

Aromatic Displacements. I. The Brominative Cleavage of Arylcarbinols. Stoichiometry¹

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Activated benzhydrols (and some derivatives) are cleaved by bromine to give the corresponding bromobenzene and carbonyl compound. The reaction appears to be an excellent one for studying the effect of substitution on electrophilic aromatic displacement mechanisms, especially with respect to the role of the leaving group. It is found that the cleavage reaction only occurs to an important extent when at least one ring is activated by a substituent as effective as methoxy. The most important competing processes when the reaction is run in 80% aqueous acetic acid are substitution ortho to the activating group and oxidation of the carbinol function to a carbonyl group, the latter being much favored for less activated benzhydrols. In the present paper the products of brominating a series of *p*-methoxybenzhydrols and related compounds in 80% aqueous acetic acid are described. For the most part the cleavage yield is relatively insensitive to the nature of the leaving group although there are several interesting complications. The hydroxyl (or related oxygenated group) accelerates attack at the cleavage site, dianisylmethane being scarcely cleaved under conditions where dianisylcarbinol gives a 75% cleavage yield. Synthetic details and careful analytical procedures for studying the cleavage reaction are described.

Introduction

By far the largest and best known class of electrophilic aromatic reactions are those involving the displacement of a proton. In principle, however, an almost unlimited number of displacement reactions are possible since any electrophile which may form a stable substituent on the aromatic nucleus might be displaced by any other if suitable conditions could be found. This hypothesis is partially supported by a large number of reactions involving the mutual displacement of electrophiles; however, the literature is extremely diffuse, and we do not intend to review it here.²⁻⁴ Usually such displacements have been discovered as unexpected and unwelcome side reactions (such as the displacement of alkyl groups from polyalkylbenzenes

during nitration)⁵ during electrophilic attack on a highly substituted aromatic system. It will be our aim in this series of papers to exploit these reactions for the elucidation of the detailed mechanism of aromatic displacement. Hopefully, any theoretical insights may provide new control and flexibility to the use of aromatic displacements in synthesis as well as being interesting in their own right.

We will first consider the cleavage of certain arylcarbinols by bromine (eq. 1) where Ar is a highly



activated benzene ring and Ar' may be nearly any organic moiety, aromatic, aliphatic, or even hydrogen. This reaction was discovered in 1911 by Clarke and Esselen⁶ (although precedent for it may be found as far back as 1845⁷). The brominative cleavage was then subjected to further study by Clarke and Patch and their co-workers.⁸⁻¹⁰ However, since 1916 no further work has been done on the reaction and it has been referred to in passing only two or three times, although the cleavage of activated benzhydrols by diazonium salts has been examined by Ziegler¹¹ and developed into a simple and elegant aldehyde synthesis by Stiles and Sisti.¹²

The results of Clarke and his colleagues suggest very strongly that the cleavage is an example of electrophilic displacement. It may be applied to suitable mono-, di-, and triarylcarbinols and some of their ethers but not aryl methanes or ketones under these conditions. In addition to bromine, it was found that chlorine and nitrous and nitric acids could be used as displacing agents in chloroform or acetic acid solutions. These observations and the response of the reaction to substitution on the aromatic nuclei led Kohler and Patch¹⁰ to conclude in summary that. . . . "cleavage and replacement of hydrogen are similar processes, promoted equally by the same groups, hindered in the same way, therefore the result of the same mechanism." Our research supports both their experimental work and their conclusions and establishes that the reaction (when carried out in aqueous acetic acid) is indeed an excellent example of electrophilic

(1) This research was supported by a grant from the Petroleum Research Fund of the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund. The work described here is taken from the Ph.D. Thesis of G. B. K., University of Pittsburgh, 1963.

(2) An extensive review of this field may be found in the thesis of G. B. K. Partial coverage will be found in ref. 3 and 4.

(3) P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution," Academic Press Inc., New York, N. Y., 1959, Chapter 16.

(4) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 364, 365.

(5) D. Nightingale, *Chem. Rev.*, **40**, 117 (1947).

(6) L. Clarke and G. J. Esselen, Jr., *J. Am. Chem. Soc.*, **33**, 1135 (1911).

(7) R. Piria, *Ann.*, **56**, 35 (1845).

(8) L. Clarke and R. H. Patch, *J. Am. Chem. Soc.*, **34**, 912 (1912).

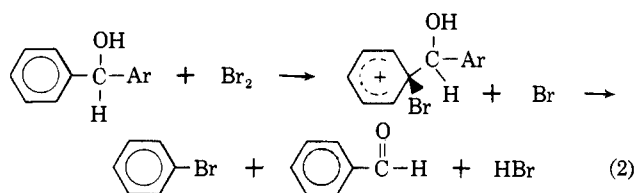
(9) L. Clarke and G. J. Esselen, Jr., *ibid.*, **36**, 308 (1914).

(10) E. P. Kohler and R. H. Patch, *ibid.*, **38**, 1205 (1916).

(11) E. Ziegler and G. Snatzke, *Monatsh.*, **84**, 278 (1953).

(12) M. Stiles and A. J. Sisti, *J. Org. Chem.*, **25**, 1691 (1960).

substitution which may be formulated in present day terms as follows



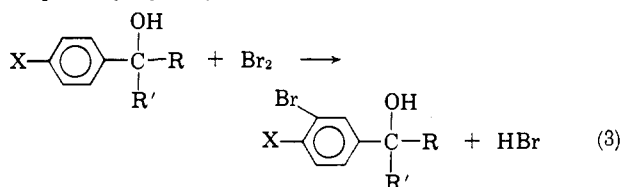
Such a cleavage of benzhydrols would seem at once to present an almost unrivaled opportunity for comparing the influence of substituents on aromatic reactivity through examination of the product ratios when two competing groups are placed in the *para* positions. Actually, this approach is not practical. However, the reaction is a good one for studying the effect of the leaving group and it is also useful for revealing a number of matters about the timing of aromatic substitution.

The present paper will be concerned with a careful evaluation by modern separation methods of the products obtained from treating various benzhydrols and related compounds with bromine in aqueous acetic acid, a solvent chosen for its superiority in kinetic studies of aromatic bromination. In subsequent papers we will consider the effect of structure on the rate of the cleavage and side reactions, the demonstration of an unstable intermediate by variation of bromide ion concentration, a detailed discussion of the reaction energy profile, and some general conclusions about the influence of the leaving group in this and other electrophilic aromatic displacements.

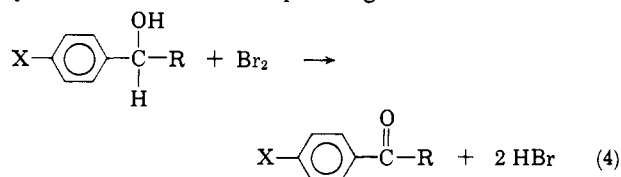
Results

Clarke and his co-workers limited their studies mostly to the cleavage of amino-activated benzhydrols which give high yields in this reaction. We soon discovered that our ability to do a careful kinetic investigation was severely limited by the fact that amino groups have such a powerful activating effect that reaction rates were too high for convenient study under the desired conditions. However, the replacement of the amino (or dimethyl-amino) group with alkyl substituents reduced the cleavage rate so sharply that several competing reactions with smaller ρ -values easily gained the upper hand and made it difficult to get measurable cleavage at all. Numerous other difficulties, which will be discussed at appropriate points, also showed that in reality we would be severely limited in our scope for studying the reaction. We were forced to settle for a careful investigation of systems bearing at least one *p*-methoxybenzene residue, and it will be seen that this still permitted observation of a wide variation of rates and yields as the cleavage competed more or less successfully with other reactions.

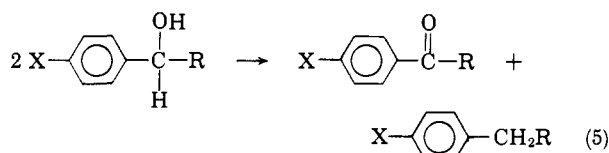
One might anticipate the following side reactions under suitable conditions: (a) substitution *ortho* to the activating substituent when these positions are occupied by hydrogen



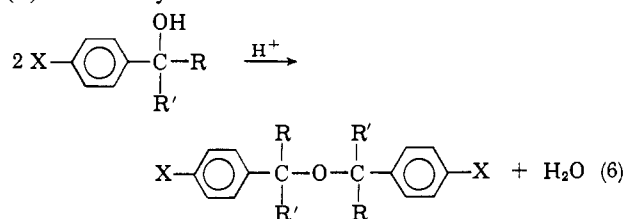
(b) oxidation of the hydroxyl group (when $\text{R}' = \text{H}$) by bromine to the corresponding ketone^{13a}



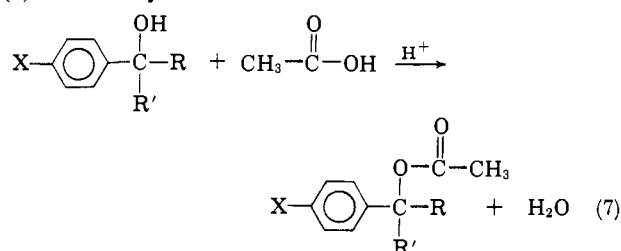
(c) disproportionation under the influence of the acidic properties of the solvent and/or hydrogen bromide formed in the course of the reaction^{13b}



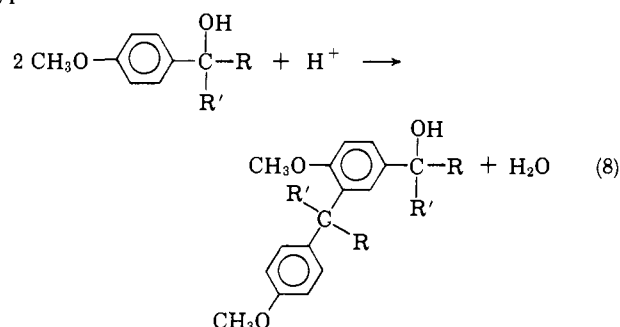
(d) acid-catalyzed formation of the bis ether



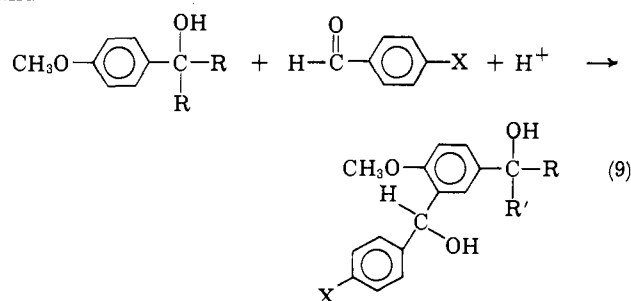
(e) acid-catalyzed esterification with solvent



(f) and condensations of the Baeyer-Villiger^{14,15} type



and



(13) (a) C. G. Swain, R. A. Wiles, and R. F. W. Bader, *J. Am. Chem. Soc.*, **83**, 1945 (1961); (b) P. D. Bartlett and J. D. McCollum, *ibid.*, **78**, 1441 (1956).

(14) A. Baeyer and V. Villiger, *Ber.*, **35**, 1197, 3013 (1902).

(15) E. F. Pratt and L. Q. Green, *J. Am. Chem. Soc.*, **75**, 275 (1953).

Table I. Cleavage Yields from Bromination of Arylmethyl Derivatives in 80% Aqueous Acetic Acid at Room Temperature as Determined by Gas Chromatography

Compd.	Brominating agent	NaBr, mole/l.	NaClO ₄ , mole/l.	Yield of bromoanisole fragment, %	Yield of carbonyl fragment, %	Other reactions
4,4'-Dimethoxybenzhydrol	Br ₂	0.2	...	73.1	68.6	R.B. ^d
4,4'-Dimethoxybenzhydrol	Br ₂	0.5	...	70.0	65.9	...
4,4'-Dimethoxybenzhydrol	Br ₂	0.1	0.4	72.1	62.5	...
4-Methoxy-4'-methylbenzhydrol	Br ₂	0.2	...	72.5 ^a	...	R.B. ^d (estd.)
4-Methoxybenzhydrol	Br ₂	0.2	...	65.2	72.5	R.B. ^d
4-Methoxy-4'-nitrobenzhydrol	Br ₂	0.2	...	39.2	...	R.B. ^d
4-Methoxy-4'-nitrobenzhydrol	Br ₂	0.5	...	32.2
4-Methoxy-4'-nitrobenzhydrol	Br ₂	0.1	0.4	51.9
4-Methoxy-4'-bromobenzhydrol	Br ₂	0.2	...	59.6 ^a	...	R.B. ^d (estd.)
3,5-Dimethyl-4-methoxybenzhydrol	Br ₂	0.2	...	83.0	82.4	Ox. ^e (ca. 10%)
4-Methoxybenzyl alcohol	Br ₂	0.2	...	61.0	...	R.B. ^d (estd.)
4-Methoxyphenylcyclohexylcarbinol	Br ₂	0.2	...	2.9	...	R.B. ^d and ox. ^e
4-Methoxytriphenylcarbinol	Br ₂	0.2	...	0.5	...	R.B. ^d (99.5%)
Bis-4,4'-dimethoxybenzhydryl ether	Br ₂	0.2	...	64.4	61.3	...
4-Hydroxybenzhydrol ^{b,c}	Br ₂	0.2	14.9	R.B. ^d
3,5-Dibromo-4-hydroxybenzhydrol ^b	Br ₂	None detected	None detected	No reaction
4,4'-Dimethylbenzhydrol	Br ₂	0.2	...	None detected	None detected	Ox. ^e ca. quant.
Benzhydrol	Br ₂	0.2	...	None detected	None detected	Ox. ^e ca. quant.
2-(4-Methoxyphenyl)ethanol	Br ₂	0.2	...	None detected	...	R.B. ^d and ox. ^e
4,4'-Dimethoxybenzophenone	Br ₂	0.2	...	None detected	...	R.B. ^d
4,4'-Dimethoxydiphenylmethane	Br ₂	0.2	...	0.2	...	R.B. ^d
4,4'-Dimethoxydiphenylmethane	Positive bromine	0.2	...	1.0

^a Estimated from a plot of per cent cleavage yield vs. the log of the over-all second-order rate constant (k_2) for the bromination of 4,4'-dimethoxybenzhydrol, 4-methoxybenzhydrol, and 4-methoxy-4'-nitrobenzhydrol in 80% aqueous acetic acid at 0.2 M sodium bromide. ^b Reaction run in 50% aqueous acetic acid. ^c Carbonyl fragment determined by ultraviolet spectroscopy as benzaldehyde. ^d Ring bromination. ^e Oxidation to ketone.

As may be seen from Table I and the detailed descriptions of bromination products in the Experimental section, only ring bromination (eq. 3) and oxidation to the ketone proved to be of any importance. The former reaction was the more serious competitor in the group of *p*-methoxyarylcarbinols and their cognates to which we devoted most of our attention. The latter side reaction was only of importance for 4,4'-dimethylbenzhydrol and benzhydrol itself in which the rate of substitution at any ring position is so depressed that oxidation of the hydroxyl function is able to assert itself. *In no case was there the slightest indication of cleavage occurring through attack on the less activated ring.*

Clarke and his co-workers followed the amount of cleavage by steam distillation of the products and a rough estimation of the amount of benzaldehyde produced. We were able to take advantage of gas chromatography and infrared spectrophotometry for more complete and accurate product analysis. In the *p*-methoxybenzhydrol series the amount of cleavage was determined within ± 2 -3% by gas chromatographic analysis for the *p*-bromoanisole produced (see Experimental). Since the products of ring bromination and oxidation were insufficiently volatile for this technique, they were estimated by infrared methods.

Ring Bromination. The product mixtures from the treatment of *p*-methoxybenzhydrols usually gave infrared spectra which matched quite well those of synthetic mixtures of the expected cleavage products, *p*-bromoanisole and a *para*-substituted benzaldehyde.

However, it was noticed that the product spectra often showed an additional strong band at $1052 \pm 6 \text{ cm.}^{-1}$ which was not present in the starting materials, cleavage products, or the expected materials that might have been formed from oxidation or disproportionation. This appears to be specific for bromination *ortho* to a methoxy group on a benzene ring. Thus it is present in the spectrum of *o*-bromoanisole but absent from that of anisole and present in 3-bromo-4-methoxytriphenylcarbinol but absent in the parent carbinol. Significantly, 3,5-dimethyl-4-methoxybenzhydrol which has its activated *ortho* positions blocked is exactly the carbinol which gave the highest cleavage yield. It is also the only one which produced both cleavage products in equal yield showing that in this case none of the cleavage product from the activated ring had been diverted by *ortho* bromination before or after cleavage. This was also the only compound in the methoxy series in which the 1050-cm.^{-1} band was missing from the bromination products. In Table II it is shown that this band was a remarkably constant feature of the residues from bromination of methoxylated compounds. No attempt was made to use this as a quantitative tool for estimating the amount of ring bromination, but it may be assumed that this reaction accounted for essentially all of the products that were not assigned specifically to cleavage or oxidation.

Oxidation. Only the less reactive (see paper II of this series) benzhydrols suffer oxidation to benzophenones. Among the *p*-methoxybenzhydrols no more than 5% oxidation occurred in any case except that of

Table II

Bromination products of	Wave no., cm. ⁻¹
4,4'-Dimethoxybenzhydrol	1049
4-Methoxybenzhydrol	1055
4-Methoxy-4'-nitrobenzhydrol	1046
4,4'-Dimethoxydiphenylmethyl acetate	1055
4,4'-Dimethoxydiphenylmethyl bromide	1053
4,4'-Dimethoxybenzophenone	1046
4,4'-Dimethoxydiphenylmethane	1050
4,4',4''-Trimethoxytriphenylmethane	1050
2-(4-Methoxyphenyl)ethanol	1055
4-Methoxybenzyl alcohol	1057

3,5-dimethyl-4-methoxybenzhydrol which as we have shown above is blocked from undergoing ring bromination. Thanks to steric inhibition of resonance from the methoxy group, this compound is considerably deactivated for substitution relative to the other *p*-methoxycarbinols and so about 10% of the product results from oxidation.

In view of our success in eliminating ring bromination in the above case, a sample of 3,5-dimethyl-4-methoxyphenylphenylmethylcarbinol was prepared in the hope that replacement of the hydrogen on the carbinol carbon would also rule out the oxidation reaction and hence give at least one compound for which a quantitative cleavage reaction could be measured at a convenient rate. Unfortunately, this compound eliminated the elements of water rapidly under the reaction conditions to give 1-phenyl-1-(3,5-dimethyl-4-methoxyphenyl)ethylene and so was useless to us.

The extent of oxidation was estimated from comparison of the diaryl ketone carbonyl stretching bands (1670–1650 cm.⁻¹) with the corresponding bands (1700–1680 cm.⁻¹) from the benzaldehyde fragments, the yield of which was established accurately by gas chromatography. The assumption was made that the molar absorptivity indices of the two peaks were equal. If anything, we have seriously overestimated the oxidation yields for ketones determined by this method.¹⁶

Benzhydrol and 4,4'-dimethylbenzhydrol gave no evidence of cleavage at all. Product isolation showed that oxidation to the ketone was essentially the only path followed by these compounds.

Other Reactions. It might be argued that some of the traces of diaryl ketone observed in these reactions could have arisen from acid-catalyzed disproportionation. However, no trace of the corresponding diaryl methane which should have been formed simultaneously was ever found. Furthermore, it was observed in the kinetic studies to be described in the following paper that reproducible rates could always be obtained with fresh carbinol solutions so that even though disproportionation might have been a problem with aged solutions it was avoided by the choice of conditions.

Evidence for the products of the other side reactions was routinely sought for but never found in quantities greater than 1%.

Detailed descriptions of the bromination and work-up of each compound will be found with its method of preparation in the Experimental section.

(16) R. E. Richards and W. R. Burton, *Trans. Faraday Soc.*, **45**, 874 (1949).

Discussion

The data presented here are hopefully of value in themselves but will also be used in the following papers on kinetics of the cleavage reaction in order to convert the over-all bromination rates to those for cleavage alone. The kinetic measurements were performed in 50% aqueous acetic acid, a medium which has been amply demonstrated by other workers to be the best for obtaining simple kinetics in aromatic brominations. However, although the benzhydrols and other compounds studied by us were sufficiently soluble for good kinetic measurements at the rather low (10⁻³ *M*) concentrations employed, it was impossible to scale up the reaction in this medium to large enough quantities for good yield estimates. Accordingly, the stoichiometric runs were performed in 80% aqueous acetic acid with concentrations of about 0.15 *M* and the assumption made that the slight change in medium would not influence yields appreciably. It is also assumed that the change in concentration will not affect the kinetics, a supposition which holds good only if (as is true) all of the important reactions are of the same order.

Table I shows that in the series of *p*-methoxybenzhydrols, CH₃OC₆H₄CHOHC₆H₄X, where X is methoxy, methyl, hydrogen, and bromine, the leaving group has little effect on the cleavage yield. This is true even if it is changed fairly drastically as in the case of 4-methoxybenzyl alcohol or bis(4,4'-dimethoxybenzhydryl) ether. It is seen, however, that the cleavage yield is decreased somewhat by the presence of strong electron-withdrawing substituents in the leaving group, this effect becoming important for X = nitro.

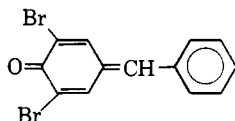
The low cleavage yields for 4-methoxyphenylcyclohexylcarbinol and 4-methoxytriphenylcarbinol are the result of depression of the cleavage rate relative to the other *p*-methoxybenzhydrols while a fast bromination of the ring at the position *ortho* to the methoxy group continues at an unchecked rate. Examination of molecular models of these two compounds shows that very likely steric congestion at the site where attack for the cleavage reaction must occur is responsible for the reduced rate and yield. It is also likely that the relatively high yield in the case of 4-methoxybenzyl alcohol is to some extent a reflection of small hindrance to formation of the cleavage transition state.

The low cleavage yield in the case of 4-hydroxybenzhydrol is partially the result of very successful ring bromination. When equivalent amounts of this carbinol and bromine were caused to react, a 14.9% yield of benzaldehyde could be obtained. When the amount of bromine was doubled, an 87.5% yield of 3,5-dibromo-4-hydroxybenzhydrol was found.

The attempted bromination of 3,5-dibromo-4-hydroxybenzhydrol itself raises an interesting point, since we could not cleave it with bromine nor could Kohler and Patch¹⁰ with bromine or nitric acid. Cannell¹⁷ in his study of the bromodesulfonation reaction was able to demonstrate the formation of a stable quinonoid intermediate in the bromination of sodium 3,5-dibromo-4-hydroxybenzenesulfonate and this decomposed smoothly to give 2,4,6-tribromophenol. In view of the marked similarity of the cleavage and de-

(17) L. G. Cannell, *J. Am. Chem. Soc.*, **79**, 2927 (1957).

sulfonation reactions in every other way there is no obvious reason why cleavage should not occur readily here and perhaps an intermediate be directly observable. Careful examination of the crystalline starting compound showed by analysis, molecular weight, and infrared spectrum that the assigned structure was in all likelihood correct. However, a solution of it in 50% aqueous acetic acid showed strong bands in the ultraviolet spectrum (2890 Å., ϵ 13,600, and 2830 Å., ϵ 13,200). This is inconsistent with the benzhydryl structure but would be very reasonable for its dehydration product, 3,5-dibromo-1-benzal-2,5-cyclohexadien-4-one, obtained by Zinke and Walter¹⁸ when they treated 3,5-dibromo-4-hydroxydiphenylmethane with bromine in carbon tetrachloride. This suggests the high resistance of this compound to bromination.



Another more recent precedent for bromination of a system like this leading to elimination and formation of a cyclohexadienone intermediate is that of Coppinger and Campbell¹⁹ who suggest such a path for the conversion of 2,6-di-*t*-butyl-4-methylphenol to 3,5-di-*t*-butyl-4-hydroxybenzaldehyde as a result of treatment with 2 equiv. of bromine in slightly aqueous acetic acid. Of relevance to our present case is the fact that when they treated 3,5-di-*t*-butyl-4-hydroxybenzyl alcohol with bromine in alcoholic solution only the corresponding aldehyde was obtained. In view of the facile cleavage of 4-methoxybenzyl alcohol observed by us, one might have expected to obtain 3,5-di-*t*-butyl-4-hydroxybromobenzene.

We have seen that in the absence of steric hindrance or other complications the cleavages of *p*-methoxybenzhydryls, a corresponding ether, and benzyl alcohol all occur with considerable facility and with little regard for the nature of the leaving group. One might therefore expect that 4,4'-dimethoxydiphenylmethane would undergo ready cleavage to give *p*-bromoanisole and a *p*-methoxybenzylcarbonium ion resulting in the formation of the corresponding alcohol, acetate, or further cleavage to *p*-bromoanisole and formaldehyde. It is found, however, that under our conditions 99.8% of the bromination occurs to displace hydrogen from the ring while cleavage competes to the extent of only 0.2% (although this may be raised to 1% by use of the more vigorous "positive" bromine; ref. 4, Chapter 8). Discussion of this effect from the oxygen functions is deferred to the third paper in this series.

Experimental

Analysis of Reaction Mixtures for Cleavage Products. A Burrell Model K-2 gas chromatograph with thermal conductivity detector and disk integrator for comparison of peak areas was used for most analyses. In a few cases qualitative comparisons were made from spectra obtained with a Perkin-Elmer Model 21 spectrophotometer. Whenever cleavage of compounds bearing the *p*-methoxyphenyl residue occurred *p*-

bromoanisole was formed, and this could be determined accurately by the procedure to be described below. Cleavage of *p*-methoxybenzhydryls also resulted in formation of an aldehyde which could sometimes be determined quantitatively by gas chromatography but in other cases (e.g., *p*-nitrobenzaldehyde) was not sufficiently volatile for this treatment. Other nonvolatile products were those resulting from ring bromination, oxidation to ketones, and small amounts of acids from oxidation of aldehyde products.

After considerable testing it was found that the two best column packings for these systems are 10% LAC-3-R-728 (Cambridge Industries) and 25% Apiezon L (James G. Biddle), both on 60-80 mesh Chromosorb W support. The life of these columns was short because of accumulation of the nonvolatile fractions referred to above which would bleed slowly from the column under operating conditions and disrupt the base line of the recording.

Stoichiometry studies were conducted in 80% aqueous acetic acid solution containing 20% water by weight and 0.2 *M* sodium bromide (for reasons to be discussed in the following paper on kinetics). The solution was 0.15 *M* with respect to bromine and the reacting carbinol compound and stood at room temperature until reaction was complete as shown by previous kinetic measurements on the system. A 25-ml. portion of the solution was then pipetted into a special 250-ml. separatory funnel modified for use with a Fisher Vibromixer²⁰ where it was neutralized (cooling) with aqueous sodium hydroxide and then extracted for 5 min. with thiophene-free benzene. The separated benzene layer was dried by filtration through a fluted Whatman No. 41 filter paper following which a 50- μ l. sample was injected into the gas chromatograph.

Final analyses were usually obtained by a bracketing procedure. A 50- μ l. sample of a synthetic solution of cleavage products which had been worked up in exactly the same way as the reaction solution was injected immediately following complete elution of the sample undergoing analysis. Comparison of peak areas then allowed an accurate evaluation of product composition. The successive approximations required by the bracketing procedure is perhaps unnecessary since it was shown that the molar response of the thermal conductivity detector-integrator system was linear down to at least 4×10^{-7} mole of *p*-bromoanisole; however, in view of the importance of exact yield values for our kinetic analysis the extra labor was expended. The value for each individual run is the average of at least three g.l.c. determinations agreeing within an error of $\pm 3\%$ (absolute) and reported yields are based on at least two replica runs differing by no more than $\pm 2\%$ from their average.

Elemental analyses and molecular weight determinations were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

Solvents and Reagents. ACS reagent grade (J. T. Baker Chemical Co.) acetic acid was purified by distillation from chromium trioxide (20 g./l.)²¹ through a 1-m. vacuum-jacketed column packed with $1/8$ -in. glass helices and rated at 17 theoretical plates. The acetic

(18) Th. Zinke and W. Walter, *Ann.*, **334**, 377 (1904).

(19) G. M. Coppinger and T. W. Campbell, *J. Am. Chem. Soc.*, **75**, 734 (1953).

(20) E. M. Arnett, C.-Y. Wu, J. N. Anderson, and R. D. Bushick, *ibid.*, **84**, 1674 (1962).

(21) K. J. P. Orton and A. E. Bradfield, *J. Chem. Soc.*, 960 (1924).

acid was refluxed first with chromium trioxide for 30 min. and then distilled at total take-off, and a main fraction (90%) was collected. This main fraction was then redistilled through the same column at a 5 to 1 reflux ratio and a main fraction, b.p. 116–117° (85%), was collected and used to prepare the reaction solvents. The acetic acid thus treated had the following physical constants: n_D^{20} 1.3719 (lit.²¹ n_D^{20} 1.3716), f.p. 16.2° (lit.²¹ 16.63). Using a value for the freezing point depression of 0.2° per 0.1% water,²¹ the difference between observed and reported freezing points corresponds to the presence of 0.2% water.

The reaction solvent, 80 wt. % acetic acid, was prepared by mixing suitable volumes of glacial acetic acid purified as described above with freshly boiled distilled water.

Mallinckrodt analytical reagent grade bromine was used without further purification and the Fisher certified reagent grade sodium bromide was dried at 110° for 4 hr. before preparation of solutions.

The arylcarbinols used in this work and for the kinetic measurements described in the following papers are often very difficult to purify, being low-melting solids with a strong tendency to form bis ethers and also to disproportionate to the corresponding ketone and diarylmethane. In some cases (none of them crucially important) all efforts to obtain a good analytical sample failed. Often, special pains had to be taken in the preparation and purification of individual compounds; also there were often slight differences in the work-up and analysis of stoichiometric runs. For this reason the preparation and treatment with bromine are described below individually for each compound in the order that they are presented in Table I.

4,4'-Dimethoxybenzhydrol was prepared through zinc dust reduction of 4,4'-dimethoxybenzophenone (Eastman White Label grade, m.p. 143.5–145°) by stirring a mixture of 50 g. of the ketone, 50 g. of sodium hydroxide (technical flake grade), 50 g. of zinc dust, and 500 ml. of 95% ethanol for 1 hr. during which time the temperature rose to 56° and then dropped to 29°. The reaction mixture was then refluxed and stirred for 2 hr. The filtered solution was poured into 2 l. of ice-water acidified with 100 ml. of concentrated hydrochloric acid. The precipitated white solid (crude yield, 83.5%) was collected by suction filtration and dried. Recrystallization of the product four times from an ethyl ether–Skellysolve B mixture gave white needles, m.p. 71–72° (lit.²² m.p. 72°).

The cleavage products from brominolysis of this compound were identified as 4-bromoanisole and 4-methoxybenzaldehyde by comparison of their infrared spectra and gas chromatographs with authentic samples (Eastman White Label, purified just prior to use) in the way described above. In addition, the 2,4-dinitrophenylhydrazone of the aldehyde was isolated, its melting point agreeing with the literature value of 254°.²³

As noted in Table I both cleavage products were determined quantitatively, a slightly greater amount of *p*-bromoanisole being found than the aldehyde. Two

factors are probably responsible for this. Firstly, we might expect that some of the starting carbinol will suffer *ortho* bromination to give 3-bromo-4,4'-dimethoxybenzhydrol which on cleavage will give *p*-bromoanisole and 3-bromo-4-methoxybenzaldehyde. The latter is nonvolatile under our gas chromatography conditions and will not be counted in with the aldehyde assay. Secondly, it is known that some anisaldehyde was lost through oxidation by air and bromine since small amounts of anisic acid (m.p. 184°) were isolated. Infrared analyses showed that less than 5% 4,4'-dimethoxybenzophenone was present in the bromination products.

4-Methoxy-4'-methylbenzhydrol when made by the Grignard reaction of *p*-tolylmagnesium bromide with anisaldehyde produced a yellow glass which was subjected to vacuum distillation after all attempts at recrystallization failed. This treatment caused nearly complete dismutation to the corresponding 4-methoxy-4'-methylbenzophenone and the corresponding diarylmethane. The latter was dissolved away from the ketone by trituration with Skellysolve F. Reduction of the ketone as described above for 4,4'-dimethoxybenzhydrol followed by recrystallization from a mixture of Skellysolve F and B gave white crystals melting at 62.6–63.6° (lit.²⁴ m.p. 61–62°).

Such a small amount of this carbinol was prepared that insufficient material was retrieved from the reaction with bromine to allow g.l.c. determination of the cleavage products. Accordingly, in this case (and that of 4-bromo-4-methoxybenzhydrol), the yield was estimated from the kinetic data in the following paper by construction of a plot of the logarithms of the over-all bromination rate constants against cleavage yield for those *p*-methoxybenzhydrols giving the best yield data. Although this is a questionable procedure, objections to it may be partially removed by the fact that the cleavage yield for these compounds would be expected from Table I to be almost the same as those from 4,4'-dimethoxybenzhydrol or 4-methoxybenzhydrol and also that these are not important compounds for any of our arguments.

4-Methoxybenzhydrol prepared by the Grignard reaction of phenylmagnesium bromide and *p*-anisaldehyde (Eastman White Label) formed its bis ether very readily, and this was nearly impossible to remove by recrystallization. The carbinol was therefore purified by distillation at 11 mm. Under these conditions it boiled at 206–207°, the distillate setting to a white crystalline mass which melted at 65–67°. Recrystallization of the distillate from ether–Skellysolve B mixture gave white needles melting at 66–67° in agreement with the literature value.²⁵ The distillation residue was recrystallized from ether to give white crystals of bis(4-methoxybenzhydryl) ether melting at 120–122°²⁴ in an amount suggesting that the crude product from the Grignard reaction contained 20–30% of the ether before distillation.

The bromination products were examined in the usual way and both cleavage fragments were determined. In contrast to the case of 4,4'-dimethoxybenzhydrol, the aldehyde fraction was found in this case to be

(22) J. Schmidlin and R. von Escher, *Ber.*, **45**, 898 (1912).

(23) I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953.

(24) M. P. Balfe, *et al.*, *J. Chem. Soc.*, 797 (1946).

(25) M. P. Balfe, M. A. Doughty, J. Kenyon, and R. Poplett, *ibid.*, 605 (1942).

appreciably larger than the *p*-bromoanisole one, although the reason is probably the same as that given above. Ring bromination of the starting carbinol will give 4-methoxy-3-bromobenzhydrol which will cleave to give benzaldehyde plus nonvolatile 2,4-dibromoanisole, thus raising the apparent proportion of aldehyde. As a check on this hypothesis the product from bromination of this carbinol with an equivalent amount of bromine was neutralized and steam distilled. The distillate yielded a mixture whose infrared spectrum was identical with an equimolar mixture of *p*-bromoanisole and benzaldehyde. This method of analysis is not accurate enough to detect any slight differences in yield of these products. The extracted residue from steam distillation yielded after fractional crystallization the bis ether of the carbinol as shown by mixture melting point and infrared spectrum. Also 3-bromo-4-methoxybenzhydrol (m.p. 79°)¹⁰ could be isolated in an amount corresponding to about 13% of ring bromination under conditions where the products in the steam distillate amounted to about 38% cleavage.

No 4-methoxybenzophenone could be found in the product mixture, albeit the ketone band might have been obscured by that of benzaldehyde. In any event much less than 5% oxidation could have occurred.

4-Methoxy-4'-nitrobenzhydrol has not been described before in the literature. It was prepared by potassium borohydride reduction of 4-methoxy-4'-nitrobenzophenone following the failure of sodium borohydride and aluminum chloride in diglyme or tetrahydrofuran. The ketone was prepared by the Friedel-Crafts reaction of anisole and *p*-nitrobenzoyl chloride following Auwers.²⁶ This gave a 55% yield of material melting at 119–122° (lit.²⁶ m.p. 121°). A slurry of 25.7 g. (0.1 mole) of this ketone in 200 ml. of methanol was stirred while a solution of 2 g. of potassium borohydride and 2 ml. of 2 *N* sodium hydroxide in 20 ml. of water was added to it at a rate of 0.5 ml./min. during which time the temperature was kept between 20 and 25°. After 64 hr. of stirring a small amount (2.5 g.) of unreacted ketone was removed by filtration and the filtrate was concentrated by evaporation, during which operation small amounts of white solid (probably bis ether) precipitated and were removed. The remaining concentrate was diluted with water and extracted with three 150-ml. portions of ether, which were combined, washed with water, dried, and evaporated. The resulting yellow crystalline solid (21.1 g., 81% yield) was recrystallized twice from Skellysolve C (90–100° petroleum ether) to give feathery white needles, m.p. 79.0–79.2°.

Anal. Calcd. for C₁₄H₁₃NO₄: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.00, 64.77; H, 5.14, 5.04; N, 5.50, 5.64.

Although the cleavage yield could be based in this case on the usual g.l.c. determination of *p*-bromoanisole, the aldehyde is a solid and cannot be analyzed in this way under these conditions. Instead it was isolated by heating the product mixture with a few milliliters of water and on cooling pale yellow needles of *p*-nitrobenzaldehyde melting at 104–105° (lit.²³ m.p. 106°) were deposited which gave an infrared spectrum identical with that of an authentic (Eastman Organic Chemicals) sample.

An infrared spectrum of the reaction products showed

(26) K. Auwers, *Ber.*, **36**, 3893 (1903).

no absorbance at 1667 cm.⁻¹ where the carbonyl stretching frequency of 4-methoxy-4'-nitrobenzophenone occurs, so that little if any oxidation occurred in this case. However, a strong hydroxyl band and a very strong band at 1046 cm.⁻¹ for bromine *ortho* to methoxy (see above) indicated that there had been considerable ring bromination to give 3-bromo-4-methoxy-4'-nitrobenzhydrol.

4-Bromo-4'-methoxybenzhydrol was prepared by the Grignard reaction of 4-bromophenylmagnesium bromide²⁷ with *p*-anisaldehyde. After many recrystallizations from an ether-Skellysolve F mixture, a small quantity of granular white solid of dubious purity was obtained melting at 71–74° (lit.²⁸ m.p. 75°). The extent of cleavage of this carbinol was estimated in the same manner as described above for 4-methoxy-4'-methylbenzhydrol.

3,5-Dimethyl-4-methoxybenzhydrol has not been previously reported. It was prepared by the reaction of benzaldehyde with the Grignard reagent of 3,5-dimethyl-4-methoxybromobenzene, made according to Bruce, Kharasch, and Winzler.²⁹

3,5-Dimethyl-4-methoxyphenylmagnesium bromide was prepared from 6.08 g. (0.25 g.-atom) of magnesium and 47.8 g. (0.25 mole) of 2,6-dimethyl-4-bromoanisole. Ten milliliters of a solution of the latter compound in 125 ml. of dry tetrahydrofuran was run into the reaction flask containing the magnesium and a small crystal of iodine under nitrogen. Initiation of the reaction required gentle heating after which it was kept at reflux by the addition of the remainder of the solution over a period of 30 min. After addition was complete the solution was refluxed for 1 hr. Freshly distilled benzaldehyde (24.4 g., 0.23 mole) in 125 ml. of tetrahydrofuran was then added at a rate to maintain gentle reflux. The Grignard addition compound was decomposed with ice and saturated ammonium chloride and the crude product was isolated by ether extraction. Short-path vacuum distillation of the steam distilled product (crude yield, 91%, b.p. 210° at 0.3 mm.) gave a yellow-white solid which was easily recrystallized four times from Skellysolve B and melted at 92.5–94°.

Anal. Calcd. for C₁₆H₁₈O₂: C, 79.31; H, 7.49. Found: C, 78.89; H, 7.35.

The cleavage products of this compound were identified as 2,6-dimethyl-4-bromoanisole and benzaldehyde by comparison of infrared spectra and g.l.c. retention times with *bona fide* samples and the cleavage yield was determined in the usual way. The 10% oxidation to ketone was estimated by infrared examination of the product mixture.

4-Methoxybenzyl alcohol (Eastman White Label) was vacuum distilled twice and fractions boiling from 120 to 121° at 5 mm. were used.

The *p*-bromoanisole cleavage fragment was identified and determined in the usual way and the formaldehyde fragment demonstrated by a strong carbonyl band at 1745 cm.⁻¹. Anisaldehyde, the expected product from bromine oxidation of the alcohol, was sought carefully by infrared and g.l.c. but not found, indicating this side reaction to be unimportant.

(27) E. Bergmann, *ibid.*, **64**, 1483 (1931).

(28) M. Am. Mihăilescu and St. P. Caragea, *Bull. sect. sci. acad. roumaine*, **12**, 7 (1929); *Chem. Abstr.*, **24**, 2116 (1930).

(29) T. C. Bruce, N. Kharasch, and R. J. Winzler, *J. Org. Chem.*, **18**, 86 (1953).

4-Methoxyphenylcyclohexylcarbinol was prepared through the Grignard reagent of cyclohexyl bromide (Eastman White Label) and *p*-anisaldehyde following the procedure of Schmidlin and von Escher.²² Three recrystallizations from Skellysolve B gave fine white crystals melting at 87.5–88° (lit.²⁹ m.p. 92°).

The small amount of cleavage in this case was shown by g.l.c. analysis for *p*-bromoanisole. The infrared spectrum of the product mixture showed a very strong band at 1053 cm.⁻¹ and an OH absorption indicating that ring bromination was the main reaction. There was also a strong band at 1669 cm.⁻¹ corresponding to the formation of considerable 4-methoxyphenyl cyclohexyl ketone by oxidation. There also appeared a strong band at 1727 cm.⁻¹ from an unidentified source. It was too strong to be attributed to the small amount of cyclohexylaldehyde that would have been formed from cleavage but might have been due to the formation of some acetate of the carbinol.

4-Methoxytriphenylcarbinol was prepared by the reaction of 4-methoxyphenylmagnesium bromide with benzophenone. This compound was exceedingly difficult to crystallize and may be polymorphic as suggested by the variety of melting points reported for it. We obtained large rectangular crystals melting sharply between 79 and 80° by repeated recrystallization from a mixture of ether, Skellysolve F, and Skellysolve B. Baeyer and Villiger¹⁴ however report 58–61° while a sample sent to us by Professor N. C. Deno melted at 69–70° but was labeled as melting between 57.5 and 59°. The infrared spectrum of Professor Deno's sample was identical with ours which in turn supported the assigned structure.

Anal. Calcd. for C₂₀H₁₈O₂: C, 82.73; H, 6.25. Found: C, 82.46, 82.40; H, 6.55, 6.57.

Treatment of this carbinol with bromine gave a detectable amount of cleavage as shown by g.l.c. analysis for *p*-bromoanisole. The weight of the sticky yellow product approximated that to be expected if ring bromination were the only reaction and a very strong infrared band at 1055 cm.⁻¹ for bromine *ortho* to the methoxyl group was seen. Fivefold recrystallization from an ether–Skellysolve B mixture gave pale yellow crystals melting at 97.1–97.8° with the correct analysis, molecular weight, and infrared spectrum for 3-bromo-4-methoxytriphenylcarbinol.

Anal. Calcd. for C₂₀H₁₇BrO₂: C, 65.05; H, 4.64; Br, 21.64; mol. wt., 369.26. Found: C, 65.82, 65.78; H, 4.75, 4.66; Br, 21.86, 21.68; mol. wt., 366, 370.

A small band at 1658 cm.⁻¹ corresponding to a trace of ketone from the cleavage reaction by bromine was removed from the crude product by the recrystallizations. Accordingly, the result of bromination is to give 99.5% bromodeprotonation and 0.5% cleavage.

Bis(4,4'-dimethoxybenzhydryl) ether was prepared by elution of a chloroform solution of 4,4'-dimethoxydiphenylmethyl acetate (prepared according to Schnackenberg and Scholl)³⁰ through a 2-ft. column of activated alumina. After crystallization from 95% ethanol white crystals melting at 78–80° (lit.³¹ m.p. 81–82°) were obtained.

(30) H. Schnackenberg and R. Scholl, *Ber.*, **36**, 655 (1903).

(31) M. P. Balfé, J. Kenyon, and E. M. Thain, *J. Chem. Soc.*, 790 (1952).

Bromination of this compound gave a 64.4% yield of *p*-bromoanisole and 61.3% yield of anisaldehyde based on the assumption that each mole of ether is capable of yielding 2 moles of the cleavage products when the reaction is carried out in aqueous solution.

4-Hydroxybenzhydrol was prepared by Döbner's³² sodium amalgam reduction of 4-hydroxybenzophenone (Dow Chemical Co.). Recrystallization from hot water gave an 83% yield of white needles melting at 160.5–163° (lit.³¹ m.p. 161°).

In view of the low volatility and small cleavage yield of 4-bromophenol, the extent of cleavage was determined in this case by spectrophotometric determination of benzaldehyde through its band at 280 mμ in the aqueous acetic acid solvent. This procedure was possible because no oxidation of the carbinol to the corresponding ketone occurred in this case. The presence of 4-hydroxybenzophenone would have spoiled such an analysis.

3,5-Dibromo-4-hydroxybenzhydrol was obtained by bromination of 4-hydroxybenzhydrol when it was found that reduction of 3,5-dibromo-4-hydroxybenzophenone with sodium amalgam gave only hydrogenolysis of carbon–bromine bonds. Two equivalents of bromine dissolved in 100 ml. of 50% aqueous acetic acid was added over a period of 4 hr. to 3.27 g. (0.0163 mole) of the carbinol in 450 ml. of the same solvent while the temperature was maintained at 5–10°. Steam distillation after neutralization with sodium bicarbonate gave an amount of 4-hydroxybenzhydrol in the distillate corresponding to 12.5% cleavage. Acidification of the pot residue with 10% hydrochloric acid precipitated a white material which was removed by filtration, washed with water, and dried (5.17 g.). Recrystallization from aqueous ethanol gave white needles melting at 164–165° in agreement with the literature value.¹⁰ The result of an attempted bromination of this compound has already been considered in the Discussion section.

4,4'-Dimethylbenzhydrol was prepared by zinc dust reduction³³ of 4,4'-dimethylbenzophenone (Eastman White Label).

The 48.8 g. (96.6% yield) of crude product was recrystallized from 375 ml. of Skellysolve B to give white needles, m.p. 70–71° (lit.³⁴ m.p. 69°).

A careful examination of the bromination products by gas chromatography with several columns failed to reveal a trace of cleavage products and only a very weak sodium fusion test for bromine was found. The infrared spectrum was identical with that of 4,4'-dimethylbenzophenone which indeed could be obtained in nearly quantitative yield on recrystallization from ethanol as white crystals melting at 94–95° (lit.²³ m.p. 99°). Clearly oxidation alone is the result of bromine treatment here.

Benzhydrol was obtained from Eastman Chemicals and recrystallized twice from Skellysolve B. The infrared spectrum of its bromination products showed no trace of benzaldehyde absorption, but only a strong band at 1658 cm.⁻¹ for benzophenone showing that oxidation is the only important reaction in this case.

(32) O. Döbner, *Ann.*, **210**, 246 (1881).

(33) F. Y. Wiselogle and H. Sonneborn, III, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 90.

(34) J. Weiler, *Ber.*, **7**, 1184 (1874).

2-(4-Methoxyphenyl)ethanol was prepared by lithium aluminum hydride reduction of ethyl (4-methoxyphenyl)acetate in ether as solvent. This in turn was prepared by the alcoholysis of 4-methoxyphenylacetonitrile (Eastman Yellow Label). To a solution of 70 g. (0.48 mole) of 4-methoxyphenylacetonitrile in 115 ml. of 95% ethanol was added 51 ml. of concentrated sulfuric acid. The reaction mixture was refluxed for 2 hr. with stirring during which time it separated into two layers. It was then poured into 2 l. of ice-water and the upper layer was separated and washed with 10% sodium bicarbonate. The crude product was distilled under reduced pressure and the fraction boiling from 125 to 128° at 2 mm. was collected (70 g., 75% yield).

For the reduction 65.1 g. (0.34 mole) of ethyl (4-methoxyphenyl)acetate in 130 ml. of ethyl ether was added with stirring over a period of 2 hr. to 7.2 g. (0.19 mole) of lithium aluminum hydride in 250 ml. of ethyl ether. After refluxing with stirring for 2 more hr., the excess hydride was destroyed with ethyl acetate. The reaction mixture was then poured into 200 ml. of ice-water and 500 ml. of cold 10% sulfuric acid added. The ethereal layer was separated, washed with 10% sodium bicarbonate and water, and dried over Drierite. After removal of the ether on a water bath, the crude product was distilled under reduced pressure and the fraction boiling from 129 to 130° at 5 mm. (39.8 g., 77.6% yield) was collected. The product was redistilled twice and shown by gas chromatography to be free of anything which might interfere with the interpretation of the results of its bromination. Its infrared spectrum was identical with that of the product of an independent Grignard synthesis. The melting point of the final product was 26° (lit.³⁶ m.p. 24°).

The products of brominating it were very carefully examined by gas chromatography under a number of conditions but not the slightest trace (less than 0.1%) of *p*-bromoanisole could be found. That oxidation and ring bromination are the main reactions were shown by a strong aldehyde band at 1739 cm.⁻¹ and a strong band for bromine *ortho* to methoxy at 1055 cm.⁻¹.

4,4'-Dimethoxybenzophenone (Eastman White Label) gave no indication of forming *p*-bromoanisole by brominative cleavage but a strong band which appeared at 1046 cm.⁻¹ after treatment with bromine shows that the major reaction is bromination *ortho* to the methoxy group.

(35) V. Grignard, *Ann. chim. phys.*, **10**, 30 (1907).

4,4'-Dimethoxydiphenylmethane was prepared by condensing methylal (Fisher certified reagent) and anisole (Fisher certified reagent) in a cooled (5–10°) solution of sulfuric acid in glacial acetic acid following Matsumura.³⁶ A 56.5% yield of oil boiling at 157.5–160° (1.5 mm.) was obtained.

Gas chromatographic analysis showed that 0.2% cleavage was obtained under the standard bromination conditions, the main reaction being ring bromination as shown by a very strong 1054-cm.⁻¹ band in the product mixture. Treatment with positive bromine in about 80% acetic acid was effected by adding a solution of 1.56 g. of the diarylmethane in 25 ml. of glacial acetic acid to a solution of 1.16 g. of silver sulfate, 0.35 ml. of bromine, and 6.15 ml. of concentrated sulfuric acid in 25 ml. of 40% aqueous acetic acid. This gave a 1% cleavage yield. The possibility that cleavage had occurred in either case through preliminary oxidation to the carbinol which then suffered cleavage was ruled out by the absence of anisaldehyde in both product mixtures.

3,5-Dimethyl-4-methoxyphenylphenylmethylcarbinol was prepared by a Grignard reaction of methylmagnesium bromide and 3,5-dimethyl-4-methoxybenzophenone. The ketone was made by a Friedel-Crafts reaction of 2,6-dimethylanisole (prepared by C. Y. Wu)³⁷ and benzoyl chloride in carbon disulfide with aluminum chloride, following the procedure of Auwers and Markovits.³⁸ The crude product (a brown oil) would not crystallize and was purified by short-path vacuum distillation, b.p. 280–290° at 0.3 mm. The infrared spectrum of this product was in good agreement with that of the product of chromium trioxide oxidation of 3,5-dimethyl-4-methoxybenzhydrol.

A procedure for the preparation of diphenylmethylcarbinol³⁹ was followed for the Grignard reaction of methylmagnesium bromide with 3,5-dimethyl-4-methoxybenzophenone. The crude product was obtained as an oily, orange-red, crystalline mass which was recrystallized six times from Skellysolve B to give white needles, m.p. 96.6–97.6°. This compound has not been reported previously.

Anal. Calcd. for C₁₇H₂₀O₂: C, 79.65; H, 7.86. Found: C, 80.19, 80.23; H, 8.05, 8.07.

(36) K. Matsumura, *J. Am. Chem. Soc.*, **57**, 128 (1935).

(37) C. Y. Wu, Ph.D. Thesis, University of Pittsburgh, 1961.

(38) K. Auwers and Th. Markovits, *Ber.*, **41**, 2339 (1908).

(39) M. S. Kharasch and P. O. Towney, *J. Am. Chem. Soc.*, **63**, 2315 (1941).