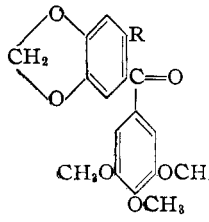
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MARYLAND]

Synthesis of Some Compounds Related to Podophyllotoxin[1]

BY WILKINS REEVE AND JOHN D. STERLING, JR.[2]

The synthesis of a number of compounds related to podophyllotoxin has been studied. Podophyllotoxin[3] has previously been shown to have tumor-damaging activity.[4,5]

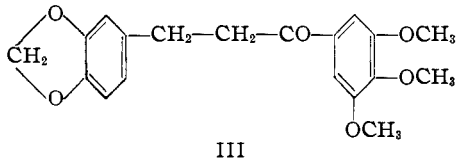


I, R = CH_3
II, R = COOH

3′,4′,5′-Trimethoxy-2-methyl-4,5-methylenedioxybenzophenone (I) was prepared by the reaction of trimethylgalloyl chloride with 3,4-methylenedioxytoluene in carbon disulfide solution using stannic chloride catalyst. Attempts to use aluminum chloride as the catalyst for this type of reaction have proven unsatisfactory presumably because of cleavage of the methoxy and methylenedioxy groups.[6] Attempts to convert I to the corresponding acid II by oxidation were not successful. The stannic chloride-catalyzed condensation of trimethylgalloyl chloride with a number of 4-substituted-methylenedioxybenzenes was tried to determine the limitations of this reaction. It was found that safrole, 3,4-methylenedioxybenzyl acetate, ethyl piperonylate, piperonal diethyl acetal, and piperonal would not react.

The 3,4-methylenedioxytoluene for the above reaction was prepared by the hydrogenation over copper–chromium–barium oxide catalyst at 160° of piperonal in dioxane solution to piperonyl alcohol, and the hydrogenolysis of this in dioxane solution over the same catalyst at 280° and 210 atmospheres starting pressure. This method has not previously been used to prepare 3,4-methylenedioxytoluene. It is of interest that the hydrogenolysis occurs under much more difficult conditions than does the hydrogenolysis of benzyl alcohol. The latter undergoes hydrogenolysis readily at 150–200° and 250 atmospheres starting pressure over this catalyst.[7]

Attempts to prepare I by condensing trimethylgallic acid with 3,4-methylenedioxytoluene in the presence of phosphorus pentoxide by Kosolapoff's procedure[8] yielded a tan colored solid, m. p. 112–120°, believed to be a mixture of compounds containing no isolatable amounts of I.



III

3,4,5 - Trimethoxy - α - piperonylacetophenone (III) was prepared by the reaction of piperonyl bromide with ethyl 3,4,5-trimethoxybenzoylacetate in alcohol solution using sodium ethoxide catalyst followed by hydrolysis and decarboxylation with barium hydroxide solution. This compound had been previously reported by Bargellini and Monti,[9] but the reported melting point was not in agreement with ours. They reported the preparation of the compound by the reduction of piperonylidene-3,4,5-trimethoxyacetophenone, but the reported melting point of this intermediate did not agree with that of other workers.[10] In view of the doubt concerning the starting compound, the uncontrolled nature of the hydrogenation reaction, and the lack of evidence that the ketone was properly characterized, it seems certain that they did not obtain ketone III.

Experimental

All melting points are "corrected."

Piperonyl Alcohol.—Ninety grams of freshly distilled piperonal in 70 ml. of dioxane (purified by refluxing over odium) was hydrogenated under 4500 lb. pressure (300 atm.) of hydrogen at 160–175° over 5 g. of copper chromite catalyst.[11] The reduction was nearly complete at 160° in fifteen minutes but was continued at 175° for another hour. Distillation gave 90 g. of piperonyl alcohol (98% yield), m. p. 51°, b. p. 125–128° at 6 mm. pressure. Reported[12]: m. p. 51°, b. p. 161° at 20 mm. pressure.

3,4-Methylenedioxytoluene.—Seventy-six grams of piperonyl alcohol in 60 ml. of purified dioxane was hydrogenated under 5500 lb. pressure (375 atm.) hydrogen at 280° over 4 g. of copper chromite catalyst.[11] The theoretical amount of hydrogen was absorbed in approximately two hours. The reaction mixture, after filtering and drying over calcium chloride, gave 58 g. of 3,4-methylenedioxytoluene (84.5% yield), b. p. 78–81° at 12–14 mm. pressure; reported[13] b. p. 81–83° at 11 mm.

Trimethylgalloyl Chloride.—This was prepared in 84% yield by stirring 191 g. of trimethylgallic acid with 175 ml. of thionyl chloride and 400 ml. of benzene at 60° for five

(1) The work reported herein was supported by a grant from the National Institute of Health.

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(3) The chemistry of podophyllotoxin is reviewed in the Ann. Repts. Progress Chem. (Chem. Soc. London), **30**, 191 (1933); **33**, 275 (1936).

(4) Ormsbee, Cornman and Berger, *Proc. Soc. Exp. Biol. and Med.*, **66**, 586 (1947).

(5) Hartwell, THIS JOURNAL, **69**, 2918 (1947); Hartwell and Shear, *Cancer Research*, **7**, 716 (1947).

(6) Spath, Wessely and Nadler, *Ber.*, **66**, 125 (1933); Frank and Tarbell, THIS JOURNAL, **70**, 1276 (1948).

(7) Folkers and Adkins, *ibid.*, **54**, 1145 (1932).

(8) Kosolapoff, *ibid.*, **69**, 1651 (1947).

(9) Bargellini and Monti, *Gazz. chim. ital.*, **44**, II, 28 (1914).

(10) Harding, *J. Chem. Soc.*, **105**, 2796 (1914).

(11) Prepared by a method similar to that described by Adkins in "Organic Syntheses," Coll. Vol. 2, p. 144, note 11 (1944).

(12) Mastagli, *Ann. chim.*, **10**, 281 (1938); Carothers and Adams, THIS JOURNAL, **46**, 1681 (1924).

(13) Schepss, *Ber.*, **46**, 2572 (1913).

hours,[14] b. p. 130° at 2 mm.; m. p. after crystallization from cyclohexane, 77–78°; reported[14] b. p. 168–170° at 14 mm., m. p. 77–78°.

3′,4′,5′-Trimethoxy-2-methyl-4,5-methylenedioxybenzophenone (I).—In a 250-ml. three-necked flask were placed 10 ml. (0.084 mole) of 3,4-methylenedioxytoluene, 50 ml. of anhydrous carbon disulfide and 4.5 ml. (0.037 mole) of anhydrous stannic chloride. To this was added slowly with cooling and stirring 10 g. (0.043 mole) of freshly distilled trimethylgalloyl chloride dissolved in 50 ml. of carbon disulfide. The reaction mixture was stirred at ice-bath temperature for six hours; during this time, the product separated as a red complex. The reaction mixture was decomposed with ice-cold 7% hydrochloric acid, extracted with ether, and the ether extract washed with dilute hydrochloric acid, water, dilute sodium hydroxide and with water. The ether solution was dried with calcium chloride, the ether distilled off, and the residue refluxed with a solution of potassium hydroxide in methyl alcohol for twenty minutes. The resulting mixture was diluted with water and extracted with ether. The ether solution was washed with water, dried with calcium chloride, and the ether removed by distillation. The residue was crystallized from methyl alcohol or cyclohexane giving 6.2 g. (43% yield) of product, m. p. 108–110°. The product gave a positive test for the methylenedioxy bridge when warmed with sulfuric acid and a trace of gallic acid.[15]

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45; OCH_3, 28.15. Found: C, 65.60; H, 5.61; OCH_3, 27.94.

3,4,5-Trimethoxy-α-piperonylacetophenone (III).—In a 100-ml. flask fitted with a condenser and drying tube were placed 50 ml. of absolute alcohol and 0.46 g. (0.02 mole) of sodium. The sodium ethoxide solution thus prepared was cooled in an ice-bath and 5.6 g. (0.02 mole) of ethyl 3,4,5-trimethoxybenzoylacetate[16] was added. Four and one-half grams (0.029 mole) of piperonyl bromide,[17] dissolved in 10 ml. of absolute ether was then added to the cold alcohol solution. Sodium bromide began to precipitate. After ten minutes, the ice-bath was removed, and the reaction allowed to proceed for half an hour while warming up to room temperature. The reaction mixture was then acid. It was diluted with water and extracted with ether. The ether solution was dried, the ether distilled off, and a viscous residual oil obtained. This was hydrolyzed by dissolving in 400 ml. of methanol and adding a solution of 45 g. of barium hydroxide octahydrate in 800 ml. of water at room temperature. A white solid soon formed; after twelve hours, it was removed by filtration. The organic material was separated from inorganic salts by dissolving in chloroform, the chloroform solution dried with anhydrous magnesium sulfate, and the chloroform removed by distillation. There remained 3.8 g. (55% yield for the two steps) of a white crystalline mass which after recrystallization from methanol gave 3.4 g. of product, m. p. 146–147°; reported[9] 96–98°.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.83; OCH_3, 27.03. Found: C, 66.14; H, 5.95; OCH_3, 26.87.

Dinitrophenylhydrazone of III.—Accurately weighed samples of III dissolved in alcohol reacted with excess dinitrophenylhydrazine in 2 *N* hydrochloric acid to give the 2,4-dinitrophenylhydrazone according to the quantitative procedure of Iddles, *et al.*[18] Quantitative yields were obtained. After two recrystallizations from benzene, approximately half the material remained, m. p. 188.5–189°.

Anal. Calcd. for $C_{25}H_{24}O_9N_4$: C, 57.25; H, 4.61; N, 10.68. Found: C, 57.47; H, 4.62; N, 10.84.

Acknowledgment.—The authors wish to express their appreciation to the National Institute of Health for the financial assistance which made this work possible, and to Mrs. Mary H. Aldridge and Mr. Byron Baer for carrying out the microanalyses.

Summary

1. 3′,4′,5′-Trimethoxy-2-methyl-4,5-methylenedioxybenzophenone (I) has been prepared by the stannic chloride catalyzed condensation of 3,4-methylenedioxytoluene with trimethylgalloyl chloride.

2. 3,4,5-Trimethoxy-α-piperonylacetophenone (III) has been prepared by an acetoacetic ester type of synthesis.

3. 3,4-Methylenedioxytoluene has been prepared by the hydrogenolysis of piperonyl alcohol. The latter is more resistant to hydrogenolysis over a copper–chromium–barium oxide catalyst than is benzyl alcohol.

(14) Asano and Yamaguti, *J. Pharm. Soc.* (*Japan*), **60**, 34 (1940).
(15) Labat, *Bull. soc. chim. biol.*, **15**, 1344 (1933).
(16) Perkin and Weizmann, *J. Chem. Soc.*, **89**, 1655 (1906).
(17) Robinson and Robinson, *ibid.*, **105**, 1463 (1914).
(18) Iddles, Low, Rosen and Hart, *Ind. Eng. Chem., Anal. Ed.*, **11**, 102 (1939).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Spirobarbituric Acids Containing a Six-membered Carbocyclic Ring

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Several spirobarbituric acids have been described by Dox and Yoder[2] in which the 5-carbon atom of the barbituric acid nucleus forms part of an unsubstituted cyclobutane or cyclohexane ring, but no pharmacological data were reported for these compounds. The spirobarbituric acids present points of structural similarity and dissimilarity to the 5,5-dialkylbarbituric acids which have led us to prepare a number of such compounds for pharmacological evaluation. In both classes the two acidic hydrogen atoms in the 5-position of the barbituric acid nucleus have been replaced by establishment of carbon-to-carbon linkages, but the spiro compounds differ uniquely from the 5,5-dialkylbarbituric acids in the spatial arrangement of the two rings in perpendicular planes. Since the pharmacological characteristics of 5,5-dialkylbarbituric acids vary widely according to the size and structure of the alkyl substituents, properties of the spiro compounds could not be predicted.

The intermediate esters required for the synthesis of spirobarbituric acids were prepared by the addition of butadiene to diethyl methylene-

(1) Sharp and Dohme Research Associate.
(2) Dox and Yoder, THIS JOURNAL, **43**, 677, 1366, 2097 (1921).