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Part I. Attempted synthesis of cyclopropanone. Part II. A new ether synthesis.

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PART I

ATTEMPTED SYNTHESIS OF A CYCLOPROPANONE

PART II

A NEW ETHER SYNTHESIS

BY

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1964

Approved

Roger J. Tilbert

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ABSTRACT

Part I.

Attempts to synthesize a cyclopropanone derivative from the reaction of triphenylmethyl sodium and some alpha-haloketones are reported. The reactions of 3-bromo-3-methyl-2-butanone, 2-methyl-2,4-dimethyl-3-pentanone, methyl-1-bromocyclohexyl ketone, and 1-bromo-1,1,3,3-tetraphenylacetone with triphenylmethyl sodium as well as 3-bromo-3-methyl-2-butanone and 1-bromo-1,1,3,3-tetraphenylacetone with dimsylsodium were investigated. 3-bromo-3-methyl-2-butanone and 1-bromo-1,1,3,3-tetraphenylacetone when treated with triphenylmethyl sodium gave a considerable amount of the reduction product. Elimination was also observed when 3-bromo-3-methyl-2-butanone and 2-bromo-2,4-dimethyl-3-pentanone were treated with triphenylmethyl sodium. Although a cyclopropanone derivative was not obtained, a better insight into the general reaction of alpha-haloketones and base was realized.

Part II

A new synthesis of ethers from triaryl and benzhydryl alcohols has been found. Thus, triphenylcarbinol and benzhydrol when reacted with iodine in the presence of some aliphatic alcohols yield the corresponding ethers. This procedure has proven more convenient than known methods. Cinnamyl alcohol was also found to be amenable to this synthetic procedure, while benzyl alcohol did not yield the

the desired products, when subjected to the same reaction conditions. The course of the reaction involves iodine as a true catalyst which generates a carbonium ion from the trityl and benzhydryl systems.

ACKNOWLEDGEMENTS

The author wishes to express his deep gratitude and appreciation to Dr. K.G. Rutherford for his guidance and his patient advice.

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PART I

APPROACHES TO SYNTHESES OF CYCLOPROPANONES

CHAPTER I

INTRODUCTION

The cyclopropanone structure has eluded the organic chemists for many years. Although one would expect compounds of this nature to be highly reactive and hence difficult to prepare, it must be realized that cyclopropene and methylene cyclopropene have been well characterized in the literature.[1,2]

These compounds would have strain comparable to that of cyclopropanones. The preparation of 2,3-diphenylcyclopropenone has recently been reported by McElvain and Kundiger,[3] as well as by Breslow and co-workers.[4] Although this compound derives certain stability from resonance considerations, (Fig. 1) here again the structure suffers from the effect of very strained bond angles.

The cyclopropanone structure has been proposed by

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[1] M.J. Schlatter, J. Am. Chem. Soc., 63, 1733 (1941).

[2] A. Muller, Nature, 135, 994 (1935).

[3] S. McElvain and D. Kundiger, J. Am. Chem. Soc., 64, 254 (1942).

[4] R. Breslow, and J. Posner, and A. Krebs, J. Am. Chem. Soc., 85, 234 (1963).

In a similar manner, suitable dihaloketones produce unsaturated carboxylic acids (Fig. 3.).

$$CH_3CCl_2COCH_3 + 2OH^{\ominus} \longrightarrow CH_2 = C(CH_3)CO_2H + 2Cl^{\ominus} + 2H_2O$$

Fig. 3. Favorskii rearrangement of dihaloketones.

Analogous rearrangement of trihaloketones can give rise to unsaturated halo acids (Fig. 4.).

$$(CH_3)_2CBrCOCHBr_2 + 2OH^- \longrightarrow (CH_3)_2C\text{-}CBrCO_2H + 2Br^-$$

Fig. 4. Favorskii rearrangement of trihaloketones.

The concept of cyclopropanone intermediates in the reactions of α-haloketones with bases was well established in the German chemical literature prior to 1900.[6,7,8,9] In the Favorskii rearrangement the initial step is the removal of a proton from the α'-carbon atom to give the haloketone enolate anion IV. Concerted or subsequent ejection of halide ion leads to a cyclopropanone which is rapidly cleaved by alkoxide to give the rearrangement product.

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[6] Pauly and Rossbach, Ber., 32, 2000 (1899).

[7] Hantzsch and Schiffer, Ber., 25, 728 (1892).

[8] Wolff, Ann., 260, 79 (1890); Ber., 26, 2220 (1893).

[9] Conrad, Ber., 32, 1005 (1899).

In the Loftfield experiment,[10] random cleavage of the cyclopropanone V, having radio-carbon distributed as marked, would lead to the isotope distribution observed in the ester fraction (Fig. 5.).

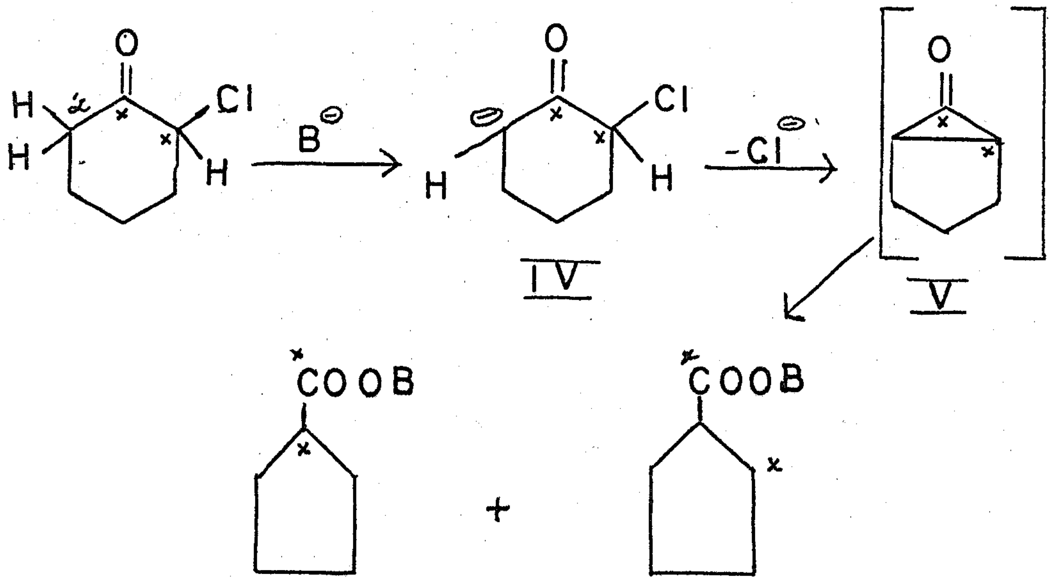

Fig. 5. Loftfield mechanism of Favorskii rearrangement.

Thus the cyclopropanone is undoubtedly an intermediate in the Favorskii rearrangement. The Loftfield mechanism, in particular, leads to the correct prediction that rearrangement of unsymmetrical α-haloketones leads to the product formed through cleavage of the cyclopropanone intermediate so as to give the more stable of the two possible transient carbanions (Fig. 6.).

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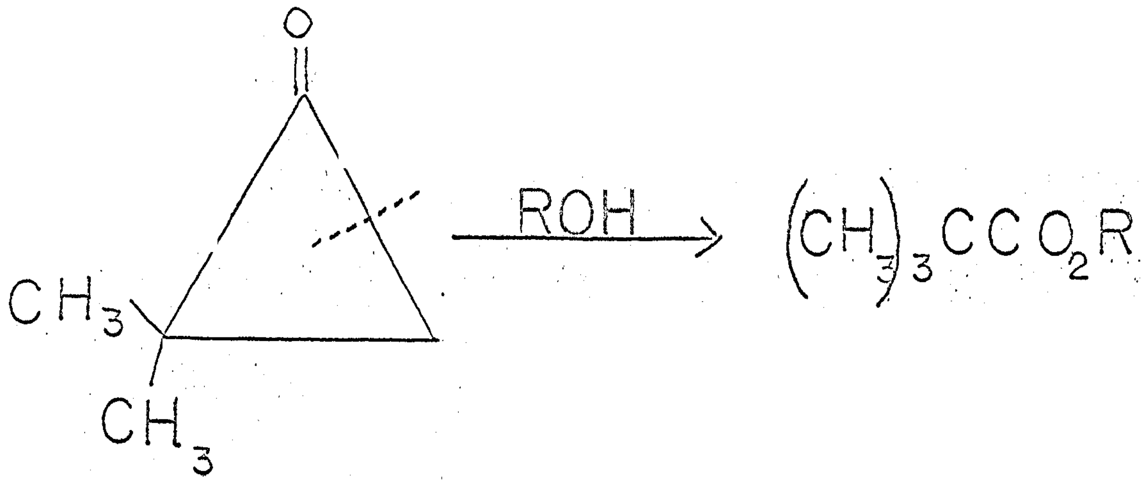
[10] R.B. Loftfield, *J. Am. Chem. Soc.*, 72, 632 (1950).



VI

Fig. 6. Cleavage of an unsymmetrical cyclopropanone intermediate.

Stabilities of unconjugated carbanions decrease in the order benzyl > tertiary > secondary > primary.[12] Thus the cyclopropanone VI derived from 3-bromo-3-methylbutan-2-one cleaves to give the tertiary trimethylacetic ester, forming a transient primary rather than tertiary carbanion.[13] Similarly, the cyclopropanone from 1-chloro-1-phenylacetone cleaves by way of a benzylic carbanion to give 3-phenylpropionic acid derivatives.[14]

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[12] G.S. Hammond, in Newman, Steric Effects in Organic Chemistry, New York, p. 439

[13] J.G. Aston and R.B. Greenburg, J. Am. Chem. Soc., 62, 2590 (1940).

[14] W.D. McPhee and E. Klingsberg, J. Am. Chem. Soc., 66, 1132 (1944).

Although the cyclopropanone mechanism has been generally accepted enabling one to predict the formation of a preferred position isomer, its stereochemical implications are less firmly established. Loftfield suggested that cyclopropanone formation is synchronous with an internal S_N2-type displacement on the halogen-bearing carbon atom with consequent inversion at that centre. This view has been questioned by Burr and Dewar on quantum mechanical grounds.[15] These workers suggested that the geometry of the enolate π-orbital is not suitable for effective S_N2-type overlap with the σ-orbital of the halogen-bearing α-carbon atom. In effect, they, along with Aston and Newkirk,[16] postulated that the loss of halide ion precedes cyclopropanone formation, and thus involves the generation of a species variously represented as a mesomeric zwitterion, (VII), or as a "no-bond" canonical form (VIII) of a cyclopropanone. Subsequent collapse of this species to the more stable cyclopropanone would lead to the products predicted from the Loftfield mechanism (Fig. 7.). The synchronous and nonsynchronous mechanisms are kinetically indistinguishable if enolate formation is rate-determining, but they clearly differ in stereochemical implications. The synchronous

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[15] J.G. Burr and M. Dewar, J. Chem. Soc., 1201 1954.

[16] J.G. Aston and J.D. Newkirk, J. Am. Chem. Soc., 73, 3900 (1951).

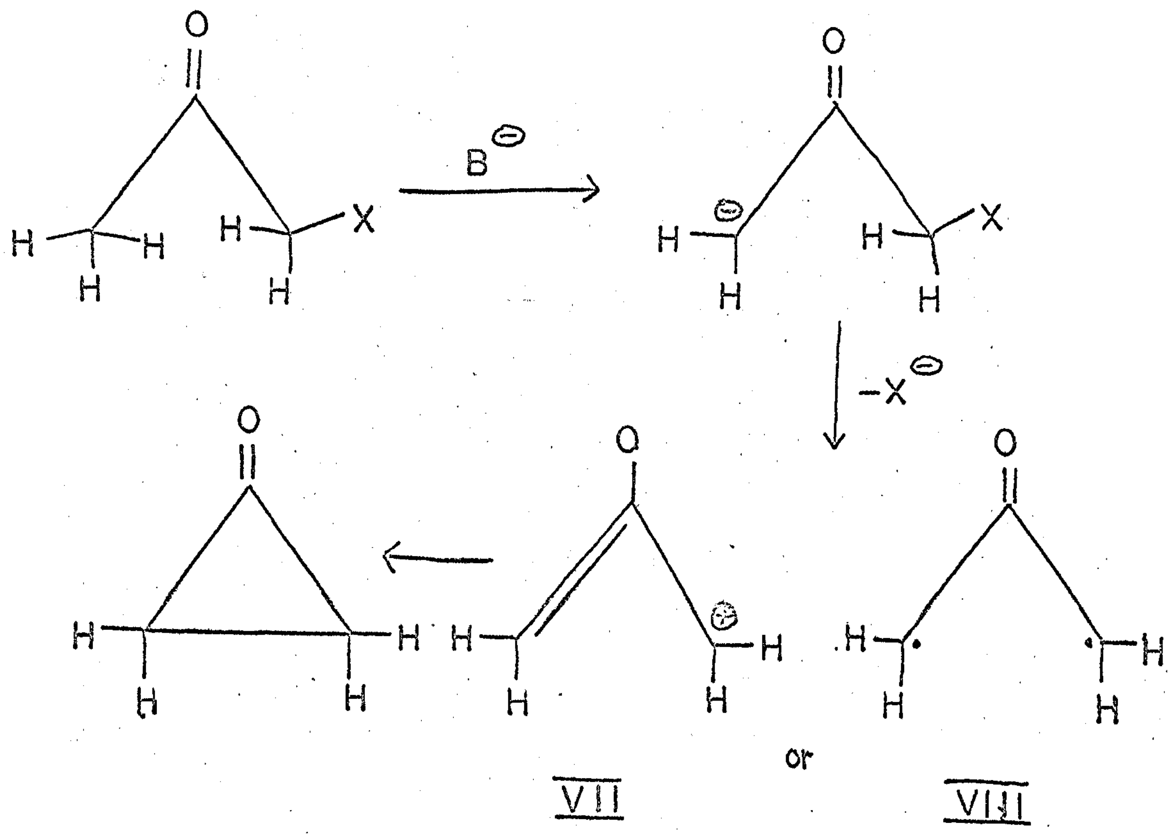
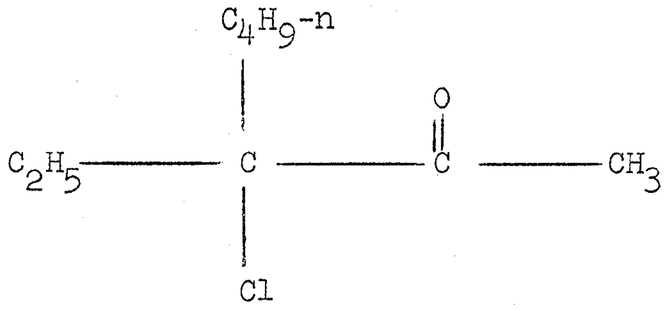


Fig. 7. Aston and Newkirk pathway of cyclopropanone formation.

process would necessarily involve steric inversion at the halogen-bearing carbon with the overall maintenance of essentially sp^3 hybridization at this same site. However, the nonsynchronous process entails the formation of an intermediate discrete species (VII or VIII) of high resonance energy, which would lead to the prediction of racemization of the halogen-bearing carbon atom. The pathways could thus be differentiated by the rearrangement of a suitable optically active haloketone, such as IX, into a trialkylacetic acid



$$\mathrm{C_2H_5{-}\overset{C_4H_9\text{-}n}{\underset{Cl}{C}}{-}\overset{O}{\overset{\|}{C}}{-}CH_3}$$

IX

which would indicate by its optical purity the degree of participation of the synchronous as against the nonsynchronous mechanism. Unfortunately, only meager evidence has been presented in the literature for the above rearrangement. However, G. Stork and I. Borowitz[17] have recently demonstrated a clearcut example of a stereospecific rearrangement using a pair of epimeric 1-chloro-1-acetyl-2-methylcyclohexanes (X and XII) of proven configuration (Fig. 8.). Rearrangement of (X) with sodium benzyloxide gave a benzyl ester, which was then converted by hydrogenolysis into a single 1,2-dimethylcyclohexane carboxylic acid (XI). The stereochemistry of this acid was clearly demonstrated by independent synthesis which involved the stereospecific Diels-Alder addition of butadiene to tiglic acid. Rearrangement of the epimeric chloroketone (XII) gave in turn exclusively the benzyl ester of the diastereomeric acid (XIII). In

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[17] G. Stork and I. Borowitz, J. Am. Chem. Soc., 82, 4307 (1960).

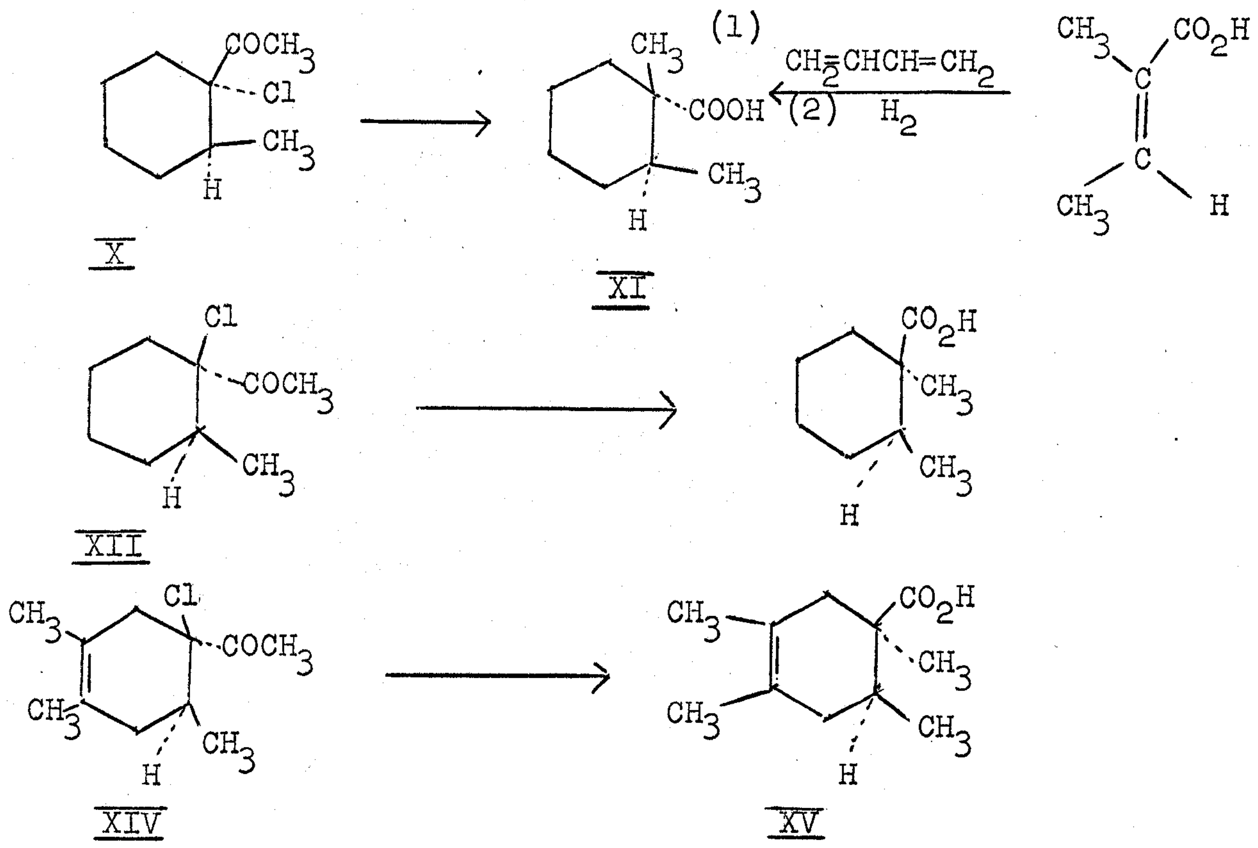
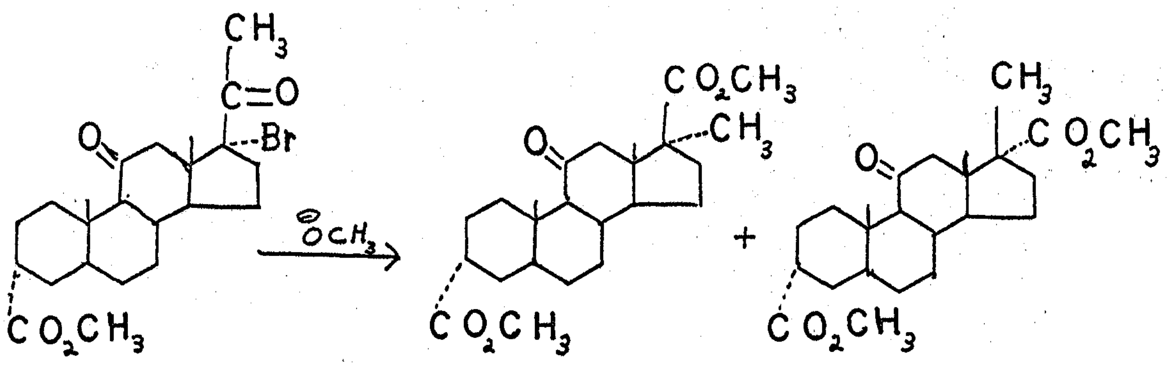


Fig. 8. Stereospecific rearrangement of epimeric 1-chloro-1-acetyl-2-methylcyclohexanes.

addition, the chloroketone (XIV) was shown to rearrange to the ester of (XV), which was proven to have carboxyl and methyl cis by its nonidentity with the adduct of tiglic acid and 2,3-dimethylbutadiene. These results are consistent with Loftfield's mechanism and suggest that cyclopropanone formation and halide loss are synchronous or very nearly so; as a minimum they would require that any intermediate zwitterion or "no-bond" species, if formed, should collapse stereospecifically to a cyclopropanone before the halide ion moves beyond the range for orbital overlap and hence cyclopropanone formation. However, the zwitterion mechanism may have significance for systems wherein steric barriers retard ring closure in the normal direction and thus allow the halide ion to travel beyond the range of stereoselective electrostatic interaction before bond formation has occurred.[18] Such has been suggested to be the case in the steroid field where Wendler[19] has shown that 17-bromo-3-acetoxypregnane-11,20-dione (XVI) of proven configuration gives, on rearrangement with alkoxide ion, a 3:2 mixture of the epimeric 17-methyl-17-carboxylic esters (XVII and XVIII), (Fig. 9.) respectively.



XVI XVII XVIII

Fig. 9. Favorskii rearrangement of 17-bromo-3-acetoxypregnane-11,20-dione with methoxide ion.

This result, which is unexplainable via the synchronous

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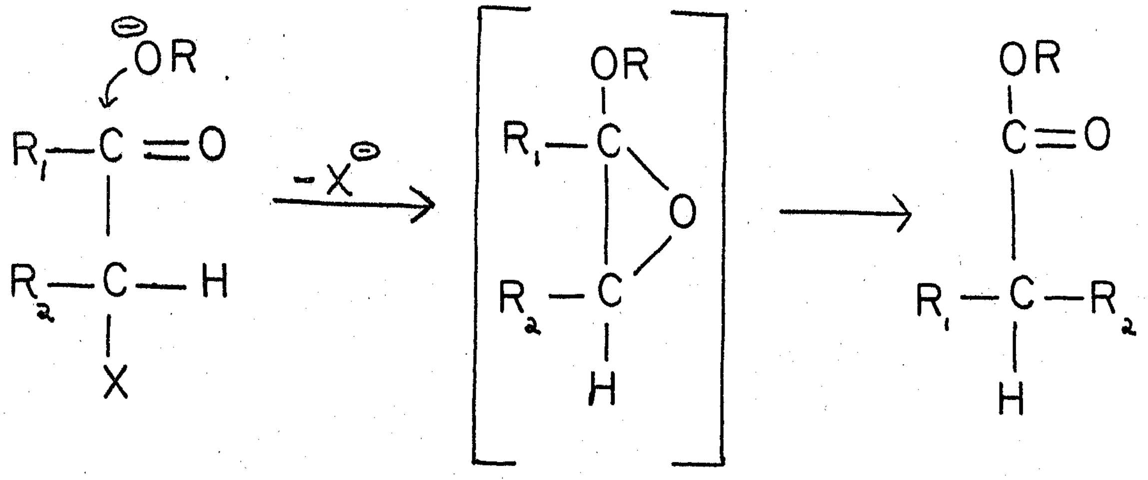
[18] C.K. Ingold, *Structure and Mechanism in Organic Chemistry*, p. 382-384.

[19] N.L. Wendler, R.P. Graber, and G.G. Hazen, *Chem. & Ind.* (London) 1956, 847; *Tetrahedron*, 3, 144 (1958).

Loftfield mechanism, was also rationalized by presupposing bromine migration to C-21 prior to rearrangement, although independent evidence for such a shift was not obtained.

The rearrangement originally was considered by Favorskii[20] to proceed by addition of alkoxide to the carbonyl carbon atom, followed by ejection of halide ion, to produce an epoxyether XIX. This, in turn, further reacted with the base to yield the products (Fig. 10). This, of course, was an attempt to explain the mechanism of the Favorskii rearrangement before the radioisotopic work of Loftfield was made known. The formation and isolation of epoxyethers from the action of alkoxides on certain α-halo-



XIX

Fig. 10. Epoxyether formation in Favorskii rearrangement.

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[20] A. Favorskii, J. prakt. Chem., (2) 88, 641 (1913).

ketones has been well established by Stevens and others.[21,27] The postulated rearrangement of the epoxyether XIX to products is highly improbable, and, in fact, such a transformation is experimentally precluded by failure to effect this rearrangement starting with pure epoxyethers synthesized by other means. The epoxyether intermediate usually reacts with alcohols or water to form hydroxyketals or hydroxyketones (Fig. 11.).

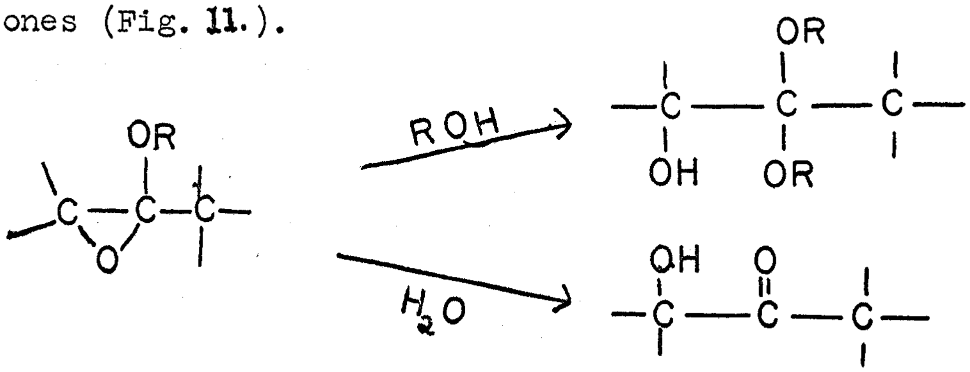

Fig. 11. Reaction of Epoxyethers with alkoxide ion.

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[21] C.L. Stevens, W. Malik, and R. Pratt, J. Am. Chem. Soc., 72, 4758 (1950).

[22] C.L. Stevens, J.J. Beereboom, and K.G. Rutherford, ibid, 77, 4590 (1955).

[23] R.B. Loftfield, J. Am. Chem. Soc., 72, 632 (1950); 73, 4707 (1951).

[24] A.M. Ward, J. Chem. Soc., 1541 1929.

[25] M. Mousseron, Jacquier, and Fontaine, Bull. soc. chim. France (5) 19, 767 (1952).

[26] C.L. Stevens and E. Farkas, J. Am. Chem. Soc., 74, 618 (1952).

[27] C.L. Stevens and J. Tazuma, ibid, 76, 715 (1954).

Stevens and others[26] have obtained pure epoxyethers by the action of alkoxides on α-halopropiophenones and α-halocyclohexylphenyl ketones. These epoxyethers rapidly gave α-hydroxyketals in the presence of methanol or methanolic methoxide ion, but no rearrangement to esters was observed. The hydroxy ketones which result on treatment of α-haloketones with hydroxide ion may undergo hydrolytic or oxidative cleavage to give carboxylic acids. The formation of 21% of cyclohexanecarboxylic acid from chloromethycyclohexyl ketone and sodium methoxide has been ascribed to hydrolysis of the intermediate hydroxymethyl ketone, since formation of the acid was eliminated by the use of anhydrous reaction conditions.[28]

The extent to which side reactions such as indicated above interfere with the normal Favorskii reaction must depend on the rate of epoxyether formation compared to the rate of rearrangement. This ratio is primarily a function of the structure of the haloketone and the nature of the halogen. Other important factors are, of course, the polarity of the reaction medium and the nature of the alkoxide. Side reactions, which must also be considered, involve direct substitution of certain α-haloketones by alkoxide (especially methoxide ion) to form α-alkoxy ketones.

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[28] R.B. Loftfield and L. Schaad, J. Am. Chem. Soc., 76, 35 (1954).

Stevens and DeYoung[29] reported replacement of chloride by methoxide ion when 1,1,3,3-tetraphenyl-1-chloroacetone was treated with sodium methoxide. Examples of replacement, however, are not too abundant owing to the fact that most of the other side reactions occur more readily. In order for replacement to occur, most other possible reaction paths must be eliminated either by steric hindrance at the carbonyl, lack of an enolizable α'-hydrogen atom or by weak nucleophilic strength of base being used. Cases have been cited in the literature by Jullien and others[30,31] where the use of amine bases as Favorskii reagents have led to the formation of α-amino ketones. Rutherford[32] was able to isolate an 85% yield of 2,4-dimethyl-1-penten-3-one from the action of triphenylmethyl sodium with 1-bromo-2,4-dimethylpentan-2-one. Examples of dehydrohalogenation such as this are common whenever very strong bases are used and beta hydrogen atoms are present in the starting haloketone. Although the mechanism of the Favorskii rearrangement appears now to be well established, the critical intermediate, the cyclopropanone, has yet to be isolated. The isolation of such

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[29] C.L. Stevens and J.J. DeYoung, *J. Am. Chem. Soc.*, 76, 718 (1954).

[30] A. Jullien *et al.*, *Bull. soc. chim. France*, (5) *20*, 374 (1953).

[31] R.M. Dodson, F. Morello, and W.G. Daubeau, *J. Am. Chem. Soc.*, *76*, 606 (1954).

[32] K.G. Rutherford, (unpublished results).

an intermediate represents not only the final conclusive step in the elucidation of the mechanism, but it also suggests an area of organic chemistry heretofore not explored - that of the fundamental chemistry of cyclopropanone and its derivatives.

Staudinger[33] was the first worker in the field to report attempts to prepare the parent compound, cyclopropanone.

C.K. Ingold[34] reported, in 1921, the isolation of a cyclopropanone as a semicarbazone when cyclopropanol-1,2-dicarboxylic acid was heated in concentrated sulfuric acid. He also obtained propanoic and succinic acids.

In 1931, Lipp and Koster[35] postulated that a cyclopropanone was an intermediate in the reaction of ketene with diazomethane. The final product of the reaction was cyclobutanone. The postulated mechanism for the conversion is shown in Figure **12**. One year later, Lipp, Buchkremer and Steeles[36] found that the action of diazomethane on an excess of ketene in the presence of methanol gave cyclopropanone monomethylacetal. The mono ethyl acetal could not be isolated in a pure state, but rather, in the presence of

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[33] H. Staudinger, Ber., 21, 312, (1930).

[34] C.K. Ingold, J. Chem. Soc., 119, 305-29 (1921).

[35] P. Lipp and R. Koster, Ber., 64, 2823 (1931).

[36] P. Lipp, J. Buchkremer, and H. Steeles, Ann., 499, 1-25 (1932).

ethanol, treatment of diazomethane with excess ketene gave cyclopropanone hydrate. All attempts to prepare a monomolecular cyclopropanone resulted in a polymeric form, so that one might conclude that the monomolecular form appears to exist only in solution. Lipp's mechanism of the formation of cyclobutanone from the treatment of excess ketene with diazomethane was substantiated by Roberts, Cox and Semenow[37] with the use of radioisotopes. They treated ketene with radioactive diazomethane (C^{14}) and obtained cyclobutanone. The radioisotopic distribution in the cyclobutanone was consistent with theoretical calculations within the limits of experimental error. The results were consistent with initial formation of cyclopropanone from which cyclobutanone was formed by introduction of a methylene group on either side of the carbonyl function with equal probability. These results are shown in Figure 13 .

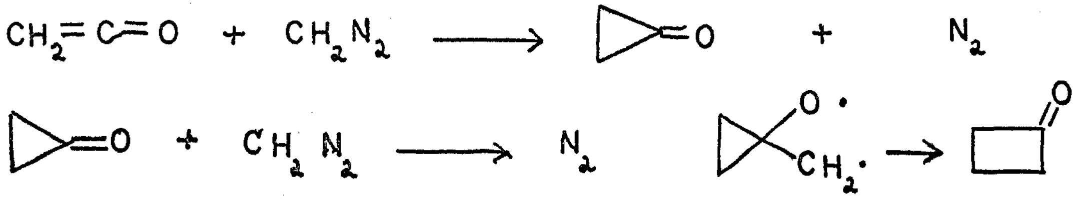

Fig. 12. Reaction of ketene with diazomethane.

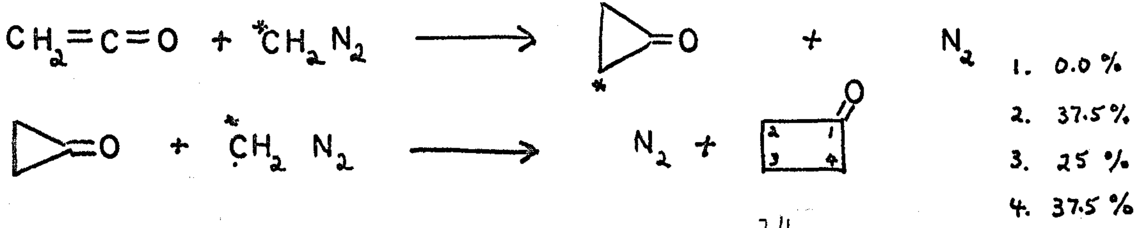

Fig. 13. Reaction of ketene with C^{14} diazomethane.

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[37] D. Semenow, E. Cox, J.D. Roberts, J. Am. Chem. Soc., 78, 3221 (1956).

All of these workers were of the opinion that the failure to isolate the intermediate cyclopropanone was due to its higher reactivity with diazomethane as compared with ketene.

Dechamps[38] reported the isolation of traces of cyclopropanone when a mixture of betaine and lime was pyrolyzed under reduced pressure. He also thought that traces of cyclopropanone were isolated when calcium succinate was heated. However, repetition of this work revealed that the actual products were methyl ethylketone and diethyl ketone.

Ingold, Shinichi and Thorpe[39] reported the isolation of a cyclopropanone from the treatment of 1-hydroxycyclopropanecarboxylic acid with concentrated sulfuric acid. However, Dem'yanov and Feofilatov[40] repeated the above experiment and reported negative results. They suspected that the actual structure of the 1-hydroxycyclopropanecarboxylic acid reportedly used by Ingold was in fact trans-γ-hydroxycrotonic acid.

Loftfield[41] clearly demonstrated the existence of a cyclopropanone when C^{14}-labelled 2-chlorocyclohexanone was

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38 G. Dechamps, <u>Bull</u>. <u>soc</u>. <u>chim</u>. <u>Belg</u>., <u>39</u>, 67 (1930).

39 C.K. Ingold, S. Shinichi, and J.F. Thorpe, <u>J</u>. <u>Chem</u>. <u>Soc</u>., <u>121</u>, 1177 (1922).

40 M. Ya. Dem'yanov, Feofilatov, V.V., <u>J</u>. <u>Gen</u>. <u>Chem</u>. (USSR), <u>9</u>, 340 (1939).

41 R.B. Loftfield, <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>., <u>72</u>, 632 (1950); <u>73</u>, 4707 (1951).

treated with methoxide ion. Examination of the cyclopentanecarboxylic acid products gave unequivocal proof of the existence of a cyclopropanone intermediate. However, the intermediate could not be isolated because of its high reactivity, and methanol, the conjugate acid of methoxide ion, is able to cleave the cyclopropanone ring resulting in ring contraction and formation of the methyl ester of cyclopentanecarboxylic acid. This elegant work of Loftfield was the first concrete evidence for the existence of a cyclopropanone.

Kistiakowsky and Sauer[42] attempted the formation of cyclopropanone by the flash photochemical decomposition of ketene in the presence of methylene. It was thought that the methylene would react with ketene to form cyclopropanone, but this was not isolated.

Kende[43] attempted to isolate a cyclopropanone by treatment of ketene with ethyl diazoacetate. It is well known that ethyl diazoacetate attacks ketene to give diazonium betaines. The aromatic betaines then lose nitrogen and collapse to the furan derivative as shown in Figure 14 .

[42] G. Kistiakowsky, and K. Sauer, J. Am. Chem. Soc., 78, 5699 (1956).

[43] A. Kende, Chem. and Ind. (London) 1053 1956 .

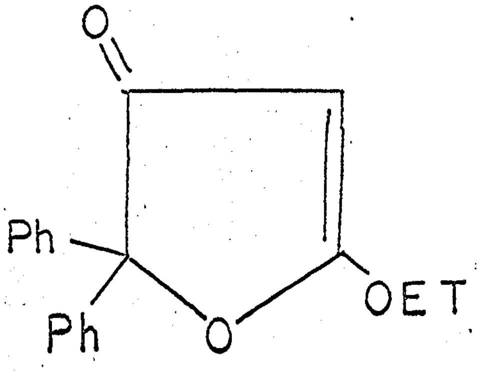

Fig. 14. 1,1-Diphenyl-2-keto-4-ethoxy-furan.

The aliphatic betaines lose nitrogen by concerted cyclization to give cyclopropanone intermediates which rearrange to the succinic anhydride enol or lose carbon monoxide to form the acrylic derivative. However, all attempts to isolate a cyclopropanone intermediate in this reaction have failed.

Several attempts to isolate a cyclopropanone by treatment of ketene acetals with diazomethane have been reported. Dull and Abend[44] treated several ketene acetals with different substituted diazomethanes and always obtained the cyclopropanone ketal in fairly good yield. A few of the results are shown in Figure 15. However, the main attempts to convert these ketals to cyclopropanones failed. McElvain and Weyna[45] also obtained cyclopropanone ketals from the treatment of ketene acetals with dichlorocarbene. Several cyclo-

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[44] M.F. Dull and P.G. Abend, J. Am. Chem. Soc., 81, 2588 (1959).

[45] S.M. McElvain and P.L. Weyna, J. Am. Chem. Soc., 81, 2579 (1959).

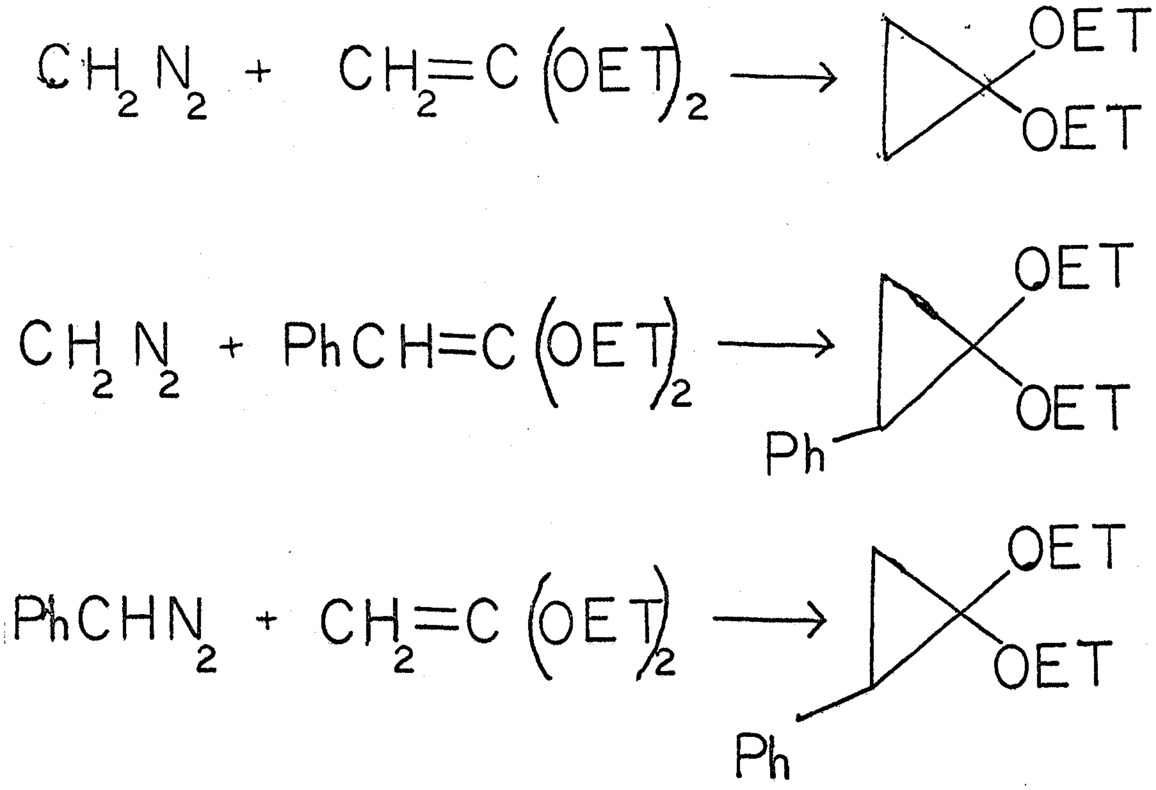

Fig. 15. Reaction of diazomethane with ketene ketal.

propanone ketals were isolated with different substituted ketene acetals. Again, the cyclopropanone itself could not be isolated.

Attempts to isolate a cyclopropanone from the Favorskii rearrangement have been reported, but all have failed. Bases such as alkoxide and amines have failed to give a cyclopropanone. α-Haloketones capable of undergoing the Favorskii rearrangement usually give esters or amides instead of the intermediate cyclopropanone. It has also been reported that 2-bromo-2,4-dimethylpentanone when treated with triethylamine gave a good yield of the unsaturated ketone.

Stevens and Farkas[46] and others have reported the formation of epoxy ethers in the Favorskii rearrangement of certain α-haloketones. However, the presence of an enolizable α'-hydrogen atom remains a requirement for the rearrangement under normal conditions. Most epoxyether formation results in systems which do not fulfill these requirements. Stevens and Rutherford[47] have reported that haloketones lacking this feature, such as 1-chloro-1-benzoylcyclohexane or 2-chloro-1-tetralone, do not give rearrangement products on treatment with alkoxides.

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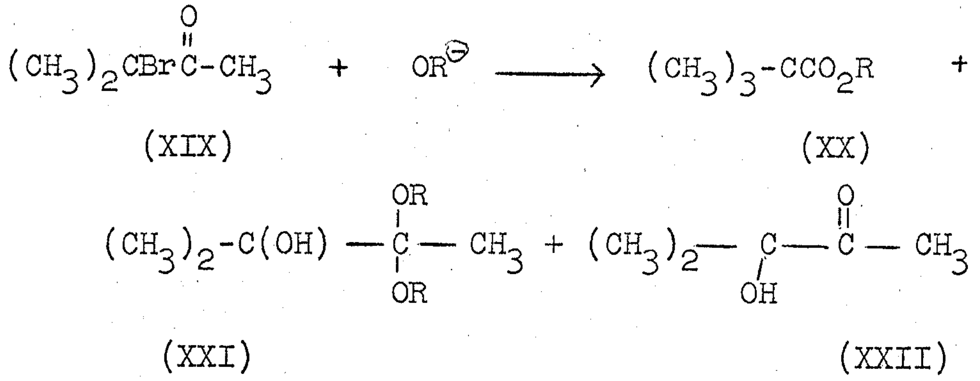
[46] C.L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, 74, 618 (1952).

[47] C.L. Stevens and K.G. Rutherford, *J. Am. Chem. Soc.*, 77, 4590 (1955).

CHAPTER II

DISCUSSION OF EXPERIMENTAL RESULTS

From a review of the previous attempts to prepare and isolate a cyclopropanone, it is evident that no cyclopropanone can exist if, in the dehydrohalogenation procedure, the conjugate acid of the base possessed nucleophilic character. With this in mind, the approach taken in this laboratory was to investigate the reaction of α-haloketones with triphenylmethyl sodium, a base, the conjugate acid (triphenylmethane) of which is inert and hence unreactive. Theoretically, if the cyclopropanone intermediate is capable of formation by such a method, isolation should be possible since the side reaction (cleavage) is eliminated. From a consideration of bond angles it should be expected that ring opening of a cyclopropanone nucleus should be spontaneous in the presence of any nucleophilic species. Conjugate acids of alkoxide bases are fairly strong nucleophiles, and hence one would predict immediate attack and subsequent ring cleavage in the presence of such nucleophiles. Table 1 shows the aliphatic series of bromo-isopropyl-methyl ketone in which the Favorskii ester (XX), the hydroxyl ketal (XXI), and the α-hydroxy ketone (XXII) may be formed. The table gives a good index of the profound effect the choice of base and solvent has on the yield of the Favorskii reaction (Figure 16).



$$(CH_3)_2CBr\overset{O}{\overset{\|}{C}}-CH_3 \quad + \quad OR^{\ominus} \longrightarrow (CH_3)_3-CCO_2R \quad +$$

(XIX) (XX)

$$(CH_3)_2-C(OH)-\underset{OR}{\overset{OR}{C}}-CH_3 + (CH_3)_2-\underset{OH}{C}-\overset{O}{\overset{\|}{C}}-CH_3$$

(XXI) (XXII)

Fig. 16. Favorskii reaction of bromo-isopropylmethyl ketone with alkoxide ion.

TABLE 1

Reaction of $(CH_3)_2$-$CBrCOCH_3$ (XIX) under conditions of the Favorskii Reaction

Base	Solvent	Yield (%) of (XX)	Yield % of By-product	Ref.
Sodium isopropoxide	Diethyl ether	64%	0%	1
Sodium ethoxide	Diethyl ether	61%	0%	1
Sodium methoxide	Diethyl ether	39%	20% XXI	1
Sodium isopropoxide	Isopropyl alcohol	20%	8% XXI	1
Sodium ethoxide	Ethyl alcohol	14%	32% XXI	1
Sodium methoxide	Methyl alcohol	0%	77% XXI	1
Barium carbonate	Water	3%		2
Potassium hydroxide	Water	0%	76% (XXII)	2

A survey of Table 1 reveals that no single alkoxide-solvent combination is clearly superior for α-monohaloketones in general. The use of diethyl ether as solvent is indicated for the simpler haloketones, and theoretical considerations suggest that solvents of low polarity, might have a generally favourable effect. The optimum choice of base and solvent appears to vary with the structure of the individual haloketone. The use of hydroxides or carbonates generally leads to extensive hydroxyketal formation, (Table 1). Significant exceptions include the conversion of 2-chlorocycloheptanone to cyclohexanecarboxylic acid (69% yield) on treatment with hot potassium carbonate.[1,2,3]

Thus our choice of base and solvent was sodium triphenylmethide and diethyl ether. The conjugate acid of sodium triphenylmethide, namely triphenylmethane, is inert and hence unreactive since it does not have electrons readily available. It was thought, therefore, that the cyclopropanone could be trapped and isolated in diethyl ether. However, in all cases attempted, no evidence of the independent existence of a cyclopropanone was obtained. When 3-bromo-3-methyl-2-butanone was treated with sodium triphenylmethide

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1 J.G. Aston and R.B. Greenburg, J. Am. Chem. Soc., 62, 2590 (1940).

2 Uenus-Danilova, J. Gen. Chem., USSR., 11, 847 (1941).

3 C.D. Gutsche, J. Am. Chem. Soc., 71, 3513 (1949).

in diethyl ether, three products were obtained; methyl isopropenyl ketone, methyl isopropyl ketone, and unreacted 3-bromo-3-methyl-2-butanone. The products were identified by gas phase chromatography. The chromatographic evidence indicates an equal amount of methyl isopropyl ketone and unreacted 3-bromo-3-methyl-2-butanone, along with approximately one third as much methyl isopropenyl ketone. All attempts at separation by distillation, both at atmospheric pressure and under reduced pressure, resulted in decomposition and polymerization. Three fractions could be separated crudely under reduced pressure. The refractive indices, however, indicated that separation was incomplete.

When 3-bromo-3-methyl-2-butanone was treated with dimsylsodium[4] in dry dimethylsulfoxide, a cyclopropanone still could not be isolated. Again, three fractions were isolated by distillation under reduced pressure. The refractive indicies and infra red spectra were not comparable with those of the expected reaction products. We might mention here that the chances of isolating a cyclopropanone in this reaction were diminished somewhat due to the fact that the original reaction mixture was poured on ice and water before extraction with diethyl ether. As was seen earlier, the cyclopropanone ring would open up immediately in the presence of

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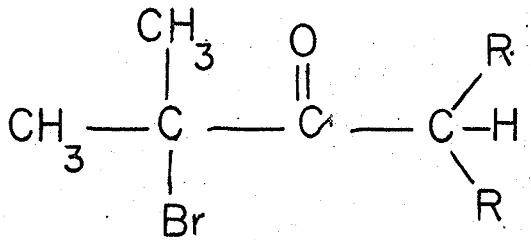
[4] E.J. Corey, J. Am. Chem. Soc., 84, 866 (1962).

water to give the normal Favorskii product. However, no evidence for 2,2-dimethyl propionic or trimethylacetic acids was obtained. Hence no Favorskii products were obtained.

When 2-bromo-2,4-dimethyl-3-pentanone was treated with sodium triphenylmethide in diethyl ether, isopropyl isopropenyl ketone was obtained in 85% yield. Perhaps the availability of the proton in Fig. 17. when R = CH_3 can explain



XXIII

Fig. 17. A monohaloketone.

the difference in the results obtained. When R = CH_3, there occurs approximately 85% elimination. When R = H, the elimination reaction seems to occur, but to a much lesser extent. This may be due also to the fact that when R = H, there are three α′-hydrogen atoms and thus the possibility of attack by base at the α′-carbon atom is greatly enhanced. This should undoubtedly decrease the amounts of elimination reaction and increase the normal Favorskii reaction. However, no evidence of Favorskii products was obtained.

When 1-bromo-1,1,3,3-tetraphenylacetone was treated with sodium triphenylmethide in diethyl ether, immediate decolourization of the reddish-coloured base occurred. When allowed to stand, a fine yellowish precipitate appeared. After filtration and removal of the solvent _in vacuo_, a reddish-yellow crystalline product, which exhibited a wide melting point range was obtained. Continued experimentation on this crystalline product afforded only small amounts of triphenylmethane and tetraphenylacetone. No evidence for the presence of 2,2,3,3-tetraphenylcyclopropanone was obtained. When dimsylsodium was substituted for sodium triphenylmethide, the starting bromo-ketone was the only identifiable product.

It is evident that reduction of the bromo-ketone resulted, at least in part, as well as the expected proton removal. This was not totally unexpected since at least three other cases of a reaction of this type appear in the literature.[5,6,7] The explanation of this reduction lies in the cationoid character of the halogen atom of the bromo-ketone. Lyle and Covey[5] reported the reduction of 7-bromo-2,2-diphenylcycloheptanone by means of dimethylaniline to yield the unhalogenated ketone. Similarly, Rosenkranz _et al._[6] found reduction of 21-iodo-20-ketopregnanes when boiled for long period of time with collidine or dimethylaniline. Stevens and Rutherford[7]

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[5] R.E. Lyle, and R.A. Covey, _J. Am. Chem. Soc._, _75_, 4973 (1953).

[6] G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, _J. Am. Chem. Soc._, _72_, 4077 (1950).

[7] C.L. Stevens and K.G. Rutherford, _J. Am. Chem. Soc._, _77_, 4590 (1955).

obtained small amounts of tetralone when α-halotetralones were treated with sodium methoxide.

The unsuccessful attempts to prepare a cyclopropanone using sodium triphenylmethide and dimsylsodium can be attributed to the strength of the base which results in non-selectivity of proton attack. The first attempt involved the use of 2-bromo-2,4-dimethyl-3-pentanone in which only one α′-hydrogen atom is present. However, the highly non-selective sodium triphenylmethide attacked a β-hydrogen atom to give an 85% yield of the elimination product. It was felt that by increasing the number of α′-hydrogen atoms, the chances of forcing the reaction to proceed according to the Loftfield mechanism would be enhanced. Hence, the next bromo-ketone used was 3-bromo-3-methyl-2-butanone. However, when this ketone was treated with sodium triphenylmethide, no evidence for either cyclopropanone or Favorskii products was obtained. Although the extent of the elimination reaction was greatly decreased, again the non-selectivity and strength of the base were evidenced, in that a considerable amount of reduction of the haloketone to the unhalogenated ketone occurred. Sodium triphenylmethide and dimsylsodium were simply too strong and hence much too non-selective to afford attack only at the α′-carbon atom. In fact, no evidence was obtained to show any attack at this site. The next obvious step was to use a bromo-ketone in which all other possible sites of attack except the α′-carbon atom were removed. Such a bromo-ketone is 1-bromo-1,1,3,3-tetraphenylacetone in which there is only one α'-hydrogen atom present. Both the carbonyl and the α-carbon atom are too sterically hindered to be attacked by the bulky triphenylmethide ion. Stevens and DeYoung[7] have found that weaker bases, such as methoxide ion, will afford replacement of the halogen atom in the corresponding chlorotetraphenylacetone. However, when 1-bromo-1,1,3,3-tetraphenylacetone is treated with sodium triphenylmethide, no replacement reaction occurs. Instead, the removal of the single α'-hydrogen atom occurs, but enough energy to cause ring closure to yield the cyclopropanone could not obtained. Even the use of dioxane in place of diethylether as a solvent which affords much higher reflux temperatures could not supply the energetics required for ring closure. In the meantime, a small amount of reduction of the haloketone to the unhalogenated occurred.

During the preparation of tetraphenylacetone, according to the procedure of Hauser[8], an interesting by-product was obtained. Instead of obtaining tetraphenylacetone (m.p. 133-134°C.), there was obtained a white solid which melted at 180°C. When this white solid was treated with concentrated sulfuric acid, another white solid was obtained which melted at 192-193°C. Hauser suggested that a small amount

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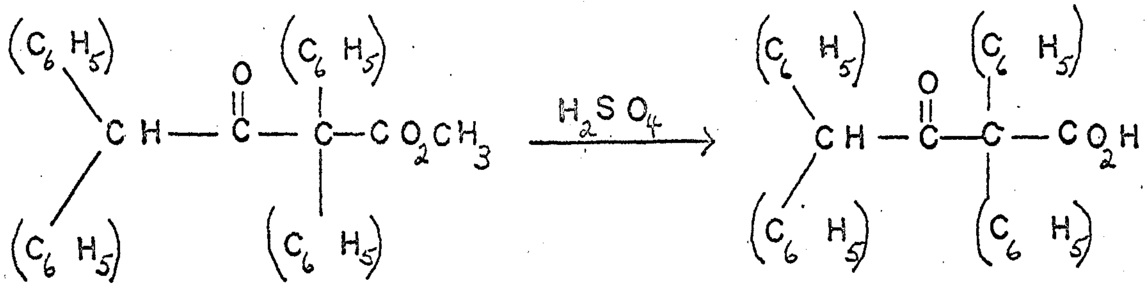
[7] C.L. Stevens and J. DeYoung, *J. Am. Chem. Soc.*, *76*, 718 (1954).

[8] C. Hauser and S.W. Kantor, *J. Am. Chem. Soc.*, *72*, 3290 (1950).

of the O-acyl derivative of the ketone was formed in the preparation of tetraphenylacetone, and that this could be hydrolyzed with alkali or acid to regenerate tetraphenylacetone. However, we suspect that the by-product obtained was the methyl ester of a β-keto acid represented below (XXIV) (Fig. 18.) and subsequent treatment with sulfuric acid would give (XXV) Compound (XXV) would be resistant to decarboxylation because of the steric hindrance to enol formation.



(XXIV)

(XXV)

Fig. 18. Conversion of β-keto ester to β-keto acid.

In general, most β-keto acids decarboxylate according to the scheme shown in Figure 19.

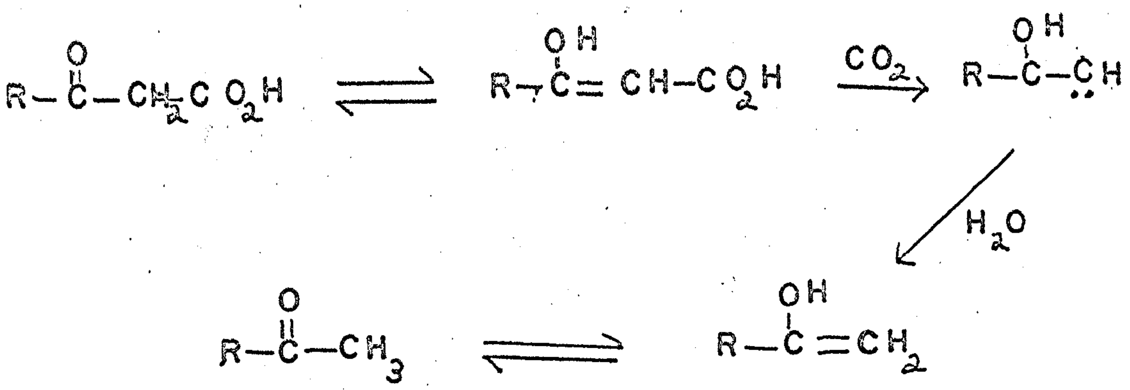


Fig. 19. Decarboxylation of a β-keto acid.

Inspection of compounds (XXIV) and (XXV) shows the resistance to decarboxylation. The interest of the structure of compound (XXIV) arose from Hauser's claim that in the preparation of tetraphenylacetone, two moles of potassium diphenylmethide were required for each mole of diphenylacetyl chloride. No reaction mechanism was given in that publication. It is suspected that the reason for the requirement of two moles of potassium diphenylmethide for each mole of diphenylacetyl chloride lies in the possibility that the reaction occurs in two steps. The first mole then of potassium diphenylmethide is used to convert diphenylacetyl chloride to diphenylketene; the second mole reacts with ketene to generate tetraphenylacetone (Fig. 20.). However, diphenylketene is known to dimerize quite readily. If this occurred, a β-keto ester

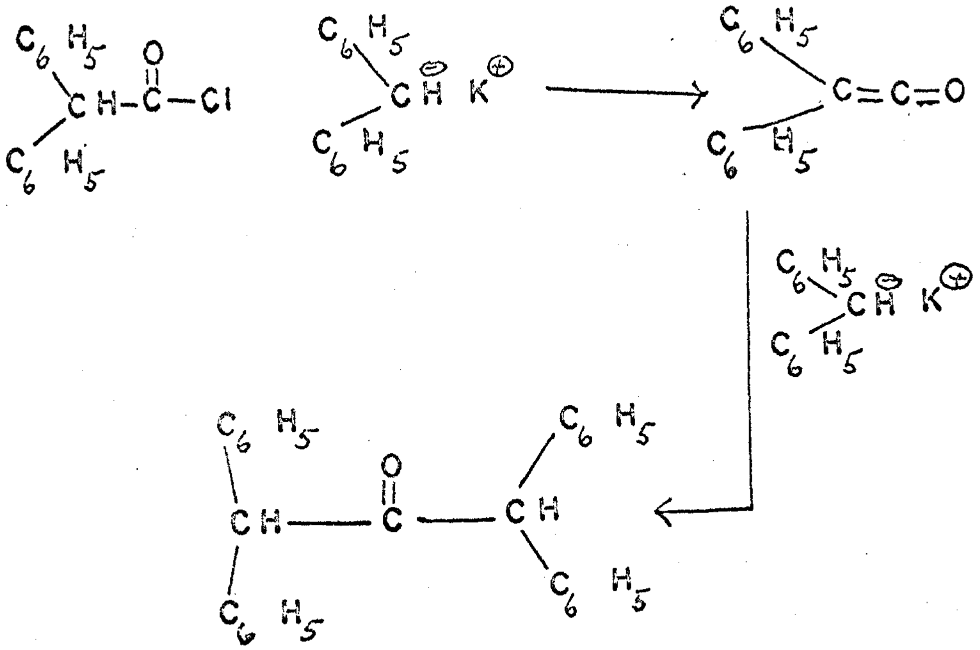


Fig. 20, Formation of tetraphenylacetone .

of the type previously described could then arise from the following reaction sequence Fig. 21.

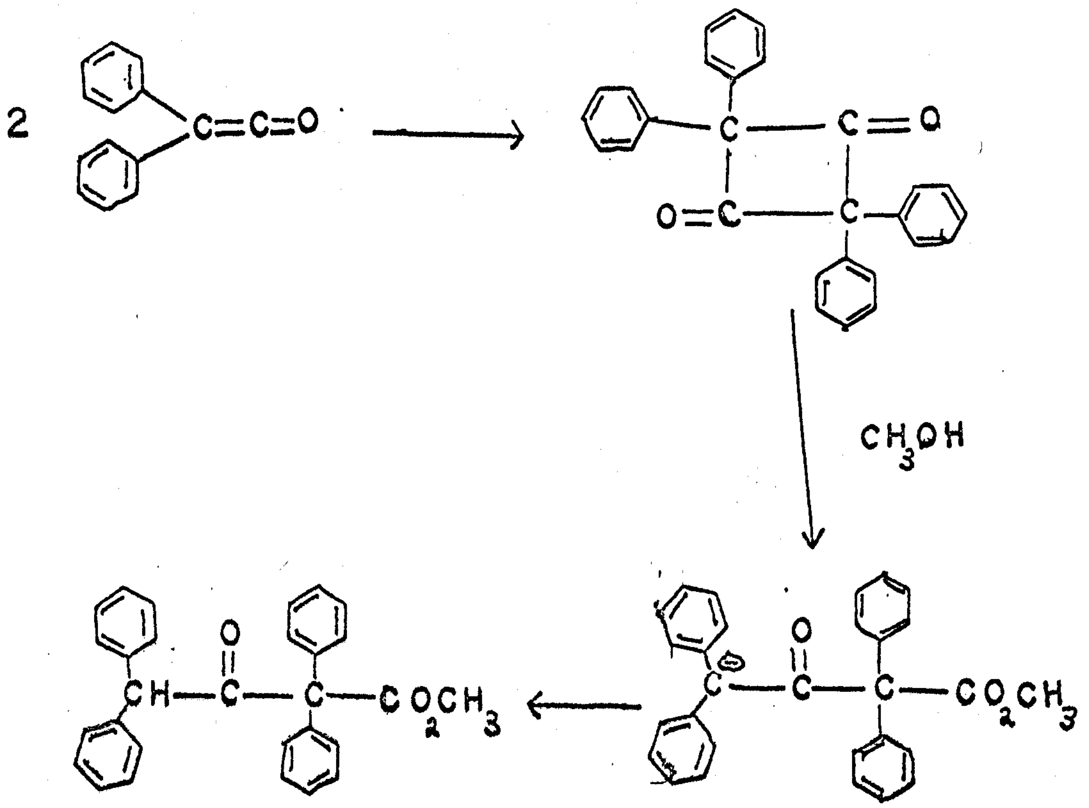


Fig. 21. Dimerization of diphenylketene and subsequent β-keto ester formation.

The treatment of one mole of diphenylketene with one mole of potassium diphenylmethide would afford unequivocal evidence for the mechanism proposed above. Investigation of this aspect is still in progress.

CHAPTER III

EXPERIMENTAL

Preparation of Triphenylmethyl sodium

(a) Triphenylcarbinol[1] - Magnesium turnings (75 g. - 3.1 m.), bromobenzene (60 ml. - 0.90 m.), ethyl ether (600 ml.) and a few crystals of iodine were placed in a dry, 3-litre, round-bottomed, three-necked flask, which was equipped with a condensor, mechanical stirrer, and a dropping funnel. After the reaction had started (decolourization of iodine and evolution of heat) an etheriel solution containing bromobenzene (180 ml. - 2.4 m.) in anhydrous ether (800 ml.) was added dropwise at such a rate to keep the reaction mixture at the reflux temperature. After the addition was complete, the reaction mixture was refluxed for an additional hour. Ethyl benzoate (240 ml.) dissolved in 600 ml. of anhydrous ether was added dropwise to the cooled Grignard reagent at such a rate to maintain a mild reflux. After the complete addition of the ethyl benzoate, an additional hour of refluxing was allowed. The reaction mixture was then poured slowly and with stirring over a mixture of 200 g. of chopped ice and 100 ml. of concentrated hydrochloric acid. The organic product was extracted with solvent ether, and dried over anhydrous sodium sulfate. The

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[1] The melting points were measured on a Fisher-Johns block and are uncorrected.

ether was removed in vacuo, whereupon the triphenylcarbinol crystallized. The yield was 273 g. (65%), m.p. 158-160°, (recorded m.p. 162°C.).[2]

(b) Triphenylchloromethane - A mixture of pure triphenylcarbinol (200 g.- 0.8 m.) and dry benzene (65 ml.) was placed in a single-necked, 1-litre, round-bottomed flask which was provided with a calcium chloride drying tube at the top. The mixture was heated on a steam bath and acetyl chloride (40 ml.) was added to the hot solution with constant shaking. During a ten minute interval additional acetyl chloride was added in 10 ml. portions and the reaction mixture refluxed for thirty minutes. The solution was cooled and petroleum ether added through the condensor. After cooling for three hours in an ice bath, white sugar-like crystals of triphenylchloromethane separated out of the reaction mixture. The product was removed by filtration and washed rapidly with 125 ml. of petroleum ether whereupon it was placed in a dessicator over soda-lime and paraffin. The dried product weighed 155 g., m.p. 111-112°C. (recorded m.p. 111.5°C.).[2] Concentration of the mother liquors in vacuo yielded an additional 24 g. of product, m.p. 111-112.5°C. The total yield was 179 g. or 89%.

(c) Triphenylmethyl sodium - Sodium amalgam[3] (approx. 2.6%) was prepared as follows: Freshly cut sodium (35 g.) was placed in an evaporating dish under nujol and heated until melted.

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[2] L.J. Fieser, Experiments in Organic Chemistry, (Boston) 1957, p. 220

[3] Organic Syntheses, Coll. Vol. 11, 609 (1943).

Mercury (85 ml.- 1150g.) was added slowly with stirring to the molten sodium. No external heating was necessary to maintain the proper temperature to keep the amalgam molten. The amalgam was allowed to cool and then washed twice with dry benzene. The amalgam was pulverized and placed in a 1.5-litre bottle (previously dried in an oven), triphenylchloromethane (200 g.- 0.72 m.) added, and the bottle filled nearly to the top with anhydrous ether. The bottle was stoppered and placed in a mechanical shaker for 8 - 10 hours, whereupon a deep red coloured solution was obtained. The bottle was then placed upright in the refrigerator to allow the mercury salts to settle out. The triphenylmethyl sodium solution was then transfered to 500-ml. bottles for storage.

5.0 ml. of the triphenylmethyl sodium solution were placed in water, ether was added to extract the triphenylmethane, and the water layer titrated with standard hydrochloric acid. The normality of the base was between 0.22-0.29N.

3-Bromo-3-methyl-2-butanone - Methyl isopropyl ketone[4] (17.2 g.- 0.2 m.) was dissolved in 50 ml. Of glacial acetic acid and 5 ml. of acetic anhydride. The temperature of the solution was lowered to 0°C. by means of an ice bath and bromine (32.0 g.- 0.2 m) was added dropwise with stirring at such a rate that each drop decolorized before another drop was added. Addition of bromine was complete in one hour, whereupon the reaction mixture was poured on ice-water containing a small

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[4] J. R. Catch, D. H. Hey, and E. H. Jones, J. Am. Chem. Soc., 70, 276 (1948).

amount of sodium bicarbonate. The bromoketone was extracted with ether, the ether layer washed twice with water, dried over anhydrous sodium sulfate and distilled. The product was collected over a distillation range of 135-139°C. The yield was 37.5 g. or 75%, (η= 1.4585); (reported η= 1.4590).[5]

Anal. Calcd. for C_5H_9BrO: C, 36.39; H, 5.49; Br, 48.42. Found: C, 36.48; H, 5.37; Br, 48.24.

Diphenylacetyl chloride - Diphenylacetic acid (10 g.- 0.05m.) was placed in a 500-ml single-necked flask which was equipped with a water cooled condensor and thionyl chloride (30 ml.) was added. The reaction mixture was refluxed for two hours yielding a dark green solution. The excess thionyl chloride was distilled off and the residue taken up in chloroform and petroleum ether. When cooled, 7.7 g. of diphenylacetyl chloride was precipitated, m.p. 49-50°C. Recrystallization from petroleum ether-chloroform afforded diphenylacetyl chloride, m.p. 53-54°C. (recorded m.p. 54-55°C.).[6]

Tetraphenylacetone -

(a) Potassium amide - In a 2000-ml., three-necked, round-bottomed flask, which was equipped with a dropping funnel, condensor, and a stirrer (to which was attached a piece of rusty wire), was placed 800 ml. of commercial anhydrous ammonia. Potassium (21.5 g. - 0.55 m.) was added with stirring to the cool-

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[5] J. R. Catch, D. H. Hey, and E. H. Jones, loc. cit.

[6] S. Kantor, and C. Hauser, J. Am. Chem. Soc., 72, 3290 (1950).

ed ammonia slowly. It was converted to a dark grey potassium amide in two hours. Conversion was indicated by discharge of the deep blue colour of the solution.

(b) Potassium diphenylmethide - The potassium amide was placed in an ice-water bath and with stirring diphenylmethane (84.0 g- 0.5 m.) in 800 ml. anhydrous ether was added, resulting in an orange coloured heterogenous solution which was allowed to come to room temperature slowly with constant stirring. The mixture was stirred overnight to allow the excess ammonia to vaporize.

(c) Tetraphenylacetone - To a suspension of 0.05 mole of potassium diphenylmethide in 800 ml. of ether, immersed in a dry ice-acetone bath, was added rapidly diphenylacetyl chloride (57.5 g.- 0.25 m.) in 400 ml. of ether. The reaction mixture was refluxed for twenty hours and then poured into 500 mls. of water, more solvent ether added, and after vigorous shaking, the aqueous-alkaline layer separated. The ether phase was washed with water, dried over sodium sulfate and the ether removed on a solvent stripper. The residue was stirred with 150 mls. of methanol giving essentially pure tetraphenylacetone, (32%), m.p. 127-129°C. Recrystallization from glacial acetic acid-water gave tetraphenylacetone (25 g. white needles), m.p. 132-134°C, (reported m.p. 133-134°C.).[7]

Note:

In one tetraphenylacetone preparation in which the exact procedure as outlined above was followed, a strange product

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[7] S. Kantor and C. Hauser, loc. cit.

was obtained. Instead of obtaining the expected tetraphenylacetone, 15 g. of a white solid was obtained which melted at 180°C. Suspicions of the compound being diphenylacetic acid anilide were removed when a mixed melting point with an authentic sample was 162-164°C. When one gram of this white solid was heated with 10 ml. of concentrated sulfuric acid and poured into water, a white solid was again obtained. Recrystallization from glacial acetic acid-water gave 0.50 g. of a white solid which melted at 192-193°C. The analyses of these two unexpected white solids were as follows:

Unexpected product from tetraphenylacetone preparation

Anal. Calcd. for $C_{29}H_{24}O_3$: C, 81.90; H, 6.13.
Found: C, 82.80; H, 5.71.

Product of heating the above compound with sulfuric acid

Anal. Calcd. for $C_{28}H_{22}O_3$: C, 82.70; H, 5.42.
Found: C, 81.74; H, 5.98.

Bromotetraphenylacetone - Tetraphenylacetone (10.0 g.- 0.03 m.) was dissolved in 60 ml. of carbon tetrachloride and placed in a 250-ml. round-bottomed flask which was equipped with a water-cooled condensor and heating mantel. A few drops of a solution of 4.45 g. (0.03 m.) bromine in 10 ml. carbon tetrachloride were added, the reaction mixture brought to reflux temperature, and then irradiated with an ultra-violet light for one hour. During this time the colour of the solution changed from red to orange. After addition of the remainder of the bromine-carbon tetrachloride solution, the reaction mixture was irradiated for an additional 12 hours. The solvent was removed on a solvent stripper, whereupon a greenish paste was obtained. The addition of approximately 25 ml. of chloroform and 200 ml. of petroleum ether gave 10.0 g. (86%) of an orange-coloured solid, bromotetraphenylacetone, m.p. 107-108°C., (reported m.p. 108-109°C.).[8] No dibromo derivative could be obtained.

Anal. Calcd. for $C_{27}H_{21}BrO$: C, 73.47; H, 4.79, Br, 18.10.
Found: C, 73.36; H, 4.65; Br, 18.10.

3-Bromobutan-2-one - Methyl ethyl ketone, (36.0 g.- 0.5 m.), was added to a 1-l. round-bottomed flask which was cooled via an ice-bath. One molar potassium chlorate solution (200 ml.) was added and a solution of bromine (80 g.- 0.5 m.) in 100 ml. water was added dropwise with stirring over a period of one and one half hours. The bromoketone was extracted with ether, washed twice with sodium bicarbonate and water, dried over anhydrous sodium sulfate and the ether removed *in vacuo*. The product was distilled under reduced pressure and the fraction which boiled at 86-88°C. at 150 mm. pressure was taken. The yield was 37.5 g. or 45%, refractive index 1.4570; (reported refractive index 1.4571).[9,10]

Methylcyclohexyl ketone

(a) Magnesium (12.5 g.- 0.5 m.) was placed in a three-necked

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[8] H. Dean *et al.*, *J. Am. Chem. Soc.*, 76, 4988 (1954).
[9] J. Catch *et al.*, *J. Chem. Soc.*, 272 (1948).
[10] E. Janetzky *et al.*, *Rec. trav. chim.*, 65, 691 (1946).

flask which was fitted with a stirrer, condensor, and dropping funnel.[11] The apparatus was flamed out, a stream of dry nitrogen passed through and 100 ml. of anhydrous ether added. A solution of methyl iodide (70.5 g.- 0.5 m.) in 250 mls. anhydrous ether was added slowly at a rate such as to maintain the reaction mixture at the reflux temperature. Upon complete addition of the methyl iodide, the Grignard reagent was refluxed for an additional one half hour.

A new flask with the same equipment was set up, dried, a stream of dry nitrogen passed through and an heterogeneous mixture of previously dried cadmium chloride (50 g.- 0.26 m.) in 100 mls. of anhydrous ether was added. To this mixture was added slowly the previously made Grignard reagent and the brownish mixture which resulted was refluxed for one half hour. To the cooled solution was added slowly a solution of cyclohexylcarbonylchloride (50 g.- 0.35 m.) in 200 mls. anhydrous ether and the reaction mixture refluxed for twenty hours. The reaction mixture was then poured carefully[12] on ice and hydrochloric acid and extracted with more solvent ether. The ether layer was washed with water, sodium bicarbonate solution, water again, and dried over anhydrous sodium sulfate. The ether was removed <u>in vacuo</u> and the ketone distilled. The yield was 17 g. (39.9%), b.p. 178-180°C., refractive index 1.4510, Se.m.p. 177°C., 2-4-Dn. m.p. 137-138°C.

(b) Bromocyclohexane (82 g.- 0.5 m.) in 200 mls. of anhydrous

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[11] J. Cason, Chem. Revs., 40, 15 (1947).

[12] $Cd(CH_3)_2$ is explosive when in contact with water or acid.

ether was added slowly to magnesium (12.0 g. - 0.5 m.) in 100 mls. of anhydrous ether. The resultant Grignard reagent was refluxed for an additional hour after all the reactants had been added.

Redistilled acetic anhydride (0.5 m. - approx. 51 ml.) in 150 mls. of anhydrous ether, was placed in a 1-litre, three-necked, round-bottomed flask[13] which was equipped with a stirrer, condensor, and dropping funnel. The solution was cooled to -70°C. with a dry ice-acetone bath and the cyclohexylmagnesium bromide solution added slowly and carefully (reaction is quite violent even at -70°C.) over a period of one and one-half hours. The stirred solution was allowed to come to room temperature and was poured over ice and sodium hydroxide. The water layer was extracted with solvent ether and this dried over magnesium sulfate after it had been washed twice with sodium bicarbonate solution and water. The ether was removed *in vacuo* and the resultant liquid, when distilled under reduced pressure, yielded 35 g. (55%) of the methylcyclohexyl ketone, b.p. 58-59°C. at 9 mm. pressure; refractive index 1.4510, (reported refractive index 1.4514).[14]

Methyl-1-bromocyclohexyl ketone - Methylcyclohexyl ketone and hydrobromic acid, (31.7 g. - 0.25 m.) was placed in a flask which was equipped with a magnetic stirrer. The solution was cooled to -10°C. with an ice-salt bath and bromine (40 g. -

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[13] M. Newman and A. Smith, *J. Org. Chem.*, *13*, 592 (1948).

[14] R. Wagner and J. Moore, *J. Am. Chem. Soc.*, *74*, 2884 (1950).

0.25 m.) added. After addition of 100 mls. of pentane, the solution was allowed to stir at 0°C. for one and one half hours, whereupon 200 mls. of water were added. The organic layer was separated, washed successively with water, sodium bicarbonate solution, water and dried over anhydrous sodium sulfate. The pentane was removed _in vacuo_ and the remaining bromoketone when distilled under reduced pressure amounted to 25 g., b.p. 58-65°C. at 3 mm. pressure. The refractive index was 1.5019-1.5043 .

Corey's Base (CH_3-S-CH_2^- Na^+)

(a) Drying of dimethylsulfoxide[15] - Dimethylsulfoxide was dried by refluxing for three hours over calcium hydride and then distilled under reduced pressure (b.p. 50-55°C. at 1 mm. pressure).

An alternate method[16] of drying dimethylsulfoxide was also used. Dimethylsulfoxide (700 mls.) was placed in a single-necked flask and approximately one gram of triphenylmethane was added. Dimsylsodium was added to this solution until a permanent red colour remained. The dimethylsulfoxide was then distilled under reduced pressure (approx. 1 mm. pressure).

(b) Dimsylsodium - Dry dimethylsulfoxide (200 mls.) was placed in a 500-ml., three-necked, round-bottomed flask which was equipped with a stirrer, condensor, and nitrogen inlet. The apparatus was placed in an oil bath and the temperature carefully

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[15] E. J. Corey and Chayakowski, J. Am. Chem. Soc., 84, 866 (1962).

[16] G. Price and M. Whiting, Chem. and Ind., 775 (May 1963).

controlled between 65-70°C. It was important not to heat above 70°C. Sodium hydride (16 g. of a 53.5% suspension in paraffin oil) was weighed out, washed twice with 60-ml. portions of dry methylcyclohexane, and added slowly in 100 mls. dry methylcyclohexane to the dimethylsulfoxide which was kept at 65-70°C. Addition was complete in about forty-five minutes and the reaction mixture was stirred continuously until all evidence of hydrogen evolution subsided. The reaction mixture was then transferred to a separatory funnel and the greyish-brown dimethylsulfoxide layer separated. The dimsylsodium was immediately stored under nitrogen in the refrigerator. Titration of 5.00 mls. of the dimsylsodium with standard hydrochloric acid resulted in a determined normality of 1.8.

Reaction of 3-Bromo-3-methyl-2-butanone with Triphenylmethyl Sodium -

(a) 3-Bromo-3-methyl-2-butanone (5.4 g. - 0.03 m.) was placed in a 500-ml. three-necked flask which was fitted with a stirrer, condensor, and nitrogen inlet, in 100 mls. of anhydrous ether. To this solution which was cooled to 0°C. by an ice bath, was added rapidly 110 mls. of 0.29 N. triphenylmethyl sodium. An orange coloured solution resulted immediately with instantaneous disappearance of the dark red-coloured base. After fifteen minutes, the solution was allowed to come to room temperature and was stirred overnight whereupon a finely divided yellow precipitate separated out. Upon filtration, 7.0 g. of this solid was obtained having a very high and wide melting point range. Extraction of the solid with chloroform left a small amount of a fine white precipitate which was soluble in water. The infrared spectrum which was taken on the chloroform extract showed signs of triphenylmethane being present. All attempts to crystallize the triphenylmethane from the chloroform failed.

The ether layer was concentrated down, yielding an orange-yellow paste, which when dissolved in chloroform and an infrared spectrum taken, again gave evidence for triphenylmethane along with a weak carbonyl band showing up at 5.75 microns.

(b) 3-Bromo-3-methyl-2-butanone (5.4 g.- 0.03 m.) was mixed with 110 mls. of 0.29 normal triphenylmethyl sodium in anhydrous ether and allowed to stir overnight at room temperature. The reaction mixture was then transferred to a single-necked, 500-ml. flask, and one gram of hydroquinone added. The ether was removed _in vacuo_ , and the pasty mass which remained, was distilled at atmospheric pressure. A small amount of an orange-coloured liquid was obtained up to 90°C., after which no more material could be obtained and decomposition occurred. An infrared spectrum of the orange liquid gave evidence of a carbonyl compound with a band showing at 5.75 microns. No infrared evidence for an alpha-beta-unsaturated carbonyl compound was observed. Bromine water was not decolourized by the orange distillate.

(c) 3-Bromo-3-methyl-2-butanone (10.0 g.- 0.06 m.) was dissolved in 100 mls. of anhydrous ether and 257 mls. of triphenylmethyl sodium (0.237 normal) added. The mixture again decolourized immediately and was allowed to stir at room temperature for two hours whereupon a colloidal precipitate was observed . The mixture was then refluxed for five hours and the fine orange precipitate allowed to settle out. Analysis of the solid which separated out from the reaction mixture showed the absence of halogen.

The clear orange etherial layer was separated with the aid of a centrifuge and the ether removed, leaving an orange pasty mass . This pasty mass was then flash distilled under reduced pressure whereupon about 5 cc. of clear distillate was obtained. Upon standing in a stoppered flask for two hours, the clear distillate was observed to turn to a light violet colour. This light violet distillate was distilled under reduced pressure and three colourless fractions were collected at 85 mm. pressure.

I 38-40°C./85 mm.
II 72-74°C./85 mm.
III above 74 (to 90°C.)/85 mm.

The orange, gummy precipitate which remained after flash distillation was poured on ice and hydrochloric acid and extracted with petroleum ether and methylcyclohexane. The solvents were removed and crystallization from methylcyclohexane attempted. No identifiable material, except a small amount of triphenylmethane, was obtained.

(d) 3-Bromo-3-methyl-2-butanone (10.0 g.- 0.06 m.) was dissolved in 100 mls. anhydrous ether, cooled to 0°C., and 257 mls. of triphenylmethyl sodium (0.237 normal) added. The mixture again decolourized immediately from dark red to orange and was allowed to stir at room temperature for one hour. After refluxing for five hours, the solution was allowed to stand and a fine yellow precipitate settled out. The ether was decanted and removed on a solvent stripper whereupon an orange pasty mass remained. The orange pasty mass was then flash distilled under reduced pressure (2 mm.) at 150°C. The clear flash distillate was passed through a gas chromatograph and the mixture was found to contain four components. By the use of known compounds, the components were found to be: ether, methylα-bromoisopropyl ketone, methyl isopropyl ketone, and methyl isopropenyl ketone. The gas chromatogram showed equal amounts of methyl isopropyl ketone and methylα-bromoisopropyl ketone while the amount of methyl isopropenyl ketone was one third that of the previous two.

Reaction of 1-Bromo-1,1,3,3-tetraphenylacetone with Triphenylmethyl Sodium - 1-Bromo-1,1,3,3-tetraphenylacetone (4.4 g.-0.01 m.) was placed in 150 mls. of anhydrous ether in a three-necked flask which was equipped with a stirrer, water-cooled condensor, and a dropping funnel. The solution was cooled to 0°C. and 37.5 mls of triphenylmethyl sodium (0.267 normal) added rapidly. Immediate decolourization of the base was noticed and the reaction mixture allowed to stir at room temperature for four hours. When stirring was discontinued, a fine yellow precipitate settled out. The precipitate was filtered off, and the ether removed in vacuo leaving a yellow-orange pasty mass. The pasty mass was placed under reduced pressure overnight and 6.6 g. of a yellow crystalline product with a wide melting point range (75 - 115°C) was obtained. The yellow solid was taken up in 125 mls. of petroleum ether, 100 mls. of ether, and 50 mls. of chloroform and the total volume concentrated down to 100 mls. The solution was then passed through a chromatographic column which was packed with alumina. It was then washed through with a 2:1 mixture of petroleum ether and ether. Approximately 10-ml. fractions were taken and concentrated down on a steam bath. A yellow solid which melted at 85-105° was obtained from fractions number four to number eleven. A white solid which melted at 100-120°C. was obtained from fractions number twenty-one to number thirty-eight. Infrared spectra of the above two solids were inconclusive. The spectra seem to indicate a mixture of triphenylmethane, bromotetraphenylacetone and tetraphenylacetone. Further attempts at separation by using a more polar effluent to wash the chromatographic column were met with little success.

All of the fractions were dissolved in glacial acetic acid, and fractional crystallization from glacial acetic acid-water attempted. Small amounts of white solids which melted at the following temperatures were obtained.

#1 fractional crystallization	m.p. 144-149°C.
#2 fractional crystallization	m.p. 131-133°C.
#3 fractional crystallization	m.p. 110-115°C.

Several attempts which involved changing reaction temperatures and periods of reflux of the original reaction mixture were tried with no noticeable change in results. The reaction was attempted using dioxane as a solvent which afforded a reflux temperature of 101°C. The results were comparable to all other attempts. A complete separation of the products of the reaction of bromotetraphenylacetone with triphenylmethyl sodium could not be obtained.

Reaction of Dimsylsodium with 3-Bromo-3-methyl-2-butanone - 3-Bromo-3-methyl-2-butanone (10.0 g.- 0.06 m.) was placed in a three-necked flask which was equipped with a stirrer, water-cooled condensor, and a dropping funnel. Dry dimethylsulfoxide (50 mls.) was added and the solution cooled to 0°C. To the cold solution was added rapidly 34 mls. of dimsylsodium (1.8 normal). The reaction mixture was allowed to come to room temperature whereupon it turned to a dark red color from the original grey. The mixture was stirred overnight, then poured over ice and water, and extracted with ether. The ether layer was dried over anhydrous sodium sulfate, and the solvent removed *in vacuo* . The liquid which remained was distilled under reduced pressure and three fractions were taken at 79 mm. pressure.

#1	57°C.	refractive index	1.4334
#2	62-73°C.	refractive index	1.4323
#3	76-78°C.	refractive index	1.4425

A sample of the above liquid before distillation was passed through the gas chromatograph. No clear separation into single components could be obtained. The small amount of dimethylsulfoxide which remained was apparently too polar and thus remained on the column for a long period of time. The refractive indices of the above three fractions are not comparable to those of fractions taken when triphenylmethyl sodium was used in place of dimsylsodium.

Reaction of 1-Bromo-1,1,3,3-tetraphenylacetone with Dimsylsodium

1-Bromo-1,1,3,3-tetraphenylacetone (4.4 g.- 0.01 m.) was placed in 50 mls. of dry dimethylsulfoxide in a three-necked flask which was equipped with a stirrer, water-cooled condensor, and dropping funnel. The solution was cooled to 0°C., and 7 mls. of dimsylsodium (1.6 normal) in 20 mls. of dry dimethylsulfoxide was added rapidly while being stirred. The reaction mixture, which turned dark brown immediately, was refluxed overnight. It was then poured on ice and water, and the light-brown oil was extracted with ether. The ether was removed leaving an oil which was crystallized from chloroform and petroleum ether. A very small amount of light-brown precipitate which melted at 105-110°C. was obtained. The infrared spectrum of this material was comparable to that of the starting bromoketone.

PART II

A NEW SYNTHESIS OF TRIARYLMETHYL AND BENZHYDRYL ALKYL ETHERS

CHAPTER I

INTRODUCTION

The synthesis of ethers has been well established in the literature. Numerous methods have been cited and, of course, some are advantages for one type of ether (e.g. aromatic) while others are more suitable for other types. Perhaps the Williamson synthesis is the most commonly used for the preparation of symmetrical and unsymmetrical aliphatic ethers. The method consists in coupling alkyl halides with sodium alkoxides as shown in Figure 1.

$$\mathrm{RONa} + \mathrm{R'X} \longrightarrow \mathrm{ROR'} + \mathrm{NaX}$$

R = aliphatic or aromatic

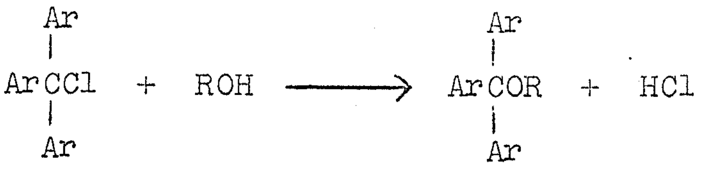
R' = aliphatic (1° or 2°)

Fig. 1. The Williamson synthesis.

Since the reaction is not reversible, it may be used to prepare mixed ethers as well as simple ethers. This synthesis is important also because it affords synthetic proof of the structure of ethers. Since an alkyl group has replaced the sodium of an alkoxide made by replacing the hydrogen of the hydroxyl group of an alcohol by sodium, an ether must have two alkyl or aryl groups combined with oxygen.

The synthesis of alkyl phenyl ethers may be carried out similarily when aqueous or alcoholic solutions of alkali phenolates are reacted with alkyl halides, but the yields in general are low.[1] However, the reactive halide in the benzyl halides is readily replaced by an alkoxyl group with yields as high as 95%.[2]

Triarylmethyl chlorides react with alcohols to form ethers according to the following reaction scheme (Fig. 2.). Nixon and Brauch[3] studied the kinetics of alcoholysis of triarylmethyl chlorides and found the reaction to be first order with respect to the trityl chloride and independent of the concentrations of hydrochloric acid and trityl ether. Either scheme (1) or (2) following can be used in consistency with the kinetic data.



$$\mathrm{Ar}\overset{\mathrm{Ar}}{\underset{\mathrm{Ar}}{\mathrm{C}}}\mathrm{Cl} + \mathrm{ROH} \longrightarrow \mathrm{Ar}\overset{\mathrm{Ar}}{\underset{\mathrm{Ar}}{\mathrm{C}}}\mathrm{OR} + \mathrm{HCl}$$

Fig. 2. Reaction of triarylmethyl chlorides with alcohols.

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[1] A. Vogel, *J. Chem. Soc.*, 616 (1948).

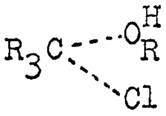
[2] T. Emmerson *et al.*, *J. Am. Chem. Soc.*, *69*, 1905 (1947).

[3] A.C. Nixon and G.K. Brauch, *J. Am. Chem. Soc.*, *58*, 492 (1936).

$$\mathrm{RCl} \overset{\text{slow}}{\rightleftharpoons} \mathrm{R^{+}} + \mathrm{Cl^{-}}$$

$$\mathrm{R^{+}} + \mathrm{R'OH} \xrightarrow{\text{fast}} \mathrm{ROR'} + \mathrm{H^{+}} \qquad (1)$$

$$\mathrm{RCl} + \mathrm{R'OH} \longrightarrow \mathrm{ROR'} + \mathrm{HCl} \qquad (2)$$

Scheme (2) represents all mechanisms in which the removal of chloride ion is assisted by the combination of an unshared electron pair of the alcohol, as for instance the formation of the transition compound  $\mathrm{R_3C}\cdots\overset{\mathrm{H}}{\mathrm{O}}\mathrm{R}\cdots\mathrm{Cl}$ with absorption of energy followed by rapid loss of hydrochloric acid. Scheme (2) implies a bimolecular reaction, but since, in their experiments, the alcohol concentration was so large with respect to the trityl chloride, a pseudo-unimolecular reaction was observed.

Substituted diaryl ethers may be prepared (Ullmann reaction) by the treatment of alkali phenoxides with aryl halides in the presence of a copper catalyst.[4,5] Further studies have shown that the yield of ether varies considerable with different copper-catalyst preparations.[6] Aromatic diethers such as 2-methoxydiphenyl ether have been prepared by the Ullmann procedure.[7]

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[4] P. Ullmann and F. Sponagel, Ann., 350, 83 (1906).

[5] C.M. Suter and F. Green, J. Am. Chem. Soc., 59, 2578 (1937).

[6] R.Q. Brewster, Org. Syntheses, Coll. Vol. II, 445 (1943). (1943).

[7] H. Ungnade and A. Orwoll, Org. Syntheses, 26, 50 (1946).

Allylic chlorides, e.g., allyl, methallyl, crotyl, and cinnamyl, are very reactive and are employed in the synthesis of unsaturated ethers.[8] Besides the usual coupling of the sodium alcoholate and halide in alcohol solutions, other conditions have been described which included the reaction of the alcohol and unsaturated halide in the presence of potassium carbonate or sodium hydroxide in acetone or water. The combination of potassium carbonate and acetone is widely used in the preparation of allyl aryl ethers, and Smith <u>et al.</u>[9] have reported that the addition of finely powdered potassium iodide not only facilitated the reaction, but resulted in greatly increased yields.

Several other examples of alkylation of hydroxy compounds by halogen compounds, e.g., preparation of haloethers, preparation of aromatic and aliphatic amino ethers or cyano ethers, have been reported in the literature.[10,11,12]

Ethers may also be prepared by the alkylation of hydroxy compounds by alkyl sulfates, sulfites or sulfonates according to the following reaction scheme (Fig. 3.).

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[8] C. Olson <u>et al</u>., <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>., <u>69</u>, 2451 (1947).

[9] L. Smith, H. Hoehn, and A. Whitney, <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>., <u>62</u>, 1863 (1940).

[10] N.L. Drake <u>et al</u>., <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>., <u>68</u>, 1536 (1946).

[11] H.H. Richmond and G. Wright, <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>., <u>67</u>, 2272 (1945).

[12] H.B. Hass and M.L. Bender, <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>., <u>71</u>, 1767 (1949).

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

Fig. 3. Alkylation of hydroxy compounds by alkyl sulfates.

Mixed aliphatic ethers containing methyl or ethyl radicals can be synthesized from the corresponding alkyl sulfate and magnesium alcoholates[13] e.g., methyl n-butyl ether, methyl cyclohexyl ether, and methyl isoamyl ether (70-78%). The method finds more general use in the alkylation of phenols. Dimethyl sulfate has also been reacted with allylic alcohols in the presence of sodium amide to produce the corresponding unsaturated ethers in 60% yield as shown in Figure 4.[14]

$$2RCH = CH - CH_2OH + (CH_3)_2SO_4 \longrightarrow 2RCH = CHCH_2OCH_3 + Na_2SO_4$$

Fig. 4. Reaction of dimethyl sulfate with allylic alcohols.

Many other groups such as hydroxy, methoxy, cyano, or halogen may be present in the alcohol or phenol during alkylations involving dimethyl sulfate. Swallen, Boord and Paul[15,16] have reported the preparation of chloro ethers from the treatment of chlorohydrins with dimethyl sulfate as shown in

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[13] B. Gredy, Bull. soc. chim., France, (5), 3, 1093 (1936).

[14] V. Cherchez, Bull. soc. chim., 43, 762 (1928).

[15] L.C. Swallen and C.E. Boord, J. Am. Chem. Soc., 52, 651 (1930).

[16] R. Paul, Bull. soc. chim., France, (10), 18, 315 (1932).

Figure 5.

$$(CH_3)_2SO_4 + 2ClCH_2CH_2OH \longrightarrow 2ClCH_2CH_2OCH_3 + Na_2SO_4$$

Fig. 5. Reaction of dimethyl sulfate with chlorohydrin.

Natelson and Gottfried[17] later reported the preparation of halo ethers from the action of dimethyl sulfate on halogenated phenols, e.g. m-bromo-anisole (91%). Alkylation by alkyl sulfates has also been used to successfully convert phenolic aldehydes to alkoxy aldehydes[18,19] (Fig. 6.).

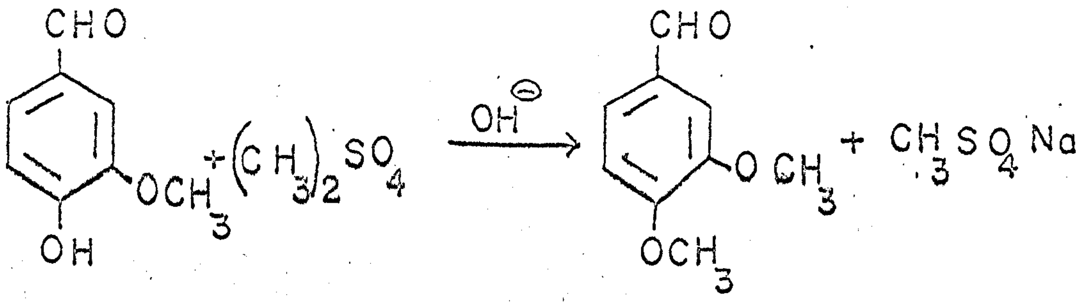

Fig. 6. Alkylation of phenolic aldehydes to alkoxy aldehydes.

Bernstein and Wallis[20] have illustrated the conversion of a phenolic ketone to an alkoxy ketone by the treatment of *p*-

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[17] S. Natelson and S. Gottfried, *J. Am. Chem. Soc.*, *61*, 1001 (1939).

[18] R.N. Icke, *Org. Syntheses*, *29*, 63 (1949).

[19] J.S. Buck, *Org. Syntheses*, *Coll. Vol. II*, 619 (1943).

[20] S. Bernstein and E. Wallis, *J. Am. Chem. Soc.*, *62*, 2872 (1940).

hydroxypropiophenone with dimethyl sulfate to give p-methoxypropiophenone (88%). Phenolic acids, esters, cyanides, and nitrophenols respond favourably to this method of methylation. Reeve and Christoffel[21] have reported the methylation of the sodium salt of mandelic acid according to the following scheme: (Fig. 7.).

$$C_6H_5CHOH\ COO^- Na^+ + (CH_3)_2SO_4 \longrightarrow \underset{42\%}{C_6H_5CH\ (OCH_3)\ COOH}$$

Fig. 7. Methylation of mandelic acid.

The dehydration of alcohols under acidic conditions is used as a general method of preparation of symmetrical aliphatic ethers (C_4 - C_{16}) (Fig. 8.).

$$2ROH \xrightarrow{H^+} ROR + H_2O$$

Fig. 8. Dehydration of alchols to form ethers.

When secondary or tertiary alcohols are used, reaction temperatures must be kept low to avoid olefin formation. However, Norris and Rigby[22] have shown that this method has special advantages in the preparation of mixed ethers containing

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

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

t-butyl and primary alkyl radicals. For example, t-butyl alcohol, when slowly added to a boiling mixture of ethanol and 15% aqueous sulfuric acid gives a 95% yield of t-butyl ethyl ether. Prolonged contact of the tertiary alcohol with the mineral acid must be avoided in order to minimize the amount of olefin formation. However, the method has little, if any, applicability in the preparation of aromatic ethers.

The interaction of Grignard reagents with halo ethers is commonly used to prepare branched ethers according to the following reaction scheme (Fig. 9.).

$$RCHClOCH_3 + R'MgX \longrightarrow RCHR'OCH_3$$

Fig. 9. Interaction of Grignard reagents with α-haloethers.

The ease of reaction of the reactive halogen atom with Grignard reagents has proven to be very useful in the preparation of some benzhydryl alkyl ethers. Unfortunately, the method has been studied more extensively only in the aliphatic series. Gredy[23] has reported that if ethers without branching on the alpha carbon atom are desired, chloromethyl ether must be made from n-butyl magnesium bromide and chloromethyl ether.

The reaction of Grignard reagents with alpha-beta dibromo ethers to form beta-bromo ethers has been developed by Boord[24]

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[23] B. Gredy, Bull. soc. chim. France, (5), 3, 1094 (1936).

[24] C.E. Boord et al., J. Am. Chem. Soc., 52, 651 3396, (1930).

and others[25,26] as the third step in the Boord synthesis of olefins. The bromine atom in the beta-position is unreactive and hence one can obtain beta-halo ethers by this method. The products from the above reaction may be put through a second process of dehydrobomination, bromination, and coupling to give more highly branched beta-bromo ethers as shown in Figure 10.

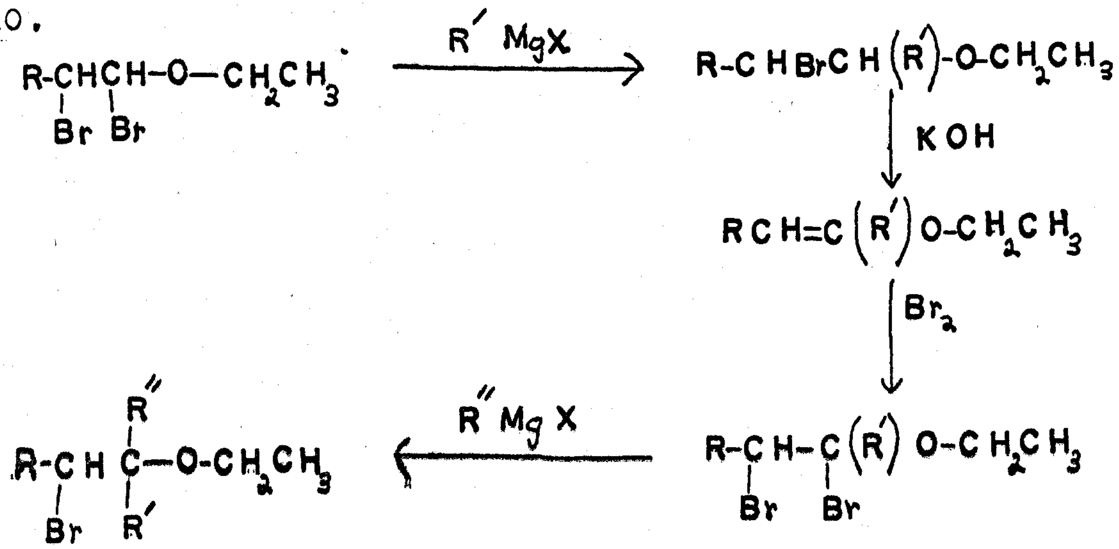

Fig. 10. Formation of branched beta-bromo ethers.

In general, primary alkylmagnesium halides give better yields than the secondary derivatives, and the tertiary Grignard reagents do not react with the alpha-beta dibromo alkyl ethers. Bossert and Brode[27] have shown that allyl and phenyl magnesium

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[25] M. Sherrill and G. Walter, J. Am. Chem. Soc., 58, 742 (1936).

[26] F. Soday and C.E. Boord, ibid, 55, 3293 (1933).

[27] R.G. Bossert and W. Brode, J. Am. Chem. Soc., 56, 165 (1934).

halides respond favourably when treated with similar dibromo ethers.

It is noteworthy, at this point, that the vast majority of the methods previously discussed for the synthesis of ethers has been applicable only to symmetrical and unsymmetrical aliphatic ethers. A survey of the literature would lead one to believe that aromatic ethers are not as well exploited. In general, aromatic trityl and benzhydryl alkyl ethers are more difficult to prepare. The Williamson synthesis is used for the preparation of compounds of this type, but in some cases the yields leave something to be desired. Also, the reaction conditions are sometimes very severe.

Although methods for the synthesis of ethers of all types are very well established, this does not preclude the search for newer methods in light of both theoretical and economic considerations.

CHAPTER II

DISCUSSION OF EXPERIMENTAL RESULTS

In the course of research on the elimination of the triphenylmethoxy group from 2-triphenylmethoxy-1-chloroethane $(C_6H_5)_3\ C\text{-}O\text{-}CH_2CH_2Cl$ using a solution of potassium iodide (excess) in acetone according to the equation illustrated by Figure 11, it was found that the addition of methanol had

$$(C_6H_5)_3C\text{-}O\text{-}CH_2CH_2Cl \xrightarrow[\text{acetone}]{\text{KI (XS)}} (C_6H_5)_3C\text{-}OH + CH_2 = CH_2 + K$$

Fig. 11. Reaction of 2-triphenylmethoxy-1-chloroethane with potassium iodide.

an outstanding effect on the main products of the reaction. Thus triphenylmethoxy methane was obtained instead of the expected triphenylcarbinol (Fig. 12.). Speculation that the triphenylmethyl methyl ether could have arisen from an iodide

$$(C_6H_5)_3C\text{-}O\text{-}CH_2CH_2Cl \xrightarrow[\substack{\text{acetone}\\ \text{methanol}}]{\text{KI (XS)}} (C_6H_5)_3C\text{-}O\text{-}CH_3 + CH_2 = CH_2 + KCl$$

Fig. 12. Reaction of 2-triphenylmethoxy-1-chloroethane with potassium iodide in acetone-methanol solution.

ion catalysed reaction of triphenylcarbinol (the normal product) with methanol was shown erroneous since an authentic sample of triphenylcarbinol was recovered unchanged under such reaction conditions. It was found, however, that triphenylcarbinol underwent facile conversion to the methyl ether when a methanolic solution was allowed to stand at room temperature in the presence of iodine. Titrimetic procedures which involve the use of sodium thiosulfate indicated that the iodine was a true catalyst in the reaction. It was also shown that iodine was liberated in the elimination reaction illustrated in Figure 11 undoubtedly as a result of the following sequence of events (Fig. 13.).

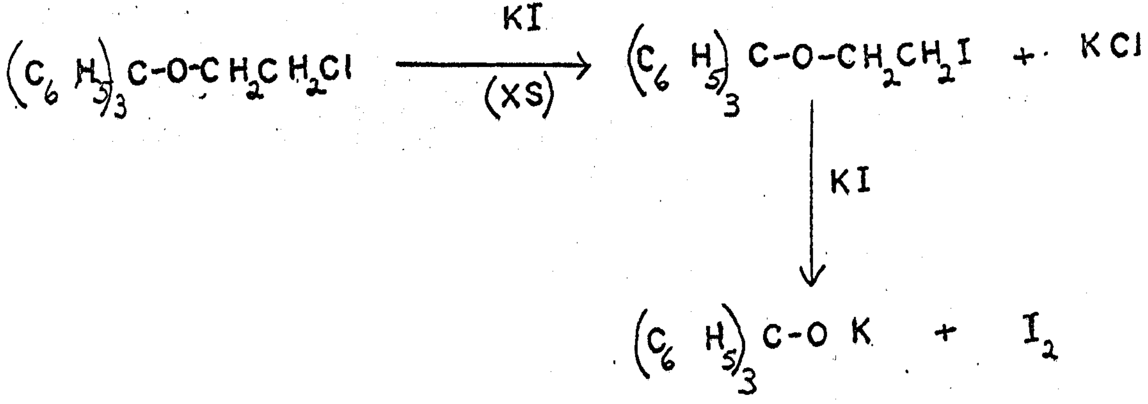


Fig. 13. Reaction of 2-triphenylmethoxy-1-chloroethane with excess potassium iodide.

The final conversion of the potassium salt to the methyl ether probably involved the initial well known equilibrium of an alkoxide salt with halogen (iodine in this case) to yield the triphenylmethoxy hypoiodite. Subsequent ionization of the hypoiodite followed by recombination of the carbonium ion with methanol then completes the sequence (Fig. 14.).

(1) $(C_6H_5)_3C\text{-}OK + I_2 \rightleftharpoons (C_6H_5)_3C\text{-}OI + KI$

(2) $(C_6H_5)_3C\text{-}OI \rightleftharpoons (C_6H_5)_3C^+ + OI^-$

(3) $(C_6H_5)_3C^+ + CH_3OH \longrightarrow (C_6H_5)_3C\text{-}OCH_3 + H^+$

(4) $HOI + KI \rightleftharpoons KOH + I_2$

Fig. 14. Conversion of alkoxide salt to methyl ether.

An analogous course of reaction can be applied to the conversion of triphenylcarbinol to the methyl ether (Fig. 15.).

(1) $(C_6H_5)_3COH + I_2 \rightleftharpoons (C_6H_5)_3C\text{-}OI + HI$

(2) $(C_6H_5)_3C\text{-}OI \rightleftharpoons (C_6H_5)_3C^+ + OI^-$

(3) $(C_6H_5)_3C^+ + CH_3OH \longrightarrow (C_6H_5)_3C\text{-}OCH_3 + H^+$

(4) $H^+ + OI^- \rightleftharpoons HOI$

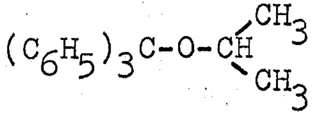
(5) $HI + HOI \rightleftharpoons H_2O + I_2$

Fig. 15. Conversion of triphenylcarbinol to the methyl ether.

Although the proposed mechanism is still under investigation in this laboratory using optically active systems, this sequence of events explains the catalytic activity of iodine. Reaction (2) in Figure 15 would be the controlling step in the sequence since it would be predicted that only those organic alcohols which form stable carbonium ions should be susceptible to ether formation under the mild conditions employed. Indeed, this investigation thus far reveals that at room temperature only trityl carbinol and benzhydrol are amenable to this new ether synthesis. Benzyl alcohol appears (at least under normal conditions) to yield only starting material although cinnamyl alcohol has been converted to the methyl ether. Undoubtedly trityl, benzhydryl and benzyl alcohols which are substituted with electron donating groups will also be converted to ethers by this procedure.

Table 1 summarizes those ethers prepared thus far by this new method.

TABLE I

Ether	Reported m.p.	Observed m.p.	Yield
$(C_6H_5)_3C\text{-}OCH_3$	69-71°	69-71°	91%
$(C_6H_5)_3C\text{-}O\text{-}CH_2CH_3$	83	74-76	93
$(C_6H_5)_3C\text{-}O\text{-}CH_2CH_2CH_3$	56	55	67
 $(C_6H_5)_3C\text{-}O\text{-}CH\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$	111-113	108-110	50
$(C_6H_5)_3C\text{-}O\text{-}CH_2\text{-}C_6H_5$	106-107	102-104	50
$(C_6H_5)_2C\text{-}O\text{-}CH_3$	B.P. 147-148	B.P. 146-148	70
$(C_6H_5)_2CH\text{-}OCH_2CH_3$	B.P. 160-161	B.P. 157-159	52
$(C_6H_5)_2CH\text{-}O\text{-}CH_2CH_2CH_3$	B.P. 161	B.P. 160-162	41.6
$(C_6H_5)\text{-}CH{=}CH\text{-}CH_2\text{-}OCH_3$	B.P. 101-102.5	B.P. 101-103	55

As can be seen from Table 1, triphenylmethyl and ethyl ethers were prepared in over 90% yields, while the yields of the higher aliphatic series decreased as the number of carbon atoms in the aliphatic alcohol increased. It was also noticed that primary aliphatic alcohols gave the best yields of the triaryl ether. The results with the benzhydryl system were somewhat analogous to the triaryl system, except that the yields in general were lower. The yields of both systems compared quite favourably with those in which other methods were employed, and in some cases, were higher. This method was also extended to an alpha-beta unsaturated alcohol (cinnamyl), where a 46% yield of cinnamyl methyl ether was obtained when cinnamyl alcohol was treated with iodine and methanol in acetone for a period of three hours. Extension of the reaction time had little or no effect on the yields.

It is interesting to note that the well known iodine dehydration of tertiary alcohols yields products which appear to result from initial carbonium ion formation. Thus, Bailey[1] reports that dehydration of 1-methylcyclohexanol with iodine yields 1-methylcyclohexene almost to the total exclusion of methylenecyclohexane. Cardew and Burwell Jr.[2] report that <u>trans</u>-1,2-dimethylcyclohexanol gives 1,2-dimethylcyclohexene in 73% yield along with 2,3-dimethylcyclohexene (24%) and 2-methyl-methylenecyclohexane (30%) whereas Hammond and DePuy[3]

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[1] W.J. Bailey and W.F. Hale, J. Am. Chem. Soc., 81, 647 (1959).

[2] M. Cardew and R.L. Burwell Jr., J. Am. Chem. Soc., 82, 6289 (1960).

[3] D.H. Froemsdorf, C.H. Collins, G.S. Hammond, and C.H. DePuy, J. Am. Chem. Soc., 81, 643 (1959).

report that pyrolysis of the corresponding acetate yields only 2,3-dimethylcyclohexene (45%) and 2-methyl-methylenecyclohexane (55%). No 1,2-dimethylcyclohexene is obtained from this kinetically controlled process. The reports are numerous in the literature on other alcohol systems which have been subjected to iodine dehydration. Invariably the Saytzeff Rule is followed, hence the conclusion that a carbonium ion as a precursor is evident in all cases. Future research plans include an investigation of methanolic iodine dehydration of many of these previously reported systems in an attempt to capture the intermediate carbonium ion as the methyl ether. Whether this "interceptor reaction" will be successful will depend on the relative rates of proton loss of the carbonium ion (leading to olefin formation) and its reaction with methanol to form the ether.

CHAPTER III

EXPERIMENTAL

Triphenylmethyl methyl ether - Triphenylcarbinol, (5.0 g. - 0.019 m.), iodine, (5.07 g. - 0.019 m.), methyl alcohol, (20 ml.) and 80 ml. of reagent grade acetone were placed in a dry 300-ml. Erlenmeyer flask and allowed to stand for three hours. The reaction mixture was then poured over a mixture of cracked ice, water and an excess of sodium thiosulfate. Decolourization of the iodine occurred simultaneously with the formation of a whitish-yellow precipitate. The removal of the acetone by air evaporation aided in the formation of an additional amount of the whitish-yellow precipitate. The solid was removed by filtration and taken up in petroleum ether. Upon evaporation of the petroleum ether, 5.0 g. of crude triphenylmethyl methyl ether was obtained. Recrystallization from petroleum ether afforded 4.7 g. of triphenylmethyl methyl ether (91%), m.p. 73-75°, reported (80-81°).[1]

Note: Reaction periods longer than three hours resulted in more tars when the reaction mixture was poured over ice and sodium thiosulfate. Also, the yields of ethers could not be increased by increasing the temperature of the reaction mixture.

Triphenylmethyl ethyl ether - Triphenylcarbinol, (5.0 g. - 0.019 m.), iodine, (5.07 g. - 0.019 m.), ethyl alcohol (redis-

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

tilled), (20 ml.) and 80 ml. of reagent grade acetone were placed in a dry 300-ml. Erlenmeyer flask and allowed to stand for three hours. The reaction mixture was then poured over a mixture of cracked ice, water, and sodium thiosulfate. Decolourization of the iodine occurred immediately simultaneous with the formation of a light-yellow precipitate. The removal of the acetone by air evaporation resulted in an additional amount of light-yellow precipitate. The precipitate was separated by filtration and dissolved in an excess of petroleum ether. Upon evaporation of the petroleum ether, 5.1 g. of crude triphenylmethyl ethyl ether was obtained. Recrystallization from a minimal amount of petroleum ether afforded 4.8 g. of triphenylmethyl ethyl ether (93%), m.p. 74-76°, reported (m.p. 83°).[2]

Triphenylmethyl n-propyl ether - Triphenylcarbinol, (5.0 g. - 0.019 m.), iodine, (5.07 g. - 0.019 m.), redistilled n-propyl alcohol, (20 ml.), and 80 ml. of reagent grade acetone were placed in a dry 300-ml. Erlenmeyer flask and allowed to stand for a period of three hours. The reaction mixture was then poured over a mixture of cracked ice, water, and sodium thiosulfate. The acetone was removed by air evaporation and the white precipitate extracted with an excess of petroleum ether. Upon evaporation of the petroleum ether, white crystals of

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

triphenylmethyl n-propyl ether separated out from the solvent. The crude yield of the desired ether was 4.2 g. Recrystallization from petroleum ether afforded 3.8 g. (67%) of the triphenylmethyl n-propyl ether, m.p. 53-54°, (reported m.p. 56°).[3]

Triphenylmethyl isopropyl ether - Triphenylcarbinol, (5.0 g. - 0.019 m.), iodine, (5.07 g. - 0.019 m.), redistilled isopropyl alcohol, (20 ml.), and 80 ml. of reagent grade acetone were placed in a 300-ml. Erlenmeyer flask and allowed to stand for a period of three hours. The reaction mixture was poured on a mixture of cracked ice, water, and sodium thiosulfate. The resultant white solid was filtered and dissolved in petroleum ether. Removal of the acetone from the water layer resulted in a small amount of light-yellow precipitate which was also dissolved in petroleum ether and combined with the first extract. Upon evaporation of the petroleum ether, 3.0 g. of white triphenylmethyl isopropyl ether was obtained. Recrystallization from petroleum ether afforded 2.7 g. of triphenylmethyl isopropyl ether (45%), m.p. 111-112°, (reported 111-113°).[4]

Triphenylmethyl benzyl ether - Triphenylcarbinol, (5.0 g. -

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

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

0.019 m.), benzyl alcohol, (20 ml.), iodine, (5.07 g. - 0.019 m.), and 80 ml. of reagent grade acetone were placed in a dry 300-ml. Erlenmeyer flask and allowed to stand at room temperature for a period of three hours. The reaction mixture was poured over a mixture of cracked ice, water, and sodium thiosulfate. The resultant white solid was extracted with petroleum ether and the water layer separated. The acetone was removed from the water layer by air evaporation and the resultant small amount of solid was taken up in petroleum ether and added to the original extract. Evaporation of the petroleum ether yielded 3.6 g. of crude triphenylmethyl benzyl ether. Recrystallization afforded 3.3 g. of the desired ether, m.p. 102-104°, (reported m.p. 106-107°).[5]

Benzylhydryl methyl ether - Diphenylcarbinol, (10.0 g. - 0.054 m.), iodine, (13.7 g. - 0.054 m.), methyl alcohol, (25 ml.), and 90 ml. of reagent grade acetone were placed in a 300-ml. Erlenmeyer flask and allowed to stand for a period of three hours. The reaction mixture was poured over a mixture of cracked ice, water, and sodium thiosulfate. The acetone was removed by air evaporation and the organic material extracted with petroleum ether. The petroleum ether solution was decolourized with Norit (decolourizing charcoal) and the solvent removed *in vacuo*. The benzhydryl methyl ether was distilled

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[5] G.L. Stadnikov, *Ber.*, *57*, 6 (1924).

under reduced pressure and a yield of 7.1 g. or 70% was obtained, which boiled at 146-148° at 17 mm. pressure. The reported boiling point and refractive index are: (b.p. 147-148° at 17 mm.), η=1.5653. The observed refractive index was 1.5648.[6]

<u>Benzhydryl ethyl ether</u> - Diphenylcarbinol, (10.0 g. - 0.054 m.), iodine, (13.7 g. - 0.054 m.), redistilled ethyl alcohol, (25 ml.), and 90 ml. of reagent grade acetone were placed in a dry 300-ml. Erlenmeyer flask and allowed to stand at room temperature for a period of three hours. The reaction mixture was poured over a mixture of cracked ice, water and sodium thiosulfate. The acetone was removed by air evaporation and the crude organic material extracted with petroleum ether. The petroleum ether solution was separated and decolourized with Norit. The solvent was removed *in vacuo* and the benzhydryl ethyl ether distilled under reduced pressure. The yield of the desired ether was 6.0 g. (52%), b.p. 158-160° at 19 mm. pressure. Reported (b.p. 160-161° at 19 mm. pressure), index of refraction 1.5544, observed index of refraction 1.5540.[7]

<u>Benzhydryl n-propyl ether</u> - Diphenylcarbinol, (10.0 g. -

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[6] E. Bergmann & J. Hervey *Ber.* *62*, 893 (1929).

[7] V. Meyer, *J. prakt. Chem.* (2) *82*, 540.

0.054 m.), iodine, (13.7 g. - 0.054 m.), redistilled n-propyl alcohol, (30 ml.), and 90 ml. of reagent grade acetone were placed in a dry 300-ml. Erlenmeyer flask and allowed to stand at room temperature for a period of three hours. The reaction mixture was poured over a mixture of cracked ice, water and sodium thiosulfate. The acetone was allowed to evaporate and the organic material extracted with petroleum ether. The petroleum ether solution was then decolourized with Norit and the solvent removed *in vacuo*. The benzhydryl n-propyl ether was distilled under reduced pressure, the fraction taken which boiled at 160-161° at 11 mm. pressure. The yield was 5.2 g. or (42%). Reported (b.p. 161° at 11 mm. pressure).[8]

Cinnamyl methyl ether - Cinnamyl alcohol (10.0 g. - 0.075 m.), iodine, (19 g. - 0.075 m.), methyl alcohol (25 ml.), and 90 ml. of reagent grade acetone were placed in a 300-ml. Erlenmeyer flask and allowed to stand at room temperature for a period of three hours. The reaction mixture was poured over a mixture of cracked ice, water, and sodium thiosulfate and the acetone removed by air evaporation. The organic material was extracted with petroleum ether and decolourized with Norit. The petroleum ether was removed *in vacuo* and the liquid which remained distilled under reduced pressure. The yield of cinnamyl methyl ether was 6.0 g. (55%), b.p. 100-103° at 11 mm. pressure.

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[8] G.L. Stadnikow, *J. prakt. Chem.* (2) *88*, 7.

Reported (b.p. 101-102.5° at 11 mm. pressure).[9] The refractive index was 1.5451, (reported 1.5452).

The reaction was repeated with the amount of methyl alcohol increased to 75 ml., but the yield of cinnamyl methyl ether remained unchanged.

Titration of Iodine

Triphenylcarbinol (2.0 g.), methyl alcohol (8 ml.) and 50 ml. of reagent grade acetone were placed in a 125-ml. Erlenmeyer flask which was fitted with a cork stopper. To this mixture was added 1.147 g. iodine (accurately weighed on an analytical balance) and the reaction mixture was allowed to stand for a period of three hours. The mixture was then titrated with 0.0449 normal freshly standardized sodium thiosulfate. The results below show the catalytic nature of iodine in the reaction.

number of equivalents thiosulfate used = 0.0449 x .1032 = 0.0046

therefore the number of equivalents iodine titrated = 0.0046

number of equivalents of iodine weighed out $\frac{1.147}{253.8}$

= 0.0045

The results of the titration are conclusive evidence that the iodine was not used up in the synthesis of the ethers.

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[9] Pschorr & Dickhauser, <u>Ber</u>., <u>44</u>, 2640.

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