

Yeast Company for generously supplying starch-free yeast and the Bureau of Standards for a sample of gentiobiose octaacetate.

Summary

1. Glucose in 0.06 molar hydrochloric acid under three atmospheres' pressure condenses to give in thirty minutes about 1.5% gentiobiose.
2. Whole corn starch under the same conditions give some gentiobiose.
3. Corn β -amylose which constitutes 85% of the starch gives no gentiobiose.
4. Corn α -amylose gives under the same hydrolytic conditions a solution of low specific rotation from which gentiobiose osazone has been isolated.
5. The gentiobiose found in solution from the hydrolysis of corn starch under the stated conditions seems to come from the direct scission of a polysaccharide in the insoluble α -amylose fraction of corn starch rather than from condensation of glucose.

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THE SYNTHESIS OF THYMOL, CHLOROTHYMOL AND HOMOLOGS OF THYMOL BY THE INTRAMOLECULAR REARRANGEMENT OF META-CRESYL ETHERS

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Theoretical Part

The syntheses of thymol may be divided into two general classes; those which begin with benzene hydrocarbons as the starting point and those which start with *m*-cresol, condensing this phenol with acetone, isopropyl alcohol or propylene. The first class may be still further divided into those which start from *p*-cymene and those which begin with benzene itself.

Béhal and Tiffeneau¹ were the first to synthesize thymol starting with *p*-cymene. Since then a number of syntheses have appeared with this substance as the starting material. These methods depend upon the occupying of the position ortho to the methyl group with an amino group and then sulfonating. Finally the amino group is replaced by hydrogen and the sulfonic acid group by hydroxyl.² Austerweil and Lemray³ have synthesized thymol starting from benzene using the standard methods.

¹ Béhal and Tiffeneau, *Bull. soc. chim.*, [4] 3, 729 (1908).

² Andrews, U. S. Patent 1,306,512 (1919); Philips, *ibid.*, 1,332,680 (1920); Austerweil, British Patent 221,226 (1923); Bert and Dover, *Compt. rend.*, 182, 634 (1926).

³ Austerweil and Lemray, *Bull. soc. chim.*, 41, 454 (1927).

The more direct manner of synthesizing thymol would be to condense *m*-cresol with isopropyl alcohol, propylene or acetone, reducing the product in the latter case. Such condensations have been tried using isopropyl alcohol, *m*-cresol and magnesium chloride or phosphoric acid.⁴

Acetone has been condensed with *m*-cresol in the presence of hydrochloric acid. The condensation product obtained was depolymerized by distillation and then reduced to give thymol.⁵

Inasmuch as in the condensation of allyl alcohol with *m*-cresol the dimer of *o*-isopropenyl-*m*-cresol can be obtained in excellent yield, the ultimate synthesis of thymol, upon reduction of this product, as in the foregoing case, ought to be possible.⁶ In this group may be included the condensation of propylene with *m*-cresol in the presence of sulfuric acid.⁷

Successful attempts have been made to condense isopropyl alcohol with substituted *m*-cresols where the position para to the hydroxyl group has been blocked off. This removed the possibility of obtaining para isomers and the yields of substituted thymols are good. Isopropyl alcohol condenses with *m*-cresol sulfonic acid with the formation of thymol sulfonic acid. The sulfonic acid group is then removed by means of superheated steam.⁸

In a similar fashion, chlorothymol has been synthesized by the condensation of isopropyl chloride or isopropyl alcohol with chloro-*m*-cresol.^{8c}

The present contribution proposes a different method for the preparation of thymol, substituted thymols and homologs of thymol. Isopropyl *m*-cresyl ether has been shown to rearrange with the formation of an isopropyl *m*-cresol which did not distil at constant temperature. The product has a strong odor of thymol, but its boiling point, acetic acid derivative (m. p. 141°) and other physical properties did not check too closely with that of thymol.⁹

In the rearrangement of unsaturated alkyl phenyl ethers and substituted diphenyl ethers by earlier investigators¹⁰ *m*-cresol had not been dealt with. It was therefore necessary to study this reaction with a view toward the determination of the position taken up by the isopropyl group, so that the structure of this and similar compounds prepared by the rearrangement

⁴ Mazzara, *Gazz. chim. ital.*, **12**, 505 (1882); Howard and Blagden, British Patent 200,151 (1922).

⁵ Jordan, Schering Kahlbaum, British Patent 279,855, 279,857, 280,924 (1928); Canadian Patent 281,114, 281,120 (1928).

⁶ Niederl, Smith and McGreal, *THIS JOURNAL*, **53**, 3390 (1931).

⁷ Howard and Blagden, British Patent 214,866 (1923).

⁸ (a) Badische Anilin und Sodafabrik, British Patent 186,202 (1921); (b) Gunther, U. S. Patent 1,412,937 (1922); (c) Raschig, Swiss Patent 127,035 (1927).

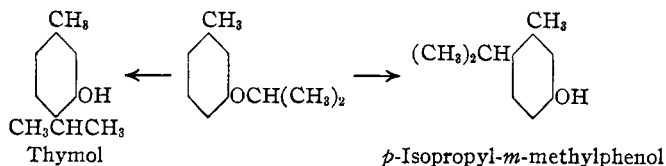
⁹ Niederl and Natelson, *THIS JOURNAL*, **53**, 1928 (1931).

¹⁰ Claisen, *Ber.*, **45**, 3157 (1912); *Ann.*, **418**, 69 (1919); *Z. angew. Chem.*, **36**, 478 (1923); Van Alphen, *Rec. trav. chim.*, **46**, 799 (1927); Kursanov, *J. Russ. Phys.-Chem. Soc.*, **48**, 1172 (1916).

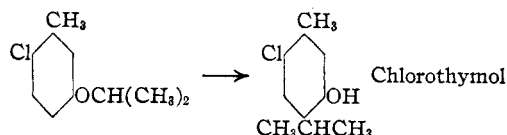
of *m*-cresyl ethers could be ascertained. Twenty-five cc. of the liquid as obtained from the intramolecular rearrangement of isopropyl *m*-cresyl ether was fractionated with a special fractionating column. The fractions obtained, and the melting points of the corresponding acetic acid derivatives after one recrystallization, were shown to be

231-235°.....	5 cc.....	146°
235-237°.....	6 cc.....	132-137°
237-244°.....	12 cc.....	125°

The derivative of the first fraction, that which boiled in the neighborhood of thymol, was identical with thymoxyacetic acid.¹¹ The highest fraction resembled more closely the product obtained by Mazzara⁴ and Read.¹² The acetic acid derivative of the middle fraction did not melt sharply, but appeared to contain largely thymoxyacetic acid. Two recrystallizations of the acetic acid derivative of the original liquid obtained after rearrangement yielded a crystalline product which melted at about 141°, showing that thymoxyacetic acid is less soluble in water than its *p*-isomer and can be crystallized from it. It appears evident from the above that after rearrangement of the isopropyl *m*-cresyl ether a mixture was obtained which consisted of about 33% thymol and about 67% of the *p*-isopropyl-*m*-methylphenol.



By blocking off the para position, a substituted thymol should be obtained in good yield. 4-Chloro-*m*-cresyl isopropyl ether was therefore rearranged and chlorothymol resulted in good yield.

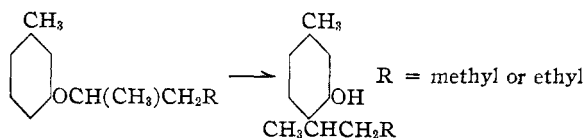


Because of the possible important antiseptic properties, homologs of thymol were prepared by rearranging secondary butyl and secondary amyl cresyl ethers. The liquid obtained from the rearrangement of *sec*-butyl *m*-cresyl ether was fractionated and the portion which distilled constantly at lower temperatures was collected. The major portion of the product came over between 246-250°. The higher boiling portion was reserved for future study. The rearrangement of *sec*-amyl *m*-cresyl ether

¹¹ Laarbach, *J. prakt. Chem.*, [2] **21**, 159 (1880).

¹² Read, Sharp and Dohme, private communication.

yielded a product which distilled more constantly. Very little of the higher boiling para isomer was obtained. It appears that rearrangement to the para position becomes more difficult the longer the chain.



The odors of thymol, methylthymol and ethylthymol were remarkably similar, the odor sweetening and becoming less phenolic the longer the chain. The odor appears to be characteristic of a tertiary carbon atom ortho to the hydroxyl group in *m*-cresol. These new compounds show extremely high phenol coefficients.

During the course of the research on these and similar compounds it was found that normal propyl, butyl and amyl *p*-cresyl ethers would not rearrange, but gave rise to the original phenol and the corresponding alkyl acetate. All of the secondary alkyl phenyl ethers studied, rearranged, while tertiary alkyl phenyl ethers gave the best yield of substituted phenol on rearrangement. The rearrangement of these ethers is a simple method for preparing the respective substituted alkyl phenols, which would be difficult to prepare otherwise.

The theoretical side of these intramolecular rearrangements may now be examined, but before any reaction mechanism is advanced the following points have to be taken into consideration: (a) the reaction appears to be unimolecular in nature; (b) the reaction is not reversible; (c) rearrangement is possible by the mere application of heat, or (d) by the use of a rearranging agent which then seems to play the part of a catalyst.

The phenomena of the rearrangement of unsaturated phenyl ethers (allyl and crotonyl phenyl ethers) have been studied extensively by Claisen and his co-workers,¹³ who advanced a reaction mechanism which states that the allyl radical does not attach itself to the cyclic nucleus through the same carbon atom which was bound to the oxygen. Such a postulate does not necessarily apply to the rearrangement of the isopropyl phenyl ethers, but in case of longer chain phenyl ethers further studies may reveal formation of metameric compounds supporting Claisen's theory.

The theory of oxonium compound formation as advanced by Van Alphen¹⁴ cannot be applied without reservation to the cases presented herein, because rearrangement of unsaturated and also of long chain saturated alkyl phenyl ethers is possible by mere application of heat.¹⁵

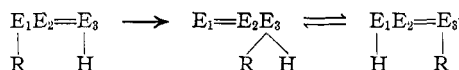
¹³ Claisen, *Ann.*, **237**, 261 (1887); **401**, 21, 119 (1914); **418**, 69 (1919); *Ber.*, **58**, 275 (1925); **45**, 3157 (1912); *Z. angew. Chem.*, **36**, 478 (1923); Claisen and Tietze, *Ber.*, **58**, 275 (1925); **59**, 2344 (1926).

¹⁴ Van Alphen, *Rec. trav. chim.*, **46**, 799 (1927).

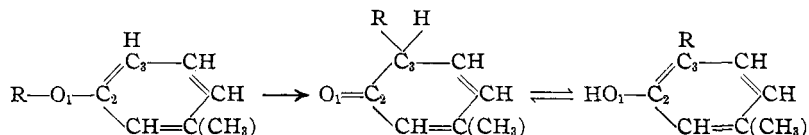
¹⁵ Niederl and Natelson, *THIS JOURNAL*, **53**, 272 (1931).

The assumption of the formation of free radicals in such intramolecular rearrangements as given by Hurd and Cohen¹⁶ will be somewhat difficult to apply to the above cases, in so far as the simultaneous formation of the possible metameric by-products demanded by rigid application of this theory could not be observed.

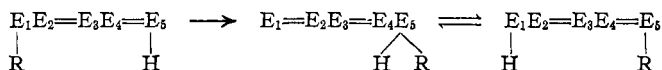
The most plausible explanation for the intramolecular rearrangements presented in this paper appears to be the reaction mechanism advanced by Lapworth¹⁷ for various other types of molecular rearrangements and which is based upon the following arrangement of atomic groupings



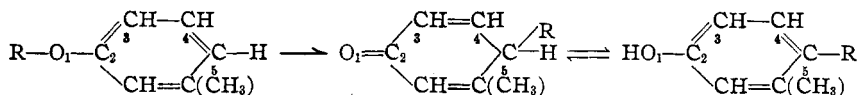
Applied to the cases presented herein the reaction mechanism could then be given for the migration of the alkyl radical to the ortho position



The formation of the para isomer necessitates the following extension of this theory

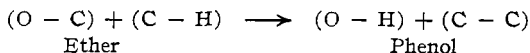


Applied to the case of the observed formation of the para isomer of thymol (the *m*-methyl-*p*-isopropylphenol) the intramolecular rearrangement can then be illustrated in the following manner



The two phases of the reaction, the disorganization (quinoid form) followed by the reorganization (benzoid form) of the molecule involving tautomeric intramolecular changes can thus be clearly indicated.

The mechanism of these intramolecular rearrangements becomes clearer when the repulsive energies of the atomic kernels in the bonds involved are taken into consideration. In the above reaction the following scheme represents the changes in the bonds during the reaction



According to Latimer,¹⁸ the values of the repulsion energies in the above linkages are

¹⁶ Hurd and Cohen, *THIS JOURNAL*, **53**, 1917 (1931).

¹⁷ Lapworth, *J. Chem. Soc.*, **73**, 445 (1898).

¹⁸ Latimer, *THIS JOURNAL*, **51**, 3185 (1929).

$$\begin{aligned}(\text{O} - \text{C}) &= 2800 \text{ kilocal. repulsion energy} \\(\text{C} - \text{H}) &= 550 \text{ kilocal. repulsion energy} \\(\text{O} - \text{H}) &= 940 \text{ kilocal. repulsion energy} \\(\text{C} - \text{C}) &= 1700 \text{ kilocal. repulsion energy}\end{aligned}$$

Substituting these values in the above equation

$$\begin{array}{ccc}(2800 + 550) & - & (940 + 1700) = 710 \text{ kilocal.} \\ \text{Ether} & & \text{Phenol}\end{array}$$

It can then be seen that these intramolecular rearrangements are accompanied by a loss of repulsion energy; the alkyl phenyl ethers with a higher total energy content change into the corresponding substituted phenols with a lower energy potential.

Experimental Part

Preparation of the Ethers.¹⁹—One molecular weight of *m*-cresol (108 g.), or 4-chloro-*m*-cresol (143 g.) was placed in a three-necked flask fitted with a reflux condenser. Slightly more than one mole of finely divided solid potassium hydroxide was added (60 g.). The whole was gently warmed with a free flame until all the alkali dissolved. Slightly more than one mole of the alkyl halide was added to the mixture drop by drop. The whole was then refluxed for four hours when a light oil separated over precipitated potassium halide. The mixture was allowed to cool and water was added so as to dissolve the potassium halide. The upper layer was separated and washed once with 10% potassium hydroxide and twice with water. The aromatic smelling oil was then dried over calcium chloride and distilled. One distillation was sufficient to obtain a colorless constant boiling liquid.

For commercial preparation of the alkyl cresyl ethers the sulfuric acid,²⁰ the diazotization,²¹ or the condensation method¹⁵ can be made use of and work in this direction is being carried out.

Rearrangement of the Ethers.—The rearrangement mixture consists of 200 cc. of concentrated sulfuric acid in sufficient glacial acetic acid to make up to a liter. The following procedure is an improvement on the one reported in a previous article.⁹

One molecular weight of the prepared ether was placed in a round-bottomed flask and 250 cc. of the above mixture added. The mixture was then refluxed for five hours. Two layers separated at first which redissolved to form a homogeneous pink colored solution. The whole was then allowed to cool and poured into an equal volume of saturated salt solution. On long standing, about five hours, a heavy oil separated at the top. This was separated off, washed once with a small quantity of water and then extracted with 600 cc. of 10% potassium hydroxide solution. A small amount of unchanged ether remained which was separated and redistilled to reclaim this starting product. The alkali extract was neutralized with concentrated hydrochloric acid, placing ice in the flask to keep it cool. An oil separated on standing, which was too viscous to handle efficiently and the whole was extracted with ether. The ether was distilled off and the residue fractionated. The colorless oil collected was finally re-fractionated in vacuum.

Preparation of the Phenoxyacetic Acid Derivatives.—Two grams of the substituted phenol was added to one gram of solid potassium hydroxide dissolved in 15 cc. of water. This mixture was warmed on a water-bath until complete solution took place. If an

¹⁹ Williamson, *J. Chem. Soc.*, **4**, 106 (1851).

²⁰ Ullmann, *Ann.*, **327**, 104 (1903).

²¹ Hantzsch and Vock, *Ber.*, **36**, 2062 (1903).

TABLE I
PHYSICAL CONSTANTS AND ANALYSES OF THE COMPOUNDS PREPARED

Compound	M. P., °C.	B. P., °C.	Sp. gr., (20°)	n_D^{20}	Carbon Analyses, %		% Hydrogen	
					Calcd.	Found	Calcd.	Found
Isopropyl <i>m</i> -tolyl ether		195	0.931	1.4959				
Sec.-butyl <i>m</i> -tolyl ether ^a		212	.927	1.4989				
Sec.-amyl <i>m</i> -tolyl ether ^a		235	.920	1.4999				
Isopropyl 4-chloro- <i>m</i> -tolyl ether		231	1.085	1.5230				
Isopropyl- <i>m</i> -cresol (from isopropyl <i>m</i> -tolyl ether)		231-244	0.994	1.5280	80.00	79.84	9.33	9.39
First fraction (thymol)		231-235						
Acetic acid derivative	146							
Mixed with thymoxyacetic acid	145				69.23	69.43	7.69	7.85
Second fraction		235-237						
Acetic acid derivative	132-137							
Third fraction (3-methyl-4-isopropylphenol)		237-244						
Acetic acid derivative	125							
Mixed with 3-methyl-4-isopropylphenoxyacetic acid ^b	125							
Chlorothymol ^c (from isopropyl 4-chloro- <i>m</i> -tolyl ether)	59-60							
Methylthymol (from sec.-butyl <i>m</i> -tolyl ether)		246-250	0.991	1.5289	Cl, calcd., 19.27.	Found, 19.34		
Methylthymoxyacetic acid	149				70.25	69.62	8.11	7.98
Ethylthymol (from sec.-amyl <i>m</i> -tolyl ether)		143-145	0.990	1.5299				
		(10 mm.)						
Ethylthymoxyacetic acid	151-153				71.19	70.77	8.48	8.61

^a M. Siegel, Research report, New York University, 1931.

^b Niederl and Natelson, *THIS JOURNAL*, **53**, 1928 (1931); Lambing, *Bull. soc. chim.*, [3] 17, 360 (1897); Spica, *Gazz. chim. ital.*, **10**, 341 (1880).

^c Bocchi, *ibid.*, **26**, 11, 103 (1896); Peratoner and Condorelli, *ibid.*, **28**, 214 (1898).

emulsion is formed it should be treated with charcoal while hot and filtered. Two grams of bromoacetic acid was dissolved in 10 cc. of water and 2 drops of phenolphthalein added; 10% potassium hydroxide solution was then added until a permanent pink color was obtained. The two solutions were then mixed and gently boiled for ten minutes. A small portion of norite was then added and the boiling continued for one minute. The mixture was filtered through a fluted filter while hot. The filtrate was allowed to cool and neutralized with concentrated hydrochloric acid. An oil separated which solidified on standing. The crystalline product was then recrystallized from water, or a mixture of benzene and ligroin. The colorless crystals were then dried in an air-bath at 110°.

The authors desire to express their appreciation to Professor Wm. C. MacTavish for the facilities placed so generously at their disposal.

Summary

The intramolecular rearrangement of isopropyl *m*-cresyl ether, under the influence of a mixture of glacial acetic acid and concentrated sulfuric acid, was studied; thymol and *m*-methyl-*p*-isopropylphenol were the products obtained, thus furnishing a new synthesis of thymol.

Methylthymol, ethylthymol and chlorothymol were prepared in a similar manner, by the rearrangement of the corresponding isomeric ethers, illustrating that the rearrangement of secondary alkyl phenyl ethers is a general reaction.

Theories underlying such intramolecular rearrangements were discussed and a reaction mechanism based upon the considerations of Lapworth and Latimer was proposed.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY, THE UPJOHN COMPANY]

BETA-ERGOSTENOL

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It was first shown by Mauthner¹ that it is possible to isomerize certain members of the sterol group by saturating chloroformic solutions with hydrochloric acid gas. Mauthner thus converted cholestene to pseudo-cholestene. He also showed that it was probable that cholesterol itself could be isomerized but it remained for Windaus² actually to separate and describe allo-cholesterol.

The isomerization of ergosterol by this process was first carried out by Reindel, Walter and Rauch,³ who also studied this reaction in the case of α -ergostenol. They state that, working with α -ergostenol prepared from

¹ Mauthner, *Monatsh.*, **28**, 1113 (1907).

² Windaus, *Ann.*, **453**, 101 (1927).

³ Reindel, Walter and Rauch, *ibid.*, **452**, 34 (1927); Reindel and Walter, *ibid.*, **460**, 212 (1928).