of compounds V and VI ($R_2 = R_3 = H$) are summarized in Table VI.

TABLE IV

RETENTION TIMES OF COMPOUNDS IV, V, AND VI (R_3 = Et)

Compd R_1	Compd R_2	Column temp, °C	He carrier gas flow rate, cc/min	Retention times, min IV	V	VI
H	H	173	80	2.0		7.6
CH_3	H	195	100	1.6		5.0
Cl	H	173	80	4.4		
OCH_3	H	173	80	5.7		
H	CH_3	173	80	4.2	6.0	8.0
CH_3	CH_3	173	80	6.2	8.5	11.2
Cl	CH_3	173	80	7.8	11.6	15.6
OCH_3	CH_3	195	100	4.7	5.8	7.8

TABLE V

ETHYL β-PHENOXYBUTYRATES (VI, $R_2 = CH_3$)

Compd R_1	Infrared cm^{-1} C=O	C—H (aromatic)	C, % Calcd	C, % Found	H, % Calcd	H, % Found
H	1742	750, 690	69.21	69.35	7.74	7.68
CH_3	1723	810	70.24	70.05	8.16	7.99
Cl	1740	825	59.41	59.39	6.19	6.15
OCH_3	1740	825	65.53	65.31	7.61	7.30

TABLE VI

IDENTIFICATION OF PRODUCTS V ($R_2 = CH_3$) AND VI ($R_2 = R_3 = H$)

Compd R_1	Mp, °C Obsd	Mp, °C Lit.	2,4-DNP, Mp, °C
V			
H	31–32	32[a]	236–237[a]
CH_3	51–52	52–54[b]	246–248
Cl	103–103.5	98–99[b]	254–256
OCH_3	63–64	65–67[b]	235–236
VI			
H	95–95.5	98[c]	
CH_3	146.5	146[d]	
Cl	135	138–139[d]	
OCH_3	110.5–111	109[e]	

[a] See ref 13. [b] See ref 7. [c] S. G. Powell, *J. Am. Chem. Soc.*, **45**, 2708 (1923). [d] D. Chakravartiand and J. Dutta, *J. Indian Chem. Soc.*, **16**, 639 (1939). [e] J. Colonge and A. Guyot, *Bull. Soc. Chim. France*, 1228 (1957).

Acknowledgment.—The authors wish to express their gratitude to Mr. T. Itakura for capable technical assistance in these experiments and to Mr. M. Kimura for help in isolating products by means of gas chromatography. The authors are also indebted to Professor S. Abe for his kind advice and to Miss T. Hara for microanalyses.

Homolytic Autoxidative Decarboxylation of Aromatic Acids[1]

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Aromatic carboxylic acids undergo homolytic decarboxylation in aromatic solvents at 125–200° in the presence of oxygen and large amounts of di-*t*-butyl peroxide or *t*-butyl hydroperoxide. Cobalt salts exert a strong catalytic effect on the reaction, and evidence that this effect results from direct oxidation of the substrate by cobalt(III) is presented. Decarboxylation of the aroyloxy radicals thus formed gives aryl radicals, whose attack upon solvent affords biaryls in yields ranging up to 50%. Yields are much lower in the absence of cobalt, under which conditions the main course of the reaction is suggested to involve abstraction of hydrogen from the carboxyl group by peroxy and/or hydroxy radicals. The preferential entrapment of aryl radicals by solvent is discussed in terms of absolute rate constants calculated from literature data; these calculations suggest that the phenyl radical does not differ significantly from other carbon radicals in its rate of reaction with oxygen.

A puzzling phenomenon encountered in the liquid phase autoxidation of alkylaromatic compounds is the extraordinary inertness of substrates containing nuclear carboxyl groups. To cite a classic example, autoxidative conversion of *p*-toluic acid to terephthalic acid occurs to only a limited extent under conditions where autoxidation of *p*-xylene to *p*-toluic acid proceeds with ease.[2,3] Although the electron-withdrawing properties of carboxyl undoubtedly retard the abstraction of benzylic hydrogen by peroxy radicals, whose electrophilicity is well established,[4] the idea that an electronic effect is the sole cause of the lowered reactivity seems to be vitiated by the observation that esters and certain other derivatives of alkylbenzoic acids autoxidize readily under conditions where the acids themselves are essentially inert.[2a,c] Alternative explanations for the behavior of the acids need to be considered, and the present investigation was undertaken to test a particularly intriguing possibility, *viz.*, that the carboxyl group is intimately involved in the autoxidation chain. Thus, if homolytic abstraction of carboxyl hydrogen were to occur, loss of carbon dioxide would follow, and reaction of the resulting aryl radicals with oxygen might eventually lead to substances (phenols, phenoxy radicals) capable of acting as inhibitors. However, at the time our work was begun there was little evidence which could be cited in support of this sequence. The very strong acid O–H bond[5] was known to be notoriously unreactive toward free radicals, and

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(1) Presented in part at the 18th Southwest Regional Meeting of the American Chemical Society, Dallas, Texas, Dec., 1962. For a preliminary account, see W. H. Starnes, Jr., *J. Am. Chem. Soc.*, **84**, 2270 (1962).

(2) For discussion and documentation of the refractivity of alkylaromatic carboxylic acids toward autoxidation, see (a) W. G. Toland and E. L. Nimer, Proceedings of the Fourth World Petroleum Congress, Section IV, Carlo Colombo Publishers, Rome, 1955, p 39; (b) D. J. Loder, U. S. Patent 2,245,528 (1941); (c) I. E. Levine, U. S. Patent 2,653,165 (1953); (d) D. S. P. Roebuck, U. S. Patent 2,644,840 (1953).

(3) Readers who are familiar with this subject will recognize that these remarks are meant to apply only to "conventional" liquid phase autoxidation systems, *i.e.*, systems containing no components other than substrate, solvent, transition metal catalysts, and small amounts of a free radical initiator. Alkyl aromatic carboxylic acids are readily oxidized by certain modified autoxidation procedures which involve use of various "promoters" (*e.g.*, cooxidants, bromine compounds), and a number of commercial processes for producing aromatic polycarboxylic acids are based on such systems. *Cf.* W. G. Toland and S. J. Lapporte, *Ind. Eng. Chem. Annual Rev. Suppl.*, 68 (1963), and other reviews in this series.

(4) (a) G. A. Russell, *J. Am. Chem. Soc.*, **78**, 1047 (1956); (b) G. A. Russell and R. C. Williamson, Jr., *ibid.*, **86**, 2357 (1964).

(5) L. Jaffe, E. J. Prosen, and M. Szwarc, *J. Chem. Phys.*, **27**, 416 (1957).

TABLE I

OXIDATION OF p-TOLUIC ACID[a]

DTBP, moles	Co^{+2},[b] (g-atom) × 10^3	Temp, °C	Reaction time, hr	Recovery of p-toluic acid, %	Yield, %[c]	
					III + IV	TPA[d]
0.075	0	127–141	6.5	65–75	1.3	10–15
0.085	1.0	135–142	6.5	65–75	Trace	15–20
0.200	0	158–177	7.0	40–50	2.1	35–40
0.200	0	171–180	9.4[e]	[f]	2.0	20–25
0.400	0	160–178	16.0	5–10	3.5	45–55
0.400	1.0	163–179	14.8	5–25	4.7	45–55
0.771	0	167–180	31.3	<5	1.2	50–60
0.800	1.0	170–181	31.8	<10	0.5	50–60

[a] p-Toluic acid, 0.200 mole; o-dichlorobenzene, 200 ml; oxygen, 31 ± 2 l./hr (uncorrected). [b] Added as the naphthenate (6% nominal cobalt content). [c] Based on initial amount of p-toluic acid. Other products detected qualitatively included methyldichlorobiphenyls, methyl dichlorobiphenylcarboxylates, methyl dichlorobiphenylcarboxylic acids, tetrachlorobiphenyls, dichlorotoluenes, dichlorobenzoic acids, dimethylbenzoic acids, and (possibly) dichlorophenols. [d] Terephthalic acid. [e] High speed stirrer replaced by glass stiffer with Teflon blade. [f] Not determined.

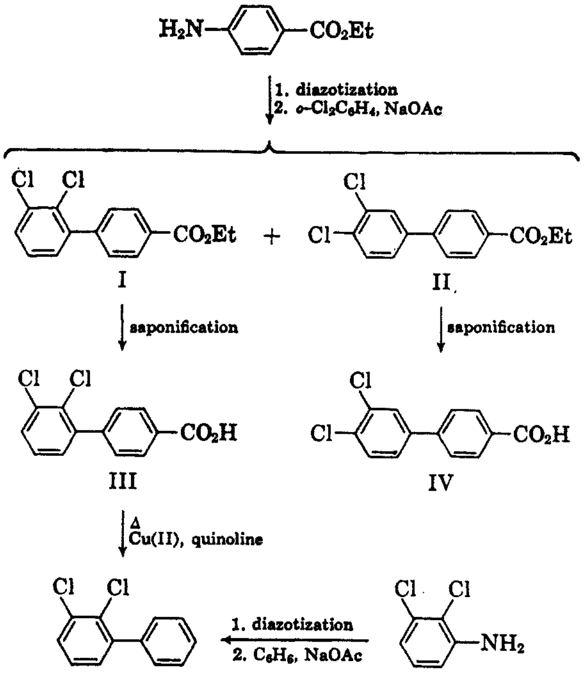
evidence for homolytic abstraction of hydrogen from the carboxyl function had been reported only for certain special systems where hydrogen bonding could be invoked.[6] There was no convincing evidence that any of the radicals involved in autoxidation chains could perform such an abstraction, or that aromatic acids could serve as substrates. Moreover, the interaction of aryl radicals with oxygen in the liquid phase had not been studied, and indeed, our results and those reported by other investigators during the course of this study (see Discussion) have revealed unexpected peculiarities in this reaction.

The initial part of the work reported here was concerned with the autoxidation of p-toluic acid in the liquid phase. Although the reaction was known to be extremely slow, it was hoped that the use of massive amounts of a free radical initiator would cause it to proceed to an appreciable extent, and that a careful examination of the products would provide clues as to the nature of possible side reactions. These possibilities were realized, and evidence for homolytic decarboxylation of the substrate was obtained. Subsequent work was concerned with the mechanism and scope of the decarboxylation reaction and its utilization as a source of aryl radicals.

Results

Table I summarizes results obtained in the oxidation of p-toluic acid in o-dichlorobenzene solution using large amounts of di-t-butyl peroxide (DTBP) for initiation. Product mixtures from these reactions were quite complex, and for this reason no attempts were made to secure quantitative material balances. The nature of certain by-products strongly suggested that all of the methyl radicals derived from the initiator were not trapped by oxygen (*cf.* Discussion), a result which is surprising in view of the extreme rapidity of this reaction in the gas phase,[7] but which may have been caused simply by low concentrations of oxygen in the liquid phase at our high reaction temperatures. Of particular significance was the formation of the isomeric dichlorobiphenylcarboxylic acids, III and IV. Although quantitative measurements of the isomer ratio were not attempted, III was shown to be the major constituent of the isolated material, and the structures of both isomers were rigorously established by Scheme I.

SCHEME I



Gomberg–Bachmann arylation of o-dichlorobenzene with diazotized ethyl p-aminobenzoate gave a mixture of esters I and II; these were separated and saponified to the corresponding acids, III and IV, which proved to be identical to the dichlorobiphenylcarboxylic acids formed in the oxidation of p-toluic acid. Decarboxylation of III with basic cupric carbonate and quinoline gave a dichlorobiphenyl which was shown to be the 2,3-isomer by its independent synthesis from 2,3-dichloroaniline and benzene under Gomberg–Bachmann conditions. Therefore, III can only be 2′,3′-dichloro-4-biphenylcarboxylic acid, and IV must be the corresponding 3′,4′-dichloro compound.

Having thus established the formation of biaryls in the oxidation of p-toluic acid, we next undertook to investigate the factors responsible for the occurrence of this important side reaction. For reasons outlined above and discussed more fully below, it was expected that benzoic acid would act as an arylating agent for o-dichlorobenzene under oxidizing conditions comparable to those to which p-toluic acid had been subjected. Table II shows that this expectation was confirmed and presents the results of a study of the reaction variables pertinent to the system. As had been the case in the

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[6] M. Szwarc and J. Smid, *J. Chem. Phys.*, **27**, 421 (1957).

[7] W. C. Sleppy and J. G. Calvert, *J. Am. Chem. Soc.*, **81**, 769 (1959).

TABLE II

PHENYLATION OF *o*-DICHLOROBENZENE WITH BENZOIC ACID[a]

Expt	Catalyst		DTBP, moles[b]	Oxygen, l./hr (uncorrected)	Temp, °C	Recovery of $PhCO_2H$, %	Dichlorobiphenyls	
	Type,	g-atom $\times 10^3$					Yield, %[c]	Ratio[d]
1	None	...	0.35	33	172–180	64[e]	3	63:37
2	Co[f]	1.0	0.41	30	172–180	38[e]	20	63:37
3[g]	Co[f]	1.0	0.43	31	172–180	36[e]	19	64:36
4[h]	Co[f]	1.0	0.93	29	171–180[i]	12[e]	22	65:35
5	Co[f]	5.0	0.38	28	172–180	20[e]	36	63:37
6	Co[j]	5.0	0.42	31	168–180	13[k]	42	65:35
7	Co[l]	5.0	0.31	26	171–180	8[k]	26	64:36
8[m]	Co[f]	5.0	0.36	28	170–180	13[e]	45	66:34
9[h]	Co[f]	5.0	0.80	27	170–180	12[e]	31[n]	60:40[n]
10	Co[f]	10.0	0.45	30	171–180	22[e]	21[n]	59:41[n]
11	None	...	0.45	38[o]	172–180	71[e]	~0.5(?)[p]	~77:23 (?)
12	Co[f]	5.0	0.41	31[o]	171–180	72[e]	~0.2(?)[p]	~75:25 (?)
13[q]	Co[f]	5.0	0.68[r]	29	76–80	103[e]	0	...
14	Mn[f]	5.1	0.37	28	172–181	77[k,s]	2	62:38
15	Cr[t]	3.6	0.41	30	164–179	55[k]	2	68:32
16	Ni[f]	5.1	0.41	29	171–179	74[k]	7	66:34
17	Fe[l]	5.1	0.43	29	164–178	47[e]	5	66:34
18	Va[u]	5.1	0.40	30	170–179	91[e]	4	70:30
19	Cu[v]	5.1	0.37	29	171–179	53[k]	5	66:34
20	Pb[w]	5.1	0.42	30	172–178	70[k]	5	65:35
21	Zn[l]	5.1	0.40	30	171–179	78[k]	3	64:36

[a] Benzoic acid, 0.200 mole; *o*-dichlorobenzene, 200 ml; reaction time, 7.0 hr. See Experimental Section for a complete list of identified products. [b] Amount actually consumed in reaction. [c] Based on initial amount of benzoic acid; limits of error are *ca.* ±0.15 × per cent yield. [d] % 2,3-:% 3,4-. Unless otherwise noted, limits of error are *ca.* ±3% for yields above 19% and ±4% for lower yields. [e] Determined by mass spectral analysis; may be high by as much as 10%. See Experimental Section. [f] Naphthenate, 6% nominal metal content. [g] A glass stirrer with Teflon blade was used. [h] Reaction time, 14.0 hr. [i] Temperature inadvertently kept at 158–168° for approximately 1 hr. [j] Octanoate, 6% nominal metal content. [k] Determined by gc procedure (*cf.* Experimental Section). [l] Stearate, assumed to be 100% pure. [m] Phthalic acid (0.0140 mole) added initially. [n] Error in analysis somewhat higher than usual, owing to contamination of 3,4-isomer peak by unidentified impurity. [o] Nitrogen. [p] Identification uncertain. [q] Reaction time, 6.8 hr. [r] *t*-Butyl hydroperoxide (91.8% pure by iodometry), total amount added. [s] Maximum value based on assumed 100% purity for fraction B (*cf.* Experimental Section). [t] Oleate, assumed to be 100% pure. [u] Naphthenate, 3.3% nominal metal content. [v] Harshaw "Uversol copper liquid," 8% nominal metal content. [w] Harshaw "Uversol lead liquid," 24% nominal metal content.

p-toluic acid work, nonquantitative entrapment of methyl radicals by oxygen was a complicating factor in all of the experiments of Table II, and attempts to account quantitatively for all of the starting acid were again frustrated by product complexities. However, it was possible to obtain a reasonably good idea of the extent of reaction by analyzing for dichlorobiphenyls, and this was conveniently done by means of gc using pure samples of 2,3- and 3,4-dichlorobiphenyl for calibration. The amounts of unreacted acid were readily determined by mass spectrometry or, more accurately, by gc analysis of the methyl esters formed from the acid fractions upon treatment with diazomethane. Unreacted DTBP was estimated by nmr analysis of the low-boiling products, and the presence of other products was inferred primarily from mass spectral evidence (see Experimental Section).

For purposes of comparison, *o*-dichlorobenzene was phenylated with benzoyl peroxide at 136–142°, and the ratio of 2,3- to 3,4-dichlorobiphenyl in the products was found to be 64 ± 3 to 36 ± 3. By using this result and assuming equal frequency factors for attack of the phenyl radical at both reactive positions of the substrate, the isomer ratio expected for homolytic phenylation of *o*-dichlorobenzene at 175° can be estimated[8] to be 63 ± 3 to 37 ±3. This value may be compared directly with the ratios obtained in most of the experiments of Table II.[9]

Further information concerning the mechanism, scope, and limitations of the new arylation procedure was provided by the experiments summarized in Table III. Here again our usual objective was to monitor the extent of reaction by analyzing for biaryls, and in no case were complete product analyses attempted. Evidence for the presence of products other than those listed is given in the Experimental Section. Biaryl yields and isomer ratios were determined by gc, using pure reference compounds in the case of the nitrobiphenyls, and assuming equal sensitivity factors for isomers in the other cases. Isomer ratios taken for comparison from the literature are corrected for temperature[8] and are believed to be based on data that are at least as reliable as any reported to date for homolytic phenylation of the compounds in question.

Discussion

Mechanism of Decarboxylation.—The results presented in Table I confirm the relative inertness of *p*-toluic acid toward liquid phase autoxidation and show that a significant part of the substrate is converted into a species capable of arylating the solvent. Indeed, the

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(8) *Cf.* G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, Inc., New York, N. Y., 1960, pp 9–11.

(9) The isomer ratio for phenylation of *o*-dichlorobenzene by the Gomberg–Bachmann procedure is reported to be 67 ± 3:33 ± 3 [H. Weingarten, *J. Org. Chem.*, **26**, 730 (1961)].

TABLE III

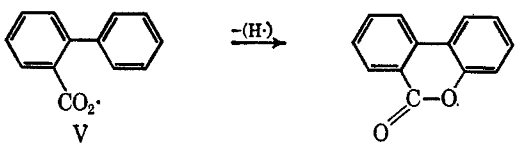
OTHER ARYLATION REACTIONS[a]

Expt	Solvent	Arylating agent	DTBP, moles[b]	Oxygen, l./hr (uncorrected)	Temp, °C	Recovery, arylating agent, %	Products[c]	Yield, %[d]	Isomer ratios[e]	
									This work[f]	Lit.[g]
22	$PhNO_2$	$PhCO_2H$	0.45	30	200–208	32[h]	Nitrobiphenyls	1	55:17:28	54:19:27
23	$PhNO_2$	$PhCO_2H$	0.42	27	171–174	62[h]	Nitrobiphenyls	10	57:15:28	55:18:27
24[i]	$PhNO_2$	$PhCO_2H$	0.42	29	172–179	51[h] (51)[j]	Nitrobiphenyls	10	58:14:28	55:18:27
25	$PhCO_2Me$	$PhCO_2H$	0.42	30	191–200[k]	13[j]	Methyl biphenylcarboxylates	50	55:22:23	53:22:25
							Biphenyl	6	...	...
26	*t*-BuPh	$PhCO_2H$	0.51	30	159–169	55[j]	*t*-Butylbiphenyls	13	21:52:27	20:52:28
							$PhCO_2Me$	12	...	...
							PhCOMe	0.6[l]	...	...
27	*t*-BuPh	$PhCO_2H$	0.39	29	160–169	59[j]	*t*-Butylbiphenyls	13	20:54:26	20:52:28
28[m]	PhCl	$PhCO_2H$	0.53	33	125–130	62[h]	Chlorobiphenyls	4	50:29:21	49:33:18
							$PhCO_2Me$	3	...	
							$(PhCO)_2O$	18	...	
29[m]	PhCl	$PhCO_2H$	0.52	28	125–130	64[h]	Chlorobiphenyls	3	56:27:17	49:33:18
30	PhCl	$PhCO_2H$	0.84[n]	29	125–132	[o]	Chlorobiphenyls	5	[o]	
31[p]	PhH	$PhCO_2H$	0.31[q]	25	74–76	95[h]	Biphenyl	0.2	...	
32[r]	PhH	$PhCO_2H$	0.33[q]	23	74–78	105[h]	Biphenyl	0.4	...	
33	*o*-$Cl_2C_6H_4$	*p*-$(CO_2H)_2C_6H_4$[s]	0.39	28	175–181	101[t]	Dichlorobiphenylcarboxylic acids	Trace	...	
34	*o*-$Cl_2C_6H_4$	*o*-$(CO_2H)_2C_6H_4$[u]	0.44	29	173–180	0	Phthalic anhydride	~90	...	
35	*o*-$Cl_2C_6H_4$	*o*-$PhC_6H_4CO_2H$[v]	0.36	25	172–179	<5	3,4-Benzcoumarin	14	...	...
							Biphenyl	5	...	...
							Dichloroterphenyls	43	...	...
36	*o*-$Cl_2C_6H_4$	$PhCO_2Me$	0.36	31	170–178	[o]	Dichlo obiphenyls	0.5	~70:30[w]	63:37[x]
37[y]	*p*-$Cl_2C_6H_4$	*p*-$ClC_6H_4CO_2H$[z]	0.33	25	138–165	87	2,4′,5-Trichlorobiphenyl	0.9	...	...

[a] Solvent, 200 ml; arylating agent, 0.200 mole; cobalt (naphthenate), 5.0×10^{-3} g-atom; reaction time, 7.0 hr. [b] Total charged, includes unreacted material. [c] See Experimental Section for other products. [d] Based on initial amount of arylating agent. [e] % *o*-:% *m*-:% *p*-substituted biphenyl. [f] Estimated accuracy, ±3%. [g] Data from the following sources are corrected to mean reaction temperature.[8] For nitrobiphenyls, *cf.* ref 21a; for methyl biphenylcarboxylates, D. H. Hey, F. C. Saunders, and G. H. Williams, *J. Chem. Soc.*, 3409 (1964); for *t*-butylbiphenyls, M. G. Gonikberg, N. I. Prokhorova, and E. F. Litvin, *Proc. Acad. Sci. USSR, Chem. Sect.*, **148**, 22 (1963); and for chlorobiphenyls, C. Shih, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 2600 (1958). [h] Maximum values, based on mass spectral analysis. *Cf.* Experimental Section. [i] Cobalt (naphthenate), 3.6×10^{-3} g-atom. [j] Determined by gc method; see Experimental Section. [k] Inadvertently allowed to reach 183–190° for ~ 15 min. [l] Based on initial amount of solvent. [m] Reaction time, 9.5 hr. [n] *t*-Butyl hydroperoxide, nominal purity 90%. [o] Not determined. [p] Cobalt (stearate), 5.0×10^{-3} g-atom; reaction time, 5.0 hr. [q] *t*-Butyl hydroperoxide, 95% pure by iodometry. [r] Reaction time, 4.0 hr. [s] 0.100 mole. [t] Crude material; see Experimental Section. [u] 0.150 mole. [v] 0.126 mole. [w] % 2,3–:% 3,4–. Analysis uncertain owing to presence of impurity with retention time close to that of 3,4 isomer. [x] See text. [y] Cobalt (naphthenate), 5.2×10^{-3} g. atom; reaction time, 6.5 hr. [z] 0.160 mole.

importance of the arylation reaction is actually greater than is indicated by the small amounts of III and IV that were isolated, since other biaryls derived from both acid and solvent also appear to have been produced in the system (Table I, footnote *c*). The major product, terephthalic acid, is almost inert under comparable reaction conditions (expt 33); thus the arylating agent must have been generated either from *p*-toluic acid itself or from an intermediate formed during oxidation of the methyl group.[10] While the latter alternative cannot be completely excluded, the occurrence of the former process is indicated by the probable formation of methyldichlorobiphenyls, whose oxidation would account for the presence of the isolated dichlorobiphenylcarboxylic acids. In any event, the experiments with benzoic acid under comparable conditions confirm the formation of an arylating agent by one or more reactions involving the carboxyl function, and conclusive identification of this agent as the free phenyl radical follows from the demonstration that the isomer ratios of the biaryls produced by phenylation of substituted aromatics with benzoic acid are identical (within experimental error) with the ratios observed in homolytic phenylations with benzoyl peroxide.

Since it seemed highly probable that phenyl radicals were formed by decarboxylation of benzoyloxy radicals, it would not have been surprising to find small amounts of products resulting from addition of benzoyloxy radicals to solvent.[11] However, mass spectroscopic examination of the neutral product fractions provided no conclusive evidence for the formation of aryl benzoates in phenylations with benzoic acid, and saponification of these fractions in the case of expt 7 and 8 gave only traces of phenols. But, on the other hand, these negative results did not necessarily rule out the presence of benzoyloxy radicals, since it was possible that their rates of addition to solvents were not fast enough to compete with decarboxylation at the relatively high temperatures employed. Therefore, we sought to confirm the presence of aroyloxy radicals by studying a system where their entrapment was more likely to occur. The *o*-phenylbenzoyloxy radical (V) was known to cyclize readily to 3,4-benzcoumarin (VI),[12] and it was anticipated that the rate of this intramolecular process might be rapid enough to compete with decarboxylation of V under our conditions. The formation of VI from 2-biphenylcarboxylic acid (expt 35) is consistent with this hypothesis and can be taken as evidence for the



V VI

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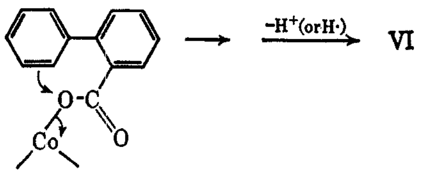
[10] One possibility is *p*-$(CO_2H)C_6H_4CO_2$·, which could decarboxylate to give an aryl radical capable of yielding II and IV directly.

[11] *Cf.* ref 8, pp 35, 65, and 116–118.

[12] (a) G. W. Kenner, M. A. Murray, and C. M. B. Tylor, *Tetrahedron*, **1**, 259 (1957); (b) D. B. Denney and P. P. Klemchuk, *J. Am. Chem. Soc.*, **80**, 3289 (1958); (c) F. D. Greene, G. R. van Norman, J. C. Cantrill, and R. D. Gilliom, *J. Org. Chem.*, **25**, 1790 (1960); (d) J. K. Kochi and R. D. Gilliom, *J. Am. Chem. Soc.*, **86**, 5251 (1964).



presence of aroyloxy radicals in the other homolytic decarboxylation reactions.[13]

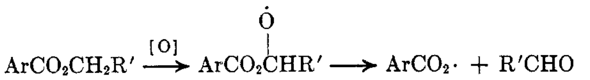
The various ways in which aroyloxy radicals might be formed from the corresponding acids may now be considered. For systems containing metal ions with more than one readily accessible valence state, direct oxidation of the acid by the metal is conceivable (eq 1).

$$ArCO_2H + M^{+n} \longrightarrow ArCO_2\cdot + H^+ + M^{+(n-1)} \qquad (1)$$

A second possibility, which *a priori* might be expected to apply to all systems, is homolytic abstraction of hydrogen from the carboxyl function (eq 2). A third

$$ArCO_2H + X\cdot \longrightarrow ArCO_2\cdot + XH \qquad (2)$$

alternative, also applicable to all cases, is that esters formed *in situ* are oxidized to alkoxy radicals capable of yielding aroyloxy radicals in a *beta*-scission process (eq 3).



$$ArCO_2CH_2R' \xrightarrow{[O]} ArCO_2\overset{\overset{\dot{O}}{|}}{C}HR' \longrightarrow ArCO_2\cdot + R'CHO \qquad (3)$$

Since the homolytic decarboxylation reaction probably does not occur at all in the absence of oxygen (*cf.* expt 11 and 12), it is clear that radicals derived from the initiator (methyl, *t*-butoxy, and radicals formed in secondary reactions) do not perform the function of X· in eq 2 under our conditions. The only other reasonable candidates for X· are peroxy and hydroxy radicals,[14] which can be formed only in the presence of oxygen.[15] It might be suggested, then, that eq 2 (X· = $RO_2\cdot$ and/or HO·) operates exclusively, and that the strong catalytic effect of cobalt results from its reaction with hydroperoxides to form peroxy radicals,[16] but,

$$RO_2H + Co(III) \longrightarrow RO_2\cdot + H^+ + Co(II)$$
$$RO_2H + Co(II) \longrightarrow RO\cdot + HO^- + Co(III)$$

if this were the case, other transition metals capable of reacting with hydroperoxides in a similar fashion would also be expected to show catalytic activity. Actually, the data of Table II reveal no significant catalytic activity for any metal other than cobalt, and from this observation it follows that the effect of cobalt must be due to some reaction other than hydroperoxide decomposition.[17a] We suggest that this reaction is, in fact, direct attack of the carboxyl group by the metal according to the over-all result depicted as eq 1. Such a process is not at all unreasonable, since in the absence of strong complexing agents cobalt(III) is one of the most powerful oxidizing agents known.[17b] In aqueous solution cobalt(III) converts alcohols to the corresponding alkoxy radicals[18] and effects the oxidative decarboxylation of aliphatic acids.[19] Moreover, in work published during the course of the present study, evidence was presented for the operation of eq 1 in the cobalt-catalyzed oxidation of pure butyric acid.[20] In view of these facts, we believe that eq 1 is responsible for most of the homolytic decarboxylation occurring in our cobalt–containing systems, and that the principal function of oxygen is simply to form peroxy radicals and hydroperoxides capable of reoxidizing the metal to its active trivalent state.

Equation 1 may actually occur in a stepwise manner, and one possibility is that it involves thermal decomposition of a cobalt(III) salt in a process similar to that which has been established for the decomposition of lead(IV) benzoate.[21] In this connection, it is of interest to compare our results with those obtained in the high temperature oxidation of aromatic acids with copper (II). The copper-catalyzed reaction also involves decarboxylation, and the final products are esters or phenols resulting from functionalization of the ring positions *ortho* to the point of attachment of the departing carboxyl.[22] Recent mechanistic studies have led to the suggestion that *o*-substituted aryl radicals [produced by thermal decomposition of the copper(II) salt of the acid] are present in this system,[23] and, in principle, mechanisms involving intermediates of this type can be considered for the cobalt-catalyzed homolytic decarboxylation. However, in this case such processes appear to be effectively excluded by the observed orientation of substituents in the biaryls produced from *p*-toluic acid and *p*-chlorobenzoic acid (expt 37).

The mechanism of homolytic decarboxylation in the absence of cobalt now needs to be considered further. Since an appreciable fraction of the methyl radicals formed from DTBP (or *t*-butyl hydroperoxide) are oxidized to methanol under the conditions of the reaction, the possibility of forming the methyl ester of the starting acid always exists, and in fact it will be noted that methyl benzoate was detected in a number of ex-

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(13) However, the possibility that VI is formed by concerted homolytic or heterolytic decomposition of a cobaltic salt cannot be completely discounted. This type of mechanism has been suggested for the analogous oxidation of 2-biphenylcarboxylic acid with chromic acid,[12a] but there is no direct evidence for its operation in oxidations with cobalt (III).

(14) However, it might be argued that the apparent failure of the *t*-butoxy radical to abstract hydrogen from the carboxyl group is a consequence of its facile β scission, and that more stable alkoxy radicals (*e.g.*, methoxy) might be capable of performing such an abstraction.

(15) A reasonable sequence is

$$t\text{-BuO}\cdot \longrightarrow (CH_3)_2CO + CH_3\cdot \xrightarrow{O_2} CH_3O_2\cdot \xrightarrow{RH} CH_3O_2H \longrightarrow HO\cdot + CH_3O\cdot$$

Cf. A. D. Kirk, *Can. J. Chem.*, **43**, 2236 (1965), and references therein. Substituted benzylperoxy radicals and benzyl hydroperoxides are probably present also (see below).

(16) *Cf.* C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp 427–428 and 574.

(17) (a) The experiments of Table I provide no evidence either for or against cobalt catalysis, since in these cases a major fraction of the biaryls derived from both acid and solvent could not be subjected to quantitative analysis (*cf.* Discussion). (b) The reduction potential of the Co(III)–Co(II) couple is 1.82 v in water at 25° [N. A. Lange, "Handbook of Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1961, p 1218].

(18) C. E. H. Bawn and A. G. White, *J. Chem. Soc.*, 343 (1951); G. Hargreaves and L. H. Sutcliffe, *Trans. Faraday Soc.*, **51**, 786 (1955); D. G. Hoare and W. A. Waters, *J. Chem. Soc.*, 2552, 2560 (1964).

(19) A. A. Clifford and W. A. Waters, *ibid.*, 2796 (1965).

(20) (a) R. van Helden, A. F. Bickel, and E. C. Kooyman, *Rec. Trav. Chim.*, **80**, 1257 (1961). (b) These workers have independently suggested that phenolic inhibitors formed by oxidation of aryl radicals are responsible for the refractivity of alkylbenzoic acids toward cobalt-catalyzed liquid phase autoxidation, the aryl radicals having been produced by homolytic decarboxylation of the substrate according to eq 1. However, no direct evidence for the operation of this process was presented [R. van Helden, A. F. Bickel, and E. C. Kooyman, *ibid.*, **80**, 1237 (1961)].

(21) (a) D. H. Hey, C. J. M. Stirling, and G. H. Williams, *J. Chem. Soc.*, 2747 (1954); (b) *ibid.*, 3963 (1955).

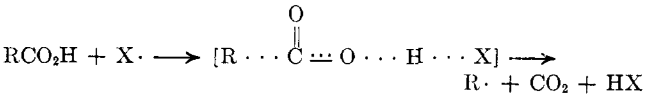
(22) W. J. Toland, *J. Am. Chem. Soc.*, **83**, 2507 (1961); W. W. Kaeding, *J. Org. Chem.*, **26**, 3144 (1961); W. Schoo, J. U. Veenland, J. A. Bigot, and F. L. J. Sixma, *Rec. Trav. Chim.*, **80**, 131 (1961).

(23) W. Schoo, J. U. Veenland, J. C. van Velzen, T. J. de Boer, and F. L. J. Sixma, *Rec. Trav. Chim.*, **82**, 959 (1963).

periments using benzoic acid. While it is certainly true that abstraction of a hydrogen atom from the methoxy group of a methyl ester is ordinarily not favored from the standpoint of energetics, the process is not impossible, and its occurrence has been demonstrated experimentally in at least one instance.[24] Furthermore, since the yields of biaryls produced in the absence of cobalt are quite small, the process responsible for production of aryl radicals under these conditions is not required to occur to a large extent. For these reasons, it was felt that oxidative attack of methyl benzoate under the forcing conditions of the homolytic decarboxylation reaction ought to be considered seriously as a possible source of aroyloxy radicals (eq 3). However, in an experiment where methyl benzoate was used as the arylating agent in place of benzoic acid, the actual yield of biaryls proved to be extremely low (expt 36). We believe this result rules out eq 3 as the major source of aroyloxy radicals in the absence of cobalt and leaves eq 2 ($X\cdot = RO_2\cdot$ and/or $HO\cdot$) as the only reasonable alternative.

Actually, when viewed in the light of several recent studies, eq 2 is now not so unreasonable as it formerly might have appeared. A plausible case has been made for the operation of this mechanism ($X\cdot = RO_2\cdot$) in the case of aliphatic acids,[25] and evidence for homolytic removal of hydrogen from the carboxyl group of aliphatic acids by hydroxy and hydroperoxy radicals is also available.[26] Numerous reports of decarboxylation during autoxidation have appeared in the literature,[27] and it is possible that eq 2 was operative in some of these cases. However, in many instances alternative explanations (*e.g.*, eq 1, thermal decarboxylation of *beta*-keto acids) cannot be ruled out.

The fact that eq 2 occurs despite the high energy of the acid O–H bond can be accounted for by formation of an intermediate hydrogen-bonded complex,[6,25] and, in fact, evidence that peroxy radicals can form such complexes with water[28] and with alcohols[29] now exists. Also, it is possible that the process is facilitated by being concerted in cases where the thermodynamic stability of the carbon radical resulting from decarboxylation is sufficiently high.[30]



$$RCO_2H + X\cdot \longrightarrow [R\cdots \overset{\overset{\displaystyle O}{\|}}{C}\mathrel{\overset{\cdots}{-}}O\cdots H\cdots X] \longrightarrow R\cdot + CO_2 + HX$$

A brief examination of the probable effects of the homolytic decarboxylation reaction upon the overall mechanism of autoxidation of alkylbenzoic acids seems worthwhile, although solution of this problem was not the objective of the present work. In this connection, we note immediately that there are already good reasons for believing that the introduction of aryl radicals into autoxidizing systems containing aromatic nuclei will lead to reductions in oxidation rate. It has been found that benzoyl peroxide is a surprisingly poor initiator for the oxidation of aralkyl hydrocarbons,[31] and this observation has been rationalized in terms of rapid termination reactions involving either the phenyl radical itself or secondary radical products derived therefrom.[31a] Moreover, it has now been shown experimentally that phenyl radicals can be converted largely to phenol in systems where the concentration of oxygen in solution is relatively high,[32] and under such conditions inhibition by phenols and phenoxy radicals would certainly occur. On the other hand, it should not be assumed that the homolytic decarboxylation reaction is necessarily the sole or even the major cause of the autoxidative refractivity of the alkylbenzoic acids. Electronic deactivation by the carboxyl group is undoubtedly important,[20b] and reduction in reactivity of peroxy radicals resulting from their conversion into hydrogen-bonded species must also be considered.[33] Further research to establish the relative importance of all these factors is clearly required.

Synthetic Aspects.—In general, there are two important restrictions on the use of the cobalt-catalyzed homolytic decarboxylation reaction as a method of synthesis for biaryls. One is the obvious requirement that both acid and solvent contain no oxidizable functional groups besides carboxyl; the other is that high boiling solvents must be used to attain practical rates. Preliminary experiments with the *o*-dichlorobenzene–benzoic acid system suggested that efficient removal of water and other low-boiling products was necessary to obtain good conversions, and for this reason most of our reactions were run near the boiling point of the solvent. As indicated previously, the concentration of oxygen in the liquid phase is so low under these conditions that reactions of methyl radicals with aromatic nuclei occur. The substituted toluenes thus formed then undergo further conversion as shown below.

$$ArH \xrightarrow[-(H\cdot)]{CH_3\cdot} ArCH_3 \xrightarrow{[O]} ArCO_2H \longrightarrow [Ar\cdot] \xrightarrow[-(H\cdot)]{ArH} Ar_2$$

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[24] J. C. Allen, J. I G. Cadogan, and D. H. Hey, *J. Chem. Soc.*, 1918 (1965).

[25] I. V. Berezin and A. M. Ragimova, *Russ. J. Phys. Chem.*, **36**, 301 (1962).

[26] W. T. Dixon, R. O. C. Norman, and A. L. Buley, *J. Chem. Soc.*, 3625 (1964); I. V. Berezin, N. N. Ugarova, A. M. Panesh, and O. R. Khrolova. *Zh. Fiz. Khim.*, **39**, 369 (1965).

[27] For examples, see E. A. Blair and J. J. Melchiore, U. S. Patent 3,013,038 (1961); N. I. Mitskevich, T. I. Soroko, and B. V. Erofeev, *Dokl. Akad. Nauk SSSR*, **115**, 103 (1957); N. I. Mitskevich, *Sb. Nauchn. Rabot, Akad. Nauk Belorussk. SSR, Inst. Fiz. Organ. Khim.*, **9**, 126 (1961) [*Chem. Abstr.*, **58**, 2347 (1963)]; N. I. Mitskevich and I. I. Uskov, *Sb. Nauchn. Rabot, Akad. Nauk Belorussk. SSR, Inst. Fiz. Organ. Khim.*, **8**, 168 (1960) [*Chem. Abstr.*, **55**, 24603 (1961)]; L. I. Shcherbak and N. I. Mitskevich, *Sb. Nauchn. Rabot, Akad. Nauk Belorussk. SSR, Inst. Fiz. Organ. Khim.*, **8**, 194 (1960) [*Chem. Abstr.*, **55**, 23986 (1961)]; N. I. Mitskevich and T. I. Soroko, *Sb. Nauchn. Rabot, Akad. Nauk Belorussk. SSR, Inst. Khim.*, **5**, 174 (1956) [*Chem. Abstr.*, **52**, 1740 (1958)]; N. I. Mitskevich, T. I. Soroko, and B. V. Erofeev, *Sb. Nauchn. Rabot, Akad. Nauk Belorussk. SSR, Inst. Khim.*, **6**, 66 (1958) [*Chem. Abstr.*, **53**, 10281 (1959)]; N. I. Mitskevich and T. I. Soroko, *Okislenie Uglevodorov z Zhidkoi Faze, Akad. Nauk SSSR, Inst. Khim. Fiz., Sb. Statei*, 238 (1959) [*Chem. Abstr.*, **55**, 606 (1961)]; B. V. Erofeev, N. I. Mitskevich, and T. I. Soroko, *Dokl. Akad. Nauk Belorussk. SSR*, **2**, 20 (1958) [*Chem. Abstr.*, **53**, 9276 (1959)]; B. V. Erofeev and N. I. Mitskevich, *ibid.*, **1**, 96 (1957) [*Chem. Abstr.*, **53**, 5838 (1959)]; N. I. Mitskevich, I. I. Uskov, and V. A. Lashitskii, *Dokl. Akad. Nauk Belorussk. SSR*, **6**, 706 (1962) [*Chem. Abstr.*, **59**, 403 (1963)]; B. V. Erofeev *et al.*, *Dokl. Akad. Nauk Belorussk. SSR*, **4**, 160 (1960) [*Chem. Abstr.*, **58**, 4399 (1963)]; B. V. Erofeev, N. I. Mitskevich, and T. I. Soroko, *Izv. Akad. Nauk Belorussk. SSR* (2), 131 (1955) [*Chem. Abstr.*, **50**, 7090 (1956)]; I. V. Berezin and A. M. Ragimova, *Dokl. Akad. Nauk Azerb. SSR*, **15**, 219 (1959) [*Chem. Abstr.*, **53**, 21630 (1959)].

[28] E. T. Denisov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 45 (1960).

[29] F. F. Rust and E. Youngman, *J. Org. Chem.*, **27**, 3778 (1962).

[30] Compare the concerted decompositions reported for peresters by P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.*, **80**, 1398 (1958), and for diacyl peroxides by M. Szwarc, "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, pp 153–174.

[31] (a) G. S. Hammond and U. S. Nandi, *J. Am. Chem. Soc.*, **83**, 1213 (1961); (b) G. A. Russell, *ibid.*, **78**, 1044 (1956).

[32] K. Tokumaru, K. Horie, and O. Simamura, *Tetrahedron*, **21**, 867 (1965).

[33] D. G. Hendry and G. A. Russell, *J. Am. Chem. Soc.*, **86**, 2368 (1965).

However, despite these limitations and complexities, arylation by the homolytic decarboxylation technique does have the advantage of not requiring conversion of the acid into peroxide or perester, and in favorable circumstances the reaction appears to be somewhat more practical than electrolysis[34] or persulfate oxidation[35] as a way of forming aryl radicals directly from acids. Improved synthetic methods might be developed using alternate ways of generating cobalt(III), and further work along these lines is indicated.

The low yields of nitrobiphenyls obtained from nitrobenzene (expt 22–24) suggest that the nitro group exerts a specific inhibitory effect on the reaction. This inhibition does not occur after formation of the aroyloxy radical, since nitrobenzene actually increases the yields of biaryls obtained in phenylations with benzoyl peroxide.[36] A possible explanation is that the activity of the catalyst is reduced by complexation with nitrobenzene;[37] however, radical reactions involving the nitro group might also be important, and the formation of unusually large amounts of tar in this particular case may be significant.

The principal reason for the low conversions obtained in experiments with terephthalic acid (expt 33) and *p*-chlorobenzoic acid (expt 37) is probably the low solubilities of these substances in the reaction media. Failure of the reaction with phthalic acid (expt 34) is apparently caused by rapid formation of phthalic anhydride rather than by conversion of catalyst into an inactive form, since phthalic acid does not reduce the yield of biaryls obtained in the *o*-dichlorobenzene–benzoic acid reaction (expt 8).

The formation of biphenyl in expt 25 and 35 requires comment. In the case of expt 35, biphenyl probably results from hydrogen abstraction by the *o*-biphenylyl radical, a process whose occurrence is of some interest in view of the very low yields of benzene obtained from the phenyl radical in aromatic solvents.[38] Abstraction in the present case is probably favored by the high temperature, the presence of materials with labile hydrogen (*e.g.*, dichlorotoluenes), and possibly by reduction in rate of the competing addition reaction, owing to steric hindrance by the bulky phenyl group.[39] Biphenylyl radicals (from homolytic decarboxylation of biphenylcarboxylic acids produced by hydrolysis) are also the probable progenitors of the biphenyl formed in expt 25, since coupling of phenyl radicals would not be expected to occur under these conditions.[38a] The absence of 3,4-benzcoumarin from the products of expt 25 does not necessarily imply the absence of the *o*-phenylbenzoyloxy and *o*-biphenylyl radicals, since it is possible that the former species undergoes decarboxylation exclusively at the high reaction temperature.

The fair yield of dichloroterphenyls obtained in expt 35 is of some practical interest in view of the low yields of aromatic substitution products which have been reported for reactions in which the *o*-biphenylyl radical was generated by other means.[39]

Reactivity of the Phenyl Radical toward Oxygen.—A particularly interesting aspect of the homolytic decarboxylation reaction is the failure of the aryl radicals formed to undergo reaction with oxygen. While this failure can be partly accounted for by the low concentrations of oxygen present in the liquid phase under the usual experimental conditions, the lack of evidence for formation of phenols or products derived therefrom under conditions where a major fraction of the methyl radicals derived from the initiator are trapped by oxygen shows that aryl radicals either react at an unusually slow rate with oxygen, or at unusually fast rates in reactions which are competitive with their oxidation. This unique behavior has been encountered in other studies,[31,32,40] and the principal cause of its occurrence has been suggested to be an abnormally low absolute rate for the reaction between phenyl radicals and oxygen.[40d] The low rate is said to result from an unfavorable polar effect in the transition state,[32,40d] with an attendant increase in activation energy.[32] However, studies of the liquid phase radiolysis of aromatic hydrocarbons have suggested that aryl radicals are extremely reactive particles,[41] and recent quantitative kinetic measurements in the gas phase have revealed unusually high rates and low activation energies for hydrogen abstraction reactions involving the phenyl radical.[42] Moreover, the absolute rate constant for addition of the phenyl radical to chlorobenzene in the liquid phase has been estimated from pulse radiolysis studies to have the remarkably high value of 4.8×10^4 l. mole^{-1} sec^{-1} at 25°.[43,44] By applying the Arrhenius equation to published data on homolytic phenylation,[45] one calculates that benzene is 0.649 times as reactive as chlorobenzene toward the phenyl radical at 25°; and from the data of Tokumaru, *et al.*,[32] the phenyl radical is calculated to be either 540 or 970 times more reactive toward oxygen than toward benzene at this temperature, depending upon whether one chooses the yield of phenol or the difference between the yields of carbon dioxide and biphenyl as the meas-

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[34] P. J. Bunyan and D. H. Hey, *J. Chem. Soc.*, 3787 (1960).

[35] J. Russell and R. H. Thomson, *ibid.*, 3379 (1962).

[36] D. H. Hey, M. J. Perkins, and G. H. Williams, *Chem. Ind.* (London), 83 (1963); C. D. Hall, *ibid.*, 384 (1965).

[37] *Cf.* N. Uri, *Nature*, **177**, 1177 (1956).

[38] See (a) ref 8, pp 34–35 and (b) R. F. Bridger and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3754 (1963).

[39] Compare the relatively low yields of *o*-terphenyl obtained from the *o*-biphenylyl radical in benzene, as reported recently by N. Kharasch and R. K. Sharma, Abstracts, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 12–17, 1965, p 10S. Also, *cf.* K. C. Chan and R. L. Huang, *J. Chem. Soc.*, 2649 (1965). *o-t*-Butylphenyl radicals (from *o-t*-butyl-N-nitrosoacetanilide) have been reported not to add to benzene at all, but to abstract hydrogen instead [J. I. G. Cadogan, D. H. Hey, and G. H. Williams, *ibid.*, 3352 (1954)].

[40] (a) J. K. Kochi, *J. Am. Chem. Soc.*, **78**, 4815 (1956); *ibid.*, **79**, 2942 (1957); (b) M. Eberhardt and E. L. Eliel, *J. Org. Chem.*, **27**, 2289 (1962); (c) R. T. Morrison, J. Cazes, N. Samkoff, and C. A. Howe, *J. Am. Chem. Soc.*, **84**, 4152 (1962); (d) G. A. Russell and R. F. Bridger, *ibid.*, **85**, 3765 (1963).

[41] T. Gäumann, *Helv. Chim. Acta*, **44**, 1337 (1961); **46**, 2873 (1963); J. Hoigné and T. Gäumann, *ibid.*, **46**, 365 (1963).

[42] (a) W. Fielding and H. O. Pritchard, *J. Phys. Chem.*, **66**, 821 (1962); (b) F. J. Duncan and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 4672 (1962).

[43] A. MacLachlan and R. L. McCarthy, *J. Am. Chem. Soc.*, **84**, 2519 (1962).

[44] By way of comparison, if chain transfer constants can be taken as a measure of rates of addition, the absolute rate constants for addition of polyethyl and polystyryl radicals to benzene are, respectively, 1.0 l. mole^{-1} sec^{-1} (at 83°) [Z. Laita and Z. Macháček, *J. Polymer Sci.*, **38**, 459 (1959)] and 5×10^{-6} l. mole^{-1} sec^{-1} (at 25°) [calculated from data given in ref 16, pp 95 and 152]. By applying the Arrhenius equation to data given by M. Levy and M. Szwarc, *J. Am. Chem. Soc.*, **77**, 1949 (1955), the "methyl affinity" of benzene is calculated to be 0.14 at 25°. Multiplication of this value by the absolute rate constant for the reaction of methyl radicals with isooctane [R. H. Schuler and R. R. Kuntz, *J. Phys. Chem.*, **67**, 1004 (1963)] gives 2.8 l. mole^{-1} sec^{-1} as the absolute rate constant for addition of the methyl radical to benzene at 25°.

[45] The data used were the relative reactivities at 20° reported by R. Itô, T. Migita, N. Morikawa, and O. Simamura, *Tetrahedron*, **21**, 955 (1965), and the revised values for 80° given by D. H. Hey, S. Orman, and G. H. Williams, *J. Chem. Soc.*, 565 (1961).

ure of reactivity toward oxygen. Therefore, the absolute rate constant for the reaction of the phenyl radical with oxygen at 25° can be estimated as $(4.8 \times 10^4)\ (0.649)\ (755 \pm 215) = (2.4 \pm 0.7) \times 10^7$ l. mole^{-1} sec^{-1}. Comparison of this value with the rate constants listed in Table IV[46] leads to the conclusion that phenyl does not differ significantly from other carbon radicals in its reactivity toward oxygen.[47]

TABLE IV

ABSOLUTE RATE CONSTANTS FOR REACTION OF CARBON RADICALS WITH MOLECULAR OXYGEN IN THE LIQUID PHASE

Radical	k, l. mole^{-1} sec^{-1} $\times 10^{-7}$	Temp, °C	Ref
Tetralyl	6.76	25	*a*
Polystyryl	4	50	*b*
1-Phenylethyl	38	60	*c*
Allylic (from ethyl linoleate)	0.9	25	*d*
Allylic (from digeranyl)	0.1	25	*d*
Alkyl (from cyclohexane radiolysis)	17	25	*e*
Alkyl (from heptane radiolysis)	3.2	25	*f*

[a] C. H. Bamford and M. J. S. Dewar, *Proc. Roy. Soc.* (London), **A198**, 252 (1949). [b] A. A. Miller and F. A. Mayo, *J. Am. Chem. Soc.*, **78**, 1017 (1956). [c] Calculated from reported values of $k/(k_1)^{1/2}$ [R. F. Vasil'ev, *Proc. Acad. Sci. USSR, Phys. Chem. Sect.*, **144**, 345 (1962)] and k_1 [A. A. Vichutinskii, *Nature*, **206**, 292 (1965)], where k_1 is the rate constant for interaction of two 1-phenylethyl radicals. [d] L. Bateman, G. Gee, A. L. Morris, and W. F. Watson, *Discussions Faraday Soc.*, **10**, 250 (1951). [e] Calculated from data given by R. W. Fessenden and R. H. Schuler, *J. Am. Chem. Soc.*, **79**, 273 (1957), taking the reduction in G(RI) they observed in air-saturated cyclohexane to be a measure of carbon radical reactivity toward oxygen, and using 3×10^8 l. mole^{-1} sec^{-1} as the rate constant for reaction of carbon radicals with iodine (*cf.* ref 44). The oxygen concentration in solution was calculated using Henry's law, the appropriate Bunsen coefficient [Landolt-Börnstein, "Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik, und Technik," Band II, Teil 2b, Springer-Verlag, Berlin, Germany, 1962, p 1-74], and the vapor pressure of cyclohexane [T. E. Jordan, "Vapor Pressure of Organic Compounds," Interscience Publishers, Inc., New York, N. Y., 1954]; the total pressure was taken to be 1.0 atm. [f] Calculated by the method outlined in footnote *e* using radiolysis data reported by P. F. Forsyth, E. N. Weber, and R. H. Schuler, *J. Chem. Phys.*, **22**, 66 (1954). Sources of other data required are given in footnote *e*.

This result can be deduced in other ways. According to Russell and Bridger,[40d] oxygen is 1200 times more reactive than carbon tetrachloride toward the phenyl radical at 60°. At this temperature carbon tetrachloride is 3.70 times as reactive toward phenyl as is the methyl group of toluene,[38b] and the rate of abstraction from the methyl group is about 1.1 times the rate of addition to the ring.[48] Calculations with the Arrhenius equation[45] show that the rate of addition of phenyl to toluene is 1.13 times the rate of addition to chlorobenzene at 60°. Therefore, the absolute rate constant for oxidation of the phenyl radical at 60° is estimated to be at least $(1200)\ (3.70)\ (1.1)\ (1.13)\ (4.8 \times 10^4) = 26 \times 10^7$ l. mole^{-1} sec.$^{-1}$ The actual value is expected to be somewhat higher, of course, since the addition of phenyl to chlorobenzene undoubtedly requires some energy of activation.[49]

Similar calculations can be made using kinetic data obtained in the vapor phase if one is willing to make the not entirely unreasonable assumption that these results can be extrapolated to reactions in solution. From data reported by Duncan and Trotman-Dickenson[42b] the rate constant for reaction of the phenyl radical with isobutane at 60° is reckoned to be 2.5×10^4 l. mole^{-1} sec.$^{-1}$ The total reactivity of isobutane relative to carbon tetrachloride can be calculated using the reactivities per hydrogen atom given by Bridger and Russell,[38b] and combination of the result with their data for cyclohexane gives 2.08 for the reactivity of cyclohexane relative to isobutane at 60°. Since the phenyl radical is known to react 1200 times faster with oxygen than with cyclohexane at this temperature,[40d] we can now obtain a second estimate of the absolute rate constant for phenyl oxidation at 60°. The result is $(2.5 \times 10^4)\ (2.08)\ (1200) = 6.2 \times 10^7$ l. mole^{-1} sec^{-1}, a value whose agreement with our earlier figure is reasonably good considering the approximations involved. An analogous but much more approximate computation based on the "apparent" rate constants reported by Fielding and Pritchard for abstraction of hydrogen by phenyl from methane[42a] leads to the value 8.5×10^7 l. mole^{-1} sec^{-1} (at 60°); whereas, use of methane data of Duncan and Trotman-Dickenson[42b] in a similar manner gives 1.4×10^6 l mole^{-1} sec^{-1} (also at 60°). Both of these values are expected to be low, since the relative reactivity of methane used in their calculation was probably too high.[50]

While the preceding calculations are not strictly reliable in a quantitative sense, the order-of-magnitude agreement of the results derived from several sources of primary data is striking and can be taken as an indication of the general validity of the values obtained. More accurate measurements of absolute rate constants for aryl radical reactions are clearly needed, but until these are made we believe the idea that the phenyl radical reacts with oxygen at an unusually slow rate should be regarded with skepticism.

Experimental Section[51]

Materials.—*o*-Dichlorobenzene usually contained about 0.1% water (Karl Fischer titration) as received but had no other impurities detectable by gc; in duplicate homolytic decarboxylation experiments this material gave results that did not differ significantly from those obtained using the redistilled solvent (bp 181.0–181.5°). Nitrobenzene was extracted with 10% sodium hydroxide solution until a water-white aqueous layer was obtained, then washed with water, dried over Drierite, and

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(46) The differences between the tabulated rate constants are probably not very meaningful, since rather large experimental uncertainties were involved in determining several of these values.

(47) This is not to say that *all* carbon radicals are equally reactive toward oxygen. Radicals which are very highly stabilized by resonance [*e.g.*, polyarylmethyl radicals; *cf.* D. G. Hendry and G. A. Russell, *J. Am. Chem. Soc.*, **86**, 2371 (1964)] are oxidized at relatively slow rates.

(48) M. V. Vazileviskii, *Russ. J. Phys. Chem.*, **38**, 122 (1964).

(49) *Cf.* G. A. Russell and R. F. Bridger, *Tetrahedron Letters*, 737 (1963).

(50) The reactivity of methane relative to that of carbon tetrachloride was calculated to be 0.0392, using the relative reactivity parameter for primary hydrogen given by Bridger and Russell.[38b] However, the bonds of methane are probably much stronger than the primary C–H bonds of the hydrocarbons they used to derive their parameter, and a comparison of bond energy values (ref 16, p 50) with their set of relative reactivity parameters for various hydrogen types suggests that the true relative reactivity of methane may be only about one-tenth our calculated value. Use of the correct relative reactivity of methane would probably increase our rate constants calculated therefrom by approximately a factor of ten.

(51) Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Boiling points and melting points are uncorrected; the latter were determined on a Fisher-Johns apparatus. The author is indebted to Mrs. M. W. Eastwood and Messrs. T. J. Denson, T. Hines, L. P. Hodges, H. W. Kinsey, G. R. Taylor, and J. L. Taylor for various analytical measurements. N. F. Chamberlain, J. G. Lillard, and Dr. F. C. Stehling assisted in the development of analytical procedures.

distilled, bp 135° at 93 mm. *t*-Butylbenzene was Phillips "Pure" grade material having a minimum nominal purity of 99%. Methyl benzoate and chlorobenzene were redistilled, bp 77.5° (11 mm) and 130.0°, respectively. Di-*t*-butyl peroxide (Wallace and Tiernan) was used as received. *t*-Butyl hydroperoxide (Wallace and Tiernan) was shown by iodometry to be 91.8% pure as received; material of 95% purity was obtained by distillation under reduced pressure. Nitrobiphenyls (Aldrich) were recrystallized from ethanol (3 and 4 isomers) or ethanol-water (2 isomer) until their melting points agreed with literature values; the purified samples were shown to be homogeneous by gc. All other chemicals used were of the highest purity available commercially.

Instrumental Analysis.—Programmed-temperature gc analyses were carried out by Mr. V. H. Rushing on an F and M instrument, Model 500. Column temperature was increased at the rate of 8°/min, and the usual temperature range was from 100 to 300° (175–340° for dichlorobiphenyl analyses; 175–260° for nitrobiphenyls). Columns used were A, 15% SE-30 on 40–60 mesh Chromosorb P (10 ft × 0.25 in.); B, 15% Carbowax 20,000 on 40–60 mesh Chromosorb P (5 ft × 0.25 in.); C, 20% OS-138 on 40–60 mesh Neutraport S (4 ft × 0.25 in.); D, 15% XE-60 on 40–60 mesh Chromosorb P (10 ft × 0.25 in.); E, 15% SE-30 on 40–60 mesh Neutraport S(10 ft × 0.25 in.). The nmr spectra were recorded with a Varian A-60 instrument using dilute solutions in $CDCl_3$, CCl_4, or CS_2; tetramethylsilane was added for internal standardization. Infrared measurements were made with a Perkin-Elmer spectrophotometer, Model 21, or with a Beckman IR-5 instrument. Mass spectra were obtained with a Consolidated Electrodynamics spectrometer, Type 21-103C.

Oxidation of *p*-Toluic Acid.—These reactions were carried out in an indented (Morton) flask (nominal volume 1 l) equipped with a gas inlet tube (Pyrex) extending to the bottom, a stirrer, a y-tube carrying two pressure-equalizing dropping funnels, an external thermometer well, and an efficient condensing assembly which allowed condensate to be either withdrawn or returned to the reaction vessel, as desired. Unless otherwise noted (Table I), a high speed stainless steel stirrer was used ("Stir-O-Vac" apparatus manufactured by Labline, Inc., catalog No. 1280). Gas was delivered from cylinders of oxygen and nitrogen connected to a manifold arrangement which permitted rapid switching from one cylinder to the other. Before entering the vessel, the gas passed through a flow meter, a wet test meter, a Drierite tower, and a t-tube safety valve filled with mercury. Effluent gases were led through a Dry-Ice trap and a second wet test meter, whose principal function was as a detector for leaks.

In a typical experiment, the desired amounts of *p*-toluic acid, solvent, and catalyst were placed in the reaction vessel, and the temperature was raised to the desired level while the mixture was stirred and bubbled with nitrogen (approximately 30 l./hr). Nitrogen was then replaced by oxygen, and a 5-ml portion of DTBP was added. The reaction was allowed to proceed for one hour, and at the end of this time enough condensate was withdrawn to bring the temperature back to the original level. The withdrawn material was then replaced by an equal volume of solvent; a second 5-ml portion of DTBP was introduced; and the procedure was repeated until all of the peroxide had been added and decomposed. In cases where mixtures were allowed to stand overnight prior to completion of the reaction, the interim shutdown and startup operations were carried out in the presence of oxygen.

Terephthalic acid was recovered by filtration of the hot mixture and washed in succession with dilute hydrochloric acid, water, and acetone. The material thus obtained was shown by infrared, mass spectral, and neutralization equivalent determinations to be 90–95% pure, with *p*-toluic acid and dichlorobiphenylcarboxylic acids as the principal contaminants. Shaking of the filtrate with 100 ml of 5% aqueous sodium hydroxide caused precipitation of the sodium salts of III and IV; these were recovered by filtering and converted to the free acids by stirring with warm concentrated hydrochloric acid. A typical mixture had mp 258–261°, melted at 259–265° upon admixture with an authentic sample of III (mp 259–261°), and gave an infrared spectrum (Nujol) which differed from that of III in only minor respects. However, by careful fractional crystallization of the mixture it was possible to isolate a small amount of IV, which was identified by its melting point (275–278°) and by infrared comparisons. The two layers of the filtrate obtained during recovery of the sodium salts were separated, and the organic phase was extracted with three additional 100-ml portions of the caustic solution. All aqueous layers were then combined and extracted with 50-ml quantities of ether until clear. The extracts were added to the organic phase, and the whole (fraction A) was washed 2–3 times with saturated sodium chloride solution, dried over Drierite, concentrated by boiling, and analyzed qualitatively by mass spectrometry. Identification of chlorine-containing substances was facilitated by the presence of peaks corresponding to the different isotopic compositions, the observed relative intensities of these peaks agreeing with values calculated from natural isotopic abundance data. The aqueous solution was acidified (pH 2) with concentrated hydrochloric acid to precipitate organic acids (fraction B); these were removed by filtering, and a second acid fraction (fraction C) was then obtained by continuous extraction of the filtrate with ether for 2–3 days. Analysis by mass spectrometry showed that the principal constituents of the acid fractions were *p*-toluic acid and dichlorobenzoic acids; semiquantitative determination of the former component was possible using the mass spectral technique.

Homolytic Decarboxylations. A. Apparatus and Procedure.—Many procedural variations were tried in an effort to maximize the yield of biaryls from the cobalt-catalyzed *o*-dichlorobenzene-benzoic acid reaction. Unless otherwise noted, all of the homolytic decarboxylation experiments reported in this paper were performed according to the procedure which gave best results in that system. In general, the preferred experimental setup was identical with that used for the *p*-toluic acid oxidations, except that changes were made in the stirrer, the condensing assembly, and the method of introducing peroxide. High-speed stirring insured efficient dispersion of oxygen and gave improved results, but the stainless steel stirrer employed previously for this purpose (see above) was found to be unsatisfactory for more lengthy operations. Extensive corrosion occurred when this stirrer was used repeatedly in cobalt-containing systems, and considerable amounts of iron oxides (identified by X-ray analysis) were formed as a result. Furthermore, a direct inverse correlation was observed between extent of conversion of the starting acid (or the yield of biaryls) and the weight lost by the stirrer during the reaction. Fortunately, it was possible to solve the corrosion problem quite satisfactorily by coating the stirrer shaft with Teflon and using a high-speed impeller constructed entirely of this material.[52] Peroxide was added through a thick-walled glass capillary (length 1 in.), fitted (standard taper joint) into a straight glass extension tube (length 12 in.), and adjusted so that liquid dropping from its tip fell directly into the reaction mixture without touching the walls of the apparatus. (Use of the extension tube was mandatory; its purpose was to keep the heat-sensitive material in the capillary away from hot vapors.) The capillary was connected with nylon tubing to a small pump capable of delivering the desired peroxide at a uniform rate. Satisfactory results were obtained with either the Beckman "Solution Metering Pump," Model 746, or the "Micro-bellows Pump" (bellows i.d. 0.5 in.) manufactured by Research Appliance Co. The gas exit arm of the flask contained an oversize Barrett trap, modified so as to allow condensate to be either removed or returned to the reaction vessel from the bottom of the collecting arm (18 in. × 9/8 in.) through a short connecting tube fitted with a stopcock. The trap carried an efficient coil-type condenser (cooled to 10° by circulated refrigerant) in series with a cold finger containing Dry Ice. Heat was supplied by a thermostatically controlled mantle.

Preliminary experiments showed that large quantities of condensate containing much water and unreacted peroxide had to be withdrawn from the Barrett trap during the course of reactions in order to maintain the desired range of temperature. However, when the collecting arm of the trap was filled with Drierite, a considerable reduction in volume of withdrawn condensate was achieved, and utilization of peroxide was greatly improved. Since several milliliters of liquid was required to wet the Drierite, it was always soaked with solvent prior to starting an experiment in order to keep the volume of the reaction mixture from undergoing an inordinate decrease during the first few minutes of operation. In general, experiments were conducted in the same way as the *p*-toluic acid oxidations, except that peroxide was pumped in continuously throughout the entire reaction periods. Periodic addition of fresh solvent was unnecessary.

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[52] We are indebted to Mr. R. V. Comeaux for aid in the design and construction of this stirrer.

Crude reaction mixtures were filtered (fritted glass) to remove small amounts of tar, then washed with 200 ml of 5% hydrochloric acid in two portions. The organic moiety was separated and processed in the manner described for the *p*-toluic acid experiments to give fractions A–C. In many experiments a white solid was deposited in the condensing assembly; this material was shown to be paraformaldehyde by melting point and spectral comparisons. Details of individual experiments are given in the following synopses.

B. Benzoic Acid and *o*-Dichlorobenzene.—In all experiments using DTBP, condensate removed during the reaction period was combined with the contents of the cold trap (never more than 4–5 g) to give a solution which was analyzed quantitatively by nmr spectroscopy using pure reference compounds to confirm peak assignments.[53] In a typical run (expt 8) this solution was found to contain 77.3% *o*-dichlorobenzene, 7.9% acetone, 4.3% DTBP, 2.8% *t*-butyl alcohol, 1.8% acetic acid, 1.1% water, 1.4% formaldehyde polymers (?), 0.7% methyl benzoate, 0.7% methyl acetate, 0.6% benzyl alcohol (?), 0.5% formic acid, 0.5% dimethoxymethane, 0.3% methyl alcohol, and 0.1% methyl formate. Independent determinations of water content (Karl Fischer titration) and total acid content (potentiometric titration) gave results which were in satisfactory agreement with those obtained by the nmr technique. In most of the experiments recovered DTBP amounted to 5–15% of the total quantity charged.

Fraction A was concentrated by distillation and analyzed for 2,3- and 3,4-dichlorobiphenyl by programmed temperature gc (column A). Peak areas obtained from known sample volumes were compared with the areas produced by known volumes of standard solutions of the two isomers in *o*-dichlorobenzene. Qualitative mass spectral analyses suggested that fraction A also contained tetrachlorobiphenyls, dichloroterphenyls, trichloroterphenyls, tetrachloroterphenyls, dichlorotoluenes, dichloroxylenes, methyl dichlorobenzoates, and methyl benzoate. In a few early experiments the mixture of dichlorobiphenyls was isolated by distillation (bp 125–135° at 3 mm), and the yields of material recovered in this way were found to be closely comparable to those indicated by gc. The presence of methyl benzoate and dichlorotoluenes in lower-boiling distillation fractions was confirmed by infrared analysis. Fraction A from expt 7 was saponified by refluxing overnight with excess ethanolic potassium hydroxide. After removal of ethanol under reduced pressure, acid salts were recovered by extraction with water, and the two acid fractions which precipitated upon adjustment of the pH of the solution to 7 and then to 2 were recovered separately and examined by mass spectrometry. The material recovered at the higher pH (0.2 g) consisted largely of biphenylcarboxylic acids, together with small amounts of benzoic acid and dichlorobiphenylcarboxylic acids, and traces of heavier materials. The other acid fraction (1.8 g) proved to be mostly benzoic acid but also contained small amounts of biphenylcarboxylic acids, a nonchlorinated material whose molecular weight was 196 (3,4-benzcoumarin ?), and substances of higher molecular weight. Fraction A from expt 8 was saponified in a similar manner, and the aqueous solution was extracted exhaustively with ether after adjustment to pH 8. Evaporation of the dried extracts gave 0.1 g of brownish oil which was shown by mass spectrometry to contain traces of dichlorophenols, dichlorohydroxybiphenyls, and (possibly) monochlorohydroxybiphenyls, as well as a number of unidentified materials. Further acidification (pH 2), followed by thorough ether extraction, gave 4.13 g of product which contained benzoic acid and dichlorobenzoic acids, but no phenolic materials. In view of the extremely low yields of phenols obtained in the saponification experiments, it is likely that the acids produced therein were derived from methyl esters or anhydrides.

Qualitative analysis of fractions B and C by mass spectrometry suggested the presence of benzoic acid, dichlorobenzoic acids, dichlorobiphenylcarboxylic acids, biphenylcarboxylic acids, toluic acids, and (in a few cases) traces of monochlorobenzoic acids, dichlorophenols, and phenol. Quantitative analysis of these fractions for benzoic acid content was accomplished in two ways. In the preferred method, a portion of each fraction was treated with excess diazomethane in ether, and the resulting mixture of methyl esters was analyzed by means of gc (column C). Mass spectral analysis of trapped chromatographic peaks confirmed the presence of methyl benzoate, methyl toluates, methyl dichlorobenzoates, methyl biphenylcarboxylates, and methyl dichlorobiphenylcarboxylates; traces of dimethyl phthalates, dimethyl biphenyldicarboxylates, methyl dichlorotoluates, and methyl trichlorobenzoates were also detected. Methyl benzoate was determined from the peak areas produced by known sample volumes, a method whose maximum limits of error were shown to be ±5% by checks with solutions of known concentration. Neutralization equivalents of fractions B and C were determined by potentiometric titration, and the benzoic acid content of each fraction was then calculated from the following equation.

$$\%\ \mathrm{PhCO_2H} = (\%\ \mathrm{PhCO_2Me})(\text{mol wt of }\mathrm{PhCO_2H})(\text{neut equiv} + 14)\ /\ (\text{neut equiv})(\text{mol wt of }\mathrm{PhCO_2Me})$$

The second method used to analyze for benzoic acid was less accurate but quicker: here the procedure was simply to compare the intensities of the low voltage mass spectral peak at *m/e* 122 produced by weighed amounts of B (or C) and pure benzoic acid. Comparisons showed that benzoic acid recoveries determined in this way were never more than 10% above the values determined by the preferred technique.

C. Benzoic Acid and Nitrobenzene.—Several filtrations were necessary to remove tarry material which separated at various stages of the work-up procedure. The method used to analyze for the isomeric nitrobiphenyls was similar to that used for dichlorobiphenyls (see above). Pure samples were used for calibration, and column B was employed.

D. Benzoic Acid and Methyl Benzoate.—The usual work-up procedure was followed using ice-cold hydrochloric acid for washing and 3 *N* sodium carbonate for extraction of acids. Fraction A was distilled at 1.5–3 mm through a spinning-band column to give a number of cuts which were analyzed separately by gc (column A). Equal response factors were assumed for all components, and the identities of the isomeric methyl biphenylcarboxylates were established by infrared, nmr, and mass spectral examination of trapped peaks. The presence of biphenyl was confirmed by spectral measurements on a trapped fraction whose retention time was identical to that of an authentic sample. Analysis of the distillation residue by mass spectrometry indicated the presence of methyl arylcarboxylates containing up to five aromatic nuclei. Recrystallization of a fraction (8.6 g) boiling at 155–165° (1.5–2.5 mm) from petroleum ether (bp 30–60°) gave 2.5 g of methyl 4-biphenylcarboxylate, mp 119–120° (lit.[54] mp 116.5°); this material was converted to 4-biphenylcarboxylic acid, mp 228–229° (lit.[55] mp 228°), by saponification with alcoholic potassium hydroxide. Mass spectral examination of fractions B and C suggested the presence of biphenylmono- and dicarboxylic acids, terphenylcarboxylic acids, benzenetricarboxylic acids, and monomethyl phthalates, but there was no evidence for the presence of 3,4-benzcoumarin in either of these fractions or in fraction A.

E. Benzoic Acid and *t*-Butylbenzene.—Fraction A from expt 26 was separated by distillation (2.5-mm pressure, spinning-band column) into a number of smaller fractions which were analyzed by gas chromatography on column A. Detector response factors were assumed to be equal for all constituents, and no attempt was made to identify all the materials present. Peaks corresponding to methyl benzoate, acetophenone, and the three *t*-butylbiphenyls were trapped and identified by the usual variety of spectroscopic methods. The material that failed to distil at 250° (2.5 mm) amounted to 2.23 g and was shown by mass spectrometry to contain *t*-butylterphenyls and heavier materials. A 2,4-dinitrophenylhydrazone was prepared from a distillation cut containing 20% of the material believed to be acetophenone; recrystallization from ethanol–acetone gave material which melted at 252–253° alone, or at 251–253° when mixed with an authentic specimen (mp 252–254°).

In expt 27 fraction A was analyzed directly for *t*-butylbiphenyls without prior distillation. The usual technique of comparing peak areas produced by known volumes of sample with the areas arising from known amounts of standard mixtures was employed, and a distillation cut containing the 2, 3, and 4 isomers in the ratio 1:5:3 (on the assumption of equal response factors) was used for calibration.

F. Benzoic Acid and Chlorobenzene.—Reaction mixtures were diluted with an equal volume of benzene and then worked

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[53] The analytical procedure was developed by Mr. R. K. Saunders.

[54] M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, **46**, 2339 (1924).

[55] H. C. Gull and E. E. Turner, *J. Chem. Soc.*, 491 (1929).

up in the usual way. In expt 28 and 30 fraction A was distilled (see above) prior to analysis. Gc analysis of the fractions obtained in expt 28 were carried out in the way described for preceding experiments, making the customary assumption with regard to response factors, and identifying products in the usual manner. Column B gave satisfactory separation of all components except 3- and 4-chlorobiphenyl; these substances were separated by column D. The yield of dichlorobiphenyls reported for expt 30 refers to material actually isolated. Fraction A from expt 29 was not distilled before analysis. Mass spectral analysis of fractions A–C from the various experiments indicated the presence of chloroterphenyls, biphenylcarboxylic acids, and the usual variety of by-products.

G. Benzoic Acid and Benzene.—The reaction mixture from expt 31 gave a negative test for peroxides with potassium iodide in acetic acid. Biphenyl yields were estimated in the usual way by gc of fraction A (column A), and the presence of this product was confirmed by its retention time and mass spectrum (of a trapped chromatographic fraction). Fractions B and C proved to be essentially pure benzoic acid, but traces of phenol were detected in these fractions by mass spectrometry.

H. Terephthalic Acid and *o*-Dichlorobenzene.—The reaction mixture was processed according to the procedure used for the *p*-toluic acid oxidates (see above). Although no sodium salts precipitated upon addition of 5% sodium hydroxide solution, the mass spectrum of the recovered terephthalic acid showed that traces of dichlorobiphenylcarboxylic acids had been formed. Fraction B (2.78 g) was shown by mass spectrometry to be mostly dichlorobenzoic acids.

I. Phthalic Acid and *o*-Dichlorobenzene.—The infrared spectrum of the total crude reaction mixture from expt 34 provided an estimate of the yield of phthalic anhydride and showed that little, if any, phthalic acid was present. Hydrolysis occurred when the mixture was processed in the usual way, and the starting acid (contaminated with small amounts of dichlorobenzoic acids) was isolated in essentially quantitative yield. Mass spectrometric examination of all product fractions gave no evidence for the presence of any substances formed *via* homolytic decarboxylation of phthalic acid.

J. 2-Biphenylcarboxylic Acid[56] and *o*-Dichlorobenzene.—The crude mixture was filtered to remove a small amount of tar and then extracted with three 100-ml portions of saturated sodium bicarbonate solution. More tar which separated during the extractions was also removed by filtering. The cloudy extracts were combined, extracted with ether until clear, adjusted to pH 2 with concentrated hydrochloric acid, chilled, and filtered to recover 0.8 g of solid, which was shown by mass spectral analysis to contain 2-biphenylcarboxylic acid and dichlorobenzoic acids. The ether extracts of the bicarbonate solution were added to the main organic phase, and the ether was boiled off. Aqueous sodium hydroxide (5%) (200 ml) was then added, and the mixture was refluxed and stirred vigorously for 20 min. The aqueous portion was separated, and the organic phase was extracted with an additional 100 ml of the caustic solution. The combined caustic layers were acidified (pH 2) with hydrochloric acid and extracted repeatedly with ether until a colorless extract was obtained. After combination, the ether extracts were washed twice with 125-ml portions of saturated sodium bicarbonate and twice with water, dried with Drierite, and evaporated *in vacuo*. The residue (5.30 g) was crude 3,4-benzcoumarin, mp 70–90°. Recrystallization of 3.67 g of this product from petroleum ether gave the purified material in two crops: 1.88 g, mp 93–94° (lit.[12c] mp 92–94°); 0.43 g, mp 91–93° (14% yield, corrected to 5.30 g basis). The infrared spectrum (Nujol) was identical with that of authentic material,[12a] and a mixture melting point showed no depression. The organic phase recovered after treatment with sodium hydroxide was washed twice with 100-ml quantities of water, dried over Drierite, concentrated by distillation at atmospheric pressure, and then fractionated through a short spinning-band column to give 0.97 g (5%) of biphenyl, bp 61–86° at 2.5 mm, mp 60–67°. Recrystallization from ethanol gave snow white prisms, mp 70–71°, which were shown to be identical with the pure substance by mixture melting point and infrared comparisons. The distillation residue weighed 16.2 g and was shown by mass spectrometry to consist almost entirely of dichloroterphenyls (43% yield), although traces of tetrachlorobiphenyls also appeared to be present. An attempt to isolate pure compounds from the residue by chromatography on alumina was not successful.

K. Methyl Benzoate and *o*-Dichlorobenzene.—The work-up procedure was identical with the one employed for expt 25. Gc analysis of fraction A for dichlorobiphenyls was carried out in the usual way. Fraction B (2.28 g) and fraction C (1.91 g) were shown by mass spectrometry to contain dichlorobenzoic acids and benzoic acid, as well as traces of dichlorobiphenylcarboxylic acids and dichlorophenols.

L. *p*-Chlorobenzoic Acid and *p*-Dichlorobenzene.—The Barrett trap was warmed with heating tape to prevent solidification of condensate during the reaction. After addition of benzene (200 ml), the total reaction product was filtered to recover 20.8 g of solid whose melting point and infrared spectrum (Nujol) were identical with those of *p*-chlorobenzoic acid. An additional 0.9 g of this material was recovered from the caustic extracts; hence the total recovery was 21.7 g, or 87%. The mass spectrum of fraction A suggested the presence of trichlorobiphenyl, tetrachlorobiphenyl, and methyl *p*-chlorobenzoate. Distillation of A through a short spinning-band column gave a fraction whose boiling point was 87–122° (inaccurate because of low distillation rate) at 2.5 mm; this material solidified upon cooling and was recrystallized from ethanol to give 0.35 g (0.9%) of white solid which melted at 64–65° and had an infrared spectrum (Nujol) identical with that of 2,4′,5-trichlorobiphenyl (see below).

Preparation of 2,3-Dichlorobiphenyl and 3,4-Dichlorobiphenyl.[57]—These compounds were synthesized by means of the Gomberg–Bachmann reaction using a procedure similar to that described by Weingarten.[9] The yield was 63% in each case, and the products were shown to be entirely homogeneous by gc.

Preparation of Ethyl 2′,3′-Dichloro-4-biphenylcarboxylate (I) and Ethyl 3′,4′-Dichloro-4-biphenylcarboxylate (II).—Reaction of the diazonium chloride of ethyl *p*-aminobenzoate with excess *o*-dichlorobenzene in the presence of sodium acetate was carried out according to the procedure used for preparation of the isomeric dichlorobiphenyls. From 33.0 g (0.200 mole) of amine and 500 ml of *o*-dichlorobenzene there was obtained 14.5 g (25%) of a mixture of I and II, bp 137–167.5° (mostly 163–167.5°) at 2.5 mm. Chromatography of 10.3 g of the mixture on 255 g of neutral alumina using petroleum ether for elution removed a small amount of yellow impurity and gave 6.8 g of white, crystalline fractions with melting points ranging from 60–67 to 58–69°. These were combined and recrystallized three times from petroleum ether with considerable loss of material to give a sample of I as clusters of needles, mp 71.2–71.8°. Programmed temperature gc (column E) showed that this sample contained no more than 0.3% of II.

Anal. Calcd for $C_{15}H_{12}Cl_2O_2$: C, 61.04; H, 4.10; Cl, 24.02. Found: C, 60.81; H, 3.99; Cl, 23.91.

In a similar experiment, that portion of the product with bp 172–178° at 3 mm (9.1 g) was chromatographed on 252 g of neutral alumina using a 1:1 mixture of benzene and petroleum ether for elution. The initial fraction of recovered solid weighed 1.3 g, melted at 67.5–69.5°, and was shown to be essentially pure I by infrared comparisons. Further elution gave a total of 5.2 g of white solid in several fractions with melting points ranging from 56–67 to 64–88°. Three recrystallizations of the combined fractions from petroleum ether gave II in the form of white needles, mp 90.0–91.7°. This material was shown by gc (column E) to contain 0.7% of I.

Anal. Calcd for $C_{15}H_{12}Cl_2O_2$: C, 61.04; H, 4.10; Cl, 24.02. Found: C, 60.87; H, 4.06; Cl, 23.75.

Preparation of 2′,3′-Dichloro-4-biphenylcarboxylic Acid (III) and 3′,4′-Dichloro-4-biphenylcarboxylic Acid (IV).—Overnight refluxing of I with excess ethanolic sodium hydroxide gave a sodium salt which was recovered by filtering, washed with fresh ethanol, dried, and dissolved in water. Acidification (pH 2) of the solution with concentrated hydrochloric acid precipitated III, mp 259–262°, in essentially quantitative yield. Recrystallization from ethanol-benzene gave tiny, snow-white needles, mp 259–261°.

Anal. Calcd for $C_{13}H_8Cl_2O_2$: C, 58.45; H, 3.02; Cl, 26.55. Found: C, 58.04; H, 3.11; Cl, 26.29.

Saponification of II in a similar manner afforded IV as a white powder, mp 278–280°. The melting point was not changed by recrystallization from ethanol–benzene.

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(56) Prepared by the method of E. H. Huntress and M. K. Seikel, *J. Am. Chem. Soc.*, **61**, 816 (1939).

(57) Dr. J. G. Houston assisted with these preparations.

Anal. Calcd for $C_{13}H_8Cl_2O_2$: C, 58.45; H, 3.02; Cl, 26.55. Found: C, 58.00; H, 2.99; Cl, 26.02.

Decarboxylation of 2′,3′-Dichloro-4-biphenylcarboxylic Acid (III).—A mixture of III (1.28 g, 4.79 mmoles), quinoline (7.0 ml), and basic cupric carbonate (100 mg) was heated rapidly to 240° with a free flame and maintained at 240–252° for 25 min. After cooling to room temperature, the mixture was diluted with 75 ml of ether and filtered. The filtrate was washed in succession with two 50-ml portions each of 2% sodium hydroxide, 1 *N* hydrochloric acid, and water, then dried over Drierite and concentrated *in vacuo* on a rotary evaporator. The residual oil weighed 0.66 g and gave an infrared spectrum (neat) differing from that of pure 2,3-dichlorobiphenyl in only minor respects. Analysis by gc (usual procedure, column A) showed that the oil contained 90% of this substance; thus, the yield was 0.59 g, or 55%.

Phenylation of *o*-Dichlorobenzene with Benzoyl Peroxide.—A solution of 12.1 g (0.0500 mole) of benzoyl peroxide in 60 ml of *o*-dichlorobenzene was added dropwise over a period of 75 min to 150 ml. of the solvent. The mixture was stirred rapidly during the addition and kept at 136–142°. After an additional 4 hr of stirring at 136–140°, the dark solution was worked up by a procedure similar to that used for most of the homolytic decarboxylation experiments. Analysis of fraction A by the usual gc technique showed that a mixture of 2,3- and 3,4-dichlorobiphenyl containing 64 ± 3% of the former isomer had been formed in 38% yield.

Preparation of 2,4′,5-Trichlorobiphenyl.—A pasty mixture of *p*-chlorobenzoyl peroxide and dibutyl phthalate (Wallace and Tiernan "Luperco BDB") was extracted repeatedly with cold methanol to remove the ester. The residual peroxide, mp 142.5–143.5° (lit.[58] mp 138°), was shown by iodometry to be 98% pure. This material (15.5 g, 0.0500 mole) was added in small portions with stirring to 200 g of *p*-dichlorobenzene kept at 79–82°. The mixture was heated at 75–97° for 18 hr, cooled, diluted with 400 ml of benzene, filtered to remove 3.6 g of *p*-chlorobenzoic acid (mp 238–241°), and then processed in the usual way (*cf.* preceding experiment). Distillation of fraction A through a spinning band column afforded 8.37 g (32% yield) of 2,4′,5-trichlorobiphenyl, bp 154° at 2.5 mm. The product solidified upon cooling and was recrystallized from ethanol to give slender, snow-white needles melting at 65.0–65.5° (lit.[59] mp 67°). The mass spectrum exhibited parent peaks at *m/e* 256, 258, 260, and 262; their intensities were in the ratio expected for a substance containing three atoms of chlorine.

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Synthesis of Protoemetine. A New Total Synthesis of Emetine

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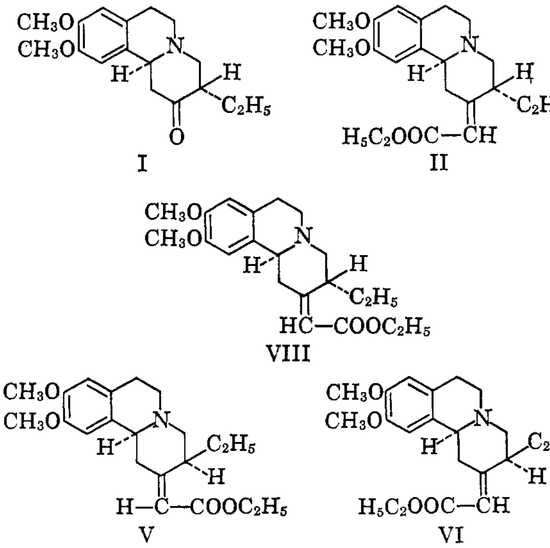
The reaction of 2-oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (I) with phosphonoacetic acid esters, in the presence of potassium *t*-butoxide, gave different stereoisomers of the α,β-unsaturated esters, depending on the conditions used. Catalytic hydrogenation of the appropriate isomer and reduction of the product with diisobutylaluminium hydride gave protoemetine in excellent yield. Pictet–Spengler condensation of the latter with 3-hydroxy-4-methoxyphenethylamine produced cephaeline as the main product besides a small amount of isocephaeline. This suggests that the biogenesis of cephaeline must involve the action of enzyme. O-Methylation of the phenolic base yielded emetine. The above reaction series was carried out both with racemic and optically active compounds.

In the last few years there has been quite extensive research activity in the field of the ipecacuanha alkaloids which are of chemical as well pharmacologic interest.[2]

By investigating the chemistry of the bases that can be obtained from heterocyclic imonium salts, we have been able to develop a simple method for producing in excellent yield[3] the benzo[*a*]quinolizine ring system, the common structural feature of ipecacuanha alkaloids. It therefore seemed feasible for us to participate in the efforts aimed at the development of a reasonable synthesis of these alkaloids. Brief mention of our results has already been made.[4,5] They are now presented in detail.

While 2-oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (I) (Chart I) is obtained in good yield,[3] it has been rather difficult to utilize this compound by subjecting it to condensation reactions. It does not react with esters of malonic acid, while the condensation product[6] with malononitrile which is obtained relatively smoothly isomerizes under the conditions of hydrolysis to give a compound which contains the originally exocyclic double bond in

CHART I



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