I hereby recommend that the thesis prepared under my supervision by James O. Koehler entitled *Amino Alcohol and Amino Ketone Derivatives of Thymol* be accepted as fulfilling this part of the requirements for the degree of.

Approved by:

[Signature]

[Prepared on Form 668—G. S. & T. C.—500—548]
AMINOALCOHOL AND AMINOKETONE DERIVATIVES OF THYMOL

A dissertation submitted to the Graduate School of Arts and Sciences of the University of Cincinnati in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY

1951

by James O. Koehler

B.Sc. in Chem. University of Akron 1947
M.Sc. in Chem. University of Cincinnati 1949
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ACKNOWLEDGMENT

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Part I

INTRODUCTION

A. Pharmacological Properties of Thymol

Thymol, 1.1, a naturally occurring aromatic compound isolated from the volatile oil of thyme and other plants, has received some attention in medicinal chemistry since it is a natural phenol and hence shows some bacteriocidal properties. It has been employed for many years as an anthelmintic and duodenal disinfectant. In particular it has been used to combat ascarides and hookworms. In dilute solution it has a pleasant taste and leaves a sensation of cleanliness in the mouth. The low toxicity (about 25 per cent that of phenol) of such dilute solutions and the bacteriocidal properties lend themselves naturally to the use of thymol as an antiseptic in mouth washes. Although its phenol coefficient is about 28, it is reported to be relatively ineffective in large amounts of organic matter.

Certain very definite fungicidal properties are demonstrated by thymol. It has been proven active against Epidermophyton, Tricophyton and Microspores. A one per cent
solution of thymol is superior to a similar solution of phenol in promoting healing in areas affected by fungus.

In recent years thymol has been studied by numerous investigators, and many new and interesting bactericidal properties of this molecule and its derivatives have been uncovered. Caujolle, Franck and Heynard (127) showed that thymol and its aliphatic ethers have the ability to localize in the lung tissues of dogs when given intravenously. This fact indicated that thymol might be employed as a tuberculocide. This assumption was verified by these investigators (127), who reported that chlorothymol carboxylic acid exerted a marked bactericidal effect in two to twenty-four hours on bovine tubercle bacilli. It has further been shown that thymol possesses a strong infertilizing power against human tubercle bacilli in vitro. It is eight times as effective as Euganol and sixteen times as effective as Guaiacol in killing tuberculous. A series of dithymyl methane derivatives was prepared by Florestane (129), who studied their bactericidal properties on tubercle bacilli in vitro. His findings are summarized in Table I.
Table I

<table>
<thead>
<tr>
<th>Name</th>
<th>Tuberculocidal Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>bis-(2-methyl-4-hydroxy-5-isopropyl-phenyl) methane</td>
<td>weak</td>
</tr>
<tr>
<td>bis-(2-hydroxy-3-isopropyl-5-chloro-6-methylphenyl) methane</td>
<td>weak</td>
</tr>
<tr>
<td>3,5'-dihydroxy-2,2'-dichloro-1-methyl-4-isopropyl) biphenylmethane</td>
<td>strong</td>
</tr>
<tr>
<td>bis-(1-hydroxy-2-isopropyl-4-chloro-5-methylphenyl) methane</td>
<td>weak</td>
</tr>
<tr>
<td>1,1'-dihydroxy-2,2'-diisopropyl-4-chloro-5,5'-dimethyl) biphenylmethane</td>
<td>weak</td>
</tr>
<tr>
<td>(1,3'-dihydroxy-2,2'-diisopropyl-4-chloro-5,5'-dimethyl) biphenylmethane</td>
<td>weak</td>
</tr>
</tbody>
</table>

Thymol has been studied to ascertain its bactericidal properties on a number of other strains of bacteria and viruses but to a much smaller extent than in the case of tuberculosis. In the following list we have summarized a number of recently reported thymol derivatives which have been tested for their bactericidal properties.

1) Burkhalter, Tendick and Jones (130) found that p-diethylaminothymol, 1.2, possessed some antimalarial properties.

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2) A one per cent thymol solution has been employed in the treatment of leprosy with good results (131).

3) Thymol proved to be effective in the treatment of anchylostomiasis (132).

4) A series of aminoalcohols was prepared by Fourneau (133), who studied their antipyretic and analgesic properties. In this series of aminoalcohols Fourneau synthesized some aminoalcohol derivatives of thymol, 1.3. The compound in which R was CH₃ possessed excellent analgesic and antipyretic properties, but could not be used clinically since it proved to be injurious to the heart.

Our investigation has dealt with the preparation of some amino alcohol isomers of Fourneau's compounds, 1.4, in which the amino alcohol group is in a position para to the hydroxyl group, thus leaving a free phenolic OH group. These compounds may have analgesic and local
anesthetic properties, and perhaps this rearrangement of the molecule will eliminate, or at least minimize, the undesirable features of Fourneau's compounds. This conclusion is based upon the evidence which follows in the succeeding sections.

B. Local Anesthetics

1. General History

The science of local anesthesia dates from the discovery by Einhorn (147) that esters of p-aminobenzoic acid produce surface anesthesia. It has been known since 1860, when Wohler (148) first tested cocaine, that his new alkaloid exerted upon the tongue "a characteristic effect in that the point touched becomes temporarily numb, almost without sensation". Approximately twenty-five years passed before the significance of this observation was appreciated: then in 1884 Koller (149) introduced cocaine as an anesthetic for the eye. However, during this time work was progressing on the determination of the structure of cocaine, and on the synthesis of compounds which give the action produced by the alkaloid.

Since the discovery of cocaine considerable work has been done to determine what may be considered to be the essential group or groups necessary for local anesthetic action.
2. Esters of Benzoic Acid and Its Derivatives

a. Primary Amino Esters

Very few esters containing an aliphatic primary amingroup have been reported to be local anesthetics. They are generally unstable substances, and are more irritating than the corresponding tertiary compounds. Table II lists some of the benzoates and aminobenzoates tested. None of the primary amines are of any practical interest from the clinical viewpoint.

Table II

\[
H_2NC(R)(R')(R")\text{CH}(R")'02CC_6H_5X-p
\]

<table>
<thead>
<tr>
<th>R</th>
<th>R</th>
<th>R</th>
<th>X</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>C_6H_5</td>
<td>H</td>
<td>151</td>
</tr>
<tr>
<td>H</td>
<td>CH_3</td>
<td>C_6H_5</td>
<td>H</td>
<td>152</td>
</tr>
<tr>
<td>H</td>
<td>C_2H_5</td>
<td>H</td>
<td>H</td>
<td>151</td>
</tr>
<tr>
<td>H</td>
<td>C_2H_5</td>
<td>C_6H_5</td>
<td>H</td>
<td>152</td>
</tr>
<tr>
<td>H</td>
<td>C_3H_7</td>
<td>C_2H_5</td>
<td>H</td>
<td>151</td>
</tr>
<tr>
<td>CH_3</td>
<td>CH_3</td>
<td>H</td>
<td>H</td>
<td>151</td>
</tr>
<tr>
<td>CH_3</td>
<td>CH_3</td>
<td>CH_3</td>
<td>H</td>
<td>151</td>
</tr>
<tr>
<td>H</td>
<td>CH_3</td>
<td>C_2H_5CO_2</td>
<td>NH_2</td>
<td>153</td>
</tr>
<tr>
<td>H</td>
<td>C_2H_5</td>
<td>H</td>
<td>NH_2</td>
<td>151</td>
</tr>
<tr>
<td>H</td>
<td>C_3H_7</td>
<td>C_2H_5</td>
<td>NH_2</td>
<td>151</td>
</tr>
<tr>
<td>CH_3</td>
<td>CH_3</td>
<td>H</td>
<td>NH_2</td>
<td>151</td>
</tr>
</tbody>
</table>
b. **Secondary Amino Esters**

The development of the secondary aminoalkyl benzoates lagged behind the tertiary amines, possibly because the secondary amino compounds are generally regarded as being more toxic and irritating than the corresponding tertiary amines. A number of such compounds have been prepared, some of which have been thoroughly investigated pharmacologically.

In the series of compounds studied by Goldberg and Whitmore (150), see Table III, the monoalkylamino-

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>iso-C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>iso-C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>2</td>
</tr>
</tbody>
</table>

propanol esters were found to be toxic, and poor anesthetics. All the ethanols were active and relatively non-toxic. Compound 5, Monocaine, showed synergism with Ephedrine and appeared to have pressor action. It has been shown by
Suter (151) that the increase in molecular weight of the symmetrical alkylamino group has no appreciable effect on the anesthetic activity.

In compounds, 1.5, with a branch chain connecting the aliphatic amine and benzoate portions of the molecule, compounds with the monosubstituent in the position generally are more effective on the rabbit cornea than are the corresponding α substituted compounds.

\[
\text{H}_2\text{N}\begin{array}{c}
\text{co}_2-(\text{CH}_2)_{n}\text{CH}-(\text{CH}_2)_{n}\text{NHR'} \\
\end{array}
\]

\[n = 0, 1 \quad n' = 0, 1\]

1.5

All of the compounds discussed thus far contain unsubstituted p-aminogroups in the benzene nucleus. Compounds containing a substituted p-aminogroup in this position have been prepared, and the compounds possessing the p-dialkylamino group are slightly less active than the molecules containing the primary aminogroup in the para position in the benzene nucleus.

Several compounds with the pridyl group acting as a secondary amine, 1.6, have been synthesized. These

\[
\text{1.6}
\]
compounds are usually quite irritating when compared with the piperidino compounds both when applied topically and when injected.

It has been found that, when an alkoxy group is substituted in the nucleus, some very desirable properties are imparted. Unfortunately the pharmacological data are sparse, but in general, introduction of the alkoxy group considerably increases the period of topical and infiltration anesthesia.

c. Tertiary Amino Esters

The dialkylaminobenzoates are poor anesthetics and are also reported to be irritating. Introducing an aminogroup into the benzene nucleus increases the anesthetic activity considerably and also avoids undesirable irritation, Procaine, 1.7, and Butyn, 1.8, are two of these N-substituted benzoates that have the aminogroup in benzene nucleus, and exhibit good anesthetic properties. The general state-

\[
\text{1.7} \quad \text{1.8}
\]

ments have been made concerning these compounds that, as the N-alkyl group increases in size, both the toxicity and anesthetic action increase but the anesthetic action increase more rapidly than the toxicity, and branched-chain
N-alkyls are less toxic and less active than the corresponding straight-chain compounds.

Since the piperidine nucleus occurs in cocaine, McElvain (154) made compounds 1.9 and 1.10. Compound 1.10 is the open-chain compound of 1.9 with the piperidine ring split between the carbon atoms which carry the substituent groups. Compound 1.10 is inactive on the rabbit cornea in two per cent concentration and compound 1.9 showed considerable anesthetic activity. The p-aminobenzoate series of compounds containing a piperidine group is considerably more active by the goldfish method than the corresponding benzoates. Alkyl substituents in the piperidino nucleus tend to enhance the anesthetic properties of the piperidino-alkyl benzoate. Metycaine, 1.11, is an example of this type of substituted piperidino compound.

In spite of the large number of benzoates and substituted benzoates that have been synthesized and tested
for anesthetic action, practically no general rules can be applied for predicting the change of activity resulting from change in structure. Following are some indications of trends of activity; however, they are only indications and sometimes do not hold even within a homologous series of compounds.

1. Practically all the dialkylamino-, piperidino-, or alkylpiperidinoalkyl benzoates and substituted benzoates are active to some degree.

2. The secondary amino groups are usually longer acting than the corresponding tertiary amines. However, they are also usually more irritating.

3. As the molecular weight of the dialkylamino portion increases, the duration of anesthesia and usually the toxicity increase.

4. As the size of the alkyl portion of the alkyl piperidine increases, the duration of the anesthesia increases, but the toxicity increases at a more rapid rate than the anesthesia.

5. As the alkylene portion connecting the amine to the ester part lengthens, the duration of activity increases.

6. The presence of a phenyl group (except for the acid precursor of the ester) any place in the compound increases the duration of anesthesia tremendously, but such compounds are quite irritating.
7. Substitution of other heterocyclic amines for the dialkylamino or piperidino portions of the molecule results in either complete destruction of activity or in increased irritation.

3. Ketones

In the year 1922 Mannich and Lammering found that the ester linkage was not essential for local anesthetic activity (138). They pointed out that ketones with the following structure

$$\text{Ar-CO-CH}_2-\text{CH}_2-\text{NR}_2$$

possessed local anesthetic activity. Table IV gives a list of some of the compounds they found to be active.

Table IV

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperidyl</td>
<td>H</td>
</tr>
<tr>
<td>Piperazyl</td>
<td>H</td>
</tr>
<tr>
<td>3,4-Benzopiperidyl</td>
<td>H</td>
</tr>
<tr>
<td>Piperidinomethyl</td>
<td>H</td>
</tr>
<tr>
<td>Piperidyl</td>
<td>OCH$_3$</td>
</tr>
</tbody>
</table>

Apparently the exchange of an ester linkage for a ketonic linkage did not destroy local anesthetic activity.

In 1945 Ray and MacGregor (155) prepared a series of ketonic derivatives of fluorene which showed local anesthetic activity when applied topically to the tip of the tongue, see Table V.
Table V

<table>
<thead>
<tr>
<th>n</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NHCH₃</td>
</tr>
<tr>
<td>2</td>
<td>N(CH₃)₂</td>
</tr>
<tr>
<td>2</td>
<td>NH₂</td>
</tr>
<tr>
<td>2</td>
<td>N(C₂H₅)₂</td>
</tr>
<tr>
<td>2</td>
<td>NH(CH₂-CH=CH₂)</td>
</tr>
<tr>
<td>2</td>
<td>N(C₃H₇)₂</td>
</tr>
<tr>
<td>2</td>
<td>NH(C₆H₅)</td>
</tr>
<tr>
<td>2</td>
<td>Piperidino</td>
</tr>
<tr>
<td>2</td>
<td>Morpholino</td>
</tr>
</tbody>
</table>

During the course of our investigation we prepared a number of ketones derived from thymol, which may show some local anesthetic properties by virtue of their similarity in structure to those prepared by Mannich (138). The series of aminoketone hydrochlorides prepared by us is shown in Table VI.
Table VI

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Y</th>
<th>H</th>
<th>CH₃</th>
<th>H</th>
<th>C₆H₅CH₂</th>
<th>H</th>
<th>C₆H₅CH₂</th>
<th>CH₃</th>
<th>C₂H₅</th>
<th>H</th>
</tr>
</thead>
</table>

C. **Analgesics**

1. **Aralkylamines**

During the past few years aralkylamines have received considerable attention as potential analgesic agents. In the present discussion the term aralkylamine is used in a restricted sense. It is applied, in general, to compounds of the type

\[
\text{Ar-(C)}_{\text{n}}\text{-NR}_2
\]

where \(n\) may vary from 1 to 6 and the chain may be substituted or unsubstituted; \(\text{NR}_2\) is a primary, secondary, or a tertiary aminogroup. Major attention has been given to those compounds that may be considered derivatives of \(\beta\)-phenylethylamine, higher or lower homologs of this basic structure, and variously substituted derivatives thereof.

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It has been considered desirable to include available data for diphenylethylamines and other compounds belonging to the class of aralkylamines, including examples in which the phenyl group is replaced by other ring systems.

a. Sympathomimetic Amines

A large number of sympathomimetic amines have been reported to exhibit a pain-threshold-elevating action. The first of these observations on epinephrine was published a few years after its structure was elucidated (156). Since that time, a number of reports have been made to the effect that epinephrine, 1.12, and ephedrine, 1.13, manifest an analgesic action in human subjects (157).

Buscaino and Pero (158) found that epinephrine markedly elevates pain thresholds in dogs and also that epinephrine, synephrine, 1.14, and amphetamine, 1.15, relieve various types of pain in man. Pero (159) furthermore advanced the hypothesis that pain is a cholinergic
and analgesia an adrenergic phenomenon. Elevation of the threshold pain stimulus in dogs was reported by Kiessig and Orzechowski (160) after administering 1-ephedrine, synephrine, amphetamine, paredrinol, desoxyephedrine, and tetrahydro-β-naphthylamine. Goetzl, Burrill, and Ivy (161) have reported that amphetamine exerts a synergistic effect on morphine analgesia. This observation suggests that significant analgesic activity may be obtained with certain aralkylamines.

More recently Puharich and Goetzl (162) reported that a discharge of epinephrine from the adrenal gland may in part explain the analgesic action of morphine. This was also noted by Gross, Holland, Carter, and Christensen (163) who found that the analgesic action of morphine in dogs is diminished after adrenalectomy.

Other aralkylamines have been reported in the patent literature to have analgesic properties. Recently a series of aminophthalidylalkanes, of which 1-amino-1-phthalidylpropane was the most active, was found to exhibit analgesic activity (164).

Suter (165) summarizes the known data on aralkylamines as follows:

1. None of the benzyl-type amines showed any activity, except 1-amino-1-phenylpropane.
2. In general, the $\beta$-phenethylamines fail to show significant activity; even the isomers of phenylephrine and synephrine showed only slight activity at or near the toxic levels.

3. Among the $\beta$-phenylisopropylamines, activity was exhibited only at or near the toxic levels except for phenylpropanolamine.

4. Among the $\beta$-phenylisopropylamines having one substituent in the ring, $\beta$-(p-aminophenyl)-isopropylamine produced a slight but consistent analgesia in the 15 mg. per kg. range. $\beta$-(p-Methylphenyl)-isopropylamine produced marked analgesia in the 10 to 20 mg. per kg. range; thus the methyl group in the ring has a pronounced effect. The $\beta$-methoxyl derivative of $\beta$-phenylisopropylamine (Amphetamine) also markedly raised the pain threshold. The nitrogen substituted derivatives of $\beta$-(p-methoxyphenyl)-isopropylamine were only slightly more active than the corresponding primary amines.

Marked pain-threshold elevation was found when a p-hydroxyl group was introduced in $\beta$-phenyl isopropylamine series, the dextro form being more active than the levo
form. The N-substituted derivatives of $\beta$-(p-hydroxyphenyl)-isopropylamine (Paredrine) were all less active than the parent compound.

The acylated derivatives of p-hydroxyphenylisopropylamine were moderately to markedly active, but all were less active than the parent substance (Paredrine).  

5. Among the $\beta$-phenyl isopropylamines having two substituent in the ring, it is striking that none of the dihydroxy compounds significantly raise the pain threshold under the conditions of testing. This is odd for, in view of the marked activity of epinephrine, one might expect these compounds to be active. The 4-hydroxy-3-methoxyphenylisopropylamine was less toxic than the dihydroxy compounds, but was only moderately active at three-fourths the toxic dose.  

6. Among the derivatives having the amino group on the third carbon from the ring only $\gamma$-phenylpropylamine was active. These compounds had a tendency to produce histopathological lesions on the central nervous system.

The inactivity of the p-hydroxy derivatives of $\gamma$-phenylpropylamine is surprising since $\beta$-(p-hydroxyphenyl)-isopropylamine is more active than $\beta$-phenylisopropylamine. The failure to obtain a similar result by introducing the p-hydroxy group in $\gamma$-phenylpropylamine is another example of the difference between even rather closely related compounds.
7. Of the compounds having the amino group on the fourth carbon from the ring, 4-amino-1-phenylpentane was of particular interest. Its pain-threshold elevating action in the range of 6 to 30 mg. per kg. was outstanding; however, this compound produced histopathological damage to the central nervous system. The p-hydroxy derivatives of 6-phenylbutylamine showed only moderate activity, and the p-methoxy compound was inactive.

8. The compound 5-amino-1-phenylhexane was only active at the toxic level, and it would thus appear that the maximum analgesic activity resides in the 4-amino-1-phenylpentane series.

Suter (165) draws the following conclusions from the known facts concerning the aralkylamines:

1. In a series of unsubstituted phenylalkylamines of the type phenyl-\(\text{C}_n\text{H}_{2n}\text{NH}_2\) where \(n\) varies from 1 to 6, the following were noted:
   a. Maximal analgesic activity was obtained with the compound having the aminogroup four carbons from the phenyl and not terminal.
   b. Partial or complete reduction of the phenyl ring did not significantly alter analgesic action but did markedly reduce toxicity and central stimulating activity.
   c. The aralkylamine-type compounds with the amino group at the end of the chain were less active than
those in which the aminogroup is located within the chain.

d. In the aralkylamine series, N-substituted compounds were less active than corresponding primary amino derivatives in most instances; however, in some cases no apparent differences were noted.
e. In the 2-amino-1-phenylpropane type substitution of a hydroxyl group on the carbon adjacent to the ring lowered toxicity and in several cases increased analgesic activity.

2. Mononuclear substitution in the para position of the 2-amino-1-phenylpropane type by a hydroxyl, methyl, methoxyl, acyloxy, benzoxy, phenylacetoxy, or a carbethoxy group increased analgesic activity, but an amino group had little effect. In general this type of substitution decreased toxicity.

3. Disubstitution in the 3,4-position of the 2-amino-1-phenylpropane type by hydroxyl groups destroyed analgesic activity. If the amino group were primary or monobenzylated, substitution of methoxyl groups increased analgesic activity; however, if the amino group was monomethylated, activity was destroyed. A methylenedioxy group in these positions enhanced analgesic activity.

4. Mononuclear substitution in the para position of 3-amino-1-phenylbutane by a methoxyl group decreased activity, whereas a hydroxyl, methyl, or chloro group destroyed activity.
5. Mononuclear substitution in the para position of 3-amino-1-phenylpentane by a hydroxyl group increased analgesic potency, but a methoxyl group had no apparent effect.

6. Disubstitution in the 3-amino-1-phenylalkane series by 3,4-dimethoxy groups increased, whereas 3,4-methylene dioxy decreased, analgesic activity.

7. Mononuclear substitution in the 4-amino-1-phenylalkane series by a p-methoxyl or a p-methyl group decreased activity; a p-hydroxyl lowered toxicity but had little effect on analgesic action.

b. Alkanolamines

Compounds of the type shown in figure 1.16 represent a varied group of aralkanolamines reported by Kupperman, Lehman and Phillips (166).

\[
\begin{align*}
\text{Alkanolamines} \\
\text{Compounds of the type shown in figure 1.16} \\
\text{represent a varied group of aralkanolamines reported by} \\
\text{Kupperman, Lehman and Phillips (166).}
\end{align*}
\]

1.16

In spite of the variations in \(X(H, \text{CH}_3, \text{Cl, OCH}_3)\), \(R(\text{H, phenyl, alkyl, C}_1-C_{18}, \text{cyclohexyl, propynyl})\), \(R'(\text{H, phenyl})\) and in \(NR''(N(\text{CH}_3)_2, \text{N}(\text{C}_2\text{H}_5)_2, \text{piperidyl, morpholyl,} \text{2-tetrahydroisoquinolyl})\) only a few of these compounds raised the pain threshold of rats. The most active of this series of compounds appears to be:
Even this compound is less active than codeine.

In this connection we prepared several amino-alkanols of thymol which are similar in structure to those cited on the preceding page, and may exhibit some analgesic activity. These compounds are shown in Table VI.

Table VI

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>HO</td>
<td>C_6H_5</td>
<td>H</td>
</tr>
<tr>
<td>CH_3O</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

The aminoketones with the following structure

\[
\begin{array}{c}
\text{Y} \\
\text{CH_3} \\
\end{array}
\]

failed to exhibit outstanding activity. Only the following compounds appear to be noteworthy:

\[
\begin{array}{c}
\text{Y} \\
\text{CH_3} \\
\end{array}
\]
Ray and MacGregor (155) prepared a series of ketone derivatives of fluorene (Table V, p. 13), which possessed local anesthetic activity when applied to the tongue. They also stated that these compounds might contain analgesic activity due to their similarity in structure to known analgesics.

A series of thymol ketone derivatives, 1.17, (Table VI, p. 14) was prepared by us which are similar in structure to those mentioned above, and may possess some analgesic activity.

\[ \text{1.17} \]
PROCEDURE AND DISCUSSION

Since thymol possesses a variety of interesting and useful pharmacological properties, further investigation of some of these properties seemed desirable. It should be pointed out, however, that in addition to the desirable properties thymol also possesses certain undesirable characteristics; for example, it has an injurious effect on the heart and may cause hemoglobinuria.

The problem concerning thymol presented two primary facets: First, to attempt to enhance its known bacteriostatic properties, or to impart new attributes to the thymol molecule; and second, to destroy its undesirable characteristics, or at least to minimize these properties.

In the past, most investigators have attempted to modify the pharmacological properties of thymol by affixing various substituents to the thymol nucleus. In particular, derivatives prepared by substitution of the hydrogen of the hydroxyl group and/or the substitution of the hydrogens in the 4 and 6 positions in thymol, 6.1, have received the most attention.

\[ \text{CH}_3 \text{CCH}_3 \]

6.1

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A discussion of some of the substituted thymol derivatives and their bacteriostatic properties has been given in the previous section. Of all the compounds cited, the aminoalcohol derivatives of thymol prepared by Fourneau (133) seemed to be the most interesting. They have very strong antipyretic and analgesic properties but, unfortunately, are injurious to the heart.

It was decided to prepare some aminoalcohol derivatives of thymol, 6.2, which, unlike those prepared by Fourneau, 6.3, would carry the aminoalcohol group in the 4 position instead of in the ether chain. This course of action was chosen for several reasons: First, Fourneau's compounds, 6.2, possess certain inherently bad qualities that have been cited above. By placing the aminoalcohol group in the 4 position it may be possible to destroy these undesirable characteristics, at the same time imparting desirable properties to the compounds of thymol; second, Fourneau's compounds possess no free hydroxy groups, but the proposed compounds will possess such a group. This fact might add desirable characteristics to the new compounds, such as enhancing their germicidal properties; and third, a series of \( \gamma \)-aminoalcohols, 6.4, have been prepared by
Mannich and Lammering (138) that are similar in structure to those proposed in this thesis. These compounds, and particularly the aminoketones, possess good anesthetic qualities that might also be embraced by the analogous thymol compounds.

The logical route to the proposed $\alpha$-aminoalcohols and $\alpha$-aminoketones was similar to that employed by Mannich and Lammering to produce their $\alpha$-aminoalcohol derivatives, 6.4. Their method was to employ the Mannich reaction (139) which consists of a simultaneous condensation between a compound containing an active hydrogen, formaldehyde or paraformaldehyde, and a desired amine, generally in the form of the amine hydrochloride.

The primary step was to prepare the necessary thymol ketones for use in the Mannich reaction. A series of thymol ketones had been prepared by Rosenmund and Schulz (140) through the Friedel-Crafts reaction. A modification of this procedure involves the preparation of the acyl thymol compounds which readily undergo a Fries rearrangement in the presence of aluminum trichloride to yield the desired ketone in yields which were up to ten per cent higher than those of Rosenmund and Schulz. This procedure had
the added advantage of eliminating the excessive foaming that had occurred in the direct Friedel-Crafts reaction. The 4-acetylthymol, 6.5, and 4-propionylthymol, 6.6, were prepared by this method.

![Chemical Structures](image)

**6.5**

**6.6**

Etherification of the thymol ketones, 6.7, yielded compounds which should be useful in determining the effects of the phenolic hydroxy group or the physiological activity of the proposed thymol derivatives. The ethers of the thymol ketones were prepared through Williamson's ether synthesis. Sodium 4-acetylthymolate was reacted with an alkyl halide in alcoholic solution. The alcohol was removed by distillation, and the ethers were distilled under reduced pressure. The methyl ethers of thymol were prepared by a slight variation in Williamson's method. Dimethylsulfate was employed in place of the methyl halide, and water was used in place of alcohol as the solvent.

![Chemical Structure](image)

**6.7**

In the Mannich reaction, equimolar quantities of a thymol ketone and piperidine hydrochloride were combined
with an excess of paraformaldehyde to give an aminoketone. A variation of this procedure involved the use of 36 to 38 per cent aqueous formaldehyde and piperidine. This variation, however, increased the number of steps employed in the synthesis of the aminoketone hydrochlorides, and resulted in a lower yield. Both the aminoketones containing the phenolic hydroxy group, 6.8, and the aminoketones of thymol, 6.9, in which the hydroxy group had been etherified were prepared in yields that varied from 60 to 70 per cent.

Several of the free ketoamines of thymol were prepared from aqueous solutions of the amine hydrochloride by the addition of ammonium hydroxide to decompose the hydrochloride. A great deal of difficulty was experienced in attempting to crystallize the free aminoketones containing asymmetric carbon atoms since they tended to separate from solution as oils instead of in crystalline form.

Reduction of the aminoketone hydrochlorides to the corresponding secondary alcohols, 6.10, was attempted by three different methods: (1) A chemical reduction of the ketoamine hydrochlorides with aluminum isopropoxide in anhydrous isopropyl alcohol. The process was analogous to that described by Wilds (141). The impurity of the
A tertiary aminoalcohol was prepared by a method employed for making certain alkyl aminoalcohols by Tiffeneau
and Ditz (142). The method involved the addition of a Grignard reagent to the ketones in a nitrogen atmosphere. The Grignard addition product was hydrolyzed with dilute hydrochloric acid, and the resulting aminoalcohol was purified by recrystallization from ethanol. This particular tertiary aminoalcohol, 6.11, was prepared in order to determine whether or not the tertiary alcohols are more physiologically active than the corresponding secondary alcohols. Jenkins and Hartung (143) intimate that in general the tertiary alcoholic grouping is less toxic and more active than the corresponding secondary alcoholic group.

All the aminoalcohols prepared contain at least one asymmetric carbon atom. As a result of this center of asymmetry the question arises whether or not one optical isomer is more active than the other. Quite often, as Jenkins and Hartung (144) state, one isomer is considerably more active than the other. For example, the l-isomer of epinephrine contains all the physiological activity, while the d-isomer is dormant. Due to the fact that the aminoalcohols contain an asymmetric carbon atom, it was important that we should separate at least one aminoalcohol into its enantiomorphs to discover whether there was a tendency in
this series of aminoalcohols to concentrate all the physiological activity in one optical isomer.

Two methods were employed for the separation of the optical isomers of the thymol aminoalcohols. The first method was the acid phthalate method that is described by Ingersoll (145) for the separation of optically active secondary alcohols. This procedure worked very smoothly and, by using brucine, no difficulty was encountered in separating the diastereoisomers. The hydrolysis of the diastereoisomers, however, produced a mixture of brucine and an aminoalcohol derivative of thymol, from which we were unable to remove completely all of the brucine. Considering this difficulty we chose a second method which proved to be advantageous.

Fuson and Ross (146) employed an optically active acid to resolve dl-phenylethylamine into its optical isomers. This procedure proved to be a successful method for the separation of the optically active aminoalcohols into their enantiomorphs. Fractional crystallization of the tartrate salts from distilled water eventually gave a compound with constant rotation. Hydrolysis of the crystalline tartrate gave the pure aminoalcohol which has $[\alpha]_D^{30} = 9$. Upon hydrolysis of the fourth crystal fraction, the other isomer having $[\alpha]_D^{30} + 9$ was obtained. Both isomers melted at 183 to 184°, and were white crystalline compounds.
EXPERIMENTAL PROCEDURE

A. Thymyl Acetate (28)

In a two liter, three-necked flask, fitted with a mechanical stirrer, and a reflux condenser equipped with a hydrogen chloride trap, are placed 362 g. (2.41 moles) of thymol and 189 g. (2.41 moles) of acetyl chloride. The mixture is stirred until the thymol dissolves, and then it is heated for one hour to complete the reaction. The crude, oily ester is distilled under reduced pressure, and the pure thymyl acetate distills at 139-142°/20 mm. (lit., 137-139°/15 mm.). The yield is 444 g. (96 per cent of the theoretical amount).

B. Thymyl Propionate (28)

The procedure and apparatus for the synthesis of this ester are the same as those described for the preparation of thymyl acetate. Thymyl propionate is a colorless, oily liquid that distills under reduced pressure at 216-220°/20 mm. (lit., 217°/15 mm.). The yield is 93 per cent of theory.

C. 4-Acetylthymol (37)

To a solution of 300 g. (1.56 moles) of thymyl acetate in 1500 g. of nitrobenzene is added, in small portions, 300 g. (2.25 moles) of anhydrous aluminum chloride. The
reaction mixture is allowed to stand for twenty-four hours, and is then poured onto ice and dilute hydrochloric acid. The crude ketone and nitrobenzene are extracted from water with ether, and the pure 4-acetylthymol crystallized from the nitrobenzene upon removal of the ether by distillation. After recrystallization from ethanol, the pure 4-acetylthymol melts at 124 to 125° (lit., 125°). The yield is 206 g. (69 per cent of the theoretical amount).

D. 4-Propionylthymol (37)

The procedure and apparatus for the synthesis of this ketone are the same as those employed for the preparation of 4-acetylthymol. 4-Propionylthymol is a white, crystalline solid that melts at 111 to 112°C after one recrystallization from ethanol (lit., 112°). The yield is 60 per cent of theory.

E. 4-Acetylthymyl Methyl Ether

In a one-liter, three-necked flask, fitted with a mechanical stirrer, separatory funnel, and reflux condenser, is placed a mixture of 86.5 g. (0.45 mole) of 4-acetylthymol and 25.2 g. (0.45 mole) of potassium hydroxide in 500 ml. of water. The mixture is cooled in an ice bath to temperatures below 10°C. There is then added through the separatory funnel, with stirring, 56.8 g. (0.45 mole) of dimethyl sulfate. This addition requires about one-half hour, and the cooling bath is not removed until the addition is...
complete. The mixture is then heated on a water bath for four hours. The 4-acetylthymyl methyl ether layer is separated from the water layer in a separatory funnel, and the crude 4-acetylthymyl methyl ether is purified by vacuum distillation. The pure ether distills at 185–190°/15 mm. The yield is 56 g. (60 per cent of the theoretical amount).

F. 4-Acetylthymyl Ethyl Ether

The procedure and apparatus for the synthesis of this ether are the same as those employed for the preparation of 4-acetylthymyl methyl ether. 4-Acetylthymyl ethyl ether is a colorless liquid which distills at 154–157°/15 mm. The yield is 54 per cent of the theoretical amount.

G. 4-Acetylthymyl Benzyl Ether

In a 500 ml., three-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a separatory funnel, are dissolved 26 g. (0.135 mole) of 4-acetylthymol and 8.9 g. (0.135 mole) of potassium hydroxide in 200 ml. of ethanol. The solution is refluxed in a water bath for one hour, and then 20.2 g. (0.135 mole) of benzyl chloride is added through the separatory funnel over a period of one-half hour. The solution is refluxed one hour longer, and it is then cooled to room temperature. The precipitated sodium chloride is removed by filtration, and the ethanol is distilled off. The 4-acetylbenzylthymyl ether is purified by vacuum distillation. It distills at 220–222°/17 mm.
The colorless oil crystallizes upon standing into white needles that melt at 59 to 60°C. The yield is 32.2 g. (86 per cent of the theoretical amount).

H. 4-Propionylthymyl Benzyl Ether

The procedure and apparatus for the synthesis of this ether are the same as those employed for the preparation of 4-acetylthymyl benzyl ether. 4-Propionylthymyl benzyl ether is a white crystalline compound that melts at 49 to 50°C. and distills at 249 to 253°C/30 mm. The yield is 83 per cent of the theoretical amount.

I. 4-(3-Piperidinopropionyl)-Thymol Hydrochloride

A mixture of 12.2 g. (0.1 mole) of piperidine hydrochloride, 0.25 ml. of concentrated hydrochloric acid, 4.5 g. (0.15 mole) of paraformaldehyde, 30 ml. of absolute ethanol, and 19.2 g. (0.1 mole) of 4-acetylthymol is heated to reflux. After one hour, 3 g. (0.1 mole) of paraformaldehyde is added to the solution, and refluxing is continued for two hours. To the hot mixture is added 250 ml. of hot acetone, and the resulting solution is cooled slowly to room temperature and finally in ice water. The white crystalline product is collected on a filter, and recrystallized from 95 per cent ethanol. The pure 4-(3-piperidinopropionyl)-thymol hydrochloride melted at 164 to 165°C. The recovery is 22.8 g. (70 per cent of the theoretical amount).

Anal. Calcd. for C₃₅H₅₇O₂NCl: Cl, 10.9
Found: Cl, 10.5, 10.7
J. 1-Methoxy-4-(3-piperidinopropionyl)-thymol Hydrochloride

A mixture of 12.2 g. (0.1 mole) of piperidine hydrochloride, 0.25 ml. of concentrated hydrochloric acid, 45 g. (0.15 mole) of paraformaldehyde, 30 ml. of absolute ethanol, and 20.6 g. (0.1 mole) of 4-acetyltymyl methyl ether is heated to reflux. The subsequent procedure in this experiment is the same as that described for the synthesis of 4-(3-piperidinopropionyl)-thymol hydrochloride. The pure 1-methoxy-4-(3-piperidinopropionyl)-thymol hydrochloride melted at 178-179° after recrystallization from 95 per cent ethanol. The yield is 22 g. (65 per cent of the theoretical amount).

Anal. Calcd. for C_{19}H_{30}O_{2}N_{2}Cl: Cl, 10.45
Found: Cl, 10.2, 10.4

K. 1-Ethoxy-4-(3-piperidinopropionyl)-Thymol Hydrochloride

A mixture of 12.2 g. (0.1 mole) of piperidine hydrochloride, 0.25 ml. of concentrated hydrochloric acid, 4.5 g. (0.15 mole) of paraformaldehyde, 30 ml. of absolute ethanol, and 22 g. (0.1 mole) of 4-acetyltymyl ethyl ether, is heated to reflux for one hour. The subsequent procedure is the same as that described for the synthesis of 4-(3-piperidinopropionyl)-thymol hydrochloride. The pure 1-ethoxy-4-(3-piperidinopropionyl)-thymol hydrochloride is a white crystalline solid that melts at 170-171° after re-
crystallization from 95 per cent ethanol. The yield is 21 g. (60 per cent of the theoretical amount).

L. l-Benzylxy-4-(3-piperidinopropionyl)-thymol Hydrochloride

The procedure and apparatus for the synthesis of this ketone is the same as those employed for the preparation of 4-(3-piperidinopropionyl)-thymol hydrochloride. The 1-benzyloxy-4-(3-piperidinopropionyl)-thymol hydrochloride melts at 191 to 192°C. after recrystallization from 95 per cent ethanol. The yield is 78 per cent of the theoretical amount.

Anal. Calcd. for C_{25}H_{34}O_{2}NCl: Cl, 8.47
Found: Cl, 8.33, 8.41

M. 4-(3-Piperidinopropionyl)-thymol

To a solution containing 20 g. (0.069 mole) of 4-(3-piperidinopropionyl)-thymol hydrochloride in 250 ml. of distilled water is added ammonium hydroxide until the solution is alkaline to litmus. The crude 4-(3-piperidinopropionyl)-thymol precipitates from the alkaline solution and is separated by filtration. The pure 4-(3-piperidinopropionyl)-thymol is a white crystalline compound which melts at 137 to 138°C.

N. 4-Piperidinomethylthymol Hydrochloride

A mixture of 61.8 g. (0.41 mole) of thymol, 40 g. (0.5 mole) of 36 per cent aqueous formaldehyde, and 35 g.
(0.41 mole) of piperidine is prepared in a 500 ml. three-necked flask equipped with a mechanical stirrer, and a reflux condenser. The mixture is heated and stirred for one and one-half hours. The brown viscous mass is washed with water, and dissolved in benzene. The benzene solution is dried over potassium carbonate and the crude 4-piperidinomethylthymol is precipitated by bubbling dry hydrogen chloride gas through the solution. Recrystallization of the crude material from the minimum quantity of ethanol yields 81 g. (73 per cent of the theoretical amount) of pure 4-piperidinomethylthymol hydrochloride, m.p. 214-215°.

**Analytical**

Calcd. for \( \text{C}_{16}\text{H}_{26}\text{O}\text{NCl} \): Cl, 12.5

Found: Cl, 12.31, 12.45

**0. 1-Benzylxy-4-(2-methyl-3-piperidinopropionyl-thymol Hydrochloride**

A mixture of 17.5 g. (0.06 mole) of 4-propionyl-thymyl benzyl ether, 7.2 g. (0.06 mole) of piperidine hydrochloride, 0.25 ml. of concentrated hydrochloric acid, 2.66 g. (0.09 mole) of paraformaldehyde, and 30 ml. of absolute ethanol is heated to reflux for one hour. The subsequent procedure is the same as that employed in the synthesis of 4-(3-piperidinopropionyl)-thymol hydrochloride. The pure 1-benzylxy-4-(2-methyl-3-piperidinopropionyl)-thymol hydrochloride melts at 147-148°C. The yield is 20 g. (78 per cent of the theoretical amount).
Anal. Calcd. for Cl: Cl, 8.24
Found: Cl, 8.12, 8.19

P. dl-l-Methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol Hydrochloride

1. Aluminum Alkoxide Reduction

In a 300 ml. round bottomed flask are placed a solution of 40 g. (0.8 mole) of purified aluminum isopropoxide in 100 ml. of dry isopropyl alcohol and 34 g. (0.1 mole) of 1-methoxy-4-(3-piperidinopropionyl)-thymol hydrochloride. A short reflux condenser is attached to the flask, but no water is run through the cooling jacket. To the top of the condenser, by means of a short, bent glass tube and cork stoppers, is attached a small water cooled condenser set for distillation. A boiling chip is added, and the solution is refluxed at such a rate that 5-10 drops of distillate are collected per minute. If more than 50-60 ml. of isopropyl alcohol distill off, 20 ml. of dry isopropyl alcohol is added to maintain the volume. When the acetone test becomes negative, water is passed through the upright condenser, and total reflux is maintained for five minutes. The water is again removed from the reflux condenser, and the first five drops of the distillate is tested for acetone. If a positive test is obtained distillation is continued to remove the acetone, then the process is repeated. When a negative test is obtained, most of the excess isopropyl alcohol is removed under slightly reduced pressure. The
cooled residue is hydrolyzed with cold 12N sodium hydroxide, and then diluted with 300 ml. of water. The crude dl-l-methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol is extracted with ether, and the ether solution is dried over sodium sulfate. The pure dl-l-methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol hydrochloride is precipitated from an ether-acetone solution; it melts at 183 to 184°. The yield is 60 per cent of the theoretical amount.

2. Catalytic Reduction

A solution of 27 g. (0.08 mole) of l-methoxy-4-(3-piperidinopropionyl)-thymol hydrochloride in 300 ml. of a 50:50 ethanol-water mixture and 0.3 g. of platinum oxide are placed in a pressure bottle. The bottle with its contents is placed in a Parr Hydrogenation Apparatus under an initial pressure of 30 psi, gauge. When the calculated pressure drop of 6.6 psi, gauge (0.08 mole) of hydrogen is reached the hydrogenation is stopped and the catalyst is removed by vacuum filtration. The solution is concentrated through distillation, and the crude dl-l-methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol hydrochloride separates out of solution. The crude aminoalcohol is recrystallized from 95 per cent ethanol, and it melts at 183-184°C. The yield is quantitative.

Anal.  Calcd. for C_{19}H_{28}O_{2}NCl:  Cl, 10.4; C, 66.7; H, 9.43
  Found:  Cl, 10.34, 10.37; C, 66.8, 66.9; H, 9.24, 9.18
Q. dl-4-(1-hydroxy-3-piperidinopropyl)-thymol Hydrochloride

In a pressure bottle are placed a solution of 32.6 g. (0.1 mole) of 4-(3-piperidinopropionyl)-thymol hydrochloride in 300 ml. of a 50:50 ethanol-water mixture and 0.3 g. of platinum oxide. The hydrogenation and purification of this compound are analogous to those employed in the case of dl-1-methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol hydrochloride. The pure dl-4-(1-hydroxy-3-piperidinopropyl)-thymol hydrochloride is a white crystalline material that melts at 187–188°C. The yield is quantitative.

Anal. Calc'd. for C_{16}H_{30}O_{2}NCl; Cl, 10.8
Found: Cl, 10.51, 10.64

R. dl-1-Methoxy-4-(1-hydroxy-1-ethyl-3-piperidinopropyl)-thymol Hydrochloride

In a 100 ml. three-necked flask, fitted with a mechanical stirrer, an efficient reflux condenser to which a calcium chloride tube is attached, and a 60 ml. dropping funnel, are placed 0.83 g. (0.034 mole) of magnesium, 25 ml. of dry ether, and 3.73 g. (0.034 mole) of ethyl bromide. The mixture is refluxed until all the magnesium is in solution. A solution of 3.3 g. (0.014 mole) of the 1-methoxy-4-(3-piperidinopropionyl)-thymol in 25 ml. of dry ether is added through the dropping funnel to the Grignard reagent, with rapid stirring. After the 1-methoxy-4-(3-piperidinopropionyl)-thymol is added, the flask is heated on a water
bath and stirring is continued for one hour. The mixture is hydrolyzed with 5N hydrochloric acid by making it acid to Congo Red. The 1-methoxy-4-(3-piperidino propionyl)-thymol is extracted with ether, and precipitated as the hydrochloride by bubbling dry hydrogen chloride through the dried ether solution. After recrystallization from ethanol, the pure dl-1-methoxy-4-(1-hydroxy-1-ethyl-3-piperidinopropyl)-thymol hydrochloride melted at 166-167°C. The yield was 1.07 g. (32.4 per cent of the theoretical amount).

**Anal. Calcd. for C_{20}H_{24}O_{2}NCl; Cl, 10**

**Found: Cl, 9.81, 9.92**

S. \( L \)-1-Methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol Hydrochloride

A solution of 3.26 g. (0.01 mole) of dl-1-methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol in 20 ml. of distilled water is mixed with 1.5 g. (0.01 mole) of d-tartaric acid; the resulting solution is heated for a short time on the steam bath, filtered into a 25 ml. beaker, and allowed to cool slowly. Upon cooling the crude \( L \)-methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol-d-tartrate is collected by suction filtration and washed on the filter with 10 ml. of ice water. The filtrate and washings are evaporated on a steam bath to a volume about two-thirds that of the original filtrate, and a second crop of crystals is obtained on cooling. By repeating the process it is possible to obtain a third and fourth crop of crystals.
The successive crops of crystals are systematically recrystallized as follows. The first crop is dissolved in about three parts of water and the hot solution allowed to deposit crystals by slow cooling. The liquor is filtered, and the remaining crops are then similarly recrystallized in succession from the same liquor, the solution being evaporated to the appropriate volume before each recrystallization. The procedure is repeated until the head fraction possesses a constant rotation.

The pure tartrate is decomposed by warming with a slight excess of slightly more than two equivalents of sodium hydroxide. The aminoalcohol is extracted, after cooling, with ether; the solution is dried over anhydrous potassium carbonate. The \( \ell \)-\( \ell \)-methoxy-4-(1-hydroxy-3-piperidinopropyl)_thymol hydrochloride is precipitated from ether-acetone solution by bubbling dry hydrogen chloride through an ether-acetone solution of the aminoalcohol, and after recrystallization from ethanol it melts at 183-184°. \( [\alpha]_D^{30} = 9 \) (C = 0.6, 95 per cent ethanol).

The fourth crystalline fraction is composed of nearly pure d-base-d-acid, and after two recrystallizations from distilled water this diastereoisomer reaches a constant rotation. This tartrate salt is decomposed, and the optically active aminoalcohol is isolated in the same manner as described above for \( \ell \)-\( \ell \)-methoxy-4-(1-hydroxy-3-piperidino-
propyl)−thymol hydrochloride. After recrystallization from ethanol, the d-l-methoxy-4-(l-hydroxy-3-piperidino-propyl)−thymol hydrochloride melts at 183–184°, and $[\alpha]^0_{D} + 9$ (C = 1.3, 95 per cent ethanol).
SUGGESTIONS FOR FUTURE THESIS PROBLEMS

A. The menthol analogs of the aminoketone and aminoalcohol derivatives of thymol might be prepared through catalytic, high pressure hydrogenation. The menthol aminoalcohols, 7.1, might possibly possess physiological properties which are superior to their thymol analogs. These compounds would contain a number of optical and geometric isomers all of which may or may not exist.

B. In the series of aminoalcohols prepared in this work, the amino group is beta to the carbonyl and carbinol group. A series of compounds, 7.2, in which the amino group is alpha to the carbonyl and carbinol group might possess superior pharmacological properties similar to those held by epinephrine.
C. Since the γ-aminoketones prepared from 4-propionylthymol possess an asymmetric carbon atom, it might be profitable to resolve these aminoketones, 7.3, into their optical antipodes. It is possible that one isomer may be superior to the other in physiological activity.

D. An analogous series of aminoketones and amino-alcohols might be synthesized by introducing the substituents in the position ortho to the hydroxy group in the thymol molecule, 7.4.
Part V

SUMMARY

A. An improvement in the method for the preparation of 4-acetylthymol and 4-propionylthymol has been reported.

B. The dl-1-methoxy-4-(1-hydroxy-3-piperidino-propyl)-thymol hydrochloride was resolved into its optical isomers.

C. In the search for compounds possessing physiological activity a series of new compounds was prepared and identified, Table XIV.
<table>
<thead>
<tr>
<th>Name</th>
<th>B.P.,°C.</th>
<th>M.P.,°C.</th>
<th>C</th>
<th>H</th>
<th>Cl</th>
<th>C</th>
<th>H</th>
<th>Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Acetyltymol Methyl Ether</td>
<td>185-190</td>
<td>15</td>
<td>1.5360</td>
<td>75.9</td>
<td>8.74</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Acetyltymol Ethyl Ether</td>
<td>160-166</td>
<td>10</td>
<td>76.4</td>
<td>9.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4-Acetyltymol Benzyl Ether</td>
<td>250</td>
<td>15</td>
<td>80.9</td>
<td>7.80</td>
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<td></td>
<td></td>
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<tr>
<td>4-Propionylthymol Benzyl Ether</td>
<td>249-253</td>
<td>30</td>
<td>81.1</td>
<td>8.11</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>4-Propionylthymol Methyl Ether</td>
<td>205-210</td>
<td>15</td>
<td>76.4</td>
<td>9.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperidinomethylthymol Hydrochloride</td>
<td>214-215</td>
<td></td>
<td>66.9</td>
<td>9.17</td>
<td>12.5</td>
<td></td>
<td></td>
<td>12.43</td>
</tr>
<tr>
<td>4-(3-Piperidinopropionyl)-thymol Hydrochloride</td>
<td>164-165</td>
<td></td>
<td>66.3</td>
<td>8.59</td>
<td>10.9</td>
<td></td>
<td></td>
<td>10.6</td>
</tr>
<tr>
<td>4-(3-Piperidinopropionyl)-thymol</td>
<td>150-155</td>
<td>1</td>
<td>74.8</td>
<td>9.71</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Methoxy-4-(3-piperidinopropionyl)-thymol</td>
<td>178-179</td>
<td></td>
<td>67.1</td>
<td>8.83</td>
<td>10.45</td>
<td></td>
<td></td>
<td>10.31</td>
</tr>
<tr>
<td>Compound</td>
<td>mp (°C)</td>
<td>¹H NMR δ (ppm)</td>
<td>¹³C NMR δ (ppm)</td>
<td>¹H NMR J (Hz)</td>
<td>¹³C NMR J (Hz)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>--------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Ethoxy-4-(3-piperidino-propionyl)-thymol Hydrochloride</td>
<td>170-171</td>
<td>68.3</td>
<td>9.05</td>
<td>10.0</td>
<td>9.91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Benzyloxy-4-(3-piperidino-propionyl)-thymol Hydrochloride</td>
<td>191-192</td>
<td>71.6</td>
<td>8.12</td>
<td>8.47</td>
<td>8.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Benzyloxy-4-(2-methyl-3-piperidinopropionyl)-thymol Hydrochloride</td>
<td>147-148</td>
<td>72.3</td>
<td>8.34</td>
<td>8.24</td>
<td>8.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dl-1-Methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol Hydrochloride</td>
<td>163-164</td>
<td>66.71</td>
<td>9.43</td>
<td>10.4</td>
<td>66.91 9.24 10.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dl-1-Methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol Hydrochloride</td>
<td>183-184</td>
<td>49</td>
<td>66.71</td>
<td>9.43</td>
<td>10.4</td>
<td>66.92 9.24 10.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1-Methoxy-4-(1-hydroxy-3-piperidinopropyl)-thymol Hydrochloride</td>
<td>183-184</td>
<td>-9</td>
<td>66.71</td>
<td>9.43</td>
<td>10.4</td>
<td>66.83 9.31 10.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dl-4-(1-hydroxy-3-piperidinopropyl)-thymol Hydrochloride</td>
<td>167-168</td>
<td>65.8</td>
<td>9.15</td>
<td>10.8</td>
<td>10.65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dl-4-(1-hydroxy-1-ethyl-3-piperidinopropyl)-thymol Hydrochloride</td>
<td>166-167</td>
<td>67.4</td>
<td>9.55</td>
<td>10.0</td>
<td>9.86</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Part VI

APPENDIX

A REVIEW OF THE CHEMISTRY OF THYMOL

I. Occurrence

Thymol, or thyme camphor, occurs as a component of the essential oils of many plants, such as ajowan, garden thyme, wild thyme, and horse mint (1). The essential oils of these plants are present, as a rule, in very small amounts, and thymol constitutes about 50 per cent of these essential oils. As a result of the small quantity of oil present, the overall yield of thymol is about 1 per cent (2). The low yield of thymol from natural sources is illustrated when we consider that it occurs to the extent of 224 ounces per acre of ajowan, and only 80 ounces per acre of horse mint (3).

II. Production

A. From Natural Sources

Thymol is extracted from its essential oils by shaking the oils with an aqueous solution of a caustic alkali. When the alkali layer, containing soluble sodium thymolate, is acidified free thymol separates and is recovered by filtration (4). Thymol recovered in this manner is invariably contaminated with carvacrol.
B. From Synthetic Sources

1) Thymol can be prepared synthetically from m-cresolsulfonic acid, which reacts with isopropyl alcohol in the presence of concentrated sulfuric acid at an elevated temperature to yield 3-cymenesulfonic acid. It has been shown that propylene may be used in place of isopropyl alcohol in the production of 3-cymenesulfonic acid (7). Steam distillation of 3-cymene sulfonic acid eliminates the sulfonic acid group to give thymol (5). Thymol may also be prepared from m-cresol by the Friedel-Crafts reaction, utilizing isopropyl chloride at -10°C. (6). Phosphoric acid may be used in place of concentrated sulfuric acid to affect a condensation between m-cresol and isopropyl alcohol at 70 to 80°C. (8).

2) p-Cymene may be employed as a starting material in one method of synthesizing thymol. The nitration of p-cymene yields nitrocymene, 1.1, which may be reduced to

```
CH(CH₃)₃
\(\text{N}^+\text{HCl}^{-}\)
```

aminocymene by iron and hydrochloric acid (9), or electrolytically in concentrated sulfuric acid. In another method nitrocymene may be reduced to cymylhydroxylamine which yields p-aminothymol upon acid catalyzed rearrangement. Deamination of p-aminothymol may be accomplished by reduction of the corresponding diazonium chloride with
hypophosphorous acid (10)(11).

3) Thymol was prepared by Kimura (12) by ferric chloride oxidation of piperitone in glacial acetic acid, manganese salts serving as catalysts. McKee (13) showed that thymol might also be prepared by treating spruce turpentine with fuming sulfuric acid, fusing the resulting sulfonic acid with sodium hydroxide to introduce the hydroxyl group. Behal and Tiffineau (14) saponified methyl methoxy-m-cresololate and obtained methoxy-m-cresotonic acid which, upon treatment with methyl magnesium iodide, produced an alcohol, C₆H₅-C₃H₃(COH)₂CH₂OH. Dehydration of tertiary alcohol yielded methyl-1-methoxy-3-pseudoallylbenezene, which could be reduced to methyl thymol by sodium and absolute alcohol. Demethylation was accomplished by the action of hydriodic acid, and thymol was the resulting product. m-Cresol isopropyl ether can be isomerized in the presence of phosphoric acid, zinc chloride, or Niederl's Reagent to give thymol (15).

III. Properties

A. Physical

1. Structural Formula:
2. Synonyms:
   2-isopropyl-5-methylphenol
   6-isopropyl-m-cresol
   3-hydroxy-4-isopropyl toluene
   3-hydroxy-p-cymene

3. Empirical Formula:
   \( \text{C}_{10}\text{H}_{14}\text{O} \)

4. Molecular Weight:
   150.21

5. Hydroxyl Number (Theory):
   342

6. Color:
   White

7. Freezing Point:
   50-51°C.

8. Boiling Point:
   233°C. at 760 mm

9. Dielectric Constant:
   \( 1.6 \times 10^{18} \)

10. Surface Pressure - dynes/cm:
    12.1

11. Vapor Pressure:
    The vapor pressure is calculated from the equation:
    \[ \log_{10} P = A + \frac{B}{T} \]
    \( A = 14.201 \)
    \( B = 4766 \)
    \( T = \text{varies from 0°C-40°C} \).
B. **Chemical Properties**

Thymol undergoes most of the reactions of the lower alkylated phenols, detailed descriptions of which are given below. Although this compound possesses two nuclear alkyl groups, it reacts in a manner similar to the reaction of m-cresol, as is illustrated below.

1. **Alkali Solubility - Formation of Phenolates**

   Thymol is only sparingly soluble in 10 per cent aqueous alkali solutions, but the material is soluble in concentrated solutions of caustic, and in alcoholic alkali solutions. In aqueous solution, sodium and potassium thymolates show a degree of hydrolysis of 10.34 per cent (21).

2. **Etherification**

   The lower alkyl ethers of thymol may be prepared by reaction of the alkali phenolate with alkyl halides, such as ethyl chloride, or with the alkyl sulfates. Table I is a list of some of these ethers and their physical constants. Substituted alkyl ethers can be prepared by the reaction of thymol with ethylene chlorohydrin, or dichloroethyl ether. Fourneau (23) produced thymoxypropene oxide by high temperature reaction of thymol with epichlorohydrin in a sealed tube. He further prepared the aminoalcohols by reacting the thymoxypropene oxide with 25 per cent dimethylamine.
Table I

Physical Properties of Some Ethers (22)

<table>
<thead>
<tr>
<th>Name</th>
<th>B.P., °C</th>
<th>Density</th>
<th>Specific Vol.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymyl methyl ether</td>
<td>216.2</td>
<td>0.9531</td>
<td>214.3</td>
</tr>
<tr>
<td>Thymyl ethyl ether</td>
<td>226.9</td>
<td>0.9534</td>
<td>240.0</td>
</tr>
<tr>
<td>Thymyl propyl ether</td>
<td>243.0</td>
<td>0.9276</td>
<td>275.5</td>
</tr>
<tr>
<td>Thymyl butyl ether</td>
<td>258.3</td>
<td>0.9230</td>
<td>289.2</td>
</tr>
<tr>
<td>Thymyl heptyl ether</td>
<td>306.7</td>
<td>0.9097</td>
<td>368.7</td>
</tr>
<tr>
<td>Thymyl octyl ether</td>
<td>319.8</td>
<td>0.9026</td>
<td>395.6</td>
</tr>
</tbody>
</table>

Ide, Baltzly, and Buck (24) produced a series of aminoethers by reacting thymol with a number of \( \omega \)-bromoalcohols. Reaction of the resultant alcohol with hydrobromic acid yielded a halogen derivative which reacted readily with substituted amines. Quaternary ammonium salts were formed with alkyl halides, see Table II. The same investigators prepared the piperidino compound, 3.1, which melted at 120°C.

![Chemical Structure](image-url)
Table II

Some Quaternary Salts Containing Aryloxyethyl and Aryloxypropyl Groups

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>R-Group</th>
<th>x</th>
<th>y</th>
<th>Mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>2</td>
<td>I</td>
<td>228</td>
</tr>
<tr>
<td>Benzyl</td>
<td>2</td>
<td>Cl</td>
<td>194</td>
</tr>
<tr>
<td>p-Chlorobenzyl</td>
<td>2</td>
<td>Cl</td>
<td>216</td>
</tr>
<tr>
<td>o-Chlorobenzyl</td>
<td>2</td>
<td>Cl</td>
<td>175</td>
</tr>
<tr>
<td>Methyl</td>
<td>3</td>
<td>I</td>
<td>229</td>
</tr>
<tr>
<td>p-Chlorobenzyl</td>
<td>3</td>
<td>Cl</td>
<td>204</td>
</tr>
<tr>
<td>p-Bromobenzyl</td>
<td>3</td>
<td>Cl</td>
<td>191</td>
</tr>
<tr>
<td>p-Chloronaphthoxypropyl</td>
<td>3</td>
<td>Cl</td>
<td>187</td>
</tr>
</tbody>
</table>

Application of the Williamson ether synthesis led to a series of substituted benzyl ethers, 3.2, as shown in Table III (25).

![Chemical Structure](image)
A p-nitrobenzyl ether, 3.3, was prepared by Reid (26), who reacted sodium or potassium thymolate with p-nitrobenzyl bromide. This compound, melting sharply at 85°C.,

![Chemical Structure](image)

3.3

may serve as a derivative useful in identification of thymol.

3. Esterification

Esters of thymol have been prepared from the alkylated phenol using such acylating agents as acetic anhydride, acetyl chloride, or benzoyl chloride. (Table IV).
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymyl formate</td>
<td>81/2mm</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Thymyl acetate</td>
<td>28</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Thymyl propionate</td>
<td>217/15mm</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Thymyl butyrate</td>
<td>222/15mm</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Thymyl isobutyrate</td>
<td>218/15mm</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Thymyl isovalerate</td>
<td>221/15mm</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Thymyl 1-bromopropionate</td>
<td>115/12mm</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Thymyl 1-bromobutyrate</td>
<td>151/12mm</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Thymyl 1-bromo-2-methylbutyrate</td>
<td>166/12mm</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Thymyl thiocyanoacetate</td>
<td></td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>4-Aminothymyl benzoate</td>
<td>119-20</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Thymyl cinnamate</td>
<td>231</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>4-Nitrothymyl benzoate</td>
<td>110</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Dithymyl oxalate</td>
<td>61</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Thymyl 4-methoxycinnamate</td>
<td>58-9</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Methyl thymoate</td>
<td>97-8</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>
Such compounds as p-nitrophenylacetyl chloride have been suggested by Ward and Jenkins (35) as reagents for identifying thymol. The p-nitrobenzoyl ester, 3.4, melts at 54.7 to 55.2°C.

Brown and Kremers (36) employed the 3,5-dinitrobenzoic acid derivative to identify thymol. This ester, 3.5, was reported to melt at 103 to 103.2°C. and crystallizes in needles with the following Miller Indices:

\[ \alpha = 1.480; \beta = 1.625; \gamma = 1.705 \]

4. Acylation

By the Fries rearrangement at low temperatures the acyl esters may be converted to the corresponding p-hydroxyketone. Higher temperatures tend to form the o-hydroxy isomers, see Table V.
Table V

Thymol Ketones

<table>
<thead>
<tr>
<th>Thymyl Ketone</th>
<th>Mp</th>
<th>Bp</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl thymyl ketone</td>
<td>125°</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>Ethyl thymyl ketone</td>
<td>118°</td>
<td>200/15 mm</td>
<td>37</td>
</tr>
<tr>
<td>Propyl thymyl ketone</td>
<td>93°</td>
<td>204/14 mm</td>
<td>37</td>
</tr>
<tr>
<td>Isopropyl thymyl ketone</td>
<td>80°</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>Isobutyl thymyl ketone</td>
<td>108°</td>
<td>201/13 mm</td>
<td>37</td>
</tr>
<tr>
<td>Phenyl thymyl ketone</td>
<td>153°</td>
<td></td>
<td>37</td>
</tr>
<tr>
<td>Heptyl thymyl ketone</td>
<td>81-82°</td>
<td>217-20/9 mm</td>
<td>38</td>
</tr>
<tr>
<td>Benzyl thymyl ketone</td>
<td>105°</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>α-Phenethyl thymyl ketone</td>
<td>122°</td>
<td></td>
<td>38</td>
</tr>
</tbody>
</table>

Houben and Fischer (39) condensed nitriles with thymol to produce ketimides, which were, in turn, hydrolyzed to ketones.

5. Hydrogenation

Thymol reacts with hydrogen to form the cis and trans-isomers of the corresponding cyclohexanol. Raney-nickel serves as an effective catalyst for this reaction.

![Chemical Reaction Diagram]

Menthol may be produced from thymol in good yields by the action of hydrogen at 150 kgm pressure at elevated temperatures in the presence of finely divided nickel catalyst (40).
6. Sulfur Derivatives

a. Reactions with Sulfur Chlorides

Thymol undergoes reactions with sulfur dichlorides to form the monosulfide, 3.6, the reaction is run in carbon tetrachloride solution at 20-30°C. The monosulfide is obtained as a white crystalline solid.

Lesser and Gad (41) produced chlorothymol sulfide, a compound similar to 3.6 with two chlorine atoms in positions para to the hydroxyl groups. It melted at 110-111°C. A series of unsymmetrical aryl sulfides was prepared by Foss, Dunning, and Jenkins (42) in a manner analogous to that used in making the monosulfide, 3.6, Table VI.

Schonberg, Vorgha, and Werner (43) produced a disulfide of thymol, by reacting thymol with thiophosgene, then with alkali.
Table VI

<table>
<thead>
<tr>
<th>Sulfide</th>
<th>Mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1-methyl-3-hydroxy-3'-nitro-4-isopropyl) biphenyl sulfide</td>
<td>116-117°C</td>
</tr>
<tr>
<td>(1-methyl-3-acetoxy-3'-nitro-4-isopropyl) biphenyl sulfide</td>
<td>77-78°C</td>
</tr>
<tr>
<td>(1-methyl-2-bromo-3-hydroxy-3'-nitro-4-isopropyl) biphenyl sulfide</td>
<td>126-127°C</td>
</tr>
<tr>
<td>(1-methyl-3-hydroxy-3'-amino-4-isopropyl) biphenyl sulfide</td>
<td>112-113°C</td>
</tr>
<tr>
<td>(1-methyl-3-acetoxy-3'-acetamido-4-isopropyl) biphenyl sulfide</td>
<td>90-91°C</td>
</tr>
<tr>
<td>(1-methyl-3-hydroxy-3'-carbamido-4-isopropyl) biphenyl sulfide</td>
<td>177-177.5°C</td>
</tr>
</tbody>
</table>

E. Sulfonic Acids

Thymol reacts readily with sulfonyl chlorides to produce the corresponding sulfonates. By this method, Sane, Chakrovartz, and Parmanick (44) produced 4,6-dinitrothymyl-p-toluenesulfonate, 4.1.

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

Sekera (45) produced the thymol ester of p-bromobenzene-sulfonic acid in 71% yield, 4.2, by reacting the appropriate sulfonyl chloride with thymol.
Thymolsulfonephthalein was produced by condensing thymol with p-sulfonyl benzoyl chloride. The principle product of this reaction, however, proved to be dithymyl-o-sulfo-benzoate (46). When p-aminobenzenesulfonamide was diazotized, and condensed with thymol, p-(4-hydroxy-5-isopropyl-2-methyl-phenylazo)-benzenesulfonamide resulted (47). Kaufmann and Weber (48) produced several sulfonic acid derivatives of thymol including 1-methyl-4-isopropyl-3-hydroxy-1-rhodan-benzene, mp 105°C.

Several methods have been proposed for the replacement of the sulfonic acid group by various other groups. Datta, Rasch, and Mitter (49) replaced the sulfonic acid group with a chlorine atom by passing a stream of chlorine gas through an aqueous solution of the sulfonic acid. Datta and Varma (50) replaced the sulfonic acid group in thymol with a nitro group using nitrogen dioxide gas in a manner similar to that described above. The sulfonic acid group in thymol may be identified by reacting the suspected compound with benzyl thiuronium chloride. Thymyl-p-sulfonic acid yields a compound melting at 212°C. (54).
An alcohol-water solution of thymol and ammonium thiocyanate was electrolyzed at 0°C. and at a current density of 0.2–0.3 amps/cm², and p-thiocyanothymol was produced. The active thiocyanating agent proved to be thiocyanagen which was produced by electrolysis of the ammonium thiocyanate (52).

7. Nitrogen Derivatives

a. Nitration

4-Nitrothymol was prepared by Ajello and Sigillo (53) by allowing a mixture of thymol and amyl nitrite to stand for three days in ether. The compound was extracted with aqueous potassium hydroxide, acidified, and crystallized from benzene. Thymol was also nitrated with a mixture of potassium nitrate and sulfuric acid (54). Monti and Cianetti (55) produced nitrothymol by passing nitrous vapors through a benzene solution of thymol. They isolated both the ortho and para nitrous thymols. Guia (56) noted that in the process of nitrating thymol, there is always a little trinitro-m-cresol produced by eliminating the isopropyl group; apparently the action of nitric acid resembled that of phosphorus pentoxide in this case. A series of polynitrated thymol derivatives have been produced by Ladenburg and Engelbrecht (57).
b. Amination

The nitro derivatives may be reduced to amines by treatment with iron and hydrochloric acid, and by all the other procedures applicable to the reduction of the nitrophenols. Hinsberg (58) produced aminobis-(4-hydroxy-2-methyl-3-isopropyl) phenyl ethane by reduction of the corresponding nitro compound with iron and hydrochloric acid. A series of Schiff's bases with p-aminothymol were produced by Sumerford, Hartung, and Jenkins (59), Table VII.

Table VII

<table>
<thead>
<tr>
<th>R</th>
<th>Mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzal</td>
<td>149°C</td>
</tr>
<tr>
<td>3-Methoxybenzal</td>
<td>160°C</td>
</tr>
<tr>
<td>3,4-Methyleneoxybenzal</td>
<td>162°C</td>
</tr>
<tr>
<td>Cinnamal</td>
<td>154°C</td>
</tr>
</tbody>
</table>

By reacting 6-aminothymol hydrochloride with nitro urea, 6-carbamidothymol was produced (60). Laborde (61) produced hexamethylenetetramine thymolate. p-Nitrosothymol was reduced to p-aminothymol and thymoquinone over palladium by Sumerford and Hartung (62). p-Aminothymol was produced by treating isonitroso-α-thujene with H₂SO₄ (63). Cheng and Sung (64) produced a series of acetamidothymol ethers, Table VIII.
Dalmer and Diehl (65) synthesized some carbocyclic alcohol esters of N-alkyl piperidinocarboxylic acids involving thymol. When 4-nitrosothymol is treated with hydrochloric acid 4-aminothymol and chloroaminothymol are isolated (66).

c. Nitroso Compounds

Lee and Lynn (67) produced p-nitrosothymol by reacting thymol with nitrosyl chloride. A quantitative yield of nitrosothymol was obtained by Dwyer, Mellor, and Trikajus (68) by reacting thymol with a mixture of K$_2$Cr$_2$O$_7$ and NaNO$_2$.

d. Azo Compounds

Ruggli and Bartusch (69) produced a series of azo compounds employing thymol in the following series of reactions.

<table>
<thead>
<tr>
<th>R</th>
<th>Mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>-</td>
</tr>
<tr>
<td>Ethyl</td>
<td>-</td>
</tr>
<tr>
<td>n-Propyl</td>
<td>131-2°C.</td>
</tr>
<tr>
<td>n-Butyl</td>
<td>104-6°C</td>
</tr>
<tr>
<td>Benzyl</td>
<td>115-7°C</td>
</tr>
</tbody>
</table>
Borsche (70) produced a series of azo compounds of thymol by reacting thymoquinone with various semicarbazides and hydrazines. Sen and Banerji (71) produced the hydrazone derivative of benzeneazothymol aldehyde by reacting benzeneazothymol aldehyde with phenyl hydrazine. Thymol-trypan-red, C_{42}H_{36}O_{16}N_{5}S_{5}Na_{4}, was produced by reacting trypan-red with thymol in 50% alcohol (72). A large number of azo compounds of thymol have been prepared and tried as azo dyes by Wheeler and his coworkers (73).

**e. Urethans**

Urethan derivatives of thymol are prepared in a manner analogous to that employed in preparing the urethans of phenol. A number of thymol urethans have been prepared by various investigators, Table IX.
### Table IX

<table>
<thead>
<tr>
<th>Name</th>
<th>Mp, °C</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymylmenthylcarbamate</td>
<td>129</td>
<td>74</td>
</tr>
<tr>
<td>Thymyl-p-chlorophenylcarbamate</td>
<td>280</td>
<td>75</td>
</tr>
<tr>
<td>Thymyl-2,4-dinitrophenylcarbamate</td>
<td>155</td>
<td>76</td>
</tr>
<tr>
<td>Thymyl-p-biphenylcarbamate</td>
<td>194</td>
<td>77</td>
</tr>
<tr>
<td>Thymylphenylcarbamate</td>
<td>107</td>
<td>78</td>
</tr>
</tbody>
</table>

### 8. Quinone Formation

Thymol was converted to thymoquinone in 85% yield by converting thymol to nitroso derivative, and reducing this compound with ammonium polysulfide to the amine. The amine was converted into the thymoquinone with nitrous acid (79). Tseng, Hu, and Chu (80) produced thymoquinone from nitrosothymol by refluxing it for two days with 8% HCl, and steam distilling the product. Krewers and Wakemann (81) oxidized the nitroso thymol with nitrous acid and recovered thymoquinone in 90% yield.

Dithymoquinone, 4.3, was prepared by Smith, Lee, and Tess (82). They exposed a film of thymoquinone to daylight for five days. Thymoquinone was produced by electrolytically oxidizing thymol in 8N sulfuric acid (83).
Thymohydroquinone was produced by reducing thymoquinone with sulfur dioxide (84). Thymoquinone was reduced catalytically by Sabatier and Mailhle (85) employing a nickel catalyst. Wakeman (86) employed a palladium catalyst for the reduction of thymoquinone. A phytochemical reduction of thymoquinone was affected by Luers and Mengele (87). They employed a mixture of hexose and yeast, and recovered a 45% yield of the hydroquinone. Through reductive acetylation of 3-hydroxythymoquinone, Erdtman (88) obtained 2,5,6-triacetoxy-1-methyl-3-isopropyl benzene. Hiroyama (89) oxidized menthone with selenium dioxide, and obtained hydroxythymoquinone. Treibs (90) bubbled oxygen gas through a methanol-KOH solution of cymorcinol and obtained dihydroxythymoquinone. Kehrmann (91) prepared a series of substituted thymoquinones, Table X. Cordone (92) produced thymoquinone diimine by reacting nitrosothymol with hydroxylamine hydrochloride, and the resulting product was reduced by tin chloride to the diamine; this diamine was oxidized to the diimine. Kehrmann (93) prepared thymoquinone monooimine by treating p-aminothymol with hydrogen sulfide.

Table X

<table>
<thead>
<tr>
<th>Name</th>
<th>Mp, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Chlorothymoquinone</td>
<td>40</td>
</tr>
<tr>
<td>6-Bromothymoquinone</td>
<td>47</td>
</tr>
<tr>
<td>6-Iodothymoquinone</td>
<td>62</td>
</tr>
<tr>
<td>3,6-Dibromothymoquinone</td>
<td>73</td>
</tr>
<tr>
<td>Tribromothymoquinone</td>
<td>65</td>
</tr>
</tbody>
</table>
Wakeman and Groffman (94) studied the action of amines on thymoquinone. They were able to prepare the normal addition products by reacting the amine and quinone in a 1:1 ratio. Hixon (95) noted that primary amines react with dibromothymoquinone to give a secondary amine, 4,4, plus methane. Borsche (96) prepared thymoquinoxime—

\[
\begin{align*}
\text{C}_4\text{H}_4
\end{align*}
\]

2-hippuryl-5-hydrozone and thymoquinoxime-3-phenyl carbamic acids hydrazone. The methyl ethers of the thymoquinone oximes were prepared by Veibel and Simesen (97). They reacted the quinone oximes with dimethyl sulfate. The hydrolysis of thymoquinoximes has been studied by Sumerford and Dalton (98). They employed hydrochloric acid and 30% hydrogen peroxide to affect the hydrolysis.

Siegmund (99) prepared two quinhydrones involving thymoquinone, Table XI. Thymoquinone gives intense reactions

Table XI

<table>
<thead>
<tr>
<th>Name</th>
<th>Ratio</th>
<th>Mp, °C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymoquinone + quinol</td>
<td>2:3</td>
<td>137 dec.</td>
</tr>
<tr>
<td>Thymoquinone + resorcinol</td>
<td>1:1</td>
<td>43-5 dec.</td>
</tr>
</tbody>
</table>

with ethyl cyanoacetate and an alcohol ammonia mixture (100). The thymoquinhydrone reduction potential has been computed by Bulmann and Muus (101). They observed that the values

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are not constant, but increase with time and temperature. The E.M.F. at 18°C. against the hydrogen electrode is 0.5927 0.0005 volt, and at 25°C. it is 0.5816 0.0005 volt.

Kehrmann and Colland (102) prepared some phenazine and fluorindine derivatives of thymol. They prepared dihydroxythymophenazine, hydroxythymophenoxyazine, and thymophenyliduline.

IV. Pharmacological Properties

A. Anthelmintic and Internal Disinfectants

Thymol has been reported to demonstrate anthelmintic action against ascaride and hookworms (103). Oral tests on dogs indicated that thymol was a good duodenal disinfectant, but it had no effect in the lower portion of the small intestine (104). Caquis and Mhaskar (105) reported that thymol was very effective in expelling round worms from animals. It compared favorably with carbon tetrachloride and cephapodium in the treatment of hookworms (106). It has been demonstrated that 25 g. doses of crystalline thymol, given daily, usually caused the disappearance of Taenia in three to four days without recurrence (107). Although thymol proved to be a good anthelmintic, Nogouchi (108) reported several cases of thymol poisoning and hemoglobinuria following treatment for hookworms.

Thymol was shown by Schulty (109) to be parasitical in large doses only; however, when it was dissolved in alcohol, it was readily absorbed and much more effective. The
primary effects were those of the alcohol, and the lethal
dose was that of the solution and not of thymol. Morgan
and Cooper (110) noted that a 30% alcoholic solution of
thymol increased considerably the apparent effect of thymol
on 3-thyphosus. They observed moreover that the phenol
coefficient of thymol was reduced by the presence of alco­
hol. The pH of the solution apparently has no great in­
fluence upon the antiseptic action of thymol (111). The
salts of chlorothymol carboxylic acid, 5.1, exhibited a
marked disinfectant action over most of the pH range (112).

\[
\begin{align*}
\text{CH} & \left(\text{CH}_3\right)_2 \\
\text{NO} & \\
\text{Cl} & \\
\text{C-OR} & \\
\text{CH}_3 & \\
\end{align*}
\]

A series of thymol amines was prepared by Stevens and
Beutel (113), and their toxicities determined, Table XII.

<table>
<thead>
<tr>
<th>Name</th>
<th>Toxicity</th>
<th>Mp,°C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Dimethyaminothymol hydrochloride</td>
<td>160.00</td>
<td>164</td>
</tr>
<tr>
<td>p-Aminothymol hydrochloride</td>
<td>23.00</td>
<td>199</td>
</tr>
<tr>
<td>Trimethylthymol ammonium iodide</td>
<td>0.72</td>
<td>171.5</td>
</tr>
<tr>
<td>p-Aminothymol methyl iodide</td>
<td>0.22</td>
<td>182</td>
</tr>
</tbody>
</table>

Thymol in concentrations of 1:2000 had some
effect in inhibiting germination of seed and growth of
bacteria. 4-Chlorothymol exhibited complete inhibition
in concentrations of 1:3000 (114). The yeast enzyme was completely unaffected by thymol, and this was explained by demonstrating that thymol had no effect on the colloidal state of the enzyme (115). The mushroom enzyme was reported by Cousin and Herissey (116) to oxidize thymol to thymoquinone.

The fixation of thymol in the red blood cells was studied by Usui (117). He concluded that the concentration of thymol in the cells was dependent upon three factors: (1) the distribution of thymol in the aqueous cell phases, (2) adsorption by the soluble cell constituents, and (3) adsorption by the insoluble cell constituents. He further observed that nucleic acid and histones were responsible for the addition of thymol by the insoluble cell constituents, and this phenomenon might be due to either chemical union or to surface condensation. Thymol depressed the isolated heart of the frog by acting on the cardiac muscle (118). It also showed the ability to increase ciliary movement (119). Recently it was employed in the etiological diagnosis of jaundice by Tallroth (120). It was used as an indicator for immune protein. Certain proteins such as β-lipoprotein and α-globulin reacted with thymol (121). In frogs, Mikleslon (122) reported a 30-70% hindering of blood cholenesterase activity by 6.5 X 10 grams of an isonarcotic dose of thymol.
B. **Fungicidal Properties**

Thymol exhibits certain very definite fungicidal properties. It has been proven active against Epidermophyton, Tricophyton, Microspores, Achorion and Sporodochium (123). Myers and Thienes (124) demonstrated that thymol was superior to 1% phenol in promoting healing of areas affected by fungus. Along with thymol, many of its derivatives, especially thymoquinone, possessed outstanding fungicidal properties (125).

C. **Bactericidal Properties**

Thymol possesses a strong infertilizing power against human tubercle bacilli in vitro. It was shown that thymol was eight times as effective as Guaiacol, and sixteen times as effective as euganol in killing tuberculosis (126). Caujolle, Franck, and Heynard (127) showed that thymol and its aliphatic ethers have the ability to localize in the lung tissues of dogs when given intravenously. In concentrations of 0.001N-0.005N chlorothymol carboxylic acid exerted a marked bactericidal effect in two to twenty-four hours on bovine tubercle bacilli (128). Florestano (129) prepared a series of dithymyl methane derivatives and studied their bactericidal properties on tubercle bacilli in vitro, Table XIII.
Table XIII

<table>
<thead>
<tr>
<th>Name</th>
<th>Tuberculocidal Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>bis-(2-methyl-4-hydroxy-5-isopropyl-phenyl) methane</td>
<td>weak</td>
</tr>
<tr>
<td>bis-(2-hydroxy-3-isopropyl-5-chloro-6-methylphenyl) methane</td>
<td>weak</td>
</tr>
<tr>
<td>(3,3'-dihydroxy-2,2'-dichloro-1-methyl-4-isopropyl) biphenylmethane</td>
<td>strong</td>
</tr>
<tr>
<td>bis-(1-hydroxy-2-isopropyl-4-chloro-5-methylphenyl) methane</td>
<td>weak</td>
</tr>
<tr>
<td>1,1'-dihydroxy-2,8'-diisopropyl-4-chloro-5,5'-dimethyl) biphenylmethane</td>
<td>weak</td>
</tr>
<tr>
<td>(1,3'-dihydroxy-2,8'-diisopropyl-4-chloro-5,5'-dimethyl) biphenylmethane</td>
<td>weak</td>
</tr>
</tbody>
</table>

Thymol has been studied to ascertain its bacterial properties on a number of other strains of bacteria and viruses, but to a much smaller degree than in the cases of tuberculosis and fungi. Burkhalter, Tendick, and Jones (130) found that diethylaminothymol, 5.2, possessed some antimalarial properties.

A 1% thymol solution has been employed in the treatment of leprosy with good results (131). Thymol also proved effective
in the treatment of anchylostomiasis (132). A large series of thymol aminoalcohols, 5.3, which possessed antipyretic and analegetic properties, was prepared by Fourneau (133). Unfortunately these proved to be injurious to the heart.

\[
\begin{align*}
5.3
\end{align*}
\]

Thymylmethyl diethyl amine, 5.4, was observed to cause convulsions in rabbits by Hildebrant (134).

\[
\begin{align*}
5.4
\end{align*}
\]

Thymylnicotinate, 5.5, produced a definite but transient fall in pressure in the carotid of the choralased dog (135).

\[
\begin{align*}
5.5
\end{align*}
\]

A series of thymyl phosphates has been prepared by Rosenmund and Vogt (136) with the intention of studying their bactericidal properties.
Dunning, Dunning, and Drake (137) recently prepared some thymyl sulfides, but as yet they have not reported the results of their bactericidal studies.
Part VII

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