moval of the catalyst and solvent left a thick oil. This was dried several days *in vacuo* over phosphorus pentoxide to give the solid hydriodide salt, m.m.p. 66–67°.

Anal. Calcd. for $C_{17}H_{25}N_2I$: C, 53.13; H, 6.56. Found: C, 53.04; H, 6.86.

Decomposition of the salt with sodium hydroxide resulted in the hygroscopic free base. Much of the water present was removed by codistillation with benzene. The benzene solution was decanted from a small amount of insoluble material. Removal of the solvent and extensive drying of the residue gave 5.1 g. (75%) of the white compound, m.m.p. 131.5–132°.

Anal. Calcd. for $C_{17}H_{24}N_2$: basic N, 5.58. Found: basic N, 5.63.

Hydrochloride. The hydrochloride salt was formed by passing dry hydrogen chloride through a solution of 4.0 g. (0.0156 mole) of 1-ethyl-2-(3-indolylethyl)piperidine in 75 ml. of dry ether under anhydrous conditions. As soon as the formation of the salt appeared complete the reaction flask and contents were placed in a desiccator until the compound had settled. The ether was removed by decantation and the salt washed twice with anhydrous ether. The white hygroscopic salt thus obtained was dried *in vacuo* to give 3.8 g. (90%), m.m.p. 170–173°.

Anal. Calcd. for $C_{17}H_{24}N_2$, HCl: Cl, 12.32. Found: Cl, 12.22.

5-Ethylcarbamyl-2-(3-indolylethyl)-1-methylpiperidine (IId). In the manner described above, 6.35 g. (0.0147 mole) of 5-ethylcarbamyl-2-(3-indolylethenyl)-1-methylpyridinium iodide was hydrogenated. The required hydrogen uptake was complete in 36 hr. at room temperature. After removal of the catalyst and solvent the free base was obtained by decomposition of the crude hydriodide salt with sodium hydroxide. The hygroscopic compound was dehydrated by codistillation with benzene followed by prolonged storage *in vacuo* over phosphorus pentoxide. Recrystallization, with charcoal treatment, from benzene-ligroin was accomplished by suitable protection from atmospheric moisture. After redrying, 3.5 g. (76%) of the compound was obtained, m.m.p. 138–140°.

Anal. Calcd. for $C_{19}H_{27}N_3O$: basic N, 4.54. Found: basic N, 4.40.

Hydrochloride. Observing the same precautions to exclude moisture and in the same manner as above the hydrochloride salt was prepared. Three g. (89%) of the salt was obtained from 3.0 g. (0.0098 mole) of the free base. Because even the slightest exposure to the atmosphere resulted in a hydrate, accuracy in melting point determinations was difficult. A melting point of 174–176° was obtained by filling and sealing a capillary in a dry box. This was checked by heating the compound on a hot stage 10° below its melting point for 0.5 hr. before redetermining the melting point.

Anal. Calcd. for $C_{19}H_{27}N_3O \cdot HCl$: Cl, 10.29. Found: Cl, 10.08.

5-Diethylcarbamyl-2(3-indolylethyl)-1-methylpiperidine (IIe) and hydriodide. 5-Diethylcarbamyl-2-(3-indolylethenyl)-1-methylpyridinium iodide, 10.0 g. (0.0215 mole) was hydrogenated in the same manner as above. Hydrogen uptake was steady but sluggish; 5 days at 60° were required for completion. Removal of the catalyst and solvent produced the solid hydriodide salt. An analytical sample was recrystallized from ethyl acetate, m.m.p. 110–112°.

Anal. Calcd. for $C_{21}H_{31}N_3O \cdot HI$: N, 8.95. Found: N, 8.76.

The salt was decomposed with sodium hydroxide and the resulting free base extracted into 600 ml. of benzene. This solution was dried over anhydrous calcium sulfate. Removal of the benzene by flash evaporation left an oil which slowly solidified. This was recrystallized from benzene–ethyl acetate to give 3.9 g. (57%) of the white compound, m.m.p. 213–214°.

Anal. Calcd. for $C_{21}H_{31}N_3O$: basic N, 4.11. Found: basic N, 4.08.

Tartrate. To a solution of 2.9 g. (0.00903 mole) of 5-diethylcarbamyl-2(3-indolylethyl)-1-methylpiperidine in 200 ml. of ethanol was added 0.78 *g.* (0.00045 mole) of tartaric acid. The solution was evaporated to *ca.* 20 ml., cooled, and 200 ml. of anhydrous ether was added. In contrast to previously prepared hydrochloride salts the tartrate salt was only mildly hygroscopic and easily dried *in vacuo*. Recrystallization from ethyl acetate, under anhydrous conditions, afforded 3.1 g. (82%) of the white salt, m.p. 124–126°.

Anal. Calcd. for $C_{42}H_{62}N_6O_2 \cdot C_4H_6O_6$: C, 68.97; H, 8.55. Found: C, 68.71; H, 8.91.

Absorption spectra of 2-(3-indolylethenyl)-1-methylpyridinium iodide. The absorption spectra of 2-(3-indolylethenyl)-1-methylpyridinium iodide in 1*N* sodium hydroxide, 0.1*N* hydrochloric acid, and distilled water were obtained from 220 mμ to 600 mμ of a Beckman DU spectrophotometer. Identical spectra were obtained in acidic and neutral media; in base a bathochromic shift was observed as summarized in Table IV.

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

Preparation of Some Simple Structural Analogs of Khellin[1,2]

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2,3,4,6-Tetramethoxy-5-ethylacetophenone, as well as several related hydroxytrimethoxyethylacetophenones have been synthesized.

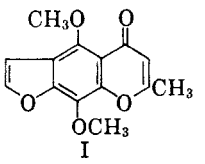
The chemistry and physiological activity of khellin (I) and related compounds isolated from *Ammi visnaga* L and *Ammi majus* L have been investigated rather extensively.[4] In addition, synthetic compounds which possess some of the structural features of khellin have been reported widely. Further studies have been directed also

(1) Presented in part at the 10th Annual Kansas City, Missouri, Chemistry Conference, November 14, 1958.

(2) From the Ph.D. thesis of D. W. Rosenburg.

(3) McNeil Laboratories, Inc. Fellow, 1957–58.

(4) C. P. Huttrer and E. Dale, *Chem. Revs.*, **48**, 543 (1951).



I

toward the preparation of derivatives of these materials.

The present investigation was concerned with the synthesis of the tetramethoxyacetophenone (VI) and related compounds which may be considered to be simple structural analogs of khellin.

The scheme chosen for the preparation of the desired 2,4,5,6-tetramethoxy-3-ethylacetophenone (VI) is summarized in Chart I.

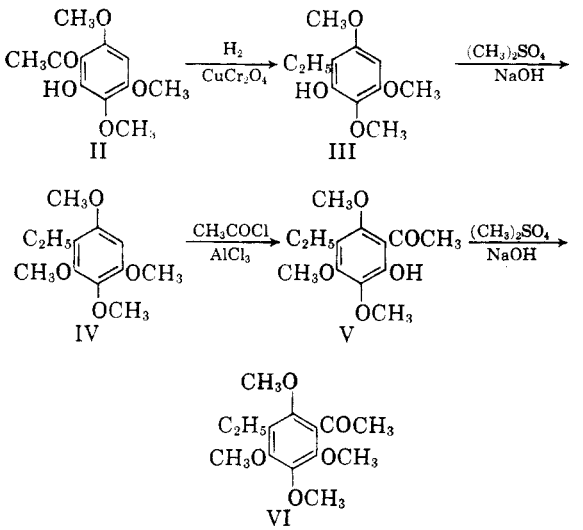


CHART I

2 - Hydroxy - 3,4,6 - trimethoxyacetophenone (II) was reduced at high pressure over copper–chromium oxide catalyst to 2,3,5-trimethoxy-6-ethylphenol (III) which then was methylated with dimethyl sulfate. The resulting 2,3,4,6-tetramethoxyethylbenzene (IV) was caused to react with acetyl chloride and aluminum chloride in dry ether. The product of this reaction afforded the correct analytical data for a hydroxytrimethoxyethylacetophenone (V), but the positions of the hydroxyl group and one of the methoxy groups were unknown. For characterization purposes, the compound was converted to a chalcone (VII) derived from piperonal. In one such experiment, the major product of the reaction was found to be the isomeric flavanone (VIII). This result established the position of the hydroxyl group as *ortho* to the acetyl function. In any event, methylation of the free hydroxyl group of V produced the sought after compound, VI.

It was presumed that V was either 2-hydroxy-3,4,6 - trimethoxy - 5 - ethylacetophenone or 2 - hydroxy-4,5,6-trimethoxy-3-ethylacetophenone (IX).

When V was caused to react with 6% hydrogen bromide in acetic acid, according to the method of Gardner, Horton, and Pincock,[5] a crystalline product was isolated which gave correct analytical data for a dihydroxydimethoxyethylacetophenone. However, it was found that the unknown differed in its chemical behavior from an authentic sample of 2,3-dihydroxy-4,6-dimethoxyacetophenone. In contrast to the latter, it failed to give a positive Tollen's test and dissolved readily in concentrated ammonium hydroxide solution. Both compounds decolorized potassium permanganate solution and gave reddish to reddish brown colors with alcoholic ferric chloride.

Since the results of the hydrogen bromide cleavage experiment were indeterminate, it was decided to synthesize the isomeric structures V and IX by unequivocal procedures.

Accordingly, the preparation of 2-hydroxy-4,5,6-trimethoxy-3-ethylacetophenone (IX) was undertaken as outlined in Chart II.

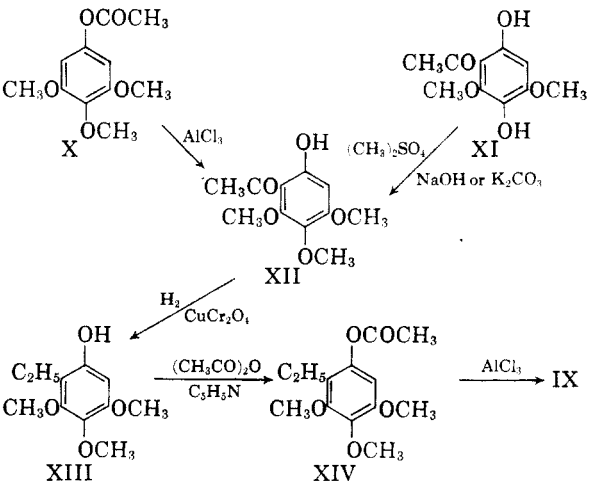


CHART II

2-Hydroxy-4,5,6-trimethoxyacetophenone (XII) was obtained by the Fries rearrangement of antiarol acetate (X) according to the method of Oliverio and Bargellini,[6] and by the selective methylation of 2,5-dihydroxy-4,6-dimethoxyacetophenone (XI) either with dimethyl sulfate and potassium carbonate in benzene[7] or with dimethyl sulfate and sodium hydroxide in aqueous solution. The 2-hydroxy-4,5,6-trimethoxyacetophenone (XII) prepared by any of the three methods melted at 30.5–31.5° on the Fisher-Johns melting-point apparatus (hereafter designated F-J). Oliverio and Bargellini[6] have recorded the melting point of this compound as 41–42°. The identity of the product obtained in the present work was confirmed by analysis and by the melting point of its benzoate.

(5) P. D. Gardner, W. J. Horton, and R. E. Pincock, *J. Am. Chem. Soc.*, **78**, 2541 (1956); see also W. J. Horton and J. T. Spence, *J. Am. Chem. Soc.*, **77**, 2894 (1955); **80**, 2453 (1958).

(6) A. Oliverio and G. Bargellini, *Gazz. chim. ital.*, **78**, 372 (1948).

(7) W. Baker, *J. Chem. Soc.*, 662 (1941).

Catalytic reduction of the 2-hydroxy-4,5,6-trimethoxyacetophenone (XII) over copper–chromium oxide catalyst converted it to 2-ethyl-3,4,5-trimethoxyphenol (XIII). The acetate (XIV) of the latter was caused to undergo a Fries rearrangement and 2-hydroxy-4,5,6-trimethoxy-3-ethylacetophenone (IX) was isolated in low yield. The piperonal chalcone of IX depressed the melting point of the corresponding derivative of the original hydroxytrimethoxyethylacetophenone (V). Further proof of the nonidentity of the two compounds was furnished by a comparison of their infrared spectra. The Fries rearrangement also gave several solid by-products which were not identified.

2 - Hydroxy - 3,4,6 - trimethoxy - 5 - ethylacetophenone (V) then was synthesized by the reactions shown in Chart III.

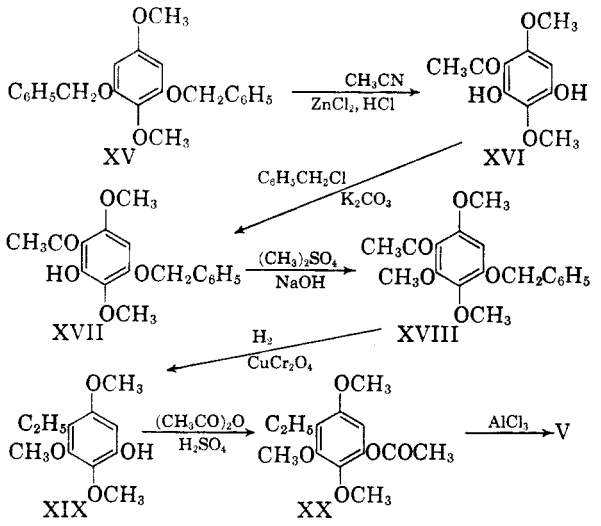


CHART III

1,4 - Dimethoxy - 2,6 - dibenzyloxybenzene (XV)[8] was converted to 2,4-dihydroxy-3,6-dimethoxyacetophenone (XVI) by means of the Hoesch reaction according to the method of Sastri and Seshadri.[9] Gardner, Wenis, and Lee[10] reported that attempts to monobenzylate 2,4-dihydroxy-3,6-dimethoxyacetophenone with benzyl bromide and potassium carbonate led to an inseparable mixture of the 2- and 4-benzyl ethers. In the present work, the 4-benzyl ether (XVII) was obtained without difficulty by the directions of Geissman.[11] It was methylated to give 2,3,6-trimethoxy-4-benzyloxyacetophenone (XVIII) which upon catalytic hydrogenation afforded 2,3,5-trimethoxy-4-ethylphenol (XIX). The acetate (XX) of this compound was subjected to a Fries rearrangement and a low yield of impure 2-hydroxy-3,4,6-trimethoxy-5-ethylacetophenone (V) was isolated. It was shown to be identical with the original hydroxytrimethoxyethylacetophenone (V) by comparison of the melting points and infrared spectra of the piperonal chalcones (VII) of the two samples.

(8) T. A. Geissman and T. G. Halsall, *J. Am. Chem. Soc.*, **73**, 1280 (1951).

(9) V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **24A**, 243 (1946).

(10) T. S. Gardner, E. Wenis, and J. Lee, *J. Org. Chem.*, **15**, 841 (1950).

(11) T. A. Geissman, *J. Am. Chem. Soc.*, **73**, 3514 (1951).

EXPERIMENTAL[12]

2-Hydroxy-3,4,6-trimethoxyacetophenone (II). This material was prepared from pyrogallol according to the procedure of Baker.[7] The over-all yield was approximately 35%, m.p. 113–115°; lit.,[7] yield, 40%, m.p. 103–105°; lit.,[9] m.p., 113–114°.

2,3,5-Trimethoxy-6-ethylphenol (III). A mixture of 50 g. (0.22 mole) of 2-hydroxy-3,4,6-trimethoxyacetophenone (II), 150 ml. of methanol, and 3.5 g. of copper–chromium oxide catalyst was shaken under an initial hydrogen pressure of 2700 p.s.i., and heated to 165–175° for 3.5 hr. It was allowed to cool, the catalyst was removed by filtration, and the solvent was evaporated *in vacuo*. The dark residue was distilled, and the material which boiled at 147–155°/3 mm. was crystallized from dilute methanol to afford 31.6 g. (67%) of white crystals which melted at 46–48°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.13; H, 7.71.

2,3,4,6-Tetramethoxyethylbenzene (IV). A solution of 12 g. (0.3 mole) of sodium hydroxide in 25 ml. of water was added slowly to a well stirred mixture of 32 g. (0.15 mole) of 2,3,5-trimethoxy-6-ethylphenol (III), 38 g. (0.3 mole) of dimethyl sulfate, and 25 ml. of ethanol during a period of 1.5 hr. while the temperature was maintained at 10–20°. Stirring was continued at room temperature for 4.5 hr., on the steam bath for 0.5 hr., and then the mixture was poured into an ice-water mixture and allowed to stand overnight. The low-melting solid was taken up in ether, the solution was dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was distilled under reduced pressure, b.p. 152–155°/20 mm., to give 30.6 g. (90%) of a colorless distillate which crystallized on standing; m.p. 38.5–41°. A sample, purified by two crystallizations from petroleum ether (b.p. 65–70°) at Dry Ice temperature, melted at 38.5–39° (F-J).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.71; H, 8.19.

2-Hydroxy-3,4,6-trimethoxy-5-ethylacetophenone (V). A solution of 10 g. (0.044 mole) of 2,3,4,6-tetramethoxyethylbenzene (IV) in 10 ml. of dry ether was added slowly to a stirred solution of 12 g. (0.09 mole) of aluminum chloride in 50 ml. of dry ether at −15 to −20°. This was followed by the dropwise addition of 6 g. (0.08 mole) of acetyl chloride. The pale yellow mixture was stirred at 0° for 4 hr. during which time the yellow, liquid complex began to separate. It was stirred for 2 hr. at room temperature and then allowed to stand overnight. The mixture, which had darkened on standing, was cooled to 0° and stirred vigorously while a solution of 12 ml. of concentrated hydrochloric acid in 80 ml. of water was added. A voluminous, vivid yellow precipitate appeared during the hydrolysis and disappeared subsequently. The hydrolysis mixture was heated on the steam bath for 0.5 hr., the ether was allowed to evaporate, the product was taken up in benzene, and the organic solution was extracted repeatedly with 5% sodium hydroxide. Acidification of the alkaline solution with dilute hydrochloric acid, extraction of the oily product with benzene, and evaporation of the solvent provided 6.0 g. (53%) of a dark brown oil. This was distilled under

(12) The carbon-hydrogen analyses were performed by Arthur Mendel of this Laboratory and by Drs. Weiler and Strauss, Oxford, England. All melting points and boiling points are uncorrected.

reduced pressure and a clear, orange-colored fraction which boiled at 117–127°/2 mm. was taken which weighed 5.22 g. (46%). A sample distilled at 0.3 mm. boiled at 117–118.5°. Molecular distillation of a portion of the latter at 24 microns gave a clear, orange-colored oil, n_D^{25} 1.5421.

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.38; H, 7.07.

An unsuccessful attempt was made to fractionate the nonphenolic portion of the product from the acetylation reaction. The oily material crystallized when it was cooled and seeded with 2,3,4,6-tetramethoxyethylbenzene, but melted when allowed to warm to room temperature. Treatment of the material with piperonal and aqueous sodium hydroxide produced a small yield of 2′,3′,4′,6′-tetramethoxy-5′-ethyl-3,4-methylenedioxychalcone (see below).

A sample of the phenol (V) was converted to 2,3,5-trimethoxy-4-ethyl-6-acetophenyl acetate by treatment with acetic anhydride and pyridine; m.p. 76–78°.

Anal. Calcd. for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 61.00; H, 6.50.

2,3,4,6-Tetramethoxy-5-ethylacetophenone (VI). A mixture of 7.6 g. (0.03 mole) of 2-hydroxy-3,4,6-trimethoxy-5-ethylacetophenone (V), 7.6 g. (0.06 mole) of dimethyl sulfate, and 5 ml. of ethanol was stirred and kept at about room temperature while a solution of 2.4 g. (0.06 mole) of sodium hydroxide in 5 ml. of water was added slowly. After the addition, a second quantity of 7.6 g. of dimethyl sulfate was added slowly, followed by 2.4 g. of sodium hydroxide in 5 ml. of water. During the latter addition, no attempt was made to control the temperature. The mixture was stirred for 1 hr. at room temperature, 0.5 hr. on the steam bath, cooled, and poured onto crushed ice. The product, which was solid at ice water temperature, was dissolved in benzene. The benzene solution was washed with sodium hydroxide and then washed free of alkali with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The pale yellow oil which remained weighed 7.2 g. (90%). It was distilled under reduced pressure; b.p. *ca.* 115°/0.9 mm.; n_D^{25} 1.5039. The product of a larger run was fractionated and a center cut, n_D^{25} 1.5033, was submitted for analysis.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.84; H, 7.26.

2′,3′,4′,6′-Tetramethoxy-5′-ethyl-3,4-methylenedioxychalcone. A mixture of 1.0 g. (0.0037 mole) of 2,3,4,6-tetramethoxy-5-ethylacetophenone (VI), 0.56 g. (0.0037 mole) of piperonal, and 4 ml. of ethanol was treated with a solution of 0.19 g. (0.0047 mole) of sodium hydroxide in 1.7 ml. of water at room temperature. As the somewhat dark, clear solution was stirred, the product began to separate as an oil, and after about 1 hr. it began to crystallize. The mixture was stirred 2 hr., allowed to stand 3 hr., and was then placed in the refrigerator overnight. The chalcone was collected, washed free of alkali with water, and recrystallized from dilute ethanol. The yield of nearly white needles, which melted at 108–109.5° with slight softening from 107°, was 1.44 g. (97%). The product of a larger run was recrystallized three times from ethanol-water; m.p. 108.5–109.5° (F-J).

Anal. Calcd. for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 66.17; H, 6.16.

2′-Hydroxy-3′,4′,6′-trimethoxy-5′-ethyl-3,4-methylenedioxychalcone (VII). One g. (0.0039 mole) of 2-hydroxy-3,4,6-trimethoxy-5-ethylacetophenone (V) was mixed with 4 ml. of ethanol, 0.60 g. (0.004 mole) of piperonal, and 2 ml. of 10% aqueous sodium hydroxide solution. The solution, which began to turn dark red when the base was added, was stirred for 3 hr. at room temperature. It was diluted with an equal volume of water, cooled, and acidified with dilute hydrochloric acid. The liquid phase was decanted from the orange-red, sticky precipitate and the residue was washed with water at 0°. It was dissolved in alcohol-water and cooled slowly with scratching to give orange needles. After recrystallization from ethanol-water, there was obtained 0.35 g. (23%) of the chalcone which melted at 106–107.5°. A sample, purified for analysis by several crystallizations from ethanol-water, melted at 108–109° (F-J).

Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 65.58; H, 5.90.

5,7,8-Trimethoxy-6-ethyl-3′,4′-methylenedioxyflavanone (VIII). This compound resulted when the preceding experiment was carried out on a 3-g. scale and was allowed to stand for 40 hr. without stirring. There was obtained 3.4 g. (76%) of yellow platelets which melted at 134–137°. After several recrystallizations from ethanol and ethanol-water, the flavanone was isolated in the form of square, colorless platelets which melted at 139–141° (F-J).

Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 65.11; H, 5.75.

The flavanone (VIII) and the isomeric chalcone (VII) were interconvertible by the action of small quantities of aqueous sodium hydroxide in alcoholic solution.

Reaction of 2-hydroxy-3,4,6-trimethoxy-5-ethylacetophenone (V) *with hydrogen bromide in acetic acid.* Following the general procedure outlined by Gardner, Horton, and Pincock,[5] a solution of 2.97 g. of 2-hydroxy-3,4,6-trimethoxy-5-ethylacetophenone (V) in 37 ml. of glacial acetic acid was treated with 7.5 ml. of 30% hydrogen bromide in glacial acetic acid. The solid product was recrystallized from benzene to give 0.37 g. (13%) of bright yellow crystals which melted at 113–114.5°. Evaporation of the mother liquor to dryness and recrystallization of the residue from petroleum ether (b.p. 65–70°) yielded 1.1 g. (39%) of additional material which melted at 105–110°. After several crystallizations from petroleum ether and ethanol-water, the product was obtained as bright yellow needles which melted at 114–115°.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.32; H, 6.78.

3,4,5-Trimethoxyphenyl acetate (X). Ten g. (0.054 mole) of 3,4,5-trimethoxyphenol (antiarol) was acetylated according to the method of Chapman, Perkin, and Robinson.[13] There was obtained 8.8 g. (71%) of white platelets which melted at 73–75° (F-J); lit.,[13] m.p. 74°. Neutralization of the mother liquor with solid sodium bicarbonate afforded a second crop of crystals which weighed 1.45 g. (12%); m.p. 73–74° (F-J).

2-Hydroxy-4,5,6-trimethoxyacetophenone (XII). (*A*) *By Fries rearrangement.* This compound was obtained in 45% yield by the Fries rearrangement of antiarol acetate (X) according to the method of Oliverio and Bargellini,[6] m.p. 29–30.5°; the reported yield was 54%, m.p. 41–42°.

(*B*) *By selective methylation of 2,5-dihydroxy-4,6-dimethoxyacetophenone* (XI). Eight g. (0.038 mole) of 2,5-dihydroxy-4,6-dimethoxyacetophenone (XI), prepared according to the method of Mauthner,[14] was dissolved in a solution of 3.75 g. (0.094 mole) of sodium hydroxide in 26 ml. of water. Six g. (0.048 mole) of dimethyl sulfate was added in one portion with vigorous shaking, which was continued for 15 min. and then occasionally for 1 hr. The mixture was diluted with 1 volume of water and extracted repeatedly with benzene. Evaporation of the solvent left a yellow oil which was dissolved in ether, and this solution was extracted with 10% sodium hydroxide. Removal of the ether gave 1.4 g. of crude 2,3,4,6-tetramethoxyacetophenone which melted at 50–54° (F-J).

The aqueous alkaline extract of the ether solution was acidified with dilute hydrochloric acid and the resulting oil was taken up in ether. Evaporation of the solvent gave a yellow oil which crystallized when it was cooled and seeded; yield, 2 g. (23%); m.p. near room temperature.

The original aqueous reaction mixture, which remained after the benzene extraction, was acidified with dilute hydrochloric acid, and extracted repeatedly with benzene. This

(13) E. Chapman, A. G. Perkin, and R. Robinson, *J. Chem. Soc.*, 3015 (1927).

(14) F. Mauthner, *J. prakt. chem.*, **147**, 287 (1936).

solution was washed with dilute hydrochloric acid, extracted with 5% sodium hydroxide, the alkaline solution was acidified, and the dark brown oil which separated was taken up in benzene and the solvent was evaporated. The residual oil was digested with ether to obtain 0.4 g. of a yellow, crystalline residue which was recrystallized from dilute ethanol; yield, 0.3 g.; m.p. 113–117° (F-J). This material, presumably the alternate monohydroxy isomer, *i.e.*, 3-hydroxy-2,4,6-trimethoxyacetophenone, was not characterized further. The ether was evaporated and the dark, semisolid product was stirred 3 times with petroleum ether (b.p. 65–70°). The residue weighed 0.73 g. and melted at 114–130° (F-J). On evaporation of the solvent, the filtrate afforded 2.2 g. (25%) of crude 2-hydroxy-4,5,6-trimethoxyacetophenone which melted at about room temperature.

The product of a larger run, based on 26 g. of 2,5-dihydroxy-4,6-dimethoxyacetophenone, was distilled and the distillate was treated with petroleum ether to remove high-melting components. The soluble portion was distilled again, the distillate, 14.4 g. (52%), b.p. 182–185°/14 mm., was chromatographed on alumina, and the portion which was eluted by petroleum ether was distilled. A fraction of the distillate, b.p. 121–122°/0.35 mm., was crystallized 3 times from dilute ethanol. The melting point of the pale yellow needles was 30.5–31.2° (F-J).

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.34; H, 6.20.

A sample of the 2-hydroxy-4,5,6-trimethoxyacetophenone was converted to its benzoate by the action of benzoyl chloride and pyridine; m.p. 86–87° (F-J); lit.[15] m.p. 87–88°

2,5-Dihydroxy-4,6-dimethoxyacetophenone (XI) also was converted to 2-hydroxy-4,5,6-trimethoxyacetophenone (XII) by the procedure of Baker,[7] yield, 17.5%, b.p. 178–181°/14 mm., m.p. 25° (F-J); lit.,[7] yield 15%, b.p. 184–186°/27 mm.

2-Ethyl-3,4,5-trimethoxyphenol (XIII). Nine g. (0.04 mole) of 2-hydroxy-4,5,6-trimethoxyacetophenone (XII), 30 ml. of methanol, and 0.63 g. of copper–chromium oxide catalyst were placed in a high-pressure hydrogenation apparatus. Hydrogen was admitted to an initial pressure of 2550 p.s.i. at room temperature, and the temperature was raised gradually to a maximum of 165° with shaking. The contents of the bomb were allowed to cool and were filtered through Filter-Cel to remove the catalyst. Evaporation of the solvent gave a white solid which weighed 8.14 g. (96%); m.p. 70–90° (F-J). It was recrystallized from methanol-water and then from petroleum ether (b.p. 65–70°) to give 6.5 g. (76%) of white needles; m.p. 95–95.5° (F-J). Three additional recrystallizations from petroleum ether failed to change the melting point.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.28; H, 7.53.

The identity of the compound was further confirmed by converting 0.2 g. of it to 2,3,4,6-tetramethoxyethylbenzene (VI) by means of an excess of dimethyl sulfate and aqueous sodium hydroxide solution. The product weighed 0.12 g. (56%), melted at 37.5–38.5° (F-J), and did not depress the melting point of an authentic sample of 2,3,4,6-tetramethoxyethylbenzene.

2-Ethyl-3,4,5-trimethoxyphenyl acetate (XIV). A mixture of 0.5 g. (0.002 mole) of 2-ethyl-3,4,5-trimethoxyphenol (XIII), 2.5 ml. of acetic anhydride, and 12 drops of anhydrous pyridine was refluxed for 1 hr. and then poured onto ice. Isolation of the product gave 0.56 g. (93%) of a pale yellow oil. The product of a larger run was obtained in 98.5% yield; n_D^{25} 1.5041. A portion was distilled in order to obtain a sample for analysis. Two fractions were taken; (I) b.p. 112–113°/1 mm., n_D^{25} 1.5041; and (II) b.p. 112–113°/1 mm., n_D^{25} 1.5041. The refractive index of the undistilled portion remained at n_D^{25} 1.5041.

(15) V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **23A**, 262 (1946).

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 60.94; H, 7.07.

2-Hydroxy-4,5,6-trimethoxy-3-ethylacetophenone (IX). A solution of 10 g. (0.039 mole) of 2-ethyl-3,4,5-trimethoxyphenyl acetate (XIV) in 30 ml. of dry nitrobenzene was added gradually to a cooled, stirred solution of 5.25 g. (0.039 mole) of anhydrous aluminum chloride in 30 ml. of dry nitrobenzene. The mixture was stirred as it warmed slowly to room temperature, and then was allowed to stand for 60 hr. The dark brown reaction mixture was hydrolyzed with ice and hydrochloric acid, extracted with ether, and the ether solution was extracted several times with excess 5% sodium hydroxide. None of the desired product was isolated from the alkaline extracts, although two crystalline, unidentified substances were obtained in low yield. The ether and nitrobenzene were removed by steam distillation from the solution which remained after the alkali extraction. The residual oil was separated from the water by means of methylene chloride, the organic solution was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Treatment of the brown, oily residue with petroleum ether (b.p. 65–70°) furnished a solid, crystalline material which melted at 146.5–148.5° (F-J). It was not identified. Extraction of the remaining solution several times with 10% sodium hydroxide, acidification of the extracts, isolation and distillation of the dark red-brown oil which separated afforded *ca.* 0.2 g. of impure 2-hydroxy-4,5,6-trimethoxy-3-ethylacetophenone (IX). An additional quantity of product was isolated from the solution which remained after the alkali extraction by evaporating the solvent from the dried solution, dissolving the residue in petroleum ether, and filtering the latter solution through alumina. The alumina was washed with petroleum ether until no yellow color appeared in the filtrate, the filtrates were combined, and the solvent was evaporated to obtain 2.25 g. of a red-brown oil, n_D^{25} 1.5260, which was distilled under reduced pressure. Three fractions were taken: (I) 0.24 g., b.p. 96–99°/0.15 mm., n_D^{25} 1.5300; (II) 0.35 g., b.p. 98–102°/0.15 mm., n_D^{25} 1.5293; and (III) 0.22 g., b.p. 102–105°/0.15 mm., n_D^{25} 1.5294. Fraction II was submitted for analysis.

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 60.85; H, 7.14.

2'-Hydroxy-3'-ethyl-4',5',6'-trimethoxy-3,4-methylenedioxychalcone. A mixture of 0.16 g. of 2-hydroxy-4,5,6-trimethoxy-3-ethylacetophenone (IX), 1 ml. of 10% aqueous sodium hydroxide, 0.16 g. of piperonal, and 4 ml. of ethanol was allowed to stand for several hours at room temperature. It was diluted with water, cooled, and acidified with dilute hydrochloric acid. The resulting orange-colored, gummy precipitate was crystallized 4 times from ethanol-water to give orange needles which melted at 103–104° (F-J).

Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 65.18; H, 5.87.

A mixture of this compound and the piperonal chalcone of 2-hydroxy-3,4,6-trimethoxy-5-ethylacetophenone (m.p. 108–109°) melted at 86–97°. The infrared spectra of these isomers were similar, but not identical.

2,4-Dihydroxy-3,6-dimethoxyacetophenone (XVI). This material was prepared from 1,4-dimethoxy-2,6-dibenzyloxybenzene (XV)[8] in 47% yield by the method of Sastri and Seshardi[9]; m.p. 125–130°. When the crude product was recrystallized from water, a small quantity of a molten material was recovered by filtering the hot mixture. It was crystallized from methanol and found to be 2-hydroxy-3,6-dimethoxy-4-benzyloxyacetophenone (XVII); m.p. 111–111.5° (F-J).

2-Hydroxy-3,6-dimethoxy-4-benzyloxyacetophenone (XVII). This compound was prepared in 53% yield, m.p. 110–111.5° (F-J), from the proportions of 2,4-dihydroxy-3,6-dimethoxyacetophenone (XVI), benzyl chloride, potassium carbonate, and acetone suggested by Geissman[11] with a reflux period of 24 hr. Geissman reports a melting point of 109–110°.

2,3,6-Trimethoxy-4-benzyloxyacetophenone (XVIII). A mixture of 4.0 g. (0.013 mole) of 2-hydroxy-3,6-dimethoxy-4-benzyloxyacetophenone (XVII), 10 g. (0.08 mole) of dimethyl sulfate, and 10 ml. of ethanol was stirred while a solution of 3.2 g. (0.08 mole) of sodium hydroxide in 8 ml. of water was added during the period of about 1 hr. After stirring the mixture for an additional 2 hr., it was poured onto ice, and stirring and scratching caused the oily product to solidify. It was collected by filtration, washed free of alkali with water, and dried in the air. The yield of white, crystalline powder was 4.2 g. (100%); m.p. 74–75° (F-J). After 1 recrystallization from petroleum ether (b.p. 65–70°), it melted at 74.5–75.5° (F-J).

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.39; H, 6.23.

2,3,5-Trimethoxy-4-ethylphenol (XIX). A mixture of 4.0 g. (0.013 mole) of 2,3,6-trimethoxy-4-benzyloxyacetophenone (XVIII), 0.5 g. of copper chromium oxide catalyst, and 100 ml. of methanol, under hydrogen at a pressure of 2500 p.s.i. at 22°, was shaken and heated to 150–155° for 1.5 hr. The mixture was cooled, filtered, and the solvent was evaporated to obtain an oil which crystallized. The tan crystals, 2.61 g. (97.5%), melted at 50–58° (F-J). After 3 recrystallizations from petroleum ether and one from methanol-water, the product melted at 62–63° (F-J).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.13; H, 7.62.

2,3,5-Trimethoxy-4-ethylphenyl acetate (XX). Six ml. of acetic anhydride and 1 drop of concentrated sulfuric acid were added to 1.1 g. (0.0052 mole) of 2,3,5-trimethoxy-4-ethylphenol (XIX). The mixture, which warmed slightly, was allowed to stand for 1 hr. at room temperature, then was warmed on the steam bath for 10 min., and finally was poured onto crushed ice. After several hours, the oil was taken up in carbon tetrachloride, the organic solution was washed with water, dried over anhydrous sodium sulfate, and the solvent was evaporated *in vacuo*. A pale yellow, viscous oil remained; yield, 1.33 g. (100%); n_D^{25} 1.5007. A center cut (b.p. 115–116°/1 mm.) from the fractionation of the product of a larger run was submitted for analysis; n_D^{25} 1.5022.

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 60.99; H, 7.46.

Fries rearrangement of 2,3,5-trimethoxy-4-ethylphenyl acetate (XX). A solution of 0.65 g. (0.0049 mole) of anhydrous aluminum chloride in 25 ml. of anhydrous nitrobenzene was stirred at 0° while a solution of 1.2 g. (0.0047 mole) of 2,3,5-trimethoxy-4-ethylphenyl acetate (XX) in 25 ml. of nitrobenzene was added dropwise during about 20 min. The mixture was stirred while it warmed slowly to room temperature, and it was allowed to stand for about 60 hr. It was treated at 0° with a solution of 1 ml. of concentrated hydrochloric acid in 9 ml. of water, and hydrolysis was completed at room temperature. The mixture was extracted with benzene, the benzene solution was washed with water and then extracted several times with 10% aqueous sodium hydroxide. The alkaline extracts were combined, cooled, and acidified with dilute hydrochloric acid. The precipitated oil was taken up in methylene chloride, the solution was washed with water, dried over anhydrous magnesium sulfate, and the solvent was evaporated. There was obtained 0.47 g. (about 39%) of a brown, viscous oil which smelled faintly of nitrobenzene; n_D^{25} 1.5328. A drop of this crude product, treated with 10% sodium hydroxide solution and piperonal in ethanol, gave a few orange crystals; m.p. 106–107° (F-J). Further alkali extraction of the original organic solution provided an additional 0.15 g. (12%) of brown oil; n_D^{25} 1.540.

The latter material was converted to its piperonal chalcone. The purified product melted at 108–109°, and when mixed with the previously prepared 2′-hydroxy-3′,4′,6′-trimethoxy-5′-ethyl-3,4-methylenedioxychalcone (VII), it melted at 107–108.5° (F-J). The infrared spectra of the two compounds were found to be identical.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF UNION CARBIDE CHEMICALS COMPANY]

Reaction of *o*-Alkenylphenols with Peracetic Acid

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The reaction of *o*-allylphenol and *o*-propenylphenol with peracetic acid has been reported to give *o*-2,3-epoxypropylphenol and *o*-1,2-epoxypropylphenol, respectively. Investigation of these reactions has shown that the product from *o*-allylphenol is 2-hydroxymethylcoumaran. *o*-Crotylphenol forms a similar heterocyclic derivative. The epoxides appear to be intermediates in this reaction. The product from *o*-propenylphenol is 1-(*o*-hydroxyphenyl)-2-propanone. This compound is formed by the loss of acetic acid from an intermediate product, 1-(*o*-hydroxyphenyl)-2-hydroxypropyl acetate, rather than by rearrangement of an epoxide intermediate.

The study of the synthesis and reactions of peracetic acid was initiated in this laboratory several years ago. In connection with this work the reaction of peracetic acid with *o*-alkenylphenols was briefly investigated. This reaction has been reported[1] to give the expected epoxides in reasonable yield; thus, *o*-allylphenol and *o*-propenylphenol reportedly gave *o*-2,3-epoxypropylphenol and *o*-1,2-epoxypropylphenol, respectively, by treatment with concentrated (73–93%) peracetic acid. It was further reported that the *o*-2,3-epoxypropylphenol, upon boiling with acetic anhydride, yielded *o*-2,3-epoxypropylphenyl acetate and that *o*-1,2-epoxypropylphenol, upon standing in a desiccator over sulfuric acid, gave 2-methylcoumarone.

In our study *o*-allylphenol was allowed to react with a 28% solution of peracetic acid in ethyl acetate at 20–30° and a product was obtained which had the same physical properties as that reported by the previous workers,[1] but which contained no epoxide group as determined by HBr analysis. The product was converted to a monoacetate by boiling with acetic anhydride; however, this acetate was markedly different from an authentic sample

(1) V. I. Pansevich-Kolyada and Z. B. Idel'chik, *J. Gen. Chem. U.S.S.R.*, **24**, 809 (1954) (Eng. Trans.)