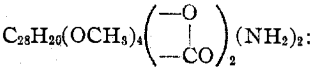
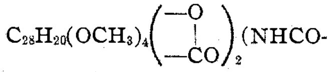
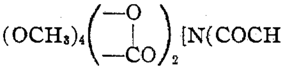
0.38 g. of bright orange platelets, and on dilution of the mother liquors there was obtained an additional 80 mg. of what was largely unreduced nitro compound.

Recrystallization of the main portion several times from slightly diluted acetic acid (with the addition of a small amount of iron) resulted in the formation of bright orange platelets, m. p. 293–294° (corr.), with decomposition.

Anal. Calcd. for  $C_{28}H_{20}(OCH_3)_4\left(\begin{array}{l}-O\\ \;\,|\\ -CO\end{array}\right)_2(NH_2)_2$: C, 68.00; H, 6.00; N, 4.67. Found: C, 67.52; H, 6.09; N, 4.54.

The compound gives a pale yellow color with concentrated sulfuric acid and is readily soluble in methanolic hydrochloric acid (but not in methanol) or in a mixture of acetic acid and hydrochloric acid. Upon the addition of hydrochloric acid to the orange solution of the compound in acetic acid the color fades to pale yellow. It dissolves with some difficulty in warm alcoholic alkali with the formation of a yellow solution which rapidly turns deep blue in air.

Acetylation of Amino Derivative.—A solution of 0.27 g. of the diamine and 0.1 g. of anhydrous sodium acetate in 5 cc. of acetic anhydride was refluxed for one hour. The initially deep orange solution soon became a pale yellow. The excess acetic anhydride was decomposed with water and the product, which weighed 0.29 g., was recrystallized twice from methanol, from which it formed pearly-white leaflets, m. p. 252–253° (corr.).

Anal. Calcd. for  $C_{28}H_{20}(OCH_3)_4\left(\begin{array}{l}-O\\ \;\,|\\ -CO\end{array}\right)_2(NHCOCH_3)_2$: C, 66.66; H, 5.85; N, 4.10. Calcd. for $C_{28}H_{20}$-  $(OCH_3)_4\left(\begin{array}{l}-O\\ \;\,|\\ -CO\end{array}\right)_2[N(COCH_3)_2]_2$: C, 65.63; H, 5.73; N, 3.65. Found: C, 66.03; H, 5.71; N, 3.71.

The compound is insoluble in alcoholic hydrochloric acid.

Summary

Gossylic acid lactone tetramethyl ether has been shown to be a *peri*-naphthalene lactone. It can be hydrolyzed to the corresponding hydroxy acid which can be methylated with diazomethane or alkali and dimethyl sulfate to the ether ester. The hydroxy acid is oxidized with dilute nitric acid to gossypolonic acid tetramethyl ether, the same water-insoluble quinone obtained by the oxidation of gossypol hexamethyl ether with nitric acid. The color indicates a *p*-quinone which demonstrates the probability of unsubstituted hydrogens para to the hydroxyls in the hydroxy acid.

The lactone is resistant to oxidation but is nitrated to a dinitro derivative. The nitro groups presumably occupy the unsubstituted positions para to the hydroxyls.

Gossypol can be considered as having two naphthalene nuclei each containing the following substitutions: 1-aldehydo, 5-hydrogen, 8-hydroxyl.

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

Structure of Gossypol. XIII.[1] Conversion of Gossic Acid to Apogossypolic Acid

BY ROGER ADAMS AND R. C. MORRIS

Two products are obtained by oxidation of gossypol hexamethyl ether with nitric acid, a water-insoluble, gossypolonic acid tetramethyl ether, and a water-soluble, gossic acid. The former is converted into the latter by the action of potassium permanganate.[2] Gossic acid has approximately half the molecular weight of the original compound and consequently knowledge of its structure would be of unusual value in clarifying the structure of gossypol.

It was shown previously that gossic acid contains two methoxyls, one carboxyl, and one dibasic acid anhydride linkage formulated as I. These facts were deduced from a Zeisel determination, titration for a tribasic acid in aqueous solution, formation of a monomethyl ester (II) by the action of diazomethane and a molecular weight determination. Various derivatives and degradation products now have been prepared. Gossic acid is hydrolyzed by alkali to a tribasic acid (III) which could not be isolated in a pure state due to its tendency to revert to gossic acid. However, an ether solution of the hydrolyzed gossic acid was methylated with diazomethane and a stable crystalline trimethyl ester (IV) obtained. This confirms the presence of a carboxyl and a dibasic acid anhydride residue in gossic acid. By demethylation of gossic acid, the corresponding dihydroxy acid (V) was isolated readily. That no rearrangement was involved was indicated by the action of diazomethane on the demethylated product. The methyl ester

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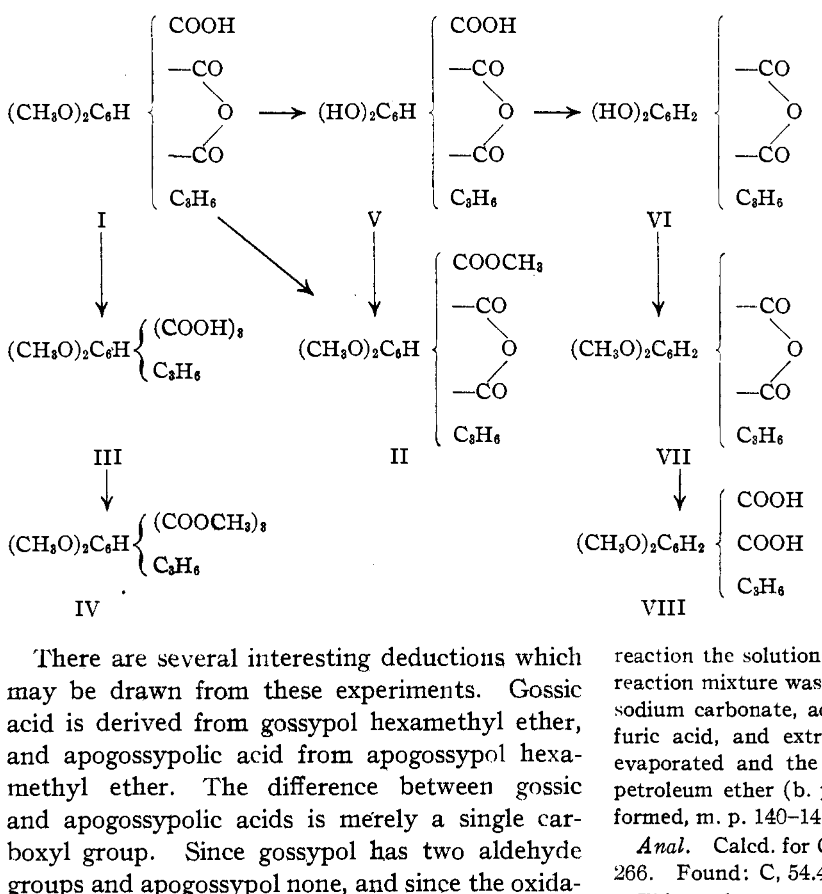
[1] For previous paper in this series see Adams and Geissman, THIS JOURNAL, **60**, 2184 (1938).

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

of gossic acid (II) previously prepared from gossic acid resulted. The demethylated gossic acid, when heated with quinoline and copper bronze, lost carbon dioxide to give a dihydroxy dibasic acid anhydride, $C_{11}H_{10}O_5$ (VI). This in turn, upon methylation with diazomethane, gave a dimethoxy dibasic acid anhydride (VII), which proved to be identical with apogossypolic acid anhydride and which hydrolyzed to apogossypolic acid (VIII).[3] This series of reactions is shown as



There are several interesting deductions which may be drawn from these experiments. Gossic acid is derived from gossypol hexamethyl ether, and apogossypolic acid from apogossypol hexamethyl ether. The difference between gossic and apogossypolic acids is merely a single carboxyl group. Since gossypol has two aldehyde groups and apogossypol none, and since the oxidation products are obtained by not dissimilar reactions, it is a reasonable speculation that one of the aldehyde groups in the gossypol hexamethyl ether accounts for the carboxyl group which is present in gossic acid and which is not found in apogossypolic acid anhydride.

The dihydroxy compounds (V and VI) both give a green color with ferric chloride indicative of two ortho hydroxyls. These compounds are oxidized by blowing air through the alkaline solutions. Upon acidification of the oxidized solutions they both yield the same red crystalline compound, which has the formula $C_9H_{10}O_4$, and which appears to be a quinone, since it can be reduced with sodium hydrosulfite and the colorless solution thus obtained can be reoxidized by shaking in air.

Experimental

Trimethyl Ester of Hydrolyzed Gossic Acid.—A solution of 0.100 g. of gossic acid in 5 cc. of 10% aqueous sodium hydroxide was prepared by warming for a few minutes on the steam-bath and then cooling in an ice–salt mixture. The cooled solution was acidified carefully with dilute hydrochloric acid and extracted a number of times with ether. The ether extracts were combined and washed with cold water. To this solution was added an ether solution of diazomethane from 0.5 g. of nitrosomethyl urea. The reaction mixture was allowed to stand overnight at room temperature, then washed with dilute sodium hydroxide. The ether was evaporated and the residue purified by crystallization from petroleum ether (30–60°), m. p. 70–71°.

Anal. Calcd. for $C_{17}H_{22}O_8$: C, 57.6; H, 6.21. Found: C, 57.56; H, 5.92.

Demethylation of Gossic Acid.—A suspension of 0.15 g. of gossic acid was refluxed very gently with 5 cc. of constant boiling hydrobromic acid for twenty to twenty-five minutes. The material dissolved in a short time and at the end of the reaction the solution had only a light yellow color. The reaction mixture was diluted with water, neutralized with sodium carbonate, acidified to congo red with dilute sulfuric acid, and extracted with ether. The ether was evaporated and the residue crystallized from acetone–petroleum ether (b. p. 60–110°). Long colorless needles formed, m. p. 140–141°.

Anal. Calcd. for $C_{12}H_{10}O_7$: C, 54.2; H, 3.76; mol. wt., 266. Found: C, 54.43; H, 3.80; mol. wt. (Rast), 280.

This product gave a green color with alcoholic ferric chloride, and a very light yellow color when dissolved in cold concentrated sulfuric acid. The material dissolved easily in 10% aqueous sodium hydroxide to give a light yellow solution, which became bright red upon shaking with air.

Action of Diazomethane on Demethylated Gossic Acid.—To an ether solution of 0.10 g. of the demethylated gossic acid was added an ether solution of diazomethane from 0.15 g. of nitrosomethyl urea. The reaction mixture was allowed to stand overnight at room temperature, then the ether was evaporated and the residue purified by sublimation at 15 mm., followed by crystallization from petroleum ether (b. p. 30–60°); white needles, m. p. 106°. The mixed melting point gave no lowering with the ester of gossic acid previously described.

Oxidation of Demethylated Gossic Acid.—A solution of 0.10 g. of the demethylated gossic acid in 5 cc. of 10%

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(3) Adams and Butterbaugh, THIS JOURNAL, 60, 2174 (1938).

aqueous sodium hydroxide was oxidized by blowing a stream of air through it. The alkaline solution was at first a bright yellow, changing to a deep orange, and finally to a bright red. After nine hours the solution was acidified with dilute sulfuric acid and the flocculent precipitate filtered, washed, and dried. The residue was purified by sublimation at 15 mm., and subsequent crystallization from benzene; large red plates, m. p. 179–181°.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.5; H, 5.49. Found: C, 59.56; H, 5.55.

Sodium hydrosulfite causes the red color to disappear from an aqueous alkaline solution of the compound; on shaking in the air the red color reappears immediately.

Decarboxylation of Demethylated Gossic Acid.—To a solution of 0.20 g. of demethylated gossic acid in 0.8 cc. of dry quinoline was added 0.1 g. of copper bronze. The reaction mixture was heated in a Wood's metal bath at 160–165°. At this temperature there was a vigorous evolution of gas.

When the evolution of gas ceased, the tube was cooled and the reaction mixture diluted with ether. The ether solution was filtered and washed a number of times with dilute hydrochloric acid. The ether was evaporated and the residue purified by sublimation at 15 mm. It crystallized from ether–petroleum ether (b. p. 60–110°) in white plates, m. p. 165–166°.

Anal. Calcd. for $C_{11}H_{10}O_6$: C, 59.5; H, 4.52. Found: C, 59.62; H, 4.40.

The compound gave a green color with alcoholic ferric chloride. It dissolved in aqueous alkali to a yellow solution which changed to red on standing. It was soluble in water and a spontaneous evaporation formed long needles.

Oxidation of Demethylated Decarboxylated Gossic Acid.—Air was blown through a solution of 0.10 g. of demethylated decarboxylated gossic acid in 5 cc. of 10% aqueous sodium hydroxide for nine hours. The material dissolved to give a yellow solution which quickly turned to a bright red on passing through the air.

The solution was acidified with dilute sulfuric acid and extracted with ether. The ether was evaporated and the residue purified by sublimation and crystallization from benzene, m. p. 179–181°. It was shown by mixed melting point to be identical with the product obtained by the alkaline–air oxidation of the demethylated gossic acid.

Diazomethane on Demethylated Decarboxylated Gossic Acid; Apogossypolic Acid Anhydride.—To a solution of 0.10 g. of the demethylated decarboxylated gossic acid in 10 cc. of ether was added an ether solution of diazomethane from 0.15 g. of nitrosomethyl urea. The reaction mixture was allowed to stand at room temperature overnight.

The ether was evaporated and the residue purified by sublimation at 15 mm., followed by crystallization from petroleum ether (b. p. 30–60°); white needles, m. p. 93–94°. The compound gave no depression in melting point when mixed with apogossypolic acid anhydride.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.60; $2OCH_3$, 24.8. Found: C, 62.1; H, 5.39; OCH_3, 23.6.

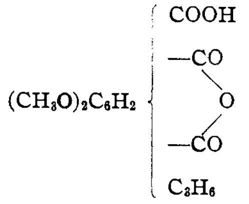
A solution of 0.050 g. of this product in 10% aqueous sodium hydroxide was cooled in an ice-bath and carefully acidified with dilute sulfuric acid. The suspension that formed was extracted with ether, the ether extract dried and evaporated. The residue was crystallized from petroleum ether (b. p. 30–60°), m. p. 170–171° with decomposition. This compound gave no depression in melting point when mixed with *apogossypolic* acid.

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.3; H, 5.97; neut. equiv., 134. Found: C, 58.31; H, 6.24; neut. equiv., 134.

On sublimation at 15 mm. dehydration takes place with formation of apogossypolic acid anhydride as shown by melting point and mixed melting point.

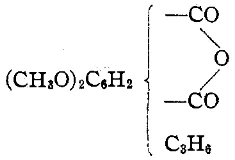
Apogossypolic acid was very stable to alkaline permanganate and was recovered unchanged even on long refluxing.

Summary

Gossic acid, 

$(CH_3O)_2C_6H_2\left\{\begin{array}{l} COOH \\ -CO \\ \quad\ \ \diagdown \\ \qquad O \\ \quad\ \ \diagup \\ -CO \\ C_3H_6 \end{array}\right.$

, obtained by oxidation of gossypol hexamethyl ether has been degraded through (1) demethylation with hydrobromic acid followed by (2) heating with quinoline and copper bronze and subsequent (3) methylation with diazomethane. The final product proved to be apogossypolic anhydride,



$(CH_3O)_2C_6H_2\left\{\begin{array}{l} -CO \\ \quad\ \ \diagdown \\ \qquad O \\ \quad\ \ \diagup \\ -CO \\ C_3H_6 \end{array}\right.$

, the product obtained by oxidation of apogossypol hexamethyl ether. It appears likely that the carboxyl group in gossic acid is produced from an aldehyde group in gossypol.

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