

A STUDY OF THE THERMAL STABILITY OF BENZYL
2,4-DIMETHYL-6-PROPENYLPHENYL ETHER

by

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Typed by Mary Adams

To My Mother
in memory of
My Father

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INTRODUCTION

The mechanism by which the migrating allyl group in the Claisen rearrangement becomes attached to the ortho or para position has now been elucidated (11,16,17,21,23, 28,29,30,32,33,34). However, the mechanism of the Claisen rearrangement to an o-propenyl side chain has not been satisfactorily shown or proved.

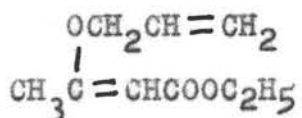
Walter M. Lauer and Donald W. Wujciak (22, p.5601-5606) have suggested two intramolecular mechanisms to explain the migration of the allyl group to an o-propenyl side chain. The first is analogous to the mechanism proposed by Hurd and Pollack (16, p.550-596) to explain the para Claisen rearrangement. This would involve the successive formation of two six-membered ring activated complexes, with the final migration of a proton to the oxygen, thus regenerating the benzenoid structure (part A, figure 5). The second mechanism posed, involves the formation of only one six-membered activated ring complex, bond formation being directly between the alpha carbon of the allyl group and the beta carbon of the o-propenyl side chain (part B, figure 5).

In an attempt to distinguish between the two proposed

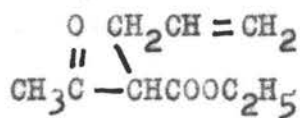
mechanisms, we synthesized and attempted to rearrange the benzyl ether of 2,4-dimethyl-6-propenylphenol under typical Claisen rearrangement conditions. If it is assumed that the mechanism operating is analogous to the para rearrangement and that the rearrangement is intramolecular, there should be no benzyl substituent observed on the beta carbon of the o-propenyl side chain. If, however, the second mechanism is possible then 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene-1 would be one of the observed rearrangement products. By independent synthesis the expected product was prepared and compared with the rearrangement product.

HISTORICAL

In 1912, Claisen originally reported (7, p.3157-3166) the rearrangement of ethyl O-allylacetoacetate to ethyl alpha-allylacetoacetate, which is known today as the Claisen rearrangement.



I



II

The reaction has since been shown to be general for ethers with the structure $\overset{\text{a}}{\text{C}}=\overset{\text{b}}{\text{C}}-\text{O}-\text{C}=\text{C}$ in which the double bond b may be aliphatic or aromatic but bond a must be aliphatic (36, p.495-546). The majority of the compounds reported to undergo the Claisen rearrangement are of the allyl aryl type. Benzyl phenyl ethers, although they possess the necessary bond arrangements, do not rearrange under the conditions for the rearrangement of allyl phenyl type ethers (8, p.210-245; 27, p. 646-658). However, they do rearrange under more drastic conditions to give a mixture of ortho and para isomers (4, p.1368-1377), while the allyl ethers give predominately the ortho isomer if an ortho position is open.

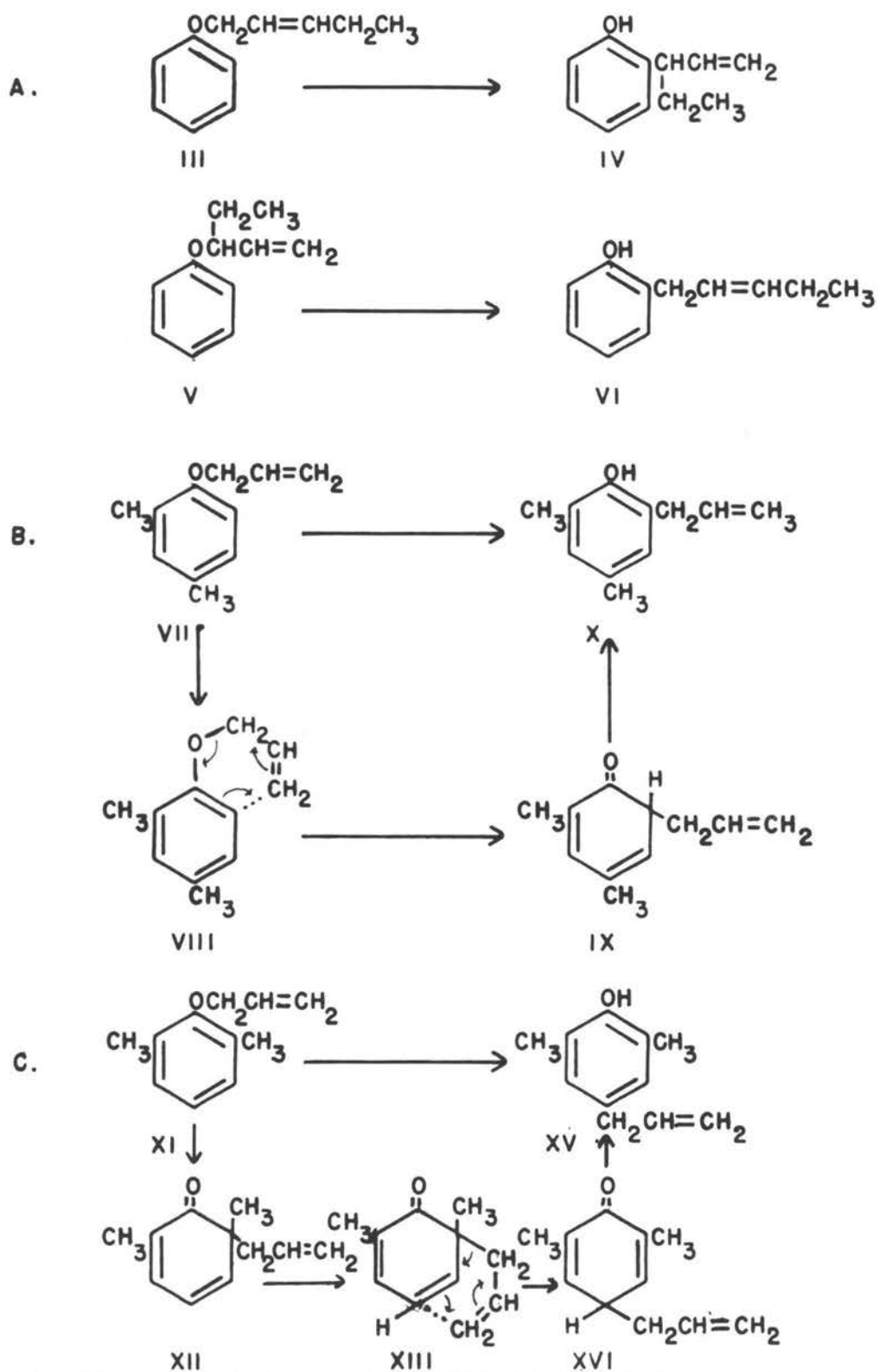
In the rearrangement the mechanism by which the allyl group migrates has attracted special interest. Three types of rearrangement products have been observed: In the first type, the allyl group becomes attached to the ortho

position with inversion. This has been clearly shown (21, p.1388) by the use of ethers containing alpha and gamma substituents on the allyl group (part A, figure 1).

The mechanism proposed by Hurd and Pollack (16, p.550-596), generally regarded as providing the best explanation of the phenomenon, is the formation of a six membered ring activated complex, VIII, in which the breaking of the carbon oxygen bond and the attachment of the gamma carbon to the ortho position occur simultaneously. This is followed by a proton shift to the oxygen thus regenerating the benzenoid structure, X, (part B, figure 1).

The second type, the para rearrangement product, is observed when both ortho positions are blocked. As a single cyclic intermediate is not possible, Hurd and Pollack suggested that the rearrangement might go by two steps (part C, figure 1): first a shift of the allyl group to the ortho position with inversion, XII, as described for the ortho rearrangement. A second cyclic intermediate can be formed, XIII, to shift the allyl group to the para position again with inversion, XIV. Finally, the migration of a proton to the oxygen regenerates the phenol, XV. The shift of the allyl group from the ortho position, XII, to the para position, XV, resembles the route traversed by an allyl group in the Cope rearrangement (12, p.441-444) in that the bond arrangement is the

FIGURE 1.



same and it, too, migrates from one carbon atom to another.

The effect of the double inversion is that of no inversion; the original allyl group structure is retained. Mumm and Moller reported (26, p.2214-2227) this to be true for gamma substituted allyl phenyl ethers but Mumm and Diederichsen (24, p.1523-1525) and Mumm, Hornhardt and Diederichsen (25, p. 100-111) reported that the gamma-ethyl allyl ether gave the same product as the alpha-ethyl allyl ether (part A, figure 2). It appeared then that an alpha substituent led to an inverted product while a gamma substituent did not. In an attempt to explain these results, which were inconsistent with all those previously reported, the authors suggested cleavage of the molecule in ions or radicals.

It appeared then, that no fixed rule could be established for the para-Claisen rearrangement as could be done in the case of the ortho rearrangement. However, the obstacle to the acceptance of the two-step Hurd and Pollack mechanism was removed in 1952, when Rhoads, Raulins and Reynolds (29, p.2531-2532) repeated the work of Mumm, Hornhardt and Diederichsen and found that both the alpha and gamma substituted allyl ethers did rearrange without inversion (part B, figure 2).

Marvell, Logan, Friedman and Ledeen (23, p.1922-1926) have also shown that the rearrangement to the para position

yields a product with no inversion of the allyl group by the rearrangement of the alpha methyl allyl and crotyl ethers of 2,6-dimethyl phenol (part C, figure 2).

Ryan and O'Connor (30, p.5866-5869) reported more evidence of non-inversion with the synthesis and rearrangement of gamma-C¹⁴ allyl-2,4-dimethyl phenyl ether.

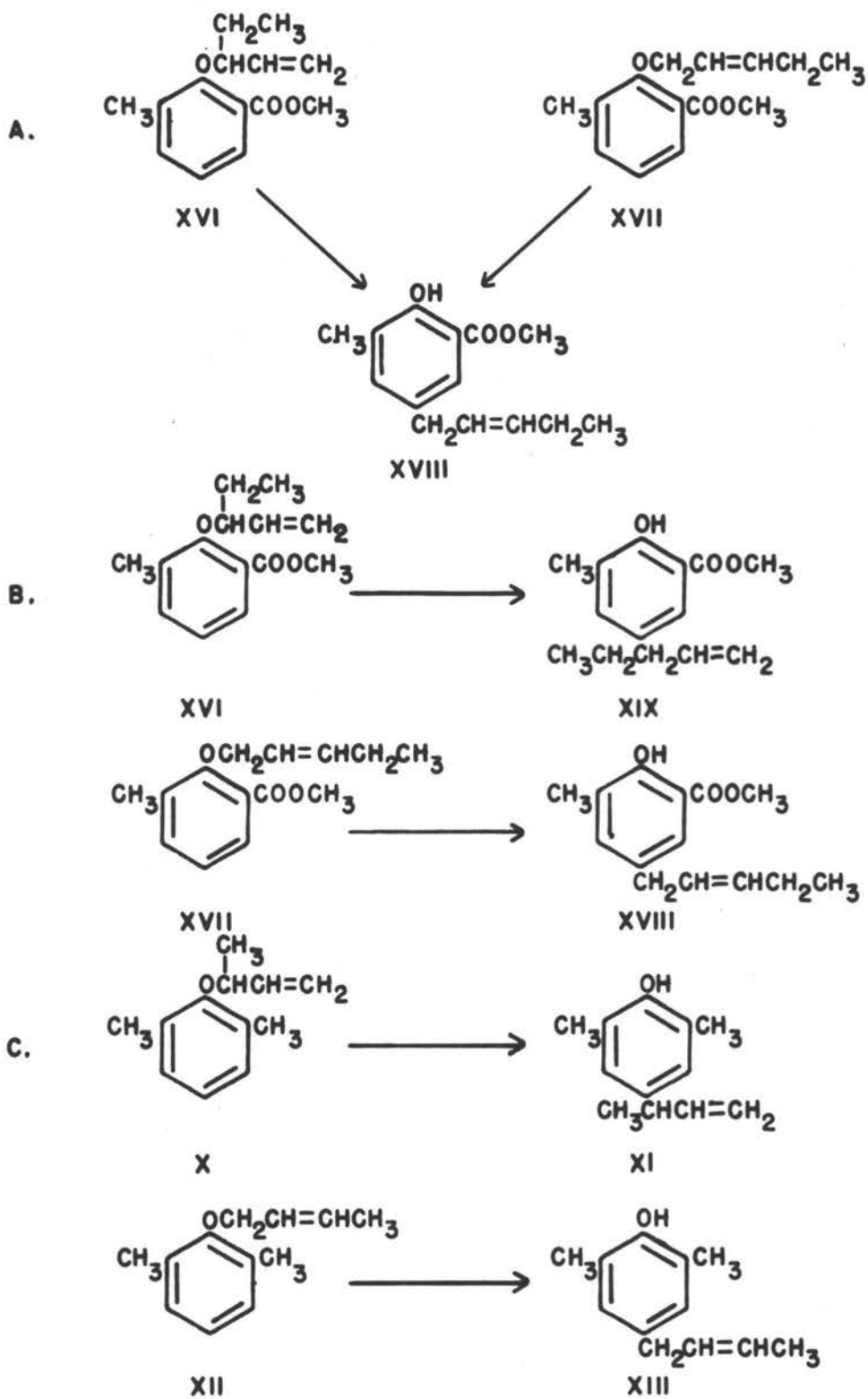
Analysis of the rearrangement product showed the activity to be solely in the gamma carbon of the allyl group (part A, figure 3).

Recently, Schmid and Schmid published three articles (32, p.1879-1890; 33, p.489-500; 34, p.687-690) all of which are in agreement with the Hurd and Pollack mechanism. Both Ryan and O'Connor, and Schmid and Schmid verify that there is inversion to the ortho position, no inversion to the para position, and that the allyl group is never free at any time in the thermal rearrangement as a free ion or radical. If the allyl group did exist as a free radical or ion, the radioactivity would be randomized between



the alpha and gamma carbons of the allyl group. Both groups of authors found, to the limit of experimental error, that all of the radioactivity was in the predicted position.

FIGURE 2.

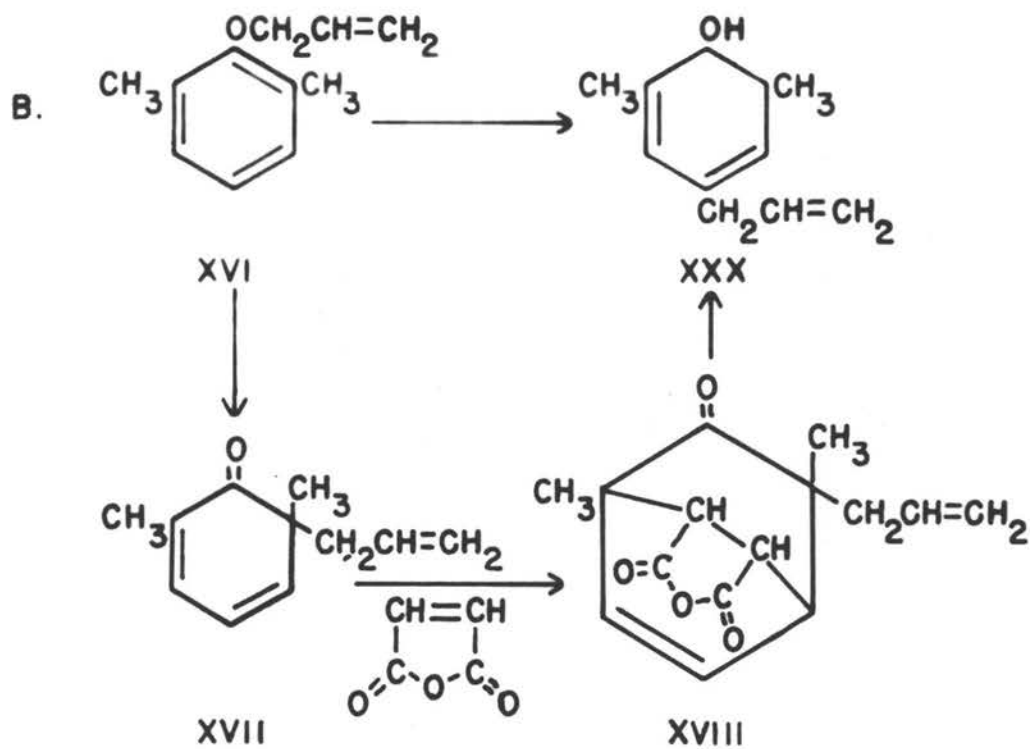
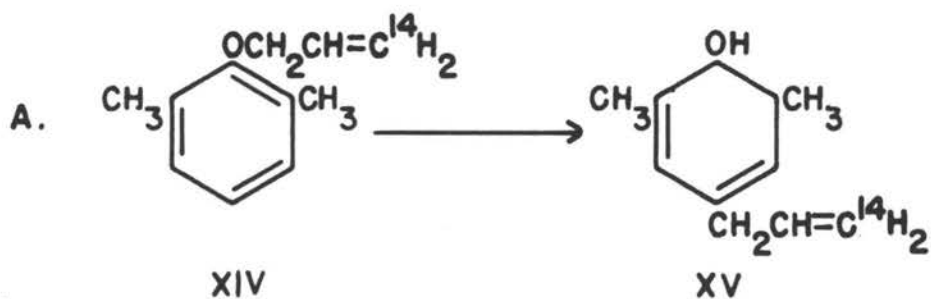


Evidence of the primary ortho migration was shown by Conroy and Firestone (11, p.177-203). On the assumption that the intermediate dienone should undergo a Diels-Alder type condensation, they carried out a rearrangement in the presence of maleic anhydride (part B, figure 3). They were able to isolate a 6.3 percent yield of a compound, XVIII, whose analysis corresponded to one of the isomeric Diels-Alder adducts of the dienone intermediate, XVII. As further evidence that XVIII is the true intermediate in the para-Claisen rearrangement of XVII, the adduct XVIII was pyrolyzed at 200° and XIX obtained as the product, XIX being the expected product from the rearrangement of XVI.

The intramolecular nature of the reaction was further verified by the work of Hurd and Schmerling (17, p.107-109) and by Fomenko, Melklukhin and Sadovneko (14, p.91-92). The migration of the H-atom to the oxygen as a proton was shown by the experiments of Kestiakowsky and Tichenor (18, p.2303-2304) using deuterium labeled compounds.

When Karasch and co-workers (19, p.309) subjected phenyl allyl ethers to ultraviolet radiation at room temperature, they observed equal parts of phenol and p-allyl phenol and postulated that an allyl free radical was an intermediate. Using gamma-C¹⁴ labeled allyl phenyl ether Schmid and Schmid found, as predicted, the radioactivity was distributed between the alpha and gamma carbon atoms

FIGURE 3.



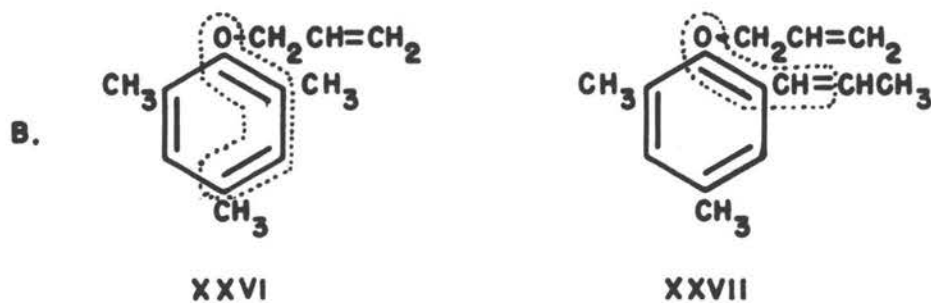
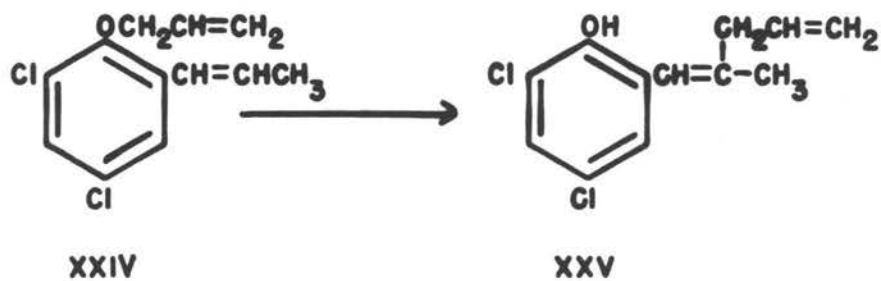
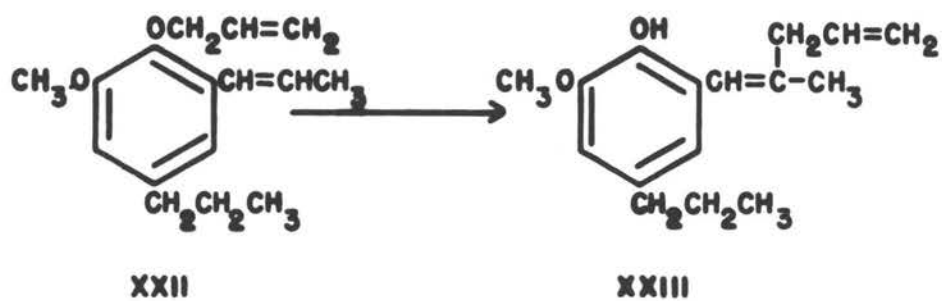
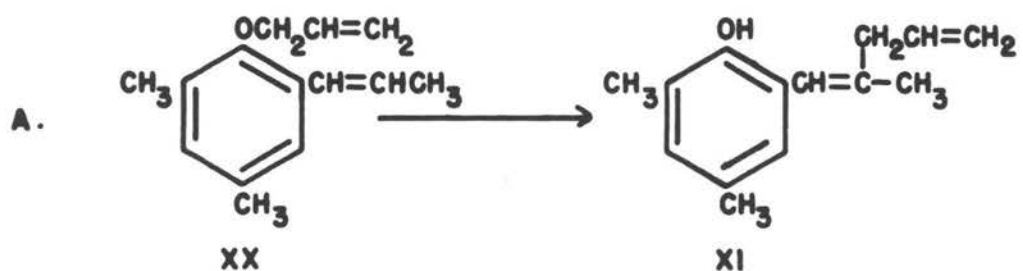
in the rearrangement catalyzed by ultraviolet radiation. Thus the thermal rearrangement is an intramolecular reaction and the ultraviolet radiation rearrangement is free radical in nature.

The third type product was reported in 1929, by Claisen and Teitze (9, p.81-101) after they had observed the rearrangement of the allyl ethers of 2,4-dimethyl-6-propenylphenol, 2-methoxy-4-propyl-6-propenyl phenol and 2,4-dichloro-6-propenyl phenol to the corresponding 2,4-disubstituted-6-(2-methyl-1,4-pentadienyl)phenol (part A, figure 4).

These reactions differ from all others previously reported for allyl phenyl ethers in that here the allyl group becomes attached to the beta carbon of the propenyl side chain, whereas it had usually been found attached directly to the benzene ring.

An interesting similarity of this rearrangement to that of the para-Claisen rearrangement was posed by the authors. If one compares the routes traversed by a migrating allyl group in the two rearrangements, the same general configuration is found. The main difference in the two paths is shown by the two encircled portions of figure 4, part B. In structure XXVI both of the double bonds in the butadiene type configuration are part of the benzene ring while in structure XXVII one of the bonds is aliphatic.

FIGURE 4.



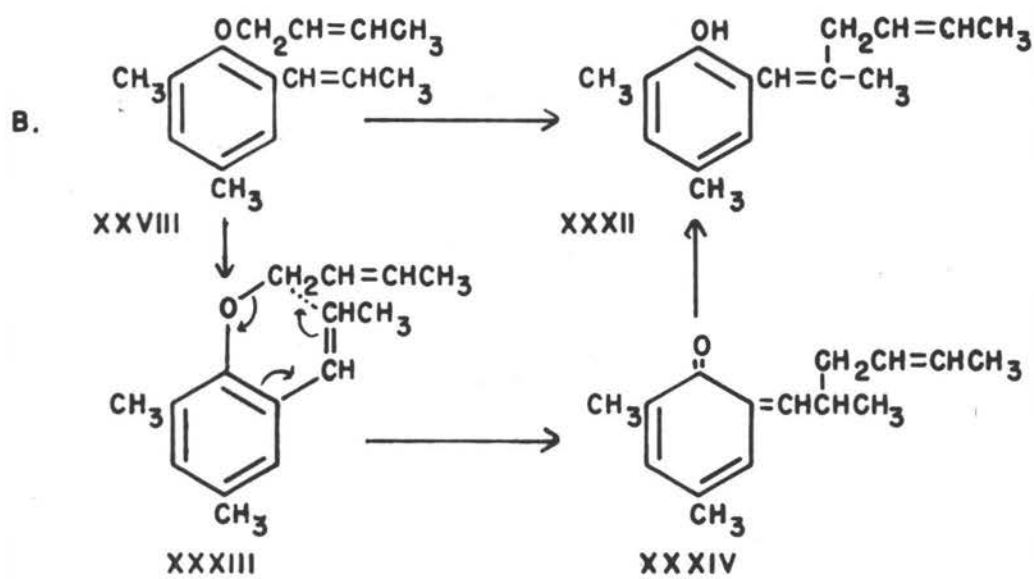
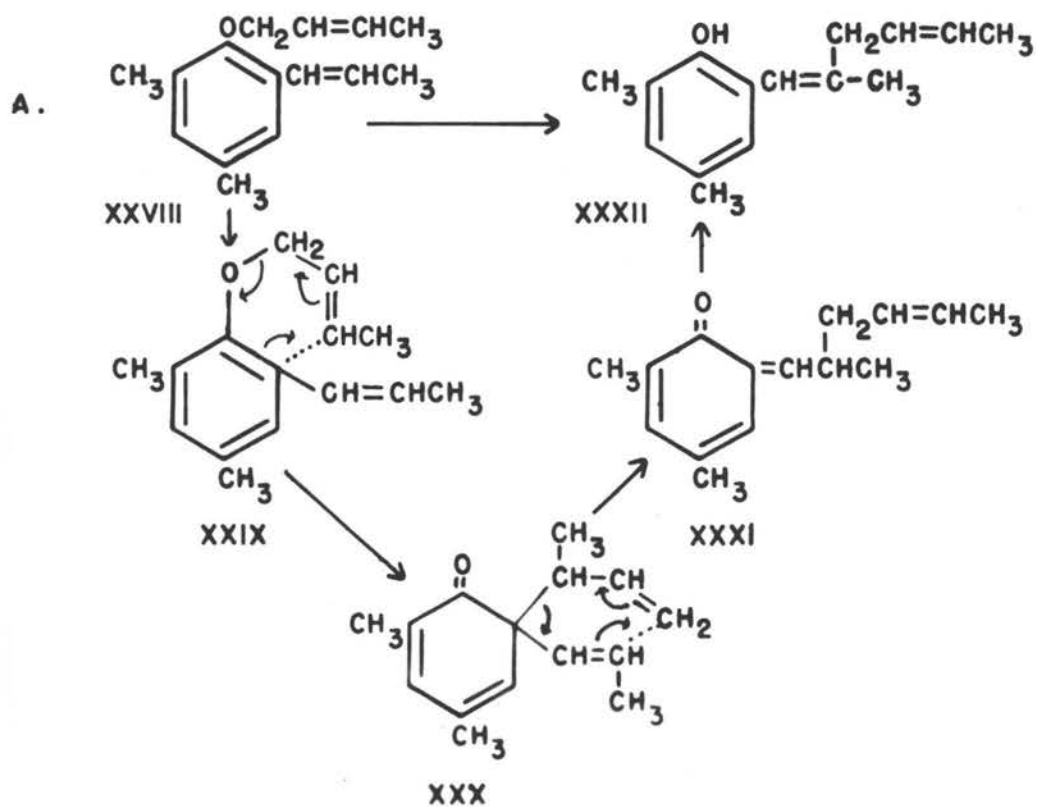
Nevertheless both structures are capable of undergoing the same two-step mechanism proposed for the para rearrangement.

In order to characterize the products observed by Claisen and Tietze, Lauer and Wujciak (22, p.5601-5606) repeated the rearrangement of 2,4-dimethyl-6-propenyl-phenyl allyl ether as well as rearranging the crotyl ether of 2,4-dimethyl-6-propenyl phenol XXV. They found that the allyl groups did migrate to the beta carbon of the propenyl side chain without inversion.

In an effort to explain this phenomenon, the authors proposed a two-step mechanism. The first, outlined in the introduction and shown in part A. of figure 5, closely resembles the mechanism already shown for the para rearrangement. However, they stated that their work does not eliminate the possibility of a second path involving only one six-membered ring transition state (part B, figure 5). They add that this mechanism is an attractive possibility.

Supporting evidence for the non-inversion of the migrating allyl group has been reported by Schmid, Fahrmi and Schmid (31, p. 708-721). After rearranging the gamma-C¹⁴ allyl ether of 2,4-dimethyl-6-propenyl phenol by the methods described by Claisen, they found that 84 percent of the radioactivity was present in the epsilon carbon of the 2-methyl-1,4-pentadienyl side chain. The

FIGURE 5.



remainder of the activity, 16 percent, was found to be at gamma position of this side chain but the authors were unable to give a satisfactory explanation for the 16 percent activity.

After observing that upon heating, the allyl ethers of 2,4-dimethyl-6-allyl phenol and 2,4-dimethyl-6-propyl phenol undergo thermolysis to propene, diallyl, 2-propyl and 2-allyl phenol, respectively, as well as higher boiling products, the authors concluded that the reaction did not proceed by a free radical mechanism. They then suggested two possible paths for the migrating allyl group. One consisted of the formation of three six-membered-activated rings by the reverse Claisen rearrangement and the second involved the formation of an eight-membered ring. However, no definite explanation was given and they admitted that their work did not rule out the alternate mechanism proposed by Lauer and Wujciak.

DISCUSSION

The object of this work was to show whether the second mechanism (part B, figure 5) proposed by Lauer and Wujciak is a possible route in the Claisen rearrangement to an o-propenyl side chain. In order to distinguish between the two proposed mechanisms, a compound had to be selected that could not undergo the two-step (double cyclic) mechanism (part A, figure 5) yet possessed the requisite bond structure.

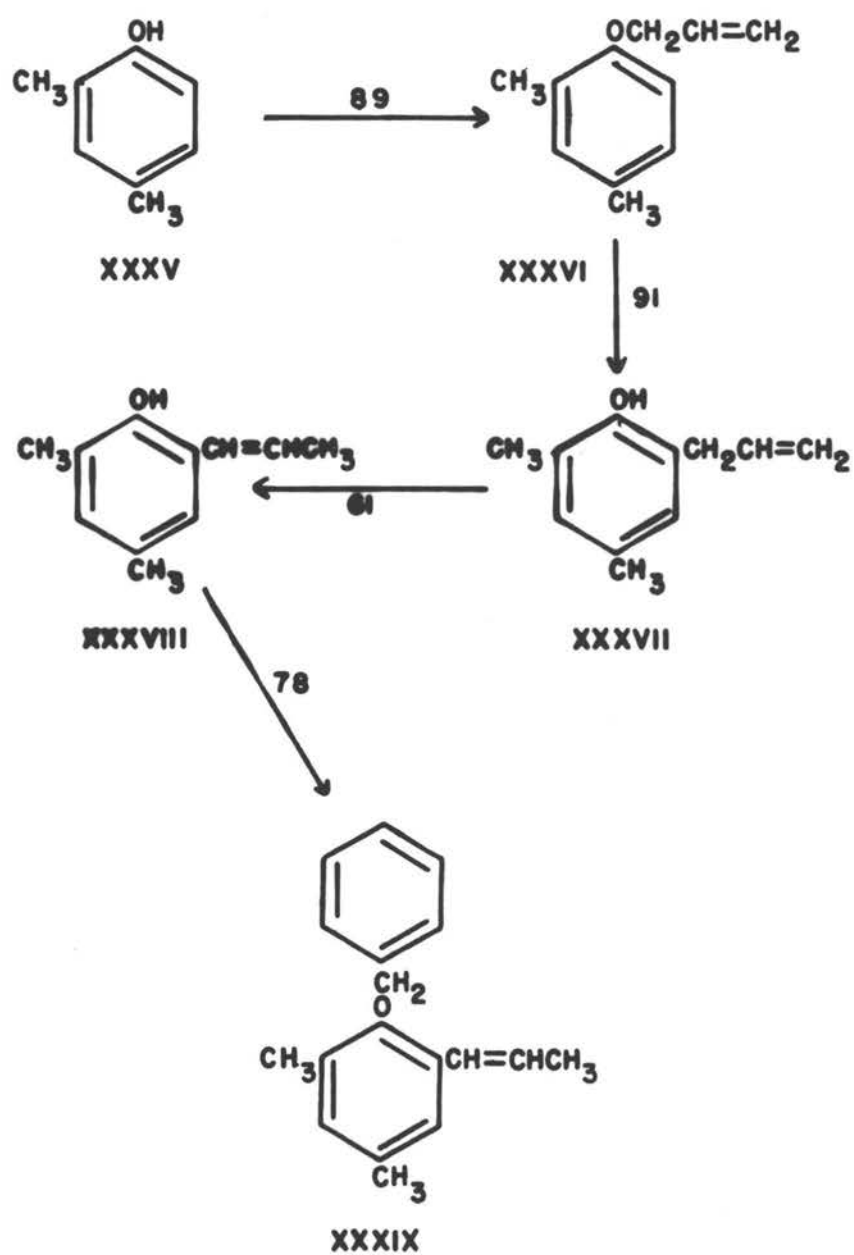
It has been known for some time that benzyl-phenyl ethers do not rearrange under the conditions of the Claisen type rearrangement (8, p.210-245; 27, p. 646-658) even though they possess the requisite groups. The conditions for their rearrangement are much more drastic, 250-300°C, (4, p.1368-1377) and a mixture of ortho and para substituted products is usually obtained (15, p.830) because of intermolecular reactions. If the benzyl group is considered to be nothing more than an alpha-gamma substituted allyl group, the benzyl ether might be expected to undergo rearrangement to an o-propenyl side chain under Claisen conditions. Because of steric hindrance a benzyl ether of 2,4-dimethyl-6-propenylphenol could not undergo the two-step mechanism. If then, the rearrangement is carried out under conditions of the Claisen

rearrangement, only the second mechanism (part B, figure 5) could account for a benzyl substituent on the *o*-propenyl side chain.

As is shown in figure 8, the *o*-propenyl side chain could form a six-membered ring intermediate with the methylene group of the benzyl ether similar to that already shown on page 14. If this is the case, 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene (XLIX) would be one of the rearrangement products.

Thus, the benzyl ether of 2,4-dimethyl-6-propenylphenol (XXXIX) was synthesized by a series of reactions (see figure 6 for schematic equations) similar to those outlined by Claisen and Teitze (9, p.81-101). Allyl bromide was reacted with 2,4-dimethylphenol in an anhydrous mixture of acetone and potassium carbonate and the resulting 2,4-dimethylphenylallyl ether (XXXVI) recovered by vacuum distillation. The purified allyl ether was rearranged by heating at 200°C for an hour under an atmosphere of nitrogen and again the product, 2,4-dimethyl-6-allylphenol (XXXVII) was obtained by vacuum distillation. Treatment of this phenol with 50 percent methanolic potassium hydroxide at 130°C for one hour gave the isomerized product, 2,4-dimethyl-6-propenylphenol (XXXVIII) whose phenylurethan checked with that reported in the literature (22, p.5601-5606). The reactions went smoothly

FIGURE 6.



and no difficulties were encountered.

The benzyl ether of 2,4-dimethyl-6-propenylphenol was obtained by a Williamson (28, p.5060-5062) type ether synthesis by first forming the sodium salt of the 2,4-dimethyl-6-propenylphenol using an equivalent amount of sodium methoxide and then treating the sodium phenoxide with benzyl chloride. After purification, infrared analysis showed only a trace of unreacted phenol remained. A negative phosphomolybdic acid test again showed the absence of unreacted phenol. Attempts to distill the ether were unsuccessful and lead to decomposition of the product if heated above 125°C. As it was necessary to obtain the product without the contamination of thermal decomposition products, no further purification by distillation was attempted.

Two general sets of rearrangement conditions appear in the literature. The first consists of heating the allyl type ether at 175-200°C under reflux conditions. With higher boiling compounds this necessitates reducing the pressure until a desirable reflux temperature is obtained. The first attempt to rearrange the benzyl ether (XXXIX) was carried out under such conditions. There was no detectable increase of phenolic material in the reaction mixture as shown by infrared analysis. However, 1.4 ml. (approx. 6%) of liquid was found frozen in the cold trap

of the apparatus. From physical constants and infrared analysis, it was identified as isobutyl benzene b.p. 167°C , n_{D}^{20} 1.4867 (reported b.p. 172°C ; n_{D}^{20} 1.4865). Because of the absence of phenols, no other attempts were made to examine the reaction mixture.

In the second method of rearrangement, compound (XXXIX) was heated at 200°C in a nitrogen atmosphere. Any volatile material that could be swept from the reaction flask was collected in a cold trap and again a liquid was obtained. In this instance, a single compound was not obtained but rather a mixture of compounds, for upon distillation, three fractions were obtained. However, the second fraction was the same as the compound collected in the first rearrangement attempt, b.p. 167°C ; n_{D}^{24} 1.5052. After separation of the remaining reaction material into a phenolic fraction and a neutral fraction by extracting a petroleum ether solution of the reaction mixture with Claisen's alkali, attempts to isolate either a solid compound or to obtain a solid derivative were unsuccessful. Paper chromatography (butanol, acetic acid and water solvent system) and chromatography over silica gel (chloroform as solvent) were also unsuccessful in the quest for a means of separation.

In order to have some knowledge of the physical characteristics of the predicted rearrangement product,

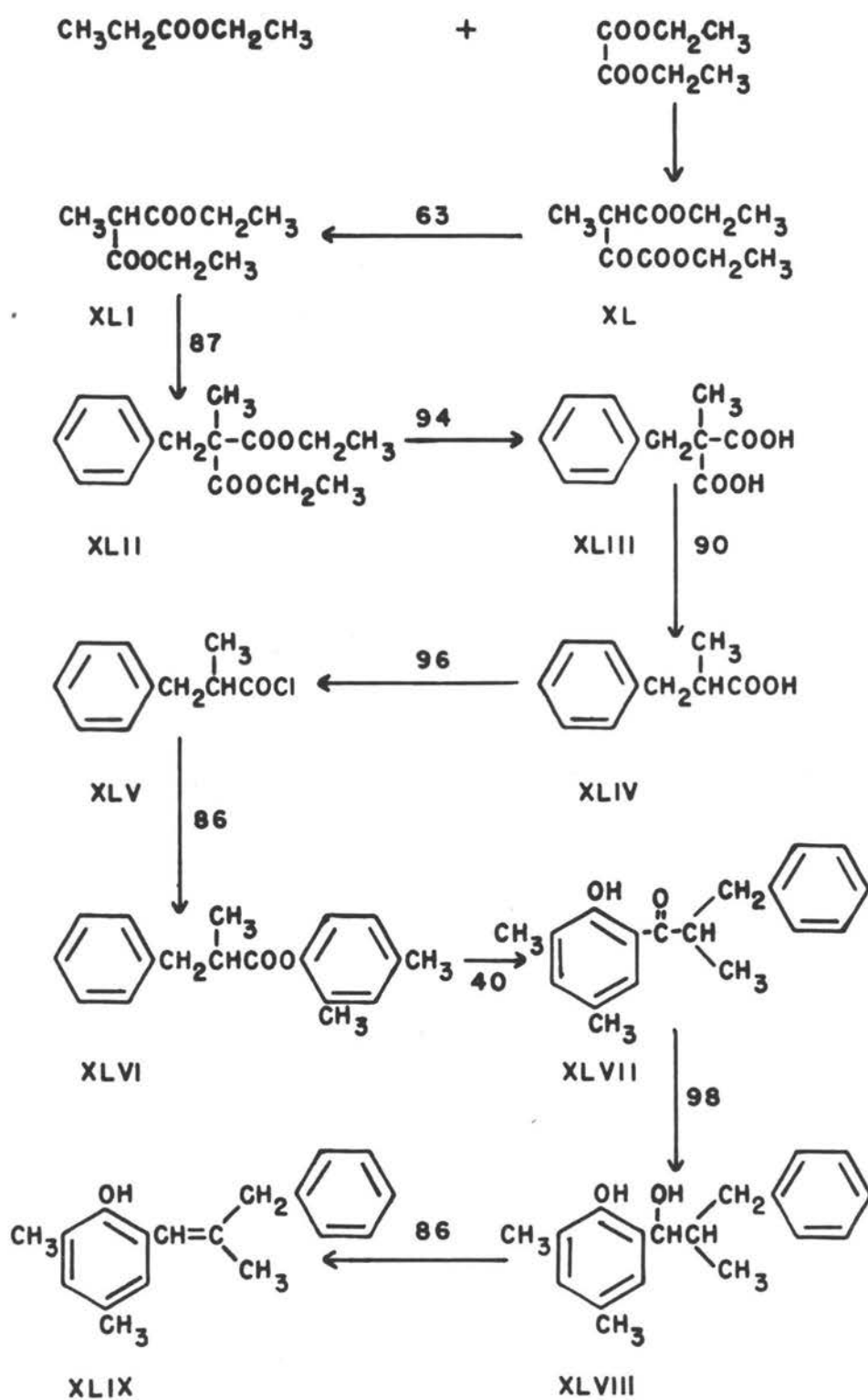
the following independent synthesis was undertaken (see figure 7 for schematic equations).

Ethyl propionate was condensed with ethyl oxalate in the presence of sodium ethoxide to give ethyl ethoxylpropionate (XL). This compound is superior for the preparation of diethyl methylmalonate for the malonic ester can be easily separated from the reaction medium. This is not true when diethyl malonate is the starting material for the substituted esters' boiling points lie too close to one another to afford good separations (10, p.177-203). The impure ethyl ethoxylpropionate was heated at 130-150°C, causing it to lose carbon monoxide, and the resulting diethyl methylmalonate (XLI) obtained pure by distillation. It, in turn, was converted to diethyl benzylmethylmalonate (XLII) by a typical malonic ester synthesis in good yield. The purified diethyl benzylmethylmalonate was hydrolyzed to the corresponding benzylmethylmalonic acid and then decarboxylated giving pure benzylmethylacetic acid (XLIV).

The physical constants, boiling point or melting point and density check closely with those reported in the literature. The molar refractivities were determined from experimental data and found to be in close agreement with the calculated values.

Benzylmethylacetyl chloride (XLV) was obtained from

FIGURE 7.



the treatment of benzylmethylacetic acid with an excess of thionyl chloride. The product isolated by vacuum distillation was kept in a sealed all-glass container, for the acid chloride was decomposed by moist air, attacked rubber and possessed a most unpleasant and sickening odor in low concentrations.

A search of the literature showed that the Fries rearrangement might be a convenient way to obtain benzylmethyl-3,5-dimethyl-2-hydroxyacetophenone (XLVII) with a certainty of structure. Ballio and Almerante (3, p.464c) reported a 42 percent yield of 3,5-dimethyl-2-hydroxyacetophenone and only 0.4 percent yield of 2,4-dimethyl-5-hydroxyacetophenone from the Fries rearrangement of 2,4-dimethylphenyl acetate. Their work shows the absence of displacement reactions or meta substitution.

On this basis, the 2,4-dimethylphenyl ester of benzylmethylacetic acid (XLVI) was prepared by reacting benzylmethylacetyl chloride with 2,4-dimethylphenol in a slurry of calcium carbonate and dry benzene. After isolation of the ester by distillation, several sets of reaction conditions were tried for the conversion of this compound to the corresponding ketone via the Fries rearrangement (5, p.342-369). It seemed wise to keep the conditions as mild as possible to prevent troublesome side reactions. As it was, the best results were obtained when mild

temperature conditions were employed and a two to four mole excess of aluminum chloride was used. It seemed that the duration of contact made little difference as a 34 percent yield was obtained after mixing the reactants and allowing them to stand at room temperature for four hours before heating and a 38 percent yield was obtained when the standing period was increased sixfold. Even increasing the heating period did not change the yield significantly. However, increasing the temperature to 140°C for 45 minutes, as mentioned in a procedure of Dutton *et al* (13, p.837-841), gave no yield at all, only a dark oil boiling over a wide range from which no pure fraction was obtained. At first, distillation was used as a means of purification, but it was found that if the oil resulting from the decomposition of the aluminum chloride complex was allowed to stand for about 24 hours, the solid ketone separated. Recrystallization from 90 percent ethanol gave well-formed crystals of the benzylmethyl-3,5-dimethyl-2-hydroxyacetophenone (XLVII).

From the ketone (XLVII) the desired product, 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene, might have been obtained by a Meerwein-Ponndorf-Verley reduction at elevated temperatures. Wilds (38, p.178-223) mentioned that in some cases, secondary and tertiary alcohols dehydrate to olefins when higher boiling solvents, toluene and xylene, were

employed in this reduction. Thus, several attempts were made to reduce the carbonyl group by this method, but none proved successful and only low yields of the alcohol were obtained. Finally, lithium aluminum hydride was used as the reducing agent, giving good yields of the two isomeric alcohols of 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropanol. The isomers were separated by fractional crystallization and tested for optical activity; however, no activity was found. Both isomers were then easily dehydrated by heating with potassium bisulfate at temperatures slightly above their melting point. The expected rearrangement product, 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene, was obtained by distillation of the resulting oil.

The physical constants and analytical data were in agreement with the reported and calculated values. Attempts to prepare derivatives of XLVI, XLVII, XLVIII and XLIX by methods outlined by Schriner and Fuson (35) were unsuccessful. It was concluded then that the functional groups were so hindered as to not undergo reaction. As examples: none of the compounds yielded phenylurethanes when treated with phenylisocyanate. It was impossible to prepare the methyl ethers either by Williamson ether synthesis, treatment with diazomethane, or dimethylsulfate. Other less common derivatives were attempted, but in each case only the starting material could be recovered.

After finding that the expected product 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene (XLIX) was an oil, b.p. 124-125°C (0.15 mm); n_D^{21} 1.5795, the phenolic fraction of the second rearrangement attempt was distilled in vacuo giving a viscous yellow oil, b.p. 132-134°C (0.15 mm), n_D^{21} 1.5578. Comparative tests showed this material to be quite different from the expected product. The refractive index differed by 0.0217 units; the boiling point was eight degrees higher at the same pressure. Carbon-hydrogen analysis showed a 3 percent increase in hydrogen with a 2.5 percent decrease in carbon. Another significant difference was found when testing the two compounds with bromine in carbon tetrachloride. As would be expected, compound XLIX gave an oily dibromide addition product which decomposed upon heating, but the unknown phenolic compound instead of adding bromine underwent a substitution reaction as evidenced by the liberation of hydrogen bromide gas. An attempt to purify this bromo-substituted phenol by either distillation or crystallization failed.

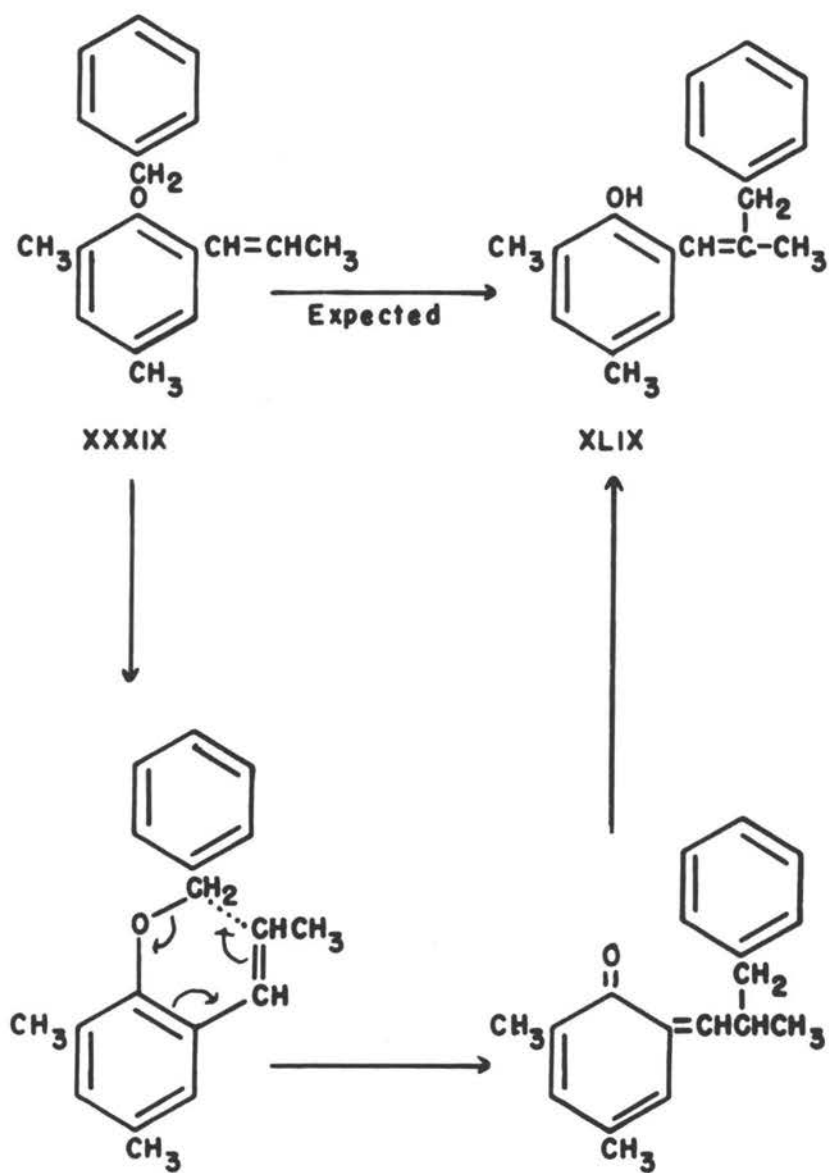
In trying to separate the neutral polymer by distillation techniques, nothing was obtained at temperatures up to 170°C (0.15 mm). When higher temperatures were used, decomposition occurred.

From the comparison of the expected rearrangement

product 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene with the isolated rearrangement material, it appears that the benzyl ether of 2,4-dimethyl-6-propenyl phenol is thermally unstable and decomposes to an unknown mixture of products most of which are high boiling liquids. This is in agreement with the work of Powell and Adams who reported the decomposition of benzyl-phenyl ethers upon heating. The presence of the isobutyl benzene as well as the structure of the phenolic material isolated from the rearrangement mixture remains unexplained on the basis of the present work.

It must be concluded that, in this case, the alternate mechanism proposed by Lauer and Wujciak does not operate as a path for this type "allyl" group to migrate to an o-propenyl side chain. This, then, leaves the two-step mechanism proposed by Lauer and Wujciak as the most acceptable explanation of the migration of an allyl group to an o-propenyl side chain.

FIGURE 8.



EXPERIMENTAL

Synthesis A.

General equations with yields obtained are given in figure 6.

2,4-Dimethyl-6-propenylphenol (XXXVIII)

The synthesis was patterned after that described by Claisen and Teitze (9, p.81-101). Allyl bromide was reacted with pure 2,4-dimethylphenol (XXXV) to yield the allyl ether of 2,4-dimethylphenol (XXXVI); b.p. 104-106°C (7 mm); n_D^{20} 1.5363. Heating of XXXVI at 200-210°C in an atmosphere of oxygen-free nitrogen gave the corresponding 2,4-dimethyl-6-allylphenol (XXXVII); b.p. 125-128°C (23 mm); n_D^{20} 1.5327. The 2,4-dimethyl-6-propenylphenol was obtained by isomerizing 2,4-dimethyl-6-allylphenol with 50 percent methanolic potassium hydroxide at 133°C for one hour. After neutralization of the caustic the white asbestos-like product separated with an overall yield for the three steps of 49 percent, m.p. 72-73°C (reported 73-74°C). A phenylurethane (m.p. 137-139°C) was prepared from this phenol.

Benzyl-(2,4-dimethyl-6-propenylphenyl) ether (XXXIX)

To a freshly prepared solution of sodium methoxide (7.1 g., 0.31 mole of sodium in 150 ml. of methyl alcohol) in absolute methanol was added 50 g. (0.31 mole) of 2,4-dimethylphenol. Thirty-nine grams (0.31 mole) of benzyl

chloride was added to the boiling solution of sodium phenoxide over a period of 20 minutes. The mixture was then heated under reflux for an additional three hours. The product was taken up in petroleum ether (b.p. 30-60°C), exhaustively extracted with Claisen's alkali until no more coloration of the alkali was observed and dried over anhydrous sodium sulfate. Distillation of the solvent at atmospheric pressure with the removal of traces of petroleum ether and benzyl chloride in vacuo at 100°C for two hours gave the benzyl ether of 2,4-dimethyl-6-propenylphenol, 70.5 g. (78%); n_D^{20} 1.5711; d_{23}^{25} 1.0395.

Anal: Calc. for $C_{18}H_{20}O$: C, 85.71; H, 7.93

Found: C, 84.03; H, 7.89

M_D : Calc. for $C_{18}H_{20}O$: 79.31

Found: 79.66

I.R. maxima at 700, 735, 790, 810, 865, 915, 975, 1025, 1085, 1110, 1150, 1220, 1275, 1305, 1385, 1470, 1490, 1510, 1600, 1660, 1765, 1900, 1975, 3000 cm^{-1} .

U.V. maxima at 2100, 2550, 2950 Å.

Synthesis B.

General equations with yields are shown in figure 7.

Benzylmethylacetic acid (XLIV)

Ethyl ethoxypropionate (XL) obtained from the condensation of ethyl propionate with ethyl oxalate in the presence of sodium ethoxide (6, p.272) was heated at 130-150°C yielding pure diethyl methylmalonate (XLI); b.p. 84-85°C (8 mm); n_D^{21} 1.4139; d_{23}^{21} 1.0230. This was then treated with benzyl chloride in the presence of sodium ethoxide under the usual conditions for malonic ester synthesis (6, p.278-280) giving diethyl benzylmethylmalonate (XLII); b.p. 137-138°C (3 mm); n_D^{21} 1.4859; d_{23}^{21} 1.0622. Hydrolysis of XLI was easily accomplished by heating it under reflux with a 50 percent excess of potassium hydroxide in twice its volume of 20 percent ethanol for ten hours. The resulting benzylmethylmalonic acid (XLIII) was decarboxylated (10, p.177-203) by heating at 180-200°C until no more gas was evolved. The overall yield of the benzylmethylacetic acid was 46 percent through the five steps. B.p. 150-152°C (8 mm); reported (20, p.1006) 160°C (12 mm); n_D^{21} 1.5142; d_4^{22} 1.0644; M_D : 46.54 calc.; 46.32 found. The physical constants of the intermediates check closely with those found in the literature.

Benzylmethylacetyl chloride (XLV).

Forty-four grams (0.27 mole) of benzylmethylacetic

acid (XLIV) and 64 g. (0.54 mole) of thionyl chloride were mixed, allowed to stand at 40°C for 14 hours and then heated under reflux for an additional two hours. The unreacted thionyl chloride was removed by distillation at atmospheric pressure and the product distilled in vacuo. Yield 47.2 g. (96%); b.p. 116-117°C (10 mm); n_D^{22} 1.5162; d_{23}^{26} 1.0908; M_D : 50.68 found; 49.88 calc. for $C_{10}H_{11}OCl$.

2,4-Dimethylphenyl benzylmethylacetate (XLVI)

2,4-Dimethylphenol, 85.5 g. (0.70 mole), was added to a slurry of 50 g. of calcium carbonate in one liter of dry benzene contained in a two liter three-necked flask equipped with a stirrer, dropping funnel and reflux condenser protected by a calcium chloride drying tube. After the dropwise addition of 118 g. (0.65 mole) of benzylmethylacetyl chloride (XLV), the mixture was heated under reflux for three hours. The condenser was turned down for distillation and 500 ml. of solvent were removed. Solid calcium carbonate and calcium chloride were removed by vacuum filtration and the remainder of the solvent removed; the last traces being removed under reduced pressure. Distillation of the residual pale yellow oil gave 148.5 g. (86%); b.p. 146-147°C (0.5 mm); n_D^{23} 1.5372; d_{23}^{26} 1.0437.

Anal: Calc. for $C_{18}H_{20}O_2$: C, 80.59; H, 7.46

Found: C, 80.65; H, 7.44

M_D : Calc. for $C_{18}H_{20}O_2$: 79.79

Found: 80.16

I.R. maxima at 700, 750, 785, 814, 875, 915, 950, 1020, 1065, 1125, 1150, 1205, 1260, 1290, 1380, 1465, 1510, 1620, 1760, 3000 cm^{-1} .

U.V. maxima at 2600, 2650, 2740 \AA .

Benzylmethyl 3,5-dimethyl-2-hydroxyacetophenone (XLVII)

Compound XLVI, above, (107 g., 0.4 mole) was mixed with an excess of aluminum chloride (160 g., 1.21 moles) in a 500 ml. three-necked round bottom flask equipped with a stirrer and protected by a calcium chloride drying tube. The mixture was allowed to stand for 20 hours at room temperature and then heated with stirring at 100°C for two hours on a steam cone. The aluminum chloride complex was hydrolyzed with cold concentrated hydrochloric acid and allowed to stand overnight. The solid ketone was obtained by filtration and two crystallizations from 90 percent ethanol gave pale yellow needles of benzylmethyl-3,5-dimethyl-2-hydroxyacetophenone, 43 g. (40%), m.p. $67-67.5^\circ\text{C}$.

Anal: Calc. for $C_{18}H_{20}O_2$: C, 80.59; H, 7.46

Found: C, 80.37; H, 7.37

I.R. maxima at 700, 720, 745, 802, 862, 910, 985, 1070, 1110, 1185, 1232, 1275, 1292, 1315, 1368, 1387, 1450, 1480, 1510, 1620, 1640, 2950 cm^{-1} .

U.V. maxima at 2600, 3500 Å.

1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropanol (XLVIII)

In a 500 ml. three-necked round bottom flask equipped with a stirrer, dropping funnel and reflux condenser protected by a calcium chloride drying tube were placed 0.9 g. (0.024 mole) of lithium aluminum hydride and 200 ml. of dry ether. After the dropwise addition of 11.0 g. (0.041 mole) of the ketone XLVII dissolved in 100 ml. of dry ether, the excess lithium aluminum hydride was destroyed by the careful addition of a few milliliters of water. The mixture was poured into 500 ml. of iced 10 percent sulfuric acid and extracted with an additional two-100 ml. portions of ether. The ether extract was washed with dilute ammonium hydroxide, then with water until neutral and finally dried over anhydrous sodium sulfate. Evaporation of the ether solution under a stream of warm air gave 10.8 g. (98%), m.p. 105-154°C of the two isomers of 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropanol (XLVIII). Crystallization from a 50-50 mixture of benzene and hexane separated the two isomers. Further purification of the higher melting isomer was accomplished by chromatography over silica gel (chloroform was the solvent) giving a pure product m.p. 157-158°C. The lower melting isomer was obtained by repeated crystallizations from benzene (m.p. 104-106°C). Yields of the individual isomers after the

purification were 4.7 g. (43%) of the higher melting isomer and 3.1 g. (28%) of the lower melting isomer.

Anal: Calc. for $C_{18}H_{22}O_2$: C, 80.00; H, 8.15

Found: C, 80.05; H, 8.21

I.R. maxima at 700, 720, 740, 755, 775, 850, 860, 905, 960, 1005, 1035, 1085, 1115, 1160, 1230, 1245, 1275, 1350, 1387, 1470, 1615, 2950, 3335, 3480 cm^{-1} .

U.V. maxima at 2850 Å.

1-(3,5-Dimethyl-2-hydroxyphenyl)-2-benzylpropene (XLIX)

A. A mixture of 1.2 g. (0.0044 mole) of the 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropanol (m.p. 157-158°C) and 1.5 g. (0.019 mole) of freshly fused potassium bisulfate was heated at 160-170°C for 30 minutes. After cooling the reaction mixture was extracted with small portions of ether, the extracts combined, and the solvent removed by distillation. Vacuum distillation of the residual oil yielded the 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene, 0.96 g. (86%), b.p. 124-125°C (0.15 mm), n_D^{21} 1.5795, d_{23}^{25} 1.0267.

Anal: Calc. for $C_{18}H_{20}O$: C, 85.71; H, 7.93

Found: C, 86.09; H, 8.12

M_D : Calc. for $C_{18}H_{20}O$: 79.18

Found: 80.21

B. A 2.5 g. (0.0093 mole) sample of the 104-106°C m.p. alcohol was mixed with 3 g. (0.038 mole) of potassium

bisulfate and heated at 140-150°C for 30 minutes. The solid residue was extracted with several portions of ether, the solvent removed on a steam cone and the residual light yellow oil distilled in vacuo. A yield, 2.15 g. (93%), of 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene (XLIX), b.p. 124-125°C (0.15 mm), n_D^{21} 1.5795, d_{23}^{25} 1.0267, was obtained.

Anal: Calc. for $C_{18}H_{20}O$: C, 85.71; H, 7.93

Found: C, 85.31; H, 7.71

Rearrangement and Thermal Stability.

Rearrangement of the Benzyl Ether of 2,4-Dimethyl-6-propenylphenol (XXXIX)

Attempt I: Twenty grams of the benzyl ether were placed in a 50 ml. round bottom flask equipped with a thermometer well. The flask was connected to a reflux condenser which was in turn attached to the cold trap (dry ice-carbon tetrachloride-chloroform) of a high vacuum system. With the pressure reduced to 0.01 mm., the temperature of the ether was raised until refluxing began, 135°C. After three hours the temperature had been raised to 146°C (0.007 mm) and the liquid appeared to be more viscous and dark red-brown in color. Heating was continued for an additional five hours with no more degradation products appearing in the trap. Samples were taken each hour from the reaction vessel and analyzed by infrared in the hydroxyl region, 3400-3700 cm^{-1} , with no detectable increase in the absorption band being observed.

At the end of the three hours 1.4 ml. of liquid, b.p. 167°C, n_D^{18} 1.4980, was found frozen in the cold trap. Infrared analysis showed maxima at 697, 738, 908, 928, 972, 1030, 1105, 1158, 1205, 1390, 2915, 3022, 3718, 3777 cm^{-1} .

Attempt II: A second sample (14.5 g.) of the benzyl ether was heated at 200-210°C (bath temperature) under an

atmosphere of nitrogen in the absence of light. Nitrogen was passed through the system to sweep out the volatile products which in turn were frozen in a liquid nitrogen cold trap. After six hours the reaction flask was cooled, weighed and found to have lost 2.5 g. (17%) of which 1.5 g., n_D^{22} 1.5001, was collected in the cold trap (a small quantity of the trapped material was lost). Distillation of the 1.5 g. of liquid gave three fractions: 0.3 ml., b.p. 105-166°C; 0.8 ml., b.p. 167-170°C, n_D^{24} 1.5052; 0.2 ml., b.p. 171-189°C; with a 0.2 ml. residue.

The benzyl ether residue was taken up in petroleum ether, extracted first with 6 N sodium hydroxide and finally with Claisen's alkali. Each of the basic extracts were neutralized with acetic acid and extracted with petroleum ether. Evaporation of the petroleum ether solutions yielded: no product from the 6 N sodium hydroxide extract, 2.8 g. (19%) from the Claisen's alkali and 9.2 g. (63%) of neutral polymer from the original solution. Distillation of the phenolic fraction gave 1 g. of a viscous light yellow oil, b.p. 132-134°C (0.15 mm), n_D^{23} 1.5278, d_{23}^{26} 1.0151.

Anal: found: C, 83.09; H, 11.58. Infrared absorption showed maxima for the phenolic polymer at 700, 740, 750, 765, 910, 955, 970, 1020, 1035, 1080, 1160, 1205, 1250, 1280, 1312, 1390, 1460, 1500, 1615, 1750, 1890,

1975, 2960, 3620 cm^{-1} . An ultra violet maximum was obtained at 2800 Å.

Test of Stability of 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene (XLIX)

A 1.2 g. sample of 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene was heated at 200 to 210°C (bath temperature) for two hours under an atmosphere of nitrogen. The effluent gases were passed through a cold trap containing liquid air. No liquid was collected in this trap and distillation of the sample gave 1.1 g. of oil, b.p. 124-125°C (0.15 mm), n_D^{21} 1.5797; prior to heating b.p. 124-125°C (0.15 mm), n_D^{21} 1.5795.

SUMMARY

In an attempt to further clarify the mechanism of the Claisen rearrangement to an o-propenyl side chain, the benzyl ether of 2,4-dimethyl-6-propenylphenol was synthesized and rearranged under typical Claisen rearrangement conditions. By independent synthesis the expected rearrangement product was prepared and compared with the rearrangement products.

The following conclusions can be drawn:

1) The benzyl ether of 2,4-dimethyl-6-propenylphenol is thermally unstable.

2) It does not rearrange under Claisen rearrangement conditions to give the expected product, 1-(3,5-dimethyl-2-hydroxyphenyl)-2-benzylpropene.

3) The double cyclic (two-step) mechanism would be the more logical explanation of a migration to an o-propenyl side chain in the Claisen rearrangement.

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