propyl groups are replaced by nitro groups. The same compound also may be produced directly by nitration of gossypolone tetramethyl ether.

2. Gossypolonic acid tetramethyl ether by a similar procedure is converted into a derivative with the isopropyl groups replaced by nitro groups.

3. Just as gossypolone tetramethyl ether can be oxidized to the corresponding carboxylic acid by means of dilute nitric acid, so can the nitration product of gossypol hexamethyl ether or gossypolone tetramethyl ether be converted into the corresponding nitration product of gossypolonic acid tetramethyl ether.

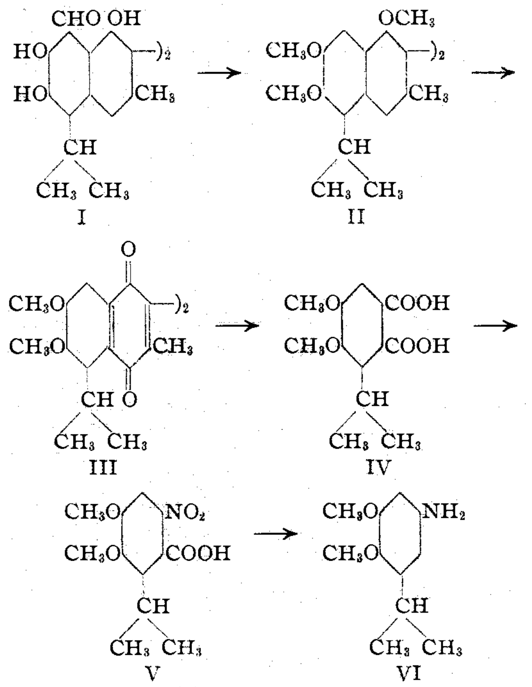
URBANA, ILLINOIS RECEIVED OCTOBER 17, 1938

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

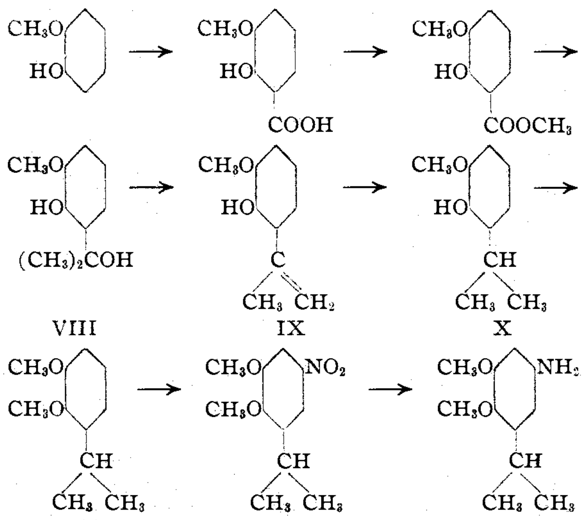
Structure of Gossypol. XVIII. Synthesis of 1,2-Dimethoxy-3-isopropyl-5-aminobenzene, a Degradation Product of Gossypol[1]

BY ROGER ADAMS, MADISON HUNT AND R. C. MORRIS

Structure I has been assigned to gossypol.[2] By the action of concentrated alkali, gossypol loses two aldehyde groups and is converted into the unstable apogossypol. The latter product is stabilized by the formation of the hexamethyl ether. Apogossypol hexamethyl ether (II) upon oxidation with chromic acid gives apogossypolone tetramethyl ether (III) which is further oxidized with potassium permanganate to apogossypolic acid (IV). Nitration of this last product results in a mononitro monocarboxylic acid (V) which upon reduction and sublimation of the product gives a decarboxylated amine (VI).[3] The amine is converted to a diacetyl derivative by the action of acetic anhydride and sodium acetate. Whether the 5-carboxyl or the 4-carboxyl in apogossypolic acid (IV) is replaced by a nitro group was not certain so that the amine which was assigned structure VI might have an isomeric formula, with the amino group in the 4-position.



The compound 1,2-dimethoxy-3-isopropyl-5-aminobenzene has now been synthesized by methods leaving little doubt as to its complete structure and no doubt as to the relative positions of the two dimethoxy and the isopropyl groups. It proved to be identical with the compound VI obtained by degradation of gossypol as shown by melting point and mixed melting points of the two amines and their acetyl derivatives. The synthesis employed is shown by the following series of reactions



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[1] For previous paper see Adams, Geissman and Morris, THIS JOURNAL, 60, 2970 (1938).

[2] Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, *ibid.*, 60, 2193 (1938).

[3] Adams, Morris, Butterbaugh and Kirkpatrick, *ibid.*, 60, 2191 (1938).

The structure of compound XI, 1,2-dimethoxy-3-isopropylbenzene, cannot be questioned. The 5-position for the nitro group in compound XII was assigned after consideration of the nitration of the analogous 1,2-dimethoxy-3-methylbenzene which was proven in two ways to give the 1,2-dimethoxy-3-methyl-5-nitro derivative.[4] The amino group in compound VI is, therefore, in the 5-position.

The identity of the synthetic product, 1,2-dimethoxy-3-isopropyl-5-aminobenzene, and the gossypol degradation product allows important conclusions to be drawn concerning the gossypol molecule. It confirms (1) the presence of isopropyl groups, and (2) the relative positions of two hydroxyls to the isopropyl groups in the gossypol molecule.

If these established facts are considered in conjunction with the method of preparation and relationship of gossic to apogossypolic acid, it may be deduced that the aldehyde groups in gossypol are in the same rings as the isopropyl groups and indeed *para* to these groups. The lactone formation in gossypol derivatives containing the aldehyde groups oxidized to carboxylic acid groups makes positive the presence of hydroxyl groups in the positions *peri* to the aldehyde groups. Thus, proof of the substituent groups in the 1-, 5-, 6-, 7- and 8-positions of the two naphthalene nuclei of gossypol is conclusive.

Experimental

3-Methoxysalicylic Acid.—To a mole equivalent of sodium in absolute ethanol, 124 g. of guaiacol was added. The alcohol was removed by distillation and the residue washed with dry ether. The solid product was dried *in vacuo* at room temperature. The solid sodium guaiacolate was finely ground and heated for eight hours under pressure at 115° with excess of carbon dioxide. The reaction mixture was dissolved in 400 cc. of water and the solution extracted with ether to remove unchanged guaiacol. The aqueous layer was acidified with hydrochloric acid, and the product separated. The yield was 55 g. (33%) which melted low and required a crystallization from water to bring it up to 150° (corr.). The yield depends to a large extent on the dryness of the sodium guaiacolate. Heyden reported a melting point of 148–150°.[5]

Methyl 3-Methoxysalicylate.—The esterification was carried out by refluxing for twelve hours a mixture of 25 g. of crude 3-methoxysalicylic acid, 65 cc. of methanol and 5.7 cc. of concentrated sulfuric acid. Dilution with ether and extraction of the ether solution with aqueous sodium bicarbonate, then distillation, gave essentially a quantitative yield of product, b. p. 134–136° (2 mm.). The distilled product solidified and was purified by crystallization from dilute methanol, m. p. 61° (corr.). Fritsch reported a melting point of 63°.[6]

Dimethyl-(3-methoxy-2-hydroxyphenyl)-carbinol (VIII).—A dry ether solution of 22 g. of methyl 3-methoxysalicylate was added with cooling to a cooled solution of Grignard reagent prepared from excess methyl chloride and 13.9 g. of magnesium. The reaction mixture was then refluxed for three hours. It was decomposed with dilute acetic acid and the product extracted with ether. After washing with water and aqueous 5% sodium bicarbonate, the ether solution was dried over anhydrous magnesium sulfate and the ether removed. The solid residue was purified by crystallization from benzene–petroleum ether (b. p. 60–110°) and formed white needles, m. p. 126° (corr.); yield, 10.5 g. (48%).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.89; H, 7.75. Found: C, 65.86; H, 7.80.

1-Methoxy-2-hydroxy-3-isopropenylbenzene (IX).—Upon heating 5 g. of the dimethyl-(3-methoxy-2-hydroxyphenyl)-carbinol for ten minutes at 195–200°, water was lost. The product distilled at 122–124° (14 mm.); $n^{20}\text{D}$ 1.5518; d^{20}_{20} 1.072; yield, 4.2 g. (93%).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.13; H, 7.37. Found: C, 73.14; H, 7.50.

1-Methoxy-2-hydroxy-3-isopropylbenzene (X).—A solution of 4 g. of 1-methoxy-2-hydroxy-3-isopropenylbenzene in 25 cc. of 95% ethanol was hydrogenated at 2–3 atm. pressure with Raney nickel as a catalyst. The product distilled at 123–125° (8 mm.); $n^{20}\text{D}$ 1.5203; d^{20}_{20} 1.049; yield, 3.8 g. (94%).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.25; H, 8.49. Found: C, 72.38; H, 8.50.

1,2-Dimethoxy-3-isopropylbenzene (XI).—To a solution of 2.3 g. of 1-methoxy-2-hydroxy-3-isopropylbenzene in 14 cc. of normal sodium methylate was added 1.3 cc. of dimethyl sulfate. The solution was refluxed for ten minutes and then treated with a second similar portion of sodium methylate and dimethyl sulfate and the heating repeated. After evaporating almost to dryness, the reaction mixture was treated with 15 cc. of water and extracted with ether. After extraction of the ether solution twice with 10% aqueous sodium hydroxide, the solvent and then the product was distilled; b. p. 119–121° (24 mm.); $n^{20}\text{D}$ 1.5068; d^{20}_{20} 1.019; yield, 2.1 g. (84%).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.28; H, 8.95. Found: C, 73.34; H, 8.99.

1,2-Dimethoxy-3-isopropyl-5-nitrobenzene (XII).—To a cold solution of 1 g. of 1,2-dimethoxy-3-isopropylbenzene in 8 cc. of glacial acetic acid was added 0.24 cc. of nitric acid (sp. gr. 1.50). The mixture was kept at 0° for thirty minutes and then was poured into 35 cc. of ice water. The oil which separated was extracted with ether and the ether solution washed with bicarbonate solution. After drying and removing the ether, the residue was dissolved in methanol. Upon cooling in an ice–salt mixture, the product separated and was recrystallized from methanol, yellow crystals, m. p. 53° (corr.); yield, 0.85 g. (68%).

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[4] (a) Cain and Simonsen, *J. Chem. Soc.*, **105**, 156 (1914); (b) Majima and Okazaki, *Ber.*, **49**, 1482 (1916).

[5] Heyden, *ibid.*, **23**, 418 (1890).

[6] Fritsch, *Ann.*, **301**, 352 (1898).

Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.64; H, 6.72; N, 6.22. Found: C, 58.91; H, 6.60; N, 6.36.

1,2-Dimethoxy-3-isopropyl-5-aminobenzene (VI).—The corresponding nitro compound was reduced in absolute ethanol solution at 2–3 atm. with Raney nickel as catalyst. The product was purified by sublimation, white crystals, m. p. 75° (corr.). The yield was 0.055 g. from 0.1 g. of nitro compound.

Anal. Calcd. for $C_{11}H_{17}O_2N$: C, 67.70; H, 8.72; N, 7.18. Found: C, 67.55; H, 8.77; N, 7.14.

This substance gave no depression in melting point when mixed with the compound assumed to have this structure and prepared from apogossypolic acid.[3]

1,2-Dimethoxy-3-isopropyl-5-diacetaminobenzene.—The amine was acetylated with acetic anhydride and sodium acetate in an 81% yield. The product was purified by washing the ether solution with 5% hydrochloric acid, evaporation of the solvent and sublimation. It formed white crystals, m. p. 86° (corr.).

Anal. Calcd. for $C_{15}H_{21}O_4N$: C, 64.52; H, 7.53; N, 5.02. Found: C, 64.57; H, 7.41; N, 5.01.

A mixed melting point of this product with the diacetyl derivative of the amine obtained by degradation of apogossypolic acid gave no depression.[3]

1,2-Dimethoxy-3-isopropyldinitrobenzene.—By nitrating 1,2-dimethoxy-3-isopropylbenzene as previously described except that excess nitric acid was used, a dinitro derivative was obtained. It was purified from methanol in yellow crystals, m. p. 106° (corr.).

Anal. Calcd. for $C_{11}H_{14}N_2O_6$: N, 10.31. Found: N, 10.10.

Whether the two nitro groups are both in the benzene ring or one in the ring and the other replacing the tertiary hydrogen of the isopropyl group was not determined. By analogy to the dinitro derivative of 1,2-dimethoxy-3-methylbenzene, it is probable that the two nitro groups occupy the 5-, 6-positions.[4b]

1,2-Dimethoxy-3-isopropyldiaminobenzene.—The reduction of the dinitro compound in absolute ethanol with Raney nickel as catalyst gave a diamine which was purified by sublimation to white crystals, m. p. 75° (corr.). This product was very unstable to atmospheric oxygen and turned brown rapidly.

Anal. Calcd. for $C_{11}H_{18}O_4N_2$: N, 13.13. Found, N, 13.14.

Summary

The synthesis of 1,2-dimethoxy-3-isopropyl-5-aminobenzene has been accomplished. It proved to be identical with the compound prepared from apogossypolic acid by nitration, subsequent reduction and sublimation.

This synthesis confirms the character of the functional groups in the 1-, 5-, 6-, 7- and 8-positions of the naphthalene nuclei in the previously postulated formula for gossypol.

URBANA, ILLINOIS RECEIVED OCTOBER 17, 1938

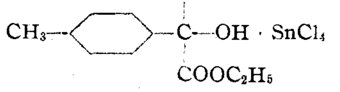
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUW UNIVERSITY]

The Preparation of Substituted Mandelic Acids and their Bacteriological Effects. II

BY J. L. RIEBSOMER, ROBERT BALDWIN, JACK BUCHANAN AND HOWARD BURKETT

It has been shown previously by work in this Laboratory[1,2] that alkyl substituted mandelic acids can be prepared readily from alkyl benzenes and ethyl oxomalonate when treated in the presence of anhydrous stannic chloride or certain other condensing agents. The intermediate condensation products are hydrolyzed and decarboxylated to form the corresponding mandelic acids. The purpose of the present work was to extend the studies reported in the first paper of this series[2] and to point out certain additional observations made on the general reaction mentioned above.

In nearly every case when anhydrous stannic chloride is added to an alkyl benzene–ethyl oxomalonate mixture a thick sticky solid separates out. With the hope that a knowledge of the composition of such a typical solid might contribute to an understanding of the mechanism of the general reaction, the solid which separated when toluene, ethyl oxomalonate and stannic chloride were mixed was purified and analyzed. This solid was very hygroscopic and immediately decomposed when added to water with the production of an oily layer. The aqueous solution gave qualitative tests for tin and chloride. The oily layers when hydrolyzed produced *p*-methylmandelic acid. A quantitative analysis for chloride indicated the compound to be an addition product as follows



$$CH_3-C_6H_4-C(COOC_2H_5)_2-OH \cdot SnCl_4$$

This result is what would be expected from a consideration of the work of Voskresenskaya[3] who showed that the esters of several dibasic acids react with stannic chloride to form similar addition

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[1] Riebsomer, Irvine and Andrews, *Ind. Acad. Sci.*, **47**, in press (1937).

[2] Riebsomer, Irvine and Andrews, THIS JOURNAL, **60**, 1015 (1938).

[3] Voskresenskaya, *C. A.*, **32**, 2551 (1938).