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PART I

REACTIONS OF ARYLCARBINOLS WITH BROMINE AND IODINE

PART II

ACYL-OXYGEN FISSION IN BENZHYDRYL HYDROGEN PHTHALATE ESTERS

BY

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A Thesis

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ABSTRACT

PART I

A report is presented on the study of the reactions of arylcarbinols with bromine and iodine in various organic solvents. It was found that triarylcarbinols in reaction with bromine or iodine in methanol solution were converted to the methyl triarylmethyl ethers. Ketones and aldehydes were obtained when benzhydrols and benzyl alcohols were treated with bromine in methanol solution. Some of the corresponding methyl benzhydryl ethers could be obtained from the reaction of several benzhydrols with iodine in solution with methanol, in yields depending on the nature of the aryl substitution. The probable presence of a carbonium ion intermediate in the reaction was demonstrated by the isolation of bis-(4-methoxyphenyl)-methane in 82% yield from the reaction of 4-methoxybenzyl alcohol with iodine in solution with anisole and acetone. The possible mechanisms of the reaction which were studied are discussed and methods of proving these mechanisms are advanced. The preparations of several previously unreported compounds are described.

PART II

A mechanistic study of the base catalyzed methanolysis and hydrolysis of several hydrogen phthalates is reported. The hydrogen phthalate esters of the following benzhydrols were prepared for this study: 4-nitrobenzhydrol, 4-bromo-4'-nitrobenzhydrol, 4-nitro-4'-t-butylbenzhydrol, 4-chlorobenzhydrol, and 4-methylbenzhydrol. The tendency of these esters to undergo these solvolytic reactions is discussed in terms of possible mechanisms and related in a qualitative manner to Hammett σ values. A new kinetic approach to studying the base catalyzed solvolysis of benzhydryl hydrogen phthalate is described. The results of the kinetic study are interpreted to elucidate the mechanistic path involved. Two esters were at least partly resolved into their optical isomers, and some solvolytic reactions involving these active esters are presented. A description of a new preparative method leading to benzhydryl hydrogen phthalate esters is included. The preparations are reported of several compounds that are unknown in the chemical literature.

ACKNOWLEDGEMENTS

The author wishes to acknowledge with sincerest gratitude the patience and direction shown by Dr. K. G. Rutherford during the period of these studies.

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PART I

REACTIONS OF ARYLCARBINOLS WITH BROMINE AND IODINE

CHAPTER I

INTRODUCTION

Reactions of alochols with bromine and iodine have long been known in the chemical literature. One of the earliest systematic approaches to the problem of an interaction between halogens and solvents was reported in 1903 by Lachman[1] who attempted to explain the observed colours of iodine in solution with several organic solvents. He showed that solvents which contained available non-bonded electrons (e.g. methyl alcohol, ethyl ether, acetone, ethyl acetate, thiophene, acetonitrile and pyridine) always gave a brown solution with iodine. Solvents which did not contain one or more free available electron pairs (e.g. hexane, toluene, chloroform, bromobenzene, nitroethane and carbon disulfide) invariably produced the normal violet solution. He accounted for these observations by proposing the existence of an unstable addition product (eqn. 1) which is formed between iodine and a solvent molecule when the latter is capable of donating a pair of electrons. It is interesting to note that Beckmann[2] had earlier suggested the formation of such a complex.

$$\text{Solvent} + I_2 \longrightarrow (\text{Solvent} + I_2) \qquad (1)$$

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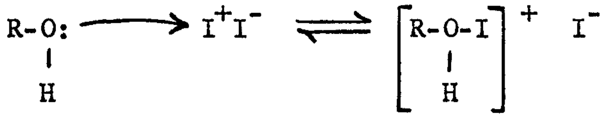
[1] A. Lachman, *J. Am. Chem. Soc.*, **25**, 50 (1903).

[2] E. Beckmann, *Z. Physik. Chem.*, **5**, 76 (1889).

In 1947, Fairbrother[3] suggested that complex formation between halogen and alcohol molecules was due to polar factors within the halogen molecule. It was proposed that the symmetrical ionic structures $X^- X^+$, $X^+ X^-$ may contribute more to the actual normal state of the halogen bond, especially in bromine, and still more iodine, than had been heretofore supposed. Thus the presence of an electron donor, like the oxygen atom in an alcohol molecule for example, may result in donation of an electron pair by the donor into the empty 5p orbital of the I^+ species or into the polarized iodine molecule (eqn. 2), hence



$$\underset{\displaystyle H}{\overset{}{R\text{-}\underset{|}{O}\!:}} \longrightarrow I^+I^- \rightleftharpoons \left[\underset{\displaystyle H}{R\text{-}\underset{|}{O}\text{-}I}\right]^+ \; I^- \qquad (2)$$

destroying the electronic symmetry and effecting a permanent ionization of the iodine molecule. Fairbrother supported his conclusion by correlating the tendency of iodine to form brown solutions in some solvents, with the apparent dipole moment of iodine in those solutions. Values of the dipole moment, (a measure of the extent of polarization of the iodine molecule), were determined to be 0.6 D in benzene (red-violet solution), 0.9 D in para-xylene (dark red), 1.3 D in 1,4-dioxane (brown), and 1.5 D in diisobutylene (brown). These solvents were chosen because they have very little polar nature yet exhibit the observed variety of colouration with iodine in solution.

A photometric study of a 1:1 complex between iodine and ethanol (eqn. 3) has been reported by Hamm.[4] The equilibrium constant for

$$CH_3CH_2OH + I_2 \rightleftharpoons CH_3CH_2OH\cdot I_2 \qquad (3)$$

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[3] F. Fairbrother, Nat., 160, 87 (1947).

[4] J. S. Hamm, J. Chem. Phys., 20, 1170 (1952).

equation 3 was determined to be 6.0 mole fraction units.

Andrews and Keefer[5] studied the reaction between bromine and tertiary amyl alcohol (eqn. 4). The authors assumed that trimethylethylene

$$Br_2 + C_5H_{11}OH \xrightarrow[-H_2O]{slow} (C_5H_{10}) + Br_2 \xrightarrow{fast} (CH_3)_2BrCCHBrCH_3 \qquad (4)$$

(C_5H_{10}) was the intermediate product which resulted from a bromine induced dehydration of the alcohol. The olefin then underwent rapid bromination to produce trimethylethylene dibromide.

The rate of disappearance of bromine was determined to be first order in bromine and second order in alcohol, and was faster than the rate of diminution of the oxidizing power of the solution. This was explained by suggesting that the rate-determining step involved a reaction of a 1:1 alcohol-bromine complex with another molecule of alcohol to yield a reducible colourless intermediate (eqns. 5,6).

$$C_5H_{11}OH + Br_2 \xrightarrow{fast} C_5H_{11}OH\cdot Br_2 \qquad (5)$$

$$C_5H_{11}OH\cdot Br_2 + C_5H_{11}OH \xrightarrow{slow} \text{Reducible Colourless Intermediate} \qquad (6)$$

The authors concluded that the reducible colourless intermediate was not the alkyl hypobromite since one would expect that such a moiety would decompose much too rapidly to allow for the high concentration observed. Again, the presence of hypobromite as an intermediate would result simultaneously in an equimolar concentration of hydrogen bromide (eqn. 7). Only traces of hydrogen bromide could be detected. Finally it was

$$C_5H_{11}OH + Br_2 \rightleftharpoons C_5H_{11}OBr + HBr \qquad (7)$$

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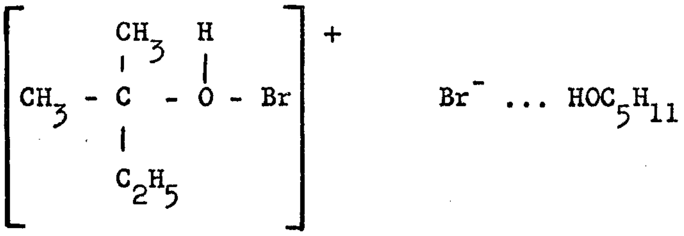
[5] L. J. Andrews and R. M. Keefer, J. Am. Chem. Soc., 75, 3557 (1953).

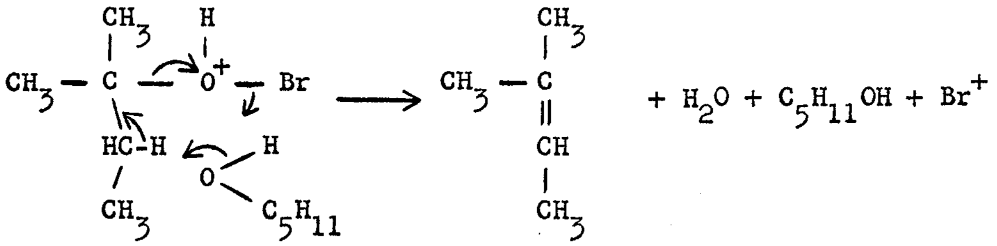
shown that the terminal reaction product was formed by a reaction whose rate was dependent on the concentration of the intermediate to the first power only, and is independent of the acid concentration.

Since the intermediate was formed through the reaction of the alcohol-bromine complex with a second molecule of alcohol, the authors suggested as a probable structure



$$\left[CH_3-\overset{CH_3}{\underset{C_2H_5}{C}}-\overset{H}{O}-Br \right]^+ \qquad Br^- \ldots HOC_5H_{11}$$

and that the breakdown is possibly initiated by the attack of a third alcohol molecule (eqn. 8).



(8)

There is not sufficient evidence to substantiate any predictions concerning the details of the breakdown process.

Keefer and Andrews in a subsequent publication[6] reported on the results of the determination of the equilibrium constant for the general reaction

$$ROH + X_2 \underset{}{\overset{K_c}{\rightleftharpoons}} ROH\cdot X_2 \qquad (9)$$

where R = t-amyl, i-propyl, and t-butyl.

$$K_c = \frac{(ROH\cdot X_2)}{(ROH)(X_2)}$$

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[6] R. M. Keefer and L. J. Andrews, J. Am. Chem. Soc., 75, 3561 (1953).

The values of K_c for the reactions of iodine with tertiary amyl alcohol, isopropyl alcohol, and tertiary butyl alcohol, and of bromine with tertiary butyl alcohol were all within the range of 0.5 to 1.6 litres per mole. They concluded that the stability of the complex ($ROH \cdot X_2$) is substantial and that its concentration is significant.

The above proposed mechanism is in contrast with one suggested by Ingold and his co-workers[7] to explain the iodine induced dehydration of tertiary alcohols (eqns. 10,11, 12).

$$ROH + 2I_2 \rightleftharpoons ROHI^+ + I_3^- \qquad \text{(fast)} \qquad (10)$$

$$ROHI^+ \longrightarrow R^+ + HOI \qquad \text{(slow)} \qquad (11)$$

$$R^+ \longrightarrow \text{Olefin} + H^+ \qquad \text{(fast)} \qquad (12)$$

This scheme was proposed as an analogy with a unimolecular elimination mechanism that Ingold had found successful in explaining the decomposition of sulfonium salts.

Several reactions of alcohols and halogens to give products other than complexes or olefins have been reported. Bugarszky[8] has reported that ethyl acetate was obtained when ethanol (two parts) was treated with bromine (one part) in aqueous solution (76%). Although no mechanism was proposed, the reaction proved to be first order in bromine concentration. In a separate experiment the same author has shown that tribromide ion (Br_3^-) does not enter into reaction with ethanol.

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[7] M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Woolf, J. Chem. Soc., 2113 (1948).

[8] S. Bugarszky, Z. Physik. Chem., 38, 561 (1901).

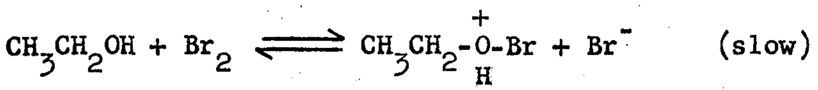
Further investigation of the above reaction by Farkas[9] and his co-workers has shown the presence of acetaldehyde as an intermediate. The authors proposed the following scheme (eqns. 13,14).

$$CH_3CH_2OH + Br_2 \longrightarrow CH_3CHO + 2HBr \qquad (13)$$

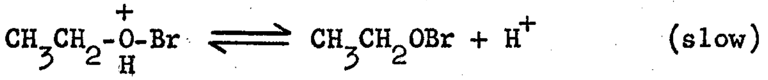
$$CH_3CHO + Br_2 + H_2O \longrightarrow CH_3COOH + 2HBr \qquad (14)$$

The rate of the reaction was found to be independent of the hydrogen ion concentration at pH less than 3 and it was shown that hypobromous acid is not involved in any rate determining step. Three possible mechanisms that are supported by experimental results were suggested by the authors.

The first mechanism (eqns. 15,16,17) involves the formation of ethyl hypobromite.



$$CH_3CH_2OH + Br_2 \rightleftharpoons CH_3CH_2\text{-}\overset{+}{\underset{H}{O}}\text{-}Br + Br^- \qquad \text{(slow)} \qquad (15)$$



$$CH_3CH_2\text{-}\overset{+}{\underset{H}{O}}\text{-}Br \rightleftharpoons CH_3CH_2OBr + H^+ \qquad \text{(slow)} \qquad (16)$$

$$CH_3CH_2OBr \longrightarrow CH_3CHO + HBr \qquad \text{(fast)} \qquad (17)$$

The decomposition of the ethyl hypobromite (eqn. 17) to give the aldehyde is supported by the known elimination of hydrogen chloride by alkyl hypochlorites to produce an aldehyde[10] (eqn. 18).

$$RCH_2OCl \longrightarrow RCHO + HCl \qquad (18)$$

However, equation 16 should be sensitive to H^+ concentration and the rate should therefore be dependent not independent as observed by the authors on the hydrogen ion concentration.

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[9] L. Farkas, B. Perlmutter, and O. Schnachter, *J. Am. Chem. Soc.*, *71*, 2829 (1949).

[10] F. D. Chattaway and O. G. Backeberg, *J. Chem. Soc.*, 3000 (1923).

The reaction represented by the second mechanism is initiated by a hydride abstraction:

$$CH_3CH_2OH + Br_2 \longrightarrow CH_3\overset{+}{C}HOH + HBr_2^- \qquad \text{(slow)} \qquad (19)$$

$$CH_3\overset{+}{C}HOH \longrightarrow CH_3CHO + H^+ \qquad \text{(fast)} \qquad (20)$$

$$HBr_2^- \longrightarrow H^+ + 2Br^- \qquad \text{(fast)} \qquad (21)$$

The third possible mechanism involves the displacement of a hydrogen atom by a bromine atom:

$$CH_3CH_2OH + Br_2 \longrightarrow CH_3CHBrOH + HBr \qquad \text{(slow)} \qquad (22)$$

$$CH_3CHBrOH \longrightarrow CH_3CHO + HBr \qquad \text{(fast)} \qquad (23)$$

This last mechanism was dismissed by the authors as untenable because of the lack of precedence for this type of reaction occurring at room temperature.

Kaplan[11] has reported on the results of a study on the effect of the substitution of tritium for protium on the α-carbon of ethanol on the rate of oxidation by bromine. This was done to distinguish if possible between the three proposed mechanisms of Farkas, Perlmutter and Schachter. In the second and third mechanisms a carbon-hydrogen bond is ruptured in the rate-determining step (eqns. 19 and 22 respectively). In the first mechanism this bond is broken in a subsequent fast step (eqn. 17). The two cases can be distinguished by comparing the rate of reaction of the normal compound with that of one which has been isotopically substituted

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[11] L. Kaplan, *J. Am. Chem. Soc.*, *76*, 4645 (1954).

at the position of bond rupture. There is experimental evidence[12,13] and theoretical justification[14-16] that if a bond involving the isotope is broken in the rate-determining step, the molecule containing the heavy isotope will react more slowly than that containing the light isotope. The rather large isotope effect, 0.57 in this study, requires that the rupture of the carbon-hydrogen bond occur in the slowest step. Again, due to the lack of dependence of the reaction rate on the hydrobromic acid concentration, Kaplan concluded that the hypobromite is not a precursor of acetaldehyde. Hence, the first mechanism of Farkas and co-workers (eqns. 15-17) appears to be ruled out as the mechanism of the reaction. The third mechanism (eqns. 22,23) was eliminated on similar grounds proposed previously by Farkas and his co-workers that it requires that hydrogen be replaced by bromine in a second order reaction at room temperature. Farkas' second mechanism (eqns. 19-21) appears much more reasonable in the light of Kaplan's work because it involves the rupture of a carbon-hydrogen bond in the slow step and because similar values of the kinetic isotope effect have been reported by Melander[17] in the reactions of ethanol with ortho and meta-nitrobenzenediazonium salts.

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[12] C. Reitz, Z. Physik. Chem., A179, 119 (1937).

[13] F. H. Westheimer and N. Nicolaides, J. Am. Chem. Soc., 71, 25 (1949).

[14] J. Bigeleisen, J. Chem. Phys., 17, 675 (1949).

[15] L. Melander, Arkiv. Kemi, 2, 211 (1950).

[16] H. Eyring and F. W. Cagle, Jr., J. Phys. Chem., 56, 889 (1952).

[17] L. Melander, Arkiv Kemi, 3, 525 (1952)

Support for the formation of methyl hypobromite was claimed by Meinel[18,19] as an intermediate in the reaction of a variety of olefins with bromine in methanol solution. Excellent yields were obtained of products corresponding to what one would expect if the elements of methyl hypobromite were to add as CH_3O^- and Br^+ across the ethylenic double bond. Meinel concluded from his studies that the following sequence was operative (eqns. 24,25):

$$CH_3OH + Br_2 \rightleftharpoons CH_3OBr + HBr \qquad (24)$$

$$CH_3OBr + R_2C{=}CR_2 \longrightarrow R_2C(OCH_3)CBrR_2 \qquad (25)$$

The author noted a great increase in the reaction rate upon the addition of silver nitrate, and this kinetic effect was explained by the precipitation of bromide ion. When bromide ion is removed from the first step (eqn. 24) the reaction becomes irreversible and the concentration of the methyl hypobromite intermediate will increase.[20]

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[18] K. Meinel, Ann., 510, 129 (1934).

[19] K. Meinel, Ann., 516, 237 (1935).

[20] The same effect may possibly be noted if the following scheme represents the reaction studied by Meinel:

$$R_2C{=}CR_2 + Br^+ - Br^- \longrightarrow R_2\overset{+}{C}\text{-}CBrR_2 + Br^- \qquad (26)$$

$$R_2\overset{+}{C}\text{-}CBrR_2 + CH_3OH \longrightarrow R_2C(CH_3O)CBrR_2 + H^+ \qquad (27)$$

$$Br^- + Br_2 \rightleftharpoons Br_3^- \qquad (28)$$

An alternate first step could be the formation of the bridged bromonium ion which may then be opened by a nucleophilic attack involving methanol. The increase in the rate of reaction on the addition of silver nitrate would accompany the removal of bromide ion as silver bromide, thus preventing the conversion of free bromine to the unreactive tribromide ion (eqn. 28). Silver may also aid in the heterolytic dissociation of bromine (eqn. 29), to increase the concentration of the active bromine species in the initial attack (eqn. 26).

$$Br_2 \rightleftharpoons Br^+ + Br^- \xrightarrow{Ag^+} Br^+ + AgBr \qquad (29)$$

Bartlett and Tarbell[21] have studied the reaction of stilbene with bromine in methanol solution in order to investigate the nature of the reaction between bromine and methanol. The addition of equivalent amounts of sodium bromide or hydrogen bromide had the same rate retarding effect. However, acidification with either hydrogen chloride or sulfuric acid had very little effect on the reaction rate. If methyl hypobromite is formed as the reactive intermediate (eqn. 30) the

$$CH_3OH + Br_2 \rightleftharpoons CH_3OBr + H^+ + Br^- \qquad (30)$$

addition of either hydrogen or bromide ions should have decreased the reaction rate by decreasing the methyl hypobromite concentration. The authors concluded that methyl hypobromite is not the intermediate that attacks the ethylenic bond. They suggested that instead, the initiator of the reaction must have been something whose concentration is reduced by the addition of bromide ion but not by the addition of hydrogen ion. Bromine was proposed to be that initiator (eqns. 31,32).

$$(C_6H_5)CH{=}CH(C_6H_5) + Br_2 \longrightarrow (C_6H_5)\overset{+}{C}H\text{-}CHBr(C_6H_5) + Br^- \qquad (31)$$

$$(C_6H_5)\overset{+}{C}H\text{-}CHBr(C_6H_5)+CH_3OH \longrightarrow (C_6H_5)CH(OCH_3)\text{-}CHBr(C_6H_4)+H^+ \qquad (32)$$

Swain[22] has studied the oxidation of isopropanol with bromine in aqueous solution and has shown that the reaction is first order in the concentrations of both bromine and alcohol (eqn. 33).

$$CH_3CHOHCH_3 + Br_2 \longrightarrow CH_3COCH_3 + 2HBr \qquad (33)$$

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[21] P. D. Bartlett and D. S. Tarbell, J. Am. Chem. Soc., 58, 46 (1936).

[22] C. G. Swain, R. A. Wiles, and R. F. Bader, J. Am. Chem. Soc., 83, 1945 (1961).

It was also shown that the reaction rate was independent of the concentrations of Br^- and H^+ in the range pH 1 to pH 3. The essential differences between the transition states for hydride and proton transfer in similar systems with the same force constants and hydrogen isotope effects were presented in a discussion that shows that these two transition states have different electron distributions. In a proton transfer the transition state may resemble

$$R_1 \overset{\rightarrow}{:} H \overset{\rightarrow}{:} R_2$$

where the hydrogen is being transferred from R_2 to R_1. In the hydride transfer the transition state may resemble

$$R_1 \; \overset{\curvearrowleft}{H :} \; R_2$$

In a transition state which involves proton transfer the electron density is higher both relatively and absolutely on R_1 and R_2. These groups are farther apart, and the distance as well as the force constants are much more sensitive to substituents because the antibonding makes energy a weak function of distance.[23]

The CH isotope effect of 2.94 ± 0.1 in isopropanol-2-d shows that this bond is broken in the rate determining step. In 1-fluoroisopropanol-2-d the CH isotope effect is 2.83 ± 0.1. Thus the relative insensitivity of the isotope effect to the electron-seeking nature of the fluorine substitution shows by the above argument that hydride transfer occurs from the 2-carbon in isopropanol. Conversely the change in the isotope effect for OH from 1.49 to 2.06 for the unfluor-

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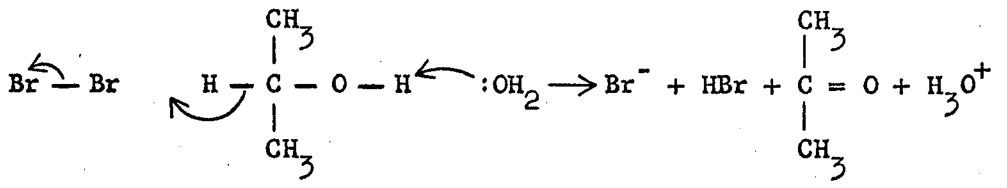
[23] H. C. Longuet-Higgins, *Rec. trav. chim.*, *75*, 825 (1956).

inated and fluorinated isopropanols respectively, shows the substitutive sensitivity that is associated with a proton transfer from the oxygen atom. The authors concluded that the mechanism (eqn. 34) for the



$$Br-Br \quad H-\overset{CH_3}{\underset{CH_3}{C}}-O-H \; :OH_2 \longrightarrow Br^- + HBr + \overset{CH_3}{\underset{CH_3}{C}}=O + H_3O^+ \qquad (34)$$

oxidation of isopropanol by bromine in aqueous solution must involve hydride transfer from carbon and proton transfer from oxygen.

It has been shown by Clarke and Esselen[24] that when 2,5-dibromo-4-aminobenzhydrol is treated with bromine in chloroform solution a splitting takes place whereby 2,4,6-tribromoaniline and benzaldehyde are produced (eqn. 35).

$$C_6H_5CHOHC_6H_2Br_2NH_2 + Br_2 \longrightarrow C_6H_5CHO + C_6H_2Br_3NH_2 + HBr \qquad (35)$$

Clarke and Patch[25] extended the research to include aminoarylcarbinols containing an aliphatic residue and also to tertiary carbinols. Ethyl-4-dimethylaminophenylcarbinol and isobutyl-4-dimethylaminophenylcarbinol were found to undergo an elimination reaction with bromine, yielding in both cases the hydrobromide of p-bromodimethylaniline along with propionaldehyde and isovaleraldehyde respectively. When 4-dimethylaminodiphenylmethylcarbinol was treated in the same manner, the same aniline derivative was obtained along with acetophenone. Similar treatment of triphenylcarbinols substituted at one, two, or three para

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[24] L. Clarke and G. J. Esselen, Jr., J. Am. Chem. Soc., 33, 1135 (1911).

[25] L. Clarke and R. H. Patch, J. Am. Chem. Soc., 34, 912 (1912).

positions by the dimethylamino group yielded the same derivatives as before along with the corresponding substituted benzophenone.

Kohler and Patch[26] were the first to note the oxidation of p-dimethylaminobenzhydrol as a minor side reaction to the cleavage reaction with bromine. Nitric acid, nitrous acid and other reagents that are capable of forming substitution products by direct action upon aromatic compounds, split these hydrols in the same manner and with the same ease as do the halogens. The compounds that give a large proportion of cleavage product when treated with halogens undergo an equally extensive cleavage with these reagents.

Kohler and Patch concluded 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."

A recent investigation[27] of the factors affecting the relative rates of cleavage, oxidation and ring bromination in the arylcarbinol system has shown that the cleavage yield is best in the benzhydrol system when both aromatic rings are substituted in the para position by the methoxyl group. Ring bromination occurs as a competing reaction in nearly all the reactions reported, while oxidation was important when ring bromination was blocked by other substitution, and when the compound was not sufficiently activated for cleavage to occur. In the case of benzhydrol and 4,4'-dimethylbenzhydrol, ring bromination was so depressed that a quantitative oxidation of the alcohol to the cor-

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[26] E. P. Kohler and R. H. Patch, J. Am. Chem. Soc., 38, 1205 (1916).

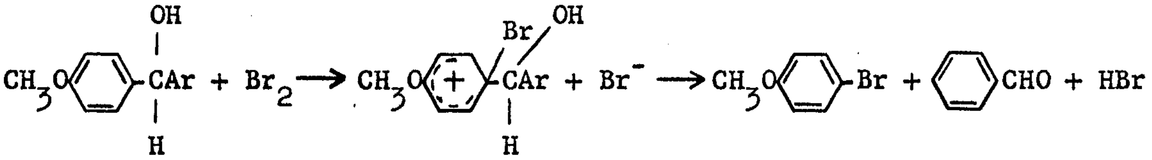
[27] E. M. Arnett and G. B. Klingensmith, J. Am. Chem. Soc., 87, 1023 (1965).

responding ketone was obtained. 4-Methoxybenzyl alcohol underwent cleavage with bromine to produce a 61% yield of 4-bromoanisole. 4-Methoxytriphenylcarbinol gave a very small yield of the cleavage product. Kinetic studies on the above reaction[28] have shown that the rate of brominative cleavage of methoxy-activated benzhydrols is determined by the nature of the substitution on both aromatic rings of the system. Variation of the 4'-substituent in 4-methoxy-4'-X-benzhydrol produces a significant change in the rate of cleavage (eqn. 36).

$$CH_3OC_6H_4CHOHC_6H_4X + Br_2 \longrightarrow CH_3OC_6H_4Br + HCOC_6H_4X + HBr \qquad (36)$$

As X is varied in the series: methoxyl, methyl, hydrogen, bromo to nitro, a 19 fold decrease in the reaction is observed.

A mechanism[29] was proposed that was in conformity with the kinetic data and the general theory of electrophilic aromatic displacements.



(37)

It was shown that the benzhydrol hypobromite was not the intermediate by preparing the 4,4'-dimethoxydiphenylmethyl hypobromite according to the method of Padwa[30] and subjecting it to the reaction

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[28] E. M. Arnett and G. B. Klingensmith, J. Am. Chem. Soc., 87, 1032 (1965).

[29] E. M. Arnett and G. B. Klingensmith, J. Am. Chem. Soc., 87, 1038 (1965).

[30] C. Walling and A. Padwa, J. Org. Chem., 27, 2976 (1962).

conditions. No cleavage product was obtained, instead the 4,4'-dimethoxybenzhydrol and its acetate were recovered in nearly quantitatively yield.

A compound of some interest was obtained by treating 4,4',4"-trimethoxytriphenylcarbinol with bromine in dichloromethane solution. Red needles were obtained from the reaction and on the basis of an analysis of an ultraviolet absorption spectrum and a nuclear magnetic resonance spectrum the compound was suggested to be trianisylcarbonium tribromide. The compound exhibited remarkable stability but quenching with water regenerated the carbinol.

The reactions of arylcarbinols with bromine and iodine became of interest in our laboratory with the observation that the methyl ether of triphenylcarbinol was obtained when a mixture of the carbinol and iodine was allowed to react in a solution of acetone and methanol. It was decided to investigate the limitations of the reaction and to determine whether it would be of value as a preparative procedure.

Previously Reported Synthetic Methods for Ethers

The Williamson[31] synthesis of asymmetric ethers involves the alkylation of hydroxy compounds by organic halides. This is usually accomplished by the addition of the alkyl halide to the alkali salt of the alcohol (eqn. 38).

$$\mathrm{RONa} + \mathrm{R'X} \longrightarrow \mathrm{ROR'} + \mathrm{NaX} \qquad (38)$$

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[31] A. W. Williamson, Phil. Mag., (3) 37, 350 (1850).

Syntheses of alkylphenyl ethers are carried out by heating under reflux conditions, an alkali phenoxide in aqueous or alcoholic solution with alkyl halides.[32,33]

Benzyl halides undergo a facile reaction with alkoxides to yield ethers[34,35] while triarylmethyl chlorides react directly with the alcohol[36] (eqn. 39).

$$Ar_3CCl + ROH \longrightarrow Ar_3COR + HCl \qquad (39)$$

Asymmetric ethers may also be prepared by the alkylation of alcohols by alkyl sulfates[37], sulfites[38] or sulfonates[39] (eqn. 40).

$$2RONa + (CH_3)_2SO_4 \longrightarrow 2ROCH_3 + Na_2SO_4 \qquad (40)$$

The preparation of higher analogues of unsymmetrical ethers is complicated by the preparation of the required sulfates.

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[32] A. I. Vogel, J. Chem. Soc., 616 (1948).

[33] W. T. Olson, et al., J. Am. Chem. Soc., 69, 2451 (1947).

[34] W. J. Monacelli and G. F. Hennion, J. Am. Chem. Soc., 63 1722 (1947).

[35] W. S. Emmerson, et al., J. Am. Chem. Soc., 69, 1905 (1947).

[36] A. C. Nixon and G. E. K. Branch, J. Am. Chem. Soc., 58, 492 (1936).

[37] W. Cerchez, Bull. Soc. Chim. France, 43, 762 (1928).

[38] W. W. Carlson and L. H. Cretcher, J. Am. Chem. Soc., 69, 1952 (1947).

[39] V. M. Rodionow, Bull. Soc. Chim. France, (4) 45, 118 (1929).

Alcohols can be made to lose water under acidic conditions to yield symmetrical aliphatic ethers[40] (eqn. 41).

$$2ROH + H^+ \longrightarrow ROR + H_3O^+ \tag{41}$$

Good yields are very dependent upon the reaction temperature, because high temperatures favour olefin formation.[41] Some unsymmetrical ethers may be prepared by acid catalyzed dehydration. For example, t-butyl alcohol added slowly to a boiling mixture of ethanol and 15% aqueous sulfuric acid gives a 95% yield of t-butyl ethyl ether[42] (eqn. 42). Sodium hydrogen sulfate can be used to obtain an 82% yield of

$$(CH_3)_3COH + H^+ + C_2H_5OH \longrightarrow (CH_3)_3COC_2H_5 + H_3O^+ \tag{42}$$

t-butyl i-propyl ethers[43], starting with t-butyl and i-propyl alcohols.

Of relatively minor importance is the gas phase dehydration of alcohols by solid catalysts such as alumina[44-46] (eqn. 43). Thorium

$$2ROH \xrightarrow[-H_2O]{Al_2O_3} ROR \tag{43}$$

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[40] P. P. Schorigin and Ya. Makaroff-Semlhanski, Ber., 65, 1293 (1932).

[41] A. I. Vogel, J. Chem. Soc., 616 (1948).

[42] I. N. Hultman, A. W. Davis, and H. T. Clarke, J. Am. Chem. Soc., 43, 366 (1921).

[43] J. F. Norris and G. W. Rigby, J. Am. Chem. Soc., 54, 2088 (1932).

[44] R. H. Clark, W. E. Graham, and A. G. Winter, J. Am. Chem. Soc., 47, 2748 (1925).

[45] V. N. Ipatieff and R. L. Burwell, Jr., J. Am. Chem. Soc., 63, 969 (1941).

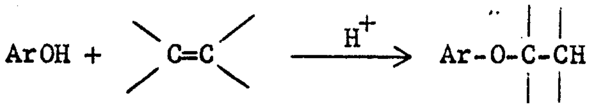
[46] N. M. Gullinane and S. J. Chard, J. Chem. Soc., 821 (1945).

dioxide at 450° is used to obtain diphenylether from phenol in 64% yield.[47]

The addition of alcohols to olefinic compounds provides an easy method for making ethers which may otherwise be difficult to obtain, particularly those which contain a second functional group. The reaction is often catalyzed by dilute sulfuric acid. Generally, alkylated olefins and primary alcohols are the most suitable reactants. Tertiary alcohols are practically non-reactive. For example, trimethylethylene and ethanol give a 90% yield of ethyl t-amyl ether[48] (eqn. 44).

$$CH_3CH{=}C(CH_3)_2 + C_2H_5OH \longrightarrow C_2H_5\text{-}O\text{-}C_5H_{11} \qquad (44)$$

Mineral acids[49] and boron trifluoride[50] can be used to condense phenols with unsaturated compounds in the cold (eqn. 45). Three molecules of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methanol can be added to vinyl acetylene in the presence of boron trifluoride and mercuric oxide to yield 2,2,4-trimethoxybutane in 65% yield.[51] However, in the presence of sodium methoxide, 4-methoxy-1-

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[47] E. Briner, J. Bron-Stalet, and H. Paillard, Helv. Chim. Acta, 15, 619 (1932).

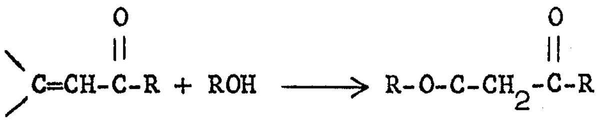
[48] T. W. Evans and K. R. Edlund, Ind. Eng. Chem., 28, 1186 (1936).

[49] J. B. Niederl and S. Natelson, J. Am. Chem. Soc., 53, 272 (1928).

[50] F. J. Sowa, H. D. Hinton, and J. A. Nieuwland, J. Am. Chem. Soc., 54, 2019, 3695 (1932).

[51] D. B. Killian, G. F. Hennion, and J. A. Nieuwland, J. Am. Chem. Soc., 56, 1786 (1934).

butyne is obtained in 61% yield.[52] Unsaturated ketones undergo a reaction with alcohols in the presence of boron trifluoride etherate [53,54] or the sodium alkoxide[55,56] to yield β-alkoxy ketones (eqn. 46).



$$\rangle C{=}CH{-}\overset{O}{\overset{\|}{C}}{-}R + ROH \longrightarrow R{-}O{-}C{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}R \qquad (46)$$

Acrylic esters undergo a similar reaction with primary and secondary alcohols and phenols to yield the corresponding β-alkoxy- and β-aryloxypropionates.[57-59] β-Alkoxypropionitriles are obtained from a reaction of acrylonitrile with primary or secondary alcohols[60-62] (eqn. 47).

$$CH_2{=}CH{-}CN + ROH \longrightarrow R{-}O{-}CH_2{-}CH_2CN \qquad (47)$$

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[52] R. A. Jacobson, H. B. Dykstra, and W. H. Carothers, *J. Am. Chem. Soc.*, *56*, 1169 (1934).

[53] D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Am. Chem. Soc.*, *58*, 892 (1936).

[54] N. A. Milas, et al., *J. Am. Chem. Soc.*, *70*, 1602 (1948).

[55] B. Puetzer, C. H. Nield, and R. H. Barry, *J. Am. Chem. Soc.*, *67*, 835 (1945).

[56] R. C. Elderfield, B. M. Pitt, and I. Wempen, *J. Am. Chem. Soc.*, *72*, 1340 (1950).

[57] C. E. Rehberg, M. B. Dixon, and C. H. Fiser, *J. Am. Chem. Soc.*, *69*, 2970 (1947).

[58] C. E. Rehberg, and M. B. Dixon, *J. Am. Chem. Soc.*, *72*, 2205 (1950).

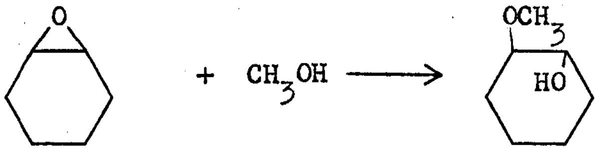
[59] R. H. Hall and E. S. Stern, *J. Chem. Soc.*, 2035 (1949).

[60] C. F. Koelsch, *J. Am. Chem. Soc.*, *65*, 437 (1943).

[61] W. P. Utermohlen, Jr., *J. Am. Chem. Soc.*, *67*, 1505 (1945).

[62] R. V. Christian, Jr., and R. M. Hixon, *J. Am. Chem. Soc.*, *70*, 1333 (1948).

Alcohols may undergo an addition reaction with oxides to give hydroxy ethers. The reaction is a trans opening of the ring and the mechanism and stereochemistry are well known.[63] For example, cyclohexene will suffer methanol addition to yield trans-2-methoxycyclohexanol in 82% yield[64] (eqn. 48). When a unsymmetrical epoxide reacts,



(48)

either a primary or a secondary alcohol is formed, depending on which carbon-oxygen bond is broken.[65-68]

Preliminary studies on the synthesis of ethers using iodine have been carried out[69,70] and have shown that the reaction is of synthetic value when applied to di- and triaryl carbinols (eqn. 49). It was

$$Ar_3COH + CH_3OH \xrightarrow{I_2} Ar_3COCH_3 \qquad (49)$$

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[63] S. Winstein and R. B. Henderson, "Heterocyclic Compounds", R. C. Elderfield, ed., Vol. I, John Wiley and Sons, New York, 1950, pp. 22-42.

[64] S. Winstein and R. B. Henderson, J. Am. Chem. Soc., 65, 2196 (1943).

[65] H. C. Chitwood and B. T. Freure, J. Am. Chem. Soc., 68, 680 (1946).

[66] A. R. Sexton and E. C. Britton, J. Am. Chem. Soc., 70, 3606 (1948).

[67] P. D. Bartlett and S. D. Ross, J. Am. Chem. Soc., 70, 926 (1948).

[68] W. Reeve and I. Christoffel, J. Am. Chem. Soc., 72, 1480 (1950).

[69] J. M. Prokipcak, Ph.D. Thesis, Faculty of Graduate Studies, University of Windsor, 1964.

[70] R. F. A. Jobin, Ph.D. Thesis, Faculty of Graduate Studies, University of Windsor, 1964.

found by titrimetric methods that the role of the iodine is that of a catalyst only. Triphenyl carbinol afforded the methyl ether (90%), the ethyl ether (80%), the n-propyl ether (78%), the i-propyl ether (45%), and the benzyl ether (50%) when allowed to react with the corresponding alcohols in the presence of iodine. Benzhydrol proved amenable to the preparation of a similar series of ethers, with corresponding yields significantly smaller: the methyl ether (70%), the ethyl ether (52%), and the n-propyl ether (42%). Benzyl methyl ether could not be prepared in even small yields from benzyl alcohol and methanol in the presence of iodine. Furthermore, 4-nitrobenzhydrol, 4-nitro-4'-bromobenzhydrol and 4-nitro-4'-t-butylbenzhydrol failed to undergo ether formation.

It was subsequently decided to make a study of the effect of nuclear substitution on the ability of an aryl carbinol to undergo iodine catalyzed ether formation and also to determine if it would be possible to induce the above mentioned nitro substituted benzhydrols to undergo ether formation with bromine as the catalyst.

In the course of these investigations it was found that with triarylcarbinols and simple alcohols, bromine and iodine yielded exclusively the corresponding unsymmetrical ethers. With benzhydrols, bromine effected oxidation to the corresponding ketone with yields greatly dependent on the nature of the aromatic substitution, while iodine gave the corresponding mixed ethers in yields also greatly dependent on the nature of the aromatic substitution. Only one benzyl alcohol was observed to undergo ether formation with iodine. Several benzyl alcohols were capable of being oxidized to the corresponding aldehyde by bromine.

Previously Reported Oxidative Synthetic Methods for Aryl Aldehydes and Ketones:

Aryl aldehydes can be prepared by the oxidation of aromatic side chains with chromium trioxide in acetic anhydride solution. The corresponding diacetates are the intermediates which are stable to further oxidation (eqn. 50). These compounds are readily hydrolyzed

$$ArCH_3 \xrightarrow[Ac_2O]{CrO_3} ArCH(OCOCH_3)_2 \xrightarrow[H_2O]{HCl} ArCHO \qquad (50)$$

in acid solution to the corresponding aldehydes.[71-73] The procedure is generally applicable to the preparation of benzaldehydes carrying nitro, halo, and cyano substituents. Manganese dioxide in an acidic medium has been used to prepare 3,5-dimethylbenzaldehyde from mesitylene.[74] Chromyl chloride[75] is often used to effect the oxidation of a hydrocarbon to yield an aldehyde (eqn. 51).

$$ArCH_3 \xrightarrow{CrO_2Cl_2} ArCHO \qquad (51)$$

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[71] S. V. Lieberman and R. Connor, *Org. Syntheses* Coll. Vol. II, 441 (1943).

[72] A. F. Walton, R. S. Tipson and L. H. Cretcher, *J. Am. Chem. Soc.*, *67*, 1501 (1945).

[73] S. M. Tsang, E. H. Wood and J. R. Johnson, *Org. Syntheses*, *24*, 75 (1944).

[74] C. S. Marvel, J. H. Saunders and C. G. Overberger, *J. Am. Chem.* Soc., *68*, 1085 (1946).

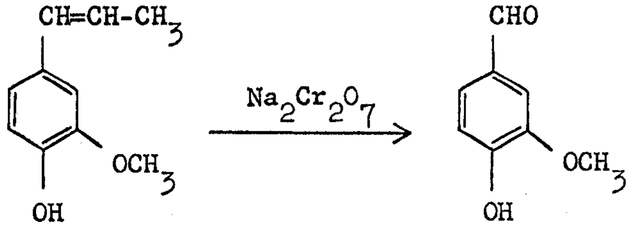
[75] M. D. Law and F. M. Perkin, *J. Chem. Soc.*, 259 (1907)

Selenium dioxide[76] or copper nitrate[77] can be used to oxidize benzyl halides directly.

Aliphatic aldehydes may be obtained by the hydrolysis of ozonides which are intermediates formed in a reaction between ozone and olefinic compounds (eqn. 52). However, the oxidation of olefinic side chains on an aromatic nucleus to form aromatic aldehydes often gives erratic results and as a consequence, other oxidants are employed. Usually nitrobenzene in dilute alkali solution will effect the desired oxidation.[78]

$$\mathrm{RCH = CH_2 \xrightarrow[H_2O]{O_3} RCHO + CH_2O} \qquad (52)$$

Sodium dichromate in the presence of sulfanilic acid gives excellent yields in the oxidation of isoeugenol[79] (eqn. 53).



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[76] C.H. Fisher, *J. Am. Chem. Soc.*, *56*, 2056 (1934).

[77] J.W. Baker, W.S. Nathan and C.W. Shoppee, *J. Chem. Soc.*, 1848 (1935).

[78] L.N. Ferguson, *Chem. Revs.*, *38*, 227 (1946).

[79] R.R. Davies and H.H. Hodgson, *J. Soc. Chem. Ind.* (London), *62*, 90 (1943).

The controlled oxidation of benzyl alcohols by chromic acid in aqueous acid solution (eqn. 54) is a useful method of preparing aromatic

$$ArCH_2OH \xrightarrow[H^+]{CrO_3} ArCHO \qquad (54)$$

aldehydes.[80] Nitrogen tetroxide has been reported as having been used to oxidize p-cyanobenzyl alcohol in chloroform solution to p-cyanobenzaldehyde.[81] The oxidations of ortho and para-nitrobenzyl alcohols with nitric acid to produce the corresponding aldehydes has been reported.[82] Phenolic benzyl alcohols have been oxidized to the corresponding aldehydes by m-nitrobenzenesulfonic acid in basic media.[83]

The Oppenauer reaction has been applied to the preparation of benzaldehydes.[84] The benzyl alcohol, a high boiling aldehyde, and an aluminium alkoxide catalyst are heated together, and the volatile benzaldehyde product is allowed to distill from the reaction mixture (eqn. 55).

$$ArCH_2OH + RCHO \xrightarrow{Al(OR)_3} ArCHO + RCH_2OH \qquad (55)$$

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[80] L. I. Smith et.al., J. Org. Chem., 4, 323 (1939).

[81] J. N. Ashley et.al., J. Chem. Soc., 115 (1942).

[82] B. F. Helferich, R. Streech and E. Gunther, J. Prakt. Chem., 151, 251 (1938).

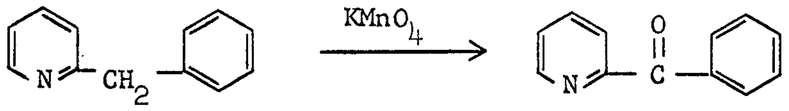
[83] F. Manus, J. Prakt. Chem., 158, 254 (1941).

[84] C. Djerassi, Organic Reactions, Vol. 6, John Wiley and Sons, New York, 1951, p.207.

The hydrolysis of gem-dihalides has been useful in the preparation of benzaldehyde (eqn. 56). Toluenes substituted with chloro, bromo, fluoro, or cyano groups can be dibrominated and the resulting benzal bromides hydrolyzed directly to the corresponding aldehydes in the presence of calcium carbonate or sulfuric acid.[85,86]

$$ArCH_3 \xrightarrow{Br_2} ArCHBr_2 \xrightarrow{H_2O} ArCHO \qquad (56)$$

The oxidative preparative methods of aryl ketones are somewhat similar to those for aryl aldehydes. Methylene groups may be oxidized readily to the corresponding ketone by a variety of oxidizing agents, such as selenium dioxide[87] and oxides of nitrogen.[88] The chromic acid oxidation of 4,4'-diacetylaminodiphenylmethane yields the corresponding benzophenone in 70% yield.[89] Also 2-benzoylpyridine is prepared from 2-benzylpyridine (eqn. 57) in 86% yield by the action of potassium per-



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[85] G. H. Coleman and G. E. Honeywell, Org. Syntheses, Coll. Vol. II, 89 (1943).

[86] W. L. McEwen, Org. Syntheses, Coll. Vol. II, 133 (1943).

[87] G. R. Waitkins and C. W. Clark, Chem. Revs., 36, 235 (1945).

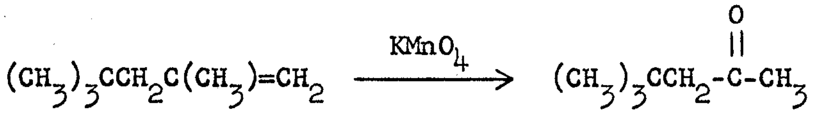
[88] J. L. Riebsomer, Chem. Revs., 36, 157 (1945).

[89] H. Rivier and A. Farine, Helv. Chim. Acta, 12, 865 (1929).

manganate.[90] Tetralin has been found to be oxidized to α-tetralone (eqn. 58) by passing dispersed air through the liquid and then hydrolyzing the mixture with an aqueous alkali solution.[91]

(58)

The preparation of aryl ketones by the ozonolysis of 1,1-diaryl olefins has little synthetic value. The oxidation of olefins with potassium permanganate or chromic acid to furnish ketones has been reported. An example (eqn. 59) is the oxidation of diisobutylene to methyl neopentyl ketone.[92] This procedure, however, seems to have its best application in the aliphatic system.



$$(CH_3)_3CCH_2C(CH_3)=CH_2 \xrightarrow{KMnO_4} (CH_3)_3CCH_2\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}CH_3 \qquad (59)$$

The oxidation of secondary alcohols has a wide application in the synthesis of aryl ketones. With chromic acid as the oxidant, m-biphenylmethylcarbinol and 2-phenylcyclohexanol are oxidized in acetic

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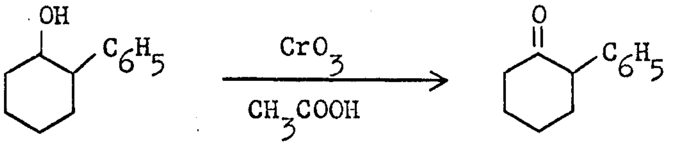
[90] E. H. Huntress and H. C. Walter, J. Am. Chem. Soc., 70, 3704 (1948).

[91] E. B. Thompson, Org. Syntheses, 20, 94 (1940).

[92] W. A. Mosher and J. C. Cox, Jr., J. Am. Chem. Soc., 72, 3701 (1950).

acid solution to the corresponding ketones (eqn. 60).[93,94] Similarly,



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α-nitroacetophenone has been obtained by the chromic acid oxidation of the corresponding alcohol.[95] The mechanism of the chromic acid oxidation of alcohols has been extensively treated in the chemical literature.[96-98] The Oppenauer reaction can be used as a means of oxidizing secondary alcohols to ketones in a manner similar to that previously described for aldehydes (eqn. 61). An extensive investigation of the reaction using

$$R_2CHOH + R'_2CO \xrightarrow[\text{alkoxide}]{\text{metal}} R_2CO + R'_2CHOH \qquad (61)$$

aluminum tertiary butoxide has been published,[99] and the literature pertinent to this synthetic method has been reviewed.[100]

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[93] C. C. Price and J. V. Karabinos, J. Am. Chem. Soc., 62, 1160 (1940).

[94] W. F. Huber et.al., J. Am. Chem. Soc., 68, 1109 (1946).

[95] L. M. Long and H. D. Troutman, J. Am. Chem. Soc., 71, 2469 (1949).

[96] Q. A. Mosher and E. O. Langerak, J. Am. Chem. Soc., 71, 286 (1949).

[97] F. H. Westheimer, Chem. Revs., 45, 419 (1949).

[98] H. A. Neidig, et. al., J. Am. Chem. Soc., 72, 4617 (1950).

[99] H. Adkins and R. C. Franklin, J. Am. Chem. Soc., 63, 2381 (1941).

[100] C. Djerassi, Organic Reactions, Vol. 6, John Wiley and Sons, New York, 1951, p.207.

The hydrolysis of gem-dihalides (eqn. 62) to give ketones has been

$$R_2CX_2 \xrightarrow{H_2O} R_2CO + 2HX \qquad (62)$$

reported in the chemical literature[101-104] and is similar to that previously mentioned for aldehydes.

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[101] C. S. Marvel and W. M. Sperry, Org. Syntheses, Coll. Vol. I, 95 (1941).

[102] L. A. Bigelow and R. S. Hanslick, Org. Syntheses, Coll. Vol. II, 244 (1943).

[103] G. Wittig and F. Vidal, Chem. Ber., 81, 368 (1948).

[104] L. Schmerling, J. Am. Chem. Soc., 68, 1650 (1946).

CHAPTER II

DISCUSSION OF EXPERIMENTAL RESULTS

The novel synthetic route to mixed arylmethyl-alkyl ethers described here seems to be a useful one particularly from the viewpoints of facility and absence of side-reactions. The facility arises from the single-step nature of the synthesis; other syntheses require the preparation of at least one of the reactants from more readily available starting materials. For example, in the Williamson synthesis of methyl triphenylmethyl ether, the readily available triphenylcarbinol must first be converted to the triphenylmethyl chloride, which then is made to react with methanol. Usually aryl carbinols are much more readily available than the halides because the former are frequently the direct result of a Grignard synthesis.

Table I summarizes the results obtained on the application of this method to the aryl carbinols studied. In addition, the following aryl carbinols failed to yield ethers with methanol and iodine: 4-nitrobenzhydrol, 4-bromo-4'-nitrobenzhydrol, 4-nitro-4'-t-butylbenzhydrol, and benzyl alcohol. It is seen that yields tend to decrease as the carbinol which undergoes the reaction becomes less substituted with groups that would tend to stabilize the corresponding carbonium ion formed through a heterolytic cleavage of the carbinol at the CO bond. For example 4-methylbenzhydrol gave a good yield of the ether with methanol while benzyl alcohol showed no evidence of ether formation under the same conditions. This is consistent with the known greater stability of the 4-methylbenzhydrol carbonium ion when compared to the benzyl carbonium ion.

Table I

Ethers Prepared From Aryl Carbinols With Iodine Catalysis

Ether	Yield (%)
Methyl triphenylmethyl ether	91
Ethyl triphenylmethyl ether	87
n-Propyl triphenylmethyl ether	80
i-Propyl triphenylmethyl ether	61
Benzyl triphenylmethyl ether	52
Methyl α-naphthylphenyl-p-tolylmethyl ether	100
Methyl phenyl-p-tolylmethyl ether	96
Methyl 4-chlorodiphenylmethyl ether	85
Methyl 4-bromo-4'-chlorodiphenylmethyl ether	100
Methyl 4-methoxybenzyl ether	73
1-Phenylphthalan	82
1,1-Diphenylphthalan	85

However, 4-nitrobenzhydrol shows no evidence of ether formation while 4-methoxybenzyl alcohol gave a good yield of the corresponding methyl ether. The presence of a nitro group in the para position on one of the aromatic rings evidently makes the carbonium ion so unstable through the inductive effect of the nitro group transmitted across the ring that the ion does not form. On the other hand, the 4-methoxyl group probably is able to contribute enough to carbonium ion stability that heterolytic cleavage of the 4-methoxybenzyl alcohol under the influence of iodine is probably more facile than the corresponding step in 4-nitrobenzhydrol.

The well-known stability of the triphenylmethyl carbonium ion again corresponds with the excellent yield obtained of the methyl and ethyl ethers of triphenylcarbinol.

The presence of a carbonium ion which was suggested as an intermediate in the iodine catalyzed dehydration of alcohols[1] was shown by the isolation of a good yield (82%) of bis-(4-methoxyphenyl)-methane from a solution of 4-methoxybenzyl alcohol, anisole and iodine in acetone. This product is the one expected in an electrophilic attack by 4-methoxybenzyl carbonium ion on anisole. If the carbonium ion is generated in the presence of a simple aliphatic alcohol, it will undergo nucelophilic attack by the alcohol to yield the ether (eqn. 63).

$$\mathrm{ROH} + \mathrm{I_2} \rightleftharpoons \mathrm{R^+} + (\mathrm{OH\cdot I_2})^- \xrightarrow{\mathrm{R'OH}} \mathrm{ROR'} + \mathrm{H^+} \qquad (63)$$

Nucleophilic attack by the aliphatic alcohol on the carbonium ion probably is governed to a large extent by the relative bulkiness of the former. Aliphatic alcohols having greater bulk will be hindered in their attack at the carbonium ion site and the yields will be correspondingly smaller. This trend was observed in both the triphenylcarbinol and benzhydrol systems. Again, aryl carbinols which form more stable carbonium ions will do so more rapidly, and the ether yield will be correspondingly larger. This trend was also noted in the experimental data.

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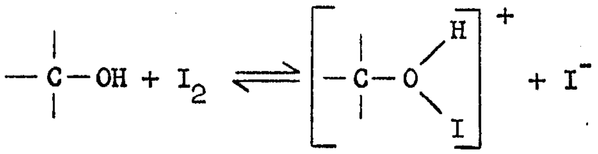
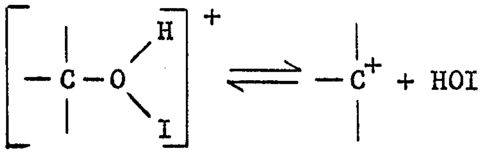
[1] M. L. Dhar, et al., J. Chem. Soc., 2113 (1948).

The mechanism for the ether formation is probably best represented in the following manner:



(64)



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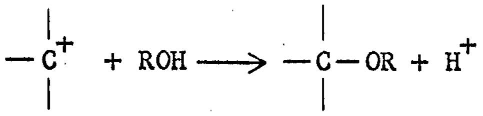
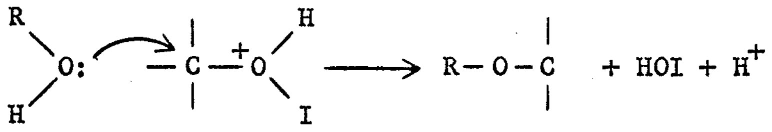


$$-\overset{|}{\underset{|}{C^{+}}} + ROH \longrightarrow -\overset{|}{\underset{|}{C}}-OR + H^{+} \qquad (66)$$

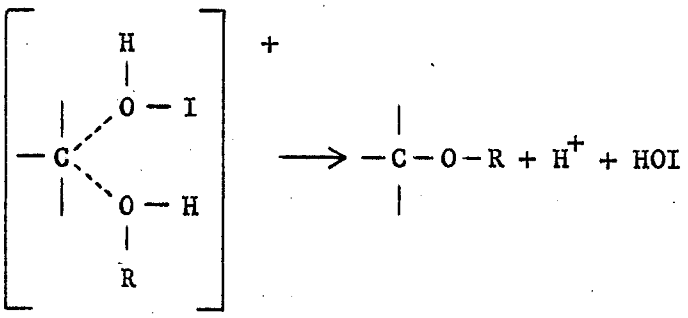
$$HOI + HI \longrightarrow H_2O + I_2 \qquad (67)$$

The regeneration of iodine would also explain the catalytic activity as determined by the titration of the reaction mixture with a standardized solution of sodium thiosulfate. Alternately, hypoiodous acid may also be eliminated in a bimolecular mechanism:



(68)

It may be possible to distinguish between the two mechanisms by preparing the methyl ether of an optically active carbinol where the asymmetric center is at the carbinyl carbon atom. If an optically inactive ether is the product, the open carbonium ion must have been formed in a unimolecular reaction which was followed by planarization and loss of optical activity. However, if the ether is optically pure, the mechanism representing its formation must not involve an open carbonium ion. Either the second mechanism described above (eqn. 68) must have prevailed, or possibly yet another, a coordinated collapse of an ion pair intermediate (eqn. 69). The existence of ion pair intermediates in solvolytic reactions is well documented.[2]



(69)

Absolute configuration studies on the optically active carbinol and ether would show whether the reaction occurred by the inversion (eqn. 68) or the retention of configuration (eqn. 69) about the carbinyl carbon atom.

It would be of interest to determine the scope and limitations of the Friedel-Crafts reaction catalyzed by iodine. Of interest may also be any reversible character in the reaction when catalyzed by iodine, as well as the ratios of ortho, meta and para substitution obtained by this reaction when compared to those obtained by metal halide or acid catalysis.

The methyl triarylmethyl ethers prepared by bromine catalysis were probably the result of a reaction scheme analogous to that for iodine. However, the reactions involving the oxidation of mono- and diaryl carbinols to aldehydes and ketones respectively probably do not count as a fruitful step the formation of the corresponding carbonium ions by the heterolytic cleavage of the carbinol. If this were not so, one would

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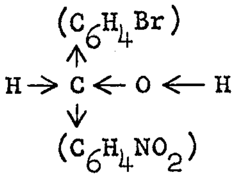
[2] J. Hine, *Physical Organic Chemistry*, 2nd ed., New York, McGraw-Hill Book Company, Inc., 1962, pp. 154-155.

expect that some of the corresponding methyl ether would be obtained, as the reaction is conducted in methanol solution. No methyl ether has been detected in any of the oxidation reactions using bromine.

The course of the reaction may only be speculated upon at this point because kinetic and isotope effect data are needed for a more complete interpretation of the experimental results. The general trend in the yield data summarized in Table II seems to be that aryl carbinols substituted with a nitro group give better yields of oxidation product than those that are halo-substituted which in turn give better yields than the remainder. This trend is in the opposite sense for that noted in the ether formation with the same compounds and iodine. It thus appears that those carbinols that yield least stable carbonium ions in reaction with iodine and as a result produce the smallest yields of ethers, give the best yields of oxidation product in reaction with bromine.

For example, 4-bromo-4'-nitrobenzhydrol proved unreactive with iodine in methanol, yet gave 100% yields of 4-bromo-4'-nitrobenzophenone in reaction with bromine in methanol. Due to the electronegativity of the bromo substituent and the inductive effect of the nitro group, the bonding electrons in the carbinol group would be displaced from their 'normal' orientation in benzhydrol in the directions indicated:



$$\begin{array}{ccccccc} & & (C_6H_4Br) & & & & \\ & & \uparrow & & & & \\ H & \rightarrow & C & \leftarrow & O & \leftarrow & H \\ & & \downarrow & & & & \\ & & (C_6H_4NO_2) & & & & \end{array}$$

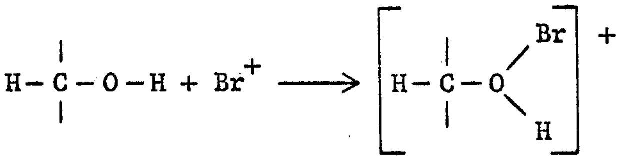
This would increase the acidities of the α and hydroxyl hydrogens.

Table II

Products Obtained On Oxidation With Bromine

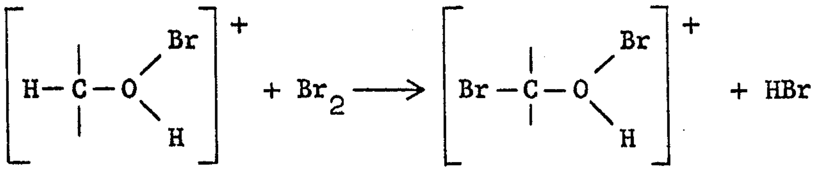
Product	Yield (%)
4-Nitrobenzophenone	100
4-Bromo-4'-nitrobenzophenone	100
4-Nitro-4'-t-butylbenzophenone	95
4-Chlorobenzophenone	100
4-Bromobenzophenone	100
4-Bromo-4'-chlorobenzophenone	100
4-Methylbenzophenone	81
Benzophenone	37
Benzaldehyde	93
3-Bromobenzaldehyde	10
4-Bromobenzaldehyde	40
4-Nitrobenzaldehyde	82
4-Methoxybenzaldehyde	61

In addition, the free electrons residing on the hydroxyl oxygen would be less available for donation to a positively charged bromine ion. As a final consequence, the complex formed between the alcohol and the positive bromine ion (eqn. 70) will not eliminate hypobromous acid as easily because of the increase in the strength with which the oxygen



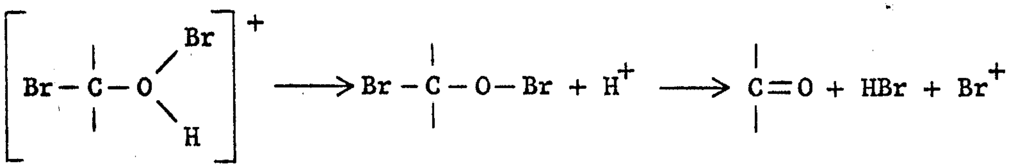
(70)

atom is bound to the carbon atom. The positive charge of the complex may further increase the acidity of the α hydrogen to a point where it may be readily replaced in a simple bromination step (eqn. 71).

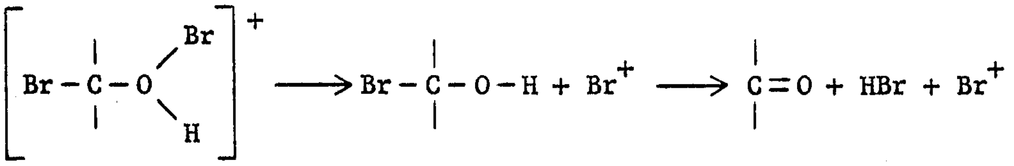


(71)

This would then be followed by one of two possible eliminations:



(72)



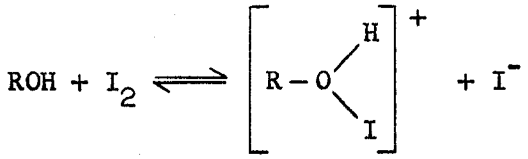
(73)

The greatly reduced yields of the corresponding benzophenones which were obtained when the oxidations of 4-nitrobenzhydrol and 4-bromo-4'-chlorobenzhydrol were attempted in ether or carbon tetrachloride solutions may have been caused by a simple decrease in the reaction rate. This is an effect that a decrease in solvent dielectric constant (methanol: 32.6; ethyl ether: 4.3; carbon tetrachloride: 2.2) often has on ionic processes.

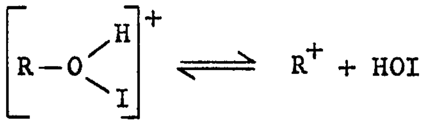
This oxidative procedure may have useful applications in the oxidations of aryl carbinols in systems where other synthetic procedures may be at a disadvantage. For example, there appears to be little tendency for benzyl alcohols to undergo oxidation to benzoic acids when nearly equimolar amounts of bromine are used.

Summary And Conclusions

It appears that alkyl arylmethyl ethers may be prepared in a facile manner by an iodine-induced dehydration of the corresponding alcohols. The arylmethyl carbonium ion probably is the moiety that undergoes nucleophilic attack by the aliphatic alcohol, and the mechanism which is consistent with the experimental results is represented below.



$$\mathrm{ROH} + \mathrm{I_2} \rightleftharpoons \left[\mathrm{R{-}O}\begin{matrix}\diagup\mathrm{H}\\ \diagdown\mathrm{I}\end{matrix}\right]^{+} + \mathrm{I^-} \qquad (74)$$



$$\left[\mathrm{R{-}O}\begin{matrix}\diagup\mathrm{H}\\ \diagdown\mathrm{I}\end{matrix}\right]^{+} \rightleftharpoons \mathrm{R^+} + \mathrm{HOI} \qquad (75)$$

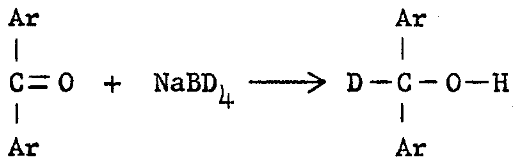
$$\mathrm{R^+} + \mathrm{R'OH} \longrightarrow \mathrm{ROR'} + \mathrm{H^+} \qquad (76)$$

$$\mathrm{H^+} + \mathrm{I^-} + \mathrm{HOI} \longrightarrow \mathrm{H_2O} + \mathrm{I_2} \qquad (77)$$

It is seen by this proposed mechanism that iodine is regenerated as it is used which is consistent with the observation that it is not consumed in the reaction. In the situation where oxidation is not possible, the reaction of triaryl carbinols with bromine in methanol solution to yield methyl ethers probably occurs by a mechanism analogous to that for iodine.

The determination of the mechanistic path of the brominative oxidations of mono- and diaryl carbinols requires kinetic and isotope data, but at least the procedure may be of some practical use as a synthetic method.

The preparation of several benzhydrols substituted on the α carbon with deuterium is currently in progress (eqn. 78). It is anticipated



$$\mathrm{Ar_2C{=}O} + \mathrm{NaBD_4} \longrightarrow \mathrm{D{-}CAr_2{-}O{-}H} \tag{78}$$

that a study of the kinetic isotope effects observed in the oxidation of these benzhydrols with bromine will elucidate the mechanistic path of the reaction. It may be possible to correlate the effect of aryl substitution on the kinetic isotope effect with hydride or proton abstraction mechanisms by a technique similar to one previously described by Swain.[3]

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[3] C. G. Swain, R. A. Wiles, and R. F. Bader, *J. Am. Chem. Soc.*, **83**, 1945 (1961).

CHAPTER III

EXPERIMENTAL PROCEDURE

Preparation of Ketones

Benzophenone, 4-nitrobenzophenone, and 4-chlorobenzophenone were obtained commercially from Aldrich Chemical Company. The preparation of 4-bromo-4'-chlorobenzophenone will serve as an example of the general procedure used in the syntheses of the remaining benzophenones.

4-Bromo-4'-Chlorobenzophenone. - Bromobenzene (200 g., 1.27 mole) and 4-chlorobenzoyl chloride (175 g., 1.0 mole) were placed in a two-litre three necked resin kettle equipped with a mechanical stirrer, condenser and drying tube. Aluminum chloride (150 g., 1.1 mole) was added in small portions with stirring to keep the reaction mixture in the temperature range 60-80°. Stirring was discontinued when the mixture became too viscous to allow for efficient stirring. After six hours of reaction time the mixture had set to a black solid. The apparatus was disassembled and the solid product was chipped out and hydrolyzed with ice-water. The crude product was recovered by filtration, washed with water and air dried. Recrystallization of the product from a chloroform-petroleum ether (b.p. 30-60°) solvent pair gave flaky buff-coloured crystals of 4-bromo-4'-chlorobenzophenone (251 g., 85%) melting in the range 149-150°. This melting point corresponds with that previously reported.[1] The infrared absorption spectrum of the compound showed a

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[1] M. Gomberg and J. C. Bailer, Jr., *J. Am. Chem. Soc.*, *51*, 2233 (1929).

carbonyl absorption band at 1660 cm^{-1} and aromatic ring skeletal absorption bands at 1485 and 1590 cm^{-1}.

4-Bromo-4'-Nitrobenzophenone. - In the manner described above, 4-nitrobenzoyl chloride (186 g., 1.0 mole), bromobenzene (200 g., 1.3 mole) and aluminum chloride (150 g., 1.1 mole) were used to prepare 4-bromo-4'-nitrobenzophenone after ten hours of reaction time. A purification scheme similar to the one above was followed and gave the pure ketone (260 g., 85%) in the form of pale yellow flakes melting sharply at 124.5°. A melting point of 125° has previously been reported.[2] The infrared spectrum of the product showed a carbonyl band at 1675 cm^{-1}, an aromatic ring skeletal absorption band at 1595 cm^{-1}, and nitro absorption bands at 1530 and 1360 cm^{-1}.

Analysis: Calcd. for $C_{13}H_8BrNO_3$: C, 51.00; H, 2.64.

Found: C, 50.89; H, 2.55.

4-Nitro-4'-t-Butylbenzophenone. - t-Butylbenzene (150 g., 1.1 mole), 4-nitrobenzoyl chloride (230 g., 1.25 mole) and aluminum chloride (200 g., 1.5 mole) were similarly used to prepare 4-nitro-4'-t-butylbenzophenone in a period of five hours. Following the purification scheme previously described, the pure ketone (218 g., 70%) was obtained as a pale yellow solid melting in the range 112-113°. The infrared spectrum of this previously unreported ketone showed a carbonyl absorption at 1670 cm^{-1}, and nitro absorption bands at 1530 and 1360 cm^{-1}.

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[2] P. J. Montagne, Ber., 49, 2256 (1916).

Analysis: Calcd. for $C_{17}H_{17}NO_3$: C, 72.2; H, 6.05.

Found: C, 72.6; H, 6.13.

4-Bromobenzophenone. - Bromobenzene (157 g., 1.0 mole) benzoyl chloride (141 g., 1.0 mole) and aluminum chloride (150 g., 1.1 mole) were used to prepare 4-bromobenzophenone in a similar manner to that above in a period of ten hours. Following the usual purification scheme gave the pure ketone (195 g., 75%) melting in the range 79.5-80°, (in agreement with that previously reported[3]). In the infrared spectrum, a carbonyl absorption at 1670 cm^{-1} and aromatic ring absorptions at 1595 and 1490 cm^{-1} were noted.

4-Methylbenzophenone. - Toluene (138 g., 1.5 mole), benzoyl chloride (141 g., 1.0 mole) and aluminum chloride (150 g., 1.1 mole) were used to prepare 4-methylbenzophenone in a manner similar to that above. On recrystallization from petroleum ether (b.p. 30-60°), the pure ketone was obtained as white needles (176 g., 90%) melting in the range 57-58°. The observed melting point is in fair agreement with 59.5° previously reported.[4] A carbonyl absorption band at 1665 cm^{-1} and an aromatic ring absorption band at 1620 cm^{-1} were evident in the infrared spectrum.

Preparation of Carbinols

Benzyl alcohol, benzhydrol, triphenylcarbinol, 4-methoxybenzyl alcohol and 4-nitrobenzyl alcohol were obtained from commercial sources.

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[3] W. D. Cohen, *Rec. trav. chim.*, *38* 113 (1919).

[4] A. G. Davies, et al., *J. Chem. Soc.*, 3475 (1954).

The remaining benzhydrols were prepared by the reduction of the corresponding benzophenones. Lithium aluminum hydride was used for the reduction of those ketones which were not nitro-substituted. Sodium borohydride was used to reduce the nitro-substituted benzophenones as this reagent will reduce a keto carbonyl in a much more facile manner than it will reduce the nitro group. The reduction of 4-chlorobenzophenone will serve as an example of a reduction with lithium aluminum hydride, and the reduction of 4-nitrobenzophenone with sodium borohydride will serve as an example of a reduction with that reagent.

4-Chlorobenzhydrol. - A suspension of lithium aluminum hydride (6.0 g., 0.16 mole) in ether (200 ml) was prepared in a one litre, round bottom, 3 necked flask which was fitted with a reflux condenser, magnetic stirrer and an externally applied ice bath. To this suspension was added a solution of 4-chlorobenzophenone (108 g., 0.5 mole) in tetrahydrofuran (500 ml). The addition rate was adjusted to maintain gentle reflux. When the addition was complete, ethyl acetate was added drop-wise (ca. 10 ml) to destroy the excess lithium aluminum hydride. The mixture was then made acid to litmus with Normal hydrochloric acid. The apparatus was disassembled and the reaction mixture was poured into one litre of cold water contained in a two litre beaker. A stream of air was directed over the stirred mixture for a period of fourteen hours, during which time the crude carbinol crystallized. The solid was isolated by filtration and allowed to dry in a stream of air. Recrystallization of the crude product from a chloroform-petroleum ether (b.p., 30-60°) solvent pair yielded the pure 4-chlorobenzhydrol (103 g., 94%), melting in the range 60-61°. This is in agreement with previous workers.[5] The infrared spectrum of the product showed the following bands: free OH stretching at 3560 cm^{-1}, aromatic skeletal vibrations at 1600 and 1493 cm^{-1}, and CO stretching at 1018 cm^{-1}.

4-Bromobenzhydrol. - In a similar manner 4-bromobenzophenone (26 g., 0.1 mole) was converted with lithium aluminum hydride (2 g., 0.05 mole) in ether solution (250 ml) to 4-bromobenzhydrol (23.5 g., 89%). This carbinol melted in the range 58-60° in agreement with that previously reported.[6] The following bands were observed in the infrared spectrum of the product: free OH stretching at 3560 cm^{-1}, aromatic skeletal vibrations at 1595 and 1492 cm^{-1}, and CO stretching at 1017 cm^{-1}.

4-Bromo-4'-Chlorobenzhydrol. - By a similar method 4-bromo-4'-chlorobenzophenone (50 g., 0.17 mole) was reduced with lithium aluminum hydride (3.0 g., 0.08 mole) in tetrahydrofuran solution (400 ml) to yield as a white crystalline solid, 4-bromo-4'-chlorobenzhydrol (48 g., 94%) melting in the range 99-100° which is slightly lower than a previously reported[7] melting range of 103-104°. The infrared spectrum of the product included the following bands: free OH stretching at 3570 cm^{-1}, aromatic skeletal vibrations at 1600 and 1498 cm^{-1}, and CO stretching at 1020 cm^{-1}.

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[5] J. O. Halford and E. B. Reid, J. Am. Chem. Soc., 63, 1873 (1941).

[6] C. F. Winans, J. Am. Chem. Soc., 61, 3564 (1939).

[7] R. Baltzly, S. DuBreuil, W. S. Ide, and E. Lorz, J. Org. Chem., 14, 775 (1949).

4-Methylbenzhydrol. - By a similar method 4-methylbenzophenone (39.2 g., 0.20 mole) was reduced with lithium aluminum hydride (4 g., 0.1 mole) to yield 4-methylbenzhydrol (31 g., 79%) in the form of white feathery crystals that melted in the range 52-53°. The range 51-53° has previously been reported.[8] The following bands were noted in the infrared spectrum of the product: free OH stretching at 3590 cm^{-1}, aromatic skeletal vibrations at 1620 and 1500 cm^{-1}, and CO stretching at 1025 cm^{-1}.

4-Bromobenzyl Alcohol. - By a similar method commercially available 4-bromobenzoic acid (100 g., 0.5 mole) was reduced with lithium aluminum hydride (16 g., 0.42 mole) during one hour of heating at reflux temperature in ether solution. 4-Bromobenzyl alcohol (90 g., 96%) was obtained as a white solid melting in the range 75-76°, in excellent agreement with other workers.[9] In the infrared spectrum, the following bands were noted: free OH stretching at 3550 cm^{-1}, aromatic skeletal vibrations at 1595 and 1490 cm^{-1}, and CO stretching at 1010 cm^{-1}.

3-Bromobenzyl Alcohol. - Commercially available 3-bromobenzoic acid (20 g., 0.1 mole) was reduced in a similar manner with lithium aluminum hydride (4 g., 0.1 mole) during one hour of heating at reflux temperature in ether solution. 3-Bromobenzyl alcohol (15.5 g., 83%) was isolated by distillation at atmospheric pressure in the range 252-254°. Previous authors have reported a range of 255-257°.[10] The infrared spectrum of

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[8] A. G. Davies, J. Kenyon, B. J. Lyons, and T. A. Rohan, *J. Chem. Soc.*, 3475 (1954).

[9] W. H. Carothers and R. Adams, *J. Am. Chem. Soc.*, *46*, 1675 (1924).

[10] J. K. Koch and G. S. Hammond, *J. Am. Chem. Soc.*, *75*, 3443 (1953).

the compound included the following bands: free OH stretching at 3610 cm^{-1}, a doublet at 1570 and 1596 cm^{-1} of which at least one represents aromatic skeletal vibrations, and CO stretching at 1015 cm^{-1}.

4-Bromo-4'-Chlorotriphenylcarbinol. - Magnesium turnings (24.3 g., 1.0 mole) and ether (200 ml) were placed in a one litre, three necked, round bottom flask fitted with a reflux condenser, addition funnel and a nitrogen inlet tube. While the mixture was magnetically stirred, a few ml. of a solution of bromobenzene (157 g., 1.0 mole) and ether (300 ml.) were added from the funnel. A small crystal of iodine was used to initiate the preparation of the phenylmagnesium bromide Grignard reagent. The rate of addition of the bromobenzene solution was adjusted to maintain the reaction mixture in a state of gentle reflux. Following the completion of the addition, the reflux was maintained for an additional thirty minutes by the external application of heat. The reaction mixture was then cooled in an ice-bath, while finely divided 4-bromo-4'-chlorobenzophenone (200 g., 0.68 mole) was added slowly enough to ensure complete absorption by the reaction mixture. The mixture was again heated under reflux conditions for a period of thirty minutes, and then cautiously quenched with the drop-wise addition of distilled water. When the mixture showed no evidence of reaction with the further addition of water, it was poured into one litre of rapidly stirred ice-water made acid with concentrated hydrochloric acid (200 mls). The organic layer was separated from the aqueous layer. The former was reduced by evaporation *in vacuo* to a heavy oil. The oil was made to crystallize from a chloroform-petroleum ether (b.p. 30-60) solvent pair and 4-bromo-4'-chlorotriphenylcarbinol was obtained as a solid melting in the range 96-100°. A second recrystallization in the same manner as the first yielded the pure compound melting sharply at 103.5°, in agreement with previous workers.[11,12] The infrared spectrum of the compound included the following bands: free OH stretching at 3570 cm^{-1}, aromatic skeletal vibrations at 1600 and 1500 cm^{-1}, and CO stretching at 1018 cm^{-1}.

α-Naphthylphenyl-p-tolylcarbinol. - By a synthesis similar to that described above, the Grignard reagent prepared from α-bromonaphthalene (104 g., 0.5 mole) and magnesium (13 g., 0.53 mole) was made to react with 4-methylbenzophenone (98 g., 0.5 mole) to yield α-naphthylphenyl-p-tolylcarbinol. The product melted in the range 112.5-113.5°, (reported 109°).[13] The following bands were noted in the infrared spectrum: free OH stretching at 3550, aromatic skeletal vibrations at 1600 and 1494 cm^{-1}, and CO stretching at 1010 cm^{-1}.

2-Benzoylbenzoic Acid. - In a manner similar to that previously described the Grignard reagent formed from bromobenzene (118 g., 0.75 mole) and magnesium (19 g., 0.78 mole) was added to an ether solution of phthalic anhydride (111 g., 0.75 mole). Purification of the product by recrystallization from a chloroform-petroleum ether (b.p. 30-60) solvent pair gave 2-benzoylbenzoic acid (98 g., 58%) m.p. 123-125, (reported[14] 126-127°). In the infrared spectrum the following bands were noted: a broad hydrogen-bonded OH stretching which merged with CH stretching at 3000 to

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[11] B. A. Stagner, J. Am. Chem. Soc., 38, 2078 (1916).

[12] J. M. Prokipcak, Ph.D. Thesis, Faculty of Graduate Studies, University of Windsor, 1964, p.96

[13] C. L. Arcus, J. Kenyon and S. Levin, J. Chem. Soc., 407 (1951).

[14] W. J. Gensler, et al., J. Am. Chem. Soc., 78, 1713 (1956).

3100 cm^{-1}, a doublet carbonyl band at 1690 and 1670 cm^{-1}, and aromatic skeletal vibrations at 1600, 1580 and 1490 cm^{-1}.

Diphenylphthalide. - By a method previously described, the Grignard reagent prepared from bromobenzene (118 g., 0.75 mole) and magnesium (19 g., 0.78 mole) was slowly added to phthalic anhydride (50 g., 0.34 mole) to yield diphenylphthalide (86 g., 83%) m.p. 117-121°, (reported[15] 115°). The infrared absorption spectrum included the following bands: a broad hydrogen-bonded OH stretching band centered at approximately 3500 cm^{-1}, carbonyl stretching at 1760 cm^{-1}, and aromatic ring skeletal vibrations at 1612, 1600 and 1493 cm^{-1}. The spectrum was too complex to assign a band corresponding to CO single bond stretching.

2-Methylolbenzhydrol. - By a method similar to one previously described, 2-benzoylbenzoic acid (22.6 g., 0.1 mole) was reduced with lithium aluminum hydride (7.6 g., 0.2 mole) in ether solution (300 ml) under reflux conditions over a period of one hour. The diol was obtained as a white solid, m.p. 115-117°, (reported[16] 76°). The infrared spectrum of the compound showed the following bands: free OH stretching at 3600 cm^{-1}, hydrogen-bonded OH in an intense broad band centered at 3340 cm^{-1}, aromatic ring skeletal vibrations at 1600 and 1492 cm^{-1}, and CO stretching at 1004 cm^{-1}. There was no evidence of a carbonyl absorption.

2-Methyloltriphenylcarbinol. - Similarly, diphenylphthalide (10 g., 0.033 mole) was reduced with lithium aluminum hydride (1.9 g., 0.05 mole)

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[15] J. S. Chamberlain and M. F. Dull, J. Am. Chem. Soc., 50, 3091 (1928).

[16] P. Pernot and A. Willemart, Bull. soc. chim. France, 321 (1953).

at the reflux temperature in ether (200 ml) during a period of one hour. 2-Methyloltriphenylcarbinol was obtained as a pure white solid melting in the range of 162-163°, (reported[17] 159°) and having the following bands in the infrared spectrum: free OH stretching at 3595 cm^{-1}, an intense broad hydrogen-bonded OH band centered at 3360 cm^{-1}, aromatic skeletal vibrations at 1596 and 1487 cm^{-1}, and CO stretching at 1001 cm^{-1}.

<u>4-Nitrobenzhydrol</u>. - A solution of 4-nitrobenzophenone (22.7 g., 0.1 mole) and tetrahydrofuran (300 ml) was prepared in a one litre erlenmeyer flask. While the solution was being magnetically stirred, sodium borohydride (3 g., 0.08 mole) was added in 0.5 gram portions, each dissolved in 5 millilitres of ice-cold distilled water. The temperature of the reaction mixture was kept below 35° by increasing the length of time between the additions of the sodium borohydride solutions. When the addition was complete, the mixture was allowed to stir for a period of fifteen minutes. The mixture was then poured cautiously on a slurry of ice (500 g.) and hydrochloric acid (25 ml). The tetrahydrofuran was allowed to evaporate from the hydrolyzed mixture in a stream of air which caused the crystallization of the 4-nitrobenzhydrol. The solid was isolated by filtration and air dried (22.2 g., 97%) m.p. 64-67°. Recrystallization of the crude material from methanol gave the pure compound melting in the range 74-75° (reported[18] 73-75.5°). The infrared

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[17] A. Guyot and J. Catel, <u>Bull</u>. <u>soc</u>. <u>chim</u>. <u>France</u>, (3) <u>35</u>, 567 (1907).

[18] B. B. Smith and J. E. Leffler, <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>., <u>77</u>, 2509 (1955).

spectrum of the compound included the following bands: free OH stretching at 3560 cm^{-1}, aromatic ring skeletal vibrations at 1606 and 1495 cm^{-1}, and nitro group stretching at 1523 and 1350 cm^{-1}.

4-Nitro-4'-t-Butylbenzhydrol. - In a manner similar to that described above, sodium borohydride (5 g., 0.13 mole) was used to reduce 4-nitro-4'-t-butylbenzophenone (94 g., 0.33 mole). 4-Nitro-4't-butylbenzhydrol was obtained as a white crystalline solid (93 g., 98%) m.p. 110-111°. The infrared spectrum of this previously unreported compound showed a free OH absorption at 3545 cm^{-1}, aromatic skeletal absorptions at 1607 and 1492 cm^{-1}, and nitro group absorptions at 1523 and 1354 cm^{-1}.

Analysis: Calcd. for $C_{17}H_{19}NO_3$: C, 71.7; H, 6.72.

Found: C, 72.3; H, 6.91.

4-Bromo-4'-Nitrobenzhydrol. - By a method similar to that described above, 4-bromo-4'-nitrobenzophenone (10 g., 0.033 mole) was reduced with sodium borohydride (1.3 g., 0.035 mole). 4-Bromo-4'-nitrobenzhydrol was obtained after recrystallization of the crude material from an acetone-water solvent pair (8.0 g., 80%), m.p. 160-161°. This compound, which is previously unreported, showed the following bands in the infrared spectrum: free OH stretching at 3560 cm^{-1}, aromatic akeletal vibrations at 1608 and 1489 cm^{-1}, and nitro group stretching bands at 1525 and 1351 cm^{-1}.

Analysis: Calcd. for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.28.

Found: C, 50.45; H, 3.27.

Reactions Of Carbinols With Iodine

In the reactions with iodine, the alcohols and iodine were usually dissolved in acetone and allowed to remain at room temperature for two hours. The iodine was then destroyed with aqueous sodium thiosulfate, the acetone solvent was removed by evaporation and the crude product was recrystallized. Authentic samples of some of the ethers were prepared by previously known methods, (usually by the Williamson synthesis) and mixed melting points were determined to demonstrate that the reaction product was in fact the ether. The preparation of methyl triphenylmethyl ether will illustrate the general procedure followed in the remainder of the preparations.

Methyl Triphenylmethyl Ether. - A solution of triphenylcarbinol (10 g., 0.0385 mole), methanol (16 g., 0.5 mole) and iodine (12.7 g., 0.05 mole) was prepared in acetone (100 mls). The mixture was magnetically stirred for a period of two hours at room temperature. The mixture was then poured into a slurry of ice and water containing enough sodium thiosulfate to consume the iodine. The acetone and methanol were allowed to evaporate in a stream of air, which caused the crude ether to precipitate. The crude material was isolated by filtration, air-dried and recrystallized from petroleum ether (b.p. 30-60°), to yield methyl triphenylmethyl ether (9.6 g., 91%) m.p. 73-77°. A second recrystallization from hot ethanol produced the pure ether (9.1 g., 86%) m.p. 81.5-82.5°, (reported[19] 80-82°). An authentic sample of the ether was prepared from

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[19] H. H. Hart, J. Chem. Soc., 483 (1938).

triphenylmethyl chloride (5 g., 0.018 mole), methanol (50 mls) and pyridine (20 mls). After recrystallization from hot ethanol the authentic ether sample had a melting point 82.5-83.5°. The melting point of a mixture of the two ether samples was determined to be 83-83.5°.

In the following preparations only the pertinent data such as quantities of reagents, yields and melting points will be given.

Ethyl Triphenylmethyl Ether. -

10 g., (0.0385 mole) triphenylcarbinol
12.7 g., (0.05 mole) iodine
23 g., (0.5 mole) ethanol
100 ml. acetone
Yield, 9.7 g., (87%)
Melting point, 82.5-83.5°, (reported[20] 83°)
Mixed melting point with authentic sample, 82-83°
Mixed melting point with methyl triphenylmethyl ether, 54-63°.

n-Propyl Triphenylmethyl Ether. -

10 g., (0.0385 mole) triphenylcarbinol
12.7 g., (0.05 mole) iodine
30 g., (0.5 mole) n-propanol
100 ml. acetone
Yield, 9.3 g., (80%)
Melting point, 54-55°, (reported[21] 56°)
Mixed melting point with authentic sample, 52-53°.

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[20] A. C. Nixon and G. E. K. Branch, J. Am. Chem. Soc., 58, 492 (1936).

[21] B. F. Helferich, P. E. Speidel and W. Toeldte, Ber., 56, 767 (1923).

i-Propyl Triphenylmethyl Ether. -

10 g., (0.0385 mole) triphenylcarbinol

12.7 g., (0.05 mole) iodine

30 g., (0.5 mole) i-propanol

100 ml. acetone

Yield, 7.1 g., (61%)

Melting point, 112-113°, (reported[22] 111-113°)

Mixed melting point with authentic sample 112-114°.

Benzyl Triphenylmethyl Ether. -

10 g., (0.0385 mole) triphenylcarbinol

12.7 g., (0.05 mole) iodine

10.8 g., (0.1 mole) benzyl alcohol

100 ml. acetone

Yield, 7.0 g., (52%)

Melting point, 105-106°, (reported[23] 106-107°)

Mixed melting point with authentic sample, 105-106°.

Methyl α-Naphthylphenyl-p-Tolylmethyl Ether. -

3.24 g., (0.01 mole) α-naphthylphenyl-p-tolylcarbinol

2.6 g., (0.01 mole) iodine

16 g., (0.5 mole) methanol

100 ml. acetone

Yield 3.28 g., (100%)

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[22] J. F. Norris and R. C. Young, J. Am. Chem. Soc., 46, 2582 (1924).

[23] G. L. Stadnikov, Ber., 57B, 6 (1924).

Melting point, 50-52°, (reported[24] 121-122°).

Infrared spectrum, aromatic skeletal vibrations: 1605 and 1495 cm^{-1},

CO stretching: 1076 and 1027 cm^{-1},

no OH stretching.

Analysis: Calcd. for $C_{25}H_{22}O$: C, 88.73; H, 6.54.

Found: C, 88.70; H, 6.61.

Methyl Phenyl-p-Tolylmethyl Ether. -

4.0 g., (0.02 mole) 4-methylbenzhydrol

5.5 g., (0.022 mole) iodine

16 g., (0.5 mole) methanol

100 ml. acetone

Yield, 4.1 g., (96%)

Boiling point 160-162/10 mm, (reported[25] 160-165/10 mm).

Infrared spectrum, aromatic skeletal vibrations: 1605, 1510 and 1492 cm^{-1},

CO stretching: 1085 cm^{-1},

no OH stretching.

Analysis: Calcd. for $C_{15}H_{16}O$: C, 85.4; H, 7.16.

Found: C, 84.9; H, 7.49.

Methyl 4-Chlorodiphenylmethyl Ether. -

11 g., (0.05 mole) 4-chlorobenzhydrol

12.7 g., (0.05 mole) iodine

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[24] W. Dilthey, et al., J. Prakt. Chem., 109, 313 (1925).

[25] A. G. Davies, et al., J. Chem. Soc., 3474 (1954).

3 g., (0.1 mole) methanol

50 ml. acetone

Yield 9.9 g., (85%)

Melting point, 27-29°, (not reported).

Infrared spectrum, aromatic skeletal vibrations: 1610 and 1500 cm^{-1},

CO stretching: 1100 and 1022 cm^{-1},

no OH stretching.

Methyl 4-Bromo-4'-Chlorodiphenylmethyl Ether. -

10 g., (0.033 mole) 4-bromo-4'-chlorobenzhydrol

12.7 g., (0.05 mole) iodine

3 g., (0.1 mole) methanol

100 ml. acetone

Yield, 10.3 g., (100%)

Melting point 87-88°, (not reported).

Infrared spectrum, aromatic skeletal vibrations: 1600 and 1493 cm^{-1},

CO stretching: 1020 and 1097 cm^{-1},

no OH stretching.

Analysis: Calcd. for $C_{14}H_{12}BrClO$: C, 54.00; H, 3.88.

Found: C, 54.24; H, 3.68.

Methyl 4-Methoxybenzyl Ether. -

10 g., (0.0725 mole) 4-methoxybenzyl alcohol

12.7 g., (0.05 mole) iodine

16 g., (0.5 mole) methanol

100 ml. acetone

Yield, 8.0 g., (73%)

Boiling point 220-225°/745 mm. (reported[26] 225.5°/758 mm.).

Index of refraction, 1.5150 (18.5°, D line of sodium).

An authentic sample of the diether was prepared according to the method of Cannizzaro in which 4-methoxybenzyl chloride (prepared by the action of thionyl chloride on 4-methoxybenzyl alcohol) is made to react with methanol. The compound prepared according to this method was observed to distil in the range 220-225° and had the index of refraction 1.5147 (18.5° D line of sodium). The infrared spectra of the two products were identical: aromatic skeletal vibrations at 1610 and 1507 cm^{-1}, CO stretching at 1087 and 1030 cm^{-1}. No OH stretching was noted in either spectrum.

<u>1-Phenylphthalan.</u> -

2 g., (0.00935 mole) 2-methylolbenzhydrol

3 g., (0.012 mole) iodine

25 ml. acetone

Yield, 1.5 g., (82%)

Melting point, 32-35° (reported[27] 35°)

Infrared spectrum, aromatic skeletal vibrations: 1603 and 1494 cm^{-1},
CO stretching (intense): 1025 cm^{-1},
no OH stretching.

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[26] von S. Cannizzaro, <u>Ann</u>., <u>137</u>, 246 (1866).

[27] A. Pernot and A. Willemart, <u>Bull</u>. <u>soc</u>. <u>chim</u>. <u>France</u>, 321

1,1-Diphenylphthalan. -

1.5 g., (0.0052 mole) 2-methyloltriphenylcarbinol

2 g., (0.0079 mole) iodine

50 ml. acetone

Yield, 1.2 g., (85%)

Melting point, 101-102° (reported[28] 99-101°).

Infrared spectrum, aromatic skeletal vibrations: 1598 and 1490 cm^{-1},

CO stretching (intense doublet): 1015 and 1024 cm^{-1},

no OH stretching.

Reaction of 4-Bromo-4'-Chlorotriphenylcarbinol With Iodine. -

5 g., (0.0134 mole) 4-bromo-4'-chlorotriphenylcarbinol

4 g., (0.0158 mole) iodine

3 g., (0.1 mole) methanol

50 ml. acetone

When the reaction mixture was poured into the sodium thiosulfate-ice slurry, a solid precipitate was obtained almost immediately. Recrystallization of the crude product from a chloroform-petroleum ether (b.p. 30-60°) solvent pair yielded a white crystalline solid, (5 g.) which melted and resolidified in the range 87-89° and again melted with decomposition in the range 170-175°. The same reaction product was obtained when tetrahydrofuran was substituted for acetone as the reaction solvent.

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[28] A. M. Creighton and L. M. Jackman, *J. Chem. Soc.*, 3144 (1960)

Again, the same reaction product was obtained when the methanol was absent from the reaction mixture entirely. The melting point of an intimately ground mixture of the product and the carbinol was over the range 110-170°.

Subtle differences in the infrared spectra of the carbinol and the reaction product were evident: the free OH stretching band was shifted slightly to 3580 cm^{-1}; a broad intense hydrogen bonded OH stretching band made its appearance at 3360 cm^{-1} where in the spectrum of the carbinol there was only a very weak corresponding band; a new CH stretching band at 2875 cm^{-1} was evident in the spectra for the reaction product; similarly, a new band at 1053 cm^{-1} was noted which usually is the result of CO single bond stretching in alcohols and in some ethers; finally, a band at 1448 cm^{-1}, corresponding to aromatic skeletal vibrations, which was evident in the carbinol spectrum was absent in the spectrum of the product.

Analysis: C, 55.79; H, 4.49; Br, 22.06; Cl, 9.79.

No iodine was detected in the elemental analysis of the compound. The analysis corresponds to a compound of stoichiometry $C_{17}H_{16}BrClO_2$.

Iodine-Catalyzed Friedel-Crafts Reaction. -

5.4 g., (0.05 mole) anisole
6.9 g., (0.05 mole) 4-methoxybenzyl alcohol
12.7 g., (0.05 mole) iodine
40 ml. acetone

The mixture was allowed to stand with stirring for a period of one-half hour, during which the temperature of the mixture spontaneously rose to approximately 45°. The mixture was hydrolyzed by pouring it into a solution of sodium thiosulfate and ice-water. The mixture was extracted twice with 50 ml. portions of ether. The ether extracts were dried over anhydrous potassium carbonate, treated with decolourizing charcoal and reduced in vacuo to an oil which crystallized on standing at 10° (9.4 g., 82%) m.p. 35-41°. The product was dissolved in ethanol and cooled whereupon white crystals of bis-(4-methoxyphenyl)-methane (1.3 g.) m.p. 44-46° (reported[29] 46-47°) was obtained. The infrared spectrum of the product showed the following bands: aromatic ring skeletal vibrations at 1613, 1585, 1506 and 1464 cm^{-1}, multiple CO stretching bands in the region 1300 to 1030 cm^{-1}, methoxyl CH stretching at 2830 cm^{-1}, and aromatic CH 'out of plane' bending overtones at 1875 and 1775 cm^{-1} which corresponds with 1,4 disubstitution on the benzene nucleus.

The nature of the product was confirmed by oxidizing 1.5 g. of the material with chromic oxide (2 g.) in acetic acid (25 ml.). After two recrystallizations from methanol, 4,4'-dimethoxybenzophenone (0.6 g., 30%) was obtained in the form of sand-coloured crystals that melted in the range 144-145° (reported[30] 143.5-145°).

Reactions Of Carbinols With Bromine

In the reactions with bromine, the carbinols and bromine were usually dissolved in methanol and the resultant solution was allowed to

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[29] P. D. Bartlett and J. D. McCollum, J. Am. Chem. Soc., 78, 1448 (1956).

[30] E. M. Arnett and G. B. Klingensmith, J. Am. Chem. Soc., 87, 1028 (1965).

remain at room temperature for twelve hours. The excess bromine was consumed by sodium thiosulfate and the reaction products were isolated and purified. The reaction of 4-nitrobenzhydrol with bromine in methanol solution will serve as an example of the general procedure followed.

Oxidation of 4-Nitrobenzhydrol. -

To a stirring solution of 4-nitrobenzhydrol (5 g., 0.022 mole) in anhydrous methanol (50 ml.), contained in a 125 ml. erlenmeyer flask, bromine (15 g., 0.094 mole) was added cautiously. A pronounced increase in the temperature of the solution was noted upon the completion of the bromine addition. The loosely stoppered reaction mixture was allowed to stand overnight and then poured into a slurry of ice (200 g.) and sodium thiosulfate (15 g.). The hydrolyzed mixture was extracted twice with 50 ml. portions of methylene chloride. The organic phase was dried over sodium sulfate and was reduced to approximately 40 ml. in volume by distillation of some of the volatile solvent under reduced pressure. Petroleum ether (b.p. 30-60°) was added, which caused the precipitation of 4-nitrobenzophenone (5 g., 100%) m.p. 135-136°. The mixed melting point with an authentic sample was undepressed, and the infrared spectrum of the product was identical with that for 4-nitrobenzophenone.

The following reactions were completed in a manner similar to that described above. Only the pertinent information is given in the following examples.

Oxidation Of 4-Bromo-4'-Nitrobenzhydrol. -

5 g., (0.0162 mole) 4-bromo-4'-nitrobenzhydrol
10 g., (0.0625 mole) bromine

50 ml. anhydrous methanol

Yield, 5.0 g., (100%) 4-bromo-4'-nitrobenzophenone

Melting point, 123-124°; mixed melting point, 123-124°.

Infrared spectrum: identical with that for 4-bromo-4'-nitrobenzophenone.

Oxidation Of 4-Nitro-4'-t-Butylbenzhydrol. -

5 g., (0.0175 mole) 4-nitro-4'-t-butylbenzhydrol

5 g., (0.031 mole) bromine

50 ml. anhydrous methanol

Yield, 4.7 g., (95%) 4-Nitro-4'-t-butylbenzophenone

Melting point, 109-111°; mixed melting point, 110-112°.

Infrared spectrum: identical with that for 4-nitro-4'-t-butylbenzophenone.

Oxidation Of 4-Chlorobenzhydrol. -

5 g., (0.023 mole) 4-chlorobenzhydrol

5 g., (0.031 mole) bromine

50 ml. anhydrous methanol

Yield 5 g., (100%) 4-chlorobenzophenone

Melting point, 73-75°; mixed melting point, 74-75°.

Infrared spectrum: identical with that for 4-chlorobenzophenone.

Oxidation of 4-Bromobenzhydrol. -

5 g., (0.019 mole) 4-bromobenzhydrol

5 g., (0.031 mole) bromine

50 ml. anhydrous methanol

Yield 5 g., (100%) 4-bromobenzophenone

Melting point, 79-80°; mixed melting point, 79-80°.

Infrared spectrum: identical with that for 4-bromobenzophenone.

Oxidation Of 4-Bromo-4'-Chlorobenzhydrol. -

5 g., (0.017 mole) 4-bromo-4'-chlorobenzhydrol

5 g., (0.031 mole) bromine

50 ml. anhydrous methanol

Yield 5 g., (100%) 4-bromo-4'-chlorobenzophenone

Melting point, 148-150°; mixed melting point 147-150°.

Infrared spectrum: identical with that for 4-bromo-4'-chlorobenzophenone.

Oxidation Of 4-Methylbenzhydrol. -

5 g., (0.025 mole) 4-methylbenzhydrol

10 g., (0.063 mole) bromine

50 ml. anhydrous methanol

Yield, 4 g., (81%) 4-methylbenzophenone

Melting point, 53-56°; mixed melting point, 53-55°.

Infrared spectrum: identical with that of 4-methylbenzophenone.

Oxidation Of Benzhydrol. - Bromine (60 g., 0.375 mole) was added to a solution of benzhydrol (54 g., 0.294 mole) in anhydrous methanol (450 ml.) at a slow rate to maintain the temperature of the mixture below 40°. After stirring for a period of two hours, the solution was poured into a rapidly stirred slurry of sodium thiosulfate (50 g.) and ice (1 Kg.). The mixture was extracted with two 100 ml. portions of petroleum ether (b.p. 30-60°) which were then combined, dried over sodium sulfate and distilled. The fraction boiling in the range 295-305° was collected and was crystallized from petroleum ether (b.p. 30-60°). The solid thus obtained, (19.8 g., 37%), m.p. 46.7°, was shown to be benzophenone by the undepressed mixed melting point with an authentic sample.

In the distilling flask there remained approximately 10 ml. of material that crystallized on cooling. One gram of a white crystalline material melting in the range 208-211° was isolated from this mass. A careful analysis[31] of the infrared spectrum of the compound showed that it was probably 1,1,2,2-tetraphenylethane: aromatic CH stretching, 3100-3000 cm^{-1}; aliphatic CH stretching, 2900 cm^{-1}; monosubstituted benzene 'out of plane' CH bending overtones, 1949, 1875, 1800, and 1730 cm^{-1}; aromatic skeletal stretching vibrations, 1597, 1580, 1490, and 1446 cm^{-1}; monosubstituted benzene CH 'in plane' bending, 690 cm^{-1} (770-730 band possibly obscured by chloroform solvent). Tetraphenylmethane has been reported[32] to melt at 210°.

Analysis: Calcd. for $C_{26}H_{22}$: C, 93.36; H, 6.64.

Found: C, 93.41; H, 6.53.

Oxidation Of Benzyl Alcohol. -

20 g., (0.185 mole) benzyl alcohol

30 g., (0.187 mole) bromine

50 g., anhydrous methanol

Yield, 5.0 g., (25%) benzaldehyde

Boiling point, 178-182° (reported[33] 178.1°)

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[31] With the assistance of Introduction To Practical Infra-red Spectroscopy, A. D. Cross. London: Butterworths Scientific Publications, 1960. p.59.

[32] K. M. Johnston and G. H. Williams, J. Chem. Soc., 1170 (1960).

[33] E. Brauer and C. von Rechenberg, J. Prakt. Chem.,(2) 101, 119 (1921).

When a 50% by weight aqueous solution of sodium thiosulfate (enough to discharge the bromine colour) was added to the reaction mixture instead of the normal hydrolysis previously described, much better yields (18.2 g., 93%) could be obtained. When the reaction mixture was analyzed by gas chromatographic techniques (diethyleneglycol succinate column, 3 meters long, flow rate: helium, 60 ml./min., column temperature: 160°) the major component (at least 90% of total peak area excluding water and methanol peaks) had the same retention time as benzaldehyde in a synthetic mixture with methanol under the same operating conditions. The characteristic odour of benzaldehyde was noted at the column exit when the major component had been eluted. By a similar technique benzyl alcohol was shown to be completely absent in the analyzed reaction mixture.

When the hydrolysis step was completely omitted, and the reaction mixture was distilled directly upon completion of the reaction period, the following fractions were obtained:

1 65-100°: 45 ml. methanol-bromine mixture
2 100-120°: 1 ml. water
3 126°: 2 ml. constant boiling aqueous hydrobromic acid
4 178-182°: 15.8 g., (79%) benzaldehyde.

Benzoic acid (0.45 g., 0.0037 mole) was isolated after two recrystallizations of the residue in the distillation flask first from petroleum ether (b.p. 30-60°) and then from water, m.p. 122°, mixed m.p. 121-122°.

The infrared spectrum of the benzaldehyde prepared in this manner was identical to that of authentic benzaldehyde. A few drops of the product placed on a watch glass underwent air oxidation to yield benzoic acid, m.p. 121-122°.

Oxidation Of 3-Bromobenzyl Alcohol. -

5 g., (0.026 mole) 3-bromobenzyl alcohol

8 g., (0.05 mole) bromine

50 ml. anhydrous methanol

Yield 0.5 g., (10%) 3-bromobenzaldehyde.

Boiling point, 228-232°/741 mm. (reported[34] 228-230°/726 mm.).

Infrared spectrum, no OH stretching,

carbonyl stretching: 1697 cm^{-1},

aromatic skeletal vibrations: 1590 and 1440 cm^{-1}.

Oxidation Of 4-Bromobenzyl Alcohol. -

10 g., (0.053 mole) 4-bromobenzyl alcohol

15 g., (0.094 mole) bromine

50 ml. anhydrous methanol

Yield 4 g., (40%) 4-bromobenzaldehyde.

Melting point, 54-56°, (reported[35] 57°).

Infrared spectrum, very weak OH stretching: 3605 cm^{-1},

carbonyl stretching: 1700 cm^{-1},

aromatic skeletal vibrations: 1590 cm^{-1}.

Oxidation Of 4-Nitrobenzyl Alcohol. -

10 g., (0.065 mole) nitrobenzyl alcohol

15 g., (0.094 mole) bromine

100 ml. anhydrous methanol

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[34] C. Mettler, *Ber.*, **38**, 2810 (1905).

[35] J. B. Bowen and E. M. Wilkinson, *J. Chem. Soc.*, 751 (1950).

Yield 8.1 g., (82%) 4-nitrobenzaldehyde.

Melting point, 105-106°, (reported[36] 106.5°).

Infrared spectrum, OH stretching (very weak): 3600 cm^{-1},
carbonyl stretching: 1710 cm^{-1},
aromatic skeletal vibrations: 1605 cm^{-1},
nitro group vibrations: 1524 and 1345 cm^{-1}.

Oxidation Of 4-Methoxybenzyl Alcohol. -

20 g., (0.145 mole) 4-methoxybenzyl alcohol
24 g., (0.15 mole) bromine
100 ml. anhydrous methanol

Yield 12 g., (61%) 4-methoxybenzaldehyde.

Boiling point, 240-245°/740 mm., (reported[37] 2480°/760 mm.).

Infrared spectrum, no OH stretching,
carbonyl stretching: 1695 cm^{-1},
aromatic skeletal vibrations: 1600 and 1486 cm^{-1},
multiple peaks in the region 1300 to 1000 cm^{-1}.

Oxidation Of 4-Bromo-4'-Chlorobenzhydrol In Carbon Tetrachloride And In Ether Solution. -

When the oxidation of 4-bromo-4'-chlorobenzhydrol (5.7 g., 0.019 mole) with bromine (15 g., 0.094 mole) was attempted in carbon tetrachloride (100 ml.) solution, it was noted that the apparent rate of reaction was greatly diminished. Where 100% yield of the ketone was obtained with

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[36] O. L. Brady and S. Harris, *J. Chem. Soc.*, 492 (1923).

[37] F. V. Grimm and W. A. Patrick, *J. Am. Chem. Soc.*, *45*, 2799 (1923).

methanol as the solvent, only 1 gram (18%) was obtained with carbon tetrachloride as the solvent after fifteen hours of reaction time. Approximately 4 grams of an unidentified oil was obtained which could not be crystallized and showed a weak carbonyl absorption (1660 cm^{-1}) in the infrared spectrum. Similar results were noted when ether was used as the solvent.

Oxidation Of 4-Nitrobenzhydrol In Carbon Tetrachloride. -

Only a small yield of 4-nitrobenzophenone (1.5 g., 15%) m.p. 136-137.5°, was obtained when 4-nitrobenzhydrol (10 g., 0.0655 mole) was treated with bromine (15 g., 0.094 mole) in carbon tetrachloride (100 ml.). The infrared spectrum of the unidentified oil showed a very weak carbonyl absorption at 1661 cm^{-1}, the usual nitro bands at 1520 and 1340 cm^{-1}, and aromatic skeletal vibrations at 1600 and 1490 cm^{-1}.

Ether Formation With Triphenylcarbinol. -

10 g., (0.0385 mole) triphenylcarbinol
8 g., (0.05 mole) bromine
100 ml. anhydrous methanol
Yield 10.1 g., (98%) methyl triphenylmethyl ether.
Melting point, 81-83°; mixed melting point 81-83°.

When the preparation of isopropyl triphenylmethyl ether by the above procedure was attempted, triphenylcarbinol was recovered in 95% yield, and a powerful lachrymator was produced. The lachrymator was thought to be bromoacetone.

Ether Formation With α-Naphthylphenyl-p-Tolylcarbinol. -

10 g., (0.031 mole) α-naphthylphenyl-p-tolylcarbinol

10 g., (0.0625 mole) bromine

100 ml. anhydrous methanol

Yield 10.1 g., (100%) methyl α-naphthylphenyl-p-tolylmethyl ether.

Melting point, 50-55°.

Infrared spectrum, identical with that for methyl α-naphthylphenyl-p-tolylmethyl ether prepared by iodine catalysis.

PART II

ACYL-OXYGEN FISSION IN BENZHYDRYL HYDROGEN PHTHALATE ESTERS

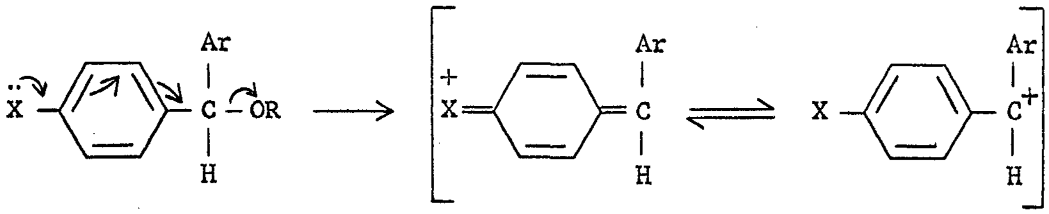
CHAPTER I

INTRODUCTION

It has been demonstrated in the chemical literature that when the α-carbon atom of an alcohol is substituted with one or more aryl groups, these compounds and their carboxylic esters have an increased tendency to undergo a base catalyzed solvolysis by a unimolecular alkyl-oxygen fission mechanism. Many reports have been published in the literature describing the effect that substitution on the aryl groups has on that mechanism. Of particular interest in this Dissertation is the mechanism of the hydroxide and methoxide catalyzed solvolytic reactions of hydrogen phthalate esters of substituted benzhydrols.

The previous work reported thus far has dealt almost exclusively with esters of aryl carbinols that are substituted in the para position of one or more of the aryl rings with groups that are able to release electrons to the aromatic ring(s). This provides an additional means of stabilization of the arylmethyl carbonium ion which is formed as an intermediate by a heterolytic alkyl-oxygen fission in the unimolecular mechanism.

It would be expected that electron release by the para substituents in the benzhydryl system would facilitate the heterolytic fission of the alkyl-oxygen bond of the hydrogen phthalate ester in a unimolecular process. The benzhydryl carbonium ion formed in such a manner could be stabilized by these para substituents in the following manner (eqn. 1).



(1)

where X = alkyl, alkoxyl, dialkylamino, or other electron donor.

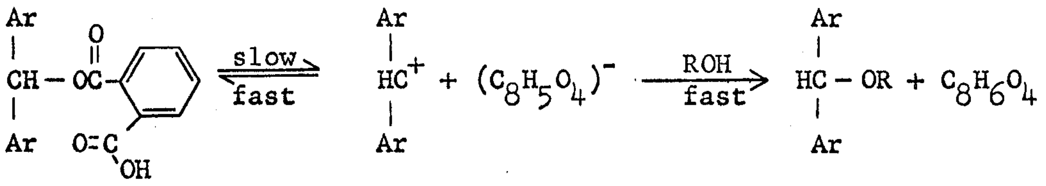
R = hydrogen phthaloyl.

No systematic study has hitherto been reported on the effect of electron withdrawing groups in the para position of the aryl groups on the mechanism of the solvolysis of benzhydryl hydrogen phthalates. Nitro substitution for example should prevent the stabilization of the benzhydryl carbonium ion by the aryl groups and thereby inhibit the unimolecular dissociation. It was decided to make a study of some solvolytic reactions of the hydrogen phthalate esters of several benzhydrols, some of which were substituted with the nitro group.

Possible Mechanisms Involved In The Solvolysis Of Hydrogen Phthalate Esters Of Benzhydrols

I Unimolecular Dissociation

The initiating step in the unimolecular mechanism is a heterolytic dissociation of the alkyl-oxygen bond in the ester portion of the molecule to yield two fragments: the benzhydryl carbonium ion and the hydrogen phthalate anion (eqn. 2).



(2)

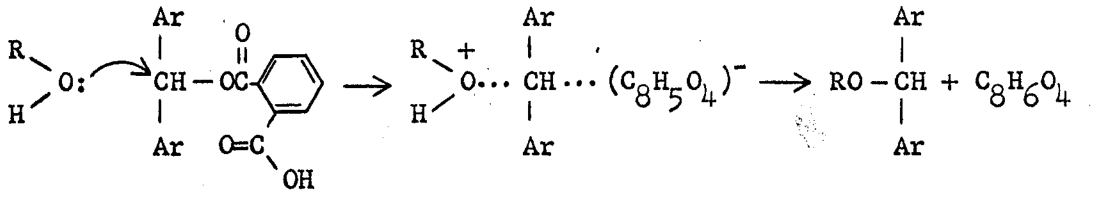
R = alkyl or hydrogen

If the ester undergoes solvolysis with an alcohol, the products are phthalic acid and the corresponding alkyl benzhydryl ether. Aqueous solvolysis yields the benzhydrol and phthalic acid as products.

Electron releasing substituents in the para positions of the aryl groups will enhance the rate of solvolysis of the benzhydryl hydrogen phthalate by the unimolecular mechanism by contributing to the stability of the carbonium ion, and increasing the rate of its formation. If the carbinyl carbon atom is a seat of asymmetry, racemization will occur on alcohol solvolysis through planarization of the carbonium ion. As a result the alkyl benzhydryl ether obtained will be racemic. This type of mechanism is termed S_N1 (from Substitution, Nucleophilic, Unimolecular).[1]

II Bimolecular Nucleophilic Substitution (S_N2)[1]

This mechanism involves a one-step nucleophilic attack on the carbinyl carbon of the ester (eqn. 3) with a simultaneous loss of hydrogen phthalate anion. The nucleophilic attack is on the side of the carbinyl carbon opposite to the leaving hydrogen phthalate anion. This results in a Walden inversion[2] about the carbinyl carbon atom. Racemiz-


(3)

R = alkyl or hydrogen

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[1] J. L. Gleave, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 236 (1935).

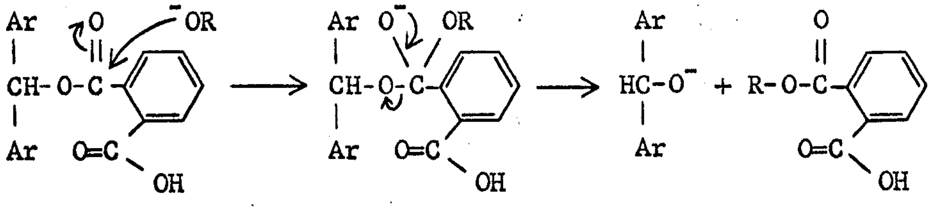
[2] P. Walden, *Ber.*, 30, 3146 (1897).

ation of the asymmetric centre in resolved optically active benzhydryl hydrogen phthalates does not occur by this mechanism and the ether product which is obtained in the alcoholysis reaction, will possess the same degree of optical purity as the ester.

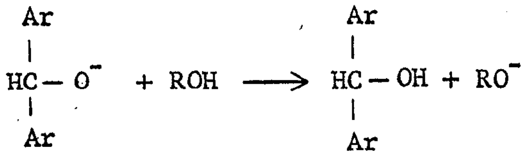
Very often, S_N1 and S_N2 processes occur competitively in the same solvolytic reaction. A measure of the relative contributions of each of the two processes to the overall hydrolysis or alcoholysis reaction is the optical purity of the alcohol or ether product: the greater the optical purity of the product, the greater the S_N2 character of the mechanism. A necessary condition for the formation of the alkyl benzhydryl ether by either of the two processes is the cleavage of the alkyl-oxygen bond in the original ester.

III Ester Interchange By Nucleophilic Attack At Ester Carbonyl By Solvent

Nucleophilic attack by a solvent molecule (water or alcohol) at the ester carbonyl of the hydrogen phthalate ester leads to ester interchange (eqns. 4,5). Because acyl-oxygen fission occurs, the nature of the



(4)



$$\underset{Ar}{\overset{Ar}{HC}}-O^- + ROH \longrightarrow \underset{Ar}{\overset{Ar}{HC}}-OH + RO^-$$

(5)

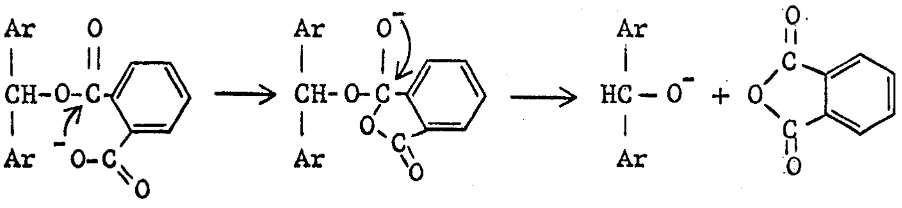
R = alkyl or hydrogen

asymmetry at the α carbon atom of the benzhydryl moiety remains intact.

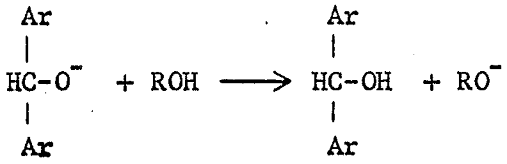
If the hydrogen phthalate ester undergoes solvolysis by an aliphatic alcohol, the products are the free benzhydrol and the hydrogen phthalate ester of the aliphatic alcohol. If the original ester was optically active, the benzhydrol obtained after solvolysis will also be optically active.

IV Ester Interchange Through Phthalic Anhydride Intermediate

Ester interchange in the case of base catalyzed solvolysis may occur through an intramolecular nucleophilic attack at the ester carbonyl by the carboxylate anion (eqns. 6,7,8). As in the third mechanism described

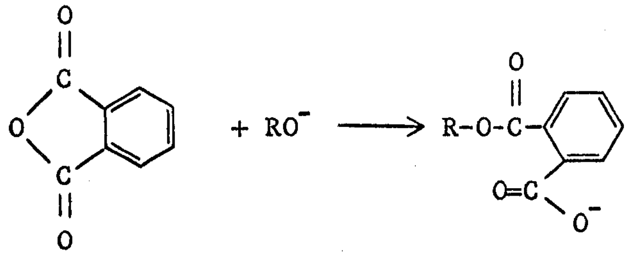


(6)



$$Ar_2CH{-}O^- + ROH \longrightarrow Ar_2CH{-}OH + RO^-$$

(7)



(8)

R = alkyl or hydrogen

above, the free benzhydrol and the alkyl hydrogen phthalate are again the reaction products. Acyl-oxygen fission occurs in this mechanism also.

This is responsible for the retention of configuration about the α carbon atom in the benzhydryl group.

One may distinguish between the above described four mechanisms in the following manner. In the solvolysis with an alcohol, mechanisms I and II have the alkyl benzhydryl ether as one of the products; mechanisms III and IV yield the free benzhydrol. Further, racemic ethers are obtained from the alcoholysis of the optically active ester by mechanism I while the ether is obtained with optical activity intact by mechanism II. Mechanisms III and IV may be distinguished between by a study of the kinetics of the reaction which will be described later.

Discussion of Previous Work

An extensive treatment of hydrogen phthalate esters of benzhydrols and other aryl carbinols has been undertaken by Balfe, Kenyon and co-workers. Their studies extend mostly to aryl carbinols that carry electron-releasing groups in the para positions of the aryl rings. The reactions that were studied are generally characterized by an alkyl-oxygen fission mechanism associated with the S_N1 process.

For example Balfe and co-workers have reported on the facile alkyl-oxygen fission in the ester and other derivatives of 4-methoxybenzhydrol.[3] It was reported that (+)-4-methoxybenzhydryl hydrogen phthalate when treated with 10 N aqueous sodium hydroxide yielded 4-methoxybenzhydrol that had underwent extensive racemization (eqn. 9). Saponification

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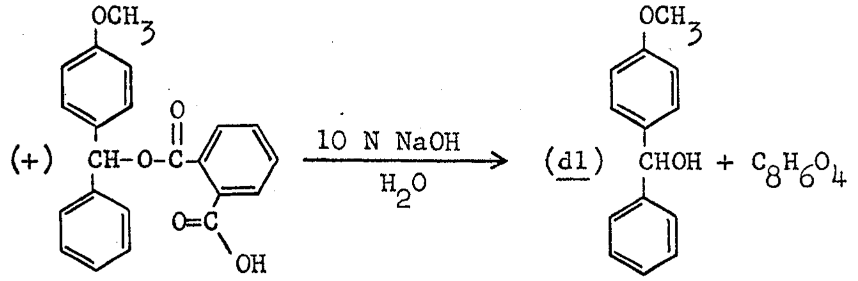
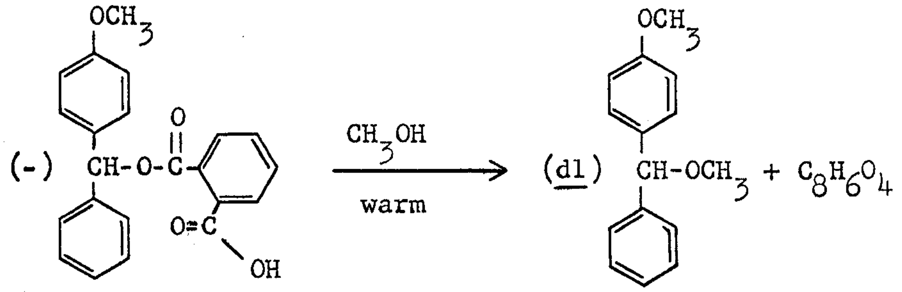
[3] M. P. Balfe, M. A. Doughty, J. Kenyon, and R. Poplett, J. Chem. Soc., 605 (1942).



(9)

of benzhydryl hydrogen phthalates in concentrated aqueous sodium hydroxide solution tends to be favourable for the conservation of optical purity, because when the same reaction is carried out in more dilute solution, more racemization occurs. Again, the trituration of the optically active esters and ethers of 4-methoxybenzhydrol with cold concentrated hydrochloric acid yielded racemic 4-methoxybenzhydryl chloride. It was also reported that (-)-4-methoxybenzhydryl hydrogen phthalate on warming in methanol solution produces a quantitative yield of the racemic methyl 4-methoxybenzhydryl ether (eqn. 10). Racemization of the alcohol occurs even on heating in contact with water.



(10)

In another paper, Balfe and co-workers have reported that the (+) hydrogen phthalate ester of α-naphthylmethylcarbinol in reaction with formic acid yielded the inactive formate ester[4] (eqn. 11). On treatment with acetic acid, the inactive acetate ester was obtained. Similar

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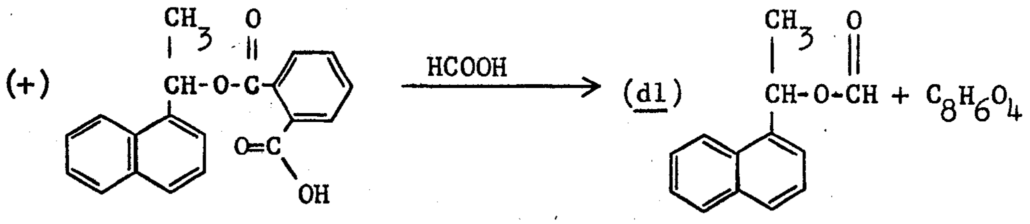
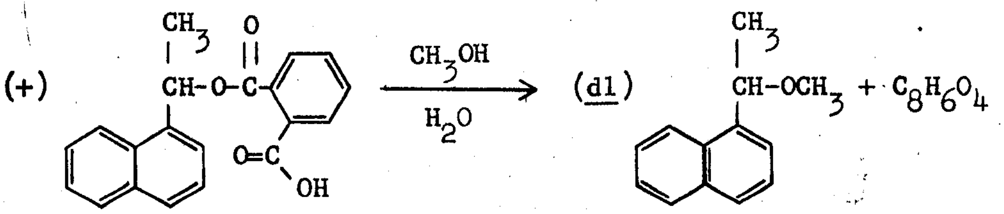
[4] M. P. Balfe, et al., J. Chem. Soc., 797 (1946).



(11)

results were noted in the formic and acetic acid solvolysis of the (-) benzoate and acetate esters. Furthermore, the corresponding racemic methyl ether was obtained on heating the same (+) hydrogen phthalate ester with aqueous methanol (eqn. 12).



(12)

Extensive racemizations were observed in a similar series of reactions of carboxylic esters of phenylmethyl carbinol, and the reactivity of these compounds by the S_N1 mechanism was not as great as in the α-naphthylmethylcarbinol series.

The authors observed that the tendency of the hydrogen phthalate esters of α-naphthylmethylcarbinol and phenylmethylcarbinol to undergo racemization during hydrolysis with weak alkali is less marked than for the hydrogen phthalate ester of 4-methoxybenzhydrol.

In a subsequent study of the hydrogen phthalate esters of p-anisyl-α-naphthylcarbinol and p-anisylmethyl-carbinol, it was shown by Balfe and co-workers that these compounds react with carboxylic acids and alcohols to give racemic products.[5] It was observed that the hydrogen phthalate

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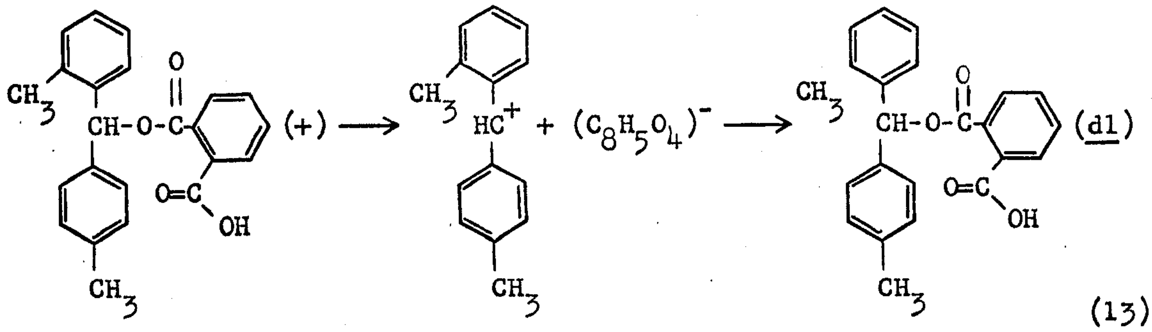
[5] M. P. Balfe, et al., J. Chem. Soc., 804 (1946).

esters of the following carbinols showed a decreasing tendency to give racemic reaction products in the order given: p-anisyl-α-naphthylcarbinol, 4-methoxybenzhydrol, p-anisyl alcohol, α and γ substituted allyl alcohols, α-naphthylmethylcarbinol, 2-chlorobenzhydrol, 3-methoxybenzhydrol and phenylmethylcarbinol. This is also the order in which one might arrange these carbinols so that they are in order of decreasing electron availability at the carbinyl carbon atom. The authors concluded that the experimental results are in accord with the unimolecular mechanism and that the cleavage of the hydrogen phthalate esters is promoted by electron release to the carbinyl carbon atom. An augmenting factor in the racemizations studied was claimed by the authors to be the dissociating influence of solvents with high dielectric constants through ion solvation.

The racemization of (+)-2,4'-dimethylbenzhydryl hydrogen phthalate has been observed to occur in anhydrous formic acid in ten minutes to yield the inactive hydrogen phthalate esters.[6] This suggests that the carbonium ion formed in the alkyl-oxygen bond dissociation is stable enough to undergo spontaneous racemization (eqn. 13).



(13)

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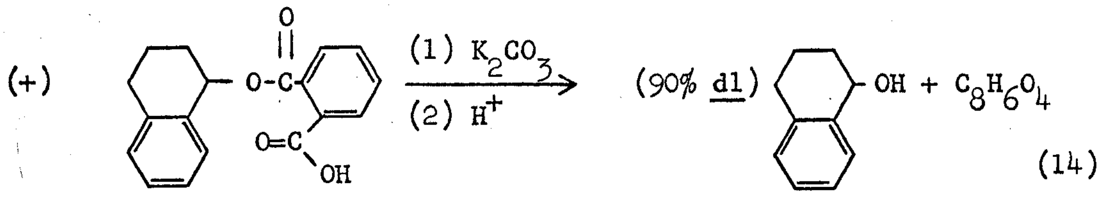
[6] M. P. Balfe, M. K. Hargreaves, and J. Kenyon, J. Chem. Soc., 375, (1951).

Davies and White have observed a facile alkyl-oxygen unimolecular heterolysis in several reactions of the hydrogen phthalate ester of 1,2,3,4-tetrahydro-1-naphthol.[7] They found that the optically active ester undergoes 90% racemization on being dissolved in an aqueous sodium carbonate solution and rapidly reprecipitated by acidulation of the solution (eqn. 14). 1,2,3,4-Tetrahydro-1-naphthyl-p-tolyl sulfone is



(14)

obtained as the product of the reaction 1,2,3,4-tetrahydro-1-naphthol or its hydrogen phthalate ester with sodium p-tolyl sulfinate in formic acid solution. Again, spontaneous racemization of the ester occurs in acetic acid solution containing a trace of sulfuric acid. Finally, Davies and White reported that the ester decomposed into 1,2-dihydronaphthalene, if left for long periods of time in formic acid solution. It was concluded by the authors that the reactions that were studied are characteristic of a unimolecular alkyl-oxygen heterolysis.

Several more papers are to be found in the literature describing additional experimental evidence supporting the S_N1 mechanism in the solvolysis of benzhydrol hydrogen phthalates. The effect of a para methyl group[8] was shown to be a stabilizing influence on the 4-methylbenzhydryl carbonium ion, which increased the tendency for carboxylate

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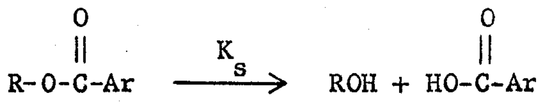
[7] A. G. Davies and A. M. White, J. Chem. Soc., 3300 (1952).

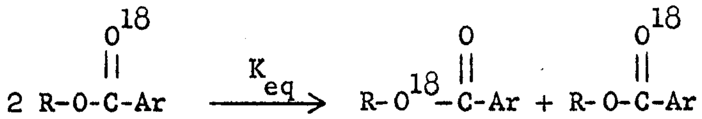
[8] A. G. Davies, et al., J. Chem. Soc., 3474 (1954).

derivatives of the corresponding alcohol to undergo the unimolecular heterolysis. Similar effects are reported for para alkylthio[9] and para dialkylamino[10] substituents.

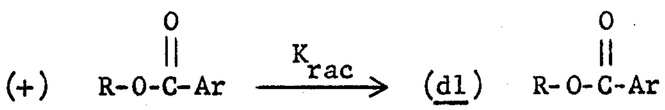
Goering recently has reported the randomization of the carboxyl oxygen atoms and the racemization of the unsolvolyzed ester in the solvolysis of optically active 4-chlorobenzhydryl 4-nitrobenzoate-carbonyl-O^{18} in 80 and 90% aqueous acetone.[11] Solvolysis (eqn. 15) is accompanied by the randomization of the carboxyl oxygen atoms (eqn. 16) and the racemization of the unsolvolyzed ester (eqn. 17). The mechanism for the reaction was proposed to involve an ion pair in which the carboxyl oxygen atoms are equivalent (eqn. 18).



$$\mathrm{R{-}O{-}\overset{\overset{O}{\|}}{C}{-}Ar} \xrightarrow{K_s} \mathrm{ROH + HO{-}\overset{\overset{O}{\|}}{C}{-}Ar} \tag{15}$$



$$2\ \mathrm{R{-}O{-}\overset{\overset{O^{18}}{\|}}{C}{-}Ar} \xrightarrow{K_{eq}} \mathrm{R{-}O^{18}{-}\overset{\overset{O}{\|}}{C}{-}Ar + R{-}O{-}\overset{\overset{O^{18}}{\|}}{C}{-}Ar} \tag{16}$$



$$(+)\quad \mathrm{R{-}O{-}\overset{\overset{O}{\|}}{C}{-}Ar} \xrightarrow{K_{rac}} (\underline{dl})\quad \mathrm{R{-}O{-}\overset{\overset{O}{\|}}{C}{-}Ar} \tag{17}$$

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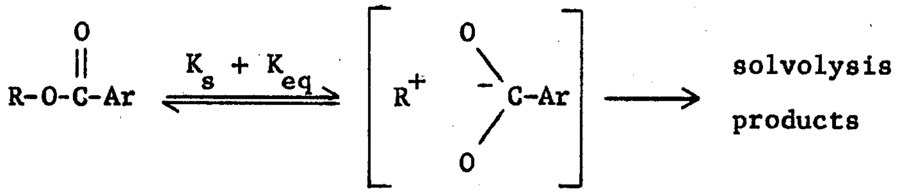
[9] M. P. Balfe, R. E. Darby and J. Kenyon, *J. Chem. Soc.*, 382 (1951).

[10] M. P. Balfe, et al., *J. Chem. Soc.*, 790 (1952).

[11] H. L. Goering, R. G. Briody and J. F. Levy, *J. Am. Chem. Soc.*, **85**, 3061 (1963).



(18)

Where R = 4-chlorobenzhydryl

Ar = 4-nitrophenyl

The data show that an ion pair return mechanism is responsible for the randomization and racemization effects observed in the original ester. In 90% aqueous acetone 72% of the ion pair intermediate (eqn.18) returns to substrate. Of the portion that returns the authors have shown that 81% regenerates the original ester and 19% is converted to the enantiomer. In 80% acetone, 60% of the intermediate returns, and of this fraction 78% is by retention of configuration and 22% by inversion to the enantiomer.

Interesting consequences were noted when the above reaction was studied in the presence of azide ion.[12] The randomization of the carboxyl oxygen atoms associated with ion pair return occurs, but the unsolvolyzed ester does not undergo racemization. This is apparently the result of the interception of the intermediate pair by azide ion that would normally return with loss of activity, but not the ion pair which returns with retention of activity. They determined furthermore that in the presence of azide ion, 82% of the 4-chlorobenzhydrol liberated is formed by acyl-oxygen fission, whereas solvolysis in the absence of azide ion occurs exclusively by alkyl-oxygen fission. This shows that in the presence of

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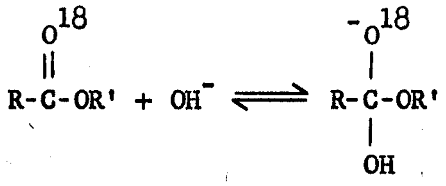
[12] H. L. Goering and J. F. Levy, *J. Am. Chem. Soc.*, *86*, 120 (1964).

azide ion, carboxyl oxygen equilibration will continue while ion pair return to give the racemic ester does not occur. The authors conclude that there are two intermediates which are involved; an ion pair that returns with retention of configuration, and one that returns with racemization.

The nucleophilic attack by solvent on the ester carbonyl which leads to ester interchange (solvolysis mechanism III, eqns. 4,5) has been extensively reported on in the literature. As an example, Bender[13] has reported on the alkaline hydrolyses of ethyl, isopropyl, and t-butyl benzoates. The object of his investigation was to determine which of the two possible mechanisms for carbonyl attack by hydroxyl ion was operative in these examples. The first mechanism is the addition of hydroxyl ion to the carbonyl group followed by a complex sequence of possible steps. The second is the simple displacement of the alkoxide ion in a one step concerted reaction. The alkaline solvolyses were carried out on the esters bearing O^{18} in the carbonyl group. The hydroxyl addition mechanisms for one of the isotopically substituted esters is represented below (eqns. 19-24).



$$R\text{-}\overset{O^{18}}{\overset{\parallel}{C}}\text{-}OR' + OH^- \rightleftharpoons R\text{-}\underset{\underset{OH}{|}}{\overset{{}^-O^{18}}{\overset{|}{C}}}\text{-}OR' , \qquad (19)$$

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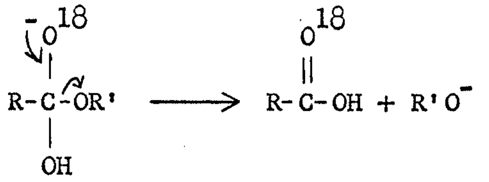
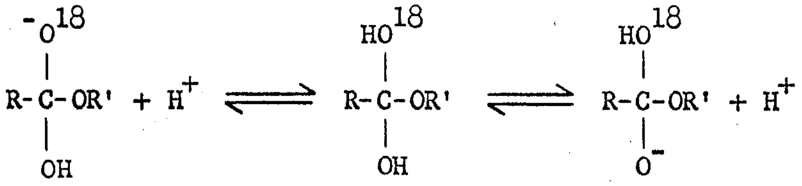
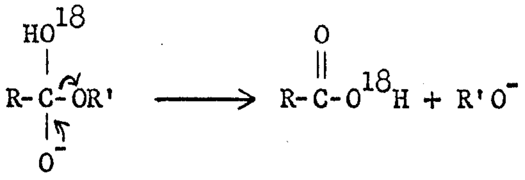
[13] M. L. Bender, *J. Am. Chem. Soc.*, *73*, 1626 (1951).



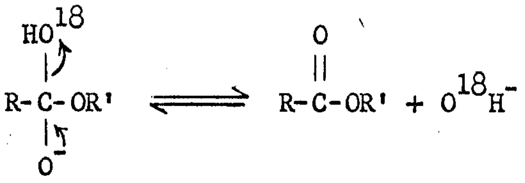
$$\mathrm{R{-}\overset{{}^{-}O^{18}}{\underset{OH}{C}}{-}OR'} \longrightarrow \mathrm{R{-}\overset{O^{18}}{\overset{\|}{C}}{-}OH} + \mathrm{R'O^{-}} \qquad (20)$$



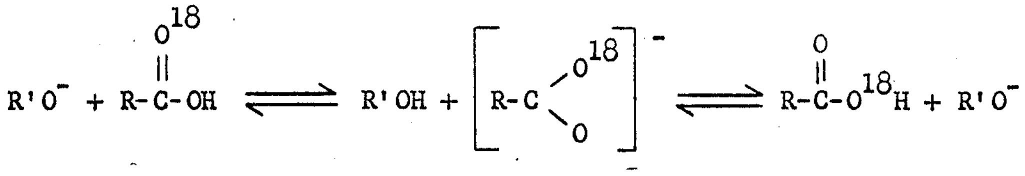
$$\mathrm{R{-}\overset{{}^{-}O^{18}}{\underset{OH}{C}}{-}OR'} + \mathrm{H^{+}} \rightleftharpoons \mathrm{R{-}\overset{HO^{18}}{\underset{OH}{C}}{-}OR'} \rightleftharpoons \mathrm{R{-}\overset{HO^{18}}{\underset{O^{-}}{C}}{-}OR'} + \mathrm{H^{+}} \qquad (21)$$



$$\mathrm{R{-}\overset{HO^{18}}{\underset{O^{-}}{C}}{-}OR'} \longrightarrow \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}O^{18}H} + \mathrm{R'O^{-}} \qquad (22)$$



$$\mathrm{R{-}\overset{HO^{18}}{\underset{O^{-}}{C}}{-}OR'} \rightleftharpoons \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}OR'} + \mathrm{O^{18}H^{-}} \qquad (23)$$

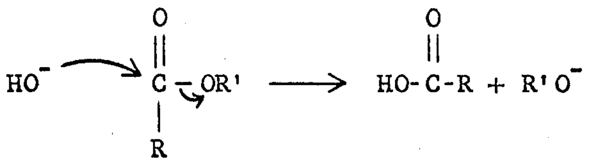


$$\mathrm{R'O^{-}} + \mathrm{R{-}\overset{O^{18}}{\overset{\|}{C}}{-}OH} \rightleftharpoons \mathrm{R'OH} + \left[\mathrm{R{-}C}\begin{smallmatrix}\diagup O^{18}\\ \diagdown O\end{smallmatrix}\right]^{-} \rightleftharpoons \mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}O^{18}H} + \mathrm{R'O^{-}} \qquad (24)$$

Where R = phenyl

R' = ethyl, isopropyl, and t-butyl.

By stopping the reactions before completion, Bender was able to isolate unhydrolyzed ester that had a smaller O^{18} content (eqn. 23) than the original ester. This observation could be explained by the above mechanism quite well, and not by the concerted one-step displacement (eqn. 25), which has no provision for the loss of O^{18} by the unhydrolyzed ester.



$$\mathrm{HO^-} \;\; \underset{\displaystyle \mathrm{R}}{\overset{\displaystyle \mathrm{O}}{\overset{\|}{\mathrm{C}}}}\mathrm{-OR'} \longrightarrow \mathrm{HO{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}R} + \mathrm{R'O^-} \qquad (25)$$

A study of the kinetics of the alkaline hydrolysis of methyl hydrogen phthalate[14] has been reported by Bender, Chloupek and Nevue in which it was shown that the o-carboxylate anion has an intramolecular catalytic effect on the hydrolysis.

The hydrolysis rate constant was reported by the authors to be dependent on the pH of the reaction solution as shown in figure 1.

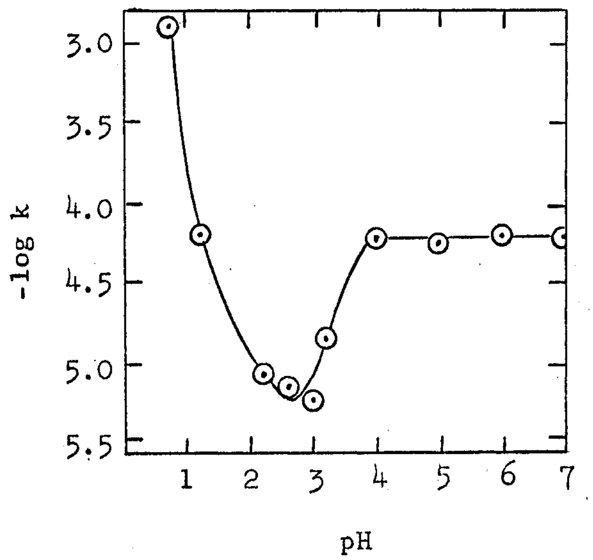


Fig. 1. - The rate of hydrolysis of methyl hydrogen phthalate with pH.

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[14] M. L. Bender, F. Chloupek and M. Neveu, *J. Am. Chem. Soc.*, *80*, 5384 (1958).

It is significant that the pK of methyl hydrogen phthalate (3.22)[15] coincides very nearly with the inflection point in the pH-rate profile.

The plateau reached in the value of the hydrolysis rate constant for pH greater than 4 is explained by the authors as representing the rate of the intramolecular carboxylate-catalyzed hydrolysis. Increasing the pH beyond 4 will not generate more carboxylate anion, and as a result, the rate does not significantly change up to pH 7, which was the upper limit of the study. As a result, the authors proposed that phthalic anhydride is generated through an intramolecular nucleophilic attack by carboxylate anion on the ester carbonyl (mechanism IV, eqns. 6,7,8).

A recent report has been made by Thanassi and Bruice[16] on the participation of the carboxyl group on the hydrolysis of several monoesters of phthalic acid. Their data shows that phenyl and 2',2',2'-trifluoroethyl hydrogen phthalates hydrolyze more slowly at pH 2 than at pH 5. The authors propose that this shows that the reaction rate is dependent on the mole fraction of the ester in the ionized form and that it is carboxylate anion that participates in the hydrolysis.

On the other hand, methyl and 2'-chloroethyl hydrogen phthalates show a decrease in the rate as the pH is increased from 2 to 5. The authors conclude from this that the rate is dependent on the mole fraction of ester that is not ionized, and that in these two examples the neutral carboxyl group (COOH) catalyzes the hydrolysis.

The rate of the hydrolysis of propargyl hydrogen phthalate showed

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[15] F. H. Westheimer and O. T. Benfey, J. Am. Chem. Soc., 78, 5309 (1956).

[16] J. W. Thanassi and T. C. Bruice, J. Am. Chem. Soc., 88, 747 (1966).

no alteration with pH changes, and therefore appears to be equally catalyzed by both the carboxylate and neutral carboxylic groups.

The experimental evidence seems to support the authors' statement that the hydrogen phthalate esters having good leaving groups (phenoxyl, 2',2',2'-trifluoroethoxyl) hydrolyze with the catalysis of the carboxylate anion, and those that have poor leaving groups (methoxyl, 2'-chloroethoxyl) hydrolyze with the catalysis of the neutral carboxyl group. Propargoxyl is apparently a borderline case, being lost on hydrolysis catalysed equally by both the carboxylate anion and the neutral carboxyl group.

The authors offer no explanation for the apparent disagreement of their data with that of Bender's[17] in relation to the work on methyl hydrogen phthalate.

Puckowski and Ross[18] have demonstrated the reluctance of the hydrogen phthalate esters of some nitro substituted benzhydrols to undergo a unimolecular dissociation which is associated with racemization of the substrate ester. The resolution of 2-, 3-, and 4-nitro-, 3,5-dinitro, and 3-bromobenzhydrol and some reactions of the alcohols and their esters in a unimolecular alkyl-oxygen fission have been reported by these authors. The tendency to react by this mechanism was investigated by studying the hydrolysis of the optically active esters, the solvolysis in methanol, formic acid and acetic acid, and the reactivity towards p-tolyl sulfinic acid.

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[17] M. L Bender, F. Chloupek and M. Nevue, loc. cit.

[18] R. T. Puckowski and W. A. Ross, J. Chem. Soc., 3555 (1959).

Hydrolysis of these esters in ethanolic sodium hydroxide solution, in 0.2 N aqueous sodium hydroxide, or in an excess of 10% aqueous sodium carbonate solution at reflux temperature yielded the optically active alcohols with little racemization. The hydrogen phthalate esters showed little reaction with boiling glacial or 70% acetic acid. Racemic formate esters were obtained in good yields from the reaction of the optically active hydrogen phthalate esters with hot 98% formic acid. The alcohols were obtained when the esters were treated with sodium p-tolylsulfinate. The authors conclude that the following substituents are arranged in the order of decreasing tendency to aid in the alkyl-oxygen fission mechanism: 4-NH_2, 2-NH_2, 3-NH_2, 3-Br, 2-, 3-, 4-NO_2, 3,5-$(NO_2)_2$. No mechanisms were discussed by the authors which may have led to acyl-oxygen cleavage of the hydrogen phthalate esters of the nitro-substituted benzhydrols.

Our interest in this problem was to determine the effect on the base catalyzed hydrolysis and methanolysis reactions of benzhydryl hydrogen phthalates when the benzhydryl moiety was substituted at one or both of the 4-positions with electron seeking groups.

CHAPTER II

DISCUSSION OF EXPERIMENTAL RESULTS

The preparation of the benzhydryl hydrogen phthalates was designed with the purpose in mind of determining whether, at least qualitatively, a transition point in the algebraic sum of the Hammett σ values[1] could be reached that would represent the point where the unimolecular solvolytic mechanism was becoming energetically unfavourable.

Jaffe has treated the problem of the additive nature[2] of the Hammett σ values in a review of work reported by other authors. It was shown that the Hammett equation (eqn. 26) applies very well

$$\log \frac{K}{K_o} = \sigma\rho \qquad (26)$$

where K is the rate or equilibrium constant in the reaction of a series of substituted aryl compounds,

K_o is the ionization constant for each of the benzoic acids substituted with the groups referred to in the definition of K,

σ is the substituent constant for the substituent,

ρ is a proportionality constant and is dependent on the conditions and nature of the reaction.

to a series of diaryl compounds where only one of the rings is substituted and equally well to a series carrying substitution on both rings

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[1] L.P. Hammett, Physical Organic Chemistry, chaps. 3, 4 and 7, McGraw-Hill Book Company, Inc., New York, 1940.

[2] H. H. Jaffe, Chem. Revs., 53, 247 (1953).

if one of the substituents is the same in the whole series. The Hammett equation in a modified form (eqn. 27) can be applied to a compound having

$$\log \frac{K}{K_o} = n\sigma\rho \qquad (27)$$

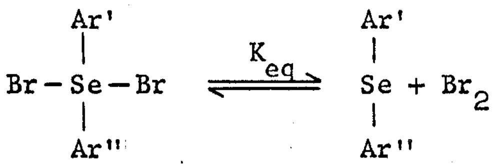
n rings that are symmetrically substituted with the same groups.

If a diaryl compound has different substitution on each of the two rings another version of the Hammett equation may apply (eqn. 28). This

$$\log \frac{K}{K_o} = \rho\,(\sigma_1 + \sigma_2) \qquad (28)$$

form of the equation implies the additivity of the σ values which has no theoretical basis but which can be verified empirically.

For example, McCullough and Barsh[3] have reported a study which shows that in the dissociation of some unsymmetrically substituted diphenylselenium dibromides (eqn. 29), the logarithm of the equilibrium



$$\mathrm{Br{-}\overset{Ar'}{\underset{Ar''}{Se}}{-}Br} \overset{K_{eq}}{\rightleftharpoons} \mathrm{\overset{Ar'}{\underset{Ar''}{Se}} + Br_2} \qquad (29)$$

constant for the dissociation shows a linear dependency on the algebraic sum of the σ values of the aryl substituents.

The hydrogen phthalate esters of the following benzhydrols were prepared: 4-nitrobenzhydrol, 4-bromo-4'-nitrobenzhydrol, 4-nitro-4'-t-butylbenzhydrol, 4-chlorobenzhydrol, and 4-methylbenzhydrol. It should

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[3] J. D. McCullough and M. K. Barsh, J. Am. Chem. Soc., 71, 3031 (1949).

be noted here that the procedure previously described by Rutherford and co-workers[4] for the preparation of hydrogen phthalate esters of tertiary alcohols did not prove adequate with the nitro substituted benzhydryl alcohols. After much experimentation it was found that sodium hydride removed the proton from the alcohol group quite readily and without complications. The resultant sodium benzhydrylate reacted rapidly with phthalic anhydride to give excellent yields of the hydrogen phthalate esters.

Table I

Values Of $(\sigma_1 + \sigma_2)$ For Benzhydryl Hydrogen Phthalates

p-Substituent	σ_1 [5]	p'-Substituent	σ_1 [5]	$\sigma_1 + \sigma_2$
NO_2	+0.778	Br	+0.232	+1.010
NO_2	+0.778	H	0.000	+0.778
NO_2	+0.778	$(CH_3)_3C$	-0.197	+0.581
Cl	+0.227	H	0.000	+0.227
CH_3	-0.170	H	0.000	-0.170

It can be seen from the table that the sum of the Hammett σ-values $(\sigma_1 + \sigma_2)$ ranges from +1.010 in the case of 4-brom-4'-nitrobenzhydryl hydrogen phthalate to -0.180 for the 4-methylbenzhydryl ester. Since

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[4] K. G. Rutherford, J. M. Prokipcak, and D. P. C. Fung, J. Org. Chem., 28, 582 (1963).

[5] Values from compilation of D. H. McDaniel and H. C. Brown, J. Org. Chem., 23, 420 (1958).

Davies and his co-workers[6] had previously reported that optically active 4-methylbenzhydryl hydrogen phthalate yielded racemic 4-methylbenzhydryl methyl ether when solvolyzed with methanol it was decided to subject the above prepared esters to the same conditions (24 hr. reflux). Davies' observation in the case of the 4-methylbenzhydryl ester ($\sigma_1 + \sigma_2 = 0.170$) was confirmed since only the methyl ether of 4-methylbenzhydrol was obtained (20% yield) as well as unreacted ester (74%). No 4-methylbenzhydrol was detected. Hence no acyl-oxygen cleavage of the ester occurred.

In the case of the remaining hydrogen phthalate esters the results were not conclusive. High yields of unreacted starting materials were obtained at the end of 24 hours (Table II). Although some neutral product was obtained in the case of 4-nitro-4-t-butylbenzhydryl and 4-chlorobenzhydryl esters, a carbonyl band was noted in the infrared spectrum of each. This could have resulted from a competing esterification reaction with the carboxylic acid group of the hydrogen phthalate ester and methanol. It was decided then to resort to sodium methoxide catalyzed solvolysis in order to enhance the reaction rate.

Table II summarizes the results of the solvolysis of the hydrogen phthalate esters with methanolic sodium methoxide and with methanol.

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[6] A. G. Davies, et al., J. Chem. Soc., 3474 (1954).

Table II

Influence Of $(\sigma_1 + \sigma_2)$ Values On Yields Of Solvolysis Products Of 4-X-4'-Y-Benzhydryl Hydrogen Phthalate

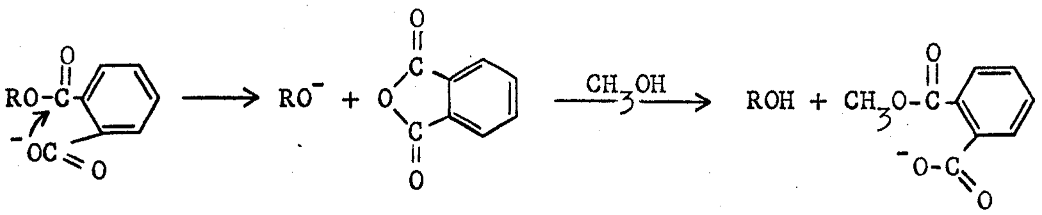
X	Y	$(\sigma_1 + \sigma_2)$	Alcohol % Yield[a]	Ester Recovery[b]
NO_2	Br	+1.010	97	92
NO_2	H	+0.778	96	94
NO_2	$(CH_3)_3C$	+0.581	91	82
Cl	H	+0.227	93	86
CH_3	H	-0.170	84	74

[a] From the solvolysis of the ester with methanolic sodium methoxide (5 minutes at room temperature).

[b] From 24 hour reflux in anhydrous methanol.

It can be seen that from the yields of benzhydrols obtained, acyl-oxygen fission occurs to the exclusion of alkyl-oxygen fission with those esters which have positive $(\sigma_1 + \sigma_2)$ values. Indeed, even in the case of the 4-methylbenzhydryl ester $(\sigma_1 + \sigma_2 = -0.170)$ 84% of the reaction occurred by acyl-oxygen cleavage. Only 10% of the alkyl-oxygen cleavage product (methyl ether) was obtained. Although it would be of interest to examine similar solvolysis of benzhydryl hydrogen phthalate esters which possessed higher negative values of $(\sigma_1 + \sigma_2)$, it was decided that at least a trend had been established and that the more interesting path of research for the present would involve the determination of the mechanism of the acyl-oxygen fission.

There are two possible mechanisms for the sodium methoxide solvolysis of the benzhydryl esters (eqns. 30,31,32).



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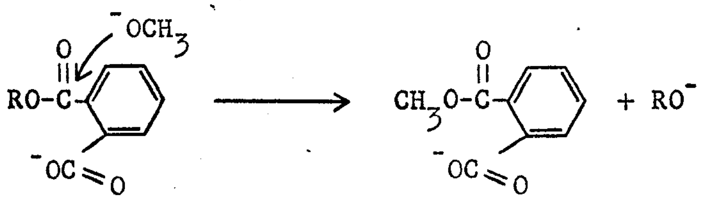


(31)

$$RO^- + CH_3OH \longrightarrow ROH + CH_3O^- \qquad (32)$$

R = Substituted Benzhydryl

The anhydride mechanism as depicted by equation (30) is attractive in view of Bender's work (p. 82 Chapt. I) which shows the intramolecular catalytic effect of the carboxylate anion. In our case, since the reaction is studied in basic solution, this intramolecular catalytic effect of carboxylate anion should be enhanced. Thus the addition of increasing amounts of base up to the equivalent point should result in a proportional rate enhancement in methanolysis. This was shown to be an erroneous assumption. Figure 2 shows the results of adding increasing amounts of sodium methoxide to 4-bromo-4'-nitrobenzhydryl hydrogen phthalate. It can be seen from the graph that as we progressively add sodium methoxide to a methanolic solution of the ester (0.01 mole), no appreciable methanolysis occurs even at the end of twenty-four hours

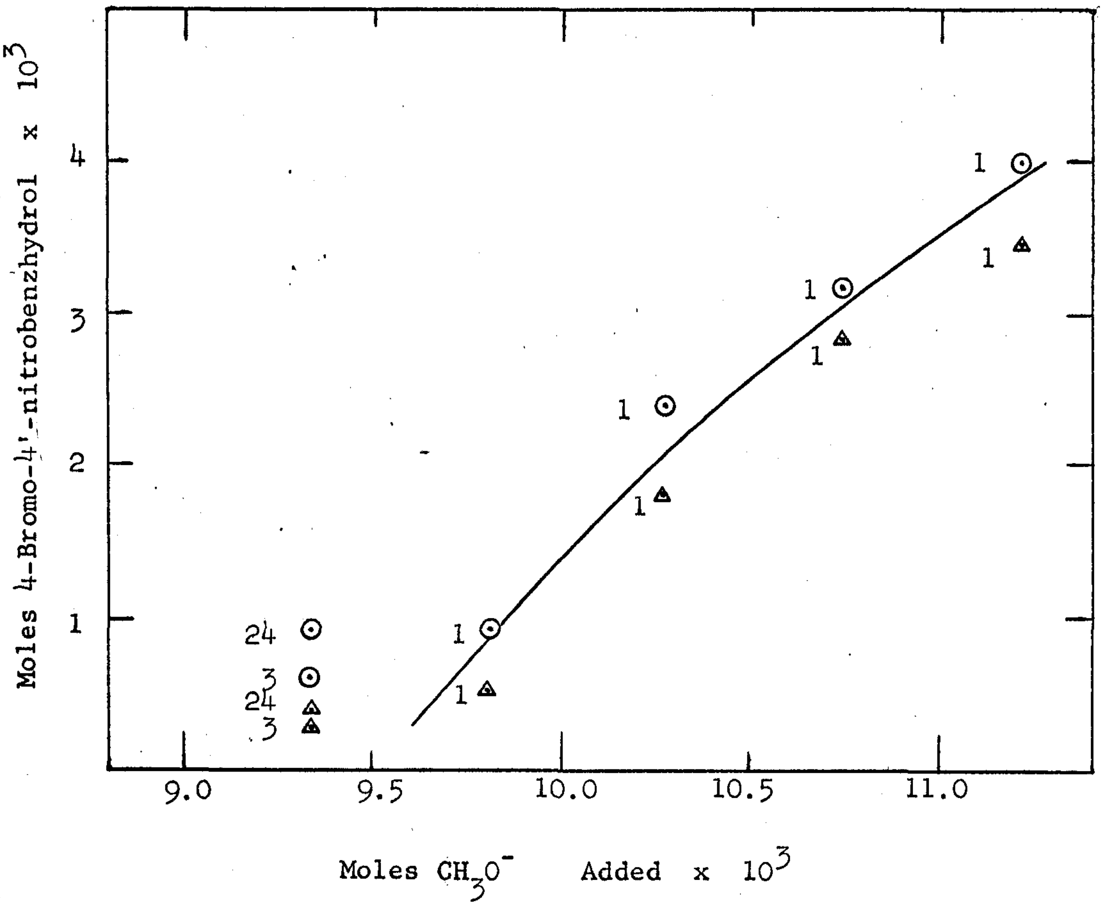


Fig. 2. - Methoxide catalyzed methanolysis of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate. Moles hydrol obtained vs moles methoxide added per 0.010 mole ester. Numbers indicate length of reaction period in hours.

⊙ Yield of hydrol calculated from precipitate weights.

▲ Yield of hydrol calculated from neutralization equivalent.

(25°) until the equivalent point is reached. Further addition of methoxide results in a progressive increase in the amounts of 4-bromo-4'-nitrobenzhydrol produced after one hour reaction time. Thus when 11.2 mmoles of methoxide is added to 10 mmoles of ester, approximately 40%

methanolysis is realized at the end of one hour. When 10.3 mmoles of methoxide are added to 10 mmoles of ester, 20% methanolysis occurs in the same length of time.

It is to be noted at the left portion of the graph that when 9.34 mmoles of methoxide is added to 10 mmoles of ester, no appreciable difference in yields of 4-bromo-4'-nitrobenzhydrol is observed at the end of three and twenty-four hours (3%-10%). The product of some of the alcohol before equivalency was reached could result from the initial pouring of the methoxide solution into the solution of benzhydryl ester. Thus high local concentrations of methoxide were probably formed giving rise to high rates of methanolysis in these regions.

It would appear from the above considerations that the intramolecular catalyzed methanolysis of the benzhydryl ester is relatively insignificant and that this mechanism can be discounted as a reaction path. It was decided however to substantiate this indirect evidence with a study of the kinetics of the reaction. If the 'anhydride' mechanism (eqn. 30) prevails, then the addition of base in excess of an equivalent amount of ester should cause no rate enhancement. If however methanolysis occurs by the normal path (eqn. 31) a rate increase should be observed paralleling that which is observed in normal hydrolysis of esters. Thus the rate equation should take the form:

$$\frac{d[\text{ester}]}{dt} = -k_2[\text{ester}][CH_3O^-]_{\text{excess}}$$

Such kinetic studies for methoxide catalyzed methanolysis present a major problem. Since the concentration of base (OCH_3^-) does not change regardless of the mechanistic path, the titrimetric methods usually followed in normal ester hydrolysis cannot be employed. It was decided to follow the rate of reaction by the gravimetric method. The following procedure proved convenient both for methoxide and subsequent hydroxide reactions with 4-bromo-4'-nitrobenzhydryl hydrogen phthalate.

The ester was dissolved in tetrahydrofuran. A methanol solution containing a known amount of methoxide anion was added. Aliquots of the reaction mixture were removed at specified intervals and rapidly acidified. From the weights of the precipitates obtained, the concentration of the unchanged ester anion was calculated in the following manner.

By mass balance $N_A + N_B = N_{A_i}$

and $N_A M_A + N_B M_B = W$

where N_A = number of moles of ester or ester anion in the precipitate.

N_B = number of moles of alcohol in the precipitate

N_{A_i} = number of moles of ester or ester anion at time = 0 in the precipitate

$$= \frac{\text{volume of aliquot}}{\text{Reaction Volume}} \times \text{number of moles of ester used in the experiment.}$$

M_A = molecular weight of the ester = 458

M_B = molecular weight of the alcohol = 308

W = precipitate weight.

Substituting with $N_B = N_{A_i} - N_A$

we obtain $N_A M_A + (N_{A_i} - N_A)M_B = W$

$$N_A M_A + N_{A_i} M_B - N_A M_B = W$$

$$N_A(M_A - M_B) = W - N_{A_i} M_B$$

$$N_A = \frac{W - N_{A_i} M_B}{M_A - M_B}$$

Finally, $[\text{ester}] = \dfrac{N_A}{\text{volume of aliquot}}$

$$= \frac{W - N_{A_i} M_B}{(M_A - M_B)V_{aliq.}}$$

Thus it can be seen that the above method enables the convenient determination of the concentration of unchanged ester in each of the experiments. From the slopes and the base concentrations, dependency of methoxide in excess of equivalency can be determined.

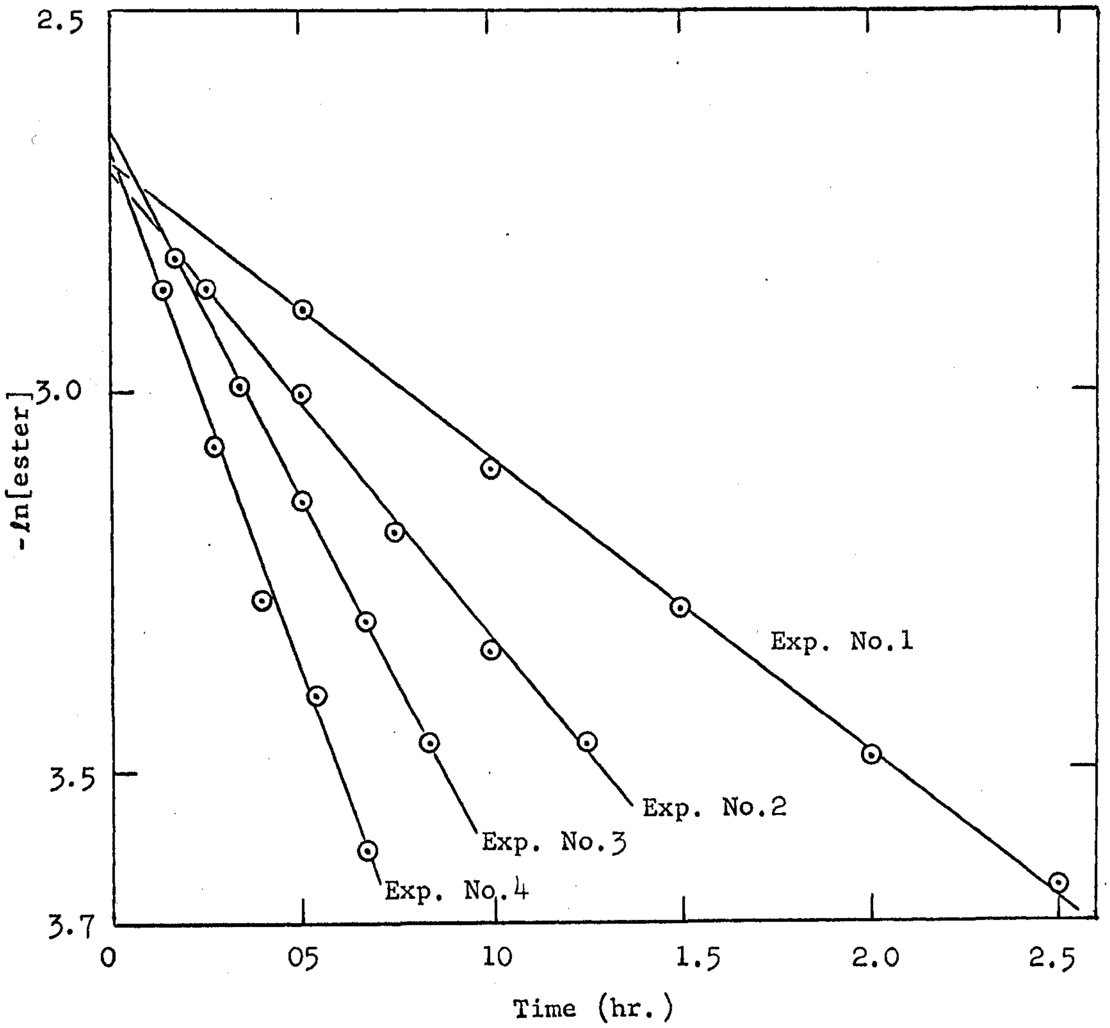


Fig. 3. - Methoxide ion catalyzed methanolysis of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate. First order in ester concentration. Excess methoxide ion: exp. No.1, 0.0010; exp. No.2, 0.0020; exp. No.3, 0.0030; exp. No.4, 0.0040 mole methoxide ion per 0.020 mole ester in 275 ml. reaction volume.

Fig. 3 shows the first order dependency of ester anion concentration in experiments which involved increasing concentrations of methoxide ion in excess of equivalency. When the slopes (Table III) were plotted against the concentration of excess methoxide anion the

Table III

Proportionality Of Ester Methanolysis Rates With Excess Methoxide Ion Concentration

Experiment No.	Methoxide Ion Added In Excess of Equivalency: moles per 0.020 moles ester in 275 ml.	Methoxide Ion Added In Excess of Equivalency: (mole lit.$^{-1}$)	k_1=Slopes [a] (hr^{-1})
1	0.0010	0.00364	-0.382
2	0.0020	0.00728	-0.596
3	0.0030	0.01091	-0.952
4	0.0040	0.01454	-1.374

[a] Taken from the first order plot (ℓn[ester] *vs* time; Fig. 3)

straight line observed in Fig. 4 was obtained indicating first order dependency of methoxide. There can be no doubt then that the 4-bromo-4'-nitrobenzhydryl ester undergoes methoxide ion catalyzed methanolysis by a path which involves attack of methoxide ion at the ester carbonyl group in accordance with the known path followed by the hydroxide ion catalyzed hydrolysis of esters.

Thus the second order rate law for the reaction is then:

$$\frac{d[\text{ester}]}{dt} = -k_2[\text{ester}][CH_3O]_{\text{excess}} \qquad (33)$$

where k_2 = -slope of plot of k_1 vs $[CH_3O]_{\text{excess}}$ in Fig. 3

k_2 calc. = 92.0 ℓ.mole^{-1}hr.$^{-1}$

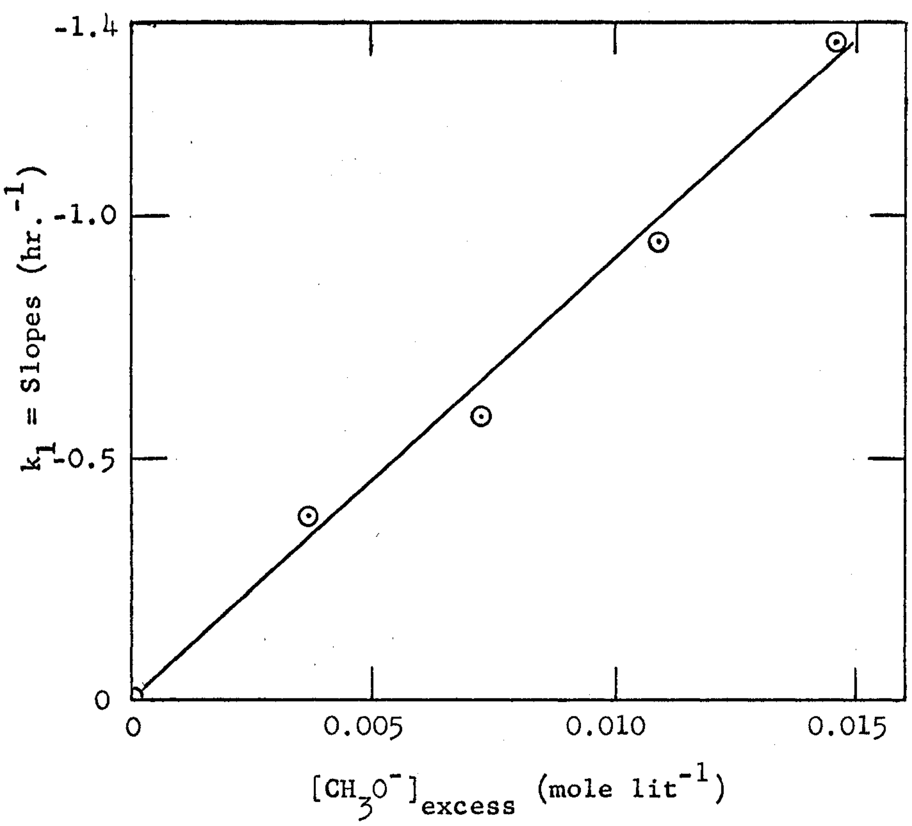


Fig. 4. - First order slopes (from Fig. 3) vs concentration of excess methoxide ion in the methanolysis of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate. First order dependency of rate on methoxide ion concentration.

It then became of interest to see if the same mechanism was operative in the hydroxide ion catalyzed hydrolysis of the same ester. Although intuitively one would expect the same mechanism to prevail, (bimolecular reaction), it should however not be assumed because a different solvent is used and hydroxide ion has less nucleophilic character than does methoxide. Thus it is conceivable that the rate of carbonyl addition of hydroxide would be slower thus enhancing the possibility of intramolecular participation of the carboxylate anion.

The kinetics will again differentiate between the two mechanisms.

Figures 5 and 6 show the kinetic dependency of both ester and hydroxide ion in the hydrolysis of 4-nitro-4'-bromobenzhydryl hydrogen phthalate. In order to effect reaction within the period of time observed for the methanolysis reaction, the concentration of hydroxide was of necessity increased about ten-fold over the methoxide concentration used in the previous study. The kinetic data resemble those of the methanolysis studies for the same ester. Hydroxide ion shows the same catalytic behaviour when added in excess of equivalency with

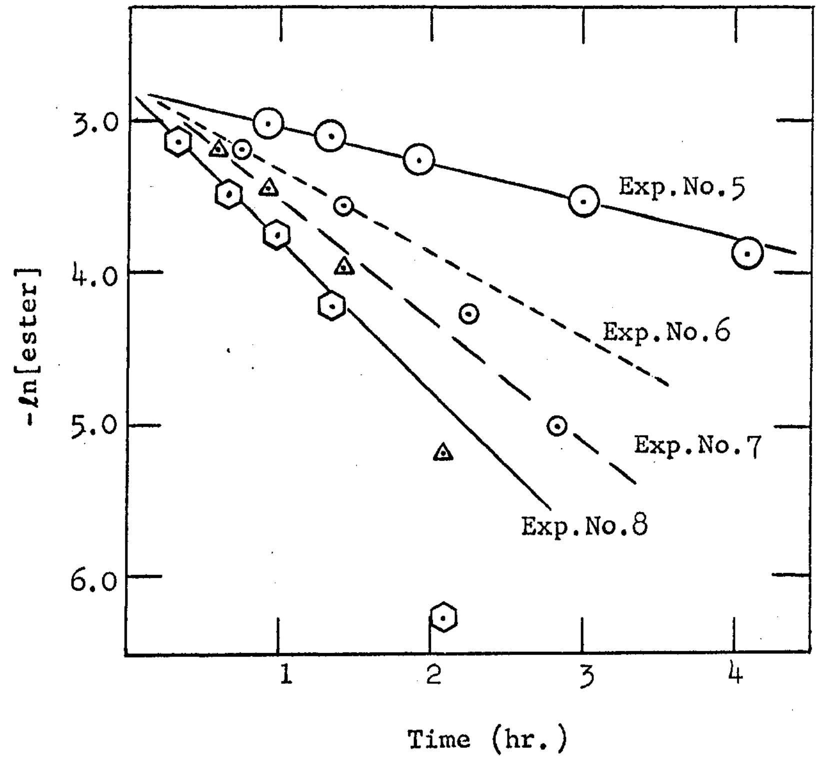


Fig. 5. - Hydroxide ion catalyzed hydrolysis of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate. First order in ester concentration. Excess hydroxide ion: exp. No.5, 0.0134; exp. No.6, 0.0252; exp. No.7, 0.0368; exp. No.8, 0.0816 mole hydroxide ion per 0.010 mole ester in 137.5 ml. reaction volume.

respect to the ester. Thus when the logarithm of the unhydrolyzed ester concentration was plotted against the reaction time, lines were obtained that showed first order rate dependency on the ester concentration (Fig. 5).

The lines in Figure 5 are straight at least in the range of the percentages of conversion found in the methanolysis study (Fig. 3). The apparent increase in the hydrolytic rate with increasing conversion is probably not a kinetic effect, but only a mechanical error caused by an incomplete precipitation of the reaction products or incomplete transfer of the products to the weighing crucibles. This gravimetric method becomes increasingly sensitive to errors arising from incomplete collection of the products as the hydrolysis nears completion. A loss or gain of 2 mg. of precipitate, for example, at 98% completion (last datum point in experiment No. 8, Fig. 5) will cause an uncertainty of 0.60 logarithm units at that point.

With the exception of the initial slope of the line representing the kinetic data of experiment No. 8 (Fig. 5) the initial slopes (first order rates) obtained from the hydrolysis experiments were directly proportional to the concentrations of hydroxide in excess of equivalency (Table IV, Fig. 6).

Table IV

Proportionality Of Ester Hydrolysis Rates With Excess Hydroxide Ion Concentration

Experiment No.	Hydroxide Added In Excess of Equivalency		k_1=Slopes [a] initial (hr^{-1})
	moles per 0.010 mole ester in 137.5 ml.	(mole lit.$^{-1}$)	
5	0.0134	0.0975	-0.250
6	0.0252	0.1833	-0.580
7	0.0368	0.2676	-0.800
8	0.0816	0.5934	-0.954

[a] Taken from the first order plot (ℓn[ester] vs time; Fig. 5)

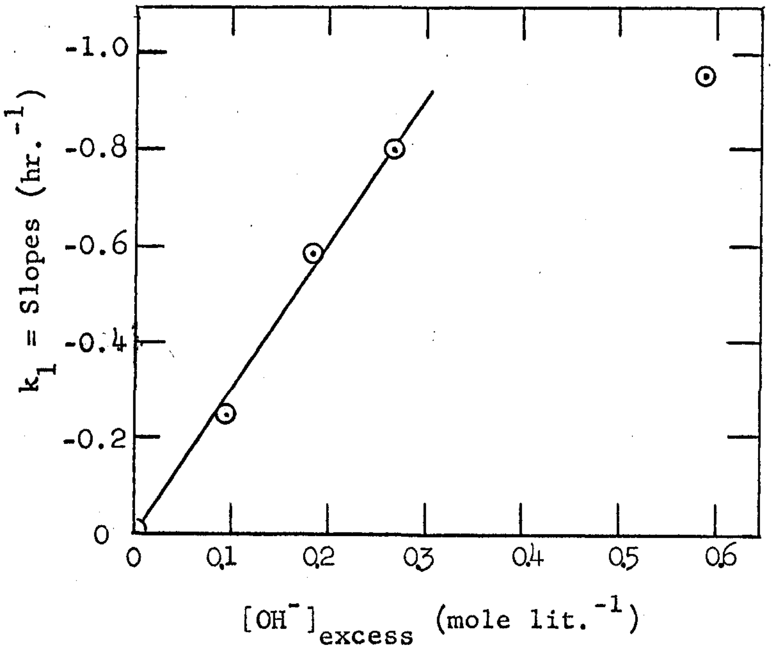


Fig. 6. - First order slopes (initial slopes from Fig. 5) vs concentration of excess hydroxide in hydrolysis of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate. First order dependency on excess hydroxide concentration.

It may then be concluded that the hydrolysis of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate in alkaline solution is first order in the concentration of the ester anion and first order in the concentration of the hydroxide ion which is added in excess of equivalency (eqn. 34).

$$\frac{d[\text{ester}]}{dt} = -k_2[\text{ester}][\text{OH}^-]_{\text{excess}} \qquad (34)$$

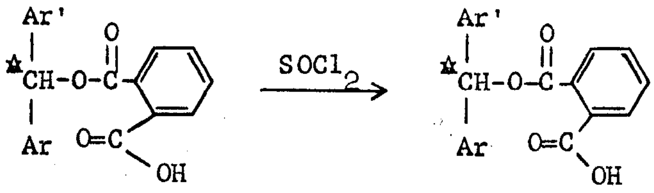
where k_2 = -slope of plot of k_1 vs $[\text{OH}^-]_{\text{excess}}$ (Fig. 6)

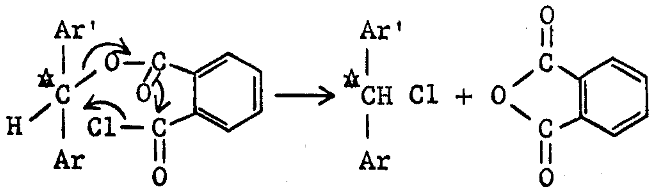
k_2 calc. = 3.05 lit. mole^{-1} hr.$^{-1}$

The second order nature of the alkaline hydrolysis of this ester indicates that the ester anion and the hydroxide ion are both involved in the rate determining step. In the interpretation of these kinetic results a problem arises here which did not arise in the methanolysis studies. Thus the absence of 4-bromo-4'-nitrobenzhydryl methyl ether in the methanolysis of the benzhydryl ester discounted any arguments that the kinetics could be explained by a classical methoxide induced Walden inversion resulting in alkyl-oxygen cleavage. However, 4-bromo-4'-nitrobenzhydrol only is obtained from the hydrolysis of the benzhydryl ester whether alkyl-oxygen or acyl-oxygen cleavage occurs. Thus the second order kinetics obtained from the hydrolysis experiments can differentiate between carboxylate anion participation and normal ester hydrolysis (both of which result in acyl-oxygen cleavage), but cannot differentiate between normal ester hydrolysis and bimolecular elimination (S_N2) of phthalate anion (bimolecular alkyl-oxygen cleavage). The problem was solved quite conveniently in the following manner: The optically active hydrogen phthalate ester of 4-bromo-4'-nitrobenzhydrol was prepared. Methanolysis of this ester yielded optically active 4-bromo-4'-nitrobenzhydrol ($[\alpha]_D^{25} + 0.23^\circ$). Since the methanolysis reaction was shown unequivically to result in acyl-oxygen cleavage, the configuration of the hydroxyl group was then established. When the same optically active ester was subjected to hydroxide ion catalyzed hydrolysis, the same optical activity ($[\alpha]_D^{25} + 0.50^\circ$) was noted in the benzhydrol. If the reaction would have proceeded with Walden inversion, then a change in sign of rotation would have been realized. It was thus shown conclusively that the hydroxide ion catalyzed hydrolysis of the benzhydryl ester followed the same mechanistic path as the methoxide catalyzed methanolysis reaction.

Some interesting offshoots developed as a result of some of the synthetic procedures used in the course of this program. Attempts to prepare the sodium salt of some nitro-substituted benzhydrols by treatment of the latter with triphenylmethyl sodium resulted in near quantitative amounts of bis-triphenylmethylperoxide. It appears that hexaphenylethane is the intermediate which undergoes an oxidation. This may prove to be of interest not only from a mechanistic standpoint, but also as a synthetic route to triarylmethyl peroxides since the reaction occurs with nitrobenzene as well.

Again, the reaction of the hydrogen phthalate ester of 4-bromo-4'-nitrobenzhydrol with thionyl chloride yields the benzhydryl chloride and phthalic anhydride. The sequence of probable steps is indicated by equations (35) and (36). It would be interesting to study the reaction from the mechanistic standpoint. If the reaction is stereospecific it may prove fruitful for the synthesis of some optically active benzhydryl chlorides.


(35)


(36)

Summary And Conclusions

The hydrogen phthalate ester of 4-methylbenzhydrol undergoes partial alkyl-oxygen cleavage with 'oxide' catalyzed methanolysis and hydrolysis although the major portion of the reaction follows acyl-oxygen cleavage. Alkyl-oxygen fission is minor with the introduction of electron seeking groups in the para position of one or both of the rings such that the algebraic sum of the Hammett σ values is positive. When high positive values are reached (> 0.5), aryl-oxygen fission occurs.

Acyl-oxygen fission occurs by normal ester solvolysis in the case of 'oxide' catalyzed methanolysis and hydrolysis of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate. No carboxylate anion participation is evident. Again, classical bimolecular elimination (S_N2) was not observed. Thus solvolysis studies on optically active 4-bromo-4'-nitrobenzhydryl ester indicated no bond breaking at the carbinyl carbon atom.

Although the hydrogen phthalate ester which was studied kinetically possessed a relatively high Hammett ($\sigma_1 + \sigma_2$) value it is proposed that carboxylate anion participation in the 'oxide' solvolysis of benzhydryl esters which undergo acyl-oxygen cleavage is probably not very significant although other compounds should be studied to substantiate this postulate.

CHAPTER III

EXPERIMENTAL PROCEDURE

Preparation Of Substituted Benzhydrols

4-Nitrobenzhydrol, 4-bromo-4'-nitrobenzhydrol, 4-nitro-4'-t-butylbenzhydrol, 4-chlorobenzhydrol and 4-methylbenzhydrol were prepared by methods described in Part I of this Dissertation.

Preparation Of Hydrogen Phthalate Esters

It was found in the course of these studies that the hydrogen phthalate esters of the nitro-substituted benzhydrols could not be prepared in useful yields by any of the common preparative methods. Some of the attempts to prepare 4-bromo-4'-nitrobenzhydryl hydrogen phthalate will be described below.

4-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate. - A solution of 4-bromo-4'-nitrobenzhydrol (1 g., 0.00325 mole), phthalic anhydride (0.48 g., 0.00325 mole), anhydrous tetrahydrofuran (25 ml.) and pyridine (10 ml.) was heated under reflux for a period of two hours. At the conclusion of the reaction period it was poured into a slurry of ice (300 g.) and concentrated hydrochloric acid (25 ml.). A crystalline precipitate was collected, dried and recrystallized from chloroform. This proved to be 4-bromo-4'-nitrobenzhydrol (0.9 g., 90% recovery) melting in the range 157-161°. Similar results were obtained when the reflux period was extended to five hours in length.

It was decided to attempt to prepare the ester by a method found in this laboratory to be useful in preparing hydrogen phthalate esters of aryl carbinols.[1] 4-Bromo-4'-nitrobenzhydrol (1 g., 0.00325 mole) was dissolved in anhydrous tetrahydrofuran (25 ml.) and to this was added an ethereal solution of sodium triphenylmethyl until a red colouration in the reaction mixture persisted. Phthalic anhydride (0.5 g., 0.0033 mole) was then added and the solution was allowed to stir overnight in a tightly stoppered flask. When hydrolyzed with water, the reaction mixture produced two immiscible phases. Where the organic layer was in contact with air the formation of yellow crystals could be seen. When the space above the solution was swept with nitrogen the crystallization process ceased. With the readmittance of air to the flask the crystallization process resumed. The precipitate was collected by filtration, air dried, and recrystallized from boiling tetrahydrofuran. A white solid (1 g.), m.p. 190°, was obtained that was shown to be triphenylmethyl peroxide. Identical results were obtained when nitrobenzene was substituted for the 4-bromo-4'-nitrobenzhydrol.

Also unsuccessful was the heating under reflux conditions a solution of 4-bromo-4'-nitrobenzhydrol (5 g., 0.016 mole) and phthalic anhydride (2.4 g., 0.016 mole) in tripropylamine (50 ml.) for a period of ninety minutes. Unidentifiable oils were obtained.

Equally unsuccessful were the reactions of the alcohol with sodium dispersion in the presence of phthalic anhydride at room temperature and at 0°. Phthalic acid was the only recognizable product obtained.

Again unsuccessful was the reaction of potassium hydrogen phthalate

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[1] K. G. Rutherford, J. M. Prokipcak, and D. P. C. Fung, J. Org. Chem., 28, 582 (1963).

with 4-bromo-4'-nitrobenzhydryl chloride prepared from the alcohol and a slight excess over equivalency of thionyl chloride.

Of limited success was the following reaction: To a solution of 4-bromo-4'-nitrobenzhydrol (15.4 g., 0.05 mole) in tetrahydrofuran (100 ml.) was added a solution composed of phthaloyl chloride (7.2 g., 0.05 mole) and tetrahydrofuran (25 ml.). The mixture was magnetically stirred and heated under reflux for ten minutes in a 500 ml. round bottom single neck flask equipped with a reflux condenser. Pyridine (20 ml.) was added to the hot solution which caused the immediate precipitation of pyridine hydrochloride. The entire mixture was quenched on a slurry of ice (500 g.) and hydrochloric acid (50 ml.) and from this resulting mixture a yellow oil was obtained. The oil was dissolved in chloroform (100 ml.). The organic phase was separated, dried over anhydrous calcium chloride and mixed with petroleum ether (b.p. 30-60°) (ca. 50 ml.). The precipitate which formed was collected by filtration, air dried and then dissolved in cold 2% aqueous potassium carbonate solution (500 ml.). The basic solution was clarified by filtration through a fine sintered glass disk and then rapidly poured into a slurry of ice (500 g.) and hydrochloric acid (50 ml.). The white solid which was obtained was recrystallized again from a chloroform-petroleum ether (b.p. 30-60°) solvent pair. 4-Bromo-4'-nitrobenzhydryl hydrogen phthalate (2.3 g., 10%) was obtained as a white crystalline solid, m.p. 185°, neutralization equivalent 458, ($C_{21}H_{14}BrNO_6$ requires 456.3). The infrared spectrum of the compound showed the following bands: a broad OH band beginning at 3500 cm^{-1} and merging with CH stretching at 3000 cm^{-1} (characteristic of carboxyl OH stretching), an ester carbonyl stretching at 1736 cm^{-1} and an acid carbonyl stretching at 1702 cm^{-1}, aromatic skeletal vibrations at 1602 and 1490 cm^{-1}, and nitro group stretching at 1524 and 1350 cm^{-1}.

Analysis: Calcd. for $C_{21}H_{14}BrNO_6$: C, 55.3; H, 3.60.

Found: C, 54.7; H, 3.23.

Near quantitative yields of the same ester could be obtained in the following manner. A solution of 4-bromo-4'-nitrobenzhydrol (31 g., 0.10 mole), phthalic anhydride (16.3 g., 0.11 mole) and pyridine (100 ml.) was prepared in a 300 ml. conical flask. While stirring the solution, sodium hydride (5.28 grams of a 50% dispersion in mineral oil, 0.11 mole) was added at a rate adjusted to keep the temperature of the solution below 35°. When the addition was complete, the flask was loosely stoppered and the mixture was magnetically stirred for a period of six hours. The mixture was then poured very slowly into one litre of 2 N hydrochloric acid. The organic material was extracted twice with chloroform (200 ml.). The organic material was washed several times with 0.1 N hydrochloric acid, dried over anhydrous sodium sulfate and reduced *in vacuo* to a gum. The gum was dissolved in 0.2 N. sodium hydroxide (750 ml.), and the resulting solution was filtered through a fine sintered glass plate. The solution was slowly acidified with dilute hydrochloric acid yielding the crude ester (42 g., 92%) melting in the range 171-180°. Recrystallization of the crude from a chloroform-petroleum ether (b.p. 30-60°) solvent pair produced the pure ester (38 g.) melting in the range 184-185°. This product gave an undepressed melting point on admixture with the ester prepared by the previous method. The infrared spectrum of this product was identical with that previously described.

4-Nitro-4'-t-Butylbenzhydryl Hydrogen Phthalate. - By a method similar to the one described above, 4-nitro-4'-t-butylbenzhydrol (28.5 g., 0.10 mole), phthalic anhydride (16.3 g., 0.11 mole), sodium hydride (5.28 g., 50% dispersion, 0.11 mole) and pyridine (100 ml.) were used to prepare 4-nitro-4'-t-butylbenzhydryl hydrogen phthalate (35.5 g., crude, 91%). Recrystallization of the crude ester from a chloroform-petroleum ether (b.p. 30-60°) solvent pair yielded the pure ester (31 g.), melting in the range 103-105°, neutralization equivalent 436, ($C_{25}H_{23}NO_6$ requires 433). The infrared spectrum of the product included the following bands: a broad OH band extending from 3500 to approximately 3000 cm^{-1} where it merged with CH stretching, an ester carbonyl band at 1730 cm^{-1}, an acid carbonyl band at 1702 cm^{-1}, aromatic skeletal vibrations at 1600 and 1492 cm^{-1}, nitro stretching bands at 1521 and 1349 cm^{-1}, and an ester CO single bond stretching band at 1270 cm^{-1}.

4-Nitrobenzhydryl Hydrogen Phthalate. - By a similar method 4-nitrobenzhydrol (23 g., 0.10 mole), phthalic anhydride (16.3 g., 0.11 mole), sodium hydride (5.28 g., 50% dispersion, 0.11 mole) and pyridine (100 ml.) were used to prepare 4-nitrobenzhydryl hydrogen phthalate (33 g., crude, 88%). Recrystallization of the crude material in the manner previously described yielded the pure ester m.p. 157-158° (reported[2] 158°). The infrared spectrum included the following bands: a broad OH stretching band extending from 3500 cm^{-1} into the CH stretching bands at 3000 cm^{-1}, an ester carbonyl stretching band at 1736 cm^{-1}, an acid carbonyl stretching band at

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[2] R. T. Puckowski and W. A. Ross, *J. Chem. Soc.*, 3560 (1959).

1708 cm^{-1}, aromatic skeletal vibrations at 1600 and 1494 cm^{-1}, nitro group stretching bands at 1529 and 1354 cm^{-1}, and an ester CO single bond stretching at 1292 cm^{-1}.

4-Chlorobenzhydryl Hydrogen Phthalate. - By a method similar to that described above, 4-chlorobenzhydrol (22 g., 0.10 mole), phthalic anhydride (16.3 g., 0.11 mole), sodium hydride (5.28 g., 50% dispersion, 0.11 mole) and pyridine (100 ml.) were used to prepare 4-chlorobenzhydryl hydrogen phthalate (27 g., crude, 74%). The pure ester (22 g.), m.p. 152-153° (unreported) was obtained on the recrystallization of the crude material from a chloroform-petroleum ether (b.p. 30-60°) solvent pair.

Analysis: Calcd. for $C_{21}H_{15}O_4Cl$: C, 68.76; H, 4.12.

Found: C, 68.36; H, 4.01.

The infrared spectrum of the compound showed the following bands: a broad OH stretching band extending from 3500 to approximately 2750 cm^{-1}, an ester carbonyl at 1730 cm^{-1}, an acid carbonyl at 1710 cm^{-1}, aromatic skeletal vibrations at 1600 and 1498 cm^{-1}, and an ester CO single bond stretching at 1282 cm^{-1}.

4-Methylbenzhydryl Hydrogen Phthalate. - By a method similar to one previously described, 4-methylbenzhydrol (20 g., 0.10 mole), phthalic anhydride (16.3 g., 0.11 mole), sodium hydride (5.28 g., 50% dispersion, 0.11 mole) and pyridine (100 ml.) were used to prepare 4-methylbenzhydryl hydrogen phthalate (32 g., crude, 90%). After recrystallization, the pure ester was obtained as feathery white crystals (22 g.) m.p.120-122° (reported[3] 120-122°). The infrared spectrum of the compound showed the

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[3] A. G. Davies, et al., *J. Chem. Soc.*, 3474 (1954).

following bands: a broad carboxyl OH stretching in the range 3500 to 3100 cm^{-1}, an ester carbonyl stretching at 1728 cm^{-1}, an acid carbonyl stretching at 1703 cm^{-1}, aromatic skeletal vibrations at 1483 cm^{-1}, and an ester CO single bond stretching at 1287 cm^{-1}.

(+)-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate. - A solution of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate (20 g., 0.044 mole), brucine (16 g., 0.041 mole) and acetone (250 ml.) was heated at the boiling point for ten minutes. Without allowing the solution to cool, the solvent was removed by evaporation at reduced pressure. The salt, which was obtained as a bright yellow spongy glass-like material, was dissolved in toluene (400 ml.) and to the resultant solution was added methylcyclohexane (200 ml.). Chilling the solution caused the precipitation of the brucine salt as a bright yellow powder (15 g.) m.p. 100-110°. Two recrystallizations of this powder from a similar toluene-methylcyclohexane solvent pair gave the apparently optically pure salt as a brilliant yellow powder (10.5 g.), m.p. 138-140°. The specific rotation of the salt could not be measured because of the intense colouration imparted to even dilute solutions by the salt. The melting point of the salt could not be increased nor the range decreased by further recrystallizations. The salt was dissolved in acetone (200 ml.) and the solution was poured into a rapidly stirred cold solution of hydrochloric acid (400 ml., 0.2 N). The ester recrystallized readily and was isolated by filtration and air dried. The ester was recrystallized once more from a chloroform-petroleum ether (b.p. 30-60°) solvent pair. The ester was obtained as a white solid (5.1 g., 23% on resolution) m.p. 180-181°C, $[\alpha]_D^{25} + 0.87^\circ$ (l,2; c, 4.0 in acetone). All rotations were determined with a Rudulph polarimeter, Model No.80.

(+)-4-Nitro-4'-t-Butylbenzhydryl Hydrogen Phthalate. - By a method similar to that previously described, the brucine salt (5.2 g.) m.p. 180-185° was obtained from an ethanol solution of the racemic 4-nitro-4'-t-butylbenzhydryl hydrogen phthalate (7.7 g., 0.0178 mole) and brucine (6.9 g., 0.0175 mole). The crude salt had a specific rotation $[\alpha]_D^{25}$-9.9° (ℓ, 2; c, 2.0). The specific rotation of the salt increased to -10.4° after one more recrystallization from ethanol. A third recrystallization from ethanol yielded the apparently pure diastereoisomer, $[\alpha]_D^{25}$ -10.5° (ℓ, 2; c, 2.0), m.p. 184-186°, (4.0 g.). By means of an acid decomposition similar to that previously described the brucine salt (4.0 g.) was decomposed to yield the optically active 4-nitro-4'-t-butylbenzhydryl hydrogen phthalate (1.5 g., 29% on resolution), m.p. 113°, having $[\alpha]_D^{25}$ +1.87°, (ℓ, 2; c, 3.3 in chloroform).

Solvolytic Reactions of Hydrogen Phthalate Esters

I With Sodium Methoxide

4-Nitrobenzhydryl Hydrogen Phthalate. - The ester (3.8 g., 0.01 mole) was dissolved in anhydrous tetrahydrofuran (30 ml.) and to this was added a methanol solution of sodium methoxide (1.0 g., 0.044 mole sodium; 30 ml. methanol). The solution was stirred for five minutes and then poured over a slurry of ice (20 g.) and concentrated hydrochloric acid (5 ml.). 4-Nitrobenzhydrol (2.2 g., 96%) was precipitated, melting in the range 72-75°. The infrared spectrum of the product was identical with that previously described for this compound. The mixed melting point was undepressed.

4-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate. - In a manner similar to that described above, 4-bromo-4'-nitrobenzhydrol (3.0 g., 97%), m.p. 150-154°, was obtained on reaction of the corresponding hydrogen phthalate ester (4.5 g., 0.01 mole) with sodium methoxide (1.0 g., 0.044 mole sodium; 30 ml. methanol). The infrared spectrum of the product was identical with that of the authentic compound. The cold aqueous phase which was obtained as the filtrate in the isolation of the 4-bromo-4'-nitrobenzhydrol was saturated with potassium chloride and extracted with ether (50 ml.). The organic phase was reduced in volume by evaporation at reduced pressure to 10 ml. and cooled. Methyl hydrogen phthalate (0.2 g., 12%) m.p. 82-83° was collected as a fine crystalline solid.

4-Nitro-4'-t-Butylbenzhydryl Hydrogen Phthalate. - In a manner similar to that described above, 4-nitro-4'-t-butylbenzhydryl hydrogen phthalate (4.3 g., 0.01 mole) underwent solvolysis with sodium methoxide (1.0 g., 0.044 mole sodium; 30 ml. methanol). 4-Nitro-4'-t-butylbenzhydrol (2.6 g., 91%) was obtained melting in the range 106-109°. Recrystallization of the product from a chloroform-petroleum ether (b.p. 30-60°) solvent pair yielded the pure compound (2.1 g.) m.p. 109-111°. The infrared spectrum of the product and of the authentic alcohol were identical. The mixed melting point was undepressed.

4-Chlorobenzhydryl Hydrogen Phthalate. - In a manner similar to that described previously 4-chlorobenzhydrol (0.83 g., 93%), m.p. 53-55°, was obtained on the reaction of 4-chlorobenzhydryl hydrogen phthalate (1.5 g., 0.0041 mole) with sodium methoxide (0.5 g., 0.022 mole sodium; 30 ml. methanol). Recrystallization of the product from a chloroform-petroleum ether (b.p. 30-60°) solvent pair yielded the pure alcohol (0.6 g.), m.p. 58-59°. A mixed melting point with an authentic sample was undepressed. The infrared spectrum of the product was identical with that of the authentic compound.

4-Methylbenzhydryl Hydrogen Phthalate. - In a manner similar to that described above, 4-methylbenzhydryl hydrogen phthalate (5.0 g., 0.0145 mole) underwent reaction with sodium methoxide (1.0 g., 0.044 mole sodium; 30 ml. methanol) to yield 4-methylbenzhydrol (2.4 g., 84%), m.p. 49-50°. The infrared spectra of the product and the authentic alcohol were identical. An oil (0.3 g., 10%) was also obtained having an infrared spectrum identical with that for 4-methylbenzhydryl methyl ether which was prepared by the previously described iodine synthesis.

(+)-4-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate. - (+)-4-Bromo-4'-nitrobenzhydryl hydrogen phthalate (4.0 g., 0.0088 mole) was dissolved in anhydrous tetrahydrofuran (30 ml., distilled from P_2O_5 and stored over sodium) and the resulting solution was poured into a methanol solution of sodium methoxide prepared by the dissolution of sodium (0.5 g., 0.022 mole) in 30 ml. anhydrous methanol (distilled from magnesium methoxide). After five minutes of reaction time, cold dilute hydrochloric acid (400 ml., 0.075 N) was added to the solution and the resulting mixture was cooled. A precipitate of (+)-4- bromo-4'-nitrobenzhydrol (2.15 g., 80%), m.p. 157-159°, was collected having $[\alpha]_D^{25}$ +0.23° (ℓ,2; c, 2.15 in acetone).

(+)-4-Nitro-4'-t-Butylbenzhydryl Hydrogen Phthalate. - When (+)-4-nitro-4'-t-butylbenzhydrol hydrogen phthalate (1.3 g., 0.0030 mole) was solvolyzed with sodium methoxide in a manner similar to that previously described,

(+)-4-nitro-4'-t-butylbenzhydrol (0.6 g., 71%), m.p. 109-110° was obtained. It possessed a very feeble rotation in solution with chloroform (25 ml.). The observed rotation in chloroform solution (0.6 g. in 25 ml.) was approximately +0.01°, $[\alpha]_D^{25}$ +0.21°;(ℓ, 2; c, 2.4).

II With Methanol

4-Nitrobenzhydryl Hydrogen Phthalate. - 4-Nitrobenzhydryl hydrogen phthalate (5.0 g., 0.013 mole) was dissolved in anhydrous methanol (50 ml.) and heated under reflux for a period of twenty-four hours. At the end of that time, cold water was added to the warm solution until the mixture became cloudy. Upon cooling the solution, a total of 4.7 grams (94% recovery) of the unreacted ester was obtained as a crystalline powder, m.p. 155-158°. The product was identified by a mixed melting point with an authentic sample and by its infrared spectrum.

4-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate. - When treated in a similar manner with methanol (50 ml.), 4-bromo-4'-nitrobenzhydryl hydrogen phthalate (5.0 g., 0.011 mole) yielded the unreacted ester (4.6 g., 92% recovery), m.p. 181-184°.

4-Nitro-4'-t-Butylbenzhydryl Hydrogen Phthalate. - When 4-nitro-4'-t-butylbenzhydryl hydrogen phthalate (5 g., 0.0115 mole) was treated with methanol (50 ml.) in a manner similar to that described above, the unchanged ester m.p. 97-102°, was recovered (4.1 g., 82% recovery), along with an uncrystallizable oil (0.3 g.). The infrared spectrum of the oil showed a broad and weak carbonyl band at 1725 cm^{-1} and broad nitro absorption bands at 1525 and 1350 cm^{-1}.

4-Chlorobenzhydryl Hydrogen Phthalate. - In a similar manner, unchanged 4-chlorobenzhydryl hydrogen phthalate (4.3 g., 86% recovery), m.p. 150-151°, was recovered from the treatment of the ester (5.0 g., 0.0135 mole) with anhydrous methanol (50 ml.) at the reflux temperature for twenty-four hours.

4-Methylbenzhydryl Hydrogen Phthalate. - When 4-methylbenzhydryl hydrogen phthalate (5.0 g., 0.0145 mole) was heated in boiling anhydrous methanol (50 ml.) for twenty-four hours, the unchanged ester (3.8 g., 74% recovery) was obtained, along with an oil, (0.6 g., 20%) that had an infrared spectrum identical to that of methyl 4-methylbenzhydryl ether prepared by the previously described iodine synthesis.

III With Aqueous Sodium Hydroxide

(+)-4-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate. - A solution of (+)-4-bromo-4'-nitrobenzhydryl hydrogen phthalate (2.25 g., 0.0049 mole), $[\alpha]_D^{25^\circ}$ + 0.31° (ℓ, 2; c, 9 in tetrahydrofuran) in tetrahydrofuran (25 ml.) was poured into an aqueous solution of sodium hydroxide (400 ml., 2 N). The mixture was allowed to stand with stirring for a period of thirty minutes. During this time a crystalline precipitate was formed. The solution was made neutral (pH 7) with dilute hydrochloric acid. The precipitate was then collected by filtration and air dried. The precipitate was identified as (+)-4-bromo-4'-nitrobenzhydrol (1.2 g., 80%), m.p. 156-158°, $[\alpha]_D^{25}$ + 0.50 (ℓ, 2; c, 6 in acetone). The filtrate from the above separation was further acidified which caused a cloudiness to appear probably due to the precipitation of unhydrolyzed ester.

Reaction Of 4-Bromo-4'-Nitrobenzhydrol With Thionyl Chloride. - To a mixture of 4-bromo-4'-nitrobenzhydrol (3.1 g., 0.01 mole) and chloroform (10 ml.) was added thionyl chloride (1.5 g., 0.02 mole). The resultant mixture was heated on a steam bath for one hour taking care to exclude moisture with a calcium chloride drying tube. The volatile material was removed by evaporation at reduced pressure. Prolonged extraction of solvent *in vacuo* caused the red oil to crystallize (m.p. 45-48°). The crystalline mass was dissolved in dry benzene (100 ml.), and decolourized with activated charcoal. Petroleum ether (b.p. 30-60°) was added to the solution which was then cooled. 4-Bromo-4'-nitrobenzhydryl chloride was obtained in the form of needles (2.6 g., 80%), m.p. 51°. The infrared spectrum of the compound showed the following bands: aromatic skeletal vibrations at 1607 and 1493 cm^{-1}, nitro group stretching at 1528 and 1353 cm^{-1}. No OH band was evident in the spectrum. After storage for thirty months in an unsealed jar, the product still melted sharply at 51°.

Analysis: Calcd. for $C_{13}H_9BrClNO_2$: C, 47.81; H, 2.78.
Found: C, 47.85; H, 2.78.

Reaction Of 4-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate With Thionyl Chloride. - To a solution of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate (4.6 g., 0.01 mole) and chloroform (50 ml.) was added thionyl chloride (3.0 ml., 0.042 mole). The resulting solution was heated on a steam bath under reflux for two hours. The volatile materials were completely removed by evaporation at reduced pressure. The heavy oil so obtained was boiled in petroleum ether (100 ml.). Cooling the solution induced the crystallization of phthalic anhydride (1.4 g., 95%), m.p.

129-130°. When the petroleum ether was removed in vacuo an uncrystallizable oil (3.0 g.) having an infrared spectrum identical with that for 4-bromo-4'-nitrobenzhydryl chloride except for three weak bands (1850, 1780, and 1262 cm^{-1}) which are found in the phthalic anhydride infrared spectrum.

Reaction Of 4-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate With Aqueous Potassium Hydroxide. - 4-Bromo-4'-nitrobenzhydrol (3.0 g., 97%) was completely precipitated from solution after two hours when 4-bromo-4'-nitrobenzhydryl hydrogen phthalate (4.6 g., 0.01 mole) was dissolved in 5 N aqueous potassium hydroxide (100 ml.) and maintained at 40°. The ester (4.5 g., 98%) however, was precipitated unchanged by the addition of hydrochloric acid to a potassium carbonate solution (5%, 100 ml.) of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate (4.6 g., 0.01 mole) even though the solution was maintained at 40° for five hours.

Kinetic Study On The Solvolysis Of 4-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate

I With Methoxide

The kinetics of the solvolysis of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate with methanolic sodium methoxide were followed initially by two methods. Known amounts of the ester (4.58 g., 0.010 mole) were dissolved in anhydrous tetrahydrofuran (40 ml. volumes). To these solutions were added carefully pipetted amounts of standard methanolic sodium methoxide solution (0.934 N) prepared from anhydrous methanol (500 ml.) and freshly cut sodium (11.5 g., 0.5 mole). The resulting solutions were tightly stoppered and kept in a constant temperature bath ($25^{\circ} \pm 0.5^{\circ}$) for varying lengths of time. The samples were then poured quantitatively into ice-cold water (300 ml.) and the resulting solutions were rapidly made acid (pH 2) with 2 N hydrochloric acid. The precipitates were allowed to remain in contact with the mother-liquor for one-half hour to ensure high yield of recovery of the precipitates. The precipitates were collected in pre-weighed sintered glass crucibles (medium porosity), washed with distilled water, air-dried for six hours, and finally dried *in vacuo* for twelve hours. The weights of the precipitates were noted, and their neutralization equivalents were determined. From the weight of the precipitate, the extent of solvolysis for each sample may be calculated as shown below.

Setting: N_A = number of moles of ester in the precipitate.

N_B = number of moles of alcohol in the precipitate.

M_A = neutralization equivalent of ester = 458.

M_B = molecular weight of alcohol = 308.

W = weight of precipitate.

Then by mass balance:

$$N_A + N_B = 0.010$$

and

$$N_A M_A + N_B M_B = W$$

Substituting:

$$(0.010 - N_B)M_A + N_B M_B = W$$

$$0.010M_A - N_B M_A + N_B M_B = W$$

$$4.58 - N_B(M_A - M_B) = W$$

$$N_B = \frac{4.58 - W}{150}$$

Table V below summarizes the amounts of methoxide solution, reaction time, precipitate weights and the number of moles of alcohol obtained under these conditions.

Table V

Methoxide Solvolysis Of 4-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate - Gravimetric Study

Run No.	Methoxide Stock Solution (0.934N)		Reaction	W	N_B
	(ml.)	(moles)	(Hr.)	(g.)	(moles)
1	10.0	0.00934	3	4.49	0.00060
2	10.0	0.00934	24	4.44	0.00093
3	10.5	0.00981	1	4.44	0.00093
4	11.0	0.01027	1	4.22	0.00240
5	11.5	0.01074	1	4.11	0.00319
6	12.0	0.01121	1	3.98	0.00400

Sample calculation

Run No. 1:

$$N_B = \frac{4.58 - 4.49}{150}$$

$$= 0.00060 \text{ moles alcohol}$$

The number of moles of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate may also be determined from the neutralization equivalent (N.E.) of the precipitate obtained from the kinetic experiments.

Let $$\text{N.E.} = M_A + N_B'M_B$$

where M_A = N.E. of the pure ester (458 g.)

M_B = molecular weight of the alcohol (308 g.)

N_B'= number of moles of alcohol associated with each mole of ester in the precipitate

$$\therefore \frac{N_B'}{N_B' + 1} = \text{mole fraction of alcohol in the precipitate}$$

But $N_A + N_B = 0.010$ = total number of moles in the precipitate

$$\therefore \quad N_B = \frac{0.010N_B'}{N_B' + 1}$$

Substituting $N_B' = \dfrac{\text{N.E.} - M_A}{M_B}$

$$N_B = 0.010 \frac{\text{N.E.} - M_A}{\text{N.E.} - M_A + M_B}$$

$$= 0.010 \frac{\text{N.E.} - 458}{\text{N.E.} - 150}$$

Table VI summarizes the reaction conditions and the extent of solvolysis of each sample determined through its neutralization equivalent.

Table VI

Methoxide Solvolysis Of 4-Bromo-4'-Nitrobenzhydryl Hydrogen Phthalate - Neutralization Equivalent Study

Run No.	Methoxide Stock Solution (0.934 N)		Reaction Time	N.E.	N_B
	(ml.)	(moles)	(Hr.)	(g.)	(moles)
1	10.0	0.00934	3	467	0.00028
2	10.0	0.00934	24	470	0.00038
3	10.5	0.00981	1	475	0.00052
4	11.0	0.01027	1	527	0.00183
5	11.5	0.01074	1	581	0.00285
6	12.0	0.01121	1	622	0.00347

<u>Sample Calculation</u>

Run No. 1:

$$N_B = 0.010\ \frac{467 - 458}{467 - 150}$$

$$= 0.00028 \text{ moles alcohol}$$

Since the titrimetric determinations of the extent of solvolysis were in fair agreement with the gravimetric determinations, the former method was abandoned and subsequently the kinetics were studied by only the gravimetric method.

A second, slightly different, method of conducting the kinetic study was used in the remaining kinetic experiments with sodium methoxide. The ester samples (9.16 g., 0.020 mole) were dissolved in volumes of anhydrous tetrahydrofuran (150 ml.). Varying amounts (22.5 to 25.7

ml.) of the methanolic sodium methoxide stock solution previously described (0.934 N) were pipetted into volumes of anhydrous methanol (100 ml.). The methanol solutions were then poured rapidly and with stirring into the ester solutions to start the kinetic experiments. Immediately, the reaction solutions were diluted to exactly 275 ml. with anhydrous methanol (less than 5 ml. being sufficient), and tightly stoppered. The solutions were kept in a constant temperature bath ($25^\circ \pm 0.5^\circ$). At intervals during the length of the reaction period, aliquots (50 ml.) were removed from the reaction flasks and were quenched and finally weighed in exactly the manner described above.

The concentration of unsolvolyzed ester remaining in each 50 ml. aliquot can be calculated in the following manner. Since 0.020 mole of the ester was originally dissolved in 275 ml., each 50 ml. aliquot of the reaction mixture will contain $\frac{50}{275}$ x 0.020 or 0.00364 mole of alcohol and ester together. Therefore we may write by the mass balance law:

$$N_A + N_B = 0.00364 \text{ mole/50 ml.}$$

and

$$N_A M_A + N_B M_B = W/50 \text{ ml.}$$

Substituting as previously described, we obtain for a 50 ml. aliquot,

$$N_A = \frac{W - 1.120}{150} \text{ moles of unhydrolyzed ester/50 ml.}$$

and

$$[\text{ester}] = \frac{N_A}{0.050} \text{ mole lit.}^{-1}$$

$$= \frac{W - 1.120}{7.50} \text{ mole lit.}^{-1}$$

Tables VII to X summarize the kinetic data obtained from the methoxide catalyzed methanolysis of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate.

Table VII

Kinetic Experiment No.1

9.16 g., 0.020 mole ester; 22.5 ml. methoxide stock solution (0.021 mole $NaOCH_3$); 275 ml. initial volume; 50 ml. aliquots.

Sample No.	Time (Hr.)	W (g.)	[Ester] mole lit^{-1}	ℓn[Ester]
1	0.50	1.537	0.0556	-2.89
2	1.00	1.459	0.0452	-3.10
3	1.50	1.402	0.0376	-3.28
4	2.00	1.352	0.0309	-3.48
5	2.50	1.314	0.0259	-3.65

Sample Calculation

Sample No.1

$$[\text{Ester}] = \frac{1.537 - 1.120}{7.50}$$

$$= 0.0556 \text{ mole lit.}^{-1}$$

Table VIII

Kinetic Experiment No.2

9.16 g., 0.020 mole ester; 23.6 ml. methoxide stock solution (0.022 mole $NaOCH_3$); 275 ml. initial volume; 50 ml. aliquots.

Sample No.	Time (Hr.)	W (g.)	[Ester] mole lit.$^{-1}$	ℓn[Ester]
1	0.25	1.548	0.0570	-2.86
2	0.50	1.495	0.0500	-3.00
3	0.75	1.432	0.0416	-3.18
4	1.00	1.385	0.0353	-3.34
5	1.25	1.354	0.0312	-3.46

Table IX

Kinetic Experiment No.3

9.16 g., 0.020 mole ester; 24.7 ml. methoxide stock solution (0.023 mole $NaOCH_3$); 275 ml. initial volume; 50 ml. aliquots.

Sample No.	Time (Hr.)	W (g.)	[Ester] mole lit.$^{-1}$	ℓn[Ester]
1	0.167	1.564	0.0598	-2.82
2	0.333	1.497	0.0503	-2.99
3	0.500	1.440	0.0426	-3.16
4	0.667	1.397	0.0369	-3.30
5	0.833	1.357	0.0316	-3.46

Table X

Kinetic Experiment No.4

9.16 g., 0.020 mole ester; 25.7 ml. methoxide stock solution (0.024 mole $NaOCH_3$); 275 ml. initial volume; 50 ml. aliquots.

Sample No.	Time (Hr.)	W (g.)	[Ester] mole lit.$^{-1}$	ℓn[Ester]
1	0.133	1.547	0.0570	-2.86
2	0.267	1.468	0.0464	-3.07
3	0.400	1.406	0.0381	-3.27
4	0.533	1.368	0.0331	-3.40
5	0.667	1.325	0.0273	-3.60

II With Hydroxide

The kinetics of the alkaline hydrolysis of 4-bromo-4'-nitrobenzhydryl hydrogen phthalate were followed by a gravimetric technique similar to that described above. In all the kinetic experiments with aqueous hydroxide, the following method was used. Samples of the ester (4.58 g., 0.010 mole) were dissolved in volumes of anhydrous tetrahydrofuran (30 ml.) and these solutions were quantitatively added to volumes of aqueous potassium hydroxide solution (100 ml.) of different concentrations. The solutions were immediately diluted to 137.5 ml. (less than 10 ml. being sufficient). The solutions were kept in a constant temperature bath ($25^\circ \pm 0.5^\circ$). At intervals during the length of the reaction period, aliquots (25 ml.) were withdrawn from the reaction flasks and were quenched and the precipitates weighed in exactly the manner described previously.

The concentration of the unhydrolyzed ester in each 25 ml. aliquot can be calculated in the following manner. Since 0.010 mole of the ester was originally dissolved in 137.5 ml. of total solution, each 25 ml. aliquot of the reaction mixture will contain $\frac{25}{137.5}$ X 0.010 or 0.001816 mole of alcohol and acid together. Therefore we may write by the mass balance law:

$$N_A + N_B = 0.001816 \text{ mole/25 ml.}$$

and $$N_A M_A + N_B M_B = W/25 \text{ ml.}$$

Substituting as before, we obtain for each 25 ml. aliquot:

$$N_A = \frac{W - 0.560}{150}$$

$$[\text{Ester}] = \frac{N_A}{0.025}$$

$$= \frac{W - 0.560}{3.75} \text{ mole lit.}^{-1}$$

Table XI

Kinetic Experiment No.5

4.58 g., 0.010 mole ester; 100 ml. 0.468 N potassium hydroxide solution (0.0468 mole KOH); 137.5 ml. initial volume; 25 ml. aliquots.

Sample No.	Time (Hr.)	W (g.)	[Ester] mole lit.$^{-1}$	ℓn[Ester]
1	0.583	0.715	0.0413	-3.19
2	0.917	0.679	0.0317	-3.45
3	1.416	0.632	0.0192	-3.95
4	2.084	0.581	0.0056	-5.18

Sample Calculation

Sample No.1

$$[\text{Ester}] = \frac{0.715 - 0.560}{3.75}$$

$$= 0.0413 \text{ mole lit.}^{-1}$$

Table XII

Kinetic Experiment No.6

4.58 g., 0.010 mole ester; 100 ml. 0.352 N potassium hydroxide solution (0.0352 mole KOH); 137.5 ml. initial volume; 25 ml. aliquots.

Sample No.	Time (Hr.)	W (g.)	[Ester] mole lit.$^{-1}$	ℓn[Ester]
1	0.75	0.715	0.0413	-3.18
2	1.42	0.667	0.0285	-3.56
3	2.25	0.613	0.0141	-4.26
4	2.83	0.585	0.0067	-5.01

Table XIII

Kinetic Experiment No.7

4.58 g., 0.010 mole ester; 100 ml. 0.234 N potassium hydroxide (0.0234 mole KOH); 137.5 ml. initial volume; 25 ml. aliquots.

Sample No.	Time (Hr.)	W (g.)	[Ester] mole lit.$^{-1}$	ℓn[Ester]
1	0.917	0.745	0.0493	-3.01
2	1.333	0.729	0.0451	-3.10
3	1.917	0.703	0.0382	-3.26
4	3.000	0.670	0.0293	-3.53
5	4.083	0.637	0.0205	-3.89

Table XIV

Kinetic Experiment No.8

4.58 g., 0.010 mole ester; 100 ml. 0.916 N potassium hydroxide (0.0916 mole KOH); 137.5 ml. initial volume; 25 ml. aliquots.

Sample No.	Time (Hr.)	W (g.)	[Ester] mole lit.$^{-1}$	ℓn[Ester]
1	0.333	0.724	0.0437	-3.13
2	0.667	0.676	0.0304	-3.49
3	1.000	0.649	0.0237	-3.74
4	1.333	0.616	0.0149	-4.21
5	2.083	0.567	0.00187	-6.29

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