REACTIONS OF SUBSTITUTED QUINONES

by

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science.

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September, 1971.

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Reactions of Substituted Quinones

Abstract.

The reaction of some substituted 1,4-benzoquinones and 1,4-naphthoquinones with acetone and acetylacetone was attempted, but only the reaction of 2,6-dimethoxy-1,4-benzoquinone and acetone was successful in yielding the desired product. The nuclear magnetic resonance spectrum and mass spectrum, hitherto unreported, have been shown.

The reactions of various p-quinones with methylmagnesium chloride were performed. New compounds prepared included the methyl-addition products of 2,6-dimethoxy-1,4-benzoquinone, 2-methoxy-1,4-naphthoquinone, 2-hydroxy-1,4-naphthoquinone and 2-methyl-1,4-naphthoquinone. Attempts to establish definitely the position of nucleophilic attack (at the carbon atom of the 1- or 4-carbonyl group) have been largely unsuccessful, but available experimental results indicate that reaction occurred at the 4-carbonyl position.
To my parents
Acknowledgements

I would like to thank my research director, Dr. H. I. Bolker, without whose invaluable help this thesis could not have been written.

The discussions with my wife and fellow workers in the laboratory were very helpful, as well.

I would like to convey my gratitude to the Spruce Falls Power and Paper Company, and to the Pulp and Paper Research Institute of Canada, for financial assistance for the duration of this work, and to extend my appreciation to my parents for their support during the course of my studies.

Thanks are due to Mr. Victor Yu for the recording of nuclear magnetic resonance spectra, and to Mr. Peter Currie for the measurement of mass spectra.

Finally, I wish to express my deepest appreciation to my wife for her encouragement, patience and helpful suggestions during the course of my studies and especially during the preparation of this thesis.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>II. Review of the Literature</td>
<td>2</td>
</tr>
<tr>
<td>A. Nucleophilic reactions occurring only at the</td>
<td></td>
</tr>
<tr>
<td>&quot;unhindered&quot; 4-carbonyl group of substituted</td>
<td></td>
</tr>
<tr>
<td>1,4-quinones</td>
<td>2</td>
</tr>
<tr>
<td>1) Oximes</td>
<td>2</td>
</tr>
<tr>
<td>2) Hydrazones</td>
<td>10</td>
</tr>
<tr>
<td>3) Semicarbazones</td>
<td>15</td>
</tr>
<tr>
<td>B. The anomalous reactions of 2-hydroxy-1,4-naphthoquinone with</td>
<td></td>
</tr>
<tr>
<td>hydroxylamine, hydrazines and</td>
<td></td>
</tr>
<tr>
<td>semicarbazides</td>
<td>17</td>
</tr>
<tr>
<td>C. Nucleophilic reactions occurring only at the</td>
<td></td>
</tr>
<tr>
<td>1-carbonyl group of substituted 1,4 quinones</td>
<td>24</td>
</tr>
<tr>
<td>1) The base-catalyzed reaction of 2,6-di-methoxy- and other</td>
<td></td>
</tr>
<tr>
<td>2,6-dialkox-y-1,4-benzoquinones with acetone and methyl ethyl</td>
<td>24</td>
</tr>
<tr>
<td>ketone</td>
<td></td>
</tr>
<tr>
<td>2) The acetate-catalyzed reaction of 2-substituted- and</td>
<td></td>
</tr>
<tr>
<td>2,6-disubstituted-1,4-benzoquinones with acetic anhydride</td>
<td>30</td>
</tr>
<tr>
<td>3) Reaction of substituted p-quinones with diazomethane</td>
<td>36</td>
</tr>
<tr>
<td>4) Replacement of the oxygen-16 atoms in the carbonyl groups of</td>
<td></td>
</tr>
<tr>
<td>substituted 1,4-benzoquinones by oxygen-18</td>
<td>48</td>
</tr>
</tbody>
</table>
D. Conclusions ........................................ 49

III. Results and Discussion ............................ 52

A. The base-catalyzed reaction of 2,6-disubstituted-1,4-benzoquinones and 2-substituted-1,4-naphthoquinones with acetone and acetylacetone .................................................. 52

B. The reaction of 2,6-disubstituted-1,4-benzoquinones and 2-substituted-1,4-naphthoquinones with the Grignard reagent, methylmagnesium chloride ............................................... 60

IV. Experimental ........................................ 79

A. 1-acetonyl-1-hydroxy-2,6-dimethoxycyclohexa-2,5-diene-4-one (LXV); Method A .................... 79

B. Attempted preparations of the addition product of 2,6-dichloro-1,4-benzoquinone and acetone; Methods B and C .................................................. 80

C. Attempted preparation of the addition product of 2-hydroxy-1,4-naphtoquinone and acetone ..... 82

D. 2-methoxy-1,4-naphtoquinone ......................... 82

E. Attempted preparation of the addition product of 2-methoxy-1,4-naphtoquinone and acetone ..... 83

F. Attempted preparation of the addition product of 2-amino-1,4-naphtoquinone and acetone ..... 83

G. Attempted preparation of the addition products of various 1,4-quinones and acetylacetone ... 83
H. Determination of the concentration of a solution of methylmagnesium chloride in tetrahydrofuran (THF) 84
I. The methyl-addition product of 2,6-dimethoxy-1,4-benzoquinone and methylmagnesium chloride 85
J. Reduction of the carbonyl group of the methyl-addition product of XVI 86
K. The methyl-addition product of 2-methoxy-1,4-naphthoquinone and methylmagnesium chloride 87
L. Methylation of the methyl-addition product of LIX 88
M. The methyl-addition product of 2-hydroxy-1,4-naphthoquinone and methylmagnesium chloride 88
N. Attempted dehydration of the methyl-addition product of LI 89
O. Methylation of the methyl-addition product of LI 90
P. The methyl-addition product of 2-methyl-1,4-naphthoquinone and methylmagnesium chloride 91
V. Spectra 92
VI. Bibliography 100
## LIST OF ILLUSTRATIONS

<table>
<thead>
<tr>
<th>Fig. no.</th>
<th>Title</th>
<th>Page no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Suggested Fragmentation Pattern of LXV</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Suggested Fragmentation Pattern of CXIV</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>Suggested Fragmentation Pattern of CXIX</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Suggested Fragmentation Pattern of CXXII</td>
<td>72</td>
</tr>
</tbody>
</table>
Introduction

Nucleophiles attacking the carbonyl groups of 2-substituted and 2,6-disubstituted-1,4-benzoquinones, and of 2-substituted 1,4-naphthoquinones, might react in three ways: (1) exclusively at the 1-carbonyl group; (2) exclusively at the 4-carbonyl group; (3) at both positions. The nucleophiles known to be members of the first classification are acetonyl anion, the anion of acetic anhydride and diazomethane; while those thus far found to be members of the second classification are hydroxylamine, various hydrazines and certain semicarbazides. No nucleophilic reagents have yet been discovered which may react both at the 1- and 4-carbonyl groups of these 1,4-quinones.

The following factors appear to govern the relative rate of nucleophilic attack at one or other carbonyl group: steric hindrance of reaction at the 1-carbonyl group by substituents at the ring positions adjacent to it; activation or deactivation of the 1-carbonyl group toward nucleophilic attack by the inductive effect of the substituents at the ring positions adjacent to it; and deactivation of the 4-carbonyl group towards nucleophilic attack by the mesomeric (resonance) effect of the ring substituents. Also, it seems quite likely that the nature of the nucleophile is of great importance in determining the position of attack, since those known to attack carbon-1 of the quinone all form carbon-carbon bonds, while those attacking at carbon-4 all form carbon-nitrogen bonds.

The object of this study is to determine the relative importance of these effects during nucleophilic attack on substituted quinones.
Review of the Literature

Nucleophilic reactions occurring only at the "unhindered" 4-carbonyl group of substituted 1,4-quinones

With only one exception, 2-substituted- and 2,6-disubstituted-1,4-benzoquinones and 2-substituted-1,4-naphthoquinones react with hydroxylamine, alkyl and aryl hydrazines and semicarbazides to form mainly the corresponding mono-oximes, mono-hydrazones and mono-semicarbazones, the nucleophilic attacks occurring at the "unhindered" carbonyl group (i.e., at the 4-position). The one anomalous compound, 2-hydroxy-1,4-naphthoquinone, undergoes reaction at the 1-carbonyl group, and will be discussed later.

1) Oximes

One of the first workers in this field, F. Kermann, reported the reactions of many mono-substituted-1,4-benzoquinones and 2,6-disubstituted-1,4-benzoquinones with hydroxylamine. Among the mono-substituted benzoquinones, he found that either mono- or di-oximes were formed, and if a mono-oxime was isolated, the oximino group was located only at the 4-position. With disubstituted benzoquinones, only the mono-oximes were formed, again solely at the 4-position. For example, when 2-chloro-(or 2-bromo)-6-methyl-1,4-benzoquinone (I) was treated with hydroxylamine hydrochloride in the presence of base, a mono-oxime (II) was formed. On reduction to the amine and subsequent oxidation to the nitro compound, the product was identical to that prepared by chlorination or bromination of 4-nitro-2-cresol (III), and Kermann concluded that
oximation had occurred at the 4-position. Because of the o-directing effect of the hydroxyl group, and the m-directing effect of the nitro group of III toward halogenation, this conclusion seems quite logical.

In connection with a study of the tautomerization of 2- and 3-substituted-4-nitrosophenol and the corresponding 2- and 3-substituted-1,4-benzoquinone-4-oximes, Ramart-Lucas and Martynoff prepared the mono-oxime (IV) of toluquinone (V) and compared it with the products of the reactions of o- and m-cresol (VI and VII, respectively) with sodium nitrite and acid. They determined that the nitrosated o-cresol product was identical with the mono-oxime by comparing the melting points and ultraviolet spectra. These authors similarly prepared the 4-mono-oxime (VIII) of 2-chloro-1,4-benzoquinone (IX) by treating IX with hydroxylamine, and by nitrosating 2-chlorophenol (X).
Metro; and Cook and co-workers\(^4\) obtained a mono-oxime (XI) by oximation of 2,6-di-tert-butyl-1,4-benzoquinone (XII), but made no claim as to the position of attack. However, the melting point of this compound, variously reported as 219-220\(^\circ\)\(^3\) and 218.5-220\(^\circ\)\(^4\), is the same as that reported by Dexter et al.\(^5\) for the product of nitrosation of 2,6-di-tert-butylphenol (XIII). Mueller and Ley\(^6\) chemically confirmed the structure of the mono-oxime XI by treating it with nitric acid in acetic acid, which yielded 2-tert-butyl-4,6-dinitrophenol (XIV). Compound XIV was also prepared by treating 2,4,6-tri-tert-butylphenol (XV) with the same acid mixture. The products from these two reactions were proven identical by a mixed melting-point determination, and by their infrared spectra.
Finally, Bolker and Kung\textsuperscript{7} reported that oximation of 2,6-dimethoxy-1,4-benzoquinone (XVI) afforded only the mono-oxime. They proved that this product was, in fact, 2,6-dimethoxy-1,4-benzoquinone-4-oxime (XVII) by preparing it independently from 5-nitro-1,2,3-trimethoxybenzene (XVIII), and by mass spectral studies.
Among benzoquinones substituted at positions adjacent to both carbonyl groups, steric hindrance appears to play an important role in determining the position of nucleophilic attack by hydroxylamine. For example, when Kermann reacted 2-isopropyl-3-chloro-5-methyl-1,4-benzoquinone (3-chlorothymoquinone) (XIX) with hydroxylamine, and oxidized the resulting mono-oxime (XX) to the corresponding nitro compound (XXI), he was able to prove that the nitro group, and hence the original oximino group, was at the 1-position, by preparing the identical compound from 2-methyl-4-nitro-5-isopropylphenol (4-nitrocarmacrol) (XXII) by chlorination of the latter.

\[
\begin{align*}
\text{XIX} & \xrightarrow{\text{H}_2\text{NOH}\cdot\text{HCl}} \text{XX} \\
\text{Cl} & \text{CH}_3 \\
\text{(CH}_3\text{)}_2\text{HC} & \text{Cl} \\
\text{OH} & \text{NOH} \\
\end{align*}
\]

\[
\begin{align*}
\text{XII} & \xrightarrow{\text{Cl}_2} \text{XXI} \\
\text{NO}_2 & \text{CH}_3 \\
\text{O} & \text{Cl} \\
\text{(CH}_3\text{)}_2\text{HC} & \text{Cl} \\
\end{align*}
\]

Similarly, Kermann found that 6-chlorothymoquinone (XXIII) reacts with hydroxylamine at the 4-position.

\[
\begin{align*}
\text{XXIII} & \xrightarrow{\text{H}_2\text{NOH}\cdot\text{HCl}} \text{XXIV} \\
\text{CH}_3 & \text{Cl} \\
\text{(CH}_3\text{)}_2\text{HC} & \text{Cl} \\
\text{CH}_3 & \text{NOH} \\
\text{O} & \text{Cl} \\
\end{align*}
\]
Ramart-Lucas and Martynoff\(^2\) claimed that the reaction of 2-isopropyl-5-methylphenol (thymol) (XXIV) with nitrous acid, and of "thymoquinone" (XXVa) with hydroxylamine gave identical products, whose structure was 2-isopropyl-5-methyl-1,4-benzoquinone-4-oxime (XXVIa); while the reaction of 2-methyl-5-isopropylphenol (carvacrol) (XXVII) with nitrous acid, and of "2-methyl-5-isopropyl-1,4-benzoquinone" (XXVb) with hydroxylamine both gave 2-methyl-5-isopropyl-1,4-benzoquinone-4-oxime (XXVIb).
Since "thymoquinone" and "2-methyl-5-isopropyl-1,4-benzoquinone" are just two different names for the same compound, it is patently obvious that the two different oximes XXVIa and XXVIb could not both have been formed from the parent quinone in identical reactions. The melting points of the two nitrosated phenols are quite close, and it is conceivable that the comparison of the compounds obtained from the two different types of reactions may have been complicated by incomplete purification of either or both products. Furthermore, the ultraviolet spectra of the two oximes are reproduced in the paper, and are almost identical. However, since it is not indicated whether the compounds used to obtain these spectra were the products of the nitrosation reactions (in which case the positions of the oximino groups are assured), or those of the oximation reactions, no conclusions may be drawn concerning the validity of the authors' claim. If the spectra were those of the products of the oximation reactions, one would expect them to be extremely similar, since they would presumably have been obtained from the same compound. Clarification of this matter would appear to require repetition of the reactions, and more accurate experimental data, to determine the correct structure of the oxime.

Except for 2-hydroxy-1,4-naphthoquinone, 2-substituted-1,4-naphthoquinones undergo oximation in much the same manner as 2,6-disubstituted-1,4-benzoquinones; i. e., hydroxylamine attacks the 4-carbonyl group. Early workers in the field included Anderson and Newman\(^9\) and Dam et. al.\(^10\), who prepared the mono-oxime of 2-methyl-1,4-naphthoquinone (menadione) (XXVIII) while studying the
biological activities of compounds related to Vitamin K. No attempt was made by either group to determine the position of hydroxylamine attack. Veldstra and Wiardi, however, proved that the mono-oxime formed upon treating XXVIII with hydroxylamine hydrochloride in acidic alcohol-water solution was 2-methyl-1,4-naphthoquinone-4-oxime (XXIX) by reducing it to the amino compound, acetylating the product and comparing this with the product obtained by treating 2-methyl-1-naphthol (XXX) with p-nitrophenyl diazonium chloride, reducing the resulting hydroxyazo compound to the amino, and acetylating.

\[
\begin{align*}
\text{XXVIII} & \xrightarrow{\text{NH}_2\text{OH} \cdot \text{HCl}} \text{XXIX} \\
\text{EtOH/H}_2\text{O} & \\
\text{SnCl}_2/\text{HCl} & \xrightarrow{(\text{CH}_3\text{CO})_2\text{O}} \text{NHCOCH}_3
\end{align*}
\]
Finally, Chuang and Han\textsuperscript{12} having obtained 5,8,9,10-tetrahydro-2-methyl-1,4-naphthoquinone (XXXI) by condensation of toluquinone with butadiene, prepared the mono-oxime of this compound. They suggested that the product was the 4-oxime, but gave no proof of this assignment.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{XXXI} & \quad \text{NOH}
\end{align*}
\]

2) Hydrazones

Hydrazine and hydrazides react as does hydroxylamine with \(p\)-quinones: attack occurs at the "unhindered" carbonyl group. Unlike the oximes, however, the resulting hydrazones tend to tautomerize to the corresponding hydroxyazo compounds. Determination of the structure of the product (i. e., the position of nucleophilic attack) is usually accomplished by treating the corresponding \(p\)-substituted phenol or naphthol with a diazonium salt. This gives a hydroxyazo compound which may be compared with the product of reaction of the parent quinone and a hydrazide. For example, McPherson and Dubois\textsuperscript{13} treated chlorobenzoquinone (XXXII) with \(\alpha,\alpha\)-phenylacetyl hydrazide in 80\% aqueous alcohol, and obtained a product which they suggested was 2-chloro-1,4-benzoquinone-4-(phenylacetyl hydrazone) (XXXIII). To prove this, they hydrolyzed the hydrazone with sulphuric acid and obtained 4-phenylazo-2-chlorophenol (XXXIV), which they synthesized independently by reacting \(p\)-chloro-
phenol with benzene diazonium chloride.

\[
\begin{align*}
\text{XXXII} & \xrightarrow{\text{N(}Ac\text{)(Ph)}NH_2, 80\% \text{ aqueous EtOH}} \text{XXXIII} \\
\text{XXXIV} & \xrightarrow{\text{PhN}_2^+\text{Cl}^-} \text{XXXV}
\end{align*}
\]

Smith and Irwin\textsuperscript{14} studied the reactions of the series of polymethyl-1,4-benzoquinones with \( p \)-nitrophenylhydrazine. First, they proved that the product of the reaction of toluquinone and the hydrazine was identical with that of the reaction of \( o \)-cresol (VI) with diazotized \( p \)-nitroaniline, namely \( 4-(p\text{-nitrophenylazo})-2\text{-methylphenol} \) (XXXV). They repeated these experiments, using 2,6-dimethyl-1,4-benzoquinone (XXXVI) and 2,6-dimethylphenol (XXXVII), respectively, and obtained \( 4-(p\text{-nitrophenylazo})-2,6\text{-dimethylphenol} \) (XXXVIII) as the reaction product. Similarly, 2,3,6-trimethyl-1,4-benzoquinone (XXXIX) was found to react only in the 4-position, giving \( 4-(p\text{-nitrophenylazo})-2,3,6\text{-trimethylphenol} \) (XL). Finally, when 2,3,5,6-tetramethyl-1,4-benzoquinone ( duroquinone) (XLI) was reacted with \( p \)-nitrophenylhydrazine, the product was the hydroxyazo compound XLII. In this respect, the reaction of hydrazine is different from that of hydroxylamine, which does not react with XLI.
It has been reported that 2,6-di-tert-butyl-1,4-benzoquinone (XLIII) formed only a mono-hydrazone upon treatment with phenylhydrazine, but no claim was made as to the position of substitution. Unfortunately, no mention of the reaction of 2,6-di-tert-butylphenol with diazotized aniline has been found in the literature. It would seem logical to predict, nonetheless, that the product is the 4-hydrazone. Similarly, it has been suggested that 2,6-dimethyl-1,4-benzoquinone (XXXVI) formed only a mono-hydrazone when treated with p-tosylhydrazine or with benzoyl hydrazine, but again no attempt was made to confirm the position of attack, which was claimed to be at the 4-carbonyl group in both instances.
Borsche and Ockinga\textsuperscript{18} studied the reaction of thymoquinone (XXV) with benzoic acid hydrazide. They proved that they had prepared the 4-hydrazone of the quinone, which subsequently tautomerized to the corresponding hydroxyazo form (XLIV), by brominating the product to give the 6-bromo compound XLV. (The 6-position is the only logical position for bromine substitution). The bromo compound was compared with the product of the reaction of 6-bromothymoquinone with benzoic acid hydrazide, which Kermann\textsuperscript{8} had shown to react at the 4-position.

Later, Borsche\textsuperscript{19} reported that thymoquinone reacts both with o-nitrophenylhydrazine and 2,4-dinitrophenylhydrazine to give the 4-hydrazones, with subsequent tautomerization to the hydroxyazo forms. He proved these structural assignments by preparing both compounds by independent routes: the treatment of 2-isopropyl-5-methylphenol (thymol) (XXIV) with diazotized o-nitro- and 2,4-dinitroanilines, respectively.
Veldstra and Wiardi have prepared the mono-phenyl-hydrazone (XLVI) of menadione (XXVIII), the only 1,4-naphthoquinone for which the preparation of a hydrazone has been reported. They established that the 4-substituted product had been formed by reducing the quinone hydrazone (more likely the hydroxyazo tautomer) to the amine, and acetylating to obtain a product identical with that prepared in their studies of oximation (see above).

The preparation of other hydrazones of XXVIII, specifically the p-carboxyphenyl hydrazone (by reaction of the quinone with p-hydrazinobenzoic acid) and the guanylhydrazone has also been reported, but no mention was made of the position of substitution.
3) Semicarbazones

Semicarbazide itself, as well as various substituted semicarbazides, have been found to react with the 4-carbonyl groups of 2-substituted- and 2,6-disubstituted-1,4-quinones. For example, Heilbron and Henderson\textsuperscript{21} have proved this to be true in the reactions of 2-chloro-1,4-benzoquinone (IX) and 2,6-dichloro-1,4-benzoquinone (XLVII) with semicarbazide. The mono-semicarbazones formed, which appear to exist mainly in their tautomeric forms XLVIII and XLIX, respectively, were boiled in dilute sodium hydroxide solution, yielding phenols, nitrogen, carbon dioxide and ammonia. The phenols obtained were proved to be 2-chlorophenol (X) and 2,6-dichlorophenol (L), respectively, by comparison with authentic samples of these compounds. No 1-semicarbazone or 1,4-di-semicarbazone could be found.
Similarly, when toluquinone was reacted with semicarbazide, and the product was boiled with dilute sodium hydroxide, only o-cresol (VI) was isolated; and when thymoquinone (XXV) was treated in the same way, only thymol (XXIV) was obtained. There was no trace of the isomeric carvacrol (XXVII).

There was evidently an error made in the naming of the tautomer of the semicarbazone derivative of XXV, since it was called the "3-methyl-4-hydroxy-5-isopropyl derivative" in the discussion, and the "2-methyl-4-hydroxy-5-isopropyl derivative" in the experimental section. The latter, of course, is the correct I. U. P. A. C. name of the product.

In connection with the preparation of certain azophenols, Heesing and Hoppe reacted 2,6-dimethyl-1,4-benzoquinone (XXXVI) with 4-\( \eta \)-butylsemicarbazide hydrochloride to give a mono-semicarbazone which they suggested was the 4-derivative, but they did not confirm this assignment. Palande et al. on the other hand, prepared the mono-semicarbazone, mono-phenylsemicarbazone
and other mono-arylsemicarbazones of 2-methyl-1,4-naphthoquinone (XXVIII), and proved that the products were the 4-semicarbazones by reducing them with stannous chloride and acid to the known 4-amino-2-methyl-1-naphthol.

Finally, Sah and Daniel\textsuperscript{24} reported the formation of a mono-thiosemicarbazone of XXVIII, but they did not make any assignment of the position of substitution. Of course, from the above results it would seem logical to conclude that it was the 4-thiosemicarbazone.

**The anomalous reactions of 2-hydroxy-1,4-naphthoquinone with hydroxylamine, hydrazines and semicarbazides**

One \( p \)-quinone which does not follow the usual pattern of oxime, hydrazone and semicarbazone formation is 2-hydroxy-1,4-naphthoquinone (lawsone) (LII), whose derivatives are of interest as possible anti-malarial agents. Since the compound LII should, in theory, exist as well in the tautomeric 4-hydroxy-1,2-naphthoquinone form, Goldstein and Grandjean\textsuperscript{25} predicted in 1943 that oximation should be possible at any or all of the 1-, 4- and (theoretically) 2-carbonyl positions, and prepared the mono-oxime by reaction with hydroxylamine hydrochloride in both acidic and basic solution. They discovered, however, that only one of the three possible mono-oximes had been formed, and proved that the product was 2-hydroxy-1,4-naphthoquinone-1-oxime (LIII) by comparing it with the product of nitrosation of 1,3-dihydroxynaphthalene (LIII). They also proved the identity of the aminonaphtho-
diols prepared from each, as well as the acetylated 4-amino-1,3-napthodiols (LIV). The tri-acetylated product LIV is a known compound.

There the matter rested until 1969, when Dudley et al. proposed that the reason for the abnormal behaviour of LI is that in basic solution the anion of the hydroxyquinone is formed and that, since 2- and 4-oxygens are engaged in stabilizing the negative charge, only the 1-carbonyl group remains susceptible to nucleophilic attack.
To test this theory, they prepared a mono-hydrazone (LV) of LI by reacting it with one equivalent of cyclohexanecarboxylic acid hydrazide in weakly basic solution. The infrared and p.m.r. spectra of LV were compatible with a 2-hydroxy-1,4-naphthoquinone mono-hydrazone structure, as opposed to the hydroxyazo tautomer of the hydrazone, or the 2-hydrazino-1,4-naphthoquinone derivative. Presumably relying on the "anion" theory to support the spectroscopic results, the authors do not stress the point that they have proved that the mono-hydrazone which they prepared was the 1-derivative. Nevertheless, they have indirectly confirmed their proposed structure: in another phase of their work, they treated ammonium
1,2-naphthoquinone-4-sulfonate (LVI) with cyclohexanecarboxylic acid hydrazide, and obtained a product whose infrared spectrum indicated that it was the 2-hydroxy-1,4-naphthoquinone-4-hydrazone (LVII), rather than the 4-hydrazino-1,2-naphthoquinone derivative. (Also, the ultraviolet spectrum of LVII did not correlate at all with that of 4-amino-1,2-naphthoquinone, which would be expected if the product were, indeed, the hydrazino-1,2-quinone.)

The authors had therefore prepared two different 2-hydroxy-1,4-naphthoquinone mono-hydrazones, and it is therefore possible to compare them. Compound LV (the proposed 1-hydrazone) had a melting range of 205-208° (dec.), while that of compound LVII was 272-278° (dec.). Also, the p.m.r. spectrum of LV contained a peak at $\delta 5.95$ (from TMS) attributable to the quinone ring proton; while in the spectrum of LVII, this peak had shifted to $\delta 7.50$. Since the latter compound is known to be the 4-hydrazone, it follows that the former must, indeed, be the 1-hydrazone.

The same workers also reacted LI with various acyl hydrazides in 80% acetic acid solution, and found that reaction occurred only at the 2-position of the quinone. This assignment
was indicated by the infrared and p.m.r. spectra of the product, and confirmed by preparing the known 2-amino-1,4-naphthoquinone (LVIII) from it.

Also, when 2-methoxy-1,4-naphthoquinone (lawsone methyl ether) (LIX) was reacted with the acyl hydrazides in the same acidic reaction medium, the product was the same as that of LI. The reaction sequence in both cases presumably consists first of protonation of the oxygen atoms of the 2-substituents, then loss
of water or methanol (leaving identical carbonium ions, which are stabilized by resonance) simultaneous with attack of the acyl hydrazide. Since only the 2-substituted product is obtained when these reactions are performed in acidic medium, the reaction rate at the 2-position (via the above sequence) appears to be greater than that of nucleophilic attack of the hydrazides at either carbonyl group.

Carroll et al. extended this study by reacting LI with thiosemicarbazide in acidic and basic solution. They found that from acidic solution the product was, as expected, 2-thiosemicarbazo-1,4-naphthoquinone (LX). This was confirmed by subjecting the compound to hydrogenolysis, followed by ferric chloride oxidation, yielding the known 2-amino-1,4-naphthoquinone (LVIII).
In basic solution, however, 2-hydroxy-1,4-naphthoquinone-1-thiosemicarbazone (LXI) was formed. The structure of this compound was confirmed by reducing it with stannous chloride and hydrochloric acid to give 4-amino-1,3-dihydroxynaphthalene hydrochloride, which was then air-oxidized at pH 8 and acetylated to give the known phenoxazone LXII. This series of reactions was then repeated, using aminoguanidine carbonate in place of thiosemicarbazide.
Interestingly, when LI was reacted with aminoguanidine in aqueous trifluoroacetic acid solution, the product was LXIV, and not LXIII as expected. The authors suggested that the conjugate base of LI exists even in the trifluoroacetic acid solution, to an extent sufficient to effect exclusive condensation at the 1-position, although they did not appear to have any experimental results at all which indicated the presence of this conjugate base in the solution. It is equally possible, of course, that the rate of reaction of the aminoguanidine with LI simply happens to be greater at the 1-position than at the 2-position.

Nucleophilic reactions occurring only at the 1-carbonyl group of substituted 1,4-quinones

1) The base-catalyzed reaction of 2,6-dimethoxy- and other 2,6-dialkoxyl,4-benzoquinones with acetone and methyl ethyl ketone

In 1953 Aghoramurthy et al. reported that when a solution of 2,6-dimethoxy-1,4-benzoquinone (XVI) in dry acetone was refluxed in the presence of solid potassium carbonate (or 10% alcoholic potassium hydroxide solution), a 1:1 condensation occurred. Solely on the basis that the 1-carbonyl group of XVI is sterically hindered, whereas the 4-carbonyl group is not, the authors suggested that the product was 4-hydroxy-4-acetonyl-2,6-dimethoxycyclohexa-2,5-diene-1-one (LXIV) rather than the isomeric 1-hydroxy-1-acetonyl-2,6-dimethoxycyclohexa-2,5-diene-4-one (LXV). They prepared the 2,4-dinitrophenylhydrazone and the semicarbazone derivatives of this compound, but did not consider at all the complica-
tion that the addition product had more than one carbonyl group able to react with the hydrazine or semicarbazide. Actually, the isolation of only a mono-hydrazone product (as determined by elemental analysis) would appear to favour their choice of the isomer LXIV, since the unreacted carbonyl group would be at the 1-position, which is sterically hindered by the substituents at the 2- and 6-positions. As discussed earlier, hydrazone formation seems to be affected by steric hindrance. On the other hand, the isomer LXV would appear to have two carbonyl groups at which hydrazone formation could occur. However, close examination of the experimental data reveals the important fact that only very little more than one equivalent of the hydrazine was used in the reaction. If, as would seem logical, the rate of reaction of the hydrazine at the side-chain carbonyl group is considerably greater than that at the ring carbonyl group, again only one mono-hydrazone would be isolated. Therefore no conclusion may be drawn concerning the position of acetone addition from this experiment.

\[
\begin{align*}
\text{XVI:} & \quad \text{CH}_3\text{O} & \quad \text{OCH}_3 \\
\text{K}_2\text{CO}_3 \text{ or KOH} & \quad \text{acetone or methyl} \\
\rightarrow & \quad \text{CH}_3\text{O} & \quad \text{OCH}_3 \\
\text{LXIV:} \quad \text{R} = \text{CH}_3 & \quad \text{LXVI:} \quad \text{R} = \text{CH}_2\text{CH}_3 \text{ or} \\
\text{LXVII:} & \quad \text{CH}_3\text{O} & \quad \text{OCH}_3 \\
\text{HO} & \quad \text{CH}(_3)\text{(COCH}_3) & \quad \text{HO} \quad \text{CH}_2\text{COCH}_3 & \quad \text{OCH}_3 \\
\text{LXV:} & \quad \text{HO} & \quad \text{CH}(_3)\text{(COCH}_3) & \quad \text{HO} \quad \text{CH}_2\text{COCH}_3 & \quad \text{OCH}_3
\end{align*}
\]
The authors then repeated this reaction, using methyl ethyl ketone instead of acetone, and proposed that the product was 4-hydroxy-4-propionylmethyl-2,6-dimethoxycyclohexa-2,5-diene-1-one (LXVI). However, not only did they not confirm the position of nucleophilic attack, they did not even rule out the possibility of formation of 4-hydroxy-4-(α-methyl-α-acetylmethyl)-2,6-dimethoxycyclohexa-2,5-diene-1-one (LXVII), although this product is unlikely because of the relative stabilities of the anions formed after removal of a 1- or 3-proton from methyl ethyl ketone.

In the course of separating XVI from other compounds by chromatography on alumina, using acetone as eluant, Magnussen isolated a compound which elemental analysis indicated was an addition product composed of equal amounts of the quinone and acetone. He also discovered, not surprisingly, that the same compound was obtained by heating a solution of XVI in acetone, in the presence of aluminum oxide. He wrote that "spectrographic examination of this compound, and its reduction to a phenol, to which the structure of 3,5-dimethoxy-4-acetonylphenol could be ascribed", indicated that the compound formed was the 1-acetonyl derivative LXV. Since he did not give experimental details in this paper, and since his later work was concerned with the reaction of various o-quinones with acetone (and hence did not include the results from the reaction of acetone with XVI), it is impossible to evaluate the validity of his proof. At no time did he appear to be aware of Aghoramurthy's earlier paper.

During his later study of the reaction of o-quinones
with acetone, Magnussen postulated a mechanism for the abstraction of a proton from acetone by aluminum oxide, followed by nucleophilic attack of the anion at the carbon atom of a carbonyl group. Revised to describe the reaction of a \( \pi \)-quinone instead of an \( \sigma \)-quinone, the mechanism was:

\[
\text{Al}_2\text{O}_3 + \text{CH}_3\text{COCH}_3 \rightleftharpoons \text{Al}_2\text{O}_3\text{H}^+ + \text{CH}_2\text{COCH}_3
\]

Magnussen presented no evidence to prove that aluminum oxide acts as a base in this reaction, but did mention that with \( \sigma \)-quinones the acetonyl group appears to prefer the more positive of the two carbonyl carbon atoms - a preference consistent with the concept of nucleophilic attack. Therefore, if the attacking species is not the acetonyl anion it is, at least, an acetone molecule with one of the carbon-hydrogen bonds greatly polarized - an effect which does not occur in the absence of aluminum oxide (or any other base).

In 1962, the structure of the addition compound was fi-
nally ascertained by Aghoramurthy et al. The compound was reduced by the zinc dust-acetic acid method to give a hydroxydimethoxyphenylacetone (LXVIII), which was methylated and then subjected to Clemmenson reduction.

\[
\begin{align*}
\text{LXV} & \quad \xrightarrow{\text{Zn/HOAc}} \quad \text{LXVIII} \\
\text{LXIX} & \quad \xrightarrow{\text{Zn(Hg), HCl}} \quad \text{LXX}
\end{align*}
\]

The final product, \( \text{n	ext{-}propylphloroglucinol trimethyl ether (LXIX), was obtained independently from phloroglucinol trimethyl ether (LXX), as shown below:} \)

\[
\begin{align*}
\text{LXX} & \quad \xrightarrow{\text{AlCl}_3, \text{CH}_3\text{CH}_2\text{COCl}} \quad \text{LXX} \\
\text{LXIX} & \quad \xrightarrow{(\text{CH}_3)_2\text{SO}_4, \text{anhydrous K}_2\text{CO}_3, \text{acetone}} \quad \text{LXIX}
\end{align*}
\]
(No explanation was given for the demethylation which seems to have occurred during the Friedel-Crafts reaction.) Also, the products obtained during the preparation of LXIX from LXV gave a positive test for the phloroglucinol system (reaction with vanillin and hydrochloric acid in ethanol), thus providing further confirmation of the proposed structure assignments.

It was suggested by these authors that the preference of acetonyl anion for the carbon atom of the 1-carbonyl group is due to deactivation of the carbonyl group in the 4-position by the mesomeric effect of the two methoxy groups, and that this effect overshadows the opposing steric hindrance effect:

Finally, in 1966 Sarngadharan and Seshadri prepared the acetone-addition product of 2,6-dibenzyloxy-1,4-benzoquinone (LXXI), in order to demonstrate the predominance of the resonance effect (deactivation of the 4-carbonyl group toward nucleophilic attack) over the steric hindrance effect. They proved the structure of the product LXXII by reducing it to a phenol (LXXIII), which gave a positive phloroglucinol-system test, and then subjecting it to successive debenzylation, methylation and Clemmenson reduction, to give the phloroglucinol trimethyl ether derivative (LXIX) which Aghoramurthy and co-workers had prepared earlier.
Since the acetone-addition product of LXXI was no more difficult to prepare than that of XVI, they concluded that the steric hindrance effect of the alkoxy groups is, indeed, negligible with respect to the mesomeric effect.

The authors also reported that 2-methoxy-1,4-naphthoquinone (LIX) did not react under the same conditions, and that 2,6-dimethyl-1,4-benzoquinone (XXXVI) gave unidentifiable polymeric material.

2) The acetate-catalyzed reaction of 2-substituted- and 2,6-disubstituted-1,4-benzoquinones with acetic anhydride

Lounasmaa studied the reaction of toluquinone (V) and 2,6-dimethyl-1,4-benzoquinone (XXXVI) with acetic anhydride in the
presence of sodium acetate. He found that the products were the result of nucleophilic attack at both carbonyl carbon atoms, with attack at the 1-carbonyl predominating to some extent.

\[
\begin{align*}
\text{V: } R &= \text{H} \\
\text{XXXVI: } R &= \text{CH}_3 \\
+ \\
\text{LXXV: } R &= \text{H} \\
\text{LXXVI: } R &= \text{CH}_3
\end{align*}
\]

When \( R = \text{H} \), the ratio of products \( A:B:C:D \) was 30:3:7:60, while when \( R = \text{CH}_3 \), the ratio was 20:4:6:70 (as determined by gas-phase chromatography). The formation of \( A \) is very simple to explain, and that of \( D \) occurs because of tautomerization:

Compounds LXXIV, LXXV, LXXVI and LXXVII result from a series of reactions, of which the key intermediates are LXXVIII and LXXIX and their isomers.

\[
\begin{align*}
\text{LXXVIII: } R &= \text{H} \\
\text{LXXIX: } R &= \text{CH}_3
\end{align*}
\]
With toluquinone, the relative rate of formation of compounds LXXV and LXXIV (indicative of the relative rate of nucleophilic attack at positions 1 and 4) is 7:3, and with 2,6-dimethyl-1,4-benzoquinone the ratio of LXXVII to LXXVI is 3:2. Methyl p-quinones should exhibit a mesomeric effect which deactivates the 4-carbonyl group toward nucleophilic attack; however, the 1-carbonyl group is also deactivated to some extent by the inductive effect of the same methyl group(s), as shown below:

\[
\begin{align*}
\text{Mesomeric effect} & \quad \begin{array}{c}
\text{Inductive effect}
\end{array} \\
\begin{array}{c}
\text{R} \\
\text{O} \\
\text{CH}_3
\end{array} & \quad \begin{array}{c}
\text{R} \\
\text{O} \\
\text{CH}_3
\end{array}
\end{align*}
\]

This tends to complicate the substitution pattern, as the two effects oppose each other. The difference in the ratios may be totally due to experimental error, but it is possible that the steric effect of two methyl groups adjacent to the 1-carbonyl is a more significant factor than the presence of only one methyl group, and that, therefore, the predominance of nucleophilic attack at the 1-carbonyl group diminishes. In any event, the pattern of substitution is not as clear-cut here as it is for other quinones.

In the same paper, Lounasmaa reported that when 2,6-di-tert-butyl-1,4-benzoquinone (XLIII) was reacted with acetic anhydride in the presence of sodium acetate, only 4-acetyl-2,6-di-tert-
butylphenol (LXXX) could be detected by gas-phase chromatography, as well as a small amount of starting material. The author suggested that this result was due to the ability of the two tert-buty1 groups to stabilize a positive charge, so that the mesomeric effect, which causes deactivation of the 4-carbonyl group toward nucleophilic attack, is very strong. Also, while the 1-carbonyl group remains relatively active electronically, it is very seriously "blocked" by the two bulky tert-buty1 groups. Therefore the anion of acetic anhydride is prevented from attacking both carbonyl groups, and only reductive acetylation of XLIII may occur.

In 1968 Lounasmaa further reported34,35 that 2,6-di-methoxy-1,4-benzoquinone (XVI), when treated with sodium acetate in acetic anhydride, gave only one of the two possible isomers, namely the one which results from nucleophilic attack at the 1-carbonyl group (LXXXI), as the major product, and LXXXII as the minor product.
To determine whether the original attack of the anion had occurred at the 1- or 4-carbonyl position, Lounasmaa treated syringyl alcohol (LXXXIII) with acetic anhydride in pyridine, and obtained a product (LXXXIV) with the same elemental analysis, and essentially the same infrared spectrum as LXXXIII. In their respective p.m.r. spectra, however, the chemical shifts of LXXXII and LXXXIV were somewhat different, as were the physical properties. Since the latter compound was known to be 4-acetoxy-3,5-dimethoxybenzyl acetate, the former (product of the acetylation of XVI) had to be the isomeric 4-acetoxy-2,6-dimethoxybenzyl acetate.
The structure of the major product LXXXI, however, was never confirmed. Only the methyl ester derivative was prepared, giving no information about the position of substitution. The chemical shift of the aromatic protons of LXXXI (δ 6.34) lay between the values for the corresponding protons of LXXXII and LXXXIV (δ 6.26 and δ 6.50, respectively). Lounasmaa's main reason for advancing the structure LXXXI, rather than its isomer (aside from the fact that only compound LXXII was isolated from this reaction - no compound LXXIV was detected), was the following theoretical consideration: the mesomeric effect of the two methoxy groups in XVI results in very strong deactivation of the 4-carbonyl group toward nucleophilic attack, even more than in 2,6-dimethyl-1,4-benzoquinone (XXXVI). Unlike XXXVI, however, the inductive effect of the two methoxy groups is such that the 1-carbonyl group becomes more positive, and hence more susceptible toward nucleophilic attack.
Since the two electronic effects are acting in the same direction in XVI, the net result should be that nucleophilic attack is directed almost entirely at the 1-carbonyl group. Although Lounasmaa was not able to isolate any of the isomers of either of the compounds LXXXI or LXXXII, he did not rule out the possibility that there may have been a small amount of either or both of these present in the reaction mixture.

3) Reaction of substituted p-quinones with diazomethane

Early workers in the field of the reactions of p-quinones with diazomethane found only pyrazoloquinones as products. Thus, Pechmann \(^{36}\) reported the reaction of diazomethane with 1,4-naphthoquinone itself, and suggested that the product was 2,3-pyrazolo-1,4-naphthoquinone (LXXXV).

\[
\begin{align*}
\text{CH}_2\text{N}_2 & \quad \text{LXXXV} \\
& \\
\end{align*}
\]

With alkyl-substituted 1,4-quinones, however, the results were not as certain. Some quinones of this type, such as 2-methyl-1,4-naphthoquinone (XXVIII), did not give the pyrazolino derivatives analogous to LXXXV \(^{37}\), while others formed non-nitrogenous compounds which were probably either quinones which had been further methylated, or dimers coupled at unsubstituted positions.
on the rings through an extra methylene group. In 1937, however, Smith and Pings\textsuperscript{38} reacted 2,3,5,6-tetramethyl-1,4-benzoquinone (XLI) with diazomethane, and obtained four different compounds; two were found to have the composition \( \text{C}_{11}\text{H}_{14}\text{N}_{2}\text{O}_{2} \) (LXXXVI and LXXXVII) (corresponding to 1:1 adducts of the quinone and diazomethane), and two had the composition \( \text{C}_{12}\text{H}_{16}\text{N}_{4}\text{O}_{2} \) (LXXXVIII and LXXXIX) (corresponding to 1:2 adducts of the quinone and diazomethane). Further reaction of LXXXVI with diazomethane yielded LXXXIX, and of LXXXVII yielded LXXXVIII.
When LXXXVI and LXXXVII were oxidized with ferric chloride the parent compound XLI was regenerated; and when LXXXVIII and LXXXIX were heated with dilute hydrochloric acid XLI was isolated as well. This series of reactions proved that the derivatives LXXXVI, LXXXVII, LXXXVIII and LXXXIX were all due to addition of diazo-methane 1,2- to either or both carbonyl groups of XLI.

Decomposition of LXXXVI during steam distillation gave a product with the composition C_{11}H_{14}O_{2}; i.e., the nitrogen was removed from the compound, which was assigned the structure 2,3-, 5,6-tetramethylcyclohepta-2,5-diene-1,4-dione (XC). Compound LXXXVII, on the other hand, was stable when steam-distilled.

![Diagram](image)

An oxime of compound XC was prepared, but no hydrazones could be formed. The compound could not be acetylated nor oxidized, and was insoluble in water, dilute hydrochloric acid and dilute sodium hydroxide. It was soluble in concentrated sulphuric acid, but was reprecipitated upon dilution. Although these experimental data are consistent with the structure proposed for the decomposition product of LXXXVI (and, indeed, were used as justification for the structural assignment), it is just possible that,
after loss of nitrogen, the free carbon and oxygen join to form an epoxy ring, rather than rearranging to the proposed tropone derivative. The experimental results, admittedly, do not really support this supposition.

Similarly, the decomposition product of LXXXVIII was assigned either of the two possible structures 2,3,6,7-tetramethylcycloocta-2,6-diene-1,4-dione (XCI) or 2,3,6,7-tetramethylcycloocta-2,6-diene-1,5-dione (XCII), while the product of decomposition of LXXXIX was assigned one of the two possible structures XCIII or XCIV.
Although the structural assignments were not really confirmed to any great degree, owing to the instability of many of these compounds, the fact remains that this was one of the first examples of diazomethane addition to the carbonyl groups of a quinone, rather than to the double bond(s).

In 1954, Marini-Bettolo and Paolini\textsuperscript{39} reported the reaction of 2,6-dimethoxy-1,4-benzoquinone (XVI) with diazomethane. Carbon, hydrogen and methoxyl analyses indicated that the quinone had incorporated a methylene (or methyl) group without an increase in the number of methoxyl groups. The product did not exhibit the properties of a quinone or hydroquinone (in that it did not form a semicarbazide or 2,4-dinitrophenylhydrazone - the fact that this would be true of any quinone which had already reacted in the 4-position did not, evidently, occur to the authors); nor did it react with those compounds which are reactive toward the ethyleneoxy group (there appear to be no experimental data given to support this claim). When hydrogenated, the product gave an unstable compound which could not easily be purified or identified. The authors concluded that the product of the reaction of XVI with diazomethane had to be a tropone, with one of the following structures:

\begin{align*}
\text{XCV} & \quad \text{XCVI} \\
\begin{array}{c}
\text{CH}_3\text{O} \\
\text{OCH}_3
\end{array} & \quad \begin{array}{c}
\text{CH}_3\text{O} \\
\text{OCH}_3
\end{array}
\end{align*}
They invoked the observations of Smith and Pings on the reaction of duroquinone (XLI) with diazomethane to support their proposal. They also compared the infrared spectrum of their product with that of 3,3,7-trimethylcyclohepta-4,6-diene-1-one (XCVII), and

![Chemical Structure](image)

noted that the spectra of both compounds included peaks at 1661 and 1603 cm\(^{-1}\) (attributed to the 1-carbonyl group and a carbon-carbon double bond conjugated with the carbonyl group, respectively). Furthermore, the authors assigned the band at 1621 cm\(^{-1}\) to the 4-carbonyl group of the proposed tropone (they mentioned that "strongly conjugated carbonyl groups in seven-member rings usually exhibit stretching frequencies in the range 1640-1620 cm\(^{-1}\)", but gave no justification or reference to support this assertion). Because of the similarity between the infrared spectra of their "tropone" and the known compound XCVII, they concluded that they had prepared compound XCVI, which must have been formed through the original attack of diazomethane at the 1-carbonyl group of XVI.

Eistert and Bock\(^{10}\) studied the reactions of various substituted quinones with diazomethane as well. From 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil) (XCVIII) they obtained a product which, when hydrogenated, gave the known 2,3,5,6-tetra-
chloro-4-hydroxybenzyl alcohol (XCIX). This led them to conclude that they had prepared 2,3,5,6-tetrachloro-1,1-ethyleneoxycyclohexa-2,5-diene-4-one (C). To prove that this was, indeed, the correct structure, they prepared the identical compound by treating 2,3,5,6-tetrachloro-1-hydroxy-1-chloromethylcyclohexa-2,5-diene-4-one (CI) with sodium hydroxide.
Thus, these reactions established for the first time the possibility of formation of an ethyleneoxy ring at the site of one of the carbonyl groups of a substituted quinone.

When Eistert and Bock reacted 2,6-dimethoxy-1,4-benzoquinone (XVI) with diazomethane, they improved upon the method of Marini-Bettolo and Paoloni by adding a small amount of methanol to the reaction mixture. This enabled them to obtain a considerably more stable form of the product than that which had been prepared by the Italian workers (although both products had melting points of 159°). When they treated the product with nitric acid they obtained the regenerated starting material, and thus proved conclusively that a tropone could not have been produced in the reaction of XVI with diazomethane. They then proposed two possible isomeric structures for the reaction product:

![Reaction Product Structures]

To determine which of these was correct, they hydrogenated the reaction product, expecting to obtain the known syringyl alcohol (LXXXIII), which has a melting point of 135°, if CIII were the actual structure. Instead, they obtained a product which they suggested was the hitherto unknown 4-hydroxy-2,6-dimethoxybenzyl alcohol (CIV). This compound had a melting point of 132° after
purification; but the mixed melting point of LXXXIII and CIV was 120-122°. Furthermore, the infrared spectra of the two compounds, while very similar, were not completely identical.

In discussing their results, the authors disagreed with the infrared band assignments of Marini-Bettolo and Paoloni. They suggested that the peak at 1661 cm\(^{-1}\) was due to the single carbon-yl group, and that the peaks at 1621 and 1603 cm\(^{-1}\) were due to "split" carbon-carbon double bond stretching frequencies. Although their interpretation of the infrared spectrum of the product was not necessarily more believable than that of the Italian workers, their chemical evidence is such that it may safely be concluded that their proposed ethyleneoxy compound (CII or CIII), rather than the tropone postulated by Marini-Bettolo and Paoloni, is the correct structure and, furthermore, that it is indeed the 1-carbonyl group which undergoes attack by diazomethane. (Unfor-
fortunately, lack of an alternate route for the preparation of CIV made it impossible to compare the product of hydrogenation with an authentic sample. The corollary of these two conclusions is that, as deduced by Eistert and Bock, the product of the reaction of XVI with diazomethane is CII.

In 1962, Eistert et al. continued this study by treating 2-methoxy-1,4-naphthoquinone (LIX), among other compounds, with diazomethane. They proposed the structure CV for the product which, when reacted in boron trifluoride-ether solution, gave the methyl ether (CVII) of the known naphthoresorcinaldehyde (CVI). The products of methylation of CVI and of CVII were found to be the identical compound 2,4-dimethoxy-1-naphthaldehyde (CVIII). Also, when CV and CVII were hydrogenated, the product of both reactions was CIX.

\[
\text{LIX} \xrightarrow{\text{CH}_2\text{N}_2} \text{CV} \xrightarrow{\text{BF}_3/\text{ether}} \text{CVII}
\]

\[
\text{CVI} \xrightarrow{\text{CH}_2\text{N}_2} \text{CVIII} \xrightarrow{\text{H}_2} \text{CIX}
\]
Since the preference of diazomethane for nucleophilic attack at the l-carbonyl group of LIX was definitely established by this series of reactions, one extra piece of information has been added to the list of factors which indicate that diazomethane attacks the l-carbonyl group of 2,6-dimethoxy-l,4-benzoquinone (XVI) as well.

In order to demonstrate that the mesomeric deactivation of the 4-carbonyl group of these compounds is one of the major reasons for the predominance of l-substitution, Eistert and co-workers tried to react 2,5-dimethoxy-1,4-benzoquinone (CX) with diazomethane. Since both carbonyl groups of this compound are affected in the same way as the 4-carbonyl group of XVI or LIX, one would expect that little or no product would be formed. Indeed, the starting material was recovered quantitatively from the reaction mixture.

When 2,6-di-tert-butyl-1,4-benzoquinone (XLIII) was reacted with one equivalent of diazomethane in etheric solution, the only product was the pyrazolino derivative CXI. However, when the reaction was performed in methanol-ether solution, a yield of approximately 30% of 4-hydroxy-3,5-di-tert-butylbenzal-
dehydrate (CXII) was obtained, as well as the aforementioned CXI. The proposed reaction path is as follows:

Since the reaction of XLIII with diazomethane to give CXII is so surprising (in view of the proven mesomeric deactivation of the 4-carbonyl group by the two tert-butyl groups), it is most unfortunate that no evidence whatsoever was given for the proposed formation of the aldehyde, nor for the validity of the postulated reaction path. No later articles by the same or other authors clarifying this controversy have been found.
Replacement of the oxygen-16 atoms in the carbonyl groups of substituted 1,4-benzquinones by oxygen-18: nucleophilic attack of oxygen-18-enriched water on quinones

Very little work has been done on the exchange of the oxygen atoms in the carbonyl groups of quinones. The mechanism of exchange is, presumably, nucleophilic attack of $\text{H}_2\text{O}^{18}$ at the carbon atom of the carbonyl group, transfer of a proton to give the diol and loss of $\text{H}_2\text{O}^{16}$:

In 1965, Samuel and Silver\textsuperscript{43} reported that the rate of oxygen-18 exchange decreases with increased alkyl- or fused-ring-substitution in the quinones, but they did not distinguish between exchange at the 1- and 4-carbonyl groups. Dahn and Aubort\textsuperscript{44} studied oxygen-18 exchange in halogenated benzoquinones (specifically 2,3,5,6-tetrachloro-1,4-benzoquinone (XCVIII) and 2,6-dichloro-1,4-benzoquinone (XLVII), and found that the rate of exchange was greater for XCVIII than for XLVII. They concluded, not surprisingly, that the rate of nucleophilic attack of water at the carbonyl carbon atoms must be affected more by the inductive effect of the chloro ring substituents than by the mesomeric (deactivating) effect, and that steric hindrance has little or no importance in determining the rate. Combining the results of their work with those of Samuel and Silver, they obtained the fol-
lowing order for the effect of substituents of 1,4-benzoquinones on the rate of oxygen-18 exchange (and therefore, on the rate of nucleophilic attack of water):

\[ \text{Cl} > \text{Br} > \text{H} > \text{CH}_3 \]

The order of this series agrees with the corresponding order of the inductive effects of these substituents.

Although the authors did not differentiate between exchange at the two different carbonyl groups of the 2,6-disubstituted quinones, the rate of exchange at the 1-carbonyl group is quite likely to be considerably greater than that at the 4-carbonyl group in 2,6-dichloro-1,4-benzoquinone (XLVII), if the proposal is correct that it is the inductive effects of the substituents which is the important factor in the nucleophilic attack of water. Quinones having other substituents with a strong (-I) effect, such as methoxy groups, should exhibit the same preference.

Conclusions

Three factors appear to have major roles in determining the position of attack of various nucleophilic reagents on substituted p-quinones; these are: "steric hindrance" by substituents adjacent to the carbonyl groups, electronic effects (inductive and mesomeric) due to the substituents and the nature of the nucleophile.
In the formation of the mono-oximes, -hydrazones and -semi-carbazones, the first factor seems to be of prime importance. The derivatives of thymoquinone (XXV), in particular, support this conclusion, since the carbonyl group which undergoes nucleophilic attack is the one adjacent to the methyl group rather than the one adjacent to the isopropyl group. Also, formation of only the 4-oxime of 2,6-dimethoxy-1,4-benzoquinone (XVI), studied by Bolker and Kung,7 appears to indicate the importance of the steric hindrance effect in oxime production: despite both the inductive effect (which makes the 1-carbonyl group more positive) and the mesomeric effect (which makes the 4-carbonyl group more electronegative) it is, nonetheless, the 4-oxime which is formed.

The anomalous reactions of 2-hydroxy-1,4-naphthoquinone (LI) with hydroxylamine, hydrazines and semicarbazides has been satisfactorily explained by the suggestion that the anion of LI has only the 1-carbonyl group available for nucleophilic attack. It may also be pointed out that the inductive effect of the 2-hydroxy group further enhances the susceptibility of the 1-carbonyl group towards nucleophilic reactions.

Some reagents appear to be able to "ignore" the effect of steric hindrance, and to follow the logical path dictated by the electronic effects of the substituents: acetone, acetic anhydride and diazomethane. Thus, acetonyl anion and diazomethane were found to react solely at the 1-carbonyl carbon atom of 2,6-dialkoxyo-1,4-benzoquinones and the anion of acetic anhydride reacted at both carbonyl positions of 2,6-dialkyl-1,4-benzoquinones (except
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for 2,6-di-tert-butyl-1,4-benzoquinone (XLIII), which did not react at all in this manner) and at the 1-carbonyl position of 2,6-dimethoxy-1,4-benzoquinone.

The factors which cause the predominance of the steric hindrance effect or the electronic effects, and the importance of the nature of the nucleophilic reagent, are not yet established, although it is probably of great significance that all the nucleophiles which have so far been shown to react at the 1-carbonyl group of the quinones form carbon-carbon bonds, whereas those which react at the 4-carbonyl position form carbon-nitrogen bonds.
Results and Discussion

The base-catalyzed reaction of 2,6-disubstituted-1,4-benzoquinones and 2-substituted-1,4-naphthoquinones with acetone and acetylacet-one

As described above, preparation of a 1:1 adduct of 2,6-dimethoxy-1,4-benzoquinone (XVI) and acetone was reported by Aghoramurthy et al.28 and by Magnussen,29,30 and this product was proved to be 1-hydroxy-1-acetonyl-2,6-dimethoxycyclohexa-2,5-diene-4-one (LXV) by Aghoramurthy and co-workers.31 Furthermore, it was found that 2,6-dibenzylxyloxy-1,4-benzoquinone (LXXI) underwent exactly the same reaction.32 These results suggested the relative unimportance in the course of this reaction of the steric hindrance of the 1-carbonyl group by the substituents at the 2- and 6-positions. Also, it was noted by certain of these authors that other simple quinones do not give this type of compound, the reactions resulting either in recovery of starting material, or in formation of a polymeric product.

In connection with the study of factors affecting the attack of nucleophilic reagents at the 1- and 4-carbons of p-quinones, it seemed of interest to try to prepare the acetonyl adducts of p-quinones with different substituents at positions adjacent to one of the carbonyl groups. Accordingly, a series of reactions was performed, with a singular lack of positive results in most cases.

First, the known addition product (LXV) of the reaction of XVI and acetone was prepared by the method of Aghoramurthy et al.,28 i.e., by refluxing a solution of the quinone in acetone, in
the presence of anhydrous potassium carbonate. The melting point and infrared spectrum of the purified product were in accord with published results. Although the compound was sparingly soluble in most organic solvents, and rather unstable in water (tending to revert to the starting quinone and acetone), a p.m.r. spectrum of the compound in deuterochloroform was obtained, although the concentration was too low to allow for integration of the peaks. The spectrum consisted of peaks at $\delta 5.50$ (due to the ring protons), $\delta 3.81$ (methoxyl protons), $\delta 3.07$ (methylene protons) and $\delta 2.20$ (acetyl protons). There was no peak attributable to the hydroxyl proton.

The mass spectrum of the compound exhibited a molecular ion peak at m/e 226. A partial suggested fragmentation pattern is shown in Figure 1. Neither the p.m.r. spectrum nor the mass spectrum of this compound have been previously reported.

Unfortunately, these reaction conditions were not suitable for preparing the acetone-addition products of other n-quinones. Reaction of 2,6-dichloro-1,4-benzoquinone (XLVII), for example (chosen because of the similarity of the electronic properties of chloro and methoxy substituents), resulted in essentially 100% recovery of starting material. Similarly, 2-hydroxy-1,4-naphthoquinone (LI), 2-methoxy-1,4-naphthoquinone (LIX) and 2-amino-1,4-naphthoquinone (LVIII) gave only starting material, as confirmed by the infrared spectra of the products, although in most cases the reaction mixtures did become much darker in colour.
Figure 1: Suggested Fragmentation Pattern of LXV
(especially when they were refluxed for longer periods of time). One likely explanation for this behaviour is the probability that these are equilibrium reactions, with the position of equilibrium far to the side of starting material. The forward reaction gives an inherently unstable product (the acetonyl compound), which reverts quickly to quinone and acetone. In other words, the rate of the forward reaction is considerably less than that of the reverse reaction.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} & \quad \text{K}_2\text{CO}_3, \text{acetone} & \quad \text{Cl} \\
\text{Cl} & \quad \text{O} & \quad \text{Cl} & \quad \text{HO} & \quad \text{CH}_2\text{COCH}_3
\end{align*}
\]

**XLVII**

Therefore it appears possible that the required product was formed in at least some of the above reactions but, except for the addition product of XVI itself, the resulting compound decomposed either during the course of the reaction or during work-up, giving back only the starting quinones with, perhaps, very small amounts of unknown impurities.

When 2,6-dichloro-1,4-benzoquinone was reacted for 18 hours, a brown, gummy solid was obtained. The infrared spectrum of this material dissolved in chloroform included peaks around 3440 and 1710 cm\(^{-1}\) (corresponding to hydroxyl and aliphatic carbonyl group stretching, respectively), which would be expected of the required addition compound. The product, however, could
not be crystallized, or even dried completely. It was finally concluded that this was some kind of polymeric material, but its exact nature has not been established.

This series of reactions was then repeated, with the modification that, instead of an excess of acetone, only slightly more than one molar equivalent was present, and dioxane was used as the solvent. The mixtures were stirred at 70° for one hour, rather than being refluxed for several hours, in order to prevent excessive loss of the acetone by evaporation.

From the reaction of 2,6-dichloro-1,4-benzoquinone a yellowish-brown wet solid and a brown, very viscous liquid were obtained. The infrared spectrum of the former dissolved in chloroform included strong peaks, as before, around 3450 and 1720 cm⁻¹. The product, being completely soluble in all organic solvents tried, was crystallized from dioxane-water solution, but only starting material was isolated. Although it is quite possible that the required addition product was formed, and then decomposed, another explanation for the presence of the two abovementioned peaks in the infrared spectrum may be postulated. Acetone does not self-condense in the presence of a base which is soluble in it (since the reverse reaction, whose rate is greater than that of the forward reaction, is also catalyzed by the readily available base). Using a base which is insoluble in acetone, however, it is possible to prepare the self-condensation product, because this product may then move away from the site of catalysis, thus inhibiting the reverse reaction.
Although the same series of events must, of course, occur with the addition product of the quinone and acetone, it seems likely that this addition product would be considerably less stable than 5-hydroxy-~h-6-hexan-2-one (CXIII), the self-condensation product of acetone, and so basic catalysis of the reverse reaction would not be as necessary.) If CXIII, which is very likely formed during the course of the reaction, is not easily removed from the quinone, or quinone:quinone-adduct equilibrium mixture, it would account for the presence of the two peaks in the infrared spectrum of the chloroform solution of the product, since the same groups would be present. Since nothing but starting material was isolated after the attempted recrystallization of the product, it would appear to be quite reasonable that this postulate is valid. (It was, unfortunately, impossible to purify the product by chromatography, since acetone-addition compounds of this type are known to be unstable when passed through a chromatographic column.)

The compounds 2-hydroxy-, 2-methoxy- and 2-amino-1,4-naphthoquinone were also reacted under the modified conditions. The first gave a reddish-brown wet precipitate which, when recrystallized, gave only starting material. The second and third also yielded only starting material. All three reactions were
accompanied by immediate changes in the colours of the solutions as acetone was added, perhaps indicating that a 1:1 complex of the various quinones and acetone can form even without the presence of base: the heterogeneous potassium carbonate could not possibly have catalyzed the complete reaction of the quinones in such short periods of time. An attempt was also made to prepare the oxime of the addition product LXV of 2,6-dimethoxy-1,4-benzoquinone, but only a brown, viscous liquid was obtained.

Although the use of methyl ethyl ketone in place of acetone has been reported in the literature, no other ketones appear to have been tried in this reaction. It seemed of interest, therefore, to attempt the reaction of the quinones with acetylacetone (2,4-pentadione). In acetylacetone there are two possible sets of acidic protons: those at the 1- and 5-carbons, and those at the 3-carbon. Although the protons at the 3-carbon are α to both carbonyl groups, and are therefore more acidic than the 1- and 5-protons, the anion formed (B) may be more seriously sterically hindered from attacking at the 1-carbonyl carbon atom of 2- or 2,6-substituted quinones. The anion (A), on the other hand, should be no different from the acetonyl anion itself in nucleophilic attack at the 1-carbonyl group of the quinone.
Accordingly, various quinones were dissolved in acetylacetone, anhydrous potassium carbonate was added, and the suspensions were refluxed for about six hours. When 2,6-dimethoxy-1,4-benzoquinone (XVI) was treated in this manner, the product was a dark brown, viscous oil which could not be dried or crystallized. The infrared spectrum of the product dissolved in chloroform was of no help in identification. Similarly 2,6-dichloro-1,4-benzoquinone and 2-methoxy-1,4-naphthoquinone yielded only unidentifiable brown syrup, which gave only dark brown gums after attempts at crystallization.

These reactions were performed a second time, as in the acetone reactions, by using only equimolar amounts of acetylacetone in dioxane in order to decrease the likelihood of self-condensation of the acetylacetone itself. Again, however, only brown, viscous oils or liquids were obtained.

It appears, therefore, that except for 2,6-dimethoxy-1,4-benzoquinone, reaction of acetone with the quinones examined either does not occur at all, or else results in the formation of addition products so unstable that they decompose during work-up or isolation, giving back only starting material. The infrared absorption peaks corresponding to hydroxyl and aliphatic carbonyl group stretching, which were sometimes observed, have been attributed to the presence of either some polymeric product, or the self-condensation product of acetone, which is presumably quite stable under the reaction conditions used. One last possibility, of course, involves the further reaction of the acetone self-conden-
sation product with additional acetone, eventually leading to a polymer as well.

Reactions of the quinones with acetylacetone (with or without dioxane as solvent) gave only unidentifiable, apparently polymeric products.

The reaction of 2,6-disubstituted-1,4-benzoquinones and 2-substituted-1,4-naphthoquinones with the Grignard reagent, methylmagnesium chloride

The study of the reaction of various substituted p-quinones with a Grignard reagent was undertaken for several reasons. First, it was reasonable to expect that, unlike the addition products of these quinones and acetone, the products of the reaction of the quinones with an alkyl Grignard reagent would be stable compounds. Second, determination of the position of nucleophilic attack would be particularly interesting since, by analogy with the other nucleophiles which form carbon-carbon bonds only at the 1-carbonyl groups of 1,4-quinones, one would expect to obtain the 1-hydroxy-1-methyl derivatives. On the other hand, the presently accepted mechanism for the reaction of Grignards with carbonyl groups is the following:\textsuperscript{45}

\[
2RMgX \rightarrow R_2Mg\cdot MgX_2
\]

\[
\begin{align*}
\text{C} & \quad \text{Mg} \\
\text{O} & \quad X \\
\text{Mg} & \quad X
\end{align*}
\]

\[
\begin{align*}
\text{C} & \quad \text{R} \\
\text{O} & \quad \text{Mg} \\
\text{X} & \quad \text{X}
\end{align*}
\]

\[
\begin{align*}
\text{C} & \quad \text{R} \\
\text{O} & \quad \text{Mg} \\
\text{X} & \quad \text{X}
\end{align*}
\]
Since the first step in either case involves coordination of the carbonyl oxygen with the magnesium (displacing one molecule of ether, according to the second mechanism), it seems logical to postulate that this reaction would occur at the more electronegative carbonyl group of the quinones, i.e., the 4-carbonyl group.

Finally, the reactions of \( \text{p} \)-benzoquinones and \( \text{p} \)-naphthoquinones with equimolar amounts of Grignard reagent had never been reported in the literature: indeed, the methyl-addition products of these quinones (see later) were unknown. Kharasch and Reinmuth\(^\text{46}\) wrote that "with a few exceptions the quinones react with Grignard reagents to give only small percentage yields of readily isolatable and identifiable products. In most cases the major portion of the reaction product consists of a refractory oil or tar, or both". Most of the exceptions mentioned were quinones with three or more fused rings.
The Grignard reagent which we chose to use in these reactions was methylmagnesium chloride. A solution of this compound in tetrahydrofuran (THF) is commercially available, requiring only confirmation of the concentration of the reagent by titration before use. (Because of the method of reaction used, it was necessary to have a previously prepared solution of the Grignard reagent: formation of the Grignard in situ was not possible.) Furthermore, because methyl is the smallest of the alkyl groups, the steric hindrance of reaction at the 1-carbonyl position of the quinone was minimized as much as possible, to allow reaction of the Grignard at this position if it were the preferred position of reaction of alkyl Grignards in general.

The first quinone reacted with methylmagnesium chloride was 2,6-dimethoxy-1,4-benzoquinone (XVI). Rather than following the "normal" method of reaction with Grignards (which involves the addition of a solution of the compound to an etheric solution of an excess of the Grignard), we reversed the procedure by adding to a solution of the quinone in anhydrous benzene (it was insoluble in ethyl ether and THF) a slightly less than equivalent amount of methylmagnesium chloride in THF, in order to protect the quinone from an excess of the Grignard reagent at all times. After work-up, a pale yellow, crystallize material was obtained. The infra-red spectrum of this product differed from that of XVI in that it included peaks at about 3270 cm⁻¹ and at 1370 cm⁻¹ (tertiary hydroxyl group) and at 1470 cm⁻¹, and it no longer exhibited a peak at about 1700 cm⁻¹ (although the peak at 1650 cm⁻¹ was still
present). This peak at 1700 cm\(^{-1}\), which was included in the spectrum of XVI, but absent from that of the methyl-addition product, is obviously due to one of the two carbonyl groups of XVI. Since this same peak was missing from the spectrum of the known 2,6-dimethoxy-1,4-benzoquinone-4-oxime (XVII) (and the peak at 1650 cm\(^{-1}\) was again present), it seems logical to postulate, at least, that it was the 4-methyl compound which had been formed, i.e., 4-hydroxy-4-methyl-2,6-dimethoxycyclohexa-2,5-diene-1-one (CXIV).

\[ \text{CH}_3\text{O} \quad \text{OCH}_2 \quad \text{CH}_3\text{O} \]

\[ \text{CH}_2\text{MgCl/THF} \quad \text{benzene} \quad \text{R. T.} \]

The p.m.r. spectrum of the compound (in deuterochloroform solution) consisted of three singlets at $\delta 5.50$ (2H), $\delta 3.85$ (6H) and $\delta 1.68$ (3H), corresponding to the two ring protons, the six methoxyl protons and the three methyl protons, respectively. There was also a small, broad band centred around $\delta 3.5$ (1H), corresponding to the hydroxyl proton. This last band disappeared when deuterium oxide was added to the deuterochloroform solution. This spectrum is significant in two ways: first, it eliminates the possibility that the Grignard reagent added 1,4 to the quinone (which would have given a product with either of the following structures:}
And second, the shift in the position of the peak due to the quinone ring protons, from 85.93 (in the spectrum of the parent compound, XVI) to 85.50, would appear to indicate that the environment of these two protons has changed, probably because the 4-carbonyl group has become a 4-hydroxy-4-methyl system (which would, indeed, be expected to shift the peak position to higher field). Since the six carbon atoms of the ring are planar in the product (the 1- or 4- carbon is kept in this plane by the rigid system of the two double bonds conjugated with the remaining carbonyl group), the molecule is still symmetric around the C-1 : C-4 axis, and the two ring protons are still in equivalent environments, and together exhibit one singlet in the p.m.r. spectrum of this product.

The mass spectrum of the compound exhibited a molecular ion peak at m/e 184. The rest of the spectrum was very similar to that of LXV, with peaks at m/e's 169, 154, 143, 137 and so on, but also included peaks at m/e's 153, 125, 124 and others, which were not present in the spectrum of the other compound. A partial suggested fragmentation pattern is shown in figure 2.

To confirm the proposed structure (CXIV) of the product, several attempts were made to reduce the remaining carbonyl group to give the hydroxyl compound, and cause the reduced product to
Figure 2: Suggested Fragmentation Pattern of CXIV
lose a molecule of water, which would yield a dimethoxy-\(\mu\)-cresol:

\[
\begin{align*}
\text{CXIV} & \quad \overset{[\text{H}]}{\longrightarrow} \quad \text{CXVI} & \quad \overset{-\text{H}_2\text{O}}{\longrightarrow} \quad \text{CXVII} \\
\end{align*}
\]

If the product of this reduction were the known 2,6-dimethoxy-\(\mu\)-cresol (CXVII) (which may easily be prepared by reducing commercially-available syringaldehyde (CXVIII)), then the original addition product must have been CXIV.

\[
\begin{align*}
\text{CXVIII} & \quad \overset{\text{Zn(Hg)} \quad \text{HCl}}{\longrightarrow} \quad \text{CXVII} \\
\end{align*}
\]

If, however, the two cresols were not identical, then the original addition compound must have been CXV.

Great difficulty was encountered in reducing the compound, quite possibly because of the steric hindrance of the two methoxy groups, assuming that it was the \(1\)-carbonyl which had to be reduced. Finally, however, from one reduction with sodium borohydride, approximately 57 mg. of CXVI (or its isomer) was obtained, as identified by its p.m.r. spectrum. Surprisingly, this compound did not spontaneously lose water, and thus far attempts to cause dehydration have failed.
Compound CXVI, itself (or its structural isomer), is quite interesting in its own right. It appears to be most stable in the boat form, and there are two possible pairs of non-interchangeable isomers:

Both boat forms of each isomer may exist, and rapid interconversion of conformations seems likely. This means that all the protons exist in different environments in the two isomers (because of the loss of symmetry of the molecule) and that, therefore, each type of proton should give rise to two singlets, rather than one, in the p.m.r. spectrum of the product (which is, in fact, a mixture of the two different isomeric compounds). The actual spectrum (in acetone-$d_6$: $D_2O$) consists of a broad signal (unresolved doublet) around $\delta 5.7$, a doublet around $\delta 4.0$, a doublet around $\delta 3.6$ and another doublet around $\delta 1.3$, corresponding to the 3,5-ring protons, the 1-ring proton, the methoxy protons and the methyl protons, respectively. (No signals arising from the hydroxyl protons would be expected, because of exchange with the $D_2O$, and none are seen.)

Additional work is required to prepare one of the two possible dimethoxy-$p$-cresols. In the meantime, however, one may postulate that the product of the reaction of XVI with methylmagn-
Nesium chloride is the compound CXIV, from the infrared and p.m.r. spectral studies.

When 2-methoxy-1,4-naphthoquinone (LIX) was reacted with methylmagnesium chloride under the conditions described, a product was obtained, whose infrared spectrum differed from that of the parent compound in that it had additional peaks at 3400 and 1360 cm\(^{-1}\) (tertiary hydroxyl group) and at 1415 cm\(^{-1}\) (methyl group). As in the spectrum of the previous reaction product, the carbonyl peak at higher frequency (at about 1680 cm\(^{-1}\)) disappeared, allowing a prediction to be made that the Grignard reagent reacted at the 4-carbonyl group of this quinone as well. The p.m.r. spectrum (in deuterochloroform) consisted of a multiplet in the range \(\delta 8.2-7.6\) (corresponding to the protons on the "B" ring), a singlet at \(\delta 5.7\) (corresponding to the proton on the "A" ring, which had shifted from \(\delta 6.2\) in the spectrum of the parent compound), a broad peak around \(\delta 4.4\) (hydroxyl proton) and a singlet at \(\delta 1.7\) (methyl protons).
Again, the simplicity of the spectrum precludes the possibility that addition had occurred 1,4 to the quinone, and the shift in the position of the "A" ring proton appears to indicate that its environment has changed in the same way as in the reaction product of XVI (loss of the effect of the adjacent carbonyl group upon reduction). Therefore the spectral data again point to the formation of CXIX rather than CXX in this reaction. Unfortunately, no integration of the p.m.r. peaks was possible, because of the relative insolubility of the compound in suitable organic solvents. The postulated fragmentation sequence (occurring in the mass spectrometer) is shown in Figure 3.

The reaction of 2-hydroxy-1,4-naphthoquinone (LI) with methylmagnesium chloride was successfully accomplished only after two or three preliminary attempts had failed. In order to obtain the desired product it was necessary to react the quinone with two equivalents of the Grignard reagent, and to reflux the mixture for a while, rather than allowing it to react at room temperature. The proposed reaction sequence is:

\[
\text{LI} + \text{CH}_3\text{MgCl/THF} \rightarrow \text{CXXII or CXXIII}
\]
Figure 31 Suggested Fragmentation Pattern of CIX
Accordingly, it is suggested that it is not 2-hydroxy-1,4-naphthoquinone itself which undergoes nucleophilic attack at one of its carbonyl groups, but rather, 2-0-magnesium ether-1,4-naphthoquinone (CXXI). This substituent increases the steric hindrance (with respect to hydroxyl) towards nucleophilic attack at the 1-carbonyl, but its influence upon the electronic effects felt by the two carbonyl groups is unknown.

The infrared spectrum of the product differed from that of the starting material in the "usual" manner, i.e., the peak at 1675 cm\(^{-1}\) disappeared, while a new peak at 1425 cm\(^{-1}\) (methyl group) and a shoulder at about 1370 cm\(^{-1}\) (tertiary hydroxyl group) were present. The broad band centred about 3190 cm\(^{-1}\) became much more intense.

The p.m.r. spectrum consisted of a multiplet centred around 8.80, a singlet at 8.575, a broad peak around 8.467 and a singlet at 5.157, corresponding to the protons on the "B" ring, the one proton on the "A" ring, the hydroxyl protons and the methyl protons, respectively. As before, the "A" ring proton signal was shifted upfield, although not to the same extent as in the previous examples; and the solution was too dilute to permit integration of the peaks. The tentative conclusion which may be drawn from the spectral data is that the correct structure of the product is CXXII.

The mass spectrum of the product exhibited a molecular ion peak at m/e 190. A partial postulated fragmentation sequence is given in Figure 4.
Figure 41: Suggested Fragmentation Pattern of CXXII
Various attempts were made to confirm chemically the proposed structures of the reaction products of 2-hydroxy- and 2-methoxy-1,4-naphthoquinone; these have not, as yet, been fruitful. One such attempt involved efforts at dehydration of the reaction product of LI. The logic behind this was as follows: if this product can be dehydrated, then the correct structure must be CXXII, since CXXIII is capable only of tautomerization:

\[ \begin{array}{c}
\text{CXXII} \\
\text{OH} \\
\text{HO} \\
\text{CH}_3 \\
\end{array} \rightarrow \begin{array}{c}
\text{CXXIV} \\
\text{OH} \\
\text{HO} \\
\text{CH}_3 \\
\end{array} \]

Dehydration of CXXII would result in the formation of 4-methyl-1,2-naphthoquinone (CXXIV), which is a known compound.

For this reason the addition product was acidified, both with Amberlite IR-120 cationic exchange resin, and with aqueous hydrochloric acid; but no dehydrated product has yet been isolated. However, this negative result is not conclusive: other reaction conditions must still be tried before the inference may be drawn that it is actually the compound CXXIII which was formed in
the reaction.

At the same time as the above reaction was being attempted, an effort was made to link together the reaction products of 2-hydroxy- and 2-methoxy-1,4-naphthoquinone, with respect to the positions of methyl-addition. Both addition products were treated with methanolic hydrochloric acid, in order to form the dimethoxy derivatives. The idea was that if both quinones had been substituted at the same carbonyl group, the products of the methylations would be identical. Even more interestingly, if the two quinones had been methylated at different carbonyl groups, both isomers of the dimethoxy derivatives would have been prepared, and a direct comparison between the two would be made possible.
In particular, the effect on the "A" ring proton of the presence or absence of the 4-carbonyl group would be immediately evident in the p.m.r. spectra of the two isomers, and a general rule concerning the shifting of this peak upon removal of this neighbouring carbonyl group could be proposed.

When the addition product of 2-methoxy-1,4-naphthoquin-one was reacted under the abovementioned conditions, the infrared spectrum of the product in chloroform solution was almost identical with that of the starting material, with the exception that, instead of one hydroxyl peak around 3400 cm⁻¹, there were two peaks around 3560 and 3490 cm⁻¹ (perhaps due to water). Also, several peaks in the range 1300-1200 cm⁻¹ had disappeared. The p.m.r. spectrum of the product had changed quite considerably, however: instead of singlets at 85.7, 83.88 and 81.7, there were doublets centred around each of the aforementioned positions. Since the two rings of the of the product, and all substituents but those at the site of the reacted carbonyl group, are in the same plane, one would expect that the "A" ring proton and the 2-methoxyl protons would be in the same environment regardless of the orientation of the methyl and hydroxyl (or methoxyl) substituents and that, therefore, the possibility of racemization at this site could not explain the appearance of these "doublets". Furthermore, if this were actually the correct reason for the appearance of the doublets, then the original addition product would have been expected to exhibit exactly the same phenomenon in its p.m.r. spectrum, since both orientations are presumably possible in this compound as well.
When 2-hydroxy-1,4-naphthoquinone was treated with methanolic hydrochloric acid, thin-layer chromatography of the reaction product showed three spots and the p.m.r. spectrum indicated the presence of at least some starting material. The mixture was therefore separated by preparative thin-layer chromatography and three bands, with RF's of 0.17, 0.75 and 0.90 were isolated. The p.m.r. spectrum of a sample of the material in the lowest band indicated that it contained the remaining starting material, while the spectra of samples taken from the second and third bands showed that they did not contain this impurity. Surprisingly, the spectra of these samples were identical, and exhibited exactly the same peaks as that of the product of methylation of the 2-methoxy-1,4-naphthoquinone addition product (CXXV or CXXVI), with the exception that the relative intensities of the two peaks within each "doublet" varied from sample to sample. Furthermore, the p.m.r. spectrum of a solution containing about equal amounts of the prod-
ucts from each of the two reactions was identical to the spectra of samples of either one alone, except for the relative peak intensities within each "doublet". Integration of the methyl and methoxyl doublets of all samples indicated that they contained equal numbers of protons (in other words, there was only one methoxyl group in each compound, if the integration was correct). Also, the infrared spectra of samples from the second and third chromatographic bands (dissolved in chloroform) were 100% identical with that of the other methylated product.

A reasonable explanation of these experimental results has not been found. One possibility is that both products are still mixtures, but thin-layer chromatography has not been able to separate them, if so. Although the integration of the methyl and methoxyl doublets indicated that they were due to equal numbers of protons, this would tend to imply that the addition product of 2-methoxy-1,4-naphthoquinone has not reacted at all, a suggestion which is negated by the appearance of the doublets. It would appear to be necessary to methylate the addition products by another method, in order to accomplish the original purpose.

The reactions of 2,6-dichloro-1,4-benzoquinone (XLVII) and of 2-methyl-1,4-naphthoquinone (XXVIII) with methylmagnesium chloride have been performed as well. The product of the first reaction was a brown, viscous oil from which no identifiable compounds have been isolated (presumably because of reaction of the Grignard reagent with the chloro-substituents on the ring), and
that of the second reaction was a brown, wet solid which has not yet been crystallized. The infrared spectrum of this product indicated that it was a mixture of starting material and the desired addition product, and the mass spectrum supported this proposal: there were peaks at m/e 188 (due to the molecular ion of the suggested product), at m/e 172 (due to the molecular ion of the starting material), and at m/e 173 (due to the ion resulting from loss of methyl radical from the product - this peak was much too intense to be merely a (M + 1) peak) of the m/e 172 molecular ion peak). Purification and crystallization of this product will be necessary to confirm that the proposed reaction has, in fact, occurred.
Experimental

All melting points are uncorrected. Infrared spectra were measured as the KBr pellets (except where otherwise noted) on a Unicam Model SP200G Grating Infrared Spectrophotometer. P.m.r. spectra were determined on a Varian A-60 or T-60 spectrometer, with tetramethylsilane as internal standard. Mass spectra were recorded on a Model MS902 mass spectrometer (AEI).

1-acetonyl-1-hydroxy-2,6-dimethoxycyclohexa-2,5-diene-4-one (LXV); Method A

A suspension of 2,6-dimethoxy-1,4-benzoquinone (XVI) (5.0 g.) and anhydrous potassium carbonate (5 g.) in dry acetone (100 ml.) was refluxed for six hours, according to the method of Aghoramurthy et al.\textsuperscript{28} After approximately one hour the quinone went into solution. The dark brown reaction mixture was then filtered, and the potassium salt was washed with hot, dry acetone. The combined filtrate and washings were evaporated to dryness. The residue consisted of 5.0 g. of yellowish-brown material (about 75% crude yield). This was crystallized from a mixture of dry acetone and dry ethyl ether (60:40). Part of the residue failed to dissolve, and was filtered off and dried under vacuum, giving a yellowish-brown solid (2.9 g.) which melted at 155-57°. The filtrate was cooled and filtered again, yielding 1.3 g. of pale yellow, crystalline material (m.p. 157-8°). The infrared spectra of the two products were essentially identical, consisting of major peaks at 3370 cm\(^{-1}\) (hydroxyl group stretching), 1712 and 1670
cm$^{-1}$ (side chain- and ring-carbonyl groups, respectively), 1620
and 1595 cm$^{-1}$ (carbon-carbon double bond stretching), 1375 cm$^{-1}$
ter (tertiary hydroxyl group) and 1250 cm$^{-1}$ ($0$-$CH_3$ ether linkage).
This correlated exactly with the published spectrum of this com-

pound. The p.m.r. and mass spectra of LXV are discussed in the
previous section, and are reproduced on pp. 95 and 98.

Attempted preparations of the addition product of 2,6-dichloro-

\[ 1,1\-benzoquinone \text{ and acetone; Methods B and C} \]

A sample of 2,6-dichloro-$1,1$-benzoquinone (XLVII) (2.5

\[ g. \]) was reacted according to Method "A", yielding 2.3 g. of brown

material, whose infrared spectrum indicated that it was mainly
starting material. This product was crystallized from a mixture
of dry acetone and dry ethyl ether (50:50). A small part of the
residue did not dissolve, and was filtered off and dried incom-

pletely. The infrared spectrum of this dark brown, slightly gummy
material (measured in chloroform solution) was of no use in deter-
minating the structure of the product. The filtrate was cooled
and filtered again, yielding a yellowish-brown, crystalline materi-

al: its infrared spectrum indicated that it was pure starting mat-

erial.

A second attempt to prepare the desired product differed
from the first only in that the mixture was refluxed for eighteen
hours (Method "B"). After work-up, a brown, gummy solid was ob-
tained. Crystallization of this material yielded a very dark
brown solid product, whose infrared spectrum included peaks at
3440 and 1720 cm$^{-1}$, as well as those attributable to starting material. No p.m.r. spectrum of this material could be obtained, because of its insolubility in suitable solvents. The mass spectrum of the compound contained many peaks at m/e's greater than 400, and none at m/e 234, 236 or 238, the molecular weights of the expected product - more than one molecular weight because of the chlorine atoms. It is therefore concluded that the product formed was polymeric, and that none of the desired addition compound was obtained.

A final attempt (Method "C") involved the reaction of 2.5 g. of the quinone with 2.0 ml. of anhydrous acetone (1.64 g., about a 1:2 molar ratio) and 2.5 g. of anhydrous potassium carbonate, in 50 ml. of dry dioxane, at 70$^\circ$ for one hour. The reaction mixture was filtered, and the potassium salt was washed with hot, dry dioxane. The filtrate and washings were evaporated separately. The former yielded a yellowish-brown, somewhat wet solid residue, and the latter, an unidentifiable brown syrup. The infrared spectrum of the yellowish-brown material (dissolved in chloroform) included peaks at about 3450 and 1730 cm$^{-1}$, as well as those attributable to starting material. The product was dissolved in dioxane and water was added to the solution, which was then cooled. Yellowish-green crystals separated out, and these were filtered off. The infrared spectrum of this crystalline material was identical with that of the starting material. The mother liquor was evaporated, leaving a brown, gummy solid residue which could not be identified.
Attempted preparation of the addition product of 2-hydroxy-1,4-naphthoquinone and acetone

Reaction of 2-hydroxy-1,4-naphthoquinone (LI) with acetone according to Method "A" yielded a brown, solid residue, whose infrared spectrum showed that it was only slightly impure starting material. Similarly, reaction of LI with slightly more than an equivalent amount of acetone (according to Method "C") gave only starting material.

2-Methoxy-1,4-naphthoquinone (LIX)

A solution of 2-hydroxy-1,4-naphthoquinone (LI) (20.0 g.) and concentrated hydrochloric acid (10 ml.) in 500 ml. of anhydrous methanol was refluxed for six hours. When the solution was cooled, a light-brown, crystalline material separated out. This was filtered off, washed with cold methanol and dried under vacuum, yielding 19.2 g. (approximately 88% yield) of product. The filtrate was evaporated, leaving a small amount of a dark brown, viscous liquid, which was discarded. The infrared spectrum of the crystalline product contained major peaks at 1670 and 1650 cm\(^{-1}\) (attributable to the two carbonyl groups of a 1,4-quinone), various peaks in the range 1600-1575 cm\(^{-1}\) (carbon-carbon double bond stretching), a peak at 1445 cm\(^{-1}\) (methoxyl group carbon-hydrogen bending) and a strong peak at 1245 cm\(^{-1}\) (methoxyl O-C ether linkage), among others. The latter two peaks were not present in the spectrum of LI. The p.m.r. spectrum (deuterochloroform) contained a multiplet centred around 0.79 (H\(^{13}\)), a singlet at 5.62
(1H) and a singlet at 8.392 (3H). These chemical shifts are consistent with the expected product. The melting point of the product was 180-2° (literature value 181.3°), and it was used without further purification.

**Attempted preparation of the addition product of 2-methoxy-1,4-naphthoquinone and acetone**

Reaction of 2-methoxy-1,4-naphthoquinone (LIX) with acetone was attempted using Method "A", Method "B" and Method "C". Only slightly impure starting material was recovered from each reaction mixture.

**Attempted preparation of the addition product of 2-amino-1,4-naphthoquinone and acetone**

Reaction of 2-amino-1,4-naphthoquinone (LVIII) with acetone was attempted using both Method "A" and Method "C", but only starting material was recovered.

**Attempted preparation of the addition products of various 1,4-quinones and acetylacetone**

There were two general procedures followed (more or less equivalent to Method "A" and Method "C" above). The first consisted of refluxing a suspension of 2.0 g. of the quinone and 2 g. of anhydrous potassium carbonate in dry (redistilled) acetylacetone (50 ml.). This gave, in all cases, dark brown mixtures, which were filtered. The potassium salts were washed with several portions of hot, dry acetylacetone, and the combined filtrates and
washings were evaporated incompletely. The products were dark brown, viscous liquids (or wet solids) in all cases, from which no identifiable material could be isolated. The quinones treated in this manner were 2,6-dimethoxy-1,4-benzoquinone, 2,6-dichloro-1,4-benzoquinone and 2-methoxy-1,4-naphthoquinone.

The second procedure consisted of reacting a mixture of 2.5 g. of the quinone, 2.5 g. of anhydrous potassium carbonate and 1.9 ml. (1.85 g., about 1:1.25 molar ratio) of acetylacetone in 50 ml. of anhydrous dioxane at 80° for 2.5 hours. The quinones treated were 2,6-dimethoxy-1,4-benzoquinone and 2,6-dichloro-1,4-benzoquinone. Both gave dark brown mixtures, which were filtered. The potassium salts were washed with several portions of hot, dry dioxane, and the combined filtrates and washings were evaporated incompletely. Again, the products were dark brown, viscous liquids or wet solids, and unidentifiable.

**Determination of the concentration of a solution of methylmagnesium chloride in tetrahydrofuran (THF)**

A solution of methylmagnesium chloride in THF (0.5 ml.) was added to 5 ml. of distilled water, in order to hydrolyze the Grignard reagent to Mg(OH)Cl, and the mixture was heated for several minutes to assure complete hydrolysis. Sulphuric acid (8.0 ml., 0.244N) and three drops of phenolphthalein were added to the mixture, which was then titrated to the endpoint with sodium hydroxide (0.242N). In two runs, 1.65 and 1.76 ml. of base were required. The concentration of the solution was calculated to be 3.1M.
The methyl-addition product of 2,6-dimethoxy-1,4-benzoquinone and methylmagnesium chloride

To a solution of 2,6-dimethoxy-1,4-benzoquinone (XVI) (3.4 g.) in anhydrous benzene (25 ml.) was slowly added a solution of methylmagnesium chloride (3.1 moles/litre) in THF (6.5 ml.). During the addition of the Grignard reagent, which was accomplished over a period of 2.5 hours, the colour of the solution changed from yellow to green. The mixture was stirred at room temperature for another 2.5 hours, and was then poured into a solution of aqueous sulphuric acid (0.25N, 20 ml.). After dilution with a further 50 ml. of water and neutralization with base, the aqueous solution was extracted with chloroform (3 x 100 ml.), and the combined extracts were dried over anhydrous magnesium sulphate, filtered and evaporated, leaving a wet, yellow, crystalline material. This was extracted with a small amount of acetone: part of the residue failed to dissolve, and was filtered off and dried. It was found to be pure starting material, from its infrared spectrum. The filtrate was evaporated and washed with carbon tetrachloride. The dried residue was a pale yellow, crystalline material, with a melting point of 147-8°. The infrared, p.m.r. and mass spectra of this compound indicated that it was the desired methyl-addition compound, with the structure CXIV or CXV. The yield of the pure product was 0.70 g., or about 20%. A further small yield of impure product was obtained by acidifying the original aqueous layer and extracting again with chloroform.
Reduction of the carbonyl group of the methyl-addition product of XVI

After several abortive attempts to reduce the addition product CXIV (or CXV) with sodium borohydride or lithium aluminum hydride (the unidentifiable products were probably mixtures of reduction products in some cases, because of the susceptibility toward reduction of double bonds conjugated with carbonyl groups, and recovered starting material in other cases), a successful method of reduction of the compound was found. One hundred milligrams of the addition compound was dissolved in 20 ml. of 70% aqueous ethanol, and the solution was stirred at room temperature while a solution of 150 mg. of sodium borohydride in 70% aqueous ethanol (15 ml.) was added dropwise. The mixture was stirred for twenty-four hours, and then the excess of sodium borohydride was destroyed by adding Amberlite IR-120 cationic exchange resin. After filtration, the solution was evaporated, methanol was added, and the methanolic solution was evaporated again. This addition and evaporation was repeated several times, in order to remove all the remaining borates as the low-boiling $\text{B(OCH}_3\text{)}_3$. The residue was a yellow oil (57 mg.), and its p.m.r. spectrum showed that it was a mixture of the two isomers of the desired reduced compound. This compound did not spontaneously lose water to give the corresponding dimethoxy-$p$-cresol; in fact, even treatment of the compound with moderately strong (0.5N) aqueous hydrochloric acid failed to give the cresol.
The methyl-addition product of 2-methoxy-1,4-naphthoquinone and methylmagnesium chloride

To a solution of 2-methoxy-1,4-naphthoquinone (LIX) (3.0 g.) in anhydrous benzene (50 ml.) at room temperature was slowly added a solution of methylmagnesium chloride (3.1 moles/litre) in THF (5.1 ml.). During the addition of the Grignard reagent, which was accomplished over a period of one hour, the colour of the solution changed from brown to very dark green. The mixture was stirred at room temperature for a further eight hours, and then added to 25 ml. of aqueous hydrochloric acid (1N). After dilution with another 25 ml. of distilled water, the mixture was extracted with chloroform (3 x 75 ml.), and the combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaporated, leaving a slightly gummy reddish-brown precipitate. This was recrystallized from ethanol: part did not dissolve, and was filtered off. The infrared spectrum of this compound showed that it was unreacted starting material. The filtrate was cooled, causing more reddish-brown crystalline material to separate out. This was filtered and dried, and again found to be starting material. The mother liquor was then evaporated, and the infrared spectrum of the residue (measured in chloroform solution) indicated that it contained some of the desired product. Therefore the residue was dissolved in chloroform, and petroleum ether was added to the solution, which caused a brown, powdery material and a reddish-brown, gummy material to separate out. The brown solid
was filtered off (the gummy material remaining attached to the wall of the flask) and dried, giving 0.40 g. of product (about 13% yield) with a melting point of 141-3°. The infrared, p.m.r. and mass spectra all indicated that this was the desired product. The gummy material, presumably polymeric, was not identifiable by its infrared spectrum (measured in chloroform solution).

Methylation of the methyl-addition product of LIX

One hundred milligrams of the methyl-addition product of LIX was dissolved in 25 ml. of anhydrous methanol, and hydrogen chloride gas was bubbled through until one gram had been absorbed. The solution was stirred (in a closed flask) for eighteen hours, and then neutralized with sodium carbonate. The mixture was filtered, evaporated, extracted with acetone (in which sodium carbonate is not soluble), filtered and evaporated again, leaving a residue of brown oil, the p.m.r. spectrum of which has been reported above.

The methyl-addition product of 2-hydroxy-1,4-naphthoquinone and methylmagnesium chloride

After several previous attempts to prepare the methyl-addition product of 2-hydroxy-1,4-naphthoquinone (LI) had failed, the following procedure was used successfully to obtain the desired product: 3.0 g. of LI was dissolved in 50 ml. of anhydrous benzene, and the solution was stirred vigorously while 11.1 ml. of methylmagnesium chloride solution (slightly less than twice
the molar amount of LI present in the solution) was added dropwise. The mixture was refluxed (instead of being stirred at room temperature, as in the previous attempts) for fifteen hours, and then added to 50 ml. of distilled water containing 4 ml. of concentrated hydrochloric acid. This was extracted with chloroform (3 x 100 ml.), and the combined organic layers were dried over magnesium sulphate, filtered and evaporated, leaving a dark brown, wet solid residue. On addition of chloroform, part of this residue did not dissolve, and was filtered off. This gave a beige powder, which was dried under vacuum (0.97 g., approximately 30% yield). The infrared, p.m.r. and mass spectra, described above, indicated that this was the desired methyl-addition product. Evaporation of the chloroform from the filtrate left a brown, slightly wet solid, of undetermined composition. The melting point of a small recrystallized sample of the methyl-addition product was 145.1-145.5°.

**Attempted dehydration of the methyl-addition product of LI**

The methyl-addition product of LI (250 mg.) was dissolved in 15 ml. of ethyl acetate, and Amberlite IR-120 cationic exchange resin (which had been equilibrated in ethyl acetate) was added to the solution. The mixture was refluxed for thirty-six hours, filtered and evaporated, leaving 230 mg. of a beige solid, which was slightly impure starting material, as judged from its infrared spectrum. When the reaction was repeated, using 1 ml. of concentrated hydrochloric acid instead of the resin, a yellow-
brown liquid remained after neutralization with sodium carbonate, filtration and evaporation. The infrared spectrum of this liquid (measured in chloroform solution) was not helpful in identifying the product (which may be polymeric), but it ruled out the possibility of the formation of the desired 4-methyl-1,2-naphthoquinone (CXXIV).

Methylation of the methyl-addition product of LI

In 25 ml. of anhydrous methanol, 150 mg. of the methyl-addition product of LI was dissolved, and IR-120 resin (which had been equilibrated in methanol) was added. The mixture was stirred at room temperature for twenty-one hours, and the reaction was followed by thin-layer chromatography, using chloroform-methanol (15:2) as developer. The Rf value of the starting material was 0.2 and, to some extent, this spot remained as the reaction continued, while two new spots gradually appeared at Rf's 0.75 and 0.9. The reaction mixture was separated by preparative thin-layer chromatography on Kodak "Chromagram" coated sheets. Extraction of the samples from the sheets was accomplished by washing the bands in chloroform, and evaporating the solvent, leaving brown liquids in all cases. The p.m.r. and infrared spectra of the three samples are reported in the previous section.
The methyl-addition product of 2-methyl-1,4-naphthoquinone and methylmagnesium chloride

To a solution of 2-methyl-1,4-naphthoquinone (XXXI) (3.0 g.) in anhydrous ethyl ether (60 ml.) was added dropwise, with vigorous stirring, a solution of methylmagnesium chloride (3.1 moles/litre) in THF (5.6 ml.). The solution turned orange, and then red, as the Grignard solution was added. The mixture was refluxed for six hours, and then added to 50 ml. of distilled water containing 2 ml. of concentrated hydrochloric acid. The solution was then extracted with chloroform (3 x 100 ml.), and the combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaporated, leaving 3.3 g. of dark brown, wet solid, which has resisted all attempts at crystallization. However, the infrared and mass spectra of the product indicate that it is a mixture of the desired product and starting material.
SPECTRA

IR spectrum no. 1 (CHCl₃): Product of the reaction of 2,6-dichlo­ro-1,4-benzoquinone (XLVII) with acetone.

IR spectrum no. 2 (CHCl₃): Product of the reaction of 2,6-dime­thoxy-1,4-benzoquinone (XVI) with acetylacetone.

IR spectrum no. 3 (KBr): Methyl-addition product (CXIV or CXV) of 2,6-dimethoxy-1,4-benzoquinone (XVI).
IR spectrum no. 4 (KBr): Methyl-addition product (CXIX or CXX) of 2-methoxy-1,4-naphthoquinone (LIX).

IR spectrum no. 5 (KBr): Methyl-addition product (CXXII or CXXIII) of 2-hydroxy-1,4-naphthoquinone (LI).

IR spectrum no. 6 (CHCl₃): Product of the reaction of 2-methyl-1,4-naphthoquinone (XXVIII) with methylmagnesium chloride.
IR spectrum no. 2 (CHCl₃): Product of the reaction of CXIX or CXX with methanolic hydrochloric acid.

P.m.r. spectrum no. 1 (acetone-d₆/D₂O): Product of the reduction of CXIV or CXV.
Figure spectrum no. 2 (CDCl₃): 1-Hydroxy-1-acetyl-2,6-dimethoxy-cyclohexa-2,5-diene-4-one (LXV).

Figure spectrum no. 3 (CDCl₃): Methyl-addition product (CXIV or CXV) of 2,6-dimethoxy-1,4-benzoquinone (XVI).
P.m.r. spectrum no. 4 (CDCl₃): Methyl-addition product (CXXIX or CXX) of 2-methoxy-1,4-naphthoquinone (LIX).

P.m.r. spectrum no. 5 (acetone-d₆): Methyl-addition product (CXXII or CXXIII) of 2-hydroxy-1,4-naphthoquinone (LII).
**P.m.r. spectrum no. 6 (CDCl₃):** Product of the reaction of CXXIX or CXXX with methanolic hydrochloric acid.

**P.m.r. spectrum no. 7 (CDCl₃):** Product of the reaction of CXXII or CXXIII with methanolic hydrochloric acid.
Mass spectrum no. 1: 1-Hydroxy-1-acetonyl-2,6-dimethoxycyclohexa-2,5-diene-4-one (LXV).

Mass spectrum no. 2: Methyl-addition product (CXIV or CXV) of 2,6-dimethoxy-1,4-benzoquinone (XVI).

Mass spectrum no. 3: Methyl-addition product (CXIX or CXX) of 2-methoxy-1,4-naphthaquinone (LIX).
Mass spectrum no. 4: Methyl-addition product (CXXII or CXXIII) of 2-hydroxy-1,4-naphthoquinone (II).

Mass spectrum no. 5: Product of the reaction of 2-methyl-1,4-naphthoquinone (XXVIII) with methylmagnesium chloride.
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