

The same compound was similarly prepared by heating the aldehyde for 13 min. with 36.0% perchloric acid and decomposing the resulting red solid by boiling with aqueous sodium hydroxide.

A sample of the red solid from the perchloric acid was recrystallized from glacial acetic acid giving beautiful red crystals with gold faces, m.p. 167–172°.

*Anal.* Calcd. for  $C_{28}H_{24}O_9 \cdot HClO_4$ : C, 54.6; H, 5.73; mol. wt., 615.1. Found: C, 54.07; H, 5.68; mol. wt. (titration with alkali), 607.

*2,4,6,2',4',6'-Hexamethoxydiphenylcarbinol.* To a solution of 0.2 g. of 2,4,6-trimethoxybenzaldehyde and 0.4 g. of 1,3,5-trimethoxybenzene in 30 ml. of glacial acetic acid was added 3.0 ml. of 42.0% perchloric acid. Heating for 9 min. on the steam bath followed by cooling in ice and recrystallizing from glacial acetic acid produced brown-red crystals (with gold-green faces) of 2,4,6,2',4',6'-hexamethoxydiphenylcarbinyl perchlorate, m.p. 190–192° dec.

*Anal.* Calcd. for  $C_{19}H_{23}O_7Cl$ : C, 51.2; H, 5.18; mol. wt., 446.9. Found: C, 51.07; H, 5.18; mol. wt. (titration with alkali), 441, 447, 443.

Heating an identical reaction mixture for 20 min. gave only the 2,4,6,2',4',6',2'',4'',6''-nonamethoxytriphenylmethane-perchloric acid adduct.

The brown-red solid was warmed with 25% aqueous sodium hydroxide. The resulting yellow solid was recrystallized three times from alcohol-water to yield a white solid, m.p. 150–152°.

*Anal.* Calcd. for  $C_{19}H_{23}O_7$ : C, 62.6; H, 6.57; mol. wt., 364.4. Found: C, 62.21; H, 6.41; mol. wt. (Rast), 371.

In addition to other expected spectral features, strong absorption at 3610  $cm^{-1}$ , typical for the alcohol group, was observed.

Several attempts to prepare this compound by treatment of 2,4,6-trimethoxybenzaldehyde alone in either hydrochloric or perchloric acid for different lengths of time resulted in recovering the starting aldehyde, in isolating 2,4,6,2',4',6',-

2'',4'',6''-nonamethoxytriphenylmethane and/or in isolating 1,3,5-trimethoxybenzene.

*1,3,5-Trimethoxybenzene.* A mixture of 0.2 g. of 2,4,6,2',4',6',2'',4'',6''-nonamethoxytriphenylmethane and 1 ml. of 25% hydrochloric acid was heated for 20 min. on the steam bath. After cooling the reaction mixture, the resulting tan solid was filtered and recrystallized from petroleum ether, yielding white needles, m.p. 52–53°. A mixture of this compound with authentic 1,3,5-trimethoxybenzene melted at 52–53°. Treatment of 2,4,6,2',4',6'-hexamethoxydiphenylcarbinol in the same way gave the same product.

*Kinetic experiments.* The reactions were run in a thermostated bath placed in the light path of the Beckmann DU Spectrophotometer. The solvent acid for all determinations was taken from a stock solution made by mixing one volume of glacial acetic acid and two volumes of 70–72% perchloric acid. The temperature was controlled at 60° to  $\pm 0.05^\circ$ . The rate of disappearance of the 2,4,6-trimethoxybenzaldehyde was followed by observing the decrease in the absorption in the region of 318  $\mu$ . In each case data were obtained at three or more wave lengths and at least two separate runs were made. The reactions were followed for at least three half-lives. The plot of  $\log(D - D_\infty)$  vs. time was linear within  $\pm 0.01$  log unit except for an occasional stray point and except for the one experiment in which the curvature of the plot was the significant observation.

Three plots are shown in Fig. 1. The results are summarized in Table I.

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## Synthesis of 5-(2',3',4'-Trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 and Derivatives

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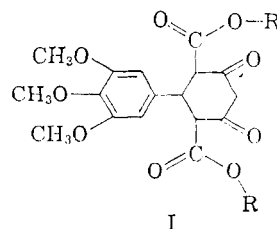
The synthesis of 2,3,4-trimethoxybenzaldehyde (III) from trimethoxybenzene, *N*-methylformanilide and phosphorus oxychloride has been described. Ethyl 2,3,4-trimethoxybenzylidenemalonate (IV) and 5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 (V) were prepared. The syntheses of the following derivatives of III and V are described: 2,4-dinitrophenylhydrazone of III; bisdiphenylhydrazone of V; 2,2-(vanillydene)-bis[5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3] (IX) and *N,N'*-bis[2-[5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexane-1,3]-*p,p'*-bisazodiphenyl (X).

The preparation of 5-(1',2',3'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 (I) was reported in a previous publication.<sup>1</sup> The syntheses involved the conversion of 3,4,5-trimethoxybenzoylchloride to 3,4,5-trimethoxybenzaldehyde by the Sonn and Muller method<sup>2</sup> and further the preparation of I according to the method previously described.<sup>3</sup>

(1) P. E. Papadakis and R. Mathiesen, *J. Org. Chem.*, **21**, 593 (1956).

(2) Sonn and Muller, *Ber.*, **52**, 1934 (1919).

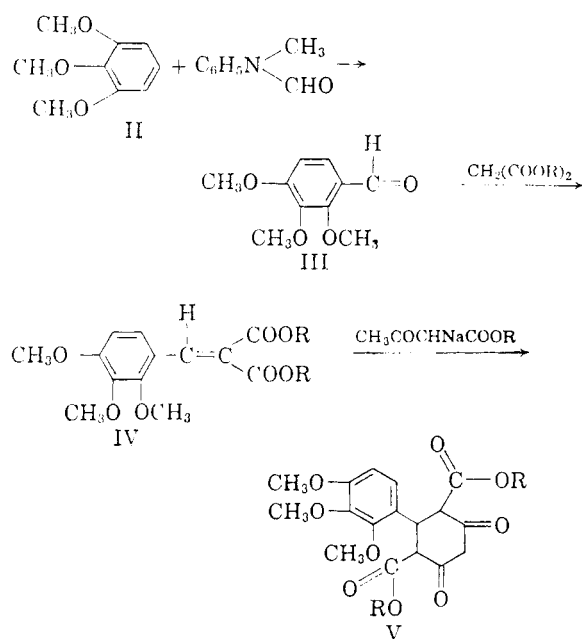
(3) P. E. Papadakis, *J. Am. Chem. Soc.*, **67**, 1799 (1945).



Mathiesen tried to prepare trimethoxybenzaldehyde directly from 3,4,5-trimethoxybenzoylchloride using the Rosemund's reduction method. He

obtained a derivative, m.p. 161°, identical with that of Emil Fischer and Freudenberg.<sup>4</sup> The carbon-hydrogen analysis of this derivative was not the same as that of 3,4,5-trimethoxybenzaldehyde. As the Sonn-Muller method used for the preparation of the trimethoxybenzaldehyde involves several steps, it was desirable to use a method giving direct formylation of trimethoxybenzene.

There are several known methods of formylation. The present report describes the syntheses of: a) 2,3,4-trimethoxybenzaldehyde (III) by the direct formylation of trimethoxybenzene with methylformanilide<sup>5</sup> and phosphorus oxychloride; b) ethyl-(2,3,4-trimethoxybenzylidene)malonate (IV); and c) 5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 (V). The sequence of the synthesis is shown below:



Details of the method of preparation of trimethoxybenzaldehyde, m.p. 32°, are described in the experimental part. As the melting point of 3,4,5-trimethoxybenzaldehyde<sup>1</sup> is 76°, it is obvious that the compound with m.p. 32° must be the 2,3,4-trimethoxybenzaldehyde (III). It may be observed that in the trimethoxybenzene (II), two out of the three trimethoxy groups influenced the activation of the carbon to which the aldehyde group was attached to form III. Barger and Ewins<sup>6</sup> used the method of Gatterman and Koebner<sup>7</sup> to prepare 2,3,4-trihydroxybenzaldehyde from pyrogallol, hydrogen cyanide, hydrogen chloride, and zinc chloride. The product was methylated to the trimethoxy derivative, m.p. 30°, b.p. 166–170°.

(4) Emil Fischer and Freudenberg, *Ber.*, **46**, 1116 (1913).

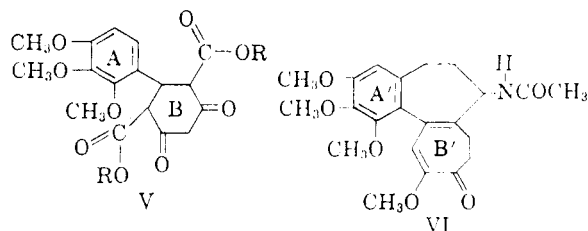
(5) L. F. Fieser and J. E. Jones, *J. Am. Chem. Soc.*, **64**, 1666 (1942).

(6) G. Barger and A. J. Ewins, *J. Chem. Soc.*, **97**, 2255.

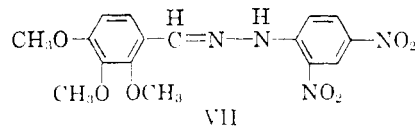
(7) L. Gatterman and M. Koebner, *Ber.*, **32**, 287 (1899).

The syntheses of compounds IV and V were by methods<sup>8</sup> previously described.

In structure V the cyclohexanedione ring (B) is connected to the trimethoxyphenyl (A) in the same position as one of the seven member rings (B') is connected to the trimethoxyphenyl (A') in the structure of colchicine (VI). Much research has been done lately on colchicine and related compounds in connection with the problem of cancer. Further work is in progress using compound V as an intermediate.



The following derivatives of III and V were made and analyzed: a) 2,4-dinitrophenylhydrazone of 2,3,4-trimethoxybenzaldehyde (VII); b) bisdiphenylhydrazone of [5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3] (VIII); c) 2,2-(vanillydene)bis[5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3] (IX); and d) *N-N'*-bis[2-[5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3]]-*p,p'*-bisazodiphenyl (X).



## EXPERIMENTAL

**2,3,4-Trimethoxybenzaldehyde (III).** A mixture of 15.3 g. of phosphorus oxychloride and 13.5 g. of *N*-methylformanilide was stirred for 45 min. in a 400-ml. ground glass stoppered flask equipped with a Teflon magnetic stirring bar. To the mixture 16.8 g. of trimethoxybenzene (III) was added over a period of 2 hr. The stirring continued for an additional 3-hr. period then the mixture was poured in ice water and allowed to stand for 12 hr. The water solution was then extracted twice with ethyl ether. The ether solution of the extract was stirred with a saturated solution of sodium bisulfite for 3 hr. The water layer containing the aldehyde-bisulfite addition compound as well as some unchanged bisulfite was separated, filtered and, warmed to 60°. This solution was treated with excess sodium carbonate. The heating was continued for 3 hr. A white, oily material separated and was extracted with ethyl ether. After evaporation of the ether the aldehyde crystallized, m.p. 32–37°, yield 11.7 g.

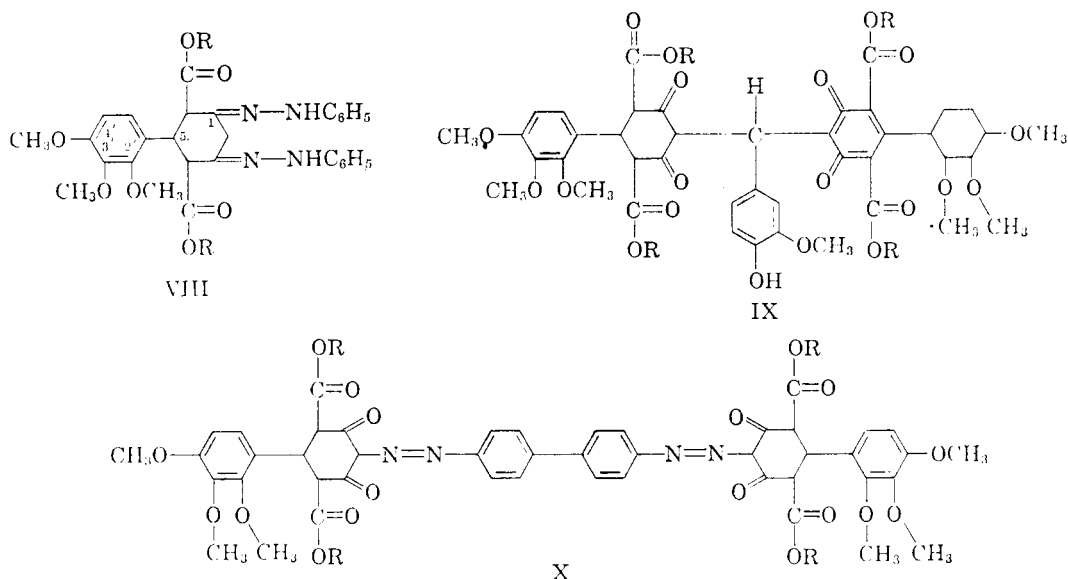
**2,4-Dinitrophenylhydrazone of 2,3,4-trimethoxybenzaldehyde (VII).** The procedure outlined in Kamm<sup>9</sup> was followed for the preparation of VII.

The product melts at 190–191°; mixed m.p. with 2,4-dinitrophenylhydrazine 161°, 166° dec.

*Anal.* Calcd. for C<sub>16</sub>H<sub>11</sub>N<sub>4</sub>O<sub>7</sub>: N, 14.89. Found: 14.70.

(8) P. E. Papadakis, *J. Am. Chem. Soc.*, **67**, 1799 (1946).

(9) Kamm, *Qualitative Organic Analysis*, Wiley, New York, 1945, p. 578.



*Ethyl 2,3,4-trimethoxybenzylidenemalonate* (IV). A mixture of 6.2 g. of 2,3,4-trimethoxybenzaldehyde, 5.1 g. of diethyl malonate, and 0.3 ml. of piperidine was refluxed for 5 hr. at an oil bath temperature of 150°. A Dean-Stark water trap was placed in the system to remove the water. The resulting product was a light yellow oil. The yellow liquid was extracted with ethyl ether and the solution was treated with anhydrous sodium sulfate. After filtering the ether solution, the ether was distilled under reduced pressure. A residue of 4.3 g. of a viscous liquid of the product was obtained which was not purified further. By repeating the experiment more material was obtained and used for the following experiment.

5-(2',3',4'-Trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3- (V). To a solution of 0.4 g. of sodium in absolute ethanol 2.2 g. of ethyl acetoacetate was added and the mixture was refluxed for 0.5 hr. To this, 5.4 g. of ethyl 2,3,4-trimethoxybenzylidenemalonate was added and the mixture was further refluxed for 4 hr. The reaction mixture flask was equipped with an air condenser, which allowed the alcohol to distill slowly. After refluxing, the mixture containing the product was dissolved in 100 ml. water and the solution cooled to 10°. Some gum formed which was extracted with ether. The water layer containing the product was acidified with cold 1*N* hydrochloric acid. The pale yellow material formed was filtered, washed with distilled water, and dried. It was washed further on porous tile with a mixture of ether and petroleum ether. The melting point was not sharp. The material sinters at 90°, liquifies at 120° without meniscus and bubbles at 160°. Yield 3.4 g.

*Anal.* Calcd. for  $C_{21}H_{26}O_9$ : C, 59.71; H, 6.16. Found: C, 59.68; H, 6.34.

*Phenylhydrazine derivative of 5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3* (VIII). To a solution of 1 g. of 5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 (V) in ethyl alcohol a solution of phenylhydrazine acetate was added. The mixture was

heated on a water bath. Orange red crystals formed which melt at 110–120°.

*Anal.* Calcd. for  $C_{33}H_{38}O_7N_{1.5}H_2O$ : C, 64.81; H, 6.38. Found: C, 64.62; H, 6.10.

2,2-(Vanillydene)bis[5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3] (IX). A 2.6-g. sample of 5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3, 0.2 g. of vanillin and 0.5 drop of piperidine were dissolved in the least amount of 75% methanol and the solution was refluxed for 30 min. The methanol was evaporated and the yellow oil formed was treated with cold water and a drop of dilute hydrochloric acid. A pale yellow material was formed which was filtered and recrystallized from 50% methanol. It sinters at 70° and melts at 95°.

*Anal.* Calcd. for  $C_{50}H_{58}O_{20}$ : C, 61.34; H, 5.93. Found: C, 61.12; H, 6.30.

*N-N'*-Bis[2-[5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3]]-p,p'-bisazodiphenyl.

Benzidine tetrazonium dichloride<sup>10</sup> was prepared by diazotizing 2.57 g. of benzidine dichloride with 1.35 g. of sodium nitrite at 0°. To the diazotized solution was added a cold solution of 10.44 g. of 5-(2',3',4'-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 dissolved in an excess of dilute sodium hydroxide. The mixture was allowed to stand for 1 hr. at 0°. The solution was then made acid to litmus with hydrochloric acid. The dark brown crystals were redissolved in dilute sodium hydroxide and reprecipitated with dilute hydrochloric acid. The material was washed with distilled water and dried on a vacuum dessicator; m.p. was too high.

*Anal.* Calcd. for  $C_{54}H_{58}O_{18}N_4 \cdot 2 H_2O$ : C, 59.66, H, 5.74. Found: C, 59.28; H, 5.76.

OMAHA 2, NEB.

(10) P. E. Papadakis, J. Seigliana, Carl Chin, and Adrienne Adrian, *J. Am. Chem. Soc.*, **72**, 4256 (1950).