Experimental

Diphenylphosphonic Acid.—Phenylmagnesium bromide (from 31.4 g. of bromobenzene and 4.86 g. of magnesium in 200 cc. of absolute ether) solution was diluted to 500 cc. by absolute ether, filtered with exclusion of air and added slowly (three and one-half hours) to a gently refluxing stirred solution of 30.6 g. of phosphorus oxychloride in 500 cc. of absolute ether; after standing overnight the ether solution was decanted from the solid precipitate and the latter treated with 200–300 g. of ice-water. The white solid which was insoluble in water was washed with water and triturated with 1 l. of warm dilute sodium hydroxide solution, filtered and filtrate acidified with dilute hydrochloric acid. The precipitated diphenylphosphonic acid was filtered, dried and recrystallized from dilute alcohol; m. p. 190–192°; yield 12 g., 55%. The sodium hydroxide-insoluble solid on repeated recrystallization yielded 4 g. of triphenylphosphine oxide, m. p. 152–153° (from dilute alcohol).

***bis-p*-Chlorophenylphosphonic Acid.**—The Grignard reagent from 39 g. of *p*-chlorobromobenzene was diluted to 400 cc. with absolute ether and added in the course of one and one-half hours to a gently refluxing stirred solution of 30.6 g. of phosphorus oxychloride in 500 cc. of absolute ether. After standing overnight, the reaction mixture was worked up as above, yielding 15 g. (51%) of *bis-p*-chlorophenylphosphonic acid, m. p. 133–135° (from dilute alcohol) and 4.5 g. of *tris-p*-chlorophenylphosphine oxide, m. p. 171–2.5° (from dil. alcohol).

Anal. Calcd. for $C_{12}H_9O_2PCl_2$: eq. wt., 287; Cl, 24.7. Found: eq. wt., 283; Cl, 24.58.

Summary

An improved method for the preparation of *bis*-arylphosphonic acids has been devised in which phosphorus oxychloride is treated with Grignard reagents in dilute solution.

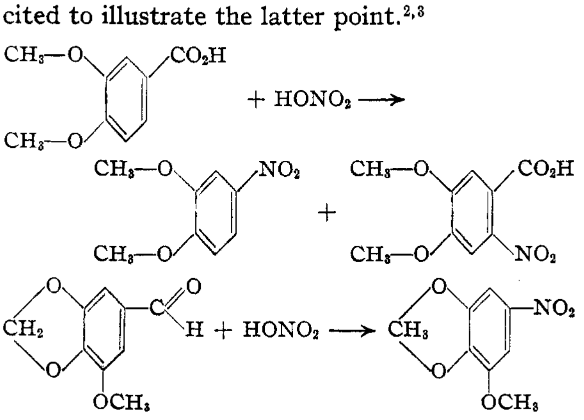
DAYTON, OHIO RECEIVED AUGUST 13, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

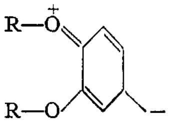
Studies in the Veratrole and Methylenedioxybenzene Series

BY RICHARD T. ARNOLD AND FREDERICK BORDWELL[1]

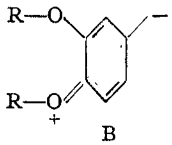
Interest in the veratrole (*o*-dimethoxybenzene) and methylenedioxybenzene (1,3-benzodioxole) compounds has been aroused largely for two reasons. First, these nuclei frequently make up important component parts of well known naturally occurring substances (opium alkaloids, apioles, etc.); and, second, the parent substances have exceedingly reactive benzenoid rings which orient incoming substituents in a unique and (according to the classical orientation rules) unpredictable manner. Two typical examples may be cited to illustrate the latter point.[2,3]



The remarkable susceptibility of these aromatic rings to attack by electrophilic reagents at the positions para to the oxygen atoms can be accounted for by resonance contributing structures of the type A and B.



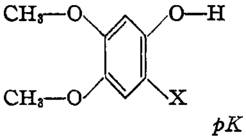
A

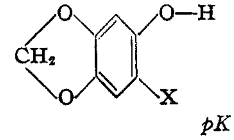


B

In spite of the easily recognizable similarities, it is well established that the benzenoid ring of methylenedioxybenzene is more reactive than that of veratrole.[4]

To enable us to make a comparative study of the aromatic bond types in these two series we have prepared a number of substituted phenols (I–IX below) and have measured their *pK* values under identical circumstances. These values were determined by measuring the *p*H of half-





	pK		*pK*
I, X = —CHO	9.12	V, X = —CHO	8.90
II, X = —CN	8.69	VI, X = —CN	8.41
III, X = —NO₂	8.33	VII, X = —NO₂	8.17
IV, X = —CO₂H	4.60	VIII, X = —CO₂H	4.58

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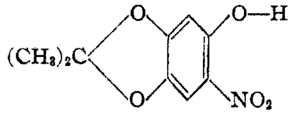
[1] Abstracted from a Ph.D. thesis submitted to the Graduate School in July, 1941.

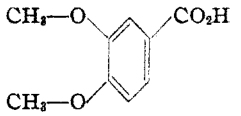
[2] Tiemann and Matsumoto, *Ber.*, **9**, 937 (1876).

[3] Salway, *J. Chem. Soc.*, **95**, 1155 (1909).

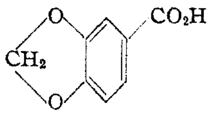
[4] Hudson and Robinson, *J. Chem. Soc.*, 715 (1941).



IX, $pK = 8.68$
(8.28 calcd. for 50% ethanol)



X, $pK = 6.21$



XI, $pK = 6.19$

neutralized solutions of the phenols in ethanol solutions (50% by volume). The value for compound IX was measured in 67% ethanol because of its relative insolubility.

It will be noticed that the pairs of related compounds X and XI, as well as IV and VIII, have the same acidity. The high acidity of *o*-hydroxy acids has been adequately explained by Branch and Yabroff.[5]

A comparison of I, II and III with V, VI and VII reveals that the methylenedioxy derivatives are more acidic than those of the veratrole series by 0.2–0.3 *pK* units. Such slight differences may be due to a combination of factors: a slight increased double bond character in the methylenedioxybenzene ring between the carbon atoms attached to groups OH and X,[6] dipolar effects and resonance effects.[7]

Nevertheless, the above discussed differences are so small that one must conclude that the benzenoid rings in the two series under consideration are very much alike. As Sutton and Pauling[8] have pointed out, however, "a small influence exerted on the benzene ring can produce important changes in reaction velocity."

Failures to prepare a number of the compounds described here have been reported.[9,16] In several other cases worthwhile modifications of reported syntheses are described.

Experimental

Methyl Veratrate.—Veratraldehyde was oxidized by a procedure similar to that used for the oxidation of piperonal[10]; the yield of veratric acid was 88%. This material was dissolved in ten times its weight of methanol and saturated with hydrogen chloride. After standing overnight the solution was distilled and yielded 73% of the ester; b. p. 165° (15 mm.); m. p. 58–59°.

Methyl 5-Nitroveratrate.—Since the method of Zincke and Francke[11] gave poor results in our hands, the following procedure was employed. Twenty-one grams of methyl veratrate was dissolved in 50 cc. of glacial acetic acid and while this solution was being stirred and cooled in an ice-bath, 100 cc. of nitric acid (d. 1.59) dissolved in 50 cc. of acetic acid was added during the course of one hour. Stirring was continued for two hours and the solution was then poured into ice water. The nitro ester was recrystallized from 600 cc. of methanol; yield 23.2 g.; m. p. 144–145°.

Methyl 5-Aminoveratrate.—The corresponding nitro compound dissolved in five times its weight of methanol was reduced at 110° with Raney nickel and hydrogen at 1000 pounds pressure; yield 80%; m. p. 128–129°. Zincke and Francke,[11] using stannous chloride, report a melting point of 133°.

Methyl 5-Hydroxyveratrate.—This substance has been obtained by direct esterification of the hydroxy acid[12] and from the amino ester.[11] Zincke and Francke[11] claimed poor yields and did not describe their procedure.

The amino ester (11.9 g.) was powdered and added to a warm solution of 13 cc. of sulfuric acid in 60 cc. of water. Cooling gave a thick paste of the amine salt which was diazotized with 4.0 g. of sodium nitrite in 15 cc. of water. The hydroxy ester was obtained pure by adding the diazonium solution dropwise to boiling copper sulfate solution. The yield of ester which steam distilled was 8.7 g.; m. p. 95–96° after one recrystallization from methanol.

5-Hydroxyveratric Acid.—The acid was obtained from the ester by refluxing the latter with sodium hydroxide (5%) until solution was effected. Acidification gave a white solid; m. p. 204–205° (dec.). Clark[13] reports 201–202°.

5-Hydroxyveratraldehyde.—Six grams of aminoveratraldehyde[14] was added to 400 cc. of water and treated with 6.0 g. of sulfuric acid in 100 cc. of water to form a suspension. Two grams of sodium nitrite in a saturated solution was added to the cold, well-stirred suspension. After one and one-half hours the solution was filtered and decomposed in boiling copper sulfate solution. The steam distillate was extracted with ether and there was obtained 2.8 g. of hydroxyaldehyde. Recrystallization from ethanol gave a product melting at 106–107°. Robertson[15] reports 107°.

Methyl 6-Aminopiperonylate.—The method described below is a modification of Bogert and Elder's[9] procedure which gave a much more pure product.

The amino ester (9.3 g.) was suspended in a mixture of 10 cc. of sulfuric acid and 50 cc. of water. Diazotization was accomplished with 3.4 g. of sodium nitrite dissolved in 20 cc. of water. The diazonium solution was diluted with four times its volume of water and added dropwise to a boiling solution of copper sulfate (50%). The steam distilled ester was perfectly white and weighed 6.9 g. after recrystallization from aqueous methanol solutions; 100–101°. The over-all yield to this point is 36% as compared to 18% reported earlier.[9]

6-Hydroxypiperonal.—The diazotization of aminopiperonal proved difficult and the use of dilute solutions was found to be distinctly advantageous.

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(5) Branch and Yabroff, THIS JOURNAL, **56**, 2568 (1934).

(6) Arnold and Sprung, *ibid.*, **61**, 2475 (1939).

(7) Kossiakoff and Springall, *ibid.*, **63**, 2223 (1941).

(8) Sutton and Pauling, *Trans. Faraday Soc.*, **31**, 939 (1935).

(9) Bogert and Elder, THIS JOURNAL, **51**, 534 (1929).

(10) Shriner and Kleiderer, "Organic Syntheses," Vol. 10, J. Wiley and Sons, New York, N. Y., 1930, p. 82.

(11) Zincke and Francke, *Ann.*, **293**, 190 (1896).

(12) Hemmelmayr, *Monatsh.*, **35**, 6 (1914).

(13) Clark, THIS JOURNAL, **53**, 3434 (1931).

(14) Rilliet, *Helv. Chim. Acta*, **5**, 547 (1922).

(15) Robertson and Head, *J. Chem. Soc.*, 2434 (1930).

The aminoaldehyde (10.6 g.) was powdered and suspended in 300 cc. of water. To this mechanically stirred suspension was added 10 cc. of sulfuric acid in 80 cc. of water. To the cool well-stirred suspension 4.5 g. of sodium nitrite in 50 cc. of water was added dropwise. After standing for thirty minutes the solution was filtered and slowly decomposed with copper sulfate solution as described above. Six to eight liters of distillate was collected; yield 5.2 g.; m. p. 125–126°.

Anal. Calcd. for $C_8H_6O_4$: C, 57.82; H, 3.64. Found: C, 57.68; H, 3.69.

6-Hydroxypiperonal Oxime.—The oxime was obtained quantitatively by treating 1.0 g. of the aldehyde in 7 cc. of ethanol with 0.8 g. of hydroxylamine hydrochloride and 0.6 g. of sodium carbonate in a few cubic centimeters of water. The mixture was warmed on a steam-bath for thirty minutes and then poured into water. After recrystallization from benzene the compound melted at 142.5–143.5°.

Anal. Calcd. for $C_8H_7O_4N$: C, 53.02; H, 3.90. Found: C, 53.17; H, 3.86.

6-Hydroxypiperononitrile.—6-Hydroxypiperonal oxime (3.1 g.) was refluxed for twenty minutes with 15 cc. of acetic anhydride and the solution was poured into 50 cc. of cold water. In one hour the solution was filtered and the solid product was gently refluxed with 15 cc. of sodium hydroxide (10%). About 15 cc. of water was added to keep the sodium salt in solution. After ten minutes the solution was neutralized with hydrochloric acid. The precipitate tenaciously held water and was dried overnight in a vacuum desiccator. Several recrystallizations from alcohol and a final one from benzene gave a substance (2.0 g.) melting at 220–225° (dec.).

Anal. Calcd. for $C_8H_5O_3N$: C, 58.87; H, 3.09. Found: C, 59.02; H, 3.00.

5-Hydroxyveratraldehyde Oxime.—This oxime was prepared as described above for the corresponding piperonal derivative; yield 90%; m. p. 146–147°.

Anal. Calcd. for $C_8H_5O_3N$: C, 54.82; H, 5.58. Found: C, 55.01; H, 5.79.

5-Hydroxyveratronitrile.—This compound was obtained in a 90% yield as described above for 6-hydroxypiperononitrile. The nitrile sinters at 120° and melts with decomposition at 142–145°.

Anal. Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.02. Found: C, 60.18; H, 4.99.

6-Acetoxypiperonal.—Following the directions given by Robertson and Head[15] in their preparation of 5-acetoxyveratraldehyde, 1.0 g. of hydroxypiperonal was dissolved in 4 cc. of pyridine and the solution was cooled until the whole solidified. To this was added 12 cc. of acetic anhydride and the mixture was kept at 35–40° for twenty hours before pouring into 125 cc. of water. The precipitate was recrystallized from aqueous alcohol and appeared as beautiful needles; yield 4.4 g.; m. p. 126–127°. A mixed melting point determination with the original aldehyde gave a value of 100° with considerable range.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.69; H, 3.85. Found: C, 57.36; H, 3.92.

6-Acetoxypiperonylic Acid.—While the phenolic hydroxyl group of the hydroxy acid could be acetylated readily in the presence of sulfuric acid and acetic anhydride, a pure product could be obtained only after numerous recrystallizations. The difficulties encountered by Bogert and Elder[9] are readily understandable. The oxidation of the corresponding aldehyde proved most satisfactory.

One gram of the acetoxyaldehyde was dissolved in 25 cc. of acetone and to this was added 1.3 g. of potassium permanganate in 30 cc. of water. After warming on a water-bath for fifteen minutes the mixture was treated with sulfur dioxide. The acetone was evaporated and the acetoxy acid was filtered immediately. The product was thoroughly dried in a vacuum desiccator and recrystallized from benzene; yield 0.67 g.; m. p. 149–150° (dec.).

Anal. Calcd. for $C_{10}H_8O_6$: C, 53.55; H, 3.60. Found: C, 53.78; H, 3.78.

5-Hydroxy-6-nitro-1,3-benzodioxole.—One gram of the nitroamine was added to a mixture of 25 cc. of water and 5 cc. of concentrated sulfuric acid. The cold solution was diazotized with a slight excess of sodium nitrite and the resulting diazonium salt was decomposed by boiling copper sulfate solution. The yellow nitrophenol steam distilled as it was formed; yield 0.4 g.; m. p. 82.5–84°.

Balaban[16] has reported an unsuccessful attempt to prepare this substance.

Anal. Calcd. for $C_7H_5O_5N$: C, 45.90; H, 2.73. Found: C, 46.24; H, 2.65.

4-Hydroxy-5-nitroveratrole.—This phenol is best prepared from 4-acetamido-5-nitroveratrole.[17]

The acetanilide (2.6 g.) was refluxed with 10 cc. of sulfuric acid in 24 cc. of water for fifteen minutes. The deep red solution was cooled and diazotized with 0.8 g. of sodium nitrite dissolved in a few cubic centimeters of water. Decomposition by the copper sulfate method followed by steam distillation gave 1.4 g. of the nitrophenol; m. p. 142–143°.

Anal. Calcd. for $C_8H_9O_5N$: C, 48.24; H, 4.55. Found: C, 48.58; H, 4.68.

5-Acetamido-2,2-dimethyl-1,3-benzodioxole.—From 5-nitro-2,2-dimethyl-1,3-benzodioxole[18] dissolved in two volumes of ethanol there was obtained an 85% yield of amine by reduction with hydrogen and Raney nickel. Acetylation in the usual way with acetic anhydride and a trace of sodium acetate gave a 95% yield of the acetanilide derivative; m. p. 108.5–109.5°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.77; H, 6.47. Found: C, 63.68; H, 6.40.

5-Hydroxy-6-nitro-2,2-dimethyl-1,3-benzodioxole.—Four grams of the above described nitroacetanilide was hydrolyzed by warming for twenty minutes with 35 cc. of methanol containing 2.0 g. of potassium hydroxide. The nitroamine weighed 3.0 g.; m. p. 127–128°. Sloof[18] reports 127°.

Diazotization of the amine was exceedingly slow. Approximately 0.8 g. of amine was suspended in a mixture containing 6 cc. of sulfuric acid (d. 1.84) and 50 cc. of water. The cooled suspension was diazotized with 0.33 g. of sodium nitrite in a few cubic centimeters of water, and after standing for one hour the solution was decomposed

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(16) Balaban, *J. Chem. Soc.*, 1088 (1929).

(17) Jones and Robinson, *ibid.*, **111**, 903 (1918).

(18) Sloof, *Rec. trav. chim.*, **54**, 995 (1935).

with boiling copper sulfate; yield 0.1 g.; m. p. 148–149°. All attempts to raise this yield by a variation of conditions failed.

Anal. Calcd. for $C_9H_9O_5N$: C, 51.18; H, 4.26. Found: C, 51.24; H, 4.00.

Summary

1. Nine negatively substituted phenols in the veratrole and methylenedioxybenzene series have been prepared.

2. A measure of the relative acidities of these compounds strongly indicates that the benzenoid rings in the two series are very comparable in structure.

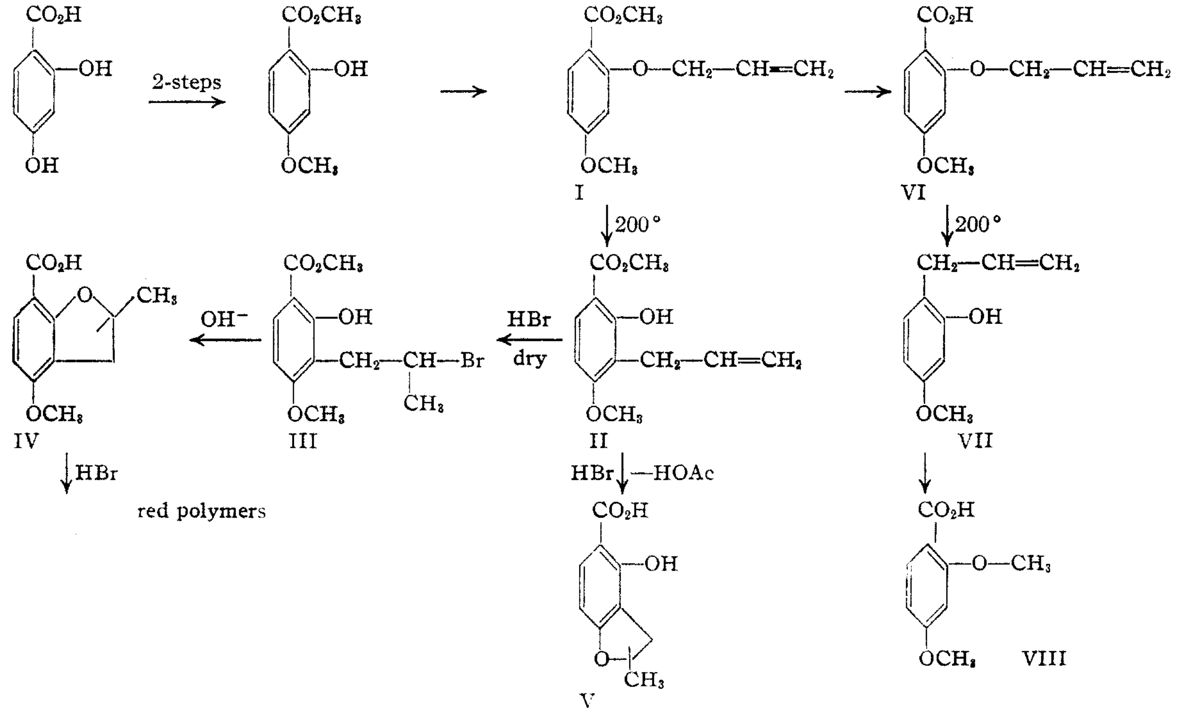
MINNEAPOLIS, MINN. RECEIVED SEPTEMBER 21, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Studies in the Coumaran Series

BY RICHARD T. ARNOLD AND JOHN MORAN

In an attempt to ascertain whether or not the coumaran heterocyclic ring is partially cleaved to an opened chain intermediate in the presence of reagents which split ordinary ethers, we have prepared 2-methyl-4-methoxy-7-carboxycoumaran IV and subjected this molecule to treatment with concentrated solutions of hydrobromic acid. Unfortunately no successful conditions were found for effecting this transformation directly. All experiments dealing with the cleavage of IV gave unidentifiable red polymers.[1,2] We wish to describe, however, a number of syntheses carried out during the course of this investigation. These can be summarized as follows



If during the cleavage of the methoxyl group the cyclic ether does form an opened chain derivative, it is to be expected that recyclization would involve the hydroxyl group para to the carboxyl group rather than that in the ortho position since the latter is rather firmly held in a chelate ring structure.

Substitution studies have repeatedly shown that the resorcinol nucleus is preferentially attacked at that position ortho to one hydroxyl group and para to the other. The thermal rearrangement of monoallylresorcinol[3] leads to the 1,2,4 configura-

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[1] Schales, *Ber.*, **70**, 116 (1937).

[2] Niederl and Storch, THIS JOURNAL, **55**, 4549 (1933).

[3] Hurd, Greengard and Pilgrim, *ibid.*, **52**, 1700 1930).