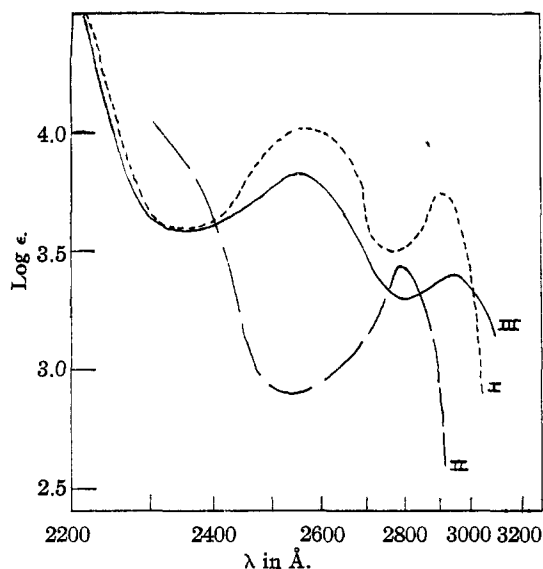


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol.<sup>1</sup> XIV. Apogossypolic AcidBY ROGER ADAMS, R. C. MORRIS, D. J. BUTTERBAUGH<sup>2</sup> AND E. C. KIRKPATRICK<sup>2</sup>

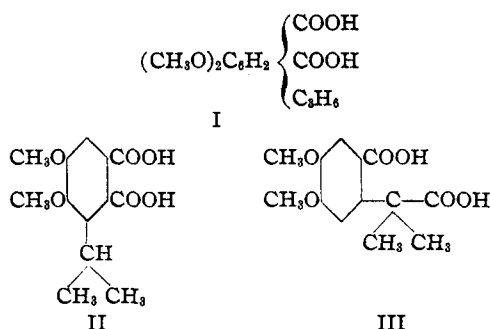
Apogossypolic acid<sup>1,3</sup> which can be obtained from gossypol hexamethyl ether by oxidative and degradation reactions and from apogossypol hexamethyl ether by oxidation has the formula shown in I. The possible position or positions for the  $C_3H_5$  residue have been discussed previously.<sup>3</sup>



I, Veratric acid; II, homoveratric acid; III, decarboxylated apogossypolic acid.

Fig. 1.

The two most likely structural formulas are assumed to be II and III.



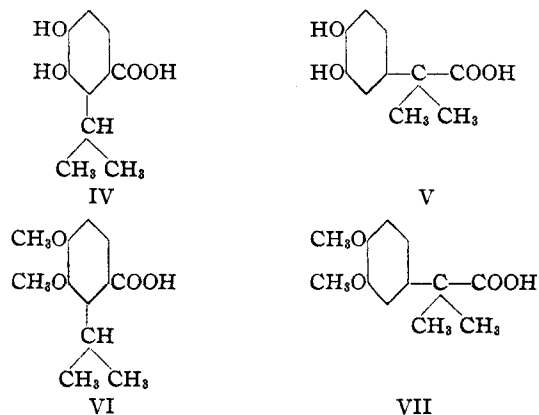
By extended boiling with hydrobromic acid, two methoxys are converted to hydroxyls and one

(1) For previous paper in this field see Adams and Morris, *THIS JOURNAL*, **60**, 2188 (1938).

(2) Portions of theses submitted in partial fulfillment of the degree of Doctor of Philosophy by D. J. Butterbaugh, Chemical Foundation Fellow 1935-1938, and E. C. Kirkpatrick, Solvay Process Fellow, 1936-1938.

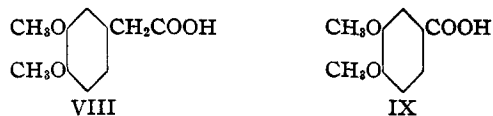
(3) Adams and Butterbaugh, *THIS JOURNAL*, **60**, 2174 (1938).

molecule of carbon dioxide is lost. The compound thus produced is postulated as IV or V. Upon treatment of this substance with diazomethane, methylation of the hydroxyl and car-



boxyl groups occurs and upon saponification the dimethoxy acid (VI or VII) results. The fact that the ester saponifies with reasonable ease is in favor of structure VI, for esters of the type of the acid shown in VII saponify only with great difficulty. This monobasic acid (VI or VII) is surprisingly resistant to oxidation and no satisfactory results were obtained after repeated experiments. Moreover, the carboxyl from compound IV or V could not be eliminated by any of the usual procedures which decarboxylate 1,2-dihydroxy-4-benzoic acid.

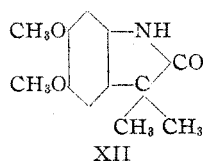
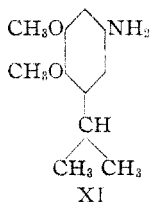
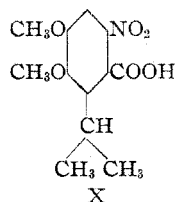
The absorption spectra of homoveratric acid (VIII) and of veratric acid (IX) were compared with that of compound VI or VII. The results are shown in Fig. 1. It is clearly apparent that



the absorption spectra of veratric acid and the acid from gossypol resemble each other closely and differ from that of homoveratric acid. Formula V, therefore, was assumed to be that of decarboxylated apogossypolic acid. The presence of the isopropyl group ortho to the carboxyl may account for the difficulty in eliminating the carboxyl in compound IV. The difficulty with which the compound apparently is

oxidized may be explained by the hindrance of the isopropyl group by ortho substituents.

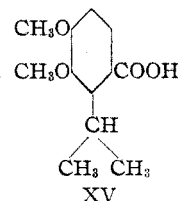
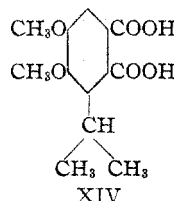
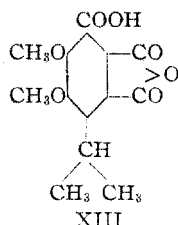
Apogossypolic acid reacts with nitric acid and a carboxyl group is replaced by a nitro. Two alternative structures, based on formula V, are possible but compound X is the more likely because oxidation of the nitro compound failed and oxidation might have been expected if the nitro were ortho to the isopropyl group. This replacement is analogous to that reported for the



substitution of the carboxyl group in veratric acid by a nitro group.<sup>4</sup> Upon reduction of the mononitromonocarboxylic acid (X), an amino compound was formed which was purified by sublimation. The product proved to be not the expected amino acid but an amine (XI) due to loss of carbon dioxide. A lactam (XII) undoubtedly would have resulted if the structure of the apogossypolic acid was III. The decarboxylation of the amino compound upon sublimation resembles the reaction of *o*-aminobenzoic acid under similar conditions. These facts leave little doubt that the  $C_3H_7$  is present in the molecule as a propyl or isopropyl substituent in the benzene ring. It cannot be present as two groups, an ethyl and methyl, because apogossypolic acid may be formed from gossic acid which contains in the ring two methoxys and three carboxyls and hence only a single position for the  $C_3H_7$  residue is available. The group is probably isopropyl since experimental evidence indicated that isopropyl alcohol was lost in the conversion of apogossypol hexamethyl ether to desapogossypol hexamethyl ether.

It is true that the experimental facts available do not allow a conclusive deduction concerning the relative positions of the methoxyl, isopropyl, and carboxyl groups in apogossypolic acid. However, indirect evidence adduced from the study

of the various degradation products of gossypol and apogossypol is very helpful<sup>5</sup> and practically limits the structures of gossic acid to XIII, apogossypolic acid to XIV and decarboxylated apogossypolic acid to XV. The absolute proof of these must await synthesis.



### Experimental

**Action of Hydrobromic Acid on Gossic Acid, Apogossypolic Acid or Apogossypolic Acid Anhydride.**—The same product was obtained by the action of constant boiling hydrobromic acid on gossic acid, apogossypolic acid or its anhydride. Since from a preparative standpoint gossic acid is the most convenient raw material, the detailed directions below involve this product. The procedure for the other compounds is exactly the same except that only two hours of boiling with hydrobromic acid instead of four is necessary.

A suspension of 0.10 g. of gossic acid was refluxed for four hours with 5 cc. of constant boiling hydrobromic acid. At the end of this time the reaction mixture was poured into a beaker. On cooling there separated a precipitate of light pink crystals. The product was filtered and purified by sublimation and crystallization from benzene or toluene. It formed colorless plates, m. p. 216–217°. The product may be heated until it distills and is recovered unchanged.

*Anal.* Calcd. for  $C_{16}H_{12}O_4$ : C, 61.2; H, 6.12. Found: C, 61.21; H, 6.55.

The compound gave a green color with alcoholic ferric chloride. A solution of the compound in dilute aqueous sodium hydroxide rapidly becomes yellow and on standing longer changes to deep orange.

**Diazomethane on Demethylated Decarboxylated Apogossypolic Acid.**—To a solution of 0.02 g. of the demethylated decarboxylated apogossypolic acid in ether was added an ether solution of diazomethane. The reaction was allowed to stand overnight at room temperature. The ether solution was then washed with cold 2% aqueous sodium hydroxide and evaporated. The residue was purified by sublimation and then crystallization from petroleum ether (b. p. 30–60°); colorless prisms, m. p. 106–107°.

*Anal.* Calcd. for  $C_{15}H_{10}O_4$ : C, 65.6; H, 7.56. Found: C, 65.42; H, 7.20.

**Saponification of the Methyl Ester of Decarboxylated Apogossypolic Acid.**—A suspension of 0.10 g. of the ether was refluxed with 10% aqueous sodium hydroxide until solution was complete. The reaction mixture was then cooled, acidified with dilute sulfuric acid, and extracted with ether. The ether was evaporated and the residue

(4) Zincke and Franke, *Ann.*, **293**, 177 (1896). See also Wegscheider and Klemenc, *Monatsh.*, **31**, 740 (1910); Rossin, *ibid.*, **12**, 493 (1891).

(5) See papers VII–XIII of this series.

purified by sublimation followed by crystallization from benzene; colorless plates, m. p. 167–169°.

*Anal.* Calcd. for  $C_{12}H_{16}O_4$ : C, 64.4; H, 7.15. Found: C, 64.85; H, 7.42.

**Action of Dilute Nitric Acid on Apogossypolic Acid.**—A mixture of 0.15 g. of apogossypolic acid, 3 cc. of concentrated nitric acid and 9 cc. of water was refluxed for two hours. Upon cooling, fine white crystals separated. These were purified by crystallization from cyclohexane, m. p. 155–158°; yield 0.105 g.

*Anal.* Calcd. for  $C_{12}H_{16}O_4N$ : C, 53.55; H, 5.58; N, 5.21; neut. equiv., 269. Found: C, 53.79; H, 5.75; N, 5.19; neut. equiv., 268.

**Reduction of the Nitric Acid Product of Apogossypolic Acid.**—The product just described was reduced with Raney nickel and hydrogen under 2.5 atm. pressure in ethanol solution. The product was purified by twice subliming at 25 mm.; white crystals, m. p. 74–76°, that turn dark after standing a few hours in air.

*Anal.* Calcd. for  $C_{11}H_{17}O_2N$ : C, 67.7; H, 8.72; N, 7.18. Found: C, 67.84; H, 8.62; N, 6.96.

This material was insoluble in dilute aqueous sodium hydroxide but soluble in 5% aqueous hydrochloric acid. It diazotized with nitrous acid and the solution gave a red color on treatment with a solution of  $\beta$ -naphthol.

**Acetylation of the Amine.**—A mixture of 30 mg. of the amine just described, 2 cc. of acetic anhydride and 50 mg. of fused sodium acetate was refluxed gently for thirty minutes. After cooling, the excess acetic anhydride was decomposed by the addition of three to four volumes of water. The solution was evaporated to dryness under a stream of air and the amine acetate extracted from the sodium acetate by means of ether. From this extract a

colorless oil was obtained which crystallized after standing for two to three hours. Purification of this crystalline material was accomplished by two sublimations at a bath temperature of 100–125° (18 mm.). This was followed by a dilute acid wash and by a third sublimation; white crystals, m. p. 85–86°.

*Anal.* Calcd. for diacetate,  $C_{15}H_{21}O_4N$ : C, 64.52; H, 7.53; N, 5.02. Found: C, 64.73; H, 7.49; N, 5.11.

### Summary

Apogossypolic acid is decarboxylated and demethylated by the action of hydrobromic acid. The product, upon methylation with diazomethane and subsequent saponification gives a monobasic acid, decarboxylated apogossypolic acid. A discussion of the structure of this latter product is given.

Apogossypolic acid is converted to a mononitro monocarboxylic acid by the action of nitric acid. The nitro compound upon reduction followed by sublimation gives an aromatic amine containing no carboxyl group. This must be a dimethoxy *n*- or isopropyl aminobenzene. Its structure and the analogous compounds from gossypol are discussed.

The absorption spectrum of decarboxylated apogossypolic acid is similar to that of veratric and dissimilar to homoveratric acid.

URBANA, ILLINOIS

RECEIVED JUNE 27, 1938

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

## Structure of Gossypol. XV.<sup>1</sup> An Interpretation of its Reactions

BY ROGER ADAMS, R. C. MORRIS, T. A. GEISSMAN, D. J. BUTTERBAUGH AND E. C. KIRKPATRICK

A large number of reactions of gossypol and of its degradation products have been studied. As the result of this accumulation of experimental evidence, it is now possible to formulate deductively a reasonable structure for the gossypol molecule. The purpose of this communication is to correlate and interpret the physical and chemical properties of gossypol in terms of this structure.

The absorption spectra of gossypol<sup>2</sup> and its derivatives and the formation of many of its

degradation products are indicative of a molecule containing two naphthalene nuclei connected either directly or through an alkylene chain. The formula for gossypol must be essentially symmetrical and probably completely so, for an even number of moles of reagent reacts in every instance. The diverse and unusual reactions of gossypol as well as the absorption spectra show every indication that the molecule is tautomeric.

The postulated structure of gossypol is represented by Ia with Ib and Ic representing two possible tautomeric forms.

The structural configuration of gossypol will be discussed and formulas will be assigned for all the significant derivatives and degradation products.

(1) For previous paper in this series, see Adams, Morris, Butterbaugh and Kirkpatrick, *THIS JOURNAL*, **60**, 2191 (1938).

(2) Adams and Kirkpatrick, *ibid.*, **60**, 2180 (1938); Marchlewski, *J. prakt. Chem.*, **60**, 84 (1899); Grünbaumowa and Marchlewski, *Biochem. Z.*, **286**, 295 (1936); Zamyshlyayeva and Krivich, *J. Gen. Chem.*, (U. S. S. R.), **7**, 1989 (1937).