acid chloride.[10] Cyclopentyl, cyclohexyl and cycloheptyl methyl ketone were prepared by an adaptation of the procedure of Newman and Booth,[11] involving the addition of the appropriate alkylmagnesium halide to acetic anhydride at −70°. Cycloheptyl methyl ketone (b.p. 86–87° at 16 mm.; $n^{20}D$ 1.4622; *Anal.* Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.27; H, 11.36) formed a 2,4-dinitrophenylhydrazone, orange-yellow needles from ethanol, m.p. 117–118°, and a semicarbazone, colorless plates from 50% ethanol, m.p. 175–176°.

Commercial samples of cyclopropyl methyl ketone and isopropyl methyl ketone were purified by distillation. Perbenzoic acid was prepared according to Braun.[12]

Preparative Scale Reactions.—In a typical reaction of the series given in Table I, approximately 0.1 mole of the ketone was mixed with that volume of a standardized chloroform solution of perbenzoic acid containing roughly a 10–15% stoichiometric excess of the peracid, and the reaction progress was followed by removal of 1-ml. aliquots of the reacting solution at intervals and determination of residual peracid iodimetrically.[3]

On completion of the reaction, the benzoic and perbenzoic acids were removed by extraction with a 1 *M* sodium bicarbonate solution, followed by a water wash. The combined aqueous phases were extracted with ether, and the ether and chloroform solutions combined and dried. Distillation of the solvent, followed by fractionation of the residual oil, gave the ester products whose properties are indicated in Table I.

Further identification of each ester was provided by its saponification equivalent and the preparation of a derivative of the alcohol and/or acid fraction after alkaline hydrolysis.

Rate Runs.—A known amount of the ketone was weighed, or pipetted from a standard solution of the ketone in dry chloroform, into a glass-stoppered volumetric flask used for the reaction. An aliquot of a standard solution of perbenzoic acid was added and the solution made nearly to volume with dry chloroform. The flask was placed in a constant temperature bath controlled to 0.02°, allowed to come to temperature and made to volume, and the course of the reaction followed by the withdrawal of 2-ml. aliquots for iodimetric determination of residual peracid.

In runs designed to investigate acid catalysis, weighed amounts of acetic or benzoic acid were added to the ketone solution before the addition of the perbenzoic acid.

When 40 or 60% *sym*-tetrachloroethane in chloroform was employed as the solvent, a 10-ml. aliquot of a standard solution of the ketone in a tetrachloroethane was placed in a 25-ml. volumetric flask and a 10-ml. aliquot of standard chloroform solution of perbenzoic acid added. After thermostating, the solution was made to volume with chloroform or tetrachloroethane, providing a 40 or 60% solution, respectively.

Runs for the evaluation of any one factor were carried out at the same time, using identical aliquots of the same solution of perbenzoic acid.

Infrared Spectra.—Sample and blank tracings in the carbonyl region were obtained using a Perkin-Elmer Recording Infrared Spectrometer, Model 12 A-B. Purified liquid samples were used without solvent in a cell of 0.025 mm. thickness.

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[10] R. Pinson, Jr., and S. L. Friess, THIS JOURNAL, **72**, 5333 (1950).

[11] M. S. Newman and W. T. Booth, *ibid.*, **67**, 154 (1945).

[12] G. Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 431.

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

Reactions of Peracids. VII. Nuclear Oxidation of Aromatic Ethers with Perbenzoic Acid

BY S. L. FRIESS,[1] A. H. SOLOWAY,[2] B. K. MORSE AND W. C. INGERSOLL

The methyl ethers of certain phenols have been found to undergo extensive and rapid nuclear oxidation on treatment with perbenzoic acid in chloroform solution. In general, sensitivity to peracid attack in terms of moles of peracid consumed per mole of compound was observed to be a function of both the degree of methoxylation present in the molecule and the relative positions of these groups. The fully methylated ethers of hydroquinone, phloroglucinol, pyrogallol and resorcinol furnished *p*-quinones as isolable products following spontaneous reaction with limited amounts of peracid; veratrole yielded dimethyl muconate as a primary fragment. No stable product could be isolated from the peracid reaction with anisole, although the ether consumed well over two moles of peracid in a reaction characterized by the usual production of color. Some kinetic studies were made at −12.4° on the initial portion of the highly exothermic reaction of phloroglucinol trimethyl ether with perbenzoic acid. The results obtained seem to be best fitted by a reaction scheme involving the consumption of two moles of peracid in the initial oxidation phase.

Introduction

Previous work in the field has indicated that aromatic nuclei which are quite reactive toward electrophilic agents are also readily attacked by peracids. For example it was found[3] that active aromatic carcinogens such as methylcholanthrene and benzpyrene react rapidly with perbenzoic acid. It has also been noted[4] that mesitylene, acetomesitylene and trimethylgallic acid spontaneously consume more than two moles of perbenzoic acid per mole of each respective compound. From the reactions of the latter two compounds, products were isolated which indicated that extensive ring cleavage had accompanied the general peroxidation process.

Also, several naphthols and phenols were found[5] to react with peracetic acid, with the formation of *o*- and *p*-quinones in appreciable yield accompanying the normal ring cleavage[6] process. Similarly, Fernholz[7] has observed that certain phenyl and naphthyl ethers are oxidized by perbenzoic and peracetic acids to yield quinones and esters as isolable products. Finally, in quite recent work, Christensen and co-workers[8] and also Bader[9] have observed the formation of a complex naphthoquinone in the molybdate-catalyzed hydrogen peroxide oxidation of β-naphthol.

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[1] Naval Medical Research Institute, Bethesda, Md.

[2] Beaunit Mills Fellow in Chemistry, 1950–1951.

[3] H. J. Eckhardt, *Ber.*, **73**, 13 (1940).

[4] S. L. Friess and A. Miller, THIS JOURNAL, **72**, 2611 (1950).

[5] J. Böeseken and M. L. von Konigsfeldt, *Rec. trav. chim.*, **54**, 313 (1935); J. Böeseken and C. F. Metz, *ibid.*, **54**, 345 (1935).

[6] A. von Wacek and R. Fiedler, *Monatsh.*, **80**, 170 (1949).

[7] H. Fernholz, *Angew. Chem.*, **60A**, 62 (1948); *Ber.*, **84**, 110 (1951).

[8] I. D. Raacke-Fels, C. H. Wang, R. K. Robbins and B. E. Christensen, *J. Org. Chem.*, **15**, 627 (1950).

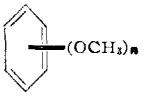
[9] A. R. Bader, THIS JOURNAL, **73**, 3731 (1951).

Discussion and Results

In the present work it was of interest to study a series of reactants in which the number and relative positions of methoxyl groups on a benzene ring were systematically varied, in order to observe sensitivity toward peracid attack as a function of these factors. Accordingly, each member of the following sequence of compounds (Table I) was treated with the indicated excess of perbenzoic acid in chloroform solution at room temperature, and uptake of peracid with time determined by the usual iodimetric titration method.

Table I

Ethers Treated with Perbenzoic Acid



	Initial molar ratio (peracid)/(ether)
Anisole (I)	3.0
1,2-Dimethoxy (II)	4.0
1,3-Dimethoxy (III)	5.0
1,4-Dimethoxy (IV)	5.0
1,2,3-Trimethoxy (V)	6.0
1,3,5-Trimethoxy (VI)	8.0

The results of these qualitative runs are shown in Fig. 1.

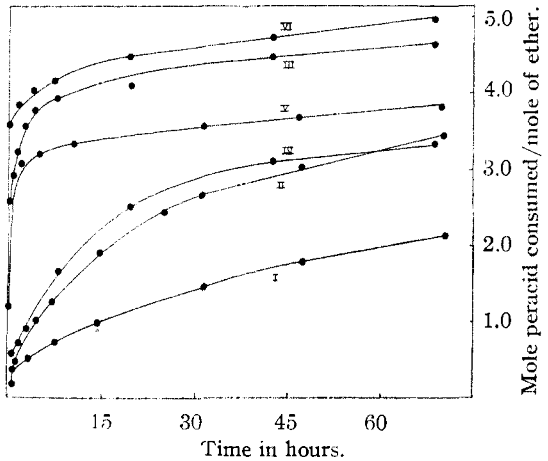


Fig. 1.—Reaction of ethers I–VI with perbenzoic acid. See Table I for peracid: ether ratios used.

From Fig. 1 it is seen that the order of increasing reactivity toward peracid in the series, as measured by maximum spontaneous uptake of peracid, is I < II = IV < V < III < VI. Further, with the exception of unusual reactivity on the part of resorcinol dimethyl ether (III) as compared to compounds II and IV, it appears that an increase in the number of electron-supplying methoxyl groups on the benzene ring produces a corresponding increase in sensitivity to peracid attack. The relatively high activity of III in the reaction may perhaps be traced to the presence of a ring position of very high electron density between the two methoxyl groups, leading to great ease of oxidation by the electrophilic peracid (or some reactive fragment derived from the peracid). The presence of three of these equivalent ring positions of high electron-density in VI could similarly account for the very high degree of reactivity found for this compound.

Curiously, the fact that both anisole and veratrole consumed several moles of peracid under the given conditions is not in accord with the observations of Fernholz[7] on oxidations using benzene as the reaction solvent. In benzene neither of these ethers consumed an appreciable quantity of peracid, and the contrast between their behavior in chloroform as compared to benzene points up Fernholz' statement that the nature of the solvent is of fundamental importance in these oxidations.

Product Studies.—As a means of gaining further insight into the character of the facile oxidation of these ethers by peracid, under the mild conditions used in this study, attempts were made to isolate the various products present in the highly colored reaction mixtures. It was found that each of the ethers III, IV, V and VI reacted with perbenzoic acid in chloroform solution at room temperature to yield a *p*-quinone as a primary nuclear oxidation product. Surprisingly, the production of *p*-quinones from V and VI occurred, even though the loss of a ring methoxyl group[10] was a necessary prerequisite to formation of the quinone. The reaction of III to yield a *p*-quinone is further complicated by an apparent loss of a methoxyl function and the introduction of a new hydroxyl substituent on the ring. The course of these oxidations to yield *p*-quinones and other isolable products corresponding to more extensive oxidative degradation of the reactant ethers is indicated in the following flow diagram. Also indicated in this scheme are known syntheses used to prepare unambiguous samples of materials for comparison with the products obtained from the peracid reaction, and transformations effected on these oxidation products for further identification purposes.

It is to be noted that both V and VI yield the same quinone by oxidation and group elimination processes which leave the carbocyclic ring intact and in addition furnish small yields of oxalic acid derivatives[11] by a ring cleavage process resulting in these two-carbon fragments. The operation of many different oxidation steps is quite probable in all these reactions, and is consistent with the low (5–38%) yields of quinones observed from the reactions of ethers III–VI.

Another factor contributing somewhat to the low yields of quinones obtained was the method of isolation required by the products. Since these benzoquinones and their hydroxy derivatives are sensitive to dilute basic reagents such as sodium bicarbonate, it proved to be impractical to separate the quinones from the accompanying large amounts of benzoic and perbenzoic acids by a basic extraction procedure. Accordingly, the quinones were isolated by fractional crystallization from mixed solvents. In this same connection it is probable that quinones were formed to some extent in the reactions of veratrole and anisole too, since these reaction mixtures were highly colored as in the sequence of reactions of III–VI, but isolation of even small amounts of quinones from I and II was not realized.

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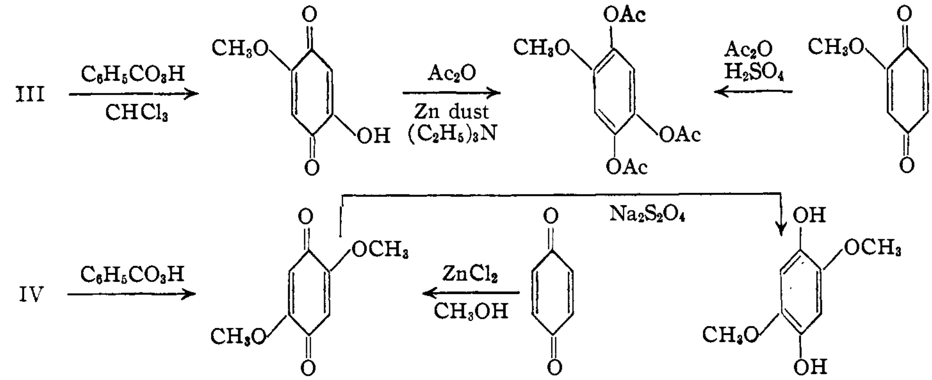
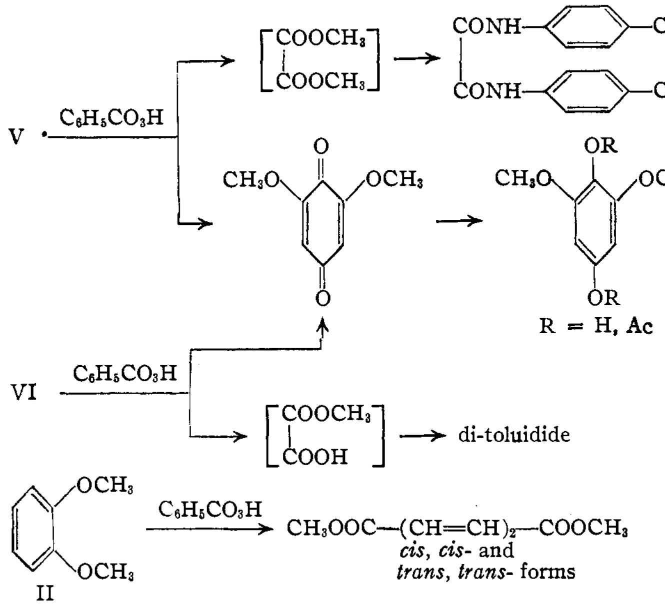
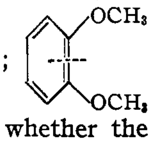
(10) See ref. 7 for a similar reaction in the naphthyl ether series.

(11) See ref. 4 for similar cleavage of trimethylgallic acid.





The single product isolated from veratrole (II) was dimethyl muconate, a product derivable from II by a single stage of nuclear cleavage;



The method of isolation determined whether the *cis,cis*- or *trans,trans*-modification of the ester was obtained; reduced pressure distillation of the residual solution following bicarbonate extraction yielded the *cis,cis*-dimethyl muconate, while concentration of this solution in the cold resulted in crystals of the *trans,trans*-dimethyl muconate.[12] This work on II is paralleled by the nuclear cleavage result found by Fernholz[7] for 1,2-dimethoxynaphthalene in its reaction with peracid.

Kinetic Study of the Oxidation of VI.—The symmetry and high reactivity of VI made it a most logical member of the series on which to study the kinetics of the initial phase of oxidation. However, since the previous qualitative studies had shown this reaction to be very rapid and highly exothermic (a reaction mixture initially at ice temperature spontaneously rose to the boiling point in about 90 seconds), it was necessary to thermostat at −12.4° in order to slow the reaction to the point of permitting analytical evaluation of its rate. A series of rate runs was made at various (ether)/(peracid) ratios, with the ether always present in excess to help ensure that its initial oxidative attack by peracid was being observed as the major reaction process. Progress of a given run was followed by iodimetric estimation of the peracid concentration remaining at various times. Since the reactions were extremely rapid, over 25% of the peracid added was consumed before an initial sample could be pipetted from the thermostatted reaction mixture. Accordingly, observations of the rates in general were made over the interval 25–80% consumption of peracid.

The kinetic data obtained are summarized in Table II.

In Table II are given values for an apparent second order rate constant k_2. These values were obtained under the assumption of a slow, bimolecular reaction step involving peracid and ether, followed by a very rapid step consuming a second mole of peracid. Under this assumption, a plot of the function $\log (E_0 - X)/(P_0 - 2X)$ against time (where E_0 and P_0 represent initial concentrations of ether and peracid, respectively) for a given run gave a straight line from whose slope the rate constant k_2 could be calculated. A plot for a representative run is shown in Fig. 2. Only under this assumed kinetic order could rate constants be obtained which remained essentially constant (within experimental error) over the range of ether/peracid ratios employed.

TABLE II

KINETIC STUDIES ON PERACID REACTION OF VI

Peracid batch	Initial concentrations, (mole/l.) $[C_6H_5CO_3H]_0$	$[Ether]_0$	$[Ether]_0/[Peracid]_0$	k_2, l./mole min.
A	0.0564	0.120	2.13	0.163
A	.0568	.0905	1.59	.164
A	.0571	.175	3.07	.136
A	.0568	.177	3.12	.155
B	.0719	.075	1.04	.138
B	.0716	.226	3.16	.140
B	.0717	.298	4.16	.125
B	.0716	.289	4.04	.116
C	.0941	.197	2.09	.144
D	.0504	.318	6.31	.144
			Mean	0.14 ± 0.01

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[12] For the known facile interconversion of the muconates, see ref. 21 and also C. Grundman, *Ber.*, **69**, 1755 (1936).

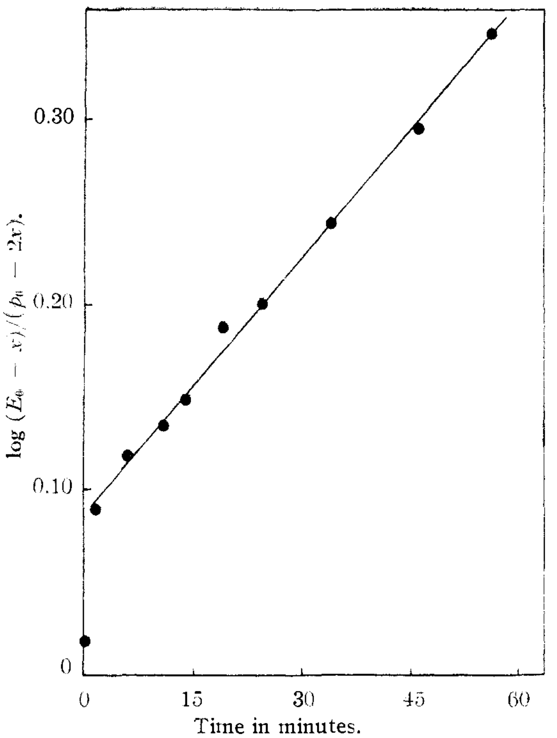
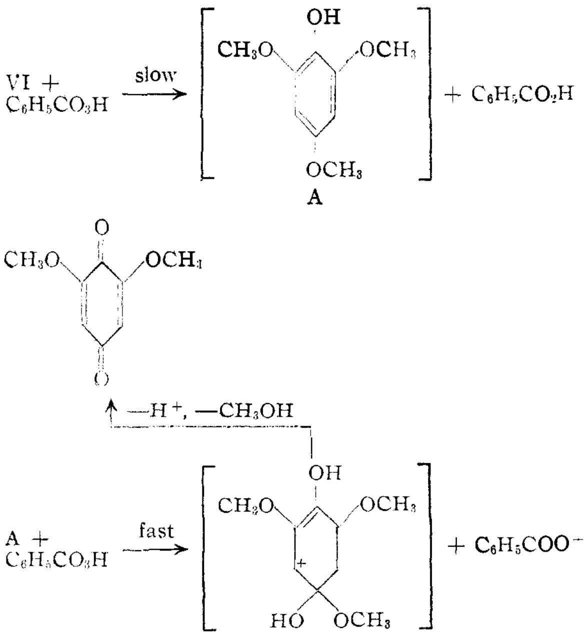


Fig. 2.—Rate run at −12.4°; initial (ether):(peracid) ratio, 1.04.

These kinetic observations on VI, in addition to the previously observed fact that a methoxyl group is lost in the formation of 2,6-dimethoxy-*p*-quinone as the major reaction product of nuclear oxidation without nuclear cleavage, would appear to be accommodated by some such reaction scheme as



Experimental[13]

Materials.—Of the six methoxy benzenes used in this study, three (I, II and III) were commercially available from Eastman Kodak Co., and were purified by distillation before use. The remaining members of the series were prepared from their respective phenols by methylation[14] with methyl sulfate and potassium carbonate.

Preliminary Stoichiometric Studies (Table I and Fig. 1).—In a representative run to determine spontaneous uptake of peracid, a weighed amount of the ether concerned was placed in a glass-stoppered 100-ml. volumetric flask to which was then added an aliquot of a standardized perbenzoic acid solution[15] in dry chloroform. Weights of ether and aliquot sizes were selected to give a molar ratio of peracid: ether of at least 3:1 for the least reactive ether, and correspondingly higher ratios for the more reactive ethers. Zero time was noted on making the solution to volume with chloroform. Immediately following mixing, and at regular time intervals during the next 72 hours, 1-ml. aliquots of solution were withdrawn and analyzed for peracid content by iodimetric titration.[15] Reactions were allowed to proceed at room temperature (25–28°), neglecting the initial rise in temperature due to the exothermic character of these reactions.

Product Studies. Oxidation of IV.—To a solution of 2.00 g. (0.0145 mole) of IV in 25 ml. of chloroform was added 100 ml. of a chloroform solution containing 0.029 mole of perbenzoic acid. The mixture was swirled and set aside at room temperature for 24 hours. The solution was then concentrated by removal of solvent, and the resulting paste taken up in 30 ml. of ethyl ether and cooled. The bright yellow quinone, m.p. 220° with sublimation,[16] separated from solution. The yield of 2,5-dimethoxy-1,4-benzoquinone was 375 mg., or 16% based on complete reaction with IV.

The residual ether solution was washed with 10% sodium bicarbonate solution (aqueous phase turned dark red immediately) and with water, dried, and solvent removed to give 1.19 g. of residue. From this was recovered sufficient starting ether IV to make the yield of quinone 38% when based on unrecovered (and presumably reacted) ether.

A 50-mg. portion of the quinone was reduced in standard fashion with 0.3 g. of sodium hydrosulfite, yielding 30 mg. (60%) of the hydroquinone; white needles from methanol-water, m.p. 166–167° (lit. value[17] 168°).

In an independent synthesis of the quinone for comparison purposes, 2.5 g. of *p*-benzoquinone and 3.0 g. of anhydrous zinc chloride were added to 18 g. of methanol, and the resulting mixture refluxed for 20 minutes. At the end of this time, 0.52 g. of the yellow quinone, m.p. 220° with sublimation,[16] had precipitated. The hydroquinone prepared by reduction of this sample gave no depression of melting point on admixture with the hydroquinone above.

Oxidation of III.—In the oxidation of 3.09 g. (0.0224 mole) of III with 0.0448 mole of peracid in 132 ml. of chloroform solution, the color of the reaction mixture progressed from colorless, to red, to brown within four hours. Concentration of the reaction mixture and cooling after the addition of 20 ml. of hexane–ethyl ether mixture gave 593 mg. (17% based on III) of 2-hydroxy-5-methoxy-1,4-benzoquinone, orange plates from chloroform–ethyl ether mixture, m.p. 177–179° (lit. value[18] 179° with decomposition).

A 100-mg. sample of the above quinone was reductively acetylated by warming on the steam-bath with a mixture of 0.5 g. of zinc dust, 1 g. of acetic anhydride and a drop of triethylamine as catalyst. After filtration and decomposition of excess acetic anhydride with water, cooling resulted in 70 mg. of 1-methoxy-2,4,5-triacetoxybenzene, white cubes from methanol-water, m.p. 138–140° (lit. value[19] 142°).

Proof of structure for this triacetoxy derivative was furnished by its independent synthesis from 154 mg. of 2-methoxy-1,4-benzoquinone in a Thiele type reaction with 1 g. of acetic anhydride and four drops of sulfuric acid. After heating this reaction mixture on the steam-bath, decomposition of excess acetic anhydride with water and cooling resulted in 151 mg. of 1-methoxy-2,4,5-triacetoxybenzene which did not depress the melting point of the above sample obtained from the oxidation product of III.

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[13] Melting points are uncorrected.

[14] The Claisen procedure using acetone as solvent was employed.

[15] G. Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 431.

[16] In agreement with findings of R. Nietzki and F. Schmidt, *Ber.*, **21**, 2374 (1888).

[17] R. Nietzki and F. Rechberg, *ibid.*, **23**, 1217 (1890).

[18] W. K. Anslow and H. Raistrick, *J. Chem. Soc.*, 1446 (1939).

[19] H. G. H. Erdtman, *Proc. Roy. Soc. (London)*, **143A**, 177 (1933).

Oxidation of V. A. Isolation of an Oxalic Acid Derivative.—When 5.66 g. (0.0337 mole) of V were allowed to react at ice temperature with 0.13 mole of perbenzoic acid in 292 ml. of chloroform, a deep red coloration developed during the highly exothermic reaction. After spontaneous evolution of heat ceased, the mixture was allowed to stand at room temperature for 11 days. It was then extracted with portions of water, 10% sodium bicarbonate solution (which turned from red-orange to purple), and then water again. After drying the chloroform solvent was removed under reduced pressure, and the residue heated on a steam-bath for eight hours with 5 g. of *p*-toluidine. The resulting solid was washed with 6 *N* hydrochloric acid and recrystallized from glacial acetic acid to give a small yield (< 1% based on one mole per mole of ether) of oxal-di-*p*-toluidide; m.p. and mixed m.p. with an authentic sample, 271° (uncor.).

B. **Isolation of 2,6-Dimethoxy-1,4-benzoquinone.**—From the oxidation of 2.44 g. (0.0145 mole) of V with just 0.0290 mole of perbenzoic acid in 100 ml. of chloroform, with a reaction time of three hours and using the product isolation scheme described for IV, there was obtained 105 mg. (5%) of the yellow quinone. This was reduced with aqueous sodium hydrosulfite to the hydroquinone; m.p. and mixed m.p. with an authentic sample of 2,6-dimethoxyhydroquinone, 154–156°.

Oxidation of VI. A. Isolation of an Oxalic Acid Derivative.—In a controlled reaction of 3.5 g. of VI with 335 ml. of 0.50 *M* perbenzoic acid in moist chloroform, the reaction mixture was kept at 0° for thirty minutes. Titration after fourteen minutes indicated the consumption of five moles of peracid per mole of ether. The reaction mixture was extracted with 10% sodium bicarbonate solution. The bicarbonate extract (containing CH_3OOC–COOH as a possible component) was chilled in ice and acidified with hydrochloric acid. The precipitated benzoic acid was filtered, and the filtrate then allowed to evaporate. The residual solid was then continuously extracted with ether. This final ether extract was evaporated, and a portion of the residue heated with *p*-toluidine on a steam-bath. Recrystallization of the product from acetic acid gave a small yield of oxal-di-*p*-toluidide, m.p. 273–275° (cor.).

B. **Isolation of 2,6-Dimethoxy-1,4-benzoquinone.**—Using the procedure previously described for the oxidation of IV to yield quinone, the following variations in reaction conditions were found to have little effect on the yield of 2,6-dimethoxy-1,4-benzoquinone obtained.

Expt.	Mole of reactants		Reaction time, hr.	Temp., °C.	Yield of quinone, %
	Ether	Peracid			
1	0.0156	0.0167	3	−20 ± 5°	28
2	.0237	.0238	6	Room	27

The quinone was reduced with aqueous sodium hydrosulfite to the known hydroquinone, white needles from water, m.p. 154–156°. Acetylation of a portion of the hydroquinone with acetic anhydride and pyridine gave the diacetoxy derivative, white flakes from dilute acetic acid, m.p. 126–127° (lit. value[20] 128°).

Oxidation of Veratrole (II).—Oxidation of 3.32 g. (0.0241 mole) of II with 0.0670 mole of perbenzoic acid in 185 ml. of solution, for a period of five days at room temperature, gave a red reaction mixture. This was washed with 10% sodium bicarbonate solution and with water, dried, and the solvent distilled on the steam-bath.

The residue was distilled under reduced pressure, giving a fraction distilling at 87–95° (16 mm.) which solidified on standing to 60 mg. (*ca.* 1%) of a white solid. This material was recrystallized from methanol-water mixture, m.p. 72–73° (lit. value[21] for *cis,cis*-dimethyl muconate, 75°). *Anal.* Calcd. for $C_8H_{10}O_4$ (dimethyl muconate): C, 56.47; H, 5.92. Found: C, 56.57; H, 6.09. The infrared spectrum of the compound (in nujol) was consistent with that to be expected for the conjugated system in dimethyl muconate, with absorption peaks at: 1706, 1582, 1440, 1364, 1224, 1163, 999, 903, 835 and 730 cm.$^{-1}$.

In a second run on II similar to that described above, 2.66 g. of a viscous oil was obtained from the chloroform phase and subjected to crystallization from an ether-hexane mixture. There was obtained 54 mg. (1%) of the *trans,trans*-dimethyl muconate, which was recrystallized from methanol, m.p. 157–158° (lit. value[21] 156°).

Kinetic Studies on VI.—The rate determinations were made at −12.4° in a large dewar flask equipped with a mercury thermoregulator, stirrer, and a 40-watt bulb as a heater. The bath liquid was a brine solution cooled by pumping through a copper coil immersed in a Dry Ice-carbon tetrachloride mixture in a second dewar flask.

The chloroform solution of perbenzoic acid was thermostated at −12.4° and its concentration determined by the usual iodimetric titration. To a weighed sample of VI in a volumetric flask was then added the desired aliquot of precooled peracid solution, after which chloroform was added to volume at room temperature. An aliquot of the reaction mixture was titrated immediately after its return to the thermostat. Usually, only one or two minutes elapsed between solution of the ether and the first titration. Since the reactions were quite rapid, the first titration represented at least 25% uptake of peracid. Aliquots were withdrawn for analysis and pipetted into acidulated potassium iodide, at two to three minute intervals during the reaction.

Because of the heat of solution of the ether and the warming involved in making the solution up to volume, the first two or three points in each run did not fall on the straight line plot determined by the subsequent values.

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(20) O. Hesse, *Ann.*, **276**, 328 (1895).

(21) E. H. Farmer, *J. Chem. Soc.*, **123**, 2531 (1923).