231°. A few derivatives were prepared. Oxidation with chromic acid gave retenequinonecarboxylic acid.

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THE FORMATION OF A COMPLEX MIXTURE OF MANY RMgX COMPOUNDS FROM THE REACTION BETWEEN A SIMPLE RX COMPOUND AND MAGNESIUM

BY HENRY GILMAN AND NINA B. ST. JOHN

Introduction

The simplest expressions for the reaction between an RX compound and magnesium in ether are the following

$$RX + Mg \longrightarrow RMgX \qquad (I)$$
$$2RX + Mg \longrightarrow R{\cdot}R + MgX_2 \qquad (II)$$

Reaction II is the chief side reaction in the preparation of Grignard reagents, and the extent of this reaction varies markedly with the nature of the RX compound, the relative proportions of reactants and experimental conditions.[1] The hydrocarbon (or their equivalent) by-products are not pure R·R compounds, but may contain R(+H) and R(−H) compounds[2] as well as R·R compounds having R-groups unlike those contained in the original RX compound.[3]

Furthermore, Reaction I gives an incomplete picture of the more important compounds contained in Grignard solutions inasmuch as these reagents are involved in the following equilibria[4]

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \qquad (III)$$
$$RMgX \rightleftharpoons R- + -MgX \qquad (IV)$$
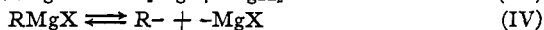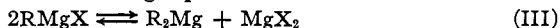
In short, a Grignard reagent is not simply an RMgX compound, but a mixture of $RMgX$, R_2Mg, MgX_2, R− and $-MgX$[5] in a series of equilibria

[1] Gilman, Zoellner and Dickey, THIS JOURNAL, 51, 1576, 1583 (1929); Gilman and McGlumphy, *Bull. soc. chim.*, 43, 1322 (1928); Gilman and Zoellner, THIS JOURNAL, 52, 3984 (1930).

[2] Gilman and Fothergill, *ibid.*, 50, 3334 (1928).

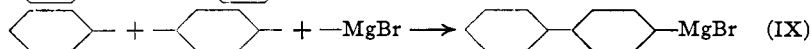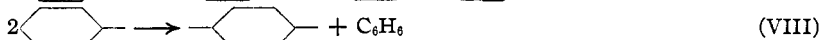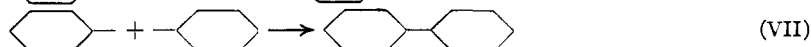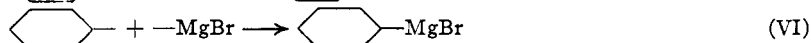[3] Gilman and Kirby, *ibid.*, 51, 1571 (1929).

[4] Gilman and Fothergill, *ibid.*, 51, 3149 (1929); Gilman and Zoellner, *ibid.*, 52, 3984 (1930). These articles contain leading references to other work. For recent related studies see Gomberg and Bachmann, *ibid.*, 52, 2455 (1930); Bachmann, *ibid.*, 52, 3287 (1930).

[5] Gilman and Brown, *ibid.*, 52, 1128 (1930). This article contains leading references to the chemistry of the interesting magnesious halides or the binary systems (MgX_2 + Mg) of Gomberg and co-workers. Better reviews of these systems are to be had in the chapters entitled "Metallo-Organic Compounds," in Vol. III (1927–1928) and Vol. IV (1928–1929) of the Annual Survey of American Chemistry, published for the National Research Council by the Chemical Catalog Co. of New York.

with only additional experiments to determine the extent of the equilibrium in Reaction III and the degree of dissociation illustrated by Reaction IV.

When the halide used to prepare the Grignard reagent contains two or more halogens which are reactive toward magnesium, then it is theoretically possible to have an infinite number of Grignard reagents. This[6] development has been illustrated with the relatively simple *p*-dibromobenzene, BrC_6H_4Br. Obviously, with an infinite number of organomagnesium halides derivable from a simple dihalogen compound, there is also present an infinite number of equilibria and dissociation reactions (III and IV).

This very complex state of affairs is apparently not restricted to organomagnesium halides prepared from a polyhalogen compound. It now appears that the reaction of a simple RX compound, having but one halogen, can give rise to a very complex mixture of RMgX compounds. The explanation for such mixtures almost certainly lies with the initial and intermediate formation of free radicals. If we select the reaction between bromobenzene and magnesium as a type, we have the following general representation[7]

$$\langle\bigcirc\rangle\!-\!Br + Mg \longrightarrow \langle\bigcirc\rangle\!-\ + -MgBr \qquad (V)$$

$$\langle\bigcirc\rangle\!-\ + -MgBr \longrightarrow \langle\bigcirc\rangle\!-MgBr \qquad (VI)$$

$$\langle\bigcirc\rangle\!-\ + -\langle\bigcirc\rangle \longrightarrow \langle\bigcirc\rangle\!-\langle\bigcirc\rangle \qquad (VII)$$

$$2\langle\bigcirc\rangle\!-\ \longrightarrow -\langle\bigcirc\rangle\!-\ + C_6H_6 \qquad (VIII)$$

$$\langle\bigcirc\rangle\!-\ + -\langle\bigcirc\rangle\!-\ + -MgBr \longrightarrow \langle\bigcirc\rangle\!-\langle\bigcirc\rangle\!-MgBr \quad (IX)$$
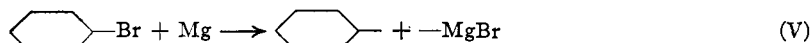
That is, the first[8] step in the reaction between an RX compound and magnesium is the formation of free radicals. These radicals may unite (Reaction VI) to give the RMgX compound; or the R-groups may unite to give the coupling (R·R) compound (Reaction VII); or the radical may disproportionate to give new free radicals, like the *p*-phenylene radical in Reaction VIII; and the radicals (mono or polyvalent) may combine with each other and with the $-MgX$ (or its equivalent, $MgX_2 + Mg$) or with magnesium to give a miscellany of Grignard reagents.

[6] Gilman, Beaber and Jones, *Rec. trav. chim.*, **48**, 597 (1929).

[7] Gomberg and Bachmann, THIS JOURNAL, **49**, 236 (1927); Gilman and Zoellner *ibid.*, **52**, 3984 (1930); and, particularly, Bachmann and Clarke, *ibid.*, **49**, 2089 (1927), for an excellent theoretical and experimental development of the mechanism of the Wurtz-Fittig reaction.

[8] We are omitting here the probable prior formation of oxonium compounds with ether and the several possible coördination formations involving each of the participating elements [Gilman and Fothergill, *ibid*, **51**, 3149 (1929)]. See, also, Gilman and Zoellner, *ibid.*, **52**, 3984 (1930), and Gilman and Brown, *ibid.*, **52**, 5045 (1930), for that interpretation involving combination of free radicals with magnesium.

We have illustrated the formation of but one RMgX compound other than phenylmagnesium bromide: namely, p-biphenylmagnesium bromide (Reaction IX). This has been done advisedly because we now have experimental evidence for the formation of p-phenylbenzoic acid, p-$C_6H_5C_6H_4$-COOH, when carbon dioxide is passed into a Grignard reagent (or reagents) prepared from bromobenzene and magnesium.

There is no reason, a *priori*, for confining consideration to the reactions (V) to (IX) as we have done. For example, it appears altogether probable that two phenyl radicals might disproportionate to give not only p-phenylene (Reaction VIII), but also a lesser quantity of o-phenylene.[3] Furthermore, multiples of these phenylene radicals might unite with a phenyl radical and $-MgBr$ (Reaction IX) to give $C_6H_5(C_6H_4)_nMgBr$.[9] Many other combinations are possible, such as the union of a phenylene radical with two $-MgBr$ groups to give $BrMgC_6H_4MgBr$.

The theoretical possibilities of even more complex mixtures are patent with the use of halides like the mono-bromotoluenes or benzyl chloride, inasmuch as we have here the opportunity of free radicals formed from the side chain as well as from the nucleus. Finally, we are unaware of any valid objection to a like condition with *alkyl*magnesium halides. A good case has been made for the short life of alkyl radicals,[10] and their disproportionation,[2] as well as for the disproportionation and rearrangements of arylalkyl radicals such as benzyl.[3] If we grant the possibility of an alkyl radical to disproportionate to an alkylene[11] radical by analogy with Reaction VIII, and to rearrange to a different free radical, then there exists the same opportunity for the formation of a complex mixture of Grignard reagents from a simple mono-halogen[12] alkyl halide.

The above development has a theoretical reasonableness and part of it, as mentioned, has found experimental confirmation. Fortunately, the extent of these many possible side reactions leading to the formation of complex mixtures of RMgX compounds is strictly limited because of preferential reactions. If a so-called single Grignard reagent is in reality very slightly contaminated with many other RMgX compounds, then the products obtained from them and reactants are also approximately of a like

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[9] Actually, the residues which yielded p-phenylbenzoic acid contained highly complex, intractable materials which so far have resisted purification, primarily because of the small quantities of starting materials used.

[10] Paneth and Hofeditz, *Ber.*, 62B, 1335 (1929).

[11] The general evidence for alkylene (or bivalent) radicals is at present hardly as convincing as that for alkyl (or trivalent) radicals and although there is essentially no experimental evidence for monovalent carbon radicals, one can conceive of an alkylene group acting as a donor of hydrogen in its disproportionation reactions.
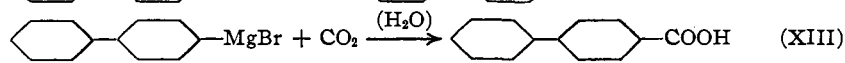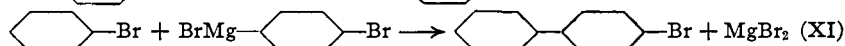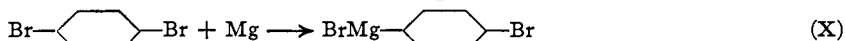
[12] With polyhalogen-alkyl compounds there is, of course, the same opportunity for an infinite number of Grignard reagents that is present in the case of p-dibromobenzene (see Ref. 6 of this paper).

degree of impurity. One important conclusion to be drawn from the several studies is that the world of organic chemicals is relatively "impure." This is hardly a situation peculiar to organomagnesium compounds[2] because it is altogether likely that most reactions of organic chemistry are accompanied by side reactions which give rise to slight impurities. Ordinarily these trivial side reactions deserve no consideration and get no consideration partly because the extent of impurities appears to be of no apparent consequence[13] and partly because we are blissfully ignorant of the impurities for the reason that our present analytical procedures do not reveal them.[14]

Discussion of Results

The isolation of p-phenylbenzoic acid came as a result of studies on the purported addition of RMgX compounds to an ethylenic linkage. In order to determine whether phenylmagnesium bromide might add to 1,1-diphenylethylene, $(C_6H_5)_2C=CH_2$, in solvents other than ether, the reactants were heated, and then the mixture was carbonated. If no addition took place, then benzoic acid alone should result. However, if some addition occurred a new Grignard reagent would result and this on carbonation would reveal itself by affecting the melting point and neutralization equivalent of the benzoic acid formed from the excess of phenylmagnesium bromide.[15] The acid obtained from this reaction was impure, and in order to identify the acidic impurity the benzoic acid was carefully removed, leaving a small quantity of p-phenylbenzoic acid.

The p-phenylbenzoic acid was also obtained in a like very small quantity when no diphenylethylene was present. There is a possibility that the p-phenylbenzoic acid, or the p-biphenylmagnesium bromide from which it was formed, came from impurities in the bromobenzene. The following reactions illustrate one of several possible methods for its formation.
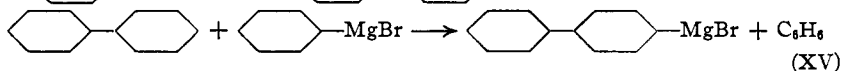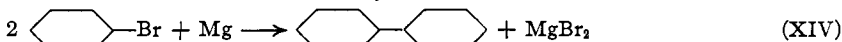
$$Br\text{—}\langle\bigcirc\rangle\text{—}Br + Mg \longrightarrow BrMg\text{—}\langle\bigcirc\rangle\text{—}Br \qquad\qquad (X)$$

$$\langle\bigcirc\rangle\text{—}Br + BrMg\text{—}\langle\bigcirc\rangle\text{—}Br \longrightarrow \langle\bigcirc\rangle\text{—}\langle\bigcirc\rangle\text{—}Br + MgBr_2 \ (XI)$$

$$\langle\bigcirc\rangle\text{—}\langle\bigcirc\rangle Br + Mg \longrightarrow \langle\bigcirc\rangle\text{—}\langle\bigcirc\rangle\text{—}MgBr \qquad (XII)$$

$$\langle\bigcirc\rangle\text{—}\langle\bigcirc\rangle\text{—}MgBr + CO_2 \xrightarrow{(H_2O)} \langle\bigcirc\rangle\text{—}\langle\bigcirc\rangle\text{—}COOH \quad (XIII)$$

[13] We say "no apparent consequence" advisedly, because there is always the irritable or pleasant phenomenon of catalysis due to small impurities to plague or to delight us depending on one's point of view.

[14] We are confident that other Grignard reagents postulated as being formed in small quantities will be characterized in large-sized runs. In this connection see Footnote 10 of Ref. 3 of this paper on the special contributions to be made to such problems by manufacturers and dealers in research chemicals.

[15] Leading references to the application of this and other devices to establish the non-addition of RMgX compounds to an ethylenic linkage may be traced from an article by Gilman and Schulz, THIS JOURNAL, **52**, 3588 (1930).

Reaction X is plausible because small quantities of p-dibromobenzene might be present in supposedly pure bromobenzene, and if so it would readily react with magnesium to give the mono-Grignard reagent.[6]   However, Reactions XI and XII are less reasonable because they take place with uncommon difficulty and to a limited extent.[16]   The bromobenzene used by us was highly purified.   Not content with this, we prepared some bromobenzene by a reaction other than that used technically (the bromination of benzene): namely, a Sandmeyer reaction starting with freshly distilled and pure aniline.   We do not say that no p-dibromobenzene is formed in such a reaction, but it does appear to be distinctly superior to the reaction of direct bromination and should yield a bromobenzene as pure and as free of dibromobenzene as that obtained by any reaction.   This bromobenzene also yielded p-phenylbenzoic acid.

There is another possible explanation for the p-biphenylmagnesium bromide and this is illustrated by the reactions

$$2\ \langle\ \rangle\!-\!Br + Mg \longrightarrow \langle\ \rangle\!-\!\langle\ \rangle + MgBr_2 \qquad\qquad (XIV)$$

$$\langle\ \rangle\!-\!\langle\ \rangle + \langle\ \rangle\!-\!MgBr \longrightarrow \langle\ \rangle\!-\!\langle\ \rangle\!-\!MgBr + C_6H_6$$
$$(XV)$$

The diphenyl of Reaction XIV is always formed to a small extent[17] in the preparation of phenylmagnesium bromide, and Reaction XV has been postulated in an interpretation of the Wurtz reaction using sodium.[18] However, the metathesis pictured in Reaction (XV) has been shown not to apply with Grignard reagents, even at elevated temperatures.[19]   To further test the unlikelihood of this reaction, the phenylmagnesium bromide was prepared and heated in the presence of a large quantity of diphenyl, but there was no increase in the yield of p-phenylbenzoic acid on subsequent carbonation.

No p-phenylbenzoic acid was isolated from a 0.5 mole preparation of phenylmagnesium bromide in ether.   Very likely the preparation of this Grignard reagent at more elevated temperatures, with no ether, and with an uncommonly large initial excess of bromobenzene gives a higher concentration of phenyl radicals.

[16] This applies to reactions in ether and not to those in the absence of ether and in the presence of an excess of hot bromobenzene, the condition of our experiments. The difficulty mentioned here is even greater when chlorobenzene is used because of its distinctly lesser activity than bromobenzene to magnesium.   Notwithstanding this, we did get a small quantity of p-phenylbenzoic acid from the preparation of phenylmagnesium chloride in the absence of ether.

[17] The extent of this side reaction can be markedly decreased with the use of an excess of magnesium; see Gilman and Fothergill, *Iowa State Coll. J. of Science*, **4**, 351 (1930).

[18] Bachmann and Clarke, THIS JOURNAL, **49**, 2089 (1927).

[19] Gilman and Leermakers, *Rec. trav. chim.* **48**, 577 (1929); see also, Gilman and Leermakers, *ibid.*, **49**, 208, 532 (1930).

Phenylmagnesium chloride prepared in the absence of ether also gave some p-phenylbenzoic acid.[20]

Experimental Part

In a typical preparation, 470.7 g. (3.0 moles) of bromobenzene was refluxed with 6.1 g. (0.25 atom) of magnesium and a crystal of iodine for one hour in a flask provided with a trap[21] to exclude air. The mixture was cooled and then carbonated. A positive color test[22] for Grignard reagent was obtained even after an eighteen-hour passage of carbon dioxide. The weight of crude benzoic acid was 10.05 g. or 32.93%, and it melted at 104–106°. Purification by crystallization from hot water gave benzoic acid melting at 122° and a dark brown oily residue which was essentially insoluble in water. This residue on crystallization from benzene gave 0.15 g. of p-phenylbenzoic acid. The p-phenylbenzoic acid was converted to its methyl ester and the identity of both the acid and the ester was confirmed by respective mixed melting point determinations with authentic specimens. Wherever elsewhere p-phenylbenzoic acid was isolated it was identified by a mixed melting point determination.

In order to test the validity of Reaction XV, 50 g. (0.32 mole) of diphenyl was added to 470.7 g. (3 moles) of bromobenzene and 6.1 g. (0.25 atom) of magnesium. After refluxing the mixture for twelve hours it was cooled to 0° and then carbonated for twelve hours. The viscous violet colored mixture gave a negative test for Grignard reagent.[22] The products recovered were a few crystals (not weighed) of p-phenylbenzoic acid, 4.23 g. of benzoic acid and 43.6 g. or 87.2% of the diphenyl.

Using the same proportions of reactants (but omitting the diphenyl) the yield of p-phenylbenzoic acid was 0.02 g. In this experiment the bromobenzene was that prepared from aniline.[23]

Phenylmagnesium bromide (0.3 mole) was prepared in a sealed tube[24] by heating for one hour at 150°, extracted by ether and then carbonated.[25] The yield of p-phenylbenzoic acid was 0.6 g. In this method of preparation the reaction between bromobenzene and magnesium is unusually rapid, and actually appears to proceed of itself on the local application of heat. The preparation in an open flask (in the absence of ether) goes much more slowly and so may give rise to a lower concentration of phenyl radicals.

Phenylmagnesium chloride was prepared[26] in a like manner from 21.8 g. (0.25 mole) of chlorobenzene and 7.3 g. (0.3 atom) of chlorobenzene, transferred to a flask containing 337.5 g. (3.0 moles) of chlorobenzene, refluxed for thirty minutes and then cooled and carbonated. The yield of crude benzoic acid melting at 104–105° was 9.26 g. (30.35%), and from this was isolated a very small quantity of p-phenylbenzoic acid. It is interesting to note that phenylmagnesium chloride in chlorobenzene is carbonated more rapidly than is phenylmagnesium bromide in bromobenzene.

Summary

The carbonation of phenylmagnesium bromide and of phenylmagnesium

[20] It has been suggested that it would be interesting to know how iodobenzene and magnesium behave in this reaction. With sodium and chlorobenzene (see Ref. 18 of this paper), there is formed a relatively large quantity of o-phenylene radicals.

[21] Gilman and Hewlett, *Rec. trav. chim.* **48**, 1124 (1929).

[22] Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

[23] This bromobenzene was synthesized by Catherine Vinton.

[24] See, Gilman and Brown, THIS JOURNAL, **52**, 3330 (1930), for a description of this method for the preparation of some Grignard reagents.

[25] This experiment was carried out by K. E. Marple.

[26] By R. E. Brown.

chloride, each prepared in the absence of ether, gave in addition to benzoic acid very small quantities of p-phenylbenzoic acid, $C_6H_5C_6H_4COOH$. The formation of the latter acid is almost certainly due to free phenyl radicals initially developed in the preparation of the C_6H_5MgX.

Attention is directed to the theoretical, and in some cases practical, formation of a large and complex variety of Grignard reagents starting with a single and simple RX compound. Although the degree of these side reactions is fortunately very limited and in most cases insignificant, it emphasizes the difficulty or impossibility of preparing absolutely pure compounds. This difficulty is undoubtedly not confined to organomagnesium compounds.

AMES, IOWA

THE CHEMISTRY OF THE LIPOIDS OF TUBERCLE BACILLI. XXI. THE POLYSACCHARIDE OCCURRING IN THE PHOSPHATIDE FROM THE HUMAN TUBERCLE BACILLI[1]

BY R. J. ANDERSON AND E. GILMAN ROBERTS[2]

Introduction

Previous investigations in this Laboratory of the water-soluble constituents which are obtained on hydrolyzing the phosphatide A-3 from the human tubercle bacillus have shown that mannose,[3] inosite[4] and some other reducing sugar, probably invert sugar,[5] are present in about equal amounts in the aqueous solution. The phosphatide fractions isolated from the avian and bovine tubercle bacilli also yielded mannose and inosite on hydrolysis.[6]

In all of these cases prolonged boiling of the phosphatides with dilute acid was necessary before reducing sugars appeared in the solution. It seemed evident, therefore, that the various sugars which were liberated on complete hydrolysis existed in the original phosphatide molecules in firm chemical combination; possibly sugar complexes or polysaccharides

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[1] The present report is a part of a coöperative investigation on tuberculosis and it has been supported partly by funds provided by the Research Committee of the National Tuberculosis Association. (An abstract of this paper was read before the Division of Medicinal Chemistry, at the meeting of the American Chemical Society, Cincinnati, Ohio, September, 1930.)

[2] Holder of a National Tuberculosis Association Fellowship at Yale University 1929–1930.

[3] Anderson and Renfrew, THIS JOURNAL, **52**, 1252 (1930).

[4] Anderson, *ibid.*, **52**, 1607 (1930).

[5] Anderson, Roberts, and Renfrew, *Proc. Soc. Exptl. Biol. Med.*, **27**, 387 (1930).

[6] Unpublished data.