THE REACTION OF PROPYLENE OXIDE WITH METHANOL

and

THE PREPARATION OF 2,6-DIMETHYL-1-HYDROXY-4-METHOXYCYCLOHEXANECARBONITRILE

by

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1949
The author wishes to express his appreciation for the valuable suggestions and guidance offered by Dr. E. Wilkins Reeve, who directed this investigation.

The author also should like to express his thanks to Miss Eleanor Werble, Mrs. Mary Aldridge, and Mr. Byron Baer for their aid in analysing the various compounds encountered during the course of this investigation.
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FORWARD

Part I of this thesis deals with the synthesis of two of the isomeric methoxypropanols, the determination of their physical constants, the preparation of derivatives, and a comparison of these isomers with the materials obtained from the condensation of propylene oxide and methanol.

Part II is concerned with the preparation of 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile. This is an intermediate in a proposed synthesis of a sterically hindered bicyclo carboxylic acid. Reactions of the cyano hydrin and its derivatives are described.
PART I

THE REACTION OF PROPYLENE OXIDE
WITH METHANOL
INTRODUCTION

The condensation of propylene oxide and methanol can yield the two isomeric alcohols shown in Figure I.

\[
\begin{align*}
\text{CH}_3\text{CHCH}_2\text{OH} & \quad \text{CH}_3\text{CHCH}_2\text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OH}
\end{align*}
\]

2-methoxypropanol-1 \quad 1-methoxypropanol-2

Figure I

J. G. Davidson (12) reported that the condensation of propylene oxide and methanol yielded a compound boiling at 123°C to which he assigned the structure 1-methoxypropanol-2. His reaction conditions were not completely described; the reaction was apparently uncatalysed, and the structure of the product was not proved. Later, Dewael (13) studied the sulfuric acid catalysed condensation of propylene oxide and methanol, and reported a boiling point of 126°C for the product to which he assigned the structure of 1-methoxypropanol-2. This assignment was based on the relationship of the boiling point of the product to the boiling point of the mono-ether of ethylene glycol.

A. A. Petrov (26) was the first to realize that the reaction of propylene oxide and methanol, when acid catalysed gave a mixture of the isomeric alkoxypropanols, but when base catalysed yielded only one isomer. In a subsequent publication (27) Petrov established the structure by oxidation studies as shown in Figure II.
He found that the product obtained from the alkaline catalysed reaction, boiling point 118°, yielded methoxyacetone on oxidation in fifteen per cent of the theoretical yield, while the product from the acid catalysed reaction gave a mixture of ten per cent of the theoretical quantity of α-methoxypropionic acid and 13% of the theoretical quantity of methoxyacetone. Petrov (26) tried unsuccessfully to obtain 2-methoxypropanol-1 in a pure state by acetyling the reaction mixture from the acid catalysed condensation with less than the theoretical amount of acetic anhydride and separating the acetate from the unreacted methoxypropanol. The unreacted methoxypropanol should be the less easily acetylated 1-methoxypropanol-2, and hydrolysis of the acetate should yield the 2-methoxypropanol-1. However, both isomers were acetylated.

In a recent paper, Chitwood and Freure (10) reported similar results from the condensation of propylene oxide and ethanol. The isomers were separated by careful fractionation and characterized by reacting the isomeric alkoxypropanols with acetic anhydride and sulfuric acid. The isomer containing the secondary ether linkage formed a diacetate,

\[
\text{CH}_3\text{CHCH}_2\text{OCH}_3 + \text{K}_2\text{Cr}_2\text{O}_7 + \text{H}_2\text{SO}_4 \rightarrow \text{CH}_3\text{CHCH}_2\text{OCH}_3
\]

\[
\text{CH}_3\text{CHCH}_2\text{OCH}_3 \text{ and CH}_3\text{CHCH}_2\text{OH} + \text{K}_2\text{Cr}_2\text{O}_7 + \text{H}_2\text{SO}_4 \rightarrow \text{CH}_3\text{CHCH}_2\text{OCH}_3 \text{ and CH}_3\text{CHCOOH}
\]

(mixture of isomers)

**Figure II**
while the one containing the more stable primary ether linkage formed a monoacetate only.

No unequivocal syntheses of any of the isomeric alkoxypropanols have been reported, nor have crystalline derivatives of these compounds been prepared. Most of the physical data on the products obtained by acid catalysis are questionable because of the difficulty of separating the mixture of isomers formed.

The objects of this investigation were to develop unequivocal syntheses for 2-methoxypropanol-1 and 1-methoxypropanol-2, to prepare suitable derivatives of these, and to compare these compounds with the products obtained by reacting propylene oxide with methanol.
DISCUSSION

Introduction

The isomeric methoxypropanols cannot be made from the corresponding propylene chlorohydrins and sodium methoxide. Chitwood and Freure (10) have reported data indicating the presence of propylene oxide as an intermediate in the reaction of 1-chloropropanol-2 with sodium ethoxide. Kalesch (16) has shown that 1-methoxy-3-butene-2-ol is formed regardless of which butadiene monochlorohydrin is used as the starting material.

Other alkoxy alcohols have, however, been prepared. Dewael (13), for example, has prepared 2-ethoxypropanol-1 by the following series of reactions:

\[
\begin{align*}
\text{CH}_3\text{CHCH}_2\text{Cl} + (\text{C}_2\text{H}_5)_2\text{SO}_4 &\rightarrow \text{CH}_3\text{CHCH}_2\text{Cl} + \text{CH}_3\text{COH} \\
\text{CH}_3\text{CHCH}_2\text{Cl} &\rightarrow \text{CH}_3\text{COOCH}_3 \\
\text{CH}_3\text{CHCH}_2\text{OCOCCH}_3 + \text{KOH} &\rightarrow \text{CH}_3\text{CHCH}_2\text{OH}
\end{align*}
\]

Figure III

Faloomaa (24) has reported the synthesis of 1-methoxy-2-methylpropanol-2 by the action of methyl magnesium iodide on methyl methoxyacetate. Neither of these methods are practical for the unequivocal synthesis of 1-methoxypropanol-
2 and 2-methoxypropanol-1.

Synthesis of Pure 2-Methoxypropanol-1 from Ethyl α-Methoxypropionate

2-Methoxypropanol-1 was prepared by the copper chromite catalysed hydrogenolysis of ethyl α-methoxypropionate. The hydrogenolysis of the ester proceeded normally, and no by-products were detected. In view of its successful use in this case, this method holds promise of being generally applicable in the synthesis of pure 2-alkoxy-substituted primary alcohols. Levene (11,18) and coworkers have reduced the methyl esters of various uronic acids and amino acids over copper chromite catalysts, and this reaction has also been used recently by Fuson (17) to prepare 2-diethylaminopropanol-1. Levene (20,23) and Adkins (1) have also reduced esters of amino acids using Raney nickel as a catalyst. Adkins states that this method has been applied successfully to a number of α-hydroxy esters, and to ethyl α-tetrahydrofuroate. However, the copper chromite catalysed hydrogenolysis of α-alkoxy esters does not appear to have been used previously.

An attempt was made to prepare α-methoxypropionaldehyde which would be expected to hydrogenate to 2-methoxypropanol-1. None of the aldehyde could be obtained by a lead tetraacetate oxidation of α-hydroxy-β-methoxybutyric acid using acetic acid as a solvent. The lead tetraacetate was reduced in the course of the reaction, and the resulting mixture gave a slight 2,4-dinitrophenylhydrazine test. No derivative or free aldehyde could, however, be isolated after the acetic
acid was removed by fractionation and partial crystallization. The failure to isolate the aldehyde could have been due to the difficulties involved in separating it from the acetic acid solvent. Gedda (21) has reported the lead tetraacetate oxidation of lactic, mandelic and several other α-hydroxy acids to the aldehyde containing one less carbon atom.

**Synthesis of Pure 1-Methoxypropanol-2 from Methoxyacetone**

1-Methoxypropanol-2 was prepared by the hydrogenation of methoxyacetone over Raney nickel catalyst. The methoxyacetone was prepared from methoxyacetonitrile and methyl magnesium bromide (15). Methoxyacetone could not be made from the reaction of bromoacetone and sodium methoxide; no identifiable product was obtained when these materials were allowed to react. The bromoacetone probably underwent condensation reactions in the presence of the sodium methoxide.

**1-Methoxypropanol-2 by the Alkaline Catalysed Condensation of Propylene Oxide and Methanol**

From the sodium methoxide catalysed reaction of methanol and propylene oxide in a sealed tube at 100° for four hours as described by Petrov (26), 1-methoxypropanol-2 was obtained in 63 per cent of the theoretical yield. Its physical properties agreed in all respects with the material prepared by the reduction of methoxyacetone. Careful fractionation of 80 ml. of the sodium methoxide catalysed reaction mixture through a
50 cm. long helices packed column failed to indicate the presence of any of the other isomer. This did not, however, preclude the possibility that traces of another constituent were present in the material held up in the column. The preferred procedure for preparing 1-methoxypropanol-2 was by the alkaline catalysed condensation of propylene oxide and methanol.

2-Methoxypropanol-1 and 1-Methoxypropanol-2

by the Acid Catalysed Reaction of Propylene Oxide and Methanol

The sulfuric acid catalysed reaction of propylene oxide and methanol at atmospheric pressure as described by Chitwood and Freure (10) gave 15 per cent of the theoretical yield of 1-methoxypropanol-2, six per cent of the theoretical yield of 2-methoxypropanol-1, and an additional estimated 25 per cent yield of the mixed isomers in the form of low boiling and intermediate fractions. Since the isomers differ in boiling point by only twelve degrees, it was difficult to obtain either isomer in a reasonably pure state except by fractionation through a thirty plate Oldershaw (22) column. Even after such careful fractionation, the methoxypropanols had an unpleasant odor. On standing, and after redistillation, the odorous material was gradually removed. Even after repeated fractionations, the higher boiling isomer, 2-methoxypropanol-1, gave a positive Schiff test and a slight precipitate with 2,4-dinitrophenylhydrazine reagent. Because of the difficulty of separating the isomeric methoxypropanols,
the low yields, and the presence of residual impurities, it was more practical to obtain pure 2-methoxypropanol-1 by the reduction of ethyl α-methoxypropionate than from propylene oxide.

Comparison of the Physical Properties of the Methoxypropanols and Their Derivatives

The physical properties of the methoxypropanols and the melting points of their derivatives are given in Table I.

The physical constants given in Table I show clearly that the lower boiling isomer is 1-methoxypropanol-2, and the higher boiling isomer is 2-methoxypropanol-1. The physical constants for the 1-methoxypropanol-2 are in agreement with those previously reported by Petrov (26). A comparison of the physical constants given in Table I with those reported by Dewael (13) show that Dewael's "1-methoxypropanol-2" obtained by the acid catalysed reaction of propylene oxide and methanol was actually a mixture of the two isomers, and not a pure compound. The physical properties of Petrov's "2-methoxypropanol-1" obtained by partial acetylation of the mixture of isomers, show that it was still contaminated with large amounts of 1-methoxypropanol-2.

1-Methoxypropanol-2 is now commercially available from the Dow Chemical Company, Midland, Michigan under the name of "Dowanol 33 B". The physical properties of the commercial product agree well with those given in Table I for the material obtained by the base catalysed reaction of propylene oxide and methanol. A comparison of these values is given in
### TABLE

Physical Properties of the Methoxy 2-Methoxypropanol-1

<table>
<thead>
<tr>
<th>Property</th>
<th>from ethyl</th>
<th>from propylene oxide, acid catalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>b.p.</td>
<td>130-130.2°</td>
<td>130-130.5°</td>
</tr>
<tr>
<td></td>
<td>758 mm.</td>
<td>758 mm.</td>
</tr>
<tr>
<td>€20</td>
<td>1.4070</td>
<td>1.4076</td>
</tr>
<tr>
<td>€25</td>
<td>1.4048</td>
<td>1.4055</td>
</tr>
<tr>
<td>d420</td>
<td>0.938</td>
<td>0.938</td>
</tr>
<tr>
<td>d425</td>
<td>0.934</td>
<td>0.934</td>
</tr>
<tr>
<td>m.p.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,5-dinitrobenzoateα</td>
<td>96.5-97°</td>
<td>95.5°</td>
</tr>
<tr>
<td>m.p.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-naphthylurethaneβ</td>
<td>60-60.5°</td>
<td>60-60.5°</td>
</tr>
</tbody>
</table>

αMelting points of the two dinitrobenzoates, m.p.s 95.5-97°, were not depressed on mixing; m.p.s of the three dinitrobenzoates, m.p.s 83.5-85° were not depressed on mixing; m.p. of mixture of isomers, 74-82°.

βMelting points of the two urethanes, m.p.s 60-60.5°, were not depressed on mixing; m.p.s of the three urethanes, m.p.s 71-73° were not depressed on mixing; m.p. of mixture of isomers, 55-64°.

cPreviously reported values: Dewael (13) (assigned 1-methoxypropanol-2 structure but actually mixture of isomers)

b.p., 126-127°; €20, 1.4070; d420, 0.9260.
propanols and Their Derivatives

<table>
<thead>
<tr>
<th>1-Methoxycropanol-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>from methoxy acetone</td>
</tr>
<tr>
<td>118°/750 mm.</td>
</tr>
<tr>
<td>1.4038</td>
</tr>
<tr>
<td>1.4020</td>
</tr>
<tr>
<td>0.923(^e)</td>
</tr>
<tr>
<td>0.920(^e)</td>
</tr>
<tr>
<td>84-85°</td>
</tr>
<tr>
<td>71-73°</td>
</tr>
</tbody>
</table>

\(^d\)Previously reported values: Petrov (26) (isomer incompletely purified by partial acetylation) b.p., 122-127°; \(n^2_0\), 1.4062; \(d^2_4\), 0.9315.

\(^e\)Determined with small pycnometer.

\(^f\)Previously reported values: Petrov (26) b.p., 118-118.5°/740 mm.; \(n^2_0\), 1.4040; \(d^2_4\), 0.9213.

\(^g\)Previously reported values: Petrov (26) (isomer incompletely purified by partial acetylation) b.p., 119-123°; \(n^2_0\), 1.4046; \(d^2_4\), 0.9260.
Table II.

**Table II**

A Comparison of the Physical Properties of Dowanol 33B and with those of 1-Methoxypropanol-2 from the Base Catalysed Reaction of Propylene Oxide and Methanol

<table>
<thead>
<tr>
<th></th>
<th>Dowanol 33B</th>
<th>1-Methoxypropanol-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>b.p.</td>
<td>117.3-121.1(^\circ)</td>
<td>118.5-119(^\circ)/765 mm.</td>
</tr>
<tr>
<td>(\rho_{25})</td>
<td>1.401</td>
<td>1.4017</td>
</tr>
<tr>
<td>(d_{25}^2)</td>
<td>0.916</td>
<td>0.917</td>
</tr>
</tbody>
</table>

**Mechanism of the Base and Acid Catalysed Reactions of Propylene Oxide and Methanol**

All of the facts concerning the addition of methanol to propylene oxide are consistent with the electronic explanations previously advanced by Petrov (26), Kadesch (16), Bartlett (3), and Chitwood and Freure (10).

\[
\begin{align*}
\text{OCH}_3 \\
\text{CH}_3 & \quad \text{CH-CH}_2
\end{align*}
\]

**Figure IV**

In basic solution, the methoxide ion attacks the number one carbon from the rear, because the positive inductive effect of the methyl group creates a slightly higher electron density around the number two carbon as shown in Figure IV. As the methoxyl group enters the molecule, the carbon-oxygen bond to the number one carbon ruptures, and the oxygen takes up a proton to give 1-methoxypropanol-2.
In acid solution, there is no methoxide ion present to attack the number one carbon. Instead, the proton coordinates with the epoxide oxygen as shown in Figure V.

\[
\text{CH}_3\text{-CH-CH}_2\text{O}^+\text{H}^+
\]

*Figure V*

Either of the weakened carbon-oxygen bonds is then broken by the attack of the methyl alcohol. There are not enough data available to decide whether this attack of the methanol involves the preliminary rupture of the epoxide ring as the rate controlling step, or the attack of the methanol possibly from the rear as the rate controlling step. The fact that more of the 1-methoxypropanol-2 is obtained than of the other isomer can be interpreted to mean the attack of the methyl alcohol from the rear predominates.
EXPERIMENTAL

Introduction

Materials. The dioxane was purified by refluxing over sodium metal for two hours and distilling. The first fourth of the distillate was discarded and the middle half of the material saved. All of the other materials were used without further purification. Propylene oxide was obtained from the Eastman Kodak Company, Rochester, New York.

Apparatus. Hydrogenations were conducted in the standard high pressure hydrogenation equipment as supplied by the American Instrument Company, Silver Spring, Maryland.

Physical constants. All melting points are uncorrected.

Refractive indices were determined with a Spencer Abbe Refractometer. Densities were determined with a pycnometer having a volume of approximately 1.2 ml., except in the case of the 1-methoxypropanol-2 from the reduction of methoxyacetone, where a pycnometer having a volume of approximately 0.2 ml. was used. Both of the methoxypropanols are hygroscopic in air of approximately 50 per cent relative humidity; necessary precautions against this fact were taken.

2-Methoxypropanol-1 from Ethyl α-Methoxypropionate

α-Methoxypropionic acid. α-Methoxypropionic acid was prepared in 60 per cent of the theoretical yield from α-chloropropionic acid and sodium methoxide by the procedure described in Organic Synthesis (6) for ethoxyacetic acid. It distilled at 103-106° at 25 mm.; the reported boiling point is 95-96°
at 12 mm. (9), and 108-110° at 30 mm. for the levorotatory material (28).

**Ethyl α-methoxypropionate.** Ethyl α-methoxypropionate was prepared in 54 per cent of the theoretical yield by the esterification of α-methoxypropionic acid using hydrogen chloride as a catalyst. This procedure was taken from the preparation of ethyl ethoxyacetate described in Organic Synthesis (6).

The fraction distilling at 140-142° at 760 mm. was collected, refluxed over Raney nickel, and redistilled before use. The previously reported boiling point for this compound was 135.5° at 760 mm. (29).

**2-Methoxypropanol-1.** A 300 ml. capacity hydrogenation vessel was charged with 80 g. of ethyl α-methoxypropionate, 50 ml. of purified dioxane, and 10 g. of copper chromite catalyst (5). The vessel was assembled, filled with hydrogen to a pressure of 3650 lbs., and heated at 250° with shaking until no further pressure drop occurred; this required two hours. After cooling, the material was removed from the vessel, the catalyst filtered through a Whatman number 50 filter paper and washed. Distillation of the reaction mixture at atmospheric pressure through a 2 cm. diameter by 45 cm. long glass helices packed column yielded 25 g., 40 per cent of the theoretical yield, of 2-methoxypropanol-1 distilling at 129.5-130.5°. The low yield was due to the hold-up of the column. The alcohol was redistilled through a small claisen flask, and the fraction distilling at 130-130.2° at 758 mm. was taken for analysis and physical constants.
The physical constants are summarized in Table I.

The following analyses were obtained for the 2-methoxy-propanol-1.

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C₄H₁₀O₂</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>53.33</td>
<td>53.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53.28</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>11.11</td>
<td>11.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.21</td>
</tr>
</tbody>
</table>

The 3,5-dinitrobenzoate, made in the usual way, was re-crystallized from 60-80° petroleum ether; it melted at 96.5-97°. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C₁₁H₁₀N₂O₇</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>46.46</td>
<td>46.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46.63</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>4.23</td>
<td>4.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.47</td>
</tr>
<tr>
<td>Nitrogen (Dumas)</td>
<td>9.85</td>
<td>10.02</td>
</tr>
</tbody>
</table>

The α-naphthylurethane, prepared in the usual way, was re-crystallized from 30-60° petroleum ether; it melted at 60-60.5°. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C₁₆H₁₇NO₃</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>69.50</td>
<td>69.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>69.61</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>6.56</td>
<td>6.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.74</td>
</tr>
</tbody>
</table>

**Attempted Preparation of α-Methoxypropanaldehyde**

α-Hydroxy-β-methoxybutyric acid. α-Bromo-β-methoxybutyric acid, prepared by the method described in Organic Synthesis (2), was hydrolysed by allowing 108 g. of it to stand in an excess of sodium hydroxide solution at room temperature for
24 hours. The solution was acidified, and the water evaporated at reduced pressure and room temperature. The residue was extracted with acetone, and the acetone evaporated. Approximately 60 g. of a white toffy-like material remained. This material was assumed to be \( \alpha \)-hydroxy-\( \beta \)-methoxybutyric acid and represented 80 per cent of the theoretical yield.

**\( \alpha \)-Methoxypropionaldehyde.** The \( \alpha \)-hydroxy-\( \beta \)-methoxybutyric acid was reacted with lead tetraacetate (8) using acetic acid as the solvent, according to the directions of Ceda (21). After the addition of the lead tetraacetate was complete, the mixture was allowed to stir until all of the lead tetraacetate had been reduced.

A small sample of the reaction mixture was washed with sodium sulfate to remove the lead, and then tested with 2,4-dinitrophenylhydrazine reagent. The test was positive, but no aldehyde or pure aldehyde derivative could be isolated either by distillation or partial crystallization of the major portion of the material.

**1-Methoxypropanol-2 from Methoxyacetone**

**Methoxyacetone.** Attempts to prepare methoxyacetone from bromoacetone (4) and sodium methoxide failed. When a methanol solution of sodium methoxide and a methanol solution of bromoacetone were mixed in equimolar quantities, a small yield of an unidentified solid melting at 110-114\(^\circ\) was obtained; no methoxyacetone was present. Further experiments in which dioxane and ether were used to dissolve the bromoacetone also failed.
Methoxyacetone was prepared in 20 per cent of the theoretical yield by reacting methoxyacetonitrile (7) with methyl magnesium bromide as described by Gauthier (15). The material distilled at 114.5-115.5° at atmospheric pressure.

The p-nitrophenylhydrazone was prepared and recrystallized from water. Its melting point was 108-109°; Leonardi (19) reported a melting point of 110-111°. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C₁₀H₁₂N₂O₃</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>53.81</td>
<td>53.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53.58</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>5.84</td>
<td>5.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.13</td>
</tr>
<tr>
<td>Nitrogen (Dumas)</td>
<td>18.83</td>
<td>19.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.97</td>
</tr>
</tbody>
</table>

The 2,4-dinitrophenylhydrazone was also prepared. After recrystallization from 95 per cent ethanol, it melted at 157-159°. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C₁₀H₁₂N₄O₅</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>44.78</td>
<td>44.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44.94</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>4.51</td>
<td>4.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.76</td>
</tr>
<tr>
<td>Nitrogen (Dumas)</td>
<td>20.88</td>
<td>20.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.62</td>
</tr>
</tbody>
</table>

1-Methoxypropanol-2. A 100 ml. capacity hydrogenation vessel was charged with 5.5 g. of methoxyacetone, 45 ml. of anhydrous ether, and approximately 2 g. of Raney nickel catalyst (25). The vessel was filled with hydrogen to a pressure of 3800 lbs. and heated to 140°. After the reduction was complete, the catalyst was removed by filtration and the
material fractionated. After two fractionations through a Vigreux column, 3 g. of 1-methoxypropanol-2 distilling at 118° at 750 mm. was obtained.

The physical constants of this material are given in Table I.

The 3,5-dinitrobenzoate was recrystallized from 60-80° petroleum ether and methanol; it melted at 84-85°. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C_{11}H_{10}N_{2}O_{7}</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>46.46</td>
<td>46.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46.55</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>4.23</td>
<td>4.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.35</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>9.85</td>
<td>9.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.38</td>
</tr>
</tbody>
</table>

The α-naphthylurethane was recrystallized from 60-80° petroleum ether. It melted at 71-73°. There was insufficient material for analysis. When this material was mixed with equal quantities of the α-naphthylurethane of the 118° isomer obtained from the acid catalysed condensation, and the α-naphthylurethane of the isomer obtained from the alkaline catalysed condensations, there was no depression in the melting point.

**Alkaline Catalysed Condensation of Propylene Oxide and Methanol**

1-Methoxypropanol-2 was made by the sodium methoxide catalysed condensation of propylene oxide and methanol according to Petrov (26). Forty-eight milliliters of propylene oxide and 35 ml. of methanol, in which 1.7 g. of sodium had
been dissolved, were reacted in a steel vessel with shaking at 100°C for four hours, and then fractionated through a 2 cm. diameter by 50 cm. long helices packed column. A yield of 40 g. distilling at 118.5-119°C at 765 mm. was obtained. This represents 68 per cent of the theoretical yield.

The physical constants are given in Table I.

The 3,5-dinitrobenzoate was recrystallized from 60-80°C petroleum ether and methanol; it melted at 84-85°C. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C₁₁H₁₂N₂O₇</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>46.46</td>
<td>46.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46.52</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>4.23</td>
<td>4.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.27</td>
</tr>
<tr>
<td>Nitrogen (Dumas)</td>
<td>9.85</td>
<td>10.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.91</td>
</tr>
</tbody>
</table>

The α-naphthylurethane was recrystallized from 30-60°C petroleum ether; it melted at 72-73°C. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C₁₆H₁₇NO₃</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>69.50</td>
<td>69.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>69.41</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>6.56</td>
<td>6.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.90</td>
</tr>
</tbody>
</table>

**Acid Catalysed Condensation of Propylene Oxide and Methanol**

To a mixture of 1068 g. (33.4 moles) of dry methanol (14) and 15.6 g. (8.5 ml.) of concentrated sulfuric acid, 387 g. (6.7 moles) of propylene oxide was added dropwise at
the reflux temperature of the mixture, according to the direc-
tions of Chitwood and Freure (10). The reaction mixture was
refluxed an additional one and a half hours, cooled, and
neutralized with 10 per cent sodium hydroxide. The sodium
sulfate was removed by filtration, and the filtrate distilled
through a 30 plate Oldershaw column (22). A methanol fraction
of 857 ml. distilling at 67° was obtained first, then 120 ml.
of a fraction distilling from 66-82°; 97.3 ml. distilling from
82-98°, and finally 200 ml. distilling at 98°. Evidence of
decomposition was then found; the remaining material was there­
fore distilled rapidly from a plain distilling flask. The
resulting distillate was treated with potassium carbonate,
the two layers obtained separated, and the organic layer dried
over anhydrous potassium carbonate. The 200 ml. fraction
distilling at 98° obtained above was found to be an azo- trope
which separated into two layers when saturated with potassium
carbonate. The upper layer was separated from the water
layer, dried over anhydrous potassium carbonate, and com-
bined with the similarly treated distillate from the plain
distillation. Fractionation of these combined materials
through the Oldershaw column was resumed, and the following
fractions obtained:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Temperature</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>62-97.5°</td>
<td>68 ml.</td>
</tr>
<tr>
<td>II</td>
<td>97.5-100°</td>
<td>28.5 ml.</td>
</tr>
<tr>
<td>III</td>
<td>100-120°</td>
<td>13.0 ml.</td>
</tr>
<tr>
<td>IV</td>
<td>120-120.5°</td>
<td>99.5 ml.</td>
</tr>
<tr>
<td>V</td>
<td>120.5-131°</td>
<td>48 ml.</td>
</tr>
<tr>
<td>VI</td>
<td>131-132°</td>
<td>36.0 ml.</td>
</tr>
<tr>
<td>VII</td>
<td>Residue</td>
<td>85 ml.</td>
</tr>
</tbody>
</table>

Fractions IV and VI, consisting predominately of the
isomeric methoxypropanols, were considered to be impure as evidenced by their objectionable odors. The two fractions represent yields of 15 per cent of the calculated yield of 1-methoxypropanol-2 and 6 per cent of the calculated yield of 2-methoxypropanol-1. The low boiling fractions, consisting of the methoxypropanol water azeotropes, together with the intermediate fractions, were estimated to contain 155 g. of the isomeric methoxypropanols corresponding to an additional 25 per cent of the theoretical yield.

Fraction IV, 1-methoxypropanol-2, was redistilled through a 2 cm. diameter by 45 cm. long glass helices packed column, and the center portion, which had a boiling point of 118.3° at 750 mm. was used for the physical constants given in Table I, and derivatives. This material still had a slightly unpleasant odor. The 3,5-dinitrobenzoate melted at 83.5-84.5° after recrystallization from 60-80° petroleum ether. The α-naphthylurethane melted at 72-73° after recrystallization from 60-80° petroleum ether. 1-Methoxypropanol-2 and water formed an azeotrope which distilled at 97.2-98.0°. When this azeotrope was saturated with potassium carbonate, the decrease in volume was such as to indicate the azeotrope contained 65 per cent of the alcohol.

Fraction VI, 2-methoxypropanol-1, was redistilled through a 60 cm. long Widmer column and 20 ml. was obtained which had a boiling point of 130°. The middle half of this fraction was redistilled through a small claisen flask. It had a boiling point of 130-130.5° at 758 mm. and was used for the physical constants given in Table I, and derivatives. This
material still had an unpleasant odor. The 3,5-dinitrobenzoate melted at 95.5° after recrystallization from 60-80° petroleum ether. The α-naphthylurethane melted at 60-60.5° after recrystallization from 60-80° petroleum ether. The above material, boiling point 130-130.5°, gave a positive Schiff's test and a positive test with 2,4-dinitrophenylhydrazine reagent. 2-Methoxypropanol-1 and water also formed an azeotrope boiling at 98°, and on treatment with potassium carbonate the decrease in volume indicated that the azeotrope contained 33 per cent of the alcohol.
SUMMARY

1. The structures of 1-methoxypropanol-2 and 2-methoxypropanol-1, previously obtained only from propylene oxide and methanol, have been established by independent syntheses. 1-Methoxypropanol-2 was made by the Raney nickel catalysed hydrogenation of methoxyacetone. 2-Methoxypropanol-1 was made by the copper chromite catalysed hydrogenolysis of ethyl α-methoxypropionate.

2. 2-Methoxypropanol-1 was best prepared in a pure state by the copper chromite catalysed hydrogenolysis of ethyl α-methoxypropionate.

3. 1-Methoxypropanol-2 was best prepared by the sodium methoxide catalysed reaction of propylene oxide and methanol. None of the isomeric 2-methoxypropanol-1 was detected in the material prepared by this method.

4. The acid catalysed condensation of propylene oxide and methanol gave a mixture of both isomers from which 2-methoxypropanol-1 was separated in less than ten per cent of the theoretical yield. Aldehyde impurities were present.

5. The isomeric methoxypropanols were characterized by their 3,5-dinitrobenzoates and α-naphthylurethanes. The following melting points were obtained:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Melting Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-naphthylurethane</td>
<td>84-85°</td>
</tr>
<tr>
<td>3,5-dinitrobenzoate</td>
<td>72-73°</td>
</tr>
</tbody>
</table>

6. Each of the isomeric methoxypropanols formed an azeotrope with water. 1-Methoxypropanol-2 formed an azeotrope
with water which contained 65 per cent of the alcohol by volume and distilled at 97.2-98°. 2-Methoxypropanol-1 formed an azeotrope with water which contained 33 per cent of the alcohol by volume and distilled at 98°.
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PART II

THE PREPARATION OF 2,6-DIMETHYL-1-HYDROXY-4-METHOXYCYCLOHEXANECARBONITRILE
INTRODUCTION

Victor Meyer (22) first noticed that 2,6-disubstituted benzoic acids would give less than ten per cent of the theoretical yields of the methyl esters when treated in the usual way with methanol and hydrogen chloride. He attributed this phenomenon to steric hindrance. This view was based upon the observation that the influence of a group in the ortho position was dependent on its size. The size of a group as measured by Meyer depended on the sum of the weights of the atoms in the group.

Sidgwick and Callow (28) have shown that ortho substituted phenols, as compared to the meta and para isomers, exhibit an increased solubility in hydrocarbon solvents, and a decreased solubility in water. In order to explain these phenomena, they proposed the theory that a six-membered chelate ring, which was stabilized by a pair of conjugated double bonds, was formed. Salicylaldehyde and o-nitrophenol could, therefore, be pictured as follows:

![Diagram of structures I and II]

Furthermore, the infra-red absorption pattern obtained for salicylaldehyde and similar compounds did not show the characteristic absorption pattern given by organic molecules con-
aining a free hydroxyl group (16).

Six-membered chelate rings containing two double bonds are the most stable type known because they are strain free. In the case of the ortho substituted phenols, amines and carboxylic acids which show the ortho effect, Dippy, Watson, et al. (13) believe that the stability is due in part to resonance. Ortho toluic acid has an abnormally high ionization constant, and a low rate of esterification and hydrolysis (31). They postulate that the high acid strength is due to the ion III shown below.

![Diagram](image)

The low rate of esterification is believed to be caused by the formation of a chelate ring, as shown above in IV, in the activated state simultaneously with the attack of the catalyst used in esterification.

Some concept of the extent of the abnormality of the ortho methyl substituted benzoic acids is shown by a comparison of the ionization constants in Table I.

<table>
<thead>
<tr>
<th>Acid</th>
<th>$K \times 10^5$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic</td>
<td>6.27</td>
<td>(31)</td>
</tr>
<tr>
<td>o-methylbenzoic</td>
<td>12.35</td>
<td>(31)</td>
</tr>
<tr>
<td>m-methylbenzoic</td>
<td>5.35</td>
<td>(31)</td>
</tr>
<tr>
<td>p-methylbenzoic</td>
<td>4.24</td>
<td>(31)</td>
</tr>
<tr>
<td>2,4,6-trimethylbenzoic</td>
<td>3.75</td>
<td>(13)</td>
</tr>
<tr>
<td>2,6-dimethylbenzoic</td>
<td>62</td>
<td>(18)</td>
</tr>
</tbody>
</table>
The low degree of ionization of 2,4,6-trimethylbenzoic acid cannot be explained.

One possible approach to an attempted elucidation of this chelate ring theory would be to build a molecule in which a similar degree of steric hindrance existed and which did not contain a conjugated system of double bonds to stabilize the chelate ring.

The first possibility considered was 2,6-dimethylhexahydrobenzoic acid in which there are no conjugated double bonds. If this molecule were planar, it would be ideal. Since it is not, the possibility of geometric isomers eliminated this compound because in some forms the methyl groups would be removed from the carbonyl group to a much greater extent than they are in 2,6-dimethylbenzoic acid. Hufferei and Noyes (18) have studied the esterification of 2,6-dimethylbenzoic, 2,6-dimethylhexahydrobenzoic, 2,6-dimethyl-2,3,4,5-tetrahydrobenzoic, 2,6-dimethyl-1,2,5,6-tetrahydrobenzoic, and 2,6-dimethyl-2,3-dihydrobenzoic acids and have obtained the results given in Table II. The esterification was conducted by refluxing the acid for four hours with an excess of anhydrous methanol, containing three to four per cent of hydrochloric acid.

**TABLE II**

<table>
<thead>
<tr>
<th>Acid</th>
<th>% Esterified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoic</td>
<td>96</td>
</tr>
<tr>
<td>2,6-Dimethylbenzoic</td>
<td>3.5</td>
</tr>
<tr>
<td>2,6-Dimethyl-2,3,4,5-tetrahydrobenzoic</td>
<td>41</td>
</tr>
<tr>
<td>2,6-Dimethyl-1,2,5,6-tetrahydrobenzoic</td>
<td>75</td>
</tr>
<tr>
<td>2,6-Dimethyl-2,3-dihydrobenzoic</td>
<td>47</td>
</tr>
<tr>
<td>2,6-Dimethylhexahydrobenzoic</td>
<td>52</td>
</tr>
</tbody>
</table>
The result obtained for the hexahydrobenzoic acid is inconclusive because of the possibility of geometric isomers. The value obtained for 2,6-dimethyl-2,3-dihydrobenzoic acid is questionable because there is some doubt as to whether the compound studied had the structure assigned.

A more satisfactory molecule would be 2,6,7-trimethylbicyclo-[2.2.2]-octane-1-carboxylic acid pictured below.

\[
\text{\begin{center}
\begin{tikzpicture}
\node at (0,0) (V) {V};
\path
draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
draw (0,0) -- (0,1);
draw (1,0) -- (1,1);
draw (0,1) -- (1,0);
\end{tikzpicture}
\end{center}}
\]

\[
\text{\(\text{COOH}\)}
\]

In such a molecule, the ring structure would be rigid. A molecular model of this compound showed that only one geometric isomer was possible, and the distance between the o-methyl groups and the carboxyl group was approximately the same as in 2,6-dimethylbenzoic acid. The compound finally chosen was 2,6,7,8-tetramethylbicyclo-[2.2.2]-octane-1-carboxylic acid because its synthesis was deemed to be more feasible. The extra methyl group in the 8 position should not affect the reactivity of the carboxylic acid group.
DISCUSSION OF SYNTHETIC REACTIONS EMPLOYED

Introduction

The steps in the synthesis of 2,6,7,8-tetramethylbicyclo-
[2.2.2]-octane-1-carboxylic acid which have been perfected are
as follows:

1. The Mannich reaction

\[
\text{CH}_3 \begin{array}{c}
\text{CH} \\
\text{CCH}_3
\end{array}
\xrightarrow{2(\text{CH}_3)_2\text{NH}+\text{HCHO}}
\text{CH}_3 \begin{array}{c}
\text{CH} \\
\text{CCH}_3
\end{array}
\]

2. Hydrogenolysis of the Mannich base

\[
\text{CH}_3 \begin{array}{c}
\text{CH} \\
\text{CCH}_3
\end{array}
\xrightarrow{\text{H}_2\text{CuCrO}_4}
\text{CH}_3 \begin{array}{c}
\text{CH} \\
\text{CCH}_3
\end{array}
\]

3. Hydrogenation of the aromatic ring

\[
\text{CH}_3 \begin{array}{c}
\text{CH} \\
\text{OCH}_3
\end{array}
\xrightarrow{\text{Ni}(\text{H})}
\text{CH}_3 \begin{array}{c}
\text{CH} \\
\text{OCH}_3
\end{array}
\]

4. Oxidation to the ketone

\[
\text{CH}_3 \begin{array}{c}
\text{CH} \\
\text{CCH}_3
\end{array}
\xrightarrow{\text{K}_2\text{Cr}_2\text{O}_7/\text{H}_2\text{SO}_4}
\text{CH}_3 \begin{array}{c}
\text{CH} \\
\text{CCH}_3
\end{array}
\]
5. Formation of the cyanohydrin

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_2 \\
\text{O} & \quad \text{+HCN} \quad \text{-(OH)-} \\
\text{GCH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

The proposed synthesis from this point would be the conversion of the 2,6-dimethyl-1-hydroxy-4-methoxycyclohexane-carbonitrile to 2,6-dimethyl-1,3-cyclohexadiene-carbonitrile, and the employment of this compound in a Diels-Alder reaction to make a bicyclo compound. A discussion of the five reactions given above follows.

**The Mannich Reaction**

The first major step in the synthesis of the compound under consideration was the alkylation of the monomethyl ether of hydroquinone in the 2 and 6 positions. The method used was based on the work of Caldwell and Thompson (8) who had reported the use of the Mannich reaction to prepare various dialkylaminomethyl substituted phenols, which would undergo hydrogenolysis to give the methyl substituted compounds. They reported the preparation in good yields of several Mannich bases, using both dimethylamine and morpholine. Included in this series was 2,5-bis(dimethylaminomethyl)hydroquinone which was obtained in almost quantitative yield. Decombe (12) reported the reaction of hydroquinone monomethyl ether with dimethylamine and formaldehyde at room temperature to give only a monosubstitution product, namely 2-dimethylaminomethyl-4-methoxyphenol. However, the preparation of 2,4,6-tridii-
methylaminomethyl)phenol was reported in 86 per cent of the theoretical yield by Bruson and MacMullen (6).

In view of the results obtained by Caldwell and Thompson (8) and Bruson and MacMullen (6), it was felt that the disubstituted product could be obtained under more drastic conditions, and since the ortho directing influence of the hydroxyl group was much greater than that of the methoxyl group, the reaction should proceed to give the desired 2,6 isomer. This was found to be the case, and a procedure was finally developed whereby the 2,6-bis(dimethylaminomethyl)-4-methoxyphenol was obtained in 75 per cent of the theoretical yield. The reaction was carried out by adding to the hydroquinone monomethyl ether a three-fold excess of dimethylamine and formaldehyde, half of the last component being added to the refluxing reaction mixture only after the first dimethylaminomethyl group had been introduced at room temperature. The material was oxidized by air, and lower yields were obtained if nitrogen was not used to exclude oxygen from the system during the distillation of the product. The product obtained was a yellow oil distilling from 143 to 152° at 3 to 3.6 mm. It was still not pure; it had the odor of dimethylamine.

When the reaction was carried out at room temperature, the monosubstitution product, 2-dimethylaminomethyl-4-methoxyphenol was obtained. This was a colorless oil distilling at 106 to 108° at 1.2 to 1.5 mm. It could be crystallized by cooling in a dry-ice acetone bath, and melted at 55-51°, after recrystallization from petroleum ether. Decombe (12), who first prepared this material, never obtained a crystalline
An attempt to use the Lederer-Manasse synthesis (21) which involved the alkaline condensation of the phenol with formaldehyde to give the hydroxymethyl substituted compound with subsequent hydrogenation to the alkyl group failed.

Hydrogenolysis of the Mannich Base

Caldwell and Thompson (8) reported a yield of 23 per cent of the theoretical amount for the preparation of 2,5-dimethylhydroquinone by the copper chromite catalysed hydrogenolysis of 2,5-bis(dimethylaminomethyl)hydroquinone. Hydrogenolysis of similar compounds obtained by using morpholine instead of dimethylamine gave yields of about 35 per cent of the theoretical amount.

The 2,6-bis(dimethylaminomethyl)-4-methoxyphenol would not undergo hydrogenolysis using a copper chromite catalyst at 165° and a hydrogen pressure of 3700 pounds for four hours in dioxane solution as described by Caldwell and Thompson (8). At 190° and a pressure of 4000 pounds the reaction did proceed in yields varying from 10 to 58 per cent of the theoretical amount. Since some of the low yields were obtained when the reaction required a long period of time, both the temperature and the pressure were raised in the hope that the rate of the desired hydrogenolysis would increase more than that of the decomposition and polymerization side-reactions. When the reaction was carried out under a hydrogen pressure of 4000 pounds measured at room temperature and heated to 235°, it was found that the reaction was complete in about one hour, and 90 per cent of the theoretical yield of crude material
The crude 2,6-dimethyl-4-methoxyphenol could be purified by any of three methods. The purest, white crystals were obtained by steam distillation of the residue which remained after the solvent had been removed from the hydrogenolysis reaction mixture; however, this proceeded too slowly to be practical. The second method was to allow the crude product which remained after the solvent had been removed to crystallize, filter from the oily impurities, and then recrystallize from 60-80°C petroleum ether or from cyclohexane. Since the material was quite soluble in these solvents, there were considerable losses. The procedure finally adopted was distillation under reduced pressure. This served to remove the tarry materials which would interfere with the next hydrogenation. No fractionation was attempted; the temperature remained constant throughout this distillation. The product was probably contaminated with hydroquinone monomethyl ether and 2-methyl-4-methoxyphenol. These could have come from the decomposition of the Mannich base during the distillation of the Mannich base itself, or during the hydrogenolysis. The distilled material was suitable for the next step in the synthesis, and the suspected impurities could be removed more easily at that point by careful fractionation.

The structure of the 2,6-dimethyl-4-methoxyphenol, prepared by the above method and steam distilled was established by the following facts:

1. A comparison of melting points.
The melting point found was 77°. The melting point reported by Bamberger (1) was 77°. Bamberger made the compound as shown below:

2. Hydrolysis to 2,6-dimethylhydroquinone, and a comparison of melting points.

The melting point of the 2,6-dimethylhydroquinone obtained by hydrolysis of the 2,6-dimethyl-4-methoxyphenol was 149 to 151°. Noelting and Bauman (23) reported a melting point of 149 to 151° for the compound prepared by the following reactions:

2,6-dimethylquinone was also prepared by Jones and Kenner (19) by the lead tetraacetate oxidation of 2,6-dimethyl-4-nitrophenol. This nitrophenol was prepared by an interesting reaction first reported by Hill (17) as follows:
2,6-Dimethylhydroquinone was also reported by Bamberger and Rising (3) as a result of the following synthesis:

3. An attempt to react the 2,6-dimethyl-4-methoxyphenol with a diazonium salt in a neutral solution.

Hydroquinone monomethyl ether, 2-methyl-4-methoxyphenol, and 2,6-dimethylhydroquinone, all of which have positions ortho to the hydroxyl group free, coupled readily to give a red precipitate with p-toluenediazonium chloride. The 2,6-dimethyl-4-methoxyphenol, in which both positions ortho to the hydroxyl group are blocked, did not react.

**Hydrogenation of the Aromatic Ring**

The Raney nickel hydrogenation of 2,6-dimethyl-4-methoxyphenol to 2,6-dimethyl-4-methoxycyclohexanol was a straightforward reaction and went in an almost quantitative yield when the starting material was pure. In the early experiments, when
small amounts of the steam distilled 2,6-dimethyl-4-methoxy-phenol were used, the yields were as high as 90 per cent of the theoretical amount in some instances. When larger amounts of the distilled material were reduced, the yield dropped to 65 per cent of the theoretical amount. This was attributed to the fact that the phenol had been distilled under reduced pressure instead of being steam distilled, and was less pure.

The hydrogenation usually went to completion in about six hours under proper conditions. In the case of the final large scale synthesis, 43 hours were required; this increase was probably caused by a slight overloading of the bomb as well as some impurities in the phenol.

**Formation and Reactions of 2,6-Dimethyl-4-methoxycyclohexanone**

The method chosen for the oxidation of 2,6-dimethyl-4-methoxycyclohexanol to the ketone was the potassium dichromate and sulfuric acid method of Beckman as outlined in Organic Synthesis for the oxidation of menthol to menthone (14).

Early experiments in which the reaction was carried out in smaller quantities, and the product distilled through a small vigreux column indicated that the yields were of the order of 60-80 per cent of the theoretical amount. It was realized, however, that since the ketone and alcohol distilled close together, the product probably contained some of the unreacted alcohol. This theory was substantiated when a large quantity of the alcohol was oxidized to the ketone and the crude ketone distilled through a 50 cm. long packed column.
The yield dropped to 32 per cent of the theoretical amount and about 30 per cent of the unreacted alcohol was recovered. The synthesis using larger quantities of material also magnified the overall loss of material; thus, after removal of the ether which was used as a solvent, only about 75 per cent of the total starting alcohol could be accounted for. The unaccounted for material was probably lost by oxidation beyond the ketone stage. No appreciable quantities of ketone were retained by the strongly acid oxidizing solution; neutralization and continued ether extraction yielded no ketone.

The fact that the alcohol was not completely oxidized to the ketone was surprising, especially since a large excess of the oxidizing agent was used. In carrying out the oxidation, it was noticed that the reaction temperature increased steadily until about half the alcohol had been added. After this period, there seemed to be no further heat evolved, and the temperature decreased. Because of this, and the fact that a considerable portion of the unreacted alcohol was recovered, it was considered desirable to increase the ratio of oxidizing mixture to alcohol still further, even though a 100 per cent excess of the dichromate mixture was used originally. This procedure, however, led to a slight decrease in the yield of ketone.

In order to prepare the diene needed for the proposed Diels-Alder reaction, the methoxyl group must be removed and a double bond introduced. There are two steps in the synthesis at which this might be accomplished; the methoxy ketone, or the methoxy cyanhydrin. When difficulties were
encountered in the attempts to cleave the methoxyl group of the methoxy cyanohydrin, some reactions of the methoxy ketone were studied.

Treatment of the 2,6-dimethyl-4-methoxycyclohexanone with hydrochloric acid resulted in a ketone which contained chlorine, and which had a higher boiling point than the starting material. A pure 2,4-dinitrophenylhydrazone could not be obtained. When this chloro ketone was distilled from quinoline (11), an unsaturated ketone was obtained. This formed a yellow 2,4-dinitrophenylhydrazone that turned red on standing. Since the formation of a red 2,4-dinitrophenylhydrazone was indicative of a conjugated system, and since the 2,4-dinitrophenylhydrazone was yellow when it first formed, some 2,6-dimethyl-3-cyclohexenone was probably formed, and the double bond shifted from the 3,4 to the 2,3 position after the 2,4-dinitrophenylhydrazone had formed.

Attempts were made to remove the methoxyl group by heating the ketone with phosphorous tribromide. A reaction appeared to occur, but on subsequent distillation of the reaction product from quinoline, only a small amount of material was obtained. This material gave positive carbonyl and unsaturation tests, but was not investigated further because of the low yield.

The use of boron trifluoride and acetic anhydride to replace the methoxyl group by an acetoxy group (29) proved unsuccessful. The reagent evidently caused the polymerization of the ketone.
Although the various attempts to introduce the double bond into the ketone showed promise, there was always the possibility that the double bond might have shifted from the 3,4 to the 2,3 position. The major efforts were, therefore, directed toward the introduction of the double bonds into the cyanohydrin to obtain the desired 2,6-dimethyl-1,3-cyclohexadienecarbonitrile.

Formation and Reactions of the Methoxy Cyanohydrin

Lapworth (10, 20) and coworkers conducted several investigations on the formation and stability of the cyanohydrins of various aldehydes and ketones, including cyclohexanone and 2-methylcyclohexanone. The results of the equilibrium studies conducted indicated that 2-methylcyclohexanone cyanohydrin did not dissociate as much as cyclohexanone cyanohydrin. The latter distilled at 140° at 15 mm. From these studies, it would be concluded that 2,6-dimethyl-4-methoxycyclohexanone cyanohydrin would not dissociate to any appreciable extent, and that it would undergo distillation under diminished pressure without decomposition. On the other hand, the cyanohydrin of 2,6-dimethylcyclohexanone is unknown; attempts to prepare it have been reported by Ruffered and Noyes (18). It was finally found that the cyanohydrin of 2,6-dimethyl-4-methoxycyclohexanone formed rapidly at room temperature when an alcohol solution of the ketone was mixed with a slight excess of an alcohol solution of hydrogen cyanide in the presence of a small amount of potassium cyanide. The
product was isolated by washing its ether solution with water to remove the alkaline materials and evaporating the solvent under diminished pressure.

Attempts to isolate the 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile (i.e. 2,6-dimethyl-4-methoxycyclohexanone cyano hydrin) from the reaction mixture by distillation invariably resulted in failure. However, later work showed that small amounts of the pure cyano hydrin could be distilled under diminished pressure. The 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile, when recrystallized from 60-80° petroleum ether, is a white stable solid melting at 99.5-100.5°. The cyano hydrin group was found to revert to the carbonyl group and cyanide ion in alkali as shown by a prussian blue test. In hot concentrated hydrochloric or hydrobromic acid solution, the cyano hydrin group was only slowly attacked.

The purpose of the experiments with 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile was to try to make 2,6-dimethyl-1,3-cyclohexadiene carbonitrile, or the corresponding ester, which could be reacted in a Diels-Alder reaction to give a bicyclo compound.

The first method of attack was to try to convert the cyano hydrin obtained into the ethyl ester of 2,6-dimethyl-1-hydroxy-4-methoxycyclohexane carboxylic acid. The procedure used was based on the method described in Organic Synthesis for ethyl α-phenyl acetoacetate (5). This consisted of saturating a solution of the nitrile in ethyl alcohol with dry hydrogen chloride to form the imino ether and then hydrolysing
this to the ester. At room temperature no reaction occurred. When carried out in a sealed tube at 100° instead of at room temperature, 1,4-dihydroxy-2,6-dimethylcyclohexanecarbonitrile was isolated in approximately 20 per cent of the theoretical yield, instead of the expected ester.

Direct attempts to make the 1,4-dihydroxy-2,6-dimethylcyclohexanecarbonitrile by hydrolysing the methoxyl group of the methoxy cyanohydrin with hydrochloric or hydrobromic acid often failed, an unidentified gum being obtained instead of the desired product. The 1,4-dihydroxy-2,6-dimethylcyclohexanecarbonitrile was obtained, although in poor yield, by refluxing with concentrated hydrochloric acid, removing the acid by distillation under diminished pressure, extracting the residue with a small amount of water, and then treating the clear extract with alkali. The difficulty in obtaining the dihydroxy compound lay in the fact that it was soluble in the acidic reaction mixture, and it had to be precipitated by the addition of alkali. If the gum, which was always present, was not removed from the acidic solution before it was made alkaline, the desired product also precipitated as a gum.

The 1,4-dihydroxy-2,6-dimethylcyclohexanecarbonitrile, on pyrolysis, should yield the desired diene. Thus, Burns and coworkers (7) have reported the pyrolysis of cyclohexanone cyanohydrin to 1-cyclohexanecarbonitrile. When this compound was subjected to pyrolysis over alumina at 345°, an unsaturated oil was obtained. The yield was very low, and the material was obviously impure. In view of the small yield and the doubtful utility of this method, this synthetic
approach was abandoned.

Another possible method of obtaining the 2,6-dimethyl-1,3-cyclohexadienecarbonitrile was dehydration of the 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile over phosphorus pentoxide; a similar reaction has been reported by Henry (15). The reaction of phosphorus pentoxide with the methoxy cyanohydrin took another course, and a small amount of m-xylene was the only product obtained. Investigations along this line were therefore discontinued.

The 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile was reacted with acetic anhydride in the presence of a small amount of concentrated sulfuric acid in the hope of forming a diacetate. The conversion of secondary ethers to the corresponding acetates by the use of these reagents has been used frequently in the aliphatic series (9), and the acetylation of cyanohydrins by the use of these reagents has been studied by Burns and coworkers (7). However, in this case 1-acetoxy-2,6-dimethyl-4-methoxycyclohexanecarbonitrile was obtained; no diacetate was isolated. Burns (7) found that the acetate of acetone cyanohydrin could be pyrolysed to give methacrylonitrile in good yield, and the pyrolysis of 2,3-butyleneglycol diacetate to butadiene in good yield is known (26). The pyrolysis of 1-acetoxy-2,6-dimethyl-4-methoxycyclohexanecarbonitrile at 450° yielded only a small amount of an unsaturated compound which was not identified.

Attempts to introduce a double bond by heating 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile with oxalic acid at 140° failed, although the preparation of
cyclohexene from methyl cyclohexyl ether by heating the ether with anhydrous oxalic acid at 150° has been reported (30). Only small amounts of the starting material could be isolated from the reaction mixture. Evolution of hydrogen cyanide during this reaction, and the fact that the reaction mixture gave a positive 2,4-dinitrophenylhydrazine test indicated that the reversal of the cyanohydrin reaction took place to some extent.

Since 1,3-cyclohexadiene has been prepared by heating 1,2-dibromocyclohexane with quinoline (11), the possibility of making the 1,4-dibromo-2,6-dimethoxycyclohexanecarbonitrile and heating it with quinoline was investigated. 2,6-Dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile was heated with phosphorous tribromide and then with quinoline. A small amount of an oil was obtained which was insoluble in dilute acid, and which decolorized aqueous potassium permanganate. The reaction of this oil with bromine in carbon tetrachloride proceeded with the evolution of hydrogen bromide, and it was therefore concluded that little, if any, diene was formed.

In several of the above experiments there were indications that some unsaturation was introduced into the molecule. In no case, however, was a pure compound isolated. One explanation for this was that, because of the low yields, separation and purification of the extremely small amount of product were difficult. Another possible explanation was that the desired diene was unstable and polymerized readily.

In general, the methoxyl group of 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile and its related compounds
was more stable to cleavage than the average methoxyl group. This was shown by its stability toward acetic anhydride and sulfuric acid, and oxalic acid.

Even though the methoxy cyanohydrin is stable in acid solution, there was some evidence for the occurrence of the reverse reaction to a small extent. This factor caused difficulty in isolating and identifying some of the products. It was because of these undesirable side reactions that attempts to remove the methoxyl group of the ketone were made. These have already been described on page 42.
EXPERIMENTAL

Introduction

Materials. The dioxane was purified by refluxing over sodium metal for two hours and distilling. The first fourth of the distillate was discarded and the middle half of the material saved. The cyclohexane used for the hydrogenation reactions was purified by refluxing over Raney nickel for two hours and distilling. The first tenth of the material was discarded and the next eight-tenths of the distillate was saved. All of the other materials were used without further purification. Hydroquinone monomethyl ether was obtained from the Tennessee Eastman Corporation, Kingston, Tennessee.

Apparatus. Hydrogenations were conducted in standard high pressure hydrogenation equipment as supplied by the American Instrument Company, Silver Spring, Maryland.

Physical constants. All melting points are uncorrected. Refractive indices were determined with a Valentine Abbe refractometer.

2-Dimethylaminomethyl-4-methoxyphenol

Twenty-four and eight-tenths grams (0.2 moles) of hydroquinone monomethyl ether was treated with 78.5 ml. (0.6 moles) of 33 per cent dimethylamine and 49.2 g. (0.6 moles) of 37 per cent formaldehyde at room temperature according to the procedure of Caldwell and Thompson (8). An oil, which would not crystallize on cooling to 0°, separated. This oil was
distilled under diminished pressure through a vigreux column and 13.6 g. of a colorless liquid which distilled from 103° at 2.5 mm. to 112° at 3.4 mm., and 2 g. of a yellow oil which distilled from 117 to 124° at 3.1 mm. were obtained. The 13.6 g. of the lower boiling oil represented 38 per cent of the theoretical yield of 2-dimethylaminomethyl-4-methoxy phenol. Decombe (12) reported the boiling point of 2-dimethylaminomethyl-4-methoxyphenol to be 115-117° at 2 mm.

2-Dimethylaminomethyl-4-methoxyphenol was crystallized by cooling the lower boiling oil to -75° in a dry ice-acetone mixture and then allowing it to warm up slowly. This solid was found to be soluble in benzene, chloroform and dioxane. It was insoluble in water, and not volatile with steam. It could be recrystallized from 60-80° petroleum ether and had a melting point of 50-51°. Another 32 g. of this material was obtained by starting with 74.4 g. of hydroquinone monomethyl ether, but instead of distilling the oil obtained, it was seeded, and the solid was recrystallized from 60-80° petroleum ether. The following analyses were obtained:

<table>
<thead>
<tr>
<th>Calculated for C_{10}H_{15}O_{2}N</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>66.27</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogen</td>
<td>8.34</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**2-Methyl-4-methoxyphenol**

Eighteen grams of the 2-dimethylaminomethyl-4-methoxyphenol dissolved in 100 ml. of purified dioxane was hydro-
generated over 5 g. of copper chromite catalyst (4) at 200° for
30 minutes with a starting pressure of 2500 lbs. of hydrogen
measured at 27°. The catalyst was removed by filtration and
the dioxane was removed by distillation at water pump pressure.
The residual material was distilled under diminished pressure
and a fraction distilling from 77° at 0.5 mm. to 85° at
1.0 mm. was obtained. This solidified on cooling to room
temperature and weighed 5.8 g., 42 per cent of the theoretical
amount of 2-methyl-4-methoxyphenol. After two recrystalliza-
tions from 60-80° petroleum ether, it melted at 70.5°. Bam-
burger and Blanjeay (2) reported a melting point of 70.5° for
2-methyl-4-methoxyphenol. The following analyses were obtained:

<table>
<thead>
<tr>
<th>Calculated for C₉H₁₀O₂</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxyl</td>
<td>22.46</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2-Diethylamino-4-methoxyphenol

Hydroquinone monomethyl ether was reacted with three
times the molar quantities of diethylamine and formaldehyde
at room temperature according to the procedure described by
Caldwell and Thompson (8). Approximately 15 per cent of the
theoretical amount of 2-diethylaminomethyl-4-methoxyphenol, an
oil, distilling at 127-130° at 3.5 mm. was obtained. This oil
would not crystallize even on cooling to -75°. Because of
the low yield, this material was not considered promising and
was not identified, but in the light of similar experiments
with dimethylamine, it was probably 2-diethylaminomethyl-4-
methoxyphenol.
2,6-Bis(dimethylaminomethyl)-4-methoxyphenol

The reaction was carried out as previously described for 2-dimethylaminomethyl-4-methoxyphenol except that after the addition of the formaldehyde was completed, the reaction mixture was refluxed gently on the steam bath for two hours and 45 minutes. Then 74.4 g. of hydroquinone monomethyl ether was reacted by this procedure, 32.8 g., 22.9 per cent of the theoretical yield, of 2,6-bis(dimethylaminomethyl)-4-methoxyphenol was obtained; it distilled from 130° at 1.9 mm. to 138° at 2.6 mm. There was some evidence of decomposition during this distillation, as could be noted from the increase in pressure during the distillation.

After several additional experiments, the following procedure was developed.

A 5-l. three-necked flask was fitted with a sealed stirrer, a 500-ml. dropping funnel with inlet arranged so that it reached nearly to the bottom of the flask, and a reflux condenser through which a thermometer was suspended. A gas absorption trap was attached to the outlet of the condenser.

Four hundred and forty-seven grams (3.6 moles) of hydroquinone monomethyl ether and 1620 g. (9 moles) of 25 per cent dimethylamine were placed in the flask and the solution cooled to 15° by an ice bath. Three hundred forty and five tenths grams (4.2 moles) of 37 per cent formaldehyde was then added dropwise through the funnel at such a rate that the temperature did not go over 25°; this addition required from 45 to 60 minutes. When the addition was almost complete, an
oil, probably 2-dimethylaminomethyl-4-methoxyphenol, separated. After completion of the addition, the ice bath was removed, and the mixture allowed to stir an additional 45 minutes. The flask was then heated to a gentle reflux, about 75°, and another 340.5 g. of 37 per cent formaldehyde added dropwise over a one hour period. During this second addition, care was taken to prevent a vigorous reflux so that a large amount of dimethylaniline and formaldehyde would not be lost through the top of the condenser. After all of the formaldehyde had been added, the temperature of the reaction mixture rose to 90°. The mixture was then stirred and refluxed gently for an additional 40 minutes, after which time it was cooled to 10° and the upper aqueous layer decanted into a 4-l. separatory funnel and washed with 500 ml. of benzene. The oil and remaining aqueous layer were then poured into the benzene solution and the flask rinsed with another 100 ml. of benzene. If the layers did not separate adequately in the separatory funnel, more benzene was added. The benzene solution was then washed with two 250-ml. portions of water, dried over anhydrous magnesium sulfate and distilled through a vigreux column under an atmosphere of nitrogen at water pump pressure to remove the benzene. When the solvent had been removed, the water pump was replaced by a vacuum pump, and the residual oil distilled. After a 50-70 g. forerun was distilled, which consisted mainly of the monosubstituted product, the desired product distilling from 143° at 3 mm. to 152° at 3.6 mm. was obtained in a 640-670 g. yield, 75-80 per cent of the theoretical amount.
2,6-Dimethyl-4-methoxyphenol

The first attempt at preparing this compound consisted of treating 0.1 mole of hydroquinone monomethyl ether with 0.2 mole of formaldehyde in 60 ml. of two per cent sodium hydroxide at room temperature for four days according to the method of Lederer and Manasse (21). The mixture was then saturated with carbon dioxide and subjected to hydrogenation over a copper chromite catalyst (4) at 3500 lbs. pressure of hydrogen and 200°. No pressure drop was obtained, nor could any product be isolated. This method was therefore discarded in favor of the Caldwell and Thompson (8) method.

2,6-Dimethyl-4-methoxyphenol was first prepared by subjecting the 2,6-bis(dimethylaminomethyl)-4-methoxyphenol to hydrogenolysis (8) at 190° and about 4000 lbs. pressure of hydrogen over a copper chromite catalyst (4). The reaction was found to give 58 per cent of the theoretical yield of 2,6-dimethyl-4-methoxyphenol. The product was recrystallized from 60-80° petroleum ether. It was volatile with steam, and could be sublimed. The melting point of the steam-distilled material was 77°; the literature value was 77° (1). The following analyses were obtained.

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C_{9}H_{12}O_{2}</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxyl</td>
<td>20.40</td>
<td>20.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.44</td>
</tr>
</tbody>
</table>

The previously unreported 3,5-dinitrobenzoate of this phenol was made according to the procedure described by Phillips and Keenan (25). The yellow needles melted 176-178°
after recrystallization from 95 per cent ethyl alcohol. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C_{16}H_{14}O_{2}N_{2}</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>55.49</td>
<td>55.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55.19</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>4.08</td>
<td>4.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.34</td>
</tr>
<tr>
<td>Nitrogen (Dumas)</td>
<td>3.09</td>
<td>7.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.12</td>
</tr>
</tbody>
</table>

2,6-Dimethylhydroquinone was prepared from 2,6-dimethyl-4-methoxyphenol by refluxing 0.5 g. of the phenol with 10 ml. of 48 per cent hydrobromic acid for two hours. A solid crystallized on cooling the reaction mixture. This solid was recrystallized from xylene. Its melting point was 149-151°. The literature value for 2,6-dimethyl hydroquinone was 149-151° (23).

The 2,6-dimethyl-4-methoxyphenol was further characterized by a comparison of its reactivity in a diazonium coupling reaction with the reactivity of various substituted phenols as follows. A small quantity of p-toluene diazonium chloride was prepared in the usual way. The excess nitrite was destroyed with urea, the solution neutralized with sodium hydroxide, and filtered. One drop of the clear solution was then added to each of several test tubes containing the various substituted phenols with the following results:
Table III

Comparison of Activity of Substituted Phenols in Diazonium Coupling Reaction

<table>
<thead>
<tr>
<th>Compound</th>
<th>Result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-methoxyphenol</td>
<td>red precipitate</td>
<td>coupling occurred</td>
</tr>
<tr>
<td>2-methyl-4-methoxyphenol</td>
<td>red precipitate</td>
<td>coupling occurred</td>
</tr>
<tr>
<td>2,6-dimethyl-4-methoxyphenol</td>
<td>white precipitate</td>
<td>no coupling</td>
</tr>
<tr>
<td>2,6-dimethylhydroquinone</td>
<td>red precipitate</td>
<td>coupling occurred</td>
</tr>
</tbody>
</table>

In subsequent preparations of 2,6-dimethyl-4-methoxyphenol by the copper chromite catalysed hydrogenolysis of 2,6-bis(dimethylaminomethyl)-4-methoxyphenol at 130° and 4000 lbs. pressure of hydrogen, it was found that the yields were much lower. These low yields were noticed especially when the quantity of starting material was increased, and a longer period of time was required for the hydrogenolysis. In order to increase the yield, the procedure was modified until the final procedure given below was evolved.

In a 2500 ml. capacity hydrogenation vessel were placed 614 g. of 2,6-bis(dimethylaminomethyl)-4-methoxyphenol, 64.5 g. of copper chromite catalyst (4) and 340 ml. of purified di-oxane. The vessel was assembled and hydrogen introduced to a pressure of 4000 lbs. The vessel was then placed in the shaker, and rocked and heated at 235° until the pressure drop observed over a ten minute period was less than 100 lbs.; this required between 1.5 and 2 hours. The hydrogenation vessel was then allowed to cool and the contents removed. The catalyst was removed from the reaction mixture by filtra-
tion through a Whatman number 50 filter paper, and washed with a small quantity of dioxane. The reaction mixture was then placed in a 2-l. flask and the dioxane was removed by distillation under reduced pressure. The residual oil was transferred to a 500-ml. flask and distilled under reduced pressure through a Claisen column using a cooled side-arm flask as a receiver. An oil bath kept at 125° was used as a source of heat during this distillation. After an 8 g. forerun, the product was obtained distilling from 81° at 1 mm. to 36° at 1.8 mm. The yield was 353.5 g., 90 per cent of the theoretical amount.

2,6-Dimethyl-4-methoxycyclohexanol

In a 2500 ml. capacity hydrogenation vessel were placed 775 g. of distilled 2,6-dimethyl-4-methoxyphenol, 600 ml. of purified cyclohexane, and approximately 80 g. of Raney nickel catalyst (24) which had been freed of water and alcohol by suspending in boiling cyclohexane. After the vessel had been assembled, it was placed in the shaker, filled with hydrogen to a pressure of 4350 lbs., and rocked and heated at 190°. After 8 hours, the pressure dropped to 3475 lbs. at 190° and the vessel was refilled to 6050 lbs. of hydrogen while shaking continued. After an additional 10 hours, the pressure had again dropped to 3150 lbs. and the vessel was recharged to 6100 lbs. at 196°. An additional 11 hours of heating and shaking gave a pressure drop to 4750 lbs. at 192°; the vessel was again filled to 6000 lbs. and the reaction continued for another 14 hours, at which time the pressure was 5375 lbs. at
191°. Further heating and shaking gave no appreciable pressure drop. The total time of reaction was 43 hours.

The vessel was allowed to cool to room temperature, the contents removed, catalyst filtered through a Whatman number 50 filter paper, and washed. The solvent was removed by distillation at reduced pressure; the residual liquid was then distilled under diminished pressure through a 2.0 cm. diameter by 60 cm. long electrically heated column packed with stainless steel helices with the following results:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Distilling Range</th>
<th>n\text{D}</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>36 to 59° at 1 mm.</td>
<td>----</td>
<td>126.1 g.</td>
</tr>
<tr>
<td>II part 1</td>
<td>59 to 66° at 1.2 mm.</td>
<td>----</td>
<td>383.8 g.</td>
</tr>
<tr>
<td>II part 2</td>
<td>70 to 80° at 1.6 to 1.8 mm.</td>
<td>1.4622</td>
<td>143.3 g.</td>
</tr>
<tr>
<td>III residue</td>
<td></td>
<td>----</td>
<td>30.3 g.</td>
</tr>
</tbody>
</table>

The 527.1 g. obtained in the combined parts of fraction II represent a yield of 65.4 per cent of the theoretical amount of 2,6-dimethyl-4-methoxycyclohexanol. The following analyses were obtained:

<table>
<thead>
<tr>
<th>Calculated for C\text{\textsubscript{2}}H\text{\textsubscript{12}}O\text{\textsubscript{4}}</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>68.31</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogen</td>
<td>11.46</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The low boiling material, fraction I, was probably 4-methoxycyclohexanol and 2-methyl-4-methoxycyclohexanol.

The 3,5-dinitrobenzoate was prepared in the usual manner and recrystallized from 60-80° petroleum ether; the melting point was 174-176°. The following analyses were obtained:
A previous hydrogenation in which a smaller quantity of steam distilled 2,6-dimethyl-4-methoxyphenol was used was found to proceed in six hours and gave 80.5 per cent of the theoretical yield of the desired 2,6-dimethyl-4-methoxycyclohexanol. In this instance, there was more free space available in the hydrogenation vessel, and the product was distilled through a small vigreux column instead of the larger packed column.

2,6-Dimethyl-4-methoxycyclohexanone

A 5-l. three-necked flask was fitted with a sealed stirrer, 500-ml. dropping funnel, and a reflux condenser through which a thermometer was suspended so that the bulb of the thermometer almost touched the bottom of the flask. The flask was charged with 440 g. (1.49 moles) of technical potassium dichromate, 2715 ml. of water and 202 ml. (3.73 moles) of concentrated sulfuric acid. The addition of the latter caused the temperature to rise to 48°. The dropwise addition of 342 g. (2.16 moles) of 2,6-dimethyl-4-methoxycyclohexanol was then started. The temperature was kept between 55 and 63°. After approximately half the alcohol had been added, there seemed to be no further evolution of heat. When the addition was completed, the reaction mixture was heated to 64° by means

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C_{16}H_{30}O_{7}N_{2}</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>54.54</td>
<td>54.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54.78</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>5.72</td>
<td>5.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.79</td>
</tr>
<tr>
<td>Nitrogen (Dumas)</td>
<td>7.95</td>
<td>7.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.92</td>
</tr>
</tbody>
</table>
of a water bath and was stirred for an additional two hours, after which time the temperature had fallen to 47°. The mixture was then cooled to 20° by an ice bath, and 400 ml. of ether added. The stirrer was stopped, and the two layers separated. The ether layer was washed with three 375-ml. portions of five per cent sodium hydroxide and dried over anhydrous potassium carbonate. The oil remaining after the removal of the ether by distillation under diminished pressure weighed 214 g.

The aqueous portion of the reaction mixture was extracted with three 250-ml. portions of ether. These ether extracts were washed with three 250-ml. portions of five per cent sodium hydroxide, dried over potassium carbonate, and the ether removed. This process yielded another 32.1 g. of crude material. A repetition of this extraction procedure on the aqueous portion yielded only an additional 5 g. of material. The total yield of crude material was 251.1 g. which accounted for 74 per cent of the starting material.

The crude material was fractionated through a 2.0 cm. diameter by 60 cm. long electrically heated column packed with stainless steel helices. After a small forerun, a ketone fraction of 107.6 g., 31.9 per cent of the theoretical amount, distilling from 102 to 112° at 24 mm. (nD 27.5, 1.4520) and 88.6 g. of recovered 2,4-dimethyl-4-methoxycyclohexanol distilling from 119 to 124° at 24 mm. (nD 27.5, 1.4621) were obtained.

In a subsequent experiment, 171 g. (1.08 moles) of 2,4-dimethyl-4-methoxycyclohexanol was added to a mixture of 440 g. (1.49 moles) of potassium dichromate, 2715 ml. of water
and 202 ml. (3.73 moles) of concentrated sulfuric acid. This concentration of oxidizing mixture represented a 300 per cent excess instead of the 100 per cent excess used previously. The higher concentration was used in order to attempt to reduce the amount of unreacted alcohol. The oxidation was conducted in a similar manner, the temperature being allowed to rise to 73°. After approximately two-thirds of the alcohol was added, the evolution of heat seemed to stop. Stirring was continued for three hours after the addition was complete. The ketone was then obtained from the reaction mixture by the process described in the previous experiment. A yield of 81 g. of crude material, which accounted for 46.8 per cent of the starting material, was obtained. On fractionation, this yielded 42.3 g., 25.6 per cent of the theoretical amount, of 2,6-dimethyl-4-methoxycyclohexanone distilling from 106 to 111° at 24 mm., and 14.3 g. of unreacted alcohol. Partial neutralization and further ether extractions of the aqueous portion of the oxidation reaction mixture did not give a further yield of ketone.

A 2,4-dinitrophenylhydrazone of 2,6-dimethyl-4-methoxycyclohexanone was made in the usual way and recrystallized from 60-80° petroleum ether. Its melting point was 78.5-80°. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C_{15}H_{20}O_{5}N_{4}</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td></td>
<td>53.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrogen</td>
<td></td>
<td>5.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrogen (Dumas)</td>
<td></td>
<td>16.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In an earlier experiment in which 0.1 mole of the 2,6-dimethyl-4-methoxycyclohexanone was oxidized, and the product distilled through a vigreux column, a fraction distilling from 61-65° at 2 mm. was obtained. This accounted for 60 per cent of the starting material, but the ketone was obviously contaminated with unreacted alcohol. This procedure was based on the preparation of menthone described in Organic Synthesis (14).

Reactions of 2,6-Dimethyl-4-methoxycyclohexanone

Reaction with hydrochloric acid. Five grams of 2,6-dimethyl-4-methoxycyclohexanone was refluxed with 50 ml. of concentrated hydrochloric acid for eight hours. At first the mixture was homogeneous when cold, but turned cloudy on heating; on cooling it became clear again. By the end of the reflux time, however, the mixture did not clear up completely on cooling. At the conclusion of the reflux period, the mixture was cooled, neutralized with sodium bicarbonate, and extracted with three 20-ml. portions of ether. The ether solution was dried over anhydrous magnesium sulfate and distilled under reduced pressure. After the removal of the ether, the following three fractions of approximately 1.5 ml. each were obtained by distillation at a pressure of 0.5 mm.:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Distilling range</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>47-53°</td>
</tr>
<tr>
<td>II</td>
<td>53-69°</td>
</tr>
<tr>
<td>III</td>
<td>70-80°</td>
</tr>
</tbody>
</table>

Fraction I gave only a slight Beilstein test for halogen, but
fraction III gave a very strong test. Although fraction III gave a positive 2,4-dinitrophenylhydrazine test, attempts at isolating a solid 2,4-dinitrophenylhydrazone were unsuccessful. Since fraction I had a low boiling point, it was probably largely recovered 2,6-dimethyl-4-methoxycyclohexanone.

A mixture of 5 g. of 2,6-dimethyl-4-methoxycyclohexanone and 25 ml. of concentrated hydrochloric acid was heated in a sealed tube at 100° for three and a half hours. The tube was then cooled and the contents removed. The reaction mixture was neutralized with sodium bicarbonate, and extracted with ether. The ether extracts were dried over anhydrous potassium carbonate, and the solvent removed by distillation. The oily residue was then mixed with 15 ml. of quinoline and the mixture distilled (11). A few milliliters of ether was added to the distillate. It was then washed with 3 N hydrochloric acid to remove the quinoline, dried over anhydrous potassium carbonate, and the ether removed. Less than one milliliter of an oil remained which decolorized aqueous potassium permanganate solution, and bromine in carbon tetrachloride. On treatment of a small sample of the oil with 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid, a yellow precipitate which turned red on standing was obtained. When the oil was treated with 2,4-dinitrophenylhydrazine reagent in hydrochloric acid and methanol, a red precipitate formed immediately in the cold. It was quite soluble in both methanol and water. The melting point of the crude material was 128 to 136°; further purification was unsuccessful. The appearance of the red color was
probably caused by a shift in the double bond from the 3,4 to the 2,3 position, forming a conjugated system.

**Reaction with phosphorous tribromide.** Two milliliters of 2,6-dimethyl-4-methoxycyclohexanone was mixed with 1.5 ml. of phosphorous tribromide. The addition of the first 0.5 ml. of phosphorous tribromide caused an evolution of heat. The mixture was heated on the steam bath in a loosely stoppered test tube for three hours and then cooled. The excess phosphorous tribromide was then hydrolysed by the addition of water.

This mixture was treated in the same manner as the mixture which had been heated with hydrochloric acid in a sealed tube. Distillation of this material from freshly distilled quinoline yielded about two drops of a material which decolorized aqueous potassium permanganate solution, and gave a positive test with 2,4-dinitrophenylhydrazine reagent.

**Treatment with boron trifluoride (22).** The 2,6-dimethyl-4-methoxycyclohexanone was treated with boron trifluoride-acetic anhydride complex. A dark brown polymer which was insoluble in ether was obtained.

2,6-Dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile (2,6-Dimethyl-4-methoxycyclohexanone Cyanhydrin)

In a 300-ml. three-necked flask fitted with a stirrer, 60-ml. dropping funnel, and a reflux condenser through which a thermometer was suspended, were placed 8.3 g. (0.31 moles) of hydrogen cyanide dissolved in 14 ml. of 95 per cent ethanol and 0.3 g. of potassium cyanide. The mixture was cooled to
0° by means of an ice bath, and 43.3 g. (0.38 moles) of 2,6-dimethyl-4-methoxycyclohexanone dissolved in 50 ml. of 95 per cent ethanol was added dropwise over a 30 minute period. The temperature was not allowed to go over 15°. After the addition had been completed, the ice bath was removed, and the mixture was stirred for an additional 30 minutes. Fifteen drops of concentrated hydrochloric acid was added, and followed by 200 ml. of ether and 20 ml. of water. A homogeneous solution was obtained. The water was removed from this solution by adding several two to five gram portions of calcium chloride and separating the layers obtained. The ether solution was finally dried over magnesium sulfate, and the ether removed by distillation at water pump pressure, using as low a temperature as was practical, not over 50°. Toward the end of the evaporation, crystals appeared in the flask. The entire residue, which weighed 50 g., was allowed to stand in the refrigerator for two days, and then filtered. The yield of crude material thus obtained was 26 g., 51 per cent of the theoretical amount. The 2,6-dimethyl-1-hydroxy-4-methoxycyclohexane carbonitrile was found to crystallize from water, and also from 60-80° petroleum ether. After two recrystallizations from petroleum ether, it melted at 99.5-100.5°. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C10H17C6N</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>65.57</td>
<td>66.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65.85</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>9.38</td>
<td>9.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.32</td>
</tr>
<tr>
<td>Nitrogen (Dumas)</td>
<td>7.65</td>
<td>7.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.56</td>
</tr>
</tbody>
</table>
In earlier experiments, a 50 per cent excess of hydrogen cyanide was used instead of the 10 per cent excess employed above. Various methods of isolating the product were tried; these included the use of benzene instead of ether for extracting the product, and direct evaporation of the acidified reaction mixture. Both of these methods gave fairly good results. All attempts to remove the cyanohydrin from the reaction mixture by distillation failed. In some cases the temperature of the reaction was allowed to go as high as 30°; the results obtained by this procedure were not consistent, and at times resulted in very small yields.

Reactions of 2,6-Dimethyl-1-hydroxy-4-methoxy-cyclohexanecarbonitrile

The reactions of the methoxy cyanohydrin are given below under the following headings:

1. Stability to cold concentrated alcoholic hydrogen chloride.

2. Conversion to 1,4-dihydroxy-2,6-dimethylcyclohexane-carbonitrile by hot alcoholic hydrogen chloride.

3. Conversion to 1,4-dihydroxy-2,6-dimethylcyclohexane-carbonitrile by concentrated hydrochloric acid.

4. Conversion to 1,4-dihydroxy-2,6-dimethylcyclohexane-carbonitrile by constant boiling hydrobromic acid.

5. Conversion to 1-acetoxy-2,6-dimethyl-4-methoxycyclohexanecarbonitrile by acetic anhydride and sulfuric acid.

Attempts to prepare an unsaturated nitrile from the methoxy cyanohydrin and its derivatives are discussed in the
Stability to cold concentrated alcoholic hydrogen chloride.
The alcoholic reaction mixture from the preparation of 2,6-
dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile was satu­
rated with hydrogen chloride and allowed to stand overnight.
A brown solid which was soluble in water formed; this solid
was finally identified as ammonium chloride. It was probably
formed from the excess hydrogen cyanide present in the origi­
nal reaction mixture. The filtrate, which remained after the
brown solid was removed, was concentrated by evaporation on
the steam bath. The residual oil was then extracted with a
small amount of hot water. A white solid was obtained which
melted at 98-100.5°, and which showed no depression in its
melting point when mixed with an equal quantity of a known
sample of 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbo­
nitrile. The yield was approximately four per cent of the
theoretical amount. This experiment was based on the proce­
dure described in Organic Synthesis (5) for the hydrolysis of
phenyl acetooacetonitrile.

Conversion to 1,4-dihydroxy-2,6-dimethylcyclohexanecarbo­
nitrile by hot alcoholic hydrogen chloride. A solution of
20 ml. of 95 per cent ethanol and 5.6 g. of 2,6-dimethyl-1-
hydroxy-4-methoxycyclohexanecarbonitrile was saturated with
hydrogen chloride and allowed to stand overnight. Approxi­
mately 0.3 g. of ammonium chloride formed; this was removed
by filtration. The filtrate was then placed in a sealed tube
and heated on the steam bath for two hours. Two layers were
found in the tube. The upper one evaporated rapidly at room
temperature; this was probably ethyl chloride. The lower layer was concentrated by distillation at reduced pressure until a viscous-oil containing some small amount of solid remained. Upon the addition of a few milliliters of water, a precipitate formed in approximately seven per cent of the theoretical yield. This solid gave a positive Beilstein test for halogen. After recrystallization from 60-80° petroleum ether, it melted at 170-175° with decomposition, and was neutral to litmus. Chlorine analysis of this material by the Parr bomb method was unsatisfactory because reproducible results were not obtained; the values obtained were 16.24, 17.61, and 18.82 per cent chlorine. The four chlorine-containing compounds which could be obtained from this reaction were 1-chloro-2,6-dimethyl-4-methoxycyclohexanecarbonitrile, 14.22 per cent chlorine; 4-chloro-2,6-dimethyl-1-hydroxycyclohexane-carbonitrile, 15.11 per cent chlorine; 1-chloro-2,6-dimethyl-4-hydroxycyclohexanecarbonitrile, 15.11 per cent chlorine; and 1,4-dichloro-2,6-dimethylcyclohexanecarbonitrile, 28.02 per cent chlorine. The material could not be purified by further recrystallization and was not identified further.

When the aqueous filtrate, which remained after the chlorine containing solid was removed from the reaction mixture, was made alkaline with 10 per cent sodium hydroxide, another white solid was obtained in about 20 per cent of the theoretical yield. This compound was soluble in water, but could be recrystallized from 60-80° petroleum ether, was neutral to litmus, gave a negative Beilstein test for halogen, and melted at 169-171°. When this chlorine-free solid was heated with a
sodium hydroxide solution and then treated with ferrous ammonium sulfate and acidified, it gave the prussian blue test which indicated the presence of the cyanohydrin grouping. The following analyses were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Calculated for CaH15C6N</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>63.88</td>
<td>63.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63.82</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>8.92</td>
<td>8.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.15</td>
</tr>
<tr>
<td>Nitrogen (Dumas)</td>
<td>8.27</td>
<td>8.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.51</td>
</tr>
</tbody>
</table>

This compound was therefore 1,4-dihydroxy-2,6-dimethylcyclohexanecarbonitrile.

The pyrolysis of this substance is described on page 76.

Conversion to 1,4-dihydroxy-2,6-dimethylcyclohexanecarbonitrile by concentrated hydrochloric acid. When a mixture of 0.95 g. of 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile and 5 ml. of concentrated hydrochloric acid were heated on the steam bath for two hours, a small amount of an unidentified oil, plus approximately 25 per cent of the starting material were obtained. The following procedure gave six per cent of the theoretical yield of the 1,4-dihydroxy-2,6-dimethylcyclohexanecarbonitrile. Five grams of the methoxycyanohydrin was refluxed with 50 ml. of concentrated hydrochloric acid for two hours. The reaction mixture was then evaporated to dryness by distillation under diminished pressure. The residue was cooled, and a few milliliters of water was added. The water solution was then filtered, and the filtrate made alkaline with sodium hydroxide. The resulting precipitate was removed, and recrystallized from 60-80°
petroleum ether. After recrystallization it weighed 0.28 g. After a second recrystallization, it melted at 156-158°, but showed no depression of the melting point when mixed with an equal quantity of a pure sample of 1,4-dihydroxy-2,6-dimethylcyclonexanecarbonitrile. Further purification was difficult.

Conversion to 1,4-dihydroxy-2,6-dimethylcyclonexanecarbonitrile by constant boiling hydrobromic acid. 1,4-Dihydroxy-2,6-dimethylcyclonexanecarbonitrile was obtained by refluxing 2.7 g. of 2,6-dimethyl-1-hydroxy-4-methoxycyclonexanecarbonitrile with 5 ml. of constant boiling hydrobromic acid for two hours. After cooling, the oily droplets which had formed were removed by filtration, and the filtrate made alkaline with 10 per cent sodium hydroxide. This procedure yielded about 0.9 g. of crude material which was sublimed. The yield of sublimed 1,4-dihydroxy-2,6-dimethylcyclonexanecarbonitrile was 0.65 g., 26 per cent of the theoretical amount. This material showed no depression of the melting point when mixed with an equal quantity of a pure sample of 1,4-dihydroxy-2,6-dimethylcyclonexanecarbonitrile. Several attempts were made to repeat this process using hydrobromic acid, but this product could not be obtained; a gum which could not be crystallized always formed.

The pyrolysis of this dihydroxy compound is described on page 76.

Conversion to 1-acetoxy-2,6-dimethyl-4-methoxycyclonexanecarbonitrile by acetic anhydride and sulfuric acid. The following procedure was based on the work of Burns and co-
workers (7). To a mixture of 19.1 g. of 2,6-dimethyl-1-hydroxy-
4-methoxycyclohexanecarbonitrile and 50 ml. of acetic anhydride,
1 ml. of concentrated sulfuric acid was added; a noticeable
amount of heat was evolved. The mixture was refluxed for
three hours. During this process, the solution became very
dark. After standing at room temperature overnight, an addi­
tional five drops of sulfuric acid was added, but no more heat
was evolved. Five grams of sodium acetate and 25 ml. of water
were added, and the solution neutralized with potassium car­
bonate. A black upper layer appeared, which was dissolved in
approximately 20 ml. of ether. The ether solution was dried
over potassium carbonate, and distilled. A 6.0 g. fraction,
40.3 per cent of the theoretical amount of 1-acetoxy-2,6-
dimethyl-4-methoxycyclohexanecarbonitrile, distilling from
103 to 107° at 1.6 mm. was obtained. This substance did not
react with bromine in carbon tetrachloride or potassium per­
manganate solution readily; the reactions with these reagents
were slight enough to have come from impurities. On boiling
with alkali and treating with ferrous ion and acid, a prussian
blue test was obtained, indicating the presence of the labile
nitrile group.

Attempts at a saponification equivalent were unsuccessful
because ammonia was evolved to some extent; a value of 178
was obtained. Methoxyl analyses were found to be difficult
since several hours were required for the reaction to go to
completion; values of 13.62 and 13.63 per cent were finally
obtained. Acetyl values according to the method described by
Shriner (27) could not be obtained readily; the compound re­
quired an abnormally long time for complete hydrolysis and
distillation; the highest value obtained was 15 per cent, and
the reaction was still not complete. All of the evidence ob­
tained indicated that this compound was 1-acetoxy-2,6-dimethyl-
4-methoxycyclohexanecarbonitrile. The analytical results are
summarized below.

<table>
<thead>
<tr>
<th></th>
<th>Calculated for C₁₂H₁₉O₃N</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon</td>
<td>63.97</td>
<td>64.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63.85</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>8.50</td>
<td>8.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.13</td>
</tr>
<tr>
<td>Methoxyl</td>
<td>13.77</td>
<td>13.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.63</td>
</tr>
<tr>
<td>Saponification equivalent 225</td>
<td>greater than 178</td>
<td></td>
</tr>
<tr>
<td>Acetyl number</td>
<td>19.1</td>
<td>greater than 15.5</td>
</tr>
</tbody>
</table>

The pyrolysis of this acetate is described in the next
section on page 76.

**Attempts to Prepare an Unsaturated Nitrile from**

**2,6-Dimethyl-1-hydroxy-4-methoxycyclohexane-
carbonitrile and its Derivatives**

These reactions are given below under the following
headings:

1. Reaction of 2,6-dimethyl-1-hydroxy-4-methoxycyclo-
hexanecarbonitrile with phosphorous pentoxide.

2. Stability of 2,6-dimethyl-1-hydroxy-4-methoxycyclo-
hexanecarbonitrile to oxalic acid.
3. Reaction of 2,6-dimethyl-1-hydroxy-4-methoxycyclo-
hexanecarbonitrile with phosphorous tribromide.

4. Pyrolysis of 1,4-dihydroxy-2,6-dimethylcyclohexane-
carbonitrile.

5. Pyrolysis of 1-acetoxy-2,6-dimethyl-4-methoxycyclo-
hexanecarbonitrile.

Reaction of 2,6-dimethyl-1-hydroxy-4-methoxycyclohexane-
carbonitrile with phosphorous pentoxide (15). Four grams of 
2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile was 
mixed with an equal quantity of phosphorous pentoxide and dis-
tilled under diminished pressure, using a free flame. A yel-
low pungent liquid was obtained. Distillation of this yellow 
liquid at atmospheric pressure yielded a portion distilling 
at 33°, which was largely hydrogen cyanide, and approximately 
five drops of a portion distilling from 133-135°. This latter 
fraction was believed to be m-xylene because of odor, index 
of refraction and insolubility in concentrated sulfuric acid. 
The index of refraction at 20° using the D line of sodium of 
m-xylene was 1.4384; the compound obtained gave a value of 
1.4945.

Stability of 2,6-dimethyl-1-hydroxy-4-methoxycyclohexane-
carbonitrile to oxalic acid. Five grams (0.027 moles) of 2,6-
dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile was heated 
at 140° for three hours with three times the molar quantity of 
oxalic acid. The starting material was recovered in 15 per-
cent of the theoretical amount. The reversal of the cyano-
hydrin synthesis was evidenced by the odor of hydrogen cyanide 
from the top of the reflux condenser, and the fact that the
reaction mixture gave a positive test with 2,4-dinitrophenyl-hydrazine reagent. This procedure was similar to the one used by Waser (30) to make cyclohexene from methyl cyclohexyl ether.

**Reaction of 2,6-dimethyl-1-hydroxy-4-methoxycyclohexane-carbonitrile with phosphorous tribromide.** A large test tube containing 5.0 g. (0.027 moles) of 2,6-dimethyl-1-hydroxy-4-methoxycyclohexane-carbonitrile and 8.1 g. (0.03 moles) of phosphorous tribromide was heated at 110-115° for two hours. The mixture bubbled vigorously at first, then turned into a clear liquid, and finally became cloudy by the end of one hour. The orange pasty mixture which resulted was poured into ice water, and allowed to warm up to room temperature. The pasty mass was stirred with the water, and as much of the water as possible was removed. The remaining material was put back in the test tube along with 25 ml. of freshly distilled quinoline, and heated at 190-200° for one hour, by which time the mixture had become deep red in color. Next, the reaction mixture was cooled, and poured into 18 ml. of ice cold 3 N hydrochloric acid. The resulting deep red aqueous mixture was extracted with three 25-ml. portions of ether. The ether extracts were washed with several small portions of water, dried over calcium chloride, and the ether removed by distillation at water pump pressure and room temperature. Approximately 0.8 ml. of a dark brown oil remained. This oil reacted with bromine in carbon tetrachloride with the evolution of hydrogen bromide, and decolorized aqueous permanganate solution. It was insoluble in dilute hydrochloric acid.

A similar use of quinoline has been reported by Crossley (11)
Pyrolysis of 1,4-dihydroxy-2,6-dimethylcyclohexanecarbonitrile. 1,4-Dihydroxy-2,6-dimethylcyclohexanecarbonitrile was pyrolysed by subliming under reduced pressure 0.65 g. of the material into an alumina packed glass tube at 345°. About 0.7 ml. of a yellow oil was obtained. This yellow oil decolorized bromine in carbon tetrachloride and potassium permanganate solution. There was insufficient material for further identification.

Pyrolysis of 1-acetoxy-2,6-dimethyl-4-methoxycyclohexanecarbonitrile. 1-Acetoxy-2,6-dimethyl-4-methoxycyclohexanecarbonitrile was pyrolysed by passing 3.67 g. (0.016 moles) of the material dropwise through an alumina packed tube at 450°. An oil was obtained which accounted for approximately half of the starting material and which darkened on standing. This oil was found to decolorize bromine in carbon tetrachloride, and potassium permanganate solution. On cooling in a dry ice-acetone mixture, it solidified, and some small amount, approximately 5-10 mgm., of a material which remained solid at room temperature was obtained. There was, however, insufficient material for further identification. The successful pyrolysis of acetates has been reported by Shlechter (26) and Burns (7).
SUMMARY

In an attempt to elucidate the well known abnormal resistance to esterification and the high ionization constant of 2,6-dimethylbenzoic acid, the preparation of 2,6,7,8-tetra-methyl-2.2.2-bicyclo[3.2.1]octane-1-carboxylic acid was undertaken; the following intermediate compounds were prepared:

1. 2,6-Bis(dimethylaminomethyl)-4-methoxyphenol was prepared in 75 per cent of the theoretical yield from hydroquinone monomethyl ether by a Mannich reaction using dimethylamine and formaldehyde. It distilled at 143° at 3 mm.

2. 2,6-Dimethyl-4-methoxyphenol was prepared in 90 per cent of the theoretical yield by the copper chromite catalysed hydrogenolysis of 2,6-bis(dimethylaminomethyl)-4-methoxyphenol. It melted at 77° and formed a 3,5-dinitrobenzoate which melted at 176-178°.

3. 2,6-Dimethyl-4-methoxycyclohexanol was prepared in 65 per cent of the theoretical yield by the Raney nickel catalysed hydrogenation of the 2,6-dimethyl-4-methoxyphenol. It distilled at 59-60° at 1-1.2 mm. and formed a 3,5-dinitrobenzoate which melted at 174-176°.

4. 2,6-Dimethylcyclohexanone was prepared in 32 per cent of the theoretical yield by the potassium dichromate-sulfuric acid oxidation of 2,6-dimethylcyclohexanol. It distilled from 106 to 111° at 24 mm. and formed a 2,4-dinitrophenylhydrazone which melted at 73.5-80°.

5. 2,6-Dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile was prepared in 51 per cent of the theoretical yield
from 2,6-dimethyl-4-methoxycyclohexanone by a cyanohydrin reaction using an alcohol solution of hydrogen cyanide and a catalytic amount of potassium cyanide. It melted at 99.5-100°.

6. 2,6-Dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile was converted into 1,4-dihydroxy-2,6-dimethylcyclohexanecarbonitrile which melted at 99.5-100°, by the action of either hydrochloric or hydrobromic acid. It was also converted into 1-acetoxy-2,6-dimethyl-4-methoxycyclohexanecarbonitrile which distilled from 103 to 107° at 1.5 mm., by the action of acetic anhydride and sulfuric acid. Neither of these latter compounds could be pyrolysed successfully to give an unsaturated nitrile.

The reactions of 2,6-dimethyl-4-methoxycyclohexanone and 2,6-dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile were studied in some detail in an attempt to develop a method of hydrolysing the methoxyl group and introducing a pair of conjugated double bonds into the ring. No pure dienes could be isolated.
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ABSTRACT

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Title of Thesis: "The Reaction of Propylene Oxide with Methanol" and "The Preparation of 2,6-Dimethyl-1-hydroxy-4-methoxycyclohexanecarbonitrile"

Thesis directed by Professor Wilkins Reeve

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Minors: Physical Chemistry, Inorganic Chemistry

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PART I

The Reaction of Propylene Oxide with Methanol

In previous work on the condensation of propylene oxide with alcohols, the structures of the alkoxypropanols obtained were not proved by unequivocal synthesis. It was known that one isomer was obtained by conducting the reaction in the presence of a catalytic amount of sodium methoxide, and both isomers were obtained by conducting the reaction in the presence of catalytic amounts of sulfuric acid.

The isomer with the lower boiling point was shown to be 1-methoxypropanol-2 by comparing its physical properties and the melting points of its derivatives with those of 1-methoxypropanol-2 prepared by the reduction of methoxyacetone. 1-Methoxypropanol-2 has the following physical properties:

b.p. 118.5-119° at 765 mm.; n^20_0, 1.4034; n^25_0, 1.4017; d^20_4, 0.922; d^25_4, 0.919. It forms a 3,5-dinitrobenzoate which melts at 84-85° and an α-naphthylurethane which melts at 72-73°.

The isomer with the higher boiling point was shown to be 2-methoxypropanol-1 by comparing its physical properties and the melting points of its derivatives with those of 2-methoxypropanol-1 prepared by the copper chromite catalysed hydrogenolysis of ethyl methoxypropionate. 2-Methoxypropanol-1
has the following physical properties: b.p. 130-130.2° at
758 mm.; n\text{D}_{20}, 1.4070; n\text{D}_{25}, 1.4048; d\text{D}_{20}, 0.938; d\text{D}_{25}, 0.934.
It forms a 3,5-dinitrobenzoate which melts at 96.5-97°, and
an α-naphthylurethane which melts at 60-60.5°.

The copper chromite hydrogenolysis of alkoxy esters has
not been used before. This reaction was found to go smoothly
at about 400 atmospheres pressure of hydrogen and 250°.

Both of the methoxypropanols formed azeotropes with
water. 1-Methoxypropanol-2 formed an azeotrope which dis-
tilled at 97.2-98° and contained approximately 65 per cent
of the alcohol by volume. The 2-methoxypropanol-1 formed an
azeotrope which distilled at 98° and contained approximately
33 per cent of the alcohol by volume.

PART II

The Preparation of 2,6-Dimethyl-1-hydroxy-4-
methoxycyclohexanecarbonitrile

In an attempt to elucidate the well-known abnormal re-
sistance to esterification and the high ionization constant
of 2,6-dimethylbenzoic acid, the preparation of 2,6,7,8-tetra-
methyl-[2.2.2]-octane-1-carboxylic acid was undertaken, and
the synthesis of many necessary intermediates developed.

Hydroquinone monomethyl ether was converted by a Mannich
reaction, using dimethylamine and formaldehyde, into 2,6-bis-
(dimethylaminomethyl)-4-methoxyphenol, distilling at 143° at
3 mm., in 75 per cent of the theoretical yield. Hydrogenolysis
of this product over a copper chromite catalyst at 235° and 400 atmospheres pressure of hydrogen gave 2,6-dimethyl-4-methoxyphenol in 90 per cent of the theoretical yield. This substance melted at 77° and formed a 3,5-dinitrobenzoate which melted at 176-178°. The 2,6-dimethyl-4-methoxyphenol was hydrogenated over Raney nickel catalyst at 130° and 400 atmospheres pressure of hydrogen, and 2,6-dimethyl-4-methoxycyclohexanol was obtained in 65 per cent of the theoretical yield. This material distilled at 53-60° at 1-1.2 mm., and its index of refraction at 25° using the D line of sodium was 1.4622. It formed a 3,5-dinitrobenzoate which melted at 174-176°. The 2,6-dimethyl-4-methoxycyclohexanol was oxidized by potassium dichromate and sulfuric acid to 2,6-dimethyl-4-methoxycyclohexanone in 32 per cent of the theoretical yield. It distilled from 106 to 111° at 24 mm., and its index of refraction at 27.5° using the D line of sodium was 1.4520. It formed a 2,4-dinitrophenylhydrazone which melted at 78.5-80°. The 2,6-dimethyl-4-methoxycyclohexanone formed a cyanohydrin in 51 per cent of the theoretical yield when it was allowed to react with an alcoholic solution of hydrogen cyanide in the presence of a catalytic amount of potassium cyanide. This cyanohydrin, 1-hydroxy-2,6-dimethyl-4-methoxycyclohexancarbonitrile, melted at 99.5-100°.

The 2,6-dimethyl-1-hydroxy-4-methoxycyclohexancarbonitrile was converted in small yields, by the action of hydrochloric or hydrobromic acid into 1,4-dihydroxy-2,6-dimethylcyclohexane-carbonitrile, which sublimed under diminished pressure and melted at 169-171°. The 2,6-dimethyl-1-hydroxy-4-methoxycyclo-
hexanecarbonitrile was also converted to 1-acetoxy-2,6-dimethyl-4-methoxycyclohexanecarbonitrile by the action of acetic anhydride and sulfuric acid. This compound distilled from 103 to 107° at 1.5 mm. Attempts to isolate an unsaturated nitrile by the pyrolysis of the dihydroxy or acetoxy nitrile were unsuccessful; small amounts of unsaturated materials which could not be purified or identified were obtained.

The reactions of 2,6-dimethyl-4-methoxycyclohexanone and 1-hydroxy-2,6-dimethyl-4-methoxycyclohexanecarbonitrile were studied in some detail in an attempt to develop a method of hydrolysing the methoxyl group and introducing a pair of conjugated double bonds into the ring. The methoxyl group could be hydrolysed in poor yield, but the attempts to introduce the conjugated double bonds into the ring were unsuccessful.
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