

# ALICYCLIC-AROMATIC ISOMERIZATION

E. C. HORNING

*Department of Chemistry, University of Michigan, Ann Arbor, Michigan*

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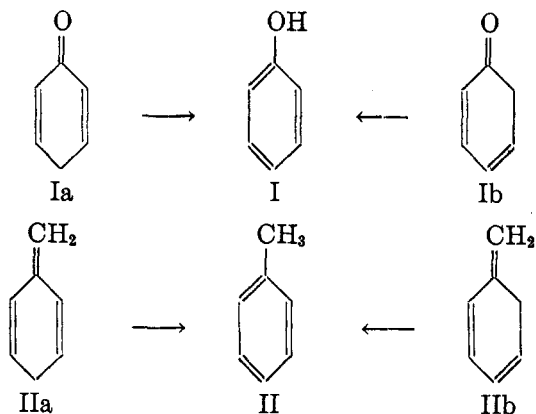
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## I. INTRODUCTION

The distinction between aromatic and alicyclic compounds is based upon a number of properties which are common to aromatic structures and whose possession gives the molecule its "aromatic character." These properties may be used to define "aromaticity," or they may be regarded as manifestations of the nature of a structure which involves a ring system of the benzene type containing alternating double and single bonds.<sup>1</sup> Of these properties one of the most fundamental is the unusual stability of the ring system as compared with the stability to be expected in the light of alicyclic considerations. Thus, benzene is far more stable than the hypothetical alicyclic cyclohexatriene with non-interacting double bonds. This unusual stability is reflected quantitatively in the thermal data for the combustion and hydrogenation of benzene and for the dehydrogenation of dihydrobenzene (when compared with the calculated "alicyclic" values); it is also responsible for the non-existence of certain alicyclic isomers of aromatic compounds. For example, the keto forms (Ia, Ib) of phenol are thermodynamically unstable with respect to the enol form (phenol), and they are apparently incapable of existence as chemical individuals. This is also true of the alicyclic isomers of toluene (IIa, IIb). Such isomers have been postulated from time to time as reaction intermediates, and methylene lines have been reported from data gathered in absorption-spectra studies of toluene (90). How-

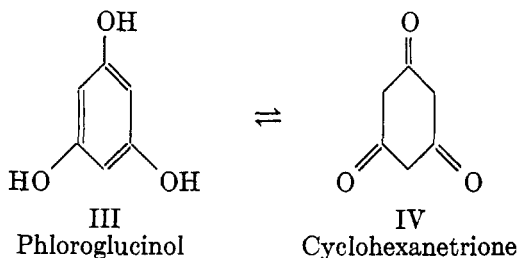
<sup>1</sup> For a critical discussion of "aromatic character" see L. F. Fieser in *Organic Chemistry*, edited by H. Gilman, 2nd edition, Vol. I, pp. 117-213. John Wiley and Sons, Inc., New York (1943).

ever, the independent existence of these isomers as chemical individuals has never been observed, because of the great difference in stability between the alicyclic



and aromatic forms, and because of the fact that the transition to the aromatic form occurs with such readiness that there is no practical way of preventing it.

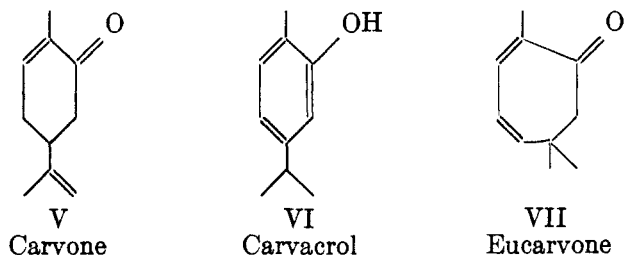
The isomerization of an alicyclic compound to an aromatic isomer is governed by two factors, and these illustrations present merely one specific form of the relation. The factors are (1) the relative thermodynamic stability of the two forms, and (2) the ease of transition from one form to the other. So far as the first factor is concerned, it is not to be assumed that the aromatic form is invariably the more stable; this will be generally true, but exceptions exist. For example, in the phloroglucinol-cyclohexanetrione equilibrium (III  $\rightleftharpoons$  IV), the



fact that both phenolic and ketonic reagents acting on phloroglucinol yield characteristic derivatives indicates that these two structures have comparable stabilities. Little is known about the effect of polyfunctionality on the stabilization of alicyclic forms, but it seems evident that comparable stabilities of the two forms (alicyclic *vs.* aromatic) may exist for polyfunctional molecules but that the number of isomers with such a relation is probably small. In the case of polynuclear compounds this condition may be altered; this point will be discussed later.

The ease of transition to the aromatic form is important in that it usually determines the possibility of separate existence for the alicyclic molecule. This is always true if the aromatic molecule has a far greater thermodynamic stability

than its alicyclic isomers, a condition which is probably realized in almost every case. For example, carvone (V) is stable under ordinary conditions; it may be



distilled under atmospheric pressure, and it may be carried through a number of reactions to yield the expected derivatives. However, the isomeric carvacrol (VI) is thermodynamically far more stable, and a variety of conditions will result in the isomerization of carvone to carvacrol. The aromatization is usually nearly complete and is generally rapid, sometimes violently so. Also, eucarvone (VII), which contains a seven-membered ring, exists as a chemical individual but the transition to the isomeric carvacrol (VI) occurs on heating.

In general, the ease with which the isomerization occurs usually determines not only the possibility of separate existence but also the possibility of preparation of a given alicyclic isomer by a given method. There are many cases known in which aromatic compounds are isolated as the result of reactions which should lead instead to one of their alicyclic isomers. It is evident that in such cases the reagents or reaction conditions are those which also induce isomerization. There are, however, many alicyclic compounds isomeric with aromatic structures which have a separate existence of their own, and in these cases isomeric aromatization awaits only the establishment of appropriate conditions.

Studies of this type of isomerization contribute to a more extensive knowledge of the relation between alicyclic and aromatic systems. They are also of considerable interest from a practical point of view. If the isomerization requires the rearrangement of hydrogen atoms only, it can usually be carried out under relatively mild conditions, and no change other than that attendant upon the rearrangement of the unsaturation occurs. The relative positions of side chains and functional groups in the aromatic molecule are predetermined by their positions in the alicyclic isomer. A synthetic route to aromatic compounds involving the preparation of an alicyclic intermediate through typical aliphatic (or alicyclic) reactions, followed by isomeric aromatization, possesses, therefore, the singular advantage that the restrictions on its use are determined for the most part by the limitations of aliphatic reactions and not by those of aromatic reactions. Methods having this advantage provide a useful complement to the usual aromatic syntheses in which the ring structure is preserved.

The recognition of the usefulness of isomeric aromatization in synthesis is apparently not widespread, although there are many examples of such aromatizations in the literature. Some few have been described as synthetic methods, others are merely incidental observations, and some have apparently been taken

as instances of anomalous behavior. The synthetic possibilities are far from exhausted, and a correlation of previous work may reveal new applications.

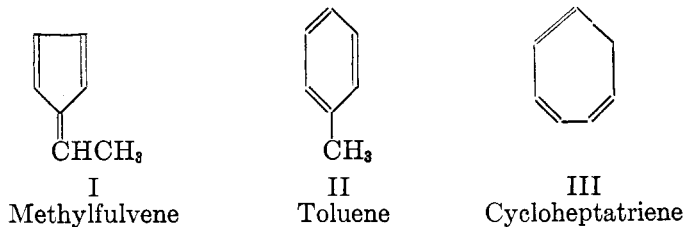
The classification scheme which has been adopted in this review is based on structural considerations. Since isomers are compounds whose only necessary relation is that they have the same molecular formula, it is apparent that a given aromatic compound may have a number of alicyclic isomers which differ in ring size, in degree of ring unsaturation, and in variety of ring or chain branching. The information now available indicates that six-membered rings in alicyclic isomers are those which are preserved, and which appear as aromatic nuclei after isomerization. Alicyclic compounds containing rings other than those of six members, such as those of five or seven members, or those with multicyclic ring systems, some of which are not six-membered, may undergo isomeric aromatization, but such rearrangements necessitate a change in the carbon skeleton of the molecule. Also, compounds containing a quaternary carbon atom in a six-membered ring cannot isomerize with aromatization of such a ring unless carbon-carbon bonds are broken and re-formed. On the other hand, if the alicyclic isomer contains a six-membered ring, appropriately substituted, it is often possible for the isomerization to proceed through the rearrangement or redistribution of the hydrogen atoms alone. There is no change in the skeleton, but the unsaturation distributed through the alicyclic structure becomes that which is associated with the aromatic ring or rings after isomerization.

Isomerizations involving fission of a carbon-carbon bond as a necessary feature of the rearrangement are treated in section II. Further classification within this group is based on the type of ring system in the alicyclic isomers. Section III deals with isomerizations which require the redistribution of hydrogen atoms alone. It is convenient to group these according to the type of multivalent links present in the alicyclic compounds. Rearrangements involving only carbon-carbon bonds form one group, those involving carbon-oxygen bonds form a second, and the third consists of rearrangements involving carbon-nitrogen bonds. Further classification in section III is based on the type of aromatic nucleus which results on isomerization.

## II. ISOMERIZATION WITH CARBON-CARBON BOND FISSION

### A. DIFFERENT RING SYSTEMS

An aromatic compound and its alicyclic isomers may have totally different ring systems. For example, methylfulvene (I) and cycloheptatriene (tropilidene) (III) are isomers of toluene (II) and contain, respectively, rings of one less and



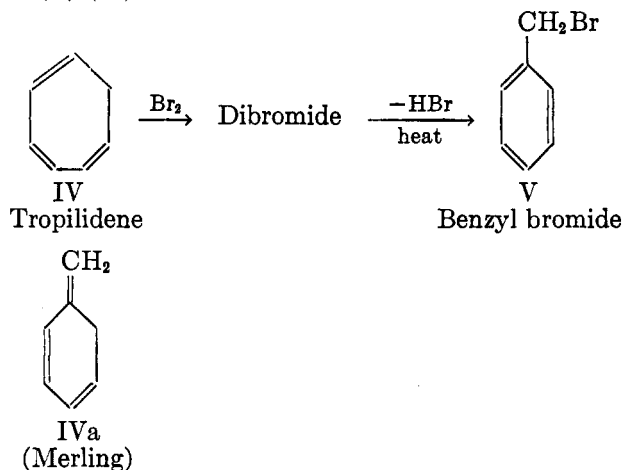
one more member than toluene. The isomeric aromatization of such molecules must involve, as a minimum change in the skeleton, the formation of a six-membered carbon ring through a new carbon-carbon bond, and the rupture of the original ring through fission of a carbon-carbon bond. An internal rearrangement of hydrogen atoms may or may not be required to complete the aromatization. While there is very little information available with regard to the relative thermodynamic stabilities of such molecules, it is probable that the aromatic compound is by far the most stable member of any such group. In the case of tropilidene, the heat of hydrogenation has been determined, and the difference between the value for tropilidene and that for cycloheptene, taken three times, is 6.7 kcal. per mole (25). This may be regarded as the resonance energy associated with the three double bonds of tropilidene. In the case of benzene the corresponding difference in energy is 36 kcal. per mole and, while these figures are not directly comparable, the order of difference is probably about the same as that for the difference in thermodynamic stability of tropilidene and toluene.

It is not to be assumed that a deviation from a ring of six members introduces a large amount of strain into the molecule and therefore confers immediately an increased thermodynamic instability on the alicyclic isomer. Alicyclic rings containing five atoms are very nearly strain free, since the bond angles in the ring are very close to those of the tetrahedral carbon atom. Six-membered rings are apparently very slightly strained, or may pass through positions of strain. Larger rings are very nearly free from strains of the Baeyer type, owing to their non-planar form, although the hydrogen blocking effect may induce a small added strain in rings of intermediate size (seven to eleven carbon atoms). These ideas are generally accepted for saturated rings, but the introduction of unsaturation should not increase the steric strain unless allene or acetylene unsaturation is introduced into a comparatively small ring. It is therefore probable that the differences in degree of stability between an aromatic compound and its alicyclic isomers of ring size of five or seven or more members are of very nearly the same order as the differences for compounds of the same ring size. Rings of less than five members are omitted here because their appearance in alicyclic compounds which are isomeric with aromatic structures is limited at present to bridged-ring systems, which are taken up separately.

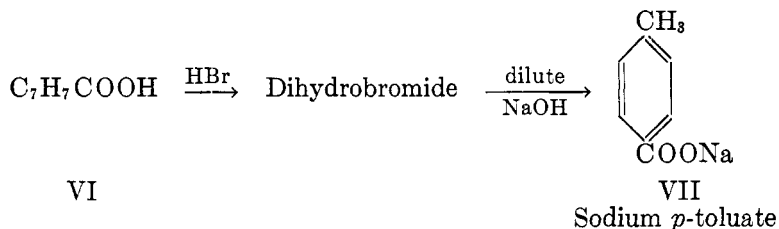
The size of the ring should therefore have comparatively little effect on the relative thermodynamic stability of an alicyclic compound with respect to an aromatic isomer, and the aromatic structure should be, in general, far more stable than any possible non-aromatic structure. So far as actual instability is concerned, most of the alicyclic isomers in this class are quite stable with regard to rearrangement. Tropilidene was isolated by both Merling and Ladenburg, and its structure was determined by Willstätter (140). It was synthesized by Willstätter from the 1,4-dibromide of cycloheptadiene by distillation from quinoline. During its purification it was in contact with dilute sulfuric acid, and it was distilled at atmospheric pressure (b.p. 115.5–116.7°C.). The preparation was repeated a few years ago (1939) and the physical properties were determined more precisely (25, 73). There is no doubt as to its structure (catalytic hydro-

genation yields cycloheptane), and the operations through which it has been carried indicate that it does not rearrange with great ease. It is true that the conditions to which tropilidene has been exposed were mild, but the preservation of the alicyclic form indicates at least moderate stability.

It is quite possible, however, to isomerize the tropilidene ring to an aromatic counterpart. The addition of one molecule of bromine, followed by heating on a water bath, results in the elimination of hydrobromic acid and formation of benzyl bromide (V) (88).



This reaction was regarded at first as a confirmation of the dihydrobenzene structure (IVa) proposed by Merling for tropilidene, but it was recognized later that a ring contraction was involved. The same ring system is present in the tropilidenecarboxylic acid derived from anhydroecgonine (34, 35). From treat-

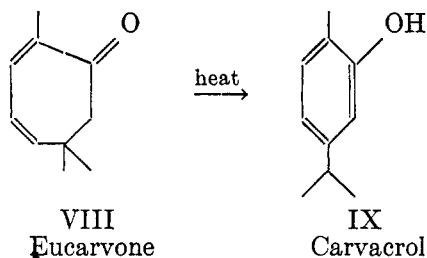


ment of this acid with hydrobromic acid in acetic acid in a sealed tube at 100°C. there was obtained a dihydrobromide, and on boiling the latter with dilute sodium hydroxide there was obtained *p*-toluic acid (as the salt, VII). Willstätter<sup>2</sup> (141) established the structure of this tropilidenecarboxylic acid; the ring

<sup>2</sup> Willstätter's dissertation, "Über die Constitution und Reduction der *p*-Methylen-dihydrobenzoësäure," was completed in 1894. The methylenedihydrobenzene structure (for tropilidene derivatives) was accepted at the time, but no ring system of this type has ever been observed in an isolated individual, and further, it is probably an impossible structure as far as isolation under any type of condition now known is concerned. This was not realized at the time, but Willstätter later demonstrated the correct structure for many compounds related to tropilidene.

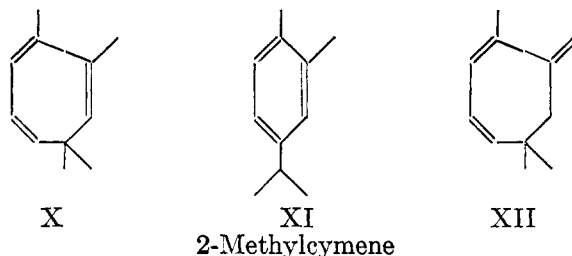
system is that of cycloheptatriene, and the rearrangement is due to an isomerization involving a contraction in ring size. It is unlikely that the addition of either bromine or hydrobromic acid to the tropilidene bond system would lead to a rearrangement, but it seems reasonable to believe that rearrangement accompanied dehydrohalogenation.<sup>3</sup>

A seven-membered ring is also present in the cyclic unsaturated ketone eucarvone (VIII). Eucarvone is an isomer of carvacrol (IX), and its rearrangement



to carvacrol may be effected by heating (11, 32). A closely related compound is the hydrocarbon X (or, less likely, XII), which has been prepared through the Grignard reaction from eucarvone and methylmagnesium iodide, followed by dehydration of the resulting tertiary alcohol (108). Isomeric aromatization of this compound to 2-methylcymene (XI) has not been observed.

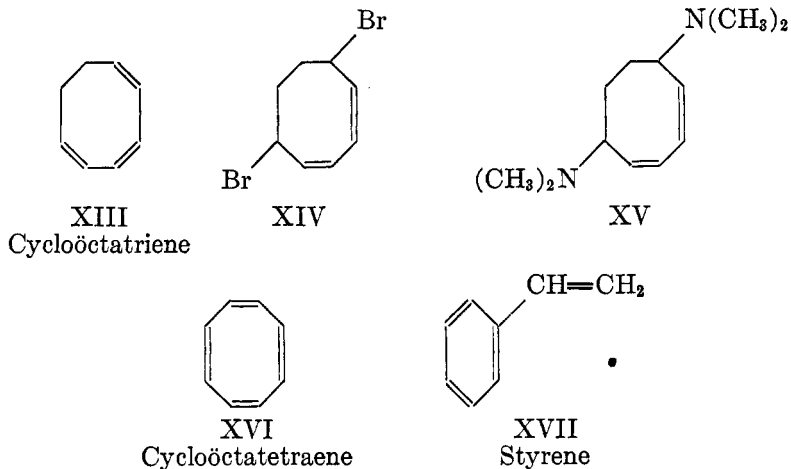
The literature with regard to alicyclic-aromatic isomerizations involving



monocyclic rings of more than seven members appears to be limited to the conflicting evidence surrounding cyclooctatetraene. Willstätter's synthesis (142, 143) of this compound was carried out by way of cyclooctatriene (XIII). Cyclooctatriene is an isomer of the xylenes and ethylbenzene, but there is no doubt

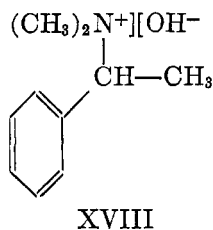
<sup>3</sup> It will be noted that the reactions which are included here, and which are termed isomerizations, may involve the formation of more or less definite intermediates. In some cases the reaction of isomeric aromatization proceeds as a rearrangement involving essentially only an initial and a final compound. In such cases a proposal of mechanism may require intermediates, but they are hypothetical in the sense that they are incapable of isolation and thus of direct experimental verification. In other cases an intermediate may have a more definite existence, in that it can actually be isolated. Reactions of the latter type are usually those in which addition of a reagent is followed later by expulsion of the elements which were added, the overall result being an isomerization. The present review includes reactions of both varieties.

as to its structure, and its isomerization to an aromatic compound was apparently not encountered. Addition of bromine led to XIV; this was converted to the di(dimethylamino)cycloheptadiene (XV), and the Hofmann procedure then yielded a hydrocarbon, presumably cycloöctatetraene (XVI).



Within recent years (since 1939) there has been less certainty that the product in question was actually cycloöctatetraene. One objection (60) rests on the fact that more than one compound, isomeric in the positions of the double bonds, might have arisen from the several Hofmann reactions which were required. Another objection to the structure lies in the observation that the properties of the product resemble those of an aromatic isomer, styrene (XVII), very closely (52, 127).

In view of the rearrangements encountered for tropilidene, it does not seem improbable that styrene could have been one of the products. An intermediate



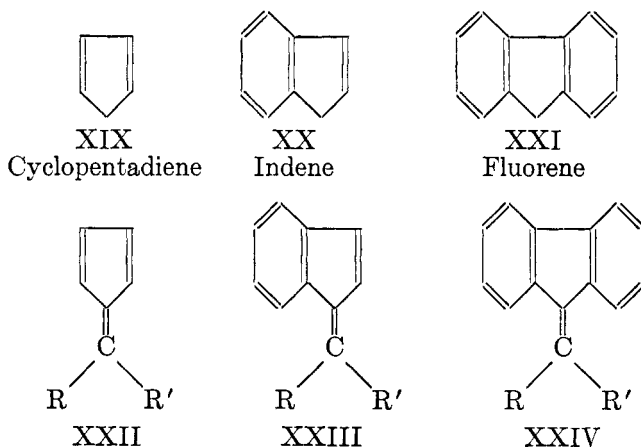
such as XVIII might have been formed through an isomerization involving ring contraction as the first step in the Hofmann procedure; this would lead to styrene on pyrolysis. A similar ring contraction might occur during the quinoline dehydrohalogenation of the dibromide XIV. This reaction, however, was not investigated beyond establishing the fact that the product was apparently not identical with the material obtained from the Hofmann reaction.

A reaction which may involve an isomerization is the conversion of cyclooctene to styrene over a chromium oxide catalyst at 425–455°C. in yields of 92–93 per cent (52). This conversion requires ring contraction and dehydrogenation



with separate or simultaneous aromatization. To describe this as including an isomerization would indicate a more intimate knowledge of the mechanism than is available at present. It is not impossible, however, that the dehydrogenation proceeded to cycloöctatetraene and that this underwent isomerization on the catalyst surface. On the other hand, the ring may have undergone contraction prior to the dehydrogenation. The facility with which aromatic rings are formed at elevated temperatures on certain catalysts from such relatively remote precursors as larger saturated or unsaturated alicyclic rings and aliphatic saturated hydrocarbons indicates the special ability of such catalysts to promote the formation of aromatic rings. The exact nature of this process, as well as that of catalytic dehydrogenation in general, is not very clear, but in some cases such reactions may well involve dehydrogenation to an alicyclic compound isomeric with an aromatic structure, followed by isomerization to the latter.

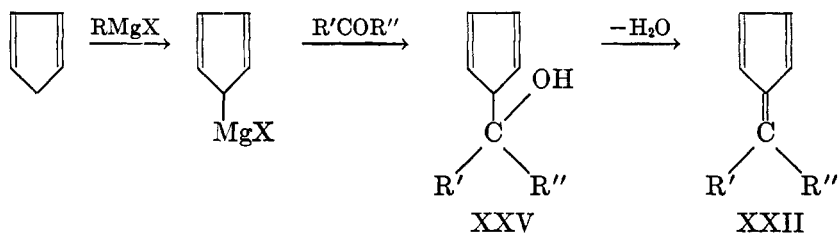
The existence of rings of less than six members in alicyclic isomers of aromatic compounds is also quite possible. Here, however, the literature is apparently limited to the five-membered rings of the fulvene derivatives. Cyclopentadiene (XIX), indene (XX), and fluorene (XXI) all contain an active methylene group.



Condensation with aldehydes and ketones should result in the structures XXII to XXIV, which are derivatives of the parent hydrocarbon fulvene (XXII; R, R' = H). The hydrocarbons from indene are benzofulvenes (XXIII), those from fluorene are dibenzofulvenes (XXIV), and in each case the compounds are isomeric with benzene, naphthalene, and phenanthrene (or anthracene) derivatives, respectively. Thiele (121, 122) obtained these compounds from condensations employing aliphatic ketones and aromatic aldehydes and ketones. Aliphatic aldehydes were unable to withstand the severity of his conditions. The reaction was reexamined recently for several aliphatic aldehydes, in the case of fluorene, and a fulvene derived from butyraldehyde was isolated (115).

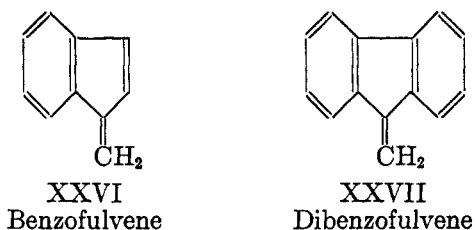
A second general investigation was described by Courtot (29), who employed a different preparative method. Cyclopentadiene and its analogs will form Grignard reagents by reaction with alkyl Grignard reagents. The reagents so

prepared react with aldehydes or ketones to yield derivatives of the structure XXV, to which Courtot gave the name fulvanols. The alcohols underwent



dehydration easily to form the fulvenes, XXII. This method has the advantage that aliphatic aldehydes may be employed in the synthesis.

The fulvenes and benzofulvenes seem to be quite stable with respect to rearrangement, although in general they are quite reactive. No investigation of the possibility of isomeric aromatization of these compounds has been found in the literature. Benzofulvene (XXVI) was obtained by Courtot (29) from the passage of the corresponding fulvanol over alumina at  $250^\circ\text{C}$ . The product had



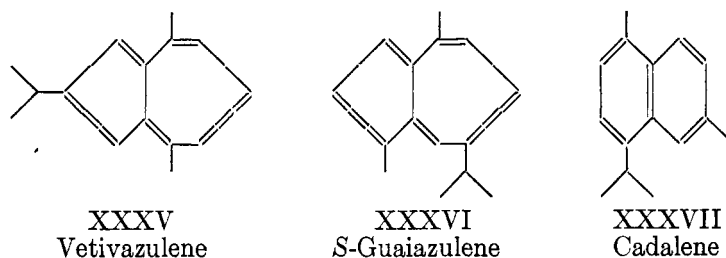
the odor of naphthalene, but did not have its physical properties (benzofulvene: m.p.  $37^\circ\text{C}$ ., b.p.  $95\text{--}97^\circ\text{C}$ . at 17 mm.). It was highly reactive, but the rearrangement to naphthalene was not encountered. Dibenzofulvene (XXVII) was reported in 1904 (84) but the compound had none of the properties to be expected for such a structure. Its preparation, which was attempted several times without success (29, 30), was finally accomplished (119). It is a low-melting solid which polymerizes readily. No isomerization to phenanthrene was noticed.

While the isomerization of dibenzofulvene (XXVII) has not been observed directly, there is at least one instance in which the isomeric phenanthrene has been obtained by a reaction which should presumably lead to dibenzofulvene. When 9-fluorenylcarbinol (XXVIII) is dehydrated by refluxing over phosphorus pentoxide in xylene there is obtained, instead of the expected dibenzofulvene (XXVII), a nearly quantitative yield of phenanthrene (XXIX) (19). The reaction probably involves a Wagner rearrangement, perhaps similar to that observed in the hydriodic acid-red phosphorus reduction of phenylbenzoylfluorene (XXX). The first product here is presumably the alcohol XXXI, which then rearranges with dehydration to yield 9,10-diphenylphenanthrene (XXXII) (139). A number of Courtot's dehydrations of the fulvanols were carried out



violet in color, which may be obtained from a number of essential oils after subjection of the oils to dehydrogenation conditions, such as heating with sulfur, selenium, or palladium-charcoal (53). The elucidation of the structure of these compounds has been due largely to the efforts of Pfau and Plattner (98, 99, 100, 101). The parent hydrocarbon, azulene (XXXIII), may be prepared by the series of reactions shown; it is an isomer of naphthalene (XXXIV) but it has one seven- and one five-membered ring instead of two six-membered rings (99). A number of alkyl- and dialkyl-azulenes have also been prepared (98, 101), as has vetivazulene (XXXV) (100). Vetivazulene and *S*-guaiazulene (XXXVI) may both be obtained from certain essential oils; they are isomers of cadalene (XXXVII).

That this bond system, isomeric with that of the aromatic naphthalene nucleus, may be produced as the result of high-temperature dehydrogenations with sulfur



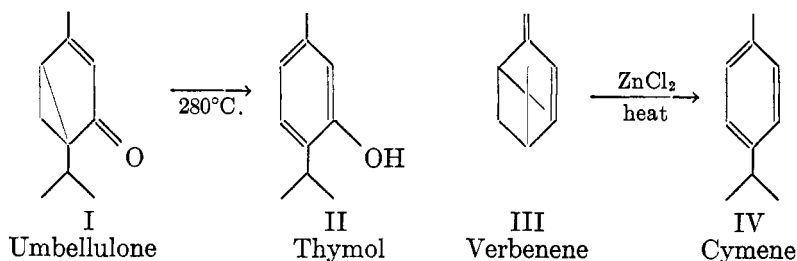
or selenium, or catalysts such as palladium-charcoal or nickel, indicates certainly that the system has a high degree of stability. Calculations based on the heats of combustion of guaiazulene and cadalene, assuming that the side chains are equivalent, indicate that the azulene molecule has only about 8 per cent less bonding energy than naphthalene (96). Dehydrogenation catalysts are apparently unable to distinguish the combination of five- and seven-membered rings from the two six-membered rings of naphthalene, or, it may be that isomerization to a naphthalene system will occur over such catalysts, but that temperatures higher than those heretofore employed are required.

#### B. BRIDGED SIX-MEMBERED RINGS

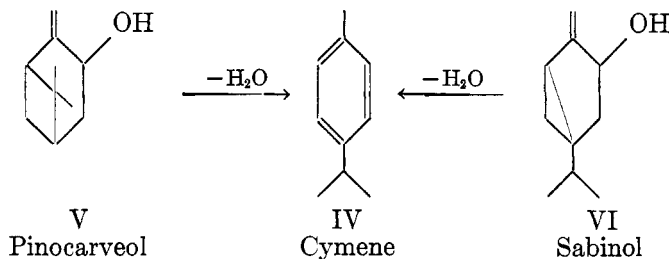
There are a number of alicyclic compounds whose molecular formulas are the same as than of aromatic compounds, and whose structures include a six-membered ring. However, the formal unsaturation, or that which is indicated by the molecular formula, is not due entirely to multiple bonds, but is contributed to, in part, by a ring bridge. The isomerization of these compounds therefore includes of necessity a rupture of one of the rings, followed by redistribution of the hydrogen atoms. The examples to be found in the literature indicate that six-membered rings are preserved, and that the rings which are likely to be broken are those with three or four members.

An example of a reaction in this group is the transformation of umbellulone (I) into thymol (II) on heating at 280°C. (33). The cyclopropane ring is broken,

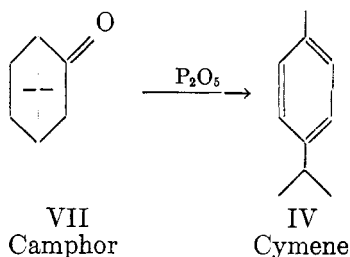
and the molecule aromatizes, the alicyclic ketone thus being converted into a phenol. Another example is the conversion of verbenene (III) into the isomeric cymene (IV), by treatment with zinc chloride (17, 111).



There are also several dehydration reactions which convert terpene alcohols into aromatic hydrocarbons, and which seem to involve rearrangements of this type. Both pinocarveol (V) (130), and sabinol (VI) (49) yield cymene (IV) under the influence of acid-type dehydrating agents. In both cases the reaction



probably proceeds through the elimination of water to yield a bicyclic hydrocarbon, followed by rearrangement of the latter under the influence of the dehydrating agent. This is almost certainly true for pinocarveol (V), since the expected product of dehydration is verbenene (III), and it is known that acidic dehydrating agents will convert verbenene to cymene. A closely related reaction may be involved in the conversion of camphor (VII) into cymene (IV)

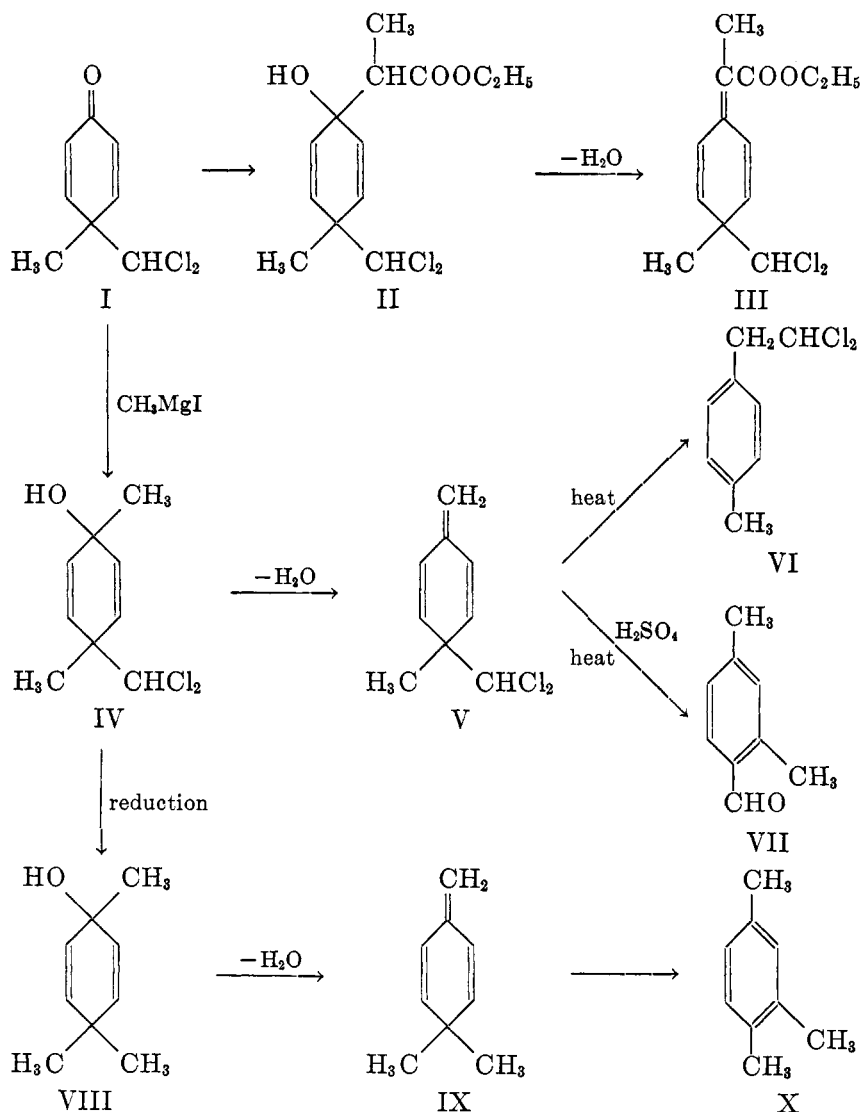


by the action of phosphorus pentoxide (5). In this case dehydration and isomerization are probably inseparable.

Another reaction which may belong in this group is the formation of carvylamine (X) from  $\beta$ -thujone oxime (IX) by the action of alcoholic sulfuric acid

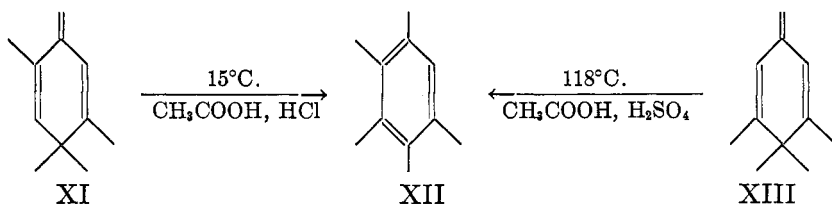


being *m*-xylylaldehyde (VII). The semibenzene IX isomerizes readily under the influence of acids to the aromatic isomer 1,2,4-trimethylbenzene (X).



The semibenzene ring system is stabilized by the presence of two substituent groups on one of the ring carbons. This quaternary carbon removes the possibility of aromatization by rearrangement of hydrogen atoms alone, but in general such compounds, while sufficiently stable to allow isolation, isomerize readily to the corresponding aromatic isomers. In the case of the semibenzenes one of the *gem*-methyl groups migrates during isomerization to the adjacent position, if this is open, and such rearrangements take place very easily. The semibenzene

XI isomerizes to pentamethylbenzene (XII) at 15°C. under the influence of hydrochloric acid in acetic acid. If both adjacent positions are blocked, the semibenzene will still isomerize but more vigorous conditions are required. For



example, compound XIII requires a much higher temperature (118°C.) for rearrangement to the same aromatic isomer, pentamethylbenzene (XII).

It is also possible to obtain trichloro compounds similar to I by the reaction of *p*-cresol with carbon tetrachloride and aluminum chloride. Phenols substituted in the ortho position, such as *o*-cresol, will also yield ketodihydrobenzenes, but the Grignard reactions of these ketones follow a different course involving 1,4-addition. The resulting products are not semibenzenes.

### III. ISOMERIZATION BY REDISTRIBUTION OF HYDROGEN

#### A. NATURE OF THE ISOMERISM

All aromatic compounds contain a certain minimum amount of unsaturation which is associated with the ring system and which finds expression in both the molecular formula and in the usual aromatic ring structures involving double and single bonds. For example, the Kekulé formula for benzene and its derivatives indicates that such compounds contain, as a minimum, an amount of unsaturation formally equivalent to three carbon-carbon double bonds, and that this unsaturation is associated with the ring. A number of alicyclic isomers of aromatic compounds have been described in section II, but they have all required for isomerization the rupture and re-formation of at least one carbon-carbon bond. It is quite possible, however, for an aromatic compound and an alicyclic isomer to differ in the distribution of the multivalent links only, or, more precisely, in the arrangement of the hydrogen atoms alone. Isomerization in these cases requires only the redistribution of the hydrogen atoms so that the ring or rings acquire, through this process, an amount of unsaturation corresponding to the Kekulé type of structure.

This type of isomerization, which might be called isoaromatization, is best defined by reference to a few simple illustrations (table 1).

It will be observed that the unsaturation which is present in the aromatic ring as a carbon-carbon double bond need not appear in this form in the alicyclic isomer. In simple cases it may appear as carbon-carbon triple bonds, or multivalent carbon-oxygen or carbon-nitrogen bonds. Presumably it could also appear in the form of other multivalent links, as those of sulfur-oxygen or nitrogen-oxygen, but no examples of isomerization involving such bonds have been found in the literature. It will also be observed that even very simple



TABLE 1  
*Examples of isoaromatization*


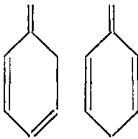
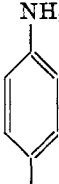
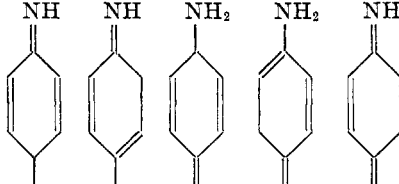
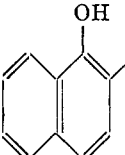
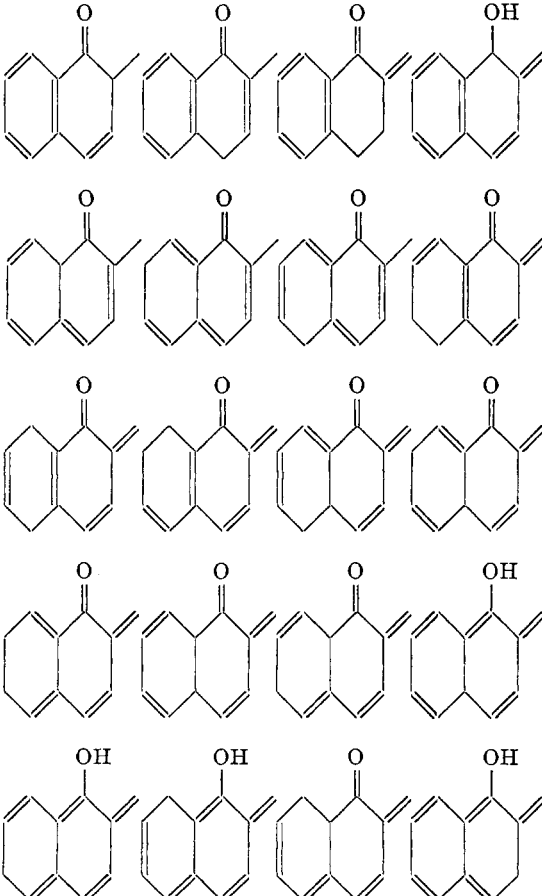
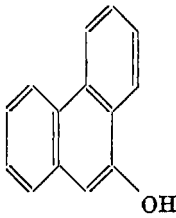
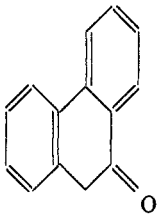
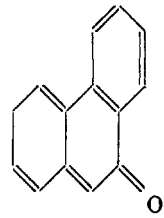
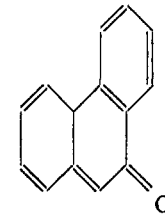
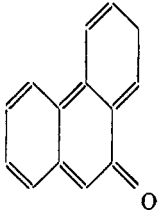
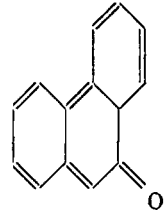
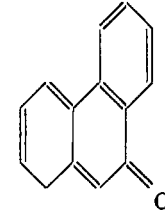
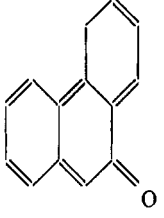
AROMATIC COMPOUND	ALICYCLIC (NON-AROMATIC) ISOMERIC STRUCTURES
Toluene, 	
<p><math>\text{NH}_2</math></p> <p><i>p</i>-Toluidine, </p>	<p>NH    NH    NH<sub>2</sub>    NH<sub>2</sub>    NH</p> 
<p>OH</p> <p>2-Methyl-1-naphthol, </p>	

TABLE 1—Concluded

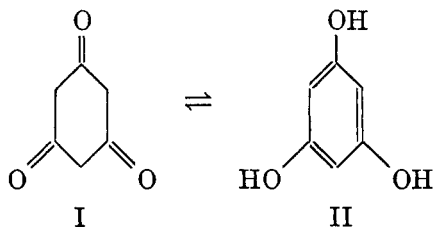
AROMATIC COMPOUND	ALICYCLIC (NON-AROMATIC) ISOMERIC STRUCTURES		
9-Phenanthrol, 			
			
			

aromatic compounds may have a large number of alicyclic isomers of this type. (There is no attempt here to classify isomers as "possible" or "impossible," except that allene and acetylene bonds have been excluded from the rings. Non-aromatic keto-enol pairs are taken as two isomers.)

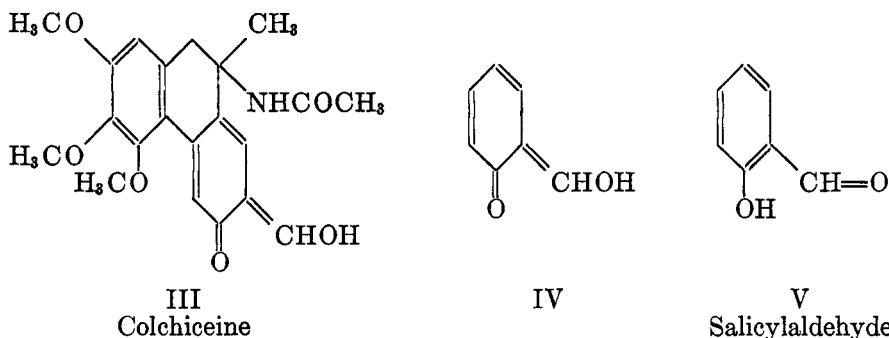
This variety of isomerism can also be extended to polynuclear compounds. In this case the alicyclic isomers are taken to include all isomers which are not entirely aromatic in nature. Thus,  $\alpha$ -naphthols have among their isomers the corresponding  $\alpha$ -tetralone derivatives. The "alicyclic isomer" here contains one aromatic ring, but the process of isomerization is essentially that of the isomeric aromatization of an alicyclic ring, and consequently these molecules are classified as alicyclic isomers. Examples of naphthalene and phenanthrene isomerism are shown in table 1.

The isomerization of any one of these alicyclic compounds to its aromatic isomer is governed by the two factors noted in the introduction: (1) the relative thermodynamic stability of the two forms, and (2) the ease of transition from one form to the other. Comparatively little quantitative data is available with respect to the first factor, but it is probable that for any monofunctional benzene or naphthalene derivative the aromatic form will be thermodynamically far more

stable than any possible alicyclic isomer.<sup>4</sup> The chief item responsible for this difference in stability derives from the resonance energy of the aromatic system. This energy differential, which arises through aromatization of the ring or rings, is large enough to overshadow any energy effects due to the transformation of a single functional group in an alicyclic isomer. In the case of polyfunctional compounds this may or may not be true. The cyclohexanetrione-phenol equilibrium (I  $\rightleftharpoons$  II) previously noted is one well-established instance in which the members of a pair of alicyclic-aromatic isomers have comparable stabi-



ties. Colchicine (III) (54) has in part a bond system corresponding to the hydroxymethylene form (IV) of salicylaldehyde (V), but the very fact that it does not isomerize during preparation casts some doubt on the proposed structure. There

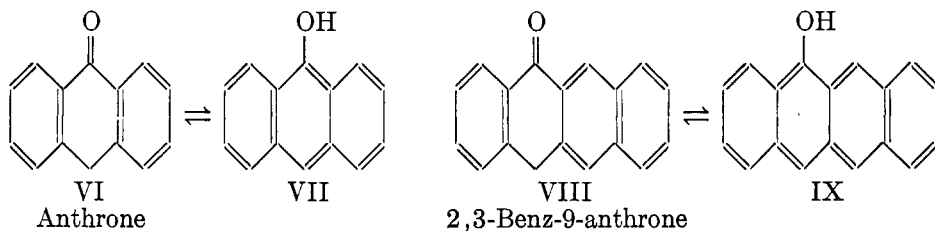


may be other cases in which two forms (alicyclic *vs.* aromatic) exist at very nearly the same energy levels, but there can be no doubt that these situations rarely occur.

For polynuclear aromatic molecules the energy relations with respect to alicyclic isomers may be quite different. As a matter of fact, in some keto-phenol pairs the alicyclic form may have a much greater thermodynamic stability than the aromatic phenolic isomer. For example, the ketones anthrone (VI) and 2,3-benz-9-anthrone (VIII) may be isomerized to the corresponding phenols VII and IX, but the equilibrium in the latter case is greatly in favor of the keto

<sup>4</sup> Quantitative estimates of the energy differences for several aromatic-non-aromatic isomeric systems have been made from time to time. Phenol, for example, is estimated to be thermodynamically more stable by 16 kcal. per mole than its keto form. A brief discussion of several current estimates of this type may be found in *The Theory of Organic Chemistry* by Branch and Calvin (18).

form. The anthrone  $\rightleftharpoons$  anthranol equilibrium (VI  $\rightleftharpoons$  VII) in some solvents lies on the side of the keto form (in alcohol the equilibrium mixture contains about 90 per cent anthrone), but the ketone is soluble in alkali, indicating complete

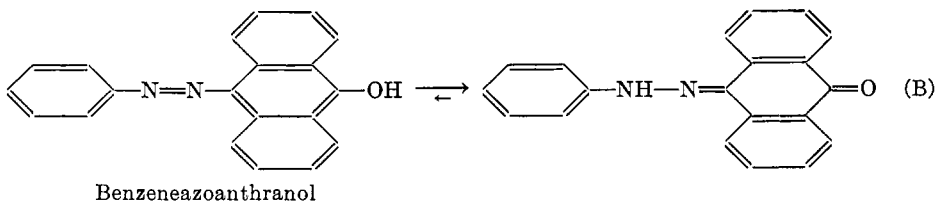
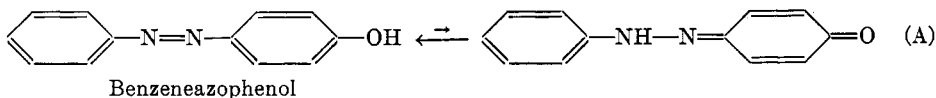


isomerization under these conditions. The ketone VIII, however, will not dissolve in alkali and forms the anthranol-type acetate very much less readily than anthranol itself (42). Any generalization about energy relationships for polynuclear molecules must therefore be made with considerable caution, and for the most part the best procedure is to treat each such case individually.<sup>5</sup>

In all cases of this type of isomerism in which the energy relations favor the aromatic compound, and therefore in the great majority of all such cases, it is apparent that the second factor is the one which will usually determine the possibility of preparation, isolation, and continued existence of a given alicyclic isomer. In the event that the aromatization requires a rearrangement of hydrogen atoms that can be accomplished by a single tautomeric shift such as that of the keto-enol variety, the alicyclic isomers of the benzene and naphthalene series have no existence as chemical individuals, so far as is now known. Any preparative method designed to yield such a compound results in the aromatic isomer instead, simply because of the ease with which the tautomeric shift is brought about.

In the event that the alicyclic isomer has more than one exocyclic set of un-

<sup>5</sup> Another example of the effect of polynuclear systems on aromatic-non-aromatic equilibria is shown by a comparison of the equilibria



encountered in the case of benzeneazophenol (A) and benzeneazoanthranol (B). The former apparently exists only as the azo compound, while the latter seems to be exclusively in the hydrazone form. The corresponding azonaphthol is an intermediate case so far as energy effects are concerned, and both structures are present in the equilibrium mixture (18).

saturated bonds, or if only one unsaturated bond set exists which is not in the ring but is distant at least one carbon from the ring, there is a possibility of independent existence as a chemical individual. In some of these instances isomeric aromatization can be brought about very readily, as for example by contact with acids. Also, since the isomerization involves essentially an intramolecular disproportionation of hydrogen, it is to be expected that catalysts which are useful for the intermolecular transfer of hydrogen should also be of value in this connection. Actually, it has been found that a number of isomeric aromatizations proceed under surprisingly mild conditions in the presence of hydrogenation catalysts.

It should be noted that it is characteristic of this type of isomerism that the skeleton of the molecule is not affected by the isomerization. Functional groups undergo transformation, such as keto-phenol transformation, but all substituents on the original alicyclic ring retain their positional relation during isomerization. This property is of considerable value from the point of view of synthetic applications of isomeric aromatizations. Many various types of specific isomerizations which have been encountered in the literature are described subsequently and provide an adequate demonstration of this point.

## B. METHODS OF AROMATIZATION

### 1. *Thermal*

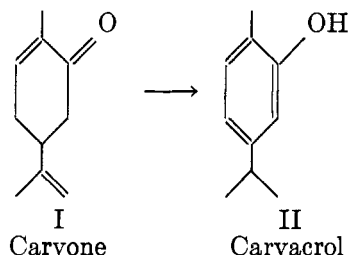
Since a number of isomeric aromatizations are known which take place easily, there have been several attempts to induce a purely thermal conversion. The disturbance of bond systems under the impact of thermal energy is a common effect, but the disturbances often result in molecular degradation, and the method is therefore not attractive. There is a report that a thermal aromatization of carvone is possible (32), but as a result of other investigations it has also been reported that a catalytic agent of some sort is necessary (11, 105). At high temperatures (heating in an autoclave with clay chips at 450°C.) a partial conversion to carvacrol has been observed (126). Since acids and hydrogenation catalysts have proved to be simple and effective agents for inducing isomerization, further investigation of thermal effects has been discouraged.

### 2. *Acids (and bases)*

The use of acids and bases to bring about rearrangements leading to aromatization involves a type of action which in the past was often referred to as catalytic, although this term is best reserved for the action of agents such as hydrogenation catalysts. Rearrangements induced by acids usually involve addition to unsaturated bonds; the addendum is subsequently lost, however, so that it does not appear in the final product. If the life span of the intermediate or intermediates is sufficiently long (under the reaction conditions), one or more of them can often be isolated from the reaction mixture. Such relatively long-lived intermediates have been isolated in a number of cases. Reactions involving the addition of hydrogen bromide or hydrogen chloride, followed by expulsion of the elements

which were added, sometimes yield such compounds. On the other hand, if the intermediate is short-lived, it may enjoy no better than a hypothetical existence. Ionic intermediates resulting from addition of a proton are of this nature.

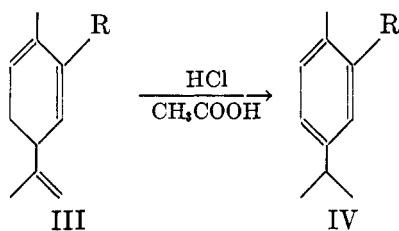
Acids, and in particular mineral acids, are usually very effective agents for



inducing isomerization. For example, the rearrangement of carvone (I) to carvacrol (II) under the influence of acids was first observed about a century ago.

Acids and acid derivatives, as phosphoric, hydrochloric, and formic acids and phosphorus oxychloride, have been employed (61, 63, 74, 93, 104, 116, 128). The compound obtained from the combination of carvone and hydrogen chloride also yields carvacrol on heating with or without added acid catalysts (93). The yields are usually high and the conversion is fairly rapid, sometimes vigorous. Under circumstances not directed to the formation of carvacrol, but which involve contact of carvone with acid, it is to be expected that carvacrol will be among the products. Such is the case in the preparation of carvone hydrate by treatment of carvone with sulfuric acid (69, 110).

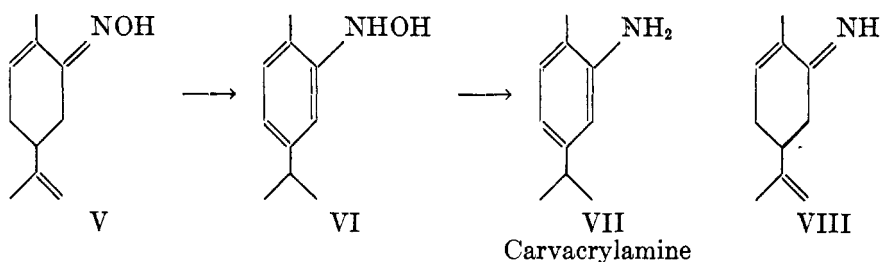
If carvone is allowed to react with a Grignard reagent ( $\text{RMgX}$ ,  $\text{R} = \text{methyl, ethyl, } n\text{-propyl, or phenyl}$ ) there results a tertiary alcohol or the product of its dehydration (64, 66, 72, 107, 109). The latter, which can be obtained from the alcohol and which has the structure III, can be aromatized readily to the cor-



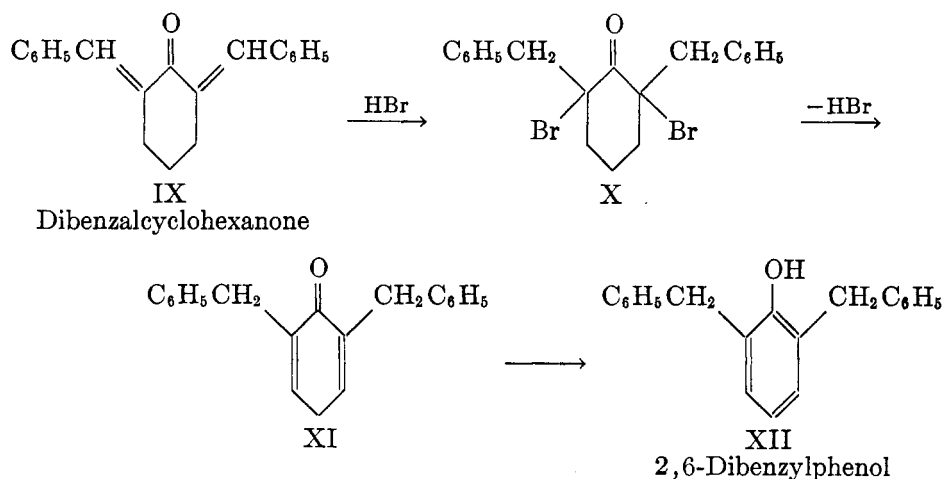
responding hydrocarbon IV by heating in a dilute (2 to 3 per cent) solution of hydrogen chloride in acetic acid.

Another compound from carvone, the oxime (V), has the same ring structure as carvone, and has been found to yield carvacrylamine (VII) under the influence of potassium hydroxide (131) and of sulfuric acid in alcohol (132). Zinc and acetic acid and potassium hydroxide will also induce the conversion of isocarvone oxime to carvacrylamine (51, 137). The carvone oxime reactions probably involve rearrangement to the corresponding aromatic isomer VI (a hydroxyl-

amine), followed by reduction to the amine VII. This seems more likely than a preliminary reduction to the imine (VIII), followed by rearrangement.



An interesting rearrangement is that described by Weiss and Ebert (138), who obtained 2,6-dibenzylphenol (XII) in the form of its acetate from treatment of dibenzalcylohexanone (IX) with a solution of hydrogen bromide in acetic acid



and acetic anhydride at 52–55°C. There is postulated an intermediate X which undergoes dehydrohalogenation to XI, which then isomerizes.

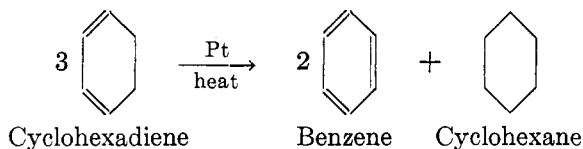
A consideration of the experimental conditions capable of inducing isomerization of the compounds presented here, together with a number of those noted later, indicates that in cases where the isomerization takes place very readily apparently all that is required is an acid environment, the nature of the acid being immaterial. In such cases the rearrangement probably proceeds through an ionic intermediate. Solutions of hydrogen chloride or hydrogen bromide in acetic acid are agents capable of inducing isomerization in a wide variety of instances, and in a number of these cases the alicyclic isomers are not susceptible to isomerization by simple contact with an acid medium. Unfortunately the limitations of this mode of aromatization, as a general method, have never been determined, and it is therefore impossible to estimate the range of usefulness of the method.

### 3. Catalytic

A method of aromatization which is both convenient and quite general in its usefulness lies in the use of catalysts of the hydrogenation group. These catalysts are capable of directing their action on portions of bond systems which show unsaturation, and their investigation in connection with this type of isomerization is therefore indicated.

Wallach, in his studies of the hydrogenation of carvone with a palladium catalyst under the usual mild conditions, found that carvacrol was always one of the products (136). Linstead encountered the same difficulty in reducing carvone to carvomenthone, and it was found in separate experiments that a slow isomerization of carvone will proceed at room temperature over the catalyst (80). Similarly, Wallach found that carvone oxime (V), when hydrogenated with the palladium catalyst of Paal, gave always some carvacrylamine (VII) (135). The latter again is probably formed from the hydroxylamine (VI) by reduction.

The effect of hydrogenation catalysts upon bond systems is a problem which has been developed very rapidly within recent years. The work of Linstead (79, 80, 81, 82) on the use of noble metals in dehydrogenations and disproportionations, and the dehydrogenation studies of Adkins (1, 2, 3, 103) indicate that hydrogenation catalysts have the ability to transfer hydrogen from one organic molecule to another, or simply to add and/or remove hydrogen from certain structures, with or without the aid of molecular hydrogen.<sup>6</sup> It is required here, however, to transform an unsaturated compound into another at the same formal level of unsaturation; there is no specific hydrogenation or dehydrogenation involved, and such a process may apparently also proceed without the intervention of molecular hydrogen. If only two molecular species are involved, the reaction is one of isomeric aromatization (or *intramolecular* disproportionation); if three or more species are involved, the reaction is one of (*intermolecular*) disproportionation or irreversible catalysis (the latter term was used by Zelinsky, and Russian workers have retained this designation). The difference between these two types of reactions, so far as the intimate mechanism is concerned, is not well defined, and it is quite possible that in some or all cases the mechanism is the same. For example, a typical disproportionation is the conversion of 1,3-cyclohexadiene into a mixture of benzene and cyclohexane through the agency of a platinum catalyst (78):



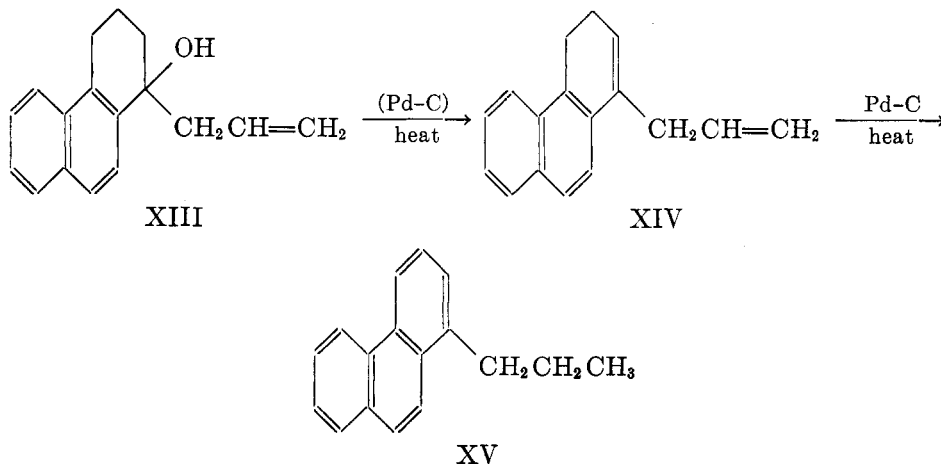
<sup>6</sup> See also Taylor (J. Am. Chem. Soc. **60**, 627 (1938)) for a discussion of dehydrogenation, particularly with respect to the Balandin multiplet theory, and Levina (J. Gen. Chem. (U.S.S.R.) **4**, 1250 (1934); **6**, 764, 1092, 1496 (1936); **7**, 353, 402, 747, 1587, 1866 (1937); **8**, 1776 (1938); **9**, 825, 1834, 2287 (1939); **10**, 913 (1940); **11**, 527, 533 (1941); **12**, 422 (1942)) for an extensive study of isomerizations and disproportionations (irreversible catalysis).

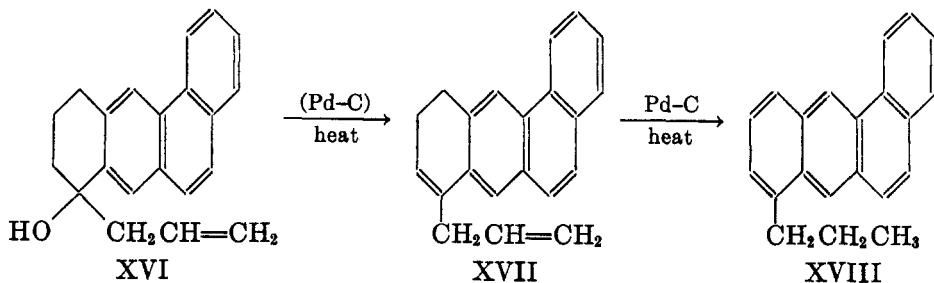


This reaction involves the transference of hydrogen atoms from one molecule of cyclohexadiene to another, the net result being the formation of benzene and cyclohexane. This process may involve a dehydrogenation on the catalyst surface, followed by desorption of the benzene molecule which is formed, but not of the hydrogen. The next cyclohexadiene molecule to be adsorbed is then hydrogenated instead of being dehydrogenated. Such a process requires the successive adsorption of cyclohexadiene molecules without desorption of hydrogen, and is essentially a two-stage process. A successive-stage process of this type could also be assumed for intramolecular disproportionation, but it is also possible that the isomerization mechanism involves a rearrangement which takes place on the catalyst surface, and that only a single adsorption is required for each rearrangement. In this case the hydrogen is merely transferred from one part of the molecule to another, and there is no intermolecular action.

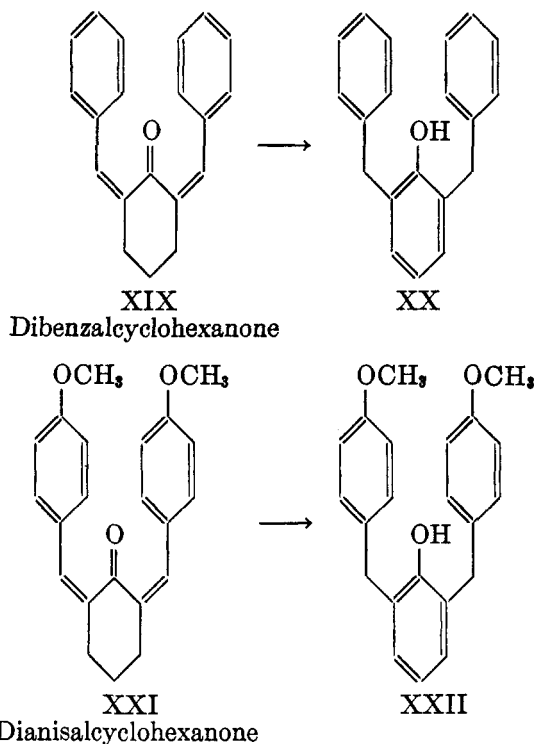
In any event, the effectiveness with which the isomerization can be carried out is dependent chiefly upon the nature of the catalyst. That a palladium catalyst is active in this respect even at room temperature, although the rate of aromatization is slow, has already been noted. At elevated temperatures with the same catalyst the reaction proceeds smoothly and rapidly. Linstead (8) heated carvone at temperatures in the range 20–230°C. for varying lengths of time with a palladium-charcoal catalyst in an atmosphere of carbon dioxide. Treatment for 12 hr. at 230°C. yielded 95 per cent of carvaerol, and 2 hr. at 228°C. 81 per cent of carvaerol. Bachmann has employed this method for synthetic purposes in several instances: the conversion of the alcohols XIII and XVI to the hydrocarbons XV and XVIII (8, 10) by heating with a palladium-charcoal catalyst evidently proceeds by way of the alicyclic intermediates XIV and XVII.

In this connection it is interesting to note a rather unusual experiment (41) in which dibenzalicyclohexanone (XIX) and dianisalicyclohexanone (XXI) were converted into the corresponding phenols (XX, XXII) in excellent yields. The alicyclic compounds were treated with hydrogen and a palladium catalyst at a temperature of 200–250°C., and after hydrogenation was complete the tempera-



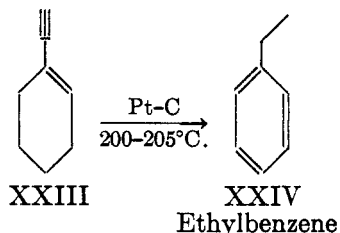


ture was raised to 325–330°C. to effect dehydrogenation. This procedure involves two steps of directly opposite natures. It should be possible to omit the hydrogen and attain the same result.



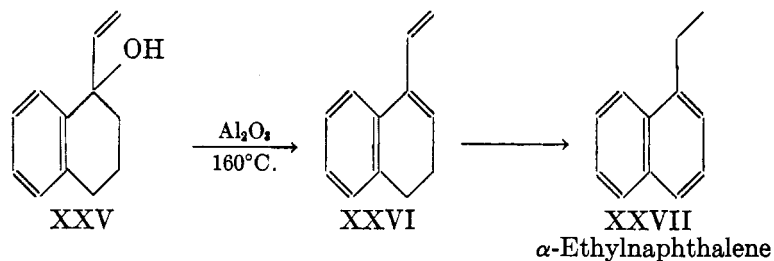
Platinum catalysts are employed less frequently than palladium catalysts for dehydrogenations, although there is little difference in the activity of the two in this connection. It is therefore likely that isomeric aromatizations can also be induced by platinum catalysts, but there are very few observations in support of this view. One interesting rearrangement which involves the use of a platinum-charcoal catalyst is the isomerization of the enyne **XXIII** to ethylbenzene (**XXIV**) (77). The acetylene bond group provides the equivalent of two double bonds.

Raney nickel has proved useful in establishing an equilibrium in certain cases of isomerism. For example, Cope (27) found that an equilibrium between the



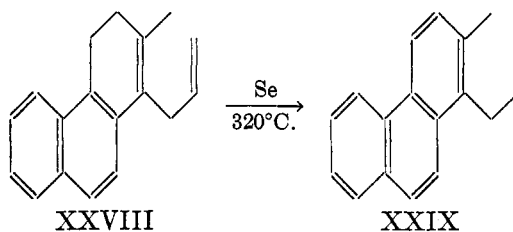
$\alpha,\beta$ - and  $\beta,\gamma$ -forms of several unsaturated (olefinic) esters could be established by heating the esters with Raney nickel at  $180^{\circ}\text{C}$ . Nickel supported on kieselguhr, chromium oxide, or alumina has been employed in dehydrogenation studies (usually at elevated temperatures and pressures) by Adkins (1). There are, however, no general observations available on the activity of nickel catalysts in inducing isomeric aromatizations.

Activated alumina is effective in establishing certain types of isomeric conversion involving unsaturated compounds. For example, isomerization equilibria among the branched-chain pentenes (40) and among dienes (56) have been investigated, employing activated alumina at relatively high temperatures. Observations of isomeric aromatization over alumina are rare, but one such example seems to be the reaction described by Goldberg (50) in which the tertiary alcohol XXV was passed over alumina at  $160^{\circ}\text{C}$ . The product was not the expected vinylidihydronaphthalene (XXVI) but the isomeric compound,  $\alpha$ -ethylnaphthalene (XXVII).



Sulfur and selenium are not ordinarily regarded as dehydrogenation catalysts, but they are capable of dehydrogenating a wide variety of alicyclic molecules to yield aromatic structures. The hydrogen is eliminated as hydrogen sulfide or hydrogen selenide, and this particular process has never been carried out in the reverse direction. Selenium, however, is capable of acting as a hydrogenation catalyst, although its activity in this respect is very low, and it also has the ability to induce isomeric aromatization. This was demonstrated by Cook's studies (24) of the hydrocarbon XXVIII. The rearrangement to the aromatic isomer XXIX was effected by heating with selenium at  $320^{\circ}\text{C}$ . for 15 hr. It was also found possible to effect the isomerization by heating for 1 hr. in acetic acid saturated with hydrogen chloride, but boiling formic acid was without action.

These examples demonstrate the possibility of the occurrence of isomeric aromatization under certain definite circumstances. Comparatively little is

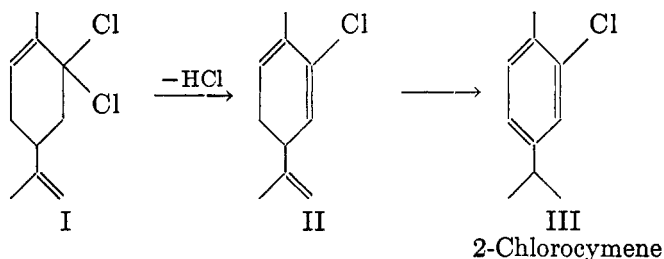


known as to the limitations of the methods for inducing such rearrangements, but the two most useful agents seem to be solutions of hydrogen bromide or hydrogen chloride in acetic acid, and palladium-charcoal catalysts.

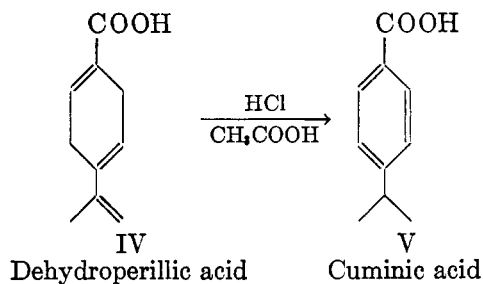
### C. ISOMERIZATIONS INVOLVING CARBON-CARBON BONDS ONLY

#### 1. Benzene derivatives

(a) *One exocyclic bond*: The unsaturated hydrocarbons derived from carvone through the Grignard reaction have been mentioned previously (page 110); their rearrangement takes place readily. The corresponding isoamyl compound ( $R = i\text{-C}_5\text{H}_{11}$ ) has been prepared (117, 118) but its aromatization has not been described. A related compound is the dichloride (I) obtained from carvone and phosphorus pentachloride. Boiling in quinoline yields 2-chlorocymene (III) (65) by way of the alicyclic compound II.

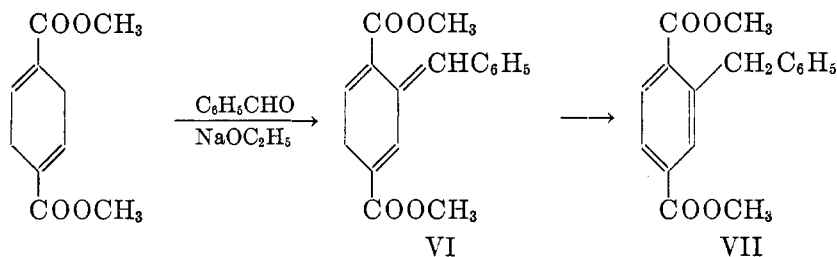


Dehydroperillic acid (IV), an alicyclic acid occurring in the western red cedar, is transformed by contact with hydrochloric acid (in acetic acid) into the iso-

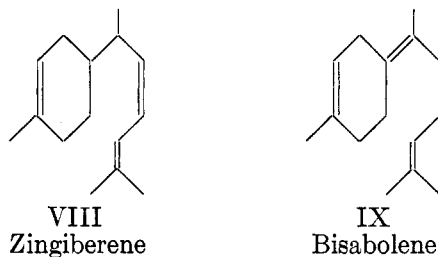


meric aromatic acid, cuminic acid (V) (4).

The methyl ester of  $\Delta^{1,4}$ -dihydroterephthalic acid will undergo condensation with aromatic aldehydes, such as benzaldehyde, to yield a diphenylmethane derivative (VII) (123). The intermediate (VI) rearranges immediately after formation to the aromatic isomer (VII).



(b) *Two exocyclic bonds:* Compounds such as zingiberene (VIII) and bisabolene (IX) fall into this class, but no record of rearrangements of these compounds to the corresponding alkylbenzenes has been found. Subjection of both

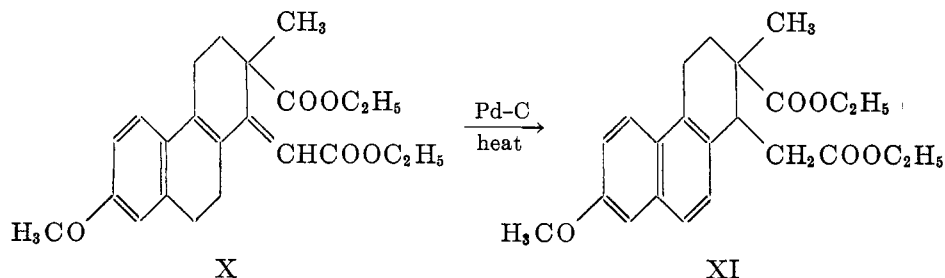


compounds to conditions which might be expected to lead to isomeric aromatization results instead in ring closure to a hydrogenated cadalene. Dehydrogenation conditions lead to cadalene, owing to this ring closure (106).

(c) *Three exocyclic bonds:* No examples in this class have been found.

## 2. Naphthalene derivatives

(a) *One exocyclic bond:* An example in this group is the rearrangement of vinyl-dihydronaphthalene previously cited (50). Another example is the isomerization carried out by Bachmann, Kushner, and Stevenson (9) in which the

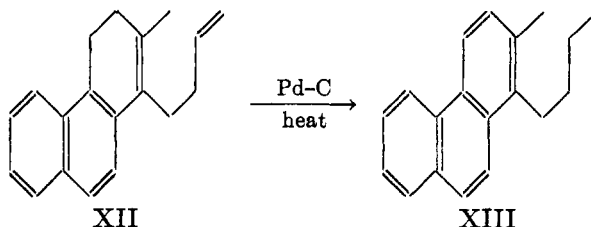


ester X was converted into its aromatic isomer, XI, by heating with a palladium-charcoal catalyst.

(b) *Two or more exocyclic bonds:* No examples in this group have been found.

## 3. Polynuclear derivatives

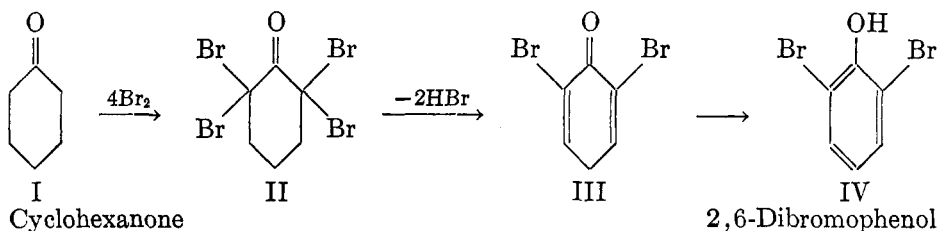
The rearrangements carried out by Bachmann (8, 10), which have been noted earlier (page 113), are examples in this class. Another such rearrangement is the transformation of the hydrocarbon XII into its aromatic isomer XIII by heating with a palladium-charcoal catalyst (21).



## D. ISOMERIZATIONS INVOLVING CARBON-OXYGEN BONDS

## 1. Benzene derivatives

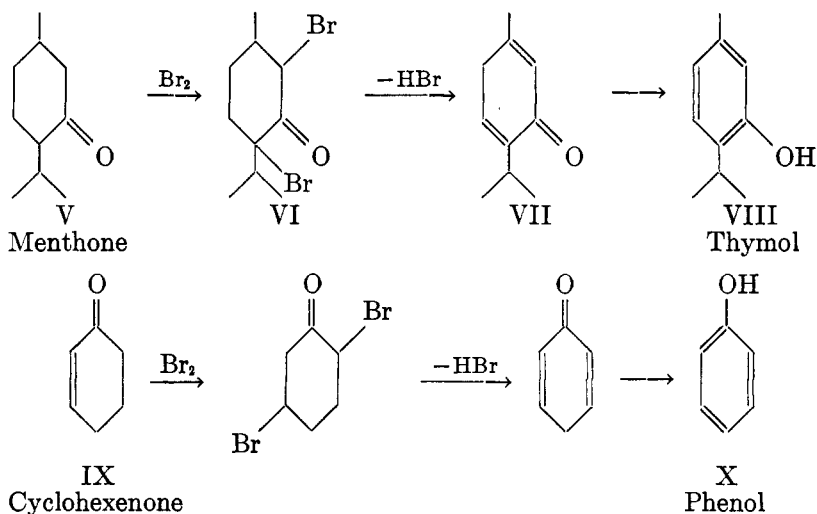
(a) *One exocyclic bond*: This group includes a number of rearrangements of intermediate compounds in certain bromination methods which have been employed for the preparation of phenols. The method in general (12) consists of the preparation of a halogen-containing derivative of a hydroaromatic ketone, followed by dehydrohalogenation to yield an aromatic compound. The halogen, which is usually bromine, may be introduced either by substitution or by addition, and the second step in the reaction is usually accomplished by boiling with a tertiary amine such as dimethylaniline or quinoline, or in some cases simply by heating. The yields vary, but are usually in the range 40 to 60 per cent. For example, cyclohexanone (I) will form a tetrabromo derivative (II) which may be converted into 2,6-dibromophenol (IV) (134); the intermediate which aromatizes is undoubtedly III. A similar series of steps will convert menthone



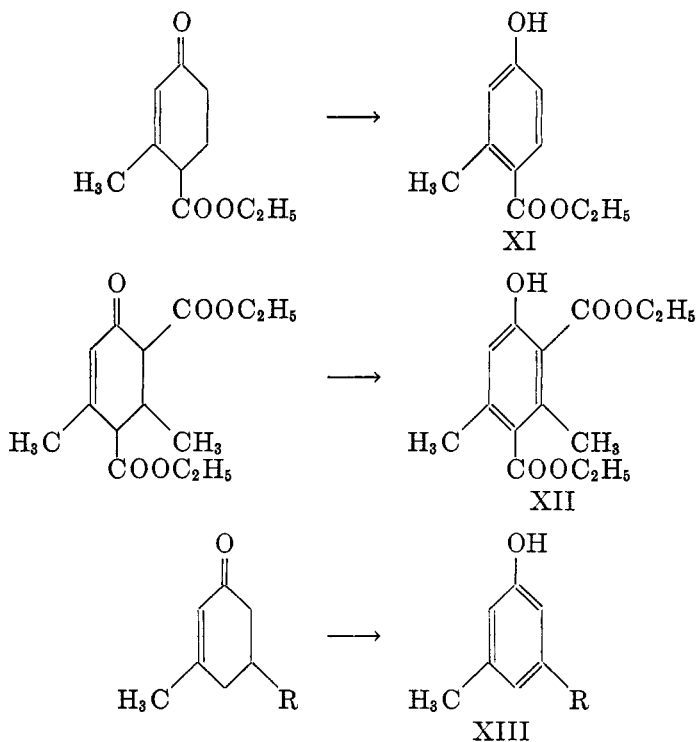
(V) into thymol (VIII) (14) by way of the dibromide (VI). The intermediate which isomerizes is probably VII. In each case the rearrangement occurs at once; the expected intermediates (III and VII) have no more than a transient existence.

$\Delta^2$ -Cyclohexenones may also be aromatized by this method. Presumably the bromine adds in 1,4-fashion to the enol form; dehydrohalogenation can usually be effected easily and the product is the corresponding phenol. This process has been carried out with cyclohexenone (IX) to yield phenol (X) (70), and with

a number of cyclohexenones derived from the bis-esters obtained from acetoacetic ester and aldehydes through the Knoevenagel condensation. The phenolic

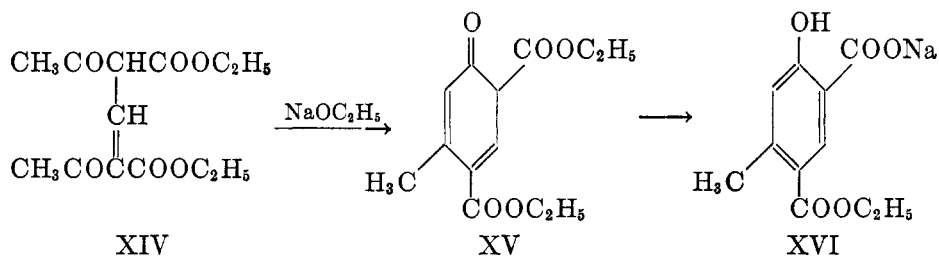


esters XI (102) and XII (67) have been obtained in this fashion. Also, a number of disubstituted phenols (XIII) in which R is an aliphatic radical or hydrogen have been prepared in the same way (68). The general nature of the latter



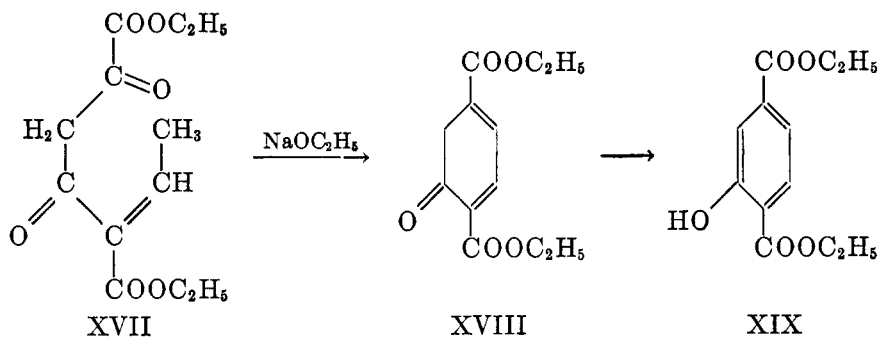
reaction has been studied by Petrov (97) and extended to include aromatic substituents.

There are also several ring-closure reactions which lead to compounds in this group. From ethyl orthoformate and acetoacetic ester there may be obtained ethyl ethoxymethyleneacetoacetate, which will undergo further reaction with ethyl acetoacetate to yield the diester XIV. Under the influence of sodium ethoxide a ring closure occurs to yield the intermediate XV. This is followed by



isomerization and partial saponification of the resulting phenolic ester. The sequence of steps is shown; the product is XVI (23). The reaction may be modified by replacement of the orthoformic ester by related compounds like chloroform or chloral (94, 95).

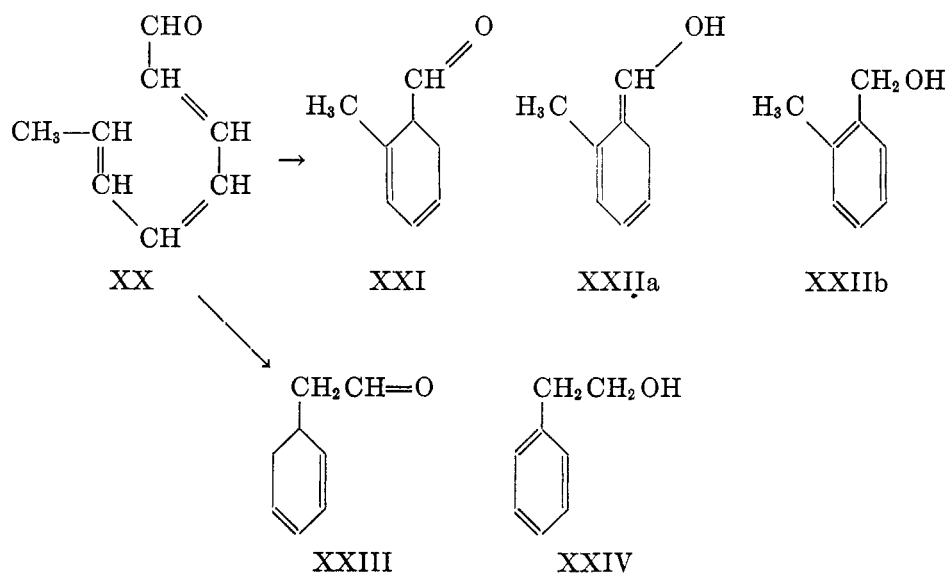
The same ring structure is present in the intermediate (XVIII) presumably obtained from the action of sodium ethoxide on ethyl  $\alpha$ -ethylidene- $\gamma$ -ethoxalylacetoacetate (XVII). The isomerization occurs immediately under the reaction conditions and the product is the hydroxyterephthalic ester XIX (113).



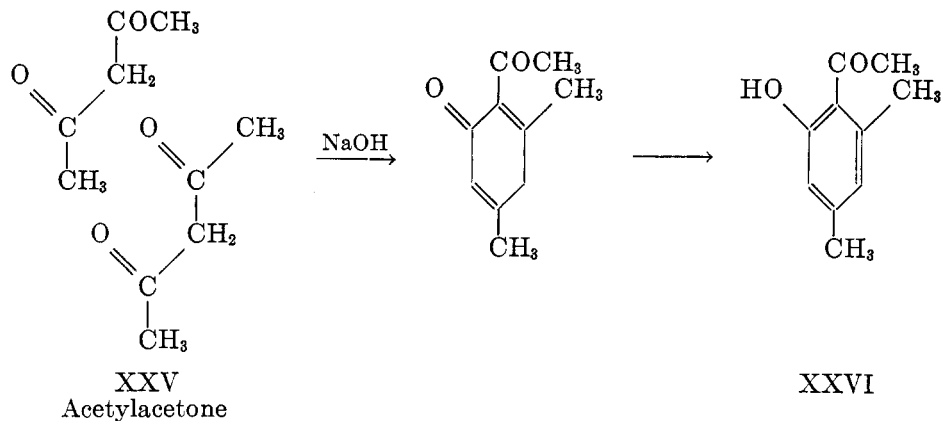
A compound whose reported structure is remarkable in that its isomerization was not observed is the aldehyde XXI. The unsaturated aldehyde XX may be obtained from the self-condensation of crotonaldehyde, and it will itself undergo further reaction through intramolecular addition to yield a cyclic unsaturated aldehyde to which the structure XXI has been assigned. The rearrangement of this compound should take place with great ease, since enolization would provide a hydroxymethylenedihydrobenzene (XXIIa), and this structure would undoubtedly instantly isomerize to the benzyl alcohol XXIIb. An alternative



formulation for the intramolecular addition is that of a Michael vinylog leading to the dihydrobenzene XXIII. This compound (XXIII) should be more stable with respect to rearrangement (to  $\beta$ -phenylethyl alcohol, XXIV) than the dihydrobenzene XXI. The investigators of the reaction, however, have obtained evidence indicating that XXI is the reaction product (15).

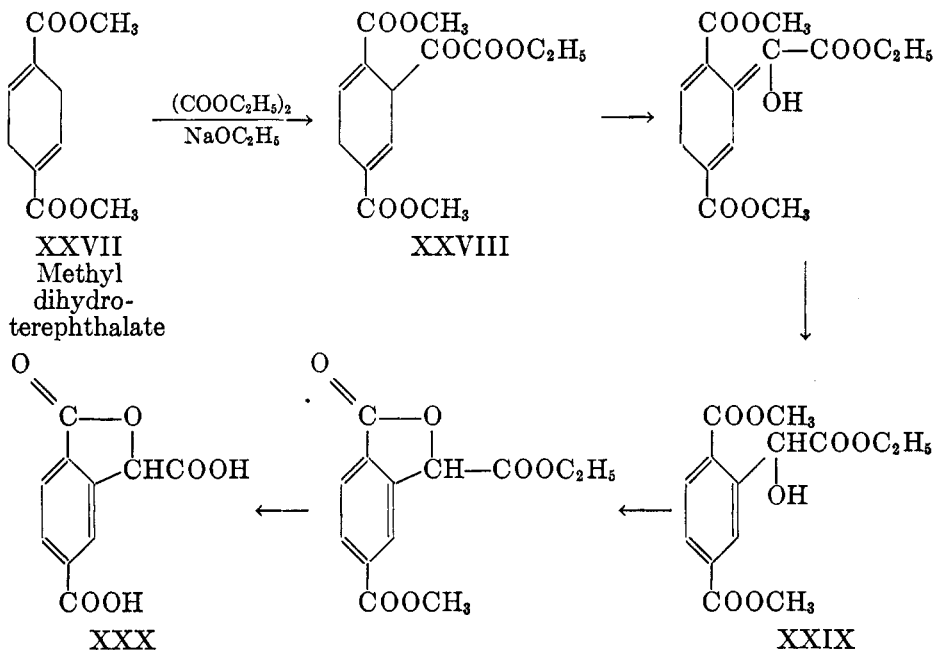


A somewhat different condensation is the reaction of acetylacetone (XXV) with itself under the influence of sodium hydroxide, the product being the hydroxyacetophenone XXVI (55).



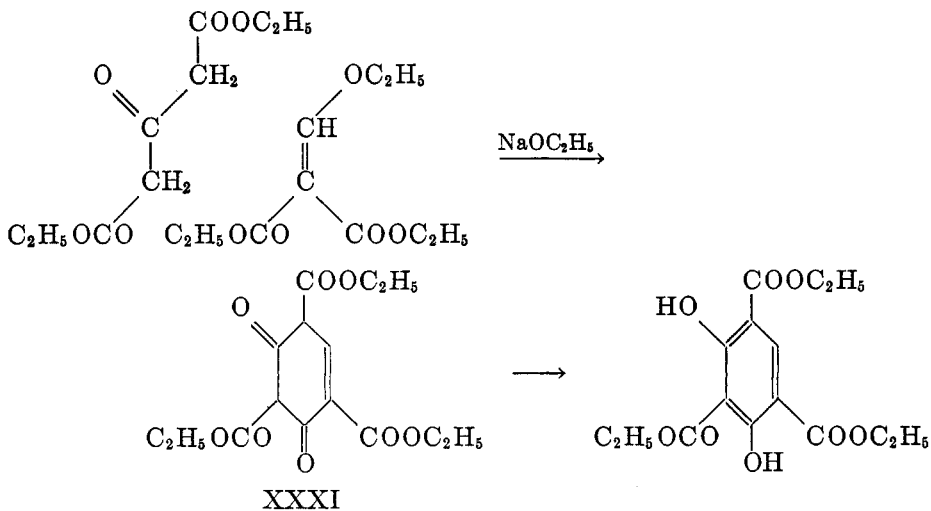
The condensation of methyl dihydroterephthalate with benzaldehyde has been noted previously. The ester (XXVII) will also react with ethyl oxalate in the

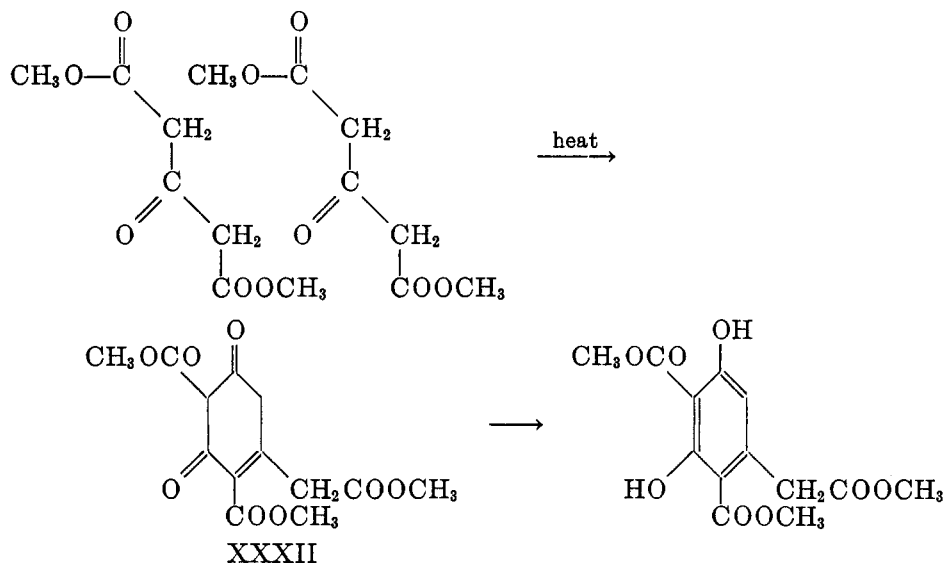
presence of sodium ethoxide. The product is not the glyoxalate (XXVIII), however, since the latter immediately isomerizes to a benzyl alcohol derivative



(XXIX). Lactonization then occurs, and saponification results in the lactonic acid XXX (123).

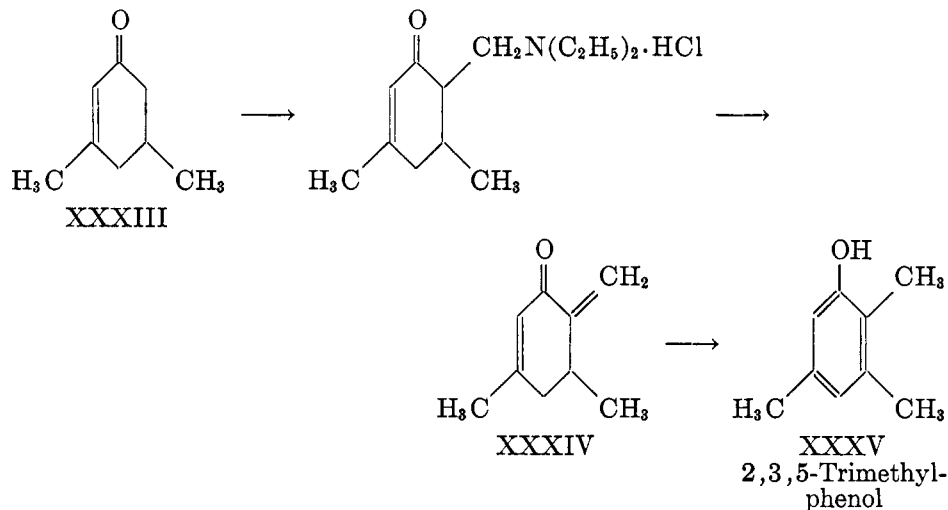
(b) *Two exocyclic bonds:* The rearrangement of carvone should be included here. The circumstances under which it aromatizes have been noted previously. Two condensations affording compounds in this group which isomerize





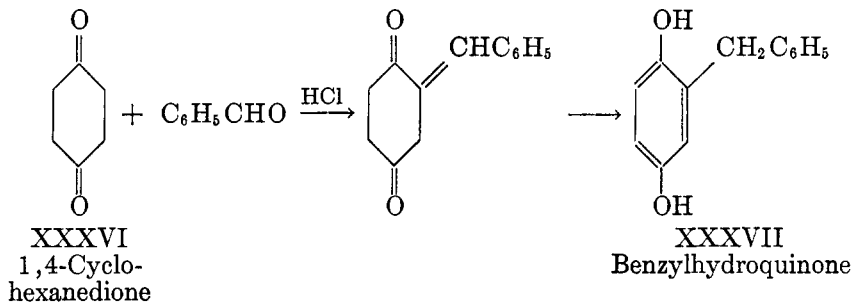
immediately are those described by Errera (XXXI) (39) and Dootson (XXXII) (31).

The  $\Delta^2$ -cyclohexenones of Knoevenagel may be employed for the production of certain trisubstituted phenols. For example, 3,5-dimethyl- $\Delta^2$ -cyclohexenone (XXXIII) may be carried through a Mannich reaction to yield an amine hydrochloride from whose pyrolysis there may be obtained 2,3,5-trimethylphenol (XXXV) (58). The probable mechanism is as shown:

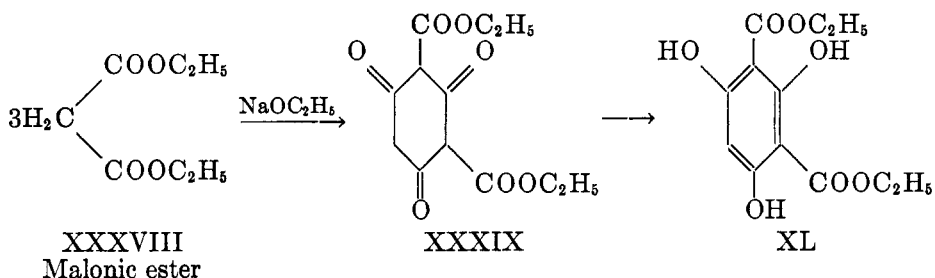


(c) *Three exocyclic bonds:* The condensation of benzaldehyde with cyclohexanone to dibenzal cyclohexanone and the rearrangement of the latter to 2,6-dibenzylphenol have been noted. If benzaldehyde is condensed with 1,4-

cyclohexanedione (XXXVI) the two keto oxygen atoms are transformed into phenolic oxygens and the product is benzyhydroquinone (XXXVII) (120).

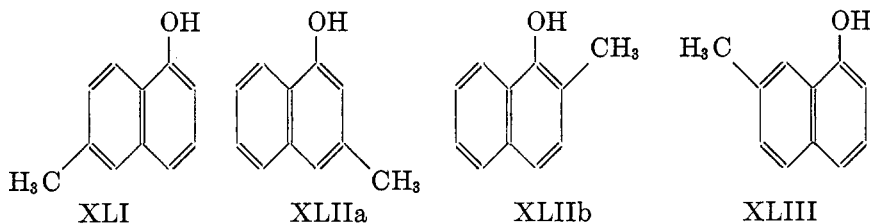


The self-condensation of malonic ester (XXXVIII) (76, 91) may result in a phloroglucinol derivative (XL), the reaction passing through the corresponding tautomeric intermediate (XXXIX).

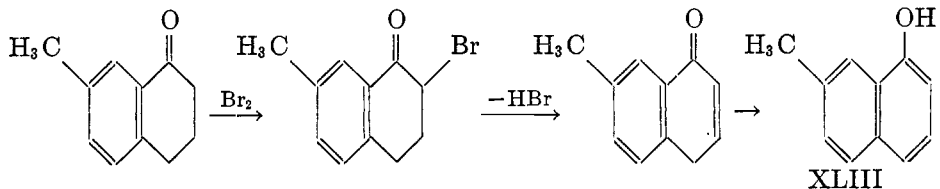


## 2. Naphthalene derivatives

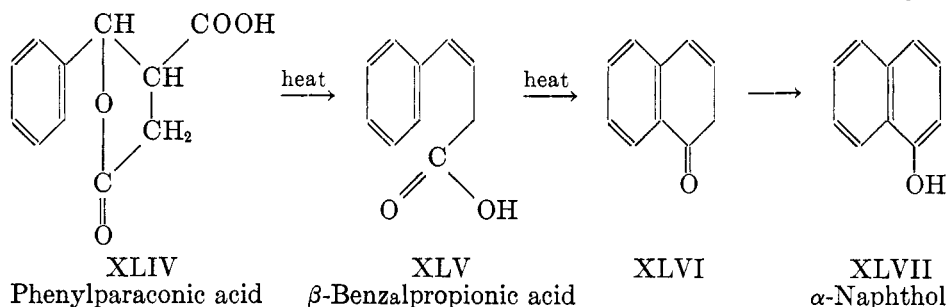
(a) *One exocyclic bond:* This group includes the intermediates in those reactions in which the bromination method of aromatization is employed to convert tetralones into naphthols. Naphthols such as XLI (43), XLIIa and XLIIb (125), and XLIII (75) have been prepared from the corresponding  $\alpha$ -tetralones



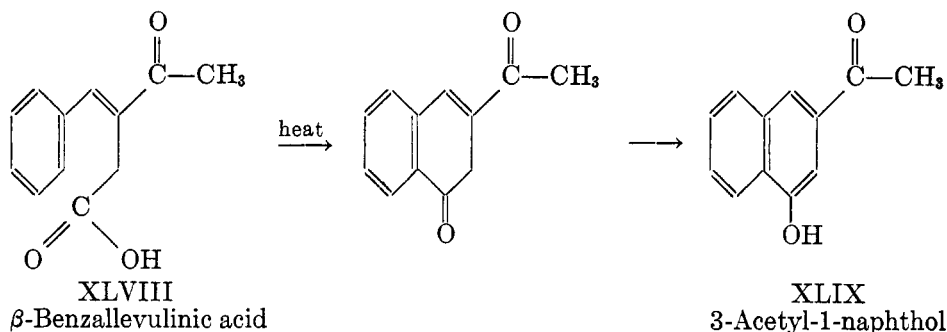
by this process. One bromine atom is introduced in the 2-position by a substitution reaction, and dehydrohalogenation accompanied by isomerization then yields the naphthols. For example:



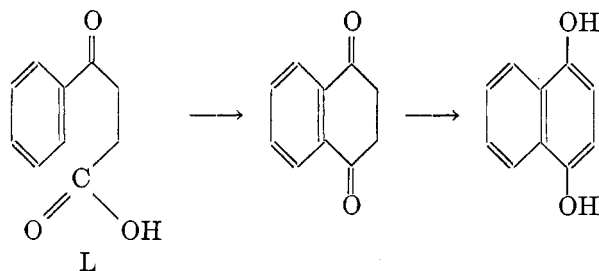
This group also includes compounds intermediate in two interesting series of ring-closure reactions, the Fittig condensation and the condensation of Menon. Both lead to  $\alpha$ -naphthols, but the intermediates involved are different. The Fittig condensation requires the ring closure, under the influence of heat, of an unsaturated acid of the basic structure XLV to a ketonic intermediate (XLVI) which immediately aromatizes to the corresponding  $\alpha$ -naphthol (XLVII). It was found by Fittig that the product of the Perkin condensation of benzaldehyde



and succinic anhydride, phenylparaconic acid (XLIV), decomposed on heating to form the simplest of such acids,  $\beta$ -benzalpropionic acid (XLV) (47). The observation was then made that further heating (distillation) of the unsaturated acid caused its conversion into  $\alpha$ -naphthol (46). The synthesis was later extended to 3-methyl-1-naphthol (48) and to chlorinated naphthols (37, 38). The same basic structure is present in  $\beta$ -benzallevalinic acid (XLVIII), and the trans-

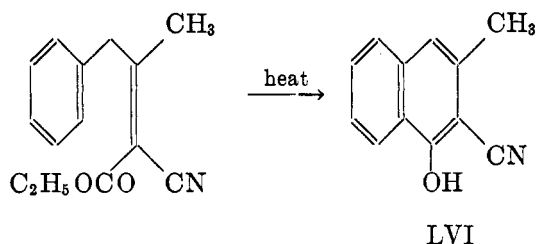
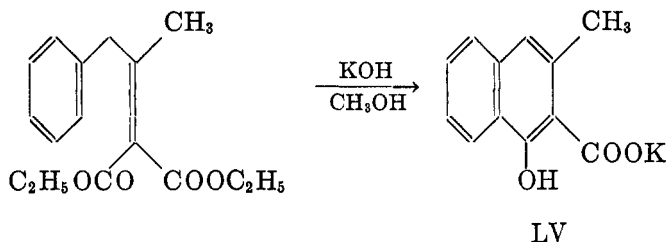
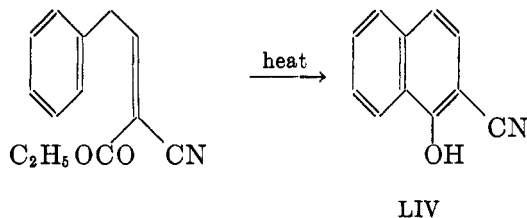
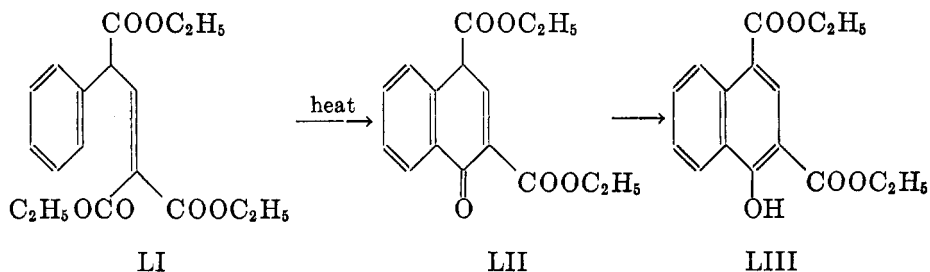


formation of this compound into 3-acetyl-1-naphthol (XLIX) by the same route has been described by Erdmann (36).



It may be of interest to point out that an attempt to cyclize the keto acid L by analogy with the Fittig reaction was unsuccessful (13).

A related condensation may be carried out with certain unsaturated esters. It was found by Menon (87) that the ester LI on heating was converted into the naphthol LIII, the intermediate being as shown (LII). Other examples of this

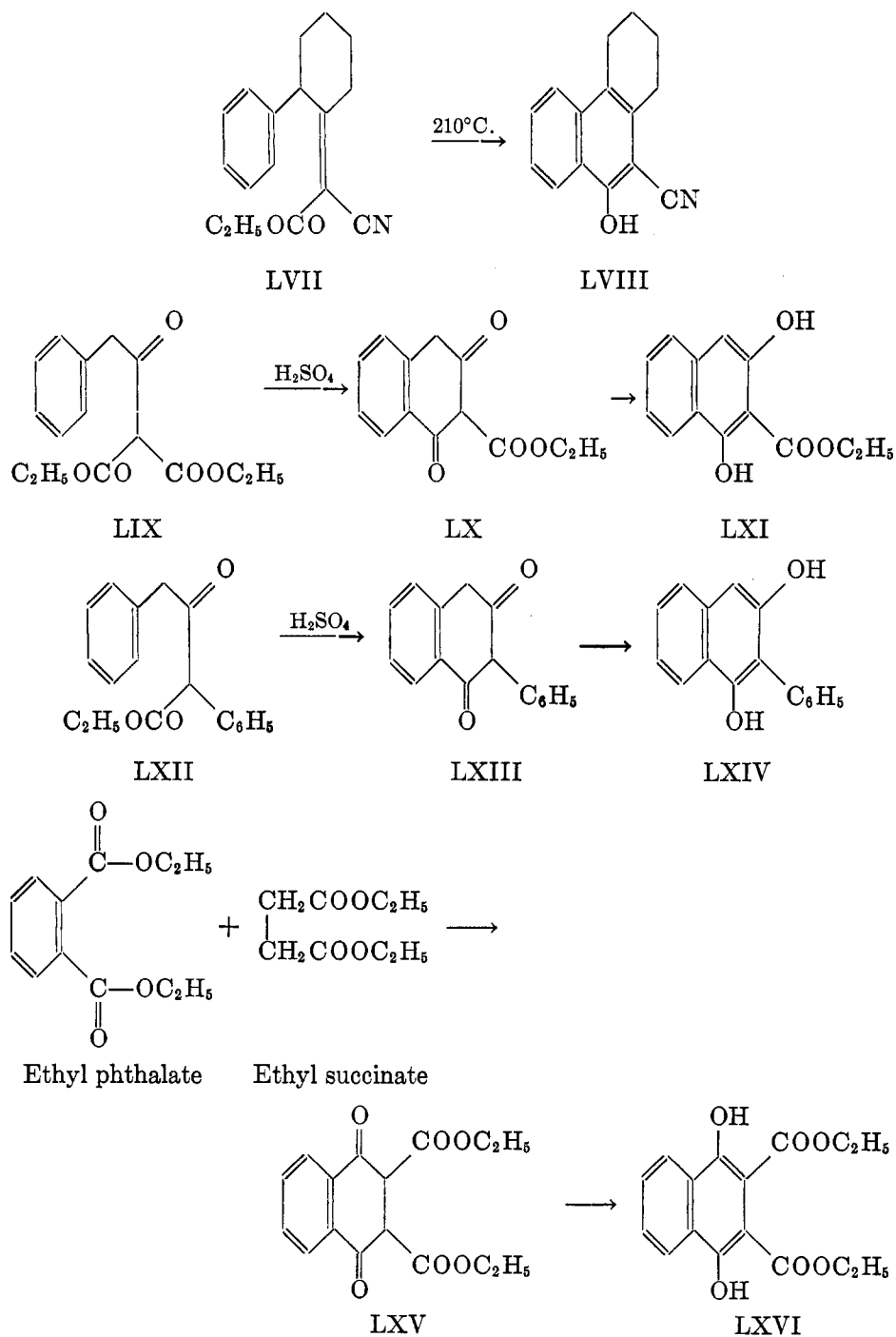


type of condensation leading to LIV, LV, and LVI were found by McRae and Marion (85, 86). The ring closure to LVI was also encountered by Cope (28), who found that the reaction proceeded smoothly in the presence of acetamide at 200–220°C.

Another ring closure of this type was found by Linstead to occur when the ester LVII was heated, the product being LVIII (83).

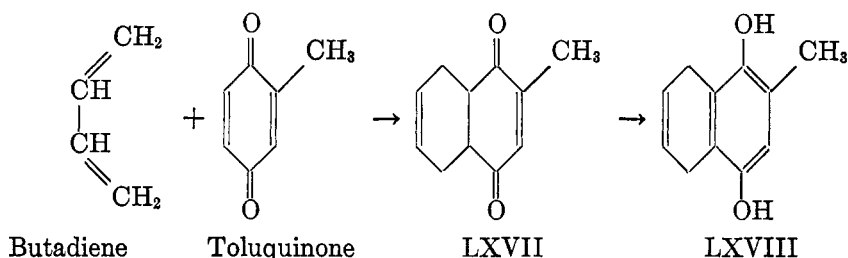
(b) *Two exocyclic bonds:* In this group are compounds resulting from a type of ring closure related to that just described. The keto esters LIX and LXII will undergo ring closure in concentrated sulfuric acid to yield the naphthols LXI (89) and LXIV (129); the probable alicyclic intermediates are as shown (LX and LXIII).

A 1,4-diketone isomeric with a naphthohydroquinone results from the Claisen condensation of ethyl phthalate and ethyl succinate, a reaction recently de-



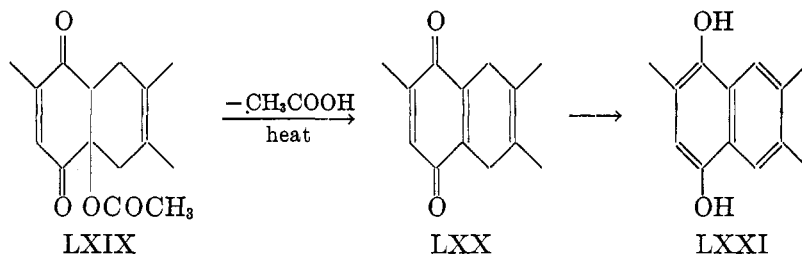
scribed by Homeyer and Wallingford (57). The normally expected product (LXV) rearranged at once under the reaction conditions to the corresponding naphthol (LXVI).

The 1,4-diketo system is also present in a number of dihydronaphthalene isomers which may be obtained from the Diels-Alder addition of benzoquinones and butadiene (44, 45). For example, toluquinone and butadiene will undergo addition to yield the diketone LXVII. This is an alicyclic isomer of the di-



hydronaphthohydroquinone LXVIII, and its isomeric aromatization to the latter may be effected simply by adding a little hydrochloric acid to an ethanol solution of the diketone. Stannous chloride is usually also added to protect the resulting hydroquinone against oxidation. In general, the rearrangement of these compounds will take place under the influence of traces of either acids or bases. (This reaction involves aromatization to a benzene ring rather than to the naphthalene structure, but is placed here because it is used for the preparation of 1,4-naphthohydroquinones.)

A similar type of intermediate, but one which in this case has no more than a hypothetical existence, results from the thermally induced expulsion of acetic acid from the diketoalcohol acetate LXIX (22). The reaction product is the 1,4-

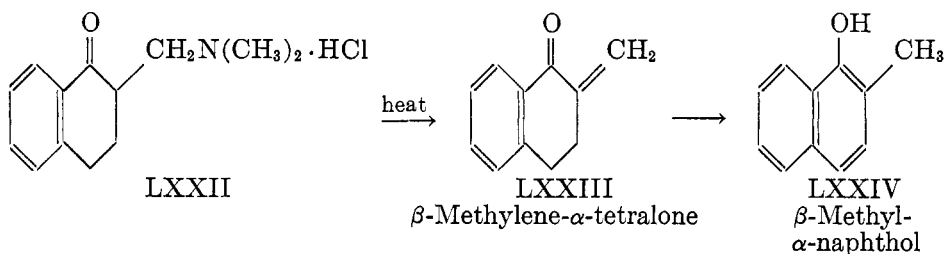


naphthohydroquinone (LXXI) isomeric with the normally expected alicyclic diketone LXX.

A product of the Mannich reaction with  $\alpha$ -tetralone is the ketoamine hydrochloride LXXII. Deamination results in the *o*-methylene ketone LXXIII. This compound is an alicyclic isomer of  $\beta$ -methyl- $\alpha$ -naphthol (LXXIV) and may be isomerized to the latter (59). The intermediate here (LXXIII) has a longer life under similar conditions than benzene analogs, and when allowed to stand the tendency to dimerize is apparently greater than the tendency to isomerize.



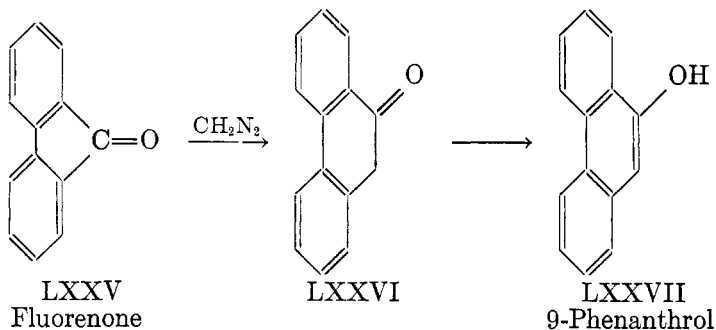
The compound reported a few years ago (62) as  $\beta$ -methylene- $\alpha$ -tetralone (LXXIII) does not have this structure, but is a dimer (59).



### 3. Polynuclear derivatives

An example is found in the production of a phenanthrol from the corresponding tetralone-like compound by the bromination method (92). The method follows that described for phenols and naphthols.

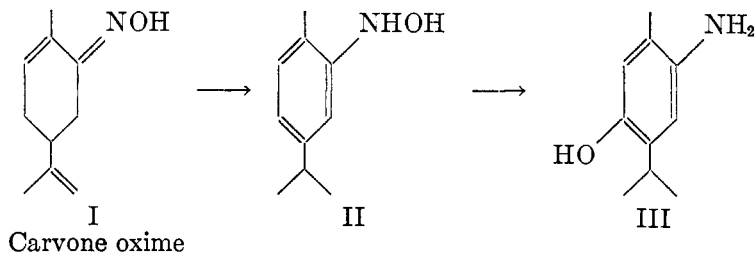
The ring-expanding effect of diazomethane when applied to alicyclic ketones can also be extended to aromatic ketones. Fluorenone (LXXV) when treated with diazomethane should provide an intermediate of structure LXXVI. The



product of the reaction is actually the aromatic isomer, 9-phenanthrol (LXXVII), principally as the methyl ether (114).

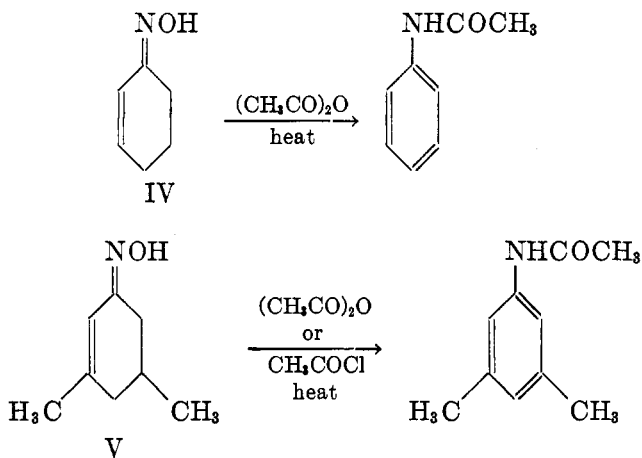
### E. ISOMERIZATIONS INVOLVING CARBON-NITROGEN BONDS

Very few such rearrangements are to be found in the literature, although the method offers a potential source of some unusual hydroxylamines and amines. Carvone oxime (I) has been mentioned previously, and another reaction of this oxime which definitely demonstrates its mode of isomerization is the formation of the *p*-aminophenol III through the action of sulfuric acid on the oxime (133).

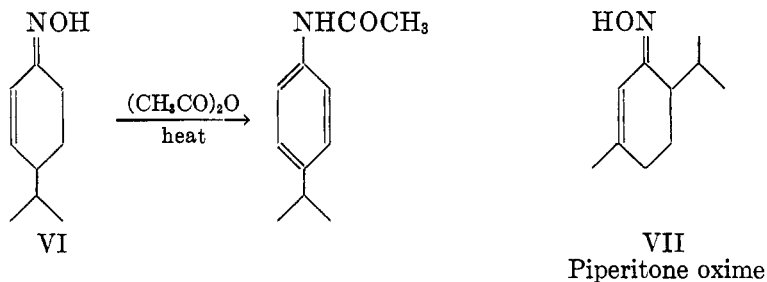


The intermediate is the hydroxylamine (II) isomeric with the oxime, and the *p*-aminophenol (III) derives from this hydroxylamine by the usual rearrangement of such compounds.

A reaction which may require inclusion at this point is Wolff's method for the conversion of oximes to amines. The oximes of certain cyclohexenones are converted to amines (in the form of the hydrochloride or the aceto derivative) by heating with such agents as hydrochloric acid, acetic anhydride, or acetyl chloride. The reaction conditions suggest a dehydration, followed by rearrangement, but it is difficult to describe the intermediate. The normal dehydration of an oxime to a nitrile is denied by the preservation of the ring structure which includes the oxime carbon atom. The simplest such rearrangement is that of  $\Delta^2$ -cyclohexenone oxime (IV) (71); another is that of the oxime of 3,5-dimethyl- $\Delta^2$ -cyclohexenone (V) (144). The same reaction was found by Macbeth (26) to



occur with the oxime VI. Piperitone oxime (VII) and carvone oxime (I) underwent the reaction much less readily.



The same type of reaction, applied this time to  $\alpha$ -tetralone and substituted  $\alpha$ -tetralone oximes, was investigated by Schroeter (112). A number of  $\alpha$ -naphthylamines were obtained, the general reaction being:



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