

# Molecular Rearrangements Related to the Claisen Rearrangement

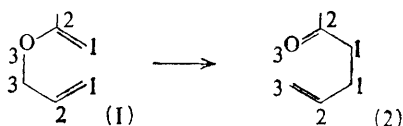
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The Claisen rearrangement involves the thermal transformation of an allyl vinyl ether into a homoallylic carbonyl compound (Scheme 1) by a concerted intramolecular pathway. The all-carbon analogue is known as the Cope rearrangement. The Claisen rearrangement is better known for the rearrangement



*Scheme 1*

of allyl phenyl ethers [(3)  $\rightarrow$  (4)  $\rightarrow$  (5) and (3)  $\rightarrow$  (6)  $\rightarrow$  (7)] where the vinyl moiety is now an integral part of an aromatic ring, and this reaction has been extensively investigated.<sup>1</sup> The more unusual aspects however have been largely beyond the scope of previous reviews, and it is now proposed to deal with some extensions of the Claisen rearrangement. Some emphasis will be given to synthetic aspects.

This Review is not comprehensive, but selects some examples which deviate from the Claisen rearrangement, and where possible correlates them in mechanistic terms. Fortunately the related rearrangements can be readily understood by first a brief consideration of the essential steps of the mechanism of the Claisen rearrangement, and by use of the selection rules for sigmatropic changes.

## 1 Mechanism of the Claisen Rearrangement

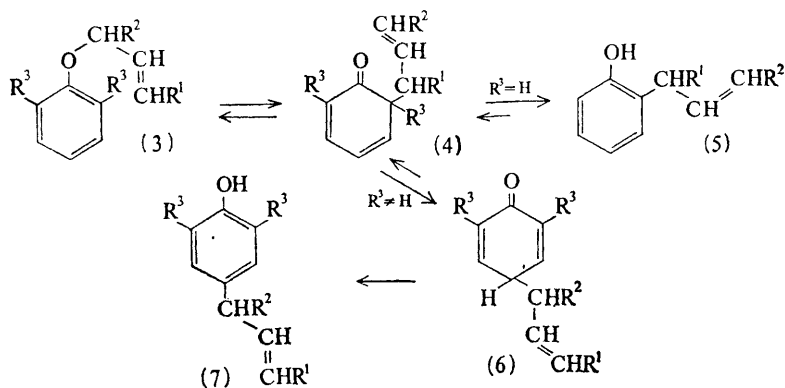
The thermal rearrangement of allyl phenyl ether (3) proceeds by an intramolecular pathway to give an *ortho*-dienone (4) which rapidly enolises to the

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2-allylphenol (5). The net result is that the  $\gamma$ -carbon atom of the allyl phenyl ether now becomes directly attached to the benzene ring in the formation of 2-allylphenol (this process is often referred to as 'inversion' of the allyl group and in this sense the term gives no information about the stereochemical properties of the rearrangement) and this has been demonstrated by labelling experiments and the use of substituents in the allyl group (Scheme 2). When the *ortho* positions are substituted (e.g.,  $R^3 = \text{alkyl}$ ) and enolisation is impossible, a Cope type rearrangement gives a *para*-dienone (6) and hence a 4-allylphenol (7). The *para* Claisen rearrangement occurs with two reversals of ends of attachment of the allyl group and labelling experiments show that the carbon atom that was attached to the ether oxygen atom is now directly attached to the benzene ring.<sup>1</sup>

Kinetic results show that both *ortho* and *para* rearrangements are first order reactions, and negative entropies of activation support the involvement of highly ordered cyclic transition states. Further details about the transition state are vague because the Claisen rearrangement is largely insensitive to the probes for ionic and free-radical character. Since the rearrangement cannot be classified in classical terms as either a homolytic or a heterocyclic reaction, it has been referred to as a reaction which proceeds by a 'no mechanism' pathway.<sup>1b</sup>

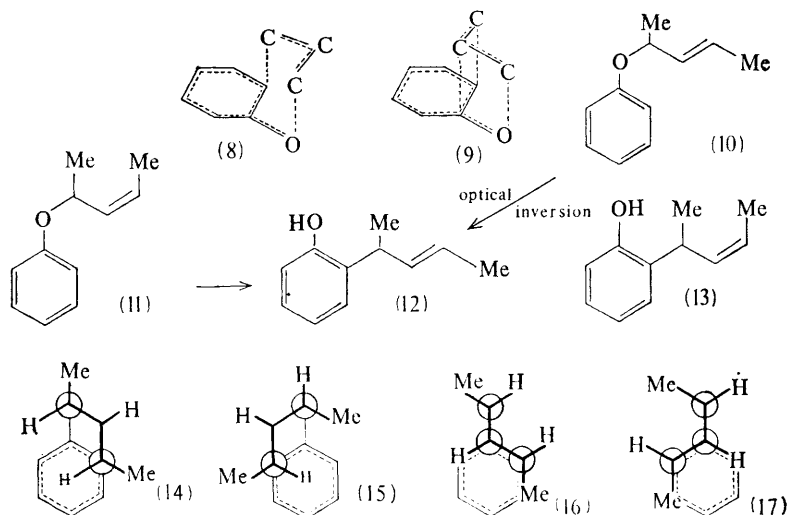


Scheme 2

The stereochemical relationship between reactant and product in the Claisen rearrangement can be derived by considering a transition state where the six atoms concerned in bond and electron redistribution can adopt either a quasi-chair ( $\alpha$ ) or a quasi-boat ( $\gamma$ ) conformation. This leads to the conclusion that the rearrangement of *trans*- and *cis*- $\alpha\gamma$ -dimethylallyl phenyl ether (10 and 11) gives

<sup>1</sup> (a) D. S. Tarbell, 'The Claisen Rearrangement in Organic Reactions', ed. R. Adams, J. Wiley, New York, 1944, vol. II, p. 1. (b) S. J. Rhoads, 'Rearrangements Proceeding through "No Mechanism Pathways"', in 'Molecular Rearrangements', ed. P. de Mayo, Interscience, New York, 1963, vol. I, p. 655. (c) H. J. Shine, 'Aromatic Rearrangements', Elsevier, Amsterdam, 1967, p. 89.

largely the *trans*-2-( $\alpha\gamma$ -dimethylallyl)phenol (12) and that asymmetry can be induced. Thus Goering and Kimoto<sup>2</sup> showed that *R*(+)-*trans*- $\alpha\gamma$ -dimethylallyl phenyl ether gave a mixture of *cis*- (13) and mainly *trans*-2-( $\alpha\gamma$ -dimethylallyl)phenol (12). Hydrogenation of this mixture gave *S*(-)-2-(2-pentyl)phenol. In an independent study<sup>3</sup> it was shown that both *cis*- (11) and *trans*- $\alpha\gamma$ -dimethylallyl phenyl ether (10) gave largely the *trans*-2-( $\alpha\gamma$ -dimethylallyl)phenol (12) on thermal rearrangement. These results do not distinguish between the quasi-boat and quasi-chair transition states since both conformations lead to the same result. This can be illustrated by use of modified Newman projection formulae (14—17). The three carbon atoms of the allyl group and their substituents are represented by the thickened lines to show that they are in a plane above, but parallel to, the benzene ring. Two possible quasi-chair transition states (14) and (15) are shown for the *trans*-ether (10) but conformation (14) will require the lower activation energy because the non-bonding interaction of the methyl groups is at a minimum. For the quasi-boat conformations (16 and 17) similar considerations favour (16). Both conformations (14 and 16) lead to the *trans*-2-( $\alpha\gamma$ -dimethylallyl)phenol (12). From the above results it is not possible to exclude the quasi-boat conformation in the transition state, but more definitive experiments which favour a quasi-chair conformation<sup>4a</sup> will be the subject of another review.<sup>4b</sup>



The advantages of the stereospecificity of the Claisen rearrangement in synthetic work are immediately obvious: not only can the rearrangement be used to create a new stereochemical centre by asymmetric induction, but in

<sup>2</sup> H. L. Goering and W. I. Kimoto, *J. Amer. Chem. Soc.*, 1965, **87**, 1748.

<sup>3</sup> E. N. Marvell, J. L. Stevenson, and J. Ong, *J. Amer. Chem. Soc.*, 1965, **87**, 1267.

<sup>4</sup> (a) H. Schmid, Chemical Society Symposium on Stereochemistry, Sheffield, December 1966. (b) *Chem. in Britain*, to be published.

addition it provides a valuable method for correlating configurations especially in alicyclic chemistry.<sup>5</sup>

## 2 Sigmatropic Rearrangements

The Cope and Claisen rearrangements have recently been classified by Woodward and Hoffmann<sup>6</sup> as sigmatropic changes of the order  $[i,j]$  where  $i$  and  $j$  each corresponds to 3. The order  $[i,j]$  refers to the extent of migration of a sigma bond along one or more  $\pi$ -electron systems during a concerted electron and bond reorganisation process, where the actual distance traversed is  $i - 1$  and  $j - 1$  atoms. Thus in the Claisen and Cope rearrangements the bond which appears to connect two 'allyl' systems at atoms designated 3,3 appears to move down two  $\pi$ -electron systems to positions 1,1 (Scheme 1). It can be shown by use of the phase relationships of the highest occupied molecular orbital that for rearrangements of the order  $[i,j]$  in which both  $i$  and  $j$  are greater than unity, thermal changes are symmetry-allowed when  $i + j = 4n + 2$  while photochemically excited transformations are permitted when  $i + j = 4n$ . This rule requires modification for migrations to a charged site.

For a pictorial interpretation of the rule based on Hückel molecular orbital theory, consider the  $\pi$ -electron system over the three carbon atoms of an allyl group.<sup>7</sup> These can be described by three molecular orbitals  $\psi_1$ ,  $\psi_2$ , and  $\psi_3$  and it must be remembered that no more than two paired electrons can occupy a given orbital. The three energy levels described as bonding, non-bonding, and anti-bonding are diagrammatically represented in Figure 1.

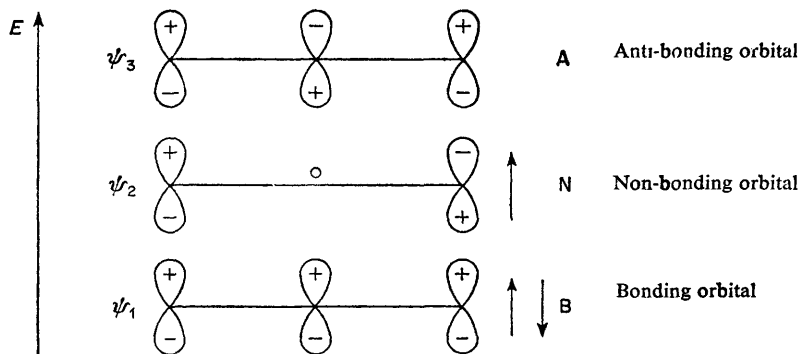


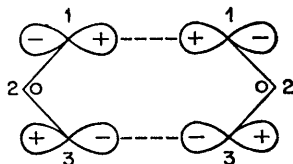
Figure 1

<sup>5</sup> R. K. Hill and A. G. Edwards, *Tetrahedron Letters*, 1964, 3239.

<sup>6</sup> R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, 1965, **87**, 2511, 4389, and personal communication from Professor R. Hoffmann.

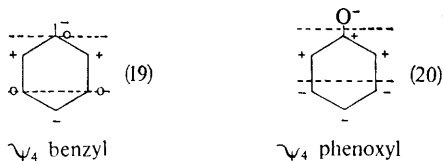
<sup>7</sup> For an introduction to molecular orbital theory see J. D. Roberts, 'Notes on Molecular Orbital Calculations', W. A. Benjamin, New York, 1962; A. Streitwieser, jun., 'Molecular Orbital Theory for Organic Chemists', John Wiley and Sons, New York, 1961.

The positive and negative signs refer to the phase of the wave function and bonding can only occur between atomic orbitals of the same phase. In the allyl radical, which has three electrons, indicated by arrows,  $\psi_2$  represents the highest occupied molecular orbital. If it is assumed that the Cope rearrangement proceeds by formation and combination of allyl quasi-radicals in the transition state, the diagram (18) of the highest occupied molecular orbitals shows that the [3,3] change is permitted whereas the [1,3] sigmatropic shift is not. [Experimental data<sup>8a</sup> show that the conclusions are identical for the rearrangement of allyl vinyl ethers.] In this concept of the transition state atoms 1,1 and 3,3 are associated in order that relative phases of the allyl orbitals are maintained, but the manner in which the two molecular orbitals perturb one another has not been considered. The Figure is consistent with the



(18)

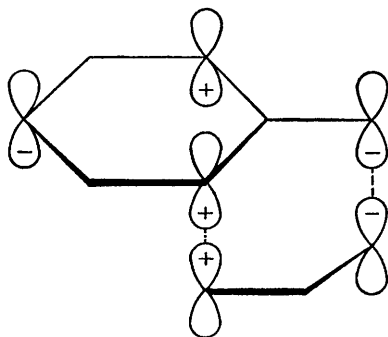
stereochemical requirements for intramolecular allylic rearrangements which demands that bond breaking and bond formation both occur on the same face of the allyl group. This is classified as a suprafacial migration in the terminology of Woodward and Hoffmann.<sup>6</sup> For the Claisen rearrangement of allyl phenyl ether and for the allyl migration in the all-carbon analogue, 4-phenylbut-1-ene,<sup>8b</sup> the highest occupied molecular orbital for the seven  $\pi$ -electrons of the phenoxy and benzyl radicals will be given by  $\psi_4$  in each case (19 and 20).<sup>9</sup> (Allyl migration to the *ortho* position in allyl phenyl ether, or in 4-phenylbut-1-ene, can be regarded as either a [3,3] or a [3,7] sigmatropic change depending on which way the sigma bond is considered to migrate along with the aromatic ring. Where there is a choice, in agreement with the views of Professor Roald Hoffmann, the lowest possible numbers have been assigned to a sigmatropic change. This means that all Claisen rearrangements can be regarded as [3,3] changes regardless of whether the reaction occurs in aliphatic or polynuclear aromatic compounds. For the theoretical interpretation, all the  $\pi$  electrons in the orbitals must be considered



<sup>8</sup> (a) Y. Pocker, *Proc. Chem. Soc.*, 1961, 141; (b) W. von E. Doering and R. A. Bragole, *Tetrahedron*, 1966, 22, 385.

<sup>9</sup> (a) G. Wagnière, personal communication; (b) E. Heilbronner and P. A. Straub, 'Hückel Molecular Orbitals', Springer-Verlag, Berlin, 1966.

which necessitates the use of aromatic orbitals in aromatic rearrangements.) It can be seen that the highest occupied molecular orbitals for the benzyl and phenoxy radicals are similar and the only differences that emerge are due to the position of the nodal planes (shown by broken lines) with respect to the substituent atom. Thus the phase of the wave function changes sign between the substituent atom and the *ortho* positions and changes again at the *para* position. The consequences of these features in the Claisen rearrangement are now clear. The transition state will be represented by  $\psi_2$  from the allyl radical and  $\psi_4$  from the phenoxy radical (21). By the very nature of the wave functions, allyl migration to the *ortho* position is allowed thermally and this may be followed by a further rearrangement of the allyl group to the *para* position. However, since the phase of the wave function is the same at both *ortho* positions an *ortho-ortho* migration with 'inversion' of an allyl group cannot occur thermally by a concerted mechanism. An alternative step-wise mechanism will be discussed in this Review to account for products arising from apparent *ortho-ortho* migrations.



(21)

A general rule for sigmatropic changes which includes migrations to charged sites and takes account of the suprafacial route can equally be given in terms of the total number of electrons involved in the transition state. Thus if there are  $(4n + 2)$   $\pi$ -electrons in the transition state, a sigmatropic change is thermally allowed by the suprafacial route. For rearrangements which occur under photochemical stimulus in the first excited state these rules may be reversed. It is a consequence of the Woodward-Hoffmann rules that a Claisen rearrangement which proceeds with 'inversion' by photochemical excitation cannot be a concerted process.

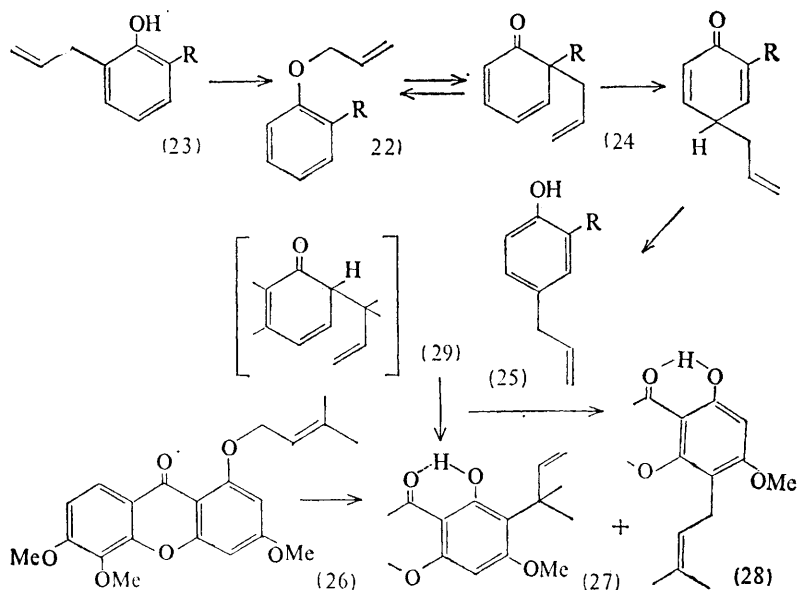
### 3 Rearrangement of Allyl Aryl Ethers

#### Rearrangement to the *para* Position in the Absence of one *ortho* Substituent.—

The thermal rearrangement of allyl aryl ethers to the *p*-allylphenol (Scheme 2) is possible by two [3,3] sigmatropic transformations and in principle can occur whenever the usually rapid enolisation of the *ortho*-dienone intermediate is hindered, or when the enolisable hydrogen is replaced by a substituent.

The 120 examples collected for an early Review<sup>1a</sup> show that an allyl group migrates almost exclusively to an *ortho* position if one is free. The few exceptions quoted, 1-(3,3-dimethyl allyl)-2-methoxyphenyl ether, allyl 2-hydroxyphenyl ether, and allyl 2,3-methylenedioxyphenyl ether all gave *para* rearrangement products. In a more recent review<sup>1b</sup> Rhoads pointed out that in the case of allyl aryl ethers which are substituted at only one *ortho* position a mixture of products can arise, and should be expected, from competitive *ortho* and *para* rearrangement. Marvell and his co-workers<sup>10</sup> confirmed this suggestion by showing that in the rearrangement of allyl 2-alkylphenyl ethers (22) the predominating product in each case, 6-allyl-2-alkylphenol (23), was accompanied by a small amount (*ca.* 10%) of the 4-allyl-2-alkylphenol (25). The size of the alkyl group which varied from methyl to *t*-butyl had a surprisingly small influence on the ratio of the products formed. The ratio of *ortho* to *para* product is dependent on the relative rates of migration to the two *ortho* positions and the partitioning of the dienone (24) between return to the ether (22) and migration to the *para* position.

Migration of the allyl group to the *para* position of ethers possessing a vacant *ortho* position has been used as a synthetic route to natural phenols with  $\gamma\gamma$ -dimethylallyl side chains. Thus the Claisen rearrangement of the  $\gamma\gamma$ -dimethylallyloxyxanthone (26)<sup>11</sup> gave the expected *o*- $\alpha$ -dimethylallylphenol



<sup>10</sup> E. N. Marvell, B. Richardson, R. Anderson, J. L. Stephenson, and T. Crandall, *J. Org. Chem.*, 1965, **30**, 1032.

<sup>11</sup> (a) E. D. Burling, A. Jefferson, and F. Scheinmann, *Tetrahedron*, 1965, **21**, 2653; (b) A. Dyer, A. Jefferson, and F. Scheinmann, *J. Org. Chem.*, 1968, **33**, 1259.

(27) but the main product (28) was due to an intramolecular *para* migration and gave the dimethyl ether of ugaxanthone (from the heartwood of *Symphonia globulifera* L.).<sup>12</sup> The circumstantial evidence here would suggest that the *para* rearrangement product was not formed from an initial rearrangement to the blocked *ortho* position because with simple 1-allyloxyxanthenes<sup>11, 13</sup> no *para* migration could be detected. Thus a more plausible explanation is that rearrangement to the free *ortho* position would yield a dienone (29) where steric factors allow a further [3,3] sigmatropic shift to become a competitive process with enolisation to the 2-( $\alpha$ -dimethylallyl)xanthone (27).

**Rearrangement to the *para* Position in Allyl Phenyl Ethers with no *ortho* Substituents.**—Borgulya, Hansen, Barner, and Schmid<sup>14</sup> observed that both *ortho* and *para* rearrangement can occur when both *ortho* positions are unsubstituted (30  $\rightarrow$  31 + 32). The observations were made with the rearrangement of  $\gamma$ -methyl and  $\gamma$ -phenylallyl phenyl ethers (30) having substituents in the 3,5-positions of the benzene ring. The *ortho* : *para* ratio depends on the substituent size in the allyl moiety and the nature of the solvent used.

On heating 3,5-dimethylphenyl  $\gamma$ -methylallyl ether (30a) in *NN*-diethylaniline for 16 hours, 79% of the *ortho* isomer (31a) and 21% of the *p*-methylallylphenol (32a) were obtained, whereas with 3,5-dimethylphenyl  $\gamma$ -phenylallyl ether (30d) the yields of *ortho* (31d) and *para* (32d) rearrangement products were 11.5% and 88.5% respectively. The effect of solvent was demonstrated by also rearranging 3,5-dimethylphenyl  $\gamma$ -methylallyl ether in decalin, benzonitrile, and dimethylformamide under comparable conditions with the result that the *ortho* : *para* ratio of the products changed from approximately 1 : 1 (decalin) to 60 : 1 (in dimethylformamide). In addition, in contrast to most Claisen rearrangements, an isotope effect was observed in the enolisation of the *o*-dienone (33 or 34). Thus replacement of the aromatic protons by deuterium in 3,5-dimethylphenyl  $\gamma$ -methylallyl ether (30a) gave more than double the amount of *para* rearrangement. Clearly therefore steric factors may retard the usually rapid enolisation process. More recent studies have shown that electronic factors can also influence the enolisation of the *ortho*-dienone (33 or 34). Thus introduction of halogens into the 3,5-positions where they can exert a strong  $-I$  effect favours enolisation and gives a high *ortho* : *para* ratio. As expected from these considerations the order of the effect is  $Cl > Br > I > CH_3$ .<sup>15</sup>

In a previous review<sup>16</sup> it was stated that the same yield of *ortho*- and *para*-allylphenols was obtained in the rearrangement of 3,5-dimethylphenyl  $\gamma$ -methylallyl ether (30a) and 3,5-diethylphenyl  $\gamma$ -methylallyl ether (30b). An inspection of the data<sup>14</sup> from both rearrangements carried out by heating in

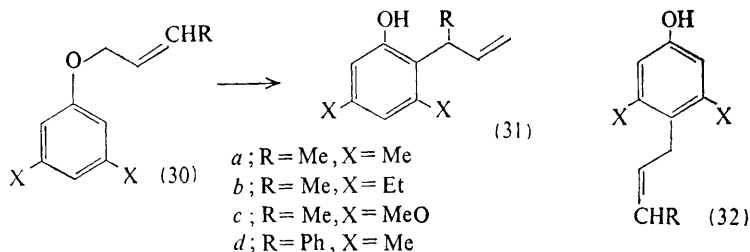
<sup>12</sup> H. D. Locksley, I. Moore, and F. Scheinmann, *J. Chem. Soc. (C)*, 1966, 2265.

<sup>13</sup> F. Scheinmann and H. Suschitzky, *Tetrahedron*, 1959, 7, 31.

<sup>14</sup> J. Borgulya, H.-J. Hansen, R. Barner, and H. Schmid, *Helv. Chim. Acta*, 1963, 46, 2444.

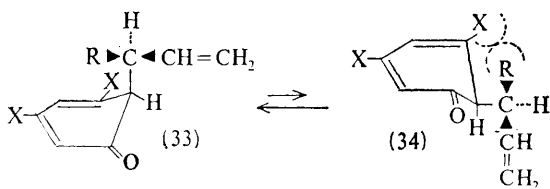
<sup>15</sup> (a) Gy. Fráter and H. Schmid, unpublished work; (b) Gy. Fráter, Ph.D. Thesis, University of Zurich, 1967.



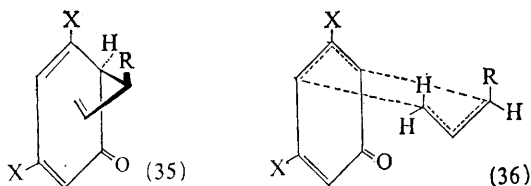


diethylaniline at  $186.5^\circ$  for 16 hr. shows that there are appreciable differences. Thus by replacing the methyl groups at the 3,5-positions by ethyl groups the extent of *para* migration increases (from 21–29%).

The mechanism for the *para* rearrangements must also account for the fact that  $\alpha\gamma$ -dimethylallyl 3,5-dimethylphenyl ether rearranges to give only the *ortho* Claisen product. An examination of a possible transition state (36) for the *para* rearrangement provides an explanation. Thus if rearrangement to give the *ortho*-dienone (33) occurs in the likely stereochemical pathway the side chain will be attached in a pseudo-axial conformation to the cyclohexadienone (33). Interaction of the methyl group on the side chain with the neighbouring groups on the ring will hinder formation of the pseudo-equatorial conformer (34) and therefore hinder enolisation to the *o*-allylphenol.

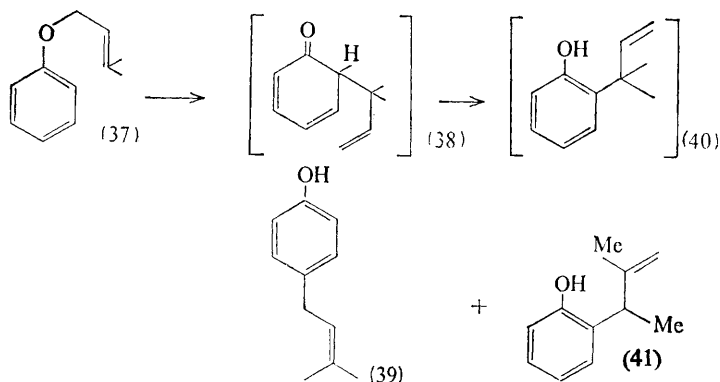


Free rotation of the side chain in the pseudo-axial conformation (33) gives a conformer (35) which has the correct orientation for the Cope-type rearrangement to the *para*-dienone. If it is assumed that the Cope rearrangement goes through the transition state with a quasi-chair conformation, the diagram (36) implies that replacement of either hydrogen atom on the unsubstituted methylene of the allyl moiety will cause a 1,3-diaxial type interaction with the groups on the ring. The experimental results suggest that such an interaction is sufficient to prevent the *para* rearrangement. Similar 1,3-interactions are also possible in a quasi-boat transition state.



That steric hindrance is the driving force for the *para* rearrangement is further illustrated by the allylphenol rearrangement. Thus for example 2- $\alpha$ -methylallyl-3,5-dimethoxyphenol (31c) gave on heating in diethylaniline for 48 hr. the thermodynamically more stable 4- $\gamma$ -methylallyl-3,5-dimethoxyphenol (32c) in 80% yield. Such a reaction presumably occurs by formation of an *ortho*-dienone (e.g., 35) followed by the Cope-type rearrangement. The failure of the 2-( $\alpha\alpha$ -dimethylallyl)xanthone (27) to rearrange further is thus attributed to hydrogen bonding which prevents formation of an *ortho*-dienone.<sup>11a</sup>

The previous examples may give the impression that in fact one *meta* substituent at least is required for the *para* rearrangement. However, recently Scheinmann, Barner and Schmid<sup>16a</sup> have shown that  $\gamma\gamma$ -dimethylallyl phenyl ether (37); rearranges in diethylaniline to 4-( $\gamma\gamma$ -dimethylallyl)phenol (39) in high yield; the other product (41) isolated arises from an abnormal Claisen rearrangement. Claisen reported,<sup>16b</sup> but without experimental details, that the  $\gamma\gamma$ -dimethylallyl ether of phenol gave the expected *ortho* product (40) when heated in sodium carbonate. Attempts to repeat this work failed to give 2-( $\alpha\alpha$ -dimethylallyl)phenol (40).<sup>16a</sup> Clearly steric interactions in the *ortho*-dienone (38) and the 2-( $\alpha\alpha$ -dimethylallyl)phenol (40) [which is the intermediate for the abnormal product (41)] allow further sigmatropic rearrangements to give thermodynamically more stable products. Product control can again be exercised by solvent: reaction in dimethylformamide favours formation of 2-( $\alpha\beta$ -dimethylallyl)phenol (41) (89%) by influencing the enolisation stage (38 $\rightarrow$ 40).

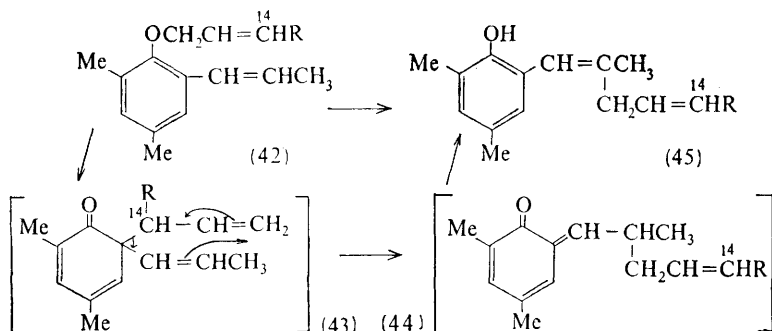


**The Out-of-ring Claisen Rearrangement.**—That the Cope rearrangement may follow a Claisen rearrangement, if such possibilities exist, can account for a more striking variation of the Claisen rearrangement. In 1926 Claisen and Tietze<sup>17</sup> found that a migrating allyl group of a phenyl ether became attached

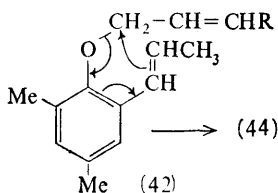
<sup>16</sup> (a) F. Scheinmann, R. Barner and H. Schmid, unpublished work; (b) L. Claisen, F. Kremers, F. Roth, E. Tietze, *J. prakt. Chem.*, 1922, 105, 65.

<sup>17</sup> L. Claisen and E. Tietze, *Annalen*, 1926, 449, 89.

to the central carbon atom of an *o*-propenyl side chain (e.g., 42 → 45). Lauer<sup>18</sup> and Schmid<sup>19</sup> and their co-workers both showed, using different methods, that rearrangement of the allyl group occurred without net 'inversion'. Thus the American group rearranged the crotyl ether (42; R = CH<sub>3</sub>) while the Swiss workers labelled the allyl ether (42; R = H) with <sup>14</sup>C at the  $\gamma$ -carbon atom and in addition showed that the reaction was intramolecular by carrying out a crossing experiment. By analogy with the mechanism for the *para* Claisen rearrangement it was suggested that the out-of-ring migration is a two-cycle process to form first the dienone (43) which rearranges to another dienone (44). Thus two 'inversions' occur during the course of the reaction. This mechanism



is therefore another example of two consecutive [3,3] sigmatropic rearrangements. However the Woodward-Hoffmann selection rules and the experimental data do not exclude the alternative mechanism (42 → 44) whereby formation of the dienone (44) occurs in one stage, because this migration represents a [1,5] sigmatropic shift of an allyl group.



Such a mechanism is not supported by experience since an allyl group does not migrate in this manner. To confirm the mechanism involving two [3,3] sigmatropic shifts it would be necessary to trap the dienone (43), possibly as the maleic anhydride adduct.

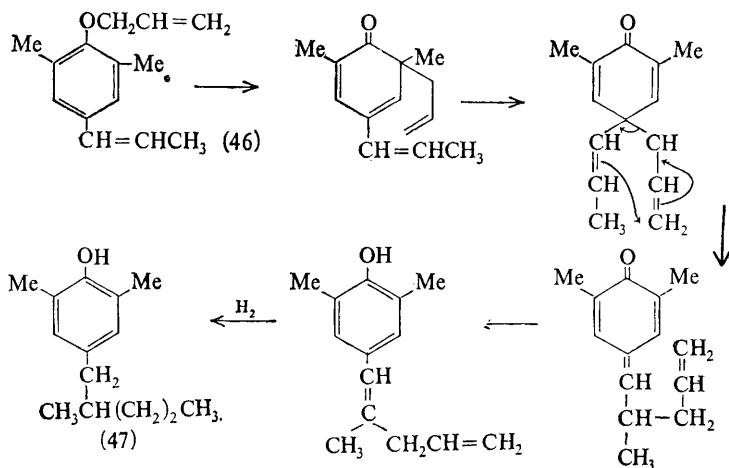
The ability of the allyl group to migrate in stages in the *para* rearrangement, and probably in the out-of-ring migrations, led Nickon and Aaronoff to investigate multistage rearrangements in which the allyl group can traverse

<sup>18</sup> W. M. Lauer and D. W. Wujciak, *J. Amer. Chem. Soc.*, 1956, **78**, 5601.

<sup>19</sup> K. Schmid, P. Fahrni, and H. Schmid, *Helv. Chim. Acta*, 1956, **39**, 708.

## Molecular Rearrangements Related to the Claisen Rearrangement

even greater distances.<sup>20</sup> Thus pyrolysis of the allyl ether of 2,6-dimethyl-4-propenylphenol (46) in ethanol at 200° followed by catalytic hydrogenation gave 2,6-dimethyl-4-(2-methylpentyl)phenol (47) by three step-wise migrations of an allyl group (Scheme 3). To test whether the olefinic unit acting as the



Scheme 3

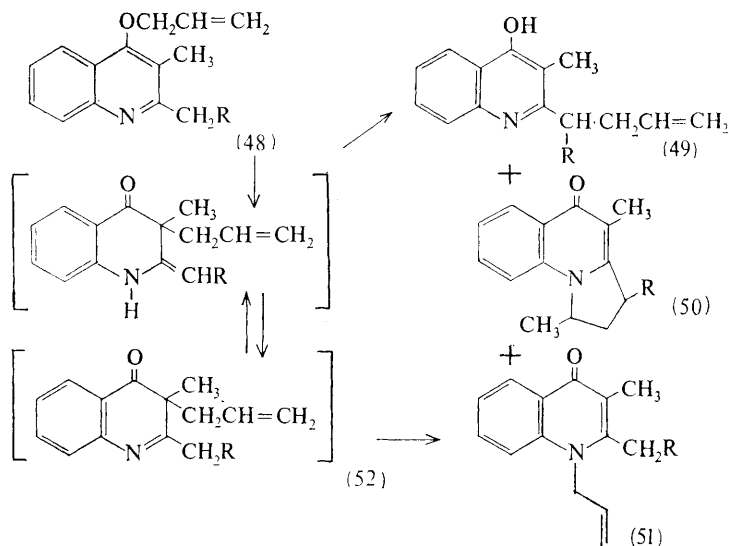
allyl acceptor in out-of ring rearrangements could be part of a second phenyl ring, the allyl ethers of several 2- and 4-hydroxybiphenols were prepared.<sup>20</sup> However on pyrolysis these allyl ethers disproportionated to the corresponding parent phenols, showing that the second phenyl ring was acting as a blocking group and not as an allyl acceptor.

Other interesting examples of out-of-ring Claisen rearrangements have been reported by Makisumu<sup>21a</sup> who studied the migrations in nitrogen heterocyclic compounds. By heating the allyl ether of 4-hydroxy-2,3-dimethylquinoline (48; R = H) at 200° migration to the *meta* methyl group (49) occurred in high yield (92%). The two other products that were isolated (50 and 51) resulted from cyclisation (49 → 50) and from *para* migration to nitrogen. If the side chain in the 2-position was extended it was shown that migration always occurred to the activated  $\alpha$ -carbon atom of the side chain. Subsequent work<sup>21b</sup> showed that rearrangement to the *meta* side chain and *para* rearrangement were competitive processes which occurred from the same dienone-type intermediate (52) (Scheme 4). Other Claisen rearrangements in nitrogen heterocyclic systems have recently been reviewed by Thyagarajan.<sup>22</sup>

<sup>20</sup> A. Nickon and B. R. Aaronoff, *J. Org. Chem.*, 1964, **29**, 3014.

<sup>21</sup> (a) Y. Makisumi, *Tetrahedron Letters*, 1964, 699; (b) 1964, 1635.

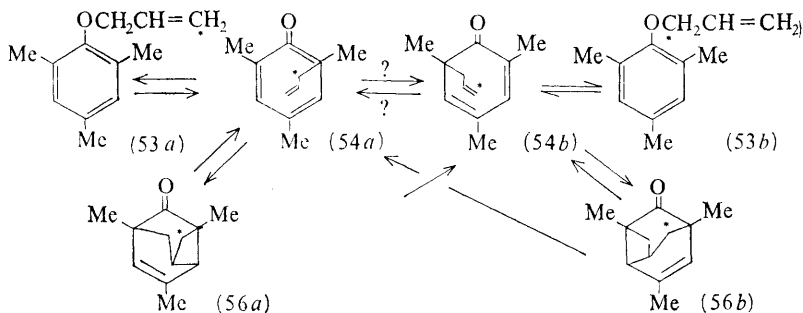
<sup>22</sup> B. S. Thyagarajan, 'Claisen Rearrangements in N-Heterocycles', in 'Advances in Heterocyclic Chemistry', ed. A. Katritzky, Academic Press, New York, 1967, vol. 8, p. 143.



Scheme 4

**The *ortho-ortho* Rearrangement.**—It has been previously stated that an *ortho-ortho* rearrangement is not allowed by the Woodward–Hoffmann selection rules.<sup>6</sup> Despite this a number of *ortho-ortho* rearrangements have been postulated in order to account for experimental phenomena and reaction products.<sup>1b</sup> These rearrangements should now be interpreted as reactions which occur by a stepwise mechanism quite different from the concerted *ortho* to *para* migration discussed previously.

In studying the reversibility of the Claisen rearrangement Schmid *et al.*<sup>23</sup> observed that on heating a [ $\gamma$ -<sup>14</sup>C] allyl ether of 2,4,6-trimethylphenol (53a), the radioactivity became distributed between the  $\alpha$  and  $\gamma$ -carbon atoms of the allyl group (53b) (Scheme 5).<sup>2b</sup> This phenomenon could be best accounted for by the occurrence of an *ortho-ortho* rearrangement with reversal of the ends of attachment (54a  $\rightleftharpoons$  54b).

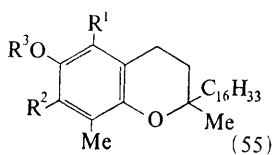


Scheme 5

<sup>23</sup> P. Fahrni and H. Schmid, *Helv. Chim. Acta*, 1959, 42, 1102.

## Molecular Rearrangements Related to the Claisen Rearrangement

In the rearrangement of the but-2-enyl ethers of  $\beta$ - and  $\gamma$ -tocopherol (55a and 55b) respectively<sup>24</sup> products arising from the expected *ortho* rearrangement (55c and 55e) and also from rearrangement without net inversion (55d and 55f) were isolated in good yield. Although the rearrangements were accompanied by cleavage of the ethers (55a and 55b) to give the original tocopherols (55g and 55h) all attempts to detect ionic, free-radical, or intermolecular character failed. Thus Green, McHale, and Marcinkiewicz<sup>24</sup> concluded that the but-2-enyltocopherols are formed by an intramolecular *ortho-ortho* migration of an *o*- $\alpha$ -methylallyldienone intermediate. N.m.r. analysis was not available for this study and the structures of the reaction products were assigned on the basis of infrared analysis and colour reactions.



- a ;  $R^1 = \text{Me}, R^2 = \text{H}, R^3 = \text{CH}_2\text{CH}:\text{CH}.\text{CH}_3$   
 b ;  $R^1 = \text{H}, R^2 = \text{Me}, R^3 = \text{CH}_2\text{CH}:\text{CH}.\text{CH}_3$   
 c ;  $R^1 = \text{Me}, R^2 = \text{CH}(\text{CH}_3).\text{CH}:\text{CH}_2, R^3 = \text{H}$   
 d ;  $R^1 = \text{Me}, R^2 = \text{CH}_2\text{CH}:\text{CH}.\text{CH}_3, R^3 = \text{H}$   
 e ;  $R^1 = \text{CH}(\text{CH}_3).\text{CH}:\text{CH}_2, R^2 = \text{Me}, R = \text{H}$   
 f ;  $R^1 = \text{CH}_2\text{CH}:\text{CH}.\text{CH}_3, R^2 = \text{Me}, R = \text{H}$   
 g ;  $R^1 = \text{Me}, R^2 = R^3 = \text{H}$   
 h ;  $R^1 = R^2 = \text{H}, R^3 = \text{Me}$

Another example of a possible *ortho-ortho* rearrangement was reported by Dinan and Tieckelmann<sup>25</sup> who showed that the Claisen rearrangement of 2-but-2-enyloxypyridine in absence of solvent gives in addition to the expected 1,2-dihydro-1- and 3-(1-methylallyl)pyridones, a product with no 'inversion', 1-but-2'-enyl-1,2-dihydro-2-pyridone. An *ortho-ortho* migration of 1,2-dihydro-3-(1-methylallyl)pyridone may account for the latter reaction product.

It has recently been suggested<sup>4a</sup> that the *ortho-ortho* rearrangement occurs in a stepwise manner by formation of an internal Diels-Alder adduct (56a, 56b) from the *ortho*-dienone (54a, 54b). Cleavage of the four-membered ring would then complete the *ortho* rearrangement with inversion ( $54a \rightleftharpoons 54b$ ). As yet an internal Diels-Alder adduct has not been isolated from the rearrangements of allyl aryl ethers. However the rearrangement of 2,6-dimethylphenyl propargyl ether does give an internal Diels-Alder adduct (see p. 411)<sup>26</sup> and this result will undoubtedly stimulate further work to isolate or trap the intermediates in the *ortho-ortho* rearrangement.

**The Abnormal Claisen Rearrangement.**—In 1936 Lauer and Filbert reported that the rearrangement of  $\gamma$ -ethylallyl phenyl ether (57) gave 2-( $\alpha$ -dimethylallyl)phenol (59).<sup>27</sup> This type of reaction became known as the abnormal Claisen rearrangement. The expected product, 2-( $\alpha$ -ethylallyl)phenol (58), was in fact also present<sup>28</sup> and further work showed conclusively that it could be converted

<sup>24</sup> J. Green, S. Marcinkiewicz, and D. McHale, *J. Chem. Soc. (C)*, 1966, 1422; *Proc. Chem. Soc.*, 1964, 228.

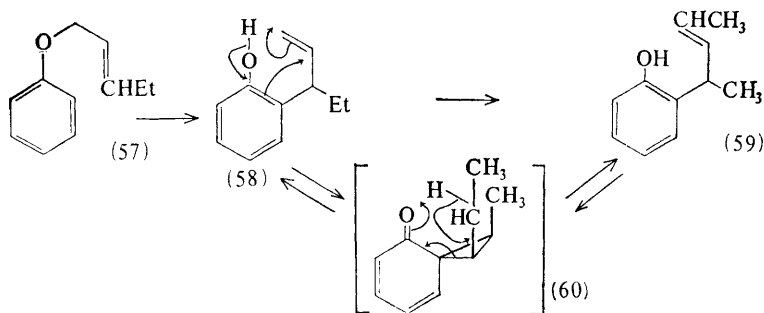
<sup>25</sup> F. J. Dinan and H. Tieckelmann, *J. Org. Chem.*, 1964, 29, 892.

<sup>26</sup> H. Schmid and J. Zsindely, *Helv. Chim. Acta.*, 1968, in the press.

<sup>27</sup> W. M. Lauer and W. F. Filbert, *J. Amer. Chem. Soc.*, 1936, 58, 1388.

<sup>28</sup> C. D. Hurd and M. A. Pollack, *J. Org. Chem.*, 1938, 3, 550.

into the abnormal product. Thus Marvell, Anderson, and Ong<sup>29</sup> demonstrated that for the abnormal reaction to occur a hydroxyl group and an allyl group must be located *ortho* to each other since the methyl ether (58; OMe instead of OH) and 4-( $\gamma$ -ethylallyl)-2,6-dimethylphenol both failed to undergo an abnormal rearrangement. The mechanism (57)–(60) was suggested in which formation of the abnormal product occurs by the reversible intramolecular hydrogen transfer of the spirocyclopropylcyclohexadienone intermediate (60).

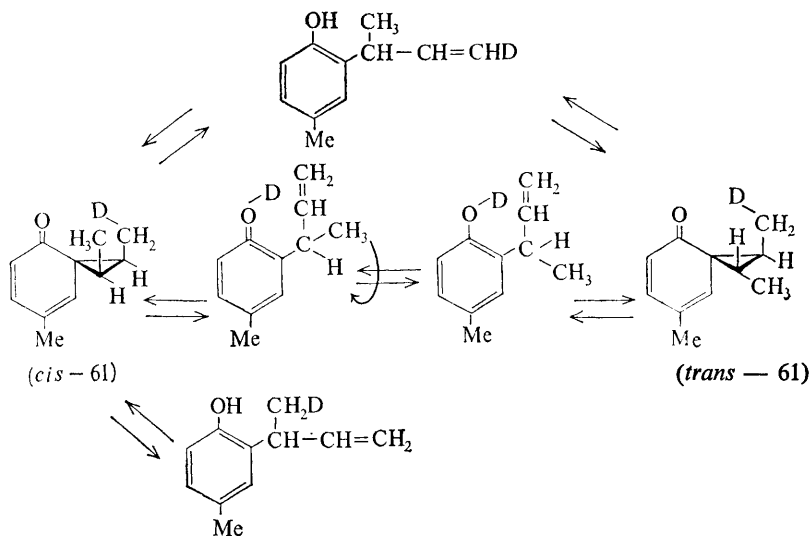


This mechanism was verified by the labelling experiments which revealed further subtle features. Thus work with 2-( $\alpha$ -methylallyl)-4-methylphenol labelled with <sup>14</sup>C at the  $\alpha$ -methyl group showed that the radioactivity became distributed between the  $\alpha$ -methyl group and the  $\gamma$ -carbon atom of the side-chain.<sup>30</sup> By use of a deuterium label it was demonstrated that deuterium could be exchanged between the terminal methylene and phenolic hydroxyl groups, and that *no* incorporation of the label occurred at the  $\alpha$ - and  $\beta$ -carbon atoms of the side-chain.<sup>31</sup> It was also shown that deuterium had been incorporated into the  $\alpha$ -methyl substituent but at a much slower rate than in the terminal methylene group. The abnormal Claisen rearrangement of *o*-allylphenols is a general reaction which in the case of unsubstituted side-chains could only be demonstrated by the exclusive deuterium exchange between the phenolic hydroxyl group and the olefinic methylene group. The mechanistic pathway for the abnormal Claisen rearrangement is summarised for the rearrangement of 4-methyl-2-( $\alpha$ -methylallyl)phenol in Scheme 6. Formation of (*trans*-61) should be favoured over formation of (*cis*-61) since in the former case steric interaction of the *cis*-methyl substituents during formation of the cyclopropane ring will be avoided. It is for this reason that deuterium exchange is faster at the terminal methylene group than at the  $\alpha$ -methyl group. In agreement with this explanation it was shown that the incorporation of deuterium at both sites

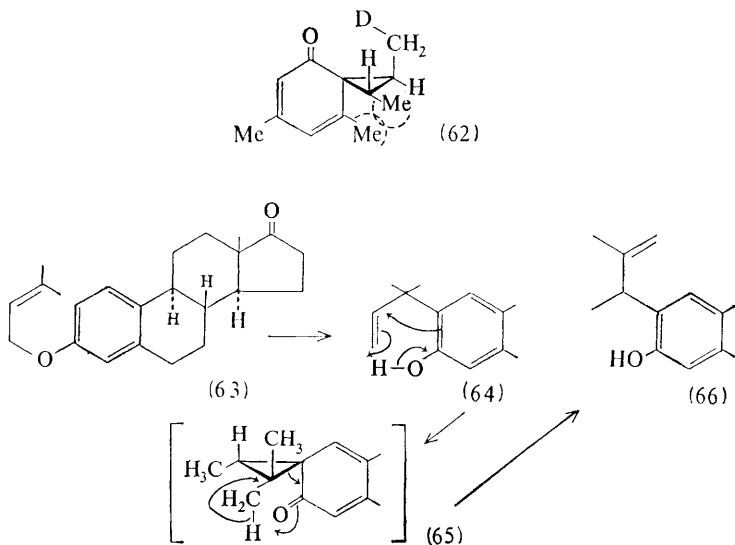
<sup>29</sup> E. N. Marvell, D. R. Anderson, and J. Ong, *J. Org. Chem.*, 1962, 27, 1109.

<sup>30</sup> A. Habich, R. Barner, R. M. Roberts, and H. Schmid, *Helv. Chim. Acta*, 1962, 45, 1943; similar conclusions were reached by W. M. Lauer and T. A. Johnson, *J. Org. Chem.*, 1963, 28, 2913.

<sup>31</sup> A. Habich, R. Barner, W. von Philipsborn, and H. Schmid, *Helv. Chim. Acta*, 1965, 48, 1297.



Scheme 6

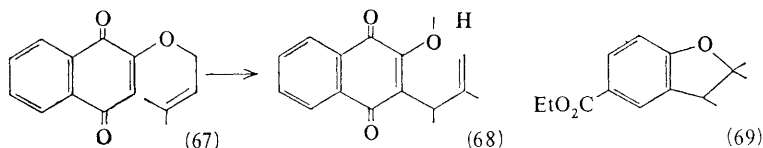


could be equalised by creating conditions in which both methyl groups in the cyclopropane ring are likely to be *cis* to one another, as in the intermediate (*cis*-61). This occurred in the rearrangement of 3,5-dimethyl-2-( $\alpha$ -methylallyl)-phenol where the presence of the 3-methyl substituent would raise the free energy of activation for the formation of the *trans*-dimethylcyclopropane intermediate



(62). The geometrical isomerism of a reaction product can also be altered by the abnormal Claisen rearrangement as demonstrated by the interconversion of *cis*- and *trans*-2-crotyl-3,5-dimethylphenol (30a) and likewise *cis*- and *trans*-2-( $\alpha\gamma$ -dimethylallyl)-3,5-dimethylphenol at 200°. <sup>32</sup>

In the examples that have been discussed, the abnormal Claisen rearrangement occurs at a slower rate than the rearrangement of the allyl aryl ether, and there has been no difficulty in isolating the normal product. This is not always the case. By heating the 3,3-dimethylallyl ether of oestrone (63) in diethylaniline none of the expected product (64) could be isolated. <sup>33</sup> Instead 2-( $\alpha\beta$ -dimethylallyl)oesrone (66) was isolated as the only rearrangement product and its formation was accounted for by the rapid transformation of 2-( $\alpha\alpha$ -dimethylallyl)oesrone (64) into the spiro-dienone (65) which could then revert into the more stable phenol (66). Thus when the rearrangement of the ether was carried out in dimethylaniline containing butyric anhydride, the normal Claisen product (64) was trapped as its butyric ester [64; CH<sub>3</sub>(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub> instead of OH]. The phenol (64) was isolated by hydrolysis and rapidly isomerised in hot diethylaniline to the abnormal product (66). The abnormal Claisen rearrangement can now be used to account for hitherto unexpected rearrangement products from 3,3-dimethylallyl aryl ethers. Thus rearrangement of 2-( $\gamma\gamma$ -dimethylallyloxy)-1,4-naphthaquinone (67) gave 2-( $\alpha\beta$ -dimethylallyl)-3-hydroxy-1,4-naphthaquinone (68). <sup>34</sup> The thermal rearrangement of ethyl 4-( $\gamma\gamma$ -dimethylallyloxy)benzoate gave isoprene and ethyl 4-hydroxybenzoate but in addition 5-ethoxycarbonyl-2,2,3-trimethyl coumaran (69) was formed, <sup>35</sup> presumably by cyclisation of an abnormal rearrangement product. <sup>36</sup> From a synthetic standpoint products arising from an abnormal Claisen rearrangement must be expected whenever an allyl ether contains a  $\gamma$ -alkyl substituent. The limiting cases appear only when the intrinsic geometry necessary for the intramolecular hydrogen transfer is missing. Thus in cases where the hydroxyl group is strongly hydrogen bonded to a carbonyl group (*e.g.*, 27) the *o*-allylphenol does not undergo further



rearrangement even after lengthy heating. The fact that the abnormal Claisen rearrangement occurs by a thermal, concerted, intramolecular suprafacial transfer of hydrogen enables it to be classified as a [1,5] sigmatropic rearrangement for migration of hydrogen from spiro-dienone to phenol (*e.g.*,

<sup>32</sup> Gy. Frater and H. Schmid, *Helv. Chim. Acta*, 1966, 49, 1957.

<sup>33</sup> A. Jefferson and F. Scheinmann, *Chem. Comm.*, 1966, 239.

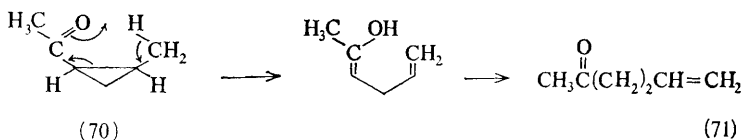
<sup>34</sup> R. G. Cooke, *Austral. J. Sci. Res.*, 1950, 3, 481.

<sup>35</sup> W. M. Lauer and O. Moe, *J. Amer. Chem. Soc.*, 1943, 65, 289.

<sup>36</sup> For examples of other abnormal Claisen rearrangements see W. M. Lauer, G. A. Doldouras, R. E. Hileman, and R. Liepins, *J. Org. Chem.*, 1961, 26, 4785.

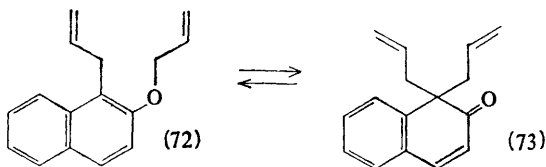
60 → 59 and 60 → 58). By the principle of microscopic reversibility the reverse reaction (*e.g.*, 59 → 60 and 58 → 60) can also be considered as [1,5] shifts.<sup>37a</sup> In classifying the abnormal Claisen rearrangement as a [1,5] sigmatropic change the lowest possible order has been assigned (see p. 394). The reactions (58) → (60) and (59) → (60) can be regarded as [1,5] changes when one neglects the  $\alpha$ -carbon atom of the side-chain in the assumption that it is a poor insulator of conjugation. The allyl side-chain and the benzene ring are homoconjugated.<sup>37b</sup>

The reaction has general application and occurs in aliphatic compounds. Thus 1-acetyl-2-alkylcyclopropanones (70) undergo easy ring-opening on heating to produce homoallylic methyl ketones (71) only when the acyl and alkyl groups are *cis* to one another.<sup>37</sup> The all-carbon analogue, the transformation of *cis*-1-methyl-2-vinylcyclopropane into *cis*-hexa-1,4-diene, occurs readily at 160°.<sup>38</sup>



### 3 Formation of a Stable Dienone and the Retro-Claisen Rearrangement

Although the Claisen rearrangement, in principle, is a reversible reaction, its preparative value is in formation of allylphenols or homoallylic carbonyl compounds. The rearrangement of 1-allyl-2-allyloxynaphthalene (72) was exceptional in that a stable dienone (73) was isolated in 55% yield.<sup>39</sup> This product partly reverted to the starting material (72) when heated at 194°. With 2-allyloxy-1-( $\alpha$ -methylallyl)naphthalene in boiling dimethylaniline a dienone was not isolated but its presence was inferred by formation of 1-allyl-2-( $\gamma$ -methylalloxy)naphthalene. Only rearrangement to C(1) is possible since no rearrangement occurs to the 3-position in 2-allyloxynaphthalenes. Similar inequality of two *ortho* positions is observed in rearrangement of allyloxy-quinolines and -isoquinolines.<sup>40</sup>



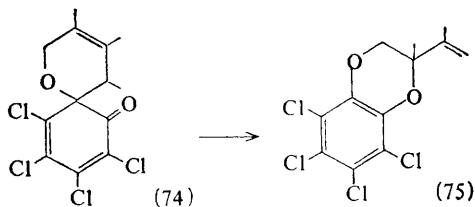
<sup>37</sup> (a) R. M. Roberts, R. G. Landolt, R. G. Greene, and E. W. Heyer, *J. Amer. Chem. Soc.*, 1967, 89, 1404 and refs. therein; (b) see S. Winstein, 'Non-classical Ions and Homoaromaticity' in 'Aromaticity', *Chem. Soc. Special Publ.*, 1967, No. 21, p. 1.

<sup>38</sup> R. J. Ellis and H. M. Frey, *Proc. Chem. Soc.*, 1964, 221; W. Grimme, *Chem. Ber.*, 1965, 98, 756.

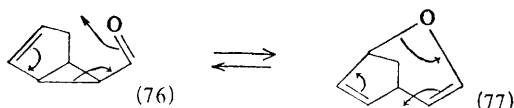
<sup>39</sup> J. Green and D. McHale, *Chem. and Ind.*, 1964, 1801.

<sup>40</sup> H. Win and H. Tieckelmann, *J. Org. Chem.*, 1967, 32, 59 and refs. therein.

An interesting case of a retro-Claisen rearrangement occurring in theoretical yield was reported by Ansell and Leslie.<sup>41</sup> The reaction of 2,3-dimethylbutadiene with *o*-chloranil gave the Diels-Alder adduct (74) which in boiling benzene rearranged to the more stable aromatic compound (75).



In the aliphatic series a reverse Claisen rearrangement probably arises in the equilibrium (76)  $\rightleftharpoons$  (77).<sup>42</sup> Here the ring structures create particularly favourable entropy factors for valence tautomerism, but molecular models show that both isomers are under ring strain. It was established that seven parts of the bicyclo[3,1,0]hex-2-ene-6-*endo*formaldehyde (76) co-exist in equilibrium with three parts of 2-oxabicyclo[3,2,1]octa-3,6-diene (77).<sup>42</sup>



#### 4 Rearrangement of Pentadienyl Phenyl Ethers

Consider the highest occupied molecular orbital  $\psi_3$  for the pentadienyl radical: the phases at C(1) and C(5) are the same but there is a change of phase at C(3) (Figure 2). To predict the outcome of the rearrangement of pentadienyl phenyl

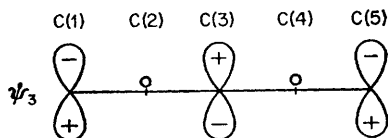


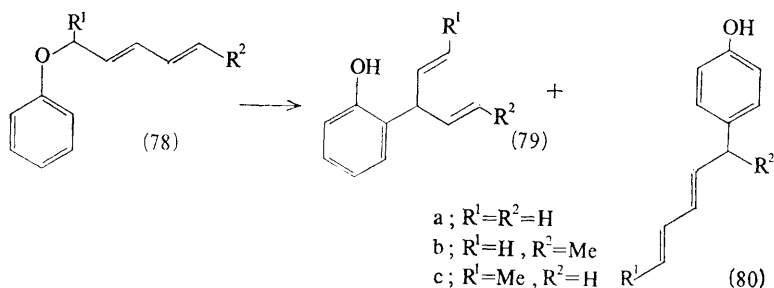
Figure 2

ether by the thermal sigmatropic process it is necessary to consider  $\psi_3$  of the pentadienyl moiety with  $\psi_4$  for the phenoxy radical (see p. 394). The same phase between oxygen and the *para* position would allow the pentadienyl group to undergo a [5,5] migration with 'inversion'. Further, since there is a change of phase between the oxygen and the *ortho* position of  $\psi_4$  for the phenoxy group it is only C(3) of the pentadienyl group which can become attached to

<sup>41</sup> M. F. Ansell and V. J. Leslie, *Chem. Comm.*, 1967, 949.

<sup>42</sup> M. Rey and A. Dreiding, *Helv. Chim. Acta*, 1965, **48**, 1985.

the *ortho* position by a suprafacial process. The experimental work of Fráter and Schmid<sup>43</sup> is in complete accord with the orbital symmetry requirements. Thus rearrangement of pentadienyl phenyl ether (78a) gives the *p*-pentadienylphenol (80a) and also the *o*-allylphenol (79a). Introduction of a methyl group at either the  $\alpha$ - or  $\omega$ -position of the pentadienyl ether (78b and 78c) gave largely the same *ortho* product (84b = 84c) but different principal *para* products (80b and 80c). [In rearrangement of (78b) both the *trans*-*o*-allylphenol (79b) and its *cis* isomer were formed. As expected for the *ortho* rearrangement of  $\alpha$ -alkylallyl phenyl ethers the *trans* product predominated (see p. 392).] Thus, consistent with a direct *para* migration with 'inversion', an  $\alpha$ -methyl group in the ether (78b) resulted in *p*-pentadienylphenol with the methyl group at the  $\omega$ -position (80b): similarly the  $\omega$ -methylpentadienyl phenyl ether (78c) gave largely the  $\alpha$ -methylpentadienylphenol (80c). These results preclude the formation of the *p*-pentadienylphenols (80) from an *ortho*-dienone intermediate, and in addition an allylphenol rearrangement could be excluded since the *o*-allylphenols (79) could not be converted into their *para* isomers (80). Thus in the rearrangement of pentadienyl phenyl ethers (78), [3,3] and [5,5] sigmatropic changes are competitive reactions, but the reaction of the higher order is significantly faster<sup>6, 43</sup>



### 5. Rearrangement of Propargyl Vinyl and Aryl Propargyl Ethers

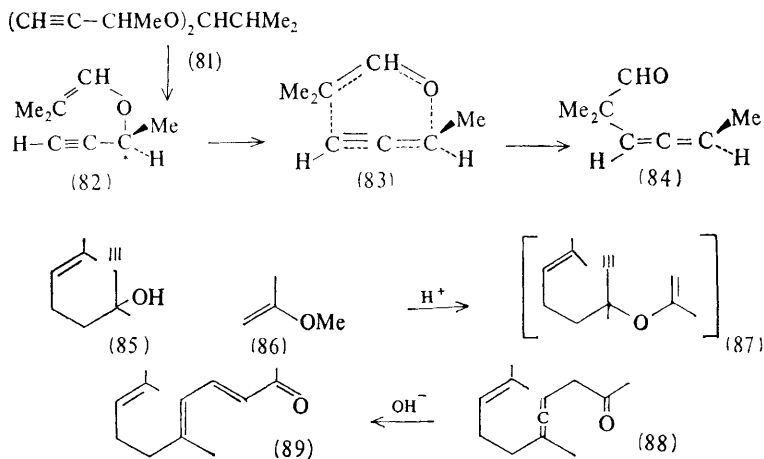
Propargyl vinyl ethers (*e.g.*, 82) undergo a Claisen-type rearrangement to give allenic carbonyl compounds (*e.g.*, 84).<sup>44</sup> The reaction conditions are more severe than for the allyl vinyl ether rearrangement but this is understandable if it is assumed that the planar transition state (*e.g.*, 83) for the formation of the allene carbonyl compound is not so favourable. In accordance with this concept of the transition state, asymmetry can be induced into the allene by the starred asymmetric atom in the ether (82). Thus, starting from (*S*)-but-3-yn-2-ol, reaction with 2-methylpropanol formed the acetal (81) which on passage over silica at 210° gave (*R*)-2,2-dimethylhexa-3,4-dienol (84).<sup>45</sup> An elegant synthesis<sup>46</sup> of pseudoionone (89) has been achieved which involves a

<sup>43</sup> Gy. Frater and H. Schmid, *Helv. Chim. Acta*, 1968, **51**, 190.

<sup>44</sup> D. R. Taylor, *Chem. Rev.*, 1967, **67**, 317, and refs. therein.

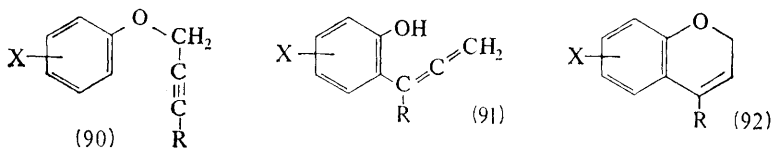
<sup>45</sup> E. R. H. Jones, J. D. Loder, and M. C. Whiting, *Proc. Chem. Soc.*, 1960, 180.

<sup>46</sup> G. Saucy and R. Marbet, *Helv. Chim. Acta*, 1967, **50**, 1158.



rearrangement of a propargyl vinyl ether (87). In this method the propargyl vinyl ether (87) is prepared *in situ* by acid-catalysed *trans* etherification of the vinyl ether (86) with the alcohol (85) and in these circumstances migration occurs under mild conditions.

In the rearrangement of aryl propargyl ethers (90) in diethylaniline an *o*-allenylphenol (91) has, as yet, not been isolated and the corresponding chromene (92) is the only product.<sup>47</sup> Iwai and Ide<sup>47</sup> concluded that direct cyclisation to form the pyran ring occurred without prior rearrangement to the *o*-allenylphenol (91). Their data can also be accommodated by formation and rapid cyclisation of an *o*-allenylphenol (91), since contrary to a previous report<sup>48</sup> *o*-allenylphenol (91; X = R = H) on heating is converted into chromen (92; X = R = H).<sup>49</sup>



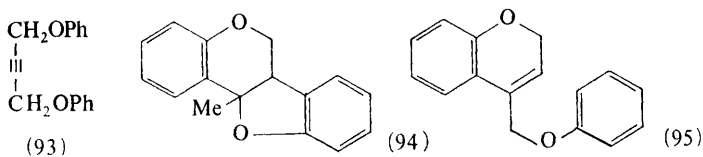
The rearrangement of 1,4-diaryloxybut-2-yne (*e.g.*, 93) gives the benzofuro-benzopyran (94) and the chromen (95) is believed to be an intermediate.<sup>50</sup>

<sup>47</sup> I. Iwai and J. Ide, *Chem. Pharm. Bull. Japan*, 1962, 10, 926; 1963, 11, 1042.

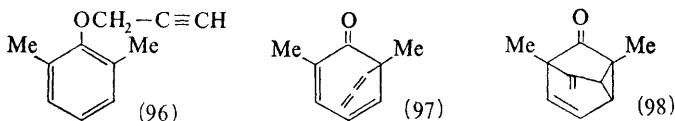
<sup>48</sup> R. Gaertner, *J. Amer. Chem. Soc.*, 1951, 73, 4400.

<sup>49</sup> J. Zsindely and H. Schmid, unpublished work.

<sup>50</sup> B. S. Thyagarajan, K. K. Balasubramanian, and R. Bhima Rao, *Tetrahedron*, 1967, 23, 1893.



The studies on the rearrangement of 2,6-dimethylphenyl propargyl ether (96) provide strong circumstantial evidence for the formation of an allene-dienone intermediate (97). The tricyclic ketone (98) was isolated and its formation was best rationalised by postulating that the allene (97) from a Claisen rearrangement undergoes an internal Diels-Alder-like reaction (Scheme 7).<sup>49</sup>



Scheme 7

## 6 The Rearrangement of Benzyl Vinyl Ethers

The success of the Claisen rearrangement of allyl phenyl ethers where the vinyl moiety is part of an aromatic ring, stimulated studies in the rearrangement of benzyl vinyl ethers where the allylic double bond is incorporated in a benzene ring. Benzyl vinyl ether (99a), however, failed to give *o*-tolylacetaldehyde (100a) and similar failures were recorded with naphthalene and anthracene analogues.<sup>51</sup> Instead, benzyl vinyl ether gave 3-phenylpropanal.

Modifications in the aromatic portion or alternatively in the vinyl moiety, however, led to the expected rearrangement.<sup>52, 53</sup> Thus 3,5-dimethoxyphenyl isopropenyl ether (99b) gave 80% of 2,4-dimethoxy-6-methylphenylacetone (100b) when heated at 240° but data on the mechanism have not been reported.<sup>52</sup> 3,5-Dimethoxybenzylacetone was also isolated and this product probably arises from a free-radical scission-recombination mechanism. It thus appears that the mesomeric donation of electrons by the methoxyl groups to the benzene ring promotes the rearrangement of the benzyl vinyl ether (99b). By the use of the acetal of *NN*-dimethylacetamide (101) it is possible to prepare 'in situ' an aminovinyl benzyl (or allyl) ether (*e.g.*, 103) which undergoes a Claisen rearrangement at 140–180°.<sup>53</sup> The Claisen intermediate is probably formed by alcohol exchange of the vinyl ether (102). By use of benzyl alcohol and the acetal of *NN*-dimethylacetamide (101) and heating at 180°, *NN*-dimethyl-*o*-tolylacetamide (104) was isolated in 50% yield. In this case resonance stabilisation of the carbonyl function by the dimethylamino-group helps to favour product formation.<sup>53</sup>

<sup>51</sup> A. W. Burgstahler, L. K. Gibbons, and I. C. Nordin, *J. Chem. Soc.*, 1963, 4986.

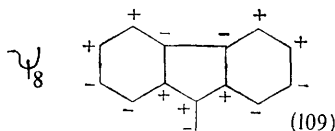
<sup>52</sup> W. J. Le Noble, P. J. Crean, and B. Gabrielson, *J. Amer. Chem. Soc.*, 1964, **86**, 1649.

<sup>53</sup> A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, 1964, **47**, 2425.



charge as in the Wagner–Meerwein and the above Wittig reactions, the rule requires modification to  $i + j = 2k + 3$  (where  $k = 0, 1, 2, 3 \dots$ ).

The Hückel molecular orbital coefficients for dibenzofulvene have been calculated and it can be shown that the anionic rearrangement of the all-carbon analogue of allyl 9-fluorenyl ether is a symmetry-allowed process. Thus the highest occupied molecular orbital for the anion of dibenzofulvene is  $\psi_8$  (109)<sup>57, 9b</sup> and the transition state for migration of an allyl radical requires change of phases between C(9) of the ring and the substituent atom.



### 8 Nitrogen, Sulphur, and Phosphorus Analogues of the Claisen Rearrangement

Before 1961, nitrogen, sulphur, and phosphorus analogues of the Claisen rearrangement were unknown. An early attempt to rearrange *N*-allylaniline at 275° gave aniline and propene.<sup>58</sup> Marcinkiewicz, Green, and Mamalis<sup>59</sup> estimated that the activation energy for rearrangement of *N*-allylaniline is about 6 kcal./mole higher than for the rearrangement of allyl phenyl ether. Thus at the higher temperatures required for allyl migration in *N*-allylaniline preferential allyl cleavage occurred.<sup>59</sup> However it was successfully predicted that *N*-allyl-1-naphthylamine would rearrange to 2-allyl-1-naphthylamine because Claisen rearrangements in the naphthalene series require a lower energy of activation.<sup>59</sup> Since the orbital symmetry requirements do not forbid the rearrangement of *N*-allylaniline<sup>60</sup> by a concerted mechanism, the problem of allyl migration essentially is how to reduce the activation energy required to reach the transition state. It is known that allyl vinyl<sup>61</sup> and allyl aryl ethers<sup>62</sup> rearrange more readily when proton acids or Lewis acids are present, probably because the resulting positive charge on the oxygen atom is further delocalised in the transition state. It has been reported that *N*-allylaniline gives 2-allylaniline<sup>63</sup> and that *N*-allyl-2,6-xylidine gives 4-allyl-2,6-xylidine<sup>64</sup> in the presence of zinc chloride. Unfortunately there were no data to show whether the rearrangements occurred by a concerted mechanism or by an intermolecular pathway.

It has recently been observed that 1-*p*-bromophenyl-2-isopropenylaziridine (110) is smoothly converted into the benzazepine (111) in high yield.<sup>65</sup> In this

<sup>57</sup> C. A. Coulson and A. Streitweiser, 'Dictionary of  $\pi$ -Electron Calculations', W. H. Freeman and Co., San Francisco, 1965, p. 140.

<sup>58</sup> F. L. Canahan and C. D. Hurd, *J. Amer. Chem. Soc.*, 1930, **52**, 4586.

<sup>59</sup> S. Marcinkiewicz, J. Green, and P. Mamalis, *Tetrahedron*, 1961, **14**, 208.

<sup>60</sup> Ref. 57, p. 263.

<sup>61</sup> G. Saucy and R. Marbet, *Helv. Chim. Acta*, 1967, **50**, 2091, 2095.

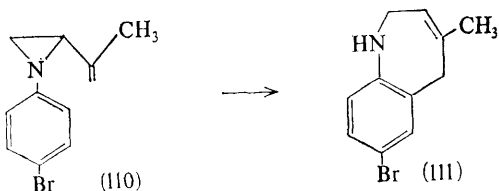
<sup>62</sup> H. Schmid, *Gazzetta*, 1962, **92**, 968, and unpublished work.

<sup>63</sup> C. D. Hurd and W. D. Jenkins, *J. Org. Chem.*, 1957, **22**, 1418.

<sup>64</sup> M. Elliot and N. F. Janes, *J. Chem. Soc.*, 1967, 1780.

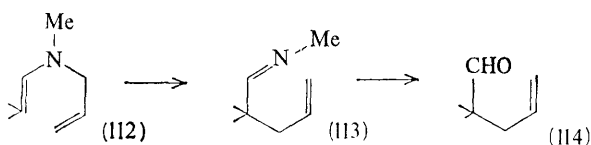
<sup>65</sup> P. Scheiner, *J. Org. Chem.*, 1967, **32**, 2628.



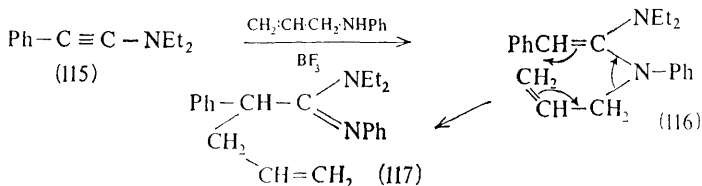


case it was suggested that an amino-Claisen rearrangement was made feasible by the relief of aziridine ring strain (12–14 kcal./mole) in the transition state.<sup>65</sup>

The rearrangement of *N*-allylenamines provides a method for alkylating aldehydes at the  $\alpha$ -position without the use of an alkylating agent or a strong base.<sup>66</sup> Thus enamines prepared from *N*-allyl amines (*e.g.*, 112) and  $\alpha$ -disubstituted aldehydes rearrange quantitatively on heating at 200–250° to give an imine (*e.g.*, 113) which on hydrolysis yields an aldehyde (*e.g.*, 114). The rearrangement proceeds with inversion and in a stereospecific manner.<sup>66</sup> A variation of this



reaction was reported by Ficini and Barbara.<sup>67</sup> An aminal (116) prepared by the reaction of an ynamine (115) with an allylamine rearranged at 280° to give the amidine (117).



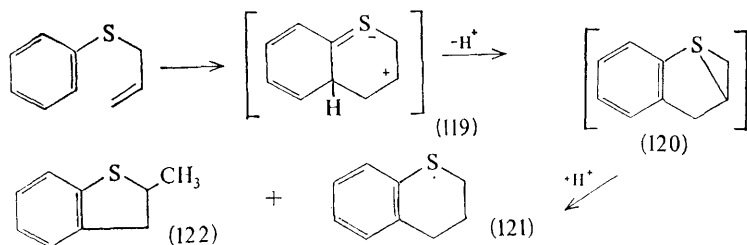
Allyl phenyl sulphide (118) on heating in either *NN*-diethylaniline or quinoline gives 2-methylthiocoumaran (122) and thiochroman (121).<sup>68a</sup> No 2-allylthiophenol was obtained but it may be one of the intermediates in the formation of the heterocyclic compounds (121 and 122).<sup>68b</sup> Thus while 2-allylthiophenol gave both the thiochroman (121) and 2-methylthiocoumaran (122) on heating under the same conditions as used for allyl phenyl sulphide, the proportions of the cyclic products were quite different. It was therefore

<sup>66</sup> R. K. Hill and N. W. Gilman, *Tetrahedron Letters*, 1967, 1421.

<sup>67</sup> J. Ficini and C. Barbara, *Tetrahedron Letters*, 1966, 6425.

<sup>68</sup> (a) H. Kwart and E. R. Evans, *J. Org. Chem.*, 1966, 31, 413; (b) H. Kwart and H. M. Cohen, *ibid.*, 1967, 32, 3135.

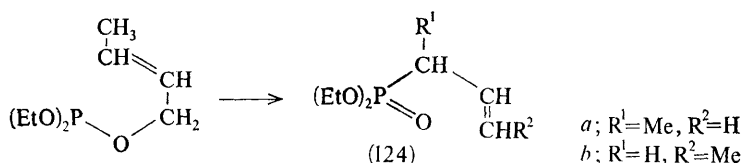
suggested by Kwart and his co-workers<sup>68</sup> that allyl phenyl sulphide can also cyclise to (119) and that octet expansion occurs to give a thiiran intermediate (120). Opening of the three-membered ring can occur in two ways to give both the 2-methylthiocoumaran and the thiochroman (Scheme 8). The later work<sup>68b</sup>



Scheme 8

suggests that in the thio-Claisen rearrangement the amine solvent plays an important role in the reaction.

The rearrangement of allyl and propargyl phosphites resembles the Claisen rearrangement in that migration to the phosphonate occurs with 'inversion'.<sup>69</sup> There may be some duality of mechanistic pathways in some cases since rearrangement of diethyl crotyl phosphite (123) gave largely the  $\alpha$ -methylallylphosphonate (124a) but in addition some of the crotylphosphonate (124b) was formed.<sup>70</sup>



## 9 Developments in Aliphatic Claisen Rearrangements

Although aromatic Claisen rearrangements have been studied in most detail, there have been some notable synthetic applications in aliphatic chemistry. The introduction of an angular group with the correct stereochemistry in polycyclic terpene and steroid syntheses has never been easy,<sup>71</sup> but with a Claisen rearrangement of the appropriate allyl vinyl ether (e.g., 125, 126) an angular group can be introduced in a stereospecific manner.<sup>72</sup>

The preparation of an allyl vinyl ether involves an ether-exchange reaction of a vinyl ether with an allyl alcohol,<sup>73</sup> and recently the procedures have been

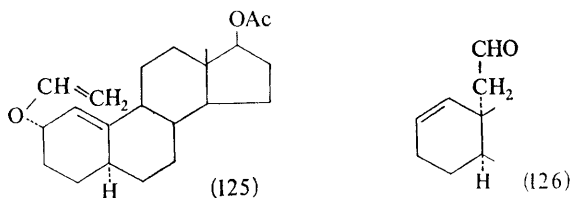
<sup>69</sup> A. N. Pudovik and I. M. Aladzheva, *Doklady Akad. Nauk S.S.S.R.*, 1963, 151, 1110.

<sup>70</sup> A. L. Lemper and H. Tieckelmann, *Tetrahedron Letters*, 1964, 3053.

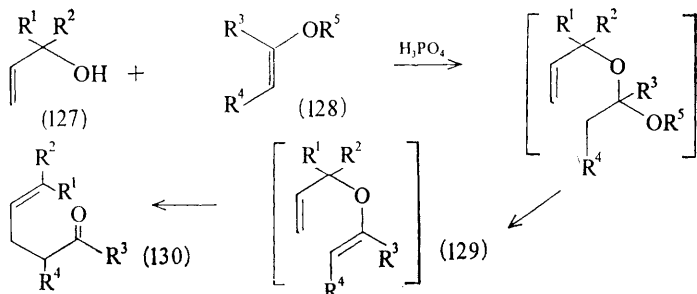
<sup>71</sup> J. W. Cornforth, 'The Total Synthesis of Steroids', in 'Progress in Organic Chemistry' ed. J. W. Cook, Butterworths, London, 1955, vol. 3, p. 1.

<sup>72</sup> M. Torigoe and J. Fishmann, *Tetrahedron Letters*, 1963, 1251.

<sup>73</sup> W. H. Watanabe and L. E. Conlon, *J. Amer. Chem. Soc.*, 1957, 79, 2828.

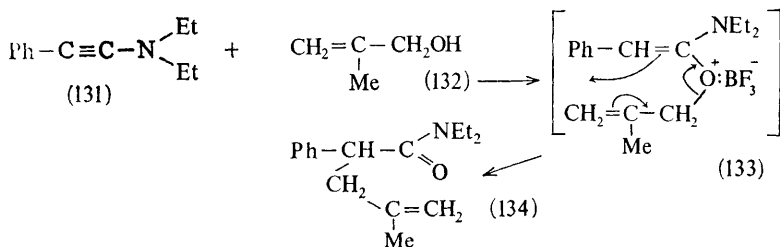


simplified. Thus by the method of Eschenmoser (see p. 411),<sup>53</sup> or by the acid-catalysed reaction of a vinyl carbinol (127) with a vinyl ether (128),<sup>61</sup> it is unnecessary to isolate the allyl ether (129) in the formation of unsaturated carbonyl compound (130) in high yield (Scheme 9).



Scheme 9

$\gamma\delta$ -Unsaturated amides (134) can be prepared by the reaction of an ynamine (131) with an allylic alcohol (132) in the presence of boron trifluoride ether complex below 30°. <sup>67</sup> The reaction is complete within 1 hr., and high yields are obtained from primary allylic alcohols. The reaction can be understood by postulating a Claisen rearrangement of a complexed ynamine-allyl alcohol adduct (133).

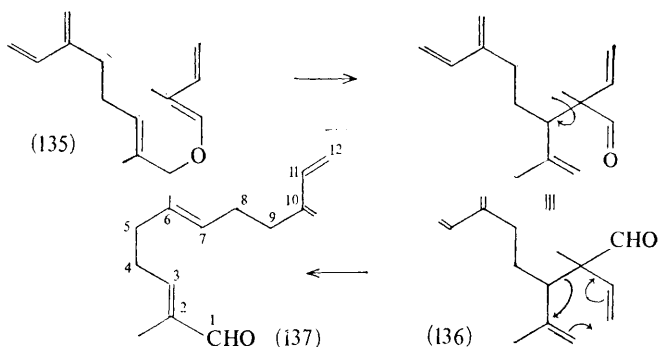


An elegant application of two [3,3] sigmatropic changes has been used by Thomas in the synthesis of  $\alpha$ -sinensal (137) which was isolated from the Chinese orange, *Citrus sinensis* L.<sup>74</sup> The basis of the synthesis was a Claisen

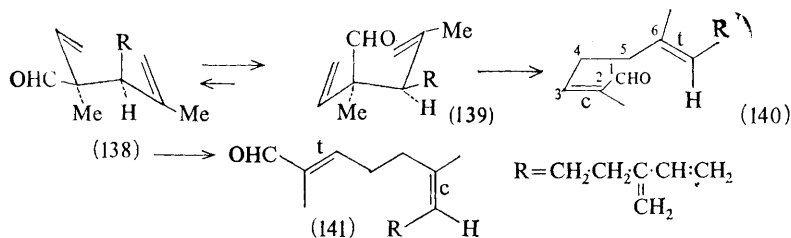
<sup>74</sup> A. F. Thomas, *Chem. Comm.*, 1967, 946, and unpublished work.

## Molecular Rearrangements Related to the Claisen Rearrangement

rearrangement of an ether (135) which gives an aldehyde (136). Free rotation as indicated would allow the 1,5-diene system to assume the correct stereochemistry for a Cope reaction to give a sinensal. If chair-like transition states are assumed for the Claisen and Cope rearrangements, stereochemical information about the reaction product can be derived.



Thus from the Claisen rearrangement the resulting aldehyde can be rotated about the single bond to give two possible chair-like conformations (138) and (139) which would lead to two different sinensals (140 and 141) from Cope rearrangements. However the conformation with the large R group equatorial (139) will be preferred and this will lead to the *trans* double bond at C(6) (140). If it is assumed that under the conditions of the reaction (50 hr. at 98°) that the aldehyde (140) would isomerise to the *trans* isomer then on the basis of the synthesis,  $\alpha$ -sinensal was postulated as 2,6-dimethyl-10-methylene-dodeca-2-*trans*,6-*trans*,11-trien-1-al (137). The consecutive Claisen and Cope



rearrangements are analogous to the *para* Claisen rearrangement in the aromatic series, and the scope of the reaction with aliphatic compounds is under investigation. For aldehyde intermediates with an  $\alpha$  hydrogen atom, the rate of  $\beta\gamma$  double-bond migration to the  $\alpha\beta$  position can be competitive and even much faster than the Cope rearrangement.<sup>74</sup>

## 10 Concluding Remarks

This survey was prompted by our observations during synthetic work that some Claisen rearrangements gave unexpected products, and that it was necessary to examine the structural features which lead to related intramolecular rearrangements. The choice of solvent has often been underestimated: from our experience a tertiary aromatic amine such as *NN*-diethyl- or *NN*-dimethylaniline has proved to be a most versatile solvent for aromatic Claisen rearrangements. Phenolic solvents, or even phenolic reaction products in neutral solvents or in absence of solvent, may catalyse the elimination of a substituted allyl group from its phenyl ether, or cause the migration of the double bond in 2-allylphenols and cyclisation to coumaran<sup>75</sup> or chroman derivatives.<sup>1a</sup> Dimethylallyl groups, for example, are particularly sensitive and care must be taken in purification of the ether.<sup>12</sup> The acid-catalysed cyclisation of 2-allylphenols to coumaran or chroman derivatives follows the rules of Markownikoff addition and these ring-closures can be used to check the structure of the side-chains.

It is remarkable that although the Claisen rearrangement was discovered in 1912, new observations and developments in this area of chemistry continue. The rate of progress during the last few years has been particularly enhanced by the use of gas and thin-layer chromatography to detect unusual products. Structural analysis by physical methods, especially n.m.r., enable the fate of an allyl group to be established rapidly without the ambiguity of the more classical methods. The Woodward-Hoffmann rules now provide a new theoretical basis for correlating earlier experimental results and for stimulating further research.

### *Appendix added in Proof*

New work by Herriott and Mislow<sup>76</sup> has shown that allyl phosphinates can rearrange to allyl phosphine oxides by an intramolecular concerted pathway with complete specificity. The duality in reaction pathways reported previously<sup>70</sup> (see page 415) can be avoided by selecting milder experimental conditions which favour only the sigmatropic process. Allyl sulphenates (142) rearrange to allyl sulphoxides (143) by a concerted cyclic pathway and this is well supported by the activation parameters and labelling experiments.<sup>77</sup>

The rearrangements of allyl phosphinates and sulphenates are formally analogous to the allyl migration in the Wittig reaction (see Section 7) in that they are [2, 3] sigmatropic processes. In this treatment the unshared *p*-electrons on phosphorus and respectively sulphur fulfill the role of the carbonion electrons for six  $\pi$ -electrons to participate in the transition state.

<sup>76</sup> A. W. Herriot and K. Mislow, *Tetrahedron Letters*, 1968, 3013.

<sup>77</sup> P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Amer. Chem. Soc.* 1968, **90**, in the press.

<sup>75</sup> A. T. Shulgin and A. W. Baker, *J. Org. Chem.*, 1963, **28**, 2468.



Steric compression of the *cis-endo* diacetyl substituents in the adduct (146) and extension of conjugation in the transition state (147) due to a developing butadiene system are responsible for rearrangement.

More recent work on the isomerisation of bicyclo [3, 1, 0] hex-2-ene-6-*endo* formaldehyde (76) shows that above 110°, in addition to the reverse Claisen rearrangement (page 408), a series of [1, 5] hydrogen shifts occur.<sup>80</sup>

This Review was initiated in 1965 and finalised while one of us (F. S.) was on leave at the University of Zürich. We thank Professor Hans Schmid and Dr. Gy. Fráter, Dr. H.-J. Hansen and Mr. J. Zsindely, for many stimulating discussions and for permission to include unpublished work. We also thank Professors Roald Hoffmann, G. Wagnière, K. Mislow, A. Dreiding, and Dr. A. F. Thomas for personal communications. We are grateful to the University of Salford for the award of a Fellowship (to A. J.) and for leave of absence (to F. S.). We thank the Royal Society for an award (to F. S.) in their European Fellowship Programme.

<sup>80</sup> F. Bickelhaupt, W. L. de Graaf, and G. W. Klump, *Chem. Comm.* 1968, 53; A. Dreiding and M. Rey, unpublished work.