A STUDY OF THE REACTION OF HINDERED NITRILES WITH SELECTED AROMATIC GRIGNARD REAGENTS

Thesis for the Degree of M. S.

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Burton Perkins Dennis

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A STUDY OF THE REACTION OF HINDERED NITRILES WITH SELECTED AROMATIC GRIGNARD REAGENTS

By

Burton Perkins Dennis

A THESIS

Submitted to the College of Science and Arts of Michigan State University of Agriculture and Applied Science in partial fulfillment of the requirements for the degree of

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AN ABSTRACT

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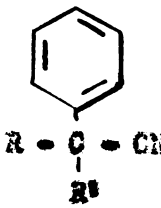
Approved Gordon L Goerner

ABSTRACT

Previous to the start of this investigation other workers in this laboratory had observed that nitriles of the type



and having an effective six-number (4) of 8 or more could not be hydrolyzed to the acid or amide even under very vigorous conditions (1,2,3). However, reduction to the amine with lithium aluminum hydride occurred in every case attempted.

This study was undertaken to see if these highly hindered nitriles would react with Grignard reagents.

In every case except one, reaction occurred between these nitriles ranging in effective six-number from 2 to 11, and the aromatic Grignard reagents employed. This indicated a difference in the mode of the two reactions. It appeared that the low energy of solvation of organometallic compounds with hydrocarbons as compared to that of ether was an important factor contributing to the greater reactivity of these highly hindered nitriles with Grignard reagents.

Hydrolysis of the Grignard complex produced ketones, ketimines or ketimine hydrochlorides, depending upon the effective six-number of the intermediate ketimine which was larger by 3 and 6 respectively than that

of the nitrile, with the addition of the o-tolyl and mesityl groups of the Grignard reagents. In general, as the effective six-number of the intermediate ketimines increased, the product of the hydrolysis of the Grignard complex went from ketone to ketimine to ketimine hydrochloride. When the effective six-number was 8 or larger the ketone was no longer obtained.

Conversion of the less hindered ketimines or ketimine hydrochlorides to oximes was possible. However, the relative reactivity of certain ketimines or ketimine hydrochlorides varied from that expected on the basis of effective six-number. It appeared that the substitution of a second methyl group on the beta carbon offered greater steric hindrance than when substituted at other positions which gave a corresponding increase in the effective six-number. The oxime could not be obtained in any case where the effective six-number of the ketimine was 14.

Starting nitrile was recovered in many of the reactions of nitriles having an alpha hydrogen atom. This appeared to be due to a side reaction in which the organic radical of the Grignard reagent was reduced by the labile hydrogen atom, followed by recovery of the nitrile from the nitrile salt upon hydrolysis.

The reactions of 2-phenylbutanenitrile with phenyl and o-tolylmagnesium bromide indicated that the reaction conditions employed had a greater effect as the steric hindrance increased.

In the reaction between 2-phenyl-2-ethyl-3-methylpentanenitrile and mesitylmagnesium bromide 83 per cent of the starting nitrile was recovered. There appeared to be no reaction.

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INTRODUCTION

During the past ten years, the alkylation of hydratroponitrile (2-phenylpropanenitrile) and 2-phenylbutanenitrile with the butyl and amyl halides in the presence of sodamide has resulted in the formation of nitriles of the general formula

where R has been methyl or ethyl and R' one of the butyl or amyl groups (1,2,3).

Some of these nitriles, such as those where R is methyl and R' is n-butyl or isobutyl, could be hydrolyzed to acids or amides. However, the greater number of these nitriles such as those where R is methyl or ethyl and R' is sec-butyl failed to undergo hydrolysis under unusually severe conditions. The failure of the latter group to undergo hydrolysis was attributed to steric hindrance. These latter sterically hindered nitriles were all observed to possess an effective six-number (4) of eight or more. Reduction of these nitriles to the primary amine by lithium aluminum hydride occurred in every case. All other reactions tried with the highly hindered nitriles failed.

It is commonly known that Grignard reagents react with nitriles to produce ketones, ketimines or ketimine hydrochlorides depending upon

the extent of hydrolysis. Kharasch and Reinmuth (5) state that this reaction was first investigated by Blaise in 1901. These authors list much of the work reported in the literature since that time regarding the reaction between nitriles and Grignard reagents. Many of the reactions listed involve nitriles which appear to be sterically hindered.

The purpose of the present investigation was to determine whether the highly hindered nitriles obtained in these laboratories would react with aromatic Grignard reagents. If the addition of phenyl magnesium bromide occurred, the reaction was to be studied further with the more sterically hindered ortho tolyl and mesityl magnesium bromides to determine at what point Grignard addition to the cyano group failed.

HISTORICAL

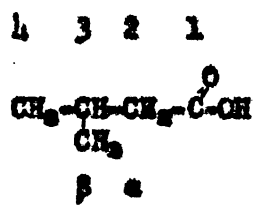
M. S. Newman (6), in his book Steric Effects in Organic Chemistry, has credited the introduction of the concept of steric hindrance to Victor Meyer and F. Kehrmann. Newman stated that as early as 1890 Kehrmann had attributed the decreased activity of certain quinones possessing an ortho substituent relative to the carbonyl group, to steric hindrance. Stewart (7) has stated that in 1894 Victor Meyer observed that substitution of methyl or nitro groups in the ortho position of benzoic acid prevented esterification of the acid with methyl alcohol. These early authors defined steric hindrance to be the retarding effect upon a reaction caused by the massing of bulky groups on the carbon atoms adjacent to the reacting group.

Kadesch (8) stated recently, however, that steric hindrance is not always due to the classical bulk effect of Meyer and Kehrmann and that in some instances ortho substitution actually increased the rate of the reaction. He reported that in some cases the presence of certain groups may sterically hinder a reaction by preventing the molecule from attaining a particular configuration necessary for reaction, rather than shielding the reacting group.

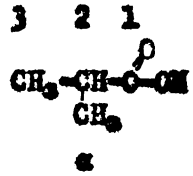
Stewart (7) reported in 1907 that Bischoff had proposed some 15 years earlier that the carbon chain is cyclic and that substituents in the 1, 5 and 1, 6 position lie closer together in space than substituents

in the 1, 3 or 1, 4 positions. Bischoff noted that accumulation of substituents in the 1, 5 or 1, 6 position with regard to an active group would hinder a reaction. Although the evidence presented by Bischoff and Stewart to substantiate this conclusion is meager, it proved to be a valid contribution to the study of steric hindrance.

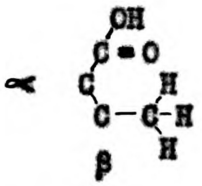
Somewhat later than this Smith (9) postulated a ring structure for carbon chains and made two significant observations. The rate of esterification of acids dropped sharply when going from propionic to butyric acid, but the change in rate when going from butyric acid to valeric or caproic acid was small. Secondly, the substitution of a methyl group on carbon atom number three of butyric acid



caused a smaller rate constant than the substitution of a methyl group on carbon atom number two of propionic acid.

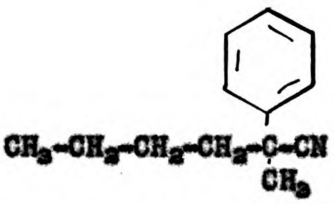


Smith explained the increased hindrance of substitution on the beta carbon atom on the basis of a coiled structure for the molecule. When the molecule assumed a ring structure, the groups attached to the beta carbon atom could shield the reacting group

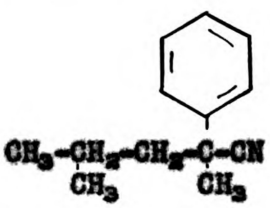


more effectively than when they were attached to the alpha carbon atom.

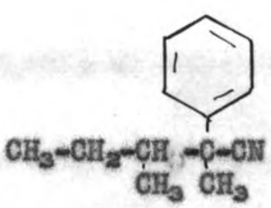
A similar observation was noted in recent investigations in this laboratory. In 1950 Workman (1) reported that it was possible to hydrolyze 2-phenyl-2-methylhexanenitrile



and 2-phenyl-2,4-dimethylpentanenitrile

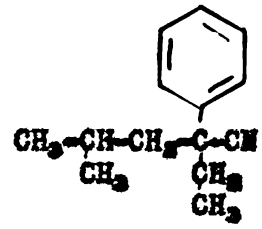


to the acid by refluxing ten hours with potassium hydroxide in amyl alcohol. However, 2-phenyl-2,3-dimethylpentanenitrile

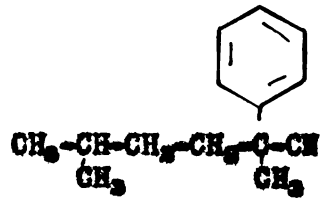


could not be hydrolyzed, even under very severe conditions.

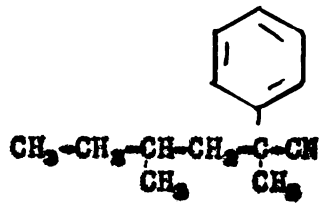
Holzschuch (3a) reported that he was unable to hydrolyze 2-phenyl-2-ethyl-4-methylpentanenitrile.



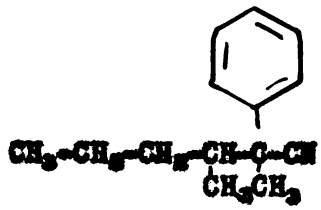
Hydratroponitrile (2-phenylpropanenitrile) on the other hand, was easily hydrolyzed. Jacobs (2) reported that 2-phenyl-2,5-dimethylhexanenitrile



and 2-phenyl-2,4-dimethylhexanenitrile



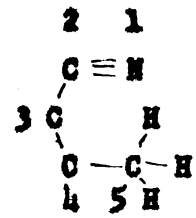
were easily hydrolyzed to the acid with potassium hydroxide in ethylene or butylene glycol at 200°. 2-Phenyl-2,3-dimethylhexanenitrile



could not be hydrolyzed even when heated at 210° for 24 hours with potassium hydroxide in butylene glycol. When a methyl substitution occurred on a beta carbon atom in the compounds mentioned the steric hindrance became great enough to prevent hydrolysis of the cyano group.

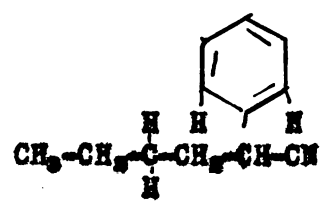
In 1950, M. S. Newman (4) published a paper on a correlation of the rate of esterification of acids. He observed that in going from acetic acid to trimethylacetic acid the rate is decreased 26.8 fold. In going from propionic acid to tert-butylacetic acid the rate is decreased 36 fold. In going from butyric acid to neopentylacetic acid the rate is almost unchanged. He also noted the difference in the effect of ethyl and methyl substitution on the alpha carbon. The rate of esterification was twice as great with acetic acid as with propionic acid. As the branching in the molecule increased, the effect of substitution of an ethyl group for a methyl group on the alpha carbon became more apparent. For example, in going from trimethyl acetic acid to triethyl acetic acid the rate is decreased by 230 fold. The rate of esterification of 2-ethyl-3,3-dimethylbutyric acid was slower than the rate for 2,2,3,3-tetramethylbutyric acid, indicating that one ethyl group on the alpha carbon had a greater effect than two methyl groups. A definite comparison was not possible as the rate of the latter was too slow to be measured.

As a result of this experimental evidence, Newman proposed the rule of six or six-number concept (4). He stated that "In reactions involving addition to an unsaturated function containing a double bond the greater the number of atoms in the sixth position, the greater will be the steric effect." The cyano group was not originally included but the concept has been extended to reactions involving unsaturated functions in general. The structure below indicates why atoms in the sixth position are effective in retarding a reaction



When the molecule assumes a coiled structure, atoms in the sixth position shield the cyano group from attack.

In compounds containing rings it is necessary to use the term "effective" six-number, which is defined as "the number of atoms in the sixth position capable of yielding a coiled structure." In molecules containing a ring such as 2-phenylhexanenitrile the two carbon atoms in the phenyl ring occupying the sixth position from the nitrogen atom are held rigidly and are not free to rotate and shield the cyano group (26). They are not counted.



Therefore, the term effective six number is used and the compound shown has an effective six-number of five.

It has not been known precisely what the steric effect of a phenyl ring is upon the reactivity of cyano or carbonyl groups attached to an adjacent carbon atom. In a comparison of the results of a recent study regarding the hydrolysis of hindered nitriles by Goerner and Holzschuh (3b) with a similar study by Tsai, Mima, and Newman (10), the former have suggested that the effect of a phenyl ring may be greater than had

been anticipated. The examination of Stuart models seems to indicate that a phenyl ring substituted on a carbon atom in the alpha position relative to a cyano group has approximately the same steric effect as an isopropyl group. An isopropyl group situated on the alpha carbon would contribute a six-number of six. On this basis, then it is important that the term effective six-number be used in compounds containing rings. Also, a comparison of the reactivity of cyclic and non-cyclic hindered compounds may not be valid when based alone on the number of atoms in the sixth position from the double bonded atom.

In further investigations Newman et al. (10) showed a definite correlation between the percent of hydrolysis of hindered amides and their six-number. Triethyl acetamide with a six-number of nine was 50.4 per cent hydrolyzed when refluxed in ethylene glycol-alkali mixtures. Di-isopropyl acetamide with a six-number of twelve was 16.7 per cent hydrolyzed and 2-(tert-butyl)-2-isopropyl acetamide with a six-number of 15 was 3 per cent hydrolyzed when treated under the same conditions.

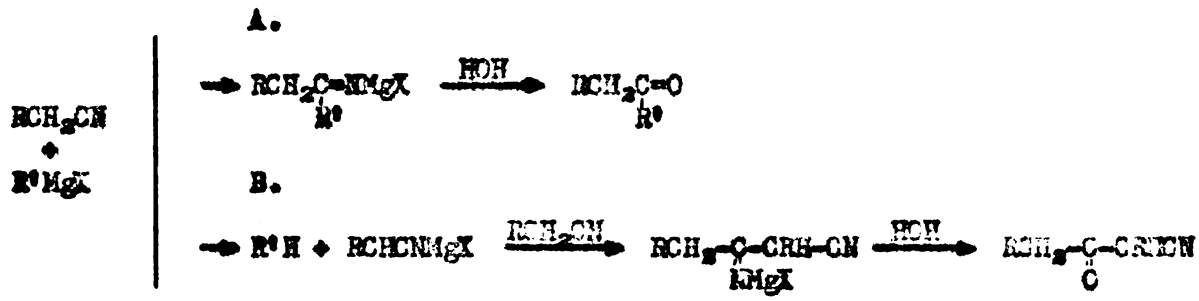
One of the earliest evidences of steric hindrance in the reaction between nitriles and Grignard reagents was reported by Kohler (11) in 1906. He observed that when 2,3-diphenyl-2-ethylpentanenitrile with an effective six-number of ten was boiled with phenylmagnesium bromide for a day, the original nitrile was recovered. The reaction between 2,3-diphenylpentanenitrile (effective six-number of 7) and phenylmagnesium bromide gave the corresponding ketone. Ramart-Lucas and

Salmon-Legagneur (12) obtained a 55 per cent yield of ketone from the reaction of 2-phenyl-2-methylbutanenitrile (effective six-number of 5) with phenylmagnesium bromide by refluxing in toluene a day and hydrolyzing with hydrobromic acid. Brodhag and Hauser (13) reported a 90 per cent yield of the ketimine hydrochloride after refluxing phenylmagnesium bromide with 2-phenyl-2-methylpentanenitrile in xylene for 12 hours and then hydrolyzing with ammonium chloride solution.

Of special interest at the start of this investigation were the reported reactions between phenylmagnesium bromide and 2,2-diethylphenylacetonitrile (effective six-number of 8). In 1928 Bumart-Lucas and Salmon-Legagneur (12) indicated that the ketimine hydrochloride was obtained as the product. Brodhag and Hauser also obtained this compound. Both reactions were carried out under similar conditions. In 1927 Bumart-Lucas and Salmon-Legagneur (14) listed their product as the ketone.

Kharasch and Reinmuth have listed many of the reactions reported in the literature between Grignard reagents and nitriles. Part of these references along with others of interest to this study are listed in Table I.

Many of these nitriles have a labile hydrogen attached to the alpha carbon atom. Hauser and Humphlett (15) have investigated the reactions of several nitriles of this type (see reactions 1-7, 9 and 10, Table I) and state that these nitriles can undergo reaction in two ways.



The course of the reaction was dependent upon the groups R and R'. These authors observed that the amount of reaction by course B increased as the R group changed from ethyl to hydrogen to phenyl. Propionitrile reacted with n-amylmagnesium bromide to give a 61 per cent yield of the ketone. The reaction of phenylacetonitrile with n-amylmagnesium bromide (reaction 6, Table I) yielded 51 per cent of the dimer of phenylacetonitrile and 31 per cent of condensed products. None of the ketone was obtained. These workers also noted that in general, aromatic Grignard reagents tended to react more by course A, the normal reaction. For example, in reaction 2, Table I ethylmagnesium bromide reacted with phenylacetonitrile to give 51 per cent of the beta ketonitrile, 36 per cent other condensation products and 10 per cent of recovered nitrile. In reaction 9, phenylacetonitrile reacted with phenylmagnesium bromide to yield 33 per cent of the normal ketone and 15 per cent of the beta ketonitrile. The amount of reaction by course A decreased in proceeding from phenyl to o-tolyl to mesitylmagnesium bromide. The reaction of phenylacetonitrile with mesitylmagnesium bromide (reaction 10, Table I) gave a 45 per cent yield of the beta ketonitrile and 43 per cent of other condensed products. As stated previously, this same nitrile

reacted with phenylacetonitrile to yield 33 per cent of the ketone and other products. Bary (18) reported that he obtained 35 per cent of the trimer, 30 per cent of the beta iminonitrile, and 10 per cent of the normal ketone in addition to diphenyl, recovered nitrile and other products in the reaction of phenylacetonitrile with phenylmagnesium bromide (reaction 8, Table I). Troger and Beck (17) reported only the normal ketone and diphenyl for this same reaction (reaction 7, Table I).

No references were found to the reaction of alpha substituted phenylacetonitriles with o-tolylmagnesium bromide or mesitylmagnesium bromide other than those reported above.

TABLE I

REACTION OF GRIGNARD REAGENTS WITH SELECTED PHENYLACETONITRILES

Nitrile	Grignard	Product	Yield %	Effective six-number	Reference
1. $C_6H_5CH_2CN$	CH_3MgI (1.1 eq.)	$C_6H_5CH_2COCH_3$ $C_6H_5CH_2COCH(CN)C_6H_5$	8 71	2	15
2. $C_6H_5CH_2CN$	C_6H_5MgBr (1.1 eq.)	Recovered nitrile $C_6H_5CH_2COCH(CN)C_6H_5$ Cond. products	10 51 36	2	15
3. $C_6H_5CH_2CN$	i-C_3H_7MgBr (1.1 eq.)	Recovered nitrile Dimer Cond. products	9 64 15	2	15
4. $C_6H_5CH_2CN$	n-C_4H_9MgBr (1.1 eq.)	Recovered nitrile Dimer Cond. products	24 23 46	2	15
5. $C_6H_5CH_2CN$	t-C_4H_9MgBr (1.1 eq.)	Dimer	80		
6. $C_6H_5CH_2CN$	n-$C_5H_{11}MgBr$ (1.1 eq.)	Dimer Cond. products	51 31	2 2	15
7. $C_6H_5CH_2CN$	C_6H_5MgBr (1.1 eq.)	$C_6H_5CH_2COC_6H_5$ Diphenyl		2	17
8. $C_6H_5CH_2CN$	C_6H_5MgBr (1 eq.)	Recovered nitrile $C_6H_5-CH_2COC_6H_5$ $C_6H_5CH_2C(=NH)CH(C_6H_5)CN$ Trimer Diphenyl, benzene, phenyl bromide	1-2 10 30 35	2	18

Continued

TABLE I - Continued

Nitrile	Grignard	Product	Yield %	Effective six-number	Reference
9. $C_6H_5CH_2CN$	C_6H_5MgBr	$C_6H_5CH_2COC_6H_5$ $C_6H_5CH_2COCH(C_6H_5)CN$	33 15	2	15
10. $C_6H_5CH_2CN$	$2,4,6(CH_3)C_6H_5MgBr$ (1.1 eq.)	$C_6H_5CH_2COCH(C_6H_5)CN$ Cond. products	45 43	2	15
11. $C_6H_5CH_2CN$	CH_3MgBr	20 l. CH_4; Recovered nitrile $C_6H_5CH_2COCH_3$ $C_6H_5CH_2CONH_2$ $C_6H_5CH_2C(=NH)CH(C_6H_5)CN$ $(C_6H_5CH_2CN)_2$	 50 10	2	19
12. $CH_3CH(C_6H_5)CN$	C_2H_5MgBr(4 eq.)	$CH_3CH(C_6H_5)COC_2H_5$		2	20
13. $CH_3CH(C_6H_5)CN$	$n\text{-}C_3H_7MgBr$(4 eq.)	$CH_3CH(C_6H_5)CO\text{-}n\text{-}C_3H_7$		2	20
14. $CH_3CH(C_6H_5)CN$	$C_6H_5CH_2MgCl$	$CH_3CH(C_6H_5)COCH_2C_6H_5$		2	20
15. $C_2H_5CH(C_6H_5)CN$	$n\text{-}C_3H_7MgBr$ (4 eq.)	$C_2H_5CH(C_6H_5)CO\text{-}n\text{-}C_3H_7$		5	20
16. $C_2H_5CH(C_6H_5)CN$	CH_3MgBr (4 eq.)	$C_2H_5CH(C_6H_5)COCH_3$		5	20
17. $C_2H_5CH(C_6H_5)CN$	$n\text{-}C_4H_9MgBr$ (4 eq.)	$C_2H_5CH(C_6H_5)CO\text{-}n\text{-}C_4H_9$		5	20
18. $CH_3C(C_6H_5)(CH_3)CN$	C_6H_5MgBr	$CH_3C(C_6H_5)(CH_3)C(C_6H_5)=NH\text{-}HCl$	60	2	31
19. $n\text{-}C_3H_7CH(C_6H_5)CN$	CH_3MgI (4 eq.)	$n\text{-}C_3H_7CH(C_6H_5)COCH_3$		5	20
20. $n\text{-}C_3H_7CH(C_6H_5)CN$	C_2H_5MgI (4 eq.)	$n\text{-}C_3H_7CH(C_6H_5)COC_2H_5$		5	20
21. $n\text{-}C_3H_7CH(C_6H_5)CN$	$n\text{-}C_4H_9MgBr$ (4 eq.)	$n\text{-}C_3H_7CH(C_6H_5)CO\text{-}n\text{-}C_4H_9$		5	20
22. $C_2H_5C(C_6H_5)(CH_3)CN$	C_6H_5MgBr(1.25 eq.)	$C_2H_5C(C_6H_5)(CH_3)COC_6H_5$	55	5	12

Continued

TABLE I - Continued

Nitrile	Grignard	Product	Yield %	Effective six-number	Reference
23. $C_2H_5C(C_6H_5)(CH_3)CN$	C_6H_5MgBr	$C_2H_5C(C_6H_5)(CH_3)COC_6H_5$		5	14
24. $C_2H_5C(C_6H_5)(C_2H_5)CN$	C_6H_5MgBr	$C_2H_5C(C_6H_5)(C_2H_5)COC_6H_5$		8	14
25. $C_2H_5C(C_6H_5)(C_2H_5)CN$	C_6H_5MgBr(1.25 eq. + HBr)	$C_2H_5C(C_6H_5)(C_2H_5)C(C_6H_5)$=NH-HBr		8	12
26. $C_2H_5C(C_6H_5)(C_2H_5)CN$	p-CH_3-C_6H_4MgBr	$C_2H_5C(C_6H_5)CO(C_6H_4CH_3)$ (Via Ketimine)		8	22
27. $C_2H_5C(C_6H_5)(C_2H_5)CN$	C_6H_5MgBr	$C_2H_5C(C_6H_5)(C_2H_5)C(C_6H_5)$=NH-HCl		8	31
28. $(C_6H_5)_2CHCN$	o-$CH_3C_6H_4MgBr$	No reaction		4	16
29. $(C_6H_5)_2CHCN$	m-$CH_3C_6H_4MgBr$	$(C_6H_5)_2CHCO(m$-$CH_3C_6H_4)$		4	16
30. $C_6H_5CH_2CH(C_6H_5)CN$	CH_3MgI (4 eq.)	$C_6H_5CH_2CH(C_6H_5)COCH_3$		4	20
31. $C_6H_5CH_2CH(C_6H_5)CN$	C_2H_5MgBr (4 eq.)	$C_6H_5CH_2CH(C_6H_5)COC_2H_5$		4	20
32. $C_6H_5CH(o$-$CH_3C_6H_4)CN$	C_6H_5MgBr	Recovered nitrile		4	16
33. $C_6H_5CH(m$-$CH_3C_6H_4)CN$	C_6H_5MgBr	$C_6H_5CH(m$-$CH_3C_6H_4)COC_6H_5$		4	16
34. $(CH_3)_2CHC(C_6H_5)_2CN$	C_6H_5MgBr	$(CH_3)_2CHC(C_6H_5)_2COC_6H_5$		10	14
35. $(CH_3)_2CHC(C_6H_5)_2CN$	C_6H_5MgBr + HBr	(ketimine hydrobromide)	30	10	12
36. $C_6H_5CH_2C(C_6H_5)(C_2H_5)CN$	C_6H_5MgBr	$C_6H_5CH_2C(C_6H_5)(C_2H_5)COC_6H_5$		7	14
37. $C_6H_5CH_2C(C_6H_5)(C_2H_5)CN$	C_6H_5MgBr + HBr	(ketimine hydrobromide)	65-70	7	12
38. $C_2H_5CH(C_6H_5)C(C_6H_5)(C_2H_5)CN$	CH_3MgI	Recovered nitrile		10	11
39. $C_2H_5CH(C_6H_5)C(C_6H_5)(C_2H_5)CN$	C_6H_5MgBr	Recovered nitrile		10	11

EXPERIMENTAL

I. Reagents

Anhydrous ether--Commercial grade anhydrous ether was obtained from the stockroom and dried over sodium.

Bromobenzene--Eastman practical grade was redistilled through a 3 x 40 cm. column packed with 3/16" glass helices. The fraction used boiled at 54.5-55° (22 mm.), n_D^{25} 1.5568.

Magnesium shavings for Grignard Reaction--Matheson, Coleman and Bell.

Mesitylene--Eastman white label. Used as received.

o-Bromotoluene--Dow Chemical Company. Redistilled through a 3 x 40 cm. column packed with 3/16" glass helices. Fractions used: 55.5° (7 mm.), n_D^{25} 1.5548, and 53.5-54° (7 mm.), n_D^{25} 1.5539.

2-Phenylbutanamide--Eastman practical grade. Used as received.

Phosphorous oxychloride--Mallinkrodt. Used as received.

Sodium Carbonate--J. T. Baker Chemical Company. Used as received.

Sodium Sulfate, Anhydrous--J. T. Baker Chemical Company. Used as received.

Toluene--Obtained from stockroom. Dried over sodium.

Other reagents obtained from stockroom and used as received.

II. Preparation of Intermediates

A. 2-Phenylbutanenitrile

The 2-phenylbutanenitrile was prepared essentially as described by Cram and Allinger (23). To 198 g. (1.2 moles) of 2-phenylbutanamide in a 2-l. flask was added 269 ml. (2.965 moles) of phosphorus oxychloride. The mixture was refluxed in an all glass apparatus on a steam bath for four hours and then cooled at 0° in an ice bath. The cold solution was poured slowly onto 2 l. of crushed ice and the mixture stirred vigorously until the organic layer rose to the surface. The oil was extracted six times with a benzene-ether mixture consisting of approximately two parts of ether to one part of benzene. The organic layer was then washed several times with water and dried over anhydrous sodium sulfate. The solvent was stripped with a water aspirator through a 3 x 40 cm. column packed with 3/16" glass helices. The 2-phenylbutanenitrile was then fractionated at reduced pressure. There was obtained 143 g. (83 per cent yield) of product boiling at 118-122° (15 mm.), n_D^{25} 1.5060. Five grams of tar remained.

In two further preparations from like amounts of starting material there were obtained 154 g. (90 per cent yield) of product, b. p. 119-122° (14.5 mm.), n_D^{25} 1.5065 and 149 g. (88 per cent yield) of product, b. p. 99-101° (5 mm.), n_D^{25} 1.5067.

Cram and Allinger report a b. p. of 122-124° (16 mm.), n_D^{25} 1.5070.

B. Bromomesitylene

Bromomesitylene was prepared as described in Organic Syntheses (24). From 318 g. (2.65 moles) of mesitylene and 450 g. (2.8 moles) of bromine there was obtained 334 g. (63 per cent yield) of desired product, b. p. 83-87° (5 mm.), n_D^{20} 1.5484. The boiling point of bromomesitylene is reported to be 105-107° (16-17 mm.).

C. Other Nitriles

The nitriles listed in Table II, on the following page, were prepared previous to the start of this investigation in other areas of research, or in course work, in this laboratory. Therefore a detailed description of the preparation of these nitriles will not be included here. The source of each nitrile, a reference to its method of preparation, and its physical constants are listed. Each of the nitriles had been stored from one to three years.

III. General Information

The preparation of all Grignard reagents unless otherwise stated was carried out in a 500 ml. three-necked flask equipped with a dropping funnel, stirrer, reflux condenser, and inlet tube for nitrogen. The dropping funnel and reflux condenser were fitted with calcium chloride drying tubes. After the titration of the Grignard reagent, a measured portion (0.395 mole Grignard to 0.25 mole of nitrile) was transferred to another 500 ml. three-necked flask fitted with a thermometer in addition to the equipment stated above. All glass reaction vessels

TABLE II

STARTING NITRILES

Nitrile	n_D^{25} When Made	When Used	Made By
Hydratropanitrile	1.5058 1.5084	1.5060 1.5080	Titus* Jacobs (2a)
2-Phenyl-2-ethylhexanenitrile	1.4969-1.4972	1.4973 1.4975-1.4976	Goerner and Holaschuh (3)
2-Phenyl-3-methylpentanenitrile	1.5034 1.5028	1.5039 1.5043	Cipriani and Powlock**
2-Phenyl-2-ethyl-3-methyl pentanenitrile	1.5028-1.5042 1.5038-1.5047 1.5038-1.5040	1.5037 1.5041-1.5048 1.5038-1.5042	Goerner and Holaschuh (3)

*Procedure of Jacobs and Workman was used.

**Made in graduate course in organic preparations by procedure described by Cope and Hancock (32).

were air dried and then stored in an oven at 50° for 12 hours previous to use. A dry nitrogen atmosphere was maintained in the flask throughout the procedure. After the addition of the nitrile the reaction flask was heated for the required period of time. The mixture was then hydrolyzed by pouring onto ice and concentrated hydrochloric acid. The principal products obtained in these reactions were ketones, ketimines, or ketimine hydrochlorides. Many times the ketimine hydrochloride separated as a solid layer immediately after hydrolysis and was recovered by

filtration. In other cases, the solid ketimine hydrochloride precipitated out of the water layer after standing for several hours. The organic layer was fractionated through one of three columns equipped with a fraction-cutting head, or through a fraction cutting head only. These columns were as follows: A, a 3 x 40 cm. column packed with 3/16" glass helices; B, a 2 x 20 cm. column packed with 3/16" glass helices and C, a 5 inch Vigreux column. All subsequent reference to these columns shall be made according to this designation.

The distillates were examined for starting nitrile, ketone or ketimine. The nitrile was identified by its boiling point range, refractive index and by a comparison of the infra-red spectra of the starting nitrile and the fraction being identified. All the ketimines boiled in the range of 170 to 210° (5 mm.). They were light yellow, viscous, sticky liquids. The refractive indices of the ketimines were above 1.55 and sometimes were so indistinct that a reading could not be made. All the ketones eventually solidified. The boiling point of the ketones was in general between that of the nitriles and ketimines. The yields have been calculated on the basis of the amount of starting nitrile.

The ketones and less hindered ketimines and ketimine hydrochlorides were derivatized as oximes. Generally, the more hindered compounds required more vigorous conditions to obtain the oxime. The highly hindered ketimines and ketimine hydrochlorides were derivatized only as the picrate. The procedure used for the preparation of these derivatives is given in

Section VI of this thesis. All derivatives were recrystallised from aqueous ethanol until a constant melting point was reached. All melting points, unless otherwise stated, were taken in capillary tubes.

IV. Preparation of Grignard Reagents

A. Phenylmagnesium Bromide

To 12.2 g. (0.5 mole) of magnesium in a 500 ml. three-necked flask equipped with a stirrer, inlet tube for dry nitrogen and a dropping funnel and reflux condenser protected with calcium chloride drying tubes was added a solution of 6 g. of bromobenzene in 40 ml. of anhydrous ether. When the reaction began, the stirrer was started and an additional 72.5 g. of bromobenzene (a total of 0.5 mole) in 160 ml. of anhydrous ether was added by means of a dropping funnel over a period of one-half hour. The flask was cooled by immersion in cold water to prevent the reaction from becoming too vigorous. The solution was stirred for three-quarters of an hour after the final addition of the bromobenzene and then titrated.

B. o-Tolylmagnesium Bromide

o-Tolylmagnesium bromide (25) was prepared in the same manner as the phenylmagnesium bromide with the following exceptions. It was necessary to initiate the reaction by heating gently on a steam bath. During the addition of the bromide, the reaction was controlled by wrapping a towel around the top of the flask and placing ice on top of the flask inside the towel. A total of 85.5 g. (0.5 mole) of

o-bromotoluene in 200 ml. of anhydrous ether was added to 12.2 g. of magnesium. After the addition of the o-bromotoluene the mixture was refluxed gently with stirring on a steam bath for 20 minutes.

C. Mesitylmagnesium Bromide

The same general procedure was used for mesitylmagnesium bromide (26) as in the preparation of phenylmagnesium bromide. The following exceptions should be noted. Initiation of the reaction was attempted by the addition of a small crystal of iodine to the reaction flask and gentle heating over a steam bath. This proved to be unsuccessful. It was found necessary to place a small amount of the bromide in ether in a test tube containing a few shavings of magnesium and grind the magnesium vigorously with a sharp glass rod. After the reaction had been initiated and had proceeded for 10 to 15 minutes, the contents of the test tube were added to the reaction flask. A total of 100 g. (0.5 mole) of bromomesitylene in 200 ml. of ether was added to 12.2 g. (0.5 mole) magnesium. After addition was complete, the flask was heated with stirring until all evidence of reaction had ceased (2 to 5 hours was required).

V. Reaction of the Grignard Reagent with the Nitrile

The reaction of 2-phenylbutanenitrile with phenylmagnesium bromide and o-tolylmagnesium bromide was investigated initially in order to determine the optimum conditions for the reaction of the nitriles with Grignard reagents. The experimental work of Brodhag and Hauser (13)

and Ramart-Lucas and Salmon-Legagneur (12) was used as a model for this investigation. Refluxing in toluene for sixteen hours with continuous stirring was found to give better yields of product than either heating at 90° for the same length of time or refluxing for a shorter period of time. The more vigorous reaction conditions, with slight modifications, were used throughout the investigation. The reaction between o-tolylmagnesium bromide and 2-phenyl-2-ethylhexanenitrile described below is a typical reaction.

After the preparation of the o-tolylmagnesium bromide, the stirrer was turned off to allow settling of the magnesium particles. The flow of nitrogen was increased to insure an atmosphere of dry nitrogen gas. Two 2 ml. aliquots of the Grignard reagent were removed from the flask by means of volumetric pipettes and were placed in two 100 ml. beakers (27). Approximately 5 ml. of distilled water was added to each beaker to hydrolyze the Grignard reagent followed by 42.07 ml. of 0.1078 N. hydrochloric acid (a known excess). The beakers were heated on a steam bath until the basic magnesium oxide was dissolved. Titration to a phenolphtalein end point required 11.07 ml. of 0.1163 N sodium hydroxide solution. The calculation to determine the volume of Grignard reagent required in order to maintain a ratio of 1.5 moles of Grignard reagent to one mole of nitrile is as follows:

Total milliequivalents of acid = 42.07 x 0.1078 N =	4.535
Total milliequivalents of base = 11.07 x 0.1163 N =	1.287
Milliequivalents of acid/2 ml. Grignard reagent	3.240

Milliequivalents/ml. of Grignard reagent = 3.248/2 = 1.624

The milliliters of Grignard reagent necessary to have the required 0.375 mole per 0.25 mole of nitrile = $\frac{375 \text{ m.e.}}{1.623 \text{ m.e./ml.}}$ = 231

The condenser was removed from the reaction flask and the Grignard reagent was filtered quickly through glass wool in a funnel into a 250 ml. graduated cylinder. The desired amount of Grignard reagent was then transferred to another 500 ml. three-necked flask equipped with gas addition tube, 250 ml. dropping funnel, stirrer, thermometer and reflux condenser. The 2-phenyl-2-ethylhexanenitrile (50.25 g., 0.25 mole) in 100 ml. of anhydrous toluene was added by means of a dropping funnel over a period of 20 minutes. The material was stirred for 15-20 minutes. The condenser was removed and the ether evaporated over a steam bath. The latter required from 45 minutes to one hour. The condenser was replaced, a heating mantle was substituted for the steam bath, and the reaction mixture refluxed for 16 hours with stirring. At the end of the 16 hour period, the reaction flask was allowed to cool for 5 to 10 minutes, after which the contents were poured over 300 ml. of crushed ice in 100 ml. of concentrated hydrochloric acid. When hydrolysis was complete, two layers appeared, a water layer surmounted by an organic layer. The two layers were separated. The aqueous phase was extracted with ether, and the extracts added to the organic layer which was washed with water, a sodium carbonate solution and again with water. The water layer was saved. From this water layer there gradually separated over a period of several hours a total of 23.2 g. (28.2 per cent) of ketimine hydrochloride.

Milliequivalents/ml. of Grignard reagent = 3.248/2 = 1.624

The milliliters of Grignard reagent necessary to have the required 0.375 mole per 0.25 mole of nitrile = $\frac{375 \text{ m.e.}}{1.623 \text{ m.e./ml.}}$ = 231

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The organic layer was dried over anhydrous sodium sulfate. The ether was stripped through an aspirator and the toluene distilled at atmospheric pressure through column A. The remaining material was fractionated at reduced pressure through the same column. The fractions obtained are shown below.

TABLE III

DISTILLATION OF KETIMINE OF 1-(o-TOLYL)-2-PHENYL-2-ETHYLHEXAN-1-ONE

Fraction	B.P., °C. (5 mm.)	Grams	n_D^{25}
1	60-90	3.95	1.5081
2	90-120	1.30	1.5140
3	120-150	.75	1.5233
4	150-182	.65	1.5277
5	182-187	2.73	1.5466
6	187-193	3.85	1.5552
7	191-193	9.85	1.5562
8	191-193	8.30	1.5568
9	193-199	3.75	1.5568 (vague)
10	199-220	1.85	

The residue and column holdup amounted to one gram. Fraction 7 gave a positive test for nitrogen. Fractions 6 through 9 were assumed to be the ketimine. These amounted to 25.8 g. or a yield of 35 per cent. The combined yield of ketimine and ketimine hydrochloride amounted to 63 per cent. When dry hydrogen chloride gas was bubbled through an ethereal solution of the ketimine, the hydrochloride precipitated.

The oxime of the corresponding ketone was prepared from the ketimine hydrochloride by two methods. In one the hydrochloride salt was combined with a mixture of sodium acetate and hydroxylamine hydrochloride in ethanol and permitted to stand at room temperature for several days. In the other, the ketimine hydrochloride was refluxed with hydroxylamine hydrochloride in an ethanol-pyridine solvent for 22 hours. The oxime could be prepared by the latter method in about 70 per cent yield. After repeated recrystallization the oxime of 1-(o-tolyl)-2-phenyl-2-ethylbenzen-1-one, $C_6H_5C(C_2H_5)(C_6H_5)C(o\text{-}CH_3C_6H_4)=NOH$, melted at 131-132.5°. Anal. Calc'd for $C_{21}H_{27}NO$: N, 4.53. Found: N, 4.47.

In an attempt to prepare the ketone, approximately 1 g. of the ketimine hydrochloride was refluxed for 24 hours in 12 N hydrochloric acid and 95 per cent ethanol. The organic layer was extracted with ether and the latter removed by evaporation over a steam bath. A small amount of thick oil remained which did not crystallize after standing for several days. The material was transferred to a 50 ml. suction flask and maintained at about 20 mm. pressure for 4 hours, and then at 2-3 mm. pressure for 4 hours with gentle heating. Crystallization was still not effected. A comparison of the infrared spectra of the reaction material with the infrared spectra of the starting ketimine indicated that some of the latter had been hydrolyzed to the ketone. A definite peak had appeared at 5.95 microns and the peak at 6.5 microns characteristic of ketimines had decreased.

A. Reaction of Hydratroponitrile

Hydratroponitrile (0.25 mole) was permitted to react with 0.375 mole of each of the three Grignard reagents. The ketimine hydrochloride could not be isolated from the three reaction mixtures, either at the time of hydrolysis or from the water layer after standing for 48 hours.

Phenylmagnesium bromide. Distillation of the organic phase through column B gave 28 g. of product boiling at 141.5-151° (5 mm.). The ketone solidified while being distilled and upon repeated recrystallization from aqueous ethanol melted at 56°. Methyldesoxybenzoin, $CH_3CH(C_6H_5)COC_6H_5$, is reported to melt at 58° (36). The oxime, prepared by the ethanol-pyridine method with five hour reflux, melted at 118-119° after recrystallization from aqueous ethanol. The oxime is reported to melt at 120° (36).

o-Tolylmagnesium bromide. Distillation of the organic layer through column B gave the following fractions:

	B. P., °C. (5 mm.)	Grams	n_D^{25}
1.	25-56	3.6	1.4928
2.	56-79	2.2	1.5202
3.	79-91	5.9	1.5178
4.	91-131	2.8	1.5271
5.	131-136	0.8	1.5540
6-11.	136-182	19.3	1.5698-1.5757
12.	182-236	3.8	
Residue		3.4	

Fractions 1 and 2 appeared to be mostly toluene. Comparison of the refractive index of fraction 3 with the reported value of n_D^{25} 1.5090 suggested that this fraction might be recovered hydratroponitrile. Although the boiling point appeared low when compared to 114-116° (19 mm.) (2a), allowing for difference in pressure, the infrared spectrum tended to prove that hydratroponitrile was indeed recovered. The infrared spectrum of this liquid showed the characteristic absorption of the cyano group at 4.45 microns and in addition was similar to the infrared absorption spectrum of a known sample of hydratroponitrile in the region of 2 to 6 microns. Fraction 3 corresponds to a 15 per cent recovery of unreacted nitrile. Fraction 4 may also contain some nitrile in addition to higher boiling material.

Fractions 6 through 11 formed a soft solid after standing several days. The solid was separated by filtration to give 11.6 g. (20.6 per cent yield) of the ketone. The melting point of 1-(o-tolyl)-3-phenylpropan-1-one, $CH_2CH(C_6H_5)CO(o\text{-}CH_3C_6H_4)$, was 54-54.5°. Anal. Calc'd. for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.85; H, 7.13.

The oxime was prepared by the ethanol-pyridine method by eight hours reflux. After repeated recrystallization from aqueous ethanol it melted at 128°. Anal. Calc'd. for $C_{16}H_{17}NO$: N, 5.85. Found: N, 6.05.

The filtrate from fractions 6 through 11 was redistilled. A small fraction distilling at 173-198° (5 mm.), the approximate boiling range of the ketimines, would not form the picrate. These fractions and fraction 12 were apparently condensed products resulting from the side reaction caused by an active alpha hydrogen.

Mesitylmagnesium bromide. After hydrolysis of the reaction mixture the water layer was separated and extracted with toluene. Distillation of the organic layer through column B yielded the following fractions:

	B. P., °C. (5 mm.)	Grams	n_D^{25}
1.	43.5-59	6.1	1.4941
2.	53-68	5.7	1.4993
3.	48-84	1.2	1.5011
4.	84-93	9.9	1.5137
5.	93-169	0.7	1.5367
6.	169-182	16.1	1.5857
7.	177-186	12.4	1.5860
8.	186-209	1.1	1.5800
Residue		4.8	

A comparison of the boiling point and refractive index of fractions 1 and 2 with the boiling point of 66° (22 mm.) and $n_D^{23.6}$ 1.4958 of mesitylene (34) suggested that these fractions were recovered mesitylene resulting from the hydrolysis of unreacted mesitylmagnesium bromide. That this liquid was mesitylene was confirmed by comparing its infrared absorption spectrum with that of a known sample mesitylene.

Fraction 4 was shown to be hydratroponitrile as in the previous reaction. It corresponds to a 30 per cent recovery of unreacted nitrile.

Fractions 6 and 7 were assumed to be the ketimine. These amounted to 28.5 g. or a yield of 45.5 per cent. The ketimine was derivatized as the oxime and picrate.

The oxime was prepared by the ethanol-pyridine method by 22 hours reflux. The oxime of 1-mesityl-2-phenylpropan-1-one, $CH_3CH(C_6H_5)C[2,4,6(CH_3)_3C_6H_2]=NOH$, melted at 139.5°. Anal. Calc'd. for $C_{18}H_{21}NO$: N, 5.24. Found: N, 5.33.

The picrate of 1-mesityl-2-phenylpropan-1-one imine, $CH_2CH(C_6H_5)C[2,4,6(CH_3)_3C_6H_2]=NH\cdot HOC_6H_2(NO_2)_3$, melted at 189-189.5°. Anal. Calc'd. for $C_{24}H_{24}N_4O_7$: N, 11.66. Found: N, 11.85.

B. Reaction of 2-Phenylbutanenitrile

As a preliminary experiment to determine the reactivity of 2-phenyl butanenitrile with Grignard reagents, the reaction was run with both phenyl and o-tolylmagnesium bromide at 90° for 17 hours. The reaction mixture was stirred for only 5 hours of this time. In the first run with each Grignard, 0.5 mole of the nitrile was permitted to react with 0.75 mole of Grignard reagent. The second reaction was carried out according to the adopted procedure as given for 2-phenyl-2-ethylhexanenitrile at the start of this section.

Phenylmagnesium bromide. First reaction. Distillation through column A gave the following fractions:

	B. P., °C. (5-6 mm.)	Grams	n_D^{28}
1.	17-46	.5	1.4766
2.	50-79	1.3	1.4932
3.	85-101	3.8	1.5260
4.	101-103	16.0	1.5254
5.	103-125	1.6	1.5480
6.	119-159	1.9	1.5645
7.	161-162	28.0	1.5709
8.	160-161-5	26.5	1.5711
Residue		9.5	

Fractions 1 through 3 appeared to be largely toluene.

The boiling point of fraction 4 compared favorably with the boiling point 99-101° (5 mm.) of 2-phenylbutanenitrile. The infrared spectrum of this liquid exhibited the characteristic absorption of the cyano group at 4.45 microns and in addition was similar to the infrared absorption spectrum of a known sample of 2-phenylbutanenitrile in the region of 2 to 6 microns. Fraction 4 represented a 22 per cent recovery of unreacted nitrile.

Fraction 6, 7 and 8 solidified while taking refractive indices and after two recrystallizations from aqueous ethanol melted at 54°. Ethyldesoxybenzoin, $C_2H_5CH(C_6H_5)CCC_6H_5$, is reported to melt at 58° (35).

Second reaction. The organic layer was fractionated through column A and a distillation pattern similar to the one immediately above was obtained. The lower fractions appeared to be mainly toluene. The fraction (2.8 g., 7.7 per cent recovery) distilling at 118-120° (14-15 mm.) compared favorably with the b. p. of 122-124° (15 mm.) reported by Cram and Allinger (23) for 2-phenylbutanenitrile. It was further confirmed as the nitrile by its infrared spectrum.

The ethyl desoxybenzoin, a total of 33.4 g., 56 per cent yield, distilling at 170-182° (14-15 mm.) solidified upon cooling and upon repeated recrystallization from aqueous ethanol melted at 55°. The oxime was prepared by the ethanol-pyridine method by 25 hours reflux and upon repeated recrystallization from aqueous ethanol melted at 129-130°. The oxime is reported to melt at 129-130° (35).

<u>o-Tolylmagnesium bromide</u>. First reaction. Upon hydrolysis 3 layers separated. The solid layer was recovered by filtration to give 25.4 g.

(18.4 per cent yield) of the ketimine hydrochloride. Distillation of the organic phase through column A gave the following fractions:

	B. P., °C. (16-17 mm.)	Grams	n_D^{25}
1.	25-26	4.6	1.4918
2.	25	5.2	1.4920
3.	25-33	1.2	1.4772
4.	33-74	1.0	1.4604
5.	74-113	3.7	1.4992
6.	113-127	7.9	1.5182
7.	127	12.8	1.5058
8.	127-142	3.2	1.5110
9.	142-178	.7	1.5329
Residue		10.	

Fractions 1 and 2 appeared to be largely toluene.

Fractions 6 and 7 were shown to be mostly unreacted nitrile by a comparison of the boiling point, refractive index and infrared absorption spectrum of this liquid with that of 2-phenylbutanenitrile as in the reaction with phenylmagnesium bromide. Fractions 6 and 7 corresponded to a 29 per cent recovery of unreacted nitrile.

It is possible that the residue contained some ketimine since the highest boiling point of the distillate is below the usual boiling point of the ketimines.

Second reaction. Upon hydrolysis, 3 layers appeared. The solid layer was separated by filtration to give 38.5 g. (56.3 per cent yield) of the ketimine hydrochloride. The organic phase was distilled through column A.

As in the previous reaction, the distillate contained mainly unreacted nitrile and toluene. The unreacted nitrile, distilling at 106-111° (13 mm.), n_D^{25} 1.5085, weighed 4.8 g. (13.5 per cent recovery).

The oxime was prepared from the ketimine hydrochloride by the sodium acetate method and by the ethanol-pyridine method with 22 hours reflux. The latter gave a 65 per cent yield of the oxime of 1-(o-tolyl)-2-phenylbutan-1-one, $C_2H_5CH(C_6H_5)C(o\text{-}CH_3C_6H_4)=NOH$, which melted at 127-128.5° After repeated recrystallization from aqueous ethanol. Anal. Calc'd. for $C_{23}H_{23}NO$: N, 5.52, Found: N, 5.53.

Mesitylmagnesium bromide. Hydrolysis produced three layers. The solid was separated by filtration and amounted to 55 g. (71.5 per cent yield) of the ketimine hydrochloride. The organic phase, distilled through column C gave largely unreacted nitrile and mesitylene, which were identified as before.

The oxime of the ketimine hydrochloride could not be prepared by the ethanol-pyridine method with 22 hours reflux. Only a sticky, viscous liquid characteristic of ketimines remained after the reflux period.

The picrate of 1-mesityl-2-phenylbutan-1-one imine, $C_2H_5CH(C_6H_5)C[2,4,6(CH_3)_3C_6H_2]=NH\ HOC_6H_2(NO_2)_3$, was prepared from the ketimine hydrochloride and melted at 180.5-182°. Anal. Calc'd. for $C_{30}H_{30}N_4O_7$: N, 11.33. Found: N, 11.45.

C. Reaction of 2-Phenyl-2-ethylhexanenitrile

2-Phenyl-2-ethylhexanenitrile (0.25 mole) was permitted to react with 0.375 mole of each Grignard reagent. The mixture of this nitrile

with phenylmagnesium bromide was heated 5 hours at 90° followed by 16 hours of refluxing without stirring.

Phenylmagnesium bromide. Hydrolysis produced 3 layers. The solid was separated by filtration to give 48 g. (61 per cent yield) of the ketimine hydrochloride. Distillation of the organic phase through a fraction-cutting head yielded one main fraction boiling at 175-183° and n_D^{25} 1.5546-1.5604. This fraction, weighing 13.6 g. (16.4 yield) was assumed to be the ketimine. The ketimine hydrochloride formed when dry hydrogen chloride was bubbled through an ethereal solution of this light yellow, sticky liquid.

The oxime of 1,2-diphenyl-2-ethylbenzan-1-one, $C_6H_5C(C_2H_5)(C_6H_5)C(C_6H_5)=NOH$, was prepared by the sodium acetate method from the ketimine hydrochloride and melted at 159-160° after repeated recrystallization from aqueous ethanol. Anal. Calc'd. for $C_{28}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.31; H, 8.53; N, 4.74.

o-Tolylmagnesium bromide. This reaction was described in detail at the beginning of this section.

Mesitylmagnesium bromide. Two layers formed upon hydrolysis. Distillation of the organic phase through column C gave the following fractions:

	B. P. °C. (5 mm.)	Grams	n_D^{25}
1.	31-38	2.0	1.4887
2.	38-40	10.8	1.4976
3.	40-42	5.9	1.4953
4.	42-80	1.5	1.4955
5.	80-91	4.0	1.5149
6.	91-95	2.9	1.5175
7.	95-110	3.4	1.5155
8.	110-126	1.5	1.5104
9.	126-137	1.6	1.5100
10.	137-200	3.1	1.5270
11.	200-210	15.8	1.5537
12.	206-212	16.8	1.5563
13.	212-215	18.0	1.5542
14.	215-218	4.8	1.5506
15.	218-252	2.9	1.5468
Residue		6.5	

Fractions 1 through 3 were shown to be mesitylene as in the reaction of hydratroponitrile.

A comparison of the boiling point and refractive indices of fractions 5 through 7 with the boiling point of 125° (5 mm.) and n_D^{25} 1.4971 of 2-phenyl-2-ethylhexanenitrile (3a) indicated these fractions were not recovered nitrile. This material was not identified.

Fractions 11 through 14 were assumed to be the ketimine. These amount to 45.4 g. or a yield of 69 per cent. The ketimine would not form when dry hydrogen chloride gas was passed into an ethereal solution of this liquid.

The picrate of 1-mesityl-2-phenyl-2-ethylhexan-1-one imine, $C_6H_5C(C_2H_5)(C_6H_5)C[2,4,6(CH_3)_3C_6H_2]=NH\cdot HOC_6H_2(NO_2)_3$ was prepared from

the ketimine and melted at 158-159.5°. Anal. Calc'd. for $C_{20}H_{24}N_2O_7$: N, 10.18. Found: N, 10.23.

D. Reaction of 2-Phenyl-3-methylpentanenitrile

2-Phenyl-3-methylpentanenitrile (0.25 mole) was permitted to react with 0.375 mole of each of the three Grignard reagents.

Phenylmagnesium bromide. Upon hydrolysis, 3 layers formed. The solid layer was separated by filtration to give 48.6 g. (67 per cent yield) of the ketimine hydrochloride. Distillation of the organic phase through column C gave the following fractions:

	B. P., °C. (5 mm.)	Grams	n_D^{25}
1.	26-110	1.3	1.5120
2.	110	.5 (solid and liquid)	1.5409
3.	108-116	4.1 (solid)	
4.	112-116	2.5 (solid and liquid)	1.5423
5.	116-121	5.0	1.5310
6	121-173	2.9	1.5366
7	173-205	3.3 (some yellow solid)	
Residue		2.8	

The solid was separated from fractions 2, 3, and 4 by filtration and after recrystallization melted at 69°. Kentress and Mulliken (33) give a melting point of 70° for biphenyl and also state that biphenyl gives a blue color with aluminum chloride in carbon tetrachloride.

A sample of the solid gave a blue color with these reagents, hence it is assumed to be biphenyl.

Fractions 1, 5 and 6, and the filtrate from the above separations were combined and redistilled through column C to give 4 fractions (15 g.) ranging in boiling point from 26 to 165° (5 mm.). The distillate did not appear to contain any separate fractions.

The oxime of the ketimine hydrochloride could not be prepared either by the sodium acetate method or the ethanol-pyridine method with 22 hours reflux. Only a sticky, viscous liquid characteristic of ketimines remained after the reflux period.

The picrate of 1,2-diphenyl-3-methylpentan-1-one imine, $C_6H_5CH(CH_3)CH(C_6H_5)C(C_6H_5)=NH\cdot HOC_6H_2(NO_2)_3$, was prepared from the ketimine hydrochloride and after repeated recrystallization from aqueous ethanol melted at 150-151.5°. Anal. Calc'd. for $C_{32}H_{30}N_4O_7$: N, 11.66. Found: N, 11.78.

o-Tolylmagnesium bromide. Three layers formed upon hydrolysis. The solid was separated by filtration to give 59 g. (78 per cent) of the ketimine hydrochloride. The organic phase was distilled through column C. The distillate appeared to contain only toluene and unreacted nitrile. The boiling point, 113-119° (5 mm.) and n_D^{25} 1.5080 of fraction 3 compared favorably with the boiling point 120° (5 mm.) and n_D^{25} 1.5039 of 2-phenyl-3-methylpentanenitrile.* The infrared absorption spectrum of this liquid exhibited the characteristic absorption of the cyano

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*Physical constants of the starting nitrile. This nitrile is not reported in the literature.

group and in addition was similar in the region of 2 to 6 microns to the infrared absorption spectrum of the 1-phenyl-3-methylpentanenitrile used in this reaction.

The oxime of the ketimine hydrochloride could not be prepared by either the sodium acetate or by the ethanol-pyridine method with 22 hours reflux. A sticky, viscous liquid remained after the reflux period.

An attempt was made to prepare the picrate of 1-(o-tolyl)-2-phenyl-3-methylpentan-1-one imine, $C_2H_5CH(CH_3)CH(C_6H_5)C(o\text{-}CH_3C_6H_4)=NH\cdot HOC_6H_2(NO_2)_3$. A dark yellow solid formed slowly, and after several recrystallizations from aqueous ethanol melted at 253-255° on a melting point block. Anal. Calc'd. for $C_{26}H_{28}N_4O_7$: N, 11.33. Found N; 22.93.

This compound may have been ammonium picrate which contains 22.67 per cent nitrogen. Other picrates or picric acid (18.3 per cent nitrogen) were excluded by the high nitrogen analysis.

Mesitylmagnesium bromide. Hydrolysis gave two layers. Distillation of the organic phase through column C gave the following fractions:

	B. P., °C. (5 mm.)	Grams	n_D^{25}
1.	39-42	5.7	1.4893
2.	40-44	13.4	1.4942
3.	42-51	4.0	1.4957
4.	51-109	2.7	1.5092
5.	109-121	3.5	1.5127
6.	121-129	1.2	1.5216
7.	129-143	1.4	1.5241
8.	143-187	2.9	1.5362
9.	186-193	22.6	1.5607

10.	188-193	18.6	1.5637
11.	193-201	4.2	1.5638
12.	201-250	4.2	1.5652
Residue		5.9	

Fractions 1 through 3 were identified as mesitylene as described previously.

Fraction 5, which corresponds to an 8.5 per cent recovery of unreacted nitrile, was identified as before.

Fractions 8 through 11 were assumed to be the ketimine. These amounted to 45.4 g. or a yield of 64 per cent. The oxime could not be prepared by the ethanol-pyridine method with 22 hours reflux.

The picrate of 1-mesityl-2-phenyl-3-methylpentan-1-one imine, $C_2H_5CH(CH_3)CH(C_6H_5)C[2,4,6(CH_3)_3C_6H_2]=NH\cdot HOC_6H_2(NO_2)_3$, was prepared from the ketimine and after repeated recrystallization from aqueous ethanol melted at 191-192°. Anal. Calc'd. for $C_{27}H_{30}N_4O_7$: N, 10.72. Found: N, 10.95.

E. Reaction of 2-Phenyl-2-ethyl-3-methylpentanenitrile

2-Phenyl-2-ethyl-3-methylpentanenitrile (0.25 mole) was permitted to react with 0.375 mole of each Grignard reagent. In an additional experiment, 0.343 mole of this nitrile was allowed to react with 0.375 mole of o-tolylmagnesium bromide.

In each reaction, hydrolysis produced only two layers.

Phenylmagnesium bromide. Distillation of the organic phase through a fraction-cutting head yielded one main fraction boiling at 183-193° (5 mm.). (The refractive index was not distinct enough to be read.)

This fraction was assumed to be the ketimine and amounted to 49 g. (71 per cent yield). The ketimine hydrochloride formed when dry hydrogen chloride gas was bubbled through an ethereal solution of this ketimine. An attempt to prepare the oxime by the ethanol-pyridine method with 22 hours reflux yielded only a sticky, viscous liquid.

The picrate of 1,2-diphenyl-2-ethyl-3-methylpentan-1-one imine, $C_6H_5CH(CH_3)C(C_2H_5)(C_6H_5)C(C_6H_5)=NH\cdot HOC_6H_2(NO_2)_3$, was prepared from the ketimine and after repeated recrystallizations from aqueous ethanol, melted at 220.5-221.5°. Anal. Calc'd. for $C_{32}H_{32}N_4O_7$: N, 11.07. Found: N, 10.93.

<u>o-Tolylmagnesium bromide</u>. Distillation of the organic phase through column C gave the following fractions:

	B. P., °C. (5 mm.)	Grams	n_D^{25}
1.	28-67	2.4	1.5208
2.	67-113	3.4	1.5137
3.	113-124	2.3	1.5081
4.	115-126	4.0	1.5063
5.	120-128	10.5	1.5053
6.	126-128	10.8	1.5051
7.	128-136	3.	1.5075
8.	136-183	1.2	1.5370
9.	183-198	6.7	1.5568
10.	195-200	8.0	1.5654
11.	200-236	1.8	
Residue		2.4	

Fractions 1 through 3 appeared to be largely toluene. The boiling range and refractive indices of fractions 4 through 7 compared favorably

with the boiling point 123-127° (5 mm.) and n_D^{26} 1.5038 of 2-phenyl-2-ethyl-3-methylpentanenitrile (3a). The infrared spectrum of this liquid exhibited the characteristic absorption of the cyano group at 4.45 microns and was similar to the infrared spectrum of a known sample of 2-phenyl-2-ethyl-3-methylpentanenitrile. Fractions 4 through 7 amounted to a 56 per cent recovery of unreacted nitrile.

Fractions 9 and 10 were assumed to be the ketimine and amounted to a 20 per cent yield. An attempt to prepare the oxime by the ethanol-pyridine method with 22 hours reflux gave only a sticky, viscous liquid.

The picrate of 1-(o-tolyl)-2-ethyl-3-methylpentan-1-one imine. $C_2H_5CH(CH_3)C(C_2H_5)(C_6H_5)C(o\text{-}CH_3C_6H_4)=NH\cdot HOC_6H_2(NO_2)_3$, was prepared from the ketimine and melted at 203-204°. Anal. Calc'd. for $C_{27}H_{30}N_4O_7$: N, 10.73. Found: N, 10.73.

In the reaction between 0.343 mole of this nitrile and 0.375 mole of o-tolylmagnesium bromide, the organic phase was distilled through a fraction-cutting head to yield two main fractions as before.

The first fraction (40 g., 58 per cent recovery) distilling at 108-125° (3-4 mm.) n_D^{25} 1.5055-1.5069 was shown to be unreacted 2-phenyl-2-ethyl-3-methylpentanenitrile as in the previous reaction.

The fraction (6.5 g., 9.5 per cent yield) boiling at 188-206° (5 mm.) was assumed to be the ketimine.

Mesitylmagnesium bromide. Distillation of the organic phase through column A yielded two main fractions.

The first fraction, distilling at 37-43° (5 mm.), n_D^{25} 1.4960-1.4961, was identified as mesitylene as in the reaction of hydratroponitrile.

The second fraction (41.7 g., 83 per cent recovery) distilling at 120-132° (5 mm.) and n_D^{25} 1.5042-1.5070, was identified as 2-phenyl-2-ethyl-3-methylpentanenitrile as before.

VI. Preparation of Derivatives

Oximes

Sodium acetate method (13). The ketimine hydrochloride gave the oxime when a solution of 2 g. (0.01 mole) of the salt in ethanol was combined with an aqueous ethanolic solution of 1.5 g. (0.02 mole) of hydroxylamine hydrochloride and 2.5 g. (0.03 mole) sodium acetate. The oxime was recrystallized from aqueous ethanol. (With the less hindered nitriles the oxime formed within a few minutes after combination.)

Ethanol-pyridine method (28). From the ketone: 2 g. of the ketone and 2 g. of hydroxylamine hydrochloride were refluxed in 6 ml. of absolute ethanol and 6 ml. of pyridine over a steam bath.

From the ketimine and ketimine hydrochloride: 3 g. of the ketimine and 3 g. of hydroxylamine hydrochloride were refluxed in 15 ml. of absolute ethanol and 25 ml. of pyridine over a steam bath.

After refluxing, the solvents were evaporated in a stream of air. The mixture was triturated with water and the solid was separated by filtration. Recrystallization was effected in aqueous ethanol.

Picrate. About 0.5 g. of the ketimine or ketimine hydrochloride in 10 ml. of absolute ethanol was combined with 10 ml. of a saturated,

The second fraction (41.7 g., 83 per cent recovery) distilling at 120-132° (5 mm.) and n_D^{25} 1.5042-1.5070, was identified as 2-phenyl-2-ethyl-3-methylpentanenitrile as before.

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From the ketimine and ketimine hydrochloride: 3 g. of the ketimine and 3 g. of hydroxylamine hydrochloride were refluxed in 15 ml. of absolute ethanol and 25 ml. of pyridine over a steam bath.

After refluxing, the solvents were evaporated in a stream of air. The mixture was triturated with water and the solid was separated by filtration. Recrystallization was effected in aqueous ethanol.

Picrate. About 0.5 g. of the ketimine or ketimine hydrochloride in 10 ml. of absolute ethanol was combined with 10 ml. of a saturated,

ethanolic solution of picric acid. The picrate crystallised from solution upon standing. The picrates were recrystallised from aqueous ethanol.

DISCUSSION

Previous to the start of this study, other workers had observed that nitriles with an effective six-number (see page 7 for the definition of this term) of 8 or more could not be hydrolyzed even under very vigorous conditions (1, 2, 3). This investigation was undertaken to see if these highly hindered nitriles would react with Grignard reagents.

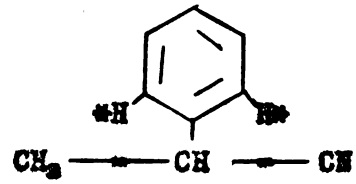
A series of nitriles of the type

were chosen with an effective six-number ranging from 2 to 11, to see if any correlation existed between the reaction of these nitriles with Grignard reagents and their observed resistance to hydrolysis. The structures of the five nitriles used are shown in Figure I. Nitriles III and V contain an ethyl group on the alpha carbon in addition to the alkyl and phenyl substituents. Nitriles IV and V have a methyl group on the beta carbon. All of these nitriles reacted with the Grignard reagents employed. Only the reaction of nitrile V with mesitylmagnesium bromide failed.

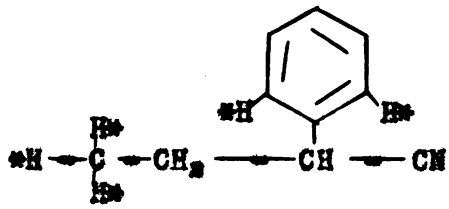
Royals (29) and Kharasch and Reinmuth (5) suggest that the reaction between nitriles and Grignard reagents proceeds according to the mechanism proposed by Swain (37). The reaction between n-butylmagnesium

FIGURE I

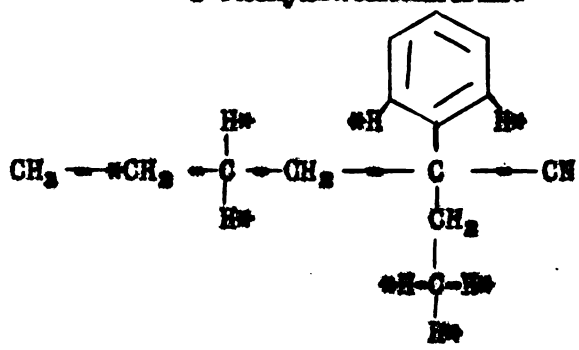
STRUCTURE OF NITRILES USED IN THIS STUDY

No.		Effective Six-Number
I		2

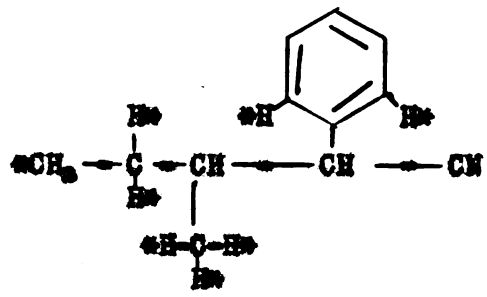
Hydratroponitrile

II		5

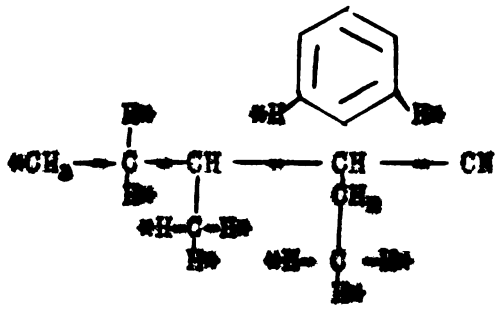
2-Phenylbutanenitrile

III		8

2-Phenyl-2-ethylhexanenitrile

IV		8

2-Phenyl-3-methylpentanenitrile

V		11

2-Phenyl-2-ethyl-3-methylpentanenitrile

Atoms in the sixth position from nitrogen are starred.

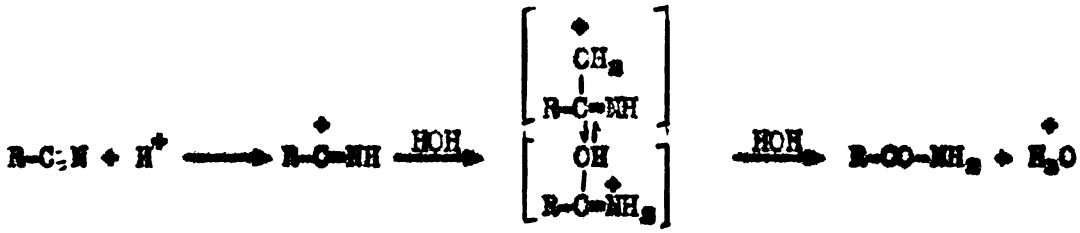
bromide and benzonitrile was studied in detail and found to be second order. The reaction may be represented as follows:

In the first step, the nitrile coordinates with the magnesium atom replacing an ether molecule. Newman (6) states that the ease of this coordinative exchange depends upon the relative electron-donating power of the two coordinating groups. In instances where the attacking group is weakly electron-donating or highly hindered, reaction may not occur. In such a case, it is found to be helpful to replace the ether with a solvent such as toluene or benzene. The principal advantage of such a solvent is not due to its higher boiling temperature, but rather to the small heat of solvation of organometallic compounds with these solvents as compared to that of ether.

In the second step, the rate determining step, an intramolecular rearrangement occurs in which the radical attached to the magnesium atom migrates to the cyano carbon. This is then followed by hydrolysis. The possibility that the second step takes place through attack of the coordination complex by a second molecule of the Grignard reagent followed by an intermolecular transfer of the organic group has been ruled out since such a process would involve third order kinetics. Also, a mechanism involving the slow solvolytic ionization of the Grignard reagent as the

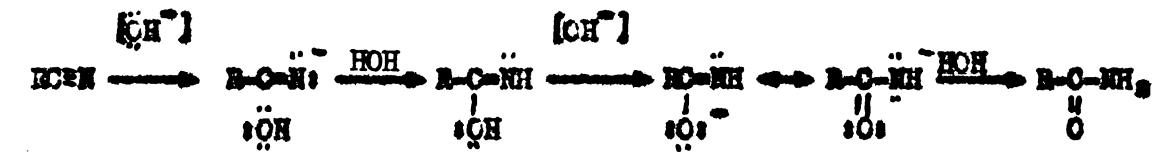
rate determining step is eliminated since it would require first order kinetics.

The fact that hydrolysis of the nitriles does not occur in many cases indicates a difference in the mode of the two reactions. Royals (29) suggests the following mechanism for the acidic hydrolysis of nitriles.



Initially the nitrile is attacked by a proton leaving a positive charge on the cyano carbon which is in turn attacked by a nucleophilic group. It is not known exactly what this group is but it seems reasonable that it may be a solvated ion or molecule. If this is the case, attack at the cyano carbon could be retarded by a highly hindered nitrile.

In the basic hydrolysis of a nitrile, Moller (30) represents the initial attack of a hydroxide ion



which again may be solvated. Such an ion again would be retarded in its attack on a hindered nitrile.

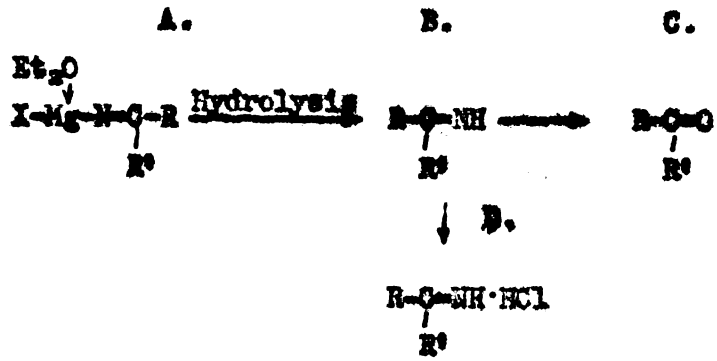
The increased reactivity of the nitrile toward Grignard reagents may be due to one or all of the following factors:

(1) The size of the attacking molecule or species may be smaller. This latter could be especially true in the case of hydrocarbon solvents since these could not form oxonium complexes with the Grignard reagent. Newman (6) has indicated that hydrocarbon solvents form only loose complexes with organometallic compounds since such solvents give only small heats of solvation.

(2) The close proximity of this radical and the cyano carbon which must exist in the Grignard complex.

(3) The greater nucleophilic character of the organic radical attached to the magnesium atom as compared to the attacking species in the nitrile hydrolysis.

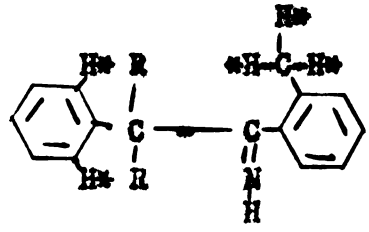
Upon hydrolysis of the Grignard intermediate A, the ketone, ketimine or ketimine hydrochloride will be produced. In every instance except one, the reaction proceeded at least to the ketimine, B.



However, hydrolysis of the ketimine to the ketone C occurred in only three reactions. These involved the less hindered nitriles. (See Figure II)

An examination of the structure of the ketimine (B) reveals first, that the molecule contains the double-bonded function C=NH, and,

as such, its reactions should be influenced by the number of atoms in the sixth position from the nitrogen, as defined by Newman (4). Secondly, the addition of the o-tolyl or mesityl groups to the ketimine carbon increases the effective six number by 3 and 6, respectively.



Thus, the addition of the o-tolyl group or mesityl group to the imino carbon would be expected to retard the reaction of the imino group.

From an examination of the following figures, it is apparent that there exists a relationship between the effective six-number of the ketimine and the ease with which the C=NH group will react.

Figures II, III, IVa and IVb show the structure of each ketimine or ketimine hydrochloride obtained in this work and its effective six-number. These are arranged according to the ease of hydrolysis and ultimately oxime formation. The ketimines shown in Figure II were not actually isolated, but are included to illustrate the effect of the effective six-number on the final product.

In Figure II are shown the intermediate ketimines which yielded ketones when the Grignard complex was hydrolyzed under the conditions used in this study. These arose from the reaction between hydratroponitrile and phenyl and o-tolylmagnesium bromide, and between 2-phenylbutanenitrile and phenylmagnesium bromide. These ketones all formed

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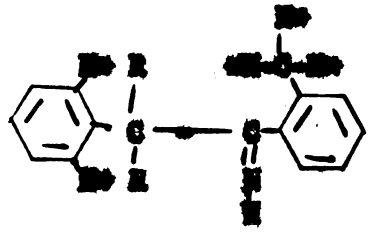


Thus, the addition of the o-tolyl group or mesityl group to the imino carbon would be expected to retard the reaction of the imino group.

From an examination of the following figures, it is apparent that there exists a relationship between the effective six-number of the ketimine and the ease with which the C=NH group will react.

Figures II, III, IVa and IVb show the structure of each ketimine or ketimine hydrochloride obtained in this work and its effective six-number. These are arranged according to the ease of hydrolysis and ultimately oxime formation. The ketimines shown in Figure II were not actually isolated, but are included to illustrate the effect of the effective six-number on the final product.

In Figure II are shown the intermediate ketimines which yielded ketones when the Grignard complex was hydrolyzed under the conditions used in this study. These arose from the reaction between hydratroponitrile and phenyl and o-tolylmagnesium bromide, and between 2-phenylbutanenitrile and phenylmagnesium bromide. These ketones all formed

FIGURE II

KETIMINES FORMING KETONES BY HYDROCHLORIC ACID HYDROLYSIS OF THE GRIGNARD COMPLEX

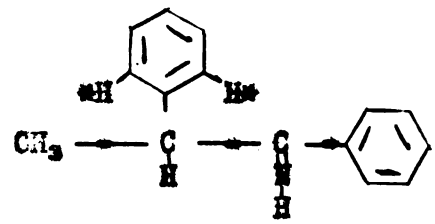
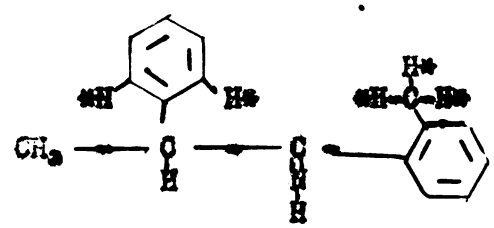
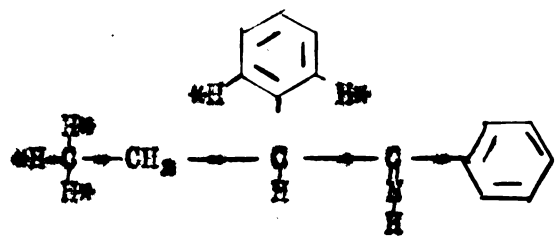
Number		Effective Six-Number
I		2
II		5
III		5

FIGURE III

KETIMINES AND KETAMINE HYDROCHLORIDES
YIELDING OXIDES

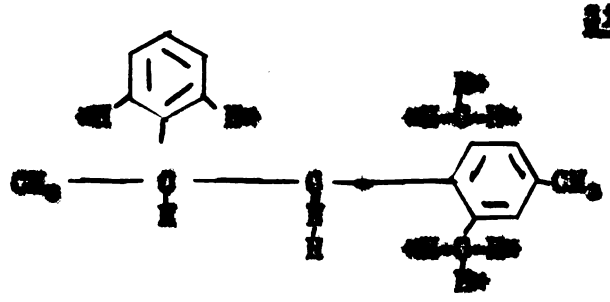
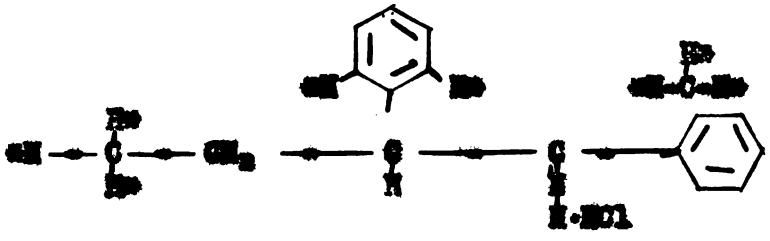
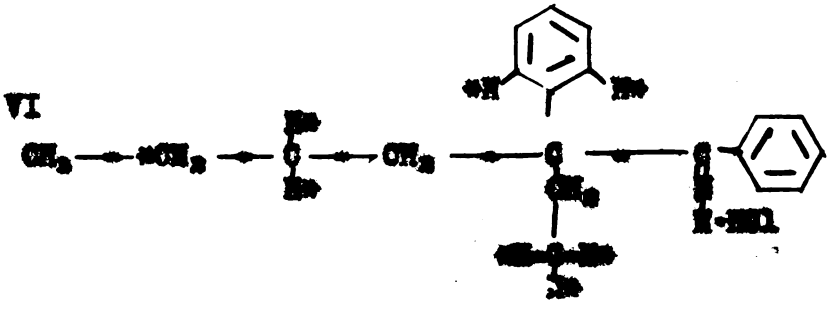
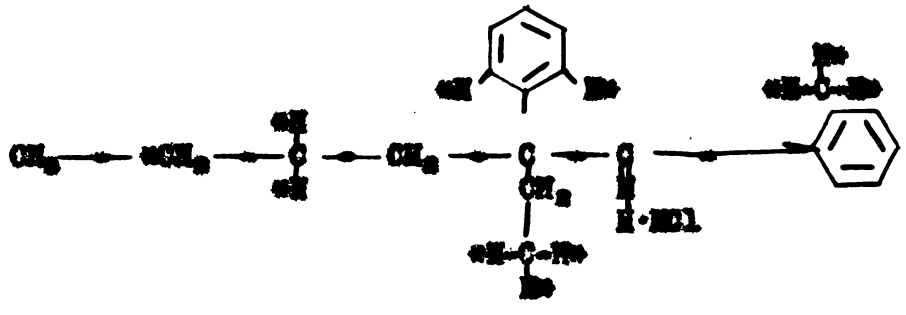
Number		Effective Six-Number
IV		8
V		8
VI		8
VII		11

FIGURE IV (a)

KETIMES AND KETIMINE HYDROCHLORIDES
FAILING TO YIELD OXIMES

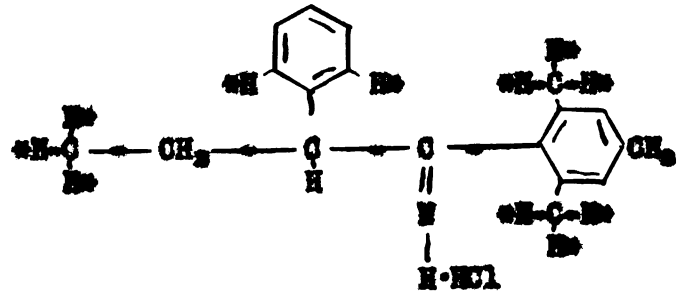
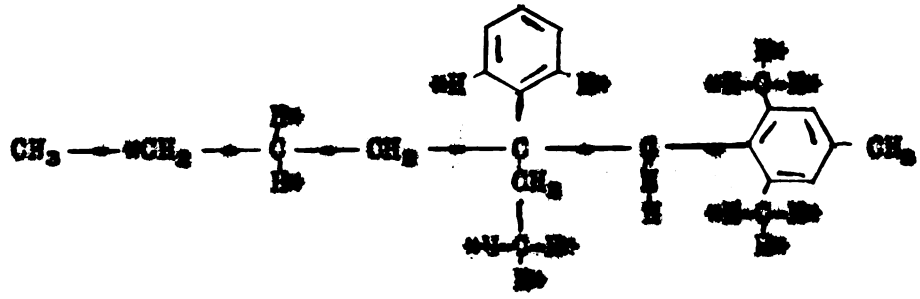
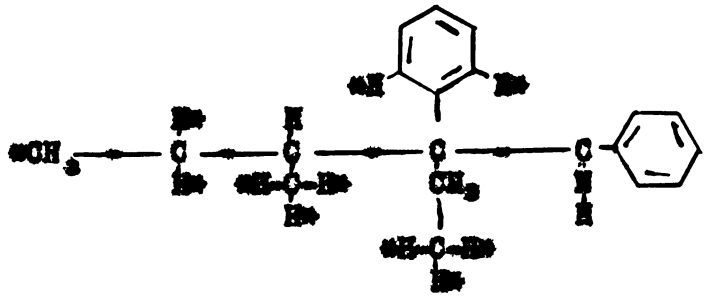
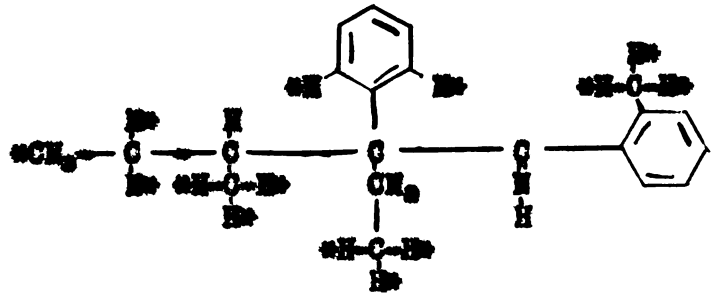
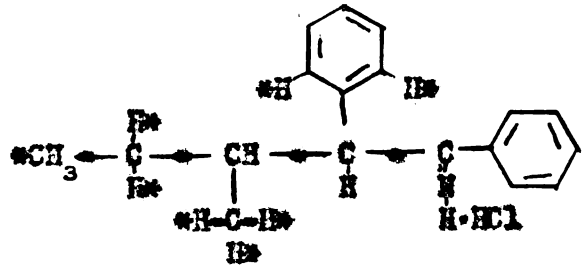
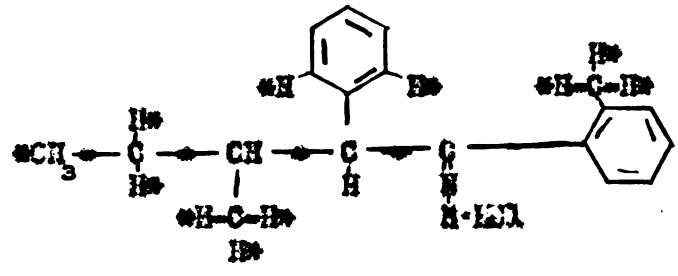
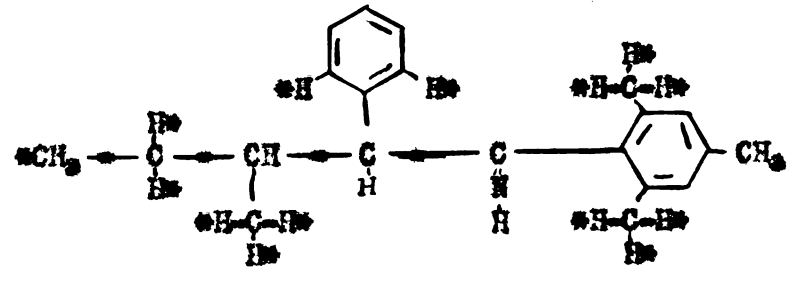
Number		Effective Six-Number
VIII		11
IX		14
X		11
XI		14

FIGURE IV (b)

KETIMINES AND KETIMINE HYDROCHLORIDES FAILING TO YIELD OXIDES

Number		Effective Six-Number
XII		8
XIII		11
XIV		14

oximes under relatively mild conditions. Ketimines II and III, with an effective six-number of 5, exhibited similar properties even though the original reactants were hydratroponitrile and 2-phenylbutanenitrile with effective six-numbers of 2 and 5 respectively. The steric hindrance appeared to be approximately the same whether the methyl radical was attached to the phenyl group as in ketimine II or to the chain portion of the nitrile as in ketimine III.

In Figure III are shown the ketimines and ketimine hydrochlorides which were isolated after hydrolysis of the Grignard complex. These ultimately yielded oximes. Ketimines IV, V and VI with an effective six-number of 8, were derived from nitriles I, II, and III (Figure I) with an effective six-number of 2, 5 and 8 respectively. This again shows that the steric effect is approximately the same whether the atoms in the sixth position are derived from either the nitrile or the Grignard reagent. An examination of Figures III and IV shows that in no case was it possible to hydrolyze any ketimine or ketimine hydrochloride with an effective six-number of 8 or more and to isolate the ketone therefrom. However, it was possible to prepare the oximes from the ketimines or ketimine hydrochlorides shown in Figure III, and this oxime formation presumably would proceed through the ketone stage. Partial hydrolysis of ketimine hydrochloride VII to the ketone after 24 hour reflux was demonstrated by the infrared absorption spectrum of the oil obtained.

On the basis of the above evidence it appears that when the effective six-number is 8 or greater: (1) hydrolysis (with ice and acid)

of the Grignard complex to the ketone fails; (2) hydrolysis of the ketimine or ketimine hydrochloride becomes very difficult or impossible.

All of the ketimines in Figure III, including ketimine VII with an effective six-number of 11 were converted to oximes by refluxing with hydroxylamine hydrochloride in an ethanol-pyridine solution for 22 hours. In contrast to this, ketimine XII, Figure IVb, with an effective six-number of 8 would not form the oxime when treated under similar conditions. In this instance the correlation between the reactivity of a molecule and its effective six-number did not hold.

Ketimines VI and XII resulted from the reaction of phenylmagnesium bromide with nitriles with the same effective six-number. Examination of their structures shows that ketimine VI has an ethyl radical substituted on the alpha carbon while ketimine XII has a methyl substituent on the beta carbon. From this, it appears that a second methyl substituent on the beta carbon atom more effectively retards reaction of the imino function than substitution of an ethyl group on the alpha carbon. Examination of Stuart models supports this belief.

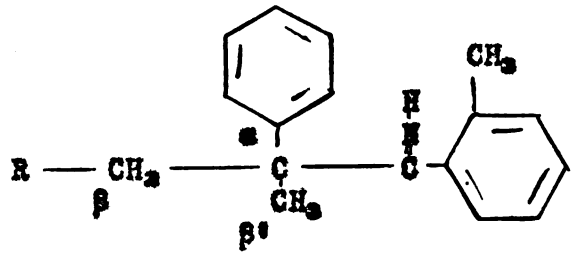
When an isopropyl or sec-butyl group is a substituent on the alpha carbon atom of one of the ketimines under consideration, rotation of the entire group to remove one methyl branch from the vicinity of the imino group causes the second methyl (or ethyl) branch to come into position so that it effectively shields the imino group.

An effect similar to that described above was observed with ketimines VII and XIII which have effective six-numbers of 11.

Also, comparison of ketimine VII with the less reactive ketimine VIII indicate that an ethyl group on the alpha carbon does not hinder reactions as much as a second methyl radical in the ortho position of the Grignard reagent.

Finally, from a comparison of ketimine IV and XII it appears that substitution of two alkyl groups on the beta carbon atom of the nitrile derived fragment prevents reaction of the imino group more effectively than the two methyl groups on the ortho positions of the Grignard derived fragment.

From these observations it appears that the order of increasing steric hindrance is as follows:



Methyl substitution at beta prime < methyl substitution at the second ortho position of the Grignard reagent < methyl substitution at beta. The effective six-number is the same in each case.

It is also of interest to observe that in general as the bulkiness of the Grignard reagent increased, the tendency for the formation of the ketimine hydrochloride decreased. This must be due to either the electrical effect or the bulkiness of the additional methyl groups. Any electrical effect that these groups may contribute would tend to make the ketimine more basic, favoring ketimine hydrochloride formation

with increasing methyl substitution. This was not found to be true. Thus, the trend from ketimine to ketimine hydrochloride as the bulkiness of the Grignard reagent increased must be due to steric hindrance.

The reactions of nitriles I, II and IV, having an alpha hydrogen atom were observed to give recovered nitrile in many instances. It appears that this may be due to the following reaction which is similar to one suggested by Noller (30) for ketones.

The hydrogen on the alpha carbon combines with the organic radical from the Grignard reagent giving the hydrocarbon and leaving the halomagnesium salt of the nitrile. Upon hydrolysis of the halomagnesium salt, the nitrile is regenerated. As the bulk of the Grignard reagent increases to such an extent that migration to the nitrile carbon becomes hindered this competing reaction becomes more favorable. It was also noted that the yields of dimers and condensation products for the reactions of these nitriles were small as compared to the corresponding reactions of phenylacetonitrile. This was evidence that the alpha substituted alkyl groups had decreased the acidity of the labile hydrogen atom thereby decreasing the side reaction causing the formation of these products (15).

Although there was insufficient evidence to establish a trend, the reactions of 2-phenylbutanenitrile showed that the reaction conditions had a definite effect upon the yield. When o-tolylmagnesium bromide was permitted to react with this nitrile for 17 hours at 90° without stirring,

the ketimine hydrochloride was obtained in 18 per cent yield. Recovered nitrile amounted to 29 per cent. When the same reaction was carried out at 110° for 16 hours with stirring the yield of ketimine hydrochloride increased to 56 per cent and the recovered nitrile amounted to 14 per cent. However, in the reaction of 2-phenylbutanenitrile with the less hindered phenylmagnesium bromide, the more vigorous reaction conditions had very little effect. The yield of ketone increased from 50.8 to 56 per cent under the more vigorous conditions.

Figure V illustrates the effect of increasing steric hindrance of the nitrile and of the Grignard reagent upon the course of the reaction. As one goes from the top left in the chart toward the bottom right, the direction of increasing hindrance, the products go in general, from ketone to ketimine hydrochloride to ketimine to "no reaction." When the effective six-number of the ketimine exceeded 5 the hydrolytic conditions used in this study no longer gave the ketone. When it exceeded 8, with the exception of ketimine VII, it was no longer possible to obtain the oxime by refluxing for 22 hours with hydroxylamine hydrochloride in an ethanol-pyridine solution. The reactions of ketimines VII and XII are anomalous since the one with higher effective six-number forms the oxime and the one of lower effective six-number does not. The steric hindrance of a methyl group varied with its location on the molecule even though the effective six-number was unchanged. Starting nitrile was recovered in seven of the nine reactions involving nitriles with an alpha hydrogen atom. The starting nitrile recovered in the two reactions at the bottom right was due to the steric hindrance in the nitrile and Grignard reagent.

FIGURE V

SUMMARY OF REACTIONS

	Grignard Reagent: Phenyl	Grignard Reagent: o-Tolyl	Grignard Reagent: Mesityl
hydro-troponitrile	Ketone I. E.S.N.(2) Oxime	Ketone II E.S.N.(5) Oxime Nitrile Recovered.	Ketimine III E.S.N.(8) Oxime, 22 hours reflux. Nitrile Recovered.
2-phenyl-butanonitrile	Ketone III E.S.N.(5) Oxime Nitrile Recovered	Ketimine Hydrochloride V E.S.N.(8) Oxime, 22 hours reflux. Nitrile Recovered.	Ketimine Hydrochloride VIII E.S.N.(11) No oxime formed. Nitrile Recovered.
2-phenyl-2-ethylpentane nitrile	Ketimine Hydrochloride VI E.S.N.(8) Oxime, 22 hours reflux.	Ketimine and Ketimine Hydrochloride VII E.S.N.(11) Oxime, 22 hours reflux.	Ketimine IX E.S.N.(14) No oxime formed
2-phenyl-2-ethyl-3-methylpentane nitrile	Ketimine Hydrochloride XII E.S.N.(8) No oxime formed	Ketimine Hydrochloride XIII E.S.N.(11) No oxime formed Nitrile Recovered.	Ketimine XIV E.S.N.(14) No oxime formed Nitrile Recovered.
2-phenyl-2-ethyl-3-methylpentane nitrile.	Ketimine X E.S.N.(11) No oxime formed	Ketimine XI E.S.N.(14) No oxime formed Nitrile Recovered.	No reaction XV E.S.N.(17) Nitrile Recovered.

E.S.N. = Effective Six Number of the Ketimine
The numbers given for the products in this figure are the same as for the corresponding compounds in Figure II, III, IVa and IVb.

CONCLUSIONS

1. Highly hindered nitriles which could not be hydrolyzed by other workers in this laboratory react with aromatic Grignard reagents to give good yields of ketimines and ketimine hydrochlorides.

2. In general, the products of the reactions go from ketone to ketimine to ketimine hydrochloride as the effective six-number of the intermediate ketimines increases.

3. When the effective six-number of the ketimine is 8 or larger, the ketone is no longer obtained.

4. Conversion of the less hindered ketimines and ketimine hydrochlorides to oximes is possible. However, the relative reactivity of certain ketimine or ketimine hydrochlorides varies from that expected on the basis of effective six-number. The substitution of the second methyl group on a beta carbon appears to offer a greater steric hindrance than when substituted at other positions which give a corresponding increase in the effective six-number. The oxime could not be obtained in any case where the effective six-number of the ketimine was 14.

5. In most of the reactions of nitriles having an alpha hydrogen atom, starting nitrile was recovered. This is believed to be due to the reduction of the organic radical of the Grignard reagent by the labile hydrogen, followed by recovery of the nitrile from the nitrile salt upon hydrolysis.

6. From the reactions of 2-phenylbutanenitrile with phenyl and o-tolylmagnesium bromide, it appears that the reaction conditions used have a greater effect as the steric hindrance increases.

7. Reaction does not occur between 2-phenyl-2-ethyl-3-methylpentanenitrile and mesitylmagnesium bromide under the reaction conditions used in this study.

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