Reaction of Methyl Cativate with Nitrosyl Chloride.—Cold, concentrated hydrochloric acid (0.7 ml.) was added dropwise to a solution of 1 g. of methyl cativate and 1 ml. of amyl nitrite in 5 ml. of chloroform at −60°. The initial yellow color turned to greenish-blue on warming to room temperature, after which time the solvent and excess hydrochloric acid were removed by vacuum distillation without heating. Chromatography of the oily residue in benzene on alumina gave a benzene–ether eluate which crystallized in the receiver after evaporation of the eluent. Recrystallization from aqueous methanol gave 0.64 g. of **methyl iso-(Δ^5)-cativ-7-one oxime**, m.p. 121.5–122°, λ_{max} 246 mμ (log ϵ 4.1); 3.07, 5.77, 6.17 μ.

Anal. Calcd. for $C_{21}H_{35}O_3N$: C, 72.16; H, 10.09; N, 4.01. Found: C, 71.97; H, 10.31; N, 4.24, 3.96.

The crystalline oxime (0.35 g.) was refluxed with 0.27 g. of pyruvic acid in 10 ml. of 50% aqueous acetic acid for 4 hr. The cooled solution was poured into 100 ml. of water, extracted with ether, and the combined extracts were washed with water, 5% aqueous sodium hydroxide solution and water. The ether layer was then evaporated, leaving 0.1 g. of a pale yellow oil which could not be crystallized but which showed expected absorption for a mono-α-, di-β-substituted, α,β-unsaturated ketone, λ_{max} 251 mμ (log ϵ 4.1).[29] Its infrared spectrum showed absorption maxima at 5.77, 6.05 and 6.22 μ.

Ozonization of Cativic Acid.—Ozonizations of cativic acid were generally carried out in ethyl acetate solution at −50° in concentrations varying from 10–20%. Similar results described below were obtained in carbon tetrachloride, chloroform, methanol and *n*-pentane solutions up to 0°. The presence or absence of moisture appeared to have little effect on the course of the reaction which was considered complete when the effluent gases passing through the ozonide solution began to oxidize potassium iodide in saturated aqueous boric acid.

The white, crystalline product which separated from solution during the course of the ozonization in *ca.* 30% yield proved to be quite stable, resisting the action of boiling water or hydrogenolysis in the the presence of Adams catalyst in ethanol at room temperature. It was recrystallized from aqueous methanol to m.p. 137–138° dec.: mol. wt. Rast, 343 (354); neut. equiv., 355 (354).

Anal. Calcd. for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 68.03; H, 9.84.

The substance gave positive starch–iodide, iodoform, Schiff, Tollens tests and negative tetranitromethane reaction. It was soluble in sodium bicarbonate and gave no crystalline oxime derivative. The compound showed no ultraviolet absorption but gave infrared bands at 3.02 (hydroxyl), 5.77 and 5.90 μ (carbonyl).

The mother liquors from the crystalline ozonolysis product were concentrated to an orange, intractable oil. This oil yielded no additional information. Decomposition attempts by treatment of the ozonolysis product with boiling water failed to fragment the molecule as shown by the neutralization equivalent of the oily product (300) and the absence of any neutral, water-soluble or low molecular weight acidic products. Attempts to isolate easily volatile degradation products were likewise unsuccessful.

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(29) Calcd. λ_{max} 249 mμ: L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publ. Corp., New York, N. Y., 1949, p. 192.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Structure and Reactions of Gossypol. IV. The Synthesis of Desapogossypol Hexamethyl Ether[1,2]

BY DAVID A. SHIRLEY AND WALTER L. DEAN[3]

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1,1′,6,6′,7,7′-Hexamethoxy-3,3′-dimethyl-2,2′-binaphthyl has been synthesized and found to be identical with desapogossypol hexamethyl ether, a degradation product of gossypol.

The extensive work of Professor Roger Adams and students on the structure of gossypol, the principal pigment of cottonseed, led to the postulation of structure X for this molecule. While a large amount of evidence was accumulated in support of this structure, an uncertainty remained in the relationship of the positions of the methyl groups and binaphthyl linkage to the positions of the other groups. An alternative possibility was the binaphthyl linkage at the 3,3′-position and the methyl groups in the 2,2′-positions. It was the objective of this research to synthesize desapogossypol hexamethyl ether (VIII) in order to answer this question as well as to provide additional general information on the structure of gossypol. After completion of this work,[4] there was reported the synthesis of a compound corresponding to the one postulated for apogossypol hexamethyl ether (IX) and the identity of the synthetic product with that obtained from gossypol.

The preparation of 3-methyl-6,7-dimethoxy-1-tetralone (I) has been reported in an earlier paper from this Laboratory[5] and by other workers.[6–8] The tetralone was converted to the 2,2-dibromo derivative II in essentially quantitative yield. Dehydrobromination of II with pyridine gave the naphthol III in about 40% yield and methylation in about 70% yield produced 1,6,7-trimethoxy-2-bromo-3-methylnaphthalene. It was found best to carry out the dehydrobromination and methylation in one step using sodium methoxide and methyl sulfate in methanol. This produced V directly from II in about 70% yield. Oxidation of the naphthol III with potassium nitrosyl disulfonate produced the quinone IV which showed an ultraviolet absorption spectrum characteristic of the 1,4-naphthoquinone system. Direct formation of the Grignard reagent of V could not be accomplished, and use of the entrainment method with a large ex-

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(2) Preceding paper: D. A. Shirley and W. C. Sheehan, *J. Org. Chem.*, **21**, 251 (1956).

(3) From a dissertation presented in December, 1955, by Walter L. Dean to the University of Tennessee in partial fulfillment of the requirements for the Ph.D. degree.

(4) J. D. Edwards and J. L. Cashaw, THIS JOURNAL, **78**, 3224 (1956).

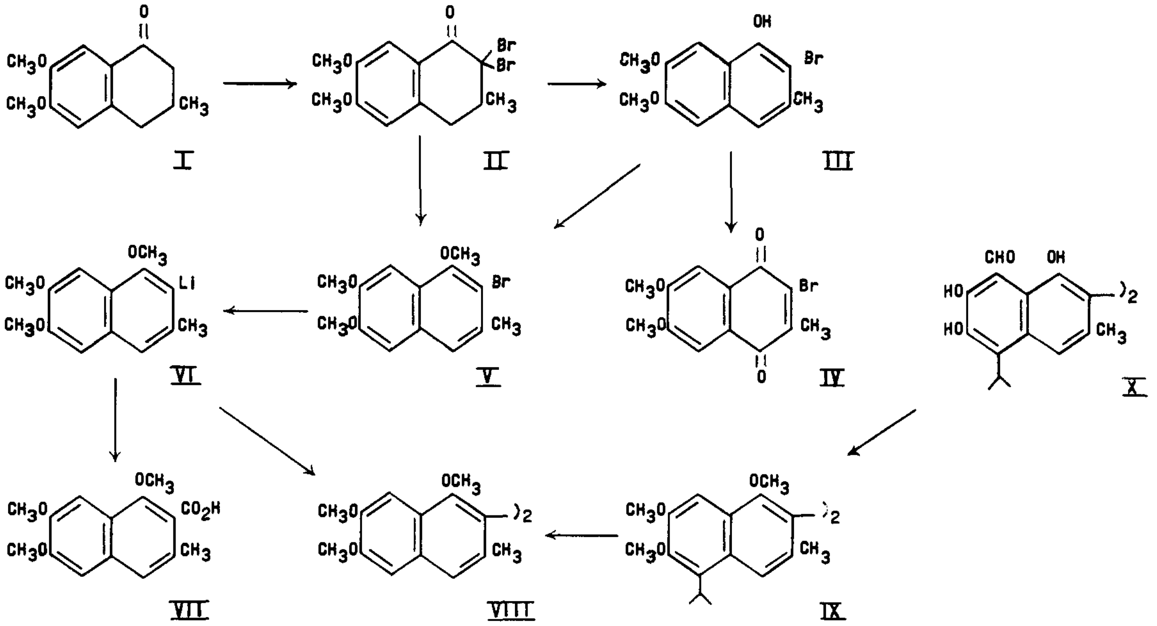
(5) D. A. Shirley and W. L. Dean, *ibid.*, **77**, 6077 (1955).

(6) J. D. Edwards and J. L. Cashaw, *ibid.*, **76**, 6188 (1954).

(7) R. D. Haworth and J. R. Atkinson, *J. Chem. Soc.*, 807 (1938).

(8) W. Borsche and J. Neimann, *Ann.*, **502**, 264 (1933).

cess of methylmagnesium iodide resulted in only a very low yield of the corresponding carboxylic acid VII on carbonation. Halogen–metal interconversion[9] of V with *n*-butyllithium followed by carbonation gave the acid VII in 82% yield. The organolithium compound VI was treated with anhydrous cobalt(II) bromide[10] to produce the binaphthyl VII in low yield. The synthetic sample was compared with one prepared from gossypol in accordance with the procedure of Adams and Butterbaugh[11] and with a sample kindly provided by Professor Adams. The samples were essentially identical in melting point, mixed melting point, ultraviolet and infrared spectra (KBr disk).



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Experimental[12]

2,2-Dibromo-3-methyl-6,7-dimethoxy-1-tetralone (II).—A solution of 36.3 g. (0.227 mole) of bromine in 150 ml. of chloroform was added over an 8-hour period to a stirred solution of 25.0 g. (0.113 mole) of 3-methyl-6,7-dimethoxy-1-tetralone (I)[5] in 500 ml. of chloroform. The mixture was stirred at room temperature for a further ten hours and the chloroform removed by distillation. The residue was dried *in vacuo* to yield 42.9 g. (99%) of yellow solid, m.p. 148–150° dec. Recrystallization from isopropyl alcohol with little loss of product gave material of m.p. 153–154°. Another crystallization from benzene–ligroin did not raise the melting point.

Anal. Calcd. for $C_{13}H_{14}Br_2O_3$: C, 41.30; H, 3.73; Br, 42.28. Found: C, 41.40; H, 3.81; Br, 42.46, 42.55.

2-Bromo-3-methyl-6,7-dimethoxy-1-naphthol (III).—A mixture of 18.9 g. (0.15 mole) of 2,2-dibromo-3-methyl-6,7-dimethoxy-1-tetralone and 200 ml. of dry toluene was refluxed and stirred under an atmosphere of dry nitrogen until all the solid had dissolved. A solution of 11.8 g. (0.15 mole) of dry pyridine in 38 ml. of toluene was added over an 8-hour period and refluxing in the presence of the inert atmosphere was continued for an additional 11 hours. The mixture was cooled to room temperature and during cooling diluted with 250 ml. of ether to keep the product in solution. The resulting solution was decanted from solid deposited on the walls of the flask. This solid was washed with ether and the combined solutions washed with dilute nitric acid, water and finally with 225 ml. of 0.35 *N* sodium hydroxide. The alkaline extract was acidified with dilute hydrochloric acid with cooling to precipitate a dark-colored solid. The entire mixture was extracted with ether and the extracts washed with water, sodium bicarbonate solution and again with water. The ether solution was then dried over magnesium sulfate and evaporated to dryness to yield 12.1 g. of a dark semi-crystalline solid. Recrystallization from 100 ml. of methanol including a Norite treatment yielded 5.97 g. (40%) of tan solid, m.p. 139–142°. Crystallizations from acetone–ligroin and again from methanol produced white crystals, m.p. 144–145°.

Anal. Calcd. for $C_{13}H_{13}BrO_3$: C, 52.54; H, 4.41; Br, 26.90. Found: C, 52.05, 52.14; H, 4.39, 4.59; Br, 27.40, 27.52.

1,6,7-Trimethoxy-2-bromo-3-methylnaphthalene (V).—The naphthol III was methylated in essential accordance with the procedure described by Smith and Hoehn[13] for the methylation of 2-bromo-3,4-diphenyl-1-naphthol. Evaporation of the ether solution gave 3.24 g. (71%) of light pink crystalline solid, m.p. 93–95°. This was recrystallized from methanol, ether–petroleum ether and isopropyl alcohol to produce white crystals m.p. 93.5–94.5°.

Anal. Calcd. for $C_{14}H_{15}BrO_3$: C, 54.04; H, 4.83; methoxyl, 29.92. Found: C, 53.85; H, 5.02; methoxyl, 29.59.

A mixture of 5.0 g. (0.0132 mole) of 2,2-dibromo-3-methyl-6,7-dimethoxy-1-tetralone (II) in 75 ml. of methanol was heated to boiling and several ml. of a saturated solution of sodium methoxide in methanol was added. The dibromotetralone went into solution on continued heating for 10 to 15 minutes. Methyl sulfate was added slowly with continual stirring until the reaction mixture was acid. About 1 ml. of sodium methoxide solution was added and heating

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(9) R. G. Jones and H. Gilman in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 339.

(10) H. Gilman and M. Lichtenwalter, This Journal, **61**, 957 (1939); M. S. Kharasch and E. K. Fields, *ibid.*, **63**, 2316 (1941); M. S. Kharasch, D. W. Lewis and W. B. Reynolds, *ibid.*, **65**, 498 (1943).

(11) R. Adams and D. J. Butterbaugh, *ibid.*, **60**, 2174 (1938).

(12) Microanalyses were by Galbraith Microanalytical Laboratories of Knoxville, Tenn. All melting points are uncorrected.

(13) L. I. Smith and H. H. Hoehn, This Journal, **61**, 2623 (1939).

and stirring continued until the mixture was alkaline. Approximately 1-ml. quantities of methyl sulfate and methanolic sodium methoxide were added alternately in the same manner as before until about 10 ml. of each had been used. The resulting solution was poured into a slurry of ice and water. The precipitated pink solid was collected and recrystallized from methanol. There was obtained 6.1 g. (74%) of light tan solid melting at 94–95°.

1,6,7-Trimethoxy-3-methyl-2-naphthoic Acid (VII). A. From the Grignard Reagent.—Approximately one-fifth of a solution of 0.37 ml. (*ca.* 6.0 mmoles) of methyl iodide in 5 ml. of ether was allowed to run into 486 mg. (20 mg. atoms) of magnesium. To the remainder of the solution was added a solution of 311 mg. (1.0 mmole) of 1,6,7-trimethoxy-2-bromo-3-methylnaphthalene in 5 ml. of dry benzene and the resulting solution added to the Grignard reagent dropwise. An additional 0.37 ml. of methyl iodide in 7 ml. of ether was added over a period of several hours. The mixture was then stirred for 24 hours at room temperature and carbonated by pouring over crushed solid carbon dioxide in the usual manner. After hydrolysis with water and hydrochloric acid, the organic layer was separated and combined with ether extracts of the aqueous layer. The resulting solution was then extracted with 0.5 *N* sodium hydroxide and the aqueous extract acidified to yield 66 mg. of acidic tan solid. This was recrystallized from water–ethanol and then from water–methanol to yield 15 mg. of nearly colorless needles, m.p. 178–180°.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.11; H, 5.96.

B. From the Halogen–Metal Interconversion Reaction.—A solution of 311 mg. (1.0 mmole) of 1,6,7-trimethoxy-2-bromo-3-methylnaphthalene in 5 ml. of ether was cooled to −30° under an atmosphere of nitrogen. To this solution was added with stirring 2 ml. of an ether solution containing 1.3 mmoles of *n*-butyllithium.[14] The mixture was held at −30 to −10° for ten minutes and then carbonated. After hydrolysis with water, the aqueous layer was separated and acidified with hydrochloric acid to precipitate a white crystalline solid (281 mg.) melting at 174.5–179° dec. This was recrystallized from benzene–petroleum ether to yield 156 mg., m.p. 176.5–179° dec., and a second crop of 70 mg., m.p. 178–180° dec. The total yield of recrystallized product was 82%. A mixture m.p. with the acid isolated in A above showed no depression.

Coupling of *o*-Anisyllithium.—A sample of 1.87 g. (0.01 mole) of *o*-bromoanisole in 25 ml. of ether was treated at −25° with 15.6 ml. of *n*-butyllithium solution containing 0.01 mole of organometallic. Approximately 0.1 g. of anhydrous cobalt(II) bromide was added which initiated a vigorous exothermic reaction. The mixture was stirred for ten minutes then carbonated and hydrolyzed in the usual manner. The ether layer was evaporated and the residual solid recrystallized from 15 ml. of petroleum ether (b.p. 90–110°). There was obtained 0.27 g. (25%) of light tan crystals, m.p. 153–154°. The melting point of 2,2′-dimethoxybiphenyl is reported to be 154°[15] and 155°.[16]

1,1′,6,6′,7,7′-Hexamethoxy-3,3′-dimethyl-2,2′-binaphthyl (VIII).—A solution of 312 mg. (1.0 mmole) of 1,6,7-trimethoxy-2-bromo-3-methylnaphthalene, m.p. 92–94°, in 5 ml. of ether was stirred and cooled to −20° under a nitrogen atmosphere while 1.5 millimoles of *n*-butyllithium in 1.9 ml. of ether was added by means of a pipet. After stirring for six minutes at −20° to −30°, approximately 100 mg. of anhydrous cobalt(II) bromide was added. Stirring was continued as the temperature of the reaction mixture was allowed to come to room temperature over a period of 25 minutes. Stirring was continued at room temperature for 20 minutes longer and then under reflux for 15 minutes. The reaction mixture was carbonated with solid carbon dioxide and hydrolyzed with water as in B above. The ether layer was separated and evaporated to yield 103 mg. of a dark semi-solid. One recrystallization from methanol–water gave 34 mg. of crystals, m.p. 93–98°, and another recrystallization from ether–petroleum ether gave 24 mg. (10%) of fine tan crystals, m.p. 98.5–100°. A mixture m.p. of this substance with a sample of 1,6,7-trimethoxy-3-methylnaphthalene,[5] m.p. 99.5–100.5°, showed no depression.

The aqueous layer contained some solids insoluble in both the ether and water layers and all of this was extracted with several portions of benzene. The benzene extracts were concentrated to 0.5 ml. and diluted with 1 ml. of methanol. On further concentration 8 mg. (3.5%) of fine white crystals precipitated. These melted at 293–295°, $\lambda_{\max}^{\text{MeOH}}$ 249 mμ, log ϵ 5.06; 314 mμ, log ϵ 3.71; 328 mμ, log ϵ 3.80. A mixture melting point with a sample of desapogossypol hexamethyl ether,[17] m.p. 293.5–295.5°, or one, m.p. 293–296°, provided by Professor Adams showed no depression.

The aqueous solution from the benzene extraction above was filtered and acidified. The precipitated product weighed 102 mg. (37% yield) and melted at 175–179°. A mixture m.p. with 1,6,7-trimethoxy-3-methyl-2-naphthoic acid, m.p. 178–180°, showed no depression.

The desapogossypol hexamethyl ether prepared above showed an infrared absorption band at 12.52 μ with a larger transmission than that shown by either sample prepared from gossypol, although all other bands were similar. The coupling reaction was repeated as above except that all the neutral material from the carbonation and hydrolysis steps was dissolved in petroleum ether (b.p. 90–110°) and the solution passed through a 1 × 20 cm. column filled with 60–100 mesh Florisil adsorbent. The column was eluted with mixed solvents of increasing polarity passing from petroleum ether to benzene to chloroform in 10% increment composition changes. Material appearing in the 60% benzene–40% chloroform and 50% benzene–50% chloroform fractions was recrystallized two times from petroleum ether (b.p. 80–110°) and a small amount of benzene to produce light tan crystals, m.p. 294–296°. This product was obtained in no better yield than the one described above and appeared to have the same physical properties, but the infrared spectrum was similar to the spectrum of desapogossypol hexamethyl ether from gossypol in all respects including the 12.52 μ band.

2-Bromo-3-methyl-6,7-dimethoxy-1,4-naphthoquinone (IV).—2-Bromo-3-methyl-6,7-dimethoxy-1-naphthol (297 mg. or 1.0 millimole) was oxidized with potassium nitrosyl disulfonate[18] in general accordance with the procedure of Teuber and Gotz[19] for the oxidation of 1-naphthol to 1,4-naphthoquinone. There was obtained 160 mg. (51%) of quinone, m.p. 209–215°. One recrystallization from acetic acid and three from acetone yielded orange needles, m.p. 232–232.5°, $\lambda_{\max}^{\text{MeOH}}$ 272–278 mμ, log ϵ 4.45; 299 mμ, log ϵ 4.13; 352 mμ, log ϵ 3.38.

Anal. Calcd. for $C_{13}H_{11}BrO_4$: C, 50.18; H, 3.56. Found: C, 50.34; H, 3.62.

3-Methyl-6,7-dimethoxy-1,4-naphthoquinone.—Oxidation of 218 mg. of 3-methyl-6,7-dimethoxy-1-naphthol[5] as described above gave 110 mg. (47%) of orange-yellow needles, m.p. 211–212.5°. Three recrystallizations from acetone raised the m.p. to 213–214°. A determination of the ultraviolet absorption spectrum showed $\lambda_{\max}^{\text{MeOH}}$ 269–275 mμ, log ϵ 4.50; 349 mμ, log ϵ 3.38.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.21; H, 5.21. Found: C, 67.01; H, 5.26.

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[16] P. Jannasch and E. Kolitz, *Ber.*, **31**, 1745 (1898).

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