

catalyst at 200°. As we have previously noted, slight variations in the preparation of the catalyst or in the condition of the experiment resulted in aromatization to ethylbenzene, which was subsequently oxidized by potassium permanganate to benzoic acid.

When 1-ethynyl-2,2,6-trimethylcyclohexanol is passed over the aluminum oxide catalyst under a variety of conditions, we could never isolate more than insignificant quantities of acetylenic derivatives. The main product consists of 1-ethyl-2,3,6-trimethylbenzene (ethylpseudocymene) accompanied by a variety of hydroaromatic compounds.<sup>2</sup>

When 1-ethynyltrimethylcyclohexanol was treated in boiling benzene with an excess of phosphorus pentoxide, the principal product was again 1-ethyl-2,3,6-trimethylbenzene.

1-Ethyl-2,3,6-trimethylbenzene had been prepared by a completely different route.<sup>3</sup> The identity of our product with the authentic sample was confirmed by conversion to the dinitro derivative, reduction of the latter to the diamino derivative, and subsequent formation of the benzimidazole by the action of formic acid on the diamino derivative. The dinitro, the diamino and benzimidazole derivatives were identical in their properties with the compounds from the literature.

The hydrogenation of the acetylenic group, employing aluminum oxide or phosphorus pentoxide, which are not hydrogenating catalysts, appears to us to be good evidence that we have in both instances predominantly an intramolecular hydrogen migration. This parallels the deductions of Levina<sup>4</sup> on the aromatization of unsubstituted cyclohexylacetylene derivatives by a platinized charcoal catalyst.

2,2,6-Trimethylcyclohexanone and 1-ethynyl-2,2,6-trimethylcyclohexanol were prepared as previously described.<sup>2</sup>

**1-Ethyl-2,3,6-trimethylbenzene (Ethylpseudocymene).** Preparation A.—Ninety-five grams of the above acetylenic carbinol was distilled at 18 mm. pressure over an aluminum oxide catalyst (prepared as previously indicated) maintained at ca. 220°. The vapors were collected and carefully fractionated: fraction 1, 6.5 g., b.p. 28–63° (11 mm.),  $n_D^{25}$  1.442–1.4833; fraction 2, 8.5 g., b.p. 63–90° (11 mm.),  $n_D^{25}$  1.4833–1.5040; fraction 3, 43.5 g. (1-ethyl-2,3,6-trimethylbenzene), b.p. 90–93° (12 mm.),  $n_D^{25}$  1.5100–1.5115; reported<sup>3</sup> b.p. 87° (10 mm.), 95° (16 mm.),  $n_D^{25}$  1.5115,  $n_D^{25}$  1.5106.

Preparation B.—A solution of 25 g. of the above carbinol in 100 ml. of dry benzene was added to 8.5 g. of phosphorus pentoxide. The mixture refluxed for one hour and after decomposition with water the organic layer was fractionated. A yield of 9 grams of 1-ethyl-2,3,6-trimethylbenzene, b.p. 94–95° (15 mm.),  $n_D^{25}$  1.5110, was obtained.

**4,5-Dinitro-1-ethyl-2,3,6-trimethylbenzene.**—The above ethylpseudocymene (from either of the two preparations) was nitrated following the procedure of Smith and Kiess; the dinitro derivative, after crystallization from alcohol, melted at 80–81°, reported<sup>3</sup> 79–80°.

Reduction of the dinitro compound by stannous chloride in HCl, according to the literature, yielded the corresponding diamino compound of m.p. 84–85° after recrystallization from alcohol, reported<sup>3</sup> 84–85°. Treatment of the diamine with formic acid yielded the benzimidazole derivative of m.p. 210°; reported<sup>3</sup> 206°.

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- (2) Cf. H. Sobotka and J. D. Chanley, *THIS JOURNAL*, **71**, 4136 (1949).  
(3) L. I. Smith and M. A. Kiess, *ibid.*, **61**, 284 (1939).  
(4) R. J. Levina, *Ann. Rept. Chem. Soc.*, **41**, 153 (1944).

## The Structure and Reactions of Gossypol. II.<sup>1</sup> The Synthesis of 1,6,7-Trimethoxy-3-methylnaphthalene, a Prototype of Desapogossypol Hexamethyl Ether<sup>2</sup>

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The extensive work of Roger Adams and his students on the structure of gossypol,<sup>3</sup> the principal pigment in cottonseed, led to a postulated structure of the molecule as shown in one of its tautomeric forms in structure IX. The work by Adams and his co-workers has resulted in a large amount of evidence for the postulated structure including synthesis of several of the degradation products of gossypol. This interpretation of the structure of gossypol has, however, not remained unchallenged.<sup>4</sup>

The degradation product of gossypol synthesized by Adams and co-workers which was most closely related to gossypol itself was desapogossypolone hexamethyl ether (X).<sup>5</sup> As pointed out by Adams and Baker,<sup>5</sup> synthesis of this compound did not establish rigorously the position of the linkage between the two naphthalene rings. An alternative possibility would be a 3,3'-linkage between rings with methyl groups in the 2- and 2'-positions.

We have undertaken to synthesize a compound more closely related to gossypol than desapogossypolone hexamethyl ether, one that would provide additional information on the correctness of structure IX for gossypol, particularly the question of the position of linkage of the two naphthalene rings. Such a compound is desapogossypol hexamethyl ether (VIII). In view of a recent paper by Edwards and Cashaw<sup>6</sup> reporting work of unstated objective but with compounds similar to ours, we have decided to present our preliminary findings.

3-Methyl-6,7-dimethoxy-1-tetralone (IV) was synthesized by the route indicated in Fig. 1. All of the yields were about 70% or above with the exception of the displacement of bromide ion with malonate anion from 1-(3',4'-dimethoxyphenyl)-2-bromopropane. A not unexpected yield of 30–35% has been the maximum obtainable here. The tetralone IV has been obtained by three earlier workers<sup>6–8</sup> by other methods. The melting point of our product agreed with that given by Edwards<sup>6</sup> and by Haworth.<sup>8</sup> Edwards<sup>6</sup> has discussed the probable reason for the different value given by Borsche.<sup>7</sup>

The tetralone was dehydrogenated to 3-methyl-6,7-dimethoxy-1-naphthol (VI) through the bromo-ketone V. Edwards<sup>6</sup> also prepared this naphthol and reported the melting point as 140–142°. Our

(1) Preceding paper, D. A. Shirley and W. C. Sheehan, *THIS JOURNAL*, **77**, 4606 (1955).

(2) A report of work carried out under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act. The contract is being supervised by the Southern Regional Research Laboratory of the Agricultural Research Service.

(3) R. Adams, T. A. Geissman, W. R. Dial and J. T. Fitzpatrick, *THIS JOURNAL*, **63**, 2439 (1941), and earlier papers.

(4) C. H. Boatner, in A. E. Bailey, Editor, "Cottonseed and Cottonseed Products," Interscience Publishers, Inc., New York, N. Y., 1948, p. 240.

(5) R. Adams and B. R. Baker, *THIS JOURNAL*, **63**, 535 (1941).

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

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

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

compound melted at 148.3–149°. We converted the naphthol VI to 1,6,7-trimethoxy-3-methylnaphthalene (VII).

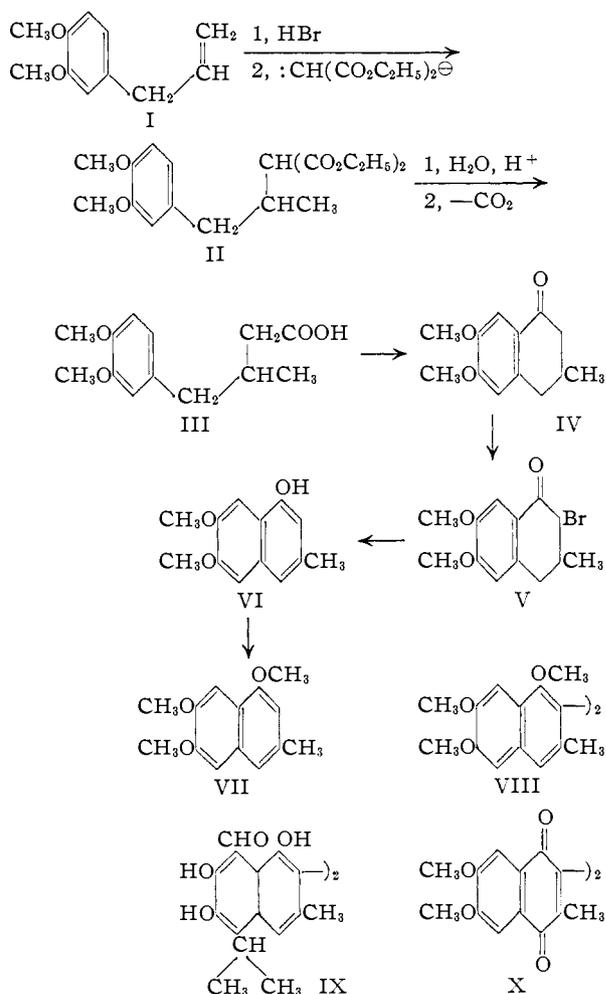


Fig. 1.

Of particular interest at this point in the investigation was a comparison of the ultraviolet absorption spectra of 1,6,7-trimethoxy-3-methylnaphthalene (VII) and desapogossypol hexamethyl ether (VIII). It has been shown<sup>9</sup> in the biphenyl series that four groups substituted in the *ortho* positions of biphenyl destroy the coplanarity of the two rings required for conjugation. In such cases the biphenyl derivative absorbs ultraviolet light as would two molecules of benzene carrying the same substituents. This has been extended into the binaphthyl series<sup>10</sup> with a comparison of the spectra of naphthalene, 1,1'-binaphthyl and 2,2'-binaphthyl. The steric inhibition to free rotation about the bonds joining the two rings in 1,1'-binaphthyl gives to its absorption spectrum a similarity to naphthalene not evident in the more fully conjugated 2,2'-binaphthyl.

The four groups in the positions adjacent to the bond joining the rings in the Adams structure for

(9) L. W. Pickett, G. F. Walter and H. France, *THIS JOURNAL*, **58**, 2296 (1936).

(10) R. A. Friedel, M. Orchin and L. Reggel, *ibid.*, **70**, 199 (1948).

desapogossypol hexamethyl ether (VIII) should offer sufficient steric hindrance to coplanarity of the rings to produce a close relationship in ultraviolet spectra to 1,6,7-trimethoxy-3-methylnaphthalene. We prepared a sample of desapogossypol hexamethyl ether by Adams' method<sup>11</sup> and determined its absorption spectrum. The comparison with the naphthalene derivative is shown in Fig. 2. The curve for 1,6,7-trimethoxy-3-methylnaphthalene is plotted as  $\log 2\epsilon$  in order to compare approximately equal numbers of molecules. We anticipated a closer resemblance of the two curves and feel that the differences could indicate that the postulated structure for desapogossypol hexamethyl ether is incorrect. For example, a point of attachment of the two rings at the 3,3'-positions with methyl groups at the 2,2'-positions would allow more freedom of rotation around the bond joining the rings and this might lead to the observed differences in the curves.

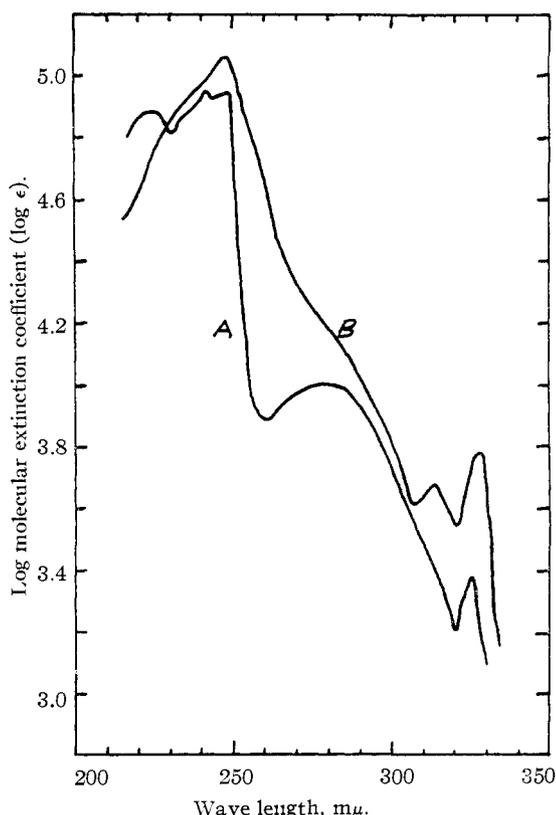


Fig. 2.—Ultraviolet absorption spectra in methanol: Curve A, 1,6,7-trimethoxy-3-methylnaphthalene (plotted as  $\log 2\epsilon$ ); curve B, desapogossypol hexamethyl ether.

In order to obtain more information we are attempting the conversion of the naphthol VI to the binaphthyl VIII in order to compare the product with desapogossypol hexamethyl ether.

We should like to acknowledge the help and encouragement of Drs. F. H. Thurber and A. M. Altschul of the Southern Regional Research Laboratory and a gift of polyphosphoric acid from the Victor Chemical Co.

(11) R. Adams and D. J. Butterbaugh, *ibid.*, **60**, 2178 (1938).

Experimental<sup>12,13</sup>

**1-(3',4'-Dimethoxyphenyl)-2-bromopropane.**—A solution of 356 g. (2.0 moles) of methyleugenol<sup>14</sup> in 700 ml. of sodium-dried petroleum ether (b.p. 35–60°) was stirred and held in the range of –7 to –3° by cooling in an ice-salt-bath while hydrogen bromide was passed into the solution. A fritted glass gas dispersal tube was used and the hydrogen bromide was passed in for seven hours. A saturated aqueous solution (600–700 ml.) of sodium bromide was added cautiously with continued stirring and cooling. Sufficient water was added to bring the precipitated sodium bromide back into solution. The top layer of petroleum ether was separated. There remained two layers and the top brown layer was separated with the aid of some ether. The resulting solution was dried and distilled. The fraction boiling at 125° with a pressure variation of 0.6 to 0.8 mm. weighed 363 g. corresponding to a 70% yield,  $n_D^{25}$  1.5546.

*Anal.* Calcd. for  $C_{11}H_{14}BrO_2$ : C, 50.99; H, 5.84; Br, 30.84;  $OCH_3$ , 23.95. Found: C, 50.90; H, 5.88; Br, 30.87;  $OCH_3$ , 23.61.

**Ethyl 2-Carboxy-3-methyl-4-(3',4'-dimethoxyphenyl)-butyrate (II).**—The 1-(3',4'-dimethoxyphenyl)-2-bromopropane (310 g., 1.20 moles) was condensed with sodium malonic ester in general accordance with the method of Carter<sup>15</sup> used for the reaction of 1-phenyl-2-bromopropane. The yield of product boiling at 190–195° (2.0 mm.),  $n_D^{25}$  1.4982, was 131 g. or 32%.

*Anal.* Calcd. for  $C_{18}H_{24}O_6$ : C, 63.88; H, 7.75. Found: C, 63.72, 63.79; H, 7.77, 7.92.

The diester was converted to the diamide with methanolic ammonia containing sodium methoxide. The product melted at 216.5–217.5° and recrystallization was from 50% aqueous ethanol.

*Anal.* Calcd. for  $C_{14}H_{20}N_2O_4$ : N, 10.00. Found: N, 9.82.

**2-Carboxy-3-methyl-4-(3',4'-dimethoxyphenyl)-butyric Acid.**—The ester (100 g. or 0.296 mole) was hydrolyzed by heating for 15 hours with a solution of 50 g. of sodium hydroxide in 450 ml. of water. The resulting clear solution was treated with charcoal and acidified to precipitate 69 g. (83%) of acid, m.p. 60–63°. A small sample was recrystallized from ethyl acetate to yield product melting at 64–65°.

*Anal.* Calcd. for  $C_{14}H_{18}O_6 \cdot H_2O$ : C, 55.99; H, 6.71;  $CH_3O$ , 20.7. Found: C, 56.87, 56.97; H, 6.73, 6.79;  $CH_3O$ , 20.99, 21.23.

**3-Methyl-4-(3',4'-dimethoxyphenyl)-butyric Acid (III).**—The crude acid isolated above was decarboxylated by heating 100 g. (0.333 mole) with 650 ml. of water and 150 ml. of concentrated hydrochloric acid under reflux for 16 hours. Extraction of the reaction mixture with ether and distillation gave 58 g. (73%) of light yellow oil, b.p. 180–181.5° (1.3 mm.),  $n_D^{25}$  1.5250. Borsche and Neimann<sup>7</sup> report b.p. 200–220° (15 mm.) for this compound synthesized by another method.

*Anal.* Calcd. for  $C_{13}H_{18}O_4$ : C, 65.53; H, 7.61;  $OCH_3$ , 26.2. Found: C, 65.79, 65.52; H, 7.67, 7.48;  $OCH_3$ , 26.05, 25.82.

On standing the oil solidified and after two recrystallizations from benzene-petroleum ether melted at 55–56°.

**3-Methyl-6,7-dimethoxy-1-tetralone (IV).**—A mixture of 58 g. (0.244 mole) of 3-methyl-4-(3',4'-dimethoxyphenyl)-butyric acid and 400 g. of polyphosphoric acid (Victor Chemical Co.) was heated in a steam-bath, with occasional mixing by rotation of the flask, for 40 minutes. The dark red-brown solution was poured into a slurry of ice and water, and the viscous mixture worked with a sturdy spatula until all the color had disappeared. The resulting white solid was filtered off, washed thoroughly with water and recrystallized from methanol. There was obtained 46.7 g. (87%) of tetralone, m.p. 133–134°.

**2,4-Dinitrophenylhydrazone** prepared in the usual manner melted at 264–265°. Recrystallization was from ethyl acetate.

(12) Microanalyses by Galbraith Microanalytical Laboratories of Knoxville, Tenn.

(13) All melting points recorded were taken on a Kofler hot-stage microscope and are uncorrected.

(14) Obtained from Givaudan-Delawanna, Inc.

(15) H. E. Carter, *J. Biol. Chem.*, **108**, 624 (1935).

*Anal.* Calcd. for  $C_{19}H_{20}N_4O_8$ : C, 56.99; H, 5.04; N, 13.99. Found: C, 56.99; H, 5.20; N, 14.02.

It was attempted to carry out a ring closure with polyphosphoric acid of 2-carboxy-3-methyl-4-(3',4'-dimethoxyphenyl)-butyric acid to a tetralone substituted by a carboxylic group in the 2-position, but in all cases decarboxylation could not be prevented and the yield of the tetralone IV was inferior to the route indicated above. It was also attempted to retain carboxyl function at the 2-position by (1) ring closure of the diester II with polyphosphoric acid and (2) by ring closure of the diacid chloride with stannic chloride. In both cases the only pure product isolated was the tetralone IV and this in poor yield.

**2-Bromo-3-methyl-6,7-dimethoxy-1-tetralone (V).**—The procedure is essentially that of Edwards and Cashaw.<sup>8</sup> An 89% yield of product melting at 108–112° was obtained. The earlier work<sup>9</sup> reported a melting point of 118–120°.

**3-Methyl-6,7-dimethoxy-1-naphthol (VI).**—The procedure for the dehydrobromination of V is a modification of one used by Schmid and Burger<sup>16</sup> on a similar compound. The bromotetralone (14.6 g.) was dissolved in 100 ml. of diethylaniline and refluxed under an atmosphere of nitrogen for 1.5 hours, cooled and poured into a mixture of excess hydrochloric acid and ice. This was extracted with ether and the extracts washed with aqueous sodium acetate, 2 *N* sulfuric acid, sodium bicarbonate solution and finally with water. Evaporation of the ether solution after drying yielded three crops of crystals; (1) 4.50 g., m.p. 147–148.5°; (2) 1.45 g., m.p. 143–145°; and (3) 0.95 g., m.p. 140.5–144°. The total yield was 6.90 g. or 65%. Two recrystallizations of the entire batch from acetone-petroleum ether gave white crystals, m.p. 148.3–149°. Edwards and Cashaw<sup>8</sup> report m.p. 140–142° in 27% yield.

*Anal.* Calcd. for  $C_{13}H_{14}O_3$ : C, 71.54; H, 6.47. Found: C, 71.48, 71.38; H, 6.42, 6.54.

**1,6,7-Trimethoxy-3-methylnaphthalene (VII).**—The naphthol VI (436 mg.) was dissolved in 2 ml. of methanol and 500 mg. of methyl sulfate was added and the mixture cooled to –5°. The cooling bath was removed and 420 mg. of potassium hydroxide in 1.5 ml. of water was added all at once. After the vigorous reaction had subsided the mixture was cooled and extracted with ether. The ether layer was washed, dried and evaporated to yield 296 mg. of a yellow gum. This was recrystallized from isopropyl alcohol-petroleum ether to yield 214 mg. (46%) of tan crystals, m.p. 89–97°. Two recrystallizations from ether-petroleum ether increased the m.p. to 99.5–100.5°.

*Anal.* Calcd. for  $C_{14}H_{16}O_3$ : C, 72.34; H, 6.94;  $OCH_3$ , 40.09. Found: C, 72.34, 72.31; H, 7.05, 6.97;  $OCH_3$ , 39.78, 39.60.

**1-Acetoxy-3,4-dihydro-3-methyl-6,7-dimethoxynaphthalene.**—A solution of 400 mg. of 3-methyl-6,7-dimethoxy-1-tetralone (IV) and 150 mg. of *p*-toluenesulfonic acid was dissolved in 10 ml. of isopropenyl acetate. The solution was heated on a steam-bath for two hours during which time a small amount of the isopropenyl acetate was distilled off. The mixture was cooled, diluted with ether and washed with water, sodium bicarbonate solution and again with water. Evaporation of the dried ether solution gave a solid (410 mg.) which upon crystallization from ether-petroleum ether gave 310 mg. (65%) of tan crystals, m.p. 82–87°. Two recrystallizations from isopropyl alcohol with one charcoal treatment allowed formation of white product, m.p. 89–89.8°.

*Anal.* Calcd. for  $C_{15}H_{18}O_4$ : C, 68.68; H, 6.92. Found: C, 68.72; H, 6.86.

Desapogossypol hexamethyl ether was prepared by Mr. W. H. Reedy, formerly of Tulane University, in accordance with the procedure of Adams and Butterbaugh.<sup>11</sup> The sample melted at 295–296°, the same as reported by Adams<sup>11</sup> and its ultraviolet absorption spectrum resembled rather closely that given by Adams and Kirkpatrick<sup>17</sup> for desapogossypol hexamethyl ether. The ultraviolet absorption spectra were obtained on a Beckman model DU spectrophotometer, using 1-cm. quartz cells.

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(16) H. Schmid and M. Burger, *Helv. Chim. Acta*, **35**, 933 (1952).

(17) R. Adams and E. C. Kirkpatrick, *This Journal*, **60**, 2182 (1938).