

crystals melting at 60–65° were obtained. Mixed with the original ester they melted at 60°.

Another sample was allowed to stand overnight in a Dewar bulb with liquid ammonia until all the latter had evaporated. A yellow oil remained which solidified after several days. From it crystals were obtained which melted at 51°, the melting point of phenyl-urethane.

Two more samples (0.5 g.) were sealed in glass tubes with alcoholic ammonia and heated for 48 hours, one at 80° and the other at 160–180°. The only substance isolated from either was phenyl-urethane.

Summary

1. A third phenyl-biuret has been prepared by the action of alkaline hydrogen peroxide upon 9-phenyl-uric acid, and clearly distinguished from the 2 isomers previously known.

2. This substance can be transformed to *asym*-phenyl-biuret, a compound of lower melting point and greater solubility, by the action of ammonia and a great variety of organic bases, but not by alkalis. No method of reversing this reaction has been discovered.

3. Although the structure theory contemplates the existence of but 2 nitrogen-substituted biurets, there is as yet no evidence that any one of the 3 existing compounds is an enol or an oxygen ether, or that it has a ring structure.

4. Certain theoretical considerations, set forth in the preceding paper, tempt one to assume the structure of symmetrical N-phenyl-biuret for the new compound.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

THE QUANTITATIVE ESTIMATION OF THE GRIGNARD REAGENT¹

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Received July 20, 1922

Introduction

In connection with a series of quantitative studies of the Grignard reagent it was necessary to devise methods for the rapid and exact estimation of this reagent in ether, the commonly employed solvent. A search of the literature disclosed that only one method has been tried. This work by Jolibois² was repeated, and the method indicated has been found quite unsatisfactory and unreliable. The present report is an account of the study of several different methods: titration with iodine, gravimetric analysis, a so-called indirect analysis, gas analysis and titra-

¹ A preliminary report of this work was made at the Rochester meeting of the American Chemical Society, April 28, 1921.

² Jolibois, *Compt. rend.*, 155, 213 (1912).

tion with acid. Of these, the last two have been found to give eminently satisfactory results, and they have already been successfully used in work to be published shortly.

Discussion of Analytical Methods

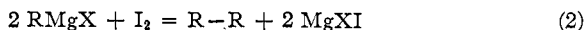
I. **Titration with Iodine.**—This method of Jolibois assumes that the following reaction occurs quantitatively when iodine is added to a solution of the Grignard reagent.



The method is to titrate the solution of unknown strength with standard iodine solution.

A brief study showed the method to be faulty in several particulars. First, the reaction is not quantitative, even on the application of heat and when a large excess of iodine is present. This was established by the presence of some unaltered reagent. Second, the end-point is not certain. When iodine solution is added at different rates to aliquot portions of a Grignard reagent, considerably more of it is required in rapid titrations than in slow titrations. Even when the rates of addition were timed to be approximately alike, the difference in iodine required was too great.

There is a likely reason for this second difficulty. In addition to the reaction assumed by Jolibois as the only one taking place, the following occurs simultaneously.



This reaction, which requires only $\frac{1}{2}$ the iodine for 1 molecule of the RMgX compound that is required by Reaction 1, probably takes place to a greater extent when the titration or addition of iodine is slow. Recent work by Datta and Mitter³ on the action of halogens on the Grignard reagent supports this explanation.

It was also observed that an excess of iodine gradually disappeared when the titration mixture was allowed to stand. This may be due, in part, to the formation of more of the RMgI compound when the RI formed in Reaction 1 combines with the magnesium which is generally left in small amounts.

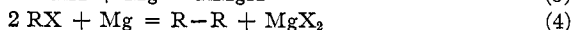
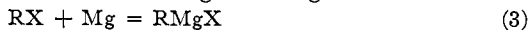
II. **Gravimetric Analysis.**—By the selection of such compounds as would supposedly react quantitatively with the RMgX compound to give a sparingly soluble product readily obtainable in a high degree of purity, it was hoped that the quantity of Grignard reagent in a solution could be determined from the weight of compound formed after reaction. With this in view, a study⁴ was made of the reaction between phenylmagnesium bromide and phenyl isocyanate. Several analyses showed the method to be quite unsuitable. The use of other compounds for the same purpose

³ Datta and Mitter, *THIS JOURNAL*, **41**, 287 (1919).

⁴ Work done by L. E. Smith.

was even less satisfactory, for not only were the results decidedly low and irregular, but the technique was too involved and time-consuming.

III. **Indirect Analysis.**—This method assumes that the following two reactions occur in the preparation of the Grignard reagent.



With some RX compounds the following typical reaction is known to take place to a small extent.

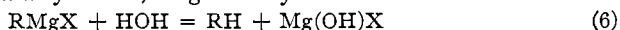


This, however, would not affect any analysis based on Reaction 4 where 2 molecules of RX react with 1 atom of magnesium to give 1 molecule of MgX_2 , and where these compounds and not the hydrocarbons formed are the basis of the analysis.

In this method it is necessary to know the weight of magnesium and the weight of RX compound which actually enter into reaction. Obviously, the weight of reacting magnesium is determined by the difference between the weight of magnesium initially used and the weight of magnesium recovered. The weight of RX which reacts is determined in another way: the halogen (X) which distributes itself between the RMgX of Reaction 3 and the MgX_2 of Reaction 4 is a measure of the RX which has entered into reaction. This halogen is conveniently determined by the Volhard method after filtration of the magnesium and addition of dil. nitric acid to the filtrate.

The greatest difficulty in this mode of analysis is the determination of unchanged magnesium. Filtration of the reaction mixture in air is accompanied by a partial decomposition of the Grignard reagent by moisture, carbon dioxide and oxygen. Any insoluble compounds so formed, particularly the basic magnesium halide, would be retained on the filter and thus make the determination of magnesium high. However, by rapid manipulation it was found that the results obtained by this method are in reasonable agreement with those by the two preferred methods. Notwithstanding the apparent value of the method, it was discarded, largely because of inherent difficulties in technique.

IV. **Gas Analysis.**—The basis of this method is the smooth decomposition of the Grignard reagent by various compounds containing "active hydrogen,"⁵ particularly water, to give a hydrocarbon.



The method, as used, is restricted to those RMgX compounds giving a hydrocarbon that is gaseous at ordinary temperatures. Zerewitinoff⁶

⁵ A common interpretation of active hydrogen is that which refers to hydrogen replaceable by a metal. The present extension, which is tolerated somewhat because of usage, includes all hydrogen atoms replaceable by MgX when treated with an RMgX compound.

⁶ Zerewitinoff, *Ber.*, **40**, 2023 (1907); **41**, 2233 (1908).

has devised, and successfully used, a sort of converse application of this principle in quantitatively estimating the number of active hydrogen atoms in a great variety of compounds.

Comparative simplicity of operation and exactness commend the method. It is necessary only to add an excess of water or dil. acid (which dissolves the basic magnesium halide) to an aliquot portion of Grignard reagent in ether, and then measure the volume of gas evolved. Unquestionably, this is the most accurate method of those studied.

V. Titration with Acid.—Reaction 6 is the basis of this method also. Inasmuch as the basic magnesium halide is a measure of the original Grignard reagent, it is necessary only to titrate with standard acid, after decomposition by water, to find the quantity of RMgX compound.

Because this method is the simplest of those mentioned, and because it is entirely comprehensive, not being restricted as is the gas analysis to RMgX compounds having 4 or fewer carbon atoms, it has been used most extensively. An apparent disadvantage is its lack of absolute accuracy, for it is inherently less exact than the gas analysis. The results always run high, but are uniformly high. A reason for this is obvious when one considers the almost insurmountable difficulties arising in preparing reagents and apparatus that are absolutely dry; and added to this is the fact that a small quantity of moisture decomposes a relatively large amount of RMgX compound.

The quantity of acid required, therefore, to neutralize this basic compound will be greater than that needed for the RMgX compound *actually available* as such. The method of gas analysis is free from this difficulty, because the quantity of gas obtained by decomposing the RMgX compound with water is a direct measure of this compound actually available. Any gas formed as a result of moisture originally present would have escaped almost entirely under the conditions of preparation, whereas the basic compound always remains and is sufficiently soluble to make the analysis run high.

It is known that oxygen also reacts with the Grignard reagent. The compound formed in largest quantity by this reaction is probably $Mg(OR)X$, likewise a basic substance.

A third substance in the air which decomposes the RMgX compounds is carbon dioxide. Here the resulting compound is $RCOOMgX$, a salt which does not affect the titration with acid, because on hydrolysis this salt gives equivalent amounts of acid and base.

In connection with these sources of error, attention should be called to a very recent paper by Clover⁷ on the auto-oxidation of ethyl ether. He found that a sample of oxidized ether which had stood, under certain conditions, for about 6 months had then a concentration of oxygen ap-

⁷ Clover, *THIS JOURNAL*, **44**, 1107 (1922).

proximately equivalent to 0.35 *N*, due almost entirely to the formation of ether peroxide. The formation of acetic acid in ether by oxidation was very much slower, and amounted to not more than a few per cent. of the quantity of ether peroxide present. Here, then, are two possible sources of error. Even under optimum conditions for the formation of these compounds, it is doubtful whether the possible error involved in methods using either the analysis of gas or titration by acid would be serious. This possible error becomes negligible when it is considered that the ether used was specially dried, had always been allowed to stand over sodium, and never was kept for longer than 4 months,—and then generally in a dark bottle or in a dark place.

Materials

The RX compound selected for most of the work on all the methods of analysis was ethyl iodide. This was fractionally distilled from phosphorus pentoxide and kept in a tightly stoppered, dark bottle. A stock lot of magnesium turnings was used without special treatment. The ether was prepared from commercial anhydrous ether by drying it with calcium chloride and then allowing it to stand for several days over freshly cut sodium. A first distillation was made with sodium present, and the distillate collected in a bottle containing sodium. There it was kept for several days, and then redistilled, this time from a large quantity of phosphorus pentoxide. The distillate was collected in a bottle containing fresh sodium and kept tightly stoppered.

Procedure

Sufficient has been said of the methods of titration with iodine and the gravimetric analysis to indicate why they were discarded. What follows concerns the other three methods which gave results in reasonable agreement when aliquot portions were taken from a single preparation. Certain preliminary operations were common to these methods. Inasmuch as these were merely incidental to procuring aliquot portions for the analyses given here they are detailed under "Procedure" in a following paper, where a special reaction flask is described.

Indirect Analysis.—After the sediment had settled, practically all of the clear supernatant liquid was siphoned off. This left for filtration only a small quantity of material, and so considerably diminished the time of filtration. No correction was made for the insoluble impurities contained in the magnesium used, because the metal was over 99.7% pure.

An aliquot portion of the clear ethereal solution containing ethylmagnesium iodide, unchanged ethyl iodide, and magnesium iodide formed according to Reaction 4 was decomposed by dil. nitric acid. The clear mixture of 2 layers was shaken in a separatory funnel, and the lower acidified aqueous solution run off. By a subsequent extraction with ether any remaining ethyl iodide was taken up in the ether while the magnesium iodide remained in the water. This aqueous solution was then diluted to a definite volume, and aliquot portions were titrated for iodine by the Volhard method.

There is a multiplication of error common to all these methods because the aliquot portion removed for analysis was generally $\frac{1}{8}$ the total volume of solution containing the Grignard reagent.

Gas Analysis.—The more important parts of the apparatus⁸ used in the gas analysis are given in the accompanying drawing.

In outline, a known volume of ethylmagnesium iodide was run from the graduate (*A*) to the reacting chamber (*C*), where it was decomposed by the dil. sulfuric acid added from *B*. The liberated ethane was bubbled through the conc. sulfuric acid washer (*D*), to remove any ether vapor, before being measured in the gas buret.

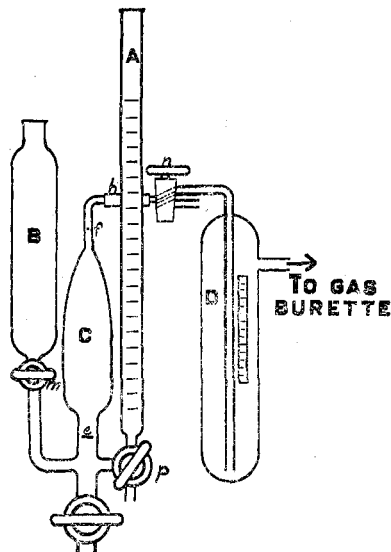
In actual manipulation the detailed technique was essentially that of related methods of gas analysis. *B* was filled about $\frac{2}{3}$ with dil. sulfuric acid (1:20). After opening the 3-way stopcock *n* to the air, the acid was allowed to run from *B* into *C* to the mark *e*. Stopcock *n* was then turned to connect *C* with the gas washer *D*, which, in turn, was connected with a 400cc. gas buret. Then Stopcock *m* was opened until *C* was about half-filled with acid.

When Stopcock *p* was opened to connect *A* and *C*, a measured volume of the Grignard reagent ran into *C* where it was immediately and smoothly decomposed liberating the hydrocarbon. A jet of steam was then directed on *C* to drive over any ethane which may have dissolved in the ether or water layers. After running acid from *B* so that the volume of liquid in *C* reached the mark *f*, the gas in the buret was brought to approximately atmospheric pressure by raising the leveling bulb connected with it. The apparatus was then disconnected at *h*, and the gas pressure in the buret brought to that of the atmosphere. Readings were noted of the gas volume, the temperature of water in the jacket surrounding the gas buret, and the barometric pressure.

Several readily ascertained corrections were then made. From the total volume of gas was deducted the volume of *C* from *e* to *f* which had previously been determined. This volume of air was forced over in the course of the analysis, a part before admitting the ethylmagnesium iodide to *C* and the remainder after the decomposition reaction was complete.

The gas washer *D* had a volume of 150 cc., and was generally $\frac{1}{2}$ filled with conc. sulfuric acid. In the course of an analysis, *D* was immersed in a beaker containing ice and water, to make the absorption of ether more complete. The quantity of ether and moisture removed in this way from the evolved gas always slightly increased the volume of acid in *D*. This increase in volume was directly measured by attaching a graduated millimeter scale to *D*, and was deducted from the total volume of gas. Experiments showed that the volume of gas obtained after it had passed through the washer suffered no diminution when subsequently washed twice with fresh conc. sulfuric acid. This proved that all of the ether vapor was retained in *D*. After every second run the contents of *D* were replaced by fresh acid. It was also proved that there was no appreciable solution of ethane in the contents of *D* under experimental conditions.

A was graduated to read to 0.1 cc. The 400cc. gas buret was specially prepared and had an enlarged upper compartment which held 200 cc.; the remaining 200 cc. was



⁸ The apparatus used has much in common with the Van Slyke apparatus for the estimation of amino acids.

graduated to 0.2 cc. The millimeter scale on *D* permitted readings with an accuracy of 0.5 cc.

Titration with Acid.—Aliquot portions of the Grignard solution were measured in tubes of 25cc. content, graduated to 0.1 cc.

As in the other methods, portions of about 20 cc. were taken for analysis. This solution was slowly poured into a 400cc. Erlenmeyer flask containing about 50 cc. of distilled water. The tube was first washed out with some of the standard sulfuric acid and then several times with distilled water, and the washings were added to the Erlenmeyer flask. About 20 cc. excess of standard acid was added, as it was found that a reasonably large excess of acid hastened solution of the basic magnesium iodide. The flask was then placed on an electric hot plate to complete the solution, and when all the basic compound had dissolved, the solution was cooled. Using methyl orange as an indicator, the excess of sulfuric acid was titrated back with standard sodium hydroxide solution.

When the acid solution was heated to the boiling temperature, free iodine was formed, by oxidation of any hydriodic acid present. As the acidity of the solution would thus be correspondingly reduced, the contents of the flask were heated only to about 60°, and until the basic magnesium iodide had just dissolved.

The odor of acetaldehyde was generally noted in the course of heating with acid to dissolve the basic compound.

Experimental Results

Table I compares the results obtained when aliquot portions were taken from two different preparations, each of which was analyzed by the in-

TABLE I
COMPARISON OF INDIRECT METHOD AND TITRATION WITH ACID

Method	Volume of aliquot Cc.	0.2584 N acid-base ^a Cc.	C ₂ H ₅ I G.	Mg. used G.	Mg. recovered G.	Total vol. reaction mixture Cc.	0.0986 N AgNO ₃ KCNS ^b Cc.	C ₂ H ₅ MgI per 20 cc. G.
1 Indirect.....	21.3	...	9.5426	1.6046	0.3322	98.2	124.9	1.757
1 Titration w. acid..	23.55	44.13	1.746
2 Indirect.....	21.38	...	9.5264	1.6052	0.2512	99.2	128.6	1.881
2 Titration w. acid..	22.8	47.06	1.923

^a 1 cc. of base = 1.344 cc. of acid. ^b 1 cc. of KCNS = 1.115 cc. of AgNO₃.

direct method and that of titration with acid. For purposes of comparison, all results are expressed in grams of ethylmagnesium iodide per 20 cc. of solution.

TABLE II
COMPARISON OF METHODS OF TITRATION WITH ACID AND ANALYSIS OF GAS

Method	Volume of aliquot Cc.	Acid-base Cc.	Ethane Cc.	C ₂ H ₅ MgI per 20 cc. G.	Average increase of results from titration over those from gas anal. %
3 Titration.....	24.0	51.86	...	2.014	...
3 Titration.....	21.25	46.39	...	2.034	4.4
3 Gas.....	15.0	...	180.6	1.939	...
4 Titration.....	24.8	47.93	...	1.801	...
4 Titration.....	20.0	39.19	...	1.826	3.4
4 Gas.....	17.0	...	185.2	1.754	...

Table II compares results obtained when aliquot portions were taken from 2 *unlike* preparations, each of which was analyzed twice by titration with acid and once by the gas method. Additional preparations gave results of the same order. All corrections have been made for the volumes of ethane recorded here.

Table III also compares typical analyses by titration with acid and analyses of gas. Analysis 5 illustrates the solubility of basic magnesium iodide in dry ether. At the conclusion of an ordinary preparation of ethylmagnesium iodide, 1 drop of water was added to the reaction mixture. A very decided precipitate of basic magnesium iodide was formed; to insure a reasonable opportunity for solution the mixture was stirred and then allowed to stand. After a short period the heavy precipitate settled, and aliquot portions were drawn off from the clear supernatant liquid.

Analysis 6 is of a clear solution of ethylmagnesium iodide which had been slowly filtered in the air, thus affording unusual opportunity for decomposition by air.

TABLE III
COMPARISON OF TITRATION WITH ACID AND ANALYSIS OF GAS AFTER PARTIAL
DECOMPOSITION OF THE REACTION MIXTURE

Method	Volume of aliquot Cc.	Acid-base Cc.	Ethane Cc.	C_2H_5MgI per 20 cc. G.	Increase of results from titration over those from gas anal. %
5 Titration.....	22.43	47.19	...	1.961	..
5 Titration.....	20.4	43.19	...	1.973	7.1
5 Gas.....	15.0	...	171.2	1.837	..
6 Titration.....	21.85	36.39	...	1.552	..
6 Titration.....	20.5	34.40	...	1.564	11.9
6 Gas.....	20.0	...	162.0	1.304	..

Discussion and Conclusion

The results in Table I show a fair agreement between the indirect method and titration by acid. They are irregular in the sense that analysis of Preparation 1 by the indirect method gives results higher than those by titration, whereas in Preparation 2 the reverse is true. The correspondence, however, is reasonably close when one considers the several difficulties incidental to analysis by the indirect method.

From Table II it is apparent that the method of titration gives results which are higher than those given by the analyses of gas. This difference was found to be rather uniform and, for the 2 preparations considered, averages 3.9%. The results give a fair indication of the reliability of the titration with acid for check results when aliquot portions of a given preparation are analyzed. An even better idea of this dependability is to be observed in the results given in Table III, and the several analyses recorded in the following paper. In justice to the value of the gas method it should be said that not only is this method more exact in an absolute

sense than the method of titration, but that it is also only slightly less reliable for check analyses from a given preparation. This latter point is illustrated in a paper⁹ which is to appear shortly.

The results of Analysis 5 in Table III bear out the reason offered for the uniformly higher results obtained by the titration method; namely, the basic magnesium halide is partially soluble in a dry ethereal solution of Grignard reagent. The larger difference in Analysis 6 is very probably connected with the action of oxygen on the Grignard reagent. Oxygen and water decompose the RMgX compounds to give basic halides of magnesium, oxygen giving a basic compound with the general formula $\text{Mg}(\text{OR})\text{X}$, and water giving a corresponding compound, $\text{Mg}(\text{OH})\text{X}$. It is reasonable to suppose that as the basic compound from oxygen contains an organic radical which makes it approximate more closely the structure of ether, it would dissolve to a greater extent than would $\text{Mg}(\text{OH})\text{X}$ in ether.

On the whole, when one considers the inherent difficulties in an analysis of this kind—the volatile solvent and the almost extraordinary sensitiveness of the RMgX compounds—the methods of analysis of the gas and titration with acid, which have been devised are quite satisfactory. Fortunately, they complement each other admirably; where one cannot be used, the other can. For example, in a quantitative study of the reaction between the Grignard reagent and unsaturated hydrocarbons titration cannot be used to indicate whether a reaction has taken place, because a molecule of any organo-magnesium halide when decomposed by water gives a molecule of basic magnesium halide. However, when a molecule of ethylmagnesium iodide is treated with an unsaturated hydrocarbon, any reaction between these compounds will diminish the quantity of ethane evolved when the reaction mixture is decomposed by water. This is so because the volume of ethane evolved is a measure of the ethylmagnesium iodide actually available.

Summary

1. A study has been made of 5 methods for the quantitative estimation of the Grignard reagent: titration with iodine, gravimetric analysis, a so-called indirect analysis, gas analysis, and titration with acid.

2. Of these, gas analysis and titration with acid give satisfactory results.

3. Both accepted methods depend on the smooth decomposition of RMgX compounds by water. The evolved gas is measured directly in one method, and the basic magnesium halide is titrated with standard acid in the other method.

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⁹ "A Quantitative Study of the Reaction Between Ethylenic Hydrocarbons and the Grignard Reagent."