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

Structure and Reactions of Gossypol. V. Methylapogossypol Hexamethyl Ether and 2,3-Dimethoxy-4-isopropyl-5-allyltoluene[1,2]

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Reduction of gossypol with lithium aluminum hydride followed by methylation yields a product designated as methylapogossypol hexamethyl ether in which the aldehyde groups of the gossypol molecule have been reduced to methyl groups and the hydroxyl groups methylated. Work directed toward the synthesis of methylapogossypol hexamethyl ether has resulted in the seven step preparation of a key intermediate, 2,3-dimethoxy-4-isopropyl-5-allyltoluene.

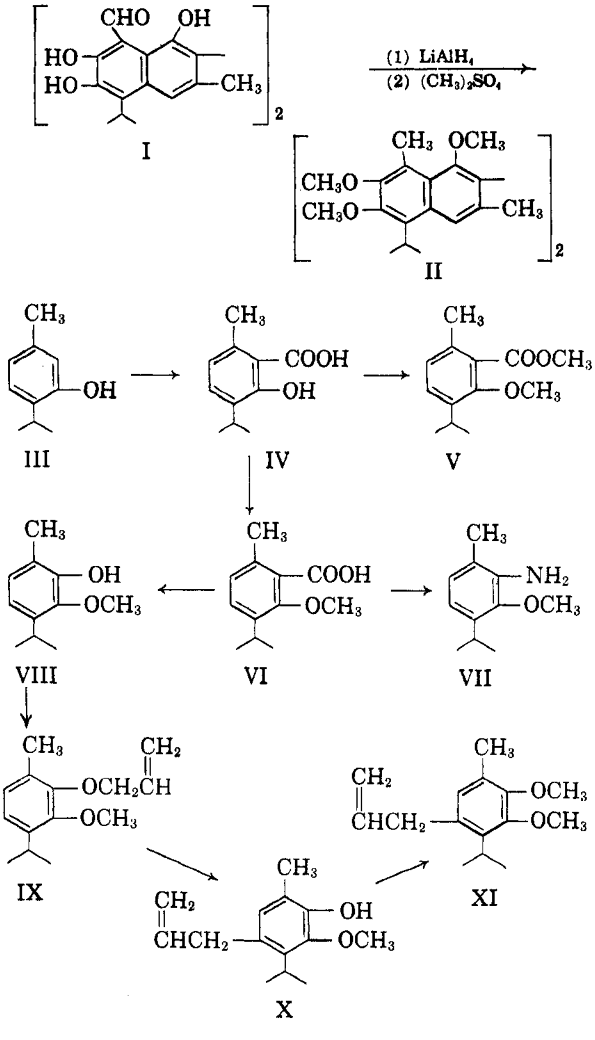
Reduction of gossypol (I) with lithium aluminum hydride followed by acetylation yielded a product, methylapogossypol hexacetate, in which the aldehyde groups were reduced to methyl groups and all hydroxyl groups were acetylated.[5] The structure of the reduction product was indicated by ultraviolet and infrared absorption spectra and characteristic reactions and reaction products, as well as the usual analytical data.

We have also produced in low yield the corresponding hexamethyl ether (II) by reduction with lithium aluminum hydride followed by methylation with methyl sulfate.

The principal infrared absorption bands for methylapogossypol hexamethyl ether (II) are given in the experimental section. There is no band in the carbonyl stretching region. The three bands at 6.88, 7.21, and 7.43 may be associated with the methyl and isopropyl groups.[6]

In view of our recent success[2,7] in the formation of a binaphthyl type corresponding to desapogossypol hexamethyl ether, we decided to undertake the synthesis of II in order to prove its structure. A key intermediate needed for this synthesis was 2,3-dimethoxy-4-isopropyl-5-allyltoluene (XI). The use of this material and the synthetic route followed earlier[2,7] should allow formation of II.

The method of synthesis of XI is indicated in the accompanying flow sheet. The readily available thymol (III) was used as the starting material. The Kolbe-Schmitt reaction to IV proceeded in 65% yield and subsequent methylation followed by alkaline hydrolysis of the ether ester (V) without isolation allowed formation of 2-methoxy-3-isopropyl-6-methylbenzoic acid (VI) in 68% yield. The Schmidt conversion of VI to the corresponding amine (VII) was realized in 48% yield, but direct conversion (without isolation of VII) by diazotization of the amine salt and hydrolysis occurred in 45% yield. Formation of the allyl ether (IX) occurred in 88% yield and Claisen rearrangement to X followed in good yield. The 2-methoxy-3-isopropyl-4-allyl-6-methylphenol (X) was not purified but methylated to XI. The overall yield from IX to XI was 49%.



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[2] Preceding paper: D. A. Shirley and W. L. Dean, *J. Am. Chem. Soc.*, **79**, 1205 (1957).

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[5] D. A. Shirley and W. C. Sheehan, *J. Am. Chem. Soc.*, **77**, 4606 (1955).

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EXPERIMENTAL[8]

Methylapogossypol hexamethyl ether (II). Five grams of powdered lithium aluminum hydride was stirred for 30 min. under an atmosphere of dry nitrogen with 200 ml. of anhydrous ether and then a solution of 5.0 g. (0.0087 mole) of gossypol–acetic acid complex[9] in 300 ml. of dry ether was added over a 40 min. period. The reaction mixture was stirred at room temperature for 18 hr., then hydrolyzed by the cautious addition of ether saturated with water followed by methanol containing 5% water, and then acidified by the addition of a dilute solution of acetic and hydrochloric acids. The ether layer was separated, the aqueous layer extracted with ether, and the combined ethereal extracts washed several times with water. The solution was dried over sodium sulfate and then filtered rapidly through a layer of sodium sulfate into a solution of 6 ml. of methyl sulfate in 25 ml. of dry methanol. The ether was removed under reduced pressure and the residue placed in a three-neck flask equipped in the usual manner with stirrer, condenser, and dropping funnel. A nitrogen atmosphere was maintained over the reactants. A 10% solution of potassium hydroxide in methanol was added until the reaction mixture was basic. After stirring for 45 min. at room temperature, 3 ml. of methyl sulfate was added, followed by the methanolic potassium hydroxide until the solution was alkaline. The mixture was stirred for 8 hr. and again made alkaline. Three ml. of methyl sulfate was added and after 3 hr. the mixture was made alkaline with the methanolic base. Stirring was then continued for 6 hr. A last 3-ml. portion of methyl sulfate was added, the solution made alkaline with methanolic base and stirred for 2 hr., after which excess base was added and the mixture heated to hydrolyze the excess methyl sulfate. The mixture was cooled and poured into 200 ml. of water. The precipitated solid was removed by filtration, washed with water, triturated with 250 ml. of hot ethanol and filtered. The major part of the product dissolved in the methanol, and no pure compound could be isolated from this fraction. The methanol-insoluble residue was recrystallized three times from benzene-ethanol to give 0.35 g. (7%) of white crystalline product m.p. 239–241°. The ultraviolet absorption spectrum in chloroform (Beckmann DU) showed the following maxima: 275 mμ (log ϵ, 4.85), 324 mμ (log ϵ, 4.14) and 340 mμ (log ϵ, 4.19).

Anal. Calcd. for $C_{36}H_{46}O_6$: C, 75.23; H, 8.07; methoxyl, 32.34; mol. wt., 575. Found: C, 75.91 and 75.98; H, 7.51 and 7.57; methoxyl,[10] 33.13, 33.22 and 31.91; mol. wt.,[10,11] 590, 597.

The infrared absorption bands[12] in microns are as follows: (S = Strong, M = Medium, W = Weak); 3.30 (M), 6.33 (W), 6.88 (S), 7.21 (S), 7.43 (S), 7.94–8.13 (M), 8.64 (M), 8.88 (M), 9.38 (S), 9.83 (M), 10.00 (W), 10.29 (M), 10.85 (M), 11.51 (W), and 11.76 (W).

Some difficulty was experienced in duplicating the above yield of methylapogossypol hexamethyl ether and this was the maximum obtained. Other methylating conditions and reagents such as methyl iodide and diazomethane were tried, but in no case was any of the above product or other pure compound isolated.

Methyl 2-methoxy-3-isopropyl-6-methylbenzoate (V). Fifty-eight and two-tenths grams (0.30 mole) of *o*-thymotinic acid[13,14] was heated with stirring until it was just molten and a solution of 57 g. (0.92 mole) of potassium hydroxide (90% KOH) in 90 ml. of water was added at a rate of 2 to 3 drops per second. About 20 sec. after initial addition of alkali, the addition of 94.5 g. (0.75 mole) of methyl sulfate was started and continued at the same rate. No external heating was used during the addition of these reagents, but the mixture was maintained at reflux temperature by the heat of reaction. After completion of the addition (15 min.), the reaction mixture was filtered and the filtrate extracted with ether. The ethereal solution was dried and distilled to give 28.4 g. (43%) of methyl 2-methoxy-3-isopropyl-6-methylbenzoate, b.p. 156–160° at 20 mm., $n_D^{27.5}$ 1.4988.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.30; H, 8.26.

2-Methoxy-3-isopropyl-6-methylbenzoic acid (VI). *o*-Thymotinic acid (233 g., 1.15 moles) was treated as described above. The addition of the methyl sulfate and aqueous potassium hydroxide solution required 45 min. The reaction mixture was stirred and heated under reflux for 1 hr. after which was added a solution of 145 g. of potassium hydroxide (80% KOH) in 135 ml. of water. The mixture was stirred and refluxed for 3 hr., filtered, cooled, and extracted with petroleum ether (b.p. 35–60°). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether, and the ethereal extract was washed with water and dried. The petroleum ether extract above was evaporated and the considerable residue refluxed for 30 min. with a solution of 135 g. of potassium hydroxide in 500 ml. of 95% ethanol. Water was added to the mixture and the alcohol removed by distillation. The mixture was acidified and extracted with ether. This ether extract was combined with the one above and the ether was distilled off. Petroleum ether (b.p. 67–75°) was added to the residue and the resulting solution decolorized with charcoal. The solution was cooled and the precipitated product recrystallized from petroleum ether (b.p. 67–75°) to yield 161.8 g. (68%) of acid, m.p. 82–83°. A maximum m.p. of 83–84° was reached on further recrystallization from the same solvent.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; neut. equiv., 208. Found: C, 69.31; H, 7.74; neut. equiv., 208.

2-Methoxy-3-isopropyl-6-methylaniline (VII).

The procedure is based on one described by Briggs and Lyttleton[15] for the preparation of various substituted aromatic amines by the use of the Schmidt reaction.

A solution of hydrazoic acid in 160 ml. of benzene, prepared from 26.0 g. of sodium azide essentially according to the procedure given in *Org. Reactions,*[16] was added to 20.8 g. (0.10 mole) of 2-methoxy-3-isopropyl-6-methylbenzoic acid. The total volume was brought to 400 ml. by addition of benzene and the mixture was heated to 40° and stirred vigorously during the addition of 32 ml. (0.6 mole) of sulfuric acid. The rate of addition of the acid was adjusted so that gas was evolved at a moderate rate. This rate was observed by passing the gas through benzene. Stirring was continued after completion of the addition as long as any gas escaped and this required about 25 min. The mixture was cooled, 300 ml. water added and the benzene layer evaporated to dryness under a hood. The aqueous layer was heated to remove any benzene and hydrazoic acid remaining and then made basic and extracted with ether. The ethereal extract was dried and dry hydrogen chloride passed through it until precipitation of the amine was complete. The amine hydrochloride was collected by filtration and crystallized from aqueous ethanol. There was obtained 10.2 g. (48%) of hydrochloride.

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(8) All elemental analyses, unless otherwise indicated, were performed by the Galbraith Microanalytical Laboratories of Knoxville, Tenn. All melting points were taken on a Kofler hot stage microscope and are uncorrected.

(9) Supplied by Southern Regional Research Laboratory, New Orleans, La.

(10) Analysis by Clark Microanalytical Laboratory, Urbana, Ill.

(11) Ebullioscopic in butanone.

(12) Determined by R. T. O'Connor and associates at Southern Regional Research Laboratory, No. IR 1095.

(13) S. C. Chou, P. J. Jannke, J. B. Burt, and L. D. Small, *J. Am. Pharm. Assoc.*, **41**, 155 (1952).

(14) R. Spallino and G. Provencal, *Gazz. chim. ital.*, **39**, II, 326 (1909); *Chem. Abstr.*, **5**, 692 (1911).

(15) L. H. Briggs and J. W. Lyttleton, *J. Chem. Soc.*, *421* (1943).

(16) H. Wolf, *Org. Reactions*, III, 327 (1946).

Anal. Calcd. for $C_{11}H_{18}ClNO$: neut. equiv., 215. Found: neut. equiv., 218.

The free base was regenerated from a small sample of hydrochloride by treatment with aqueous alkali, extraction with ether, and distillation. 2-Methoxy-3-isopropyl-6-methylaniline boils at 75–80° at 0.10 to 0.15 mm., n_D^{29} 1.5212.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.78; H, 9.82; N, 7.93.

A *benzenesulfonamide* derivative was prepared in the usual manner,[17] m.p. 118–119°.

Anal. Calcd. for $C_{17}H_{21}NO_3S$: N, 4.39. Found: N, 4.53.

2-Methoxy-3-isopropyl-6-methylphenol (VIII). While the phenol was made directly of diazotization of 2-methoxy-3-isopropyl-6-methylaniline, it was found most convenient to carry out the diazotization directly on the aqueous layer obtained in the Schmidt reaction above. A Schmidt reaction involving 160 g. (0.77 mole) of 2-methoxy-3-isopropyl-6-methylbenzoic acid, 186 g. of sodium azide and 3 l. of benzene was carried out as described above. The aqueous layer was heated to remove benzene and hydrazoic acid, cooled to 0°, and 500 g. ice added followed by a solution of 53.0 g. (0.77 mole) of sodium nitrite in 145 ml. of water. The temperature of the reaction mixture was held between 0° and 5° during this addition and until its hydrolysis in 100 ml. increments was complete.

A mixture of 200 ml. of water and 150 ml. of concentrated sulfuric acid was placed in a flask equipped for steam distillation. Addition of the diazonium salt solution was made through a water-cooled funnel designed according to the directions of Lambooy.[18] Steam distillation and addition of the diazonium salt solution were carried out according to Lambooy's directions. The distillate was extracted with ether and the residue after evaporation of the ether was recrystallized from 3:1 acetic acid-water. This gave 62.2 g. (45%) of 2-methoxy-3-isopropyl-6-methylphenol, m.p. 46–47°. A second recrystallization from alcohol-water raised the m.p. to 47–47.5°.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.14; H, 8.84.

2-Methoxy-3-isopropyl-6-methylphenyl allyl ether (IX). The procedure of Kawai and Sugiyama[19] for the formation of 4-methylguaiacol allyl ether was used. A mixture of 91.5 g. (0.507 mole) of VIII, 61.5 g. (0.507 mole) of freshly distilled allyl bromide, 71.0 g. (0.507 mole) of anhydrous potassium carbonate and 190 ml. of pure acetone was heated under reflux and stirred for 19 hr. The mixture was diluted with 500 ml. of water and extracted with petroleum ether (b.p. 35–60°). The extracts were dried over potassium carbonate to yield 98 g. (88%) of 2-methoxy-3-isopropyl-6-methylphenyl allyl ether, b.p. 82–85° at 0.7 to 1.1 mm., n_D^{27} 1.4980.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.43; H, 9.30.

2-Methoxy-3-isopropyl-4-allyl-6-methylphenol (X). A mixture of 96.5 g. (0.437 mole) of IX, 193 ml. of freshly distilled diethylaniline was heated to 220° under an atmosphere of nitrogen. At this temperature a vigorous exothermic reaction ensued and continued without application of heat for 10 min. During this period the mixture boiled vigorously. The mixture was then heated under reflux for 17 hr. The product was dissolved in petroleum ether (b.p. 35–60°) and the solution extracted with dilute hydrochloric acid to remove the diethylaniline. The petroleum ether solution was then washed with water followed by 20% aqueous sodium hydroxide solution. It was necessary to dilute the mixture with water to aid in breaking the emulsion which formed. The petroleum ether layer was dried and the solvent removed on a steam bath. The residue was extracted with aqueous base and the aqueous layer separated and added to the alkaline extract above. Acidification of the basic solution and extraction with ether followed by drying and evaporation of the ether yielded 91.0 g. (94%) of crude 2-methoxy-3-isopropyl-4-allyl-6-methylphenol (X). This product was carried directly into the next step.

2,3-Dimethoxy-4-isopropyl-5-allyltoluene (XI). The crude phenol (103.8 g. or 0.472 mole) was methylated with 89.0 g. (0.707 mole) of methyl sulfate and a solution of 59 g. (0.94 mole) of 90% potassium hydroxide in 80 ml. of water. The methyl sulfate and base were added as described above for the methylation of thymotinic acid. Thirty min. were required for addition of the reactants at 100° without application of external heat. The mixture was then stirred for 90 min. during which the temperature fell to 55°. Petroleum ether (b.p. 35–60°) was added and the precipitated salt removed by filtration. The petroleum ether layer was separated and the aqueous layer extracted three times with petroleum ether. The combined extracts were dried and distilled and three fractions collected as follows: (1) 18.2 g., b.p. 75–88° at 1.0 mm., n_D^{27} 1.4978; (2) 10 g., b.p. 84–91° at 1.0 mm., n_D^{27} 1.5007; (3) 57.5 g., b.p. 93–98° at 0.85 to 1.2 mm., n_D^{27} 1.5075. Fraction number 3 was analyzed and thus indicated to be 2,3-dimethoxy-4-isopropyl-5-allyltoluene. It was formed in 52% yield.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; methoxyl, 25.87. Found: C, 76.71; H, 9.48; methoxyl, 26.19.

It was considered possible that the alkali used in either the Claisen rearrangement (IX–X) or the subsequent methylation could have caused isomerization of the allyl group with migration of the double band to a position conjugated with the benzene ring. In order to check this point, the ultraviolet absorption spectrum of XI was determined in absolute ethanol, using a Beckmann Model DU spectrophotometer. The maximum position of absorption was at 269.5 mμ (log ε, 2.78). Herzog and Hillmer[20] have determined the ultraviolet absorption spectra of several allyl and propenyl substituted benzenes. The bathochromic shift in absorption in going from the non-conjugated (allyl) to the conjugated (propenyl) type is very pronounced. The 269.5 mμ maximum observed above corresponds to an expected absorption for the allyl type. It was concluded that little or no isomerization had occurred.

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