The Relative Reactivities of Methylmagnesium Chloride and Dimethylmagnesium

BY GEORGE F. WRIGHT

Introduction

In connection with the use of the Kohler machine[1] for the analysis of lignins with methyl Grignard reagent, it was found necessary to employ several solvents such as dioxane and pyridine in which these lignins were soluble. The observation that analyses varied with the different solvents led to investigation of these solvents as they affected the Grignard analysis in general.[2] The results of this study indicated that the solvent profoundly affected the course of reaction, with Grignard reagent, of a number of carbonyl types.

Since one of the solvents employed, dioxane, is used extensively to effect precipitation of RMgX and MgX_2 from an ether solution of the Grignard reagent, any investigation involving the former solvent raises the question of the relative reactivity of organomagnesium halide as compared with diorganomagnesium. Schlenk and Schlenk[3] consider RMgX and R_2Mg to be equally reactive in so far as addition to the carbonyl group is concerned; Bartlett[4] concurs in the opinion, but Gilman and Brown[5] state that phenylmagnesium bromide is more reactive toward valeronitrile than diphenylmagnesium, while Cope[6] finds that RMgX is more reactive toward dimethyl sulfate than is R_2Mg. By analogy with other organometallic types it would be expected that R_2Mg would be less reactive than RMgX since the corresponding mercury compounds show this tendency. Thus, phenylmercuric chloride will react with ketene to give a 20% yield of acetophenone but none of this product can be isolated when diphenylmercury is employed.[7] If such a fortunate choice of carbonyl compound could be selected for reactions with the two forms of the Grignard reagent, the relative reactivity toward the carbonyl function could be evaluated in like manner. Alternatively, such a difference in reactivity might be ascertained if it were found that whereas both forms were equally reactive toward one function, such as hydroxyl, they were of different reactivity toward another function such as carbonyl. In the present investigation the latter course has been pursued.

The preparation of dimethylmagnesium was carried out according to the procedure outlined previously,[3,9] but in spite of a reasonable delay before filtering[8] in order to shift the following equilibrium to the right

$$2RMgX \rightleftarrows R_2Mg + MgX_2$$

only 6.5% of the reagent remained in solution as dimethylmagnesium. This is much lower than that found by Cope[9] (47%). The discrepancy may be owing to a difference in concentration of the Grignard reagent before precipitation, Cope's solution being about one-fifth as strong as that described here, or it may be owing to a difference in mode of addition. It was observed that, when the precipitated RMgX + MgX_2 was washed with dioxane, subsequent to filtration of the ether-dioxane solution, a crystalline precipitate appeared when this wash liquor was added to the ether-dioxane filtrate. This precipitate redissolved upon evaporation of the ether. The precipitate gave a positive Gilman test with Michler's ketone but was halogen-free; it thus appears that dimethylmagnesium (dioxanate ?) is of limited solubility in ethyl ether. A like phenomenon was encountered when this crystalline compound was extracted with isoamyl ether, the resulting solutions being too dilute for satisfactory analysis. Because of this limited solubility in ethers it is possible that the apparent increased concentration of R_2Mg at higher temperatures as reported by Cope,[9] may be owing to change of solvent in which the diorganomagnesium compound is more soluble. No attempt was made to increase the yield of R_2Mg in the present investigation, since the halogen content of the solution was much lower than has been reported previously. The importance of excluding magnesium halide is evident since any trace of magnesium halide is a potential source of organ-

(1) Kohler, Fuson and Stone, THIS JOURNAL, 49, 3181 (1927); Kohler and Richtmyer, ibid., 52, 3736 (1930).

(2) Lieff, Wright and Hibbert, ibid., 61, 865 (1939).

(3) Schlenk and Schlenk, Ber., 62, 920 (1929).

(4) Bartlett and Berry, THIS JOURNAL, 56, 2683 (1934).

(5) Gilman and Brown, ibid., 52, 1181 (1930).

(6) Cope, ibid., 56, 1578 (1934); see also Suter and Gerhart, ibid., 57, 107 (1935).

(7) Gilman, Woolley and Wright, ibid., 55, 2609 (1933). It was subsequently found by these workers that R_2Hg reacts little or not at all. The apparent reaction with the symmetrical mercurial was caused by presence of mercuric halide as an impurity.

(8) Noller, ibid., 59, 1354 (1937), see especially note 5.

(9) Cope, ibid., 57, 2238 (1935).

TABLE I

COMPARISON OF REACTIONS WITH THE COMPONENTS OF THE GRIGNARD REAGENT

Expt.	Substance Name	Moles	Reagent Name	Solvent	Equiv.	Active hydrogen, equiv.	Carbonyl, equiv.	Products Recovered reactant mole %	Carbinol, mole %
1	Benzoin	0.001	(CH₃)₂Mg	Dioxane	0.0016	1.2	0.3	Benzoin, 38%	1,2-Diphenylpropanediol-1,2, 18%
2	Benzoin	.001	(CH₃)₂Mg	Dioxane	.0026	1.2	0.5	Benzoin, 18%	1,2-Diphenylpropanediol-1,2, 26%
3	Benzoin	.001	(CH₃)₂Mg + CH₃MgI	Isoamyl ether	.002	1.0	1.0	None	1,2-Diphenylpropanediol-1,2, 94%
4	Benzoin	.05	CH₃MgCl + MgCl₂	Dioxane	.25	..	..	None	1,2-Diphenylpropanediol-1,2, 65%
5	Benzoin	.001	(CH₃)₂Mg	Dioxane	.0013	1.3	..	Benzoic acid, 23%	1,2-Diphenylpropanediol-1,2, 25%
6	Acetophenone	.0019	(CH₃)₂Mg	Dioxane	.0027	0.6	0.3	Acetophenone,[a] 35%	Not isolated
7	Desoxybenzoin	.0011	(CH₃)₂Mg	Dioxane	.0017	.24	.71	Desoxybenzoin,[a] 18%	Not isolated
8	Diphenylaceto-phenone	.00075	(CH₃)₂Mg	Dioxane	.0015	.11	.78	...	Triphenylpropanol, 33%

[a] Isolated as the 2,4-dinitrophenylhydrazone.

omagnesium halide (see formulation), and this magnesium halide is capable of regeneration.

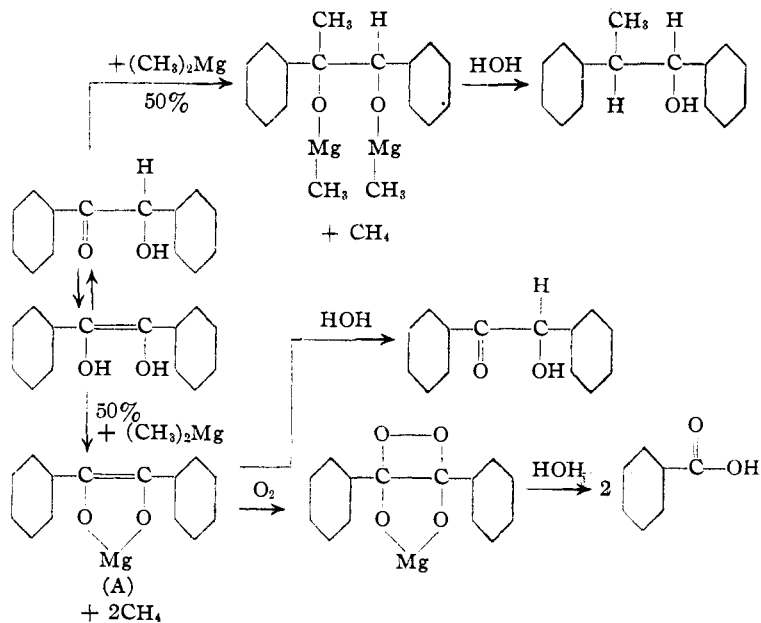$$ROMgX \rightleftarrows (RO)_2Mg + MgX_2$$
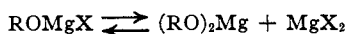
Benzoin was investigated because it has become, among Grignard machine analysts, a standardizing substance giving, within experimental error, exactly one active hydrogen and one carbonyl addition. This analysis can be duplicated when the benzoin is dissolved in xylene. When, however, dioxane is used as solvent, the gas liberated by hydroxyl becomes 1.3 equivalent per mole, while the carbonyl addition is decreased to 0.6 equivalent per mole.[2] Furthermore, benzoin can be isolated from the reaction mixture. This indicates that part of the benzoin is reacting in the ene-diol form. Reference to Table I shows that a solution of dimethylmagnesium acts in identically the same manner, so that about half reacts as ene-diol and half as ketone. The yield ratios of products isolated (Table I) substantiate the analytical figures. The existence of the magnesium salt (A) is further established if the reaction mixture is oxidized prior to hydrolysis. By this treatment with oxygen no benzoin is obtained, substantially the same yield of benzoic acid being produced in its stead. Some significance may be attached to the fact that the deep red color of the reaction mixture containing benzoin and dimethylmagnesium is bleached to

yellow on oxidation. The reaction mixture using methyl Grignard reagent[10] in isoamyl ether is colorless. It is supposed that the red color is due to compound A.

Some insight into the relative reactivity of R₂Mg as compared with the methyl Grignard rea-

gent is afforded by the data in Table I. In expts. 1 and 2 using dimethylmagnesium in dioxane, an insufficient amount of reagent was employed in

expt. 1 and an excess in expt. 2. In both runs the active hydrogen value was the same, the carbonyl being lower (0.3 compared with 0.5) in the case of the experiment in which insufficient amount of the reagent was used. Both values for carbonyl addition were lower than in the case where the ordinary Grignard reagent in isoamyl ether was added to a dioxane solution of benzoin (C=O, 0.6). Finally it was demonstrated (expt. 3) that in the ordinary analysis using methyl Grignard reagent in isoamyl ether with crystalline benzoin, the reaction goes to completion without excess of reagent. These results may be interpreted as follows. Firstly, dimethylmagnesium reacts by preference with the hydroxyl group, the resulting compound enolizing to form another molecule of methane rather than undergoing intramolecular addition to the carbonyl group. This is demonstrated by the fact that the insufficient amount of reagent used in expt. 1 (0.0008 mole per 0.001 mole of benzoin) gave as much methane as was produced in expt. 2 (0.0013 mole per 0.001 mole of benzoin). Secondly, on the basis of CH₃–Mg equivalence dimethylmagnesium is less reactive than methylmagnesium chloride since an excess of CH₃Mg (0.0026 equivalent per equivalent of benzoin) failed to give a complete reaction, whereas the Grignard reagent in isoamyl ether reacts completely when equivalent
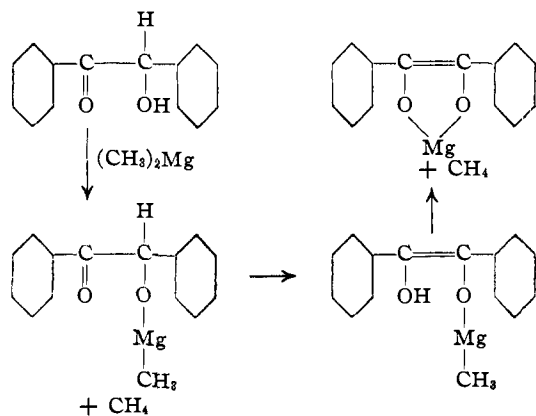
quantities are employed (expt. 3). Both of these observations can be summarized in the statement that CH₃MgOR is less reactive toward carbonyl than CH₃–Mg–CH₃ or CH₃MgCl.

There remains the possibility that the course of the reaction is altered by the presence of dioxane. This is disproved by the fact that the extremely dilute solutions of dimethylmagnesium in isoamyl ether (equiv. to 1.7 cc. of methane

per cc. of reagent), while it failed to give reproducible analyses, reacted to give the same red color with benzoin which was observed with dimethylmagnesium in dioxane but not with methyl Grignard reagent in isoamyl ether, or isoamyl ether–xylene mixture. Furthermore, the reaction products from dimethylmagnesium and benzoin in isoamyl ether were benzoin and 1,2-diphenylpropanediol-1,2, in approximately the same ratio (1:1) as was obtained using the same substances in dioxane. As additional evidence that dioxane has no effect on the benzoin, the precipitated RMgX from the methyl Grignard reagent–dioxane precipitation was suspended in the latter solvent and treated with a dioxane suspension of benzoin (expt. 4), the reaction mixture containing no red color. No benzoin was found in the product, and the comparatively low yield (65%) of 1,2-diphenylpropanediol-1,2 represents the amount of the two pure diastereomers resulting from the wasteful process of their separation.[11] RMgX and benzoin therefore react normally in dioxane as they do in isoamyl ether.

If the red color mentioned above be characteristic of the compound A in solution, then it would appear either that dimethylmagnesium does not exist in significant amount in the isoamyl ether solution of Grignard reagent from methyl iodide; or else it is so much less reactive than methylmagnesium iodide that there is little tendency toward the abnormal reaction leading to A. While the solution of methyl Grignard reagent and benzoin in isoamyl ether–xylene is apparently colorless, a yield of benzoic acid about one-fiftieth of that obtained in the reaction between dimethylmagnesium and benzoin can be obtained on oxygen treatment of the former reaction mixture.

If dimethylmagnesium reacts preferentially with active hydrogen rather than carbonyl, it would be expected that the tendency toward enolization exhibited by acetophenone, desoxybenzoin and diphenylacetophenone on reaction with methyl iodide Grignard reagent would be amplified when dimethylmagnesium was used. This expectation is realized. Kohler, Fuson and Stone[1] report active hydrogen values of 0.33, 0.10 and 0.16, respectively, for these substances. Experi-

(11) It may be noted that the diastereomer m. p. 97–98° evidently corresponds to the 1,2-diphenylpropanediol reported by McKenzie and Wren, J. Chem. Soc., 97, 477 (1910), melting at 81–82° and by Tiffeneau and Levy, Bull. soc. chim., 41, 1351 (1927), as melting at 92–93°.

ments 6, 7 and 8 (Table I) demonstrate that these values are approximately doubled when dimethylmagnesium in dioxane is the reagent. It is notable that reaction is incomplete in each case, indicating that dimethylmagnesium is less reactive than methylmagnesium iodide even when (expt. 8) equimolar portions of ketone and R_2Mg are employed. This incompleteness of reaction is in contrast to analyses using methyl iodide Grignard reagent in isoamyl ether.[1]

Experimental Part

Preparation of the Reagent.—Two hundred and fifty cc. (0.29 mole) of a stock Grignard reagent (1.17 N) prepared from methyl chloride and an excess of magnesium was stirred under nitrogen while 100 cc. (1.15 moles) of dry, peroxide-free dioxane was added over a ninety-minute period. After subsequently stirring for the same length of time the reagent was let stand overnight, then filtered through a fibrous glass plug into a nitrogen-filled Claisen flask and washed with 50 cc. of dioxane. Addition of this wash liquid (which gave a positive Gilman test with Michler's ketone) to the original filtrate caused precipitation of a crystalline solid which, however, was halogen free. Titration of the combined filtrates showed that 0.019 mole of basic magnesium (6.5% of that in the original reagent) was present; this filtrate was then evaporated under 10 mm. pressure to a volume of 25 cc., when the crystalline solid, which had disappeared as the ether evaporated, again began to separate out. This was transferred to an auxiliary reservoir on the Grignard machine and the flask washed out with 10 cc. and 5 cc. of dioxane, which dissolved the precipitated solid to give 40 cc. of clear solution of $(CH_3)_2Mg$ in dioxane. Analysis in the machine gave 10.0 cc. of methane per cc. of reagent; analysis for halogen (micro) showed that the hydrolysate contained less than 0.02% of chlorine per gram of dimethylmagnesium. No trouble was encountered because of precipitation from the reagent, but in a similar preparation wherein the filtrate from the dioxane treatment was evaporated to dryness and extracted with isoamyl ether, the solution saturated at 20° contained only 0.000041 mole of dimethylmagnesium per cc. of reagent. While this reagent in isoamyl ether was too dilute for accurate analysis, examination of the products (benzoin and 1,2-diphenylpropanediol-1,2) indicated that it reacted in the same manner as the reagent in dioxane.

Benzoin with Precipitated Grignard Reagent in Dioxane. —The washed precipitate after removal of dimethylmagnesium was suspended in 100 cc. of dioxane and stirred while a suspension of 10.6 g. (0.05 mole) of benzoin in 100 cc. of dioxane was added over a ninety-minute period. The temperature did not rise above 40° and no color change occurred. After stirring for three hours and standing for a day the reaction mixture was processed in the usual manner to yield 11.3 g. of solid, m. p. 75–83°, which, when crystallized from 500 cc. of 3:2 water–ethanol, yielded 4.73 g. of 1,2-diphenylpropanediol-1,2, m. p. 100°. No trace of benzoin was found, although this would have been less soluble in the mixed solvent than the diol which

was isolated. The filtrate, extracted with ether and the dried solution evaporated, was distilled at 192–200° (8 mm.). The distillate (3.10 g.) was fractionally crystallized from 35 cc. of carbon disulfide to yield 2.24 g. of the 104° isomer; the filtrate evaporated to dryness and then crystallized from 40 cc. of 30–60° petroleum ether yielded 0.50 g. of 1,2-diphenylpropanediol-1,2; m. p. 97–98°. A mixed melting point of the 97–98° isomer with that melting at 104° was depressed 15°. It was recrystallized from petroleum ether (b. p. 30–70°).

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.7; H, 7.01. Found: C, 78.9; H, 7.18.

The 104° isomer was obtained in 63% yield, the 97–98° isomer in 4% yield.

Products from Grignard Machine Analysis.—All analyses were carried out using approximately 0.2-g. samples dissolved in 5 cc. of dioxane which had been purified by distillation from sodium–benzophenone. A 5-cc. portion of this dioxane gave 2.1 cc. of methane from the reagent, and this blank was deducted from all active hydrogen determinations. After analysis, the Grignardized sample was poured into water; ether and dilute hydrochloric acid were added. The non-aqueous layer, after separation, was washed with water, dried with magnesium sulfate and evaporated at 10 mm. The residue was weighed, after which the recovered starting material was isolated either as the 2,4-dinitrophenylhydrazone or, in the case of some of the benzoin runs, by crystallization from 9:1 water–ethanol in which the benzoin was insoluble. Evaporation of the water–ethanol filtrate yielded 1,2-diphenylpropanediol-1,2 which was purified by crystallization from water; only the higher melting isomer was isolated. The carbinols from acetophenone and desoxybenzoin were not isolated but 1,1,2-triphenylpropanol-2 was obtained, following an abortive attempt to isolate the dinitrophenylhydrazone of triphenylethanone, by crystallizing the product from petroleum ether (b. p. 60–70°). The 1,1,2-triphenylpropanol-2, m. p. 78–80°, wt. 0.079 g. (32.5% of theoretical), was crystallized repeatedly from the same solvent to melt at 81–82°. This is lower than that reported by Levy (89°).[12]

Oxidation of Magnesium 1,2-Diphenylethenediol-1,2-ate.—The addition of Grignard reagent in isoamyl ether to benzoin gives a white precipitate. The dioxane solution of dimethylmagnesium and benzoin, on the other hand, was clear and red. After oxygen, dried through sulfuric acid, was passed at a rate of 0.5 cc. per sec. over this clear red solution at 8° for eleven hours, the resulting gel was yellow in color. It was dissolved in dilute hydrochloric acid and extracted with ether. The washed ether solution was shaken out with 2% sodium hydroxide, dried with magnesium sulfate and evaporated to yield 0.05 g. of oil which, when crystallized from boiling water, yielded 0.045 g. of impure 1,2-diphenylpropanediol-1,2 (m. p. 83°). The alkaline layer after acidification was extracted twice with ether. The ether solution on evaporation yielded 0.05 g. of benzoic acid of m. p. 100°, which crystallized without appreciable loss from water to melt at 123°, no depression being noted on admixture with an authentic sample. In like manner it was shown that in absence of oxygen treat-

(12) Levy, *Bull. soc. chim.*, **29**, 878 (1921).

ment benzoin was recovered but no benzoic acid was obtained. Benzoin (0.200 g.) in xylene treated with methyl Grignard reagent in isoamyl ether, and subsequently treated with oxygen as outlined above gave 0.001 g. of benzoic acid.

Thanks are due Miss Joan Romeyn for the microanalyses.

Summary

1. A solution of dimethylmagnesium in dioxane has been prepared under conditions which suggest that its dioxanate has a limited solubility in ether.

2. Upon reaction with benzoin, dimethylmagnesium shows such a preferential reaction with hydroxyl groups that an ene-diol magnesium salt seems to be formed.

3. The reaction of dimethylmagnesium with enolizable ketones indicates that this substance is less reactive toward carbonyl than is methylmagnesium iodide.

A New Approach to the Synthesis of Aldehydo Sugars

BY CHARLES D. HURD AND EDWARD M. FILACHIONE

Methods for the synthesis of aldehydo sugars, developed in recent years, involve these final steps in the various processes: (a) reaction of a thioacetal function with mercuric chloride, or with mercuric chloride and cadmium carbonate, (b) re-
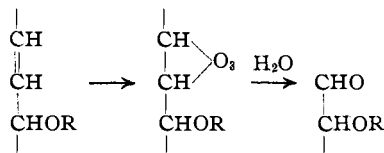
$ROCH_2(CHOR)_4CH(SEt)_2 \longrightarrow ROCH_2(CHOR)_4CHO$

moval of oxime or semicarbazone configurations by means of nitrous acid, (c) scission of a glycol

$AcOCH_2(CHOAc)_4CH{=}NOH \longrightarrow$
$\qquad\qquad AcOCH_2(CHOAc)_4CHO$

function with lead tetraacetate, (d) catalytic

$BzOCH_2CHOBzCHOHCHOHCHOBzCH_2OBz \longrightarrow$
$\qquad\qquad 2BzOCBzCHOBzCHO$

hydrogenation of an aldonyl chloride

$AcOCH_2(CHOAc)_4COCl \longrightarrow AcOCH_2(CHOAc)_4CHO$

In the present work, another approach was studied involving ozonolysis of a carbon-to-carbon double bond

$$
\begin{array}{ccc}
| & | & \\
CH & CH\!\diagdown & \\
\| & \;\;\;\diagup O_3 \;\; H_2O & \\
CH & \longrightarrow \;\; CH\!\diagup \quad\longrightarrow & CHO \\
| & | & | \\
CHOR & CHOR & CHOR \\
| & | & |
\end{array}
$$

The unsaturated compounds selected for study were of two types, namely, those with a terminal vinyl group and those possessing cyclic unsaturation as in glucal.

Originally, it was planned to test three types possessing a terminal vinyl group (I–III), for which the starting points, respectively, were glycerol, *meso*-erythritol and mannitol. Glycerol was converted into allyl alcohol (for I) by the

formic acid reaction, and erythritol into erythrol (for II) by the same general procedure.

$$
\begin{array}{ccc}
CH_2 & CH_2 & CH_2 \\
\| & \| & \| \\
CH & CH & CH \\
| & | & | \\
CH_2OCOR & CHOCOR & CHOCOR \\
 & | & | \\
 & CH_2OCOR & CHOCOR \\
 & & | \\
 & & CHOCOR \\
 & & | \\
 & & CH_2OCOR \\
I & II & III
\end{array}
$$
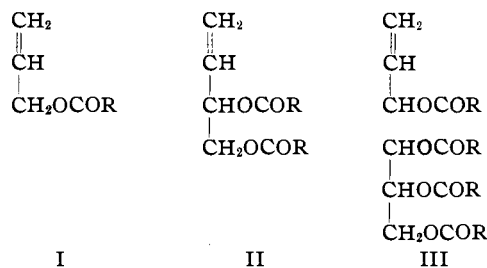
This type of reaction was not successful, however, when applied to the conversion of mannitol into the vinyltetrol related to III. This confirms the results of earlier workers,[1] who obtained a furan type of ring closure rather than production of terminal ethylenic unsaturation. The products identified were 2-vinyl-2,5-dihydrofuran, mannitan tetraformate and isomannide diformate.

In the present work additional data were obtained on this subject. A sirup was produced at 140° in the reaction between mannitol and formic acid from which mannitol triformate was obtainable in 20% yields. Vacuum distillation of the sirup yielded a water-insoluble distillate, half of which appeared to be a substance with the following structure or one closely related to it.

$$
\begin{array}{c}
CH{=}CH \\
| \qquad | \\
CH_2 \quad CHCHOHCH_2OCHO \\
\diagdown O \diagup
\end{array}
$$
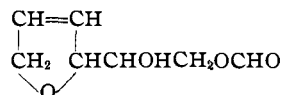
(1) Henninger, *Ber.*, **7**, 264 (1876); Fauconnier, *Compt. rend.*, **100**, 914 (1885); von Romburgh and Van der Berg, *Proc. Acad. Sci. Amsterdam*, **25**, 235 (1922); *C. A.*, **17**, 1214 (1923).