THE BEHAVIOR OF CONJUGATED SYSTEMS CONTAINING AROMATIC DOUBLE BONDS TOWARDS ORGANOMETALLIC REAGENTS

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CONTENTS

I. INTRODUCTION

Involvement of the double bonds of aromatic nuclei in reactions with Grignard reagents was first observed in 1929 by Gilman, Kirby, and Kinney (31) with benzophenone anil. Since that time similar results have been reported for aryl ketones and nitriles. In view of the considerable extent to which the field has been developed and the current interest in this type of reaction, a review of the progress that has been made seems timely.

It is the purpose of the present paper to present a survey of the work with Grignard reagents as well as with certain other organometallic compounds.

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[2] Some additions made October 19, 1949.

II. CONJUGATE ADDITION

A. 1,4-ADDITION

1. *To systems containing the grouping* $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=N-$

(a) *Anils:* The report of Gilman, Kirby, and Kinney (31) involved benzophenone anil (I) and phenylmagnesium bromide. They observed the formation of o-phenylbenzohydrylaniline (II) and suggested that the reaction proceeded with the disruption and regeneration of the aromatic double bond. The same compound was obtained by allowing the Grignard reagent to act upon phenyl isocyanate or phenyl isothiocyanate and was synthesized unequivocally by the
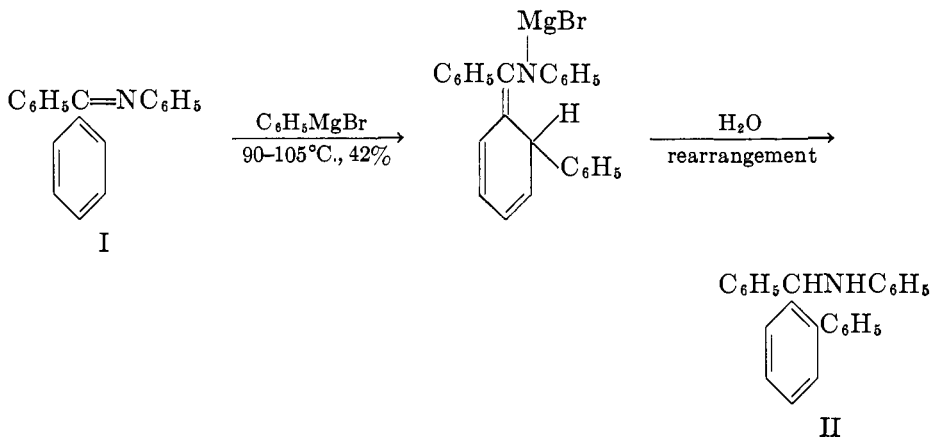
interaction of o-biphenylylmagnesium iodide and benzalaniline. Later benzophenone oxime was shown by Campbell and McKenna (8) to yield the same amine (II) on treatment with the phenyl Grignard reagent.

Very recently, Gilman and Morton (32) have shown that a similar course was taken in the "forced" addition of phenylmagnesium bromide to benzophenone β-naphthil (III); no reaction involving the naphthalene nucleus could be detected. The product (IV) was identical with that from the reaction of o-biphenylyl magnesium iodide with benzal-β-naphthylamine (V).
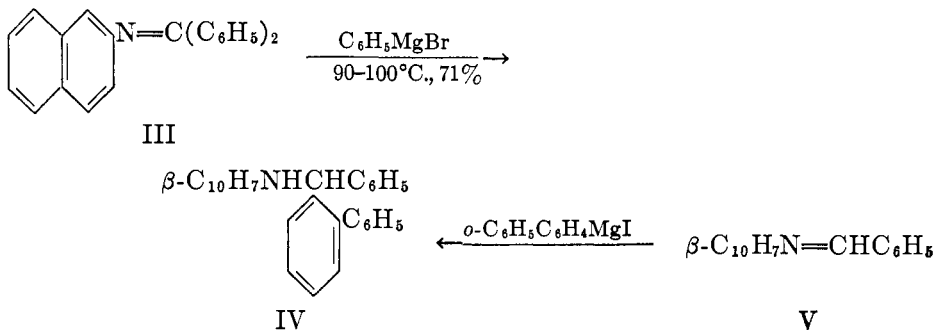
(b) *Heterocycles:* A slightly different type of activation by a hetero atom has been observed to result in 1,4-addition to a ring–chain system. Hoffman, Farlow, and Fuson (34) added phenylmagnesium bromide to benzalquinaldine (VI) and *p*-chlorobenzalquinaldine (VIII) to give α-benzohydrylquinaldine (VII) and the *p*-chloro analog (IX), respectively. The first product was also obtained by the addition of benze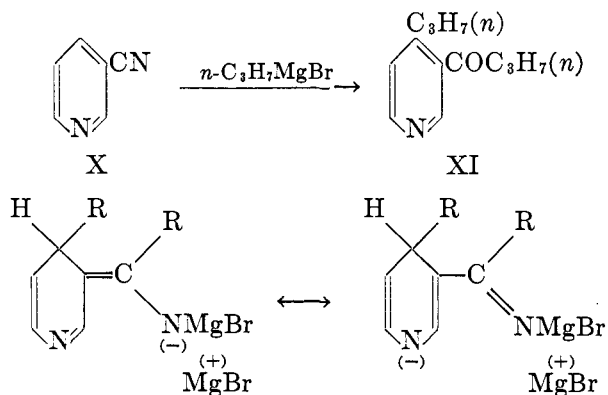ne in the presence of aluminum chloride. This compound (VII) has recently been obtained by Gilman and Gainer (30a) in quantitative yield from benzalquinaldine by the action of phenyllithium.

$$\text{VI} \quad \xrightarrow[\substack{\text{or} \\ C_6H_6,\ AlCl_3}]{\substack{C_6H_5MgBr \\ 70\%}} \quad \text{VII}$$

Quinoline-$CH{=}CHC_6H_5$ VI $\xrightarrow{}$ Quinoline-$CH_2CH(C_6H_5)_2$ VII

$$\text{VIII} \quad \xrightarrow[64\%]{C_6H_5MgBr} \quad \text{IX}$$

Quinoline-$CH{=}CHC_6H_4Cl$ VIII $\xrightarrow{}$ Quinoline-$CH_2CH(C_6H_5)C_6H_4Cl$ IX
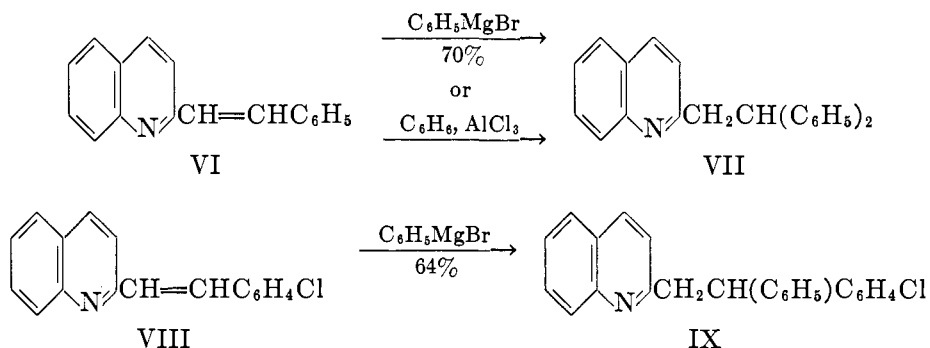
Recently the addition of the *n*-propyl Grignard reagent to nicotinonitrile (X) has been observed to yield *n*-propyl 4-*n*-propyl-3-pyridyl ketone (XI) (12). It may be pointed out that the probable intermediate would be capable of resonance.

$$\text{X} \quad \xrightarrow{n\text{-}C_3H_7MgBr} \quad \text{XI}$$

Pyridine-CN X $\xrightarrow{}$ Pyridine-$C_3H_7(n),\ COC_3H_7(n)$ XI

$$\text{(intermediate)}_1 \quad \longleftrightarrow \quad \text{(intermediate)}_2$$

Acridine and quinoline also contain the system $-\overset{|}{C}{=}\overset{|}{C}-\overset{|}{C}{=}N-$, and several authors have investigated the addition of organometallic reagents to this type of compound. It was reported by Freund (13) in 1904 that the reaction of acridine methiodide (XII) with ethylmagnesium iodide yielded 9-ethyl-10-methyl-9-phenyl-9,10-dihydroacridine (XIII). Later Bergmann, Blum-Bergmann, and von Christiani (6) allowed acridine itself to react with phenylmagnesium bromide and aryllithium compounds. The primary product in all cases was the corresponding 9-aryl-9,10-dihydroacridine (XIV), although this was partially converted to the

aromatic compound by "secondary oxidation" in the case of reaction with the Grignard reagent. Ziegler and Zeiser (51) also found that butyllithium added similarly to acridine, and that quinoline reacted with either this reagent or

$Ar = C_6H_5$, p-$CH_3OC_6H_4$, o- and m-$CH_3C_6H_4$, α-$C_{10}H_7$.
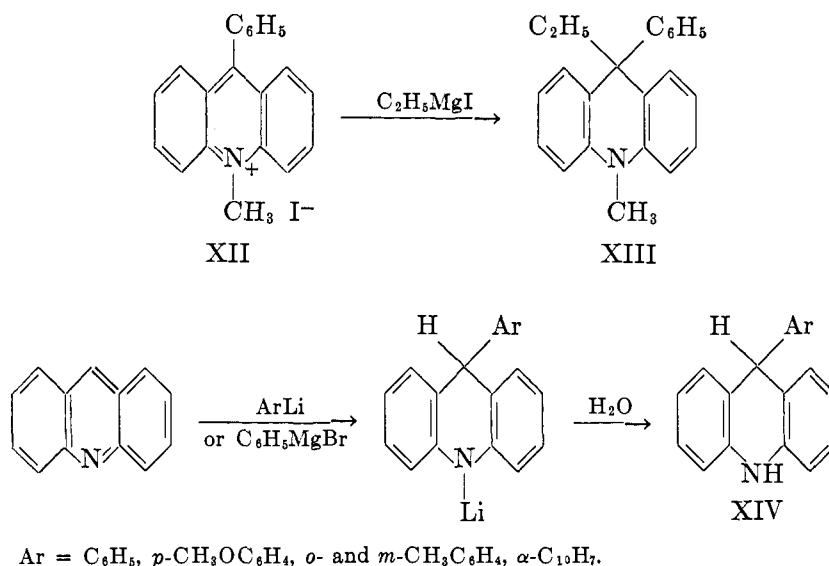
phenyllithium to give a small amount of the corresponding 4-substituted compound isolated as the picrate, as well as the normal 2-substituted compound. Similar results were reported by Bergmann and Rosenthal (7), who used benzylmagnesium chloride. Acridine gave the expected products; quinoline was reported
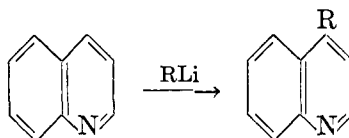

$R = n$-C_4H_9, C_6H_5.

to give both the 4-benzyl (XV) and the 2,4-dibenzyl (XVI) derivative, in addition to the 2-benzyl derivative. In view of the recent reports that phenyllithium adds in the 1,2 manner to 2-phenylquinoline (30), the identity of the dibenzylquinoline might be questioned. Bergmann and Rosenthal also reported the 1,4-
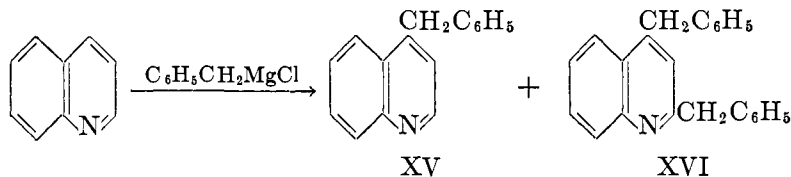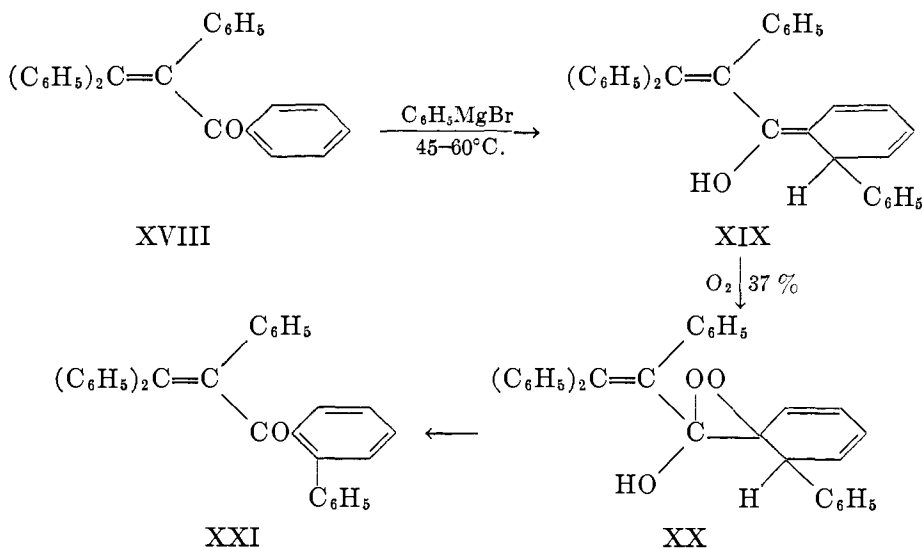
addition of benzhydrylsodium to acridine, the product being 9-benzhydryl-9,10-dihydroacridine (XVII).
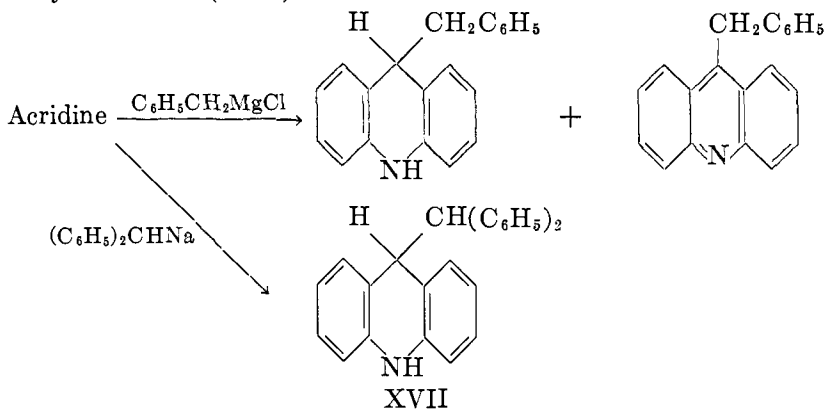
2. *To systems containing the grouping* $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$

(a) *Polycyclic ketones:* o-Arylation of an aromatic ketone was first observed by Kohler and Nygaard (43), who treated the α,β-ethylenic compound XVIII with the phenyl Grignard reagent and found to their surprise that the reaction in-

volved not the extracyclic unsaturation but a double bond in an aromatic ring. They isolated the peroxide (XX) of the enol (XIX) in 37 per cent yield and decomposed it to the corresponding aromatic ketone (XXI), from which by oxidative cleavage were obtained benzophenone and o-phenylbenzil.

This type of addition was soon extended to fused polycyclic systems. Almost simultaneously Allen and Gilman (1) and Dufraisse and Horclois (11) announced the double 1,4-addition of phenylmagnesium bromide to naphthacenequinone

(XXII). The resulting stereoisomeric tetrahydro ketones (XXIII) were converted to rubrene (XXV) by the former workers, whose formulations are shown. It is of interest that the intermediate 6,11-diphenyl-5,12-naphthacenequinone (XXIV) was unaffected by the phenyl Grignard reagent but added phenyllithium
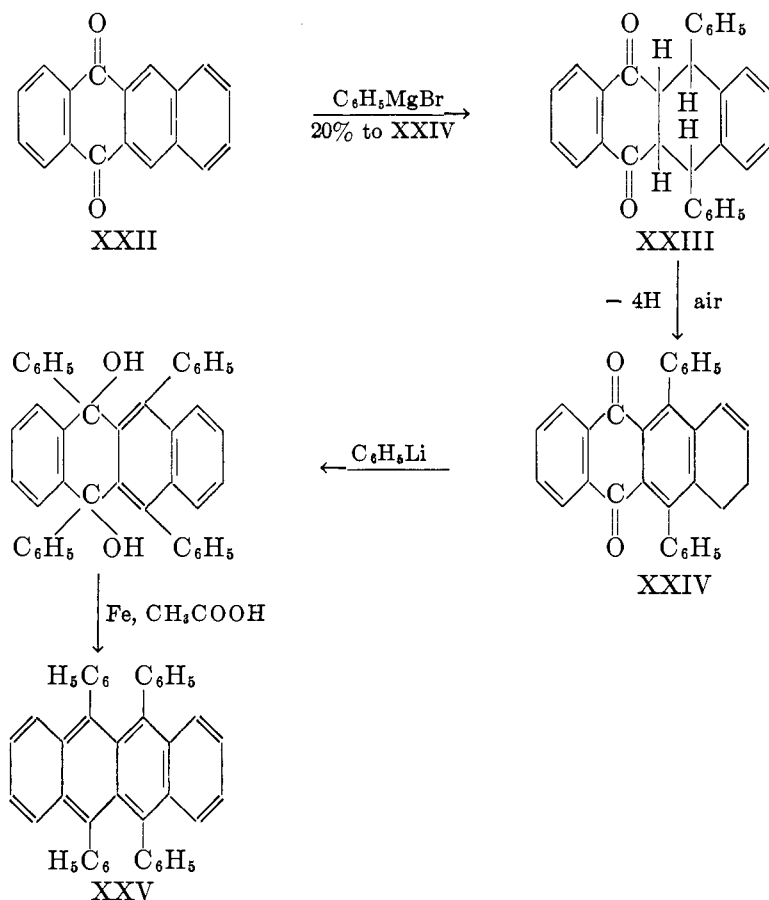

readily. This compound (XXIV) was also converted by fusion with potassium hydroxide to benzoic and 1,4-diphenyl-2-naphthoic acids, a proof of the double 1,4-addition.

Quite similar results were obtained by Allen and Bell (2) with 6,13-pentacene-quinone (XXVI). This compound reacted with phenylmagnesium bromide to give as the major product (70 per cent) the normal diol; however, the tetra-hydro ketone (XXVII) resulting from a double 1,4-addition was also isolated. Oxidation of the compound gave the fully aromatic 5,14-diphenyl-6,13-penta-cenequinone (XXVIII), which was also found to undergo a similar double conjugate addition of the same reagent to give a second tetrahydro ketone (XXIX).

Another example of a fused polynuclear ketone which undergoes 1,4-addition of Grignard reagents is benzanthrone (XXX). Both Clar (10) and Nakanishi (45) obtained what they believed to be a 1,6-addition product with the phenyl

Grignard reagent, but these claims have been disproved (4, 9). Charrier and Ghigi (9) did show that the methyl and ethyl reagents added in the 1,4 manner.
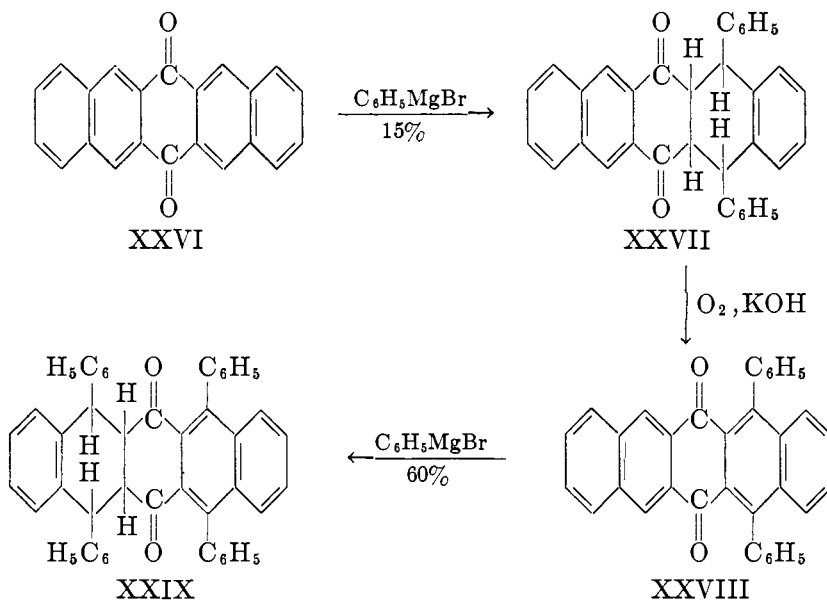
The reaction of benzanthrone with Grignard reagents was later investigated more exhaustively by Allen and Overbaugh (3), who showed that the reaction took the following path:
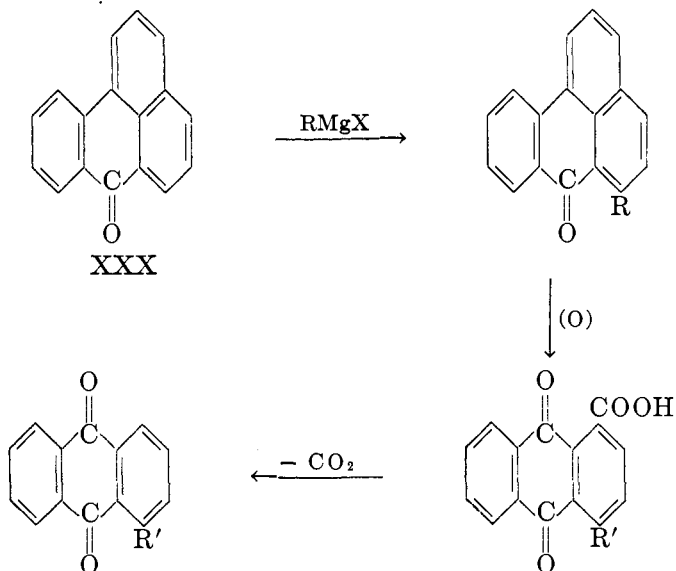

R = C_6H_5 (42%), $C_6H_5CH_2$ (22%),
    n-C_6H_{13} (61%), cyclo-C_6H_{11} (15%).
R' = C_6H_5, C_6H_5CO.

They considered their failure to isolate dihydro compounds as due probably to simultaneous oxidation and reduction, stating that yields were in accord with this assumption and that tarry by-products of these reactions might be converted to additional amounts of the substitution products by treatment with quinone. Only the *t*-butyl Grignard reagent added to the ketone in the 1,2 manner, as it did to an analog, *bz*-1-phenylbenzanthrone (XXXI). These authors found an indication of the generality of the conjugate addition by examining the behavior of the latter compound with other Grignard reagents (4).
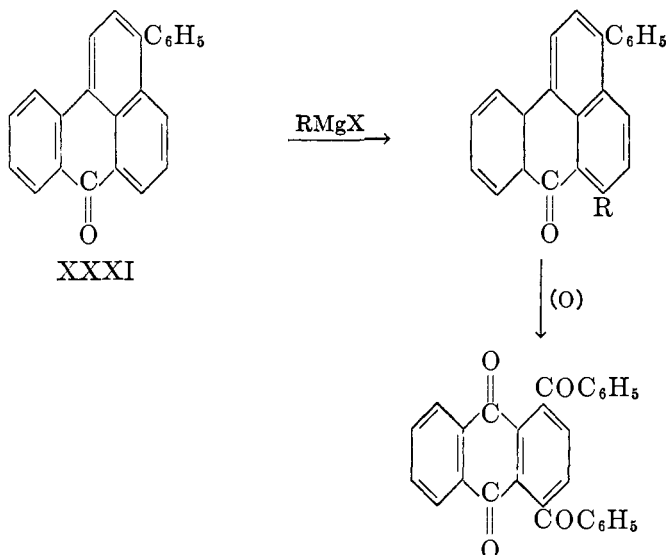
$$R = C_6H_5CH_2 \ (19\%), \ C_6H_5 \ (45\%),$$
$$C_6H_5CH_2CH_2 \ (51\%), \ cyclo-C_6H_{11} \ (22\%),$$
$$C_2H_5 \ (35\%), \ n-C_4H_9 \ (53\%), \ n-C_6H_{13} \ (47\%),$$
$$C_6H_5CH{=}CH \ (6\%).$$

A compound which possesses the affected portion of the structure of benzanthrone is 8-phenyl-*peri*-naphthindandione-7,9 (XXXII). This and a related substance (XXXIV) have been found by Koelsch and Rosenwald (41) to undergo 1,4-addition of both the Grignard reagent and phenyllithium. These and related reactions of the products are given on page 501.

The transformation of XXXII to XXXIII proceeded in good yield with phenyllithium, but only small yields were isolated with phenylmagnesium bromide; the reverse was true of the change of XXXIV to XXXV. 1,8-Diphenyl-*peri*-naphthindandione-7,9 (XXXVI) was oxidized to 2-phenylnaphthalic anhydride, which underwent ring closure and decarboxylation to the known 1,2-benzofluorenone.

Another example of conjugate addition to this type of system was found by Koelsch and Rosenwald (42) in 7-ethoxy-*peri*-naphthindenone-9 (XXXVII), which was shown to add phenylmagnesium bromide in the 1,4 manner.
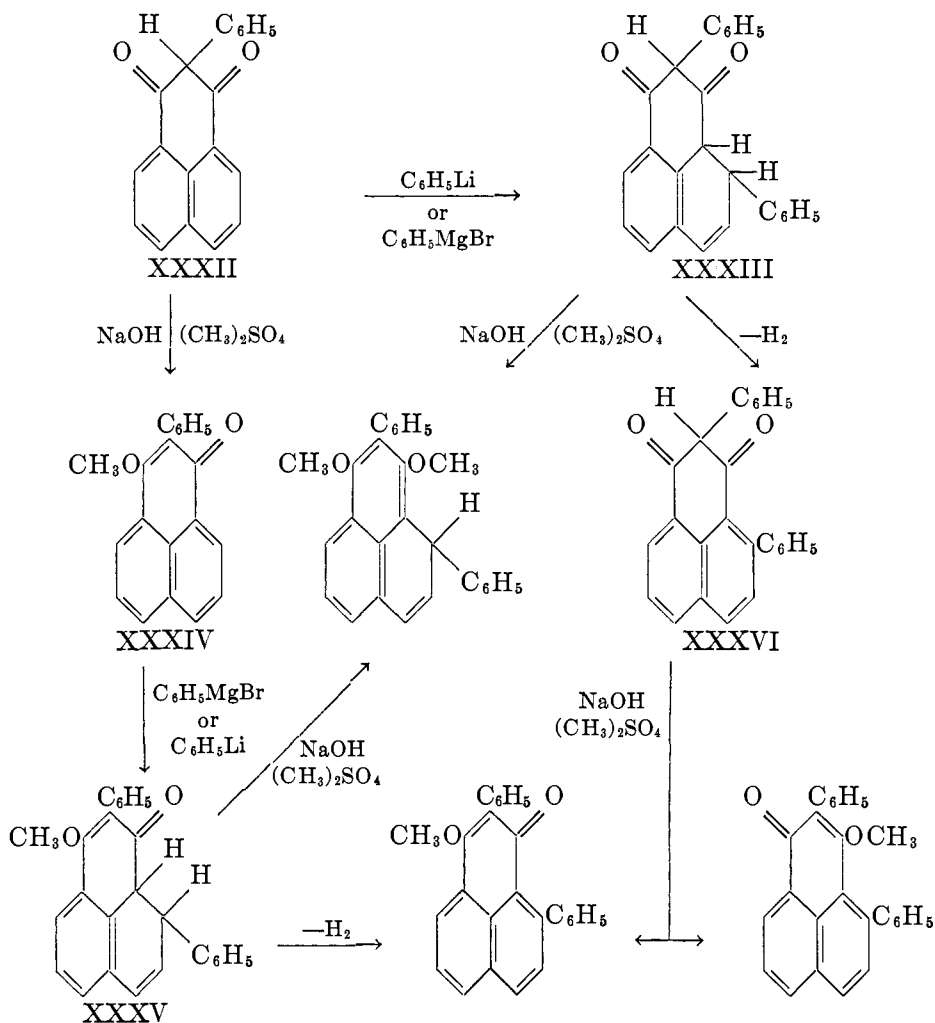
This study was extended by Geissman and Morris (29) to 8,8-dimethyl-*peri*-naphthindandione-7,9 (XXXIX), which underwent simultaneous 1,2- and 1,4-addition of two molecules of the phenyl reagent. Under milder conditions compounds resulting from either single or double normal addition could be obtained as the major product.

Similar behavior was later observed by Koelsch and Anthes (40) with the simpler *peri*-naphthenone-7 (XL). The enolic (phenolic) dihydro intermediate was dehydrogenated by distillation at reduced pressure to give 1-phenyl-*peri*-naphthenone-7 (XLI), which was also oxidized to 2-phenylnaphthalic anhydride. It is to be noted that, in this example of 1,4-addition, reaction occurred with an aromatic double bond rather than with the apparently simple ethylenic linkage between the 8 and 9 positions.
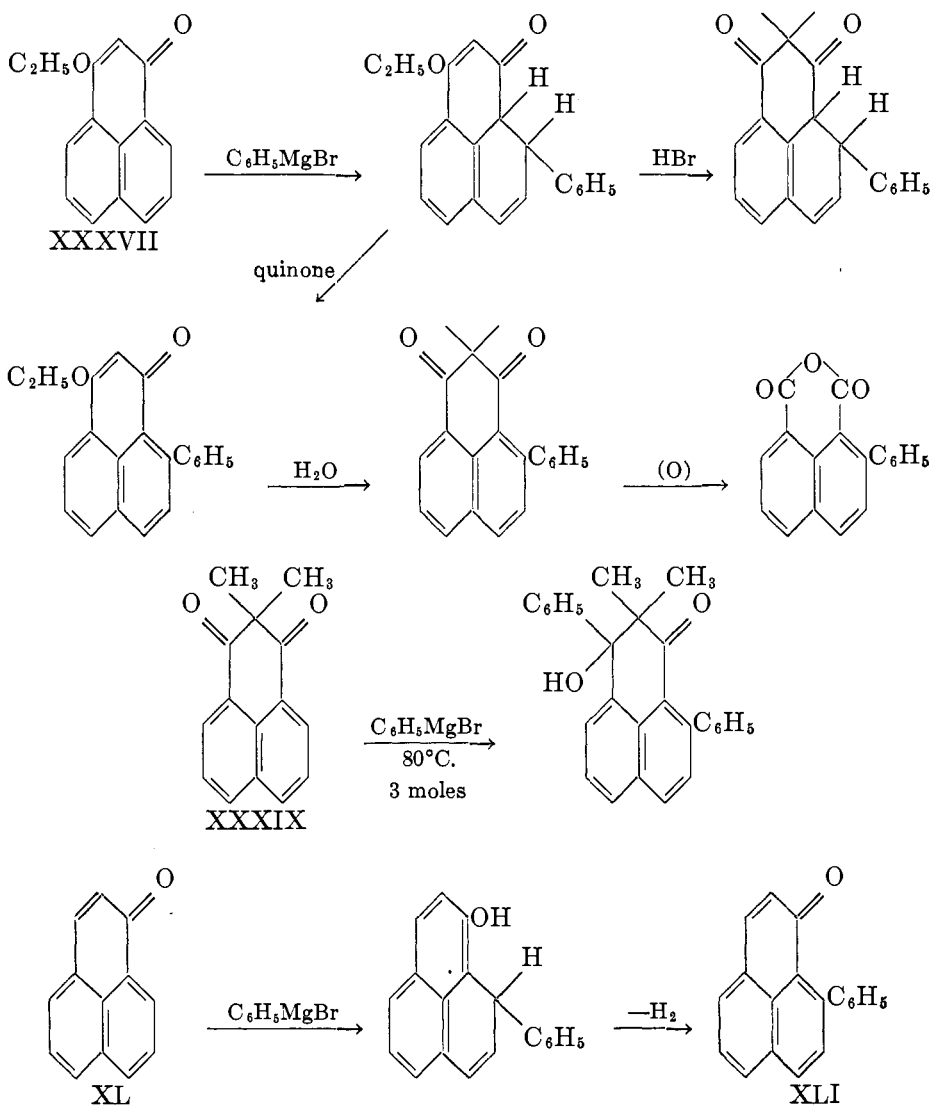
(b) *Simple hindered diaryl ketones: i. Involving the furan nucleus*—There are
two examples in which conjugate addition of a Grignard reagent disrupted a furan
nucleus. Although 2-benzoylbenzofuran adds these reagents in the normal 1,2
manner, Fuson, Kaiser, and Speck (22) used the hindering effect of the mesityl
(Mes or 2,4,6-trimethylphenyl) and tipyl (Tip or 2,4,6-triisopropylphenyl)
radicals to suppress this course with mesityl 2-benzofuryl (XLII) and tipyl
2-benzofuryl (XLIII) ketones and obtained the corresponding 2-aroyl-3-phenyl-
2,3-dihydrobenzofurans (XLV). If the intermediate enols were treated with

oxygen, the resulting enol peroxides decomposed to yield, in both cases, 3-phenyl-isocoumaranone (XLIV) as well as mesitoic or triisopropylbenzoic acid.

XLII: Ar = Mes
XLIII: Ar = Tip

XLIV

XLV
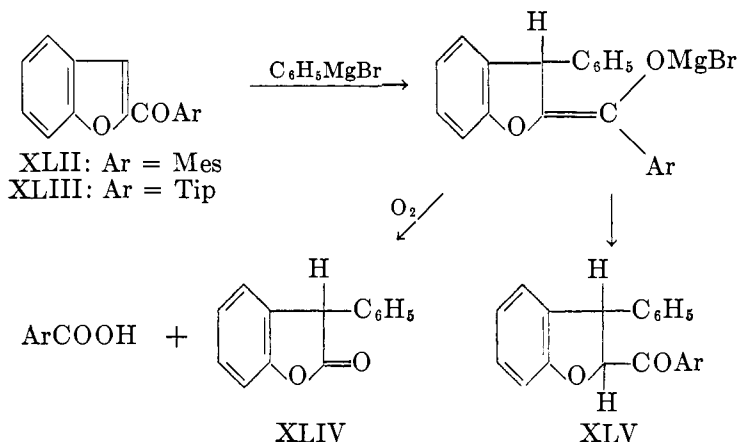
Lutz and Reveley (44) treated 3-mesitoyl-5-mesityl-2-methyl-4-phenylfuran (XLV) with methylmagnesium iodide and obtained the product which would result by a process of 1,4-addition followed by fission of the ether linkage, 2-*t*-butyl-1,4-dimesityl-3-phenyl-1,4-butanedione (XLVI). This compound was prepared by two independent methods,—hydrogenation of the corresponding butene and 1,4-addition of phenylmagnesium bromide to 2-*t*-butyl-1,4-dimesityl-2-butene-1,4-dione (XLVII).

XLV

$$C_6H_5C\text{---}C\text{===}C$$

$$MesC \qquad C(CH_3)_3 \quad Mes$$

$$OMgI$$

$$H_2O \downarrow \uparrow CH_3MgI$$

$$MesCOCH\text{===}CCOMes \xrightarrow{C_6H_5MgBr} MesCOCH\text{---}CHCOMes$$

$$\underset{\text{XLVII}}{\overset{C(CH_3)_3}{|}} \qquad \underset{\text{XLVI}}{\overset{C_6H_5 \quad C(CH_3)_3}{|\qquad|}}$$
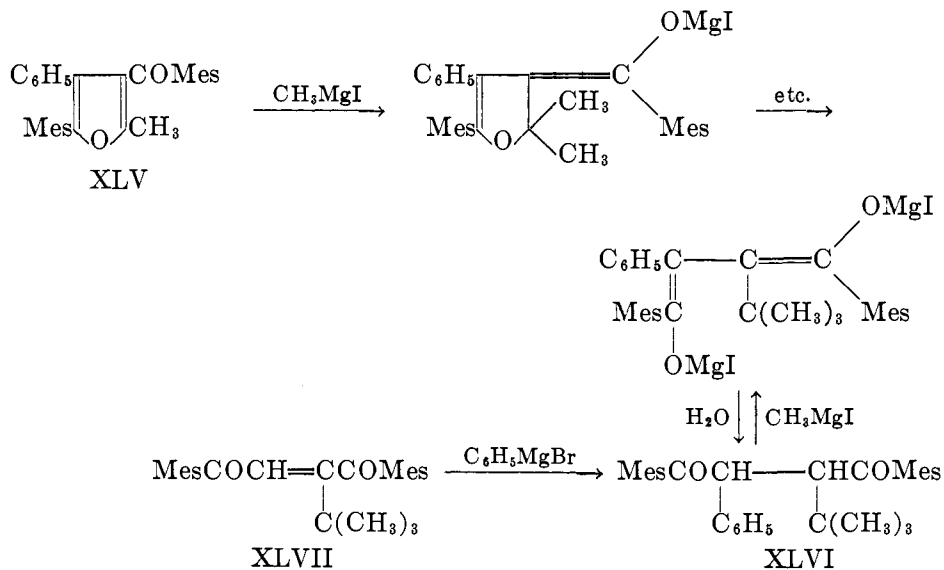
ii. Involving benzenoid nuclei—This use of steric hindrance to prevent the 1,2-addition of Grignard reagents while still retaining the powerful activating effect

of the carbonyl group has proved extremely fruitful, leading to the discovery of a number of examples of the conjugate addition of organometallic compounds into aromatic nuclei. Fuson, Botorff, Foster, and Speck (16, 17) investigated the reaction of esters of mesitoic acid with Grignard reagents. With alkyl mesitoates
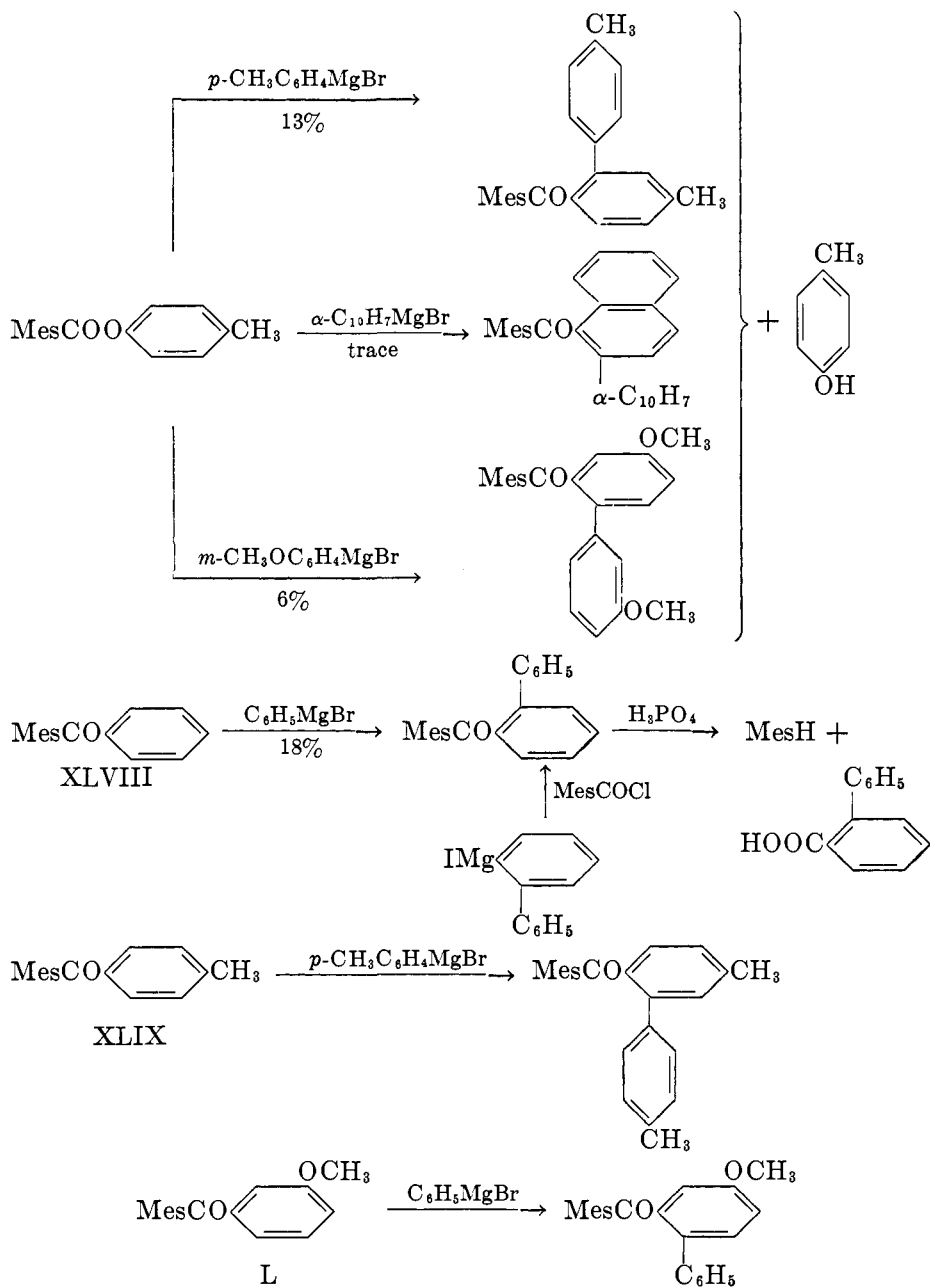
only cleavage resulted; aryl esters, however, gave with aryl reagents the products resulting from 1,4-addition to the supposedly intermediate ketones. The yields of p-cresol varied from 40 to 95 per cent. With a hindered Grignard reagent,

$$MesCO\text{—} \xrightarrow{C_6H_5MgBr} \left[MesC\text{=}\underset{OH}{} \underset{H}{} \underset{C_6H_5}{} \right] \xrightarrow{O_2}$$

LI

$$MesCOOH + HO\text{—}\underset{C_6H_5}{}$$

LII
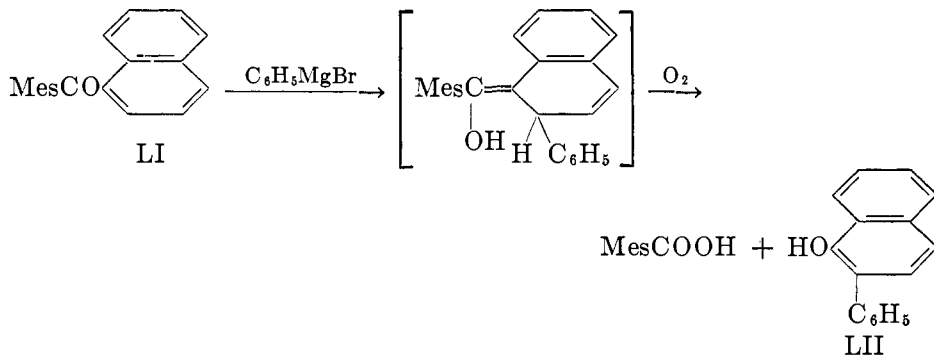
mesitylmagnesium bromide, only small amounts of dimesityl ketone and mesitil were isolated. These observations led logically to 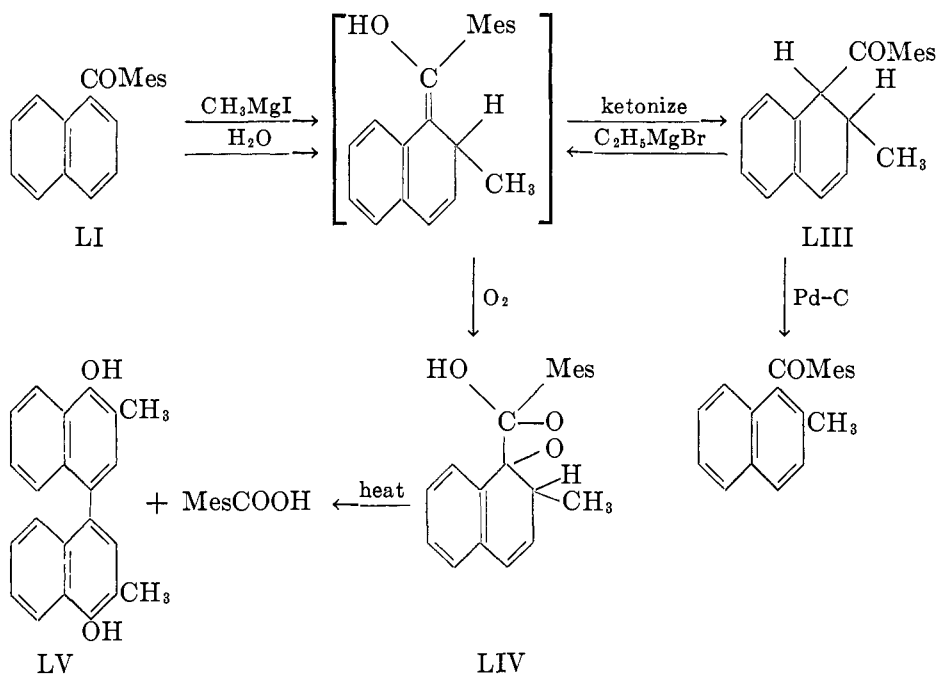the use of the mesityl ketones themselves (14). Mesityl phenyl ketone (XLVIII), mesityl p-tolyl ketone (XLIX), and mesityl m-methoxyphenyl ketone (L) reacted to give the o-arylated ketones. In the first case the structure of the product was proved by synthesis from 2-biphenylylmagnesium iodide and by cleavage with acid to o-phenyl-benzoic acid. Mesityl 1-naphthyl ketone (LI) formed an intermediate enol which was cleaved by air to 2-phenyl-1-naphthol (LII) and mesitoic acid. This ketone

$$\text{COMes} \xrightarrow[H_2O]{CH_3MgI} \left[\underset{C}{\overset{HO\quad Mes}{}} \underset{CH_3}{\overset{H}{}} \right] \underset{C_2H_5MgBr}{\overset{ketonize}{\rightleftarrows}} \underset{CH_3}{\overset{H\quad COMes}{}}$$

LI   LIII

$$\downarrow O_2 \qquad\qquad \downarrow Pd\text{-}C$$

$$\underset{LV}{\overset{OH\quad CH_3}{} + MesCOOH} \xleftarrow{heat} \underset{LIV}{\overset{HO\quad Mes}{C\text{—}O}} \qquad \underset{}{\overset{COMes}{CH_3}}$$
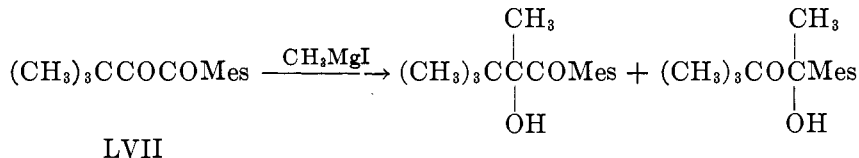
LV   LIV

(LI) was also treated with methylmagnesium iodide by Fuson, McKusick, and Spangler (25), who showed that dihydro ketones are probably intermediates in many similar reactions by isolating such compounds. They are quite stable in these cases and some of their more interesting reactions are shown in the diagram. 1,2-Dihydro-1-mesitoyl-2-methylnaphthalene (LIII) formed an acetate from which it could be regenerated by hydrolysis and liberated one mole of methane in the Grignard machine. This suggested that the enol was quite stable, and it was treated with oxygen to form a crystalline peroxide (LIV) which decomposed to the known 4,4'-dihydroxy-3,3'-dimethyl-1,1'-dinaphthol (LV).
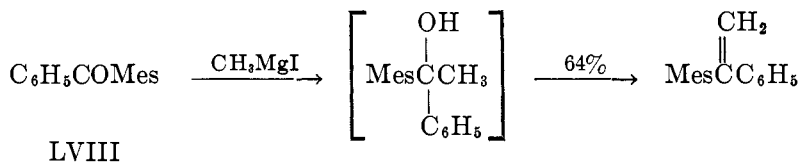
A similar series of transformations was observed with the isomeric mesityl 2-naphthyl ketone (LVI), the yield of 74 per cent in one run being one of the highest ever observed in a Grignard reaction involving an aromatic nucleus.
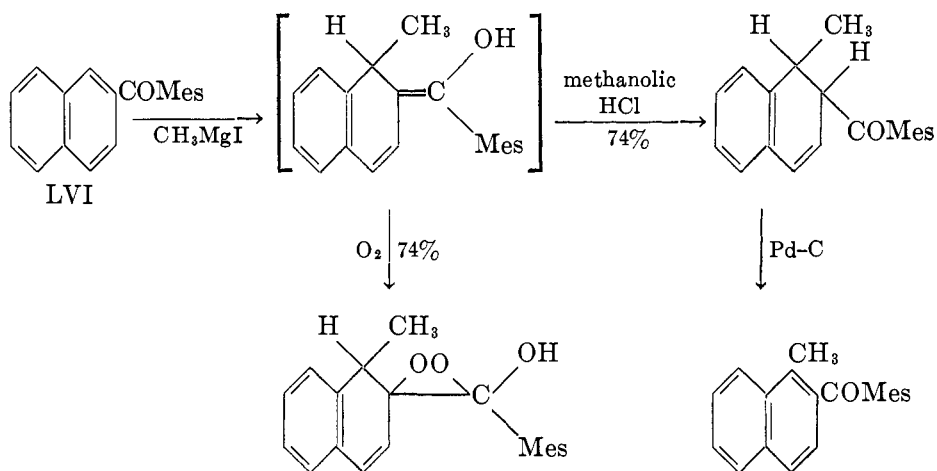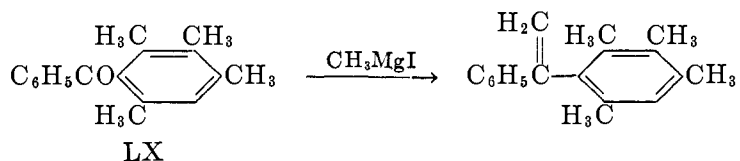

It is interesting that this type of steric hindrance is not always effective in preventing normal addition. Fuson and Robertson (26) first observed 1,2-addition to a mesityl ketone, in this case t-butyl mesityl diketone (LVII), which added the methyl Grignard reagent to give both possible products. Later Young and Roberts (50) observed this type of addition with s-butenylmagnesium bromide

$$(CH_3)_3CCOCOMes \xrightarrow{\;CH_3MgI\;} (CH_3)_3C\underset{OH}{\overset{CH_3}{C}}CCOMes + (CH_3)_3CO\underset{OH}{\overset{CH_3}{C}}Mes$$

LVII

and benzylmagnesium chloride to acetomesitylene. Mesityl phenyl ketone (LVIII), isoduryl phenyl ketone (LX), and mesityl p-tolyl ketone (LIX) were

$$C_6H_5COMes \xrightarrow{\;CH_3MgI\;} \left[Mes\underset{C_6H_5}{\overset{OH}{C}}CH_3 \right] \xrightarrow{\;64\%\;} Mes\overset{CH_2}{\overset{\|}{C}}C_6H_5$$

LVIII

also found by Fuson, Armstrong, Wallace, and Kneisley (15) to form the corresponding ethylenes, presumably by dehydration of the intermediate carbinols.
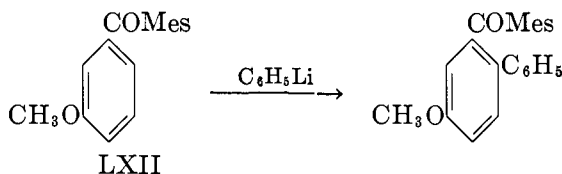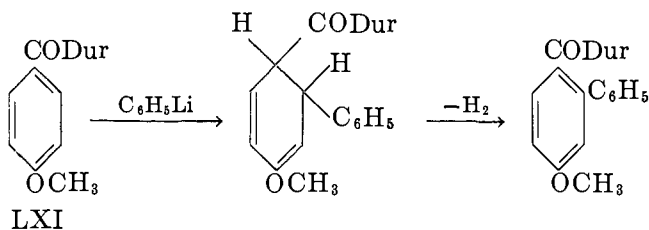
$$CH_3\text{—}\langle\text{—}\rangle\text{—}COMes \xrightarrow{CH_3MgI} CH_3\text{—}\langle\text{—}\rangle\text{—}\overset{CH_2}{\underset{\|}{C}}Mes$$

LIX

$$C_6H_5CO\text{—}\overset{H_3C\quad CH_3}{\underset{H_3C}{\langle\text{—}\rangle}}\text{—}CH_3 \xrightarrow{CH_3MgI} C_6H_5\overset{H_2C}{\underset{\|}{C}}\text{—}\overset{H_3C\quad CH_3}{\underset{H_3C}{\langle\text{—}\rangle}}\text{—}CH_3$$

LX
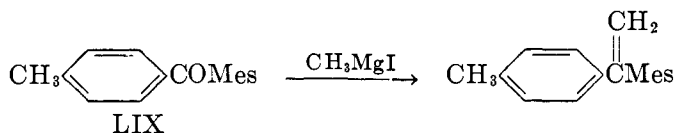
Two examples of the 1,4-addition of phenyllithium have already been mentioned. With this reagent the use of a hindering radical, e.g., mesityl, is less effective than in the case of the Grignard reagent, but with *p*-anisyl duryl ketone (LXI) and *m*-anisyl mesityl ketone (LXII) 1,4-addition was observed (20). The product of the latter reaction was identical with that previously obtained by the action of phenylmagnesium bromide (27). Strangely enough, mesityl 3,4-dimethoxyphenyl ketone (LXIII) and mesityl 2-methoxy-5-methylphenyl ketone (LXIV) yielded only the products of 1,2-addition, illustrating the strong tend-

CODur
OCH₃
LXI
$\xrightarrow{C_6H_5Li}$
H   CODur
    H
    C₆H₅
OCH₃
$\xrightarrow{-H_2}$
CODur
    C₆H₅
OCH₃

COMes
CH₃O
LXII
$\xrightarrow{C_6H_5Li}$
COMes
    C₆H₅
CH₃O

COMes
OCH₃
OCH₃
LXIII

COMes
    OCH₃
H₃C
LXIV

ency of phenyllithium to react in this manner.

Other examples of 1,4-addition to aromatic systems will be discussed later (page 515 ff.) in connection with the replacement of functional groups.
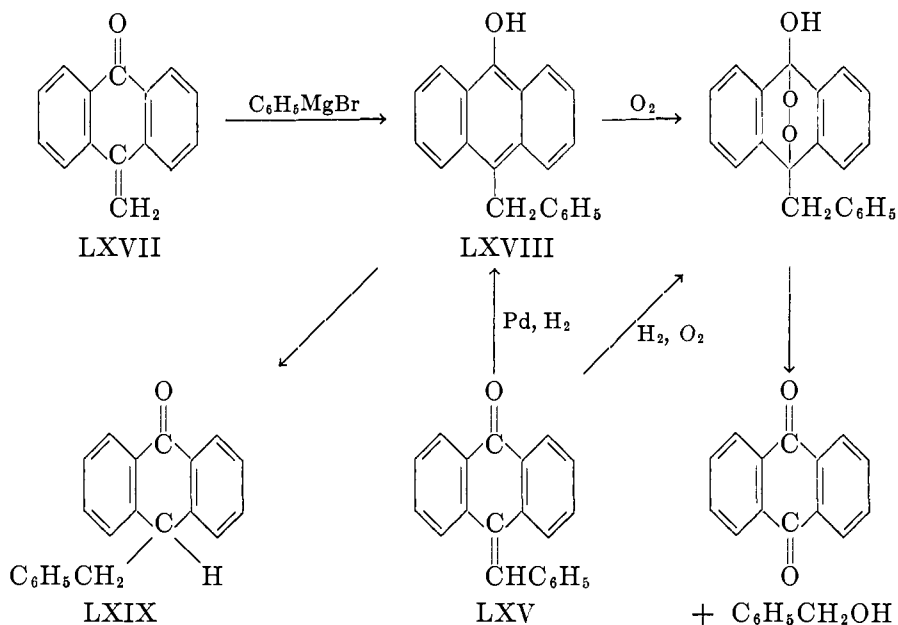
B. 1,6-ADDITION

1. To fuchsones

Claims of 1,6-addition of the Grignard reagent to aromatic systems were first advanced by both Clar (10) and Nakanishi (45) in connection with the reaction of benzanthrone with the phenyl reagent. As has been mentioned, these examples have been shown to be cases of 1,4-addition (3). However, Nakanishi also claimed to have isolated anthrafuchsone (LXVI) from the reaction of "benzylideneanthrone" or benzalanthrone (LXV) with this reagent. The reaction was subsequently investigated by Julian and Magnani (39) and by Julian and Cole (36), who were unable to duplicate these results. Only 1,2-adducts were isolated by these workers with the methyl and phenyl reagents (36, 37, 39). However, 1,6-addition was observed by Julian and coworkers with other fuchsone-like
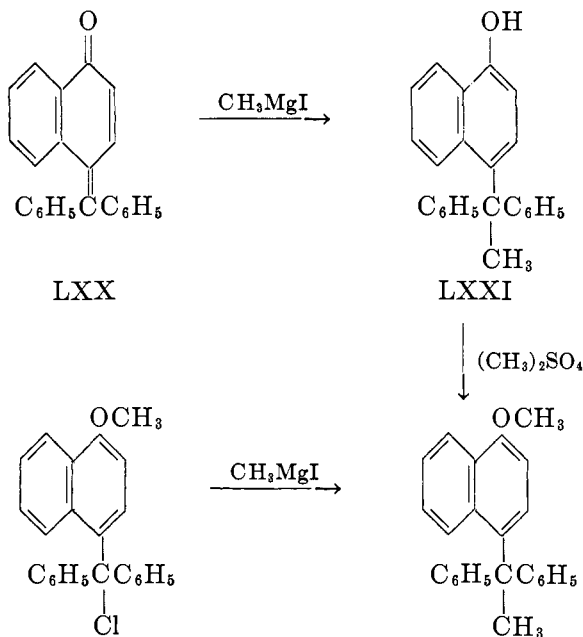

R = CH₃, C₆H₅.

R = CH_3, C_6H_5.
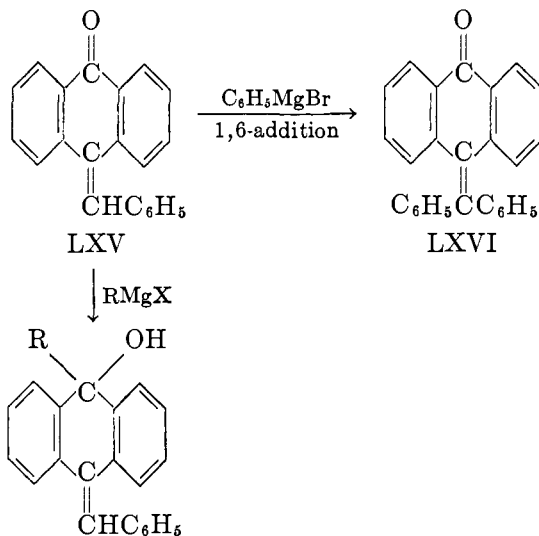
compounds. This reaction, although not resulting in substitution of a Grignard radical for hydrogen in an aromatic nucleus, is probably most accurately considered as involving addition to a system of which the "aromatic" ethylenic linkage between atoms 3 and 4 is a vital part. With methyleneanthrone (LXVII) the impure product was 10-benzylanthranol (LXVIII), characterized as a peroxide which decomposed into anthraquinone and benzyl alcohol (36, 39). The same peroxide was later synthesized by the simultaneous addition of hydrogen and oxygen to benzalanthrone (LXV), while hydrogen alone gave the anthranol (LXVIII), which rearranged to 10-benzylanthrone (LXIX) (36). The methyl and ethyl reagents were also added to methyleneanthrone; the products, isolated as peroxides, similarly decomposed yielding ethyl and propyl alcohols, respectively. Anthrafuchsone reacted with methylmagnesium iodide in only the 1,2 manner (38); however, naphthofuchsone (LXX) underwent 1,6-addition with this re-

agent. The structure of the adduct (LXXI) was proved by a coupling reaction with the same reagent. This work is an extension of a similar series of experiments

LXVII

C_6H_5MgBr →

LXVIII

O_2 →

$CH_2C_6H_5$

$CH_2C_6H_5$

Pd, H_2

H_2, O_2

$C_6H_5CH_2$ H

LXIX

CHC_6H_5

LXV

$+ C_6H_5CH_2OH$

proving the nature of the product (LXXIII) of the reaction of fuchsone (LXXII) itself with the methyl Grignard reagent. Baeyer and Villiger (5) originally pro-

$C_6H_5CC_6H_5$

LXX

CH_3MgI →

OH

$C_6H_5CC_6H_5$

CH_3

LXXI

$(CH_3)_2SO_4$

OCH_3

$C_6H_5CC_6H_5$

Cl

CH_3MgI →

OCH_3

$C_6H_5CC_6H_5$

CH_3

posed this course for the reaction in 1903, and Julian and Gist (38) were led to carry out a proof of structure analogous to that shown above. It may be pointed out that in this example and that of naphthofuchsone a benzenoid ring is generated by a process of 1,6-addition, while in the case of anthrafuchsone conjugate

LXXII   LXXIII
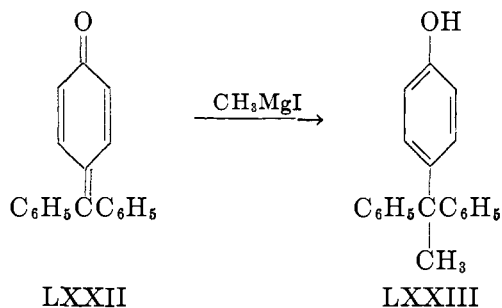
reaction could not form an additional aromatic system.

2. To hindered diaryl ketones

That 1,6-addition of Grignard reagents occurs with much simpler diaryl ketones has been shown by Fuson and coworkers. By taking advantage of the hindering effect of the duryl (2,3,5,6-tetramethylphenyl, abbreviated as Dur) radical to prevent 1,2-addition, Fuson and McKusick (23) observed conjugate reaction of the benzyl and t-butyl Grignard reagents with duryl phenyl ketone (LXXIV). These and related transformations are illustrated in the diagram.
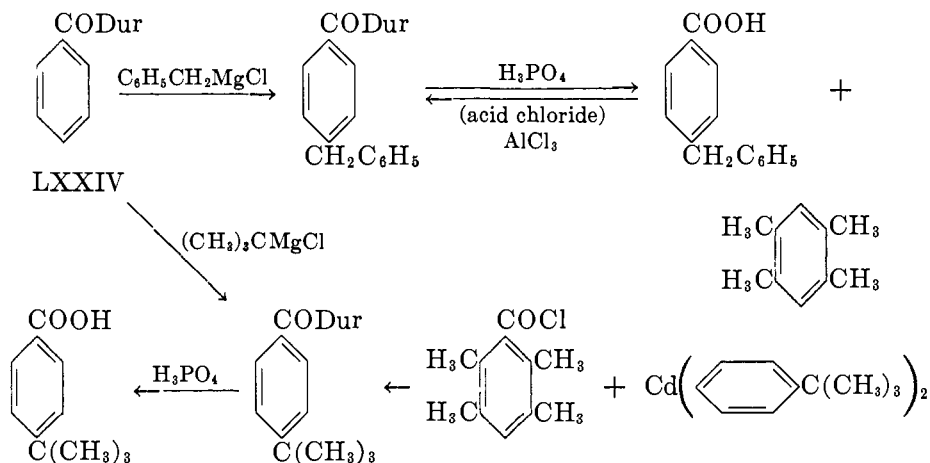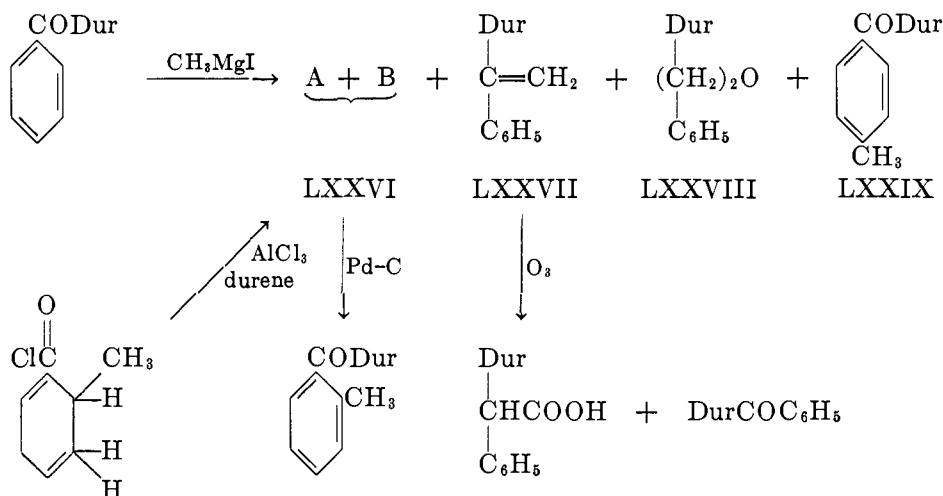

A similar reaction occurred with duryl 2-(o-methoxyphenyl)phenyl ketone (LXXV) (19). Later work (28) has shown that the isopropyl, cyclohexyl, and s-butyl reagents also react in this manner with duryl phenyl ketone, and that reaction of duryl o-tolyl and 2,6-dimethylphenyl duryl ketones with t-butyl-magnesium chloride results in t-butylation in the 4 position with low yields.

In only one case has it been possible by extensive and exhaustive investigation

of the reaction mixture to prove the occurrence of simultaneous 1,2- 1,4-, and 1,6-addition of a Grignard reagent (24). Duryl phenyl ketone reacted with
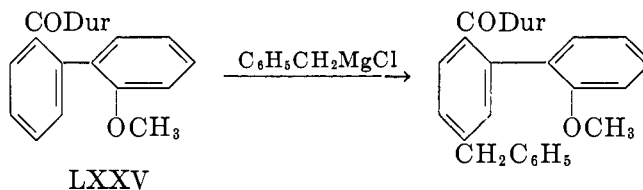
LXXV

methylmagnesium iodide to give principally two isomeric dihydro products (LXXVI) of 1,4-addition, but small amounts of compounds reulting from the other modes of reaction were also iolated. The carbinol to be expected from 1,2-addition was not obtained but two dehydration products, 1-duryl-1-phenyl-


ethylene (LXXVII) and 2,3,5,6-tetramethylbenzohydryl ether (LXXVIII), were found. 1,6-Addition produced small amounts of duryl p-tolyl ketone (LXXIX). As indicated, one of the 1,4-adducts (A) was shown to be duryl 2,3-dihydro-o-tolyl ketone by synthesis from the corresponding acid chloride. Ozonolysis of LXXVII yielded both duryl phenyl ketone and durylphenylacetic acid.

Other examples of 1,6-addition will be mentioned in the following section, since they are of interest in connection with the replacement of groups by the action of the Grignard reagent.

C. MECHANISM OF CONJUGATE ADDITION
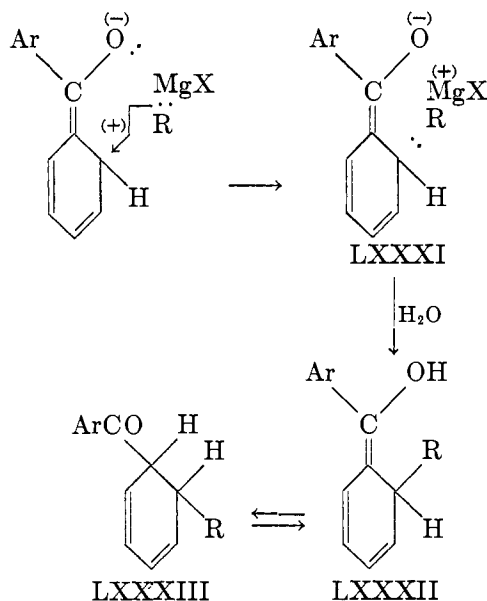
A discussion of the mechanism of the reactions which have been described must include an adaptation of well-known, previously expressed ideas concerning open systems, modern concepts of resonance, and the theory of nucleophilic attack. The Grignard reagent, or for that matter any organometallic compound, may be considered as containing a potential carbanion, and its reaction as involving

primarily attack of this negative radical upon a positive center. In the case of conjugated systems this center may be transferred from, for example, the carbonyl carbon atom to the last atom in the system. We may represent this action by the following extreme resonance structure (LXXX), where the hindered ketones are chosen as an example:


LXXX
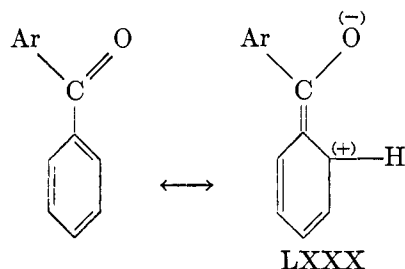
It is reasonable to assume, then, that the more positive magnesium atom of the reagent will coördinate with the negative oxygen atom and the negative carbanion will be attracted by the positive center shown above. This transition complex then reacts as indicated, with the transfer of the Grignard radical with its pair of electrons to the carbon atom in the nucleus to generate the halomagnesium enolate (LXXXI). Hydrolysis would then produce the enol (LXXXII) itself, which may ketonize to give the dihydro aromatic ketone (LXXXIII), the product usually isolated in many cases which have been mentioned. That the enol may be stable is demonstrated by those examples in which the enol peroxide

LXXXI

H_2O

LXXXIII   LXXXII

was obtained. However, the majority of products isolated from these reaction mixtures are fully aromatic, and the mechanism of elimination of hydrogen is

obscure. Several explanations might be advanced. Disproportionation of the dihydro compound would aromatize two-thirds of the material and saturate one-third. The saturated compound would be capable of existence in stereoisomeric
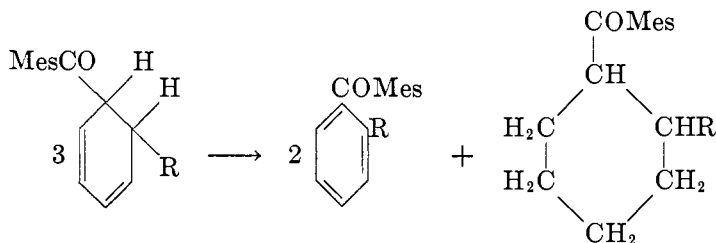
forms and this might account for the formation of the gums usually observed. The fact that a yield of aromatic material greater than 67 per cent has never been claimed is also in agreement with this mechanism. Elimination of hydride ions seems unlikely. A third course is the air oxidation of the mixture before or after hydrolysis. Probably either the first or the third explanation is near the truth.

Of course, it is realized that the mechanism proposed above, involving cyclization, cannot be applied unmodified in the case of 1,6-addition, and the reason for the tendency of certain reagents, notably benzyl, to react in this manner is again obscure. The same type of extreme polarized structure may again be suggested:
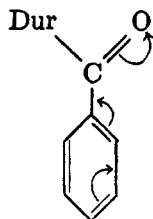
Other considerations are similar, except that no dihydroaromatic compound of this nature has ever been isolated.

III. REPLACEMENT OF FUNCTIONAL GROUPS

The preceding section has been concerned with the replacement by the radical of an organometallic reagent of hydrogen on an aromatic ring, or in some cases the formation of dihydroaromatic compounds by conjugate addition. This type of reaction has also been observed to result in the replacement of two substituents, —the methoxyl group and, in one case, a bromine atom.

A. THE METHOXYL GROUP

1. "Unactivated" methoxyl groups

In only two cases has it been claimed that an organometallic compound was capable of replacing a methoxyl group which was not ortho or para to some electron-attracting or activating group. In 1914 Späth (49) stated that he isolated what was probably isoamylbenzene from the reaction of anisole with isoamyl-

magnesium iodide. However, the principal product was phenol and no sub-
stantiating evidence was advanced for the identity of the supposed hydrocarbon,
isolated in very small amount. Although the yield was again almost negligible, the
work of Price and Meuller (46) was more convincing. These authors treated
p-methoxyphenylmagnesium bromide (LXXXIV) with 1,2-dibromocyclohexane
and isolated two minor products, 4,4'-dimethoxybiphenyl (LXXXV) and 4,4''-
dimethoxy-p-terphenyl (LXXXVI).

LXXXIV   LXXXV   LXXXVI
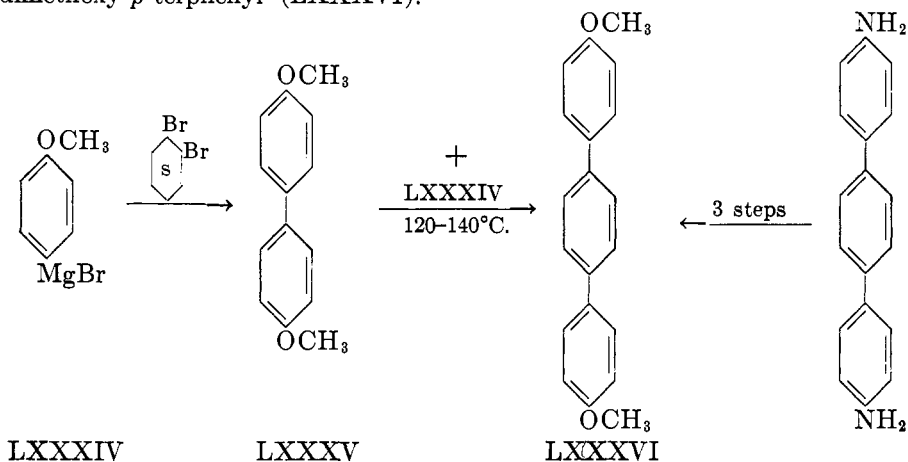
Treatment of LXXXIV with LXXXV also yielded LXXVI. The terphenyl
was finally prepared from the corresponding diamine by successive tetrazotiza-
tion, hydrolysis, and methylation. This extraordinary example is apparently the
only one of its type which has been thoroughly investigated.

2. Methoxyl groups activated by an ortho substituent

(a) *The hindered carbonyl group:* As previously discussed, the reaction of aryl
mesitoates with Grignard reagents led to conjugate addition (17). However, the
presence of an ortho methoxyl group in the reagent resulted in a new reaction,
the replacement of the substituent. Thus p-cresyl mesitoate (LXXXVII) and o-
methoxyphenylmagnesium bromide (LXXXVIII) reacted to give mesityl 2-(o-

LXXXVII   LXXXVIII
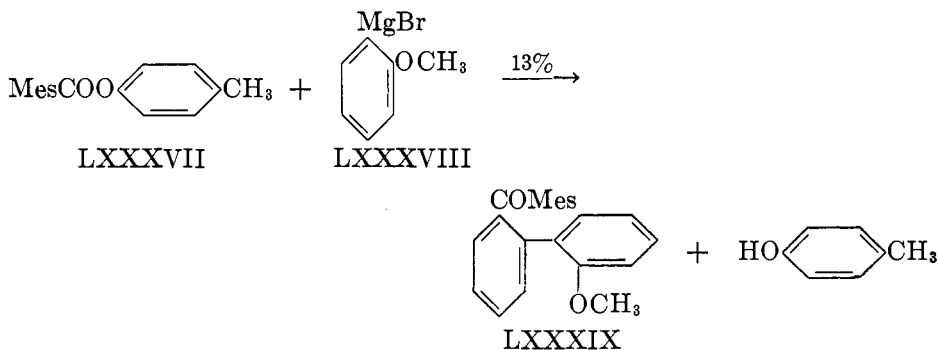
LXXXIX

methoxyphenyl)phenyl ketone (**LXXXIX**).

A similar observation was that duroyl chloride, upon treatment with the same reagent, yielded the duryl analog of LXXXIX (19).
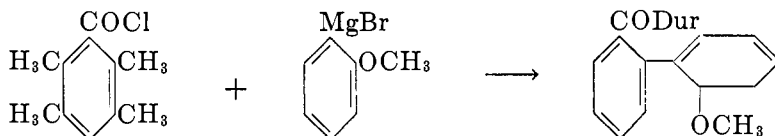

Logically, these observations led to the investigation of the methoxyaryl ketones, presumed intermediates, and it was soon discovered by Fuson and Speck (27) and others that arylation was facilitated, proceeding in better yield and under milder conditions, if it were possible for the reaction to result in the replacement of a methoxyl group ortho to the carbonyl group. As an example we compare the reactions of mesityl phenyl ketone and mesityl o-methoxyphenyl ketone (XC) with phenylmagnesium bromide. As previously stated, the former arylates in the ortho position in 18 per cent yield, while the latter undergoes replacement of the substituent to give the same product in 35 per cent yield. As in
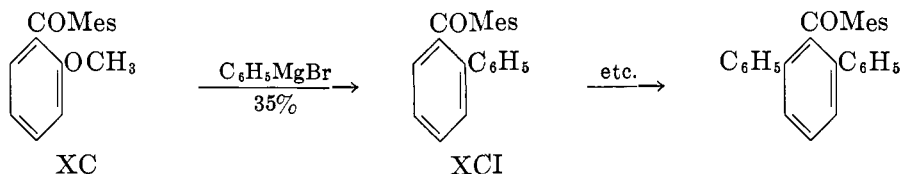
several other cases, this compound may be arylated further by the same reagent. The product of replacement may be isolated under mild conditions; thus it appears that replacement proceeds preferentially. Table 1 includes the known examples of this type of reaction. The higher yields in the examples involving the naphthalene derivative were interpreted as being another indication of the greater double-bond character between the 1 and 2 positions of that nucleus. As would be predicted on the basis of a mechanism involving conjugate addition, methoxyl groups in the meta position were unaffected, conjugate addition proceeding normally (Section III, A, 3, b).

(b) *The cyano group:* In the above reactions advantage was taken of the hindering effect of either the mesityl or the duryl radical to prevent normal 1,2-addition. That this was unnecessary was shown by Richtzenhain (47), who found that
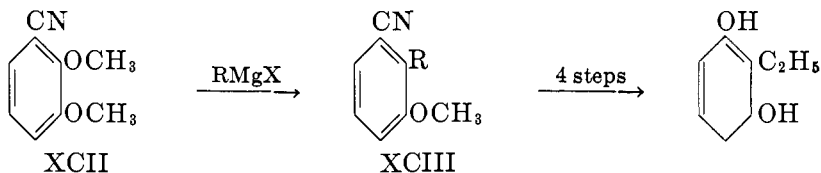
R = C_2H_5 (60%); i-C_3H_7 (81%, or 83% (21)); n-C_4H_9 (80%); i-C_4H_9 (45%); n-C_7H_{15} (62%); cyclo-C_6H_{11} (68%); C_6H_5 (31%).

activation by the sluggish cyano grouping, combined with flanking by a second methoxyl group, also permitted replacement of the ortho methoxyl group 2,3-Dimethoxybenzonitrile (XCII) reacted with Grignard reagents to yield

2-substituted compounds (XCIII) (47, 48). The structure of the ethyl derivative was proved by successive hydrolysis to the amide, degradation to the amine, diazotization, and hydrolysis to 2-ethylresorcinol. The corresponding 2-allyloxy- and 2-benzyloxy- compounds gave the same product (XCIII) with ethylmagnesium bromide but in much lower yield (47); but no replacement was observed with the 2-acetate or with a free hydroxyl group in this position. Strangely enough, methylmagnesium iodide reacted only in the normal manner. In investigating this reaction further, Fuson, Gaertner, and Chadwick (21) found that more than a slight excess of reagent is to be avoided, since under these conditions the product of *both* replacement and 1,2-addition is the major one. Steric hindrance in the reagent prevents replacement, *t*-butylmagnesium chloride adding exclusively in the 1,2 manner. These authors also found that two substituted

TABLE 1

| KETONE	R OF RMgX	POSITION OF ENTERING GROUP(S)	YIELD	REFERENCES
			per cent	
2-CH₃OC₆H₄COMes* .... {	*o*-CH₃OC₆H₄	2	47	(27)
	Phenyl	2; 2,6	35; 20	(27)
	Phenyl	2	59	(27)
	1-Naphthyl	2	76	(27)
2-CH₃OC₁₀H₆COMes .... {	Methyl	2	56	(27)
	Ethyl	2	80	(27)
	n-Butyl	2	55	(27)
2-CH₃O-5-CH₃C₆H₃COMes .... {	Ethyl	2	28	(27)
	Phenyl	2; 2,6	18; 20	(27)
2,3-(CH₃O)₂C₆H₃COMes	Benzyl	2	7	(19)
2,6-(CH₃O)₂C₆H₃CODur†	Methyl	2,6	47	(28)

*Mes = 2,4,6-triphenyl.
†Dur = 2,3,5,6-tetramethylphenyl.

2,3-dimethoxybenzonitriles, one bearing a methyl group in position 5 (XCIV) and a bromo derivative of uncertain structure substituted in either the 6 or the 4 position (XCV), also underwent replacement of the ortho methoxyl group with the ethyl reagent. Still other 2,3-dimethoxybenzonitriles which have been shown by Richtzenhain and Nippus (48a) to undergo replacement of the ortho methoxyl group with the ethyl reagent are: 2,3-dimethoxy-5-propylbenzonitrile (20 per cent, impure); 4,5-dimethoxyisophthalonitrile (75 per cent); and 2,3,4-trimethoxybenzonitrile (45 per cent).

These authors reported that the following related compounds reacted normally with Grignard reagents: 2-methoxy-3-methylbenzonitrile, 3-chloro-2-methoxybenzonitrile, 1-methoxy-2-naphthonitrile, 2,3-dimethoxybenzalaniline, *o*-isoeugenol methyl ether, 2,3-dimethoxybenzophenone, and ethyl 2,3-dimethoxybenzoate. 3-Iodo-2-methoxybenzonitrile underwent a Grignard exchange reaction to give, on hydrolysis, 2-methoxybenzonitrile. Under the usual conditions

β-(2,3-dimethoxyphenyl)acrylonitrile   and   6,7-dimethoxy-1-(2,3-dimethoxy-phenyl)isoquinoline gave unidentified products and 4-chloro-3-methoxy-2-naph-thonitrile and the 4-bromo analog did not react with Grignard reagents.

Attempts (18, 21) to replace methoxyl groups in related compounds not hav-ing the 2,3-dimethoxy grouping met with failure, only normal addition being de-tected; these will be discussed later in connection with the mechanism of this reaction.
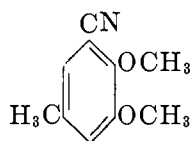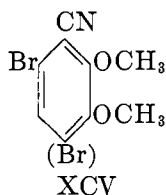

Later, Richtzenhain and Miedrach (47a) adapted the reaction to the prepara-tion of 2-naphthyl-3-methoxybenzonitriles. Unfortunately, when naphthyl re-agents themselves were used, the yields of replacement products were low (α-, 6.5 per cent; β-, 7 per cent). However, when the reagent from 2-bromo-3,4-dihydronaphthalene was used, the yield of aromatized replacement product, obtained directly, was 26 per cent. 2-Chloro-1,2,3,4-tetrahydronaphthalene led to the corresponding tetrahydro derivative in 55 per cent yield.
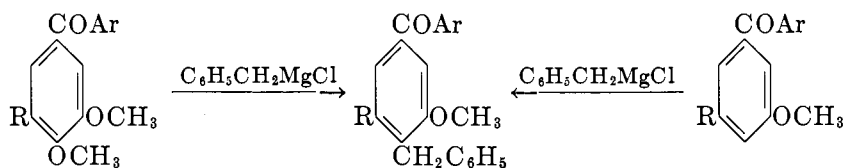
3. Methoxyl groups activated by a para substituent

(a) The cyano group: Only one example of this reaction has been described in the literature. Haller and Schaffer (33) treated 3,4,5-trimethoxybenzonitrile (XCVI) with isobutylmagnesium iodide in refluxing toluene and isolated, in
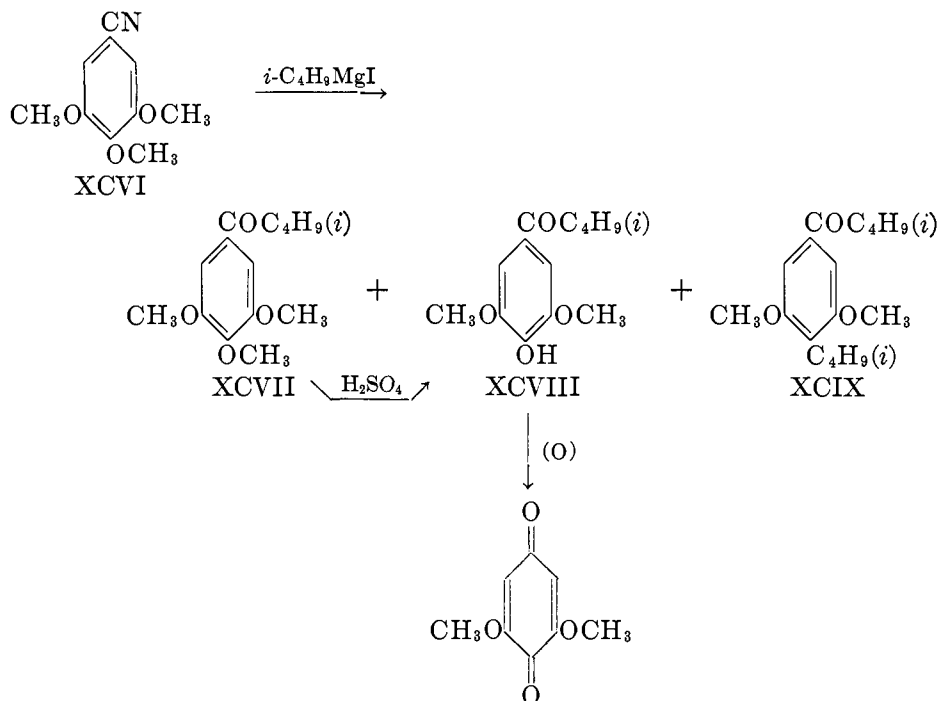
addition to the normal product (XCVII), two other ketones. That obtained in the larger amount was phenolic in nature, the assigned structure being XCVIII. This formula was later confirmed by Hurd and Winberg (35) by oxidation of the compound to 2,6-dimethoxyquinone; they also obtained the phenolic ketone (XCVIII) by the action of sulfuric acid on XCVII. The other abnormal product was presumably 3,5-dimethoxy-4-isobutylphenyl isobutyl ketone (XCIX). The latter authors believed that its formation proceeded through an abnormal ether cleavage, since only the normal product was obtained at 40°C. and pyrogallol trimethyl ether was cleaved to 1,3-pyrogallol dimethyl ether by methylmagnesium iodide at 110°C. 3,4,5-Trimethoxybenzonitrile also undergoes replacement of the para group to give 3,5-dimethoxy-4-ethylpropiophenone (22 per cent yield) when treated with ethylmagnesium bromide (48a). 3,4-Dimethoxybenzonitrile and piperononitrile react normally with Grignard reagents (21).

(b) *The hindered carbonyl group:* Although, in view of the ease of replacement of methoxyl groups ortho to hindered carbonyl groups, it was early attempted to replace similarly such groups in the para position, only dihydro compounds of uncertain structure have been obtained from duryl *p*-methoxyphenyl ketone and the mesityl analog with the benzyl Grignard reagent (19). However, the previously cited examples of replacement of ortho methoxyl groups, which appeared to be promoted by the presence of a flanking methoxyl in the meta position, led Fuson and Gaertner (19) to investigate the action of the benzyl reagent on 3,4-dimethoxyphenyl mesityl ketone (C). As hoped, the expected product (CI) of replacement was obtained, the yield being 22 per cent. The

COAr $\xrightarrow{C_6H_5CH_2MgCl}$ COAr $\xleftarrow{C_6H_5CH_2MgCl}$ COAr

| R—OCH₃, OCH₃ | R—OCH₃, CH₂C₆H₅ | R—OCH₃ |

C: R = H, Ar = Mes　　CI: R = H, Ar = Mes　　CII: R = H, Ar = Mes
CIII: R = H, Ar = Dur　CIV: R = H, Ar = Dur　CV: R = H, Ar = Dur
CVI: R = OCH₃, Ar = Dur　CVII: R = OCH₃, Ar = Dur　CVIII: R = OCH₃, Ar = Dur

structure was proved by the 1,6-addition of benzylmagnesium chloride to mesityl *m*-methoxyphenyl ketone (CII). The series of reactions was extended to the duryl analogs (CIII, CIV, and CV) and to duryl 3,4,5-trimethoxyphenyl ketone (CVI) in 42 per cent and 58 per cent yields, respectively, for the replacements. The comparatively high yield in the last case suggests that the promoting effect of the flanking methoxyl group on the replacement reaction was additive. Treatment of C with phenylmagnesium bromide, followed by bromination, gave a compound having the composition of a monobromo derivative of the corresponding replacement product. Duryl 3,4-methylenedioxyphenyl ketone did not undergo cleavage of the methylenedioxy ring (19).

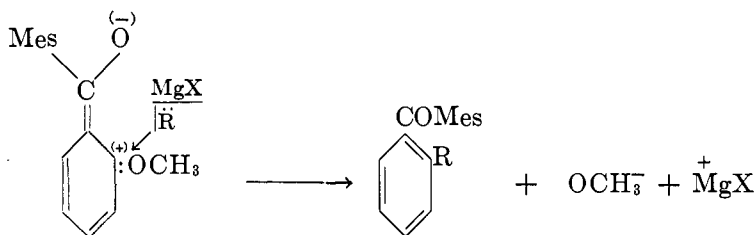<div align="center">B. A BROMO SUBSTITUENT</div>

A single report of the replacement of a bromine atom ortho to a hindered carbonyl group exists. Fuson and Speck (27) treated *o*-bromophenyl mesityl

ketone (CIX) with phenylmagnesium bromide and observed the formation of 2,6-diphenylphenyl mesityl ketone (CX) as a result of both replacement and 1,4-addition.
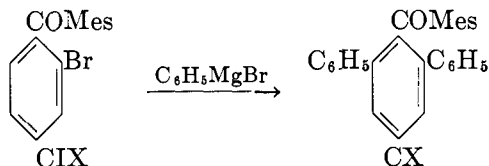

C. MECHANISM OF REPLACEMENT

Since a mechanism of simple ether cleavage appears untenable, it seems that most of the same considerations which were mentioned in connection with the mechanism of conjugate addition apply to the replacement of substituents by the organometallic compounds. Again considering the Grignard reagent as containing a potential carbanion, the replacement might proceed through nucleophilic attack of this ion on the positive center generated by resonance involving the activating group and a double bond in the aromatic nucleus. The extreme structure shown probably should be postulated as being generated at the instant of the attack and at the demand of the attacking reagent. It seems probable that this reaction involves the cyclic intermediate indicated; a six-membered ring is formed by supposing that the reagent coördinates between the oxygen atoms. There have been references (27, 47) to hydrolysis, followed by "elimination of the elements of methanol"; however, the fact that the simultaneous replace-
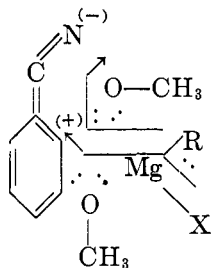

ment of two methoxyl groups without isolation of the mono-replacement product has been observed (page 515) seems to eliminate this possibility. This reaction must surely involve regeneration of the activating group before the second replacement can occur.

This mechanism alone, however, seems inadequate to explain the failure of the following nitriles to undergo replacement (18, 21).
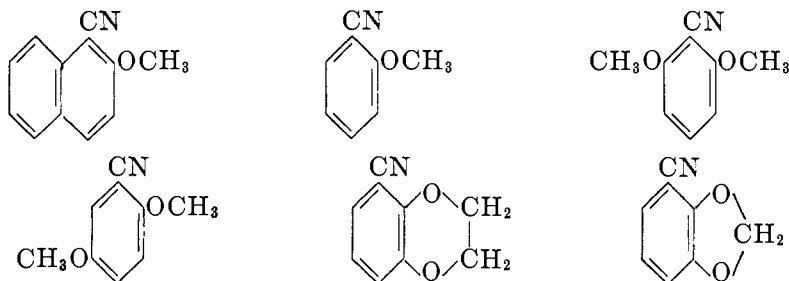
Of course, it may be argued that in these cases the reactivity of the cyano grouping merely predominated, but there must be some explanation for the promoting effect of the flanking group in the 2,3-dimethoxybenzonitriles. A quite attractive rationalization involves coördination of the reagent between the two methoxyl groups so as to provide some necessary orientation for the attack of the radical. It seems possible that the electron-attracting power of the second meth-

oxyl group may also play a part in increasing the positive nature of the attacked ortho carbon atom. Of course, it is to be remembered that R and X are thought to be in a perpendicular plane, one above the plane of the paper and the other below. Again a five-membered ring is suggested for the transition stage.

In the case of replacement of a para methoxyl group, a similar reactive complex may be formulated. Apparently the promoting effect of this sort of system is sufficiently great to make the difference between success and failure of the replacement. It is also interesting that no compound bearing both the radical of a
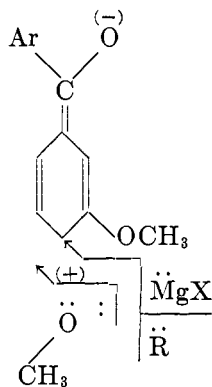
Grignard reagent and a methoxyl group on the same carbon atom has ever been shown to exist.

The author wishes to express his gratitude to Professor Reynold C. Fuson of the University of Illinois for suggesting the preparation of this review and for his helpful criticisms concerning it.

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