followed in the presence of sulfanilamide, sulfathiazole, sulfapyridine and N^1-benzoylsulfanilamide.

2. An analysis of the growth curves indicates that competitive inhibition is obtained in each case.

3. Dissociation constants for the enzyme-drug complexes have been calculated and their relation to bacteriostatic activity discussed.

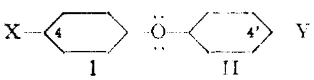
EVANSTON, ILLINOIS RECEIVED DECEMBER 4, 1944

[CONTRIBUTION FROM THE BAILEY CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

Polarization Effects in Aromatic Ethers[1]

BY RAY Q. BREWSTER AND ROBERT SLOCOMBE[2]

Several observers[3] have reported the fact that a substituent in one ring of an aromatic ether, such as diphenyl ether, has a marked effect in both rings. Thus in 4-nitrophenyl phenyl ether the substitution of bromine in the 4-nitrophenyl radical is almost precluded and occurs only slowly in the unnitrated nucleus. On the other hand 4-methoxyphenyl phenyl ether undergoes bromination in the unsubstituted phenyl group at a rate which is even faster than that of diphenyl ether itself. Inasmuch as substituting agents are electrophilic, substitution would be expected to occur at position 4′ because of the increased electron density at that position, as shown in resonance form B, and a group X at position 4 would favor or hinder this resonance form in proportion to its ability to donate electrons or accept electrons. Thus, if X is a nitro group, which has a strong attraction for electrons (form C) substitution still occurs at position 4′ but at a reduced rate. Conversely, when X is an electron donor, such as the methoxy group, the electron release in ring I increases resonance form B with the result that the rate of substitution at position 4′ is greatly enhanced. We have found also that the presence of a nitro group at position 4 (X = NO$_2$) facilitates the oxidation of a methyl radical at position 4′ (Y = CH$_3$) almost as much as if these two substituents were on the same ring as in *p*-nitrotoluene.



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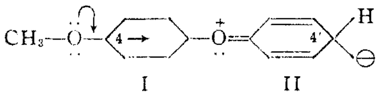

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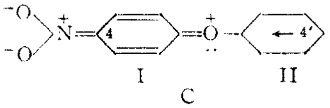

C

In order to measure the extent of these polarization effects we have conducted three series of experiments: (1) the speed of bromination of aromatic ethers, (2) the speed of benzylation in these ethers and (3) the yields of carboxylic acids obtained by the oxidation of a methyl radical in aromatic ethers.

Experimental

Materials.—All of the ethers used in this investigation were carefully purified by several crystallizations or fractional distillation. The melting points or boiling points of these ethers were: diphenyl ether, m. p. 26.8–27.0°; *p*-tolyl phenyl ether, b. p. 277° (745 mm.), 138–140° (9 mm.); *p*-bromophenyl phenyl ether, 165–167° (16 mm.); *p*-nitrophenyl phenyl ether, m. p. 58°; *p*-methoxyphenyl phenyl ether, 155–156° (6 mm.); *p*-bromophenyl *p*-nitrophenyl ether, m. p. 66°; *p*-nitrophenyl *p*-tolyl ether, m p. 69°; *o*-nitrophenyl *p*-tolyl ether, m. p. 49°; 2,4-dinitrophenyl *p*-tolyl ether, m. p. 93°.

Bromination.—Molar solutions of diphenyl ether in glacial acetic acid and of bromine likewise in glacial acetic acid were prepared and placed in a thermostat at 44°. To a 100-ml. portion of the diphenyl ether solution was added 100 ml. of the bromine solution. The combined solution, still kept in the thermostat, was thus 0.5 molar with respect to each component. Immediately upon mixing 5 ml. of the solution was removed with a pipet, run into a solution of potassium iodide and the liberated iodine titrated with 0.097 *N* sodium thiosulfate solution. At intervals of ten to twenty minutes successive 5-ml. portions of the solution were withdrawn for titration and the rate at which the bromine concentration decreased was plotted. Similar experiments were performed with 4-methoxyphenyl phenyl ether, 4-nitrophenyl phenyl ether, 4-bromophenyl phenyl ether, and *p*-tolyl phenyl ether In all of these cases mono-bromination occurred para to the ether oxygen and all of the brominated ethers were identified by mixed melting points with known samples. The relative rates at which the bromine concentration decreased are shown in Fig. 1.

The rates at which these ethers undergo bromination are in the same order as the rates of bromination of anisole, benzene, bromobenzene and nitrobenzene and confirm the predictions as to rate of substitution that could be made from the resonance theory. The fact that substitution in toluene is more rapid than in benzene would lead to the expectation that *p*-tolyl phenyl ether should be brominated more rapidly than diphenyl ether. That the converse is true may be explained on the basis of there being two chances for bromination to occur para to the oxygen in diphenyl ether and only one in *p*-tolyl phenyl ether. In no case was the substitution of any bromine at positions 2 or 2′ detected. Under the conditions of this experiment 4-nitrophenyl 4-bromophenyl ether, which might be expected to undergo further substitution ortho to the ether oxygen, failed to react as there was no appreciable diminution of the bromine concentration.

Benzylation.—The benzyl chloride and aromatic ethers used in this experiment were carefully purified by frac-

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(1) Presented before the Division of Organic Chemistry at the 107th meeting of the American Chemical Society at Cleveland, Ohio, April 3–7, 1944.

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(3) Scarborough, *J. Chem. Soc.*, **132**, 2361 (1925); Scarborough and Sweeten, *ibid.*, 52 (1934); Brewster and Strain, THIS JOURNAL, **56**, 117 (1934); Brewster and Choguill, *ibid.*, **61**, 2702 (1939).

tionation at reduced pressure. Benzyl chloride and diphenyl ether gave no sign of reaction when heated together at 150° for six hours; however, the presence of a little mercuric chloride brought about immediate reaction at 150° with the evolution of hydrogen chloride and the formation of 4-benzylphenyl phenyl ether. It was found that absorption of the hydrogen chloride in water and titration with a standard solution of a base gave a measure of the extent of the reaction which checked very closely with the yield of products obtained by fractional distillation of the mixture.

Eighty-five grams (0.5 mole) of diphenyl ether, 31.6 g. (0.25 mole) of benzyl chloride, and 2.71 g. (0.01 mole) of finely pulverized mercuric chloride were placed in a 500-ml. flask fitted with a mechanical stirrer and gas outlet tube which led into water in a titration flask. The reaction flask was heated in a thermostat maintained at 150°. Reaction soon began with evolution of hydrogen chloride which was absorbed in water and titrated with standardized alkali solution. About twenty minutes usually were required for the evolved hydrogen chloride to sweep the air out of the apparatus and the timing of the reaction was begun when the air had been expelled. The speed of the reaction was determined by titration of the hydrochloric acid solution at different intervals of time. At the end of the experiment hydrogen chloride remaining in the apparatus was swept into the absorbing solution by a slow stream of natural gas. Over most of the course of the reaction the data are in agreement with a reaction of the first order and the velocity constants are computed on that basis using the mole fraction of each constituent as a measure of its concentration. Typical data are shown in Table I.

TABLE I

RATE OF REACTION OF DIPHENYL ETHER AND BENZYL CHLORIDE (CATALYZED BY $HgCl_2$)

$HgCl_2$, 0.010 mole, mole fraction	0.013
PhOPh, 0.500 mole, mole fraction	.658
$PhCH_2Cl$, 0.250 mole, mole fraction	.329
	1.000

Time, minutes	Moles of HCl evolved	K
0	0.058	
27	.071	0.0013
94	.097	.0014
121	.107	.0014
155	.116	.0013
194	.128	.0013
236	.137	.0013
	Av.	0.0013

The mercuric chloride dissolves in the solution of diphenyl ether and benzyl chloride and its concentration affects the rate of reaction as shown in Table II.

TABLE II

MOLE FRACTIONS			
$HgCl_2$	PhOPh	$PhCH_2Cl$	K
0.009	0.495	0.495	0.00033
.018	.491	.491	.0021
.036	.482	.481	.015

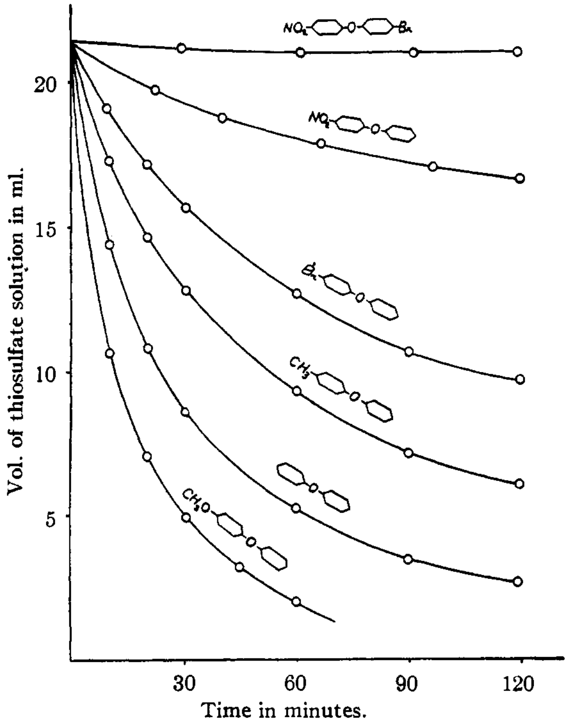


Fig. 1.—Relative rates of bromination of aromatic ethers. The most rapid decrease in bromine concentration (measured by titration against thiosulfate solution) indicates the most rapid reaction.

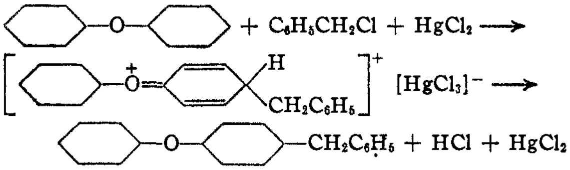
Similar experiments were performed with 4-methoxyphenyl phenyl ether, 4-nitrophenyl phenyl ether and with anisole. For purposes of comparison the mole fractions of the aromatic ether, benzyl chloride and mercuric chloride were held constant at 0.658, 0.329 and 0.013, respectively. In the case of 4-nitrophenyl phenyl ether no hydrogen chloride was evolved even when the temperature of the solution was raised to 195°. The rate of reaction was entirely too low to be measured and the velocity constant is recorded in Table III as zero.

TABLE III

COMPARATIVE RATES OF REACTION OF AROMATIC ETHERS WITH BENZYL CHLORIDE

Expt.	Ether	K
12	Diphenyl	0.0013
13	Diphenyl	.0012
14	Diphenyl	.0011
15	Diphenyl	.0013
	Av.	0.0012
16	*p*-Methoxyphenyl phenyl	0.0017
17	*p*-Methoxyphenyl phenyl	.0018
18	*p*-Methoxyphenyl phenyl	.0015
	Av.	0.0017
19	Anisole	0.0077
20	Anisole	.0073
	Av.	0.0075
21	*p*-Nitrophenyl phenyl	.0000

These rates of benzylation are in the same order as the rates of bromination in the first set of experiments and indicate that the tautomeric effects of a substituent in one benzene ring are transmitted to the other. The observation that the reactions appear to be of the first order indicates that the limiting rate of reaction is the speed of dissociation of a coördination compound and may be formulated as in the Friedel and Crafts reaction.



A solution of mercuric chloride in benzyl chloride was found to conduct an electric current but the conductance rapidly decreased upon the addition of diphenyl ether.

Oxidation of Methyl Radicals in Aromatic Ethers.—These experiments were conducted by dissolving 0.02 mole of the aromatic ether in 250 ml. of glacial acetic acid and adding 20 ml. of concentrated sulfuric acid and 50 ml. of a solution of sodium dichromate (20 g. of $Na_2Cr_2O_7 \cdot 2H_2O$ in 100 ml. of water). The flask containing this reaction mixture was placed in a constant temperature bath at 44° and stirred mechanically. The rate of reduction of the chromium was determined by removal of a 5-ml. portion of the solution with a pipet at intervals of fifteen minutes and titration against standardized ferrous ammoniun sulfate solution. At the end of two and one-half hours the reacting solution was poured into 700 ml. of cold water, chilled in ice and the precipitated aromatic acid collected on a filter. For purification the crude acid was dissolved in dilute sodium hydroxide solution, filtered from any material not soluble in alkali and reprecipitated with hydrochloric acid. The acids were identified by their melting points and "mixed melting points" with known samples.[4] The percentage yields of acids obtained by oxidizing different ethers are shown in Table IV.

TABLE IV

Ether	Acid obtained	Yield, %
Phenyl *p*-tolyl	4-Phenoxybenzoic	17
4-Nitrophenyl *p*-tolyl	4-(4-Nitrophenoxy)-benzoic	48
2-Nitrophenyl *p*-tolyl	4-(2-Nitrophenoxy)-benzoic	71
2,4-Dinitrophenyl *p*-tolyl	4-(2,4-Dinitrophenoxy)benzoic	82

According to the procedure used in this experiment *p*-nitrotoluene gave an 82% yield of *p*-nitrobenzoic acid. The volume of sodium dichromate solution reduced cannot be taken as a measure of the extent of oxidation of the methyl group because there is some cleavage of the ether at the oxygen atom and the resulting phenolic compounds consume part of the oxidizing agent. The shift of electrons from the ether oxygen atom to the *p*-tolyl nucleus facilitates oxidative cleavage of the C–O link but this action is hindered by the opposite shift of electrons to the nitro groups of the nitrated ring in those ethers where nitro groups are present. Thus the cleavage of the ether is least and the yield of carboxylic acid is greatest in 2,4-dinitrophenyl *p*-tolyl ether.

Summary

Three sets of experiments have been conducted to study the extent of the resonance effects in one ring of an aromatic ether produced by a substituent in the other ring. It has been shown that the tautomeric or inductive effects are transmitted across the ether oxygen atom from one ring to the other and that a substituent in one ring modifies the reactivity of a substituent in the other almost as much as if the two substituting groups were attached to the same benzene nucleus.

LAWRENCE, KANSAS RECEIVED DECEMBER 14, 1944

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[4] The statements in the literature (Beilstein, "Handbuch der organischen Chemie," Vierte Auflage VI, p. 394) that some of these ethers cannot be oxidized to the corresponding carboxylic acids are in error. We believe the error was caused by too high concentrations of oxidizing agent and sulfuric acid as these conditions result in cleavage of the ether linkage.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Synthesis of 1-(3',4'-Dimethoxyphenyl)-4-phenyl-butanone-2 and 1-Phenyl-4-(3',4'-dimethoxyphenyl)-butanone-2 and Related Compounds

BY E. F. LANDAU, F. LEONARD, R. H. CARROLL[1] AND P. E. SPOERRI

A comparison of the yields of the hydrolytic products obtained from the hydrolysis of 1-cyano-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2[2] (I) with 1-cyano-1,4-diphenylbutanone-2 (II)[3] indicated a marked difference in the ease of hydrolysis of these two substances. The former was hydrolyzed with great difficulty in poor yield to 1-carbamyl-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2 (III) whereas the 1-cyano-1,4-diphenylbutanone-2 was hydrolyzed easily in excellent yield to 1-carbamyl-1,4-diphenylbutanone-2 (IV). It appeared, therefore, to be of interest to attempt the preparation of 1-cyano-1-(3',4'-dimethoxyphenyl)-4-phenylbutanone-2 (V), and 1-cyano-1-phenyl-4-(3',4'-dimethoxyphenyl)-butanone-2 (VI) and compare the ease of hydrolysis of these two cyano ketones with that of the above-mentioned cyano ketones I and II by observing the yields of their respective carbamyl ketones.

Compounds of the following type were prepared:

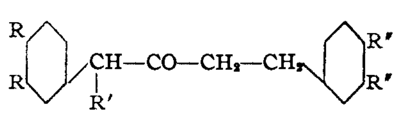

Table I lists the specific compounds discussed.

The preparations of the desired cyano ketones involved the condensation of a substituted propionate with the appropriate nitriles in the presence of a sodium alcoholate. For the synthesis of 1-cyano-1-(3',4'-dimethoxyphenyl)-4-phenylbutanone-2 (V), 3,4-dimethoxybenzyl cyanide was condensed with ethyl hydrocinnamate. Similarly by condensing benzyl cyanide with ethyl 3,4-dimethoxyphenyl propionate, the desired 1-cyano-1-phenyl-4-(3',4'-dimethoxyphenyl) butanone-2 (VI) was obtained as a viscous oil

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[1] Present address: Winthrop Chemical Co., Rensselaer, New York.

[2] Carroll and Spoerri, THIS JOURNAL, 60, 2658 (1938).

[3] Haworth, *J. Chem. Soc.*, 1426 (1934).