

1927

Part I. Some aliphatic local anaesthetics, Part II. The physical constants of organomagnesium halides

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PART I

SOME ALIPHATIC LOCAL ANAESTHETICS

PART II

THE PHYSICAL CONSTANTS OF ORGANOMAGNESIUM HALIDES

BY

Leon C. Heckert

124
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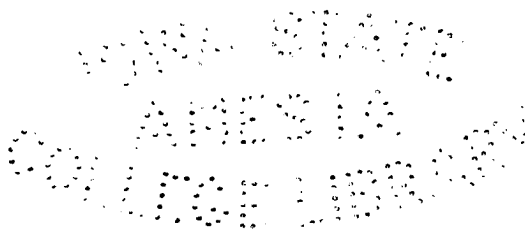
A Thesis submitted to the Graduate Faculty
for the Degree of
DOCTOR OF PHILOSOPHY
Major subject--Organic Chemistry

Approved

Signature was redacted for privacy.
In charge of Major work.

Signature was redacted for privacy.
Head of Major Department.

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Iowa State College

1927

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The author takes this occasion to express his indebtedness to Dr. Henry Gilman, of the Chemistry Department, Iowa State College, under whose direction the work was done.

T17721

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PART I

SOME ALIPHATIC LOCAL ANAESTHETICS.

INTRODUCTION.

The differences between aromatic and corresponding aliphatic compounds are largely of degree and not of kind. There are probably no rigidly exclusive aromatic characteristics. Functional groups that have the so-called aromatic properties are almost invariably attached to a tertiary carbon atom that has some degree or other of unsaturation. A fair basis of comparison would restrict correlation to aliphatic compounds that have functional groups of a related type. When this condition is met, in part or in whole, one observes that practically all the so-called distinctive aromatic properties are shown by varied aliphatic compounds.¹

The present work extends such correlation to include the comparative physiological action of some aromatic compounds with aliphatic types. Previously, Gilman and Pickens² showed a correlation based on physiological ac-

(1) Space does not permit of reference to the many works in this field. A general and leading account of some such correlations is to be found in Johnson and Hahn's translation of Henrich's "Theories of Organic Chemistry" (John Wiley and Sons, 1922). See pages 182-183, 232-235.

(2) Gilman and Pickens, J. Am. Chem. Soc., 47, 245 (1925)

tion, between some aromatic heterocyclic types (furan, thiophene and pyrrole) and benzene. For comparative purposes the same physiological action: namely, local anaesthetic action, has been studied. It has been found that the diethylaminoethyl esters of carboxylic acids (where the carboxyl group is attached to an unsaturated carbon atom) shows a distinct, although small, local anaesthetic action. Where the same grouping is attached to a saturated carbon atom there is no local anaesthetic action.

EXPERIMENTAL PART.

The hydrochlorides of the diethylaminoethyl esters were prepared by a standard technique involving the interaction of the acid chloride with diethylaminoethanol in an inert medium, generally benzene or ether.

Diethylaminoethyl Acrylate-Hydrochloride.--8 grams or 0.088 mole of acrylic acid chloride³ in 50 cc. of dry benzene was added dropwise to 11 grams or 0.094 mole of β -diethylaminoethanol in 50 cc. of benzene. The hygroscopic hydrochloride of diethylaminoethyl acrylate melted at 93 when crystallized from benzene.

Analysis. Calculated for $C_9H_{18}O_2NCl$: Cl-17.07; N-6.70
Found: Cl-16.89, 16.53; N-6.30

Preliminary to the above synthesis,⁴ β -chloroethyl α,β -dibromopropionate, $CH_2BrCHBrCO_2CH_2CH_2Cl$, was prepared by passing hydrogen chloride into a mixture of α,β -dibromopropionic acid and ethylene chlorohydrin. The yield of ester boiling at 153/20 mm. was 92.9%; n_D^{30} , 1.9080; d_4^{20} , 1.5241.

Analysis. Calculated for $C_5H_7O_2Br_2Cl$: Br-54.31; Cl-12.03.
Found: Br-54.20; Cl-12.02.

(3) Prepared according to directions of Mourou, Ann. chim. phys., (7) 2, 161 (1894).

(4) The author is indebted to Mr. Roy McCracken for the preparation and analysis of these two compounds.

Diethylaminoethyl β,β -Dimethylacrylate-Hydrochloride.--

This compound was prepared from dimethylacrylic acid chloride and diethylaminoethanol in ether. When crystallized from acetone it melted at $128-9^{\circ}$.

Analysis: Calculated for $C_{11}H_{22}O_2NCl$; Cl-15.07.

Found: Cl-15.2.

Diethylaminoethyl Trichloroacetate-Hydrochloride.--The

same general conditions were followed here as in the preparation of the β,β -dimethylacrylate ester-hydrochloride. The compound melted at 144-145.

Analysis: Calculated for $C_8H_{15}O_2NCl_4$; N-4.68.

Found: N-4.76.

Diethylaminoethyl Acetate-Hydrochloride.melted at ~~107-~~
~~109.~~ $116-117^{\circ}$

-Analysis: Calculated for $C_8H_{18}O_2NCl$: Cl- 18.16%

Found: Cl- 18.09, 18.14%.

Some preliminary reactions were carried out between diethylaminoethanol and the acid chlorides of fumaric and monochloroacetic acids. From these the hydrochloride of β -diethylaminoethanol was obtained.

PHARMACOLOGICAL TESTS.

We are indebted to Dr. Oliver Kamm of Parke, Davis and Company of Detroit for the results of the pharmacological tests. The method of testing was that described earlier.² Cocaine was selected arbitrarily as a standard and given a weight of 10. On a scale of this kind, the relative and rather approximate ratings of the hydrochlorides are as follows:

diethylaminoethyl-dimethylacrylate----1

diethylaminoethyl-acrylate-----1

diethylaminoethyl-trichloroacetate----
slightly less than-----1

diethylaminoethyl-acetate-----0

Diethylaminoethyl-trichloroacetate was selected in this study because trichloroacetic acid has, among other properties, a conductivity that places it nearer to aromatic compounds than acetic acid.

It is interesting to note that the comparative effectiveness of the diethylaminoethyl esters of acrylic and dimethylacrylic acids places them not far from two of the aromatic types previously reported²; namely, diethylaminoethyl 2-thiophene-carboxylate (with a rating of 1) and diethylaminoethyl 2-furancarboxylate (with a rating of less than 1).

SUMMARY.

A study of the local anaesthetic action of some diethylaminoethyl esters of aliphatic carboxylic acids shows that the chemical correlation of aromatic compounds with some related aliphatic compounds can be extended to include physiological action.

PART II

THE PHYSICAL CONSTANTS OF ORGANOMAGNESIUM HALIDES.

INTRODUCTION.

The important and almost specific role which ethers, notably diethyl ether, assume in the preparation of the Grignard reagents has been interpreted in three general ways; (1) as a catalyst, the ether remaining in the molecule simply as "ether of crystallization" and playing no further part in the reactions of the reagent, (2) as forming an oxonium compound, the extreme reactivity of the compound being attributed to the abnormal valence of the oxygen, and (3) as forming a complex of the Werner type, in which the reactivity is due to a rearrangement in the main and auxiliary valences.

That ether plays an important part in the preparation of these compounds cannot be denied since the substitution of other solvents, either in part or wholly, results in very unsatisfactory yields.⁽¹⁾ It is notable, however, that the only solvents, or "catalysts" in which it has been possible to obtain solutions which will give positive Grignard reactions are, in general, compounds having

(1) A complete account of the information mentioned will be published by Gilman and McCracken in a forthcoming issue of Recueil des travaux chimiques des Pays-Bas.

potentially free valences, i. e. elements in which higher valences are possible, such as ethers, tertiary amines, sulfides, tellurides, phosphines, phosphine oxides, and even brombenzene.

Ever since Grignard showed that the ether was not readily removed from solutions of his reagent, attempts have been made to include the ether in one form or another in the structure of the compounds. It must be remarked that the experimental proof of the validity of these theories is not too convincing; even the number of molecules of ether is a subject of controversy and is assumed to be either one or two to suit the convenience of the individual. The real basis for the entire argument rests on the fact that ethers, particularly diethyl ether, are practically the only solvents in which the reagents can be prepared with any degree of success. It would seem, then, that the logical method of attacking the problem would be to prepare a normal reagent and then completely remove the ether. If the resulting substance, can be shown to undergo reactions characteristic of the Grignard reagent, then it would be only logical to conclude that ether is not an essential part of the molecule of the active Grignard reagent, and it would be unnecessary

to assume either an oxonium or a coordination structure for it.

This paper reports the preparation of several dry, ether-free, Grignard reagents, their analyses and some properties.

HISTORICAL.

Grignard⁽²⁾ attempted the preparation of dry methylmagnesium iodide and found that it retained ether so firmly bound that it was necessary to heat it a full day at 150° in a vacuum to completely remove it. Heated to 50° in a vacuum for five days and then up to 80° it still retained two-thirds mole of ether.⁽³⁾ Tschelinzeff⁽⁴⁾ prepared reagents from a weighed quantity of magnesium and halide, distilled them at 80° and determined the weight of ether remaining and found that approximately two moles of ether was left. He confirmed this result by measurement of the heat evolved when ether was added to a benzene solution of amylmagnesium iodide. Equal quantities of heat were evolved for the first two moles of ether added.⁽⁵⁾

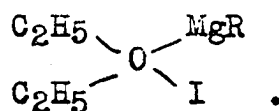
(2) Grignard, Ann. chim. phys., (7) 24, 433 (1901).

(3) When dried methylmagnesium iodide is decomposed with water, a part of the iodine is lost as hydriodic acid. Grignard determined the composition of the residue by means of magnesium and iodine determinations. The low iodine content was interpreted by him to mean a high ether content.

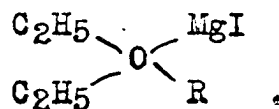
(4) Tschelinzeff, Ber., 39, 773, (1906).

(5) The determinations of ether by Tschelinzeff disagree with the theoretical by as much as 25 percent. The method used was not capable of much accuracy.

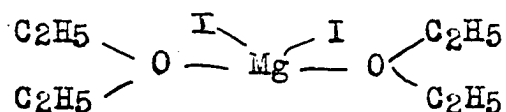
Blaise⁽⁶⁾ found that ethylmagnesium bromide and ethylmagnesium iodide retained one molecule of ether when dried up to 100°, but gradually lost it above that temperature. He also isolated some crystalline derivatives with aromatic nitriles which contained one mole of ether. Baeyer⁽⁷⁾ applied Collie and Tickles oxonium theory, and represented the substances as



Grignard⁽⁸⁾ proposed, instead,



Blaise⁽⁹⁾ isolated a di-etherate of magnesium iodide which he formulated as



which when treated with benzoyl chloride at 100° gave ethyl

(6) Blaise, Compt. rend., 132, 893 (1901).

(7) Baeyer, Ber., 35, 1201 (1902).

(8) Grignard, Compt. rend., 136, 1260 (1903).

(9) Blaise, Compt. rend., 139, 1211 (1904); 140, 661 (1905).

iodide, ethyl benzoate and magnesium chloride.⁽¹⁰⁾ He found that ethyl ether could be replaced by other ethers. Zerewitinoff⁽¹¹⁾ prepared a crystalline mono-etherate of methylmagnesium iodide with amyl ether.⁽¹²⁾ Ahrens and Stapler⁽¹³⁾ prepared crystalline derivatives of B-bromoethylmagnesium bromide with benzaldehyde and of the Grignard reagent from trimethylethylene bromide with benzaldehyde. The first formed a mono-etherate, while the second, did not, but formed the ether-free derivative.⁽¹⁴⁾

(10) It has been shown that acid chlorides, in the presence of certain metallic chlorides, notably zinc chloride, decompose ethers with the formation of products similar to those obtained by Blaise.

See Descude, Compt. rend., 132, 1129 (1901).

Wedekind and Haussermann, Ber., 34, 2081 (1901).

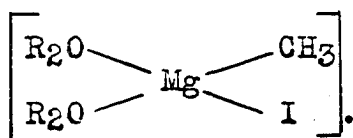
(11) Zerewitinoff, Ber., 41, 2224 (1908).

(12) The crystals were analyzed after drying between filter paper, a procedure scarcely capable of analytical accuracy.

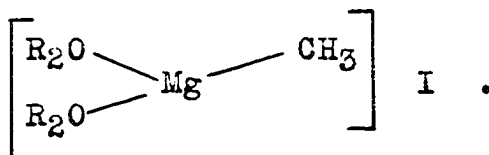
(13) Ahrens and Stapler, Ber., 38, 1296, 3265 (1905).

(14) The crystals were dried in a current of air before analysis. Grignard reagents prepared from dihalogen compounds have been shown to have a remarkable reactivity with oxygen, showing luminescence. It is noteworthy, also, that benzaldehyde formed a mono-etherate with mono-organomagnesium halide, while the di-organomagnesium halide contained no ether, as was the case with the compound of benzaldehyde with B-bromo-trimethylethylmagnesium bromide.

The experiments of Thorpe and Kamm⁽¹⁵⁾ rather decidedly disproved the oxonium theory and attention is now centered on coordination formulas. The formula proposed by Tschelinzeff⁽¹⁶⁾ received little consideration. Meisenheimer⁽¹⁷⁾ and his coworkers formulate the complex with magnesium as the central atom with a coordination number of four



Hess and Rheinboldt⁽¹⁸⁾ give magnesium a coordination number of three, and propose the formula



Jolibois⁽¹⁹⁾ found that magnesium diethyl would not dissolve in ether, but would dissolve in an ether solution

(15) Thorpe and Kamm, J. Am. Chem. Soc., 36, 1022 (1914).

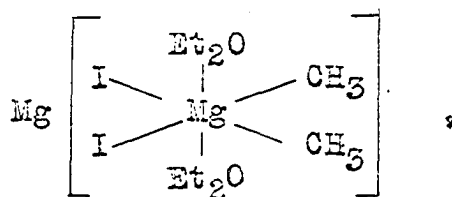
(16) Tschelinzeff, Ber., 38, 3664 (1905).

(17) Meisenheimer and Casper, Ber., 54, 1655 (1921).

(18) Hess and Rheinboldt, Ber., 54, 2045 (1921).

(19) Jolibois, Compt. rend., 155, 353 (1912).

of magnesium iodide, and that the solution possessed properties identical with those of the Grignard reagent. He proposed that the Grignard reagent was a double compound of magnesium dialkyl and magnesium halide etherate. Terentiev⁽²⁰⁾ determined the molecular weight of methylmagnesium iodide in ether and found it to correspond to the double molecule.⁽²¹⁾ Kondyrew⁽²²⁾ showed that ether solutions of organomagnesium compounds would conduct a current of electricity, and that magnesium was deposited on the cathode, but that no halogen was liberated at the anode. The formula of Meisenheimer, and that of Hess and Rheinboldt do not account for this electrolytic behavior. Terentiev⁽²⁰⁾ proposes the formula



which accounts for the electrolytic behavior, and also for the inactivity of the halogens toward sodium. The nature of the products at the anode has not been investigated.

(20) Terentiev, Z. anorg. allgem. Chem., 156, 75 (1926).

(21) The molecular weight of methylmagnesium iodide in ether solution was found to be approximately 380. This does not account for the "ether" in the molecule.

(22) Kondyrew, Ber., 58, 459; 1573 (1925). See also Nelson and Evans, J. Am. Chem. Soc., 39, 82 (1917). Gaddum and French, ibid., 49, 1295 (1927).

DISCUSSION OF METHOD.

The experiments of Grignard⁽²³⁾ and Blaise⁽²⁴⁾ indicate that it might be possible to expel the ether by careful drying in an inert atmosphere at an elevated temperature, if the compound does not decompose before losing the ether. Some preliminary experiments, confirmed later, indicated that methylmagnesium iodide was unsuited to the study because of a side reaction during the decomposition with water which resulted in the loss of iodine, apparently as hydriodic acid.⁽²⁵⁾ This side reaction is being further studied. Ethylmagnesium bromide seemingly is the most stable reagent and was used most generally.

When allowed to stand at room temperature in a closed system through which a current of pure hydrogen was passing at a fairly uniform rate, loss of ether took place rather

(23) loc. cit.

(24) Blaise, Compt. rend., 152, 839 (1901).

(25) Methylmagnesium iodide in ether solution was dried in an atmosphere of hydrogen at 150 for three hours as is later described in connection with ethylmagnesium iodide. When cooled to room temperature, surrounded by cold water, and then decomposed with water, the gas evolved contained iodine as was shown by passing the gas through aqueous silver nitrate. The residue invariably was lower in iodine than that calculated for the ether-free methylmagnesium iodide.

rapidly at first and then gradually dropped off and became very small in the course of a day. When the residue was analyzed at this point, it contained somewhat less than one mole of ether for each mole of ethylmagnesium bromide. The residue at this point was a solid somewhat resembling phenol, but not crystalline. When the temperature was raised to 60°, the solid melted and again lost weight, but the loss per day soon became almost negligible again. Analyzed at this point, it contained 0.75 mole of ether per mole of ethylmagnesium bromide. At 60° it was still a liquid, but became solid when cooled to room temperature. Experiments with α -naphthylmagnesium bromide, which forms a crystalline derivative when cooled in fairly concentrated ether solutions, paralleled the results with ethylmagnesium bromide. Drying curves for these are shown in Figure I. With α -naphthylmagnesium bromide, the crystals were drained of the excess ether, then washed several times with dry petroleum ether in which the crystals are insoluble, and the very apparent mechanically held ether driven off with a current of hydrogen and then weighed at intervals. The loss was very rapid at first, being apparently mechanically held petroleum ether. The loss soon became rather small and nearly constant. Analyzed at this point, the crystals contained very nearly one mole of ether per mole of α -naphthylmagnesium bromide. However, further loss took place

Fig. I (c)

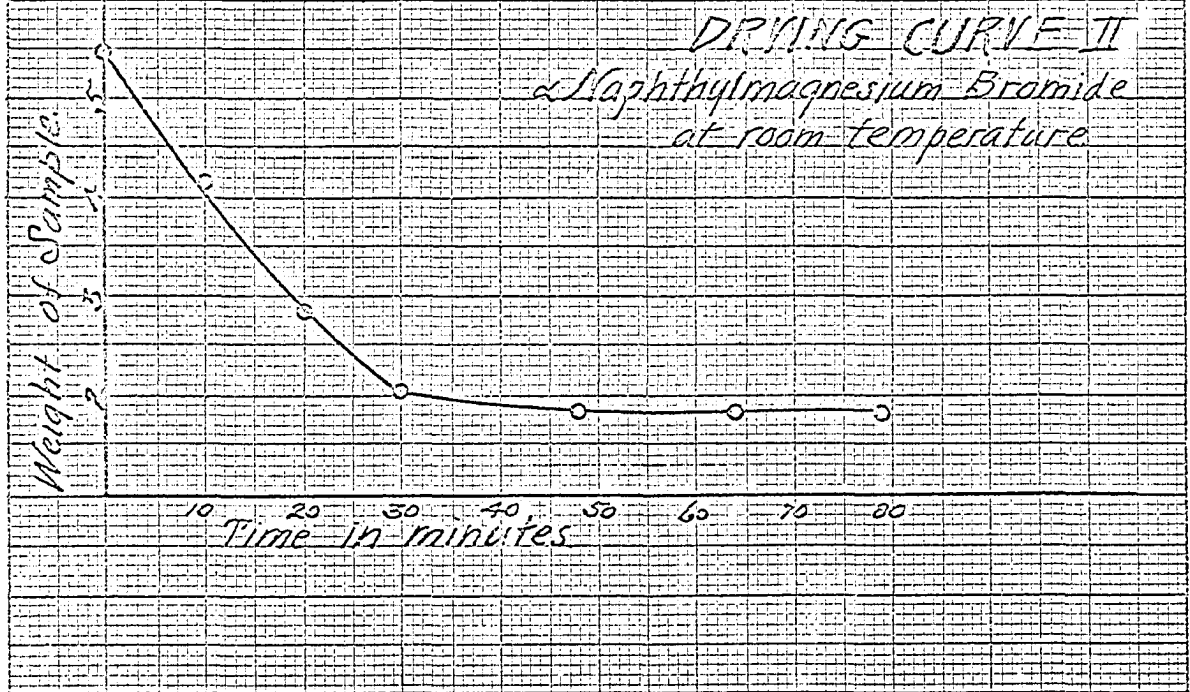
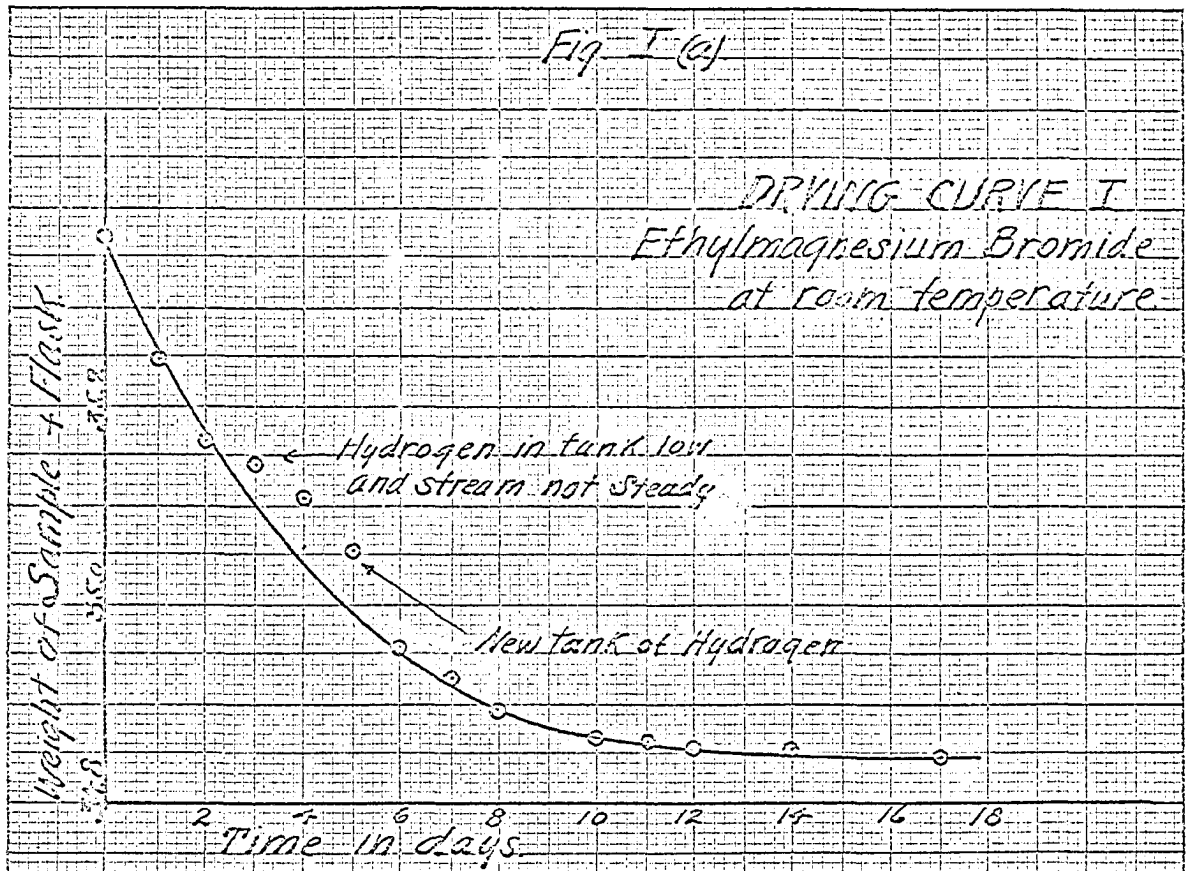
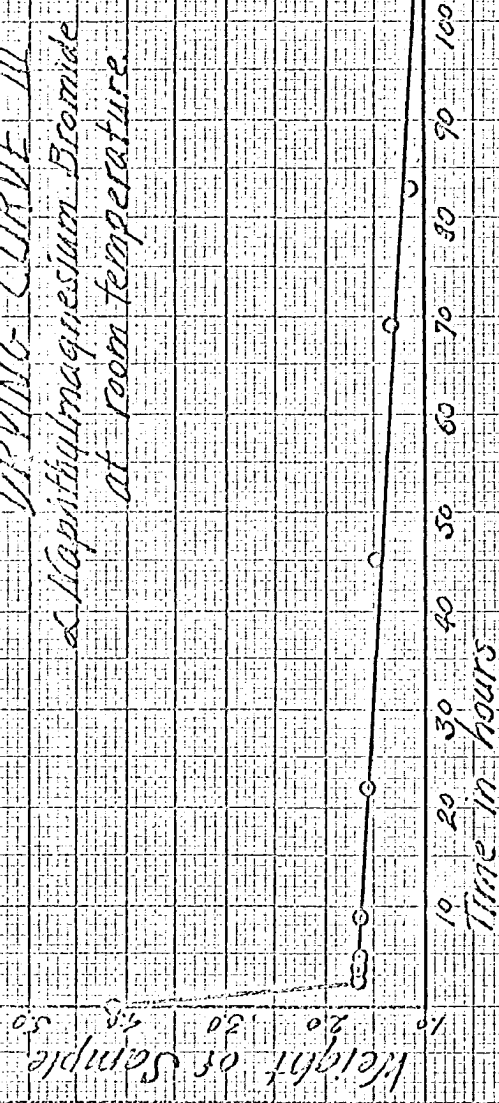
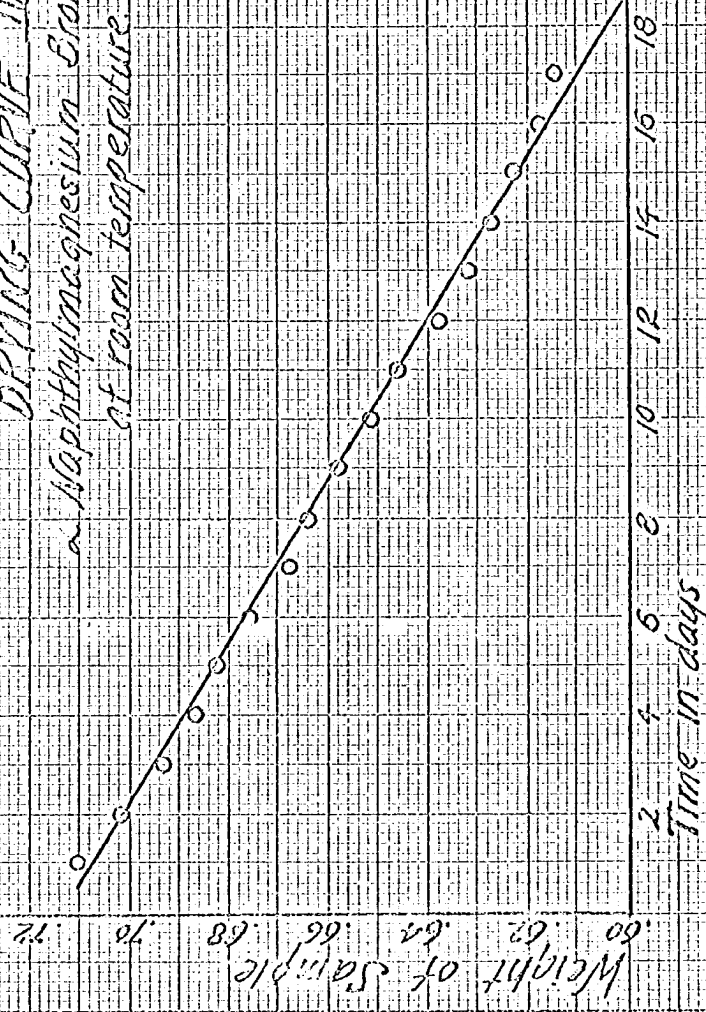


Fig. I(b)

DRYING CURVE III
 α Naphthylmagnesium Bromide
 at room temperature



DRYING CURVE III
 α Naphthylmagnesium Bromide
 at room temperature



slowly, and if kept long enough the solid very likely would lose all of the ether. It is possible that in both cases a mono-etherate is formed at room temperature, and, the vapor pressure of the ether from the mono-etherate being very low, the loss in a system in which the vapor is being constantly removed is therefore small. There is, however, a notable difference in the time required to reach the point where the loss becomes small. This is due to the fact that the solvent ether can be readily removed from the crystals of naphthylmagnesium bromide, while it must be evaporated in the cases of ethylmagnesium bromide. The rate at which the ether is lost would depend upon the temperature, the rate of removal of the vapors, the rate at which equilibrium of the etherate with the vapor is established and unknown factors, such as the extent of dissociation of the etherate into the ether-free RMgX compound and ether.

However, a similar phenomenon might be expected from the evaporation of a simple solution of an organomagnesium halide in ether. As ether is removed, the proportion of solute increases and the vapor pressure decreases, and since the rate of removal of vapors is nearly constant, the rate of loss would become less and less, and when the concentration became one mole of solvent to one mole of solute, the vapor pressure would be comparatively small, and the

form of curve would be very similar to that obtained. It is obvious that the last traces of ether in such a system might be nearly as difficult to remove as are the last traces of water from such a very soluble substance as sodium hydroxide. Extremely concentrated solutions of RMgX compounds may be obtained in ether, in fact it is possible to crystallize but very few of them.

The fact that a substance analyzing nearly exactly one mole of ether for each mole of organomagnesium halide is obtained from all Grignard reagents regardless of the size of the R group or the halogen is to be expected since in all cases as the mole fraction of solute to solvent approaches one-half, the vapor pressure of the system at the same temperature would be the same and if the rate of removal of the vapors is constant the rates of loss should be identical. Consequently an analysis at the point where the loss becomes negligible would show approximately the same molecular composition.

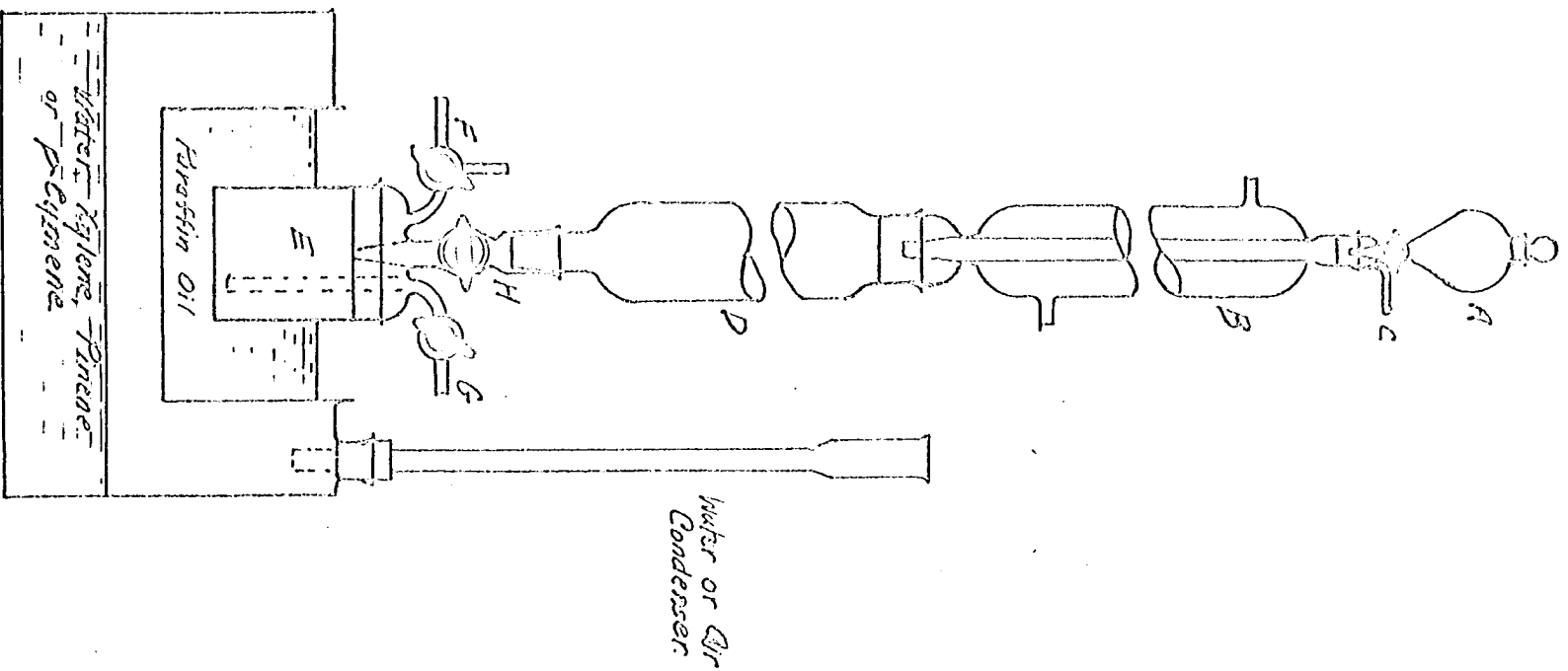
If the solution hypothesis is correct, it should be possible to remove ever increasing quantities of ether as the temperature is raised, and, depending upon the stability of the reagent, it might be possible to remove the ether practically completely. A series of experiments was made in which the solution of the Grignard reagent was dried at different temperatures in an inert atmosphere, and the

residue analyzed. Particular care was exercised in the purification of all reagents.

APPARATUS.

Preliminary experiments showed the necessity of avoiding gases such as oxygen and carbon dioxide, which react with Grignard reagents, especially since a small amount of the dry reagent was exposed to these gases at a relatively high temperature for a rather long period, and then analyzed. Even a very small amount of oxygen or carbon dioxide would decompose a relatively large proportion of the sample. Consequently an apparatus, Figure II, was designed to permit the preparation, filtration, and drying of the Grignard reagent in an inert atmosphere of hydrogen or nitrogen. It consisted of a dropping funnel (A), ground to the condenser (B), with side tube (C), for the entrance or exit of the gas. The condenser was attached by a ground glass joint to a reaction vessel (D) which in turn, was ground to a weighing bottle (E) having tubes (F), and (G), fitted with glass stopcocks so that the gas could be run in or out at either place. The glass stopcock in the tube (F) was three way, permitting the air in the tube to be flushed out after disconnecting to weigh, and reconnecting to the gas supply. The other tube (G) reached nearly to the bottom of the flask in

Fig II



order to permit complete removal of the air, and also to permit washing of the solid and forcing out of the wash liquid, if desired.

MANIPULATION.

In a typical run the apparatus was cleaned thoroughly, and dried in an oven at 110° for not less than two hours. It was cooled and then all ground glass joints and stopcocks given a light coat of vaseline except the stopcock (H) between the reaction flask and weighing bottle. This one received a small amount of vaseline on the edges, but none in the center near the opening. A small plug of previously dried absorbent cotton⁽²⁶⁾ was forced down into the narrow tube at the bottom of the reaction vessel (D), and the magnesium turnings put in. It was then assembled and the air displaced by hydrogen.

The hydrogen used was taken from a tank and purified by leading it through a red hot tube containing metallic

(26) A number of runs were made using a variety of filtering agents such as cotton, glass wool, and combinations of cotton or glass wool with white sea sand, Kieselguhr, and carbon black. A good cotton filter gave as good results as any, seemed to undergo no reaction with reagent, and was more convenient to use.

copper, through a tube containing soda lime, through two tubes containing calcium chloride, through concentrated sulfuric acid and finally through two lime towers filled with phosphorous pentoxide supported on glass wool. The hydrogen then went to a manifold so designed that the gas could be sent into the apparatus at any one of the openings, and also leave at any other one. After leaving the apparatus, the gas was run through sulfuric acid to prevent any back diffusion of air. A safety outlet through a mercury trap prevented the development of any undue pressure in any part of the apparatus or purification train. On flushing out the apparatus, the hydrogen entered at the top through the tube (C), and left through the tube (G). This permitted the ready removal of all the air. After running through, at the rate of about two bubbles per second, for an hour, the stopcock (G) was closed, then stopcock (H), the flask disconnected, and weighed.⁽²⁷⁾ In the meantime

(27) The weighing bottle was always weighed with a slight pressure of hydrogen enclosed. The maximum pressure that could be attained was that of the mercury safety trap, or about five centimeters of mercury. Ordinarily this was not reached. The maximum error thus introduced by variations in the weight of the gas was considerably less than the usual allowable error in weighing. In this way any leaks in the ground glass joints permitted loss of hydrogen rather than the ingress of air.

the hydrogen continued to flow from the bottom of the reaction vessel, preventing the admission of air. After weighing it was reconnected, stopcock (H) opened, and then stopcock (G), and the flushing continued. This was repeated at thirty minute intervals until constant weight was obtained. Usually two or three weighings sufficed.

In the meantime dry ether and ethyl bromide in the proportion of three parts ether to one part of halide were placed in the dropping funnel (A), and a small piece of freshly cut sodium added, the funnel stoppered and allowed to stand for a few minutes in order to remove any moisture absorbed from the air during the transfer. There was no indication of a reaction between the halide and the sodium in the time allowed. When the weighing bottle had attained constant weight, the stopcock (H) was closed and hydrogen run into the weighing bottle at (F) and out through tube (G). The tube (C) was also opened to the hydrogen supply so that the entire interior of the apparatus was under slight pressure of hydrogen. Any expansion was taken care of by escape of gas through the sulfuric acid trap, and any contraction was immediately offset by the admission of more hydrogen.

The ether solution of the halide was then run into the reaction vessel by opening the stopcock, and warming the funnel slightly with the hand. Usually the reaction started soon after the addition of the solution to the magnesium, and in a few instances it became so vigorous that it was necessary to cool the vessel with a cold damp towel. The contents were stirred occasionally or continually as desired by forcing the stream of hydrogen up through the vessel by adjusting the proper stopcocks. After the reaction was apparently over, the product was allowed to stand in contact with the excess magnesium for a short time or gently refluxed by carefully applying a micro-burner to the outside of the vessel. Stopcock (G) was then closed, (F) turned to connect with the exit trap, and hydrogen admitted at (C). A small pressure (regulated by the mercury safety trap) of about fifty millimeters of mercury was built up in the upper part of the apparatus, and then stopcock (H) was opened. The solution was forced by the pressure of the hydrogen through the cotton filter and into the weighing bottle. By reversing the direction of the stream of hydrogen, ether could be distilled up into the reaction vessel, condensed, and then, by again reversing the direction of the gas, wash the remainder of the Grignard solution down into the weighing bottle.

The contents of the weighing bottle were then dried under the various conditions by heating in a water bath or an oil bath, designed to maintain a constant temperature, for the designated time with a constant stream of hydrogen running through the weighing bottle.

The apparatus was then allowed to come to room temperature, the stopcocks closed, the flask disconnected, wiped clean of oil with benzene, then with dry cheesecloth, and weighed. In the drying experiments, after weighing, the apparatus was reconnected to the hydrogen manifold by tubes (F) and (H). The air in tube (F) was then flushed out by permitting the hydrogen to escape from the side tube before admitting it to the bottle. In this way admission of air was prevented. The hydrogen was then admitted to the bottle by turning stopcock (F) and opening stopcock (H) ⁽²⁷⁾ to the exit trap, and the drying continued.

(27) After the first period of drying the weighing bottle was usually connected directly to the exit trap by fitting a rubber stopper with a glass tube in the enlargement in tube (H) rather than reconnecting to the entire apparatus.

METHOD OF ANALYSIS.

(1) Gas Analysis.

In the cases where the volume of ethane evolved was to be measured, the weighing bottle was immersed in cold water, a small dropping funnel attached by means of a piece of rubber tubing to (H) and twenty five cubic centimeters of distilled water put into the dropping funnel by means of a pipette. One of the tubes (F) was attached to a eudiometer⁽²⁸⁾ for collecting the gas. After adjusting the pressure in the apparatus by leveling, the system was closed and a slight vacuum was obtained by lowering the leveling bottle. Water from the dropping funnel was then slowly and carefully admitted through (H). The reaction was very vigorous and the water was forced from the eudiometer into the leveling bottle. After all of the reagent was decomposed, the remainder of the twenty five cubic centimeters

(28) Runs with and without a sulfuric acid wash bottle to remove ether gave identical results, and, in general, on account of the danger of sulfuric acid sucking back, it was not used.

of water⁽²⁹⁾ was run in carefully so as to not admit any air. After standing for some time in order to come to equilibrium at room temperature, the pressure was adjusted by leveling, and the volume of gas measured, either by transferring to a burette, or by measuring the volume of water displaced. Generally, on account of the large volume of gas obtained, the latter method was used. After deducting the volume of water added from the measured volume of gas, it was corrected for temperature, pressure and vapor pressure. No correction was applied for solubility of ethane.

(2) Acid Titration.

The weighing bottle and contents were transferred to a casserole and sufficient standard sulfuric acid to react completely with the Grignard reagent was added by means of

(29) Since the precipitate formed by the reaction with water usually stood for an hour or more in contact with a very large excess of water, there is little likelihood that any of the Grignard reagent remained undecomposed because of a coating of the basic compound. The precipitate in nearly all cases was very slimy, much like "milk of magnesia" rather than in large particles. On a few occasions some of the solid Grignard, due to faulty manipulation, was forced into the tube (G). It was generally rather difficult to get this part to react with water since the tube was closed, and in those cases the gas analyses ran low.

a pipette. The casserole was heated on a hot plate nearly to boiling until the precipitate was completely dissolved. The liquid was then carefully transferred to a volumetric flask, the casserole and weighing bottle being thoroughly washed with distilled water. After cooling, the contents were diluted to the mark. Aliquots of this solution were then titrated with standard potassium hydroxide using methyl orange, and calculated to the corresponding RMgX compound according to the method of Gilman, Wilkinson, Fishel and Meyers.⁽³⁰⁾

(3) Halogen Determination.

An aliquot of the above solution was exactly neutralized with potassium hydroxide or a slight excess of pure, precipitated calcium carbonate⁽³¹⁾ added, and then titrated with standard silver nitrate solution, using potassium chromate as indicator.

(30) Gilman, Wilkinson, Fishel and Meyers, J. Am. Chem. Soc., 45, 150 (1923).

(31) The latter method, on account of its convenience was more generally used. Occasionally check determinations were made on the same aliquot used for the acid titration, as it was found the color of the methyl orange did not interfere seriously with the end point with potassium chromate. The results of the titrations carried out both ways on the same sample usually checked very closely.

(4) Magnesium.

The magnesium in an aliquot of the above solution was determined by precipitation as magnesium ammonium phosphate, and ignition to the pyrophosphate, and weighing as such.

MODIFIED APPARATUS.

Some difficulty was experienced in securing perfectly dry reagents, especially in the summer when the humidity was high. Even with utmost precautions in the preparation of the reagents, and in spite of the presence of freshly cut metallic sodium in dropping funnel (A),⁽³¹⁾ an opalescence often developed in the reaction vessel when the reaction started. Metallic sodium was also placed in the reaction vessel⁽³²⁾ with no better results. It seemed certain that the trace of moisture must have gained access during the transfer of the reagents through the air. To avoid this difficulty, the apparatus in Figure III was set up, identical in principle with the previously described apparatus, but permitting the distillation of the reagents directly from dehydrating agents into the reaction vessel.

Two fifty cubic centimeter distilling flasks, (A) and (B), with bent side arms were attached to a condenser (C),

(31) The liquid sodium-potassium alloy was also tried with no better results.

(32) Houben reports yields as high as 99.85% RMgX compound by the simple expedient of preparing the reagents in the presence of metallic sodium. Houben Weyl, Vol. IV., p. 725.

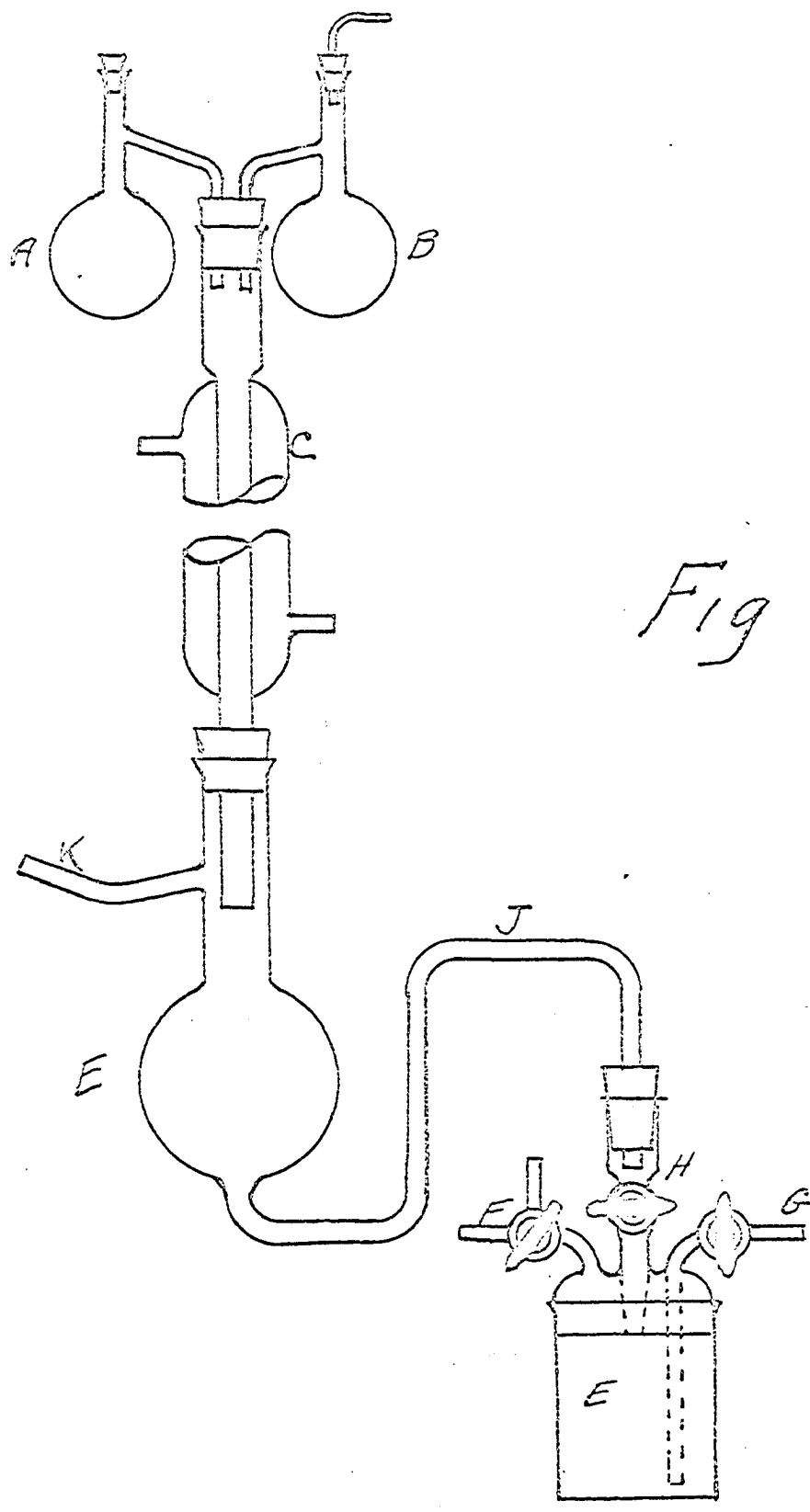


Fig III

by means of a two-holed rubber stopper. One of the flasks was connected to the hydrogen supply and to the exit trap by means of a rubber stopper fitted with a T-tube. The condenser led to a reaction flask (E) made by sealing a tube to the bottom of a fifty cubic centimeter distilling flask and bending the tube in the form of a siphon (J). The weighing bottle, as previously described, was then attached to the siphon tube by means of a piece of rubber tubing, the end of the siphon tube being drawn out so that it entered inside of tube (H) of the weighing bottle.

The apparatus was cleaned and dried for not less than two hours in an oven at 110° . A small plug of dried absorbent cotton was forced down into the siphon tube, in the position shown in Figure III, and sufficient magnesium turnings to form five to eight grams of the solid Grignard reagent⁽³³⁾ put in the flask, and then the whole dried for a few minutes at 110° . The apparatus was then assembled as shown in the diagram. About two grams of phosphorous pentoxide was put into the distilling flask (B), and the hydrogen

(33) An excess of magnesium was always put into the reaction flask in order that all of the halide could react. This was done in order to avoid the possibility of a reaction of the unchanged halide with the Grignard reagent during the drying.

then allowed to displace the air in the apparatus, entering at the top and escaping through tube (G) of the weighing bottle, all other avenues of escape being closed. The system was allowed to sweep out for two hours in contact with the phosphorous pentoxide. The weighing flask was then detached as previously described and weighed at thirty minute intervals until constant weight was attained. Then forty cubic centimeters of ether and a few cubic centimeters of a Grignard reagent (usually phenylmagnesium bromide, but in some cases, a solution of the Grignard reagent to be prepared) were run into flask (A), and ethyl bromide or other halide added to flask (B), being dried by the phosphorous pentoxide. The system was then allowed to stand for thirty minutes to permit complete drying of the reagents and to displace any air that may have entered. Stopcocks (G) and (H) were closed, and the side tube (K) of the reaction vessel opened to the exit trap. The ether was then distilled from flask (A), through the condenser and into the reaction flask. Then the halide was distilled from the phosphorous pentoxide into the reaction flask until the proportion of ether to halogen was about three or four to one. In general, sufficient halide was used to give from five to eight grams of $RMgX$ compound, as this size sample was the most convenient to handle with the solutions used. Little trouble was experienced in getting

the reaction started with reagents prepared in this way, even α-bromnaphthalene starting rather readily. The reagents secured in this way gave but a very slight opalescence at most when the reaction started and usually remained perfectly clear. The procedure from this point was identical with that previously described.

ETHYLMAGNESIUM BROMIDE.

The results obtained by drying ethylmagnesium bromide at the various temperatures are shown in Table I. Drying for a period of three hours at a temperature of 150°-160° seems to be the most desirable for ethylmagnesium bromide although it can be heated to a considerably higher temperature with little decomposition.⁽³⁴⁾ The determinations of active Grignard reagent by two different methods, entirely different in principle, proves beyond doubt that decomposition had not taken place. However, in addition to this, the solid gives a strong positive test for Grignard reagent with Gilman and Schulze's⁽³⁵⁾ reagent, reacts in xylene solution with benzophenone to give a 90% yield of diphenylethylcarbinol, and with carbon dioxide to give propionic acid. In order to get a third analytical check, the iodine titration

(34) Lohr, (Ann., 261, 72 (1890).) heated the compound obtained by the action of ethyl iodide on magnesium in a sealed tube to a temperature of 300° without decomposition. It is likely that Lohr was not dealing with ethylmagnesium iodide but rather with magnesium diethyl. Grignard (loc. cit.), however, found that ethylmagnesium bromide began to decompose at 200° and underwent violent decomposition at 300° with the formation of much gas and a brown liquid.

(35) Gilman and Schulze, J. Am. Chem. Soc., 46, 2002 (1924).

method of Job and Reich⁽³⁶⁾ was attempted. The method was very unsatisfactory for the solid reagents since it was necessary, in order to avoid side reactions, to always have an excess of iodine present. Here, the iodine solution could only be added to the solid, so that the conditions were ideal for the side reaction rather than for the estimation of the active reagent. However, in spite of this, the iodine titration showed 89.70% of active Grignard reagent, a result which proves conclusively the foregoing conclusions.

Although the determinations do not show 100% Grignard reagent, the high bromine results indicate clearly the presence of a little magnesium bromide which seems to be always present. If the difference between 100% and the percent of Grignard reagent found be calculated to magnesium bromide,⁽³⁷⁾ the bromine and magnesium found check very closely

(36) Job and Reich, Bull. soc. chim., 53, 1414 (1923).

(37) Meisenheimer and Casper, (loc. cit.) have shown that the ether is readily removed from magnesium iodide etherate by heating in a vacuum for about two hours. It is accompanied, however, by a loss of iodine. Magnesium bromide etherate lost the first mole in a vacuum at room temperature in a short time, and slowly lost a large proportion of the remaining mole in four days.

with that to be expected. These results indicate quite clearly that but a very trace of ether at the most could remain, and since a sensitive test for traces of ether is lacking, conclusions must rest on the analytical data.

The most remarkable result, however, is that the ethylmagnesium bromide remained active, gave a positive test for RMgX compound with Gilman and Schulze's reagent, and showed 87% RMgX compound by gas analysis after having been heated to 330° for three hours at ten millimeters pressure. It is hardly conceivable that any ether could remain after this treatment. However, it is possible that magnesium diethyl may have been formed with the simultaneous formation of an equal quantity of magnesium bromide. Since magnesium diethyl is not volatile, the quantitative results would have been the same in both cases.

TABLE I.

ETHYLMAGNESIUM BROMIDE.

				% RMgX	% Br	% Mg			
Temp:	Press:	Time of:	Gas :	Acid	Found:	Theor:	Found:	Theor:	
:	:	heating:	Anal.:	titration:	:	:	:	:	
Room:	Atm.:	10 day:	:	65.6 ^a	40.65:	40.65:	12.11:	12.16:	
60	"	12 "	:	68.8 ^a	42.64:	42.63:	12.75:	12.73:	
135	"	3 hrs.:	:	77.52 ^b	51.50:	59.94:	-----:	18.24:	
150	"	" "	:	99.28 ^c	61.03:	60.13:	18.12:	18.20:	
168	"	" "	:	93.36:	100.40	61.51:	61.73:	18.10:	17.90:
"	"	" "	:	93.57:	96.54	62.94:	61.67:	18.19:	17.92:
"	"	" "	:	96.73:	96.22	60.60:	60.82:	:	:
"	"	" "	:	95.06		60.6	61.27:	:	:
"	"	" "	:	96.92:	96.35	63.6	60.92:	18.68:	18.05:
100	10 mm:	" "	:	85.87:	85.03	54.05:	:	:	:
"	"	6 "	:	95.97		60.86:	61.03:	18.05:	18.04:
130	30 mm:	3 "	:	91.83:	96.59	63.09:	63.15:	:	:
330	10 mm:	3 "	:	87.03:		:	:	:	:

(a) The theoretical bromine content due to ethylmagnesium bromide, when calculated from the acid titrations, should be 39.32% and 41.24%. These, subtracted from the bromine found, leave 1.53% and 1.39% respectively, which must come from some other source. When calculated to magnesium bromide which is the most likely source, it gives 1.53% and 1.60% of that substance. This, added to 65.6% and 68.8%, and the total subtracted from 100%, gives 32.84% and 29.64% of ether. Assuming that all of the ether is associated with ethylmagnesium bromide, the empirical

formulas are $C_2H_5MgBr \cdot 0.8887(C_2H_5)_2O$ and $C_2H_5MgBr \cdot 0.7752(C_2H_5)_2O$.

- (b) These theoretical percentages are calculated on the basis of the pure, ether-free, ethylmagnesium bromide.
- (c) These, and the remainder of the theoretical percentages are calculated for a mixture of ethylmagnesium bromide and magnesium bromide, the latter being determined by subtracting the percentage of ethylmagnesium bromide found from 100%. In cases of disagreement between the percentage of ethylmagnesium bromide found by acid titration and by gas analysis, the latter value was used.

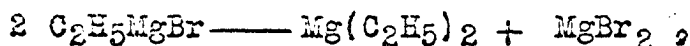
PROPERTIES.

The dry ethylmagnesium bromide prepared at 150°-155° was a white amorphous solid. It reacted vigorously with water, and decomposed in the air. If it is finely divided, the reaction in air may become rapid enough to cause ignition. This suggests the presence of magnesium diethyl and seems to indicate that the Grignard solution may, as suggested by Jolibois⁽³⁸⁾ and Terentiev⁽³⁹⁾ be a mixture of magnesium diethyl and magnesium bromide. While it is known that magnesium dialkyls are spontaneously inflammable, it is possible that the magnesium bromide raises the ignition temperature to a point where the usual reagent will not ignite. This idea is further confirmed by the fact that if a Grignard reagent (phenylmagnesium bromide or ethylmagnesium bromide) be boiled with xylene, a white precipitate forms when most of the ether is driven off. If the xylene is filtered out with suction and washed with petroleum ether, the mass ignites as soon as the petroleum

(38) loc. cit.

(39) loc. cit.

ether is evaporated.⁽⁴⁰⁾ It seems possible that the actual reagent may be a equilibrium mixture according to the equation,



and that the equilibrium is pushed to the right by an increase of temperature, various reagents, etc. This question cannot be answered until a test is developed permitting the differentiation between organomagnesium halides and magnesium dialkyls.

The solubility of the dry ethylmagnesium bromide was determined in a variety of solvents. A number of samples of the dried reagent was prepared, the solvent added, and the mixture refluxed for a few minutes in an atmosphere of hydrogen. They were then disconnected from the hydrogen and allowed to stand for a week, during which time they were shaken several times daily. The quantity dissolved was then determined by analyzing a known volume of the clear solution. The results are shown in Table II.

(40) There is little probability that the spontaneous ignition is due to metallic magnesium or other metals which by the treatment have become pyrophoric, since perfectly clear filtered solutions of ethylmagnesium bromide behave in the same manner.

TABLE II.

SOLUBILITY OF ETHYLMAGNESIUM BROMIDE.

Solvent	Solubility : grams/liter:	Method of Analysis.
Petroleum Ether	0	Acid titration and Bromine
Benzene	11.5	" " " "
Xylene	62.4	" " " "
Anisole	140.8	" "
Dibutyl ether	123.4	" "
Triethyl amine	31.96 ^(a)	Gas analysis
Dimethyl aniline	91.88 ^(b)	Bromine
Diethyl ether	Soluble completely.	

(a) The mixture became very warm, indicating a probable reaction.

(b) The end point was very indistinct, the result therefore inaccurate.

A determination of the electrical conductivity in ether solution checked the value obtained by Terentiev.⁽⁴¹⁾ In xylene no current could be detected, even with the cell directly in series with the phones, and measurement against a radio grid leak indicated a resistance in excess of 1,000,000 ohms. In dimethyl aniline and triethylamine, the conductivity of saturated solutions was found to be 1.4×10^{-5} and $.5 \times 10^{-5}$ respectively. Later experiments have shown that magnesium bromide in dry ether is an exceptionally good conductor, and it is possible that the conductivity of Grignard reagents may be due to the small amount of magnesium bromide which is always present. This seems to be indicated by the non-conductivity of xylene solutions, in which an appreciable amount of RMgX compound is dissolved, but probably no magnesium bromide,⁽⁴²⁾ This is further confirmed by experiments with phenylmagnesium bromide. The conductivity of both Grignard reagents was found to be very nearly the same. Since,

(41) Loc. cit. The value determined was as follows:-
Specific conductivity (35) ---0.0001036
Molecular " ---0.0805386

(42) There seems to be no information in the literature concerning the conductivity of magnesium bromide in ether.

in both cases, the yield of Grignard reagent is nearly equal, it is likely that the amount of magnesium bromide in the two solutions is also equal, and the conductivity should be nearly the same. One would hardly expect two Grignard reagents with such very different groups to show the same conductivity, if the conductivity is due to that substance. It is further confirmed in that the conductivity of benzylmagnesium chloride was found to be very nearly the same, notwithstanding the different halogen in the compound. For example, with a given conductivity cell, the resistance of ethylmagnesium bromide was found to be 1616 ohms, phenylmagnesium bromide 1775 ohms, and benzylmagnesium chloride 2550 ohms. The resistance of a N/50 potassium chloride solution for the same cell was 60.49 ohms. Magnesium chloride is much less soluble in ether than magnesium bromide, and it is possible that the difference noted may be due to a difference of concentration.

THE REACTION OF DRY ETHYLMAGNESIUM BROMIDE
WITH BENZOPHENONE.

Ethylmagnesium bromide was prepared as in the previous experiments and dried for five hours at 150°. A solution of benzophenone in toluene was then added with no apparent reaction. It was removed from the apparatus and connected to a reflux condenser and refluxed for fifteen minutes. As there was yet no apparent reaction, the flask was disconnected and the solid cake was broken up with a stirring rod. A small portion of the solid was removed, which reacted very vigorously with water. It was again connected to the condenser and refluxed for two hours. The white solid which initially was caked had broken up to a fine white powder. The reaction mixture was cooled and decomposed with iced hydrochloric acid, the toluene layer separated and steam distilled. The decomposition with water was very vigorous and acted very much as if unchanged Grignard reagent were present. Toluene came over first followed by heavy oil which crystallized on cooling. The crude product melted at 85°-89°, and the melting point was not depressed by mixing with some known diphenylethylcarbinol prepared in the usual manner with ether solutions. The amount of product obtained was approximately equal to the amount of benzophenone used, corresponding to a yield of 85-90%.

n-PROPYLMAGNESIUM BROMIDE.

n-Propylmagnesium bromide was prepared in the same manner from propyl bromide, ether and magnesium. It was dried at 150° for three hours, decomposed with water, and analyzed as described.

: Determination	: Found		: Calculated for 92.5% C ₃ H ₇ MgBr 7.5% MgBr ₂
	: I	: II	
: RMgX (acid titr'n)	: 92.5 ^a	:	:
: Bromine	: 56.56	: 56.56	: 56.6
: Magnesium	: 16.66	: 16.09 ^b	: 16.62

- (a) This yield checks that obtained by Gilman and McCracken, J. Am. Chem. Soc., 45, 2462 (1925).
- (b) These apparently poor checks are due largely to using too small a sample. The actual weights of magnesium pyrophosphate obtained were 0.0437 and 0.0422.

n-BUTYLMAGNESIUM BROMIDE.

Butylmagnesium bromide⁽⁴³⁾ was prepared and dried at 150° for five hours. On analysis it gave the following results:

Determination	Found		Calculated for 88.41% C ₄ H ₉ MgBr 11.59% MgBr ₂
	I	II	
RMgX (acid titr'n)	88.41		
Bromine	53.95	53.71	53.87
Magnesium	15.05	15.12	14.86

It is obvious that the compound cannot contain 11.59% (equivalent to 0.285 moles) of ether, since in that case both the bromine and the magnesium determinations would be lower. If, for example, it is assumed that the remaining 11.59% is ether, the percentages of magnesium and bromine to be expected would be 13.32% and 43.76% respectively,

(43) In one experiment, the magnesium was replaced by the more active copper-magnesium alloy. the preparation was accompanied by an evolution of considerable gas and the yield of the Grignard reagent determined by acid titration, dropped to 35.64%. Simultaneously the bromine content rose to 75.95%. For a mixture of 35.64% butylmagnesium bromide and 64.36% magnesium bromide there should be 73.56% of bromine. It is very evident that coupling took place to a considerable extent.

which are far removed from those found.

Another possibility is that magnesium bromide etherate may be present, which when hydrolyzed, would increase the titration value,⁽⁴⁴⁾ and also the bromine content. Reference to the gas analysis of ethylmagnesium bromide shows the improbability of this.

(44) Experiments in this laboratory seem to indicate that magnesium bromide etherate will give an indication of active Grignard reagent by acid titration at times when the Gilman-Schulze test is negative. No quantitative results are available, and the reason is, as yet, unknown.

PHENYLMAGNESIUM BROMIDE.

Phenylmagnesium bromide was prepared in the same way as previously described and dried at 150° at atmospheric pressure for three hours. The resulting product was a brownish yellow waxy appearing solid, and diphenyl⁽⁴⁵⁾ sublimed to the top of the weighing bottle and out into the exit tube. The substance was decomposed with water and analyzed in the usual manner.

TABLE III.

Expt. No.	%C ₆ H ₅ MgBr	% Bromine (a)		% Mg (a)	
		Found	Theor.	Found	Theor.
I	90.09	46.82	44.08	12.94	13.42
II	91.67	46.41	"	13.58	"
III	90.18	42.23	"		
IV	88.34	43.59	"		
V	84.68	50.23	"		(b)
VI	86.46	44.49	"		

(a) The theoretical percentages are calculated on the basis of the pure, ether-free Grignard reagent.

(b) Powdered copper-magnesium alloy (86%Mg - 12%Cu) was used in this experiment.

(45) The diphenyl was identified by means of a mixed melting point.

It is apparent that magnesium bromide is formed in conjunction with diphenyl during the preparation of the reagent. In the subsequent drying, a part of the diphenyl is volatilized leaving a residue of RMgX compound, magnesium bromide and some diphenyl. A small amount of diphenyl is always found when the solid is decomposed with water. In the case of the alkyl Grignard reagents, the coupling product was easily driven out, but here a part of it remains.

On the basis of this assumption, the composition of the residue seems to be as follows;

RMgX	-----	90.09%
MgBr ₂	-----	7.75%
C ₆ H ₅ C ₆ H ₅	-----	2.16% .

REACTION OF DRY PHENYLMAGNESIUM BROMIDE
WITH ETHYL BENZOATE.

Phenylmagnesium bromide was prepared in a three-necked flask from 1.216 (.05 mole) of magnesium, twenty cubic centimeters of ether and 5.23 cubic centimeters (7.85 grams, .05 mole) of brombenzene. The air was first displaced by hydrogen and the reaction started by adding a drop of previously prepared phenylmagnesium bromide. After the reaction was complete, the product was dried in an oil bath at 175° for four hours with a stream of hydrogen constantly passing through. There was a small amount of unchanged magnesium left. The solid residue had the characteristic brownish-yellow waxy appearance. It was cooled and twenty-five cubic centimeters of xylene added, and then a solution of five cubic centimeters of ethyl benzoate (0.035 mole) in fifteen cubic centimeters of xylene. There was no apparent action, so the mixture was refluxed for two hours. The xylene solution became reddish-brown and the solid changed from the original yellow waxy substance to a fine white powder. It was cooled and then cold, dilute sulfuric acid added. Again there was no vigorous reaction, and the whole of the water was added at once. The mixture was warmed to complete solution, and then transferred to a distilling flask and steam distilled. Xylene and unchanged ethyl

benzoate came over first, and a brownish crystalline residue was left in the flask. The residue was filtered off and weighed (6.7 grams), then dissolved in ether, washed with sodium hydroxide and again steam distilled. It became somewhat lighter in color and more crystalline. A very small amount of a solid substance which melted at 87° - 90° came over. This was probably triphenyl methane, formed from the triphenyl carbinol by the action of sulfuric acid on the unused magnesium. The solid remaining was recrystallized twice from alcohol, and identified by means of a mixed melting point as triphenyl carbinol. The yield was 4.2 grams, or 65%, melting at 158° - 160° .

The reaction is not as clean cut as that observed by the use of ether, and the product seems to be more difficult to purify. In working with such small quantities, the percentage loss in manipulation is large, so that the yield obtained was very encouraging and proves almost beyond doubt that the residue was active Grignard reagent for the major part.

THE PREPARATION OF A LARGE AMOUNT OF
DRY PHENYLMAGNESIUM BROMIDE.

One-half mole of phenylmagnesium bromide was prepared in a three-necked flask, in which the air had been displaced by hydrogen. An excess of magnesium was used, and the product was allowed to stand with the excess of magnesium for several days in order to completely use up the bromobenzene. It was then filtered (in the air) into a distilling flask, and the excess ether distilled off on the water bath. The vacuum pump was then attached, and an oil bath substituted for the water bath. The remainder of the ether was distilled off and the residue finally heated to 180° for three hours at ten millimeters pressure. Some diphenyl distilled over into the receiver, some stayed in the neck and side-arm of the distilling flask, and considerable remained in the top layer of the solid residue which was not immersed in the oil. The solution foamed somewhat as the ether evaporated, and as a result the solid was very porous and nearly filled the distilling flask, furnishing ideal thin films for the complete elimination of ether. After cooling, a hydrogen tank was attached to the pump, the vacuum released, and the system filled with hydrogen. It was then disconnected and tightly stoppered, taking care

not to lose hydrogen, by holding the side-arm continually downward until stoppered.

The residue obtained was nearly white at the bottom of the flask, but yellowish and waxy near the top, where it was not immersed in the oil, apparently due to the diphenyl present. With a stream of hydrogen entering in the side-arm, and the neck opening held downward, some of the solid was quickly transferred to a weighing bottle. An attempt was made to analyze the top and bottom layers separately by picking out samples from each place. The results of the analyses are as follows:-

	Top	Bottom
% C_6H_5MgBr -----	94.05	99.91
% Bromine-----	42.28	44.70

The theoretical percentage of bromine in pure phenylmagnesium bromide is 44.08%. For a mixture of 94.05% of phenylmagnesium bromide and 5.95% of diphenyl, the calculated percentage of bromine is 41.46%. Since the substance was exposed to the air on two occasions, it cannot be assumed that unaccounted for bromine will necessarily be in the form of magnesium bromide. It is evident, however, that a small amount of bromine is present either as the normal bromide or as the oxy-bromide of magnesium.

The top layer very apparently contained an inert substance, probably diphenyl, while the white solid seemed to be nearly pure phenylmagnesium bromide. The titration probably was a little high since no particular effort was made to avoid oxygen during the filtration, and the solid was transferred from one weighing bottle to another through the air in weighing out the sample. However, the amount of oxidation was relatively small. The real danger of oxidation probably is during the drying, while the substance is at a high temperature. After the substance is once dried, it can be handled in the air with about the same degree of success as with such materials as sodamide or phosphorus pentoxide.

The solid substance reacts vigorously with water with the formation of benzene. It gives a very strong test with Gilman and Schulze's reagent. A small amount, placed on a watch-glass, gave a weak positive test after twenty minutes exposure to moist air, but after an hour it gave no test.

A small amount, placed in a gas bottle and attached to an oxygen tank, exploded violently soon after the oxygen was admitted. Suspended in xylene and subjected to a slow stream of dry air, the large pieces of solid material broke up and a fine white powder was formed. A small amount exposed to moist air gave a considerable amount of a brownish solid which

appeared to be diphenyl.

The solid phenylmagnesium bromide was very soluble in ether, somewhat soluble in brombenzene, slightly soluble in xylene, but insoluble in petroleum ether and in chlorbenzene, as determined by the application of Gilman and Schulze's test to the solutions. It seemed to dissolve somewhat in dimethyl aniline with a reaction, as was evidenced by a change in the color of the solvent, which darkened considerably, and by the deposition of a solid, gelatinous substance around the top of the liquid where it came in contact with the air. It failed, however, to give a test with the reagent, even when sufficient hydrochloric acid was added to completely neutralize the dimethyl aniline.

α -NAPHTHYLMAGNESIUM BROMIDE.

α -Naphthylmagnesium bromide presented a somewhat different case than other Grignard reagents. It crystallized from concentrated ether solutions readily by simply cooling the solution with a freezing mixture. The crystals obtained in this way contain one mole of ether. The formation of these crystals lends considerable support to the etherate theory, although it must be pointed out that compounds which contain the naphthalene nucleus form addition compounds very readily, and the ether of crystallization may as well be due to that part of the molecule as to the Grignard reagent.

The α -naphthylmagnesium bromide was prepared in the usual manner, but instead of drying the solution in the weighing bottle, it was cooled with an ice-salt mixture. Slightly yellow, needle-like crystals separated. The excess ether was then forced out through tube (G) by slightly inclining the apparatus, permitting hydrogen to enter at (F), with tube (G) being opened and leading to an Erlenmeyer flask as receiver. Fresh ether was then added from the dropping funnel and forced into the weighing bottle by the proper adjustment of the stopcocks. By slightly warming the ether, the crystals redissolved. On cooling again they were re-

deposited, and the ether again forced off. In this manner, the substance could be recrystallized as many times as desired. In some experiments the crystals were washed with petroleum ether in order to remove adhering ether. Even by this change of solvent it was not possible to replace the one mole of ether.

The drying curves are shown in Figure I. The mechanically held ether was lost very rapidly, usually one or two hours at room temperature being sufficient to remove it. The mole of combined ether was lost much more slowly, although it seems probable that all of it could be removed at room temperature if sufficient time is allowed. Curve II shows the rate of loss of mechanically held ether and indicates a rather sharp break. An analysis of the substance on the basis of the weight at the "break" point showed slightly more than one mole of ether. Curve III shows the very definite character of the break, while curve IV shows the loss of ether after the break. An analysis of the substance used in securing the data for curve IV showed a molecular composition of $C_{10}H_7MgBr \cdot 0.47(C_2H_5)_2O$ after drying for seventeen days. Calculated back to the original weight (after drying for twenty-four hours at room temperature) the formula corresponded almost exactly with the mono-etherate.

α -Naphthylmagnesium bromide etherate cannot be dried at as high a temperature as the other Grignard reagents. When heated to 125° for one hour, it lost but very little of the ether. When the temperature was raised to 130°, and the period lengthened to three hours, some decomposition took place as was evidenced by the orange color of the naphthalene obtained on hydrolysis. On heating to 140° for five minutes, about half of the ether was lost with little decomposition. When heated at that temperature for a longer period considerable decomposition took place with the formation of carbon. It may be possible to eliminate most of the ether by the application of a higher temperature for a brief time. The results of the analyses are shown in Table IV.

TABLE IV.

α-NAPHTHYLMAGNESIUM BROMIDE.

Treatment	% RMeX		% Br.		% Mg.	
	Found	Theor. (a)	Found	Theor. (a)	Found	Theor. (a)
25° for 20 min	62.40	75.74	23.47	26.16	b	
25° " 24 hrs.	73.32	"	25.36	"	8.00	7.96
25° " 72 "	74.34	"	27.05	"	8.00	7.96
25° " 15 days	86.58					
100° " 3 hrs.	77.84	"	27.15	"	8.09	
120° " 1 "	77.48		27.29			
130° " 3 "c	81.5		34.01			
140° " 5 min.	88.74		30.60	30.66 ^d		

- (a) These theoretical percentages are calculated for the pure mono-etherate.
- (b) In this run the crystals were dried only until it seemed as if the adhering ether might be all driven off.
- (c) Some naphthalene sublimed into the exit tubes during this run. On treatment with water, the naphthalene obtained was orange colored, indicating decomposition.
- (d) This theoretical percentage is calculated for a mixture of 88.74% of the ether-free α-naphthylmagnesium bromide and 11.26% of ether. The naphthalene obtained was white, with no evidence of decomposition.

SUMMARY AND CONCLUSIONS.

- (1). It is possible to eliminate all, or all but a trace of ether from solutions of Grignard reagents by simple heating in an inert atmosphere.
- (2). The analysis and reactions of these dried reagents show that they are decomposed but little by the process. They show normal, typical reactions of Grignard reagents.
- (3). While the results cannot furnish absolute proof, it appears probable that the ether is not an essential part of the molecule, but acts as a catalyst or solvent.
- (4). The formation of a crystalline etherate is a specific property of α -naphthylmagnesium bromide, and not a general property of all Grignard reagents.
- (5). The solubility, conductivity, and some other general properties of several Grignard reagents is reported.