THE OXIDATION OF ALKYL ARYL ETHERS

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Contents

I. Introduction

Oxidation reactions of phenols such as oxidative coupling[1] and hydroxylation[2] have been the subject of several comprehensive reviews in recent years. In contrast, oxidation of the closely related alkyl aryl ethers has received no such attention apart from a brief survey[3] in 1956. The present review is concerned particularly with reactions of the simple alkyl aryl ethers. The oxidation of some substituted ethers involves the substituent groups rather than the less reactive ether functions. Thus alkoxyphenols give products resulting predominantly from the oxidation of the phenolic groups[4,5] while alkoxyarylamines undergo reaction at the amino groups.[6] Such compounds are therefore not included.

The term "oxidation" is applied to reactions which either involve the formal loss of one or more electrons or hydrogen atoms from a molecule, or result in the incorporation into the molecule of one or more electronegative atoms such as nitrogen, oxygen, or halogen, or of groups containing these. Because of the powerful electron-releasing properties of the alkoxyl group, alkyl aryl ethers readily undergo electrophilic substitution reactions. Nitration and halogenation, in particular, are formally oxidation reactions but will not be considered further as their salient features have recently been discussed elsewhere.[7,8] The oxidation reactions of alkyl aryl ethers show some resemblances to those of phenols. Probably the most significant difference is encountered in reactions performed in alkaline solution. Whereas phenols give the corresponding phenoxide ions which react rapidly, the corresponding alkyl aryl ethers are usually unaffected. Most oxidations of the ethers by polar reagents are effected in the presence of proton acids or Lewis acids, often with acetic acid as the solvent.

The oxidation reactions undergone by alkyl aryl ethers are conveniently classified according to the nature of the products obtained. This empirical approach is necessary as the mechanisms of many of the reactions are conjectural. Few of them have been examined kinetically, and in many cases there is little quantitative information about the products. The nomenclature used follows the IUPAC 1957 Rules as far as possible; the literature has been examined up to the end of December 1967.

II. Formation of Cation Radicals

The removal of an electron from an alkyl aryl ether, ArOR, gives the corresponding cation radical $[ArOR]^+$ which is a highly reactive species and has a transient existence. Such ions can be obtained by electron-impact ionization in the mass spectrometer, and their subsequent fragmentation reactions in the gas phase have been studied intensively.[9] Because cation radicals are thought to participate in many conventional oxidation reactions, their behavior in solution has also received considerable attention. The flash photolysis[10,11] of aqueous solutions of anisole results in the formation of hydrated

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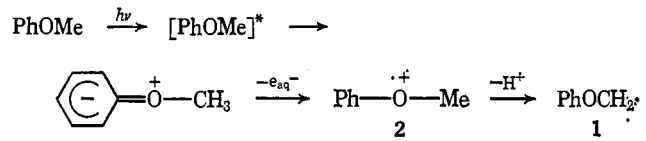
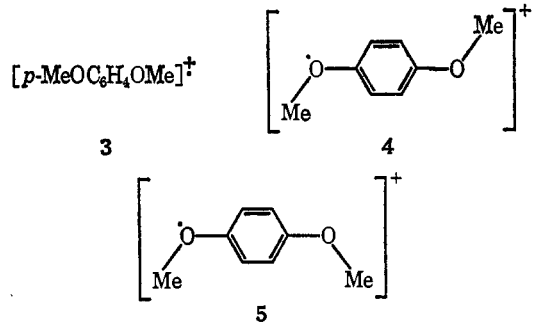
(2) J. D. Loudon, *Progr. Org. Chem.*, 5, 46 (1961).
(3) L. A. Wiles, *Chem. Rev.*, 56, 329 (1956).
(4) E. Adler, I. Falkehag, and B. Smith, *Acta Chem. Scand.*, 16, 529 (1962).
(5) F. R. Hewgill and B. S. Middleton, *J. Chem. Soc., C*, 2316 (1967).
(6) D. G. H. Daniels and B. C. Saunders, *ibid.*, 2112 (1951).
(7) G. Kohnstam and D. L. H. Williams in "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience Publishers, London, 1967, p 132.
(8) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier Publishing Co., Amsterdam, 1965.
(9) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 237.
(10) L. I. Grossweiner and H.-I. Joschek, Advances in Chemistry Series, No. 50, American Chemical Society, Washington, D. C., p 279.
(11) H.-I. Joschek and L. I. Grossweiner, *J. Amer. Chem. Soc.*, 88, 3261 (1966).

electrons and phenoxymethyl radicals **1** presumably *via* the cation radical **2**.

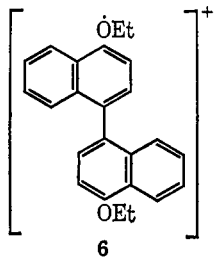


Both the ultraviolet irradiation of *p*-dimethoxybenzene[12] at 193°K and the radiolysis of anisole[13] at 123°K also probably involve similar ion formation. Luminescence results from the application of an ac potential across an electrolytic cell containing a methoxylated naphthalene or anthracene, and an electrolyte in an aprotic solvent.[14,14a] The polycyclic compound is alternately oxidized to the cation radical and reduced to the anion radical. Anode potentials have been measured for the one-electron oxidation of anisole and 1-methoxynaphthalene in acetic acid,[15] and controlled-potential electrolysis of the various methoxybenzenes gives short-lived products having the esr spectra of cation radicals.[16]

The one-electron oxidation of alkyl aryl ethers can also be effected by many chemical methods. Solutions of anisole and other methoxybenzenes in concentrated sulfuric acid give esr spectra showing the presence of cation radicals.[16-18] These result from the oxidation of the protonated ether by either the sulfuric acid or the dissolved oxygen present. The concentrations obtained are very small, that of the cation radical **3** from 1,4-dimethoxybenzene[18] being 0.025% at 20°. The esr spectrum of **3** suggests that both the *trans* and the *cis* forms (**4** and **5**) are present.[16,18] Under similar conditions 4,4′-diethoxy-1,1′-binaphthyl gives the green cation radical **6**; the reaction



is promoted by the addition of nitric acid and nitro compounds.[19] The addition of peroxodisulfate ion to a solution of anisole in concentrated sulfuric acid fails, however, to give a higher concentration of the desired cation radical.[20] Instead hydroxylation occurs with the formation, finally, of the semiquinone **7**. Mixtures of Lewis acids and nitro compounds exhibit strong electron affinity, and a solution of aluminum



6

7

chloride in nitromethane[21,22] is a much more efficient oxidizing agent than is sulfuric acid. 1,4-Dimethoxy- and 1,4-diethoxybenzene are converted nearly quantitatively into the corresponding cation radicals.[22] 4,4′-Dimethoxybiphenyl also gives a monopositive ion in this way but on treatment with nitric acid in sulfuric acid forms a dipositive ion.[21] A solution of lead(IV) acetate and boron trifluoride etherate in methylene chloride may also be used for the oxidation of anisole and related compounds to cation radicals.[23] It has been suggested that the rapid reaction of 3,4-dimethoxybenzaldehyde with cobalt(III) perchlorate[24] is a consequence of oxidation processes involving the ether functions rather than the aldehyde group. This receives support from the oxidations of methoxybenzenes and methoxynaphthalenes by manganese(III) acetate in acetic acid.[25,26] The order of reactivity of the ethers is 1-$C_{10}H_7OMe$ = 2-$C_{10}H_7OMe$ ≫ 1,4-$MeOC_6H_4OMe$ > 1,3-$MeOC_6H_4OMe$ > 1,2-$MeOC_6H_4OMe$ > PhOEt > PhOMe. All the products obtained can be accounted for if the initial step in each case is the transfer of an electron.

$$ArOMe + Mn(OAc)_3 \longrightarrow [ArOMe]\cdot^+ + Mn(OAc)_2 + AcO^-$$

Many of the reactions described in later sections of this review probably begin in a similar way.

The formation of a charge-transfer complex formally involves electron transfer from donor to acceptor in the excited state and represents a type of reversible oxidation of the donor molecule. Alkyl aryl ethers readily form such complexes with tetracyanoethylene[27,28] and other acceptors[29,30] and the ionization potentials of the ethers have been calculated from the charge-transfer spectra obtained.[28] There is ultraviolet spectral evidence for the existence of an oxygen–anisole complex.[31]

III. Formation of Compounds with New Aryl–Aryl Bonds

A. SCHOLL AND RELATED REACTIONS

Under suitable oxidizing conditions many aromatic compounds lose hydrogen and give products containing new

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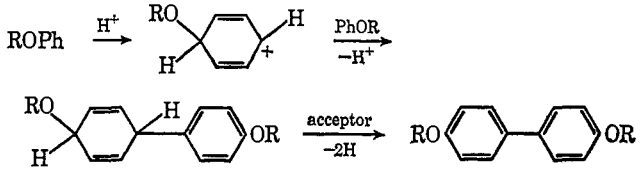
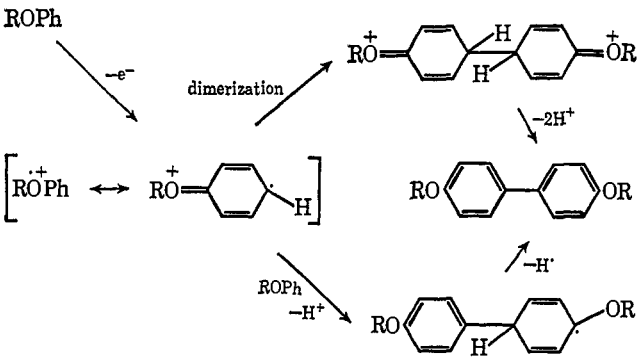
aryl–aryl bonds. Bond formation may be intermolecular, leading to biaryl formation, or it may be intramolecular, resulting in cyclization. That alkyl aryl ethers undergo such reactions more readily than do the corresponding aromatic hydrocarbons can be attributed to the powerful electron-releasing properties of alkoxyl groups which facilitate substitution reactions. Dehydrogenations of this sort which occur under the influence of Friedel–Crafts catalysts are termed "Scholl reactions," but the many closely related reactions which do not involve such catalysts suggest that this classification is of limited value.[32] Two main types of mechanism have been proposed for these reactions;[32] these are shown below in simplified form for a typical alkyl aryl ether. In the first, protonation of the aromatic molecule is followed by normal electrophilic substitution and subsequent dehydrogenation to the biaryl.

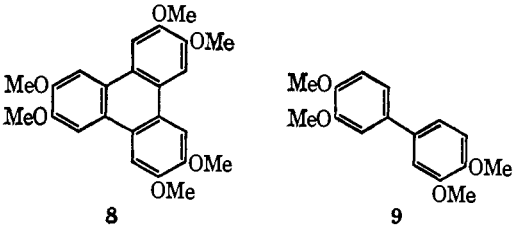


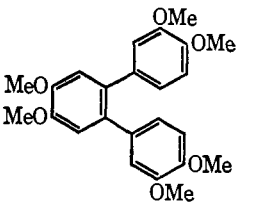
Alternatively the initial formation of a cation radical is followed by dimerization or radical substitution.



These mechanisms permit the rationalization of most of the reactions listed in Table I.[33–67]

The wide range of yields recorded for these reactions is noteworthy, and there is as yet no way of predicting if a particular combination of reagents will bring about the oxidation of a given ether efficiently. High yields of biaryls are obtained from many oxidations of 1,2,4-trimethoxybenzene and 1-alkoxynaphthalenes. In many reactions the oxidizing agent acts as a hydrogen acceptor and the observed conversions of nitrobenzene into phenylhydroxylamine,[53] and of chloranil into tetrachloroquinol,[68] probably involve hydride transfers. However, it is likely that electron transfer is the most important process in oxidations brought about by electrolysis, and by manganese(IV) oxide and sulfuric acid,[38] iron(III) chloride,[41] manganese(III) acetate,[25] and nitrogen dioxide.[52] The oxidations of 1,2-dimethoxybenzene are unusual in that they give a product which contains more than one new aryl–aryl bond. The hexamethoxytriphenylene **8** is obtained in good yields from the oxidation by chloranil in sulfuric acid both of 1,2-dimethoxybenzene and of a mixture of 1,2-dimethoxybenzene with 3,3′,4,4′-tetramethoxybiphenyl (**9**). The efficient incorporation of this biphenyl into the triphenylene **8** indicates that the latter is probably formed from 1,2-dimethoxybenzene by three consecutive Scholl reactions[42] *via* the biphenyl **9** and the hexamethoxyterphenyl **10**. 1,2-Dimethoxybenzene is apparently not oxidized under normal Scholl conditions using





aluminum chloride and nitrobenzene.[42] The oxidation of anisole by lead(IV) acetate in the presence of boron trifluoride[36] probably proceeds *via* *p*-methoxyphenyllead triacetate (**11**), and the main reaction sequence is thought to be

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Table I
Scholl and Related Reactions

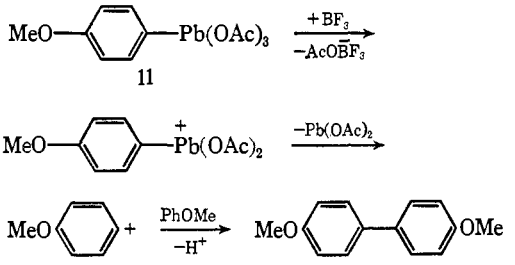
Ether	*Reagent*	*Products*	*Ref*
Anisole	γ irradiation in presence of benzoyl chloride	2,2′-, 4,4′-, and possibly 3,3′-dimethoxybiphenyl in very low yield	33
Anisole	Thermal neutron irradiation	4,4′-Dimethoxybiphenyl (low yield)	34
Anisole	Benzoyl peroxide and aluminum chloride in nitrobenzene	4,4′-Dimethoxybiphenyl (23%)	35
Anisole	Lead(IV) acetate and boron trifluoride etherate in dichloromethane	2,2′- (1%), 2,4′- (6%), and 4,4′-dimethoxybiphenyl (30%)	23, 36
Anisole	Lead(IV) acetate and boron trifluoride	2,2′- (0.5%), 2,4′- (3%), and 4,4′-dimethoxybiphenyl (2%)	36
2-Methoxytoluene	Electrolysis in aqueous acid	4,4′-Dihydroxy-3,3′-dimethylbiphenyl and its monomethyl ether	37
3-Methoxytoluene	Electrolysis in aqueous acid	4-Hydroxy-4′-methoxy-2,2′-dimethylbiphenyl (19%)	37
4-Methoxytoluene	Electrolysis in aqueous acid	2,2′-Dimethoxy-5,5′-dimethylbiphenyl and 2-hydroxy-2′-methoxy-5,5′-dimethylbiphenyl (34%)	37
4-Methoxytoluene	Manganese(IV) oxide and sulfuric acid	2,2′-Dimethoxy-5,5′-dimethylbiphenyl	38
1,2-Dimethoxybenzene	Electrolysis in aqueous acid	3,3′,4,4′-Tetramethoxybiphenyl and a hydroxytrimethoxybiphenyl (low yield)	39
1,2-Dimethoxybenzene	Aluminum chloride and acetyl chloride in toluene	2,3,6,7,10,11-Hexamethoxytriphenylene (0.08%)	40
1,2-Dimethoxybenzene	Moist iron(III) chloride	2,3,6,7,10,11-Hexamethoxytriphenylene (7%)	41
1,2-Dimethoxybenzene	Chloranil (and related quinones) in 70% v/v aqueous sulfuric acid	2,3,6,7,10,11-Hexamethoxytriphenylene (73%)	42
1,2-Dimethoxybenzene and 3,3′,4,4′-tetramethoxybiphenyl	Chloranil in 70% v/v aqueous sulfuric acid	2,3,6,7,10,11-Hexamethoxytriphenylene (154% based on 1,2-dimethoxybenzene alone)	42
1,3-Dimethoxybenzene	Aluminum chloride in nitrobenzene	2,2′,4,4′-Tetramethoxybiphenyl (2.5%)	43
1,4-Dimethoxybenzene	Diisopropyl peroxodicarbonate and aluminum chloride	2,2′,5,5′-Tetramethoxybiphenyl (30%)	44
2,5-Dimethoxytoluene	Electrolysis in aqueous acid or chromic acid	2,2′,5,5′-Tetramethoxy-4,4′-dimethylbiphenyl	37, 45
1-Chloro-2,5-dimethoxybenzene	Chromic acid	4,4′-Dichloro-2,2′,5,5′-tetramethoxybiphenyl	45
1,2,4-Trimethoxybenzene	Acenaphthenequinone or phenanthrene-9,10-quinone in polyphosphoric acid	2,2′,4,4′,5,5′-Hexamethoxybiphenyl (60%)	46
1,2,4-Trimethoxybenzene	Electrolysis in aqueous acid	2,2′,4,4′,5,5′-Hexamethoxybiphenyl (85%)	47
1,2,4-Trimethoxybenzene	"Almost any oxidizing agent" in acid solution, *e.g.*, chromic acid, iron(III) chloride, iodine chloride	2,2′,4,4′,5,5′-Hexamethoxybiphenyl	47
1-Methoxynaphthalene	Lead(IV) acetate	4,4′-Dimethoxy-1,1′-binaphthyl	48
1-Methoxynaphthalene	Aluminum chloride in nitrobenzene	4,4′-Dimethoxy-1,1′-binaphthyl (32%)	43, 49
1-Methoxynaphthalene	Concentrated sulfuric acid, or mixed nitric, sulfuric, and acetic acids	4,4′-Dimethoxy-1,1′-binaphthyl	50
1-Methoxynaphthalene	Peroxoformic acid	4,4′-Dimethoxy-1,1′-binaphthyl (70%)	51
1-Methoxynaphthalene	Manganese(III) acetate	1,1′-Diacetoxy-4,4′-dimethoxy-2,2′-binaphthyl	25
1-Methoxynaphthalene	Nitrogen dioxide in carbon tetrachloride	4,4′-Dimethoxy-3,3′-dinitro-1,1′-binaphthyl (28%)	52
1-Ethoxynaphthalene	Benzenesulfonic acid in nitrobenzene	4,4′-Diethoxy-1,1′-binaphthyl (44%)	53
1-Ethoxynaphthalene	Aluminum chloride in nitrobenzene	4,4′-Diethoxy-1,1′-binaphthyl (70%)	43, 54
1-Ethoxynaphthalene	Cation radical from 4,4′-diethoxy-1,1′-binaphthyl	4,4′-Diethoxy-1,1′-binaphthyl	19
1-Ethoxynaphthalene	Potassium anthraquinone-1,5-disulfonate, boric acid, and concentrated sulfuric acid	4,4′-Diethoxy-1,1′-binaphthyl (84%)	55
1-Ethoxynaphthalene	Isatin in concentrated sulfuric acid	4,4′-Diethoxy-1,1′-binaphthyl (11%)	56
1-Ethoxynaphthalene	Isatin in 84% sulfuric acid	4,4′-Diethoxy-1,1′-binaphthyl (22%)	57, 58
1-Ethoxynaphthalene	Phenanthrene-9,10-quinone in sulfuric acid	4,4′-Diethoxy-1,1′-binaphthyl (65%)	57
2-Methoxynaphthalene	Silver fluoride and iodine	2,2′-Dimethoxy-1,1′-binaphthyl (30%)	59
2-Methoxynaphthalene	Aluminum chloride in nitrobenzene	2,2′-Dimethoxy-1,1′-binaphthyl (5%)	43

Table I (Continued)

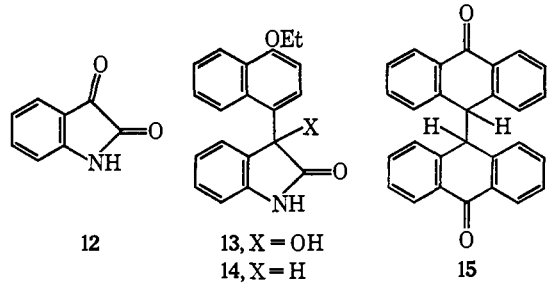
Ether	*Reagent*	*Products*	*Ref*
2-Ethoxynaphthalene	Silver fluoride and iodine	2,2′-Diethoxy-1,1′-binaphthyl	59
2-Methoxybenzil	Aluminum chloride	1-Methoxyphenanthrene-9,10-quinone (1%)	60
3,4-Dimethoxybenzil	Aluminum chloride	2,3-Dimethoxyphenanthrene-9,10-quinone (6%)	61
3,3′,4,4′-Tetramethoxybenzil	Aluminum chloride and nitrobenzene	2,3,6,7-Tetramethoxyphenanthrene-9,10-quinone (86%)	61, 62
2,2′-Dimethoxy-1,1′-binaphthyl	Aluminum chloride	1,12-Dihydroxyperylene	63, 64
2,3,6,7-Tetramethoxy-9,10-diphenylphenanthrene	Aluminum chloride in nitrobenzene	2,3,6,7-Tetramethoxyphenanthro[9,10-*l*]-phenanthrene	46
1-Benzoyl-4-methoxynaphthalene	Aluminum chloride (or aluminum chloride and sodium chloride)	3-Hydroxy-1,2-benzfluorenone (85%)	65, 66
1-Benzoyl-4-ethoxynaphthalene	Aluminum chloride	3-Hydroxy-1,2-benzfluorenone	65, 67
1-Methoxy-4-(2-naphthoyl)naphthalene	Aluminum chloride and sodium chloride	3-Hydroxy-1,2,5,6-dibenzfluorenone	66

$$Pb(OAc)_4 + BF_3 \rightleftharpoons {}^{+}Pb(OAc)_3 + AcO\bar{B}F_3$$

$$PhOMe + {}^{+}Pb(OAc)_3 \xrightarrow{-H^+}$$



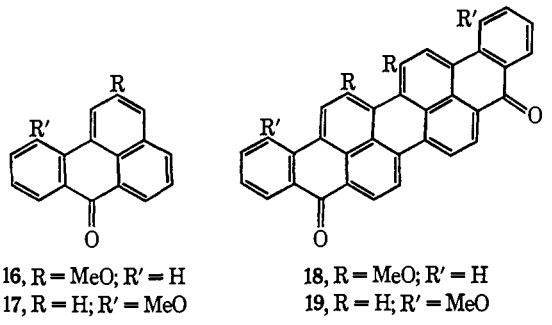
The oxidation of 1-ethoxynaphthalene to 4,4′-diethoxy-1,1′-binaphthyl by isatin (**12**) in sulfuric acid is complicated by the initial condensation[57,58,69] of part of the reactants to give the tertiary alcohol **13**. This then acts as the hydrogen acceptor in the formation of the binaphthyl, being itself reduced to the oxindole **14**.



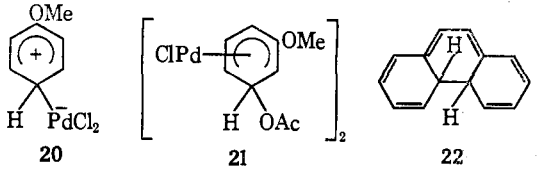
12 13, X = OH; 14, X = H 15

9,9′-Bianthronyl (**15**) is formed when 9-methoxy- and 9-ethoxyanthracene are oxidized by nitric acid or by iron(III) chloride.[70] As such ethers are easily dealkylated these reactions probably occur by the oxidative coupling of 9-anthranol rather than the direct oxidation of the ethers.

Some dehydrogenations which result in aryl–aryl bond formation occur under conditions different from those listed in Table I and clearly have completely different mechanisms. Thus fusion of the benzanthracenones **16** and **17** with potassium hydroxide in the presence of air gives the dimethoxyviolanthrenediones **18** and **19**, respectively.[71,72] Finally, treatment of anisole with palladium chloride and sodium acetate gives 4,4′-dimethoxybiphenyl (10%).[73] This unusual oxidation is thought to take place by formation of the σ complex **20** which is converted by acetate ion into the dimeric π-cyclohexadienyl complex **21**. The latter decomposes with the formation of palladium and palladium chloride; coupling of the resulting acetoxycyclohexadienyl radicals and subsequent elimination of acetic acid affords the biphenyl.



16, R = MeO; R′ = H
17, R = H; R′ = MeO
18, R = MeO; R′ = H
19, R = H; R′ = MeO



20 21 22

B. PHOTOCHEMICAL DEHYDROGENATIONS

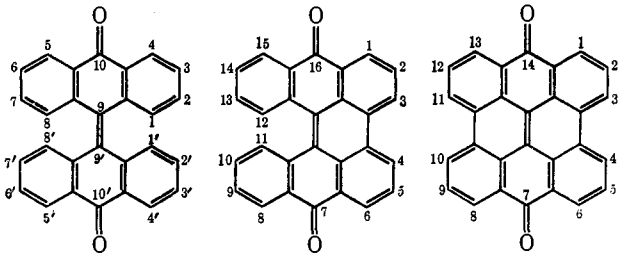
The irradiation of certain ethers brings about their cyclization. Loss of hydrogen then occurs, giving polycyclic compounds which contain new aryl–aryl bonds. Thus ultraviolet light[74] causes isomerization of a *trans*-stilbene to the *cis* isomer followed by cyclization to give a nonaromatic product **22**. In the

(69) C. Marschalk, *Bull. Soc. Chim. Fr.*, [5] 3, 129 (1936).
(70) E. de B. Barnett, J. W. Cook, and M. A. Matthews, *J. Chem. Soc.*, 123, 1994 (1923).
(71) F. G. Baddar, *ibid.*, 1088 (1948).
(72) T. Maki and A. Kikuchi, *Ber.*, 71B, 2036 (1938).
(73) R. van Helden and G. Verberg, *Rec. Trav. Chim. Pays-Bas*, 84, 1263 (1965).
(74) F. R. Stermitz in "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Edward Arnold Ltd., London, 1967, p 247.

Table II
Photochemical Dehydrogenations

Ether	*Products*	*Ref*
trans-4-Methoxystilbene	3-Methoxyphenanthrene (42%)	75
trans-2-Methoxystilbene	1-Methoxyphenanthrene (46%)	75
trans-3,3'-Dimethoxystilbene	2,5-Dimethoxy- and 2,7-dimethoxyphenanthrene (59%)	76
cis-3,3'-Dimethoxystilbene	2,5-Dimethoxy- and 2,7-dimethoxyphenanthrene (73%)	76
trans-2,3-Di(4-methoxyphenyl)but-2-ene	3,6-Dimethoxy-9,10-dimethylphenanthrene (47%)	77
trans-2,3-Di(4-methoxyphenyl)pent-2-ene	3,6-Dimethoxy-9-ethyl-10-methylphenanthrene (55%)	77
trans-3,4-Di(4-methoxyphenyl)hex-3-ene	3,6-Dimethoxy-9,10-diethylphenanthrene (63%)	76, 77
2,2'-Dimethoxybianthron-9-ylidene	3,10-Dimethoxy derivatives of **24** and **25**	78
4,4'-Dimethoxybianthron-9-ylidene	1,6-Dimethoxy derivatives of **24** and **25**	79
2,2',3,3'-Tetramethoxybianthron-9-ylidene	2,3,4,5-Tetramethoxy derivatives of **24** and **25**	79
2,2',6,6'-Tetramethoxybianthron-9-ylidene	3,4,9,14-Tetramethoxy derivative of **24** and 3,4,9,12-tetramethoxy derivative of **25**	80
1,6-Dimethoxy derivative of **24**	1,6-Dimethoxy derivative of **25**	81
1,6-Dimethoxy-2,5-dimethyl and -3,4-dimethyl derivatives of **24**	1,6-Dimethoxy-2,5-dimethyl and -3,4-dimethyl derivatives of **25**	82

presence of a suitable oxidizing agent, this is readily oxidized to the corresponding phenanthrene. Aerial oxidation is sometimes sufficient, but better yields are obtained using iodine and air, preferably in the presence of copper(II) chloride. Similar dehydrogenations are encountered when derivatives of bianthron-9-ylidene (**23**) are illuminated with visible light. The resulting dibenzoperylenequinones (**24**) can undergo further cyclization and finally substituted phenanthroperylenequinones (**25**) are obtained.



23 **24** **25**

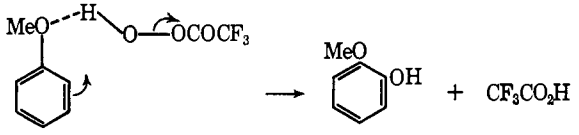
No added oxidizing agent is necessary here, the quinonoid systems presumably acting as hydrogen acceptors. The methoxy-substituted derivatives of phenanthrene and of **24** and **25** which have been obtained in this way are listed in Table II.[75-82]

IV. Formation of Hydroxylated Products

The hydroxylation of the aromatic nucleus in alkyl aryl ethers can be effected by both electrophilic reagents and radicals. In addition there are many examples of hydroxylations which take place in living organisms.

A. ELECTROPHILIC HYDROXYLATIONS

Several peroxo acids act effectively as sources of the unknown hydroxyl cation HO^+ and bring about the hydroxylation of alkyl aryl ethers.[8] Normal electrophilic substitution occurs, but as the resulting *o*- and *p*-alkoxyphenols are even more reactive toward the hydroxylating agents than are the ethers themselves, they usually undergo further oxidation to the corresponding quinones. Many of the oxidations described in section VII.B clearly occur in this way. The reaction of anisole with trifluoroperoxoacetic acid, CF_3CO_3H, is the only electrophilic hydroxylation to have been examined in detail.[83,84] The products are 2- and 4-methoxyphenol (up to 39 and 14%, respectively), but the interpretation of the results is complicated by the preferential further oxidation of the *para* isomer. The high reactivity of anisole compared with that of benzene in a similar reaction establishes that electrophilic rather than radical substitution is occurring. Hydrogen bonding between the oxygen atom of the ether and the trifluoroperoxoacetic acid is considered to be responsible for the predominance of *ortho* substitution.



The formation of quinol in the reaction between anisole, peroxodisulfate ion, and concentrated sulfuric acid may also occur by initial electrophilic substitution followed by demethylation.[20]

B. RADICAL HYDROXYLATIONS

Hydroxylation can also be brought about by the radical reactions summarized in Table III. The possibility that radical reactions might occur during the metabolism of aromatic compounds has led to attempts to devise nonenzymatic systems capable of effecting hydroxylation by homolytic processes. The most convenient source of hydroxyl radicals is a mixture of aqueous hydrogen peroxide and an iron(II) salt (Fenton's reagent).

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + HO^- + HO\cdot$$

This reacts with anisole to give a mixture (up to 20%) of

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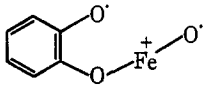
(76) P. Hugelshofer, J. Kalvoda, and K. Schaffner, *Helv. Chim. Acta*, 43, 1322 (1960).
(77) D. J. Collins and J. J. Hobbs, *Chem. Ind.* (London), 1725 (1965); *Aust. J. Chem.*, 20, 1905 (1967).
(78) A. G. Perkin and G. Yoda, *J. Chem. Soc.*, 127, 1884 (1925).
(79) G. F. Attree and A. G. Perkin, *ibid.*, 144 (1931).
(80) D. W. Cameron and P. E. Schutz, *ibid.*, *C*, 2121 (1967).
(81) A. Eckert and J. Hampel, *Ber.*, 60B, 1693 (1927).
(82) H. Brockmann and A. Dorlars, *Chem. Ber.*, 85, 1168 (1952).
(83) A. J. Davidson and R. O. C. Norman, *J. Chem. Soc.*, 5404 (1964).
(84) J. D. McClure and P. H. Williams, *J. Org, Chem.*, 27, 627 (1962).

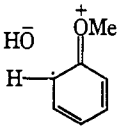
Table III
Radical Hydroxylations

Ether	*Reagent*	*Products*	*Ref*
Anisole	Fenton's reagent [iron(II) ion and hydrogen peroxide]	2-Methoxyphenol (9%) and quinol	85–87
Anisole	Fenton's reagent	2- and 4-methoxyphenol (20%)	88, 89
Anisole	Hydrogen peroxide, catalyzed by iron(III) ion and catechol	2- and 4-methoxyphenol (58%)	89–91
Anisole	Oxygen, iron(II) ion, and ascorbic acid	2-, 3-, and 4-methoxyphenol	88, 93
Anisole	γ irradiation in water	Not isolated	95
Anisole	Cyclohexyl hydroperoxide and trimethyl borate at 140°	2- and 4-methoxyphenol	96
Anisole	Peroxonitrous acid (hydrogen peroxide and nitrous acid)	4-Methoxy-2-nitro- and 2-methoxy-6-nitrophenol	97
Anisole	Peroxonitrous acid	2-Methoxyphenol, quinol, and 4-methoxy-2-nitrophenol	87
Ethoxybenzene	Peroxonitrous acid	2-Ethoxy- and 2-ethoxy-6-nitrophenol, and a little 2-ethoxy-4,6-dinitrophenol	98
Propoxybenzene	Peroxonitrous acid	A little 2,4-dinitro-6-propoxyphenol	98
4-Ethoxyacetanilide	Oxygen and complexes of iron(II), copper(I), vanadium(II), tin(II), or titanium(III)	2-Hydroxy-4-ethoxy- and 3-hydroxy-4-ethoxyacetanilide	98a

methoxyphenols (85% *ortho*, 0% *meta*, and 15% *para*).[85–89] Other products, including quinol, may also be formed.[86,87] Better yields (up to 58%) of methoxyphenols are obtained when anisole is treated with aqueous hydrogen peroxide, catechol, and a *catalytic* amount of an iron(III) salt.[89] Hydroxylation by this reagent is less selective, the proportions of the products being 65% *ortho*, <5% *meta*, and 35% *para*; no satisfactory free-radical chain mechanism explains the observed kinetics.[90,91] The lower reactivity of anisole toward this reagent, compared with Fenton's reagent, indicates that it does not provide hydroxyl radicals, and structure **26** has been suggested[91] for the species which effects the radical substitution reaction. Both of the above methods require hydrogen

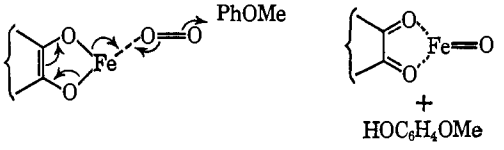


26

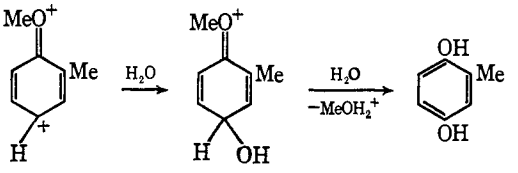


27

peroxide which is not present in living organisms, and a hydroxylating system which utilizes molecular oxygen has therefore been sought. A mixture of an iron(II) salt, ascorbic acid, and molecular oxygen[92] does bring about the hydroxylation of anisole, but the yield (8%) is poor. The proportions of the resulting methoxyphenols (43% *ortho*, 18% *meta*, and 39% *para*; in the presence of EDTA, 61% *ortho*, 9% *meta*, and 30% *para*) show that simple hydroxyl radicals are not involved.[88,93] It has been proposed that the perhydroxyl radical $HO_2\cdot$ takes part in these reactions,[88] but a more attractive suggestion[94] is that an oxygen *atom* is inserted into an aromatic C–H bond of anisole *via* an "oxenoid" intermediate.



The marked preference for *ortho–para* substitution in the above hydroxylations supports the view that the radicals concerned have electrophilic character.[88,88a] The predominant *ortho* substitution of anisole using Fenton's reagent can be explained if it is assumed that the ionic canonical structure **27** is important in the transition state.[88a] The hydroxylation of anisole and related ethers can also be brought about by the remaining systems listed in Table III[95–98a] which are likewise thought to produce hydroxyl radicals. Peroxonitrous acid gives rise to nitrogen dioxide as well as the hydroxyl radical, and this is responsible for the appearance of nitro groups in the products.[97] It has often been assumed that electrolytic oxidations occur *via* neutral radicals. By analogy with anodic



(1)

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(86) B. Fraser-Reid, J. K. N. Jones, and M. B. Perry, *Can. J. Chem.*, 39, 555 (1961).
(87) L. G. Shevchuk and N. A. Vyotskaya, *Zh. Org. Khim.*, 2, 1229 (1966).
(88) R. O. C. Norman and G. K. Radda, *Proc. Chem. Soc.*, 138 (1962).
(88a) R. O. C. Norman and J. R. L. Smith in "Oxidases and Related Redox Systems," Vol. 1, T. E. King, H. S. Mason, and M. Morrison, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965, p 131.
(89) G. A. Hamilton and J. P. Friedman, *J. Amer. Chem. Soc.*, **85**, 1008 (1963).
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(91) G. A. Hamilton, J. W. Hanifin, and J. P. Friedman, *ibid.*, **88**, 5269 (1966).
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(95) M. Anbar, D. Meyerstein, and P. Neta, *J. Phys. Chem.*, 70, 2660 (1966).
(96) Société des Usines Chimiques Rhônepoulenc, Addition 86,646 (1966) to French Patent 1,384,710 (1965); *Chem. Abstr.*, **65**, 10530 (1966); *cf.* French Patent 1,453,335 (1966); *Chem. Abstr.*, **67**, 21637*m* (1967).
(97) E. Halfpenny and P. L. Robinson, *J. Chem. Soc.*, 939 (1952).
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(98a) V. Ullrich, D. Hey, H. Staudinger, H. Büch, and W. Rummel, *Biochem. Pharmacol.*, **16**, 2237 (1967).

acetoxylation (section VI), it appears likely that the electrolyses of 2- and 3-methoxytoluene[37] in aqueous acid, which give 2,5-dihydroxytoluene, involve the removal of pairs of electrons from the aromatic compounds. The resulting ions $[MeOC_6H_4Me]^{2+}$ then react with water, *e.g*, as shown in eq 1.

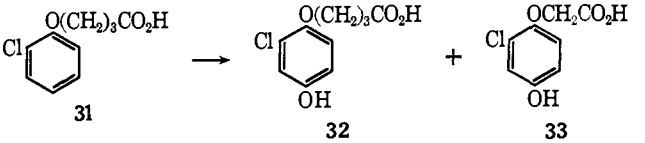
C. BIOLOGICAL HYDROXYLATIONS

Alkyl aryl ethers are metabolized by plants and animals by oxidative pathways. Both dealkylation of the ether function (see section X.B) and hydroxylation of the aromatic nucleus can occur and the resulting phenolic compounds may then be further metabolized or excreted (*e.g.*, as the corresponding glucuronides). The hydroxylations which have been investigated either have been reviewed previously[99] or are listed in Table IV.[100-120] Although knowledge of the mechanism of biological hydroxylation has increased rapidly recently,[88a,120a] the nature of the initial oxidation step is still conjectural. With animals substitution occurs mainly *para* to the ether function.

Many synthetic plant growth regulating substances are derivatives of phenoxyacetic acid (**28**) and the metabolism of this and related compounds by plants and microorganisms has received much attention.

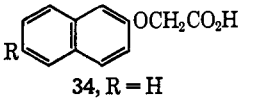
$$PhO(CH_2)_nCO_2H$$
28, $n = 1$; **29**, $n = 3$; **30**, $n = 5$

In higher plants hydroxylation of **28** and its chloro derivatives occurs *para* to the ether function[100,101] unless this position is blocked as in 2,4,6-trichlorophenoxyacetic acid.[101] However, with 2,4-dichlorophenoxyacetic acid, *para* hydroxylation does occur, the 4-chloro substituent migrating[120a] to the 3 or the 5 position.[102] The normal mode of degradation of an acid containing a polymethylene chain is by β oxidation with the subsequent formation of an acid having two carbon atoms fewer. With the higher homologs of phenoxyacetic acid, *e.g.*, 4-phenoxybutyric acid (**29**) and 6-phenoxyhexanoic acid (**30**), the final product of metabolism is 4-hydroxyphenoxyacetic acid, both modes of oxidation having occurred.[103] The fungus *Aspergillus niger* hydroxylates phenoxyacetic acid in a less selective manner, giving as the major products the *ortho* (77%) and *para* (19%) hydroxylated compounds, together with a little (4%) of the *meta* isomer.[107,111,112] Under similar conditions anisole also undergoes hydroxylation predominantly in the *ortho* position.[107] Treatment of phenoxyacetic acid with the iron(II)–ascorbic acid–molecular oxygen system described in section IV.B results in the formation of 2- and 4-hydroxyphenoxyacetic acid. This hydroxylating system therefore appears to have some features in common with that present in *A. niger*. Like the higher plants, *A. niger* can bring about β oxidation in addition to hydroxylation.[111] The isolation of the hydroxybutyric acid **32** as one of the metabolic products from the phenoxybutyric acid **31**, in addition to the expected hydroxyacetic acid **33**, indicates that β oxidation does not always occur first.[118] Some chlorine-substituted phenoxyacetic acids



31 **32** **33**

are hydroxylated in a nonspecific manner. Thus the products obtained from 2-chlorophenoxyacetic acid show that it undergoes nuclear hydroxylation at all five possible positions.[113] The metabolism of 2-naphthyloxyacetic acid (**34**) by microorganisms is generally similar,[119,120] hydroxylation occurring at C-6 to give **35**. Substitution at this position is unusual, and it is of interest that the same product is obtained using the iron(II)–ascorbic acid–molecular oxygen system,[119] together with a little of the expected isomer, 1-hydroxy-2-naphthyloxyacetic acid.[121]



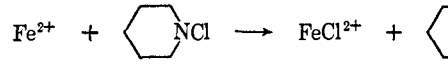
34, R = H
35, R = OH

V. Formation of Aminated Products

Just as the reaction of hydrogen peroxide with an iron(II) salt produces hydroxyl radicals so treatment of hydroxylamine with a titanium(III) salt gives amino radicals.

$$NH_2OH + Ti^{3+} \longrightarrow TiOH^{3+} + NH_2\cdot$$

These react with anisole to produce a mixture of 2- and 4-methoxyanilines (18%). The same products are obtained in better (38%) yield when a mixture of iron(II) chloride and hydroxylamine-O-sulfonic acid, H_2NOSO_3H, is used.[122,123] Under these conditions 1,3-dimethoxybenzene gives mainly 2,4-dimethoxyaniline. The simple amino radicals appear to have strong electrophilic properties, and this is also true of the piperidino radicals which are generated by the reaction of an iron(II) salt with N-chloropiperidine in methanol.



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(101) E. W. Thomas, B. C. Loughman, and R. G. Powell, *ibid.*, 204, 286 (1964).
(102) E. W. Thomas, B. C. Loughman, and R. G. Powell, *ibid.*, 204, 884 (1964).
(103) M. Wilcox, D. E. Moreland, and G. C. Klingman, *Physiol. Plant.*, 16, 565 (1963).
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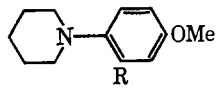
Table IV

Biological Hydroxylations

Ether	*Organism*	*Products*	*Re*
Anisole	Rabbit	4-Methoxyphenol	104
Anisole	Rabbit	4-Methoxyphenol and a little 2-methoxyphenol	105, 106
Anisole	*Aspergillus niger*	2-Methoxyphenol	107
4-Chloro-, 4-cyano-, and 4-nitroanisole	Rabbit	A little 4-chloro-, 4-cyano-, and 4-nitrocatechol	108
Ethoxybenzene	Dog	4-Ethoxyphenol	109, 110
Phenoxyacetic and ω-phenoxybutyric and -hexanoic acid	Excised roots of oats, barley, and corn	4-Hydroxyphenoxyacetic acid	103
Phenoxyacetic acid	Stem tissues of *Avena sativa*	4-Hydroxyphenoxyacetic acid	100
Phenoxyacetic acid	*A. niger*	2-Hydroxyphenoxyacetic acid	107
Phenoxyacetic and 4-phenoxybutyric acid	*A. niger*	2- and 4-hydroxyphenoxyacetic acid	111
Phenoxyacetic acid	*A. niger*	2- and 4-hydroxy- and a little 3-hydroxyphenoxy-acetic acid	112
ω-Phenoxypropionic and -pentanoic acid	*A. niger*	3-(2- and 4-hydroxyphenoxy)propionic acid	111
2-Chlorophenoxyacetic acid	*Avena sativa*	2-Chloro-4-hydroxyphenoxyacetic acid	101
2-Chlorophenoxyacetic acid	*A. niger*	2-Chloro-4- and -5-hydroxyphenoxyacetic acid and minor amounts of 2-chloro-3- and 6-hydroxyphenoxyacetic acid and 2-hydroxy-phenoxyacetic acid	113
4-Chlorophenoxyacetic acid	*A. niger*	4-Chloro-2- and -3-hydroxyphenoxyacetic acid	113
4-Chlorophenoxyacetic acid	A soil microorganism	4-Chloro-2-hydroxyphenoxyacetic acid	114
4-Chloro-2-methyl-phenoxyacetic acid	*A. niger*	4-Chloro-5-hydroxy-2-methylphenoxyacetic acid	115, 116
2,4-Dichlorophenoxy-acetic acid	Stems of *Phaseolus vulgaris*	2,5-Dichloro-4-hydroxy- and 2,3-dichloro-4-hydroxyphenoxyacetic acid	102
2,4-Dichlorophenoxy-acetic acid	Red kidney-bean plants	A hydroxy-2,4-dichlorophenoxyacetic acid	117
2,4-Dichlorophenoxy-acetic acid	*A. niger*	2,4-Dichloro-5-hydroxy- and some 2,5-dichloro-4-hydroxyphenoxyacetic acid	115, 116
2,5-Dichlorophenoxy-acetic acid	*A. niger*	2,5-Dichloro-4-hydroxyphenoxyacetic acid	115, 116
2,6-Dichlorophenoxy-acetic acid	*Avena sativa*	2,6-Dichloro-4-hydroxyphenoxyacetic acid	101
2,4,6-Trichlorophe-noxyacetic acid	*Avena sativa*	2,4,6-Trichloro-3-hydroxyphenoxyacetic acid	101
4-(2-Chlorophenoxy)-butyric acid	*A. niger*	4-(2-Chloro-4-hydroxyphenoxy)butyric, 2-chloro-4-hydroxyphenoxyacetic, and a trace of 2-chloro-3-hydroxyphenoxyacetic acid	118
4-(3-Chlorophenoxy)-butyric acid	*A. niger*	3-Chloro-6-hydroxyphenoxyacetic acid	118
4-(4-Chlorophenoxy)-butyric acid	*A. niger*	4-Chloro-2- and -3-hydroxyphenoxyacetic acid	118
2-Naphthyloxyacetic acid	*A. niger* or *Sclerotinia laxa*	6-Hydroxy-2-naphthyloxyacetic acid	119, 120
3-(2-Naphthyloxy)pro-pionic acid	*A. niger*	3-(6-Hydroxy-2-naphthyloxy)propionic acid	119
4-(2-Naphthyloxy)-butyric acid	*A. niger*	4-(6-Hydroxy-2-naphthyloxy)butyric acid and 6-hydroxy-2-naphthyloxyacetic acid	119
ω-(2-Naphthyloxy)hex-anoic, -octanoic, -decanoic, and -do-decanoic acid	*A. niger*	6-Hydroxy-2-naphthyloxyacetic acid	119
ω-(2-Naphthyloxy)-pentanoic, -hepta-noic, and -nonanoic acid	*A. niger*	3-(6-Hydroxy-2-naphthyloxy)propionic acid	119

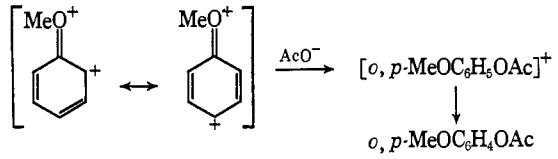
These react with anisole to give mainly 4-piperidinoanisole (**36**) and 3-chloro-4-piperidinoanisole (**37**), and with 1,3-dimethoxybenzene to give 4-piperidino-1,3-dimethoxybenzene.[123-125]



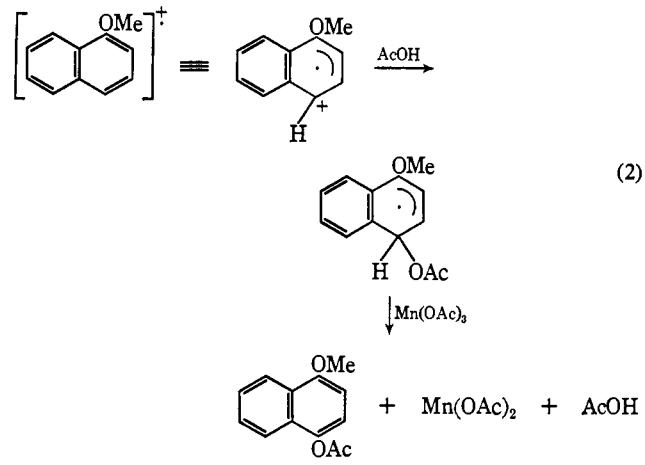
36, R = H
37, R = Cl

VI. Formation of Acyloxylated Products

The introduction of acyloxy groups, RCOO–, into alkyl aryl ethers can be brought about by reactions involving electrolysis, electron transfer, decomposition of acyl peroxides and lead(IV) acetate, and oxidation of aromatic ketones. The recorded reactions are summarized, in this order, in Table V. The electrolysis of a solution of anisole and acetate ion in acetic acid gives a mixture consisting almost entirely of 2- and 4-acetoxyanisoles,[126-129] the *ortho* isomer being predominant. The reaction was thought[126-128] to involve acyloxy radicals which would be expected to have electrophilic properties leading to the observed *ortho–para* substitution. However, the acetoxylation takes place at a potential considerably lower than those required for the oxidation of acetic acid[15] or the acetate ion[129,130] and appears to be a *two*-electron process.[131] It follows that it is the anisole which must undergo oxidation at the anode, losing two electrons to give the ion $[MeOC_6H_5]^{2+}$. The subsequent reaction of this with the acetate ion[131] may be represented as

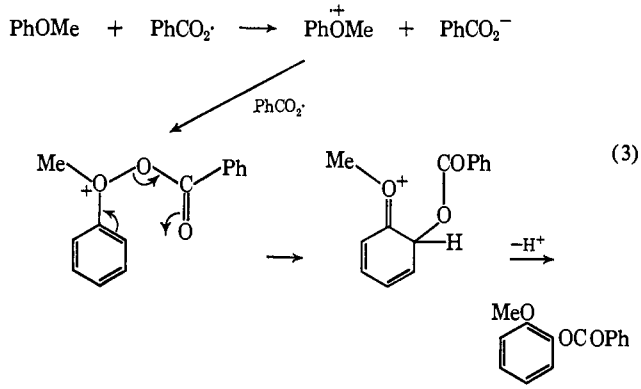


Acyloxylation involving the one-electron oxidation of an ether (see section II) occurs in the reaction between an excess of 1-methoxynaphthalene and manganese(III) acetate in acetic acid. The product, 1-acetoxy-4-methoxynaphthalene,[25,26] is thought to be formed by reaction of the resulting cation radical with the solvent, with subsequent further electron transfer (2). Few acyloxylations having a free-radical mechanism have been reported, the most important being the reaction of anisole with dibenzoyl peroxide[132] at 80°. This gives, in addition to products resulting from phenylation, a mixture of *o*- and *p*-benzoyloxyanisoles. The larger amount of the *ortho* isomer formed suggests that some interaction occurs between the ether oxygen and the benzoyl radical which leads to preferential *ortho* substitution.[132] A possible reaction sequence is shown in eq 3.



(2)

In the presence of oxygen more benzoyloxylation occurs and the proportion of *ortho* isomer formed is smaller.[133] Diacetyl



(3)

peroxide which is much less stable than dibenzoyl peroxide behaves in a different way in its reactions with alkyl aryl ethers in acetic acid.[134] Hydrogen abstraction from the solvent occurs, rather than from the ethers, and the carboxymethyl radicals formed then react with the ethers to give the corresponding alkoxyarylacetic acids.[135,136] In the presence of Lewis

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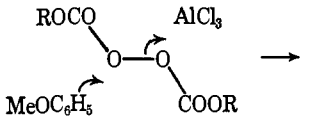
Table V
Acyloxylation Reactions

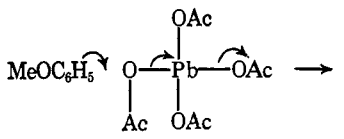
Ether	*Reagent*	*Products*	*Ref*
Anisole	Electrolysis in aqueous acetic acid	2- and 4-acetoxyanisole (40%) and a trace of the 3 isomer	126–129, 131
Anisole	Electrolysis with benzoic acid in acetonitrile	2- and 4-benzoyloxyanisole	137
Anisole	Electrolysis with 4-methoxy- and 4-methylbenzoic acid in acetonitrile	2- and 4-(4-methoxybenzoyloxy)anisole, and 2- and 4-(4-methylbenzoyloxy)anisole	137
4-Methoxytoluene	Manganese(III) acetate	Small amounts of 2- and 3-acetoxy-4-methoxytoluene	138
1-Methoxynaphthalene	Manganese(III) acetate	1-Acetoxy-4-methoxynaphthalene	25, 26
Anisole	Dibenzoyl peroxide at 80°	2- and 4-benzoyloxyanisole (20–33%)	132, 133
Anisole	Silver bromide dibenzoate	A little benzoyloxyanisole	139
1,4-Dimethoxybenzene	Dibenzoyl peroxide at 80°	1-Benzoyloxy-2,5-dimethoxybenzene	132
1,2,3-Trimethoxybenzene	Dibenzoyl peroxide at 120–160°	4- and 5-benzoyloxy-1,2,3-trimethoxybenzene	140
Anisole	Diisopropyl peroxodicarbonate and aluminum chloride	Isopropyl 2- and 4-methoxyphenyl carbonate (86%)	141
1,2-Dimethoxybenzene	Diisopropyl peroxodicarbonate and aluminum chloride	Isopropyl 2,3- and 3,4-dimethoxyphenyl carbonate (65%)	44
1,3-Dimethoxybenzene	Diisopropyl peroxodicarbonate and aluminum chloride	Isopropyl 2,4-dimethoxyphenyl carbonate (77%)	44
1,4-Dimethoxybenzene	Diisopropyl peroxodicarbonate and aluminum chloride	Isopropyl 2,5-dimethoxyphenyl carbonate (31%)	44
1,3,5-Trimethoxybenzene	Diisopropyl peroxodicarbonate and aluminum chloride	Isopropyl 2,4,6-trimethoxyphenyl carbonate (78%)	44
Anisole	Dicyclohexyl peroxodicarbonate and Lewis acids	Cyclohexyl 2- and 4-methoxyphenyl carbonate and 4-cyclohexyloxyanisole	142
Anisole	*t*-Butyl isopropyl peroxocarbonate and (a) aluminum chloride, (b) boron trichloride	2- and 4-methoxyphenol: (a) 4%, (b) 25%	143
1,3-Dimethoxybenzene	*t*-Butyl isopropyl peroxocarbonate	2,4-Dimethoxyphenol (5%)	143
1,3-Dimethoxybenzene	Dibenzoyl peroxide and aluminum chloride	1-Benzoyloxy-2,4-dimethoxybenzene (3%)	35
Anisole	Di-4-nitrobenzoyl peroxide and aluminum chloride	2- and 4-(4-nitrobenzoyloxy)anisole (7 and 21%)	35
Ethoxybenzene	Di-4-nitrobenzoyl peroxide and aluminum chloride	2- and 4-(4-nitrobenzoyloxy)-1-ethoxybenzene (10 and 12%)	35
1,3-Dimethoxybenzene	Di-4-nitrobenzoyl peroxide and aluminum chloride	1-(4-Nitrobenzoyloxy)-2,4-dimethoxybenzene (20%)	35
Anisole	Lead(IV) acetate in sunlight	2- and 4-acetoxyanisole	144
Anisole	Lead(IV) acetate in various solvents at 80°	2- and 4-acetoxyanisole	128, 134
Anisole	Lead(IV) acetate at 120°	2-Acetoxyanisole	145
Ethoxybenzene	Lead(IV) acetate	A little 1-acetoxy-4-ethoxybenzene	134
Isopropoxybenzene	Lead(IV) acetate	A little 1-acetoxy-4-isopropoxybenzene	134
Benzyloxybenzene	Lead(IV) acetate	1-Acetoxy-4-benzyloxybenzene	134
1,2-Dimethoxybenzene	Lead(IV) acetate, prolonged reaction time	4-Acetoxy-1,2-dimethoxybenzene (37%) and 4,5-diacetoxy-1,2-dimethoxybenzene (3.5%)	146
1,3-Dimethoxybenzene	Lead(IV) acetate	1-Acetoxy-2,4-dimethoxybenzene (10%) and a trace of 1-acetoxy-2,6-dimethoxybenzene	147
1,3-Dimethoxy-5-tridecylbenzene	Lead(IV) acetate	1-Acetoxy-2,4-dimethoxy-6-tridecylbenzene	148
1,4-Dimethoxybenzene	Lead(IV) acetate	Some 1-acetoxy-2,5-dimethoxybenzene	149
1-Methoxynaphthalene	Lead(IV) acetate	1-Acetoxy-4-methoxynaphthalene	48
2-Methoxynaphthalene	Lead(IV) acetate	1-Acetoxy-2-methoxynaphthalene	48
1,3,5-Trimethoxybenzene	Lead(IV) acetate in benzene	A trace of 1-acetoxy-2,4,6-trimethoxybenzene	150
Anisole	Lead(IV) acetate and boron trifluoride at 20°	4-Acetoxyanisole (5%)	36
2,5-Dimethoxyacetophenone	Peroxoacetic acid or peroxobenzoic acid	1-Acetoxy-2,5-dimethoxybenzene	151, 152
2-Acetyl-1-methoxynaphthalene	Peroxoacetic acid	2-Acetoxy-1-methoxynaphthalene	121

acids, the oxygen–oxygen bonds of diacyl peroxides undergo heterolysis rather than homolysis. The resulting acyloxy cations react with alkyl aryl ethers by normal electrophilic substitution reactions to give *ortho*- and *para*-acyloxylated products.



$$o,p\text{-}MeOC_6H_4OCOOR + ROCOOAlCl_2 + HCl$$

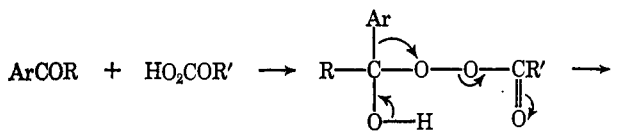
The yields from such reactions with dialkyl peroxodicarbonates are particularly good.[44,141] Lead(IV) acetate can undergo either homolytic or heterolytic decomposition depending on the conditions. With anisole in acetic acid both photochemical[144] and thermal[128,134] reactions lead, rather inefficiently, to the formation of 1- and 2-acetoxyanisole. The homolytic mechanism originally proposed for the thermal (80°) reaction[134] was later rejected in favor of the electrophilic substitution mechanism.[128]



$$MeOC_6H_4OAc + HOAc + Pb(OAc)_2$$

In the presence of boron trifluoride the reaction giving 4-acetoxyanisole occurs even at 20°.[36] Under these conditions it appears likely that 4-methoxyphenyllead triacetate (**11**) is formed initially and gives rise to the p-$MeOC_6H_4^+$ cation (section III.A) which then reacts with acetate ion.

Baeyer–Villiger oxidations of methoxyacetophenones, methoxybenzaldehydes, and related compounds, using peroxo acids, have been reviewed previously.[153,154] These reactions give the corresponding acyloxymethoxybenzenes or the derived methoxyphenols



$$RCOOAr + R'CO_2H$$

and may be considered to be special cases of intramolecular electrophilic acyloxylation.[121,151–154]

VII. Formation of Quinones

Quinones are by far the commonest oxidation products of alkyl aryl ethers. Almost all the usual acidic oxidizing agents have been used at some time, the most important being nitric acid[155,156] and chromic acid. Quinones are relatively resistant to further oxidation by these reagents and are often obtained in high yield. The poor solubility of many enables them to be separated easily from reaction mixtures. 1,2-Benzoquinones are less stable than are the corresponding 1,4 isomers and are rarely obtained; the formation of 1,4-quinones in the naphthalene series is favored for the same reason. The color of an oxidation product often indicates the type of quinonoid system present, simple 1,4-quinones being yellow while 1,2-quinones are orange or red.

Reactions resulting in quinone formation can be grouped into four categories: (A) those in which compounds undergo dealkylation of *two* methoxyl groups (Subsequent oxidation gives quinones which contain no additional oxygen atoms. The term "oxidative demethylation" is normally restricted to this type of oxidation.); (B) those in which only *one* of the quinonoid oxygen atoms results from the demethylation of a methoxyl group, the other being introduced by the oxidizing agent by, for example, hydroxylation; (C) those in which *both* the quinonoid oxygen atoms are introduced by the oxidizing agent; (D) those which involve both Scholl (and related) reactions and quinone formation.

A. OXIDATIVE DEMETHYLATION

The oxidations of substituted 1,4-dimethoxybenzenes which lead to the formation of substituted benzo-1,4-quinones are listed in Table VI. Nitric acid in various concentrations is the commonest reagent and many yields are good. The reactions are normally performed under mild conditions (0–30°) and are very rapid, some being complete in less than 1 min. Other substituent groups including methoxyl groups and, surprisingly, some phenolic and olefinic groups are largely unaffected by the oxidation conditions. The formyl group is protected from oxidation by treatment with acetic anhydride which converts it into the diacetoxymethyl group.[157] Because of the difficulty of deciding which of the various chromium(VI) species is present,[158,159] the general description "chromic acid" is used for reagents prepared from chromium trioxide or dichromate ion. Similar reactions leading to quinone formation from other types of aromatic compound are given in Table VII. Formation of *o*-quinones occurs occasionally[160–165] in certain systems, most of which contain fused rings, but once again 1,4-quinones are the predominant products. As a result oxidative demethylation with nitric acid has proved to be of considerable value in the determination of the structures of naturally occurring polymethoxyflavones and related compounds.[166] In the few cases examined, oxidation of compounds containing alkoxyl groups other than methoxyl occurs in the normal manner.

The reaction of nitric acid with anisole and its derivatives has been shown[167,168] to result in considerable demethylation in addition to nitration, the methyl group separating in effect

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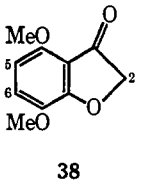
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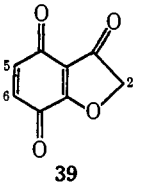
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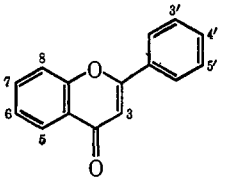
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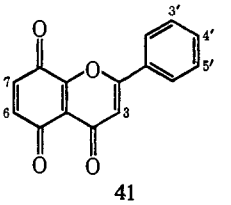
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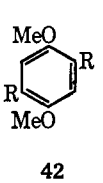
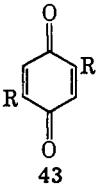
as the methylcarbonium ion which reacts with the solvent. Similar reactions would be expected to occur with other methoxylated benzene derivatives under suitable conditions. 1,4-Dimethoxybenzene is highly reactive in electrophilic substitution reactions and readily undergoes nitration[169] as do many related compounds having substituents in the 2- and 3, or 2 and 6 positions.[170-172] Substituted 1,4-dimethoxybenzenes (**42**) carrying electron-supplying groups in the 2 and 5 positions, however, frequently undergo oxidative demethylation giving the quinones **43**. It seems likely that electrophilic


42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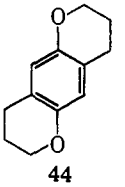
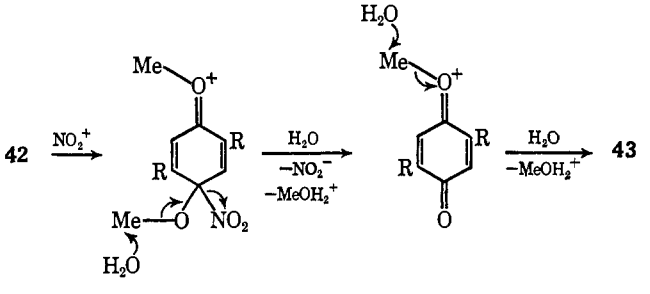
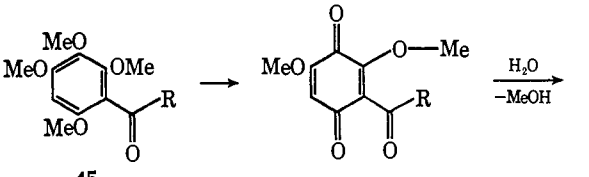

44

substitution at the 3 and 6 positions in **42** is hampered by the steric effects of the flanking groups so allowing attack by the nitronium ion to occur elsewhere. Thus compound **42** (R = $-(CH_2)_3OCH_2CH_2CN$) on treatment with nitric acid gives the corresponding quinone but, in contrast, the related cyclic ether **44** undergoes normal nitration[173] presumably because the steric requirements of the substituents are smaller. Under a wide variety of conditions[8] nitric acid acts as a source of the nitronium ion, NO_2^+, and a plausible mechanism for the formation of the quinone **43** is



It is possible that reactions involving the nitrosonium ion, NO^+, may also occur.

Oxidative demethylation is favored by the presence of additional methoxyl groups in the molecule. The orientation of the substituents is then of less importance and both 2,6- and 2,5-disubstitution facilitate quinone formation. The reaction of nitric acid with some tetra- and pentamethoxy compounds leads not only to quinone formation but also to hydrolysis, the products being mono- or dihydroxyquinones. The monohydroxyquinones are derived from 1,2,3,5-tetramethoxybenzene or, better, its acyl derivatives **45**, and their formation from the latter may be represented thus[203]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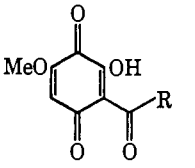
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The products **46** are no doubt stabilized by the hydrogen bonding between the phenolic group and the two adjacent carbonyl groups. The dihydroxyquinones are formed from the 1,2,3,4,5-pentamethoxy-2-acylbenzenes (**47**) in a similar manner. Here the hydrolysis of a second methoxyl group is favored by the relative stability of product **48** which has a symmetrical, strongly hydrogen-bonded structure.

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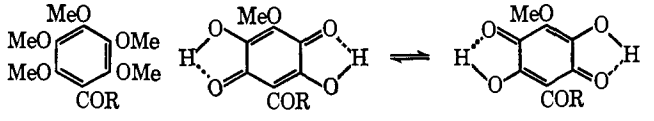
Table VI
Simple Oxidative Demethylations of Substituted 1,4-Dimethoxybenzenes

Substituted 1,4-dimethoxybenzene	*Reagent*	*Substituted benzo-1,4-quinone*	*Ref*
Unsubstituted	Electrolysis in aqueous acid	Unsubstituted (49%)	39
Unsubstituted	Peroxochromic acid and hydrochloric acid	Tetrachloro- (complex with tetrachloro-1,4-dimethoxybenzene) (44%)	174
2,5-Diacetamido-	Nitric acid (*d* 1.4)	2,5-Diacetamido- (89%)	170
2-Amino-5-methyl-	Nitric acid (*d* 1.4) and acetic anhydride	2-Acetamido-5-methyl- (78%)	170
2,5-Dimethyl-	Peroxoacetic acid	2,5-Dimethyl-	175
2-Octyl-5-pentyl-	Nitric acid in acetic acid	2-Octyl-5-pentyl-	176
2,5-Bischloromethyl-	Nitric acid in acetic acid	2,5-Bischloromethyl-	173
2,5-Di(11-methoxyundecyl)-	Nitric acid in acetic acid	2,5-Di(11-methoxyundecyl)- (74%)	173, 177
2,5-Bisethoxycarbonylmethyl-	Nitric acid in acetic acid	2,5-Bisethoxycarbonylmethyl- (72%)	173
2,5-Di-3-(2-cyanoethoxy)-propyl-	Nitric acid in acetic acid	2,5-Di-3-(2-cyanoethoxy)propyl- (91%)	173
2,5-Di(6-cyano-4-hydroxyhexyl)-	Nitric acid in acetic acid	2,5-Di(6-cyano-4-hydroxyhexyl)-	177
2,5-Dichloro-	Nitric acid (*d* 1.5)	2,5-Dichloro-	171
2,5-Dibromo-	Nitric acid (*d* 1.5)	2,5-Dibromo-	172
2,3,5-Tribromo-	Nitric acid (*d* 1.5)	Tetrabromo- (small yield)	172
2-Acetamido-5,6-dibromo-	Nitric acid in acetic acid	2-Acetamido-5,6-dibromo-3-nitro- (28%)	178
Tetramethyl-	Cerium(IV) sulfate in sulfuric acid and acetic acid	Tetramethyl-	179
2-Formyl-3,5,6-trimethyl-	Nitric acid (*d* 1.4)	2,3,5-Trimethyl-6-nitro-	180
2,5-Di(2-chlorophenyl)-	Nitric acid (*d* 1.4)	2,5-Di(2-chlorophenyl)-	181
2-Chloro-5-(2-chlorophenyl)-	Nitric acid (*d* 1.4)	2-Chloro-5-(2-chlorophenyl)-	181
2-Methoxy-	Dry chlorine in chloroform	2,3,5-Trichloro-6-methoxy-	182
2-Methoxy-	Sulfuryl chloride in chloroform	2,3,-Dichloro-5-methoxy- (15%)	183
2-Methoxy-5-methyl-	Chromic acid	2-Methoxy-5-methyl- (quantitative)	184
2,5-Dibromo-3-methoxy-6-methyl-	Nitric acid (*d* 1.4)	2,5-Dibromo-3-methoxy-6-methyl-	184
2-Methoxy-5-propyl-	Nitric acid (*d* 1.5) or chromyl chloride	2-Methoxy-5-propyl-	185–187
2-Methoxy-6-propyl-	Nitric acid	2-Methoxy-6-propyl-	188
2-Ethoxy-6-propyl-	Nitric acid	2-Ethoxy-6-propyl-	188
2-Propoxy-6-propyl-	Nitric acid	2-Propoxy-6-propyl-	188
2-Formyl-5-methoxy-	Nitric acid in acetic anhydride and sulfuric acid	2-Diacetoxymethyl-5-methoxy-	157
2,5-Dibromo-3-methoxy-	Nitric acid (*d* 1.4)	2,5-Dibromo-3-methoxy- (84%)	189
2-Bromo-5-methoxy-	Peroxoacetic acid	2-Bromo-5-methoxy-	175
2-Methoxy-5-(2′-methoxyphenylprop-1-yl)-	Chromic acid	2-Methoxy-5-(2′-methoxyphenylprop-1-yl)- [*and* 4-methoxy-5-(2′-methoxyphenylprop-1-yl)benzo-1,2-quinone]	160
2-Methoxy-5-(2′-methoxyphenylprop-2-en-1-yl)-(di-O-methyllatifolin)	Chromic acid	2-Methoxy-5-(2′-methoxyphenylprop-2-en-1-yl)- (latifolinone)	190
2-Methoxy-5-R-, where R = $MeCPh_2$-, $PhCOCPh_2$-, $PhCH_2CPhMe$-, phthalidyl-, dimethoxyphthalidyl-, and dimethoxynitrophthalidyl-	Nitric acid in acetic acid, or nitric acid (*d* 1.5)	2-Methoxy-5-R-	191
2-Acetyl-3-hydroxy-5-methoxy-	Nitric acid in ether	2-Acetyl-3-hydroxy-5-methoxy- (40%)	192
2-Cinnamoyl-3-hydroxy-5-methoxy-	Nitric acid in acetic acid	2-Cinnamoyl-3-hydroxy-5-methoxy-	192
2,5-Dimethoxy-	Nitric acid or peroxoacetic acid	2,5-Dimethoxy-	175, 193
2,5-Di(2-methoxycarbonylphenyl)-3,6-dimethoxy-	Nitric acid (*d* 1.4) in aqueous methanol	2,5-Di(2-methoxycarbonylphenyl)-3,6-dimethoxy-	194
2,6-Dimethoxy-	Chromic acid or nitric acid	2,6-Dimethoxy- (26%)	195, 196
2,6-Dimethoxy-	Nitric acid (*d* 1.25) in ethanol	2-Hydroxy-6-methoxy-	192
2,6-Dimethoxy-3-methyl-	Nitric acid or chromic acid	2,6-Dimethoxy-3-methyl-	184
2-Acetyl-3,5-dimethoxy-	Nitric acid in ether or 35% nitric acid in ethanol	2-Acetyl-3-hydroxy-5-methoxy-	192, 197
2-Bromo-3,5-dimethoxy-	35% Nitric acid in ethanol	2-Bromo-3,5-dimethoxy-	198

Table VI (Continued)

Substiiuted 1,4-dimethoxy-benzene	*Reagent*	*Substituted benzo-1,4-quinone*	*Ref*
2-Phenyl-3,5-dimethoxy-	35% Nitric acid in ethanol	2-Phenyl-3,5-dimethoxy- (70%)	198
2-Cinnamoyl-3,5-dimethoxy-	Nitric acid in acetic acid	2-Cinnamoyl-3-hydroxy-5-methoxy-	192
2,3-Dibromo-5,6-dimethoxy-	Nitric acid	2,3-Dibromo-5,6-dimethoxy-	199
2-Acetyl-3,5,6-trimethoxy-	Nitric acid in ether	2-Acetyl-3,6-dihydroxy-5-methoxy-	200
2-Cinnamoyl-3,5,6-trimethoxy- (pedicellin)	Nitric acid in acetic acid	2-Cinnamoyl-3-hydroxy-5,6-dimethoxy- and some 2-cinnamoyl-3,6-dihydroxy-5-methoxy-	201, 202
2-Dihydrocinnamoyl-3,5,6-trimethoxy-	Nitric acid (*d* 1.4) in acetic acid	2-Dihydrocinnamoyl-3,6-dihydroxy-5-methoxy- (after alkaline hydrolysis; 60%)	202



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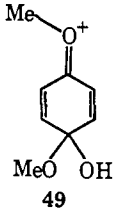

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The formation of quinones using most of the other reagents listed in Tables VI and VII can be rationalized without difficulty. For example, both electrolytic and peroxoacetic acid oxidations (*cf.* sections IV.B and IV.A) probably involve hydroxylation, by different routes, at the 4 position of the 1,4-dimethoxybenzene system. The resulting ion **49** reacts with water to form the 1,4-quinone and methanol. Reactions with chromic acid appear to follow a similar course to those with nitric acid, probably with the transient formation of aryl chromates (*cf.* section VII.B.1) while those with one-electron oxidizing agents presumably proceed *via* cation radicals.

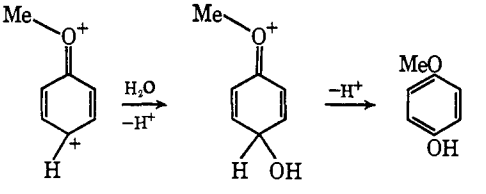
The reactions in which chlorine or sulfuryl chloride participate are of a different type.[182,183] Addition of chlorine takes place giving polychlorinated nonaromatic products (see section IX.A) which then undergo elimination reactions with the formation of chloroquinones. In aqueous solution chlorine catalyzes the demethylation of derivatives of 1,2-dimethoxybenzene.[223–225] With an excess of chlorine the resulting catechols are thought to be oxidized eventually to quinones, but no such products have yet been isolated.

B. INTRODUCTION OF ONE EXTRA OXYGEN ATOM

1. Benzoquinones

Many derivatives of anisole having an unsubstituted *para* position undergo oxidation on treatment with suitable electrophilic reagents or on electrolysis to give derivatives of benzo-1,4-quinone (Table VIII). During these reactions an oxygen-containing group enters the *para* position; this provides one of the quinonoid oxygen atoms of the product, the other being derived from the alkoxyl group of the parent ether. No derivatives of benzo-1,2-quinone have been obtained from such reactions, no doubt because of the ease with which such compounds are further oxidized. Oxidizing agents which have been used frequently are peroxoacetic acid, lead(IV) acetate, nitric acid, and chromic acid, the last two being of particular importance. Some of the simpler monoalkoxy compounds fail to give quinones with these reagents but do so on electrolysis.[37,39] Because of the widely differing natures of the oxidizing agents, each will be discussed separately.

Electrolytic oxidation of, for example, anisole,[39] presumably occurs by way of the ion $[MeOC_6H_5]^{2+}$ (see section VI) which reacts with water giving 4-methoxyphenol.



Two more electrons are then removed and further reaction with water takes place (eq 4).

The first stage in the reaction of peroxoacetic acid and peroxobenzoic acid with many alkyl aryl ethers appears to be hydroxylation. However, the resulting alkoxyphenols are so

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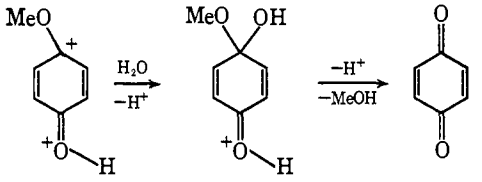
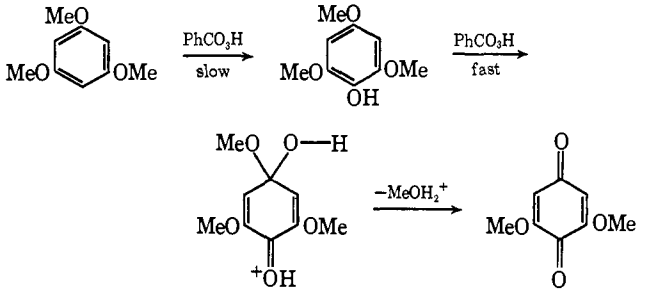
Table VII
Simple Oxidative Demethylations of Other Alkoxy Compounds

Ether	*Reagent*	*Products*	*Ref*
1-Cinnamoyl-2,3,5,6-tetraethoxy-4-methoxybenzene	Nitric acid in acetic acid	2-Cinnamoyl-3,6-dihydroxy-5-methoxybenzo-1,4-quinone and 2-cinnamoyl-3-hydroxy-6-ethoxy-5-methoxybenzo-1,4-quinone	204
2,2′-Dibromo-3,3′,5,5′,6,6′-hexamethoxybiphenyl	Nitric acid	6,6′-Dibromo-3,3′-dimethoxybiphenyl-2,5:2′,5′-diquinone	47
1,4-Dimethoxy-2-methylnaphthalene	Chromic acid or nitric acid	2-Methylnaphtha-1,4-quinone	205, 206
Di(1,4-dimethoxy-2-naphthylmethyl) disulfide	Peroxoacetic acid	2-Hydroxynaphtha-1,4-quinon-3-yl-methanesulfonic acid	207
1,2,3,6,7,8-Hexamethoxybiphenylene	Aqueous nitric acid	1,6,7,8-Tetramethoxybiphenylene-2,3-quinone (96%)	161
1,2,3,6,7,8-Hexamethoxybiphenylene	Bromine	1,6,7,8-Tetramethoxybiphenylene-2,3-quinone (29%) and the 4-bromo derivative (15%)	161
2,2′-Diiodo-3,3′,4,4′,5,5′-hexamethoxybiphenyl	Cuprous oxide	1,6,7,8-Tetramethoxybiphenylene-2,3-quinone (small amount)	162
9,10-Dimethoxy- and 9,10-diethoxyanthracene	Bromine in carbon tetrachloride	Anthraquinone	208
9,10-Benzylidenedioxy-, 9,10-(1-phenylethylidenedioxy)-, and 9,10-(diphenylmethylenedioxy)phenanthrene	Concentrated sulfuric acid	Phenanthrene-9,10-quinone	209
5,6-Methylenedioxy- and 5,6-diphenylmethylenedioxychrysene	Concentrated sulfuric acid	Chrysene-5,6-quinone	209
10,10′-Dimethoxy-9,9′-bianthryl	Anhydrous iron(III) chloride	Bianthron-9-ylidene (**23**)	70
4,4′-Di(X)-2,5-dimethoxybiphenyl-2′,5′-quinone (**70**, X = Br, Cl, MeO, Ph) and diethoxy analogs	Nitric acid or chromic acid	4,4′-Di(X)biphenyl-2,5:2′,5′-diquinone (**71**, X = Br, Cl, MeO, Ph)	45, 47
16,17-Dimethoxyviolanthrene-5,10-dione (Caledon Jade Green **17**)	Nitric acid and sulfuric acid	Violanthrene-5,17:10,16-diquinone	210
16,17-Dimethoxyviolanthrene-5,10-dione	Nitric acid	15,18-Dinitroviolanthrene-5,17:10,16-diquinone	211
Derivatives of 4,7-dimethoxy-(2H)-benzofuran-3-one (**38**)		Derivatives of (2H)-benzofuran-3,4,7-trione (**39**)	
2-Benzyl-6-methoxy-	Nitric acid (*d* 1.25)	2-Benzyl-6-methoxy-	212
2-Benzylidene-6-methoxy-	Nitric acid (*d* 1.25)	2-Benzylidene-6-methoxy-	213
2-Benzyl-5,6-dimethoxy-	Nitric acid (*d* 1.25)	2-Benzyl-5,6-dimethoxy-	212
2-Benzylidene-5,6-dimethoxy-	Nitric acid (*d* 1.25)	2-Benzylidene-5,6-dimethoxy-	212
5,6,7,8-Tetramethoxyflavanone	Nitric acid in ether	6,7-Dimethoxyflavanone-5,8-quinone	214
Derivatives of flavone (**40**)		Derivatives of flavone-5,8-quinone (**41**)	
5,7,8-Trimethoxy-	Nitric acid (*d* 1.25)	7-Methoxy-	215
3,5,7,8-Tetramethoxy-	Nitric acid (*d* 1.25)	3,7-Dimethoxy-	216
3,4′,5,7,8-Pentamethoxy-	Nitric acid (*d* 1.25)	3,4′,7-Trimethoxy-	217
3,3′,4′,5,7,8-Hexamethoxy- and 3,3′,4′,5,7-pentamethoxy-8-ethoxy-	Nitric acid (*d* 1.25)	3,3′,4′,7-Tetramethoxy-	218
3,3′,4′,5,5′,6,8-Heptamethoxy-	Nitric acid (*d* 1.25)	3,3′,4′,5′,6-Pentamethoxy-	219
3,4′,5,6,7,8-Hexamethoxy-	Nitric acid (*d* 1.25)	3,4′,6,7-Tetramethoxy-	192
1,2-Ethylenedioxy-4,5-dimethoxybenzene	Nitric acid	4,5-Ethylenedioxybenzo-1,2-quinone	163
5,8-Dimethoxy-2-methyl-6,7-furanochromone (khellin)	Nitric acid (*d* 1.2)	2-Methyl-6,7-furanochromone-5,8-quinone	220
5-Acetyl-6-hydroxy-4,7-dimethoxybenzofuran (khellinone)	Nitric acid in ether	5-Acetyl-6-hydroxybenzofuran-4,7-quinone	221
1,2,3,4-Tetramethoxy-10-methylacridone (melicopicine, **89a**)	Nitric acid	2,3-Dimethoxy-10-methylacridone-1,4-quinone and the corresponding 1,2-quinone	164
Brucine	Nitric acid or chromic acid	Strychnine-10,11-quinone (80%)	165
Dihydrobrucine	Nitric acid	Dihydrostrychnine-10,11-quinone	165
2,4-Dichloro-3,7-dimethoxy-1,5,8-trimethyldepsidone	Nitric acid in acetic acid	2-Hydroxy-3,6-dimethylbenzo-1,4-quinone	222

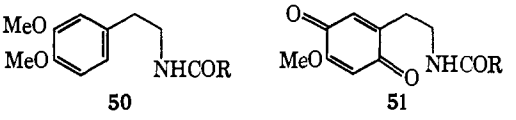


(4)

much more reactive than are the ethers that they cannot be isolated, being oxidized preferentially to the corresponding quinones.[175,226] In many cases the latter undergo further oxidation leading to the destruction of the quinonoid system (section IX.B) and yields are usually less than 30%. A kinetic study[226] of the reaction between 1,3,5-trimethoxybenzene and peroxobenzoic acid supports the mechanism shown below in which the peroxo acid acts as a source of the hydroxyl cation (HO^+).



The order of reactivity of the methoxybenzenes toward peroxobenzoic acid is mono < 1,2-di = 1,4-di < 1,2,3-tri < 1,3-di < 1,3,5-tri, which is compatible with a mechanism involving

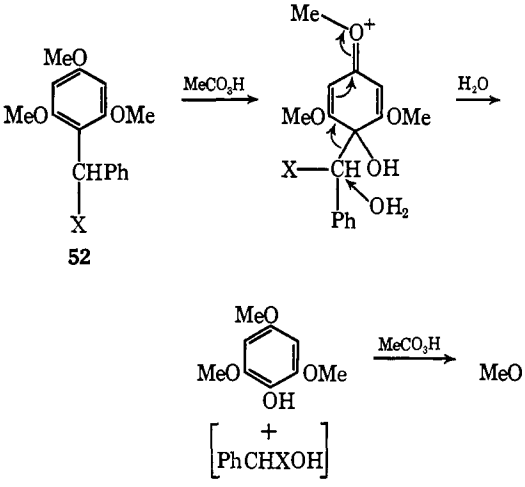


50 **51**

R = CCl_3, CH_2Cl, $SO_2C_6H_4Cl$-*p*

electrophilic attack. The oxidations effected by peroxoacetic acid[175] have similar kinetics[227] and take place in a similar manner. The ethers which fail to react are, in general, those with deactivating substituents. It is therefore surprising that 1,2-dimethoxybenzene, which is highly reactive in electrophilic substitution reactions, should react sluggishly or not at all with the peroxo acids.[175,227,228] The oxidation of some trimethoxydiphenylmethane derivatives **52** leads to the displacement of the aralkyl group [229] with the formation of the quinone **53**. Nucleophilic attack at the benzyl carbon atom would be expected to take place comparatively readily. Lead(IV) acetate normally reacts with simple alkyl aryl ethers to give acetoxy compounds (section VI). In a few cases, however,[148,150,230] quinone formation also occurs presumably as a consequence of further acetoxylation (eq 5).

The oxidative demethylation of 1,4-dimethoxybenzene derivatives with nitric acid gives benzo-1,4-quinones (section VII.A). The application of this reaction to ethers in which the

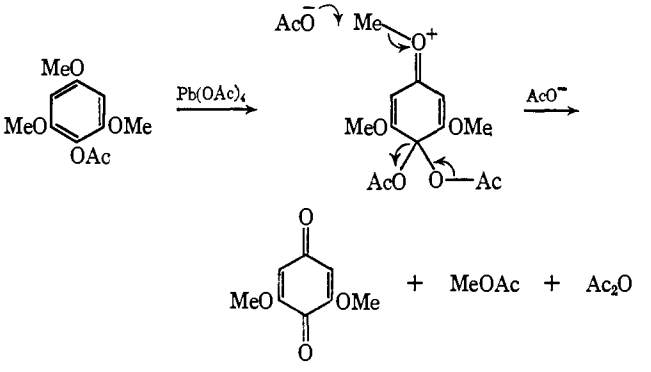


(5)

52

53

para position is unsubstituted can also lead to quinone formation. Once again a wide range of concentrations of nitric acid in several different solvents have been used. Anisole derivatives undergo nitration almost exclusively, and only a few examples[231–233] are known where small amounts of quinones



are obtained. The same is true of derivatives of 1,2- and 1,3-dimethoxybenzene. However, with 1,2,3-trialkoxybenzenes and related ethers nitration is less important and, using carefully controlled reaction conditions, good yields of 2,6-dialkoxybenzo-1,4-quinones can be obtained.[234–242] The formation from 1,2,3-trimethoxybenzene of 2,6-dimethoxybenzoquinone and of the other major product, 1,2,3-trimethoxy-5-nitrobenzene, can be explained by a reaction sequence such as that following.

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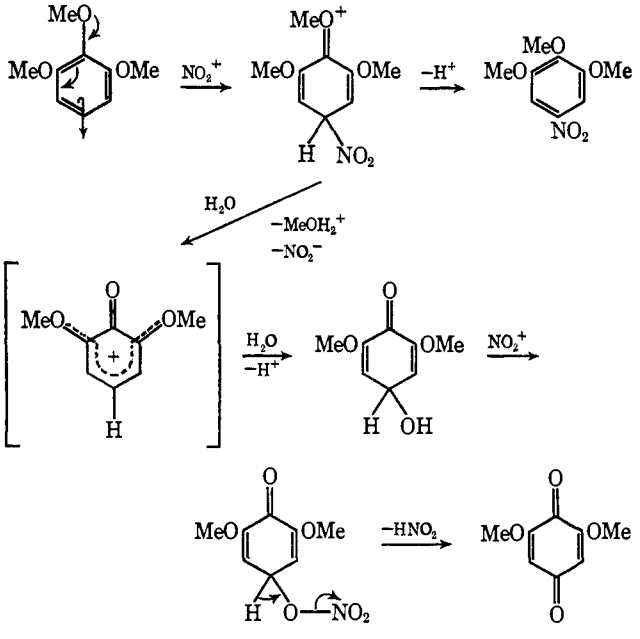
Table VIII
Benzoquinones Formed with Introduction of One Extra Oxygen Atom

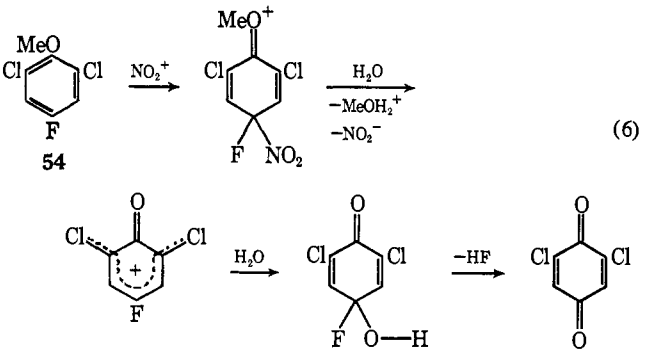
Ether	*Reagent*	*Substituted benzo-1,4-quinone*	*Ref*
Anisole, ethoxybenzene, or 3-methylbutoxybenzene	Electrolysis in aqueous acid	Unsubstituted (46–72%)	39
3-Methoxytoluene	Electrolysis in aqueous acid	2-Methyl-	37
3,5-Dimethylanisole	Peroxoacetic acid	2,6-Dimethyl-	175
2-*t*-Butyl-5-methyl- and 3-*t*-butyl-6-methylanisole	Nitric acid in acetic anhydride	2-*t*-Butyl-5-methyl- (small yields)	231–233
2-*t*-Butyl-5-ethylanisole	Nitric acid in acetic anhydride	2-*t*-Butyl-5-ethyl-	233
2,6-Dichloro-4-fluoroanisole	Nitric acid (*d* 1.5)	2,6-Dichloro-	243
2,6-Dibromo-4-fluoroanisole	Nitric acid (*d* 1.5)	2,6-Dibromo-	244
2,3-Dimethoxytoluene	Nitric acid (*d* 1.4) in acetic acid	2-Methoxy-6-methyl-	245
3,4-Dimethoxytoluene	Peroxoacetic acid	2-Methoxy-5-methyl-	175
1-(2-Acylamidoethyl)-3,4-dimethoxybenzene (**50**)	Peroxoacetic acid in ethanol	2-(2-Acylamidoethyl)-5-methoxy- (**51**)	246
1,2-Dichloro-4,5-dimethoxybenzene	Nitric acid in acetic anhydride	2-Chloro-5-methoxy- (20%)	247
2,6-Dimethoxytoluene	Chromic acid	2-Methoxy-3-methyl-	248
3,5-Dimethoxytoluene	Peroxoacetic acid or chromic acid	2-Methoxy-6-methyl-	175, 249
1-Ethyl-2,4-dimethoxybenzene	Peroxoacetic acid	2-Ethyl-5-methoxy-	175
1,3-Dimethoxy-5-propylbenzene	Chromic acid	2-Methoxy-6-propyl-	250
1-*t*-Butyl-2,4-dimethoxybenzene	Nitric acid in acetic anhydride	2-*t*-Butyl-5-methoxy- (small yield)	233
1,3-Dimethoxy-5-pentylbenzene	Chromic acid	2-Methoxy-6-pentyl-	250
1-Heptyl-3,5-dimethoxybenzene	Chromic acid	2-Heptyl-6-methoxy-	250
1-Dodecyl-3,5-dimethoxybenzene	Chromic acid	2-Dodecyl-6-methoxy-	251
1,3-Dimethoxy-5-undecylbenzene	Chromic acid	2-Methoxy-6-undecyl-	251
1,3-Dimethoxy-5-tridecylbenzene	Chromic acid or lead(IV) acetate	2-Methoxy-6-tridecyl- (18%)	148, 252
1,3-Dimethoxy-5-tetradecylbenzene	Chromic acid	2-Methoxy-6-tetradecyl-	252
2- (or 4-) Bromo-3,5-dimethoxytoluene	Peroxoacetic acid	2- (or 6-) Bromo-3-methoxy-5-methyl-	175
1-Bromo-2,4-dimethoxybenzene	Peroxoacetic acid	2-Bromo-5-methoxy-	175
1-Chloro-2,4-dimethoxybenzene	Peroxoacetic acid	2-Chloro-5-methoxy-	175
2-Bromo-3,5-dimethoxytoluene	Chromic acid	2-Bromo-5-methoxy-3-methyl-	250
1-Bromo-2,4-dimethoxy-6-propylbenzene	Chromic acid	2-Bromo-5-methoxy-3-propyl-	250
1-Bromo-2,4-dimethoxy-6-pentylbenzene	Chromic acid	2-Bromo-5-methoxy-3-pentyl-	250
Derivatives of diphenyl ether			
2,3′,4-Trimethoxy-5′,6-dimethyl-	Chromic acid or 50% nitric acid in acetic acid	2-Methoxy-6-methyl-	249
2,3′,4-Trimethoxy-5′-methyl-6-pentyl-	Chromic acid	2-Methoxy-6-methyl-	253
2,3′,4-Trimethoxy-5′,6-dipentyl-	Chromic acid	2-Methoxy-6-pentyl-	254
2,3′,4-Trimethoxy-2′,3,5′,6-tetramethyl-	Chromic acid	2-Methoxy-3,6-dimethyl-	250
2′,3,4′-Tribromo-4,5′,6-trimethoxy-3′-methyl-2-pentyl-	Chromic acid	2-Bromo-5-methoxy-3-pentyl-	253
1,2,3-Trimethoxybenzene	Various	2,6-Dimethoxy-	
	Electrolysis in acid solution	30%	47
	Nitric acid in acetic acid	64%	235
	Nitric acid (*d* 1.2) in ethanol	Up to 80%	196, 234, 236
	Nitric acid (*d* 1.38)	19%	236
	Peroxobenzoic acid in chloroform	5%	226
	Peroxoacetic acid	...	175
1,2,3-Triethoxybenzene	Nitric acid in acetic acid	2,6-Diethoxy- (16%)	235
1,2,3-Triethoxybenzene	Nitric acid in ethanol	2,6-Diethoxy- (53%)	237
1,2-Dibenzyloxy-3-methoxybenzene	Nitric acid (*d* 1.2) in acetic acid	2-Benzyloxy-6-methoxy- (44%)	238
1,2,3-Tribenzyloxybenzene	Nitric acid (*d* 1.2) in acetic acid	2,6-Dibenzyloxy- (45%)	239–241
1,2,4-Trimethoxybenzene	Peroxoacetic acid	2,5-Dimethoxy-	175

Table VIII (Continued)

Ether	*Reagent*	*Substituted benzo-1,4-quinone*	*Ref*
1,3,5-Trimethoxybenzene	Various	2,6-Dimethoxy-	
	Peroxobenzoic acid in chloroform	28%	226
	Peroxoacetic acid	...	175, 229
	Lead(IV) acetate in benzene	17%	150
	Chromic acid	...	255
	Nitric acid (10%)	...	242
2,4,6-Trimethoxybenzaldehyde	Sodium perchlorate in perchloric acid	2,6-Dimethoxy-	256
2,3',4,4',6-Pentamethoxydiphenylmethanol (or its methyl ether)	Chromic acid	2,6-Dimethoxy-	257
2,4,6-Trimethoxydiphenylmethanol (or its methyl ether)	Chromic acid or peroxoacetic acid	2,6-Dimethoxy-	229, 257
2,2',4,4',6,6'-Hexamethoxytriphenylmethane	Chromic acid	2,6-Dimethoxy-	257
2,6-Diethoxy-4-methoxydiphenylmethanol	Chromic acid	2,6-Diethoxy- (39%)	258
2-Ethoxy-4,6-dimethoxydiphenylmethanol	Chromic acid	2-Ethoxy-6-methoxy-	258
2,4,6-Trimethoxydiphenylmethyl *p*-tolyl sulfide	Peroxoacetic acid	2,6-Dimethoxy-	229
1-Acetoxy-2,5-dimethoxybenzene	Lead(IV) acetate	2,5-Dimethoxy-	230
1-Bromo-2,4,5-trimethoxybenzene	Peroxoacetic acid	2,5-Dimethoxy-	175
1-Bromo-2,4,6-trimethoxybenzene	Peroxoacetic acid	2-Bromo-3,5-dimethoxy-	175
1,3-Dibromo-2,4,6-trimethoxybenzene	Peroxoacetic acid	2,6-Dibromo-3,5-dimethoxy-	175
1,3-Dichloro-2,4,6-trimethoxybenzene	Peroxoacetic acid	2,6-Dichloro-3,5-dimethoxy-	175



Several examples are known of the formation of quinones from *p*-halogenoanisoles.[243,244,247] The displacement of fluorine in the oxidation of **54** can be accounted for by a related sequence (eq 6).



(6)

Less electronegative substituents such as alkyl groups are not removed in this way. For example, the reaction[259] of the dimethoxytetralin **55** with nitric acid stops after the formation of the nitrodienone **56**.

Many oxidations of ethers have been performed using chromic acid[158,159] in aqueous acetic acid, and all appear to involve the two-electron reduction of Cr^{VI} to Cr^{IV}. Derivatives of both di- and trimethoxybenzenes undergo oxidation to the corresponding quinones, the additional oxygen atom entering the unsubstituted *para* position. Alkyl groups are not affected but, as happens with peroxoacetic acid, a trimethoxydiphenylmethane derivative of the type **52** loses the aralkyl group[257,258] and gives the quinone **53**. The oxidation of a substituted di-

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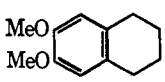

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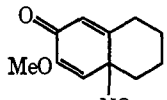
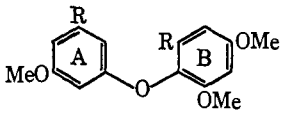


56

phenyl ether **57** with chromic acid provides the corresponding quinone **58**. Here it is not possible to decide if the product



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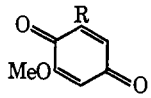
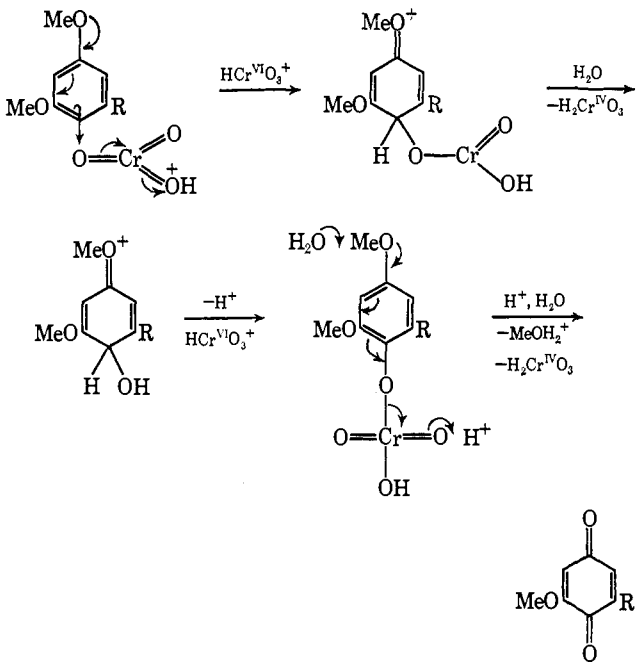


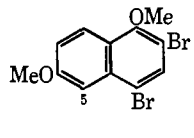
58

results from ring B by a type of oxidative demethylation, or from ring A by oxidation with the introduction of an extra oxygen atom.[249,250,254] The oxidations of two such ethers each containing two different alkyl groups[253] show that either ring A or ring B may be the precursor of the quinone **58**. The mechanism for oxidations with chromic acid may be represented as shown below, the oxidizing agent being assumed for convenience to be the $(HCrO_3)^+$ ion.[159]



2. *Naphthaquinones and Others*

Many of the naphthaquinones listed in Table IX have been obtained only in poor yield. In general, naphthalenes having an alkoxyl group in the 1 position are oxidized to 1,4-quinones, while the 2-alkoxy compounds provide 1,2-quinones. In many cases quinone formation involves the displacement of bromine or chlorine (*cf.* section VII.B.1). Most of these oxidations have been effected by nitric acid; chromic acid is less satisfactory as it frequently causes the introduction of two extra oxygen atoms into the naphthalene nucleus (see section VII.C). Treatment of the naphthyl ethers with nitric acid also results in nitration, and with the more simple compounds little oxidation may take place. Thus 2,3-dimethoxynaphthalene gives mainly nitro compounds, and only a small amount of 3-methoxy-1,2-naphthaquinone[260] is obtained. Both types of reactions can occur in the same molecule and nitronaphthaquinones are frequently produced.[261–264] Some features of the reactions are unusual. Thus the oxidation of the dimethoxynaphthalene **59** with chromic acid gives the 1,2-quinone **60**, which is different[261] from the nitric acid oxidation product, the 1,4-quinone **61**. It seems likely that the first



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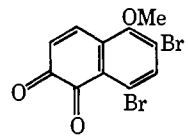

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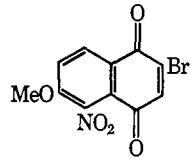
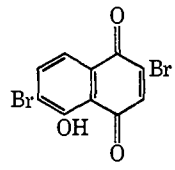


61

stage in each of these reactions is electrophilic attack at the 5 position of **59** and, with chromic acid, quinone formation follows to give **60**. Treatment with nitric acid gives first the 5-nitro derivative of **59** which then undergoes quinone formation at the more reactive 1 and 4 positions to give **61**.

The use of bromine in acetic acid as a reagent for the formation of quinones is uncommon. Apart from the simple oxidative demethylation of a hexamethoxybiphenylene,[161] the only other example[266] is the conversion of 1,5-dimethoxynaphthalene by the use of a large excess of bromine into the hydroxyquinone **62**. The reaction clearly proceeds *via* the di-



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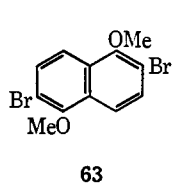

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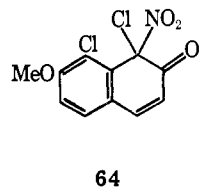
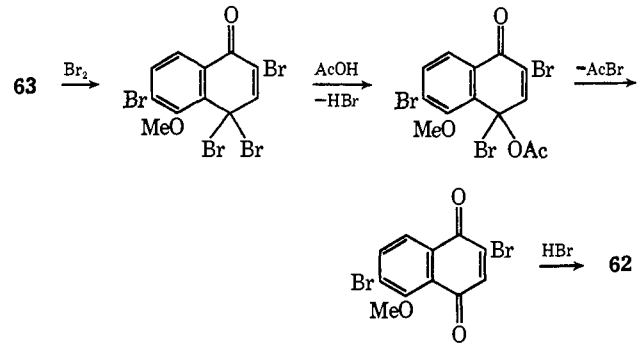


64

bromo compound **63** (which is the product of bromination under normal conditions) and may be represented thus



The oxidation of 4,5-dichloro-3,6-dimethoxynaphthalene with concentrated nitric acid yields a compound **64** which on heating at 130° loses nitrosyl chloride and gives the corresponding 1,2-quinone.[264] The structure of this intermediate provides some support for the mechanism proposed in section VII.B.1 for the oxidation of halogenoanisoles by nitric acid.

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(263) F. Bell and K. R. Buck, 6069 (1963).
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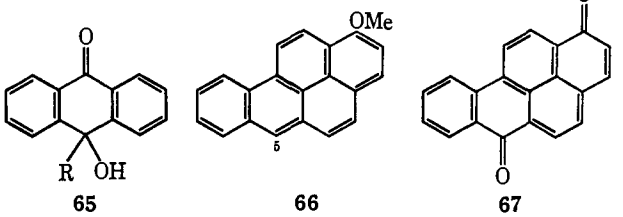
Table IX
Naphthaquinones Formed with Introduction of One Extra Oxygen Atom

Substituted naphthalene	*Reagent*	*Quinone*	*Ref*
1-Methoxy-	Peroxobenzoic acid	Naphtha-1,4-	228
2,4-Dibromo-1-methoxy-	Nitric acid (*d* 1.52)	2-Bromonaphtha-1,4-	265
1,3-Dimethoxy-	Peroxoacetic acid	2-Methoxynaphtha-1,4-	175
2,3-Dimethoxy-	35% Nitric acid	3-Methoxynaphtha-1,2- (6.5%)	260
1,4-Dibromo-2,3-dimethoxy-	Nitric acid (*d* 1.5)	4-Bromo-3-methoxy-8-nitronaphtha-1,2-	261
1,4-Dichloro-2,3-dimethoxy-	Nitric acid	4-Chloro-3-methoxy-8(?)-nitronaphtha-1,2-	262
1,4,6-Tribromo-2,3-dimethoxy-	Nitric acid in acetic acid	4,7-Dibromo-3-methoxy-5(?)-nitronaphtha-1,2-	261, 262
6-Bromo-1,4-dichloro-2,3-dimethoxy-	Nitric acid in acetic acid	7-Bromo-4-chloro-3-methoxy-5(?)-nitronaphtha-1,2-	261, 262
1,5-Dimethoxy-	Bromine	2,6-Dibromo-5-hydroxynaphtha-1,4-	266
2,4,6,8-Tetrachloro-1,5-dimethoxy-	Nitric acid in acetic acid	4,6,8-Trichloro-5-methoxynaphtha-1,2- and 2,6,8-trichloro-5-methoxynaphtha-1,4-	261
2,4-Dibromo-1,6-dimethoxy-	Chromic acid	6,8-Dibromo-5-methoxynaphtha-1,2-	261
2,4-Dibromo-1,6-dimethoxy-	Nitric acid in acetic acid	2-Bromo-6-methoxy-5-nitronaphtha-1,4-	261
1,2-Dibromo-4,6-dimethoxy-	Nitric acid in acetic acid	3,4-Dibromo-7-methoxy-8-nitronaphtha-1,2-	261, 262
1,3,5-Trichloro-4,6-dimethoxy-	Nitric acid in acetic acid	3,5-Dichloro-6-methoxynaphtha-1,4-	261
2,5-Dibromo-3,6-dimethoxy- (and diethoxy analog)	Chromic acid or nitric acid in acetic acid	3,8-Dibromo-7-methoxynaphtha-1,2- (and diethoxy analog)	263, 264, 267, 268
4,5-Dichloro-3,6-dimethoxy- (and diethoxy analog)	Nitric acid in acetic acid; product heated at 130°	8-Chloro-7-methoxynaphtha-1,2- (and ethoxy analog)	263, 264
4,5-Dichloro-3,6-dimethoxy- (and diethoxy analog)	Nitric acid (*d* 1.5)	8-Chloro-7-methoxy-3(?)-nitronaphtha-1,2- (and ethoxy analog)	263, 264
2-Bromo-5-chloro-3,6-dimethoxy-	Nitric acid in acetic acid	3-Bromo-8-chloro-7-methoxynaphtha-1,2-	264
4-Chloro-3,6-dimethoxy-5-nitro-	Nitric acid (*d* 1.5)	7-Methoxy-3(?),8-dinitronaphtha-1,2-	264
2-Bromo-5-chloro-3,6-diethoxy-	Nitric acid in acetic acid	3-Bromo-8-chloro-7-ethoxynaphtha-1,2-	263

The quinones obtained by the chromic acid oxidation of other polycyclic aromatic ethers are listed in Table X. 9-Alkoxyanthracenes are oxidized to anthracene-9,10-quinone or its derivatives even if an alkyl substituent is present at the 10 position. Using mild conditions,[269,270] it is possible to isolate the intermediate anthrone derivatives **65** (R = Et, Pr). Anthrone derivatives rather than anthraquinones are also



65 **66** **67**

obtained when oxidizing agents other than chromic acid are used. Thus nitrogen dioxide[271] converts 9-methoxy-10-phenylanthracene into the hydroxyanthrone **65** (R = Ph) while 9-nitroanthrones are formed in related reactions using nitrogen dioxide[271] or nitric acid.[70,272] 9-Bromoanthrones result from the bromination of certain 9-methoxyanthracenes which are substituted in the *peri* positions.[273] Phenanthrenes having methoxyl groups in the 1 or 4 positions are oxidized by chromic acid to phenanthrene-1,4-quinones,[274–276] but those with a 9-methoxy group give the expected phenanthrene-9,10-quinones.[277,278] Oxidation of the methoxybenz[*a*]pyrene **66**, like other electrophilic substitutions, occurs at the highly reactive 5 position[279] and gives finally the extended quinone **67**.

C. INTRODUCTION OF TWO EXTRA OXYGEN ATOMS

The reagents which have been most frequently used in the oxidations listed in Table XI are peroxo acids and chromic acid. The former appear to cause repeated electrophilic hydroxylation of ethers which have two activated positions *para* to each other. 1,4-Dimethoxybenzene is converted, in satisfactory yield, into 2,5-dimethoxybenzo-1,4-quinone,[226] but the yields of other quinones are frequently poor because of their further oxidation.[175,228] Oxidations of alkoxynaphthalenes and of their halogen derivatives by chromic acid give poor yields of naphtha-1,4-quinones. In some cases quinone

(269) F. Goldmann, *Ber.*, 21, 2505 (1888).
(270) F. Hallgarten, *ibid.*, 22, 1069 (1889).
(271) E. de B. Barnett, *J. Chem. Soc.*, 127, 2040 (1925).
(272) E. de B. Barnett and J. W. Cook, *ibid.*, 123, 2631 (1923).
(273) E. de B. Barnett and C. L. Hewett, *ibid.*, 1452 (1932).
(274) K. W. Bentley and R. Robinson, *ibid.*, 947 (1952).
(275) K. W. Bentley and R. Robinson, *Experientia*, 6, 353 (1950).
(276) P. Hill and W. F. Short, *J. Chem. Soc.*, 260 (1937).
(277) S. Keimatsu, T. Ishiguro, and K. Sumi, *J. Pharm. Soc. Jap.*, 56, 588 (1936); *Chem. Abstr.*, 32, 8409 (1938).
(278) L. Ruzicka and H. Waldmann, *Helv. Chim. Acta*, 15, 907 (1932).
(279) J. W. Cook, R. S. Ludwiczak, and R. Schoental, *J. Chem. Soc.*, 1112 (1950).

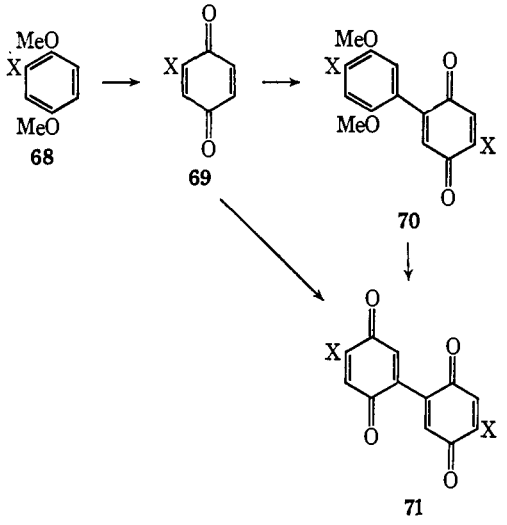
Table X
Other Quinones Formed with Introduction of One Extra Oxygen Atom

Ether	*Reagent*	*Products*	*Ref*
2,2′,4,4′-Tetramethoxybiphenyl	Peroxoacetic acid	4,4′-Dimethoxybiphenyl-2,5:2′,5′-diquinone	175
5,5′-Diisopropyl-1,1′,6,6′,7,7′-hexamethoxy-3,3′-dimethyl-2,2′-binaphthyl	Chromic acid and sulfuric acid	5,5′-Diisopropyl-6,6′,7,7′-tetramethoxy-3,3′-dimethyl-2,2′-binaphthyl-1,4:1′,4′-diquinone	280
9-Ethoxyanthracene	Chromic acid	Anthraquinone	281
9-Propoxy-10-propylanthracene	Chromic acid	Anthraquinone	270
1,2,7,10-Tetramethoxyanthracene	Chromic acid	1,2,7-Trimethoxyanthraquinone	282
9,9′-Dimethoxy-10,10′-bianthryl	Chromic acid	Anthraquinone	283
2,2′,6,6′,10,10′-Hexamethoxy-9,9′-bianthryl	Chromic acid	2,6-Dimethoxyanthraquinone (30%)	80
9-Methoxyphenanthrene	Chromic acid	Phenanthrene-9,10-quinone (90%)	278
1,7-Dimethyl-9-methoxyphenanthrene	Chromic acid	1,7-Dimethylphenanthrene-9,10-quinone	278
7-Isopropyl-9-methoxy-1-methylphenanthrene	Chromic acid	7-Isopropyl-1-methylphenanthrene-9,10-quinone	277
1-Methoxy-2-methylphenanthrene	Chromic acid	2-Methylphenanthrene-1,4-quinone	276
3,4,6-Trimethoxyphenanthrene	Chromic acid	3,6-Dimethoxyphenanthrene-1,4-quinone	274, 275
1-Methoxybenz[*a*]pyrene	Chromic acid	Benz[*a*]pyrene-1,6-quinone	279

formation results in the displacement of a halogen atom but usually it is the halogen-free ring which is oxidized. Despite the presence of the alkoxyl groups the anthracene and phenanthrene derivatives listed in Table XI undergo oxidation by chromic acid exclusively at the 9 and 10 positions as, of course, do the corresponding hydrocarbons. The stability of the resulting quinones to further oxidation permits vigorous oxidizing conditions to be used when necessary. With hot chromic acid alkyl groups at the 9 and 10 positions of alkoxyanthracenes can be removed,[284] and methoxylated 9,9′-bianthryls undergo scission of the aryl–aryl bond.[80,285] Methoxy derivatives of 9-phenylanthracene do not readily undergo dephenylation, however,[286] and are oxidized to methoxy derivatives of the phenylhydroxyanthrone (**65**, R = Ph).

D. BIARYL DERIVATIVES AND RELATED COMPOUNDS

Certain oxidations of 1,3- and 1,4-dimethoxybenzene and of related compounds result in the formation of quinones and diquinones derived from biphenyl. The products, which in some cases are obtained in high yield, are listed in Table XII. Ethers of the type **68** appear to undergo initial oxidative demethylation forming the quinones **69** which by acid-catalyzed arylation and oxidation[45,179] give the biphenylquinones **70**. Structure **70** replaces[45] an earlier incorrect formulation.[47] The biphenyldiquinones **71** may result either from further oxidative demethylation of **70** (see section VII.A) or from the oxidative coupling of two molecules of the monoquinone **69**. The formation of similar diquinones in the reactions of certain 1,3-dialkoxybenzenes with peroxoacetic acid suggests that these ethers are first oxidized to the alkoxyquinones (**69**, X = OR). The oxidations of 2-methoxynaphthalene recorded in Table XII follow a similar course. The initial formation of naphtha-1,2-quinone is followed either by dimerization[48] or, under more acidic conditions, by arylation.[51]



The conversion of 2,6-dimethoxyanthracene by sulfuric acid[80] into a tetramethoxy derivative of **24** provides an example of an oxidation which involves both quinone formation and a dehydrogenation reaction of the Scholl type (see section III.A). A somewhat similar series of reactions occurs when

(280) E. P. Clark, *J. Amer. Chem. Soc.*, **51**, 1475 (1929).
(281) F. Goldmann, *Ber.*, **21**, 1176 (1888).
(282) A. Macmaster and A. G. Perkin, *J. Chem. Soc.*, 1306 (1927).
(283) H. Meyer, *Ber.*, 42, 143 (1909).
(284) A. Müller, M. Raltschewa, and M. Papp, *ibid.*, 75B, 692 (1942).
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(287) D. Molho and C. Mentzer, *Experientia*, **6**, 11 (1950).
(288) E. Bernatek and F. Christenssen, *Acta Chem. Scand.*, 19, 2009 (1965).
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(290) G. Schroeter, L. Lichtenstadt, and D. Irineu, *Ber.*, **51**, 1587 (1918).
(291) R. D. Wilson, *J. Chem. Soc.*, 3304 (1965).
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(293) K. Fries, R. Walter, and K. Schilling, *ibid.*, **516**, 248 (1935).
(294) R. Pschorr, *Ber.*, **34**, 3998 (1901).
(295) I. R. Sherwood and W. F. Short, *J. Chem. Soc.*, 1006 (1938).
(296) L. F. Fieser and M. N. Young, *J. Amer. Chem. Soc.*, **53**, 4120 (1931).
(297) K.-J. Karrman, *Svensk Kem. Tidskr.*, 57, 103 (1945); *Chem. Abstr.*, 40, 4372 (1946).
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(300) G. M. Badger, *J. Chem. Soc.*, 2497 (1949).
(301) E. Noelting and P. Werner, *Ber.*, **23**, 3246 (1890).
(302) R. Nietzki, *Justus Liebigs Ann. Chem.*, **215**, 125 (1882).
(303) A. J. Shand and R. H. Thomson, *Tetrahedron*, **19**, 1919 (1963).

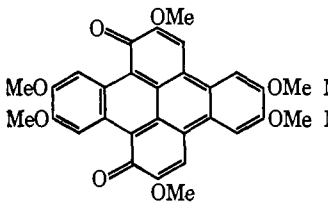
Table XI
Quinones Formed with the Introduction of Two Extra Oxygen Atoms

Ether	*Reagent*	*Products*	*Ref*
1,3-Dimethoxybenzene	Peroxobenzoic acid	2-Hydroxy-5-methoxybenzo-1,4-quinone (17%)	226
1,4-Dimethoxybenzene	Peroxobenzoic acid, or peroxoacetic acid, or lead(IV) acetate	2,5-Dimethoxybenzo-1,4-quinone (38%)	149, 175, 226
4-(4-Nitrobenzyloxy)anisole	Peroxoacetic acid	2-Methoxy-5-(4-nitrobenzyloxy)benzo-1,4-quinone	175
2,5-Dimethoxyacetophenone	Peroxobenzoic acid or peroxoacetic acid	2,5-Dimethoxybenzo-1,4-quinone (low yield)	151, 152
2-Methoxynaphthalene	Manganese(III) acetate or chromic acid or lead(IV) acetate or peroxobenzoic acid	2-Methoxynaphtha-1,4-quinone (up to 17%)	25, 26, 48, 228, 287, 288
2-Ethoxy- or 2-benzyloxynaphthalene	Peroxobenzoic or peroxoacetic acid	2-Ethoxy- or 2-benzyloxynaphtha-1,4-quinone (low yields)	228
1-Bromo-2-methoxynaphthalene	Chromic acid	5-Bromo-6-methoxynaphtha-1,4-quinone	289
1,6-Dibromo-2-methoxynaphthalene	Chromic acid	2,5-Dibromo-6-methoxy- and 6-bromo-2-methoxy-naphtha-1,4-quinone	289
1,4-Dichloro-2-methoxynaphthalene	Chromic acid	5,8-Dichloro-6-methoxynaphtha-1,4-quinone	289
2,3-Dimethoxynaphthalene	Peroxoacetic acid	2,3-Dimethoxynaphtha-1,4-quinone	175
2,3-Dimethoxy-6,7-dimethylnaphthalene	Chromic acid	6,7-Dimethoxy-2,3-dimethylnaphtha-1,4-quinone	290
1,4-Dibromo-2,3-dimethoxynaphthalene	Chromic acid	5,8-Dibromo-5,7-dimethoxynaphtha-1,4-quinone	261
1,4-Dichloro-2,3-dimethoxynaphthalene	Nitric acid	5,8-Dichloro-6,7-dimethoxynaphtha-1,4-quinone	262
2,7-Dimethoxynaphthalene	Chromic acid	2,7-Dimethoxynaphtha-1,4-quinone (15%)	268
1-Bromo-2,7-dimethoxynaphthalene	Chromic acid	8-Bromo-2,7-dimethoxynaphtha-1,4-quinone	267
1-Chloro-2,7-dimethoxynaphthalene	Chromic acid	5-Chloro-3,6-dimethoxynaphtha-1,4-quinone	291
1,6-Dibromo-2,7-dimethoxynaphthalene	Chromic acid	6-Bromo-2,7-dimethoxynaphtha-1,4-quinone	267, 268
4,5-Dichloro-3,6-dimethoxynaphthalene	Chromic acid	5-Chloro-3,6-dimethoxynaphtha-1,4-quinone	268, 291
1,3,6-Tribromo-2,7-dimethoxynaphthalene	Chromic acid	2,7-Dibromo-3,6-dimethoxynaphtha-1,4-quinone	268
3-Bromo-1,8-dichloro-2,7-dimethoxynaphthalene	Chromic acid	6-Bromo-8-chloro-2,7-dimethoxynaphtha-1,4-quinone	291
3,6-Dibromo-1,8-dichloro-2,7-dimethoxynaphthalene	Chromic acid	2,7-Dibromo-5-chloro-3,6-dimethoxynaphtha-1,4-quinone	289, 291
2,3-Dimethoxyanthracene	Chromic acid	2,3-Dimethoxyanthraquinone	292
2,3,6,7-Tetramethoxy-9,10-dimethylanthracene (and diethyl analog)	Chromic acid or nitric acid (40%)	2,3,6,7-Tetramethoxyanthraquinone	284
1,5-Dibromo-2,6-dimethoxyanthracene	Chromic acid	1,5-Dibromo-2,6-dimethoxyanthraquinone	293
2,2′-Dimethoxy-9,9′-bianthryl	Chromic acid	2-Methoxyanthraquinone	285
2,2′,6,6′-Tetramethoxy-9,9′-bianthryl	Chromic acid	2,6-Dimethoxyanthraquinone	80
3-Methoxyphenanthrene	Chromic acid	3-Methoxyphenanthrene-9,10-quinone	294
3-Methoxy-8-methylphenanthrene	Chromic acid	3-Methoxy-8-methylphenanthrene-9,10-quinone	295
2-Isopropyl-3-methoxy-8-methylphenanthrene (and ethoxy analog)	Chromic acid	2-Isopropyl-3-methoxy-8-methylphenanthrene-9,10-quinone (and ethoxy analog)	296–298
2,3-Dimethoxyphenanthrene	Chromic acid	2,3-Dimethoxyphenanthrene-9,10-quinone	299
5-Methoxy-12-methyl- and 5-methoxy-7,12-dimethyl-benz[*a*]anthracene	Chromic acid	5-Methoxybenz[*a*]anthracene-7,12-quinone	300

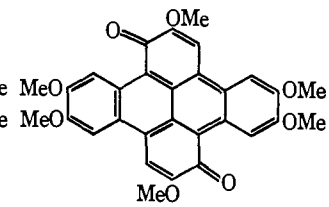
Table XII
Quinones Derived from Biaryls

Ether	*Reagent*	*Products*	*Ref*
1,3-Dimethoxybenzene (and dibenzyloxy analog)	Peroxoacetic acid	4,4'-Dimethoxybiphenyl-2,5:2',5'-diquinone (and dibenzyloxy analog)	175
1,4-Dimethoxybenzene	Cerium(IV) sulfate in sulfuric acid	Biphenyl-2,5:2',5'-diquinone (20%)	179
2,5-Dimethoxytoluene (and diethoxy analog)	Electrolysis in aqueous acid or chromic acid	2,5-Dimethoxy-4,4'-dimethylbiphenyl-2',5'-quinone (and diethoxy analog)	37, 45, 47, 301, 302
2,5-Dimethoxytoluene	Cerium(IV) sulfate in sulfuric acid, or chromic acid	4,4'-Dimethylbiphenyl-2,5:2',5'-diquinone (75%)	179, 303
1,4-Dimethoxy-2,5-dimethylbenzene	Cerium(IV) sulfate in sulfuric acid	3,3',6,6'-Tetramethylbiphenyl-2,5:2',5'-diquinone (20%)	179
1-(X)-2,5-dimethoxybenzene (**68**) where X = Cl, Br, I, Ph, 4-PhC_6H_4–, AcNH–, $HO_2CCH_2CH_2$–	Chromic acid	4,4'-Di(X)-2,5-dimethoxybiphenyl-2',5'-quinone (**70**)	45
2,5-Dimethoxybiphenyl	Chromic acid	2,5-Dihydroxy-4,4'-diphenylbiphenyl-2',5'-quinone	303
1,2,4-Trimethoxybenzene	Chromic acid	2,4,4',5-Tetramethoxybiphenyl-2',5'-quinone and a little 2,5-dihydroxy-4,4'-dimethoxybiphenyl-2',5'-quinone	45, 47
1,2,4-Trimethoxybenzene	Nitric acid (25%)	4,4'-Dimethoxybiphenyl-2,5:2',5'-diquinone	193
2-Methoxynaphthalene	Lead(IV) acetate	1,1'-Binaphthyl-3,4:3',4'-diquinone (trace)	48
2-Methoxynaphthalene	Peroxoformic acid	2-Methoxy-1,1'-binaphthyl-3',4'-quinone (64%)	51
2,6-Dimethoxyanthracene	Sulfuric acid	3,4,9,14-Tetramethoxydibenz[*a,o*]perylene-7,16-quinone (see **24**)	80
1,2-Dimethoxybenzene	Chloranil in 70% v/v aqueous sulfuric acid	2,5,6,9,12,13-Hexamethoxydibenzo[*fg,op*]naphthacene-1,10-quinone (**72**) (7%)	68
3,3',4,4'-Tetramethoxybiphenyl	Chloranil in 70% v/v aqueous sulfuric acid	2,5,6,9,12,13-Hexamethoxydibenzo[*fg,op*]naphthacene-1,8-quinone (**73**) (75%)	68
1,2-Dimethoxybenzene	Moist iron(III) chloride	**72** and **73** (1%)	68

1,2-dimethoxybenzene is treated with chloranil in sulfuric acid.[68] The polycyclic quinone **72** which results is presumably formed by the oxidative demethylation of the corresponding octamethoxy compound; the latter results from a mixed



72



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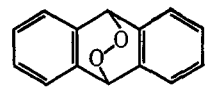
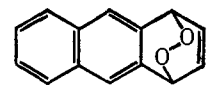
Scholl reaction between 1,2-dimethoxybenzene and the hexamethoxytriphenylene **8** which is the major product of this reaction. Oxidation of 3,3',4,4'-tetramethoxybiphenyl (**9**) in the same way[68] gives the isomeric quinone **73** in good yield. The main product of the oxidation of 1,2-dimethoxybenzene by iron(III) chloride is the hexamethoxytriphenylene **8** (section III.A), but in addition small amounts of the quinones **72** and **73** are formed.[68]

VIII. Formation of Photoperoxides

The alkoxy derivatives of anthracene listed in Table XIII readily react with oxygen on exposure to light to form addition compounds. The solvent has a marked effect on the course of the reaction and carbon disulfide and diethyl ether have been found to be the most satisfactory. The initial products are similar to those formed by the corresponding hydrocarbons and appear to have the same type of transannular peroxide structure.[304] In most cases the adducts are derivatives of the 9,10-epidioxide **74** and are relatively stable. Prolonged ir-



74



75

radiation or heating to temperatures above 135° is required to bring about their conversion into anthraquinones or dissociation into their components.[80, 292, 305–307] Several simple 1,4-dialkoxyanthracenes, however, give very labile photoperoxides which dissociate at much lower temperatures. These are now considered[311] to be derivatives of the 1,4-epidioxide **75**, as are the corresponding 9-phenyl, 9,10-diphenyl, and 9,10-di(2-pyridyl) compounds.[309, 320, 321, 327] This marked difference in behavior has not yet been explained. Photoperoxides are also formed by the related polycyclic ethers recorded in Table XIII.

(304) K. Gollnick and G. O. Schenck in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, p 255.
(305) C. Dufraisse and R. Priou, *C. R. Acad. Sci., Paris*, 204, 127 (1937).
(306) H. Meyer and A. Eckert, *Monatsh. Chem.*, 39, 241 (1918).
(307) C. Dufraisse and R. Priou, *Bull. Soc. Chim. Fr.*, [5] **6**, 1649 (1939).

Table XIII
Formation of Photoperoxides

Substituted anthracene	*Probable location of epidioxide bridge*	*Ref.*
2-Methoxy-	9,10	308
1,4-Dimethoxy-	1,4	309–311
1,4-Diethoxy-	1,4	310, 311
1,4-Dibenzyloxy-	1,4	310, 311
2,3-Dimethoxy-	9,10 (not isolated)	292
9,10-Dimethoxy-	9,10	305–307
2,6,9-Trimethoxy-	9,10 (not isolated)	80
1,3,5,7-Tetramethoxy-	? (not isolated)	80
1,4,9,10-Tetramethoxy-	9,10	308, 312
9-Methoxy-10-phenyl-	9,10	313, 314
1,4-Dimethoxy-9-phenyl-	1,4	308, 309
1,4-Dimethoxy-9,10-dimethyl-	9,10	308, 312
1,4-Dimethoxy-9-methyl-10-phenyl-	9,10	308, 312
1-Methoxy-9,10-diphenyl-	9,10	315
2-Methoxy-9,10-diphenyl-	9,10	315
1,2-Dimethoxy-9,10-diphenyl-	9,10	316
2,3-Dimethoxy-9,10-diphenyl-	9,10	315, 316
1,4-Dimethoxy-9,10-diphenyl-	1,4	309, 316–320
1,4-Dialkoxy-9,10-diphenyl- (alkoxy = ethoxy, 2-chloroethoxy, 2-bromoethoxy, propoxy, benzyloxy, isopropoxy)	1,4	320, 321
1,8-Dimethoxy-9,10-diphenyl-	9,10	322, 323
2,6-Dimethoxy-9,10-diphenyl-	9,10	322, 323
1,2,6-Trimethoxy-9,10-diphenyl-	9,10	324
1,2,5,6-Tetramethoxy-9,10-diphenyl-	9,10	324
1-Methoxy-4-methyl-9,10-diphenyl-	9,10	325, 326
1-Chloro-4-methoxy-9,10-diphenyl-	9,10	317
1,4-Dimethoxy-9,10-di(2-pyridyl)-	1,4	327
Related Compounds		
5,11-Di(4-methoxyphenyl)-6,12-diphenylnaphthacene	5,12	328
2-Methoxy-7,12-dimethylbenz[*a*]-anthracene	7,12	329
7,16-Dimethoxydibenzo[*a*,*o*]-perylene	?	330

(308) Y. Lepage, *Ann. Chim.* (Paris), [13] **4**, 1137 (1959).
(309) C. Dufraisse, J. Rigaudy, J. J. Basselier, and N. K. Cuong, *C. R. Acad. Sci., Paris*, **260**, 5031 (1965).
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(311) J. Rigaudy, N. C. Cohen, and N. K. Cuong, *ibid., Ser. C*, 264, 1851 (1967).
(312) Y. Lepage, *ibid.*, **248**, 1193 (1959).
(313) C. Dufraisse, A. Étienne, and J. Rigaudy, *Bull. Soc. Chim. Fr.*, 804 (1948).
(314) C. Dufraisse, A. Étienne, and J. Rigaudy, *C. R. Acad. Sci., Paris*, **226**, 1773 (1948).
(315) C. Dufraisse, R. Demuynck, and A. Allais, *ibid.*, **215**, 487 (1942).
(316) C. Dufraisse, C. Pinazzi, and J. Baget, *ibid.*, **217**, 375 (1943).
(317) C. Dufraisse, L. Velluz, and R. Demuynck, *ibid.*, **215**, 111 (1942).
(318) C. Dufraisse, L. Velluz, and L. Velluz, *ibid.*, **208**, 1822 (1939).
(319) C. Dufraisse, L. Velluz, and L. Velluz, *ibid.*, **209**, 516 (1939).
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(321) A. Étienne and G. Bichet, *C. R. Acad. Sci., Paris*, **228**, 1134 (1949).
(322) C. Dufraisse and L. Velluz, *Bull. Soc. Chim. Fr.*, 9, 171 (1942).
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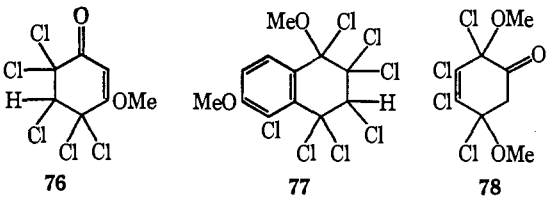
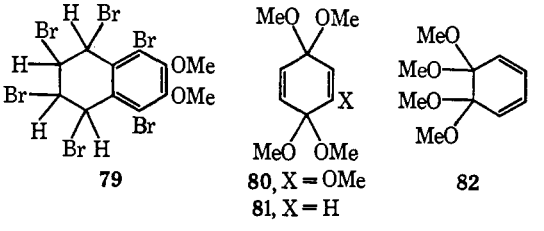
IX. Other Reactions Involving Loss of Aromaticity

A. FORMATION OF ALICYCLIC PRODUCTS

Although quinones are the commonest nonaromatic products formed in oxidations of alkyl aryl ethers, other types of alicyclic compounds are sometimes obtained. Thus sulfuryl chloride converts 1,3-dimethoxybenzene[331] into the pentachlorocyclohexenone **76**, and 1,6-dimethoxynaphthalene[261] into the heptachlorotetralin **77**. Treatment of 1,2,4-trimethoxybenzene with chlorine in chloroform[182,332] gives, as one product, the tetrachlorocyclohexenone **78**, while bromination of 1,4-dibromo-2,3-dimethoxynaphthalene under similar conditions[261] produces the hexabromotetralin **79**. In each of these cases the expected electrophilic halogenation reaction is prevented from taking its usual course by the addition of halogen to an intermediate.

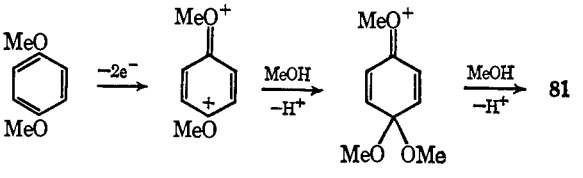


76 **77** **78**



79 **80**, X = OMe; **81**, X = H **82**

The electrolysis of 1,3- and 1,4-dimethoxybenzenes in alkaline methanol causes methoxylation with the formation of the quinone ketals **80** and **81**, respectively, in good yield.[333] The first of these products is also obtained when 1,2,4-trimethoxybenzene and 1,2-dimethoxybenzene are used. The electrolysis of 1,2-dimethoxybenzene gives, in addition, 1,2,4-trimethoxybenzene, the quinone ketal **82**, and the acyclic product **83**. All these reactions presumably involve the two-electron oxidation of the ether at the anode followed by nucleophilic attack by the solvent (*cf.* section VI), *e.g.*



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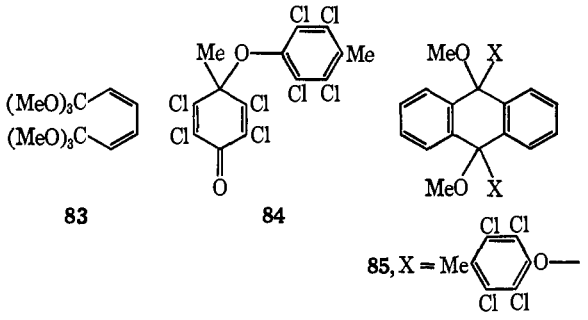
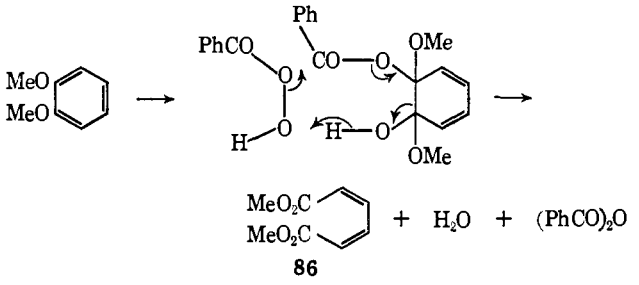
The product formed by the reaction of chlorine dioxide with 1,2-dimethoxybenzene is claimed[334] to be a transannular peroxide. Finally, treatment of 9,10-dimethoxyanthracene[335] with the aryloxydienone **84** gives the anthraquinone ketal **85**.



83 **84** **85**, X = Me

B. RING SCISSION

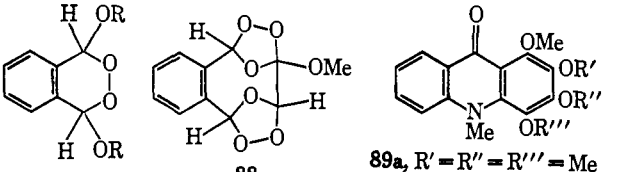
The reactions of alkoxybenzenes with oxidizing agents such as peroxoacetic acid[175] and peroxobenzoic acid[226] frequently result in some scission of the aromatic nucleus with the formation of various aliphatic compounds. Few products, however, have been isolated because of the ease with which they undergo further oxidation.[175] 1,2-Dimethoxybenzene[226] is oxidized by peroxobenzoic acid to dimethyl muconate (**86**), possibly by the sequence



86

while methyl esters of oxalic acid are obtained as minor by-products from similar reactions with 1,2,3- and 1,3,5-trimethoxybenzene[226] and with 3,4,5-trimethoxybenzoic acid.[336] The electrochemical oxidation of 1,2-dimethoxybenzene in aqueous sulfuric acid yields succinic acid as the major product,[39] but when alkaline methanol is used as the solvent hexamethyl *cis,cis*-orthomuconate (**83**) is obtained.[333] The latter product appears to be formed by the further methoxylation of the 1,2-quinone ketal **82**. Anisole is oxidized by chlorine dioxide to a mixture of oxalic, maleic, and fumaric acids;[337] it reacts rapidly with ozone to give an explosive triozonide of unknown structure.[338,339] The metabolism of 4-chloro- and 2,4-dichlorophenoxyacetic acid by soil microorganisms results in the formation of chloromuconic acids[340,341] as well as carbon dioxide.[342]

Ethers containing more than one aromatic ring are oxidized to products which, being themselves aromatic, are relatively resistant to further oxidation and are also readily isolated. Nearly all the reactions summarized in Table XIV result in the scission of the aromatic ring which carries the most alkoxyl groups, *i.e.*, that with the higher electron density. The usual products obtained by the treatment of alkoxynaphthalenes with nitric acid, chromic acid, or alkaline permanganate under vigorous conditions are derivatives of phthalic acid or of 2-carboxyphenylglyoxylic acid, but derivatives of phenylglyoxal and of 2-formylbenzoic acid have also been

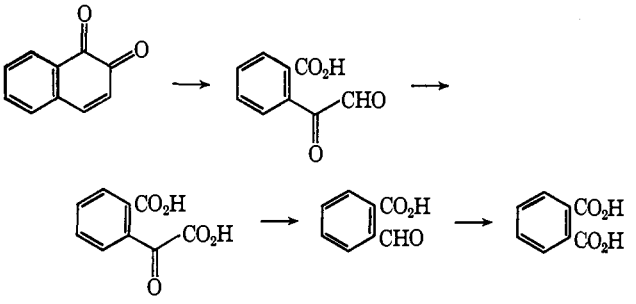


87a, R = Me
b, R = Et

88

89a, R′ = R″ = R‴ = Me
b, R′ = Me; R″R‴ = CH_2
c, R‴ = Me; R′R″ = CH_2

obtained. The formation of all these can be rationalized by assuming the initial formation of a naphtha-1,2-quinone which then undergoes further oxidative degradation thus



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(342) M. H. Rogoff and J. J. Reid, *J. Bacteriol.*, **71**, 303 (1956).
(343) J. H. Gardner, *J. Indian Chem. Soc.*, **11**, 401 (1934).
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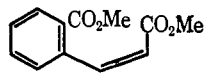
Table XIV
Ring Scission of Alkoxynaphthalenes and Related Compounds

Substituted naphthalene	*Reagent*	*Products*	*Ref*
1-Methoxy-	Peroxobenzoic acid in benzene	Methyl *o*-carboxycinnamate	228
1-Methoxy- and 2-methoxy-	Alkaline permanganate, 100°	2-Carboxyphenylglyoxylic acid and phthalic acid	343–345
2-Methoxy-	Peroxobenzoic acid in benzene or peroxoacetic acid	Methyl *o*-carboxycinnamate and *o*-carboxycinnamic acid	228, 346
2-Methoxy- and 2-ethoxy-	*Aspergillus niger*	2-Hydroxy-4-methoxy- and 2-hydroxy-4-ethoxybenzoic acid	347
2-Methoxy-	Ozone in methanol at −60°	Methyl glyoxylate (60%) and dimethoxyperoxide **87a** (68%)	348
2-Methoxy-	Ozone in ethanol at −60°	Methyl glyoxylate (46%) and diethoxyperoxide **87b** (48%)	348
2-Methoxy-	Ozone in carbon tetrachloride at −20°	Diozonide **88**	348
2-Ethoxy-	Ozone in methanol at −60°	Ethyl glyoxylate (89%) and dimethoxyperoxide **87a** (35%)	348
2-Methoxy-1-nitro-	Alkaline permanganate, 100°	4-Methoxy-3-nitrophthalic acid, phthalic acid, and 3-methoxy-2-nitrobenzoic acid	349
2-Ethoxy-6-nitro-	Nitric acid (*d* 1.14), 180–200°	4-Nitrophthalic acid	350
2-Ethoxy-8-nitro-	Nitric acid (*d* 1.14), 180–200°	Picric acid	350
1-Ethoxy-4,5-dinitro-	Nitric acid (*d* 1.14), 200°	3-Nitrophthalic acid	351
2-Ethoxy-1,8-dinitro-	Nitric acid (*d* 1.18), 160–170°	3,6-Dinitrophthalic acid	352, 353
1-Methoxy-4,5,7-trinitro-	Nitric acid at 160°, or chromic acid	3,5-Dinitrophthalic acid	354
1-Methoxy-4,5,8-trinitro-	Nitric acid, 160°	3,6-Dinitrophthalic acid	354
1,2-Dimethoxy-	Peroxobenzoic acid in benzene	Methyl *o*-methoxycarbonylcinnamate	346
1,5-Dimethoxy-	Alkaline permanganate, 100°	3-Methoxyphthalic acid and 2-formyl-3-methoxybenzoic acid (11–16%)	355, 356
1,5-Dimethoxy-4-nitro- and 1,5-dimethoxy-4,8-dinitro-	Boiling nitric acid (*d* 1.14)	3-Methoxy-6-nitrophthalic acid	357
1,7-Dimethoxy-	Alkaline permanganate, 100°	2-Carboxy-6-methoxyphenylglyoxylic acid	343
2,3-Dimethoxy-5-methyl-	Alkaline permanganate	4,5-Dimethoxyphthalic acid	358
2,6-Dimethoxy-	Alkaline permanganate	2-Carboxy-4-methoxy- and 2-carboxy-5-methoxyphenylglyoxylic acid	359
2,7-Dimethoxy-	Alkaline permanganate	2-Formyl-4-methoxy- and 2-formyl-5-methoxybenzoic acid	360
2,7-Dimethoxy-1-nitro-	Nitric acid (*d* 1.34), 100°	4-Methoxy-3-nitrophthalic acid	361
1,6-Dibromo-2,7-dimethoxy-	Chromic acid	5-Bromo-2-carboxy-4-methoxyphenylglyoxal	267
1,4,5,6-Tetramethoxy-	Alkaline permanganate	3,6-Dimethoxyphthalic acid	362
		Related Compounds	
1,2-Dimethoxy-9,10-diphenylanthracene	Chromic acid	1,2-Dibenzoyl-3,4-dimethoxybenzene	363
Melicopicine (**89a**), melicopine (**89b**), and melicopidine (**89c**)	68% Nitric acid	1-Methyl-4-quinolone-3-carboxylic acid	364
2-Methoxyphenanthrene	Peroxobenzoic acid in benzene	Methyl β-(2-carboxynaphth-1-yl)acrylate	228
3-Methoxyphenanthrene	Peroxobenzoic acid in benzene	β-(1-Carboxynaphth-2-yl)acrylic acid	228
N-Acetylcolchinol methyl ether	Peroxobenzoic acid in benzene	Dimethyl oxalate	346
2′,3′,4,4″,5′,6′-Hexamethoxy-*p*-terphenyl	Chromic acid	4-Methoxybenzoic acid and methyl 4-methoxyphenylglyoxylate	365
4,4‴-Dimethoxyquaterphenyl	Chromic acid	Biphenyl-4,4′-dicarboxylic acid (85%)	366

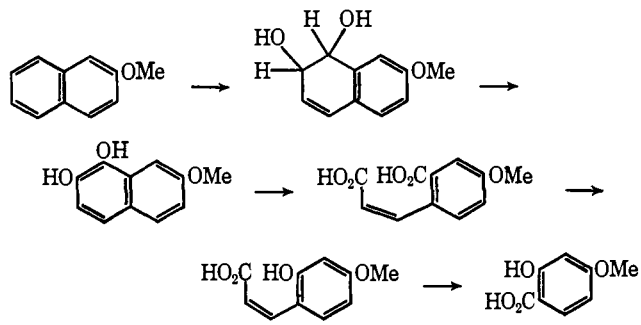
Peroxo acids cause ring scission under much milder conditions with the formation of unsaturated dicarboxylic acids and their esters. A typical example is the oxidation of 1,2-dimethoxynaphthalene[346] by peroxobenzoic acid to give the dimethyl ester **90** which is analogous to the formation of dimethyl muconate (**86**) from 1,2-dimethoxybenzene. The reactions of peroxobenzoic acid with colchicine and related compounds have been examined semiquantitatively.[228,346] Al-



90

though the oxidation products were not isolated, the amounts of oxidizing agent consumed showed that ring scission had occurred.

Treatment of 2-methoxynaphthalene with ozone in carbon tetrachloride gives the diozonide **88**, but in the presence of methanol a further reaction occurs with the formation of the dimethoxyperoxide **87a** and methyl glyoxylate.[348] Two oxidations of methoxynaphthalenes are unusual in that the rings carrying the methoxyl substituents remain intact. 2,3-Dimethoxy-5-methylnaphthalene is converted by permanganate into 4,5-dimethoxyphthalic acid[358] ("metahemipinic acid") while the metabolism of 2-methoxynaphthalene by *Aspergillus niger* results in the formation of 2-hydroxy-4-methoxybenzoic acid,[317] possibly by the following sequence of reactions.[367]

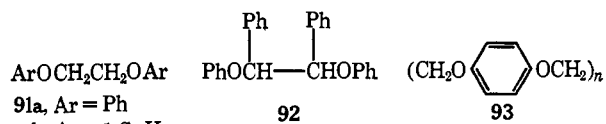


X. Oxidation of the Alkyl Group

Most oxidizing agents react with the aromatic nucleus of an alkyl aryl ether, the alkoxyl function either remaining unchanged or undergoing hydrolysis to the corresponding alcohol. Under conditions which favor homolytic reactions, however, the alkyl group can lose a hydrogen atom. The resulting radical may then undergo further oxidation to give oxygen- or chlorine-containing products.

A. RADICAL FORMATION

The flash photolysis of anisole in aqueous solution results in its photoionization and the initial production of hydrated electrons. The transient spectrum then observed is the same as that obtained in the flash photolysis of phenoxymethyl chloride and is therefore attributed to the phenoxymethyl ($PhOCH_2\cdot$) radical[10,11] (see section II). Several related ethers behave in a similar manner. Chemical support for the intermediate formation of aryloxymethyl radicals comes from the isolation of the dimerization products **91a** and **91b** which are obtained in low yield by the ultraviolet or neutron irradiation of anisole and 1-methoxynaphthalene, respectively.[34,368] Although there is some indication of radical formation at low



91a, Ar = Ph
b, Ar = 1-$C_{10}H_7$

92

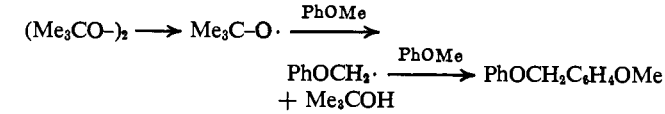
93

(367) D. Woodcock in "Phenolics in Plants in Health and Disease," J. B. Pridham, Ed., Pergamon Press, Oxford, 1960, p 75.

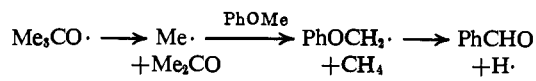
(368) K. Pfordte and G. Leuschner, *Justus Liebigs Ann. Chem.*, 643, 1 (1961).

temperature,[13] anisole is largely unaffected by γ irradiation;[33,369] a similar reaction with the more reactive benzyloxybenzene[369] gives a product considered to be the diaryloxyethane **92**.

The thermal decomposition of di-*t*-butyl peroxide in anisole at 140° leads to the formation of a mixture of *o*-, *m*-, and *p*-phenoxymethylanisole.[370] The predominance of the *ortho* isomer confirms that the reacting species is the radical ($PhOCH_2\cdot$).



The absence of the dimerization product **91a** from the reaction products is attributed to the rapid removal of the phenoxymethyl radicals, which are present in low concentration, by reaction with the excess of anisole. A similar type of reaction occurs with 1,4-dimethoxybenzene,[370] but at 200° this is reported[371] to be oxidized instead to a polymeric product formulated as **93**. When the reaction of di-*t*-butyl peroxide with anisole is effected photochemically at 40° only a little of the mixture of phenoxymethylanisoles results. Phenoxymethyl radicals are now formed in abundance and the dimer **91a** results.[370] In the gas phase above 180° the reaction of anisole with the peroxide follows a different course and the main oxidation product is benzaldehyde.[372]



In similar reactions, ethoxybenzene and isopropoxybenzene give benzaldehyde and acetophenone, respectively. Contrary to previous suggestions[373,374] there is no evidence that the thermal decomposition of dibenzoyl peroxide in anisole produces phenoxymethyl radicals.[132] The pyrolysis of ethoxybenzene at 500°, which is presumably a homolytic process, results in dehydrogenation and the formation of dihydrobenzofuran (10%).[374a]

B. INTRODUCTION OF OXYGEN

Table XV lists those reactions during which oxygen-containing substituents are introduced into the alkyl groups of alkyl aryl ethers. In most cases the yields are poor and much unchanged starting material is recovered. The wide variety of products can be rationalized by assuming that each oxidation follows the sequence

94

The product **94** may then undergo further reactions depending on the nature of the groups R and X. Thus treatment of

(369) A. F. Everard, G. A. Swan, and P. S. Timmons, *J. Chem. Soc.*, 918 (1962).

(370) H. B. Henbest, J. A. W. Reid, and C. J. M. Stirling, *ibid.*, 5239 (1961).

(371) S. L. Sosin and V. V. Vorshak, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 347 (1964); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 318 (1964).

(372) M. F. R. Mulcahy, B. G. Tucker, D. J. Williams, and J. R. Wilmshurst, *Aust. J. Chem.*, 20, 1155 (1967); *Chem. Commun.*, 609 (1965).

(373) D. R. Augood and G. H. Williams, *Chem. Rev.*, 57, 123 (1957).

(374) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, Oxford, 1960, p 65.

(374a) R. D. Obolentsev, *J. Gen. Chem. USSR*, 16, 1459 (1946); *Chem. Abstr.*, 41, 5477 (1947).

Table XV
Chemical Oxidation of Alkoxyl Groups

Ether	*Reagent*	*Products*	*Ref*
Anisole	Lead(IV) acetate in sunlight, or alkaline potassium peroxodisulfate, or iron(II) ion and hydrogen peroxide	Some formaldehyde	144, 375, 376
Anisole	Di-*t*-butyl peroxide or γ irradiation	A little phenol	369, 377
Anisole	Peroxonitrous acid	Phenol, *o*-nitrophenol, and quinol	87, 97
Anisole	Iron(II) ion and hydrogen peroxide	Quinol	87
Anisole	Lead(IV) acetate at 120°	*p*-Methoxybenzylidene diacetate	378
Anisole	Manganese(III) acetate at 100°	4-Methoxybenzoic acid, and 2- and 4-acetoxymethylanisole	25
Ethoxy- and propoxybenzene	γ irradiation	A little phenol	369
4-Methoxycumene	Air, potassium carbonate, and aluminum at 160°	4-Hydroxycumene	379
4-Ethoxyacetanilide	Oxygen and complexes of iron(II), copper(I), etc.	4-Hydroxyacetanilide	98a
1,2-Diphenoxyethane	Nitric acid in carbon tetrachloride	Oxalic acid and 2,4-dinitrophenol	380
Benzyloxybenzene	γ irradiation	Some phenol	369
Benzyloxybenzene	Prolonged boiling in air, or nitrogen dioxide in carbon tetrachloride, or N-bromosuccinimide	Benzaldehyde or benzoic acid	381–384
1-Benzyloxy-2,4-dichlorobenzene	Chlorine and phosphorus pentachloride	Benzaldehyde and benzoyl chloride	385
1-Benzyloxy-2,4,6-tribromobenzene	N-Bromosuccinimide	Benzaldehyde	383
Benzyloxybenzene	Lead(IV) acetate at 80°	Some α-phenoxybenzyl acetate	134
1,2-Dimethoxybenzene	Manganese(III) acetate at 100°	3,4-Dimethoxybenzyl acetate, 3,4-dimethoxybenzoic acid, and 3,3′,4,4′-tetramethoxybenzophenone	25
1,2-Dimethoxybenzene	Lead(IV) acetate	Small amounts of 3,4-dimethoxybenzaldehyde, 3,4-dimethoxybenzoic acid, and, after hydrolysis, 2,2′-dihydroxy-4,4′,5,5′-tetramethoxydiphenylmethane	146, 386
1,2-Dimethoxybenzene	Prolonged heating with oxygen and manganese(IV) oxide at 130°	3,4-Dimethoxybenzaldehyde and 3,4-dimethoxybenzoic acid	387
3,4-Dimethoxybenzaldehyde	Nitrobenzene and alkali at 160°	4-Hydroxy-3-methoxybenzaldehyde (31%)	388, 389
3,4-Methylenedioxypropenylbenzene	Ozonized air	Some 3,4-dihydroxybenzaldehyde	390
1,3-Dimethoxybenzene	Manganese(III) acetate at 100°	Tris-2,4-dimethoxyphenylmethanol (66%)	25
1,3-Dimethoxybenzene	Lead(IV) acetate at 70°	Small amounts of 2,4-dimethoxybenzylidyne triacetate, 2,4-dimethoxybenzaldehyde, 2,4-dimethoxybenzoic acid, and 3-acetoxyanisole	147, 378
1,4-Dimethoxybenzene	Lead(IV) acetate at 90°	2,5-Dimethoxybenzylidyne triacetate, 4-acetoxyanisole, 2,5-dimethoxybenzaldehyde, and formaldehyde	149, 230, 378
1,4-Dimethoxybenzene	Manganese(III) acetate at 100°	4-Acetoxyanisole and 2,5-dimethoxybenzyl acetate	25
1,3,5-Trimethoxybenzene	Lead(IV) acetate in benzene	3,5-Dimethoxyphenoxymethyl acetate (32%)	150
3,4,5-Trimethoxybenzaldehyde	Nitrobenzene and alkali at 160°	4-Hydroxy-3,5-dimethoxybenzaldehyde (11%)	389

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1,3,5-trimethoxybenzene[150] with lead(IV) acetate gives an acetoxymethyl ether of the type **95**. Oxidations of other methyl

$ArOCH_2OAc$ **95** $ArOCH_2OH$ **96**

ethers with either lead(IV) or manganese(III) acetate in acetic acid are complicated by the behavior of the resulting acetoxymethoxy compounds. These appear to react by two routes with the excess of the ethers giving compounds each of which contains an extra carbon atom. Formaldehyde may be formed first,[144,230] in which case the products finally isolated are methoxylated derivatives of benzaldehyde, benzoic acid, diphenylmethane, benzophenone, and triphenylmethanol.[25,146,147,149,386] Alternatively, acetoxymethylation may occur to give methoxy derivatives of benzyl acetate[25] which may undergo further acetoxylation at the methylene group to form the corresponding diacetoxy and triacetoxy derivatives.[378] From some of these reactions various demethylated products have also been isolated.

The products from the reactions of methyl ethers with either Fenton's reagent or peroxonitrous acid, both of which are sources of hydroxyl radicals, include formaldehyde and phenols.[87,97,376] These clearly result from the decomposition of hydroxymethyl ethers of the type **96**. Presumably most of the other oxidizing agents listed in Table XV produce analogous intermediates.[375,377,379,387] Benzyl ethers are also oxidized, forming benzaldehyde or benzoic acid derivatives,[381–385] while chlorophenoxyacetic acids undergo photochemical oxidation in the presence of riboflavin giving glyoxylic acid and the corresponding chlorophenols.[114] Fenton's reagent does not, however, react with the methylene group of aryloxyacetic acids. Instead the radical $ArOCH_2CO_2\cdot$ results which decarboxylates to form the aryloxymethyl radical $ArOCH_2\cdot$ and hence the dimer $ArOCH_2CH_2OAr$, formaldehyde, and the corresponding phenol.[87,391] The oxidations brought about by ozone[390] and by alkaline nitrobenzene[388,389] may involve polar reactions; the nature of the products of the reaction between selenium dioxide[392] and the methoxyl group is not known.

The metabolism of many methoxylated aromatic compounds by animals results in the formation of the corresponding phenols which are then excreted, frequently as their β-glucuronides.[99,393] These demethylation reactions, which are summarized in Table XVI, occur in the liver microsomes and can also be brought about *in vitro* using liver enzyme preparations. Direct replacement of methoxyl by hydroxyl does not occur.[394] Instead the methoxy compound ArOMe appears to be oxidized to the hydroxymethyl ether $ArOCH_2OH$ or its equivalent which then gives the phenol ArOH and formaldehyde.[108,393,395–398] Oxygen and reduced nicotinamideadenine dinucleotide phosphate ($NADPH_2$) are required for the oxidation[395–398] which presumably has a homolytic mechanism. Ethers containing alkyl groups other than methyl behave in a similar manner, but the rate of dealkylation falls as the alkyl group increases in size.[395,397,399,400] Despite the ability of the enzyme systems to effect the oxidation of a wide range of ethers each containing one alkoxyl group, polymethoxylated compounds undergo selective demethylation of only one of their ether functions with the formation of monohydric phenols.[395,397,398,401–403]

The main reaction which occurs during the metabolism of aryloxyacetic acids by microorganisms is hydroxylation of the aromatic nucleus (see section IV.C). Small amounts of phenols are obtained in some cases[107,114] showing that the carboxymethyl group also undergoes oxidation to some extent. The degradation of the higher homologs of these acids in both microorganisms and plants involves the repeated β oxidation of the polymethylene chains.[404–407] Those with odd numbers of methylene groups give finally the corresponding aryloxyacetic acids, which are active plant-growth regulators, while those with even numbers give the inactive phenols.[120,405,407]

$$ArO(CH_2CH_2)_nCO_2H \longrightarrow ArOCH_2CH_2CO_2H \longrightarrow ArOCOCH_2CO_2H \longrightarrow ArOCO_2H \longrightarrow ArOH$$

The methylenedioxybenzene grouping which is present in many alkaloids and other natural products appears to be formed in plants by the oxidative cyclization of precursors containing the *o*-hydroxyanisole system.[413–416]

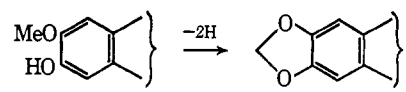

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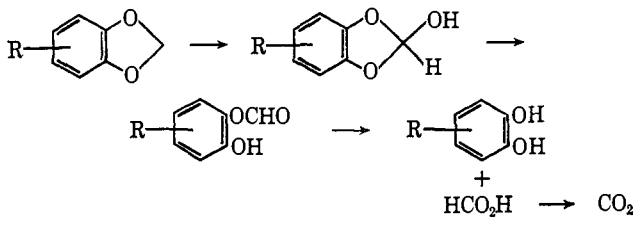
Table XVI
Biological Oxidation of Alkoxyl Groups

Ether	*Organism*	*Products*	*Ref*
Anisole	Rabbit	Phenol and formaldehyde	397
Anisole	*Aspergillus niger*	Some phenol	107
2-Nitro-, 3-nitro-, 4-nitro-, 4-chloro-, and 4-cyanoanisole	Rabbit or rat	Formaldehyde and the corresponding substituted phenols	108, 395, 396
4-Methyl-, 4-hydroxy-, 3-carboxy-, 4-carboxy-, 4-formyl-, 2-nitro-, 4-hydroxymethyl-, 4-aminomethyl-, and 4-propenylanisole	Rabbit or rat	The corresponding substituted phenols	108, 395, 396
2- and 4-methoxy-, 2- and 4-ethoxy-, 4-propoxy-, and 4-butoxybiphenyl	Rat, trout, or frog	2- or 4-hydroxybiphenyl	399
2- and 4-methoxy- and 4-ethoxyacetanilide	Rabbit, man, or rat	2- or 4-hydroxyacetanilide	394, 395, 397, 408, 409, 409a
4-Iodylanisole	Dog	4-Iodophenol	410
1,4-Dimethoxybenzene	Rabbit	Formaldehyde, 4-methoxyphenol, and quinol	108
3,4-Dimethoxyacetanilide	Rabbit	Mainly 4-hydroxy-3-methoxyacetanilide	401
3,4-Dimethoxynitrobenzene	Rabbit	4-Hydroxy-3-methoxy- (54%), 3-hydroxy-4-methoxy- (8.4%), and a trace of 3,4-dihydroxynitrobenzene	401
5,7-Dihydroxy-4′-methoxyisoflavone (biochanin A)	Rat	4′,5,7-Trihydroxyisoflavone (genistein) and formaldehyde	396, 411
3-Methyl ethers of oestrone, oestradiol, oestriol, and oestradiol 17-benzoate	Man or rat	The corresponding phenols	396, 412
Griseofulvin	Man, rat, or rabbit	6-Demethylgriseofulvin	403
Codeine, papaverine, quinine, mescaline, thebaine, colchicine, and brucine	Rabbit, mouse	Formaldehyde and the corresponding monohydric phenols	395, 397, 398, 402
4-, 5-, 6-, and 7-methoxyoxindole	Rat, guinea pig, or rabbit	The corresponding phenols	412a

Many derivatives of methylenedioxybenzene have the property of prolonging the action of drugs and, in particular, of increasing the toxicity of insecticides ("synergism"). Much of this activity results from the inhibition of the oxidative detoxification processes in the organisms concerned, presumably because of the preferential oxidation of the methylenedioxybenzene system. Both the house-fly and the mouse convert the methylene group into carbon dioxide while mouse-liver microsome $NADPH_2$ gives mainly formate *in vitro*. Accordingly the oxidation is thought to take the following path.[417]



C. INTRODUCTION OF CHLORINE

When simple methyl ethers, such as anisole and 1,2- and 1,4-dimethoxybenzene, are heated under a wide range of conditions with chlorine, complicated mixtures of products result. Nuclear chlorination predominates and little reaction occurs at the methyl groups with the formation of very small amounts of chloromethoxy compounds.[385,418,419] 4-Chloroanisole undergoes nuclear chlorination less readily, and the main product (60%) of its reaction with chlorine (1 mole/mole) at 195° is 1-chloro-4-chloromethoxybenzene (**97**). In the presence of

$4\text{-}ClC_6H_4OCH_2Cl$	$ArOCHCl_2$	$ArOCCl_3$	CCl_3CF_2OAr
97	**98**	**99**	**100**

phosphorus pentachloride chlorination of the methoxyl group is greatly facilitated and an excellent yield (93%) of the monochloromethoxy compound is obtained.[385] Other nuclear-chlorinated derivatives of anisole behave in a similar manner, but yields are lower when either a methyl or a second methoxyl group (both of which can undergo chlorination) is present in the molecule.[385,419] A selection of examples from a comprehensive study[385] of these and related reactions is given in Table XVII.

Reactions of chloroanisoles with two and three molecular proportions of chlorine[385] under similar conditions result in the efficient formation of dichloromethoxy and of trichloromethoxy compounds of types **98** and **99**, respectively (see Table XVIII). Chlorine-substituted 1,2- and 1,4-dimethoxybenzenes react in a generally similar manner.[419] The complete chlorination of the more highly substituted ethers in this way results in some replacement of the ether function by chlorine, and in the case of pentachloroanisole the main product obtained is hexachlorobenzene. Presumably with these compounds the steric congestion which results during the

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Table XVII
Monochlorination of Alkoxyl Groups

Ether	*Chlorination conditions*	*Products*	*Ref*
Anisole	Visible light at 220°, vapor phase	Mono- and some dichloromethoxybenzene	418
Anisole	145–160°	1-Chloro-4-chloromethoxybenzene (1%)	385
4-Chloroanisole	195–200°	1-Chloro-4-chloromethoxybenzene (60%) and 1,3-dichloro-4-chloromethoxybenzene	385, 425
4-Chloroanisole	Phosphorus pentachloride or disulfur dichloride at 195–200°	1-Chloro-4-chloromethoxybenzene [(a) 87–93%, (b) 80%]	385, 425
2-Chloro-, 2,4-dichloro-, 2,5-dichloro-, 2,4,6-trichloro-, and pentachloroanisole	Phosphorus pentachloride at 190–195°.	The corresponding monochloromethoxy compounds (86–98%)	385, 425
4-Methoxy- and 2-chloro-5-methoxytoluene, and 1-chloro-4-methoxy-2,6-dimethylbenzene	Phosphorus pentachloride at 190–195°.	The corresponding monochloromethoxy compounds (21–31%)	385
3-Chloro-6-methoxytoluene	Phosphorus pentachloride at 190–195°.	3-Chloro-6-chloromethoxytoluene (76%)	385
4-Nitroanisole	Phosphorus pentachloride at 160°	1-Chloromethoxy-4-nitrobenzene (20%)	385
Bis-2,4-dichlorophenoxymethane	195–200°	Bis-2,4-dichlorophenoxychloromethane (45%)	385
Ethyl 2,4-dichlorophenoxyacetate	200–205°	Ethyl 2,4-dichlorophenoxychloroacetate (62%)	385
1-Methoxynaphthalene	Phosphorus pentachloride at 190–195°	1-Chloromethoxynaphthalene (2%)	385
1-Chloro-2-methoxynaphthalene	Phosphorus pentachloride at 190–195°	1-Chloro-2-chloromethoxynaphthalene (21%)	385
1,2-Dimethoxybenzene	Phosphorus pentachloride at 190–195°	1-Chloromethoxy-2-methoxybenzene (5%)	419
1,4-Dimethoxybenzene	Phosphorus pentachloride at 190–195°	1-Chloromethoxy-4-methoxybenzene (3%)	419
1,2-Dichloro-4,5-dimethoxybenzene	Phosphorus pentachloride at 190–195°	1,2-Dichloro-4-chloromethoxy-5-methoxybenzene and some 1,2-dichloro-4,5-bischloromethoxybenzene	419
1,4-Dichloro-2,5-dimethoxybenzene	Phosphorus pentachloride at 190–195°	1,4-Dichloro-2-chloromethoxy-5-methoxybenzene (54%) and 1,4-dichloro-2,5-bischloromethoxybenzene (6%)	419

Table XVIII
Polychlorination of Alkoxyl Groups

Ether	*Chlorination conditions*	*Products*	*Ref*
Anisole	Visible light at 220°, vapor phase	Some dichloromethoxybenzene	418
Anisole	In excess; visible light; 150–160° in liquid phase	Di(3-chlorophenyl) carbonate (water-insoluble residue; formed *via* 1-chloro-3-trichloromethoxybenzene)	418
4-Chloro-, 2,4-dichloro-, and 2,4,6-trichloroanisole	2 or 3 moles/mole; PCl_5 at 190°	The corresponding dichloromethoxy compounds (90–91%) or trichloromethoxy compounds (65–91%)	385, 422, 425
2-Chloro-, 4-fluoro-, 4-cyano-, 3-chlorocarbonyl-, and 4-chlorocarbonylanisole	190–200°; PCl_5	The corresponding trichloromethoxy compounds (66–87%)	422–424
2,4-Bistrifluoromethylanisole	In excess; 20–35°	1-Trichloromethoxy-2,4-bistrifluoromethylbenzene	420
Pentachloroanisole	3 moles/mole; PCl_5 at 190°	Trichloromethoxypentachlorobenzene (25%) and hexachlorobenzene (65%)	385
Pentafluoroanisole	Ultraviolet light at bp	Trichloromethoxypentafluorobenzene	421
1,2-Dichloro-4,5-dimethoxybenzene	In excess; PCl_5 at 190–195°	1,2-Dichloro-4,5-bisdichloromethoxy- and -4,5-bistrichloromethoxybenzene, 1,2,4,5-tetrachlorobenzene, and hexachlorobenzene	419
1,4-Dichloro-2,5-dimethoxybenzene	2 moles/mole; PCl_5 at 190–195°	1,4-Dichloro-2,5-bischloromethoxybenzene and some 1,4-dichloro-2-dichloromethoxy-5-methoxybenzene	419

Table XVIII (Continued)

Ether	*Chlorination conditions*	*Products*	*Ref*
1,4-Dichloro-2,5-dimethoxybenzene	3 moles/mole; PCl_5 at 190–195°	Mainly 1,4-dichloro-2-chloromethoxy-5-dichloromethoxybenzene	419
1,4-Dichloro-2,5-dimethoxybenzene	In excess; PCl_5 at 190–195°	1,4-Dichloro-2,5-bistrichloromethoxybenzene (27%), and a little 1,4-bistrichloromethoxytetrachlorobenzene and hexachlorobenzene	419
5-Chloro-2-chloromethoxytoluene	PCl_5 at 198–215°	5-Chloro-2-dichloromethoxy- and -2-trichloromethoxytoluene	385, 426
2-Chloro-5-chloromethoxytoluene	PCl_5 at 195–215°	2-Chloro-5-dichloromethoxy- and -5-trichloromethoxytoluene	385, 426
3-(β,β,β-Trifluoroethoxy)benzoyl chloride	Ultraviolet light; PCl_3 at 150°	3-(α,α-Dichloro-β,β,β-trifluoroethoxy)-benzoyl chloride	427
β,β-Dichloro-α,α-difluoroethoxybenzene and its 3-chloro-, 4-chloro-, 2,4-dichloro-, pentachloro-, and 3-chlorocarbonyl derivatives	Ultraviolet light; PCl_3 at 150°	β,β,β-Trichloro-α,α-difluoroethoxybenzene and its corresponding derivatives	427
1,4-Bis-β,β-dichloro-α,α-difluoroethoxybenzene	Ultraviolet light; PCl_3 at 150°	1,4-Bis-β,β,β-trichloro-α,α-difluoroethoxybenzene	427
3- and 4-β,β-dichloro-α,α-difluoroethoxytoluene	Ultraviolet light; PCl_3 at 150°	3- and 4-β,β,β-trichloro-α,α-difluoroethoxybenzylidyne trichloride	427

chlorination of the intermediate **98** can be relieved by the elimination of the ether function as phosgene. Anisole derivatives containing other deactivating substituents such as -F, -CN, -COCl, and $-CF_3$ are also readily converted into trichloromethoxy compounds of type **99**.[420–424] Ultraviolet irradiation may be used to effect the chlorination of several fluorine-containing ethers.[421,427] In this way, β chlorination of β,β-dichloro-α,α-difluoroethoxybenzene and its derivatives may be effected giving good yields of the corresponding trichlorodifluoro compounds **100**.

The reaction of anisole with sulfuryl chloride, unlike the reaction with chlorine, takes place under mild conditions and gives chloromethoxybenzene in high (93 to 95%) yield.[428,429]

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