# Reactions of Lead(IV). Part XXII.[1] Radical-initiated Oxidation of Anisole

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The oxidation of anisole by lead tetra-acetate can occur by a radical-chain mechanism which leads to methylation, acetoxylation, and acetoxymethylation of the ring-carbon atoms and acetoxylation of the side-chain. The relative yields of the products vary markedly with the conditions, and especially with the addition of acetic acid; the causes of the variations are discussed. The radical-initiated reactions of anisole with lead tetrapropionate and of benzene with lead tetra-acetate are also reported.

LEAD TETRA-ACETATE effects both homolytic and heterolytic substitution in benzenoid compounds. Reactions of the former type have usually been studied in refluxing acetic acid; under these conditions, the methyl radical is generated and can bring about both methylation[2] and formation of the radical $\cdot CH_2CO_2H$ from acetic acid and thence carboxymethylation.[3] A reaction of the latter type is plumbylation, which appears to be a typical electrophilic aromatic substitution;[4] thus, it is significant only with compounds which are strongly activated towards electrophiles, such as anisole[2] and *m*-dimethoxybenzene.[5] A second reaction, acetoxylation, displays one characteristic of electrophilic substitution in that it occurs only with compounds which are activated towards electrophiles,[2] but it is nonetheless not a typical reaction of this class; for example, *m*-dimethoxybenzene, which is much more reactive than its *ortho-* and *para-*isomers towards electrophiles, is the least reactive of the three compounds in acetoxylation.[4] To account for this and other observations it has been suggested that acetoxylation is initiated by electron transfer from the aromatic compound to the oxidant, but it is not clear whether one or two electrons are transferred;[1,4] reactions (1) and (2) represent these possibilities for *p*-dimethoxybenzene. We have now examined this and some related problems in greater detail by studying the reaction of anisole with lead tetra-acetate in the presence of a source of free radicals, namely Perkadox (di-isopropyl peroxydicarbonate); complementary investigations, involving the oxidation of anisole by lead tetrapropionate and of benzene by lead tetra-acetate, are also reported.

Oxidation of Anisole with Lead Tetra-acetate.—Reactions were carried out at 80° with an excess of the aromatic compound and, except where stated otherwise,

were continued until all the lead tetra-acetate had been used. Yields are based on the lead salt, on the assumption (unless specified) that 1 mol of product is equivalent to 1 mol of lead salt. The products usually obtained were (1)—(4); in addition, traces of dimethoxybiphenyls were detected in some cases but their yields, which were never greater than 0·3%, are not tabulated.
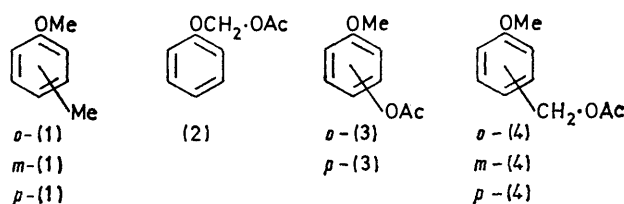
The products formed in the absence of Perkadox are set out in Table 1. In each case, small amounts of *o*- and *p*-chloroanisole, in the ratio *ca.* 1 : 6, were detected (yields of 2, 1·5, 1, and 4% in experiments 2, 3, 4, and 5, respectively) which presumably originate in heterolytic reactions noted before with the dimethoxybenzenes.[4] Table 2 shows the effect of including a catalytic amount of Perkadox; the amount added was not significant within wide limits, for under the conditions of experiment 8 variation in the quantity from 25 to 200 mg caused no change in the relative or absolute yields of products outside the experimental error.

Comparison of the times required for the total consumption of lead tetra-acetate with and without a catalytic amount of Perkadox points to the involvement of a radical-chain reaction under the former conditions. When a reaction was carried out under the conditions of the experiments in Table 2, with acetic acid (20 ml) present but with no anisole, only 27% of the lead tetra-acetate had been consumed after 15 min, as estimated by iodometry; when the amount of the lead tetra-acetate was halved, only 33% had been consumed after 20 min. It follows that anisole takes part in one or more of the propagating steps of the chain.

We shall first discuss the possible sources of the products and, later, the factors determining their relative yields. The methyl group in the methylated products (1) could be derived either from lead tetra-acetate or from Perkadox. Evidence that the latter source is un-
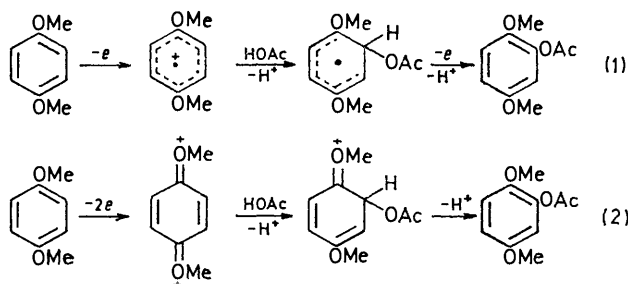
[1] Part XXI, R. O. C. Norman, C. B. Thomas, and J. S. Willson, *J. Chem. Soc.* (B), 1971, 518.

[2] D. R. Harvey and R. O. C. Norman, *J. Chem. Soc.*, 1964, 4860.

[3] E. I. Heiba, R. M. Dessau, and W. J. Koehl, jun., *J. Amer. Chem. Soc.*, 1968, **90**, 1082.

[4] R. O. C. Norman and C. B. Thomas, *J. Chem. Soc.* (B), 1970, 421.

[5] F. R. Preuss and I. Janshen, *Arch. Pharm.*, 1960, **293**, 933.

important is derived from two observations. First, in many of the experiments in Table 2 the yield of methylated products was considerably greater than could be accounted for in this way; secondly, when lead tetrapropionate was used in conjunction with Perkadox, the yield of methylated products was very small compared both with that obtained under comparable conditions with lead tetra-acetate and with that of ethylated products (Table 6; see later).

Since a radical-chain is involved in methylation, we infer that the reactive entity is either a free methyl

The isomer distribution we obtained for the methylated derivatives, $o : m : p = 62 : 29 : 9$, was significantly different from that with lead tetra-acetate $(74 : 19 : 7)$; likewise, the reactivity of anisole compared with benzene towards methylation, as estimated by product yields when a large excess of an equimolar mixture of the two compounds was oxidised, was different with di-t-butyl peroxide $(k_{rel} = 1\cdot7)$ compared with lead tetra-acetate $(k_{rel} = 1\cdot4)$.* However, selectivity in homolytic aromatic substitution can vary slightly depending on what oxidising agents are present, since the cyclohexadienyl

TABLE 1

Products from the oxidation of anisole with lead tetra-acetate (*ca.* 1 g) at 80°

					Products (%)				
Expt.	PhOMe (ml)	HOAc (ml)	Atmos.	Time (h)	(1)	(2)	(3)	Ratio (o-3) : (p-3)	(4)
1	10	0	N_2	0·3 [b]	1·3				
2	10	0	N_2	60	2·9	1·4	2·4	46 : 54	
3	10	0	Air	132	2·8	1·0	2·4	42 : 58	0·1
4	1	9	N_2	60	0·1	0·7	17·7	18 : 82	1
5	1	9	Air	132	0·1	0·1	12·0	5 : 95	
6 [a]	1	13	Air	120			14·6	4 : 96	

[a] Ref. 4; 5 g Pb(OAc)₄.   [b] Incomplete consumption of oxidant.

TABLE 2

Products from the oxidation of anisole with lead tetra-acetate in the presence of Perkadox (*ca.* 50 mg) under nitrogen at 80°

					Products (%)					
Expt.	Pb(OAc)₄ (g)	PhOMe (ml)	HOAc (ml)	Time (min)	(1)	(2)	(3)	Ratio (o-3) : (p-3)	(4)	Ratio (o-4) : (m-4) : (p-4)
7	2	200	0	20	70 [b]	31	2	41 : 59	Trace	
8	2	20	0	15	39 [b]	26	12	41 : 59	3	
9	2	18	2	15	36 [b]	20	21	24 : 76	5	
10	2	10	10	15	9 [b]	9	24	25 : 75	16	78 : 2 : 20
11	2	2	18	15	<1	4	20	24 : 76	22	80 : 6 : 14
12	0·5	5	45	15	<1	5	5	21 : 79	37	76 : 5 : 19
13	0·1	5	45	15	<1	5	2	21 : 79	34	70 : 1 : 29
14 [a]	2	2	18	15	Trace	4	24	26 : 74	4	

[a] Cu(OAc)₂ (0·05 g) was included.   [b] $o : m : p = 74 : 19 : 7$.

radical or a carrier of this species, such as lead triacetate, from which methyl could be transferred. We should not expect these alternative reagents to show the same selectivity between the *ortho-*, *meta-*, and *para*-positions of anisole, and we therefore sought information about the selectivity shown in reaction with a well established source of the methyl radical at the same temperature. Two previous studies, in both of which di-t-butyl peroxide was used to generate the methyl radical, were at much higher temperatures (140 [6] and [7] >180°), and we therefore re-investigated the reaction at 80°.

radicals which mediate in these processes require an oxidant for conversion into substitution products but not for their alternative reactions such as dimerisation (*e.g.*, ref. 10). Lead(IV) is likely to be a more effective oxidant for these radicals than is di-t-butyl peroxide; thus, there is evidence for its capacity to oxidise alkyl radicals,[11] and its oxidation of cyclohexadienyl radicals as in reaction (9) is invoked in the present work as a necessary chain-propagating step. We therefore repeated the methylation of anisole with di-t-butyl peroxide in the presence of copper(II) acetate, since copper(II) is known to be an effective oxidant for organic radicals, more so than lead(IV).[12] This resulted in an

* The methyl affinity of anisole has been reported to be *less* than unity.[8] However, the method used was one which would give an incorrectly low value if reaction of the methyl radical at 65° occurs at the methoxy-group of anisole, to give methane, as it is known to do at higher temperatures.[7,9] We also examined the isomer ratio for the methylation of anisole by di-t-butyl peroxide at 150°; the ratio $(o : m : p = 67 : 24 : 9)$ is significantly different from that reported for 140° $(74 : 15 : 11)$, probably in part because of the improvement in analytical technique since the latter measurement.[6]

[6] B. R. Cowley, R. O. C. Norman, and W. A. Waters, *J. Chem. Soc.*, 1959, 1799.

[7] M. F. R. Mulcahy, B. G. Tucker, D. J. Williams, and J. R. Wilmshurst, *Austral. J. Chem.*, 1967, **20**, 1155.

[8] W. J. Heilman, A. Rembaum, and M. Szwarc, *J. Chem. Soc.*, 1957, 1127.

[9] H. B. Henbest, J. A. W. Reid, and C. J. M. Stirling, *J. Chem. Soc.*, 1961, 5239.

[10] D. H. Hey, K. S. Y. Liang, and M. J. Perkins, *Tetrahedron Letters*, 1967, 1477.

[11] J. K. Kochi, *J. Amer. Chem. Soc.*, 1965, **87**, 3609; J. K. Kochi, J. D. Bacha, and T. W. Bethea III, *ibid.*, 1967, **89**, 6538.

[12] J. D. Bacha and J. K. Kochi, *J. Org. Chem.*, 1968, **33**, 83.

isomer distribution for the methylanisoles, $o : m : p = 73 : 18 : 10$, which is the same within the experimental error as that obtained with lead tetra-acetate, and there is therefore no reason to invoke an agent other than the methyl radical as responsible for the aromatic methylation of anisole.

The acetoxymethyl-derivatives (4) * have been previously obtained from the oxidation of anisole with manganese(III) acetate in acetic acid at 90°,[13] and the corresponding derivatives of toluene have been obtained with lead tetra-acetate in acetic acid.[3] It has been suggested that these products are formed by reaction of the methyl radical with acetic acid to give the species $\cdot CH_2CO_2H$, homolytic substitution by this species in the aromatic compound, and oxidative decarboxylation of the resulting arylacetic acid [e.g., Scheme, reactions (11)—(13)].[3,13] It is likely that this path is followed under the conditions of the experiments in Table 2, and, in accord with this, we found in a control experiment that p-methoxyphenylacetic acid is converted quantitatively in 15 min into p-methoxybenzyl acetate by lead tetra-acetate in acetic acid containing Perkadox at 80°. It is notable that the isomer distribution for the acetoxymethyl-derivatives varies with the conditions (experiments 10—13) and, in particular, that the highest relative yield of the meta-derivative occurs when the ratio of $[Pb^{IV}] : [PhOMe]$ is greatest, that is, when the further oxidation of the intervening arylacetic acids has the greatest chance of occurring. This may be due at least in part to the fact that m-methoxyphenylacetic acid is oxidised by lead(IV) less rapidly than its ortho- and para-isomers (oxidation of each of which should be facilitated by the $+M$ effect of the substituent [12]). In accord with this view, when a small amount (12 mg) of phenylacetic acid (the oxidation of which should have similar characteristics to that of its m-methoxy-derivative, since the electronic effect of m-OMe is small) was included with anisole in a reaction under the conditions of experiment 10, only 21% of it was converted into benzyl acetate. Finally, for the higher ratios of $[Pb^{IV}] : [PhOMe]$ in Table 2, the isomer distribution of the acetoxymethyl-derivatives is, within the limits of the experimental error, the same as obtained with manganese(III) acetate $(o : m : p = 78 : 5 : 17)$.[13]

Nuclear acetoxylation differs markedly from methylation and acetoxymethylation in that benzene, which undergoes the last two reactions (Table 7; see later), gives no detectable phenyl acetate. Further, when we submitted a mixture of benzene and anisole to oxidation the yield of the acetoxyanisoles was 16% whereas again no phenyl acetate was found. This observation, together with the measured sensitivity of the g.l.c. technique, shows that anisole is at least 200 times as reactive

as benzene in acetoxylation; we infer that at least one of the steps concerned in acetoxylation involves a reagent of strong electrophilic character. Now, although radicals in which the unpaired electron is associated with a strongly electronegative element display electrophilic character in their additions to aromatic rings, the effects are never so marked as we have found; a particularly pertinent comparison is with the benzoyloxy-radical which brings about the benzoyloxylation of aromatics, towards which anisole is no more than ten times as reactive as benzene.[14] Thus, we cannot envisage that either the acetoxy-radical or a neutral ' carrier ' of it such as lead triacetate brings about acetoxylation by the addition–elimination sequence which is typical of homolytic aromatic substitution.[15]

A possible mechanism for acetoxylation which combines an electrophilic step with one susceptible to initiation by Perkadox consists of electrophilic plumbylation followed by the radical-induced homolysis of the resulting aryl-lead triacetate; thus, it is established that p-methoxyphenyl-lead triacetate is formed from anisole and lead tetra-acetate [2] and converted into p-acetoxyanisole (although not efficiently) when heated at 80° in the presence of Perkadox.[4] However, this mechanism can be ruled out on two grounds. First, the electrophilic plumbylation of anisole is a relatively slow reaction [2] which could not have proceeded to a significant enough extent in 15 min to account for more than a very small proportion of the acetoxyanisoles formed under the conditions of the experiments in Table 2; moreover, it probably occurs almost entirely at the para-position of anisole [2] (cf. thalliation [16]), whereas acetoxylation is much less selective. Secondly, when p-methoxyphenyl radicals are formed from the lead(IV) derivative in the presence of anisole, they bring about homolytic aromatic substitution to give 2,4'-, 3,4'-, and 4,4'-dimethoxybiphenyl in significant amounts,[17] whereas under our conditions only traces of these dimers were detected.
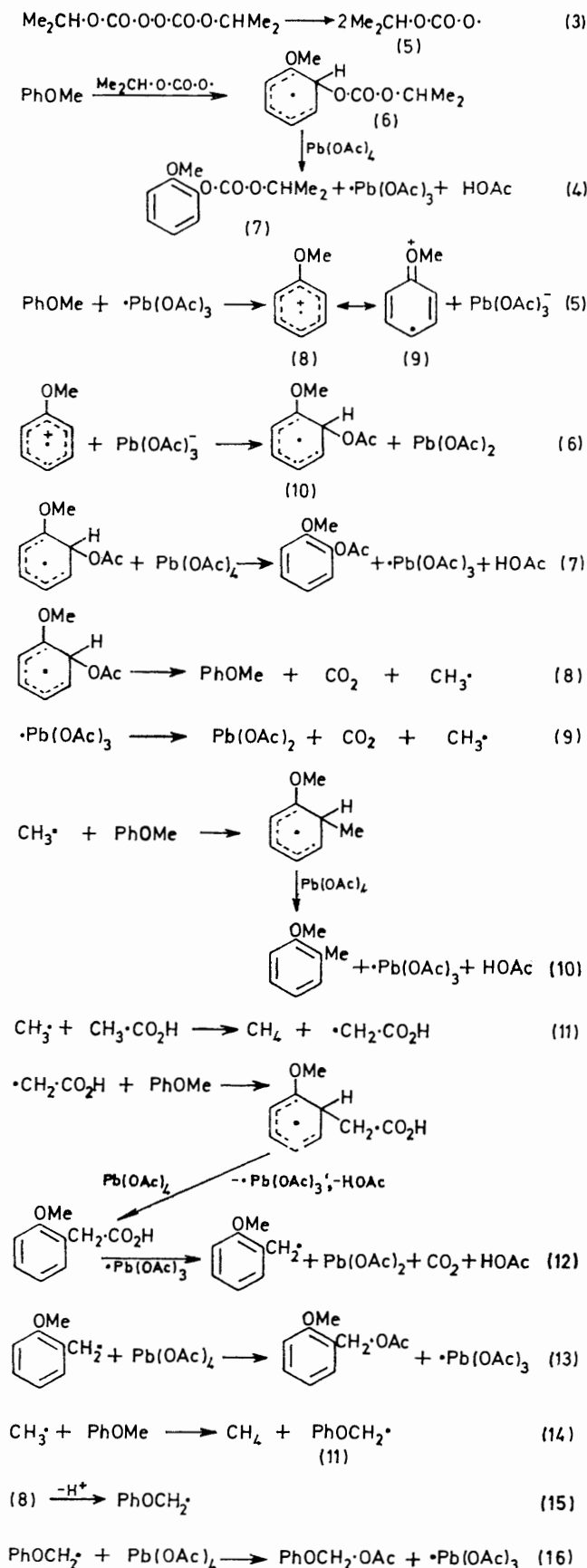
We return, therefore, to the electron-transfer mechanism suggested previously to account for acetoxylation in the absence of Perkadox, the two variants of which are the one-electron and two-electron processes. Of the two, the latter cannot apply under the conditions of the experiments in Table 2 since it cannot be associated with a radical-chain reaction. However, the one-electron mechanism fulfils both the crucial criteria; it can be part of a chain process, as shown in the Scheme [propagating steps: reactions (5)—(7)], and it is consistent with the much greater reactivity of anisole compared with benzene since the positive charge acquired by the aromatic ring as a result of electron transfer can be assimilated by oxygen [e.g. structure (9)].

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* It should be noted that formation of the acetoxymethyl-derivatives (4) requires four single-electron oxidations, i.e. 2 mol of lead(IV) per mol of product; since yields in Table 2 are based on the assumption of a 1 : 1 mol-equivalence, the material balance is significantly greater than the sum of the yields would indicate when a large proportion of the derivatives (4) is produced.

[13] E. I. Heiba, R. M. Dessau, and W. J. Koehl, jun., J. Amer. Chem. Soc., 1969, 91, 138.

[14] M. E. Kurz and M. Pellegrini, J. Org. Chem., 1970, 35, 990; T. Nakata, K. Tokumaru, and O. Simamura, Tetrahedron Letters, 1967, 3303.

[15] G. H. Williams, ' Homolytic Aromatic Substitution,' Pergamon Press, 1960.

[16] A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, Tetrahedron Letters, 1969, 2427.

[17] R. A. McClelland, R. O. C. Norman, and C. B. Thomas, J.C.S. Perkin I, 1972, 578.

$$Me_2CH\cdot O\cdot CO\cdot O\cdot O\cdot CO\cdot O\cdot CHMe_2 \longrightarrow 2\,Me_2CH\cdot O\cdot CO\cdot O\cdot \quad (3)$$
(5)

PhOMe $\xrightarrow{Me_2CH\cdot O\cdot CO\cdot O\cdot}$ (6)

 (4)
(7)

PhOMe + $\cdot Pb(OAc)_3 \longrightarrow$ $+ Pb(OAc)_3^-$ (5)
(8) (9)

 $+ Pb(OAc)_3^- \longrightarrow$ $+ Pb(OAc)_2$ (6)
(10)

 $+ Pb(OAc)_4 \longrightarrow$ $+\cdot Pb(OAc)_3 + HOAc$ (7)

 $\longrightarrow PhOMe + CO_2 + CH_3\cdot$ (8)

$\cdot Pb(OAc)_3 \longrightarrow Pb(OAc)_2 + CO_2 + CH_3\cdot$ (9)

$CH_3\cdot + PhOMe \longrightarrow$

 $+\cdot Pb(OAc)_3 + HOAc$ (10)

$CH_3\cdot + CH_3\cdot CO_2H \longrightarrow CH_4 + \cdot CH_2\cdot CO_2H$ (11)

$\cdot CH_2\cdot CO_2H + PhOMe \longrightarrow$

 $+ Pb(OAc)_2 + CO_2 + HOAc$ (12)

 $+ Pb(OAc)_4 \longrightarrow$ $+\cdot Pb(OAc)_3$ (13)

$CH_3\cdot + PhOMe \longrightarrow CH_4 + PhOCH_2\cdot$ (14)
(11)

(8) $\xrightarrow{-H^+} PhOCH_2\cdot$ (15)

$PhOCH_2\cdot + Pb(OAc)_4 \longrightarrow PhOCH_2\cdot OAc + \cdot Pb(OAc)_3$ (16)

SCHEME

Finally, the acetoxy-derivative (2) could be formed in a radical-chain process by reaction (14) (evidence for the occurrence of which has been obtained at higher temperatures [7,9]) or (15), followed in either case by (16); we should not necessarily expect to be able to detect the dimer of the intervening phenoxymethyl radical (11) since the oxygen substituent should promote the ease of oxidation of this radical by lead tetra-acetate (*cf.* the relative ease of oxidation of the benzyl and *p*-methoxybenzyl radicals discussed below). Indeed, a useful synthetic procedure for phenoxymethyl acetate was found to be the oxidative decarboxylation of phenoxyacetic acid with lead tetra-acetate at 80°; the product was formed in 70% yield (g.l.c.) (53% isolated), presumably *via* the radical $PhOCH_2\cdot$ followed by one-electron oxidation.

Initiation of the chains is likely to be *via* reactions (3) and (4), and evidence consistent with this was obtained as follows. It has already been shown that anisole reacts with the radical (5) from Perkadox to give the product (7) and its *para*-isomer,[18] and we found small quantities of two compounds in each experiment in Table 2 the g.l.c. retention times of which were of the order expected for these products and which were identified as such by their (qualitatively identical) mass spectra. Thus, the parent ions (m/e 210) fragment in a manner similar to that from isopropyl phenyl carbonate,[19] namely, by the sequential and concurrent loss of 44 (CO_2) and 42 (C_3H_6) m.u. to give base peaks at m/e 124, the further fragmentations of which closely resemble those of the parent ions from *o*- and *p*-methoxyphenol.[20] This pattern, together with weak ions of m/e 195 ($M - Me$) and stronger ones of m/e 151 (probably arising both by loss of the isopropoxy-radical from the parent ions and of the methyl radical from the ions of m/e 166) identify the two compounds as the *ortho*- and *para*-isomers of isopropyl methoxyphenyl carbonate.

The lead(III) derivative formed by the initiating reactions could act both as a one-electron oxidant for anisole [reaction (5)] and as a source of the methyl radical [reaction (9)]; in each case, lead(III) could be regenerated in subsequent steps, (7) and (10), so as to perpetuate the chain. It has been postulated that species of the type $\cdot Pb(O_2CR)_3$ mediate in the decomposition of lead tetracarboxylates and fragment to alkyl radicals,[11] but there is another likely route to the methyl radical in this case, for there is evidence that the species (10) and its *para*-isomer, formed as in reaction (6), not only provide the nuclear acetoxylated products (3) by one-electron oxidation but also fragment to anisole, carbon dioxide, and the methyl radical [reaction (8)].[21] However, there is no evidence for the mediation, during the oxidation of benzene, of the adduct corresponding to

[18] M. E. Kurz, P. Kovacic, A. K. Bose, and I. Kugajevsky, *J. Amer. Chem. Soc.*, 1968, **90**, 1818.
[19] P. Brown and C. Djerassi, *J. Amer. Chem. Soc.*, 1966, **88**, 2469.
[20] C. B. Thomas, *J. Chem. Soc. (B)*, 1970, 430.
[21] R. A. McClelland, R. O. C. Norman, and C. B. Thomas, following paper.

(10) from anisole, despite which methylation can occur in good yield (see later); we conclude that the methyl radical in that case is formed by fragmentation of the lead(III) derivative and, by analogy, that this route is also responsible at least in part for the methylation of anisole.

The inclusion of increasing amounts of acetic acid (experiments 8—11) results in an increase in the yield of the products (4) and decrease in the yields of the methyl-derivatives (1) and the side-chain acetoxy-derivative (2). These changes are consistent with the increasing importance of reaction (11) relative to reactions (10) and (14). However, the yield of the acetoxy-derivative (2) does not fall so rapidly as that of the methylated products, in accord with the suggestion that side-chain acetoxyl-ation occurs via reaction (15) as well as reaction (14). In addition to these changes, it is noteworthy that increase in the concentration of acetic acid results in a decrease in the total yield; thus, this falls from about 100% in experiment 7 to <70% in experiment 11 [even allowing for the fact that formation of 1 mol of products (4) requires 2 mol of oxidant]. This is possibly because the radical $\cdot CH_2CO_2H$ is partly removed by oxidation, to give acetoxyacetic acid; consistent with this, when experiment 11 was repeated with the inclusion of copper(II) [which is a better oxidant than lead(IV) towards organic radicals [11]], the yield of the acetoxy-derivatives (2) and (3) remained about the same but that of the products (4) fell sharply (experiment 14).

The effect of reducing the concentration of lead tetra-acetate (compare experiments 7 and 8, and 11, 12, and 13) is to decrease the yields of ring-acetoxylated products and to increase those of products from the methyl radical. This could be accounted for by partitioning of the adduct (10) and its para-isomer between one-electron oxidation [reaction (7)] and fragmentation [reaction (8)].

TABLE 3

Products from the oxidation of anisole, under the conditions of experiment 10, at various temperatures

Expt.	Temp.	Time (min)	(1) [a]	(2)	(3) [b]	(4)
15	60°	300	4	6	50	10
10	80	15	9	9	24	16
16	105	3	15	10	13	18

[a] $o : m : p = 74 : 19 : 7$. [b] $o : p = 25 : 75$.

The data in Table 3 show the effect on the product distribution of varying the temperature for reaction under the conditions of experiment 10. We infer that, as the temperature is raised, the fragmentations which lead to the methyl radical become increasingly important relative to the electron-transfer process.

We consider next the selectivity between the three nuclear positions of anisole in the acetoxylation process. First, none of the meta-derivative was found under any of the conditions we employed [an isomer distribution with <0.5% (m-3) would have been detected]. This is compatible with the suggested mechanism. Thus, if the transition states for formation of the adduct (10) and

its isomers occur relatively early along the reaction co-ordinate so that they resemble the reactants, little or no meta-substitution would be expected since the unpaired electron should be more heavily concentrated at the ortho- and para-positions in the reactant [cf. the contribution of the structure (9) to the reactant molecule]; alternatively, if the transition states resemble the products (10) and its isomers, again little meta-substitution would be expected since the methoxy-group can only take part in delocalisation of the unpaired electron for reaction at the ortho- and para-positions. Secondly, a striking feature of the data for acetoxylation is that the ortho : para ratio changes sharply when acetic acid is added to the medium. Such a change could in principle result if further oxidation of the two acetoxy-derivatives were to occur selectively and to an extent dependent upon the conditions. However, when the concentration of lead tetra-acetate was varied several-fold under otherwise identical conditions (presence of acetic acid, experiments 11—13), there was a very small change in the isomer distribution—perhaps reflecting the differential effect in the competition between oxidation and fragmentation of the intermediate (10) and its para-isomer—but nothing like so great an effect as occurs when acetic acid is excluded, and a five-fold increase in the concentration of the oxidant compared with experiment 11 had no effect on the isomer distribution. These observations argue against an explanation in terms of selective further oxidation for reaction in the presence of acetic acid; moreover, since there is a greater excess of anisole over lead tetra-acetate in experiments 7 and 8 than in experiment 11, it is unlikely that further oxidation is important in determining the ratio in the absence of added acetic acid. It is probable, therefore, that the presence of acetic acid in significant quantity (that is, greater than is available from the lead tetra-acetate) modifies the mechanism of acetoxylation and thereby leads to a change in the ortho : para ratio for the process. To investigate this possibility further, we employed some other additives as co-solvents with anisole, with the results shown in Table 4.

Three ways in which an additive might affect the ortho : para ratio for acetoxylation are: (i) by changing the dielectric constant of the medium; (ii) by acting as a (Brönsted) base; (iii) by acting as a ligand for the lead atom. Possibility (i) was eliminated by our finding that, whereas the ratio is changed by the addition of a small quantity of acetic acid, which has a somewhat larger dielectric constant than anisole (compare experiments 8 and 9), it is not changed by addition of the same quantity of acetonitrile, which has a very much larger dielectric constant (compare experiments 8 and 17), nor, to a significant extent, by the addition of a large amount of 1,2-dichloroethane, which also has a higher dielectric constant than anisole.[22] Evidence against possibility (ii) was provided by our finding that, whereas the addition

[22] A. Weissberger, E. S. Proskauer, J. A. Riddick, and E. E. Toops, 'Technique of Organic Chemistry,' vol. 7, 2nd edn., Interscience, New York, 1955.

of a small amount of pyridine greatly alters the ratio (experiments 8 and 19), the addition of the same amount of 2,6-lutidine—a slightly stronger Brönsted base than pyridine [23]—hardly affects it (experiments 8 and 20). However, pyridine and 2,6-lutidine differ markedly in their capacity to act as Lewis bases towards moderately bulky electron acceptors such as boron trifluoride,[23] so that their significantly different effects in our case suggest that the change in the *ortho* : *para* ratio is associated with the availability of a ligand for a lead species [possibility (iii)]; moreover, this view is also consistent with the fact that a small quantity of acetic acid [which provides a ligand for lead(IV) [24]] affects the ratio whereas neither acetonitrile nor 1,2-dichloroethane does so significantly. We therefore suggest that the *ortho* : *para* ratio in acetoxylation is mainly determined

products (1) and (4) is essentially completely inhibited, evidently because bromotrichloromethane traps the methyl radical efficiently, presumably giving bromomethane and the radical $\cdot CCl_3$. In contrast, acetoxylation of the aromatic ring is not inhibited, and acetoxylation of the side-chain still occurs to a significant extent. We infer from the former observation that the radical cation (8) is not efficiently trapped by the bromocompound (although such trapping may be the source of the small amounts of the bromoanisoles which are formed), and the latter observation adds support to our view that side-chain acetoxylation occurs at least in part by way of the radical cation (8).

The final inference drawn from the data in Table 5 is the following. Under the conditions of these experiments but in the absence of the inhibitor, more than 40%

TABLE 4

Products from the oxidation of anisole, under the conditions of the experiments in Table 2, with additives

Expt.	PhOMe (ml)	Co-solvent (ml)	Time (min)	(1)	(2)	(3)	Ratio (o-3) : (p-3)	(4)
17	18	MeCN (2)	15	24 [c]	18	15	40 : 60	3
18	2	$CH_2Cl \cdot CH_2Cl$ (20)	120	1	20	10	37 : 63	0
19	20	C_5H_5N [a] (2)	15	29 [c]	21	2·5	20 : 80	2
20	20	2,6-L [b] (2)	15	13 [c]	13	3	37 : 63	1

[a] Pyridine.   [b] 2,6-Lutidine.   [c] $o : m : p = 74 : 19 : 7$.

TABLE 5

Products from the oxidation of anisole, under the conditions of the experiments in Table 2, in the presence of bromotrichloromethane

Expt.	PhOMe (ml)	HOAc (ml)	$BrCCl_3$ (ml)	(1)	(2)	(3)	MeO·C_6H_4Br [a]	Ratio (o-3) : (p-3)
21	20	0	2	Trace	10	17	3	41 : 59
22	18	2	0·5	Trace	8	28	5	29 : 71
23	18	2	2	Trace	8	36	6	28 : 72

[a] $o : m : p = 4 : 0 : 96$.

by the ease with which the radical cation (8) and the associated lead species formed by reaction (5) collapse to give either the *ortho*-intermediate (10) or its *para*-isomer, and this is in turn dependent on the nature of the ligands on the lead species.

We also studied the effect of bromotrichloromethane, a typical inhibitor of radical-chain reactions, on the Perkadox-initiated oxidation of anisole by lead tetra-acetate. The results are in Table 5; none of the acetoxymethyl-derivatives (4) were detectable.

It is notable, first, that bromotrichloromethane does not inhibit the chain reaction as a whole, although it was always present in considerable excess of the initiator; thus, the oxidant was fully consumed within 15 min in experiments 21—23, in contrast to the long reaction times in the absence of both initiator and inhibitor (Table 1). We infer that bromotrichloromethane does not compete effectively with anisole for the radical (5) from Perkadox, and this may be related to the fact that the O–Br bond which would be formed by abstraction of bromine by this radical is very weak. Secondly, the formation of the

of the products are derived from the methyl radical (experiments 8 and 9); thus, at least 40% of the lead triacetate species lead, directly or *via* the adduct (10) and its *para*-isomer, to the methyl radical, so that barely more than half take part in acetoxylation. If, then, the essentially complete scavenging of the methyl radical by bromotrichloromethane were to give a non-chain-carrying radical, the maximum chain length in acetoxylation would be little greater than two so that the yields of acetoxylated products in the time available could be hardly more than four times the amount of Perkadox (each molecule of Perkadox being able to initiate two chains). In practice, yields at least ten times as great as the amount of Perkadox were obtained, from which it follows that, when the methyl radical is scavenged, a new chain-carrying radical is formed. This species is presumably $\cdot CCl_3$, and it may act by adding to anisole to give cyclohexadienyl radicals, oxidation of
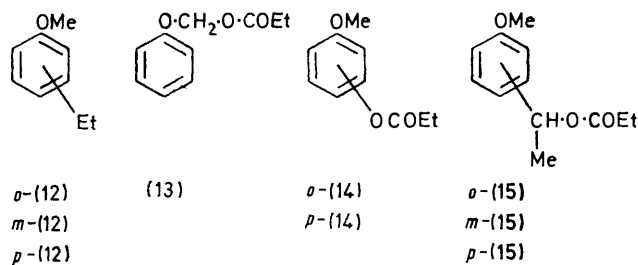
[23] H. C. Brown, *J. Chem. Soc.*, 1956, 1248.
[24] D. Benson, L. H. Sutcliffe, and J. Walkley, *J. Amer. Chem. Soc.*, 1959, **81**, 4488.

which by lead tetra-acetate gives a lead(III) species to continue the chain; in accord with this, benzotrichloride was identified as a product (45%) when benzene was oxidised under the conditions of experiment 21.

Finally, we can comment further on the course of oxidation of anisole in the absence of Perkadox (Table 1). The facts that the products are the same and that re-action is inhibited by oxygen (compare the time for con-sumption of the oxidant in experiments 2 and 3 and in 4 and 5) suggest that the same radical-chain sequences operate except for the initiation steps. However, the *ortho* : *para* ratios of the acetoxy-derivatives (3) differ from those in the Perkadox-initiated reactions, the differences being especially marked in experiments 4—6, and it is likely that an additional pathway occurs to give these products. Since electrophilic plumbylation has time to occur to a significant extent under these condi-tions and *p*-methoxyphenyl-lead triacetate is known to give some *p*-acetoxyanisole on thermolysis,[4] this con-stitutes a likely additional route; the very low *ortho* : *para* ratios for acetoxylation in experiments 4—6 are in

the propionate ligand is a somewhat stronger electron donor to lead(IV) than is acetate, so that lead tetra-propionate less readily accepts an electron than the tetra-acetate in reactions of the type (4), (7), and (10).

OMe | O·CH$_2$·O·COEt | OMe | OMe

Et | (13) | O·COEt | CH·O·COEt
| | | Me

o-(12) | (13) | *o*-(14) | *o*-(15)
m-(12) | | *p*-(14) | *m*-(15)
p-(12) | | | *p*-(15)

Oxidation of Benzene with Lead Tetra-acetate.—The products from the oxidation of benzene with lead tetra-acetate in the presence of a catalytic amount of Perkadox are set out in Table 7; in each case reaction was com-plete within 2 h, in contrast to the situation in the absence of the initiator when no products were detected

TABLE 6

Products from the oxidation of anisole with lead tetrapropionate (*ca.* 1 g) in the presence of Perkadox under nitrogen at 80°

				Products (%)						
Expt.	PhOMe (ml)	EtCO$_2$H (ml)	Time (min)	(1)	(12)	(13)	(14)	Ratio (*o*-14) : (*p*-14)	(15)
24	10	0	15 [b]	3	39 [c]	6	0·7	44 : 56	11
25	10	0	30	2	38 [c]	7	0·7	44 : 56	13
26	5	5	30 [b]	1	4	1	4	24 : 76	9
27	5	5	150		3	1	6	23 : 77	14
28	1	9	900 [b]		0·2	0·4	4	26 : 74	1
29 [a]	1	10	3600		0·2	0·3	1	12 : 88	1

[a] In air, in the absence of Perkadox, at the reflux temperature. [b] Reaction incomplete. [c] *o* : *m* : *p* = 71 : 23 : 6.

accord with the earlier suggestion that plumbylation occurs very largely at the *para*-position of anisole. Finally, the occurrence of more than one path for the acetoxylation of anisole, and the associated strong dependence of the *ortho* : *para* ratio on the reaction con-ditions, may well account, at least in part, for the widely varying ratios which have been reported previously.[2,4,25]

Oxidation of Anisole with Lead Tetrapropionate.—Data for the oxidation of anisole by lead tetrapropionate in the presence and absence of a catalytic amount of Perkadox are in Table 6. In general, they show the same features as the corresponding reactions with lead tetra-acetate, from which it follows that radical-chain sequences analogous to those in the Scheme are respon-sible for the formation of the products (12)—(15); it is also notable that the *ortho* : *para* ratio for nuclear pro-pionoxylation shows a similar dependence on solvent to that for acetoxylation. A specific feature is that con-sumption of the lead salt is slower with the propionate than with the acetate (compare experiment 24 with 8, 26 with 10, and especially 28 with 11), possibly because

after 48 h.[2] In addition, traces (0·1—0·3%) of benzyl chloride, isopropyl phenyl carbonate, xylenes, and methylbenzyl acetates were detected, but there was no trace of phenyl acetate (<0·02%). As in the oxidation

TABLE 7

Products from the oxidation of benzene with lead tetra-acetate (*ca.* 2 g) in the presence of Perkadox under nitrogen at 80°
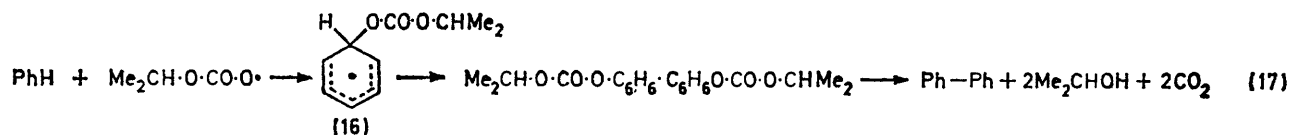
			Products (%)			
Expt.	PhH (ml)	HOAc (ml)	PhMe	PhCH$_2$-OAc	Ph·Ph	PhCH$_2$-CH$_2$Ph
30	25	0	73	0·6	1	0·3
31	10	10	15	15	0·1	3
32	1	25	1	15		0·4

of anisole, the total yield (as well as that of the methyl-ated product) decreased rapidly on the addition of acetic acid, again probably because of oxidation of the radical ·CH$_2$CO$_2$H.

The major difference compared with the oxidation of anisole is the lack of nuclear acetoxylation, and this we take to reflect the relatively high energy of the benzene radical cation; from the absence of this species, and thence of the adduct corresponding to (10) from anisole, we infer that the methyl radical is in this case entirely

[25] G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, 1955, 1404; J. Jadot and M. Neuray, *Bull. Soc. roy. Sci. Liège*, 1960, **29**, 138; Y. Yukawa, M. Sakai, and S. Suzuki, *Yuki Gosei Kagaku Kyokai Shi.*, 1966, **24**, 66 (*Chem. Abs.*, 1966, **64**, 8057).

derived from ·Pb(OAc)₃ by fragmentation. The source of biphenyl is likely to be the dimerisation of the radical (16) followed by elimination [reaction (17); cf. its formation from benzene and the hydroxyl radical²⁶]; in accord with this, biphenyl, as well as isopropyl phenyl carbonate, was obtained when Perkadox was decomposed in benzene at 80° under nitrogen. Since the yields of bibenzyl and benzyl acetate increase sharply on the introduction of acetic acid as a cosolvent, it is likely that they are formed mainly via the radical ·CH₂CO₂H, phenylacetic acid, and the benzyl radical; in a control

and ethylanisoles were analysed on a column consisting of Bentone 34 (1 part) and tricresyl phosphate (1 part) on Celite (10 parts).²⁷ All other products were analysed on the Carbowax column at 190°.

Materials.—Acetic and propionic acids were Fisons Laboratory Reagents. Anisole (Fisons Laboratory Reagent) was fractionally distilled and dried over 4A Molecular Sieves; g.l.c. analysis showed no methylanisoles as impurities. Benzene (Fisons Analytical Reagent) was distilled and dried over sodium. All other solvents were laboratory reagent grade and were distilled and dried over potassium hydroxide pellets. Lead tetra-acetate (Fisons Laboratory

$$PhH + Me_2CH\cdot O\cdot CO\cdot O\cdot \longrightarrow \underset{(16)}{\overset{H\quad O\cdot CO\cdot O\cdot CHMe_2}{\text{[ring]}}} \longrightarrow Me_2CH\cdot O\cdot CO\cdot O\cdot C_6H_6\cdot C_6H_6O\cdot CO\cdot O\cdot CHMe_2 \longrightarrow Ph-Ph + 2Me_2CHOH + 2CO_2 \quad (17)$$

experiment with phenylacetic acid in place of benzene under the conditions of experiment 32, benzyl acetate (70%) and bibenzyl (15%) were obtained. It is notable that the (mainly *o*-) methoxybenzyl radicals considered to mediate in the formation of the acetoxymethyl-derivatives (4) from anisole do not give a detectable yield of dimer, whereas the benzyl radical from benzene does so. This is likely to be because the *o*-methoxy-substituent facilitates one-electron oxidation of the substituted benzyl radical to the corresponding carbonium ion and thence the acetate (see earlier discussion).

EXPERIMENTAL

¹H N.m.r. spectra were recorded for solutions in deuterio-chloroform on a Perkin-Elmer R10 60 MHz spectrometer. Mass spectra were determined on an A.E.I. MS12 spectrometer which for some experiments was connected via a heated capillary to a gas chromatograph. M.p.s were measured on a Kofler micro-hotstage and are uncorrected. Gas chromatography was on a Pye instrument (series 104, model 24) with columns (6 ft × ¼ in) usually packed with either 20% Carbowax 20M or 10% Apiezon L coated on Celite. Products were identified by comparison of their retention times with those of authentic materials on the two columns, together with comparison of their mass spectra, obtained by combined g.l.c.–mass spectrometry, with those of authentic materials. Quantitative analysis was by gas chromatography, by addition of suitable standards to the reaction mixture. A hydrogen-inject flame ionisation detector gave a linear response, and the relationship between peak areas of product and standard was determined from synthetic mixtures. Yields (mol %) were reproducible to within ±5% of the values quoted except that, for yields of less than 2%, the reproducibility decreased. In Tables in which the same isomer distribution is reported for a number of experiments, the values were identical within the experimental error. Toluene, and the relative amounts of anisole and benzene in competitive reactions, were measured on the Carbowax column at 100° and dimethoxybiphenyls on the Apiezon L column at 230°. The methoxytoluenes

Reagent) was treated as previously described.²⁸ Lead tetrapropionate, prepared by distilling under reduced pressure a stirred mixture of lead tetra-acetate (40 g) and propionic acid (150 ml) until ca. 100 ml had been removed, filtering, and recrystallising from propionic acid–propionic anhydride, had m.p. 126—129° (lit.,²⁹ 133°); it was handled in the same manner as lead tetra-acetate. Perkadox was supplied by Novadel Ltd. Di-t-butyl peroxide (Koch–Light) was purified by column chromatography. Copper-(II) acetate (Fisons Laboratory Reagent) was the monohydrate.

o-, *m*-, and *p*-Methoxyphenyl acetate and propionate were prepared by shaking the appropriate phenol and anhydride in cold aqueous alkali.⁴ The three methoxybenzyl acetates were prepared from the alcohol and acetyl chloride. Likewise, 1-(*p*-methoxyphenyl)ethyl alcohol {obtained by the Grignard reaction between *p*-methoxybromobenzene and acetaldehyde and accompanied by a considerable amount of a higher boiling material which was probably bis[1-(*p*-methoxyphenyl)ethyl] ether ³⁰} was treated with propionyl chloride to give 1-(p-*methoxyphenyl*)*ethyl propionate*, b.p. 90° at 0·2 mmHg (Found: C, 69·3; H, 7·8. C₁₂H₁₆O₃ requires C, 69·2; H, 7·7%); τ 2·68 (2H, d, J 9 Hz, ArH), 3·13 (2H, d, J 9 Hz, other ArH), 4·11 (1H, q, J′ 6 Hz, CH), 6·22 (3H, s, OCH₃), 7·67 (2H, q, J″ 8 Hz, CH₂), 8·50 (3H, d, J′ 6 Hz, CH–CH₃), 8·87 (3H, t, J″ 8 Hz, CH₂–CH₃); m/e 208 (24%), 152 (4), 151 (4), 137 (19), 135 (78), and 134 (100). The *ortho*- and *meta*-isomers were prepared by similar reactions but were not completely purified.

Phenoxymethyl acetate was prepared as follows. A solution of lead tetra-acetate (100 g) and phenoxyacetic acid (50 g) in acetic acid (250 ml) was stirred at 80° in a nitrogen atmosphere for 20 h. The cooled solution was poured into water and the ether extract was washed with sodium hydrogen carbonate solution and dried (MgSO₄). Evaporation of the solvent and distillation of the residual liquid gave *phenoxymethyl acetate* as a colourless liquid (20 g, 53%), b.p. 71—73° at 1 mmHg (Found: C, 64·95; H, 6·1. C₉H₁₀O₃ requires C, 65·05; H, 6·1%); τ 2·55—3·05 (5H, m, ArH), 4·29 (2H, s, CH₂), 7·95 (3H, s, CH₃); m/e 166 (16%), 136 (15), 107 (15), 94 (100), 77 (14), and 43 (27), m* 111·4 (166 ⟶ 136).

²⁶ J. R. Lindsay Smith and R. O. C. Norman, *J. Chem. Soc.*, 1963, 2897.

²⁷ J. V. Mortimer and P. L. Gent, *Analyt. Chem.*, 1964, **36**, 754.

²⁸ R. O. C. Norman and C. B. Thomas, *J. Chem. Soc.* (B), 1968, 994.

²⁹ Y. Yukawa and M. Sakai, *Bull. Chem. Soc. Japan*, 1963, **36**, 761.

³⁰ M. P. Balfe, A. Evans, J. Kenyon, and K. N. Nandi, *J. Chem. Soc.*, 1946, 803.

X

The preparation of the dimethoxybiphenyls has been reported elsewhere.[1] All other samples were commercially available.

Oxidations.—The general procedure for lead(IV) oxidations was as follows. The reagents, apart from oxidant and initiator, were deoxygenated with oxygen-free nitrogen. The lead(IV) salt was added and the reagents were stirred under a nitrogen atmosphere in a bath at the appropriate temperature. After allowing sufficient time for the bath temperature to be reached, the Perkadox was introduced if required. Except where stated in the text, Perkadox was not weighed in accurately; *ca.* 50 mg was usually employed. The quantities of other materials used, as well as reaction time and temperature, are set out in the Tables. After completion of the reaction (as judged by the absence of lead dioxide when a drop of the mixture was added to water), the solution was cooled and poured into water. The ether extract was washed with sodium hydrogen carbonate solution and dried ($MgSO_4$), the ether was removed on a rotary evaporator, and the residue was submitted to the analytical procedures. (With reactions involving benzene, a small sample was set aside before solvent evaporation to allow for analysis of toluene.)

The following products were identified by g.l.c.–mass spectrometry only: phenoxymethyl propionate, m/e 180 (9%), 150 (20), 107 (27), 94 (100), 77 (28), and 57 (73), m^* 125·0 (180 ⟶ 150); two methoxyphenyl isopropyl carbonates (see text); phenyl isopropyl carbonate. The first two carbonates were present in all reactions involving Perkadox, anisole, and lead(IV), the third in those involving Perkadox, benzene, and lead(IV). Yields of phenoxymethyl propionate are based on the assumption of an identical g.l.c. response to that of phenoxymethyl acetate.

In the lead tetra-acetate oxidation of mixtures of benzene and anisole the reagents, after deoxygenation, were sealed in a tube and shaken in a bath at 80° for 30 min. After being cooled in an ice-bath, the tube was opened, standards were added, and the sample was immediately analysed for toluene, methoxytoluenes, and the anisole : benzene ratio; analysis of other products followed the usual work-up procedure. In a typical experiment, lead tetra-acetate (0·4 g) and Perkadox (*ca.* 50 mg) in a mixture (4 ml) of anisole and benzene (1·02 : 1, w/w) gave toluene (18%), methoxytoluenes (19%; $o : m : p = 75 : 18 : 7$), phenoxymethyl acetate (23%), nuclear-acetoxylated anisoles (16%; $o : p = 35 : 65$), and methoxybenzyl acetates (3%). (A 0·1% yield of phenyl acetate would have been detected.)

Phenylacetic acids were decarboxylated following the general procedure, with lead tetra-acetate (1 g), the carboxylic acid (2 g), Perkadox (*ca.* 50 mg), and acetic acid (25 ml). Reactions were run under nitrogen at 80° for 15 min with *p*-methoxyphenylacetic acid and for 2 h with phenylacetic acid; the former reaction yielded 100% *p*-methoxybenzyl acetate (g.l.c.).

Reactions with di-t-butyl peroxide were carried out by sealing the reaction mixtures [aromatic compound (5 ml) and peroxide (0·5 g)] in ampoules (under nitrogen) and standing them in a bath at the appropriate temperature; samples were analysed with no work-up. The competitive reaction involving anisole and benzene was carried out as for the corresponding reaction with lead tetra-acetate. In one reaction, copper(II) acetate (36 mg) and acetic acid (1 ml) (to dissolve the copper salt) were added. Reactions were left for 3 weeks at 80° or for 3 days at 150°; yields of methylated product were 1—4% at 80° and 15% at 150°. No attempt was made to analyse for other products.

When a solution of Perkadox (0·16 g) in benzene (25 ml) was heated at the reflux temperature under nitrogen for 2 h, biphenyl (7 mg) and phenyl isopropyl carbonate were obtained.