Influence of Alkyl Groups on the Rate of the *para* Claisen Rearrangement

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The rates of the Claisen rearrangement of allyl *o*-tolyl, allyl *o*-ethylphenyl, allyl *o*-isopropylphenyl, allyl 2,6-diethylphenyl, and allyl 2,6-diisopropylphenyl ethers have been measured. The data show that a single *ortho*-alkyl group depresses the rate of migration of the allyl group to a *para* position (half the rate of allyl *p*-tolyl ether as a standard), whereas the presence of alkyl groups in both *ortho* positions markedly enhances that rate. A rationale is offered for these observations.

The interesting series of rate constants shown in Table I prompted Schmid and Kalberer[2] to conclude that the allyl group in the allyl ether of methyl *o*-cresotinate (R = Me, R′ = COOMe) migrates to the *para* position principally *via* the *ortho* carbon bearing the methyl group, and that the allyl group in allyl 2,4-dimethylphenyl ether migrates to the open *ortho* position to an appreciable extent by going around the benzene ring *via* the 2- and 4-positions. Additional evidence in support of this interpretation was felt to be provided by the entropies of activation. It has been pointed out that this interpretation depends on the assumption that k_1, k_2, and k_3 must be independent of the nature of the group R′ present in the other *ortho* position.[3] While there seems to be no *a priori* reason to suspect that this assumption should hold, it is not the only condition involved. It must also be assumed that the carbomethoxy group deactivates the position to which it is attached so that k_1 becomes much smaller than when a methyl group is attached.[4]

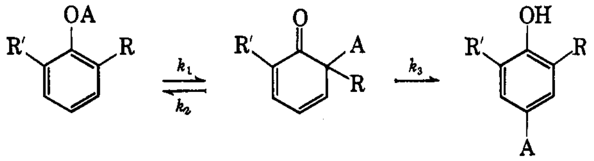

TABLE I

RATES OF SOME CLAISEN REARRANGEMENTS

Allyl ether of	$k_{170} \times 10^5$ sec.$^{-1}$
p-Cresol	0.76
2,4-Dimethylphenol	1.58
2,6-Dimethylphenol	6.46
Methyl *o*-cresotinate	3.31

We have recently obtained some experimental evidence which casts considerable doubt on the validity of the assumptions involved.[5] The rearrangement of allyl *o*-tolyl ether gives a mixture of 2-allyl-6-methylphenol and 4-allyl-2-methylphenol in the ratio of 5.6 to 1.0. Should the assumptions described above be valid, the rate of migration to a single *ortho* position should be approximately 0.38×10^{-5} sec.$^{-1}$, while that to the *para* position *via* a methyl-bearing *ortho* carbon should be 3.23×10^{-5} sec.$^{-1}$. Hence the ratio of 2-allyl-6-methylphenol to 4-allyl-2-methylphenol would have been 0.12 to 1.0. A second, but less compelling, piece of evidence pointing to the same conclusion is that the allyl ether of *o*-cresotinic acid gives 80% 2-allyl-6-methylphenol by loss of carbon dioxide.[6] If the carboxyl and carbomethoxy groups have a similar influence on the rate, as seems eminently reasonable, this shows that k_1 (R = COOH) is four times as large as k_1 (R = Me). If the k_1 (R = COOMe) is equally large, then k_2/k_3 (R = COOMe) must exceed 80 if 95% of the allyl migration is to go *via* the methyl group. Since k_2/k_3 (R = Me or allyl) is near to 0.3,[7] such a large change seems unreasonable.[4,8]

To provide further evidence bearing on the influence of substituents on the *para*-Claisen rearrangement we have measured the rates of rearrangement of a series of 2-alkyl- and 2,6-dialkylphenyl allyl ethers. The results are shown in Table II. For the cases where the alkyl group or groups were ethyl or isopropyl the rates were determined on neat samples. Under such conditions the first-order rate constants often show an upward

TABLE II

RATES OF CLAISEN REARRANGEMENT OF SOME *o*-ALKYLPHENYL ALLYL ETHERS

Allyl ether of	$k \times 10^5$ sec.$^{-1}$			
	155°	170°	180°	185°
Phenol		0.46^a		1.52^b
o-Cresol		0.92^c	1.91^d	
2-Ethylphenol		1.51		5.15
2-Isopropylphenol		1.1^c		3.86
2,6-Dimethylphenol		$6.42^{b,e}$		
2,6-Diethylphenol		10.1		36
2,6-Diisopropylphenol	2.72	9.5^c		

^{a} Calculated from the data of ref. 11. ^{b} Measured in diphenyl ether. ^{c} Calculated for 170° using E_a = 32 kcal./mole. ^{d} Measured in decalin. ^{e} Data from ref. 9.

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[2] F. Kalberer and H. Schmid, *Helv. Chim. Acta*, **40**, 13 (1957).

[3] S. J. Rhoads, "Molecular Rearrangements," part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 699.

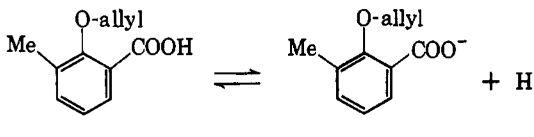
[4] Since the over-all rate is $k_{obsd} = k_1 [1/(1 + k_2/k_3)]$, the same trend can be effected by an increase in k_2 or a decrease in k_3. However, both the reactions represented by k_2 and k_3 are of a very similar nature and the substituent R might be expected to influence both in the same way so that the ratio k_2/k_3 would show only a small change.

[5] E. N. Marvell, B. Richardson, D. R. Anderson, J. L. Stephenson, and T. Crandall, *J. Org. Chem.*, **30**, 1032 (1965).

[6] L. Claisen and O. Eisleb, *Ann.*, **401**, 79 (1913).

[7] D. Y. Curtin and R. J. Crawford, *J. Am. Chem. Soc.*, **79**, 3156 (1957); W. Haegele and H. Schmid, *Helv. Chim. Acta*, **41**, 42 (1958).

[8] This analysis neglects the possibility that ionization may occur to a small degree and that the ionized ether may be the form which rearranges.



Since the carboxylate and carbomethoxy groups would not be expected to produce a similar effect on the rate, this would invalidate the conclusions reached above.

trend due to a solvent effect.[9] Our results show this effect, though it was small except in the case of allyl *o*-ethylphenyl ether. In order to make these data as reasonably comparable with the other data in Table II where the rates were determined in relatively nonpolar solvents, the rate constants given are average values for the first 50% of the reaction.

Though the data in the table are not strictly comparable because of the solvent differences noted above, the uncertainty introduced by this is not large enough to invalidate the conclusions reached.[10] Inspection immediately reveals that the *ortho*-substituted ethers fall into two groups ratewise: those with a single *ortho* substituent and those with two such substituents. The former react about eight to ten times more slowly than the latter and belong to what we will term the normal category. That is their rates are more nearly comparable with those ethers having the same substituent in a *para* position. The introduction of the second *ortho* substituent appears to provide an unusual impetus to the arrangement.

This peculiar influence is more strikingly apparent from the data of Table III. The data in the table have been corrected statistically so that the rates are for rearrangement to a single position, and the data for *ortho* to *para* product ratios[5] have been used to calculate the rates for the *para* rearrangement of allyl *o*-alkylphenyl ethers. Three specific conclusions are evident: (a) a single *ortho* substituent is more effective in increasing the rate of rearrangement to a hydrogen-occupied *ortho* position than is the same substituent in a *para* position; (b) an alkyl group in an *ortho* position *decreases* the rate of migration *via* that *ortho* position; and (c) two *ortho*-alkyl groups increase the rate of migration by a factor of 20–40-fold.[12]

TABLE III

RATES OF REARRANGEMENT TO INDIVIDUAL POSITIONS AT 170°

Allyl ether of	k_o[a]	k_p[a]
p-Cresol	0.38 (1)	
o-Cresol	0.78 (2)	0.14 (0.4)
o-Ethylphenol	1.36 (4)	0.15 (0.4)
o-Isopropylphenol	1.00 (3)	0.10 (0.3)
2,6-Dimethylphenol		3.21 (9)
2,6-Diethylphenol		5.05 (13)
2,6-Diisopropylphenol		4.75 (12)

[a] Values in parentheses are rates relative to *p*-cresol.

These interesting and somewhat unexpected results can be rationalized mainly in terms of the steric effects of *ortho* substituents on ground-state energies, and on the populations of certain conformations. When a single *ortho* position is occupied by an alkyl group, the allyloxy moiety will adopt preferentially a conformation with the allyl entity turned toward the hydrogen-occupied *ortho* position. The effects a and b noted above can both be attributed to this conformational influence. When alkyl groups are present in both *ortho* positions, we suggest that ground-state energy of the allyl ether is increased, thus accounting for the third observation. It is possible that not all of the large increase in rate caused by the introduction of the second alkyl group is due to the increase in k_1 resulting from the higher ground-state energy. This increase may be reflected to a smaller degree in the transition state. To the extent that the transition-state energy is raised by steric crowding k_2 will be decreased. Hence k_2/k_3 will be smaller than when this steric influence is absent, and thus the observed rate, $k_{\text{obsd}} = k_1[1/(1 + k_2/k_3)]$, will be larger.[13]

The postulated increase in ground-state energy can be attributed, at least in part, to the forcing of the allyloxy group out of coplanarity with the ring. This will be a less stable conformation because delocalization of the unshared pairs on the oxygen into the ring will be less effective. That steric *modus operandi* will also make itself apparent in the ultraviolet spectra of these ethers. Burawoy and Chamberlain[14] have studied the spectra of a series of methyl-substituted anisoles, and these along with our data on the allyl isopropylphenyl ethers are shown in Table IV. The data give clear evidence for the special influence due to two *ortho*-alkyl substituents and provide good support for the suggestion made here.

TABLE IV

ULTRAVIOLET SPECTRA OF SUBSTITUTED ALKYL ARYL ETHERS

Compd.	$\lambda_{\max}$, mμ	ϵ
Anisole[a]	270	1590
	277	1410
p-Methylanisole[a]	277.5	2150
	284.5	1820
o-Methylanisole[a]	271	1740
	277	1740
2,6-Dimethylanisole[a]	265	600
o-Isopropylphenyl allyl ether	270	2550
	277	2240
2,6-Diisopropylphenyl allyl ether	252	910

[a] Data of Burawoy and Chamberlain.[14]

On the basis of our data and the measured rate of rearrangement of allyl 2,4-dimethylphenyl ether we conclude that the only important route to 6-allyl-2,4-dimethylphenol must be *via* direct migration of the allyl group to the 6 position. At present we can derive no conclusions *vis-à-vis* the relative rates of migration *via* the methyl-bearing *ortho* carbon and the carbomethoxy-occupied one in the allyl ether of methyl *o*-cresotinate.

Experimental

Allyl 2-Alkylphenyl Ethers.—Allyl *o*-cresyl ether was prepared according to the procedure of Claisen and Eisleb.[15] Allyl 2-ethylphenyl and allyl 2-isopropylphenyl ethers were prepared ac-

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[9] J. F. Kincaid and D. S. Tarbell, *J. Am. Chem. Soc.*, **61**, 3085 (1939); **62**, 728 (1940).

[10] An estimate of the effect of the solvent difference on the rate can be made from the rates of allyl *o*-tolyl and allyl *o*-ethylphenyl ethers. The influence of methyl and ethyl groups in the *para* position is nearly identical.[11] Thus the difference between the rates of these two ethers probably provides a reasonable estimate of the solvent influence. The energies and entropies of activation for allyl 2-ethylphenyl and allyl 2,6-diethylphenyl ethers calculated from the data in Table II are in the normal range. Choice of 32 kcal./mole to calculate rates at 170° was made because the activation energies normally lie in the range 30–34 kcal./mole and for the temperature interval involved the use of 32 kcal./mole can introduce only minor errors.

[11] H. L. Goering and R. R. Jacobson, *J. Am. Chem. Soc.*, **80**, 3277 (1958).

[12] This is an enormous factor in relation to those usually observed in Claisen rearrangements. For example, the total spread for a group of *para* substituents ranging from nitro to dimethylamino is only 16-fold.[11]

[13] An alternate way of looking at this which is perhaps preferable is to suggest that the steric influence on the dienone is larger than on the activated complexes. Thus, as R increases in size, k_2 increases but k_3 increases more rapidly. Thus k_2/k_3 decreases and the observed rate will again be higher.

[14] A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.*, 2310 (1952).

[15] L. Claisen and O. Eisleb, *Ann.*, **401**, 21 (1913).

cording to the procedure described earlier.[4] The properties were in accord with those reported.

Allyl 2,6-Diethylphenyl Ether.—A sample of 2,6-diethylphenol, m.p. 35–36°, was prepared essentially by the method of von Auwers.[16] This was treated with allyl bromide in *t*-butyl alcohol according to the procedure of Rhoads, Raulins, and Reynolds.[17] The ether was separated from unreacted phenol by extraction with Claisen alkali and isolated by distillation, b.p. 40° (0.03 mm.), $n^{22.5}\text{D}$ 1.4990.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.92; H, 9.76.

Allyl 2,6-Diisopropylphenyl Ether.—A sample of 2,6-diisopropylphenol[18] was converted to its allyl ether as described for allyl 2,6-diethylphenyl ether above. The clear liquid was distilled, b.p. 54–57° (0.05 mm.), $n^{23}\text{D}$ 1.4972, $\bar{\nu}$ 1640 and 920 cm.$^{-1}$, 73%.

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.61; H, 10.16. Found: C, 82.35; H, 10.02.

Kinetics.—All rates were measured by the ampoule method using sealed Pyrex tubes suspended in a bath maintained at the desired temperature ±0.5°. Allyl *o*-cresyl ether was run in decalin solution[19] and the analysis was carried out by gas chromatography using a 20% Reoplex 400 on Chromosorb column. Allyl 2-ethylphenyl ether, allyl 2-isopropylphenyl ether, and allyl 2,6-diisopropylphenyl ether were rearranged neat and the reaction was followed by the change in refractive index. A Zeiss Abbe-type refractometer was used at 20.0° and the relation between refractive index and composition was shown to be linear in each case. Allyl 2,6-diethylphenyl ether and allyl 2,6-diisopropylphenyl ether were rearranged neat; the reaction was followed by n.m.r. Allyl 2,6-diethylphenyl ether has an n.m.r. band at τ 3.10 which represents the aromatic protons on carbons 3, 4, and 5, while 2,6-diethyl-4-allylphenol exhibits a band due to the aromatic protons at C-3 and C-5 at τ 3.31. The relevant bands for the diisopropyl case lie at τ 2.90 and 3.12, respectively. The relative areas under the peaks were corrected for the protons involved and the data were used directly to follow the progress of the rearrangement.[20]

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[16] K. von Auwers and W. Mauss, *Ann.*, **460**, 224 (1928); K. von Auwers and G. Wittig, *Ber.*, **57**, 1275 (1924).

[17] S. J. Rhoads, R. Raulins, and R. D. Reynolds, *J. Am. Chem. Soc.*, **76**, 3456 (1954).

[18] We are indebted to the Ethyl Corp. for a generous sample of 2,6-diisopropylphenol and are pleased to acknowledge their courteous aid to our research.

[19] We are indebted to Dr. Richard Anderson who carried out this determination, which was made in 1961 in connection with another problem.

[20] The authors are indebted to the National Science Foundation for financial assistance toward the purchase of the Varian A-60 n.m.r. spectrometer.

Claisen Rearrangement of Allyl 2-Alkylphenyl Ethers[1]

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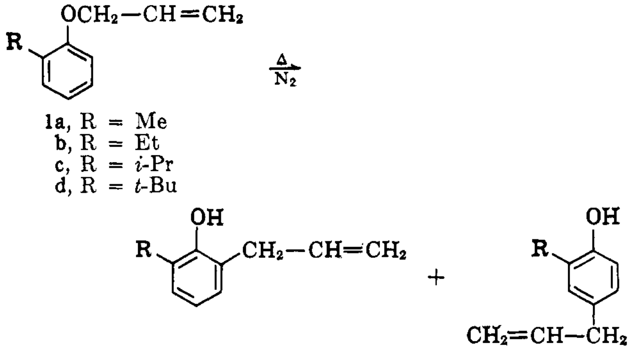
A series of allyl 2-alkylphenyl ethers with the alkyl group varied from methyl to *t*-butyl has been prepared and rearranged. The relative amounts of 6-allyl-2-alkylphenol and 4-allyl-2-alkylphenol were determined in each case by gas chromatography. For all but the *t*-butyl case the nature of the products was verified by synthesis. All rearrangements gave predominantly the 6-allyl-2-alkylphenol accompanied by smaller amounts (*ca.* 10%) of the 4-allyl-2-alkylphenol.

For many years the idea that the migratory allyl group in the Claisen rearrangement would enter an *ortho* position exclusively when at least one was available was an important rule.[2] Use of the rule has been made frequently in synthetic work,[3] but recent studies on the mechanism of the Claisen rearrangement have shown that the idea is generally untenable.[4] In fact there exists a considerable collection of examples which attests to the common formation of both *ortho* and *para* products in the rearrangement of *ortho*-substituted phenyl allyl ethers.[5] Aside from the apparently general inference that the ratio of *ortho* to *para* product is distinctly lower when the *ortho* substituent is hydroxyl or amino than when it is alkyl, no generalizations concerning the factors which influence the partitioning of the allyl group between the *ortho* and *para* positions have been developed. The work reported here will show that the size of the *ortho* substituent has a surprisingly small influence on that partitioning.

The series of allyl 2-alkylphenyl ethers **1a–d** was prepared from the 2-alkylphenols by etherification in *t*-butyl alcohol.[6] These were rearranged neat under nitrogen and the product was analyzed by gas chromatography. The results are shown in Table I. As expected, the separation between the peaks due to *ortho* and *para* product decreased with increasing size of the alkyl group. However, in every case except *t*-butyl the



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[1] A preliminary account of this work was presented at the 138th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1960; *cf.* Abstracts, p. 85P. Published with the approval of the Monographs Publication Committee, Oregon State University, as Research Paper No. 470, School of Science, Department of Chemistry. The authors are pleased to acknowledge partial financial support from the National Science Foundation under Grant G 7432, the Sigma Xi-RESA Research Fund, and the General Research Grants of Oregon State University. Paper no. 6 on the Claisen Rearrangement; paper no. 5: *J. Org. Chem.*, **27**, 1109 (1962).

[2] D. S. Tarbell, *Org. Reactions*, **2**, 8 (1944).

[3] Note, for example, the use of Claisen rearrangements of *ortho*-substituted phenyl ethers to prepare 2,6-dialkylphenols as model compounds for analytical procedures: (a) E. N. Marvell, A. V. Logan, L. Friedman, and R. Ledeen, *J. Am. Chem. Soc.*, **76**, 1922 (1954); (b) D. Y. Curtin and M. W. Johnson, Jr., *ibid.*, **78**, 2611 (1956); (c) M. J. S. Dewar and N. A. Putnam, *J. Chem. Soc.*, 4080 (1959).

[4] For an excellent review, see S. J. Rhoads, "Molecular Rearrangements," part I, P. deMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 655.

[5] References to these are listed by P. Fahrni, W. Haegele, K. Schmid, and H. Schmid [*Helv. Chim. Acta*, **38**, 783 (1955)].

[6] S. J. Rhoads, R. Raulins, and R. D. Reynolds, *J. Am. Chem. Soc.*, **76**, 3456 (1954).