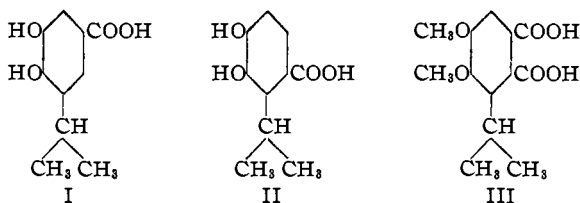


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Structure of Gossypol. XX.¹ Synthesis of 1,2-Dihydroxy-3-isopropyl-5-benzoic Acid

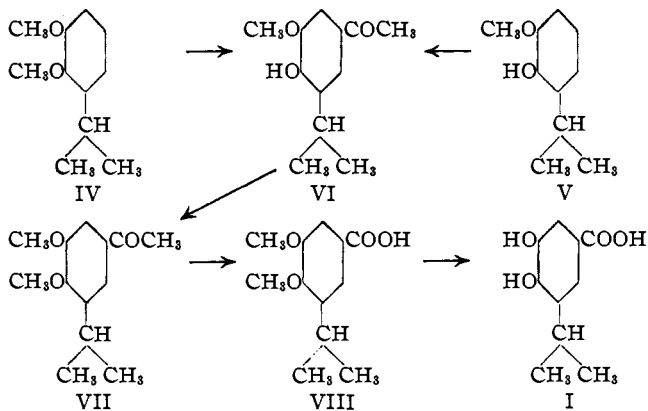
BY ROGER ADAMS, MADISON HUNT AND B. R. BAKER

Based on the postulated structure of apogossypolic acid (III) the dihydroxymonocarboxylic acid obtained by the action of hydrobromic acid on gossic acid or apogossypolic acid must have the carboxyl group in the 4- or the 5-position (I or II). The correctness of this assumption has been confirmed by the synthesis of the 6-acid reported in the previous paper;¹ this was not the same as the one obtained from natural sources.



The 1,2-dihydroxy-3-isopropyl-5-benzoic acid (I) has now been prepared by two unambiguous methods and the compound proved to be identical with the acid derived from gossic or apogossypolic acid (III). The establishment of this structure confirms again the 1,2-dihydroxy-3-isopropyl arrangement of groups in gossypol and at the same time lends support to the formula postulated for apogossypolic acid (III).

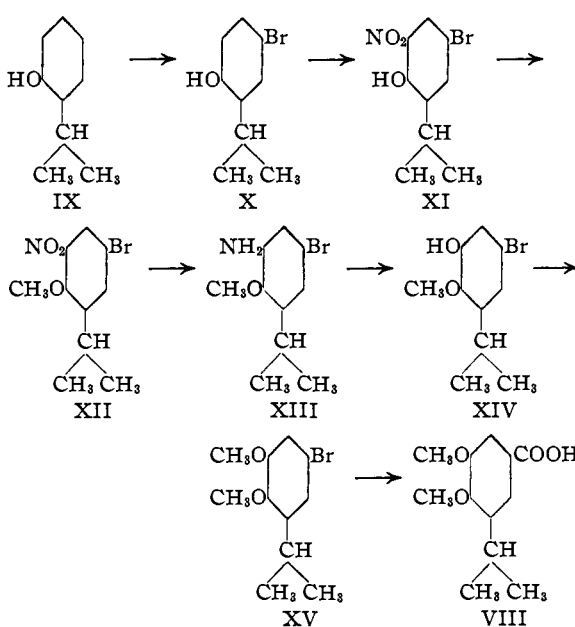
The first synthesis used in the preparation of the 5-acid (I) consisted in treating 1,2-dimethoxy-3-isopropylbenzene (IV) or 1-methoxy-2-hydroxy-3-isopropylbenzene (V) with acetic anhydride



and anhydrous aluminum chloride; the product in each instance was 1-methoxy-2-hydroxy-3-

isopropyl-5-acetophenone (VI). Upon methylation, this compound gave 1,2-dimethoxy-3-isopropyl-5-acetophenone (VII) which was oxidized to the 1,2-dimethoxy-3-isopropyl-5-benzoic acid (VIII). Demethylation of this last substance gave 1,2-dihydroxy-3-isopropyl-5-benzoic acid (I).

The assumption that the acetyl group in compound VI is in the 5-position is justified after consideration of the fact that in compounds analo-



gous to IV and V, the substituent has been shown always to enter that position.² The correctness of this has been proved by synthesizing the acid (VIII) by a second method which leaves no doubt about the position of the carboxyl group. The series of reactions is shown (IX-XV). The structure of compound XI had been established previously with certainty,³ thus fixing the position of the carboxyl group in compound VIII.

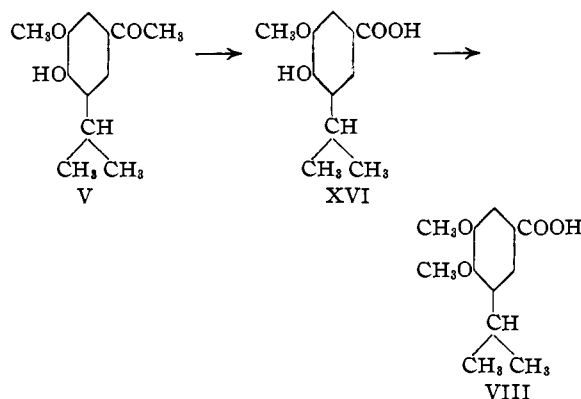
The dimethyl ether (VIII), m. p. 115°, obtained by the two methods just described as an intermediate in the synthesis of the dihydroxymonocarboxylic acid (I) proved not to be

(1) For previous paper see Adams and Hunt, THIS JOURNAL, 61, 1132 (1939).

(2) Cain and Simonsen, *J. Chem. Soc.*, 105, 156 (1914); Majima and Okazaki, *Ber.*, 49, 1482 (1916).

(3) Fileti, *Gazz. chim. ital.*, 16, 121 (1886).

identical with the substance reported previously⁴ to have this structure, m. p. 166–167°, and prepared by the methylation with diazomethane of the dihydroxymonocarboxylic acid derived from gossic acid. It has now been demonstrated that the compound previously in hand was the 1-methoxy-2-hydroxy-3-isopropyl-5-benzoic acid (XVI) formed by incomplete methylation⁵ of the dihydroxy acid. The dihydroxy isopropyl carboxylic acid derived from gossic or apogossypolic acid has been methylated again, this time first with diazomethane followed by dimethyl sulfate and alkali. The dimethyl ether thus obtained has a melting point of 115° and is identical with the synthetic product (VIII). The 1-methoxy-2-hydroxy-3-isopropyl-5-benzoic acid (XVI) was synthesized from 1-methoxy-2-hydroxy-3-isopropyl-5-acetophenone (VI) by the action of iodine and alkali. It melted at 166–167° and was identical with the compound previously reported as the dimethyl ether.



The establishment of the structure of this degradation product of gossypol adds further support to the postulated formulas for gossypol and its derivatives.

Experimental

1 - Methoxy - 2 - hydroxy - 3 - isopropyl - 5 - acetophenone.—To a cold solution of 6 g. of 1-methoxy-2-hydroxy-3-isopropyl-5-acetophenone

(4) Adams, Morris, Butterbaugh and Kirkpatrick, *THIS JOURNAL*, **60**, 2191 (1938).

(5) The synthesis of the 1,2-dimethoxy-3-isopropyl-5-benzoic acid by methylation of the corresponding dihydroxy acid, as previously described,⁴ involved unexpected difficulties. The isolation of pure methyl dimethoxyisopropylbenzoate in a crystalline state was attempted only once for analytical purposes. In general, the oily crude methyl ester from the action of excess of diazomethane on the dihydroxy isopropyl benzoic acid was saponified directly. Apparently complete methylation of this latter compound did not take place as readily as might be expected and consequently the crude product was a mixture of the mono- and dimethyl ethers which on saponification gave a mixture of the mono- and dimethyl ethers of the acid. The monomethyl ether was the more readily isolated and thus led to a misinterpretation of results. The quantities of material available at that time excluded a proper study of the compound.

droxy-3-isopropylbenzene⁶ in 75 cc. of carbon disulfide were added 14.5 g. of anhydrous aluminum chloride and 4.5 cc. of acetic anhydride. The mixture was stirred at room temperature for one hour and then decomposed with cold dilute hydrochloric acid. The product was extracted with ether and dried over anhydrous magnesium sulfate. After removal of the ether the oily residue was crystallized from benzene-petroleum ether (b. p. 60–110°). One recrystallization gave 4.3 g. (57%) of pure product, m. p. 116° (corr.).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.75. Found: C, 69.12; H, 7.63.

The same product was obtained by a similar procedure using 1,2-dimethoxy-3-isopropylbenzene. One methoxyl was hydrolyzed during the reaction.

1,2 - Dimethoxy - 3 - isopropyl - 5 - acetophenone.—A solution of 3 g. of 1-methoxy-2-hydroxy-3-isopropyl-5-acetophenone in 14.5 cc. of *N* sodium methylate was treated with 1.8 g. of dimethyl sulfate. The mixture was heated to boiling and two additional portions of 14.5 cc. of *N* sodium methylate and 1.8 g. of dimethyl sulfate were added successively. The solution was then evaporated nearly to dryness and the residue dissolved in water. The aqueous solution was extracted with ether. The product distilled at 135–137° (2 mm.); n_D^{20} 1.5279, d_4^{20} 1.066; yield 2 g. (86%).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.17. Found: C, 70.46; H, 8.25.

1,2 - Dimethoxy - 3 - isopropyl - 5 - benzoic Acid.—A mixture of 1.75 g. of 1,2-dimethoxy-3-isopropyl-5-acetophenone, 25 cc. of water, 10 cc. of acetone, 2.8 g. of potassium permanganate and 5 g. of sodium carbonate was refluxed for two hours. A few drops of alcohol was added to remove the excess permanganate and the mixture was filtered. The aqueous solution was acidified with hydrochloric acid and extracted with ether. The ether solution was, in turn, extracted with aqueous sodium bicarbonate and the aqueous layer thus obtained acidified with hydrochloric acid. The oil was extracted with ether and after evaporation of the solvent the residue was heated to boiling with excess hydrogen peroxide. On cooling, the product crystallized readily and was purified by recrystallization from dilute ethanol; yield 0.4 g. (23%) of acid, m. p. 115° (corr.).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.26; H, 7.20. Found: C, 64.31; H, 7.12.

1 - Nitro - 2 - methoxy - 3 - isopropyl - 5 - bromobenzene.—The preparation of 1-nitro-2-hydroxy-3-isopropyl-5-bromobenzene was carried out by the following series of reactions. (1) *o*-Isopropenylphenol⁷ was made by the action of methylmagnesium iodide upon methyl salicylate and distillation of the product at ordinary pressure to eliminate water, b. p. 201–205° (750 mm.) (Béhal and Tiffeneau report 204°); yield 80%. (2) *o*-Isopropenylphenol was reduced to *o*-isopropylphenol by means of Raney nickel and hydrogen at 2–3 atm., b. p. 207–208° (same as previously reported); yield 78%. (3) *o*-Isopropylphenol was brominated at low temperature in carbon tetrachloride solution to give 2-hydroxy-3-isopropyl-5-

(6) Adams, Hunt, and Morris, *THIS JOURNAL*, **60**, 2972 (1938).

(7) Béhal and Tiffeneau, *Bull. soc. chim.*, [4] **3**, 315 (1908).

bromobenzene, b. p. 150–152° (20 mm.) (Fileti³ reports boiling point of 250°); yield 82%. (4) 2-Hydroxy-3-isopropyl-5-bromobenzene was nitrated by fuming nitric acid in glacial acetic acid at low temperatures to give 1-nitro-2-hydroxy-3-isopropyl-5-bromobenzene,³ m. p. 29–30° (Fileti reports 33°); yield 95%.

To a solution of 4.7 g. of sodium in 50 cc. of absolute ethanol was added a solution of 51 g. of 1-nitro-2-hydroxy-3-isopropyl-5-bromobenzene in 200 cc. of dry toluene. After addition of 20 cc. of dimethyl sulfate, the deep red solution was refluxed for one and one-half hours. Addition of 7 cc. more of dimethyl sulfate and refluxing for one hour served to complete the reaction. The solution was washed with aqueous sodium hydroxide and with water, the toluene solution dried and the toluene distilled. The product was purified by distillation, yellowish oil, b. p. 137–139° (3 mm.), n_{20}^D 1.5589, d_{20}^{20} 1.388; yield 32 g. (59%).

Anal. Calcd. for $C_{10}H_{12}O_3NBr$: N, 5.12. Found: N, 5.03.

1 - Amino - 2 - methoxy - 3 - isopropyl - 5 - bromobenzene.—The nitro compound just described was reduced with hydrogen and Raney nickel in ethanol solution. The product, a yellowish oil, boiled at 134–137° (3 mm.), n_{20}^D 1.5672, d_{20}^{20} 1.334; yield 25 g. (90%). The amine rapidly turned dark so was converted to its hydrochloride by dissolving it in dilute hydrochloric acid. The hydrochloride salt separated and was purified by crystallization from a mixture of chloroform and ether; white felted needles, m. p. 171–174° (corr.).

Anal. Calcd. for $C_{10}H_{16}ONBrCl$: N, 4.99. Found: N, 5.22.

1,2 - Dimethoxy - 3 - isopropyl - 5 - bromobenzene.—To a cold solution of 14 g. of 1-amino-2-methoxy-3-isopropyl-5-bromobenzene in 70 cc. of water and 10 cc. of concentrated sulfuric acid was added 5 g. of sodium nitrite in 14 cc. of water. After filtration from a small amount of tarry material, the excess nitrous acid was destroyed with urea and the solution was added dropwise into a boiling solution of 60 cc. of concentrated sulfuric acid, 60 g. of anhydrous sodium sulfate and 60 cc. of water. The phenol produced was steam distilled as it formed. The temperature of the solution was kept under 150° by gradual addition of water. The addition took one hour and boiling was continued for an hour longer with the temperature under 170°. The distillate was extracted with ether; the ether solution, in turn, was extracted with 10% aqueous sodium hydroxide and after acidification again extracted with ether. After removal of the solvent, the crude phenol was dissolved in methanol and methylated according to the method of Perkin,⁸ colorless oil, b. p. 120–122° (2 mm.); n_{20}^D 1.5376, d_{20}^{20} 1.307; yield 2.5 g.

Anal. Calcd. for $C_{11}H_{16}O_2Br$: C, 50.96; H, 5.79. Found: C, 51.22; H, 5.86.

1,2 - Dimethoxy - 3 - isopropyl - 5 - benzoic Acid.—To a dry ether solution of 1 g. of 1,2-dimethoxy-3-isopropyl-5-bromobenzene was added an excess of magnesium turnings and then gradually 2 cc. of ethyl bromide. After standing for twenty hours, the solution was decanted from the magnesium and excess of dry ice was added.

After two hours, the addition compound was decomposed by pouring into dilute hydrochloric acid. The ether was evaporated from the aqueous layer; the oil remaining solidified on cooling. The crude acid was filtered and dried on a clay plate; yield 0.2 g. After recrystallization from benzene–petroleum ether (b. p. 60–110°) it melted at 115–116°. Mixed melting point with the acid prepared by the oxidation of 1,2-dimethoxy-3-isopropyl-acetophenone showed no depression.

1,2 - Dimethoxy - 3 - isopropyl - 5 - benzoic Acid from Gossic Acid.—To a solution in dry ether of 70 mg. of pure 1,2-dihydroxy-3-isopropyl-5-benzoic acid obtained from gossic acid⁴ was added a large excess of diazomethane in dry ether. After standing overnight the ether was evaporated and the residue dissolved in 5 cc. of methanol. To this was added 2 cc. of *N* sodium methylate and 0.2 cc. of dimethyl sulfate. The mixture was refluxed for ten minutes and then treated twice more with equal amounts of sodium methylate and dimethyl sulfate. The methanol was evaporated and the residue refluxed with 7 cc. of 10% aqueous sodium hydroxide solution for two hours. After cooling, filtering and acidification the organic acid was extracted with ether and the ether solution in turn extracted with aqueous sodium bicarbonate. After acidification, the product separated and was filtered, dried and purified by sublimation; white crystals, m. p. 113–114°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.26; H, 7.20. Found: C, 63.95; H, 7.23.

The mixed melting point of this product and that obtained by synthesis showed no depression.

1,2 - Dihydroxy - 3 - isopropyl - 5 - benzoic Acid.—A mixture of 3 cc. of 48% hydrobromic acid and 0.1 g. of pure synthetic 1,2-dimethoxy-3-isopropyl-5-benzoic acid was refluxed for one hour. The solution was cooled and the product which separated was removed by filtration. The material was recrystallized from ether–petroleum ether (b. p. 60–110°). A yield of 0.055 g. of compound melting at 215° (corr.) was obtained.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.19; H, 6.17. Found: C, 60.93; H, 6.25.

A mixed melting point with the product obtained by the action of hydrobromic acid on gossic or apogossypolic acid gave no depression.

1 - Methoxy - 2 - hydroxy - 3 - isopropyl - 5 - benzoic Acid.—To a solution of 6 g. of potassium hydroxide in 150 cc. of water at 0° was added 4 g. of iodine, then 0.5 g. of 1-methoxy-2-hydroxy-3-isopropyl-5-acetophenone. After standing for five minutes at 0°, the solution was filtered and 1 g. of sodium bisulfite added. The mixture was then acidified with hydrochloric acid, extracted with ether and the ether solution extracted with aqueous sodium bicarbonate solution. The alkaline solution thus obtained, deposited the desired acid upon acidification. It was purified by recrystallization from ether–petroleum ether (b. p. 60–110°). A yield of 0.025 g. of product, m. p. 167–169°, was obtained.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.83; H, 6.71. Found: C, 62.49; H, 6.72.

The product gave no depression of the melting point when mixed with the methylation product, m. p. 166–

(8) Perkin, *J. Chem. Soc.*, **89**, 1649 (1906).

167°, previously described erroneously as the dimethyl ether.⁴

This same product was obtained by a second procedure which was less satisfactory. By bromination of 1-methoxy-2-hydroxy-3-isopropylbenzene, 1-methoxy-2-hydroxy-3-isopropyl-5-bromobenzene was prepared. This product was benzyloxy to 1-methoxy-2-benzyloxy-3-isopropyl-5-bromobenzene which in turn was converted through the Grignard reagent and carbonation to 1-methoxy-2-benzyloxy-3-isopropyl-5-benzoic acid. Upon debenylation, the 1-methoxy-2-hydroxy-3-isopropyl-5-benzoic acid was obtained, m. p. 168–169° (corr.), and identical with the product prepared as just described.

1 - Methoxy - 2 - hydroxy - 3 - isopropyl - 5 - bromobenzene.—To an ice-cold solution of 1 g. of 1-methoxy-2-hydroxy-3-isopropylbenzene in 10 cc. of carbon tetrachloride was added with stirring a solution of 0.3 cc. of bromine in 10 cc. of carbon tetrachloride over a period of one hour. The solvent was then evaporated and the residue distilled, b. p. 113–114° (2 mm.), d_{20}^{20} 1.322; n_D^{20} 1.5490; yield 1.4 g. (95%).

Anal. Calcd. for $C_{12}H_{13}O_2Br$: C, 49.1; H, 5.32. Found: C 49.46; H, 5.49.

1 - Methoxy - 2 - benzyloxy - 3 - isopropyl - 5 - bromobenzene.—A mixture of 1.4 g. of 1-methoxy-2-hydroxy-3-isopropyl-5-bromobenzene, 0.8 cc. of benzyl chloride and 6 cc. of *N* sodium methylate was refluxed for two hours. The solution was poured into water and all volatile matter distilled with steam. To the cooled residual solution (25 cc.) was added 20 cc. of 10% aqueous sodium hydroxide and extracted with ether. The ether solution was washed with aqueous sodium hydroxide, dried and evaporated. The product quickly crystallized and was recrystallized from ethanol and then sublimed, m. p. 72–73° (corr.); yield 0.8 g. (43%).

Anal. Calcd. for $C_{17}H_{19}O_2Br$: C, 60.90; H, 5.67. Found: C, 61.08; H, 5.91.

1 - Methoxy - 2 - hydroxy - 3 - isopropyl - 5 - benzoic Acid.—To a dry ether solution of 0.55 g. of 1-methoxy-2-benzyloxy-3-isopropyl-5-bromobenzene was added an excess of magnesium and 1 cc. of ethyl bromide. After the initial reaction, the mixture was refluxed overnight and then carbonated with an excess of dry ice. After acidification with hydrochloric acid, the ether solution was separated and extracted with saturated aqueous sodium bicarbonate. The latter extract was acidified, extracted with ether, the ether solution dried and evaporated. The residue was refluxed ten minutes with 2 cc. of ethanol and 2 cc. of concentrated hydrochloric acid. The reaction mixture was poured into water, saturated with ammonium sulfate and extracted with ether. After drying and evaporation of the ether, the residue was sublimed at 130° (2 mm.). It was then recrystallized from ether-petroleum ether (b. p. 60–110°), m. p. 168–169° (corr.). It proved to be identical with the same product obtained in other ways. The yield was very small due to incomplete formation of the Grignard reagent.

(1,2 - Dimethoxy - 4 - phenyl) - dimethylcarbinol.—To a Grignard solution prepared from 2.5 g. of magnesium, 15 g. of methyl iodide and 70 cc. of dry ether, was added a dry ether solution of 10 g. of methyl veratrate. The mixture was cooled during the addition and then warmed a half hour on the steam-bath. Decomposition with ammonium chloride solution and working up the product gave 9.0 g. of a light brown solid which after purification from ether-petroleum ether formed white crystals, m. p. 78°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.34; H, 8.18. Found: C, 67.46; H, 8.12.

The same product could be obtained from 1,2-dimethoxy-4-acetophenone and methylmagnesium iodide but in poorer yield.

The product on attempted distillation under diminished pressure decomposed with loss of water and formation of a heavy viscous liquid, possibly a polymer.

This product was prepared as an intermediate for the synthesis of $(CH_3O)_2C_6H_3-C(CH_3)_2COOH$ before it was recognized that this structure was an unlikely one.

Summary

1. The product obtained by the vigorous treatment of gossic or apogossypolic acid with hydrobromic acid has been shown to be 1,2-dihydroxy-3-isopropyl-5-benzoic acid.

2. This compound has been synthesized by two methods. The first consisted in converting 1-methoxy-2-hydroxy-3-isopropylbenzene to 1-methoxy-2-hydroxy-3-isopropyl-5-acetophenone, methylation to 1,2-dimethoxy-3-isopropyl-5-acetophenone, oxidation to 1,2-dimethoxy-3-isopropyl-5-benzoic acid and demethylation. The second method started with 1-nitro-2-hydroxy-3-isopropyl-5-bromobenzene, a product the constitution of which previously had been proven. Methylation, reduction to the amine, replacement of the amino group by hydroxyl and methylation gave 1,2-dimethoxy-3-isopropyl-5-bromobenzene, which was then converted to the Grignard reagent and carbonated to the 5-acid.

3. The compound of m. p. 166–167° reported in a previous paper as 1,2-dimethoxy-3-isopropyl-5-benzoic acid and derived from natural sources was shown actually to be 1-methoxy-2-hydroxy-3-isopropyl-5-benzoic acid. The latter was synthesized from 1-methoxy-2-hydroxy-3-isopropyl-5-acetophenone by the action of iodine and aqueous alkali.