

To
My Father

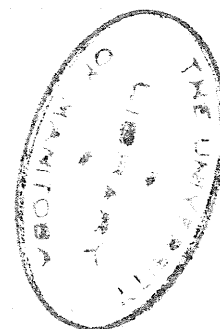
AN ISOTOPIC STUDY OF
THE REDUCING ACTION OF THE GRIGNARD REAGENT

by

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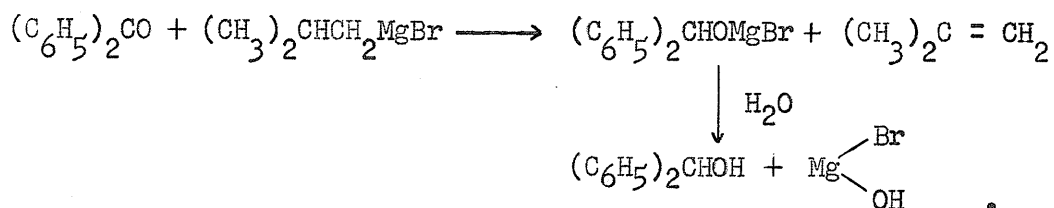
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An Isotopic Study of the Reducing Action of the Grignard Reagent

Submitted by John Warkentin.

Summary.

Benzophenone was reduced to benzhydrol by an excess of isobutyl-magnesium bromide according to the equation:



Separate samples of Grignard reagent, having some deuterium in the alpha, beta and gamma positions respectively, were used. The bromides and benzhydrols were analysed for deuterium, through their respective waters of combustion, by the gradient density tube method.

Only those benzhydrols produced by reduction of benzophenone with beta-deuterated Grignard reagent contained any deuterium, which indicates that beta hydrogen of the Grignard reagent is transferred in such a reaction. It was found that the transfer is about 2.1 times faster for protium than for deuterium.

The isotope effect accompanying the thermal decarboxylation of dimethylmalonic acid having some deuterium in its carboxyl groups was determined. The ratio $k_{\text{H}}/k_{\text{D}}$ was about 4.5.

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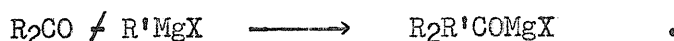
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INTRODUCTION

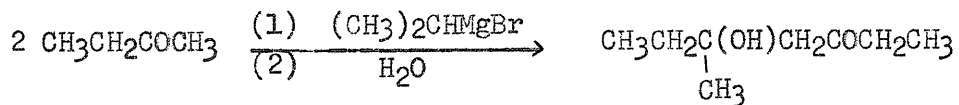
The Grignard reagent is one of the most useful reagents to the organic chemist for the synthesis of organic compounds because of its ability to add to the carbonyl group according to the general equation:



With certain specific Grignard reagents and carbonyl compounds this addition reaction may be accompanied by one or more of the following side reactions (24).

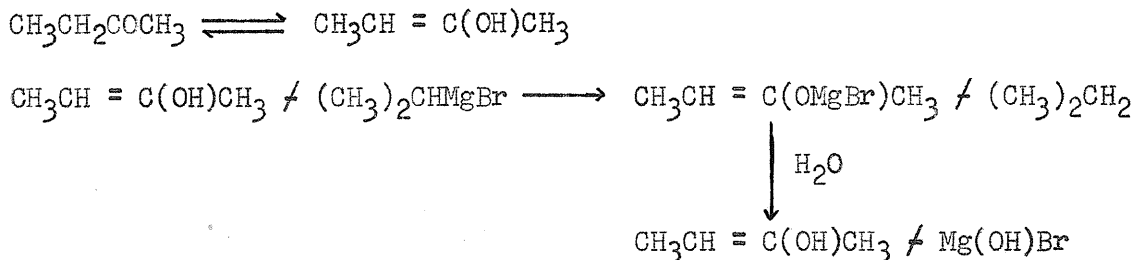
(a) Condensation:

In this reaction the Grignard reagent catalyses an aldol-type condensation between two molecules of ketone.



(b) Enolization:

In this case the Grignard reagent reacts with the enol form of the ketone to form the halo-magnesium salt, while the alkyl group of the Grignard reagent is converted to saturated hydrocarbon.

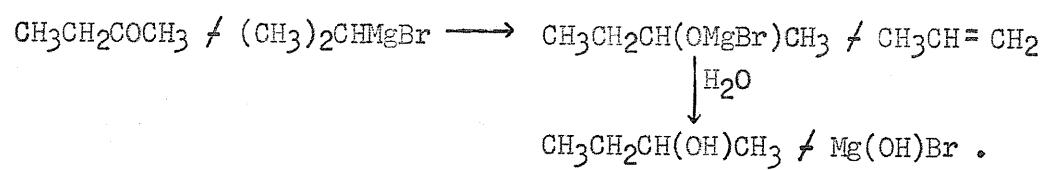


(c) Reduction:

The Grignard reagent reduces the ketone to the halo-magnesium salt of the corresponding secondary alcohol while the alkyl group of the

1.

Grignard reagent appears as unsaturated hydrocarbon.



HISTORICAL

The reducing action of the Grignard reagent was first observed by Grignard when he isolated benzyl alcohol as a product of the reaction of benzaldehyde with isoamyl Grignard reagent (11). Numerous instances of reduction by the Grignard reagent have been reported since that time and many attempts have been made to explain this reducing property. Most of these theories have been attempts to correlate the amount of reduction observed with the chemical structures of both the Grignard reagent and the carbonyl compound. Other theories have dealt with the mechanism of the reduction, including possible intermediate complexes and the mode of decomposition of, or attack on, these intermediates.

Some attempts at correlation of the amount of reduction obtained with chemical structure, and some postulated reduction mechanisms will be discussed briefly in the following pages. For an adequate review of the literature on the reducing action of the Grignard reagent the reader is referred to the recent surveys by Kharasch and Weinhouse (15) and by Kharasch and Rheinmuth (14).

Whitmore and George attempted to correlate the extent of reduction of a particular ketone with the steric conditions in the alkyl group of the Grignard reagent and with the number of substituents on its beta carbon atom (29). Diisopropyl ketone was reacted with several Grignard reagents to obtain the following results:

Grignard Reagent	% Addition	% Reduction	% Enolization
CH ₃ MgBr	95	0	0
CH ₃ CH ₂ MgBr	77	21	2
CH ₃ CH ₂ CH ₂ MgBr	36	60	2
(CH ₃) ₂ CH MgBr	0	65	29
(CH ₃) ₂ CH CH ₂ MgBr	8	78	11
(CH ₃) ₃ C CH ₂ MgCl	4	0	90

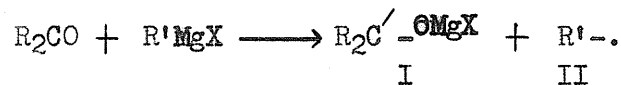
These results were interpreted in this way:

(1) The amount of addition to a particular ketone is determined by the steric conditions in the alkyl group of the Grignard reagent.

(2) The extent of reduction depends on the number and on the primary, secondary or tertiary nature of the beta hydrogen atoms of the Grignard reagent. At least one beta hydrogen atom in the Grignard reagent is necessary for reduction to occur.

Other investigators have never observed reduction of carbonyl compounds with Grignard reagents lacking beta hydrogen or with phenyl Grignard reagents. While beta hydrogen in the Grignard reagent is essential to its reducing activity, it is also generally necessary that the structures of either one of, or both, the reacting molecules be such as to provide specific steric hindrance to normal addition.

An early mechanism that was to account for the reducing action of the Grignard reagent involved the dissociation of the Grignard molecule into free radicals. Blicke and Powers (4) formulated the reaction of a Grignard reagent with a carbonyl compound as follows:



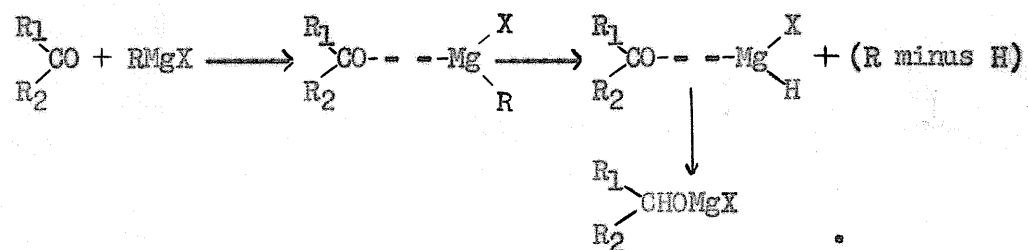
The free radicals I and II might:

- (1) unite to form, on hydrolysis, the normal addition compound,
- (2) undergo mutual oxidation-reduction with production of $R_2C(OMgX)H$ leading to secondary alcohol, and of olefin (R' minus H),
- (3) polymerize to dimolecular forms $R_2C(OMgX) - R_2C(OMgX)$ and $R' - R'$. The former of these two would yield a pinacol while the latter would appear as saturated hydrocarbon. In support of this mechanism Blicke and Powers cite the observation that triphenylmethylmagnesium chloride dissociates into free radicals and that it reduces benzophenone to benzopinacol (10).

Evidence that a pinacol and saturated hydrocarbon do not generally appear as products of the reduction of a carbonyl compound with a Grignard reagent was obtained by Noller, Grebe and Knox (22). These investigators showed that in the reduction of benzophenone with isobutylmagnesium bromide the only products obtained are benzhydrol and an equivalent amount of isobutylene containing only 0.1 percent of saturated hydrocarbon. The fact that no benzopinacol and only a negligible amount of saturated hydrocarbon were obtained indicates clearly that at least the reaction which they studied does not proceed by a free radical mechanism.

A different mechanism of reduction, involving dissociation of a complex between the Grignard reagent and the carbonyl compound prior to reduction of the carbonyl group, was advanced by Rheinboldt and Roleff (23). They reacted benzaldehyde with isobutylmagnesium bromide to obtain 58 percent of benzyl alcohol. However, when isovaleraldehyde was brought together with phenylmagnesium bromide no reduction of the aldehyde was observed. The different results in the two cases were explained by

postulating that "in the reactions of Grignard reagents with carbonyl compounds the organomagnesium halide attaches itself to the carbonyl oxygen in the manner of metallic salts". A halomagnesium hydride formed by the loss of olefin from the Grignard part of this complex was accredited with the reduction. This mechanism may be summarized in the equation:

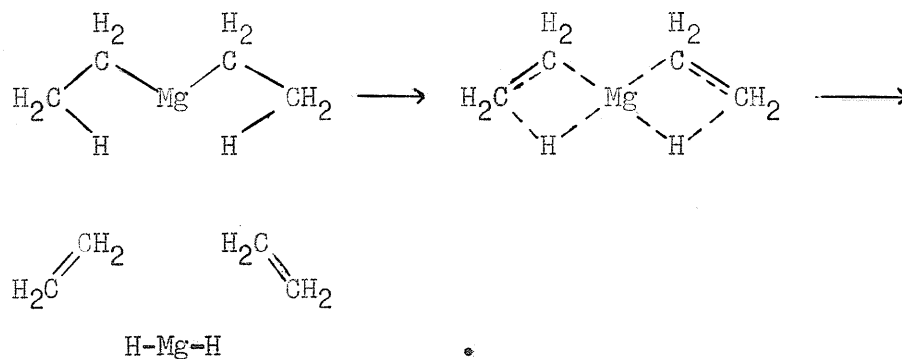


Phenyl Grignard reagents, therefore, could not reduce the carbonyl group because they could not dissociate into olefin and halomagnesium hydride.

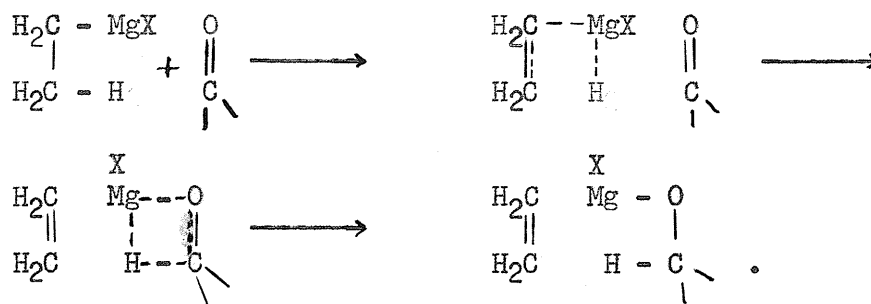
There is no other experimental evidence to indicate that halomagnesium hydrides can exist as components of complexes such as the one postulated by Rheinboldt and Roleff, but it has been shown by Noller and co-workers (22) that some intermediate other than the halomagnesium salt of the alcohol does exist after the loss of alkene from the reaction of a Grignard reagent with a carbonyl compound. These workers found that when isobutylmagnesium bromide and benzophenone react in n-butyl ether solution there is immediate evolution of isobutylene but no permanent precipitation of $(C_6H_5)_2 CHOMgBr$, even though the latter is soluble in n-butyl ether to the extent of only 0.006 g./ml. By adding solid $(C_6H_5)_2 CHOMgBr$ to the solution it was shown that supersaturation effects were absent. It was pointed out that although these observations indicate that a complex between carbonyl compound and halomagnesium hydride may

exist, they could also be explained if a soluble complex of $(C_6H_5)_2 CHOMgX$ with excess Grignard reagent is formed, or if the reduction product exists in the ether soluble form $[(C_6H_5)_2 CHO]_2 \cdot Mg$.

In a reduction mechanism recently advanced by Wiberg and Bauer (27) an analogy was drawn between the olefin loss in a Grignard reduction reaction and the pyrolytic loss of olefin from magnesium dialkyls or Grignard reagents. To explain the loss of ethylene from diethylmagnesium at $175^\circ C$. it was assumed that in the presence of suitable neighboring atoms like magnesium, carbon can form "hydrogen bonds". The formulation for diethylmagnesium then resembles that postulated for the boron hydrides and the loss of olefin on heating would go according to the scheme:



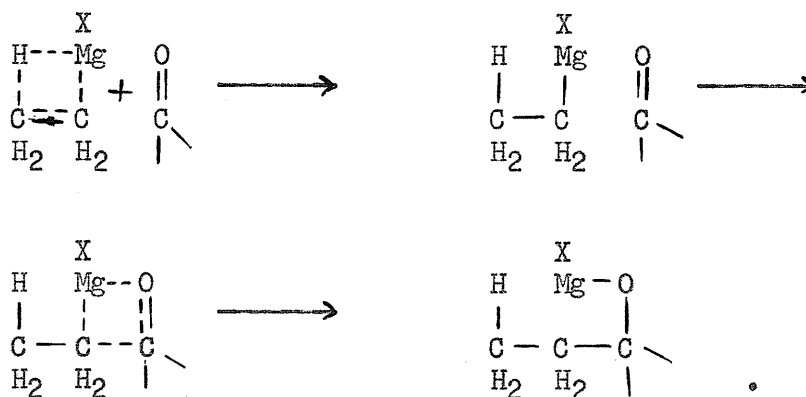
These investigators suggested, by analogy, that the Grignard reaction involving reduction of a carbonyl group and alkene formation might proceed via intramolecular cyclization of the Grignard reagent with magnesium being linked to a beta hydrogen atom. Subsequent attack by the carbonyl group would remove that hydrogen from the "Grignard molecule" to leave an alkene and reduce the carbonyl compound. The process was represented pictorially as follows:



To distinguish their mechanism more clearly from that of Rheinboldt and co-workers (page 4) Wiberg and Bauer emphasized the following main features of their mechanism:

- (1) Separated magnesium hydrogen bindings are not suggested.
- (2) The magnesium plays only the role of a hydrogen carrier.

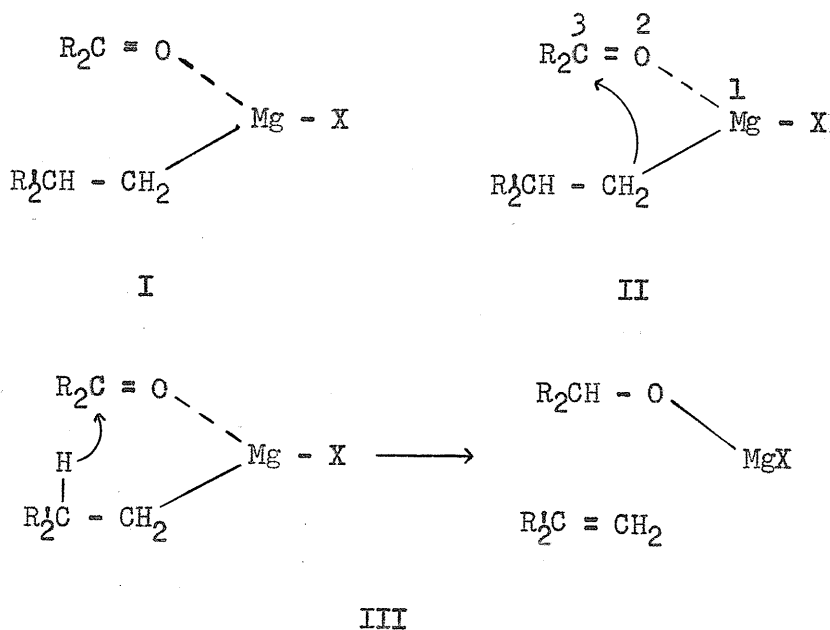
The Grignard addition reaction was assumed to proceed by a similar mechanism except that the carbonyl group attaches itself to magnesium and carbon instead of magnesium and hydrogen. Thus the preformation of olefin inside the Grignard molecule is not favoured as is seen from the following schematic representation.



No comments on the reduction mechanism of Wiberg and Bauer were found in the literature to date.

The most widely accepted mechanism for the reaction of a Grignard reagent with a carbonyl compound is probably that proposed by Whitmore at a meeting of the American Chemical Society (28). Since the paper was not published the details of the proposed mechanism are unavailable.

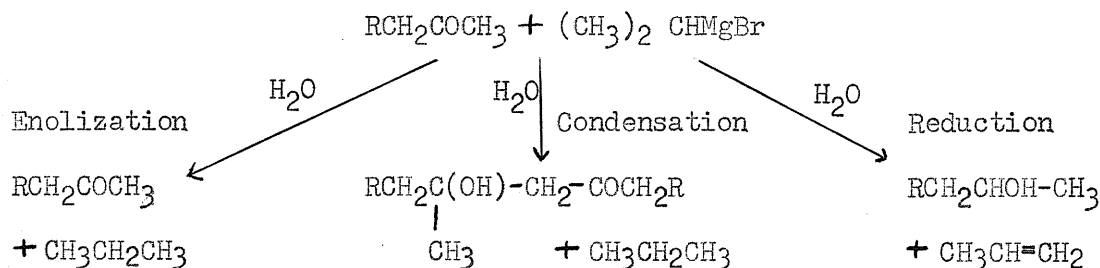
Apparently Whitmore postulated (14) that there is a co-ordinate link between the magnesium and the oxygen of the form I below, which may rearrange to form addition product by a 1-3 shift of the alkyl group from the magnesium to the carbonyl carbon atom as illustrated by II. The reduction reaction might involve a cyclic rearrangement of electrons within the complex and a subsequent transfer of hydrogen from the beta position of the Grignard reagent to the carbonyl carbon as shown in III.



Various modifications of the mechanism have been suggested.

An example is the conclusion of Shine (24) that the side reactions of the Grignard reagent, which were condensation, enolization

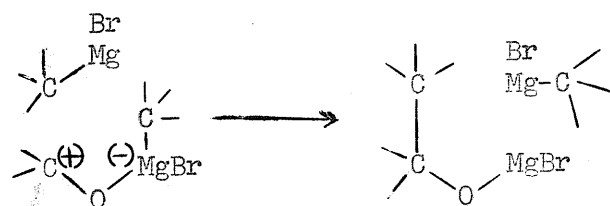
and reduction in his study, proceed by the attack of other molecules on an addition complex rather than by rearrangement of the complex as suggested by Whitmore. The reactions Shine investigated were the following:



The volume of the saturated gas obtained in a reaction was taken as a measure of the amount of enolization and condensation that had occurred, while the amount of alkene indicated the extent of reduction. It was found that the total anomalous reaction as measured by the total gas evolved was a maximum only with a large excess of Grignard reagent. The results shed little light on the mechanism of the reduction since Shine observed three reactions at once. An examination of his results reveals that the percentage of unsaturated gas and hence of reduction usually dropped somewhat when the concentration of Grignard reagent in a particular reaction was substantially increased. This seems to indicate that the extent of reduction was independent of how large an excess of Grignard reagent was used and that probably only the enolization and condensation reactions require an excess of the reagent in order to go to completion. Therefore, Shine's work cannot be cited as evidence that reduction occurs by the attack of other molecules on an addition complex rather than by rearrangement of the complex as

postulated by Whitmore.

On the other hand a mechanism in which the addition reaction proceeds by attack of another molecule of Grignard reagent on a Grignard reagent-carbonyl compound complex was suggested by Swain and Boyles (26). The addition reaction was formulated thus:



Reduction would occur by an intramolecular rearrangement of the complex as postulated by Whitmore.

Such a mechanism predicts that one should be able to increase the yield of addition product at the expense of reduction by adding magnesium bromide to the ketone prior to the addition of the Grignard reagent. The ketone should complex preferentially with the magnesium bromide since the latter is a stronger Lewis acid than the Grignard reagent. Thus in the addition reaction, magnesium bromide would play the part of the first molecule of Grignard reagent and would polarize the ketone even more strongly. The complex between ketone and magnesium bromide would be incapable of reduction by intramolecular rearrangement so that the effect of adding magnesium bromide should be to favour addition and hinder reduction.

Swain and Boyles succeeded in increasing the yield of addition product in the reaction of n-propylmagnesium bromide with diisopropyl ketone from 36 to 65 percent by adding magnesium bromide to the ketone prior to the addition of the Grignard reagent. Thus

the predictions of their mechanism were confirmed.

Additional experimental data which can be explained by the Whitmore mechanism for reduction were reported by McBee, Fierce and Higgins (18). The hydride ion transfer involved in the cyclic reduction mechanism may be assumed to be assisted mainly by a partial positive charge on the carbonyl carbon atom arising out of the complexing of the carbonyl oxygen with magnesium. This positive charge should be enhanced and hence the shift accelerated, by the introduction of electron-withdrawing substituents into the carbonyl compound. McBee, Pierce and Higgins found a pronounced increase in the amount of reduction when a fluorinated carbonyl compound is substituted for ordinary material in a Grignard reduction reaction. On the other hand they were able to decrease the amount of reduction of pentafluoropropionaldehyde by ethyl Grignard reagent by about 25 percent through the addition of magnesium bromide to the aldehyde prior to the addition of Grignard reagent. This evidence was cited in favour of a cyclic reduction process, the argument being analogous to that of Swain and Boyles (page 10).

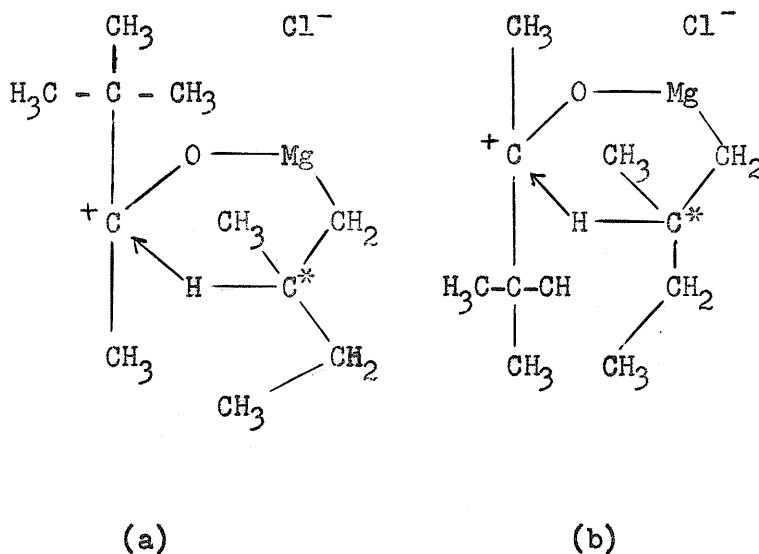
More recently McBee, Pierce and Meyer (19) reached conclusions which are incompatible with the results mentioned above. By a series of vapour pressure measurements of carbonyl compounds in phenetole, with or without added magnesium bromide, these investigators were able to show that fluorinated aldehydes, ketones and esters do not co-ordinate with magnesium bromide. Corresponding non-fluorinated compounds showed definite complex formation. Since the Grignard reagent is expected to complex even less readily with a given carbonyl compound than does magnesium bromide, the conclusion was reached that the cyclic mechanism

of Whitmore does not apply to the reduction of perfluoro compounds by Grignard reagents. Instead it was postulated that in perfluoro carbonyl compounds the carbonyl carbon is sufficiently positive, without complexing, for intermolecular transfer of hydride ion from the Grignard reagent to take place.

It is hard to see why the presence of magnesium bromide in the reaction of a fluorinated carbonyl compound with a Grignard reagent should cause an appreciable decrease in the amount of reduction, as observed by McBee and co-workers (18), if no complex is formed between the carbonyl compound and either the magnesium bromide or the Grignard reagent. The difficulty is removed by postulating that even with perfluoro carbonyl compounds a complex does form but that the equilibrium concentration of complex is so small that its presence can not be established by the method that was employed (19). A lower equilibrium concentration of complex is to be expected when the carbonyl compound is fluorinated than when it is not because the electron-withdrawing character of the fluorine atoms will decrease the tendency of the carbonyl oxygen to coordinate with a metal atom. If the equilibrium between the complex and its components is attained rapidly, then reduction can still proceed entirely by a cyclic mechanism even if the equilibrium concentration of complex is very small. The effect on the amounts of addition and reduction of adding magnesium bromide to a perfluoro carbonyl compound prior to the addition of Grignard reagent can then be accounted for.

The strongest evidence in favour of some closely associated complex as an intermediate in the reduction of a carbonyl compound with

a Grignard reagent is found in the results of reductions with optically active Grignard reagents. Mosher and LaCombe reduced methyl-*t*-butyl ketone to methyl-*t*-butyl carbinol with the Grignard reagent from (✓) 2-methylbutyl chloride (20). The carbinol obtained was optically active, indicating that partially asymmetric reduction had occurred. It had been predicted on the basis of the generalization proposed by Whitmore that such a reaction should give a preponderance of one of the optical isomers. The prediction was based on the assumption that there would be less steric interference occurring in the proposed ring complex of the transition state when the complex was arranged as in (a) than when it was arranged as in (b) below.

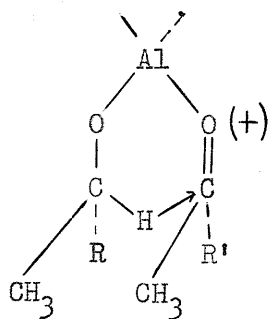


The tendency for the six-membered ring to form with the larger groups, namely, the *t*-butyl group of the ketone and the ethyl group of the Grignard reagent both on the same side of the ring as in (b), should be less than the tendency to form (a), due to steric factors. The activation energy necessary to form transition state (a) should, therefore, be less

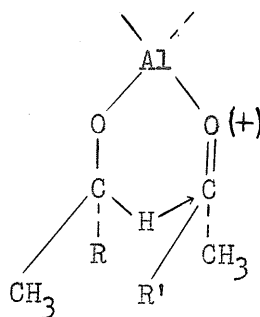
than the corresponding quantity for state (b). Thus the product of reaction resulting from state (a) should predominate and the overall product should be optically active. The fact that an optically active product was obtained is strong evidence that an intermediate of the kind postulated must exist in a stage of the reduction.

Evidence for the six-membered character of such a complex is found in other work of Mosher and LaCombe (21) who found that no asymmetric reduction is observed when the asymmetry centre of the aliphatic Grignard reagent is at the gamma position as exemplified by the action of (*ψ*) 3-methylpentylmagnesium chloride on methyl-*t*-butyl ketone. These results are best explained if the hydride ion comes from the beta carbon atom of the Grignard reagent in each case.

A similarity between the Grignard reduction and the Meerwein-Ponndorf-Verley reduction is indicated, for the latter reaction may also yield partially asymmetric products. Hypothetical mechanisms for the aluminum alkoxide and sodium alkoxide catalysed oxidation-reduction reactions of carbinol-carbonyl systems have been suggested (31,5). These mechanisms predicted that optically active products should be obtained from reductions of unsymmetrical ketones with optically active carbinols. Doering and Young (16) attempted such reactions which were formulated according to the proposed mechanism for an aluminum alkoxide catalysed reduction as follows:



(a)



(b)

As in the reductions of carbonyl compounds with optically active Grignard reagents (page 13), asymmetric reduction was expected as a result of larger steric hindrance between the groups R and R' in state (b) than in the state (a). Doering and Young found partially asymmetric reduction in two systems, in agreement with the postulated mechanism.

Studies of the Meerwein-Ponndorf-Verley reduction with deuterated carbinols (5) indicate that solvent hydrogen does not become attached to the carbonyl carbon atom and that hydrogen is probably transferred directly from the carbinol carbon to the carbonyl carbon as indicated schematically above. It was also found that hydrogen is transferred about 2.5 times faster than deuterium. In so far as the mechanism is similar to that postulated for the Grignard reduction reaction (compare page 8) it is probable that the latter also proceeds without the intervention of solvent hydrogen and that beta hydrogen of the Grignard reagent is involved.

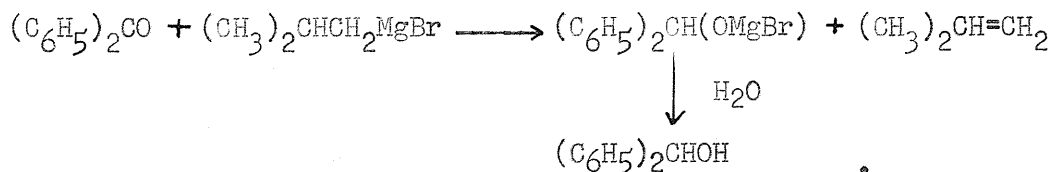
OBJECT AND METHOD OF THE PRESENT INVESTIGATION

The Whitmore mechanism for the reduction of carbonyl compounds by Grignard reagents has gained considerable support from a variety of experimental evidence. Some of that evidence, however, is of negative character and consequently inconclusive. An example is the evidence for the origin of the reducing hydrogen. Although Grignard reagents lacking beta hydrogen have never shown reducing activity it does not necessarily follow that reduction, when it does occur, involves the transfer of a hydrogen atom from the beta position of the Grignard reagent to the carbonyl carbon atom. Without evidence of a positive nature one could not entirely exclude the possibilities that the hydrogen comes from the alpha or gamma positions of the Grignard reagent, the transfer being followed by rearrangement of the Grignard reagent residue to unsaturated hydrocarbon, or that it is furnished indirectly by the solvent.

It should be possible to determine the source of the reducing hydrogen atom in a Grignard reduction reaction by using, in separate runs, Grignard reagents labelled with deuterium in different positions of the molecule. The use of excess Grignard reagent would allow competition between deuterated and non-deuterated molecules for the carbonyl compound. Therefore, by suitable analysis of the reactants and products for deuterium the source of the hydrogen appearing in the reduction product of such a reaction, as well as the relative rates of transfer of hydrogen and deuterium, should be determined.

The reduction chosen for the investigation was that of benzophenone to benzhydrol by isobutylmagnesium bromide according to the

equation:



The main reasons for this choice of reaction follow.

1. It has been shown that the reduction is almost quantitative and that the only products are benzhydrol and isobutylene (22).

2. Isobutyl bromide has alpha, beta and gamma carbon atoms to be labelled with deuterium.

3. The bromomagnesium salt of benzhydrol is insoluble in ether so that filtration of the reaction mixture is sufficient to separate it from excess Grignard reagent and from traces of unreacted benzophenone.

4. The necessary condition, that the product should not lose deuterium by exchange during the hydrolysis of the alcoholate, was satisfied. It has been shown that isopropyl alcohol produced by reduction of acetone with lithium aluminum deuteride contains practically one atom of deuterium per molecule and that no deuterium is lost when the alcohol is converted to isopropyl bromide (25). Therefore, the deuterium on the alpha carbon atom of isopropyl alcohol does not exchange when the lithium salt of the alcohol is hydrolysed. Since benzhydrol differs from isopropyl alcohol only in that benzene rings are substituted for methyl groups, deuterium attached to the aliphatic carbon atom of benzhydrol should not exchange when the magnesium alcoholate of the latter is hydrolysed.

The main steps involved in the investigation were (a) the

preparation of separate samples of alpha, beta and gamma-deutero isobutyl bromides, (b) the reduction of benzophenone to benzhydrol with the individual Grignard reagents from the labelled bromides and (c) the analysis of the bromides and benzhydrols for deuterium. The results would indicate whether the reducing hydrogen comes from the Grignard reagent and, if so, from which position.

An opportunity for a small side investigation arose out of the method used in the preparation of beta-deutero isobutyl bromide. One step in that preparation was the decarboxylation of dimethylmalonic acid having some deuterium in its carboxyl groups to form deutero isobutyric acid. From the analyses of the isobutyric acid and the isobutyl alcohol obtained from it by reduction, the relative rates of transfer of carboxyl hydrogen and deuterium in the thermal decarboxylation of dimethylmalonic acid could be calculated.

EXPERIMENTAL

The experimental section follows under four main headings which are:

1. Starting Materials
2. Preparation of Deuterated Isobutyl Bromides
3. Reduction of Benzophenone and Purification of Benzhydrol
4. Analysis for Deuterium.

Starting Materials

Anhydrous Ether. Commercial ether was dried over sodium wire, fractionated, and stored over fresh sodium wire.

Absolute Alcohol. Ethanol (95%) was refluxed with calcium oxide and distilled. It was dried further by refluxing with magnesium ethylate and redistilled.

Acetone. Acetone was dried with calcium sulphate and distilled before use. The fraction boiling in the range 55.5 - 56.5°C. (750 mm.) was collected.

Dioxane. Dioxane was purified by Fieser's method (8).

Deuterium Oxide. The deuterium oxide was obtained through the Commercial Products Division of Atomic Energy of Canada, Ltd., and was reported to have a mass-spectrometric analysis of 99.73 atom-percent deuterium.

Lithium Aluminum Deuteride. The deuteride was obtained from the National Research Council of Canada, Ltd. It was reported by the suppliers to have a deuterium content of 96 atom-percent.

Isobutyraldehyde. The aldehyde was dried with anhydrous calcium

sulphate and distilled immediately before use. The fraction boiling within the temperature range 62-64°C. (746 mm.) was collected.

Bromobenzene. The bromobenzene was distilled through a fifteen-plate column. The fraction boiling at 155°C. (740 mm.) was collected.

Kerosene. The kerosene was purified in 500 ml. portions with concentrated sulphuric acid. Four such treatments were sufficient to remove olefins and sulphur compounds. The kerosene was then dried with sodium sulphate and distilled through a fifteen-plate column. The fraction boiling in the range 190-220°C. was collected. Tests with bromine water and potassium permanganate showed that the kerosene was free from unsaturated materials.

Other Chemicals. Benzophenone, phosphorus tribromide, paraformaldehyde and methylmalonic acid diethylester were Matheson, Coleman and Bell reagent grade and were used without further purification.

Preparation of Deuterated Isobutyl Bromides

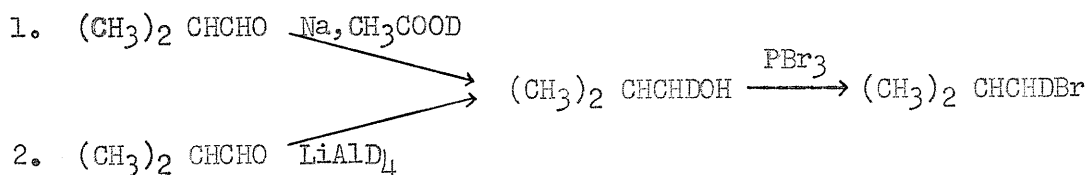
Two methods for the preparation of each of the alpha, beta and gamma-deutero isobutyl bromides were considered. After testing each scheme by means of runs with non-deuterated materials, the best one was selected for the preparation of a particular deuterated bromide.

Unless otherwise indicated, typical runs described in the following sections are those in which non-deuterated materials were used since the yields of individual steps were accurately determined. The results of similar runs with deuterated materials follow the discussion of a typical run. These yields are usually approximate only, careful purification of the intermediate deuterated materials

having been avoided in the interests of the overall yield of the desired product. In cases where intermediates were not isolated from the solvent but were reacted in solution in a further step, yields will not be given.

Preparation of Alpha Deutero Isobutyl Bromide.

Methods for preparing this compound were to reduce isobutyraldehyde either with sodium and deuterated acetic acid (1. below) or with lithium aluminum deuteride (2. below), and to convert the deutero alcohol obtained to isobutyl bromide by means of phosphorus tribromide.



Reduction of Isobutyraldehyde with Sodium and Acetic Acid. This reaction gave isobutyl alcohol in very low yield and was therefore abandoned in favour of reaction 2. (above) in making deuterated isobutyl alcohol. The following is a typical run with sodium and non-deuterated acetic acid.

Sodium (7.0g., 0.305 g. atom) was covered with 50 ml. of o-xylene in a three necked 250 ml. flask fitted with condenser, stirrer and dropping funnel. The sodium was carefully melted by heating the flask with a bare flame, and was dispersed in the xylene by rapid stirring of the mixture. Acetic acid, prepared by warming 7.1 g. (0.69 mole) of freshly distilled acetic anhydride with 1.25 g. (0.69 mole) of water was added to 10 ml. of xylene and 10 g. (0.14 mole) of

isobutyraldehyde. The resulting solution was dropped onto the rapidly stirring sodium dispersion over a period of one hour. The reaction flask was cooled with ice during this time. Water (50 ml.) was added carefully with cooling, and the aqueous layer separated. Ether extracts of this layer yielded 0.5 g. of isobutyl alcohol (b.p. 104-108°C./738 mm.). The xylene layer was dried with calcium sulphate and distilled, collecting all distillate boiling up to 140°C. (738 mm.). This first fraction was redistilled from a 100 ml. flask having a 9 x 1½ cm. fractionating arm packed with 1/8 inch glass helices and yielded 2.8 g. of isobutyl alcohol boiling in the range 104-108°C. (738 mm.). The total yield of alcohol (3.8 g.) is about 30 percent of the theoretical amount, based on the water used to make the acetic acid.

Reduction of Isobutyraldehyde with Lithium Aluminum Hydride. Isobutyraldehyde (4.2 g. 0.058 mole) in 20 ml. of dry ether was added dropwise to a stirring solution of 0.65 g. (0.017 mole) of lithium aluminum hydride in 20 ml. of dry ether. The reaction vessel was a 250 ml. round-bottomed, three-necked flask fitted with stirrer, condenser and dropping funnel. A 45 minute reflux period was followed by hydrolysis with dilute hydrochloric acid and extraction of the aqueous layer with ether. The ether extracts were dried with anhydrous calcium sulphate, the ether evaporated and the residue distilled from a 50 ml. flask. The yield of alcohol boiling in the range 90-107°C. (740 mm.) was 58 percent. A 70 percent yield was obtained in a duplicate run.

To prepare alpha-deutero isobutyl alcohol 1.97 g. (0.047 mole) of lithium aluminum deuteride was reacted with 13.5 g. (0.188 mole) of isobutyraldehyde. Material boiling in the range 60 - 106°C. (750 mm.) was collected on distillation of the product and was converted to alpha-deutero isobutyl bromide by treatment with phosphorus tribromide by the method described below.

Conversion of Isobutyl Alcohol to Isobutyl Bromide. Phosphorus tribromide (19.5 g. 0.072 mole) was added dropwise with stirring to 12.8 g. (0.173 mole) of isobutyl alcohol over a period of 45 minutes. The 250 ml. reaction flask, equipped with condenser, stirrer and dropping funnel, was cooled during the addition by means of an ice-salt cooling mixture. When the addition of tribromide was complete the cooling bath was removed and the reactants allowed to warm up to room temperature with continuous stirring. The mixture was then transferred to a 50 ml. distilling flask and slowly distilled, heating the flask by means of an electric mantel. Distillate boiling up to 96°C. (745 mm.) was collected, cooled to 0°C., and washed several times with cold concentrated sulphuric acid. Washing was repeated with cold sodium carbonate solution and with cold water. Drying with anhydrous calcium chloride preceded the final distillation which yielded 48 percent (11.5 g.) of isobutyl bromide boiling in the range 88 - 92°C. (735 mm.). Yields of similar runs were generally between 40 and 50 percent.

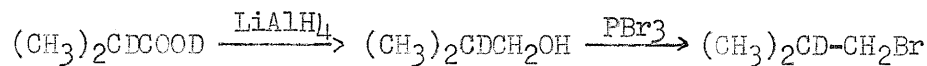
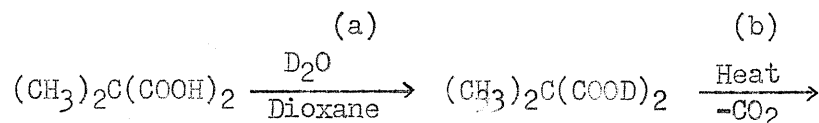
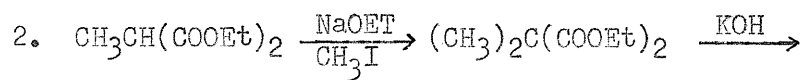
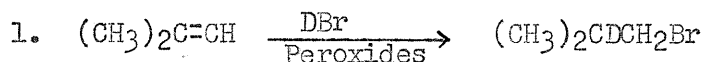
The crude alpha-deutero isobutyl alcohol obtained by reduction of isobutyraldehyde with lithium aluminum deuteride yielded 1.5 g. of

alpha-deutero isobutyl bromide on treatment with phosphorus tribromide. The low overall yield obtained in the synthesis of the deutero bromide must have been due to the use of lithium aluminum deuteride which was several years old and probably partially hydrolysed.

The deutero bromide was diluted with enough ordinary isobutyl bromide to produce 12 g. of stock material. This solution was analysed three times for deuterium and the remainder converted into two samples of Grignard reagent for reduction of benzophenone.

Preparation of Beta-Deutero Isobutyl Bromide.

The most elegant way to prepare this compound would be to add deuterium bromide, in the presence of peroxides, to isobutylene (1. below). An alternative longer method involved the use of dimethylmalonic acid (2. below).



(e)

(f)

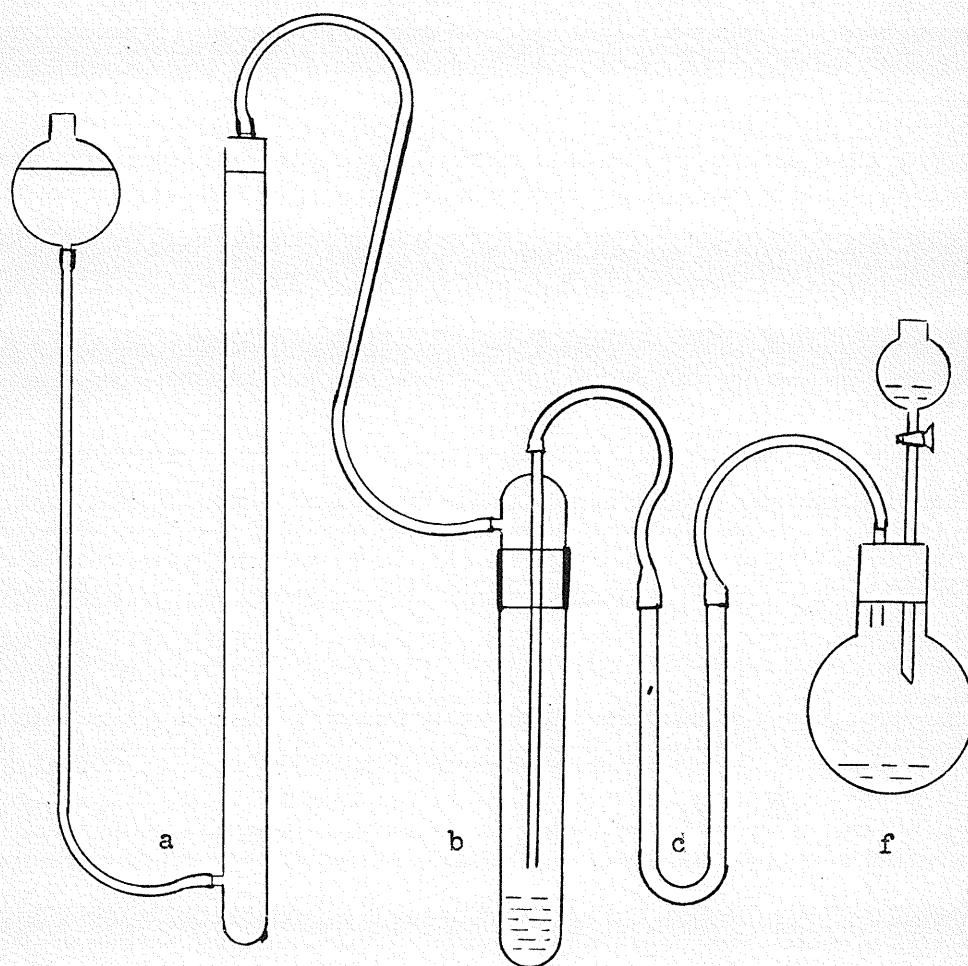
Attempted Addition of Hydrogen Bromide to Isobutylene. Isobutyl bromide has been prepared in good yield by the addition of hydrogen bromide to isobutylene in the gas phase in the presence of the peroxide ascaridole (12, 13). The runs described below in which either benzoyl

peroxide or di-t-butyl peroxide were used gave very poor yields of isobutyl bromide so that the series 2 (above) had to be used in the preparation of beta-deutero isobutyl bromide.

The apparatus used in a typical run is sketched in Figure 1. About 8 ml. of isobutylene, generated by dropping t-butyl alcohol onto warm 50:50 sulphuric acid in a three-necked flask equipped with stirrer, condenser and dropping funnel, was passed into the top opening of tube (b) (Fig. 1) and condensed in that vessel. The peroxide used in a particular run was then added to the isobutylene and the top outlet of tube (b) connected through the drying tube (c) to the hydrogen bromide generator (f). Water was dropped onto the phosphorus tribromide in (f) to generate excess hydrogen bromide which was kept over the isobutylene under a pressure of about 5 cm. of mercury above atmospheric by means of the nitrometer (a).

The tube (b) was shaken at intervals until no more hydrogen bromide was noticeably absorbed over a period of about 2 hours. The reaction vessel was then opened and allowed to reach room temperature while excess hydrogen bromide escaped. Concentrated sodium bicarbonate solution and water were used successively in washing the product. Isobutyl bromide is almost insoluble in either of these reagents but t-butyl bromide dissolves slowly in sodium bicarbonate solution. The product was dried with calcium chloride prior to distillation.

The first run, carried out at -70°C . with 2.4 g. (0.01 mole) of benzoyl peroxide, 8 ml. of isobutylene and excess hydrogen bromide yielded 4.5 g. of t-butyl bromide boiling in the range $71-72^{\circ}\text{C}$. (743 mm). Additional t-butyl bromide must have been removed in the washing process.



b and c were immersed in a mixture of Dry-Ice and acetone.

Fig. 1. Apparatus for Addition of Hydrogen Bromide to Isobutylene.

The fact that no isobutyl bromide could be isolated and that, therefore, the normal Markownikoff addition had occurred was attributed to the relative insolubility of benzoyl peroxide in isobutylene. In a modified run 0.2 g. of the peroxide was added in ether solution to the alkene. The products were t-butyl bromide and some tarry residue.

In the next run 2.0 g. (0.083 mole) of the peroxide was added in ether solution (about 50 ml.). The apparatus was modified by inserting a trap between the reaction tube (b) and the drying tube (c) (Fig. 1) to catch any liquid sucked back by sudden changes of pressure in the system. The solution was saturated with hydrogen bromide at the reaction temperature (-30 to -10°C.). Again only t-butyl bromide and tarry residues were obtained.

Further runs were made with di-t-butyl peroxide which was found to be quite soluble in isobutylene above -60°C. The same apparatus and procedure were employed except that the products were washed with sodium thiosulphate solution to remove the colour of bromine before the usual washing procedure. During the first run an attempt was made to remove excess di-t-butyl peroxide from the reaction products by washing them with ferrous sulphate solution. No reducing action of ferrous sulphate on the peroxide could be detected. Since the latter is fairly stable, distillation of the products up to the boiling point of isobutyl bromide could be carried out safely.

The first run in which 3.0 g. of di-t-butyl peroxide was used, yielded t-butyl bromide and 1.0 g. of material boiling in the range 85 - 95°C. (745 mm.). The refractive index (n_D^{18}) was 1.4100 as

compared to a literature value of 1.436 (n_D^{20}) for isobutyl bromide, and of 1.428 (n_D^{20}) for t-butyl bromide. A second run with 5.0 g. of the peroxide yielded only a negligible amount of isobutyl bromide.

In a third run with 4.0 g. of di-t-butyl peroxide, both the isobutylene and the hydrogen bromide were dried more thoroughly by passage through calcium chloride tubes in their respective delivery trains. The following fractions were collected from a 100 ml. flask having a $9 \times 1\frac{1}{2}$ cm. fractionating arm packed with $1/8$ inch glass helices:

- (a) 5.0 g. b.p. 63-73°C. (741 mm.); $n_D^{18} = 1.4200$,
- (b) 7.0 g. b.p. 73-85°C. (741 mm.),
- (c) 2.5 g. b.p. 85-92°C. (741 mm.); $n_D^{18} = 1.423$.

The fraction (c) which boiled in the range bracketing the normal boiling point (91.5°C.) of isobutyl bromide nevertheless differed widely from the latter in refractive index. Hence the yield of isobutyl bromide obtained was really quite low and the method had to be given up. The longer method (2. page 24), which gave better results, is described below.

Preparation of Dimethylmalonic Acid Diethylester. (2-a, page 24).

Sodium (3.8 g., 0.165 g. atom) was added in small amounts to 100 ml. of absolute alcohol in a 500 ml. round bottomed flask fitted with condenser. When all the sodium was dissolved, 26.0 g. (0.16 mole) of methylmalonic acid diethylester was added all at once and the flask shaken. Methyl iodide 22.7 g. (0.16 mole) was then added dropwise through the top of the condenser. After a 3 hour reflux period 2 ml. of methyl iodide was added and refluxing continued for one

additional hour. Ethyl alcohol was distilled off on a steam bath and the residue in the flask treated with water. From ether extracts of the aqueous solution 19.1 g. (68%) of ester boiling in the range 186 - 190°C. was obtained by distillation. Since the boiling points of monomethylmalonic and dimethylmalonic acid diethylesters at 750 mm. are 196°C. and 196.5°C. respectively, it was necessary to show, by means of the neutral equivalent of the corresponding acid, that the product was the dimethyl compound (page 30).

Saponification of Dimethylmalonic Acid Diethylester. (2-b, page 24).

The ester was saponified by refluxing for $2\frac{1}{2}$ hours with an equal weight of potassium hydroxide dissolved in its own weight of water. Unconverted ester was removed by neutralizing the mixture and extracting it with ether. Dimethylmalonic acid was similarly isolated after acidification of the reaction mixture with dilute acid. The saponification yields were over 90 percent. Samples of the acid that were recrystallized from benzene melted in the range 188-190°C. (corrected). By recrystallizing the acid from ether the melting point (corrected) was raised to the literature value of 193°C.

Exchange of Dimethylmalonic Acid with Deuterium Oxide. (2-c, page 24).

Dimethylmalonic acid (21.5 g., 0.163 mole), dissolved in 60 ml. of pure dioxane, was equilibrated for 70 hours with 3.3 g. (0.165 mole) of deuterium oxide. The 100 ml. distilling flask which served as vessel for the exchange, was then fitted with a condenser and receiver and kept under partial vacuum for 48 hours to evaporate the dioxane and water. To remove the last traces of solvent, the flask was heated,

under vacuum, to 90°C. by means of a water bath. A sample of exchanged acid that was withdrawn immediately after evaporation of the solvents had a neutralization equivalent of 67.5 ± 2 . The calculated values for dimethylmalonic and methylmalonic acids are 66 and 59 respectively.

Decarboxylation of Deuterated Dimethylmalonic Acid. (2-d, page 24).

The acid was decarboxylated immediately after removal of the solvents used in the exchange by heating the distilling flask above 195°C. with an oil bath. A thoroughly flamed condenser, of the type having a removable jacket, and a similarly dried receiver had been assembled to the distilling flask to collect the isobutyric acid formed. A portion of the latter was stored in a clean dry serum vial with self-sealing rubber stopper for analysis in connection with the isotope effect in the decarboxylation of dimethylmalonic acid (page 18).

A determination of the neutralization equivalent indicated a molecular weight of 91 ± 2 . The calculated value for monodeutero isobutyric acid is 89. The overall yield of the exchange and decarboxylation reactions was about 85 percent.

Reduction of Isobutyric Acid to Isobutyl Alcohol. (2-e, page 24).

The following is a typical reduction of non-deuterated acid. Isobutyric acid (12.0 g., 0.14 mole) in 15 ml. of anhydrous ether was added dropwise with stirring to a slurry of lithium aluminum hydride (7.0 g., 0.136 mole) in 30 ml. of dry ether. A 250 ml. three-necked flask fitted with condenser, stirrer and dropping funnel, served as reaction vessel. After the addition of about 15 ml. of ether to

provide for smooth stirring of the slurry, the mixture was refluxed for one hour. Excess hydride was hydrolysed with water and dilute hydrochloric acid added to dissolve lithium and aluminum salts. The ether layer was separated and the aqueous layer extracted three times with small quantities of ether. The combined extracts were neutralized by shaking with a few ml. of sodium carbonate solution and dried with anhydrous calcium sulphate. Distillation was carried out from a 50 ml. flask. The yield of isobutyl alcohol boiling in the range 96 - 107°C. (738 mm.) was 60 percent (6.1 g.). Yields up to 70 percent were obtained in some duplicate runs.

In distilling the beta-deutero isobutyl alcohol obtained by reducing beta-deutero isobutyric acid from the decarboxylation reaction (above) a cut of distillate coming over at the boiling point of pure isobutyl alcohol was saved for analysis in connection with the isotope effect accompanying the decarboxylation of dimethylmalonic acid (page 18).

Conversion of Isobutyl Alcohol to Isobutyl Bromide. (2-f, page 24).

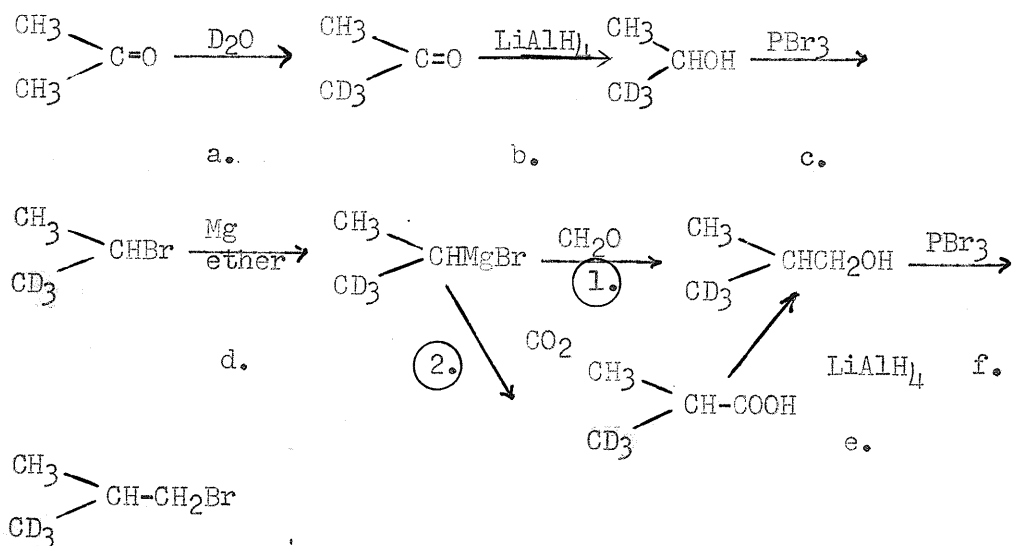
The procedure outlined on page 23 was followed. The yield of beta labelled isobutyl bromide prepared from 26.0 g. of methylmalonic acid diethylester was 1.5 g. The overall yield of the series, corrected for the amounts of isobutyric acid and of isobutyl alcohol that were removed for analysis, was about 12 percent.

The bromide was diluted with ordinary isobutyl bromide to obtain two solutions of different deuterium content. Each solution was analysed once for deuterium the remainder being converted to the

Grignard reagents and reacted with benzophenone.

Preparation of Gamma-Deutero Isobutyl Bromide.

Two series of reactions for the preparation of gamma-deutero isobutyl bromide, starting with acetone, were investigated (1. and 2. below).



Typical trial runs, followed by brief mention of the results obtained in similar runs with deuterated materials, are given below.

Exchange of Acetone with Deuterium Oxide (a. page 32). No trial runs with ordinary water were necessary. Acetone 30 g. (0.52 mole) was equilibrated with 30 g. (1.5 mole) of 99.7 percent deuterium oxide in a 100 ml. flask fitted with a short fractionating arm. A 0.2 g. pellet of sodium hydroxide was added to catalyse the exchange. After 48 hours of standing at room temperature the solution was distilled, collecting distillate boiling up to 95°C. (741 mm.). The deutero acetone was dried overnight with calcium sulphate, filtered and weighed to within 0.1 g. The yield was 30.8 g.

Reduction of Acetone with Lithium Aluminum Hydride (b. page 32). Four trial reductions were carried out, two of which were done in ethyl ether and two in diethyl carbitol solvent.

Acetone (14.0 g., 0.24 mole) was dissolved in 15 ml. of dry ether and added dropwise with stirring to 2.6 g. (0.069 mole) of lithium aluminum hydride in 35 ml. of ether. The reaction was carried out in a 250 ml. flask fitted with condenser, stirrer and dropping funnel. After all the acetone had been added (about one hour) the mixture was refluxed with stirring for one hour. Excess lithium aluminum hydride was carefully hydrolysed with water and dilute hydrochloric acid added to decompose lithium and aluminum hydroxides. The aqueous layer was extracted three times with small volumes of ether. These extracts were neutralized by shaking with a few ml. of sodium carbonate solution, and were dried with anhydrous calcium sulphate. The yield of isopropyl alcohol boiling in the range 77-80°C (738 mm.) was 23 percent (3.3 g.).

In a duplicate run the products were fractionated in a short column collecting the fraction boiling in the range 79-79.5°C. (738 mm.). The yield was 22 percent, based on the acetone. Attempts to raise the yields by using the higher boiling solvent diethyl carbitol instead of ethyl ether are described below.

The apparatus used was identical with that employed in reductions in solvent ethyl ether. Acetone (14.0 g., 0.24 mole) was dissolved in 20 ml. of diethyl carbitol and the solution added to a stirring slurry of 3.0 g. (0.08 mole) of lithium aluminum hydride in 20 ml. of diethyl carbitol. The rate of addition was so regulated that no

refluxing occurred, although the reaction mixture became quite hot. The test for lithium aluminum hydride, using Michler's ketone and iodine in glacial acetic acid (9) was positive at the end of the $1\frac{1}{2}$ hour addition period. Dilute hydrochloric acid was added carefully, with stirring. The reaction mixture was then distilled from a 500 ml. flask, collecting all distillate boiling up to 95°C . (750 mm.). This fraction was transferred to a small flask having a $9 \times 1\frac{1}{2}$ cm. fractionating arm packed with $1/8$ inch glass helices, and fractionated. The yield of isopropyl alcohol boiling in the range $78-83^{\circ}\text{C}$. (742 mm.) was 10.5 g. (74%). The refractive index (n_{D}^{20}) of this material was 1.3764 as compared to the literature value for isopropyl alcohol (n_{D}^{20}) of 1.3775.

A duplicate run yielded 80 percent of isopropyl alcohol boiling in the range $79-81^{\circ}\text{C}$. (740 mm.). The refractive index of this material ($n_{\text{D}}^{17.5}$) was 1.3772.

Reductions of deuterated acetone were carried out with a considerable excess (about 20%) of lithium aluminum hydride. The yields of deuterated isopropyl alcohol were about 80 percent of theoretical.

Conversion of Isopropyl Alcohol to Isopropyl Bromide (c. page 32).

The method described on page 23 for the analogous conversion of isobutyl alcohol to the bromide was followed. The yield of isopropyl bromide boiling in the range $56-60^{\circ}\text{C}$. (746 mm.) was 55 percent. Yields of deuterated bromides from the corresponding isopropyl alcohols were 48 percent of theoretical.

Preparation of Isopropyl Grignard Reagent (d. page 32). The Grignard

reagent was prepared in a 250 ml. flask equipped with condenser and dropping funnel. A 10 percent excess of magnesium turnings were used with 40 ml. of ether for about 0.2 moles of the halide. A third of the halide was added with a bit of iodine to the magnesium and the reaction initiated by gentle heating. The remaining halide, in 20 ml. of ether, was added at such a rate that the ether refluxed smoothly. When all the halide had been added refluxing was continued for a few hours. The solution was then decanted into a graduated cylinder and its volume determined. A one ml. portion was added to an excess of standard acid in an Erlenmeyer flask and the solution titrated to the neutral point with standard alkali. The yield of Grignard reagent could then be calculated. The percent conversion was generally between 85 and 90.

Attempted Reaction of Isopropyl Grignard Reagent with Formaldehyde

(1. page 32). Isopropylmagnesium bromide was prepared as outlined above. Formaldehyde, generated by heating paraformaldehyde in a small single-necked flask, was passed into the flask containing the Grignard reagent by means of a delivery tube reaching down almost to the surface of the liquid. The Grignard reagent was stirred vigorously to provide maximum contact with the gaseous formaldehyde. Enough formaldehyde was generated to react with all the Grignard reagent the presence of which was periodically tested for by means of the Gilman test with Michler's ketone (9). A u-tube with a little mercury in the bottom of it was connected to the third neck of the reaction flask to keep a slight pressure in excess of atmospheric in the system and also

to indicate the rate of escape of unreacted formaldehyde. A slight excess of paraformaldehyde was always sufficient to react with all the Grignard reagent present, although some of the generated formaldehyde escaped out of the reaction flask. The yields of isobutyl alcohol obtained were 30 percent or less. A titration of the paraformaldehyde with Karl Fischer reagent indicated that less than 1.8 percent of free water was present so that the low yields were not due to the use of wet paraformaldehyde.

Deuterated isopropyl Grignard reagent was converted to isobutyl alcohol by the longer method (2. page 32) which gave better overall yields. Typical trial runs follow.

Carbonation of Isopropyl Grignard Reagent (2. page 32). The Grignard reagent prepared as outlined on page 34 was poured slowly into a beaker containing crushed Dry Ice covered with anhydrous ether. When all the Grignard solution had been added, the beaker was covered with a clock glass and allowed to stand at room temperature until all the Dry Ice was gone. The isobutyric acid was liberated from its magnesium salt by the addition of dilute hydrochloric acid and was extracted from the aqueous layer with ether. Combined extracts were dried with anhydrous calcium sulphate and distilled after evaporation of the bulk of the ether. Yields of acid boiling in the range 145-150°C. (740 mm.) were 70 to 80 percent based on the Grignard reagent.

Reduction of Gamma-Deutero Isobutyric Acid to the Alcohol (2. page 32).

The reductions were carried out as outlined on page 30. The yields

obtained in the reductions of two samples of gamma-deutero isobutyric acid were 60 and 65 percent.

Conversion of Gamma-Deutero Isobutyl Alcohol to the Bromide (f. page 32).

The method outlined on page 23 was followed in this last step of the synthesis of the gamma-labelled bromide. The best overall yield of the synthesis, based on the amount of acetone exchanged with heavy water, was 13 percent. In another series the overall efficiency was 8.5 percent.

The gamma-deutero bromides obtained in the two runs were combined and diluted with ordinary isobutyl bromide to a total of 12 g., from which three samples of Grignard reagent were prepared for reductions of benzophenone. The stock bromide was analysed twice to determine the deuterium content.

Reduction of Benzophenone and Purification of Benzhydrol

Several reductions of benzophenone with non-deuterated isobutylmagnesium bromide were made in order to find a suitable procedure for a small scale reaction. The best results were obtained when the ketone was added in ether solution to the Grignard reagent. Adding the ketone in benzene solution gives good results when reductions are carried out on a fairly large scale, but when less than 2 g. of benzophenone was reduced the presence of benzene made purification of the product difficult.

A 2:1 excess of Grignard reagent over ketone was used in all reductions. The reason for this procedure was that isobutylmagnesium bromide has only one hydrogen atom in the beta position. Should the

reducing hydrogen be supplied from the beta position, a preference for hydrogen over deuterium in the transfer would not be detected unless the reagent were present in excess. For the sake of uniformity the reductions with alpha and gamma-deutero Grignard reagents were also carried out with the reagents present in 2:1 excess. The procedure followed in the preparation of isobutylmagnesium bromide and in the reduction of benzophenone with the reagent, is outlined in the following run with non-deuterated material.

Preparation of Isobutyl Grignard Reagent. Isobutyl bromide (3.0 g., 0.022 mole) dissolved in 5 ml. of dry ether, was added to a 10 percent excess of magnesium turnings (0.53 g.) in 25 ml. of dry ether. The reaction flask was of 250 ml. capacity and was equipped with a condenser and a dropping funnel. The reaction was initiated without the addition of iodine by warming the flask gently with a free flame, and was completed by refluxing for several hours. The volume of the solution was then measured by decanting it off excess magnesium into a dry graduated cylinder, from which it was immediately transferred to a dry, 250 ml., three-necked flask fitted with condenser, stirrer and dropping funnel. A 1 ml. portion was then pipetted into an excess of standard acid which was back-titrated with standard base to determine the amount of Grignard reagent present. The yield of Grignard reagent was 75 percent (0.0166 mole).

Reduction of Benzophenone. To the non-deuterated Grignard reagent prepared as outlined above was added one half of the equivalent quantity (1.51 g., 0.0083 mole) of benzophenone dissolved in 10 ml.

of anhydrous ether. The solution turned deep red as soon as the ketone was added but the color disappeared after the addition was complete and reaction solution had been refluxed for a few minutes. When the mixture had been refluxed for a few hours to ensure completion of the reaction, the bromomagnesium salt of benzhydrol was allowed to settle out and was filtered off in a 7 cm. Buchner funnel. The salt was washed immediately with about 10 ml. of anhydrous ether, returned to the reaction flask, and hydrolysed with dilute hydrochloric acid. The liberated benzhydrol was extracted with ether and recrystallized from ligroin. The yield of benzhydrol melting at 66°C. was 1.2 g. (80%). The melting point was determined on a Fischer melting point block and was read when the first crystal of the material collapsed.

The results of the reduction with the labelled Grignard reagents are summarized in Table 1.

Table 1.
Results of Reductions with Labelled Grignard Reagents

Bromide	Run	Grignard Reagent		Benzophenone		Benzhydrol		
		Yield%	moles $\times 10^3$	Gm.	moles $\times 10^3$	Gm.	Yield%	M.P. (°C)
Alpha-deutero	1	80	16.80	1.53	8.40	1.20	78	66
	2	79	15.90	1.45	7.95	1.14	78	66
	3	78	17.00	1.54	8.50	1.29	83	66
Beta-deutero	1	82	16.72	1.52	8.36	1.14	74	66
	2	87	16.09	1.46	8.04	.80	54	65
Gamma-deutero	1	72	15.90	1.44	7.95	.98	67	65
	2	68	14.14	1.29	7.07	1.05	81	66
	3	77	15.44	1.41	7.72	1.12	79	65

The low yields of benzhydrol isolated in run 2 with beta-deutero Grignard reagent and in run 1 with gamma-deutero Grignard reagent were probably

due to mechanical losses sustained in isolating the benzhydrol. The samples of benzhydrol obtained in the runs with deuterated Grignard reagents were stored in weighing bottles having tight-fitting glass stoppers.

Analysis For Deuterium

To analyse a compound for deuterium a sample large enough to yield about 0.5 g. of water of combustion was burned in a combustion apparatus and the water collected. The weight-percent deuterium oxide in the purified water was determined by a method involving the density. The amount of deuterium present in the original compound could then be calculated.

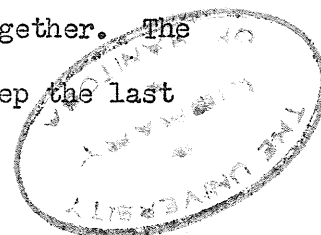
The Combustion Train. The combustion apparatus consisted of a three unit macro furnace with a Vycor combustion tube having a standard taper joint as an outlet. Near the outlet was a plug of silver wool to remove halogens. The rest of the tube up to the central heating unit of the furnace was filled with copper oxide. A roll of copper gauze, three inches long, touched the copper oxide and extended into the central section of the furnace. Oxygen from a cylinder was dried in a calcium chloride drying tower and two Greiner-Friedrichs gas-washing bottles filled with sulphuric acid before it was passed into the combustion tube. The receiver for combustion water consisted of a Pyrex glass u-tube with a standard taper joint at right angles to one end and with a capillary opening at the other end.

To prepare for a combustion oxygen was passed through the tube while the long section of the furnace heated the copper oxide in the tube to dull redness. The receiver was then assembled to the

combustion tube and thoroughly flamed while a stream of oxygen passed through it. When the u-tube had cooled sufficiently it was surrounded by a freezing mixture of Dry Ice-acetone in a Dewar flask. The combustion was then begun by introducing the sample and adjusting the rate of flow of oxygen to about 2 bubbles per second.

At the end of a combustion the receiving tube was removed, the furnace sections were opened, and the combustion tube allowed to cool with a slow stream of dry air passing through. When cool the tube was tightly stoppered. For another combustion the procedure outlined above was repeated.

Combustion of Isobutyl Bromide. Isobutyl bromide was introduced into the combustion tube in a Pyrex glass ampule of about $1\frac{1}{2}$ ml. capacity which had been loaded with 0.8 to 1.2 g. of the bromide to be analysed. The ampule was pushed far enough into the tube that the tip touched the roll of copper gauze in the centre of the combustion tube. The heat conducted to the gauze by the copper oxide with which it was in contact was sufficient to vaporize the bromide very slowly from the ampule. To assist in distilling out the sample, the central section of the furnace was turned on at a very low setting of the rheostat control. Very careful heating was necessary to prevent the occurrence of flash-backs. Until the ampule was nearly empty the temperature of the tube in its immediate vicinity was kept at about 80°C . The temperature of the central section was then increased to dull red heat along with the short heating unit which had hitherto been shut off altogether. The flow of oxygen was continued for about 15 minutes to sweep the last



traces of water into the u-tube. The total time required for the combustion of a sample of bromide was 2 hours. At the end of the process water condensed in the upper part of the receiver was "swept down" by heating the glass with a free flame and the capillary opening sealed by melting the tip. The receiver was then separated from the combustion tube and sealed with a standard taper glass stopper. The yield of water was 95-98 percent of the theoretical amount.

Combustion of Benzhydrol. With the combustion tube prepared for a run a sample of benzhydrol (about 0.8 g.) was rapidly transferred from its storage vial to a dry porcelain combustion boat and weighed as quickly as possible to within one milligram. The boat was then placed in contact with the wire gauze in the central section of the combustion tube and the heating unit above it turned on at a fairly high setting to melt the benzhydrol. The rate of heating was decreased once the benzhydrol had melted and was then kept constant until the boat was practically dry. The process was completed in a manner analogous to that outlined under the previous heading. The average duration of a combustion of benzhydrol was $1\frac{1}{2}$ hours with yields of water near 99 percent of theoretical.

Combustion of Isobutyric Acid and Isobutyl Alcohol. The method outlined under the heading "Combustion of Isobutyl Bromide" (page 41) was followed, except that the rate of heating was faster in accordance with the higher boiling points of the materials. Samples of acid and of alcohol weighing about 0.5 g. were burned in two and $1\frac{1}{2}$ hours respectively with 98 percent yields of water.

Purification of the Water Samples. The water samples obtained in the oxidation processes were purified by a modification of the method of Keston, Rittenberg and Schoenheimer (16). The purification apparatus consisted of a train of 4 Pyrex glass u-tubes having standard taper joints. These tubes were cleaned with chromic acid mixture, washed with dilute ammonium hydroxide, rinsed with distilled water and dried in an oven. The distillation train was arranged as shown in Figure 2.

Distillations were carried out under partial vacuum (about 10 mm. Hg.) supplied by a water aspirator. Before assembling tube 1., which served as receiving tube during the combustions and contained the water sample to be purified, the rest of the apparatus was evacuated and thoroughly flamed. When the apparatus had cooled to near room temperature the two-way stopcock A (Fig. 2.) was turned to allow air to enter the system through three calcium chloride tubes. These tubes had cotton batting packed above the calcium chloride to prevent fine particles of the drying agent from being swept into tube 5. Small amounts of calcium oxide and potassium permanganate were now introduced into tube 2. and tube 1. assembled to the rest of the system. The stopcock A was returned to the vacuum position and tube 2. surrounded by a Dry Ice-acetone freezing mixture. The sample was distilled into tube 2. by warming tube 1. with a beaker full of warm water. When the distillation was finished the system was restored to atmospheric pressure, tube 1. was removed, tube 2. closed with a standard taper stopper, and the freezing mixture moved to tube 3. The water in tube 2. was then heated to the boiling point under atmospheric pressure and refluxed for a moment on the calcium oxide and permanganate to remove carbon

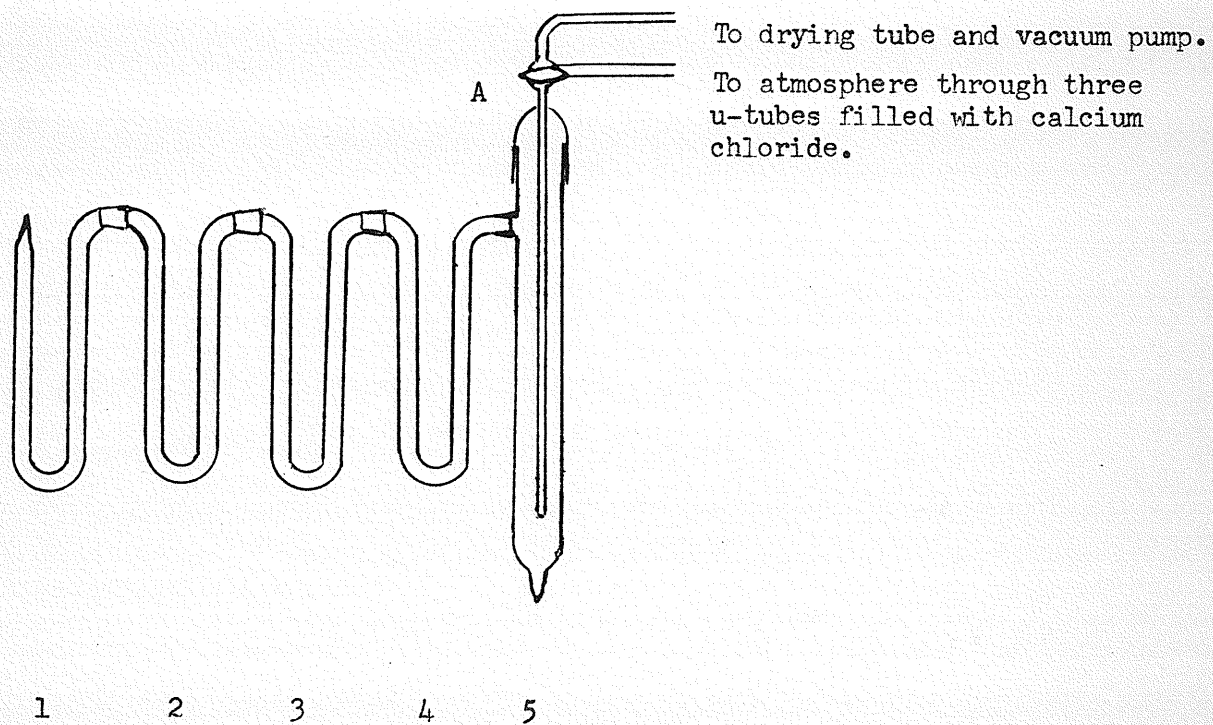


Fig. 2. Apparatus for Purification of Water Samples.

dioxide. When the water had cooled down to near room temperature the system was again evacuated and the distillation into tube 3. carried out. The process was repeated until the sample had been distilled three times after the initial distillation onto the purifying agents. The water sample was transferred from the receiver 5. to a clean dry serum vial with self-sealing hypodermic stopper, by means of Pyrex tubing with capillary tip and rubber suction bulb. Clean dry tubing for this purpose was drawn out to a capillary just before use.

Analysis of the Water Samples for Deuterium Oxide. The gradient density tube method described by C. Anfinson (1) was used to determine the percent deuterium oxide in the water samples obtained by combustion. The method is based on Fick's principle that a linear gradient of densities is produced at the juncture of two miscible liquids of unequal specific gravities. Two bromobenzene-kerosene solutions having specific gravities of 0.998 and 1.019 respectively were used for the top and bottom liquids.

The gradient tube consisted of a 35 cm. Pyrex tube of diameter 5 cm. the ends of which were sealed to the neck of a 1 l. round-bottomed flask and to the bottom of a 500 ml. round-bottomed flask respectively. The neck of the latter flask was fitted with a ground glass cap which protected the system from moisture and dust.

The apparatus was mounted vertically in a glass-fronted thermostat maintained at $25.0 \pm .1^{\circ}\text{C}$., and was filled to the mid-point with the bromobenzene-kerosene solution of specific gravity 1.019. The lighter solution was then gently layered over it by means of a funnel

the tip of which was kept just below the surface of the liquid, to fill the system to within about 4 inches of the top.

A glass rod, the end of which had been shaped into a spiral in a plane perpendicular to the rod was then lowered gently to the centre of the tube and the solutions stirred slowly with strokes of increasing length until at the tenth stroke the entire length of the tube had been traversed. The system was then allowed to stand for two days to attain equilibrium.

The linearity of the gradient was checked by introducing drops of standard water-deuterium oxide solutions and measuring their equilibrium heights with a cathetometer. The standards were prepared on a weight-percent basis and were stored in serum vials with self-sealing stoppers. It was found that a plot of weight-percent deuterium oxide against height of the standard drops in the tube was as nearly linear as the corresponding plot of density against height, for the low deuterium content of the standards. Therefore, the gradient could be used to read weight-percent deuterium oxide directly, within the error associated with the measurement of the equilibrium height of the drops concerned.

The gradient prepared as outlined above had a working range of 0-2 percent deuterium oxide. Another gradient with a range of 0-8 percent deuterium oxide was used to analyse combustion waters falling into that range of deuterium content. Plots of cathetometer readings versus percent deuterium oxide for the two gradients are shown in Figure 3.

The drop to be introduced into the gradient density tube was

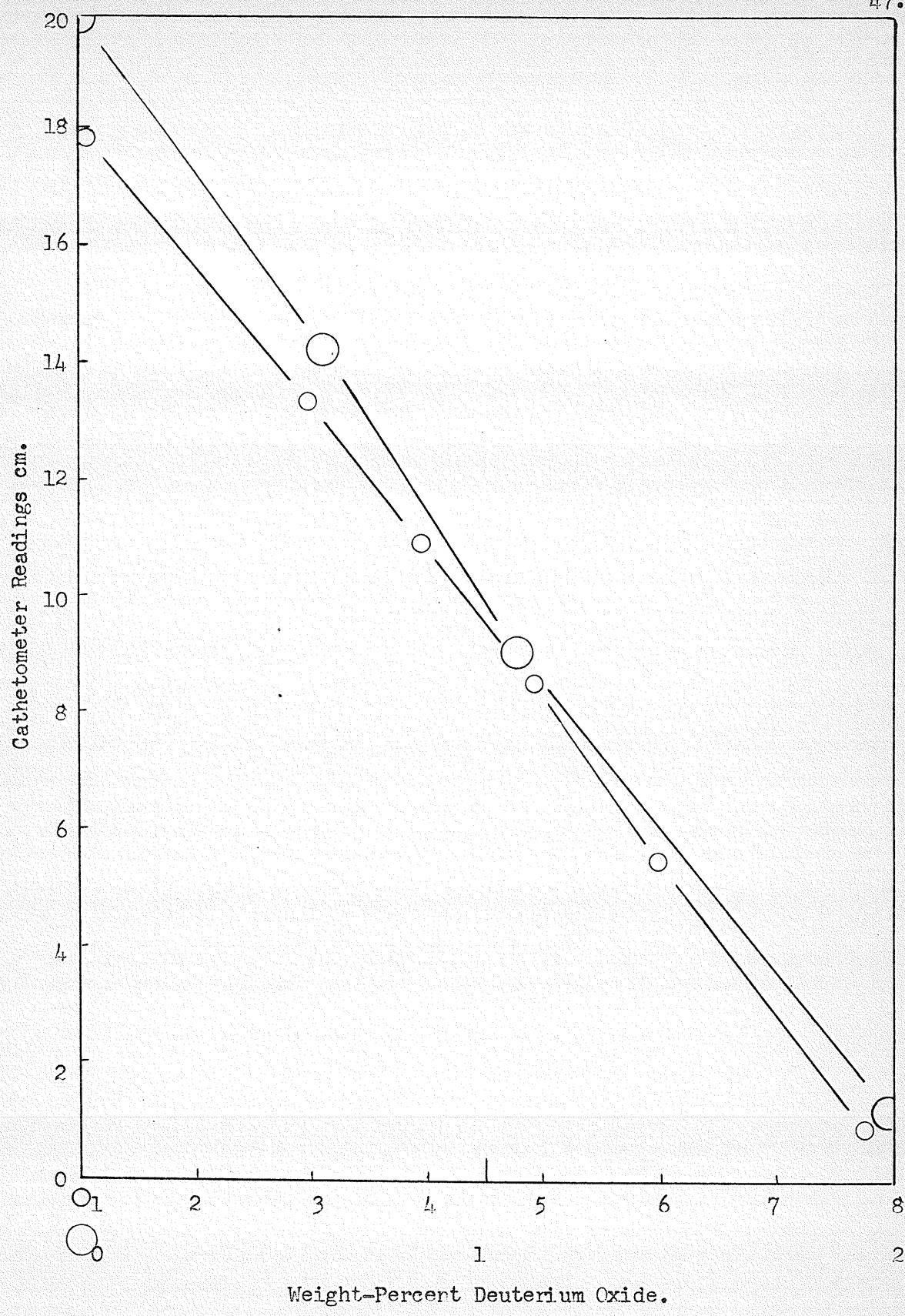


Fig. 3. Plot of Cathetometer Readings versus Percent Deuterium Oxide.

withdrawn from the serum vial with a hypodermic needle attached to a ground fitting of a capillary tube of 10 cm. length and $\frac{1}{4}$ mm. bore. A rubber policeman was slipped onto the capillary extension to serve as suction bulb. The needle was inserted into the sample through the stopper of the vial to eliminate the possibility of contaminating the sample by contact with the atmosphere. The solution was drawn halfway up the capillary by means of the rubber policeman. The needle was withdrawn from the vial and emptied; then reinserted and refilled. A drop was introduced into the density tube by lowering the tip of the needle into the gradient solution and applying gentle pressure to the rubber policeman. Drops formed in this manner were consistently of 3 mm. diameter. The needle was changed and the capillary dried before introducing a new sample.

Standard and sample drops were introduced on opposite sides of the tube to avoid confusion. The heaviest of a series was dropped in first. The drops were allowed five hours in which to attain their equilibrium levels which were recorded as the mean of the top and bottom levels read with a cathetometer accurate to 0.1 mm. From the known values of the percent deuterium oxide in the standards bracketing each unknown drop and the vertical differences in levels between the standards and the unknown the percent deuterium oxide in the sample could be calculated by interpolation.

Slight fluctuations in the linearity of the gradient occurred with changes in pressure and temperature. To follow these irregularities and so get consistent readings, new standards were introduced with each set of unknowns. As a double check the samples most pertinent

to the investigation were analysed two times with an interval of several days between the analyses. The results differed by less than 4 parts per hundred.

A loss of deuterium due to exchange with protons on the walls of the combustion tube and distillation train occurred during the combustion and purification processes. The magnitude of this loss was determined by putting standard deuterium oxide-water solutions through the combustion and purification procedures and then measuring the loss of deuterium by analysis in the gradient density tube. Standard samples of 0.585 and 2.956 percent deuterium oxide showed respective losses of 3.9 and 3.6 percent of the initial deuterium present. The mean value 3.75 percent was used in correcting results for exchange losses. To determine whether or not a greater loss of deuterium occurred when the boat instead of an ampule was used in the combustion step, the standard 7.797 percent deuterium oxide sample was put through both steps separately. The loss of deuterium in each case was 1.6 percent of the initial deuterium present.

The results of the analyses are given in the following table.

Table 2
Results of the Analyses

Source of Water Sample	Sample No.	Weight % D ₂ O	Mean Corrected Weight % D ₂ O ^a
Alpha-deutero Isobutyl Bromide	1	0.68	0.69
	2	0.65	
	3	0.67	
Gamma-deutero Isobutyl Bromide	1	20.65 ^b	21.82
	2	21.32	
Benzhydrol from Alpha-deutero Grignard reagent	1-3	nil	nil
Benzhydrol from Gamma-deutero Grignard reagent	1	nil	nil
	2	.03	
	3	nil	
Beta-deutero Isobutyl Bromide	1	1.30 ^c 1.35	1.38
	2	1.41 1.44	
Benzhydrol from Beta-deutero Grignard reagent	1	0.62 ^c 0.63	0.65
	2	0.75 0.75	
Isobutyric Acid ^d (Dimethylmalonic Acid)	1	13.62 ^b	14.32
	2	13.87	
	3	13.85	
Beta-deutero Isobutyl Alcohol	1	2.95	3.07
	2	2.97	

^a Corrected for exchange losses in the purification process.

^b Analysed on the 0-8% gradient by suitable dilution.

^c The two values for each sample are readings obtained on different days against a freshly calibrated gradient.

^d Since no loss of hydrogen occurs on decarboxylation of dimethylmalonic acid to form isobutyric acid, the analyses apply to either compound.

RESULTS AND DISCUSSION

It will be seen from the preceding table that the benzhydrols obtained by reduction of benzophenone with beta-deutero isobutyl Grignard reagents contained deuterium, while those obtained by the use of alpha and gamma-deutero Grignard reagents did not. Therefore, the reduction occurs by hydrogen transfer from the beta position of the Grignard reagent as was postulated by Whitmore. The possibility that slight intervention of alpha or gamma deuterium would not have been detected by the method of analysis is admitted. The 0-2 percent gradient was spread over a vertical distance of 17.5 cms., and drop levels read to within 0.1 mm., so that the limit of detectability of deuterium oxide in the water samples was 0.01 percent by weight. In order to use this figure to compute the maximum percentages of reaction that could have occurred by transfer of hydrogen from the alpha or gamma positions and yet have escaped detection it is necessary to obtain an equation connecting the concentrations of deuterium in starting materials and products and the percent completion of the reaction with the relative rates of transfer of hydrogen and deuterium in the reduction. Such a difference in the rate of reaction, caused by the substitution of a lighter or heavier isotopic atom for some atom in one of the reacting molecules is now referred to in the literature simply as an "isotope effect".

The absolute reaction rate theory of Eyring shows the dependence of the rate constant on the zero-point energy difference between the activated complex and the reactants. The energy of a bond is a function of the vibrational frequency which in turn depends on the

reduced mass of the atoms held together by the bond in question. It can be shown that if the reduced mass is increased by the substitution of a heavier isotope for one of the atoms forming the bond the vibration frequency and hence the zero-point energy will be decreased. On passing to the transition state a decrease in the zero-point energy will occur whether the bond under consideration is isotopically substituted or not but that decrease will be smaller for the heavier than for the normal form. Therefore, the heavier form will require a larger activation energy to reach the transition state and should react at a slower rate if the isotopically substituted position is involved in the rate controlling step of the process. For a detailed discussion of the theory of isotope effects the reader should refer to the treatment by Bigeleisen (2,3).

The isotope effect k_H/k_D may be calculated from an equation derived from the rate constants of the two species that are in competition. Thus, if the reaction can be assumed to be first order with respect to Grignard reagent, as most investigators in the field postulate that it is, then

$$k_H t = \ln \frac{a}{a-x} \quad \text{and} \quad k_D t = \ln \frac{a'}{a'-x'}$$

represent the rate expressions for the reactions of normal and deuterio Grignard reagents where

k_H = the rate constant for the transfer of hydrogen;

k_D = the rate constant for the transfer of deuterium;

a = the initial concentration of non-deuterated form;

a' = the initial concentration of deuterated form;

$a - x$ = the concentration of non-deuterated form at time t ;

$a' - x'$ = the concentration of deuterated form at time t .

The isotope effect k_H/k_D is then given by the expression

$$\frac{k_H}{k_D} = \frac{\log \frac{a}{a-x}}{\log \frac{a'}{a'-x'}} \quad 1.$$

which can be shown to be equivalent to the form

$$\frac{k_H}{k_D} = \frac{\log (1/x) - \log [1/x - P(1/A)]}{\log (1/X) - \log [1/X - P(1/A)]} \quad 2.$$

if the following substitutions are made

$$\frac{a'}{a} = A \quad ; \quad \frac{x'}{x} = X \quad ; \quad \text{and } P = \frac{x/x'}{a/a'} \quad ;$$

where A = the ratio of deuterium to hydrogen in the labelled position of the starting material;

X = the ratio of deuterium to hydrogen in the labelled position of the product;

P = the fraction of reaction completed (ratio of products to reactants).

Before equation 2. could be used to estimate the possible amount of reaction involving alpha and gamma hydrogen from the Grignard reagent it was necessary to estimate the maximum value of k_H/k_D when carbon-hydrogen and carbon-deuterium bonds are broken, and to evaluate A and X , as defined, from the analytical data which were obtained in terms of weight-percent deuterium oxide in the waters of combustion. The maximum value of k_H/k_D has been shown to be about 6 at room temperature (7) while A and X could be calculated from the equation

$$\frac{D}{H} = \frac{1}{\frac{n'}{9Qn} (1000-Q) - 1} \quad 3.$$

where D/H = the ratio of deuterium atoms to hydrogen atoms in the labelled position of the compound;

n' = the total number of hydrogen atoms (protium plus deuterium) in the labelled position of a molecule of the compound;^e

n = the total number of hydrogen atoms in a non-deuterated molecule of the compound;

Q = the weight-percent deuterium oxide in the water of combustion of the compound.

The maximum percentage of reaction involving the alpha position of the Grignard reagent which would just have escaped detection was then calculated in the following way:

1. The value of A for alpha-deutero isobutyl bromide was calculated from equation 3. using the mean corrected weight-percent deuterium oxide value from Table 2.

2. The equation 2. was solved for X by the method of successive approximation using $\frac{k_H}{k_D} = 6$ and $P = 0.5$.^f

3. The value of X for benzhydrol whose combustion water would contain the minimum detectable weight-percent (0.01) of deuterium oxide was calculated from equation 3.

^e For the benzhydrol samples the only position that could have contained deuterium was the aliphatic C-H group, so that n'=1.

^f Since the Grignard reagent was present in 2:1 excess the percent completion of the reaction with respect to Grignard reagent could not exceed 50.

4. The value of X from step 3. was multiplied by 100 and divided by the value of X calculated in step 2.

It can easily be verified that the result gives the maximum percentage of the reaction that could have proceeded by the transfer of hydride ion from the alpha position of the Grignard reagent. The result obtained for the alpha position was 17 percent and for the gamma position, by a similar calculation, one percent.

It is unlikely however that the reduction proceeds by more than one mechanism. Since the data indicate that the beta position is certainly involved, it is probable that no deuterium or hydrogen atoms were incorporated into the benzhydrol from the alpha or gamma positions of the Grignard reagent.

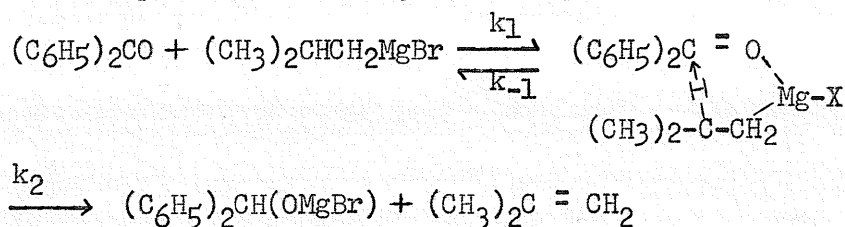
The source of the reducing hydrogen having been determined as the beta position, it was desirable to calculate the isotope effect accompanying the reduction with partially beta-deuterated material. Equation 2. was again employed. The values of A and X for each run with beta-deutero Grignard reagent were calculated from the data in Table 1 with the help of equation 3. Using $P = 0.5$ the value of $\frac{k_H}{k_D}$ could be calculated from equation 2. The ratio $\frac{k_H}{k_D}$ for the decarboxylation of dimethylmalonic acid was obtained in an analogous manner. ^g The results are given in Table 3.

^g Since only half of the carboxyl hydrogen is transferred to the beta position on decarboxylation the value $P = 0.5$ again applies.

Table 3
Calculated Values of D/H and k_H/k_D

	Q	n'	n	D/H	k_H/k_D	Mean k_H/k_D	
Beta-deutero Isobutyl Bromide #1	1.38	1	9	0.126	2.0	2.1	
Corresponding Benzhydrol	0.65	1	12	0.076			
Beta-deutero Isobutyl Bromide #2	1.48	1	9	0.137	2.2		
Corresponding Benzhydrol	0.78	1	12	0.092			
Dimethylmalonic Acid	14.32	2	8	1.096	4.5		4.5
Beta-deutero Isobutyl Alcohol	3.07	1	10	0.383			

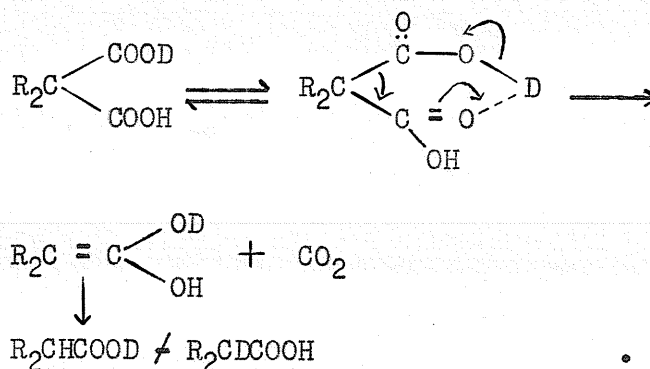
It will be seen from Table 3 that the transfer of hydrogen from the beta position of isobutyl Grignard reagent to the carbonyl carbon of benzophenone according to the equation



is about 2.1 times faster for protium than for deuterium. The observed isotope effect does not throw any light on the question of whether or not reduction proceeds by rearrangement of a complex as postulated by Whitmore and other workers. However, it may be used to predict something about the rates of formation and rearrangement of such a complex if the proposed mechanism is assumed to be correct. The facility of the formation of complex should not be affected by the presence of

deuterium in the beta position of the Grignard reagent. The relative amounts of deuterio and ordinary complex, therefore, should be the same as the relative amounts of deuterio and non-deuterio Grignard reagent used in the reaction. Now if every complex that formed were decomposed to form products then the relative amounts of deuterio and non-deuterio benzhydrol obtained should also be the same, that is, there should be no isotope effect. Since an isotope effect was observed, not every complex that forms rearranges to form products but rather an equilibrium between complex and its components must exist as written in the equation. In addition the equilibrium must be attained at a rate exceeding the rate of decomposition of complex to form products in order for competitive transfer of hydrogen and deuterium to be possible. The small magnitude of the isotope effect may indicate that k_2 is not much smaller than k_{-1} .

It is seen from Table 3 that there is an isotope effect of about 4.5 in the thermal decarboxylation of dimethylmalonic acid having some carboxyl deuterium. The following mechanism for the decarboxylation of a malonic acid has been suggested by King (17).^h



^h The deuterium in the formulae has been introduced by the present author.

The first step can not be relevant to the isotope effect since proton transfers from one carboxyl to another are expected to be practically instantaneous. Even if a preference for either hydrogen or deuterium were inherent in that step the same material would be formed in the next step in each case. The last step in which the dihydroxy compound rearranges should be accompanied by an isotope effect since competition is possible between hydrogen and deuterium.

Therefore, the observed isotope effect is in agreement with the suggested mechanism. However, the evidence is in no way confirmatory since an isotope effect would be expected for other mechanisms. The only mechanism not involving an isotope effect would be one in which the hydrogen transfer occurs in a step such that no choice between hydrogen and deuterium is presented. It seems to be impossible to visualize such a mechanism.

CONCLUSIONS

1. In the reduction of benzophenone to benzhydrol by isobutylmagnesium bromide the reducing hydride hydrogen comes from the beta position of the Grignard reagent.

2. The transfer of hydride hydrogen in the reaction is about 2.1 times faster than the transfer of deuteride deuterium.

3. The fact that an isotope effect was observed indicates that if the reduction occurs through the rearrangement of an intermediate complex as is generally postulated, the formation of such a complex must be a rapidly reversible equilibrium process.

4. The small magnitude of the isotope effect may indicate that the rate of reduction is nearly as great as the rate of attainment of equilibrium between the reactants and the proposed intermediate complex.

5. The thermal decarboxylation of dimethylmalonic acid having one carboxyl group deuterated shows an isotope effect of about 4.5. This evidence is in agreement with the postulated mechanism of such a decarboxylation, but does not confirm the mechanism.

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