

1931

Abnormal reactions of organometallic compounds

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197

ABNORMAL REACTIONS OF ORGANOMETALLIC COMPOUNDS

BY

Stanton A. Harris

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A Thesis Submitted to the Graduate Faculty
for the Degree

DOCTOR OF PHILOSOPHY

Major Subject Organic Chemistry

Approved:

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Dean of Graduate College

Iowa State College
1931

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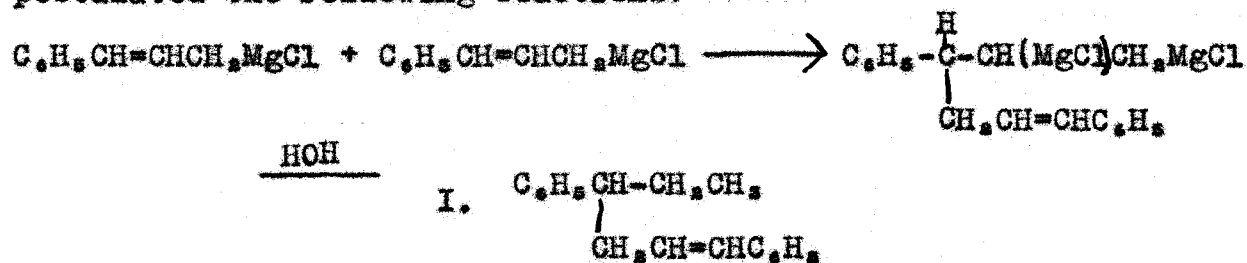
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A. THE ABNORMAL REACTION OF CINNAMYL CHLORIDE
WITH MAGNESIUM

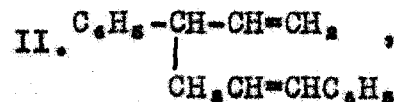
INTRODUCTION

It has been reported^{1a} that cinnamyl chloride with magnesium and carbon dioxide gave methylatropic acid ($C_6H_5-C=CH-CH_2$) instead of the expected phenylisocrotonic acid ($C_6H_5-CH=CH-CH_2-COOH$). This problem was undertaken because Rupe and Burgin² said that cinnamylmagnesium chloride added to the ethylenic linkage in another molecule of itself. They postulated the following reactions:



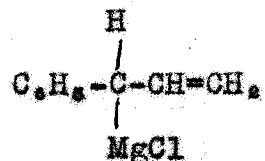
Gilman and coworkers have treated many different ethylenic compounds with the Grignard reagent and have never been able to find any evidence that addition to an ethylenic linkage took place. Leading references to this work may be found in the papers by Gilman and Harris^{1a & b}.

It has been found that the hydrocarbon obtained by Rupe and Burgin is 1,4-diphenylhexadiene-1,5



-
1. Gilman and Harris, (a) *J. Am. Chem. Soc.*, 49, 1825 (1927),
(b) *Rec. trav. chem.*, 49, 762 (1930).
 2. Rupe and Burgin, *Ber.*, 43, 172 (1910).

and not 1,4-diphenylhexene-1 as postulated by them. The Grignard reagent from cinnamyl chloride has been found to act as if it had the following structure:



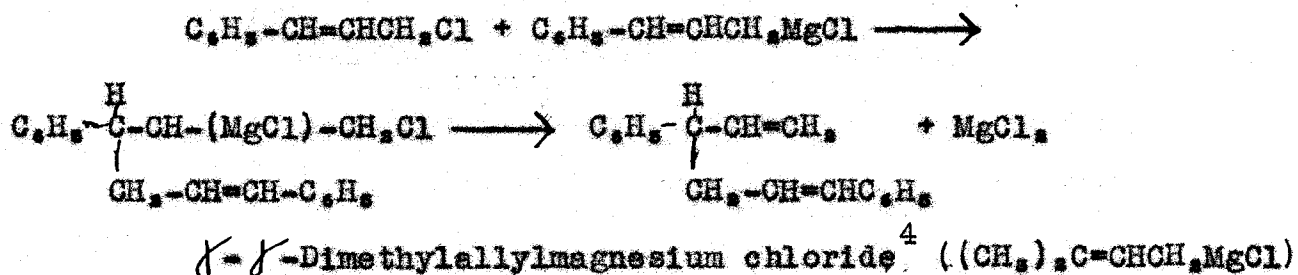
For convenience, this Grignard reagent will be called "cinnamylmagnesium chloride". On the basis of the abnormal behavior of cinnamylmagnesium chloride, a mechanism for the formation of 1,4-diphenylhexadiene-1,5 is given. Also, the reactions of this Grignard reagent, with several of the common reagents, are described. In every case, only rearranged products have been found.

In a private communication Professor Rupe has indicated that he no longer believes that the Grignard reagent adds to the ethylenic linkage.

HISTORICAL

The rearrangement that takes place in the cinnamylmagnesium chloride reaction is one that is common to a large number of compounds that contain the allylic grouping (-CH=CHCH₂-). Since there is a considerable amount of work dealing with this problem, an historical account will not be out of place here. The first part will deal with the reactions of the cinnamyl group, which will be followed by the general theories that have been proposed to explain these rearrangements.

Von Braun and Köhler³ said that Rupe and Bürgin probably obtained hydrocarbon II. instead of I. They gave the following mechanism:



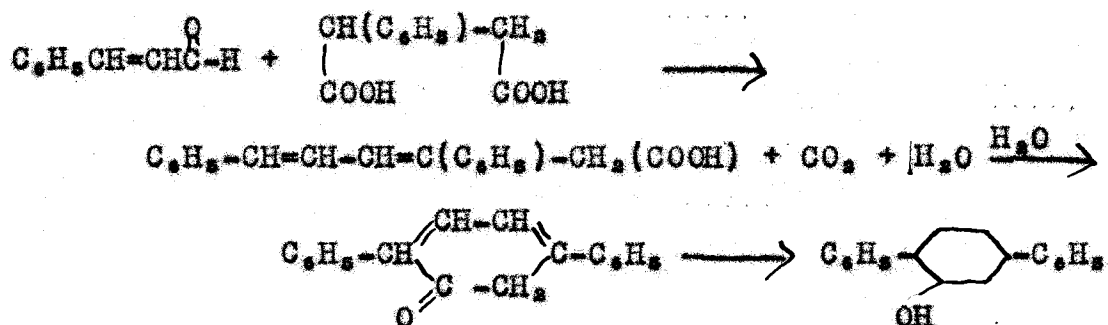
was reported to undergo a similar reaction. The normal acid ((CH₃)₂C=CHCH₂COOH) was obtained with carbon dioxide.

Kuhn and Winterstein⁵ attempted to make diphenylhexatriene by treating cinnamylmagnesium chloride with cinnamic

3. Von Braun and Köhler, Ber., 51, 83 (1918).
 4. Standinger, Kreis and Schilt, Helv. Chim. Acta, 5, 743 (1922).
 5. Kuhn and Winterstein, Helv. Chim. Acta, 11, 87 (1928).

aldehyde. Instead of obtaining the expected compound, they obtained about 10% yield of *p*-diphenylbenzene or terphenyl. They said that the Grignard reagent reacted with the carbon adjacent to the benzene ring instead of with the aldehyde group. This is another bit of evidence that the Grignard reagent from cinnamyl chloride is not $C_6H_5CH=CH-CH_2MgCl$, although the mechanism of their reaction is not clear.

Fichter and Grether⁶ gave a similar reaction between cinnamic aldehyde and phenylsuccinic acid which is as follows:



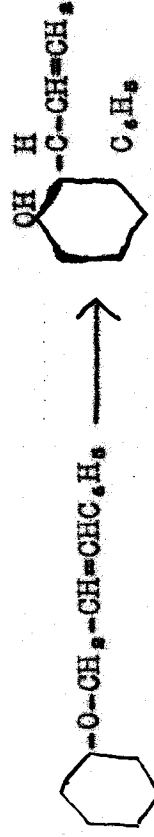
One of the first references to the fact that the reactions of the cinnamyl group were abnormal was that of J. Dupont and Labaune⁷. Cinnamyl bromide and ROH (R=CH₃ or C₂H₅) in the presence of KCN or KHCO₃ gave $C_6H_5-\overset{OR}{\underset{O}{\parallel}C}-CH-CH_2$. With silver nitrate in alcohol solution, cinnamyl bromide gave cinnamyl alcohol and its ethyl ether, and α -phenylallyl alcohol and its ethyl ether.

6. Fichter and Grether, Ber., 36, 1407 (1903).

7. Dupont and Labaune, Wiss. ind. ber. r. Bertrand, 1, 34 (1910), Chem. Zentr., (1910) II, 734, (C.A., 5, 1398 (1911).)

Moureu and Callagher⁸, in making derivatives of cinnamyl alcohol and *o*-phenylallyl alcohol, discovered that both alcohols gave the same bromide when treated with phosphorus tribromide or hydrogen bromide. This compound proved to be cinnamyl bromide because it gave benzoic acid on oxidation, and because its boiling point was higher than that of *o*-phenylallyl alcohol and lower than that of cinnamyl alcohol. This statement was based on the general fact that bromides have a lower boiling point than their corresponding alcohols.

Claisen and Tietze⁹ gave a mechanism for the rearrangement of phenyl cinnamyl ether to *o*-phenylallyl phenol. This was not only a rearrangement of the ether, but there was also a rearrangement within the cinnamyl group itself as shown by the reaction:



They proved the structure of their cinnamyl phenyl ether by reducing it to the dihydrocinnamyl phenyl ether, which was identical with the product formed in the reaction between dihydrocinnamyl bromide and sodium phenolate. The phenol obtained was not identical with the true cinnamylphenol which boiled

8. Moureu and Callagher, Bull. soc. chim., (4) 29, 1009 (1921).
9. Claisen and Tietze, Ber., 58, 275 (1925). They also refer to Klages and Klenk, ibid., 39, 2552 (1906).

higher than the α -phenylallyl derivative. It is generally true that cinnamyl derivatives boil higher than the corresponding α -allyl derivatives.

Recent work by Hurd and Cohen¹⁰ on the crotyl ethers of phenol showed that these compounds gave the same type of rearrangement as that shown by phenyl cinnamyl ether.

Valeur and Luce¹¹ made the observation that α -phenylallyl alcohol with hydrochloric acid and silver acetate gave cinnamyl alcohol. Cinnamyl alcohol was also obtained by the action of dilute sulfuric acid on α -phenylallyl alcohol.

α -Cyclohexylallyl alcohol did not undergo isomerism.

Charon¹² also made the observation that cinnamyl bromide and methyl or ethyl alcohol in alkaline solution gave the corresponding ether of α -phenylallyl alcohol.

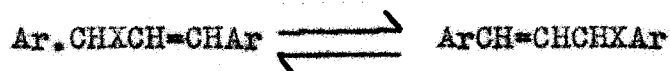
Burton and Ingold¹³ summarized this work in their paper entitled, "Preliminary Study of the Conditions of Activation of the Three Carbon System, and a Discussion of the Results in Relation to the Modes of Addition to Conjugated Systems".

They gave the following equilibrium equations:

-
10. Hurd and Cohen, J. Am. Chem. Soc., 53, 1917 (1931). These authors gave complete references to Claisen's work.
 11. Valeur and Luce, Bull. soc. chim., 27, 611 (1920).
 12. Charon, Bull. soc. chim., (4) 7, 86 (1910).
 13. Burton and Ingold, J. Chem. Soc., p. 904. (1928).

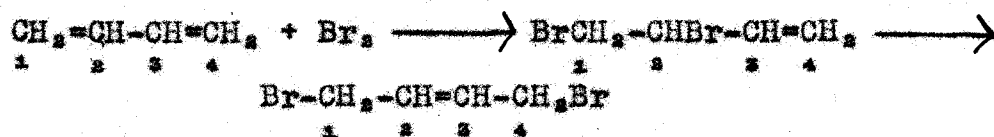


and



X = OR or Halogen.

They said that this tautomerism could be used as an explanation of 1,4-addition: namely, that 1,2-addition first took place and was then followed by anionotropic change. For example, bromine added 1,2 to butadiene, and then a bromine atom underwent rearrangement to the 4-position as illustrated:



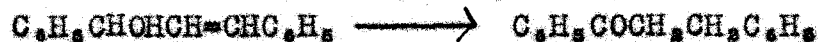
They also gave a number of references ^{14, 15}. They were not able to transform α -phenylallyl alcohol into cinnamyl alcohol as described by Valeur and Luce ¹¹. They (Burton and Ingold) also proved that Moureu and Gallagher's ⁸ interpretation of the structure of cinnamyl bromide was correct. They ozonized cinnamyl bromide and obtained benzaldehyde and bromoacetaldehyde which were identified as the semicarbazone and the bromal hydrate. Formaldehyde was not obtained.

Other references given by Burton and Ingold ¹³ were those of Tiffeneau ¹⁶ and Nomura ¹⁷. Tiffeneau ¹⁶ gave the following reactions:

-
14. Prevost, Compt. rend., 184, 1460 (1927).
 15. Farmer, Laroid, Switz and Thorpe, J. Chem. Soc., p.2937(1927).
 16. Tiffeneau, Bull. soc. chim., 1, 1209 (1907).
 17. Nomura, *ibid.*, 37, 1245 (1925).



and



These reactions took place in the presence of alcoholic alkali.

This reaction and ozonization were used to identify the products. Burton and Ingold¹³ gave the following order in which groups cause anionotropy:



This agreed with the o, p orienting sequence $\text{Cl} > \text{Me} > \text{H}$. In their experimental work, Burton and Ingold¹³ stated that

α -phenylallyl alcohol was not converted to cinnamyl alcohol with either hydrochloric or sulfuric acid, but it was converted when boiled with acetic anhydride for six hours. The p-methyl derivative was more easily converted to p-methylcinnamyl alcohol. Cinnamyl bromide was found to have a corresponding structure.

Harold Burton¹⁸ in the second paper on "Mobile anion tautomerism", gave a mechanism for anionotropic change. The experimental work gave some methods for converting α -phenylallyl alcohol and derivatives into cinnamyl alcohols. See next reference for discussion.

Burton^{19a}, in his third article on "Mobile anion tautomerism", gave a "Comparison of the activation of three-

18. Burton, J. Chem. Soc., p. 1650 (1928).

19a. Burton, *ibid.*, p. 455-8. (1929).

carbon anionotropic systems by alkyl and by aryl groups". In the previous articles the following reaction was shown to be complete:



The phenyl group activated the anionotropic system to a much greater extent than the methyl group. The stability of the system depended on the X and on some molecular property of the solvent which was closely related to the dielectric constant. In the system, $\text{CH}_2\text{CHXCH=CH}_2 \rightleftharpoons \text{CH}_2\text{CH=CH-CH}_2\text{X}$, the mobility of the X was much less, since each alcohol yielded its own acetate, and the *p*-nitrobenzoate resembled the acetates in their stability.

Burton^{19b} found that esterification of α -methylvinylcarbinol with trichloroacetic acid gave an equilibrium mixture, which consisted of 55% α -methylallylacetate and 45% of crotyl trichloroacetate. Heating either one of these esters caused the formation of the same equilibrium mixture. The *p*-nitrobenzoate of α -cyclohexylallyl alcohol underwent no change in acetic anhydride. α -2,4-Xylylallyl alcohol, when heated with acetic anhydride for six hours, gave the acetate of 2,4-dimethylcinnamyl alcohol.

Burton^{19c} was unsuccessful in attempting to prepare γ -phenyl- α -*p*-methoxyphenylallyl alcohol and δ -phenyl- α -*p*-

19b. Burton, J. Chem. Soc., p. 248 (1930).
19c. Burton, Proc. Leeds Phil. Lit. Soc. 2, pt. II. 61-4 (1930).

dimethylaminophenylallyl alcohol from the Grignard reagents. In his most recent paper, Burton^{19d} compared the activation of the three carbon anionotropic systems as shown by the phenyl, α -naphthyl and β -naphthyl radicals. The *p*-nitrobenzoate of α -phenylallyl alcohol has never yielded any of the corresponding cinnamyl derivative, when heated in pyridine for twenty-four hours. Under the same conditions, the *p*-nitrobenzoates of α -1-naphthyl and α -2-naphthylallyl alcohols were changed to the corresponding γ -allyl alcohols. This showed that the α - and β -naphthyl groups were more powerful than the phenyl group in the activation of the allylic system. This same observation was made in connection with the dissociation of the hexaphenyl and hexanaphthyl ethanes.

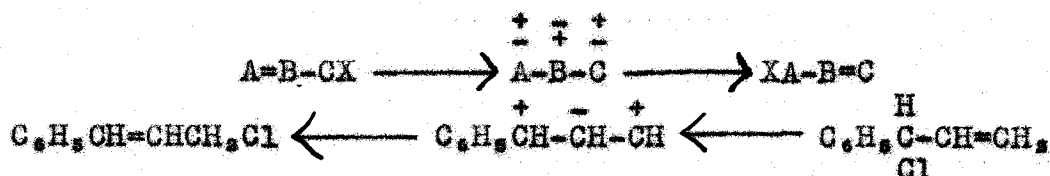
Marcel Bouis,^{20, 21, 22} while making allene hydrocarbons, used this same rearrangement. He described yields, constants and derivatives of several substituted α -allyl alcohols made by the reactions between a Grignard reagent and acrolein. He treated these alcohols with phosphorus tribromide in the presence of pyridine which removed the hydrogen bromide. In all cases, the bromide obtained was that corresponding to the rearranged product according to the following reaction:

- 19d. Burton, J. Chem. Soc., p. 759 (1931).
20. Bouis, Compt. rend., 183, 133-4 (1926).
21. Bouis, Bull. soc. chim., (4) 41, 1160 (1927).
22. Bouis, Ann. chim., 9, 402 (1928).



This compound, when treated with sodium acetate and hydrolyzed, gave the corresponding primary alcohol with no trace of the secondary alcohol. The bromides were treated with bromine to form the tribromides which were used to make the corresponding allene hydrocarbons. The last article of Bouis²², gave many references to related work.

Prevost²³ has done a considerable amount of work on this rearrangement which he named the "allylic rearrangement". This referred to the same reaction as that of Burton's which he called "mobile anion tautomerism". Prevost²³ proposed the following mechanism to explain the allylic rearrangement: he coined the word, "synionie", for the grouping which may be explained as follows:



In the example given, the "synionie" has two carbons holding a positive charge, thus the chlorine may take its choice as to which carbon it will go. The consequences of Prevost's "synionie" theory are given below.

1. If this common ion is free in a reaction momentarily, the results should be the same whatever the original isomer might be.

23. Prevost, *Compt. rend.*, 185, 132-4 (1927).

2. If X is very stable in one form and less stable in the other form, it will be transformed irreversibly to the first form.

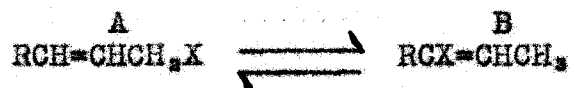
3. If X is very mobile in each of two isomers, it should be transformed reversibly from one to the other. (Desmotropism).

4. If X is slightly mobile in each of its forms, the two compounds will show no tendency to isomerize. They will be formed simultaneously in the same reaction.

5. All causes (rise of temperature for instance) which increase the mobility of X will modify the isomers of the two forms in the sense that they approach desmotropism.

These conclusions have been in part verified by the study of enol-keto isomerism. The allylic rearrangement was explained by this theory, and the five conclusions above were verified experimentally.

The following is Prevost's²⁴ summary of the allylic rearrangement:



1. Alcohols of type B isomerized in the presence of aluminum oxide at 350° to type A.

2. In presence of water at 200° geraniol isomerized to linalol.

24. Prevost, Compt. rend., 185, 1283-5 (1927).

3. Catalytic reduction of the two alcohols gave the same compound.

4. Acetyl chloride and acetic anhydride transformed the two alcohols to their corresponding acetates.

5. Esterification of both alcohols with hydrochloric acid gave partial rearrangement.

6. Both alcohols with phosphorus pentachloride gave a halogen derivative of type A.

7. Formation of the barium alcoholate and reconversion to the alcohol caused no change.

8. Saponification of the bromide of type A produced a mixture of alcohols.

9. The action of alkali salts of acetic acid on halogen ester of type A or B gave only the esters of type A.

10. The bromine derivatives of type B isomerized at 70° to type A.

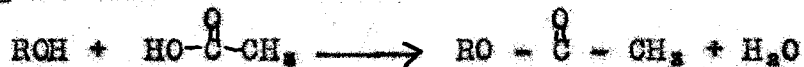
11. Crotyl bromide with dry potassium formate gave erythrene.

12. Bromides of type A with sodium ethylate gave chiefly an ethylene derivative of type A and some of type B.

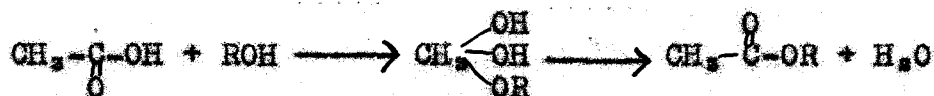
13. Dilute hydrochloric acid at 100° converted methylvinylcarbinol into a mixture of the chloride (type A), the alcohols of both types, and all the esters.

Because the reaction with acetic acid was normal,

Prevost said that esterification must be according to the following scheme:



He agreed with Carother's³¹ mechanism for esterification:

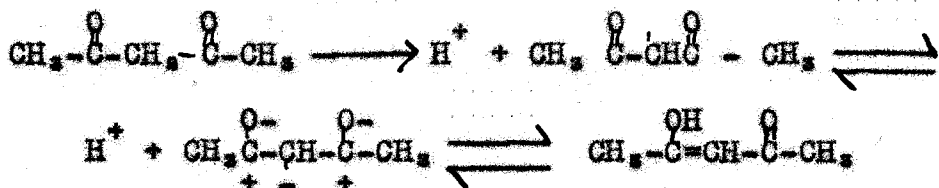


However, hydrochloric acid gave abnormal reactions, therefore the mechanism must be as follows:



Prevost²⁵ said that the allylic or α - γ -rearrangement is very general. Some examples are given here:

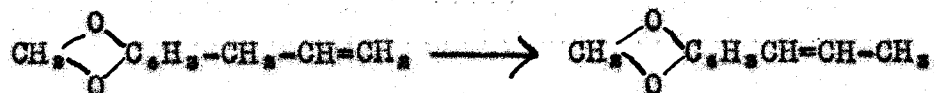
1. o, p-rearrangements.
2. semi-benzidine and benzidine rearrangements.
3. allyl-propenylic rearrangements.
4. enol-keto tautomerism.



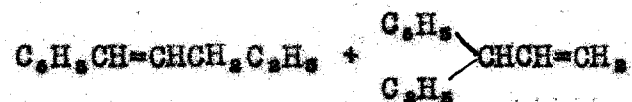
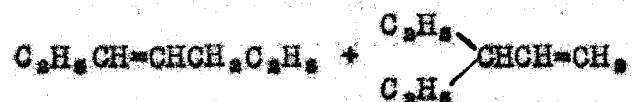
One of the oldest examples of the allylic rearrangement was the

-
25. Prevost, *Ann. chim.*, 10, 113 (1928).
 26. Prevost, *ibid.*, 10, 147 (1928).
 27. Prevost, *Bull. soc. chim.*, 43, 996-1018 (1928).
 28. Prevost, *Compt. rend.*, 187, 946-8 (1928).
 29. Prevost, *ibid.*, 187, 1052 (1928).
 30. Prevost, *Ann. chim.*, 10, 356-439 (1928).
 31. Carothers, *J. Am. Chem. Soc.*, 46, 2226 (1924).

transformation of safrol into iso safrol. A hydrogen was the mobile group.



Prevost and Daujat³² obtained abnormal reactions when they treated substituted allyl bromides with Grignard reagents. They carried out the following reactions, and obtained and identified the following compounds:



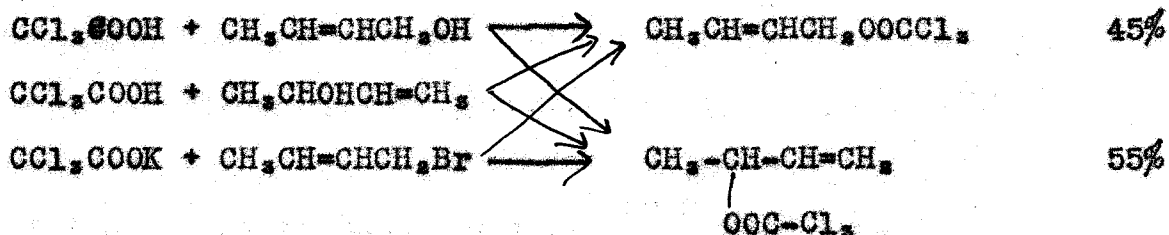
In the reaction between cinnamyl bromide and ethylmagnesium bromide, they obtained dicinnamyl and a liquid hydrocarbon which they predicted to have one of the following formulas:



The experimental part of this thesis shows that the
32. Prevost and Daujat, Bull. soc. chim., 47, 588 (1930).

liquid hydrocarbon has structure II.

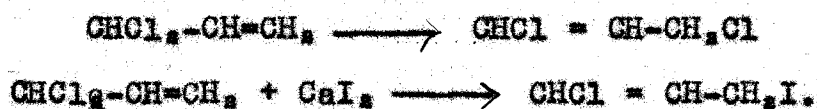
Recently, Prevost³³ had another paper on the mechanism of the allylic rearrangement. He gave the following reactions for the esterification of the isomeric crotyl alcohols with trichloroacetic acid. The reactions were carried out at 95-100° and the yields of the two products were as indicated:



These results agree with those of M. Burton^{19b} who explained the reactions differently, but Prevost objected to his explanation.

Merling³⁴ in the treatment of diallyl with a strong base obtained some diisopropenyl.

v. Romburgh³⁵ gave the following reactions:



Claisen³⁶ reported the tautomeric bromides:

$(\text{CH}_2)_2\text{CBr-CH}=\text{CH}_2$ and $(\text{CH}_2)_2\text{-C}=\text{CH-CH}_2\text{Br}$. He also mentioned the formation of cinnamyl alcohol from α -phenylallyl alcohol and

33. Prevost, *ibid.*, 49, 261 (1931).

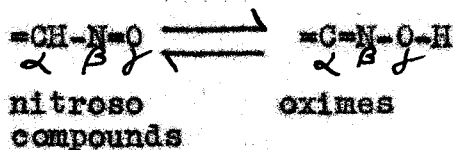
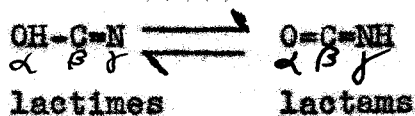
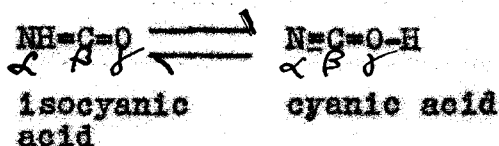
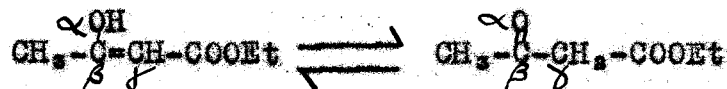
34. Merling, *Ann.*, 264, 345 (1891).

35. v. Romburgh, *Bull. soc. chim.*, (2) 36, 550 (1881) and 37, 103 (1882).

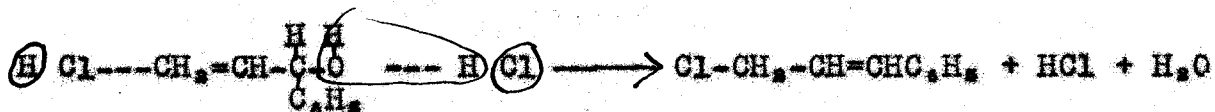
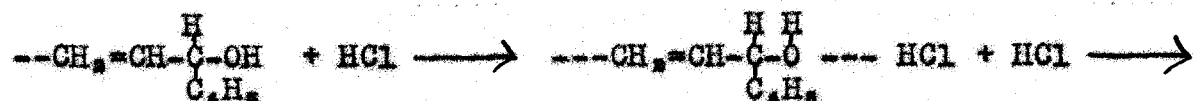
36. Claisen, Kremers, Roth and Tietze, *J. prakt. chem.*, (2) 105, 65 (1923).

hydrobromic acid. Claisen³⁷ mentioned the rearrangement of α -phenylallyl alcohol to cinnamyl bromide.

Lapworth³⁸ described many α - β -rearrangements. Some examples are given here:



Meisenheimer³⁹ gave a mechanism to explain the formation of cinnamyl chloride from α -phenylallyl alcohol.



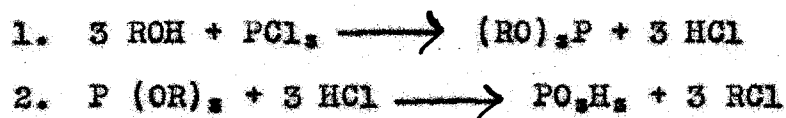
Meisenheimer and Link⁴⁰ gave an extensive paper on the rearrangement of the allyl group. They described the formation of the cinnamyl halides from cinnamyl alcohol and also from

-
37. Claisen, Ber., 58, 279 (1925).
 38. Lapworth, J. Chem. Soc., 73, 445 (1898).
 39. Meisenheimer, Ann., 456, 134 (1927).
 40. Meisenheimer and Link, Ann., 479, 211 (1930).

α -phenylallyl alcohol; the formation of alkyl ethers; the formation of acetates; and the formation of ethylcinnamylaniline. The formation of ethers and acetates gave partial rearrangements depending on the reagents used while the formation of ethylcinnamylaniline was a normal reaction.

They also gave the reactions of ethylvinylcarbinol and penten-2-ol-1. The secondary alcohol was made from ethylmagnesium bromide and acrolein. The carbinol on treatment with acetic anhydride gave a mixture of acetates. (This was contrary to Prevost's statement). The acetates were hydrolyzed and the primary and secondary alcohols were separated by careful fractionation.

Prevost^{26,29} has treated alkylvinylcarbinols with phosphorus trichloride in the presence of pyridine. Milobendzki and Sachnowski⁴¹ gave the following mechanism for the reaction between an alcohol and phosphorus trichloride:

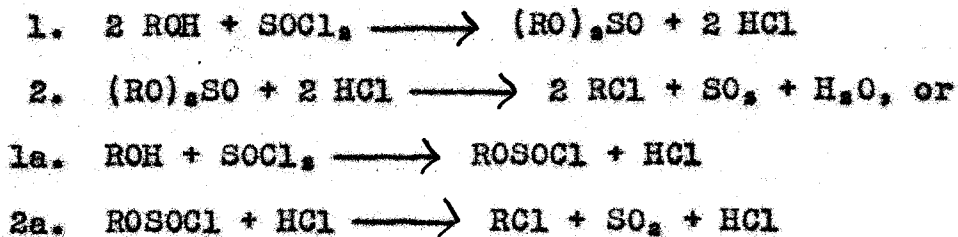


When pyridine was used it combined with one molecule of hydrogen chloride leaving behind one molecule of phosphoric acid ester. On distillation this broke down into phosphinic acid ester. In the presence of pyridine the reaction ceased unless additional dry hydrogen chloride was led in. This

41. Milobendzki and Sachnowski, Chemik. Polski, 15, 34 (1917), (C.A., 13, 2865 (1919).)

gave a 15-20% higher yield of the vinyl chloride than when dry hydrogen chloride was used.

Thionyl chloride acted according to the following scheme:

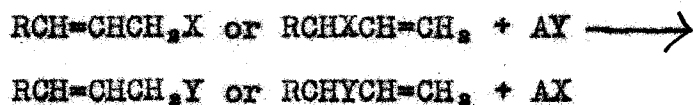


Meisenheimer and Link discussed other mechanisms for the allylic rearrangement and then gave one of their own. The following is an abstract of their discussion:

1. The rearrangement took place due either to a rearrangement of the starting materials or a rearrangement of the reaction products. This seemed unlikely.

2. Moureu and Gallagher⁸ said that the rearrangement was due to the addition of hydrogen halide followed by the splitting out of water. This was easily disproved by experiment.

3. The third explanation was that of Prevost's²¹ "synionie" which they said was worthless for the following reasons:



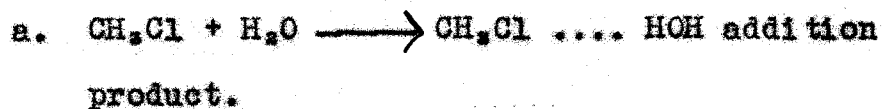
First, the course of the reaction was not independent of the nature of A. For instance, potassium and silver acetates did

not give the same results with cinnamyl chloride. Absolute alcoholic potash gave the corresponding ether with cinnamyl chloride, while silver oxide gave 30-40% of the isomeric ether.

Second, different reagents should have given the same results but they did not. Hydrogen chloride with pentenyl alcohol gave 60-70%, phosphorus trichloride gave 40-50%, and thionyl chloride gave 20-75% of the primary alcohol.

4. They did not discuss the theory of Burton and Ingold in this paper.

5. Their own theory was as follows:



In allyl compounds there were two points of affinity, thus:



The A, Y and X all took part in determining the position at which the group will add.

Several other references of minor importance were given in the articles of Prevost and Bouis. References 26 to 30,

inclusive, of Prevost were concerned chiefly with experimental work on this subject.

Straus⁴² and Straus and Berkow⁴³ gave the rearrangement of cinnamyl chloride to α -phenylallyl alcohol. They also referred to Dupont and Labaune's⁷ work.

Another allylic rearrangement was that of α -naphthylmethylmagnesium chloride and benzylmagnesium chloride by Gilman and Kirby⁴⁴. They obtained normal reactions with carbon dioxide, phenyl isocyanate, and dimethyl sulfate; and abnormal reactions with ethylchlorocarbonate and formaldehyde. Cinnamylmagnesium chloride gives abnormal reactions with carbon dioxide, phenyl isocyanate, and an indication of an abnormal reaction with diethyl sulfate.

42. Straus, Ann., 393, 252 (1912).

43. Straus and Berkow, Ann., 401, 131 (1913).

44. Gilman and Kirby, J. Am. Chem. Soc., 51, 3475 (1929).

45. A survey of the three carbon system may be found in the "Annual Reports on the Progress of Chemistry". 25, 127-133 (1928) and 26, 119-130 (1929).

THEORETICAL

As shown in the experimental part of this thesis, the structure that Rupe and Bürgin assigned to the liquid hydrocarbon, which was obtained when they treated cinnamyl chloride with magnesium, was undoubtedly wrong. The formula obtained by them, as given in the introduction, was



The compound was purified by several fractional distillations in a vacuum, which gave a compound whose boiling point, density and refractive index, agreed very closely with the constants obtained by Rupe and Bürgin. This showed that it was the same compound. The constants are given in the experimental part. However, the analysis agreed more closely with $\text{C}_{18}\text{H}_{18}$ than with $\text{C}_{18}\text{H}_{20}$ which they obtained. This indicated that the compound contained two ethylenic linkages instead of one. This fact was definitely proved by catalytic reduction, whereby exactly two molecular equivalents of hydrogen were used. This definitely established the formula $\text{C}_{18}\text{H}_{18}$.

The proof of the structure of this liquid hydrocarbon was obtained by the use of two different methods. The first method was that of reduction and comparison with a saturated synthetic hydrocarbon. In this way, the reduced liquid hydro-

carbon proved to be 1,4-diphenylhexane. The preparation of the synthetic 1,4-diphenylhexane is described in the experimental part. The boiling point, density, refractive index, molecular refraction, and analysis of these hydrocarbons showed them to be the same compound.

Oxidation reactions were used to determine the position of the ethylenic linkages in the molecule. Rupe obtained benzoic acid and phenylsuccinic acid on oxidation with dilute potassium permanganate. In repeating this oxidation reaction, no phenylsuccinic acid was obtained in several runs. Benzoic acid was always obtained. Ozonization was also tried. Benzaldehyde was the only product which was identified by a derivative. Formaldehyde was also shown to be a product by the use of the fuchsin aldehyde reagent in the presence of mineral acids. The method used was that described by Doavre⁴⁶ for the determination of formaldehyde in the quantitative ozonization of hydrocarbons.

This work showed that two fragments of the molecule were: $\text{CH}_2=$ and $\text{C}_6\text{H}_5\overset{\text{H}}{\text{C}}=$. The fact that Rupe obtained phenylsuccinic acid indicated that the third fragment was: $\text{C}_6\text{H}_5-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}-\overset{\text{H}}{\text{C}}=$.

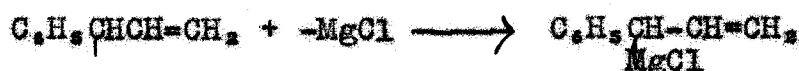
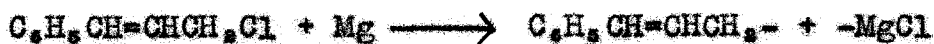
46. Doavre, Bull. soc. chim., 45, 140-52 (1929).

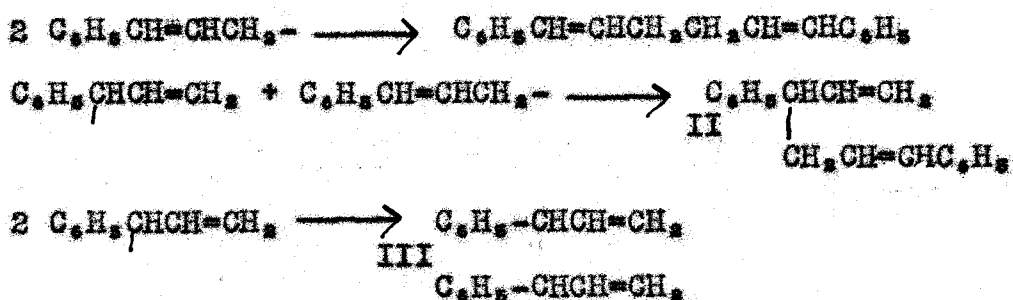
It is therefore postulated that this hydrocarbon has the following structure: $C_6H_5-\overset{H}{\underset{CH_2CH=CHC_6H_5}{C}}-CH_2=CH_2$ II. This hydrocarbon would be called 1,4-diphenylhexadiene-1,5. It is more reasonable to expect the formation of phenylsuccinic acid on the oxidation of this hydrocarbon, than it is to expect it from 1,4-diphenylhexene-1, as postulated by Rupe and Burgin.

A second hydrocarbon obtained from cinnamyl chloride and magnesium was dicinnamyl or 1,6-diphenylhexadiene-1,5. On ozonization, benzaldehyde was obtained, but no test for formaldehyde was observed.

A third possible hydrocarbon is 3,4-diphenylhexadiene-3,5. No such hydrocarbon was obtained. This structure is eliminated as a possibility for the liquid hydrocarbon because on reduction, it would give 3,4-diphenylhexane which is a solid melting at $89^\circ C$. A little of the authentic 3,4-diphenylhexane would not cause the crystallization of the reduced hydrocarbon from cinnamyl chloride and magnesium.

The following mechanism is proposed for the formation of these two hydrocarbons when cinnamyl chloride is treated with magnesium:





Moureu and Gallagher⁸, and Burton and Ingold¹², have established that the structure for cinnamyl bromide is $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{Br}$. It should, therefore, be safe to assume that cinnamyl chloride is $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{Cl}$. Other reactions of the Grignard reagent seemed to show that the $-\text{MgCl}$ group had migrated from the α - to the γ -position during its formation. This was simply an allylic rearrangement, described by Prevost and others, as cited in the historical part of this paper.

Gilman and Harris^{1a} obtained methylatropic acid from cinnamyl chloride, magnesium and carbon dioxide. This acid, however, was not obtained directly from the reaction, but was obtained by heating to boiling the liquid acid which was the direct product of the reaction. It was stated before^{1a} that this liquid acid was probably an isomer of methylatropic acid. Further investigation of this acid showed that it may be changed to methylatropic acid by three methods which are: first, heating for two or three minutes at its boiling point; second, boiling with 50% sulphuric acid; and third, heating with dilute sodium hydroxide.

The neutralization equivalent of the crude liquid acid was the same as that of methylatropic acid. It, therefore, is an isomeric form of methylatropic acid of which there are three possibilities: first, it may be a geometric isomer; second, it may be a mixture of phenylisocrotonic acid and methylatropic acid; or, third, it may be a β - γ -unsaturated acid instead of an α - β -unsaturated acid, as is the case with methylatropic acid. No direct evidence has been obtained to prove or disprove the first possibility.

The second possibility was disproved in two ways. In the first place, attempted fractional crystallization of the liquid acid would yield neither phenylisocrotonic acid nor methylatropic acid. In fact, phenylisocrotonic acid was never obtained from this reaction. This showed that the reaction was entirely abnormal. In the second place, the liquid acid was finally crystallized from petroleum ether (b.p. 40-60°) at about -10° C. and therefore proved to be a definite chemical compound. It melted sharply at 22-23° C. This acid was reduced to α -phenylbutyric acid which was identified by mixed melting points.

A β - γ -unsaturated acid is more unstable than an α - β -unsaturated acid. The β - γ -unsaturated acid should be transformed to an insoluble lactone when boiled with either dilute sulfuric acid or dilute alkali. However, in each case,

this acid was transformed to the more stable isomer which is also a characteristic of β - γ -unsaturated acids.

Direct proof of its structure was attempted by oxidation both with dilute potassium permanganate and ozone. If it were a geometric isomer of methylatropic acid, oxidation should yield benzoylformic acid. This acid was not obtained as there was no reaction with phenylhydrazine. No definite products could be obtained from the permanganate oxidation due probably to the formation of inner esters.

Ozonization of this acid yielded formaldehyde, but the other products could not be identified. From the evidence obtained, the following structure is assigned to the liquid acid:
$$\text{C}_6\text{H}_5-\overset{\text{H}}{\underset{\text{COOH}}{\text{C}}}-\text{CH}=\text{CH}_2.$$
 This would be known as phenylvinylacetic acid.

The Grignard reagent from cinnamyl chloride, when treated with phenyl isocyanate, gave one anilide which proved to be identical with the anilide made from phenylvinylacetic acid. No anilide of phenylisocrotonic acid was obtained.

In every case, the only derivatives that could be isolated were the ones that could only be explained by the rearrangement of cinnamylmagnesium chloride. It, therefore, seems that the structure of cinnamylmagnesium chloride can best be explained by the following formula:
$$\text{C}_6\text{H}_5-\overset{\text{H}}{\underset{\text{MgCl}^-}{\text{C}}}-\overset{\ominus}{\text{C}}\text{H}=\text{CH}_2.$$

Also, the evidence is in favor of the following structure for cinnamyl chloride: $C_6H_5CH=CHCH_2Cl$. Therefore, rearrangement must take place during the formation of the Grignard reagent.

Since phenylvinylmethylmagnesium chloride is actually a substituted benzylmagnesium chloride, it was thought possible that it might show rearrangement reactions to the ring, as found by Gilman and Kirby⁴⁴. Ethyl chlorocarbonate and formaldehyde are known to give abnormal reactions with benzylmagnesium chloride. These reagents were therefore added to so-called cinnamylmagnesium chloride. All of the products were oxidized with potassium permanganate according to the procedure used by Kirby⁴⁷. In no case could any *o*-phthalic or terephthalic acid be isolated. The ester formed from ethylchlorocarbonate gave methylatropic acid on hydrolysis.

47. Kirby, Unpublished Thesis, Iowa State College Library, Ames, Iowa. 1929.

EXPERIMENTAL PART

Preparation of Cinnamyl Chloride and its Grignard Reagent

This work has been submitted⁴⁸ for publication, and is only briefly outlined here. Cinnamyl chloride of high purity, for use in the preparation of its Grignard reagent, was made in good yields as follows: The cinnamyl alcohol was purified by repeated fractional distillations. The portion melting at 32-33° was used. One hundred and thirty-four grams (1.0 mole) of cinnamyl alcohol was dissolved in 100 cc. of chloroform. One hundred and two and eight-tenths grams (1.3 moles) of pyridine was dissolved in 100 cc. of chloroform and to this pyridine solution was added 142.8 g. (1.2 moles) of thionyl chloride. This addition took about five minutes while the flask was cooled in ice water. The pyridine-thionyl chloride solution was then added to the cinnamyl alcohol solution which was also cooled in ice water. This addition took one and one-half hours. Toward the end of the reaction, solid pyridine hydrochloride separated and was dissolved by gentle warming. After the addition was completed the solution was refluxed on a water bath for one hour. This was allowed to cool and the pyridine hydrochloride was extracted with three or four (50 cc) portions of water. The solution

48. Gilman and Harris, Rec. trav. chim., (1931).

was dried over calcium chloride, the chloroform distilled under a vacuum from a water pump, and the cinnamyl chloride distilled with an oil pump. The yield was 126 g. or 82.9%; the boiling point was 86-87°/2 mm, 102-103°/5 mm, 109-110°/6 mm; the melting point was 7-8°.

Cinnamyl chloride prepared in this way showed no signs of decomposing, as evidenced by the lack of residue on distillation. It gave very satisfactory yields when used for the preparation of its Grignard reagent.

Because of the unusual reactivity of cinnamyl chloride, it entered into coupling reactions with magnesium to a large extent, unless proper precautions were observed. References to the preparation of other Grignard reagents by Gilman and coworkers from reactive halogen compounds, are given in the above mentioned paper⁴⁸.

A typical run for the preparation of cinnamylmagnesium chloride is described here. The apparatus used consisted of a 500 cc. three-necked flask fitted with a reflux condenser, a mercury sealed stirrer and a dropping funnel. The apparatus was protected from the air by a calcium chloride, soda-lime tube. Fifteen grams (0.6 atom) of 30-60 mesh magnesium was placed in the flask. The reaction was started with a few drops of cinnamyl chloride in 50 cc. of ether without the aid of a catalyst. The remainder of the cinnamyl chloride

(30.5 g. or 0.2 mole) was added in 275 cc. of ether. The time of addition was 2.25 hours. The yield by acid titration was 83.3%.

The Hydrocarbons from Cinnamyl Chloride and Magnesium

Two hydrocarbons were obtained when cinnamyl chloride was treated with magnesium in ether solution. The reactions for their formation are given in the theoretical part. The structure of the liquid hydrocarbon was established by the following steps: first, separation, purification and analysis showed that the empirical formula was $C_{18}H_{18}$ instead of $C_{18}H_{20}$; second, catalytic reduction showed the presence of two ethylenic linkages which were located with the aid of ozone; third, the reduced liquid hydrocarbon was found to be identical with 1,4-diphenylhexane which was synthesized by standard reactions.

Cinnamyl chloride in ether solution was added to one-half equivalent of magnesium. The resulting hydrocarbons were obtained by fractional distillations. The total yield of unpurified hydrocarbons was 74.5%. After five fractional distillations, a 43% yield of liquid hydrocarbon was obtained. The boiling point was $175-180^{\circ}/2$ mm. An 8.75% yield of solid

dicinnamyl was obtained by freezing and filtering the higher boiling fractions. This compound melts at 82° and has been described before^{2,3}.

The following is the analysis of the liquid hydrocarbon compared with that obtained by Rupe and Bürgin²:

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74.

Found: C, 92.08; H, 7.95.

Rupe and Bürgin² obtained the following:

Anal. Calcd. for $C_{18}H_{20}$: C, 91.54; H, 8.47.

Found: C, 91.54; H, 8.51.

The constants of this hydrocarbon agreed with those obtained by Rupe and Bürgin as shown by lines 1 and 2 in Table I.

TABLE I.

Compound	B.P.	Pressure	n_D^{20}	d_4^{20}	observed m.p.	Calcd. m.p.
1. Liquid Hydrocarbon	157-160	2 mm.	1.5890	0.9919	80.1	77.5
2. Same compound obtained by Rupe	190	11 mm.	1.5880	0.9915	80.14	78.0
3. 1,4-diphenylhexane	147-148	3 mm.	1.5456	0.9608	78.38	78.14
4. Synthetic 1,4-diphenylhexane	147-149	3-4 mm.	1.5460	0.9660	78.01	78.14
5. 1,4-diphenylhexanol-4	177-179	5 mm.	1.5508 ²⁴	1.0284 ²⁴		

Reduction of Liquid Hydrocarbon

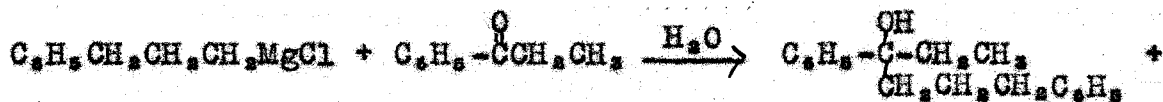
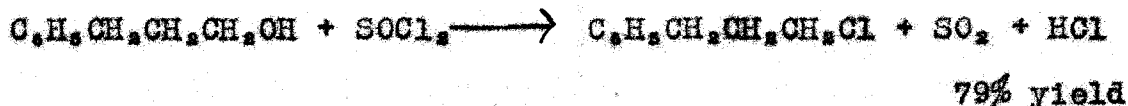
Five-hundredths mole of this hydrocarbon was reduced catalytically with platinum oxide catalyst in alcohol solution. Exactly 0.1 mole, or two equivalents of hydrogen, were taken up proving that there were two ethylenic linkages.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.75; H, 9.24.

Found: C, 90.40; H, 9.16.

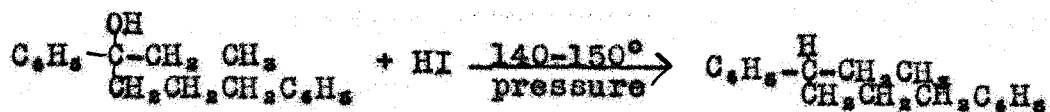
Synthesis of 1,4-diphenylhexane

This hydrocarbon was made by the following reactions:



Anal. Calcd. for $C_{18}H_{22}O$: C, 85.04; H, 8.66.

Found: C, 84.96; H, 8.69.



Anal. Calcd. for $C_{18}H_{22}$: C, 90.75; H, 9.24.

Found: C, 90.57; H, 9.19.

As shown by the agreement of the constants (lines 3 and 4 of Table I) and by the agreement of the analysis of these two compounds, they are proved to be identical. The reduced liquid hydrocarbon is therefore 1,4-diphenylhexane. It was established that the liquid hydrocarbon has two ethylenic linkages, therefore, it must be a 1,4-diphenylhexadiene. The location of the ethylenic linkages was determined by oxidation reactions.

Oxidation with potassium permanganate yielded only benzoic acid. Phenylsuccinic acid was not obtained as described by Rupe and Bürgin². Ozonization, using the quantitative methods of Deavre⁴⁶, yielded benzaldehyde and formaldehyde. This established the ethylenic linkages at the two ends of the molecule which is in agreement with the formation of phenylsuccinic acid mentioned above.

The liquid hydrocarbon from cinnamyl chloride and magnesium is, therefore, 1,4-diphenylhexadiene-1,5 which was formed by the reactions given in the theoretical part.

Structure of Cinnamyl Chloride

Because cinnamylmagnesium chloride gave abnormal reactions in every case tried, it was thought wise to definitely establish the structure of cinnamyl chloride. Burton and Ingold¹³ ozonized cinnamyl bromide and obtained benzaldehyde and bromoacetaldehyde. The ozonization of cinnamyl chloride in chloroform solution yielded benzaldehyde on hydrolysis with water.

An attempt was made to synthesize α -phenylallyl chloride, which is an isomer of cinnamyl chloride, by treating α -phenylallyl alcohol with the thionyl chloride-pyridine complex. α -Phenylallyl alcohol was prepared in 74% yield from acrolein and phenylmagnesium bromide. The alcohol was converted to the chloride in the same manner as cinnamyl alcohol was converted to cinnamyl chloride. An 83% yield of product boiling at 102-103°/5 mm. was obtained. Boiling point, melting point, mixed melting point, refractive index and density showed that this compound was practically pure cinnamyl chloride.

Two cc. of forerun was obtained which boiled at 65-67°/3-4 mm; the refractive index was 1.4830 and the density was 1.0428/20°. Fourteen hours later the refractive index was found to be 1.5300 and the density 1.0406.

Cinnamyl chloride that had stood for three months was

redistilled. The refractive indexes at 23° of three equal, successive fractions were 1.5795; 1.5810; and 1.5825. These figures, along with its sharp melting point and constant boiling point, showed that cinnamyl chloride is not a mixture. The exaltation of molecular refraction, on conjugation of an ethylenic linkage with the benzene ring, is shown in Table II of physical constants. α -Phenylallyl alcohol is not conjugated and shows absolutely no exaltation. Cinnamyl chloride and cinnamyl acetate show an exaltation of about two.

Cinnamyl acetate was made by treating cinnamyl chloride with sodium acetate and acetic acid, according to the method of Bouis²², also, by treating cinnamyl alcohol with acetyl chloride. The two products were identical. Cinnamyl acetate was ozonized. Benzaldehyde, as identified by the phenylhydrazone, was obtained.

TABLE II.

Compound	B.P.	Density	n_D^{20}	Observed mr:	Calcd. mr:	Exalta- tion
Low boiling cinnamyl chloride	65-67 3-4 mm.	1.0428	1.4830	45.27	44.56	.71
Cinnamyl chloride	102-103 at 5 mm.	1.0876	1.5825	46.72	44.56	2.16
-Phenylallyl alcohol	86-87 at 5 mm.	1.0214	1.5410	41.225	41.22	.00
Cinnamyl acetate	138-139 at 10 mm.	1.0524	1.5405 ^{25°}	52.58	50.59	1.99
-Phenylallyl acetate	100-102 at 3 mm.		1.5105			

1
53
1

Ozonization of α -Phenylallyl Alcohol

Three and three-tenths grams (0.025 mole) was dissolved in 20 cc. of glacial acetic acid and treated with ozonized air until no more test for unsaturation was obtained with bromine. This was hydrolyzed with zinc dust and water. Benzaldehyde was obtained as identified by its hydrazone. This was an unexpected result, but it did agree with the work of Verley⁴⁹ which was disputed by Doewre⁴⁶. It throws additional doubt on the value of ozonization in locating ethylenic linkages in the proximity of the benzene ring. There is of course the possibility that the structure for α -phenylallyl alcohol is not correct. The evidence from Table II points to the fact that the ethylenic linkage is not conjugated with the benzene ring as there is no exaltation in the molecular refraction. A decision would, therefore, have to be made between molecular refraction and ozonization as means of proving structure. Physical means of determining structure should be more reliable as there is a possibility that chemical reagents like ozone may cause rearrangement.

It is concluded that the accepted structure for cinnamyl chloride ($C_6H_5CH=CHCH_2Cl$) is correct. This is in agreement with Moureu and Gallagher⁸, and Burton and Ingold¹³,

49. Verley, Bull. soc. chim., 43, 854 (1928).

in their proof of structure of cinnamyl bromide.

The Carbonation of Cinnamylmagnesium Chloride

Gilman and Harris^{1a} previously reported the formation of methylatropic acid ($C_6H_5-\overset{\text{COOH}}{\underset{|}{C}}=CHCH_3$), from the reaction between cinnamylmagnesium chloride and carbon dioxide. The acid obtained directly from the reaction was a liquid, which was changed to methylatropic acid by boiling with dilute acid or alkali or by allowing it to stand for a period of time.

When carbon dioxide was run into a solution of cinnamylmagnesium chloride, the yield of acid obtained was 31.3% based on the amount of RMgX compound present. This yield was increased to 65% of the RMgX compound present by adding the cooled solution to a bottle filled with ice cold carbon dioxide. The following is the description of the bottle used for the inverse addition of a Grignard reagent to a carbon dioxide atmosphere. A bottle about twelve inches high having a wide mouth and a capacity of about two liters was used. This was fitted with a mercury sealed stirrer which had two extra sets of vanes in addition to those at the bottom. These vanes were sealed onto the stirring rod and spaced equidistant from each other. They were so shaped that the incoming

RMgX solution would be sprayed throughout the bottle. An inlet and an outlet tube were inserted in the stopper for the carbon dioxide, and another inlet tube was provided for the addition of the RMgX compound. The bottle was immersed in an ice-salt bath and the carbon dioxide was cooled by passing through a considerable length of rubber tubing immersed in the ice-salt mixture. The Grignard solution was also cooled by allowing it to flow down through a condenser whose jacket was filled with ice water. The only difficulty was to keep the solid that was formed from plugging the RMgX compound inlet tube. This trouble was avoided by using a slight pressure from a nitrogen tank at the top of the dropping funnel containing the RMgX solution.

The neutralization equivalent of the crude liquid acid was 166. The theoretical for $C_9H_9C_6H_5COOH$ is 162. It was therefore found to be an isomer of the methylatropic acid. The three possibilities were: first, that it was a geometric isomer; second, that it was a mixture of methylatropic acid and phenylisocrotonic acid, and third, that it was a β - γ -unsaturated isomer.

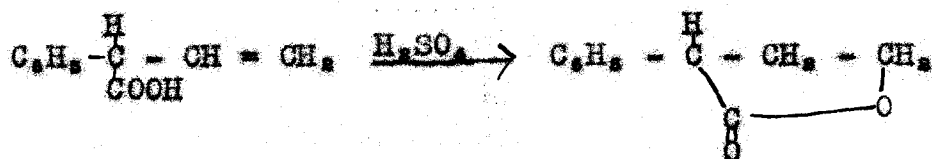
The possibility that phenylisocrotonic acid was present as an impurity was eliminated by recrystallization of the liquid acid from water. In no case was phenylisocrotonic acid isolated. This showed that the reaction with carbon

dioxide was entirely abnormal. In one case, another acid was isolated, which melted at 77-78° and had a neutralization equivalent of 161.2. This acid was not identified. α -Methylcinnamic acid, an isomer, melts at 78°. This acid was synthesized by the directions of Erdman⁵⁰. Mixed melting points with the above acid gave a depression of 15-20°.

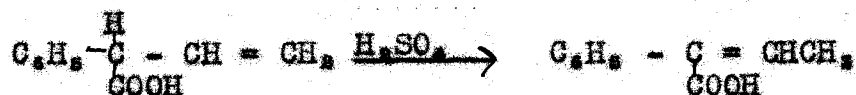
The liquid acid was finally crystallized from petroleum ether (b.p. 40-60°) by cooling to -10° C. Recrystallization gave an acid which melted at 23-24°. The liquid acid yielded no other product, hence it was concluded that it was a single compound. Liquid acid which had stood for several months would not crystallize in this manner. On treatment with dilute sodium hydroxide, methylatropic acid was obtained.

The acid melting at 23° showed an average neutralization equivalent of 162.2. On heating to boiling, in a test tube for two minutes, it was changed to methylatropic acid melting at 132°. It was then concluded that this acid was the β - γ -unsaturated isomer, phenylvinylacetic acid, since the double bond was so readily shifted to the α - β -position. Fifty percent sulfuric acid should change a β - γ -acid into an insoluble lactone. Instead, it was changed to methylatropic acid which was not a surprising fact. The reaction which might be expected is as follows:

50. Erdman, Ann., 227, 246 (1884).



The following is the reaction which actually did take place:



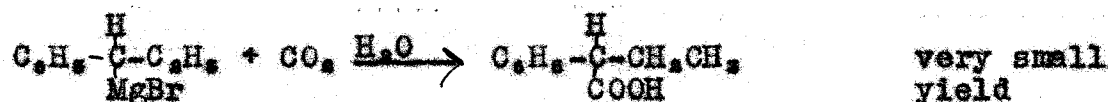
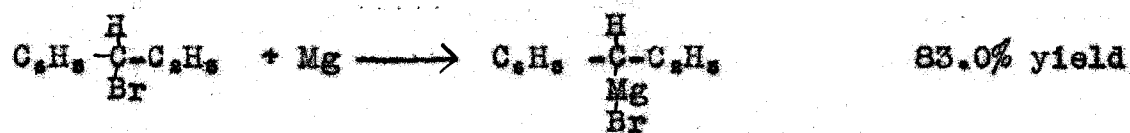
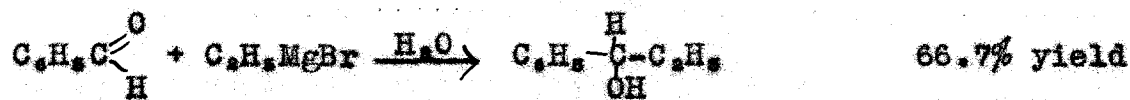
Ozonization was used to prove that the ethylenic linkage was at the end of the chain. The quantitative ozonization method of Deeuve⁴⁶ was used on liquid acid that had stood for six months. A 20% and a 17% yield of formaldehyde were obtained in two runs. The low yield might be due to partial isomerism to methylatropic acid.

Catalytic reduction was used to prove the position of the carboxyl group in the liquid acid. A small amount of liquid acid was crystallized from petroleum ether (b.p., 40-60°) and found to melt at 22-24°. This was dissolved in ethyl acetate to which was added 0.1 g. of platinum oxide catalyst. It was then shaken with hydrogen until no more was absorbed.

This solution was filtered from the catalyst, and washed with dilute alkali, which was filtered and poured into an excess of cold dilute sulfuric acid. An oily layer separated which was extracted with ether. The ethyl ether was replaced by petroleum ether, which was filtered and cooled. The acid crystallized out and was pressed dry on a suction filter.

It melted at 42°.

α-Phenylbutyric acid⁵¹ melts at 42°, so it was synthesized by the following reactions:



This acid was crystallized, filtered, and dried. The melting point was 42.5°. Mixed melting point with the acid obtained by reduction showed no depression. First, ozonization; and, second, reduction of the acid melting at 23° showed that it was phenylvinylacetic acid.

Grignard and Ono⁵² previously made phenylethylmethylmagnesium bromide, but they did not make the acid from it.

α-Phenylbutyric acid has been made by hydrolyzing phenylethylacetonitrile.

51. Neure, Ann., 250, 140 (1888).

52. Grignard and Ono, Bull. soc. chim., 39, 1589-94 (1926).

The Reaction Between Cinnamylmagnesium Chloride
and Phenyl Isocyanate

A 0.25 mole run of cinnamylmagnesium chloride was made, which gave an 87% yield by titration. To this was added an ether solution containing 20 g. (0.17 mole) of phenyl isocyanate. A negative color test was obtained after the addition. The reaction products were hydrolyzed with iced hydrochloric acid. The ether layer was dried and evaporated. The residue solidified and was recrystallized from either a small portion of benzene, or alcohol. The part of this anilide that was used for analysis was recrystallized from the following solvents in the order given: benzene, alcohol, chloroform and finally, benzene. It was then dried in the oven at 90° C. The melting point, 97-98° was not raised by these recrystallizations, so it was considered to be pure.

Anal. Calcd. for $C_{16}H_{15}ON$: C, 81.01; H, 6.33.

Found: C, 80.77; H, 6.33.

The crude liquid acid from cinnamylmagnesium chloride and carbon dioxide was changed to the acid chloride in benzene solution by the addition of thionyl chloride. The excess thionyl chloride was boiled off and the residue treated with aniline. The product was washed with dilute hydrochloric acid

to remove aniline and the residue was crystallized from petroleum ether (b.p. 40-60°). The melting point was 94-115°. Recrystallization of this product from benzene yielded a small amount of insoluble material melting at 190°. The soluble product crystallized out and was found to melt at 96-97°. A mixed melting point with the product from phenyl isocyanate and the Grignard reagent showed no depression. Therefore this compound is the anilide of phenylvinylacetic acid.

The anilide of methylatropic acid was made in the same way and found to melt at 193°. This compound was found to be identical with the 190° compound obtained from the liquid acid and aniline.

The Reaction with Ethylchlorocarbonate

A 0.25 mole run of cinnamylmagnesium chloride was made, which gave a 59% yield by titration. The RMgCl solution was decanted from the excess of magnesium and added to an ice cold solution of ether containing 126 g. (1 mole) of practical ethylchlorocarbonate. After hydrolysis, the ether solution was evaporated and the residue steam distilled. The steam distillate yielded 3.45 g. of ester which was a 12.5%

yield based on the RMgCl compound present. The boiling point was 93°/4-5 mm. The index of refraction at 28° was 1.5060.


This ester was hydrolyzed by shaking for two days with an excess of alkali. It was then extracted with ether and the alkaline solution was acidified. From this was obtained 2.35 g. or 80% of dried acid, melting at 129-130°C. A mixed melting point with methylatropic acid showed no depression. Recrystallization of this acid from water yielded pure methylatropic acid. The conditions for the hydrolysis of this ester were such as would change phenylvinylacetic acid to methylatropic acid. The probability is that the ester was ethyl phenylvinylacetate, as this would be in harmony with the other reactions of cinnamylmagnesium chloride.

The residue obtained from steam distillation was found to contain the hydrocarbons described before. All of the products from this run were oxidized with an excess of potassium permanganate. The resulting product was carefully searched for the presence of ortho and terephthalic acids. The technique used was that described by J. E. Kirby⁴⁷ in his Doctoral thesis. Since neither of these acids could be detected, it is concluded that no rearrangement to the benzene ring took place in this reaction.

The Reaction with Gaseous Formaldehyde

A 0.25 mole run of cinnamylmagnesium chloride was made, which yielded 77% RMgCl compound by titration. The solution was treated with gaseous formaldehyde until no color test was obtained. The ether soluble material after hydrolysis was steam distilled. The steam distillate was taken up in ether, dried and distilled in a vacuum. The boiling point was $90^{\circ}/2-3$ mm; n_d^{20} was 1.5365; the density was 1.0123; the yield was 9.5 g. (0.064 mole) or 33.2% based on the amount of RMgX compound present. The product was not pure as the analysis for $C_{10}H_{12}O$ was found to be low. The structure of the carbinol was not determined further than to prove that no rearrangement to the ring had taken place. This was done by oxidation, as previously described. Only benzoic acid could be isolated.

Oxidation of Residues from Cinnamylmagnesium Chloride Runs

Kuhn and Winterstein⁵³ reported a 10% yield of terphenyl () in the reaction between cinnamylmagnesium chloride and cinnamic aldehyde. Because of this observation, residues from some cinnamylmagnesium chloride

53. Kuhn and Winterstein, *Helv. Chim. Acta.*, 11, 87 (1928).

runs were oxidized with potassium permanganate. Benzoic acid alone was obtained. Terphenyl should give *p*-phenylbenzoic acid or terephthalic acid. Neither of these acids was obtained. The terphenyl is, no doubt, a product of the reaction between the rearranged cinnamylmagnesium chloride and cinnamic aldehyde.

Reaction with Oxygen and with Ethyl Sulfate

A 0.2 mole run of cinnamylmagnesium chloride was destroyed by passing dry air over the solution. Three grams of material boiling at 85-95° / 2 mm. came over at first. The refractive index at 21° was 1.5450. α -Phenylallyl alcohol boils at 86-87° / 4-5 mm. Its refractive index is 1.5410. This reaction was also abnormal.

Another run was treated with ethyl sulfate. A hydrocarbon boiling at 66° / 8-9 mm. was obtained. The refractive index was 1.5010; the density at 23° was 0.8948. The yield was 10 g. or 57% of the RMgX compound present. This hydrocarbon was ozonized in acetic acid solution. The product on hydrolysis was treated with semicarbazine hydrochloride. A white precipitate was formed which melted at 140-143°. After one recrystallization from benzene, it melted at 150-151°.

The semicarbazone of α -phenylbutyraldehyde⁵⁴ melts at 155°. This hydrocarbon also yielded formaldehyde on ozonization.

Attempted Reduction of Cinnamylmagnesium Chloride

If cinnamylmagnesium chloride could be reduced in ether solution to the saturated compound, the position of the -MgCl group could then be determined by changing it to the acid. This reduction was attempted with the use of platinum oxide catalyst and hydrogen. A drying train of calcium chloride and phosphorous pentoxide had to be used to remove the water from the hydrogen. No hydrogen was absorbed, even when a second 0.1 gram portion of catalyst was added. The remaining Grignard solution was carbonated and the usual phenylvinylacetic acid was isolated.

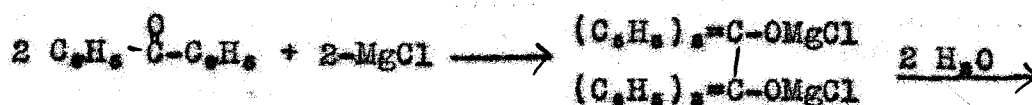
The reduction of another unsaturated Grignard was also attempted. One-tenth mole of stock styrylmagnesium bromide was treated with hydrogen in the presence of platinum oxide catalyst. Some hydrogen was absorbed, although the exact amount could not be determined because of difficulty with the apparatus. The resulting solution was carbonated and the acids worked up as usual. Crystallization from hot water gave pure cinnamic acid, which was identified by melting point and 54. Stoermer, Ber., 39, 2300 (1906).

mixed melting point. No other acid could be isolated.

The reduction of Grignard reagents is limited to the use of ether or tertiary amines as solvents. Amines are anti catalysts toward catalytic reduction. Reductions in ether usually take place very slowly, so the possibility of reduction of unsaturated Grignard reagents is not at all promising. The catalyst used was found to be effective in reducing maleic acid in ethyl acetate solution.

The Reaction with Benzophenone

Cinnamylmagnesium chloride was treated with an ether solution of benzophenone. A faint red color was obtained, but it soon disappeared. After hydrolysis, the ether solution was evaporated and the residue treated with petroleum ether (b.p. 40-60°) in which benzopinacol is quite insoluble. No benzopinacol was obtained, so it was concluded that cinnamylmagnesium chloride does not dissociate. The possible dissociation reactions are as follows:



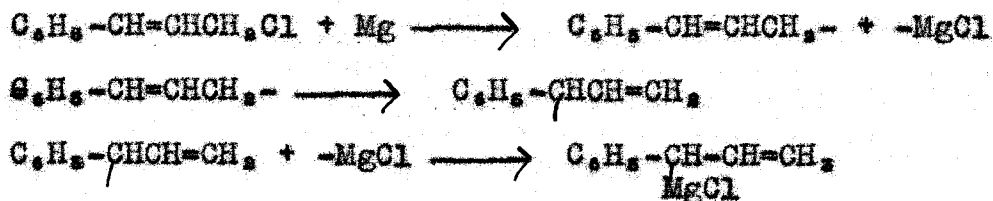


Gilman and Fothergill⁵⁵ were able to estimate qualitatively the amount of dissociation of triphenylmethylmagnesium chloride by the amount of benzopinacol that was formed, when the Grignard was treated with benzophenone.

55. Gilman and Fothergill, J. Am. Chem. Soc., 51, 3149 (1929).

SUMMARY

Cinnamylmagnesium chloride was made in 83% yield, when a large excess of 30-80 mesh magnesium and a dilute ether solution of pure cinnamyl chloride were used. The following derivatives of this Grignard reagent were obtained: phenylvinylacetic acid which rearranges to methylatropic acid, was formed with carbon dioxide; the anilide of phenylvinylacetic acid was formed with phenyl isocyanate; and the ethyl ester of phenylvinylacetic acid was formed with ethylchlorocarbonate. The liquid hydrocarbon, which was obtained as a by-product, was found to be 1,4-diphenylhexadiene-1,5 instead of 1,4-diphenylhexene-1 as it was described previously². One explanation for the formation of these derivatives is the rearrangement of the cinnamyl radical, on treatment with magnesium, to form phenylvinylmethylmagnesium chloride as illustrated:



B. GRIGNARD REAGENTS FROM HALOGENATED TERTIARY AMINES

INTRODUCTION

The object of this work was to prepare Grignard reagents that contained a tertiary amino group. Such a Grignard reagent could then be added to lead chloride or organolead halides to form an organolead compound which would contain a potentially water soluble group.

Certain compounds of lead have been found to have some value in the treatment of cancer. The literature on this subject has been reviewed by Robinson¹ in his Doctoral thesis on "Organolead compounds in cancer therapy." In Robinson's work, an attempt was made to introduce groups into the organolead compounds which would have a water solubilizing tendency. Some of the groups tried were the p-aminobenzoate, the p-bromophenyl, and the carboxy radicals. None of these was very successful.

If an amino group could be introduced into the lead compounds by the use of the Grignard reagent, it would then be possible to obtain organolead compounds whose hydrochlorides would be somewhat water soluble. Such compounds could then be tested for their effectiveness in retarding cancer growth or destroying cancer tissue.

1. Robinson, Unpublished thesis, Iowa State College Library, Ames, Iowa, 1929.

The tertiary amino group is the only one which does not react with the Grignard reagent. There are two types of tertiary amino groups; first, one which is included in a ring structure of which pyridine and quinoline are examples; and second, one which is attached to three separate radicals.

This work was initiated by Gilman and Heck² who perfected directions for the preparation of β -chloroethylmethylaniline and γ -chloropropylmethylaniline. These compounds reacted normally with magnesium to give a Grignard reagent which in turn reacted with aldehydes and ketones. Further reference to these reactions is made in the theoretical part. This work was temporarily discontinued because the reagents used in the synthesis of the halogenated amines were too expensive.

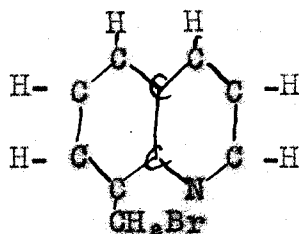
The present problem deals, first, with the attempted preparation of Grignard reagents from some of the halogenated pyridines and quinolines, and second, with the preparation of Grignard reagents from the o-halogen N-dialkylanilines. 2-Iodopyridine was found to react quite readily with magnesium in ether solution. However, the Grignard reagent was not stable and no derivatives were obtained from it. Other pyridine compounds were too unreactive with magnesium to be of any real value.

2. Gilman and Heck, Ber., 62, 1379 (1929).

Attention was then turned to the N-dialkyl halogenated anilines. It was found that the o-iodo- and the o-bromodimethylanilines reacted readily with magnesium in ether solution to form the corresponding Grignard reagents in high yields. The o-chloro compound reacted with magnesium less readily.

HISTORICAL

There is only one case in the literature where a reaction between a halogenated pyridine or quinoline compound and magnesium was reported. Howitz and Kopke³ reported that a variety of bromoquinolines would not react with magnesium. They said that only 8-quinolinemethyl bromide

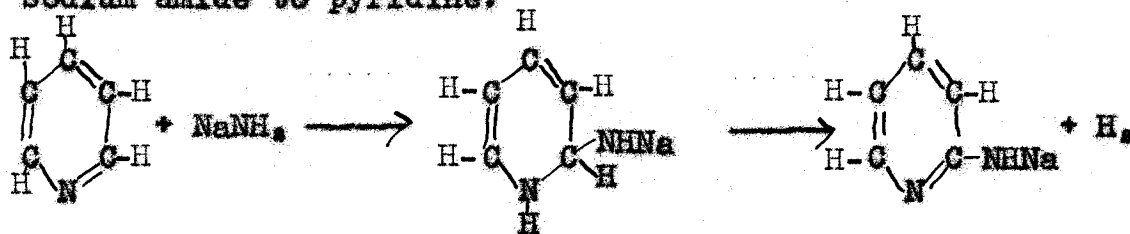


could be brought into reaction with magnesium in ether solution. Sachs and Sachs⁴ also made the statement that bromoquinolines with magnesium in ether could not be made to react.

Since no reference was found which mentioned a reaction between the halogenated pyridines and magnesium, the literature was scanned for the best methods for the preparation of these compounds. There are two recent reviews on pyridine chemistry which contain most of the important references on this subject. Horsters and Horsters⁵ in their

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3. Howitz and Köpke, *Ann.*, 396, 38 (1913).
 4. Sachs and Sachs, *Ber.*, 37, 3088 (1904).
 5. Horsters and Horsters, *Handbuch der biologischen arbeitsmethoden*, Edited by Emil Abderhalden, p. 2879-2970 (1930). (*C.A.*, 25, 1548 (1931)).

article on "New syntheses of biologically important pyridine-bodies", give directions for the preparation of 2-amino-pyridine which may be used to make the corresponding 2-iodo- and 2-chloropyridines. These directions were originally reported by Chichibabin⁶, but they were not very accessible as they were published in the Russian Journal. The second review on "Pyridine chemistry" by Maier-Bode⁷ gives a complete account of the entrance of substituents into the pyridine ring. The 3 and 5 positions in the pyridine ring were filled by direct substitution, while the 2 and 6, and to some extent the 4, positions were filled by addition reactions followed by the splitting out of hydrogen. An example of the latter reaction is shown by the addition of sodium amide to pyridine:



This reaction took place in boiling toluene. If a solvent boiling from 160-180° was used, both the 2 and the 6 hydrogens were replaced.

6. Chichibabin and Ziede, J. Russ. Phys.-Chem. Soc., 46, 1216 (1914). (C.A., 9, 1901 (1915)).

7. Maier-Bode, Z. angew. Chem., 44, 49-55 (1931).

The 2-aminopyridine was changed to the 2-iodo- or 2-chloropyridine by the diazo reaction as described by Chichibabin⁸.

The best directions for the preparation of 3-bromopyridine and 3,5-dibromopyridine are given by Englert and McElvain⁹. They heated the pyridine hydrobromide in a sodium nitrate-potassium nitrate bath at 240° for eight hours.

The 2,3 and 4-halogen substituted quinolines were made by the same reactions that were used to prepare the 2, 3 and 4 substituted pyridines. The references for these compounds were found in Beilstein¹⁰. The 5, 6, 7 and 8-halogen substituted quinolines were made by the modified Skraup's synthesis. If a mixture of *m*-bromoaniline, nitrobenzene, glycerol and sulfuric acid was heated together, a mixture of 5- and 7-bromoquinolines was obtained¹¹. LaCoste¹² prepared 6-bromoquinoline by heating a mixture of *p*-bromoaniline, glycerol, nitrobenzene and sulfuric acid. It was also made by diazotizing 6-aminoquinoline as described by Howitz, Fraenkel and Schroeder¹³. Claus and Tornier¹¹ also made

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8. Chichibabin and Rjazancev, J. Russ. Phys.-Chem. Soc., 46, 1571 (1915). (C.A., 10, 2898 (1916).)
 9. Englert and McElvain, J. Am. Chem. Soc., 51, 863 (1929).
 10. Beilstein, p. 256, vol. IV, 3rd. edition.
 11. Claus and Tornier, Ber., 20, 2872 (1887).
 12. LaCoste, Ber., 15, 557 (1882).
 13. Howitz, Fraenkel and Schroeder, Ann., 396, 53 (1912).

8-bromoquinoline by the modified Skraup's synthesis.

Hammick¹⁴ prepared α -tribromoquinaldine by adding bromine to an acetic acid solution of quinaldine which contained an excess of powdered anhydrous sodium acetate. This compound was reduced to the α -monobromoquinaldine¹⁵ with stannous chloride in acetone solution.

Howitz and Nother¹⁶ described the preparation of 8-quinolinemethyl bromide which was the only bromoquinoline compound that has been reported to react with magnesium³.

Howitz and Phillipp¹⁷ described the bromination of 6-methylquinoline. They obtained the 6-dibromomethylquinoline instead of the monobromo compound. They also obtained some 6-dibromomethyl-3-bromoquinoline.

The Grignard reagent from (β -chloroethyl) methylaniline has been prepared by Gilman and Heck². They found that this Grignard reagent reacted normally with aldehydes and ketones, which was contrary to a statement made by VonBraun, Heider and Müller¹⁸. Gilman and Heck described a method for the preparation of β -chloro- and γ -chloroalkyl tertiary amines which is illustrated as follows:

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14. Hammick, J. Chem. Soc., p. 2882 (1923).
 15. Hammick, *ibid.*, p. 1302 (1926).
 16. Howitz and Nother, Ber., 39, 2705 (1906).
 17. Howitz and Phillipp, Ann., 396, 23 (1912).
 18. VonBraun, Heider and Müller, Ber., 50, 1637 (1917), also *ibid.*, 51, 273 (1918).



The cost of the reagents used in the above reactions has delayed further development along these lines.

The dialkylaniline compounds with the halogen in the benzene ring can be made more easily and more cheaply than the previous class of compounds. The Grignard reagent of p-bromodimethylaniline¹⁹ has been made, but the reaction is unusually slow and the yields are only fair. It has also been made by Votocek and Matejka²⁰, and Hurd and Webb²¹. The Grignard reagents from o-, m- and p-iododimethylanilines were prepared by v.Baeyer²². He said that the o-compound was the most reactive, and the p-compound was the least reactive. No mention of the Grignard reagents from o-bromodimethylaniline or o-bromodiethylaniline was found in the literature.

19. Gilman and Hewlett, unpublished work.

20. Votocek and Matejka, Ber., 46, 1760 (1913).

21. Hurd and Webb, J. Am. Chem. Soc., 49, 546 (1927).

22. v.Baeyer, Ber., 38, 2759 (1905) also Ann., 354, 152 (1907).

THEORETICAL

An attempt was made to prepare the Grignard reagents from 3-bromopyridine and from 3,5-dibromopyridine. These compounds in ether solution did not react with activated magnesium-copper alloy. In the absence of ether or in a sealed tube with ether, a reaction did take place between 90 and 100°. In every case, a tarry mass which was insoluble in ether or benzene was obtained. After the reaction had gone to completion, the reaction products did not give a color test²³ when refluxed with Michler's ketone. This showed that no Grignard reagent was present.

If pure 3-bromopyridine was heated with magnesium in a test tube, a darkening of the products was noticed around 100°. If a benzene solution of Michler's ketone was added at once, so that the reaction would continue in its presence, then a color test could be obtained upon hydrolysis. This showed that the Grignard reagent was formed at least in the transient stage.

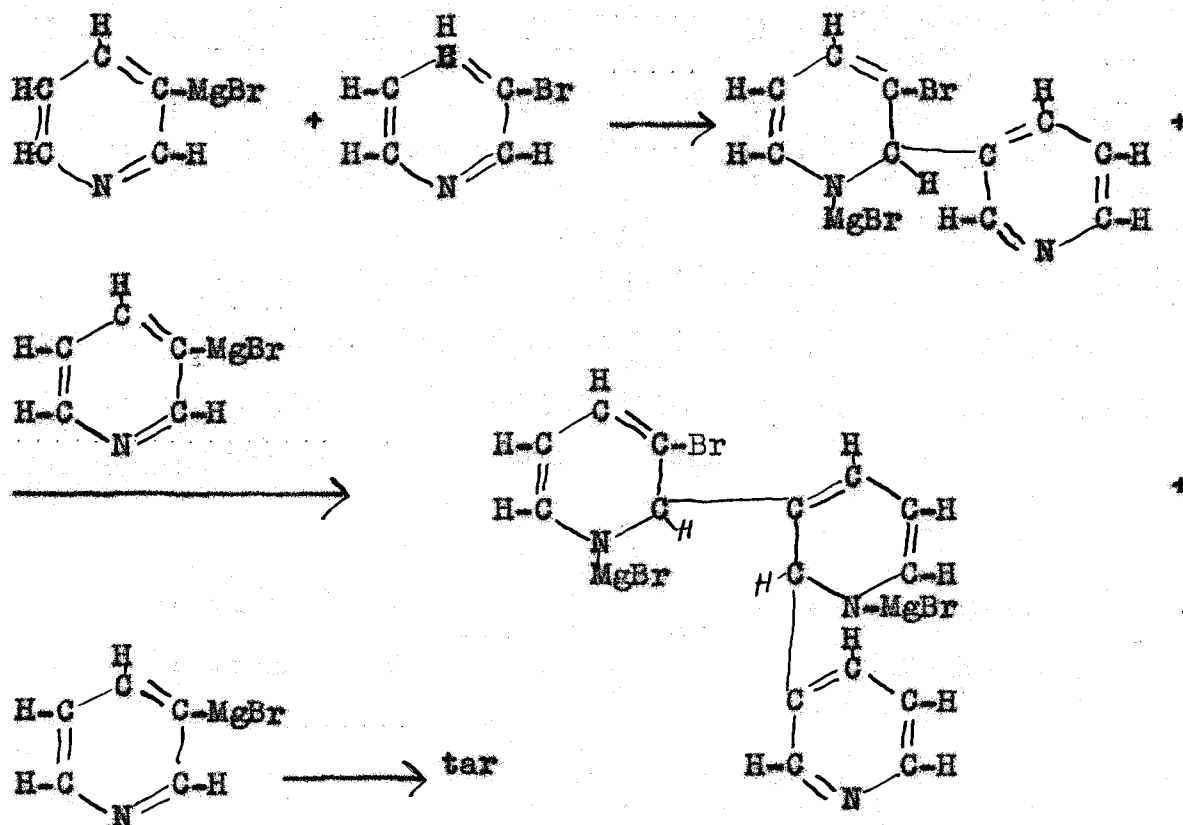
Pyridine, unlike other tertiary amines, contains a carbon nitrogen double bond which can be brought into reaction with the Grignard reagent. Bergstrom and McAllister²⁴

23. Gilman and Schulze, *J. Am. Chem. Soc.*, 47, 2002 (1925).

24. Bergstrom and McAllister, *J. Am. Chem. Soc.*, 52, 2845 (1930).

prepared 2-aryl- and 2-alkylpyridines by heating at 150-160°, the complex formed between pyridine and the desired Grignard reagent. They gave references to earlier work of this type.

This reaction would account for the polymerization reaction of 3-bromopyridine with magnesium. A molecule of 3-pyridylmagnesium bromide might add to a molecule of 3-bromopyridine, and a second molecule of the Grignard reagent might add to that molecule etc., until a large molecule was formed. A possible reaction could be illustrated as follows:



The bromine that was left in the molecule would probably react with magnesium to further complicate the results. No attempt was made to determine the constitution of the residues, since the purpose of this work was to find a halogenated tertiary amine which would give a Grignard reagent.

In the review on "Pyridine chemistry" by Maier-Bode⁷ the statement was made that 2-chloropyridine resembled the aliphatic halides in its reactivity. Also Wibaut and Overhoff²⁵ found that 2-iodopyridine reacted smoothly with copper powder to give 2,2'-dipyridyl. It was therefore hoped that 2-iodopyridine would react with magnesium at the temperature of boiling ether. The possibility of polymerization reactions seemed much less at that low a temperature.

It was found that 2-iodopyridine could be made to react with magnesium in ether solution. The reaction was started with activated magnesium-copper alloy. The ether solution became a deep green in color, but when added to Michler's ketone no green color could be obtained after hydrolysis. A color test could be obtained if the Michler's ketone was added to the solid that was formed at the bottom of the flask. However, after standing, no color test could be obtained. The mixture was carbonated and an attempt was made to isolate picolinic acid²⁶ as its copper salt. No acid

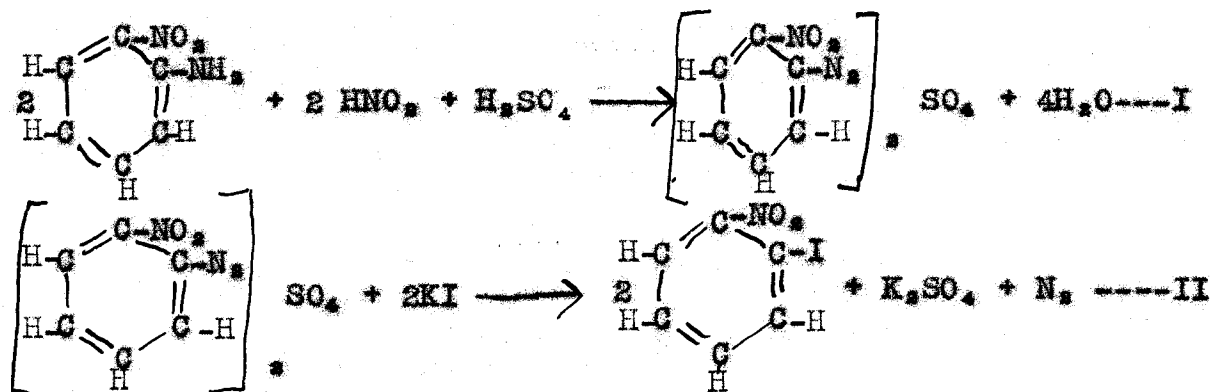
25. Wibaut and Overhoff, *Rec. trav. chim.*, 47, 761 (1928).

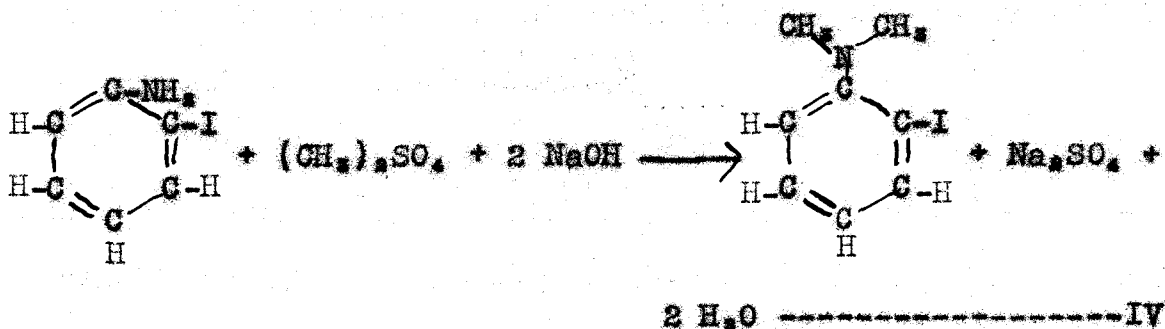
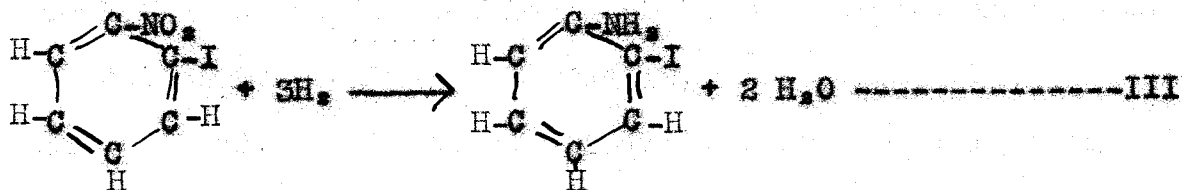
26. Weidel, *Ber.*, 12, 1989 (1879).

could be obtained. 2-Chloropyridine was also brought into reaction with activated magnesium, but the reaction was much slower. It is therefore evident that 2-iodopyridine and magnesium underwent polymerization reactions even at the temperature of boiling ether.

An attempt to prepare α -bromoquinaldine according to the reactions of Hammick¹⁴ was unsuccessful. 6-Bromoquinoline could not be made to react with activated magnesium in ether solution. The preparation of 6-iodoquinoline by the diazotization of 6-aminoquinoline gave a very low yield of the iodo compound, so its reaction with magnesium was not tried.

After the unsuccessful attempts to prepare Grignard reagents from halogenated pyridines and quinolines, attention was turned to the iodo- and bromodimethylanilines. According to von Baeyer²² the o-iododimethylaniline was more reactive than the m- or p- derivatives. o-Iododimethylaniline was made by the following reactions:





Reaction III was found to give the lowest yield of all.

Reduction with ferrous sulfate, according to the directions of Korner and Wender²⁷, gave the best results.

Both the o-iodo- and the o-bromodimethylanilines reacted readily in ether solution with magnesium when a small amount of iodine was added. The resulting Grignard reagents were titrated, and found to give yields approximating 90%. The end point with the iodine compound was not very good as there was some free iodine present. o-Chlorodimethylaniline was also made to react with magnesium in the presence of iodine and the absence of ether when it was heated to its boiling point.

27. Korner and Wender, Gazz. chim. ital., 17, 486 (1888), J. Chem. Soc. Abstracts, p. 1278 (1888).

EXPERIMENTAL PART

Preparation of 3-Bromopyridine and its

Reaction with Magnesium

The directions of Englert and McElvain⁹ were followed for the preparation of this compound. The pyridine hydrobromide was made by passing gaseous hydrogen bromide into an acetic acid solution of pyridine until the theoretical amount had been absorbed, as determined by the increase in weight. This solution was then treated directly with an acetic acid solution of bromine, and the perbromide filtered out according to the directions. In a private communication, Professor McElvain said that the best way to make pyridine hydrobromide was to treat pyridine with the theoretical amount of constant boiling hydrobromic acid, and evaporate it to a thick syrup. This syrup was cooled and filtered by suction to obtain the solid pyridine hydrobromide.

Four runs were made, starting with 158 g. or 2.0 moles of pyridine. The average yield was 28 g. (0.176 mole) or 8.8% of 3-bromopyridine and 30 g. (0.126 mole) or 6.3% of 3,5-dibromopyridine.

Neither 3-bromopyridine nor 3,5-dibromopyridine in ether solution could be made to react with activated magnesium-copper alloy. A tenth mole of 3-bromopyridine in 100 cc. of

ether solution was placed in a tube with an excess of 30-40 mesh magnesium and a small amount of iodine. The tube was evacuated, until the ether boiled, and then it was sealed off. This solution has stood over four months and there is no visible evidence that a reaction has taken place. The same thing was done with 3,5-dibromopyridine and the same results noted.

Fifteen and eight-tenths grams (0.1 mole) of 3-bromopyridine was placed in a sealed tube with 3 g. of fine magnesium. The tube was evacuated to 5 mm. pressure and sealed. It was heated at 160-180° for three hours. A tarry mass was formed from which no Grignard reagent could be extracted with ether or benzene. A second run was made, in which the temperature was kept below 108°. The material had charred after one hour. No RMgX compound could be extracted with ether or pyridine as solvents.

Ten grams of 3-bromopyridine and two grams of powdered magnesium were placed in a pyrex test tube that was evacuated to 5 mm. and then sealed. After twenty minutes in a bath of boiling water the reaction started and became vigorous, so it was cooled in running tap water. No Grignard reagent could be extracted from the tarry mass with any combination of ether, benzene and pyridine. The solid was treated with carbon dioxide and then hydrolyzed. The resulting water solu-

tion was buffered with disodium phosphate and evaporated to a small volume. No nicotinic acid was isolated.

In two test-tube experiments, a color test was obtained with Michler's ketone, if it were added as soon as the 3-bromopyridine started to react with the magnesium. In one test tube, activated magnesium-copper alloy was used, while plain magnesium was used in the other. The only difference was that it took a higher temperature to start the reaction with plain magnesium. Activated magnesium alone would not reduce Michler's ketone to give a color test. The color test could not be obtained if the reaction went to completion before the ketone was added.

3,5-Dibromopyridine and magnesium were refluxed in an ether benzene solution. No reaction took place even when a gram of iodine was added. The solvents were removed and replaced by pyridine. After refluxing for a few minutes, a reaction set in and continued until the whole mass became a thick red tar. No Grignard reagent could be extracted. When 3,5-dibromopyridine was refluxed for two days in an equal mixture of pyridine and ether, the same tarry mass was obtained.

It was concluded that 3-bromopyridine and 3,5-dibromopyridine entered into addition reactions with themselves when treated with magnesium as postulated in the theoretical part.

If any RMgX compound was formed, it was only transient in its existence.

Preparation of 2-Aminopyridine

2-Aminopyridine was made according to the directions of Horsters and Horsters⁴. One hundred grams of sodium amide was ground under toluene and transferred to a 500 cc. balloon flask where it was covered with about 250 cc. of toluene. To this was added 100 g. (1.25 moles) of pure pyridine. A reflux condenser was attached to the flask, the apparatus was swept out with dry nitrogen, and it was protected from the atmosphere by a nujol trap. It was heated in an oil bath at 120-125° for ten hours. After cooling, the solid reaction product was cautiously hydrolyzed with ice cold water in which it dissolved. The toluene layer was separated and the water layer extracted with ether. The combined solutions were dried over sodium hydroxide and distilled. The main product distilled constantly at 112-114°/25-27 mm. The melting point was 58-59°. The average yield from four runs was 86 g. (0.91 mole) or 73%.

Preparation of 2-iodopyridine and its
Reaction with Magnesium

The directions of Chichibabin⁸ were followed.

Thirty-one and three tenths grams (0.33 mole) of 2-aminopyridine and 23.5 g. (0.33 mole) of sodium nitrite were dissolved in 120 cc. of water and cooled to 0°. To this solution was added 20 cc. of acetic acid in 80 cc. of water. The resulting solution was kept in an ice mixture for eleven hours as described by Chichibabin. A solution of 128 g. of potassium iodide and 20 cc. of acetic acid in 50 cc. of water was prepared. This solution was boiled under a reflux condenser while the diazo solution was added to it dropwise. The final solution was neutralized with sodium hydroxide and steam distilled. The 2-iodopyridine was separated from the steam distillate which was extracted with ether. This solution was dried over solid sodium hydroxide and the 2-iodopyridine distilled under reduced pressure. It boiled at 94-96°/11 mm. The average yield was 14.5 g. (0.07 mole) or 21%.

Ten and twenty-five hundredths grams (0.05 mole) of 2-iodopyridine was dissolved in 50 cc. of dry ether. Seven and two-tenths grams (0.3 atom) of powdered magnesium was placed in a 200 cc. three-necked flask which was connected

with the usual stirrer, reflux condenser and dropping funnel. The apparatus was protected from the atmosphere by a nujol trap. The reaction was started with activated magnesium, and the solution continued to reflux gently during the addition of the remainder of the halide. An intense green color developed in the ether solution. Toward the end of the reaction, the magnesium stuck together in the form of lumps, which made stirring very difficult. The ether solution would not give a color test for RMgX compound with Michler's ketone.

The mixture was cooled with ice and treated with carbon dioxide for three hours. The solution was hydrolyzed with ammonium chloride solution. The water solution was made slightly acid with acetic acid, and then treated with a copper acetate solution. On evaporation to a small volume, no purple precipitate of the copper salt of picolinic acid²⁶ was obtained.

When another run was treated with phenyl isocyanate, none of the known anilide of picolinic acid could be isolated from the reaction products. Only a tarry residue was isolated.

When 2-iodopyridine was brought into reaction with magnesium and iodine in a test tube, the resulting ether solution did not give a color test for RMgX compound. However,

if the solution of Michler's ketone was added to the contents of the test-tube during the reaction or as soon as it was finished, then a good positive color test was obtained.

It is concluded that the Grignard reagent of 2-iodopyridine is also transient in its existence. There is a possibility that a derivative might be obtained if the reaction with magnesium could be made to take place in the presence of a reactant like phenyl isocyanate or carbon dioxide.

Preparation of 2-Chloropyridine and its
Reaction with Magnesium

Forty-seven grams (0.5 mole) of 2-aminopyridine was dissolved in 237 g. of hydrochloric acid. This was cooled to 0° and to it was added 34.5 g. (0.5 mole) of sodium nitrite. The solution was allowed to come to room temperature, and was then neutralized with sodium carbonate. The 2-chloropyridine was extracted with ether, dried over solid sodium hydroxide and distilled. The yield was 19 g. (0.166 mole) or 33.2%.

One gram of freshly distilled 2-chloropyridine in 5 c.c. of ether was treated with activated magnesium. The reaction did not start at once so 2-3 drops of methyl iodide were added. The reaction started very soon and continued for

about twenty minutes. The reaction mixture seemed to be entirely in solution and was dark green in color. This green color disappeared on treatment with Michler's ketone, but a good color test for RMgX compound was obtained upon hydrolysis. This color test means little because methyl iodide was used to help start the reaction. On standing for four hours the products precipitated and a color test could no longer be obtained.

2-Chloropyridine did not react as readily with magnesium as 2-iodopyridine did. No derivatives were obtained with either carbon dioxide or phenyl isocyanate.

Preparation of o-Iododimethylaniline

One hundred and thirty-eight grams (1.0 mole) of o-nitroaniline was diazotized in hydrochloric acid solution. This diazo solution was added to 167 g. (1.0 mole) of potassium iodide in 150 cc. of water. The solution was kept at 10-12° during the addition. After one hour the solution was filtered and iodine removed from the precipitate with sodium bisulfite solution. This precipitate was then dissolved in hot alcohol, filtered from a residue, and allowed to cool. The yield was 190 g. or 86%. The melting point was 45-46°. An additional

25 g. or 11% of material melting at 42-43° was obtained from the mother liquor.

Catalytic reduction of o-iodonitrobenzene with hydrogen and platinum oxide catalyst gave a 40% yield of o-iodoaniline melting at 49°. It should melt at 56°. Side reactions apparently took place during this reduction as a considerable amount of tarry material was also formed.

Reduction with ferrous sulphate according to the directions of Korner and Wender²⁷ gave the best product. Twenty-five grams of o-iodonitroaniline was added to 250 g. of ferrous sulphate in solution. The solution was made alkaline with a slight excess of ammonia and heated on a steam plate for ten to twelve hours. The precipitate was filtered out, and both the precipitate and the solution were extracted with ether. The material was then steam distilled which gave a practically pure white compound. This product was dissolved in dilute sulfuric acid to remove the unchanged nitro compound. It was then precipitated with sodium hydroxide and filtered. The yield from four runs was 40 g. (0.18 mole) or 45%. The melting point was 56°.

Forty grams (0.18 mole) of o-iodoaniline in 40 cc. of water was treated with a total of three molecular equivalents (69 g.) of methyl sulfate. After the addition of each equivalent of methyl sulfate the mixture was allowed to stand

until it became homogeneous, and then it was neutralized with sodium hydroxide before the addition of the next equivalent. The excess methyl sulfate was finally destroyed with ammonium hydroxide. The o-iododimethylaniline was extracted with ether, dried over solid sodium hydroxide and then distilled in a vacuum. The yield was 26.5 g. (0.11 mole) or 61%.

Preparation of o-Dimethylaminophenylmagnesium Iodide

Twelve and four-tenths grams (0.05 mole) of o-iododimethylaniline in 50 cc. of ether was allowed to react with magnesium in the customary three-necked flask to which was attached a mercury sealed stirrer, dropping funnel and reflux condenser. The apparatus was protected from the air with a calcium chloride tube. The reaction started readily with a crystal of iodine as a catalyst. A very good color test for RMgX compound was obtained. Two 5 cc. portions were titrated by the acid method. The end point was obscured by the presence of free iodine which was destroyed with sodium thiosulfate solution. The values obtained were 93% and 104%. The Grignard reagent was treated with carbon dioxide in the cold until no more color test was obtained. Because of the

amphoteric nature of the N-dimethylantranilic acid, it has not as yet been isolated.

Preparation of o-Dimethylaminophenylmagnesium Bromide

Commercial o-bromodimethylaniline was redistilled and used for this run. Ten grams (0.05 mole) of the bromide was dissolved in 50 cc. of ether and treated with magnesium in the same way as described for the iodide. The reaction started very readily with a small amount of iodine as a catalyst. The yield by acid titration was 91%. Another run of the same size gave an 87% yield of Grignard reagent.

SUMMARY

It is desirable to prepare Grignard reagents which contain a tertiary amine group in their hydrocarbon radicals. The radicals could then be introduced into organolead compounds to give them water solubility. Such compounds might be of use in cancer therapy.

3-Bromopyridine and 3,5-dibromopyridine react with magnesium at high temperatures to give polymerization products from which no Grignard reagent could be isolated. 2-Iodopyridine reacts with magnesium in ether solution when iodine or activated magnesium are used as catalysts. However, the Grignard reagent is unstable and yields only polymerization products.

o-Iodo- and o-bromodimethylanilines react readily with magnesium in ether solution to give high yields of their corresponding Grignard reagents. As yet, no derivatives have been made.