyl ether.

The phenylhydrazine gives an orange-yellow color in concentrated sulfuric acid and a red color with ferric chloride which changes to orange upon standing. It is insoluble in cold 10% aqueous alkali but soluble in 10% methanolic alkali.

Phenylhydrazine from Gossypol Diethyl Tetramethyl Ether.—A solution of 0.1 g. of the 271–272° form of the above ether in 10 cc. of glacial acetic acid was warmed with 0.8 cc. of phenylhydrazine for thirty minutes on a steam-bath. Upon scratching the side of the flask, 0.95 g. of product separated. After recrystallization from benzene and petroleum ether (b. p. 60–110°), yellow prisms formed, m. p. 268–269° (corr.).

Anal. Calcd. for $C_{38}H_{54}O_6N_4$: C, 73.63; H, 6.95; N, 7.16. Found: C, 73.34; H, 6.71; N, 7.16, 7.25.

The phenylhydrazine gave an orange-yellow color in concentrated sulfuric acid and gave no color with ferric chloride.

The phenylhydrazine prepared in exactly the same manner from the 228–229° form of the ether melted at 268–269° (corr.) and gave no depression when mixed with the phenylhydrazine from the 271–272° form.

The phenylhydrazine can be reconverted to the gossypol diethyl tetramethyl ether by the action of methanolic hydrogen chloride. A suspension of 1.0 g. of the phenylhydrazine in 40 cc. of absolute methanol was treated with dry hydrogen chloride until all of the phenylhydrazine went into solution. The solution was allowed to stand overnight, whereupon the crystalline ether separated. It weighed 0.7 g. and after several recrystallizations from benzene–methanol mixture, melted at 271–272° (corr.) and gave no depression in melting point when mixed with the ether obtained by the ethylation of gossypol tetramethyl ether.

Gossypol Dimethyl Tetraethyl Ether by the Action of Ethanolic Hydrogen Chloride on the Phenylhydrazine from Gossypol Diethyl Tetramethyl Ether.—The same procedure as in the methanolysis was used except for the replacement of methanol by ethanol. After standing overnight 0.75 g. of product separated which was purified by recrystallization from acetone–ethanol mixture; white prisms, m. p. 241–242° (corr.).

Anal. Calcd. for $C_{40}H_{60}O_8$: C, 72.92; H, 7.65. Found: C, 73.19; H, 7.51.

The ether gives an orange color in concentrated sulfuric acid and no color in ferric chloride.

Norgossic Acid Ethyl Methyl Ether: 1-Methoxy-2-ethoxy-3-isopropyl-4,5,6-benzene Tricarboxylic Acid Anhydride-4,5.—Gossypol diethyl tetramethyl ether was treated with dilute nitric acid exactly as was described for the formation of gossic acid from gossypol hexamethyl ether.⁵

The insoluble residue could not be purified but the acid-soluble material amounted to 0.5 g. of crude acid from 2.0 g. of diethyl tetramethyl ether. Purified from toluene, white needles were obtained, m. p. 178–179° (corr.).

Anal. Calcd. for $C_{16}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.39; H, 5.27.

The acid gave no color in concentrated sulfuric acid and no color in ferric chloride.

Gossypolone Diethyl Dimethyl Ether.—To a solution of 2.0 g. of recrystallized gossypol diethyl tetramethyl ether in 50 cc. of boiling glacial acetic acid was added in one portion 10 cc. of a 10% aqueous solution of chromic anhydride. The mixture was allowed to boil for one minute and then poured onto a mixture of 100 g. of ice and 50 cc. of water. The yellow precipitate was filtered with suction, washed with water and air dried. The product was added to 50 cc. of hot methanol and upon cooling yellow platelets separated; yield, 0.8 g. After purification by the recrystallization from methanol, it melted at 185–186° (corr.).

Anal. Calcd. for $C_{38}H_{38}O_{10}$: C, 68.56; H, 6.07. Found: C, 68.20; H, 6.02.

The product gave a brown color in concentrated sulfuric acid which changed to orange upon standing for thirty minutes. It gave no color with ferric chloride.

In this oxidation no evidence of lactone formation was noted.

Phenylhydrazine from Gossypol Hexaethyl Ether.—A solution of 0.1 g. of gossypol hexaethyl ether in 4 cc. of hot glacial acetic acid was treated with 0.5 cc. of phenylhydrazine and the mixture was heated on the steam-bath

for thirty minutes. Upon cooling 0.08 g. of product separated; yellow needles from benzene-petroleum ether (b. p. 60–110°), m. p. 241–242° (corr.).

Anal. Calcd. for $C_{60}H_{88}O_8N_4$: C, 74.05; H, 7.21; N, 6.91. Found: C, 73.91; H, 7.01; N, 6.95.

The product gave an orange color with concentrated sulfuric acid and no color with ferric chloride.

The action of ethanolic hydrogen chloride on this product reconverted it to gossypol hexaethyl ether, m. p. 211–212° (corr.).

Gossypol Tetraethyl Dimethyl Ether.—By treatment of the phenylhydrazone from gossypol hexaethyl ether with methanolic hydrogen chloride in the same manner as described for other phenylhydrazones, 1.5 g. of product was obtained from 2 g. of starting material. It formed white crystals from acetone-methanol, m. p. 206–207° (corr.).

Anal. Calcd. for $C_{40}H_{60}O_8$: C, 72.92; H, 7.65. Found: C, 73.13; H, 7.77.

The product gave an orange color in concentrated sulfuric acid and no color with ferric chloride.

Gossypolonic Acid Tetraethyl Ether.—A suspension of 2.0 g. of gossypol hexaethyl ether in a mixture of 200 cc. of water and 50 cc. of concentrated nitric acid (sp. gr. 1.42) was refluxed for twelve hours. After this time a yellow solid remained in suspension. After cooling the yellow insoluble material was filtered and dissolved in 10% aqueous sodium bicarbonate solution. The bicarbonate solution, after extraction with ether, was filtered and acidified with dilute sulfuric acid. The product weighed 0.5 g. Purified from acetone-methanol mixture, it formed yellow flakes, m. p. 272–273° (corr.).

Anal. Calcd. for $C_{38}H_{42}O_{12}$: C, 66.07; H, 6.13. Found: C, 66.04; H, 6.27.

The product gave a maroon color in concentrated sulfuric acid which changed to brown on standing. It gave no color with ferric chloride. It was soluble in aqueous alkali giving a yellow solution.

The nitric acid filtrate was worked up as described for the dilute nitric acid oxidation of gossypol hexamethyl ether, but no crystalline acid corresponding to gossic acid could be isolated.

Gossypolone Tetraethyl Ether and Gossylic Acid Lactone Tetraethyl Ether.—To a solution of 2.0 g. of gossypol hexaethyl ether in 50 cc. of boiling glacial acetic acid was added 10 cc. of a 10% aqueous solution of chromic anhydride. The mixture was boiled for a minute and then poured onto 100 g. of ice. The insoluble product was filtered and dissolved in 100 cc. of boiling methanol. A yellow insoluble product (0.19 g.) separated almost immediately and proved to be gossylic acid lactone tetraethyl ether. It was purified by dissolving in 8 cc. of boiling acetic anhydride to which was then added slowly a mixture of 3 cc. of glacial acetic acid and 1.5 cc. of water. Upon scratching the walls of the flask, crystals separated. After repetition of this procedure, a white crystalline powder resulted, m. p. 244–245° (corr.).

The methanolic filtrate from the crude gossylic acid lactone tetraethyl ether was concentrated to about 30 cc. and cooled. The precipitate of gossypolone tetraethyl ether (0.5 g.) was purified from methanol; yellow plates, m. p. 146–147° (corr.).

Anal. (Lactone, m. p. 244–245°.) Calcd. for $C_{38}H_{42}O_8$: C, 72.82; H, 6.76. Found: C, 72.54; H, 6.88. (Gossypolone, m. p. 146–147°.) Calcd. for $C_{38}H_{42}O_{10}$: C, 69.28; H, 6.43. Found: C, 69.40; H, 6.55.

The gossypolone gave a brown color in concentrated sulfuric acid and the lactone a yellow color.

The lactone was insoluble in warm aqueous alkali but soluble in warm alcoholic alkali.

Dinitrogossylic Acid Lactone Tetraethyl Ether.—To a solution of 0.08 g. of the gossylic acid lactone tetraethyl ether in 10 cc. of hot glacial acetic acid, 1 cc. of concentrated nitric acid was added. A clear brown solution resulted which was boiled and water added dropwise until crystallization started. After cooling, the product which separated was recrystallized from dilute acetic acid; pale yellow needles, m. p. 266–267° (corr.).

Anal. Calcd. for $C_{38}H_{40}N_2O_8$: N, 3.91. Found: N, 3.72.

Reduction of Gossypol Hexamethyl Ether: Desoxygossypol Tetramethyl Ether.—A solution of 2.0 g. of pure gossypol hexamethyl ether (m. p. 223–225°) in 200 cc. of warm (50°) glacial acetic acid was placed in a reduction bottle together with 0.1 g. of platinum oxide catalyst and shaken with hydrogen at room temperature under three atmospheres pressure. After four hours, the solution was filtered to remove the platinum and the filtrate was poured into 800 cc. of water. The white flocculent precipitate was filtered, washed with water until free of acid and dried in air. The 1.9 g. of white amorphous product was triturated with warm methanol. A gummy mass was at first obtained which became crystalline upon standing for a few minutes. The methanol-insoluble material was filtered and weighed 1.5 g. After recrystallization from acetone-methanol mixture, it melted at 261–263° (corr.), with decomposition.

Anal. Calcd. for $C_{34}H_{38}O_6$: C, 75.28; H, 7.01; 4 OCH_3 , 22.8; mol. wt., 542. Calcd. for $C_{34}H_{42}O_6$: C, 74.73; H, 7.69; 4 OCH_3 , 22.7; mol. wt., 546. Found: C, 74.75, 74.49, 74.31, 75.08, 74.44, 74.90, 74.65; H, 7.49, 7.37, 7.56, 7.46, 7.39, 7.42, 7.29; OCH_3 , 26.0, 26.8; mol. wt. (b. p. elev., $CHCl_3$), 529.

The compound is insoluble in alkali (aqueous or alcoholic) and gives no ferric chloride color and no color with Dimroth's pyroboracetate reagent. It gives a brilliant green color with concentrated sulfuric acid.

The compound is soluble in ether, benzene and acetone. It is slightly soluble in acetic acid or methanol and insoluble in ligroin.

Attempts to reduce gossypol hexamethyl ether in alcohol or ethyl acetate resulted in the recovery of the unchanged ether.

Phenylhydrazine, acetic anhydride and sodium acetate, pyridine and acetic anhydride, methanolic dimethyl sulfate and alkali, all resulted in recovery of unchanged starting material.

Attempted demethylation with glacial acetic acid and a drop of sulfuric acid gave no results.

Nitration with various strengths of nitric acid gave only amorphous products. The same was true of bromine, attempted Friedel and Crafts reactions with acetyl chloride, and of hydriodic acid.

Aniline and 2,4-dinitroaniline were diazotized in glacial acetic acid with butyl nitrite and sulfuric acid according to the method of Meyer.⁸

Each of the solid diazonium sulfates was dissolved in 6 parts of cold glacial acetic acid and 1 cc. of each of these solutions was added to a solution of 15 mg. of the compound to be tested in 5 cc. of glacial acetic acid. Diazotized aniline gave no color with gossypol hexamethyl ether or desoxygossypol tetramethyl ether; it did give a color with gossylic acid tetramethyl ether. Diazotized 2,4-dinitroaniline, on the other hand, gave a color with all three products.

Oxidation of Desoxygossypol Tetramethyl Ether to Gossic Acid—A suspension of 0.18 g. of desoxygossypol tetramethyl ether in a mixture of 15 cc. of water and 5 cc. of concentrated nitric acid (sp. gr. 1.42) was refluxed for fourteen hours whereupon all the material went into solution. After cooling, about 30 mg. of insoluble acidic material was filtered. This could not be purified. The dilute nitric acid filtrate was neutralized with sodium carbonate, then acidified to congo red with sulfuric acid, saturated with sodium chloride and extracted several times with ether. The ether extracts were dried with anhydrous magnesium sulfate and then petroleum ether (b. p. 60–110°) added. The ethyl ether was evaporated whereupon brown needles separated from the petroleum ether. The product was purified from toluene, yield 0.08 g. Upon sublimation (2 mm. at 180°) and then recrystallization from toluene, white needles were obtained, m. p. 185–186° (corr.). Mixed with an authentic sample of gossic acid the melting point was 185–186° (corr.).

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.15; H, 4.76. Found: C, 57.27; H, 4.78.

Oxidation of Desoxygossypol Tetramethyl Ether to Gossypolone Tetramethyl Ether.—To a solution of 0.21 g. of desoxygossypol tetramethyl ether in 15 cc. of boiling glacial acetic acid was added rapidly with vigorous stirring 2 cc. of 10% aqueous solution of chromic anhydride and the mixture was allowed to boil for one minute. It was then poured onto a mixture of 30 g. of ice and 10 cc. of water. The product was filtered with suction and the yellow residue was washed with water and air dried. This was added to 10 cc. of warm methanol and the gummy material first formed gradually became crystalline. Recrystallized from methanol, 0.1 g. of yellow plates, m. p. 154–155° (corr.), was obtained. Mixed with an authentic sample of gossypolone tetramethyl ether the melting point was 154–156° (corr.).

Anal. Calcd. for $C_{34}H_{34}O_{10}$: C, 67.77; H, 5.64. Found: C, 67.73; H, 5.81.

Reduction of Gossypol Tetramethyl Diethyl Ether to Desoxygossypol Tetramethyl Ether.—Gossypol tetramethyl diethyl ether⁵ which has two acetal ethoxy groups was reduced in the same manner as described for the hexamethyl ether. Upon recrystallization of the product from acetone–methanol, white plates were obtained, m. p. 261–263° (corr.). Mixed with the product obtained by the reduction of gossypol hexamethyl ether, it melted at 261–263° (corr.).

Anal. Calcd. for $C_{34}H_{38}O_8$: C, 75.28; H, 7.01. Found: C, 74.62; H, 7.57.

Reduction of Gossypol Diethyl Tetramethyl Ether: Desoxygossypol Diethyl Dimethyl Ether.—Gossypol diethyl tetramethyl ether⁶ which has two methoxy groups as acetal linkages was reduced as previously described for the hexamethyl ether. From 1.2 g. of starting material, 0.6 g. of desoxy compound was obtained; white plates from acetone–methanol mixture, m. p. 240–242° (corr.).

Anal. Calcd. for $C_{36}H_{42}O_6$: C, 75.76; H, 7.42. Found: C, 75.28; H, 7.58.

Reduction of Gossypol Tetramethyl Ether: Desoxygossypol Dimethyl Ether.—Gossypol tetramethyl ether⁹ which has two acetal methoxyls was reduced in the same manner as described for the hexamethyl ether but no crystalline material was obtained. The crude tan amorphous desoxygossypol dimethyl ether thus obtained weighed 1.5 g. and had a very indefinite melting point. That this material was a reduction product similar to that obtained by the reduction of gossypol hexamethyl ether was demonstrated by methylation and ethylation.

A solution of 1.5 g. of crude product in 20 cc. of methanol was treated with 5 cc. of dimethyl sulfate. To this mixture was added 16 cc. of a 20% solution of potassium hydroxide in methanol and then heated on a steam-bath for five minutes. Another 5 cc. of methyl sulfate and 16 cc. of 20% methanolic potassium hydroxide was added and the solution evaporated with stirring to a thick sludge. About 20 cc. of methanol was added and the mixture was cooled and filtered. After washing with methanol until the washings were colorless and washing with water to remove potassium salts, 0.5 g. of a cream-colored crystalline material remained on the filter. This after four recrystallizations from acetone–methanol mixture melted at 262–263° (corr.). The white platelets thus obtained proved identical with the desoxygossypol tetramethyl ether already described, mixed m. p. 262–263° (corr.).

Anal. Calcd. for $C_{34}H_{38}O_6$: C, 75.28; H, 7.01. Found: C, 74.67; H, 7.01.

By treatment of the amorphous desoxygossypol dimethyl ether with diethyl sulfate and 20% potassium hydroxide in ethyl alcohol desoxygossypol diethyl dimethyl ether was obtained. It formed white crystals, m. p. 240–242° (corr.) and gave no depression in the melting point when mixed with the sample prepared by the reduction of gossypol diethyl tetramethyl ether.

Summary

1. A number of new ethers of gossypol are described—two gossypol tetraethyl dimethyl ethers and gossypol diethyl tetramethyl ether. These had properties similar to gossypol hexamethyl ether. They could be oxidized to analogous products.

2. Gossypol hexamethyl ether was reduced in glacial acetic acid with hydrogen to desoxygossypol tetramethyl ether and an analogous compound was obtained by the reduction of gossypol diethyl tetramethyl ether. The desoxy compounds oxidize to products similar to those from gossypol hexamethyl ether.