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Title: THE AROMATIC COPE REARRANGEMENT:

ENERGETICS AND REALITY

Abstract approved: Redacted for Privacy

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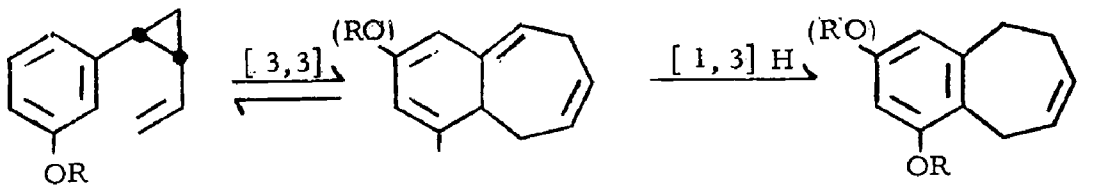
In a continuing investigation of the Cope rearrangement, the energetics associated with the first authentic aromatic-Cope rearrangement have been determined. The activation parameters for the aromatic-Cope rearrangement of cis-1-(m-hydroxyphenyl)-2-vinylcyclopropane to 6, 9-dihydro-5H-benzocyclohepten-1-ol are $\Delta H^{\ddagger} = 26.7 \pm 4.0$ kcal/mole with $\Delta S^{\ddagger} = -17.5 \pm 9.8$ e.u. In dilute solutions of cis-1-(m-hydroxyphenyl)-2-vinylcyclopropane the rate



R = H, CH_3

determining step becomes the [1, 3] hydrogen shift and no rearrangement occurs. When cis-1-(m-methoxyphenyl)-2-vinyl-cyclopropane was heated no rearrangement occurred until phenol was added to the

reaction and then a mixture which contained 6, 9-dihydro-5H-benzocycloheptenyl methyl ether and 4, 7-dihydro-3H- benzocyclohepenyl methyl ether was obtained.

Heating the anions of 1-phenyl-3-buten-1-ol, 1-α-naphthyl)-3-buten-1-ol and 2, 2-dimethyl-1-phenyl-3-buten-1-ol produced compounds derived from a double bond migration or a [1, 3] shift with none of the desired aromatic oxy-Cope products being detected. However, the anionic oxy-Cope rearrangement of 1-(α-naphyl)-2, 2-dimethyl-3-buten-1-ol produced 2-(γ, γ-dimethyl-allyl)-1, 2-dihydronaphthalene-1-carboxaldehyde in 10% yield along with the [1, 3] shift product.

The Aromatic Cope Rearrangement: Energetics and Reality

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To G. D.

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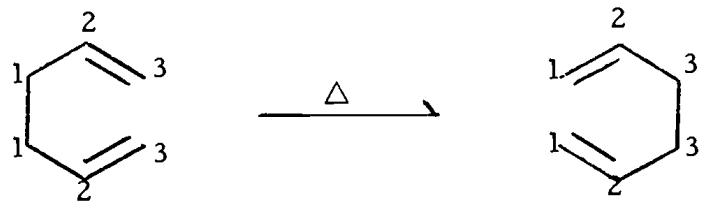
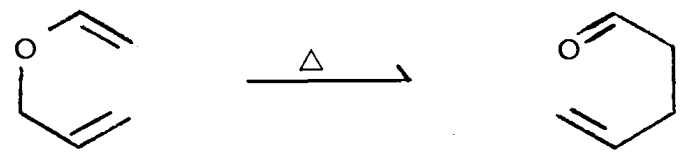
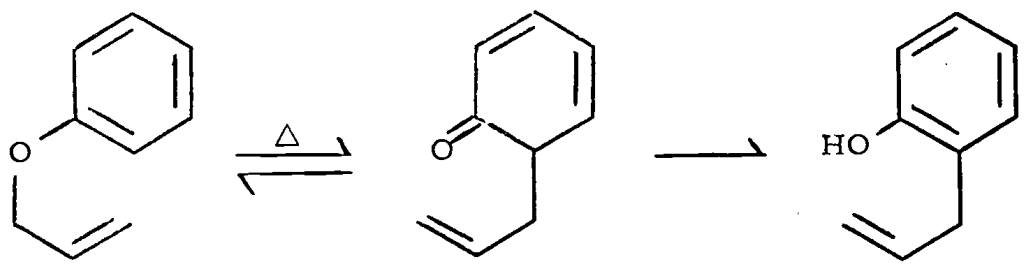
INTRODUCTION

The Cope rearrangement is the prototype for all [3, 3] sigmatropic shifts (1), and a wide variety of such shifts, having one or more



atoms of different nature in place of carbon and having various substituents on the chain, have been reported during the last seventy years (2, 3, 4, 5, 6). It is interesting that the Claisen rearrangement proceeds





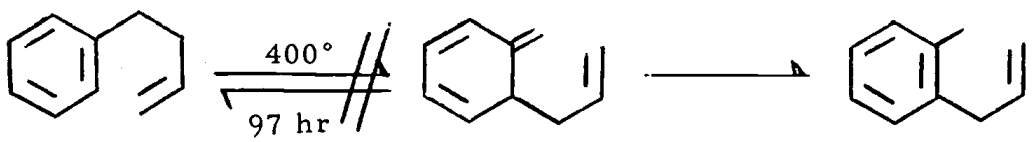
about as well when the enol double bond is incorporated in an aromatic ring as does its acyclic analog, but the Cope rearrangement fails completely when one double bond is part of an aromatic ring. Reasons can be advanced to account for this but experimental evidence bearing on this point is as sparse as are aromatic-Cope rearrangements.

Recently we have uncovered the first authentic example of an aromatic-Cope rearrangement, which opens the door to experimental examination of the problems associated with the aromatic-Cope reaction in general. Thus we propose to ascertain the activation parameters for this example and to translate these to the more general case. Then, since this example depends on the activation provided by a vanishing cyclopropane ring, we hope to use the information on energetics to light the route to other ways to activate further examples of the aromatic-Cope rearrangement.

HISTORICAL

I. The Aromatic-Cope Rearrangement

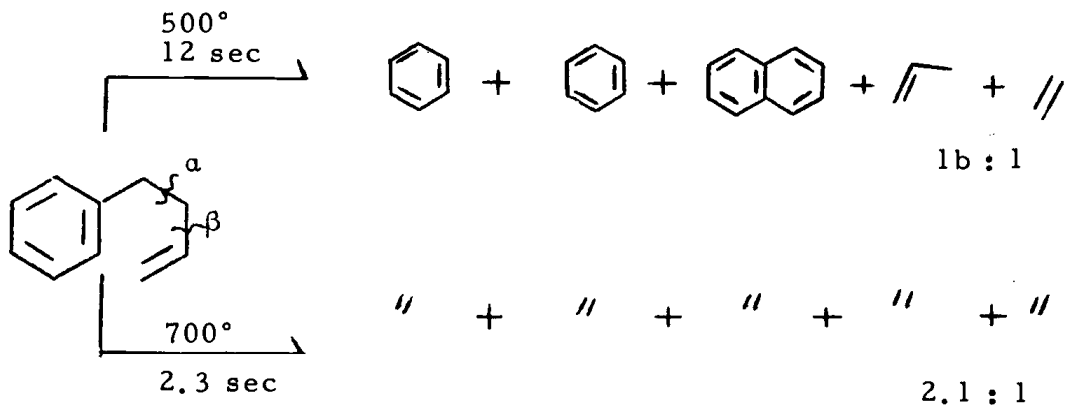
Attempts to find an Aromatic-Cope rearrangement have taken a number of different routes. The earliest study, by Hurd and Bollman in 1933 (7), was a good indication of the success to be achieved over the next forty-five years. When 4-phenyl-1-butene (1) was heated to 400° for 97 hr. in a sealed ampoule none of the Cope product, o-allyltoluene (3), was observed and only starting material was recovered.



1 2 3

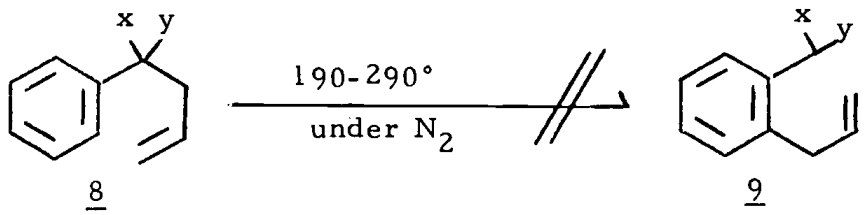
At 500-700° in a flow system (8), products from fragmentation began to appear. For example, at 500° (contact time 12 sec.) benzene, toluene, propene, ethylene and naphthalene were obtained. It was noted that propene and ethylene were derived from α- and β- cleavages. At 700° with (contact time 2.3 sec.) the ratio of α/β cleavage decreased. The authors argued that this represented a preference for α-cleavage at lower temperatures, which should aid the Aromatic-Cope rearrangement but limit the useful temperature range.

In the mid-1950's Cope and coworkers took a new look at the Aromatic-Cope rearrangement (9, 10). Cope's earlier findings showed that substitution of $-CO_2Et$, -CN or $-C_6H_5$ on the methylene carbon accelerates the Cope rearrangement (11, 12). The effectiveness is



illustrated dramatically by the relative temperatures required for the Cope rearrangement of ethyl (1-methylpropenyl)-allylcyanoacetate (4b) and 3-methyl-1, 5-hexadiene (6) of 150° and 300°, respectively.

Introduction of such activating substituents at C_4 of 4-phenyl-1-butene failed to house the Aromatic Cope reaction, only partial decomposition or no reaction occurred even at 290°.



8 9

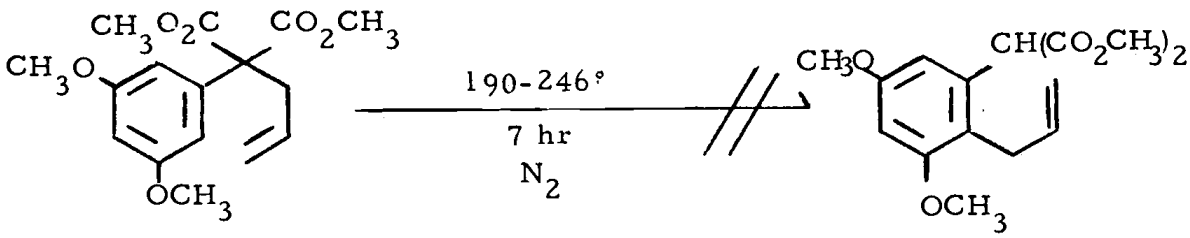
a. x = y = $-CO_2Et$

b. x = $-CO_2Et$; y = -CN

c. x = y = -CN

d. x = y = $-C_6H_5$

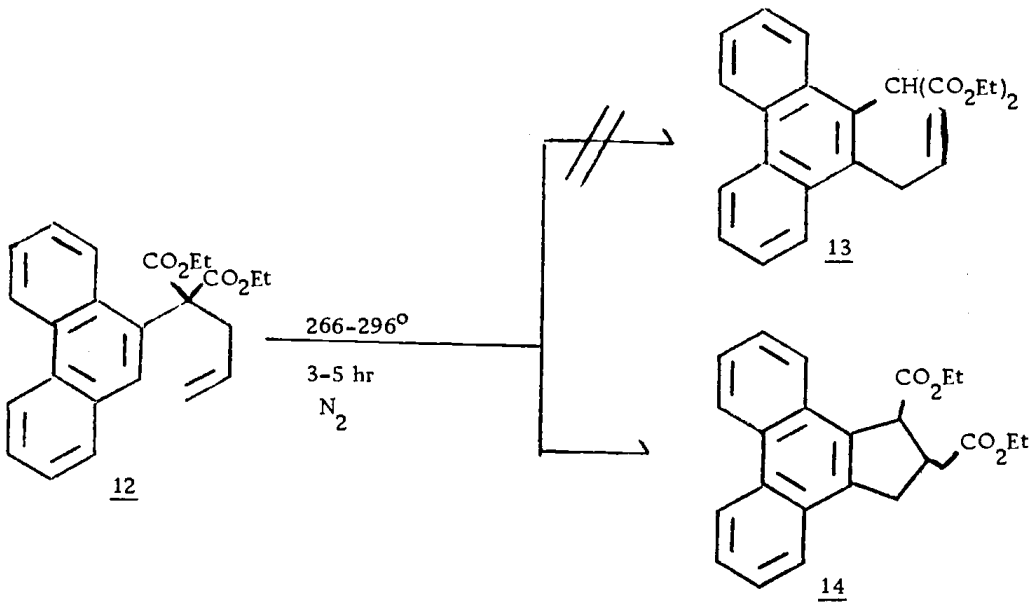
Even the incorporation of m-methoxy groups which had been shown to enhance the rate of the aromatic-Claisen rearrangement (13) proved unsuccessful. When dimethyl α-(3, 5-dimethoxyphenyl)-α-allyl-malonate (10) was heated only a little polymer and starting material were obtained.



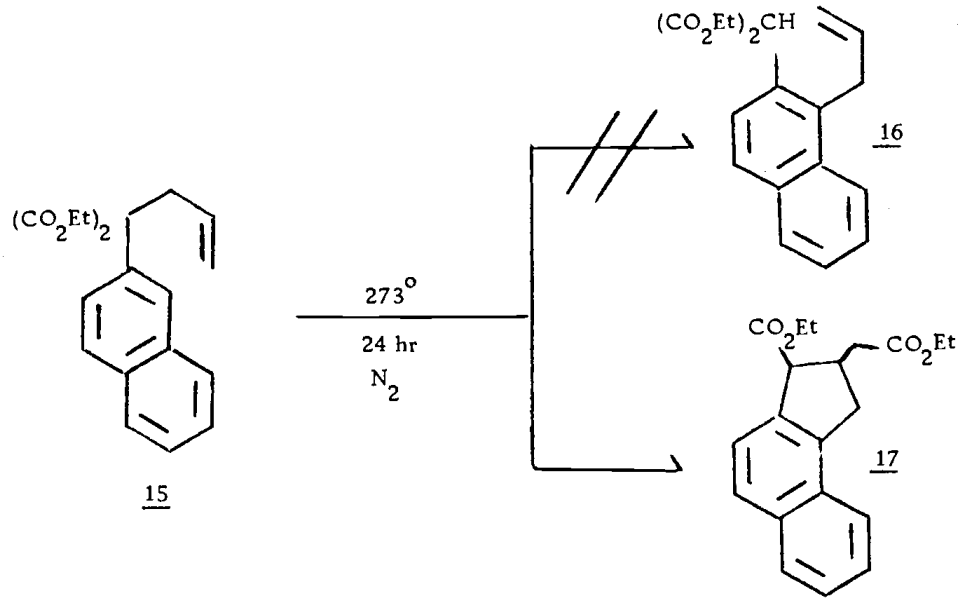
10 11

Attempting to minimize the loss of resonance energy during the reaction, Cope tried both phenanthryl and naphthyl systems (9, 10). Diethyl α-allyl-α-(9-phenanthryl) malonate (12) heated to 266-296° gave

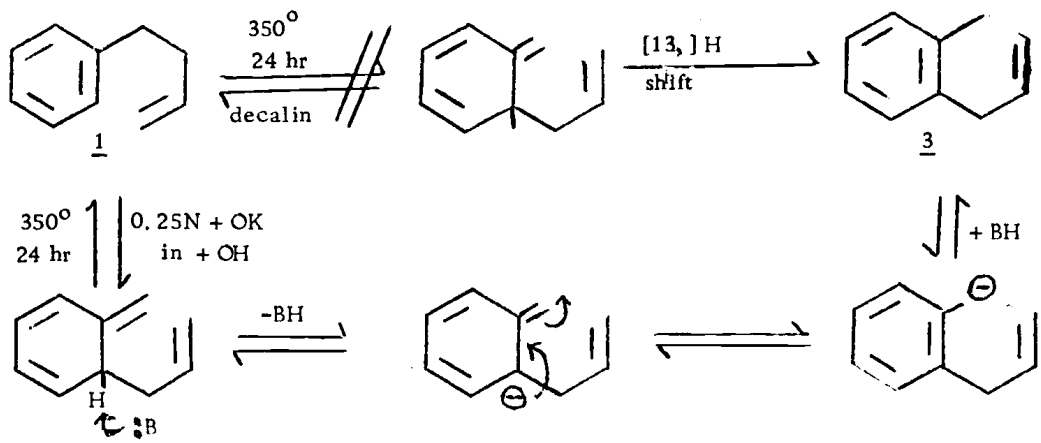
a new compound, 14, which was not the expected Cope product, 13, but could have been produced by further rearrangement of 13. A



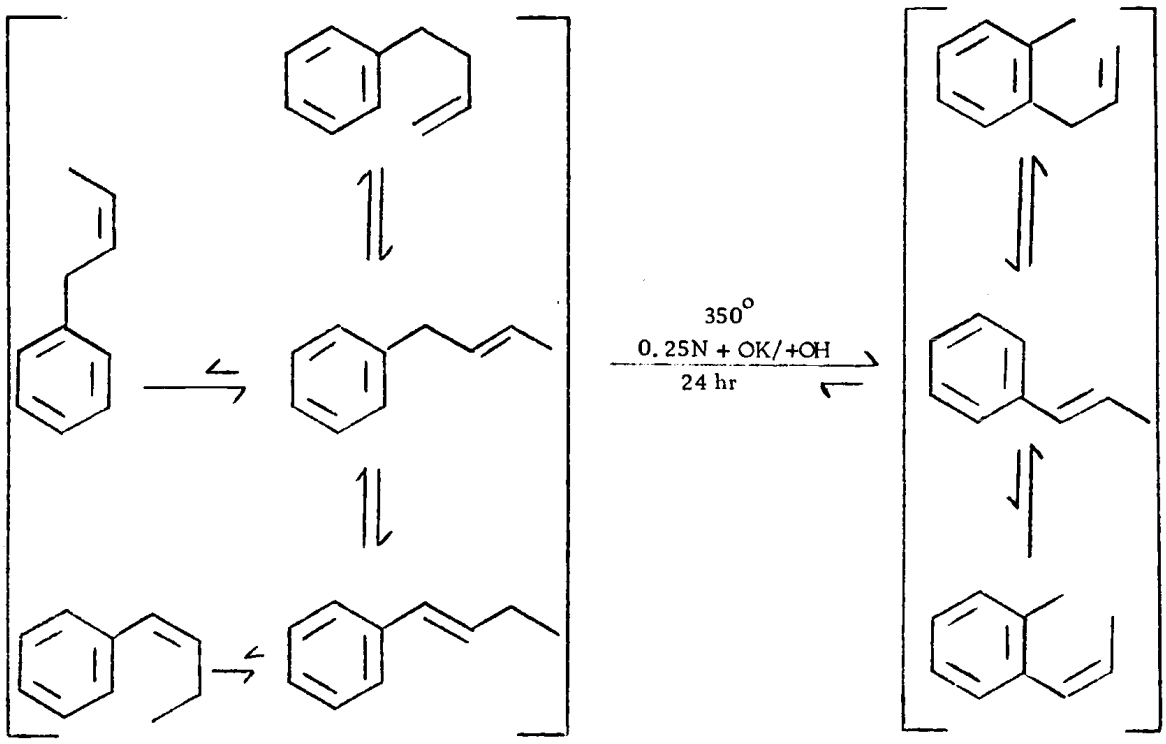
similar result was obtained when diethyl α-allyl-α-(2-naphthyl) malonate (15) was heated (10).



Bearing heavily on the Woodward-Hoffman rules, Doering suggested that the forbidden [1, 3] hydrogen shift was the inhibitor of the aromatic-Cope rather than the allowed [3, 3] shift (14). When 1 was heated in decalin none of the desired o-allyltoluene (3) was observed as expected from the results of Hurd and Bollman (7). If Doering's

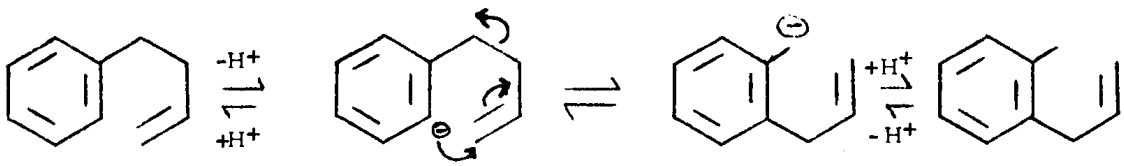


hypothesis were correct, use of a strong base would catalyze the [1, 3] H sigmatropic shift and permit formation of o-allyltoluene (3). The reasoning appeared confirmed since in the presence of 0.25N potassium t-butoxide 1 did indeed produce a moderate yield of 3 along with several isomers of both reactant and product. Unfortunately, this example has never been tied directly to the aromatic-Cope rearrangement as there are several other mechanistic possibilities.



5-10% 90-95%

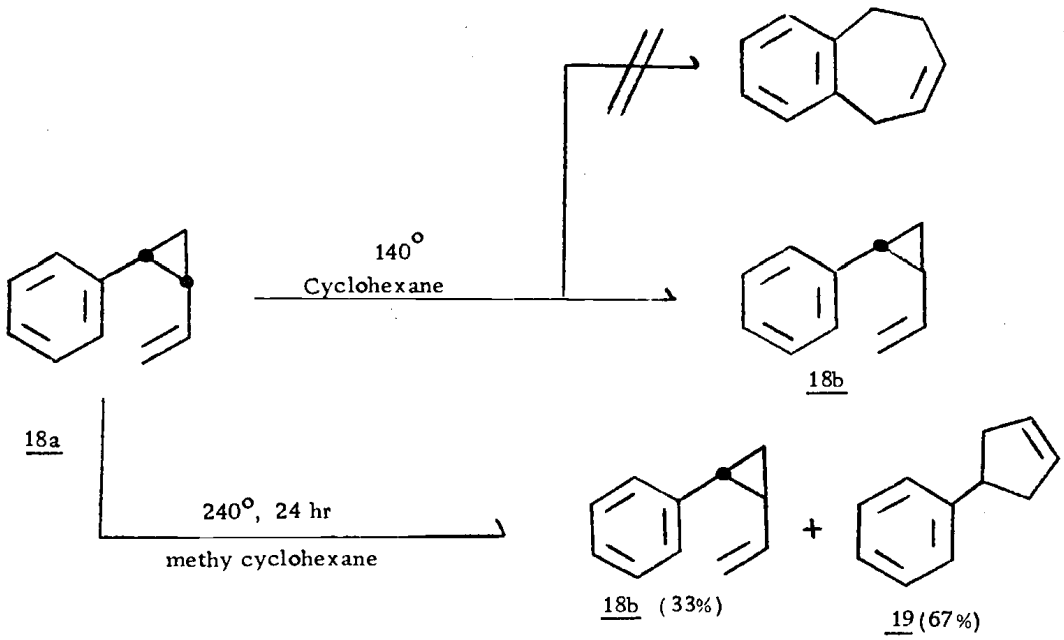
One mechanism suggested by Doering and Bragole involves removal of an o-proton. A final direct attempt to activate the aromatic-Cope



rearrangement introduced ring strain into the reactant system which could be released during the [3, 3] sigmatropic reaction (15, 16, 17). Brown and coworkers found an approximate 12 kcal/mole drop in activation energy of the Cope rearrangement of 1, 5-hexadiene when the

sp^3 carbons were incorporated into a cyclopropane ring (18).

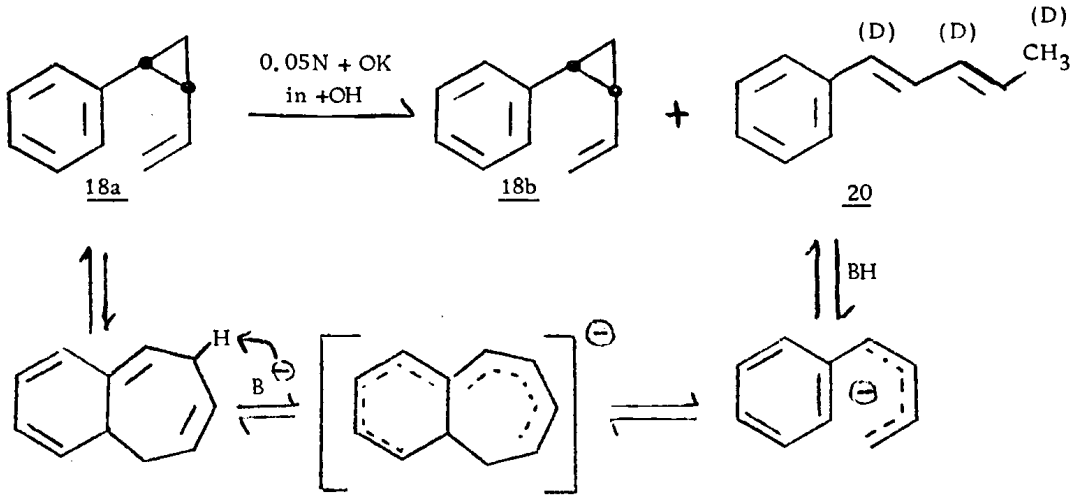
Marvell and Lin were the first to test this approach and they built a cyclopropane ring into 4-phenyl-1-butene (16). When cis-1-phenyl-2-vinylcyclopropane (18a) was heated to 140° only a mixture of cis- and trans-cyclopropanes (18a and 18b) was obtained. When 18a was heated to 240° a vinylcyclopropane-cyclopentene rearrangement was activated (19). Assuming the Doering approach they heated



18a in the presence of 0.05N potassium t-butoxide. Despite the presence of the base the product mixture contained none of the desired Cope product but only compounds 20 and 18b.

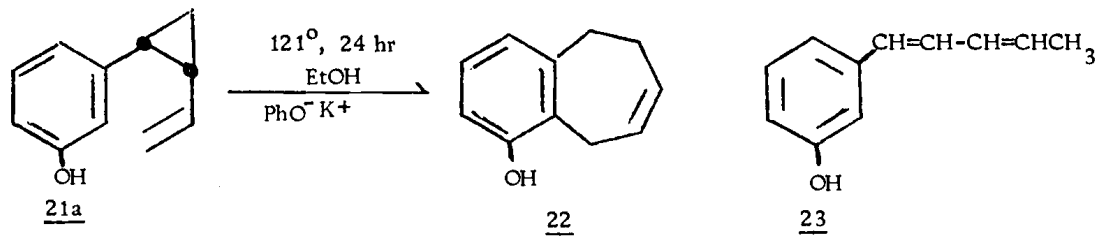
Marvell and Lin have suggested that 20 is derived from the tetranene Cope product. They argue that base treatment could remove the doubly allylic proton in the cycloheptadiene ring to produce

a 10π electron system which then undergoes an electrocyclic ring opening to regain aromaticity. The mechanism proposed has been

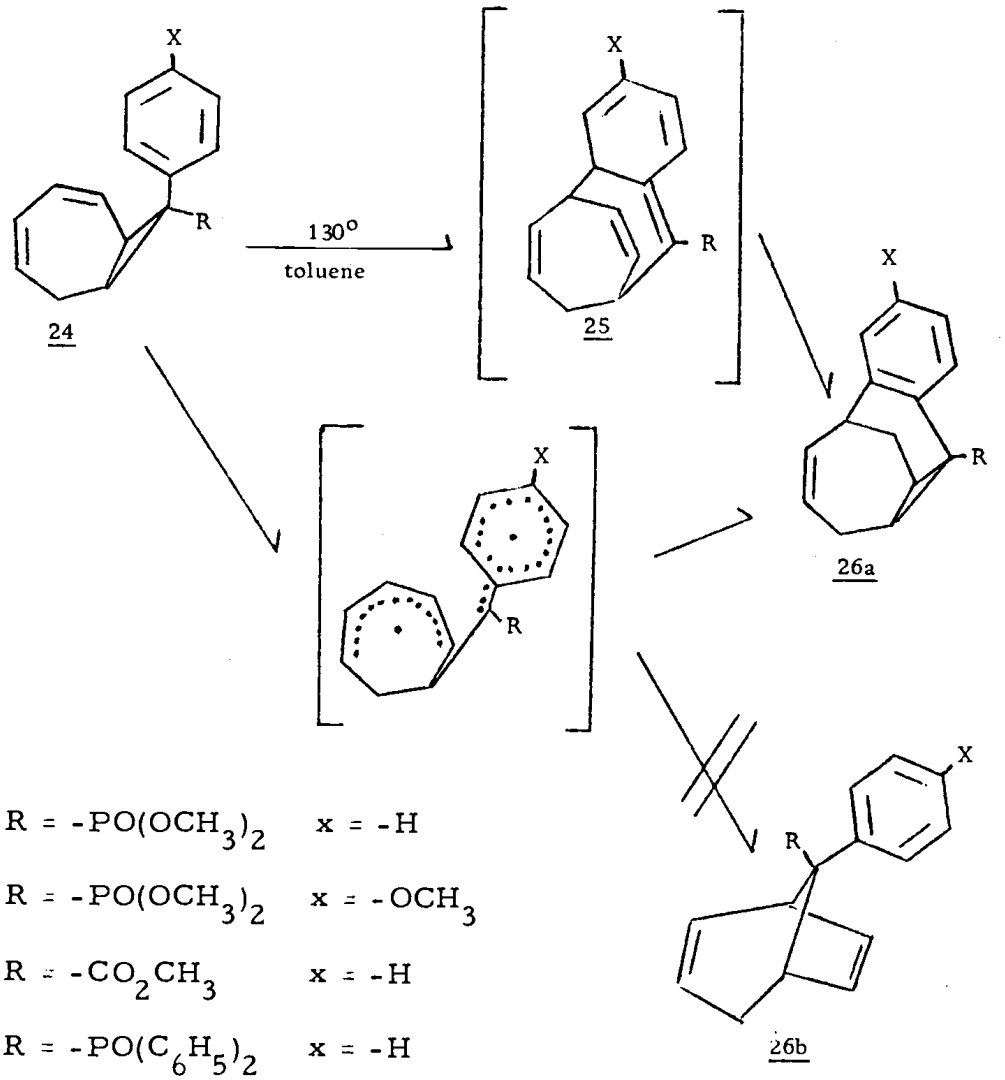


supported by the authors through a deuterium labeling experiment.

Quite different results were uncovered when cis-1-(m-hydroxyphenyl)-2-vinylcyclopropane (21a) was heated (17). After heating 21a dissolved in ethanol with a small amount of potassium phenoxide they isolated 22 along with some of the 1, 3-pentadiene product, (23). This was the first example of a true aromatic-Cope rearrangement.



Shortly after the discovery by Marvell and Lin, Maas and Regitz reported similar findings in their study of certain bicyclic systems containing a cyclopropane ring (15a). Various 8-endo-phenyl substituted bicyclo [5.1.0] octa-2,4-dienes (24) were heated in toluene and a Cope product 26a was isolated. It should be emphasized that



a) R = $-PO(OCH_3)_2$ x = -H

b) R = $-PO(OCH_3)_2$ x = $-OCH_3$

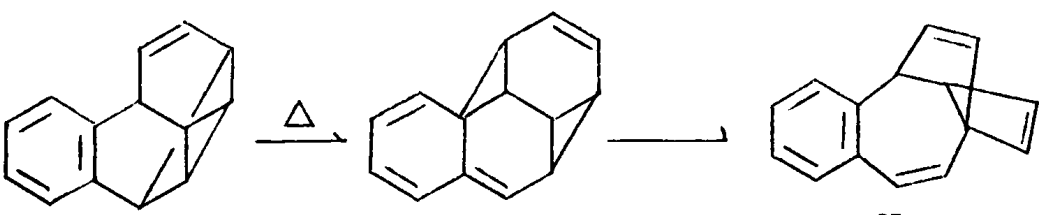
c) R = $-CO_2CH_3$ x = -H

d) R = $-PO(C_6H_5)_2$ x = -H

e) R = $-C_6H_5$

the rearrangement could proceed via a radical intermediate rather than via 25 as suggested by the authors. However, failure to isolate any 26b argues against that idea.

Vedejs and coworkers have suggested that the rearrangement of 4,5-benzotetracyclo[4.4.0.$0^{2,10}$.$0^{3,9}$]deca-4,7-diene to 27 proceeds through the aromatic-Cope intermediate as illustrated (15b). Though this is the most obvious route for the rearrangement, no evidence other than reactant and product structures to support the proposed mechanism have been reported.



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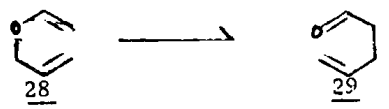
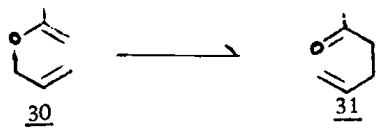
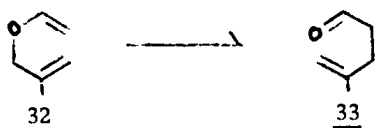
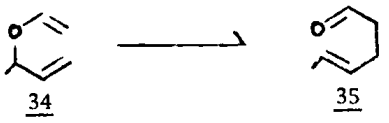
II. Activation Parameters

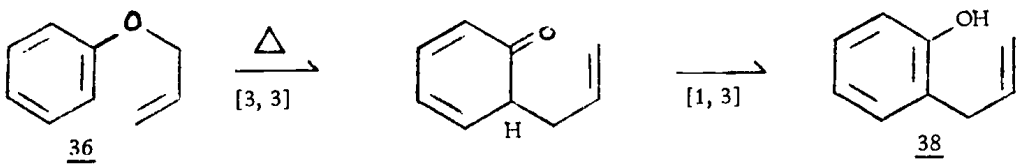
The Claisen Rearrangement

The Claisen rearrangement was discovered around 1912 some thirty years before its carbon analog (19, 20). Since then extensive investigations have revealed much mechanistic detail and a broad synthetic utility (2, 4, 5, 6). Forty years later the activation parameters associated with the Claisen rearrangement were determined (21). Schuler and Murphy reported that the conversion of allyl vinyl ether (28) to 4-penten-1-one (29) had an energy of activation of 30.6 kcal/mole and an Arrhenius frequency factor of 11.70 sec^{-1} (Table 1). The substituent effect of a methyl group on the

Table 1. Activation Parameters of Various Allyl Vinyl Ethers

Reaction	Ea(kcal/mole)	log A (sec^{-1})	Ref
 28 → 29	30.6	11.70	21
 30 → 31	29.3	11.73	22
 32 → 33	29.1	11.15	23
 34 → 35	27.9	11.32	24

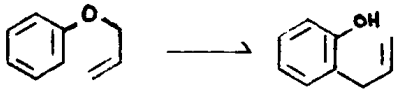
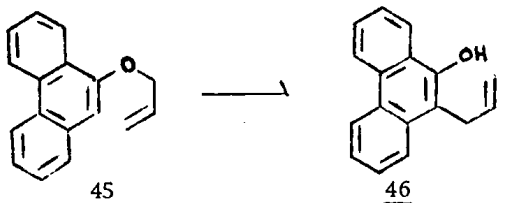
vinyl and allyl moieties appeared soon thereafter (22, 23, 24). It is interesting to note that regardless of the positioning of the methyl group on C_2, C_4 and C_5, the energy of activation is always lower than in the simple unsubstituted system. The activation parameters associated with phenyl vinyl ether were first reported by Goering and Jacobson in 1958 (13). When phenyl vinyl ether (36) was heated to 200° they obtained O-allyl-phenol (38). The mechanism generally accepted is first a concerted [3, 3] sigmatropic rearrangement to the ortho-dienone (37) followed by rapid enolization to give 38. The remarkable aspect of the aromatic-Claisen rearrangement is that

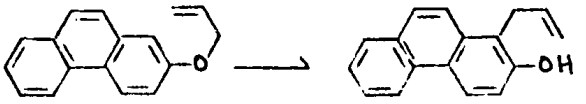


36 38

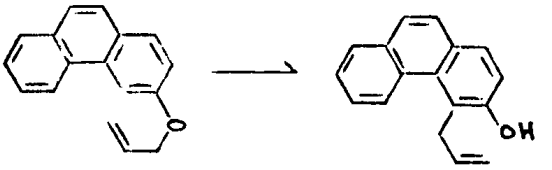
the incorporation of the phenyl ring only adds approximately 1 kcal/mole to the activation enthalpy (Table 2). Areen and coworkers (25) studied several aryl allyl ethers and reported the activation parameters (Table 2).

Table 2. Activation Parameters for the Aromatic-Claisen Rearrangements of Various Aromatic Systems

Reaction	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, e.u.	Ref.
 28 → 29	29.7	-7.7	21
 36 → 38	30.7	-12.0	13
 41 → 42	25.1	-15.9	25
 43 → 44	26.7	-12.0	25
 45 → 46	28.7	-18.1	25



47 48 28.7 -11.0 25



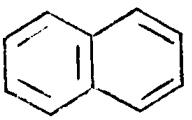
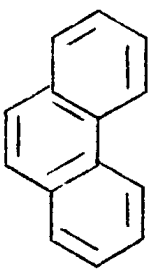
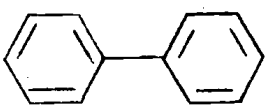
49 50 28.6 -11.0 25

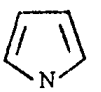
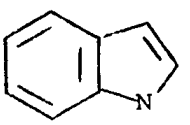
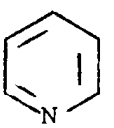
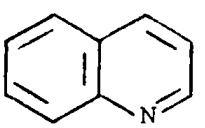
The enthalpy values generally seem to correlate well with the relative stabilization energies for each of the aromatic systems except in the case of the 9-phenanthryl systems (45→ 46). If one compares the stabilization energy of benzene (38 kcal/mole) with that of naphthalene (71 kcal/mole) a difference of 33 kcal/mole is obtained. This implies that there is a decrease of 5 kcal/mole in stabilization energy in going from the phenyl to the naphthyl system is supported by the drop in activation enthalpy in going from 36 to 41.

However, if one compares the stabilization energies of phenanthrene (111 kcal/mole) to that of biphenyl (83 kcal/mole) a difference of 28 kcal/mole is obtained. One would expect then a decrease in activation enthalpy to less than that for the naphthyl system (41) but this is not obtained. One possible explanation is that the

full stabilization energy of biphenyl cannot be obtained due to geometric restrictions of the [3, 3] intermediate.

Table 3. Stabilization Energies (or Approximate Resonance Energies) from Heats of Combustion of Some Aromatic Compounds (Ref. 26).

Compound	Structure	S. E. (kcal/mole
benzene		38
naphthalene		71
phenanthrene		111
biphenyl		83

pyrole		16[a]
Indole		48
pyridine		21[a]
quinoline		55

a) included in the table for purposes of comparison.

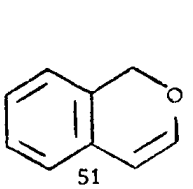
The acceleration of the Aromatic-Claisen rearrangement by substituents located in the meta- and para-positions of the phenyl ring was first noted by Goering and Jacobson (13). They found that incorporation of a m-methoxy group increased the rate three times

and lowered the activation enthalpy 1.2 kcal/mole (Table 4).

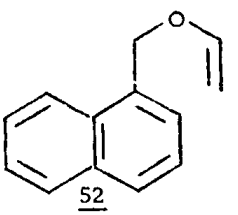
Table 4. Kinetic Data for the Ortho Rearrangement of Substituted Phenyl Allyl Ethers in Diphenyl Ether at 184-185° (13).

Substituent x	$k_o \times 10^5$ (sec^{-1}) (1%)	$\triangle H^{\ddagger}$ (kcal/mole) (1)	$\triangle S^{\ddagger}$ (e.u.) (2-3)
H	1.52	30.7	-12
p-OCH_3	4.58	32.7	-6
m-OCH_3	4.92	29.5	-13

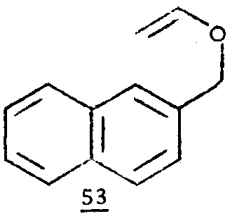
The incorporation of the allyl double bond into an aromatic system did not result in the same success as its vinyl counterpart. Burgstahler and coworkers showed that regardless of the aromatic system employed (51-55), at temperatures of 225-300° for 6-8 hr. in diglyme or decalin only partial polymerization was observed (27).



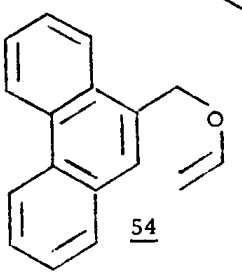
51



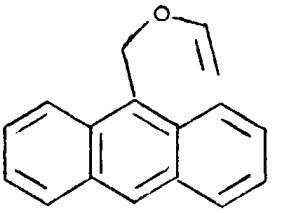
52



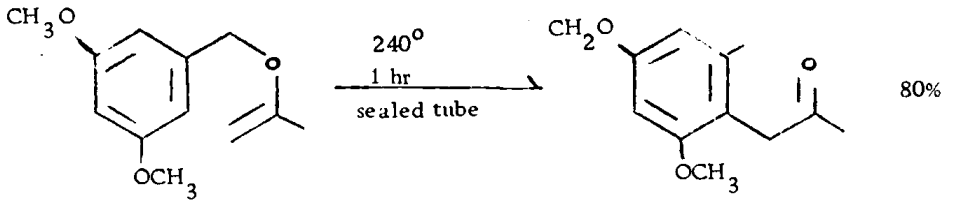
53



54

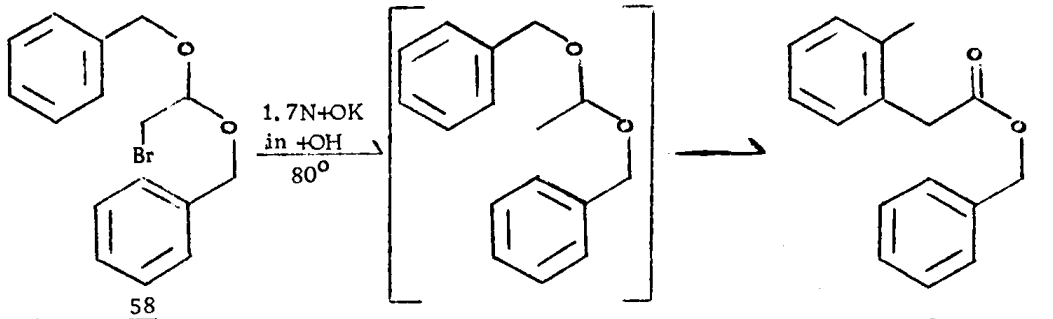


55



56 57

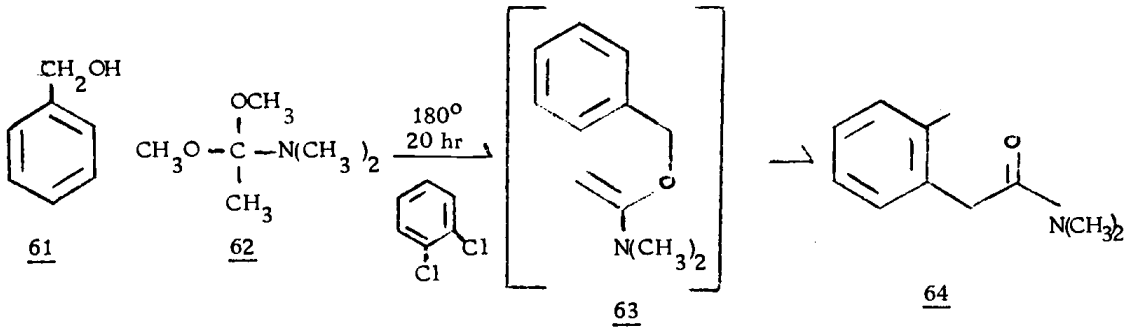
The only cases where benzyl vinyl ethers have been successfully rearranged in an Aromatic-Claisen reaction are ones in which either accelerating groups were placed on the aromatic ring (29) or where the reactant has been destabilized (30, 31). LeNoble and coworkers 29), employing the rate acceleration effect noted by Goering and Jacobson (13) obtained the Cope product, 57, by heating 3, 5-dimethoxyphenyl-2-propenyl ether (56).



58 59 60

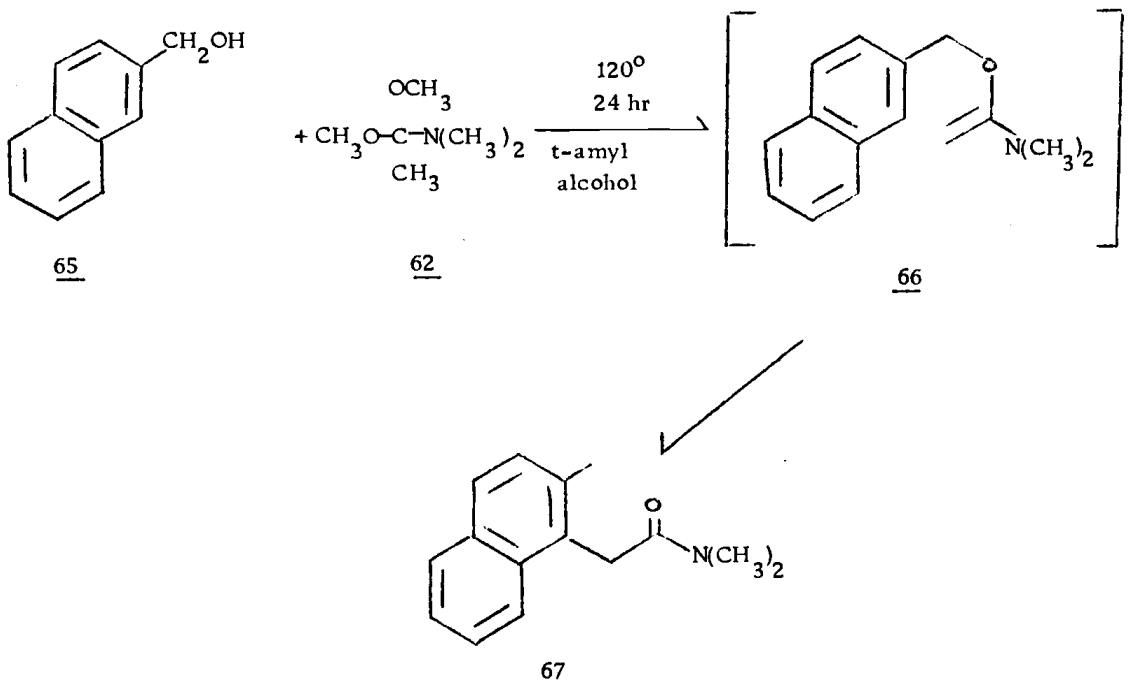
Shapiro (30) and Eschenmoser (31) used enols of esters and amides, respectively, to obtain the Aromatic-Claisen products. Shapiro treated dibenzyl bromoacetal (58) with base and obtained 60 as the major component. He proposed that intermediate 59 was

generated under the strongly basic conditions which then rearranged to 60. Eschenmoser (31) generated intermediate (63) from the



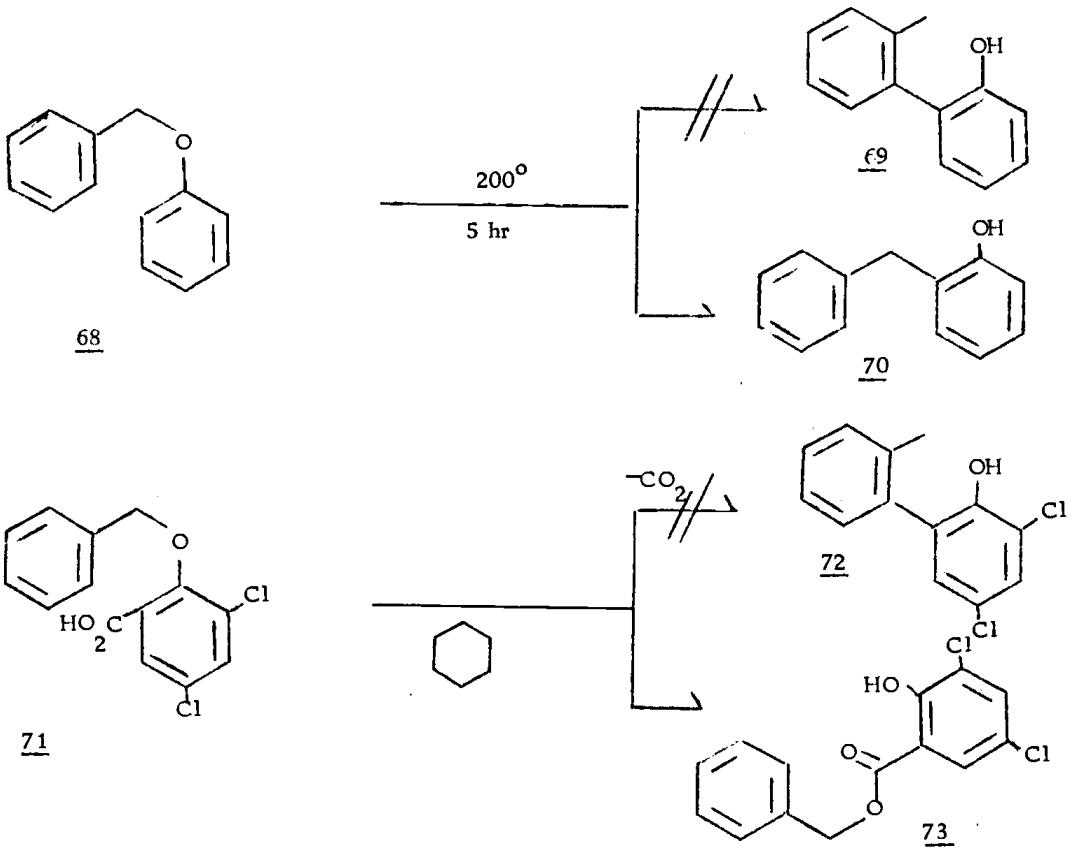
61 62 63 64

reaction of the dimethylacetal of N, N-dimethylacetamide (62) with benzyl alcohol (61) which then rearranged to N, N-dimethyl-α-(o-tolyl)-acetamide (64). In a similar reaction Eschenmoser was able to obtain 67, by heating 62 with β-naphthylcarbinol (65).



65 62 66 67

Interesting results were obtained by Hart (28) and Tarbell (32) when they built both vinyl and allyl double bonds into benzene rings. Hart investigated the thermal behavior of benzyl phenyl ether (68). He discovered that when 68 was heated a [1, 3] sigmatropic shift produced o-benzylphenol (70). No [3, 3] sigmatropic reaction was observed.

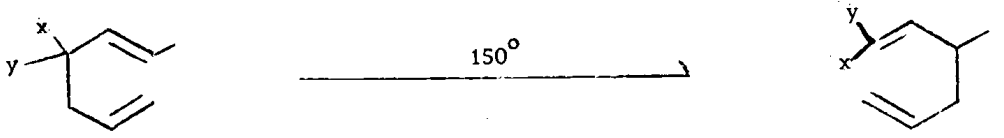


A formal [1, 5] sigmatropic shift product was obtained by Tarbell from the benzyl ether of 3, 5-dichloro-salicylic acid (71).

Instead of the [3, 3] product, 2, 4-dichloro-6-(o-tolyl)phenol (72), he obtained the benzyl ester (73).

The Cope Rearrangement

Since its discovery in 1941 (33), the Cope rearrangement has been the target of many mechanistic and synthetic studies (2, 3, 6). The basic introductory studies were done by Arthur Cope, the man the reaction was named after. Cope found that when 1, 5-hexadienes were heated to elevated temperatures the diene skeleton was inverted (11, 33, 34). For example, after heating ethyl-(1-methyl-propenyl)-allylcyanoacetate (46) at 150° Cope and coworkers isolated compound 5b.



4 5

a. x=y=-CO_2Et

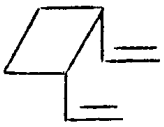
b. x=-CO_2Et;y=-CN

c. x=y=-CN

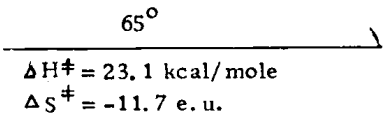
d. x=y=-C_6H_5

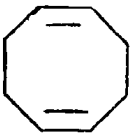
Activation parameters for several Cope rearrangements have been reported during the last forty years. These are collected in Table 5. The alkyl substituted 1, 5-hexadienes have energies of activation in the neighborhood of 33-37 kcal/mole, or about 5 kcal/mole higher than those of the non-aromatic Claisen rearrangements. The Arrhenius frequency factors are very similar, however. An interesting aspect of the Cope rearrangement is that certain substituents decrease the activation energy by approximately 10 kcal/mole (83→ 84).

Relief of ring strain has also been shown to lower the activation enthalpy of the Cope Rearrangement (42, 43, 44, 45). Hammond and DeBoer showed that thermally activated cis-1, 2-divinylcyclobutane (90) gave cis, cis-1, 5-cyclooctadiene (91)(42). The activation enthalpy was 23. 1 kcal/mole or 12 kcal/mole below that



90





91

of 1, 5-hexadiene (43).

Similar results were obtained with a cyclopropane ring in the 1, 5-hexadiene system by Brown and coworkers (45). Doering (47)

Table 5. Activation Parameters Associated with the Cope Rearrangement of Simple 1, 5-Hexadiene Compounds

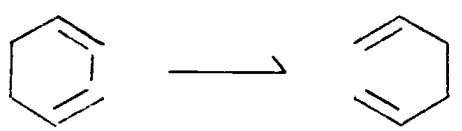
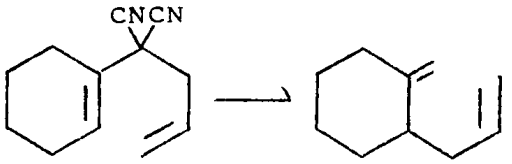
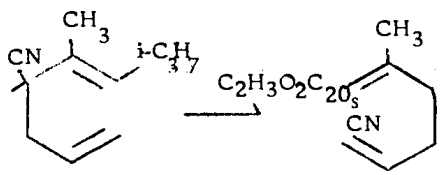
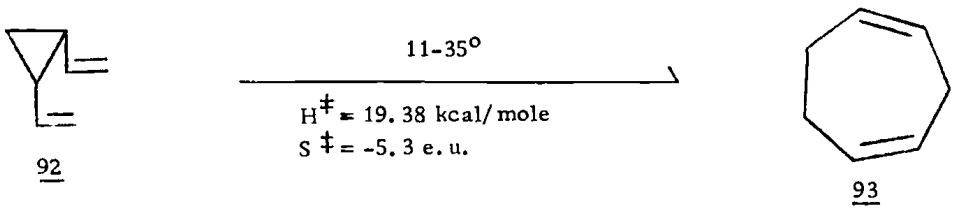
Reaction	Ea (kcal/mole)	log A (sec^{-1})	Ref
 74 → 75	35.5	11.1	35, 36
 76 → 77	34.20	10.55	37, 39
 77 → 76	35.36	10.39	37
 76 → 78	35.72	10.54	37
 78 → 76	36.72	10.66	37
 79 → 80	34.62	11.13	38

Table 5. (Continued)

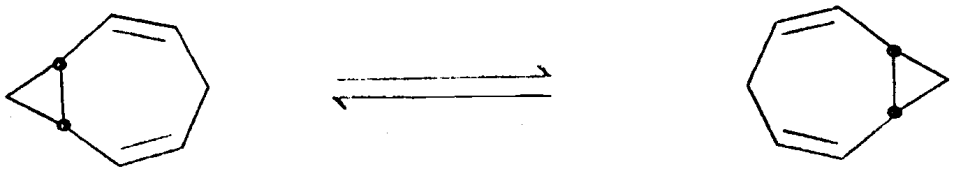
Reaction	Ea (kcal) mole	log A (sec^{-1})	Ref
 80 79	36.94	10.39	38
 81 82	26.12	10.80	40
 83 84	25.78	10.94	40
 85 86	28.62	10.35	40
 87 88	32.8	10.68	41
 87 89	36.07	10.71	41

and Vogel (44, 46) had suggested that cis-1, 2-divinyl-cyclopropane (92) would rearrange to cis, cis-1, 4-cycloheptadiene (93). However, Brown and coworkers were the first to isolate the molecule and measure the activation parameters for its Cope rearrangement (45).



92 93

When the divinyl groups of 92 are joined by a methylene bridge, as in the case of homo-tropilidene (94), the Cope rearrangement becomes degenerate. A variety of such degenerate thermal rearrangements have been reported in the literature and the free



94

energies of activation of some of these reactions are given in Table 6.

Table 6. Free Energies of Activation of Some Cope Rearrangements.

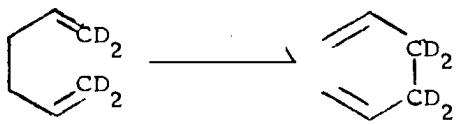
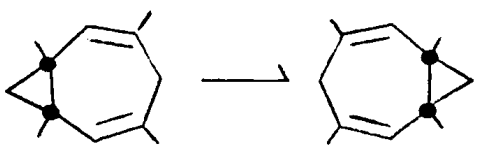
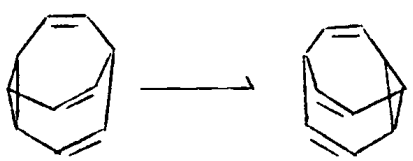
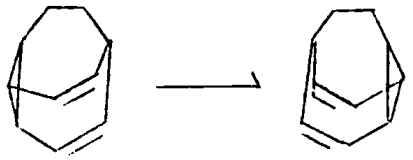
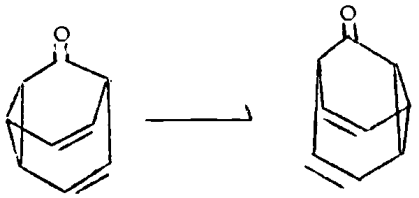
Reaction	G^{++} (kcal/mole)	Temp. (°C)	Ref
 74 75	35.5	230-350°	35
 92 93	20.6	11-35°	45
 95	13.6	0°	48
 96	12.8	25-123°	49

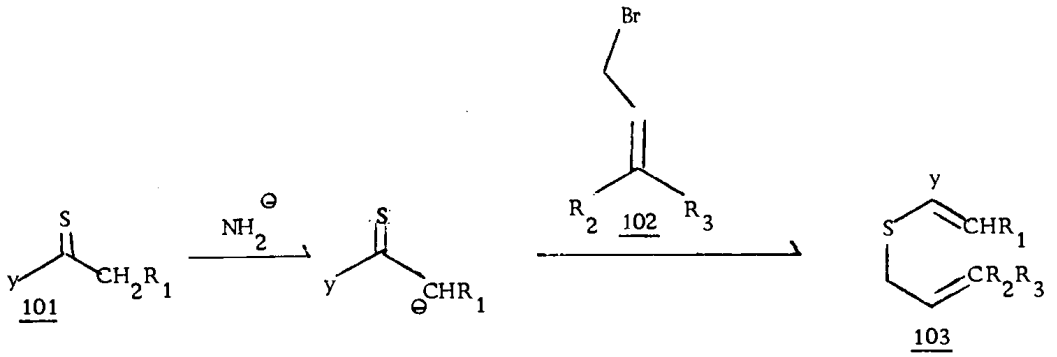
Table 6. (Continued)

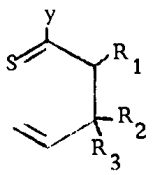
 97	9.5	-40°	50
 98	9.6	-55°	51
 99	7.8	-77°	52
 100	6.4	-141°	53

The Thio-Claisen Rearrangement

The sulfur analog to the Claisen rearrangement or the thio-Claisen rearrangement was first reported by Schuijl and Brandsma (54). When they treated sulfur compounds of type 101 with a metal amide and 102, they obtained directly products of type 104. The reaction is presumed to go through an allyl vinyl sulfide intermediate

103. Schuijl and Brandsma noted that in some cases the reaction was





104

R_1=-H, alkyl or -Ph

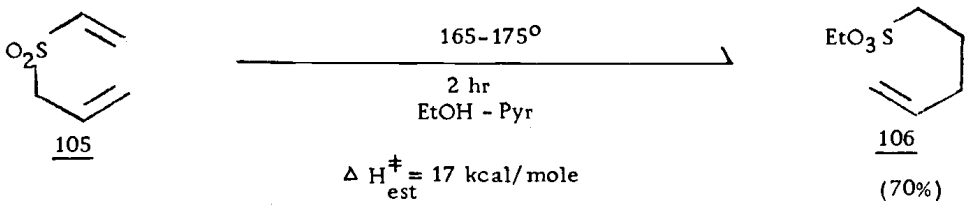
R_2=-H, $-OCH_3$

R_3=-H, $-OCH_3$

Y=-OEt, -SEt, $-N(CH_3)_2$, $-N(C_2H_4)_2$

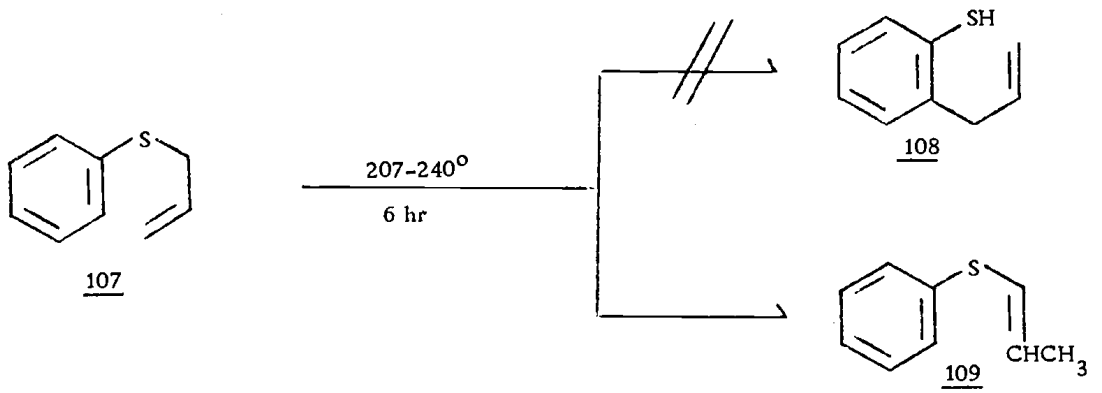
so rapid that 103 could not be detected, however, the rate could be lowered by increasing the bulk of R_1.

There have been no kinetic parameters reported for the thio-Claisen rearrangement of simple allyl vinyl sulfides. However, in 1976 King and Harding reported an approximate activation enthalpy for allyl vinyl sulfone (105) (55). They noted that when 105 was heated, they were able to isolate the thio-Claisen product, 106, with an activation enthalpy estimated at 17 kcal/mole.

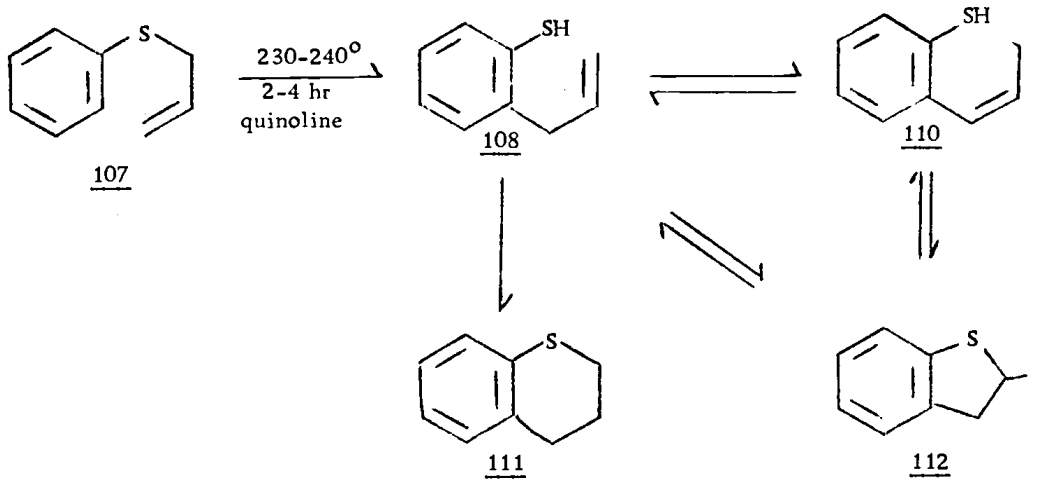


In 1930 Hurd and Greengard reported what they believed to be the first example of the sulfur analog of the Aromatic-Claisen rearrangement (56). They assigned the structure o-allylthiophenol to the product from heating allyl phenyl sulfide (107) at 207-240°.

It wasn't until 27 years later that Karauloua et al. showed the actual product was phenyl 1-propenyl sulfide (109) (57).



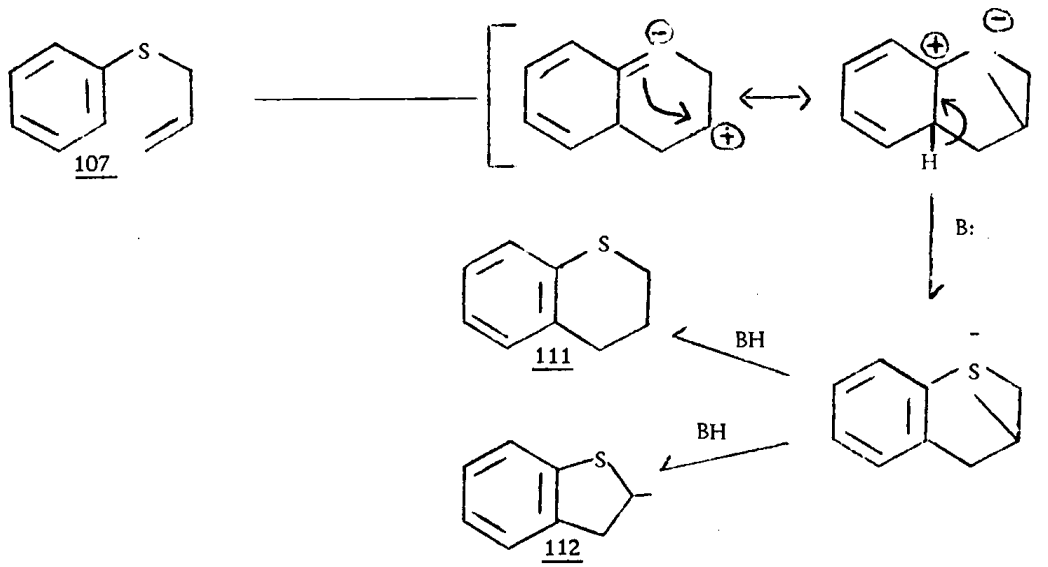
Meyers and coworkers refluxed 107 in quinoline at 230-240° and obtained 3-methylthiacoumaran (112) and thiachroman (111) (58). They argued that these products could be formed by a [3, 3] sigmatropic rearrangement, giving o-allylthiophenol (108 and 110) which could cyclize directly or rearrange and then cyclize to give the



107 108 110 111 112

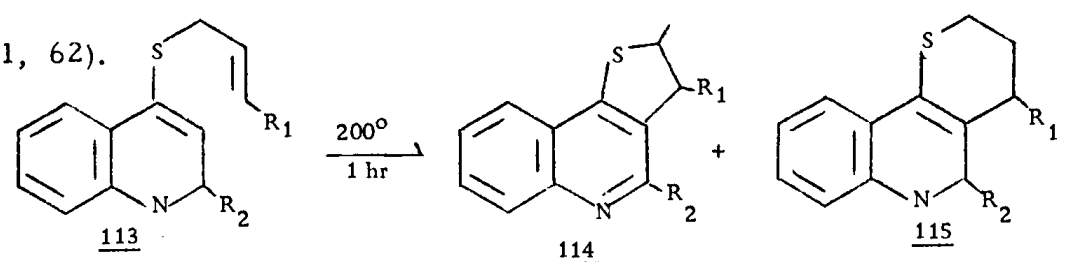
products 111 and 112.

Kwart and Evans heated allyl phenyl sulfide (107) and o-allylthiophenol (108) under the same conditions and found that the same product ratios were not obtained. For example, when a quinoline solution of 107 was refluxed for 6 hr. under nitrogen (217-241°) the products they obtained consisted of 40% 112 and 25% 111. Obviously, the mechanism proposed by Meyers and coworkers could not be entirely correct. Kwart and Evans suggested the following mechanism to explain their results (59):



Regardless of the mechanism a dearomatization step must be involved since both 111 and 112 are ortho-substitution products. Also, the presence of a base is necessary for rearrangement to occur.

Studies of other allyl aryl sulfides have been reported which involve quinoline and indole derivatives. Makisumi and coworkers reported that allyl-4-quinolyl sulfides (113) rearrange to give products similar to those reported to allyl phenyl sulfide (107) (60, 61, 62).

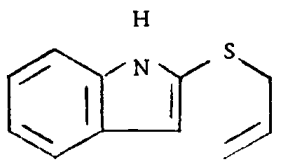


a) $R_1 = R_2 = H$

b) $R_1 = -H$; $R_2 = -CH_3$

c) $R_1 = R_2 = -H$

4.5 : 1.0

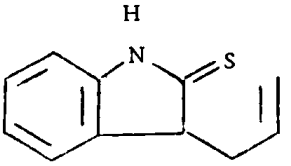


116

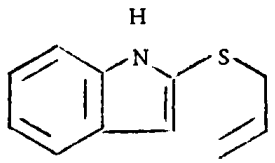
toluene
reflux

$\Delta H^{\ddagger}$ = 17.8 kcal/mole

$\Delta S^{\ddagger}$ = 19.4 e.u.



117

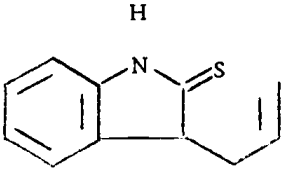


118

toluene
reflux

$\Delta H^{\ddagger}$ = 18.4 kcal/mole

$\Delta S^{\ddagger}$ = -16.8 e.u.



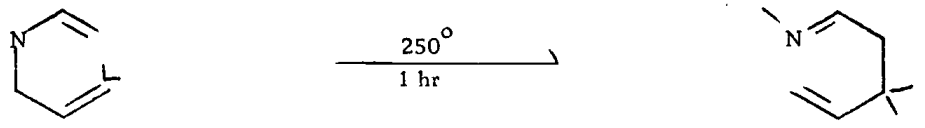
119

The only activation parameters associated with the aromatic thio-Claisen rearrangement were reported by Bycroft and Landon (63). They showed that indole derivatives undergo the [3, 3] sigmatropic rearrangement to give thiones rather than cyclized products in virtually quantitative yields. When allyl 2-indolyl sulfides 116 and 118 were heated in either polar or non-polar solvents they recovered thiones 117 and 119 and the activation enthalpies and entropies were obtained in toluene.

The low temperature at which the rearrangement occurs reflects the decrease in the aromatic character of the pyrrole system as can be seen in Table 3.

The Amino-Claisen Rearrangement

The amino-Claisen rearrangement or the nitrogen analog of the Claisen rearrangement involving N-allyl-N-vinylamine has not been reported. However, a very simple case i.e. N-allyl-N-methyl-N-isobutenylamine, (120) rearranges thermally to N-methyl-2, 2-dimethylpent-4-enimine (121) (64).

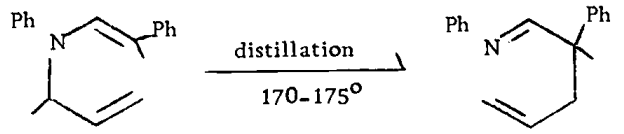
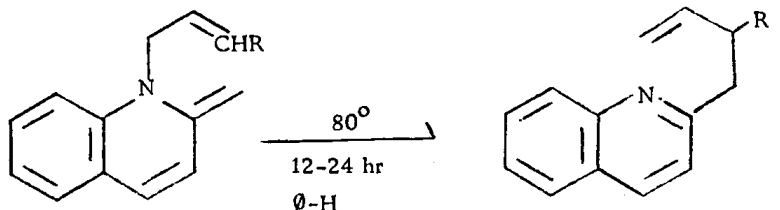
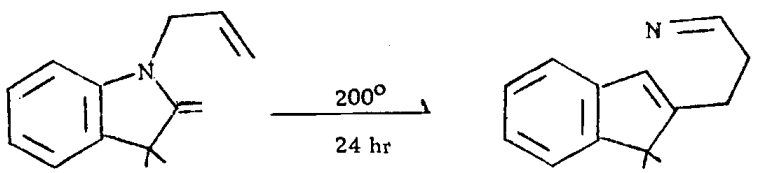


120 121

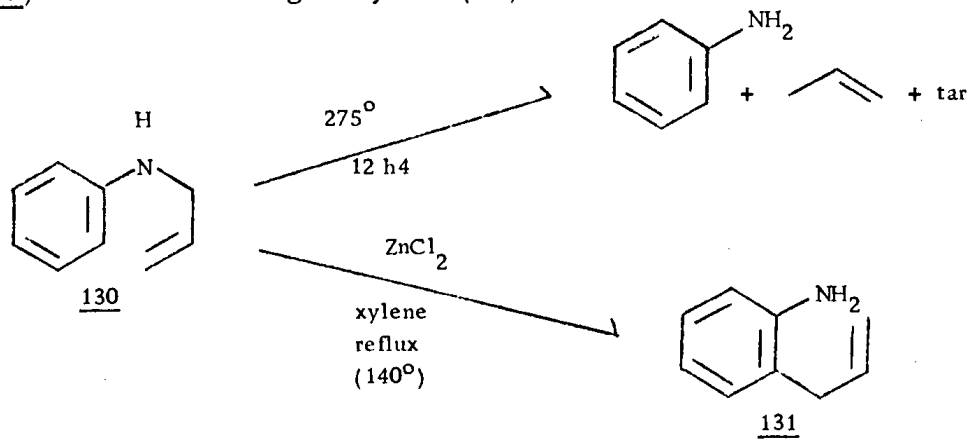
Though no activation parameters have been recorded for simple aliphatic examples, several of these rearrangements are known

(Table 7).

Table 7. Various Amino-Claisen Rearrangements of N-Allyl-N-Vinylamines.

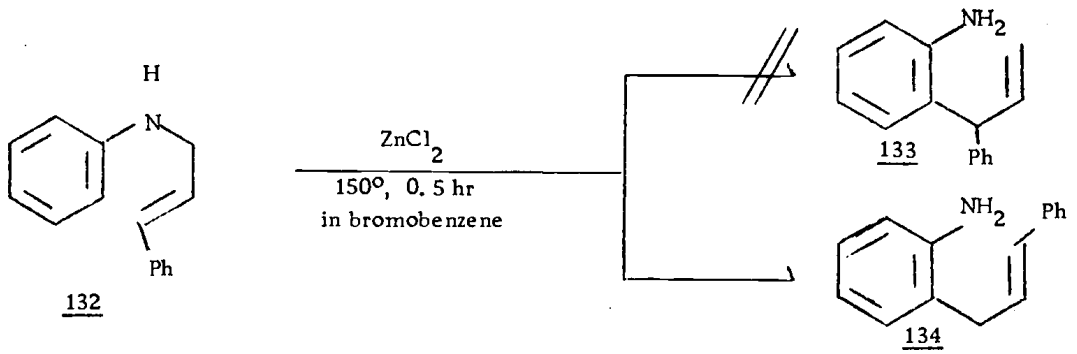
Reaction	Ref
	64
 R = -H, -CH_3, -Ph 124 125	65
 126 127	65
 128 129	66

The aromatic analog of the amino-Claisen rearrangement has been difficult to find. When N-allyl-aniline (130) was heated to 275° only aniline, propene and tar were obtained (67). However, when 130 was refluxed with zinc chloride in xylene, o-allylaniline (131) was formed in good yield (68).



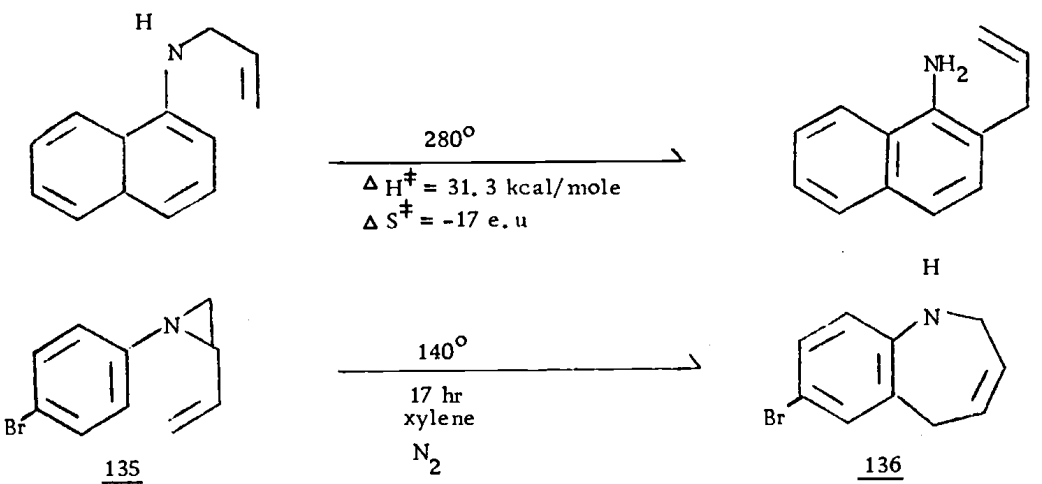
In an effort to ascertain whether the reaction proceeded via a [3, 3] sigmatropic shift and not a [1, 3] sigmatropic reaction Hurd and Jenkins heated N-cinnamylaniline (132) in the presence of zinc chloride (68). Analysis of the product mixture showed that the [1, 3] product, o-cinnamylaniline (134) and not the [3, 3] shift product o-(1-phenylprop-2-enyl)aninline (133) was produced.

Activation parameters for the aromatic amino-Claisen rearrangement were measured by Green and coworkers (25). At 280° N-allyl-1-naphthylamine rearranges smoothly to 2-allyl-1-naphthylamine. For this process $\triangle H^{\ddagger}$ is 31.3 kcal/mole and $\triangle S^{\ddagger}$ is -17 e.u.



Again, because of the non-substituted allyl group, it is not clear whether migration proceeds with inversion as required by the Claisen mechanism. However, the large negative value for $\triangle S^{\ddagger}$ (-17 e.u.) suggests that the reaction proceeds through a highly ordered transition state.

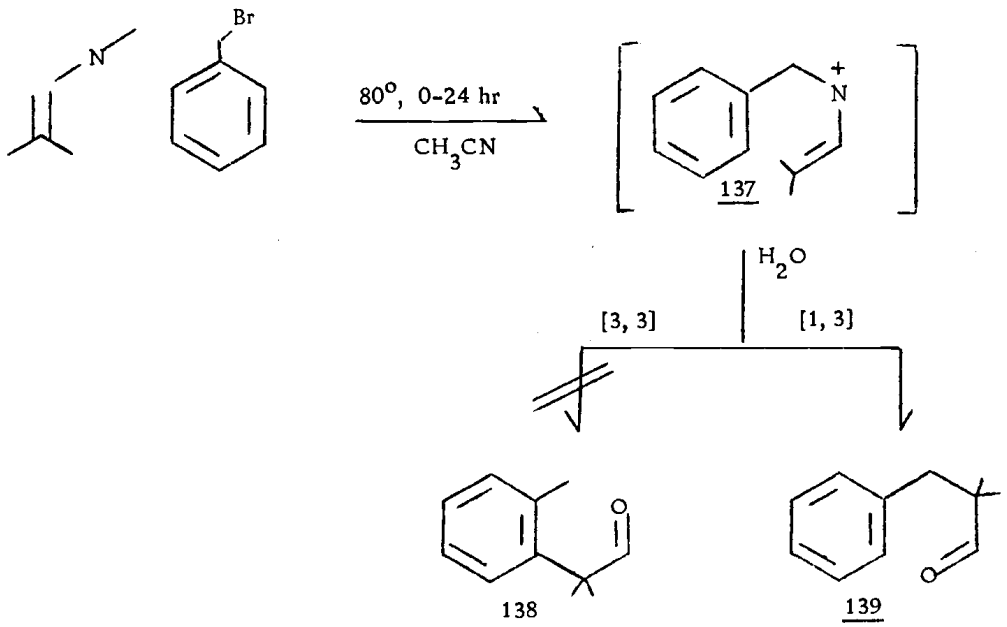
Rearrangement of an N-aryl-2-vinyl aziridine by Scheiner gave rise to the first indisputable [3, 3] shift (69). Thus refluxing a xylene solution of 135 gave the desired product 136 in excellent yield. No doubt the ring strain of the aziridine system plays an



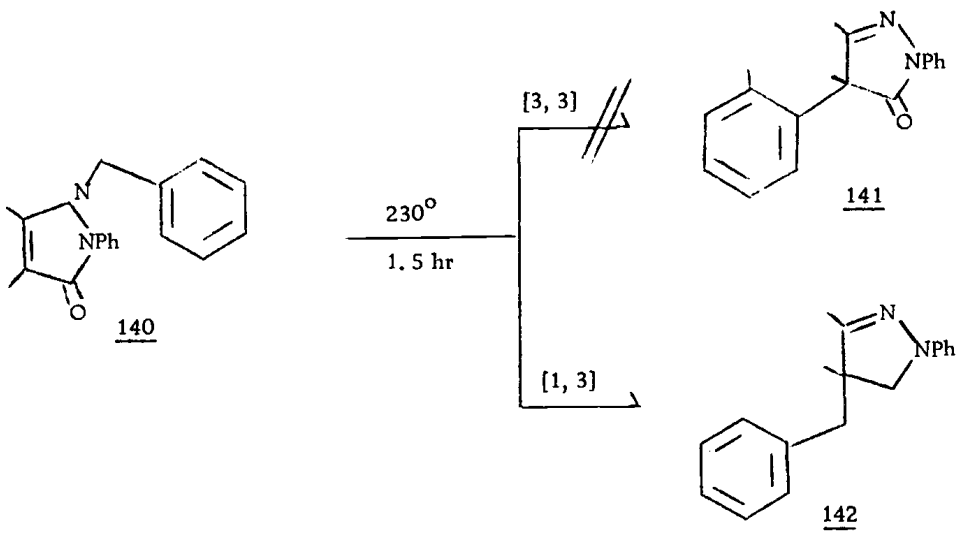
important role in the success of this rearrangement.

The rearrangements of N-benzyl-N-vinylamines have also been studied (70, 71). However, the same lack of success pertains in these systems as for the rearrangements of benzyl vinyl ethers. Again, other processes, via the [1, 3] shift, were shown to occur rather than the desired [3, 3] shift.

Ref. 70



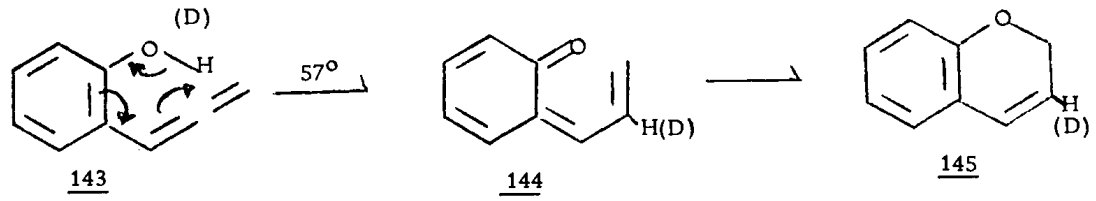
Ref. 71



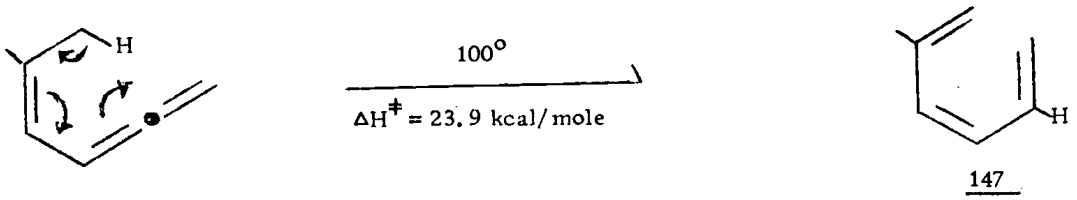
Dearomatizing [1, 5s] Sigmatropic Reactions

The [3, 3] sigmatropic rearrangements discussed above are not the only intramolecular rearrangements which lead to dearomatization (72, 73). For example, the first step in the rearrangement of o-allenylphenol (143) to Δ^3-chromene (145) (74) was proposed to involve an aromatic [1, 5s] sigmatropic hydrogen shift to give (144). This mechanism was supported by the results of a deuterium labeling experiment (73), that is o-allenylphenol-o-d (43) gave specifically deuterated 3-d, Δ^3-chromene (145).

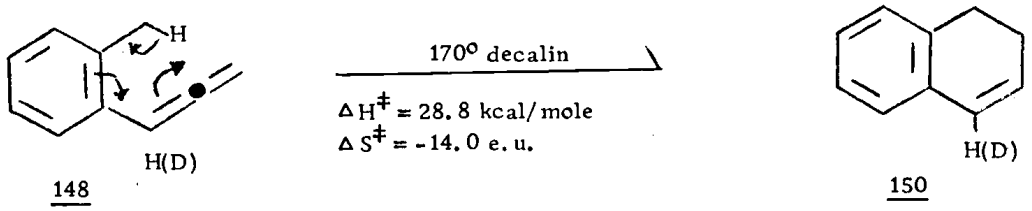
Activation parameters for both the aromatic and nonaromatic [1, 5s] sigmatropic shifts have been determined by Schmid (75) and by Skattebol (76) respectively. It is rather surprising that aromatization of one double bond cost only 4.9 kcal/mole in activation enthalpy.



143 144 145



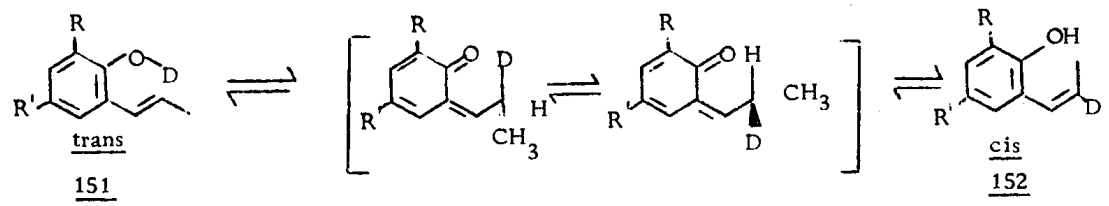
146 147



148 150

Trans-cis isomerization of o-(n-propenyl)phenols is a further example of a dearomatizing [1, 5] sigmatropic reaction (77, 78). Activation parameters for the isomerization of some o-(n-propenyl) phenols have been reported (Table 8) (77, 78).

Table 8. Activation Parameters of the Trans-Cis Isomerization of o-(n-Propenyl)phenols in Decane at 150°.

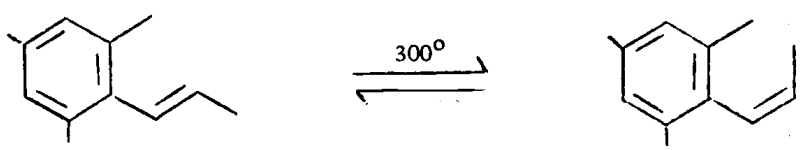


trans
151

cis
152

R	R'	$\Delta H^{\ddagger}_{t\rightarrow c}$	$\Delta S^{\ddagger}_{t\rightarrow c}$	$\Delta H^{\ddagger}_{c\rightarrow t}$	$\Delta S^{\ddagger}_{c\rightarrow t}$
CH_3	CH_3	26.2	-19	26.0	-17
t-C_4H_9	CH_3	27.9	-13	27.9	-11

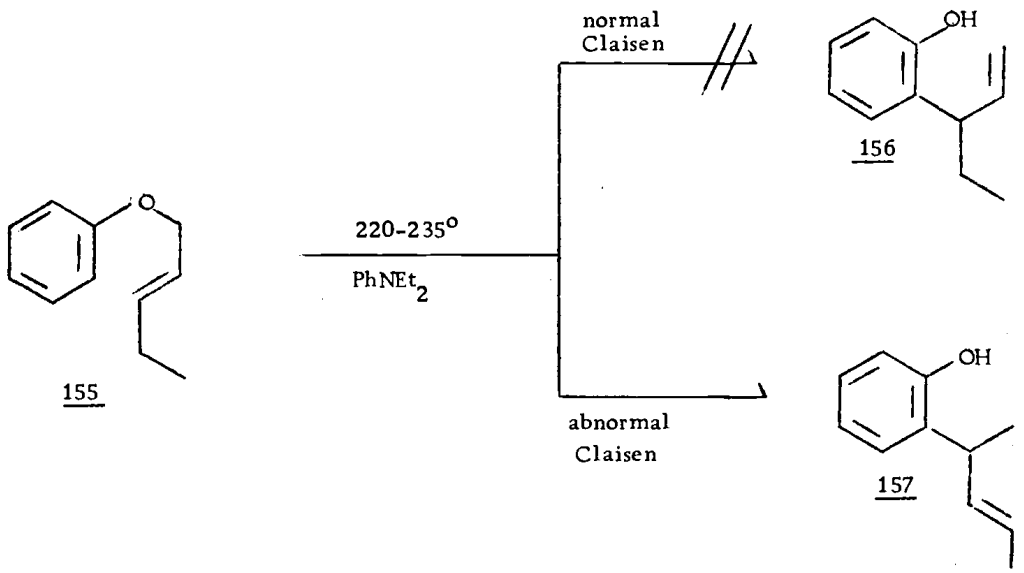
Isomerization does occur when the hydroxyl is replaced by a methyl, but requires a much higher temperature (78). For example, isomerization of 153 to 154 requires a temperature of over 300° (78). This is not too surprising since rearrangement in the aliphatic system, 1, 3-pentadiene, has an activation energy of about 35 kcal/mole (79, 80).



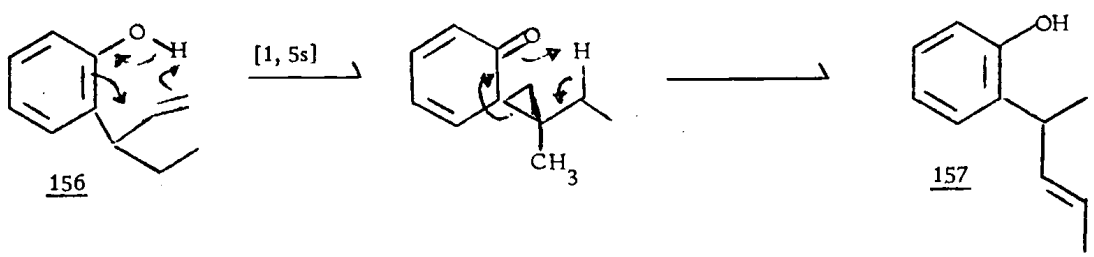
153

154

The [1, 5] homosigmatropic reaction in an aromatic system is exemplified by the abnormal Claisen rearrangement. This unusual rearrangement was uncovered when 157 was unexpectedly obtained by thermolysis of pent-2-enyl phenyl ether (155).

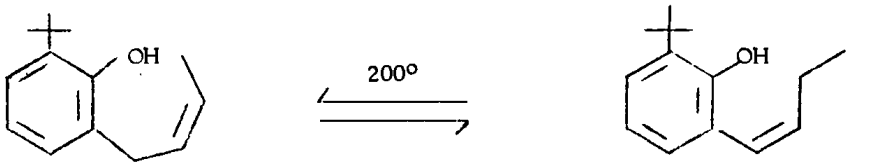


The novel homosigmatropic mechanism was proposed by Marvell and coworkers. Measurement of activation parameters



was done with 158, where the cis-trans isomerization has been shown

to occur. The parameters are listed here (82, 83).



cis-158 trans-158

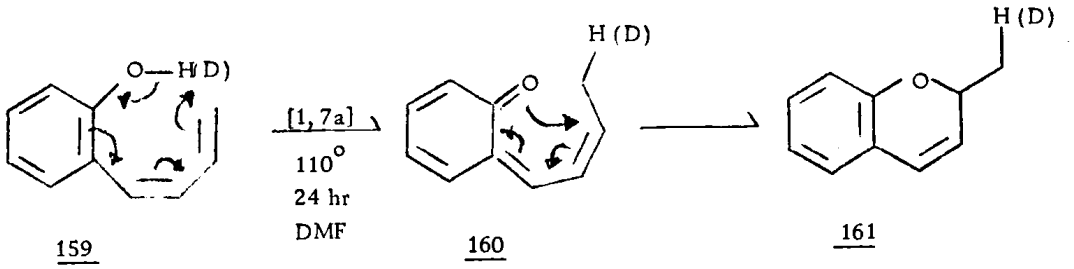
$H^{\ddagger}_{c \rightarrow t}$ = 30.9 kcal/mole $H^{\ddagger}_{t \rightarrow c}$ = 31.9 kcal/mole

$S^{\ddagger}_{c \rightarrow t}$ = -21 e.u $S^{\ddagger}_{t \rightarrow c}$ = -20 e.u.

The [1,5s] homosigmatropic shift is also known in the aliphatic system, but no kinetic studies giving the desired activation values have been made.

Dearomatizing [1, 7a] Sigmatropic Reactions

In 1969 Schweizer and his students reported the first example of a [1, 7a] sigmatropic reaction involving an aromatic system (86). Thus o-(1, 3-butadienyl) phenol (159) produced solely 161 at 110° (86). They suggested that the reaction proceeded via intermediate 160 and

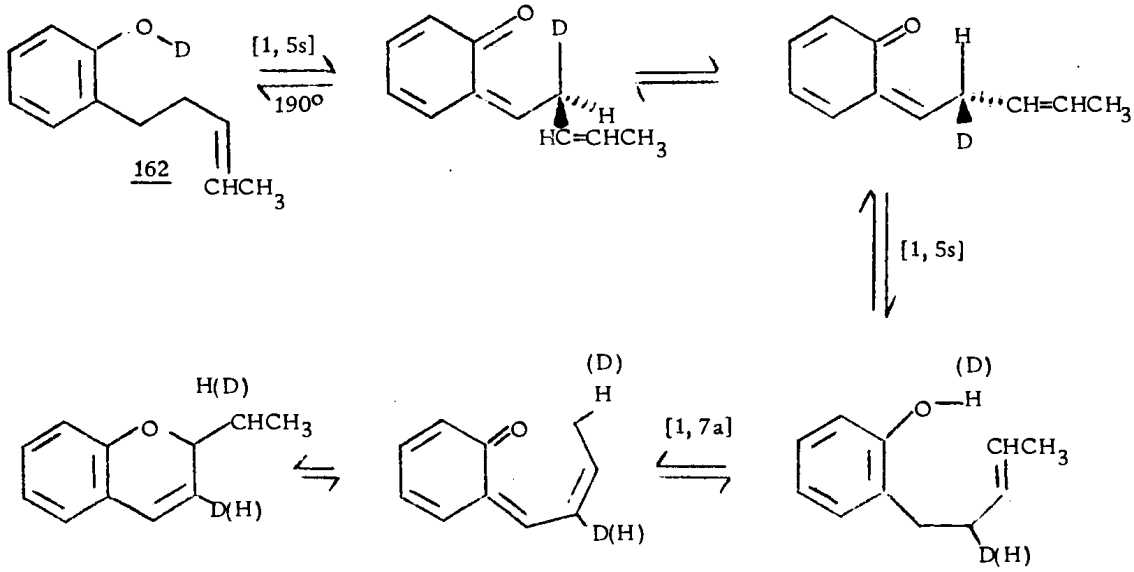


159 160 161

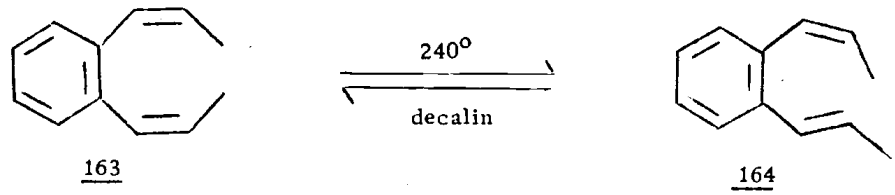
supported this mechanism with a deuterium labeling experiment.

The activation enthalpy for the reaction was 23.0 kcal/mole ($\Delta S^{\ddagger}$ = -17 e.u.).

If the double bond adjacent to the ring is trans, it has been shown, using deuterium labeling, that the reaction proceeds via a [1, 5s] sigmatropic reaction. The [1, 5s] shift is then followed by a [1, 7a] shift as shown (87).

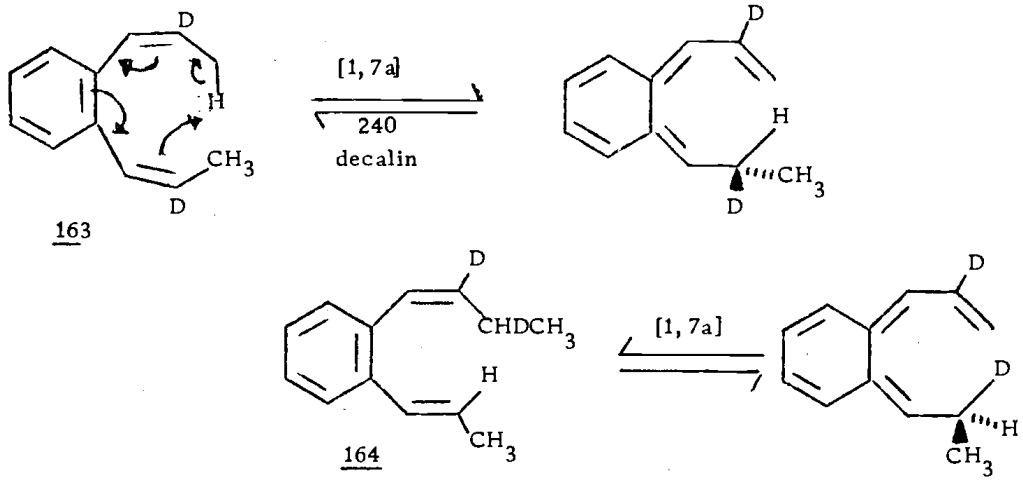


A [1, 7a] sigmatropic reaction in an all carbon system was discovered by Schmid and his coworkers. They heated cis, cis-1, 2-di-(1-propenyl)benzene(163) to 240° and recovered only the cis-trans-isomer 164 and starting material (88). At first glance, this reaction



163 164

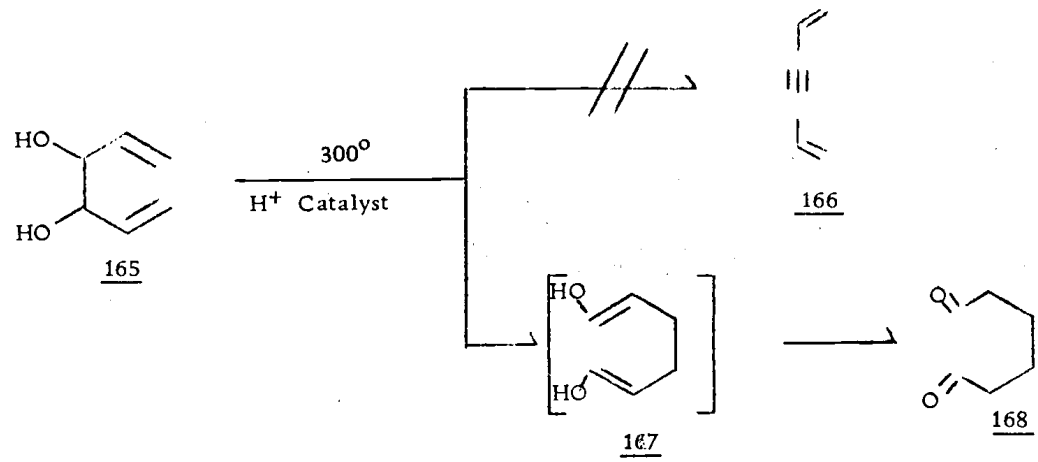
appears to be a simple cis-trans isomerization, however, deuterium labelling showed that the reaction involves a [1, 7a] sigmatropic shift (88).



163 164

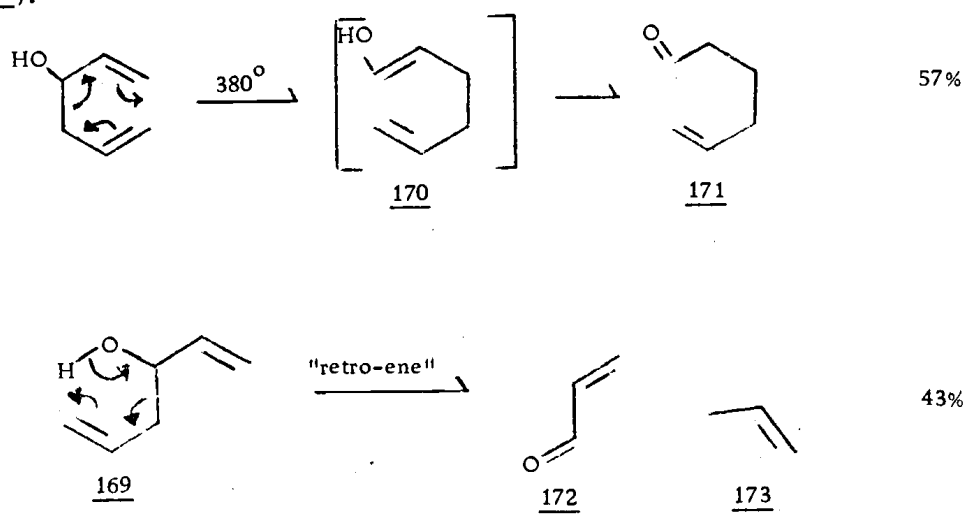
The Oxy-Cope Rearrangement

In 1930 when Urion reported obtaining 1, 6-hexadione (168) rather than 1, 5-hexadien-3-yne (166) from the acid catalyzed pyrolysis of 3, 4-dihydroxy-1, 5-hexadiene (165) he undoubtedly had no idea that this would be hailed as the first example of the oxy-Cope rearrangement (89, 90). It is presumed now, that the reaction involved

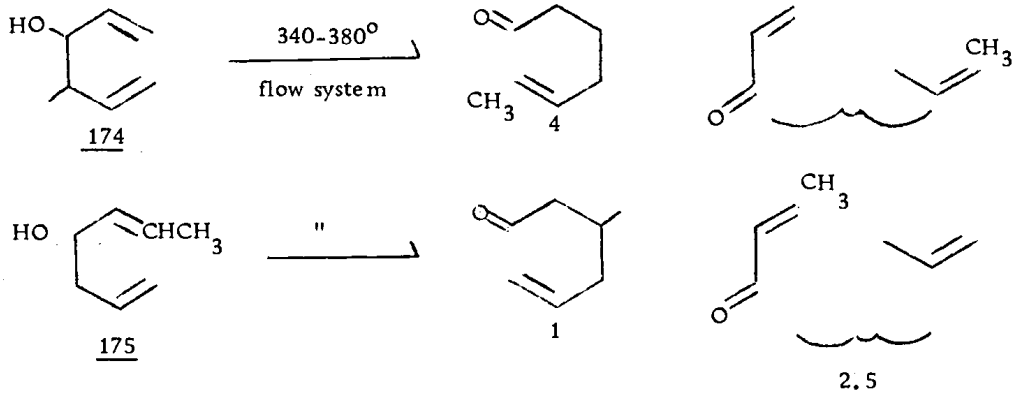


a [3, 3] shift to 167.

The oxy-Cope rearrangement has been studied extensively over the last 50 years (26). However, one of the drawbacks to the rearrangement is that it has a side reaction, the retro-ene process (91). Pyrolysis (380°) of 3-hydroxy-1, 5-hexadiene (169) gave besides the desired 5-hexen-1-al (171), a substantial amount of butenal (172) and (173).



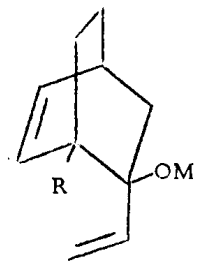
The ratio of oxy-Cope to retro-ene product has been shown to vary with the substitution. Alkyl substituents on carbons C_2, C_3, or C_4 have little effect on the ratios while substitution on C_1, C_5, or C_6 enhances the formation of retro-ene products (102).



As one might suspect the oxy-Cope rearrangement is synthetically useful for generation of 5, 6-unsaturated carbonyl compounds (94-102) and also in four carbon ring expansions (92, 93, 103-106).

The main problem with the rearrangement, until recently, has been the high temperature required. In 1975, however, Evans and Golob reported that simply replacing the hydroxyl hydrogen with a metal (Li, Na, K) gave a rate enhancement of 10^{11}-10^{17} (107). It seems rather surprising that the activation energy can be lowered by as much as 17 kcal/mole when an alkoxide is converted to an enolate, rather than an alcohol to an enol (Table 9).

Table 9. Activation Parameters Associated with Various Endo-Vinyl Bicyclo-Octadienyl Systems



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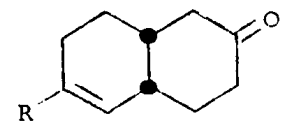


177

R	M	Reaction Temp. (°K)	Ea (kcal/mole)	log A (sec^{-1})	Ref.
$-OCH_3$	H	448-488°	35.9	12.6	96
$-OCH_3$	K	283-328°	19.4	10.3	107
$-OCH_3$	K	253-278°	18.2	11.5	107‡
-H	H	448-488°	41.8	12.5	98

‡ 3.0 equiv. of 18-C-6 added

RESULTS AND DISCUSSION

I. Energetics of the Aromatic Cope Rearrangement

The Cope rearrangement of 1, 5-hexadiene proceeds quite readily ($\triangle H^{\ddagger}$ = 34.5 kcal/mole), but not as easily as does its oxygen analog, allyl vinyl ether ($\triangle H^{\ddagger}$ = 29.7 kcal/mole). Phenyl allyl ether also rearranges ($\triangle H^{\ddagger}$ = 30.7 kcal/ mole), but with a slight increase in energy resulting from conversion of the vinyl to a phenyl moiety. In view of these observations the resistance of 4-phenyl-1-butene toward undergoing a Cope rearrangement even at 400° should seem puzzling even to the most casual of observers. If, like the Claisen rearrangement, conversion of the Cope to an aromatic type forces it to occur in two steps, then the allowed [3, 3] shift may pass its rate determining prerequisite to the forbidden [1, 3] hydrogen shift step. No hard experimental observations serve as yet to define the rate determining step, and as a result no determination of the activation parameters for the aromatic-Cope rearrangement could be obtained. With the discovery by Marvell and Lin of an authentic example of an aromatic-Cope reaction it became possible to fill this gap in our knowledge.

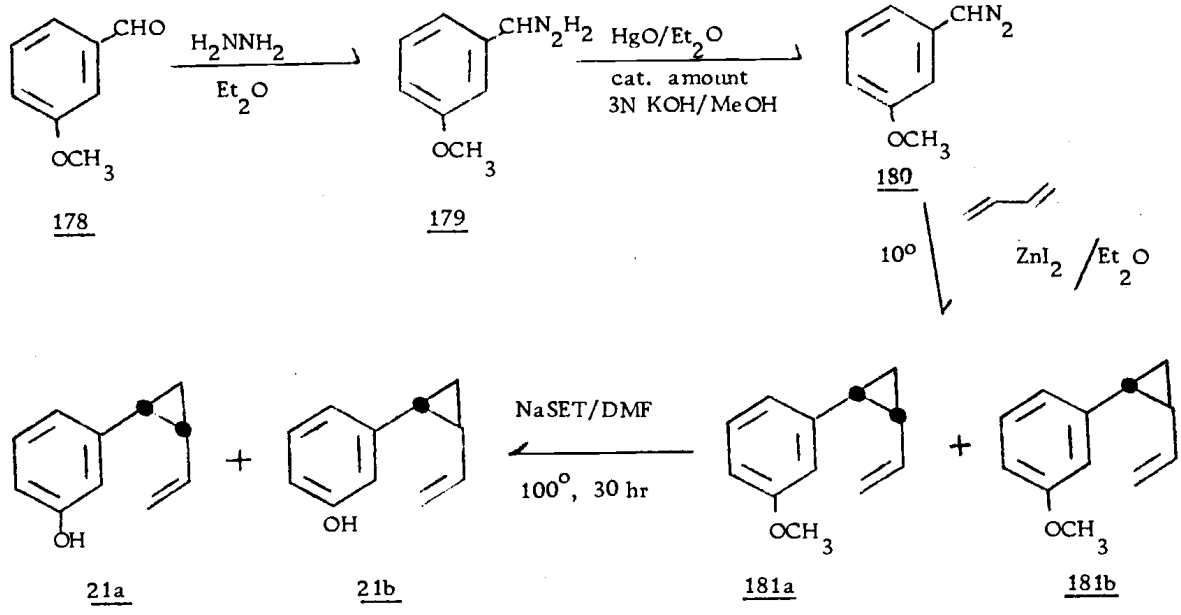
We will describe here our kinetic studies of the aromatic-Cope rearrangement of cis-1-(m-hydroxyphenyl)-2-vinylcyclopropane (21a) and discuss the possible implications of the results for the more general

aromatic-Cope rearrangement of 4-phenyl-1-butene.

Synthesis of Reactant (21a) and Product (22)

Marvell and Lin have described the synthesis of cis-1-(m-hydroxyphenyl)-2-vinylcyclopropane (21a) (17) and a modification of their procedure was used for preparation of this compound. The overall route is illustrated in scheme 1. Conversion of the aldehyde 178

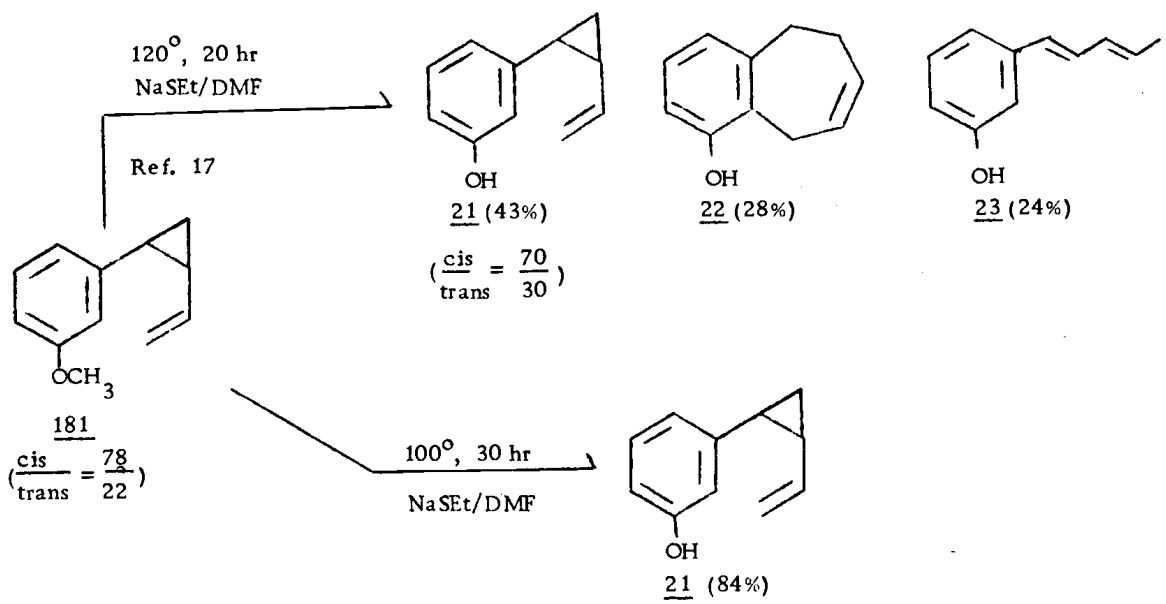
Scheme 1



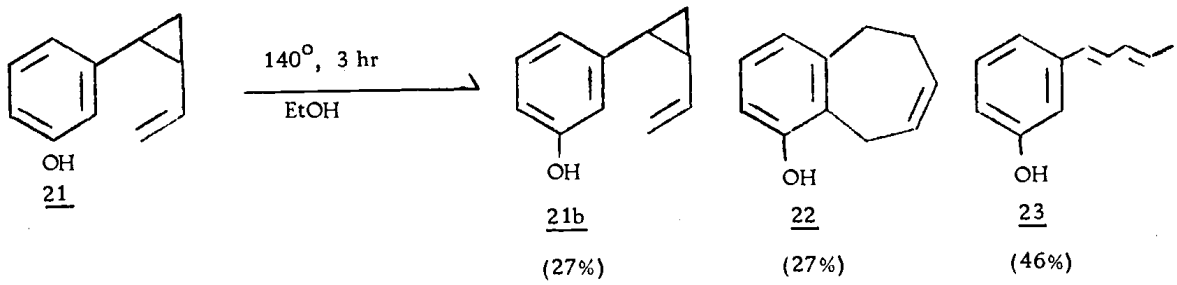
to its hydrazone (180) followed well established procedures (108). Formation of the diazo compound 181 and its elaboration to the

cyclopropane derivatives 181a and 181b was patterned after the method of Goh, Closs and Closs (109) as adapted by Lin (17). However in our hands the ring forming step proceeded in higher yield (32% as compared to 12%) when it was run at 10° rather than at -10° as described earlier.

The demethylation procedure described by Lin (110) was utilized but with one significant modification. Test runs monitored by gas chromatography showed that a lower temperature was beneficial. Though the reaction time was unavoidably increased, the better yield (84% vs. 43% at 120°) and the absence of side products provided more than adequate compensation. A mixture of cis and trans isomers was obtained, but these were not separated since the trans isomer does not interfere with the kinetic studies (see below).



A pure sample of 22 was obtained by thermal rearrangement of the above mixture under the conditions prescribed by Lin (111). The three reaction products were separated and 22 was purified by

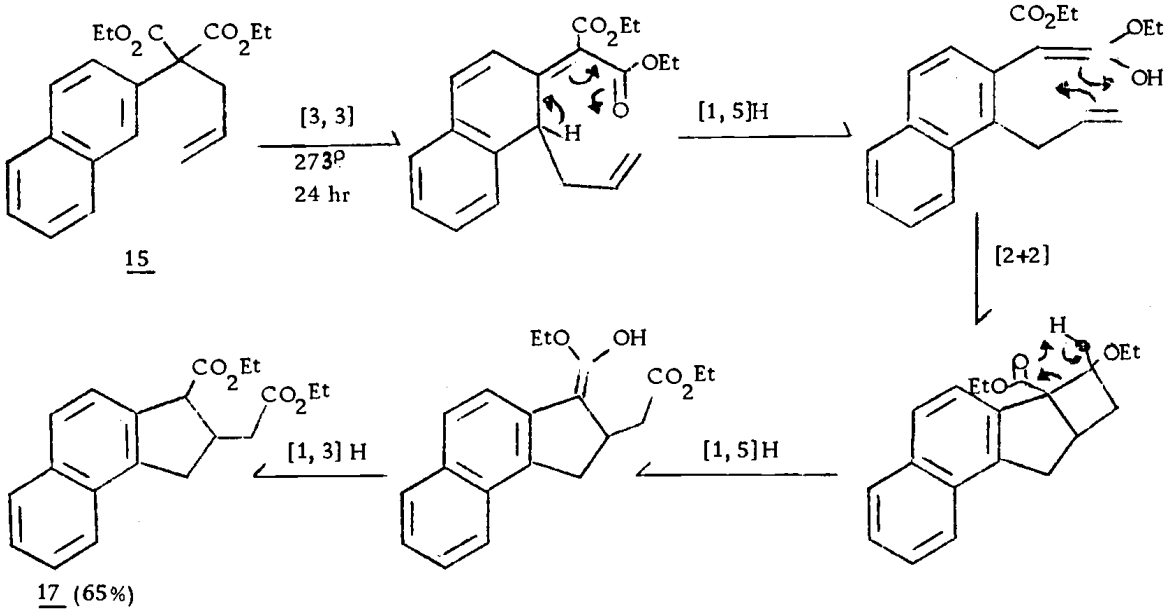


preparative glc. The spectral properties of all of the products were in complete accord with those reported (17).

Energy Estimations of the Aromatic-Cope Rearrangement of 4-Phenyl-1-butene (1)

Prior to considering the results of our kinetic studies, we will digress briefly to play some numbers games with information available from the literature. From this we hope to establish some estimates, albeit rather imprecise, for the enthalpy of activation for the Cope rearrangement of 4-phenyl-1-butene. To do this we shall adopt the view that the reaction observed by Cope (9) with allyl-2-naphthylmalonic ester (15→17) was initiated by an aromatic-Cope rearrangement. Furthermore we will assume that the initial step was rate

determining. This is reasonable since the [1, 5] hydrogen shift [$\triangle H^{\ddagger}$=35.4 kcal/mole in an acyclic system (139)] regenerates an aromatic ring and these are inevitably facile. The cycloaddition step has literature precedents which proceed at ca. 135° (123), and the

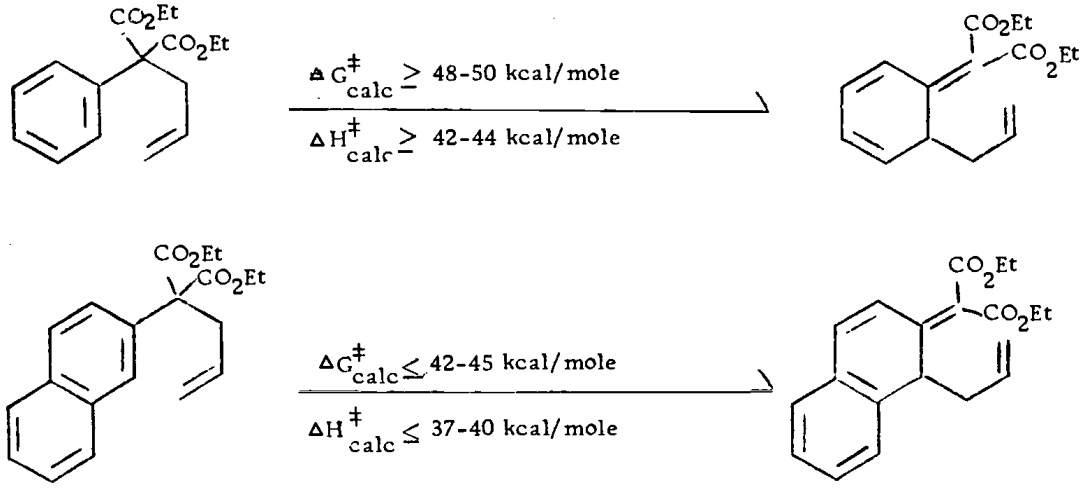


final proton shift is facilitated by cleavage of a cyclobutane ring. A similar step is involved in the so-called abnormal Claisen rearrangement and is indeed of modest activation energy (81).

Given these, we believe, entirely reasonable assumptions, we are in a position to assess some possible values of $\triangle H^{\ddagger}$ for an unactivated aromatic-Cope rearrangement. To accomplish this we will need some value for $\triangle S^{\ddagger}$ for this aromatic-Cope reaction, and we will use -10 e.u. as a convenient average value. The figure was taken from the average of a series of Claisen rearrangements (Table 2), but

the particular value adopted is of little overall significance since ±5 e.u. would merely shift the $\triangle H^{\ddagger}$ obtained by ±3 kcal/mole. Thus the $\triangle G^{\ddagger}$ for diethyl allyl-2-naphthylmalonate (15) which reacts readily at 273° is almost certainly less than 42-45 kcal/mole and sets $\triangle H^{\ddagger} \leq$ 37-40 kcal/mole. In the same sense the $\triangle G^{\ddagger}$ for diethyl allylphenylmalonate (8a), which does not rearrange at 290°, must be greater than 48-50 kcal/mole, hence $\triangle H^{\ddagger} \geq$ 42-44 kcal/mole.

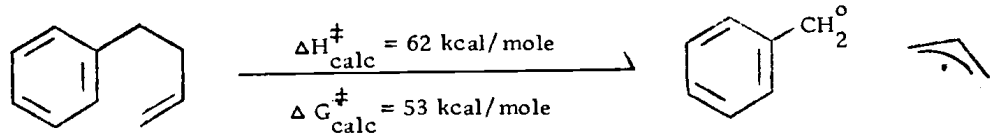
This difference ca. 4-5 kcal/mole, seems quite reasonable based on the $\triangle H^{\ddagger}$ – 5 kcal/mole between the Claisen rearrangement of allyl phenyl ether and allyl 2-naphthyl ether. It is interesting that this 5 kcal/mole difference is equivalent to the △RE (resonance energy difference) between benzene and one naphthyl ring (Table 3).



The above $\triangle H^{\ddagger}$ estimates for malonic esters can perhaps be converted to values appropriate to 4-phenyl-1-butene, if it is assumed that the carbethoxy groups influence both acyclic and aromatic-Cope

rearrangements equally. For the acyclic rearrangement each carbethoxy group decreases $\triangle H^{\ddagger}$ by ca. 5 kcal/mole, thus setting $\triangle H^{\ddagger}$ for 4-phenyl-1-butene at ca. 52-54 kcal/mole. This value should without a doubt evoke some surprise.

We can attempt to estimate this $\triangle H^{\ddagger}$ from another angle. Since 4-phenyl-1-butene has been shown experimentally to form products at 400-500° which are most reasonably explicable via cleavage into benzyl and allyl radicals with no evidence for any Cope reaction (122, 135), a lower bound to the required $\triangle H^{\ddagger}$ can be estimated. The $\triangle H^{\ddagger}$ for bond cleavage of 4-phenyl-1-butene can be established since the bond dissociation energy for ethane is 88 kcal/mole and both benzyl and allyl radicals are stabilized by ca. 13 kcal/mole. Thus the cleavage $\triangle H^{\ddagger}$ is ca. 62 kcal/mole. However, such fission processes

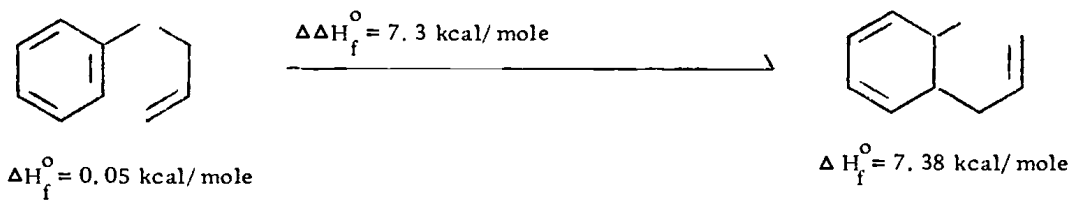


1

are usually favorable entropically, and an average value of $\triangle S^{\ddagger}$ = 12 e.u. will be used here. This was derived from the value of $\triangle S^{\ddagger}$ given by Wigfield and Tyman for 1, 5-hexadiene ($\triangle S^{\ddagger}$ = 12 e.u.) (140). With this $\triangle S^{\ddagger}$ at 450°C the $\triangle G^{\ddagger}$ for formation of the radicals is ca. 53

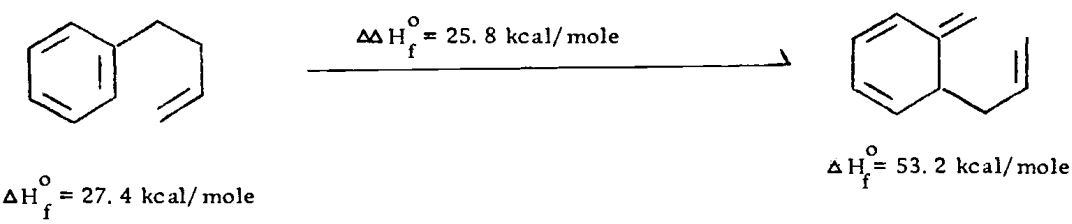
kcal/mole, and the $\triangle G^{\ddagger}$ (Cope) must be at least 4 kcal/mole higher to have avoided detection. Again employing the $\triangle S^{\ddagger}$ = -10 e.u. for the Cope rearrangement we reach $\triangle H^{\ddagger} \simeq$ 49-50 kcal/mole as a lower bound. The agreement with the first estimate is surprisingly good.

Let's try yet another route to this same $\triangle H^{\ddagger}$. Phenyl allyl ether has $\triangle H^{\ddagger}$ = 30.7 kcal/mole for the Claisen rearrangement. Using Benson's equivalents (136) with a few estimates for non-tabulated groups the $\triangle H_f^o$ for the reaction phenyl allyl ether to 2-allyl-cyclohexadienone is 7.3 kcal/mole. However for the reaction 4-phenyl-1-butene to 2-allyl-1-methylenecyclohexadiene $\triangle H_f^o$ = 25.8 kcal/mole.



ΔH_f^o = 0.05 kcal/mole

ΔH_f^o = 7.38 kcal/mole



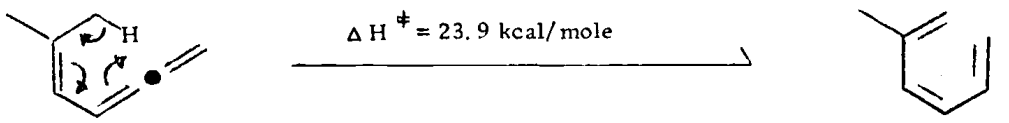
ΔH_f^o = 27.4 kcal/mole

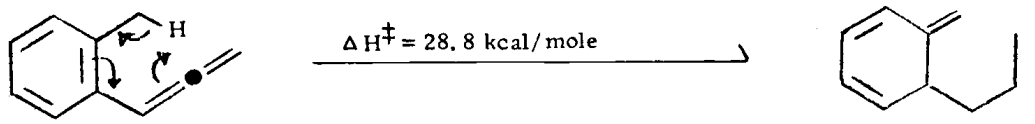
ΔH_f^o = 53.2 kcal/mole

If we assume that the entire difference in these reaction enthalpies applies at the transition states, then $\triangle H^{\ddagger}$ (Cope) for 4-phenyl-1-butene is 30.7 + (25.8-7.3) = 49.2 kcal/mole. We really seem to be stuck on the same square.

We can attempt one last effort. The $\triangle H^{\ddagger}$ for the Cope

rearrangement of 1, 5-hexadiene is 34.5 kcal/mole (36). One estimate of the enthalpic cost of converting a double bond to a benzene bond in a concerted thermal reaction can be obtained from published activation parameters for [1, 5] hydrogen shifts (shown below). Combination of





these experimental results give a $\triangle H^{\ddagger}$ (Cope) for 4-phenyl-1-butene of 34.5 + 4.9 = 39.4 kcal/mole. This value is too low because it would take an extraordinary set of $\triangle S^{\ddagger}$ values to prevent the Cope rearrangement from competing favorably with the radical cleavage reaction. Why is the cost of incorporating the benzene ring into the [1, 5] hydrogen shift reaction so low? One possible reason could be tha larger conjugate system being generated and a second could be that the reaction requires no change in hybridization of a ring carbon.

While keeping the previous calculations in mind, let's look at the experimental findings concerning the activation parameters of the Cope rearrangement of cis-(m-hydroxyphenyl)-2-vinylcyclopropane.

The Aromatic-Cope Rearrangement of 21a

A kinetic study of the Aromatic-Cope rearrangement of 21a was carried out in the temperature range 121.3-133.9° in ethanol containing a catalytic amount of phenol. The samples were analyzed by glpc using an electronic digital integrator and with n-tetradecane as an internal standard. Because of the competing processes of cis-trans isomerization, the aromatic-Cope rearrangement and formation of 1-(m-hydroxyphenyl)-1,3-pentadiene (23) it was necessary to find a column that would separate all four compounds cleanly. Unfortunately, this turned out to be more difficult than was anticipated. Several columns were tried before one was found which would provide the desired separation (Table 10). The only column tried that separated all four compounds was a 100' x 0.01" 2147 MBMA capillary column. The retention time of each compound is listed in Table 18, p. 105 in the experimental section.

Response factors (R_f) relative to n-tetradecane were measured using the method described by Grant (112). The following equation was used for the calculation:

$$R_f = \frac{A_i \times W_s}{A_s \times W_i}$$

R_f = response factor
A_i = area of sample
W_i = weight of sample
A_s = area of standard
W_s = weight of standard

Values for the response factors appear in Table 11.

Table 10. Various Columns Tried for Separation of 21a, 21b, 22 and 23.

Diameter (in.)	Length (ft.)	% liquid phase	Liquid phase	Support
1/8	12	3	SF-96	Chrom W-AW (45/60)
1/8	8	3	XF-1150	Chrom G-AW (45/60)
1/4	6	9	QF-1	Chrom W-AW (45/60)
1/4	6	15	Carbowax	Chrom P (60/80)
1/4	8	3	XF-1150	Chrom G (45/60)
1/4	4	3	SF-96	Chrom W-AW (45/60)
1/4	8	2	SE-30	Chrom W-AW (45/60)
1/4	8	9	SE-30	Chrom W-AW (45/60)
1/4	8	20	SE-30	Chrom W-AW (45/60)

Table 11. Response Factors for Compounds 21a, 21b, 22 and 23 Relative to n-Tetradecane.

Compound	Response Factor*
21a	0.98[+]
21a	0.98[+]
22	0.73[‡]
23	0.93[‡]

*Average Value of three Injections.

[+], [‡]Values Calculated from a Sample Containing Both Compounds.

In this study k_o is defined as the observed rate constant for the aromatic-Cope rearrangement of 21a. The actual rates at different temperatures and phenol concentrations are given in Table 12. The concentrations of 21a, 21b, n-tetradecane and phenol can be found in Table 17, p.103 in the experimental section.

The activation parameters for the aromatic-Cope rearrangement have been determined from a plot of log k_o versus 1/T and are presented in Table 13.

Table 12. Rates of the Aromatic-Cope Rearrangement at Various Temperatures and Phenol Concentration

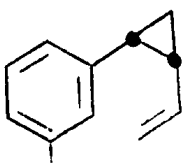
Temperature (°C)	∅-OH moles/liter	$k_o \times 10^6$ ‡ sec^{-1}
121.3	8.12×10^{-3}	1.92 ± 0.15*
127.1	none added	-0-+
127.1	2.23×10^{-2}	3.69 ± 0.37
127.1	5.67×10^{-2}	4.07 ± 0.38*
127.1	2.41	4.29 ± 0.39
133.9	8.12×10^{-2}	5.13 ± 0.38

‡95% Confidence Limits ($N \geq 20$).

*These rates were used in determination of activation parameters.

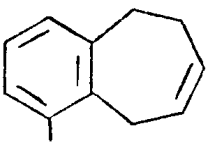
+Too slow to be accurately measured, 21a = 7.00×10^{-4} M

Table 13. Activation Parameters for the Aromatic-Cope Rearrangement of 21a.



OH

21a



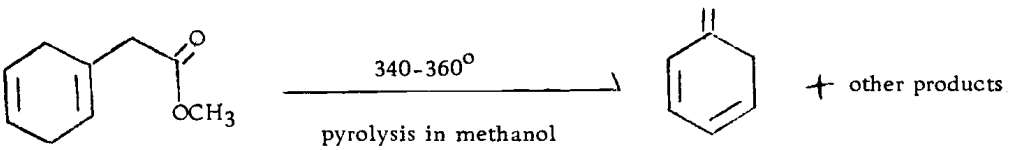
OH

22

Ea	27.5 ± 4.0 kcal/mole
log A	9.5 ± 2.1 sec^{-1}
$\triangle H^{\ddagger}$ (127.6°)	26.7 ± 4.0 kcal/mole
$\triangle S^{\ddagger}$ (127.6°)	-17.5 ± 9.8 e.u.

Based on the thought that a [3,3] sigmatropic shift is an allowed process (1) while a [1, 3] hydrogen shift is thermally forbidden (1), it seems reasonable to assume that the hydrogen shift will be the rate determining step. However the loss of resonance energy in the [3, 3] shift step could conceivably increase the activation energy for that step to a point where it becomes rate determining. There exists very little experimental evidence on which to base any estimates about the energy requirements of either step. The purely thermal intramolecular 1, 3-hydrogen shift is clearly a very slow process if it occurs at all. Thus, for example, Bailey and Baylouny were able to prepare 5-methylene-1, 3-cyclohexadiene by pyrolysis of a methyl carbonate at 350°, and to isolate that triene from a complex mixture by preparative gas

chromatography at 110° (137). However when a crude sample was



allowed to stand at room temperature isomerization to toluene was observed. While this may mean that the isomerization is very sensitive to acid or base catalysis, no more is known about the mechanism of that hydrogen migration process.

Doering has suggested that the hydrogen shift is rate limiting and has presented evidence for removal of this limiting effect by base catalysis (14). If this rearomatization step is also susceptible to acid catalysis, as the experimental evidence indicates, then the phenolic hydroxyl in both the reactant and product could act as catalysis for the proton transfer. Since this catalyst would necessarily be a bimolecular process its rate must be concentration dependent. This expectation was put to experimental test. At substrate concentrations of 7×10^{-4} M no measureable amount of product was formed, but in a preparative reaction run at a concentration of 4×10^{-2} M the Cope product was obtained though no rate measurement was made. Thus the overall rate of the reaction does appear to be concentration

dependent as would be expected for a bimolecular (or higher order) rate determining step.

This qualitative result was confirmed by quantitative rate studies. In the presence of added phenol the rate is increased until at very high phenol levels the rate becomes independent of the phenol concentration. At these levels the reaction is purely first order in substrate which indicates the Cope rearrangement step is rate determining. Kinetically then the overall process has the form

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow[C]{k_2} D$$

where A is the substrate, step 1 is the [3, 3] sigmatropy and C is the acid catalyst. Huisgen has shown that kinetic systems of this type can be treated as follows (113, 114, 115). Under conditions where the acit catalyst concentration remains constant the overall rate is

$$\text{rate} = k_c[A] = \frac{k_1 k_2 [A][C]}{k_{-1} + k_2[C]}$$

which by simple transformation converts to the form

$$k_o = k_1 - \frac{k_{-1}}{k_2} \frac{k_o}{[C]}$$

This gives a straight line when k_o is plotted against $k_o/[C]$. Treatment of the data for the rearrangement of 21a in this way gives a

straight line with $k_1 = 4.24 \times 10^{-6}$ sec^{-1} and $k_{-1}/k_2 = 0.014$ (Table 14). Clearly the first step in rate determining and under the conditions employed only 1% of 182 returns to the reactant. However the negligible rate in dilute solution shows that at very low catalyst concentrations the proton migration step probably has become rate determining.

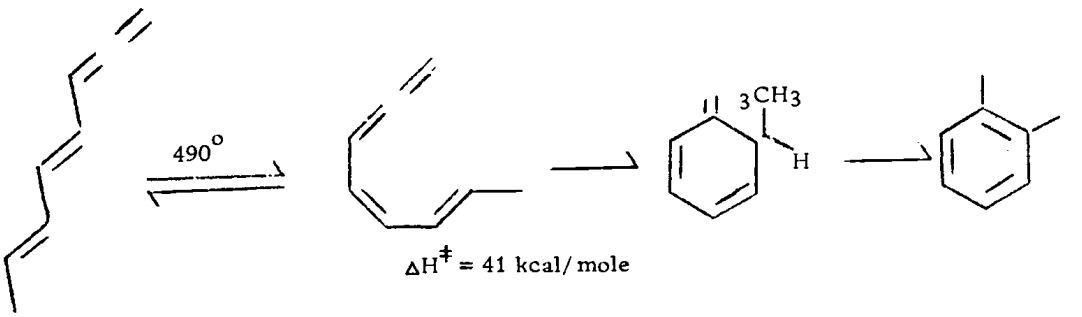
Table 14. Analysis of k_o versus $k_o/[C]$ Using a Least Squares Fit.

$k_o \times 10^6$ (sec^{-1})	$k_o/[C]$ ($\frac{liters}{mole \cdot sec}$) $[C] = [21a] + [\beta\text{-OH}]$	k_1 (sec)
3.69	3.94	
4.07	6.38	4.24×10^{-6} ‡
4.29	1.73	

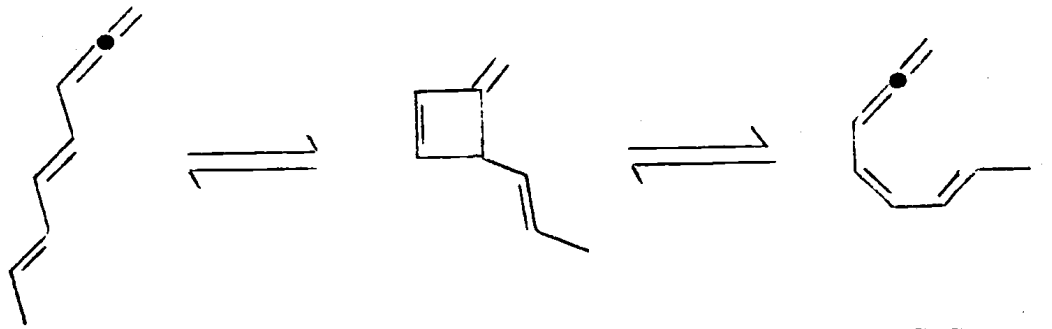
‡Correlation Coefficient = 0.96 with $k_{-1}/k_2 = 0.0143$

This explanation for the extremely slow rate under the low concentration conditions depends on the equilibrium constant for the Cope rearrangement being very small (see $\triangle\triangle H_f^\circ$), and the rate constant for the hydrogen migration being very low. The first requirement is clearly satisfied, but what should be expected for the [1, 3] hydrogen shift rate is far from certain. No authentic concerted

intramolecular shift has been uncovered. One piece of evidence which may be of value in this context is the measured $\triangle H^{\ddagger}$ of 41 kcal/mole for the reaction sequence below. The authors suggested that the cis-trans isomerization is rate determining (138),



which is in good accord with such a process provided that the reaction involves a 180° rotation about the center bond (154). It seems much more likely that the double bond isomerization goes via a cyclobutene as shown here. Methylenecyclobutene and vinylallene have about the same heat of formation (calc. from Benson's group



equivalents assuming that =C=C has the same value as C_tC_d), and since ring opening proceeds readily at 175° (155), ring closure should go equally readily. Thus the $\triangle H^{\ddagger}$ for the double bond mutation should be much less than 40 kcal/mole and probably ca. 32-35 kcal/mole. The electrocyclization is certainly not rate restrictive

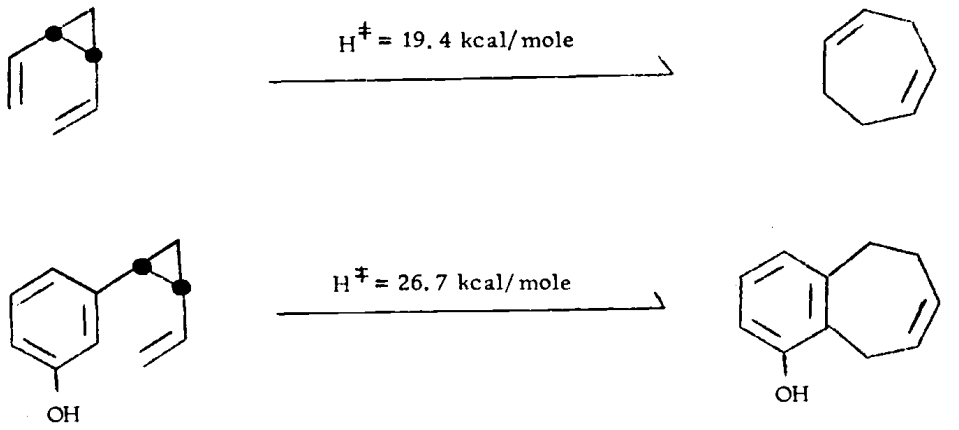
(usual $\triangle H^{\ddagger} \sim$ 30 kcal/mole) (142), and so we postulate that the hydrogen migration is the step requiring 41 kcal/mole for enthalpy of activation. If this analysis is correct and in our case the $\triangle H^{\ddagger}$ for the hydrogen shift approaches 41 kcal/mole, then it is obvious why we did not see any reaction under low concentration conditions.

Estimation of $\triangle H^{\ddagger}$ for the Cope rearrangement of 4-Phenyl-1-butene (1)

Having obtained the activation parameters for the Cope rearrangement of 21a, we are now in a position to make some estimates for $\triangle H^{\ddagger}$ of an unactivated system such as 4-phenyl-1-butene. Before doing this a note about our measured values is in order. The narrow temperature range available to us for the study of the Cope rearrangement (rate is too slow below ca. 120° and cis-trans isomerization interferes above 135°) prevents a very accurate appraisal of the activation values. Since it is known that the $\triangle S^{\ddagger}$ for a Cope rearrangement via a boat transition state is smaller than that for a chair (119, 120), we view our $\triangle S^{\ddagger}$ = -17.5 e.u. with some skepticism. That is we feel that this value is probably too high and consequently $\triangle H^{\ddagger}$ is too low. The corresponding values of Maas and Rigitz for a similar rearrangement, $\triangle H^{\ddagger}$ = 29.3 kcal/mole and $\triangle S^{\ddagger}$ = -7.1 e.u., reinforce this feeling (15a). Thus for the following discussion of the estimation of a $\triangle H^{\ddagger}$ for 4-phenyl-1-butene, we will adopt the range from our 26.7 kcal/mole to their

29.3 kcal/mole as a reasonable one.

Rearrangement of both cis-1, 2-divinylcyclopropane and 21a, must make use of the boat transition state, since reaction via a chair transition state would generate the extremely unstable trans, cis-1, 4-cycloheptadiene ring (115). Ignoring for the moment the influence of



the hydroxyl group, these two can be compared directly, and the $\Delta\Delta H^{\ddagger}$ = 7.3 kcal/mole can then be used in conjunction with Doering's value of $\Delta H^{\ddagger}$ for the rearrangement of 1, 5-hexadiene. This leads to a $\Delta H^{\ddagger}$ = 41.8 kcal/mole for 4-phenyl-1-butene from our value, or 44.4 kcal/mole from Maas and Regitz value.

Now we must consider the influence of the hydroxyl group. Unfortunately there are no data directly pertinent to the question of the quantitative effect of a m-hydroxyl on the rate of a concerted [3, 3] sigmatropic shift. The best estimate available is the 1.2 kcal/mole

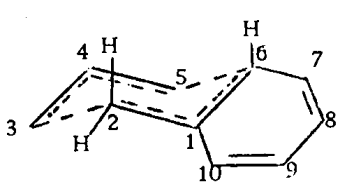
reduction of the $\triangle H^{\ddagger}$ for the Claisen rearrangement by a m-methoxyl group. Taking this directly raises the estimated $\triangle H^{\ddagger}$ (for 4-phenyl-1-butene) from our results to 43.0 kcal/mole.

A possible source of error in this approach lies in the assumption that a $\triangle H^{\ddagger}$ value obtained from a boat transition state process can be applied verbatim to a chair state process (117-121), i.e. that of a 1,5-hexadiene and 4-phenyl-1-butene. This assumption needs some examination. In effect this treatment really states that the changes made in converting a double bond into a phenyl group influence each transition state equally, and each ground state equally. We submit that the ground state effects will be very much smaller than the transition state influences, and we have ignored the former in the discussion which follows. Any large difference in the resonance stabilization of the two transition states would necessarily stem from notable differential distortions of the cyclohexadienoid moiety in the boat versus the chair transition states. Reasonable models indicate no necessity for any such distortions. Thus any important reasons for failure of the above assumption must be steric in origin.

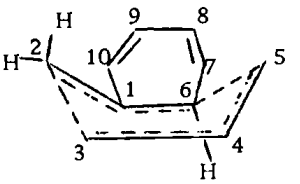
In establishing a model for the transition states having a phenyl group we have maintained the sp^2 hybridization at all the aromatic ring carbons except for that one which becomes sp^3 in the product. Consequently the ring carbons maintain their planarity throughout the

reaction. Then the major difference between the two systems results from substitution of two hydrogens by sp^2 ring carbons in each set, boat vs. chair. In each transition state one CH (C_7) is in an unhindered position, i.e. equatorial in the chair form and bowsprit or

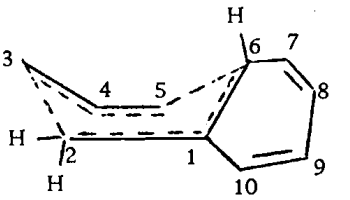
Fig. I



chair

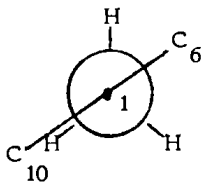


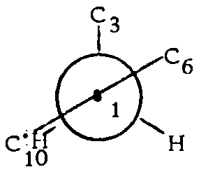
boat 1

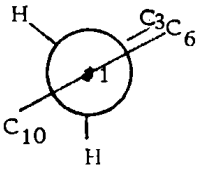


boat 2

C_7	equatorial	C_7	exo	C_7	bowsprit
C_{10}	eclipsed	C_{10}	eclipsed	C_{10}	non-eclipsed



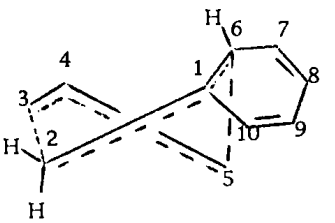




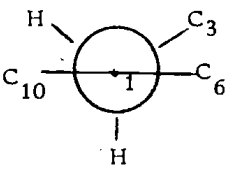
exo in the boat. We consider these to have equivalent effects on the two transition states, thus there is no differential effect. The second CH (C_{10}) is attached to a trigonal carbon of the transition state ring in each conformation. In all known examples of acyclic molecules having sp^2-sp^3 bonds the eclipsed conformation is the only one populated (156). This is the conformation naturally formed with the chair conformer and is thus presumably present in the chair transition state. Several options are available in the boat transition state. In the classic (C_{2v}) boat with one sp^2 CH (C_7) in the bowsprit the trigonal carbon has its

CH (C_{10}) in a non-eclipsed position. However if one CH (C_7) is exo the trigonal carbon has its attached CH (C_{10}) group in an eclipsed conformation (see Fig. I). In a twist boat conformation the eclipsed conformation does not appear but the dihedral angle is always less than 60° (Figure II). The most one can ascertain at present is that the presence of the benzene ring could increase the energy differential

Fig. II



twist boat



between boat and chair transition states, but probably the differential effects will be small, since equivalent conformations are available in both states. Since we can visualize no major influence we have chosen to neglect this trigonal carbon contribution also. Further support for this position is provided by the observation that for sp^2-sp^3 centers an eclipsed methyl is as favorable as an eclipsed hydrogen (156).

Summary

This leads to an estimated $\triangle H^{\ddagger}$ of 43 ± 4 kcal/mole for 4-phenyl-1-butene. Although 4-phenyl-1-butene decomposes before undergoing

a Cope rearrangement, this observation could be irrelevant with respect to the Cope process if the hydrogen migration were rate determining. The highest temperature under which an unactivated molecule has been shown to resist a Cope rearrangement is ca. 350° (135), and this would be quite compatible with the upper end of the above $\Delta H^{\ddagger}$ range. However, if our appraisal of the route to the product from β-naphthylallylmalonic ester is correct, and the quantitative effect of the carbethoxyl groups holds for the aromatic cases, only the upper extreme seems permissible.

Regardless of whether the value of 43 or 47 kcal/mole proves correct the conclusions about further studies remains obvious. Pure thermal activation of non-activated arylbutenes is not a viable route to aromatic-Cope reactions. Thus the search must be for substituents or catalysts to provide the necessary acceleration.

II. Further Studies on Rate Determining Steps

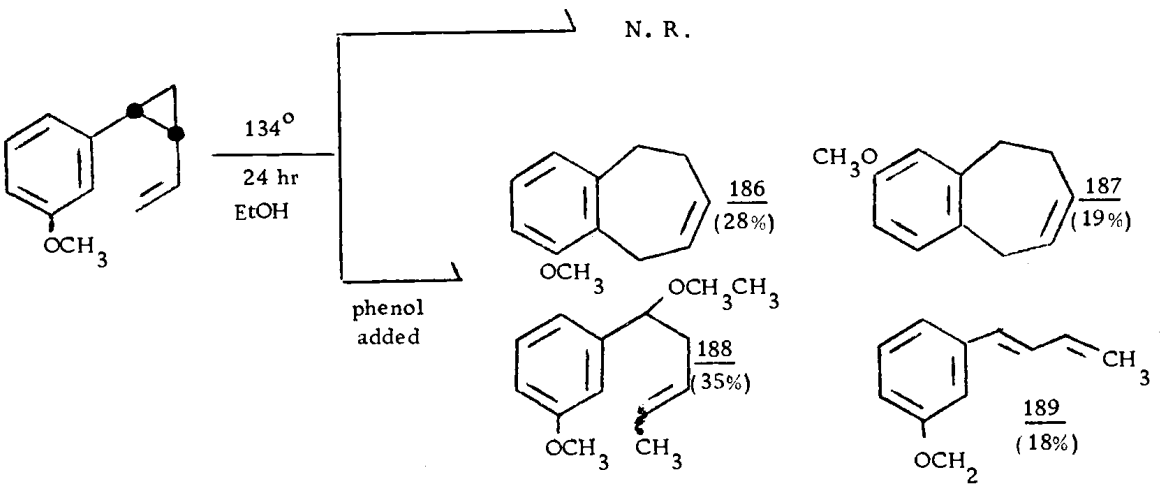
The kinetic studies noted above show that in a solution of low acid concentration the hydrogen migration step can be rate determining in the Cope rearrangement of cis-1-(m-hydroxyphenyl)-2-vinylcyclopropane. Some further studies to determine the generality of that observation were made and are described here.

A. Rearrangement of cis-1-(m-Methoxyphenyl)-2-vinylcyclopropane (181a).

If the hydrogen shift step is generally rate

determining, 181a which has no acidic moiety present should undergo no apparent thermal reaction in neutral solution, but should rearrange under appropriate acid catalysis. This simple scenario has been confirmed experimentally.

When a solution of 181a in ethanol was heated we recovered only unreacted starting material. After heating a similar solution containing added phenol, however, we obtained four new compounds.



The compounds were separated on a 4% SF-96 column and identified as 186, 187, 188, and 189. Compounds 186 and 187 are the expected Cope products. The fact that the Cope rearrangement of 181a was observed in the presence of added phenol and not observed in its absence proves that the [1, 3] hydrogen shift can generally become rate limiting in systems like 21a and 181a which require only low activation energy in the Cope step. This says nothing about systems like 4-phenyl-1-butene which require much higher activation energy in that step.

The fact that both ortho- and para-substituted products were obtained in the methoxy case (181a) and only the ortho-product was obtained in the hydroxy case (21a) is very interesting. The aromatic-Claisen rearrangement has shown little or no regioselectivity with regard to meta-methyl, methoxyl or hydroxyl group on the aromatic ring (Table 15).

Therefore one would expect a mixture of ortho- and para-substitution products as was the case with 181a. The failure of 21a to give any para- substituted product is rather intriguing but is not clearly explicable at present.

Table 15. Selectivity of the Aromatic-Claisen Rearrangement using Various Phenyl Substituents.

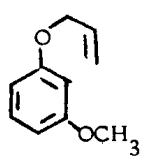
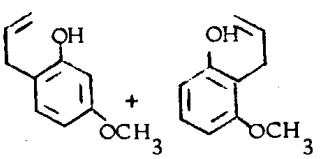
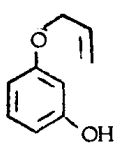
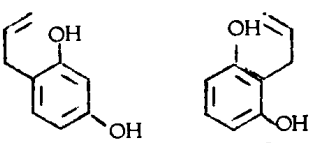
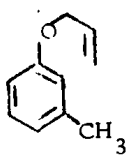
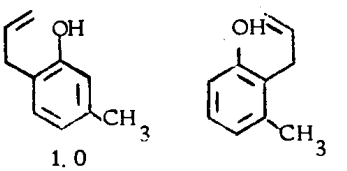
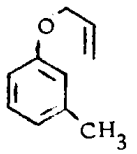
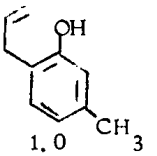
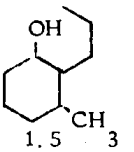
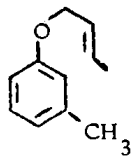
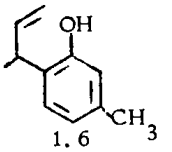
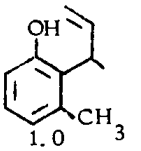
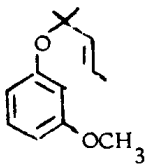
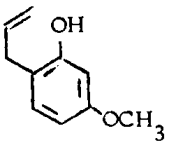
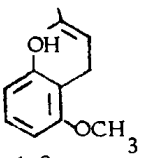
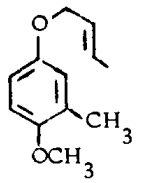
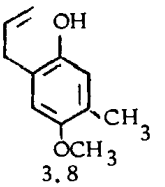
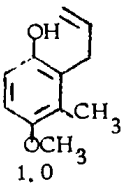
Compound	Conditions	Product	Ref.
	200° diethylene glycol sealed tube	 2.0 1.0	124
	Reflux, 1 hr, $(C_2H_5)_2NC_6H_5$	 1.3 1.0	125
	Reflux, 8.5 hr, $(CH_3)_2NC_6H_5$	 1.0 1.1	126

Table 15. (Continued)

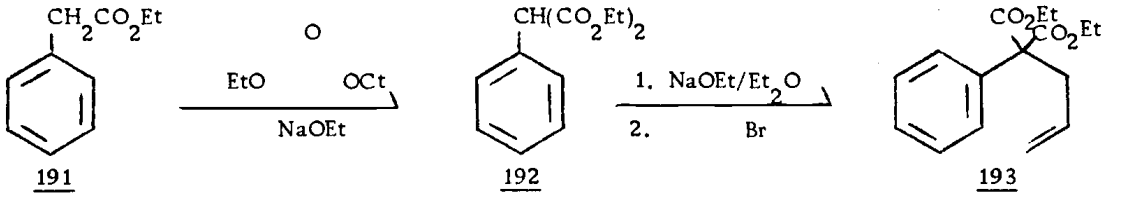
Compound	Conditions			Ref
	200°, sealed tube, carbitol	 1.0	 1.5	124
	185°, 16 hr, $(CH_2H_5)_2NC_6H_5$	 1.6	 1.0	127
	Reflux, 1 hr, $(C_2H_5)_2NC_6H_5$	 1.0	 1.0	128
	Heat, $(CH_3)_2NC_6H_5$	 3.8	 1.0	129

B. Pyrolysis of Allylphenylmalonic Ester (193)

Cope and his students investigated this reaction prior to the Woodward-Hoffman era and thus would have had little reason to suspect that the hydrogen shift might be rate determining. However, if our mechanism for the formation of 17 from allyl-2-naphtyylmalonic ester is correct, the hydrogen shift would not be rate limiting even for the phenyl case. Thus as a partial test of our mecha nism and a check on the possibility that the hydrogen shift might be rate determining, we have heated 193 with sodium ethoxide.

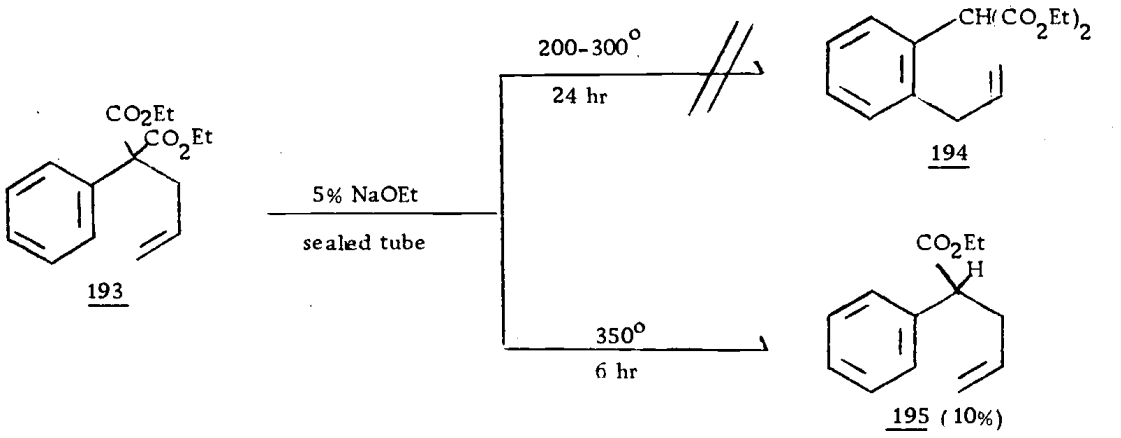
Compound 193 was synthesized in straightforward fashion from ethyl phenylacetate. The route is illustrated in scheme 2. About 5% sodium ethoside was added to a sample of pure 193 and the mixture

Scheme 2



191 192 193

was heated to 300° without incurring any rearrangement. At 350° decomposition occurred and still no evidence for Cope rearrangement

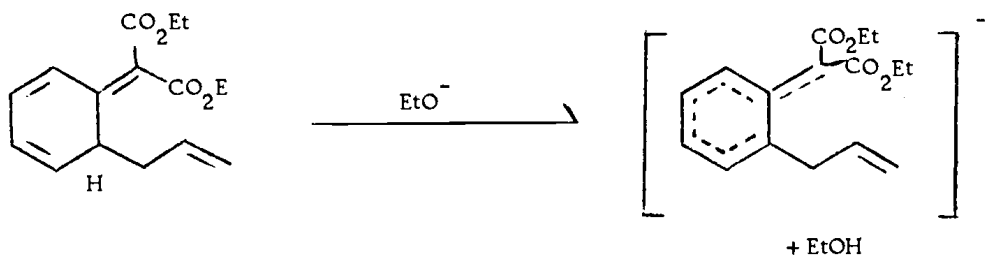


193 194 195 (10%)

was found. The above results are in full agreement with Cope's findings in the absence of the base. This then provides a rather modest measure of support for our suggested mechanism.

In comparison with the results obtained by Doering and Bragole

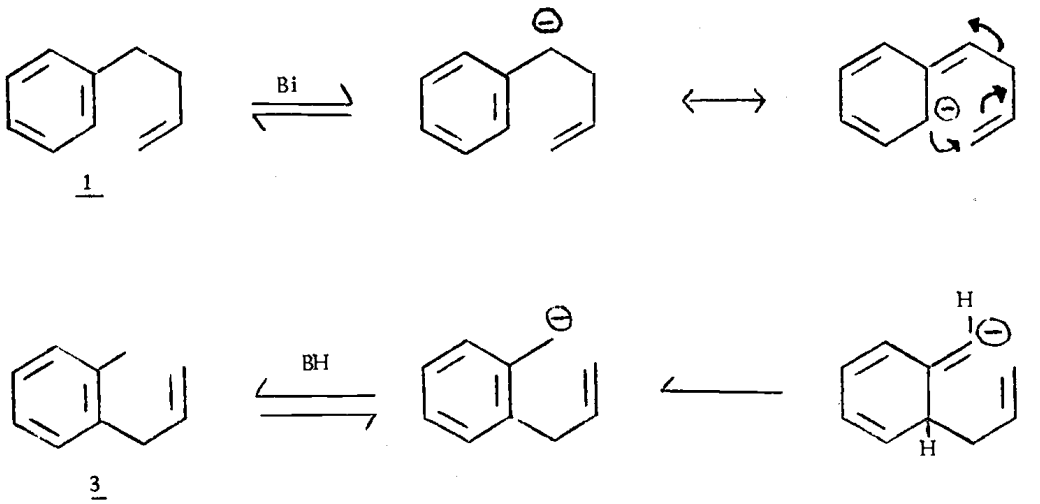
with 4-phenyl-1-butene (1) in the presence of t-butoxide at 350°, our results with 193 are very suggestive. Assuming that the carbethoxy groups lower $\triangle H^{\ddagger}$ for an aromatic Cope by the same 5 kcal/mole per carbethoxy they produced with an aliphatic Cope, rearrangement of 193 should proceed some 3×10^3 times faster than 1. Three explanations are possible - a) sodium ethoxide was not effective as a catalyst, b) the carbethoxy groups do not enhance the rate of an aromatic Cope rearrangement, c) Doering and Bragole were not observing a normal aromatic Cope reaction. While we have no evidence at present to eliminate choice a, the proton to be removed is a vinylog of malonic ester and it would certainly be surprising if ethoxide were unable to



remove it at 350°. Similarly, there exists no evidence about the influence of carbethoxy groups on the aromatic Cope rearrangement except as one accepts our postulated mechanism for the rearrangement of 15. Given that the route is correct then these groups do enhance the rate since Lambert et al. failed to find any significant rearrangement of a naphthyl analog lacking such activation (135). However even if no activation occurred we would still have seen some rearrangement

if Doering and Bragole were actually observing an aromatic Cope rearrangement. Thus we believe alternative b can be eliminated.

It seems likely that the results we have observed show that Doering and Bragole were seeing an anionic rearrangement of the type shown below. Since allylphenylmalonic ester lacks any benzyl hydrogen it cannot undergo an equivalent reaction. Until further



1

3

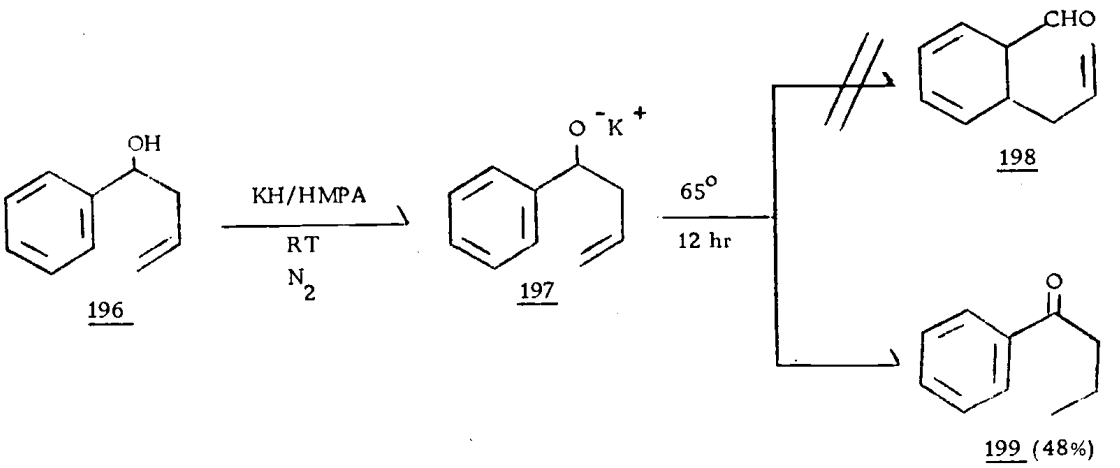
studies are made this must rest as a reasonable hypothesis.

III. Search for Alternative Methods to Activate the Aromatic Cope Rearrangement

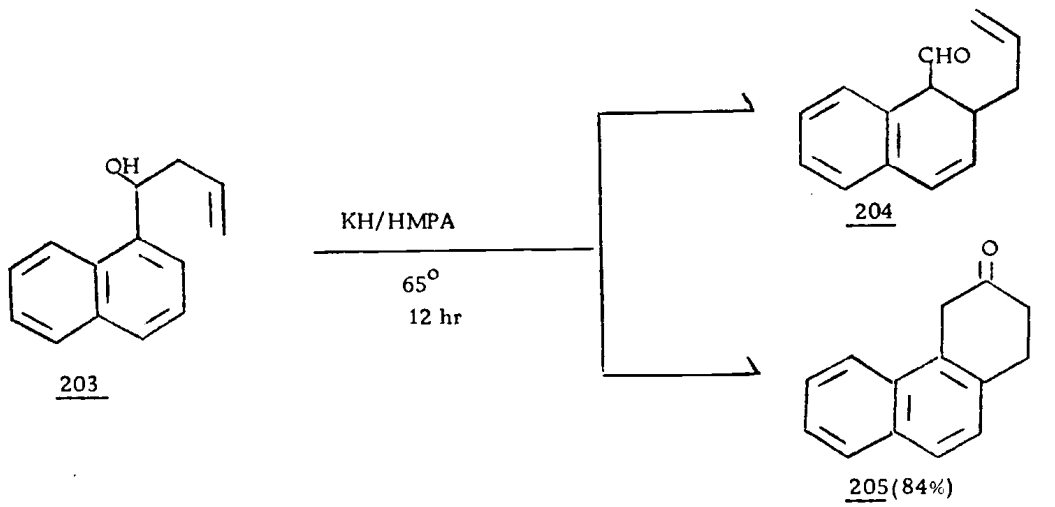
The activation energy required to bring about an aromatic Cope rearrangement with a non-activated system is so high that most potential reactants can undergo alternative reactions with lower activation requirements. Thus to search for additional examples of the aromatic Cope rearrangement really means to search for ways to lower the activation energy. The recent discovery by Evans and Golob that the normal oxy-Cope reaction can be accelerated by up to seventeen powers of ten by converting the hydroxyl group to a naked anion (94) makes this method the prime candidate for application to our problem.

A. Anionic Acceleration of Potential Aromatic-Oxy-Cope Systems

A series of 1-aryl-3-buten-1-ols was prepared by addition of an appropriate allyl Grignard reagent to an arylaldehyde. The initial molecule investigated was 1-phenyl-3-buten-1-ol (196). The anion was prepared by reaction with potassium hydride in HMPA. At 65° the anion 197 was slowly converted to the anion of butyrophenone by a base catalyzed double bond migration. No trace of 1, 2-dihydro-2-allylbenzaldehyde was obtained. Reaction of 1-α-naphthyl-3-buten-1-ol (203) under the same conditions let to an equivalent result.



196 197 198 199 (48%)



203 204 205(84%)

Evans et al. have shown that the rate of the anionic rearrangement increases with the dieletric constant of the medium (HMPA > THF > Et_2O) and decreases with increasing metal-alkoxide association (Li < Na < K) (94). A variety of metal hydrides, solvents and temperatures were tried in hopes of finding conditions where the Cope rearrangement of 196 and 203 could be observed (Table 16).

Table 16. Metal Hydride and Solvent Study of the Anionic Rearrangement of 196 and 203.

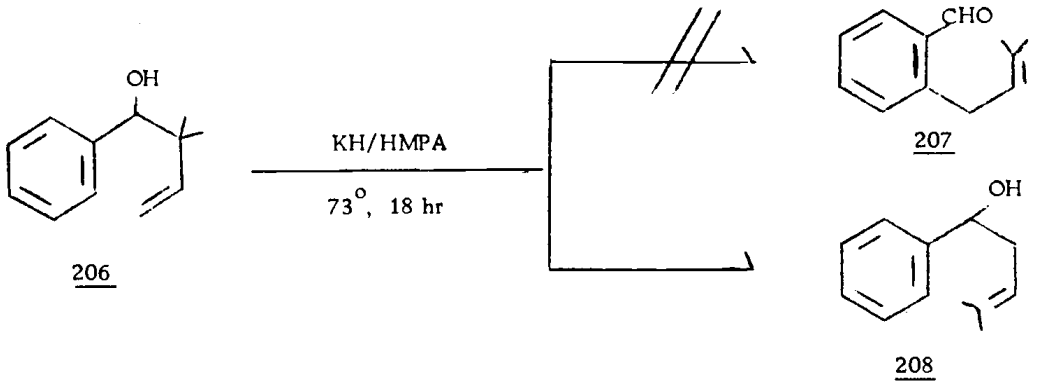
MH	Solvent	Temp. (°C)	Product
KH (1.2 eq)	DME	reflux (83-84°)	N.R.
(3.0 eq)	"	overnight	N.R.
NaH (1.2 eq)	DME	reflux, 18 hr	N.R.
(3.3 eq)	"	"	N.R.
KH (1.2 eq)	Diphenyl Ether	150°, overnight	N.R.
(3.0 eq)	"	"	N.R.
NaH (1.2 eq)	Diphenyl Ether	150°, overnight	N.R.
(3.0 eq)	"	"	N.R.
KH (1.2 eq)	THF	reflux (67°) 12 hr	N.R.
KH (1.2 eq)	DME	reflux (85°) 16 hr	199 (50%) or 205 (39%)

*all conditions shown were tried on both 196 and 203

**1.2 eq. of 18-C-6 added

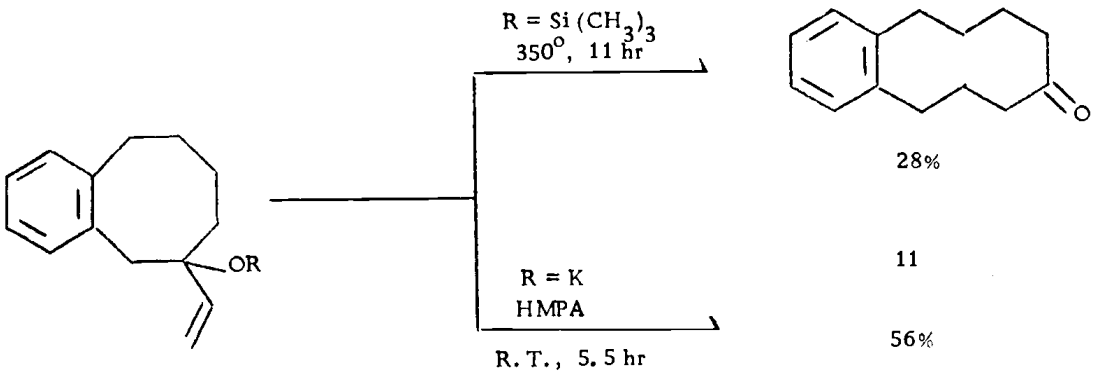
The results show that 196 and 203 are resistant to the oxy-Cope rearrangement. Unfortunately, the hydrogen migration process inevitably occurs faster than the Cope rearrangement.

In order to prevent the double bond migration we prepared 1-phenyl-2, 2-dimethyl-3-buten-1-ol (206) and studied its anion under the same conditions. At ca. 70-75* this anion undergoes a 1, 3-sigmatropic shift to give 1-phenyl-4, 4-dimethyl-3-buten-1-ol (208).



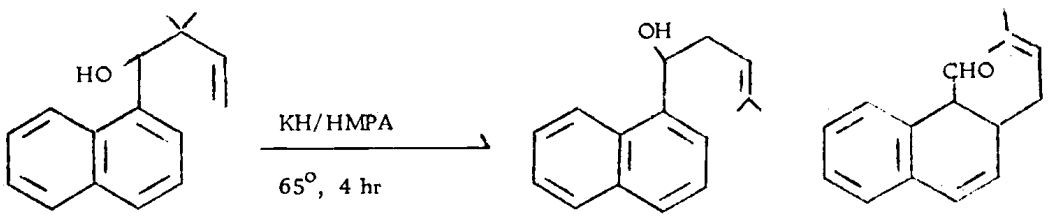
206 207 208

Many examples of facile a [1, 3] shifts in anionic systems have appeared in the literature recently (131, 132, 133). For example, Thies and Seitz have noted a dramatic rate enhancement in [1, 3] shift processes under conditions remarkably similar to ours (131). When the reaction rates of the anionic systems were compared with



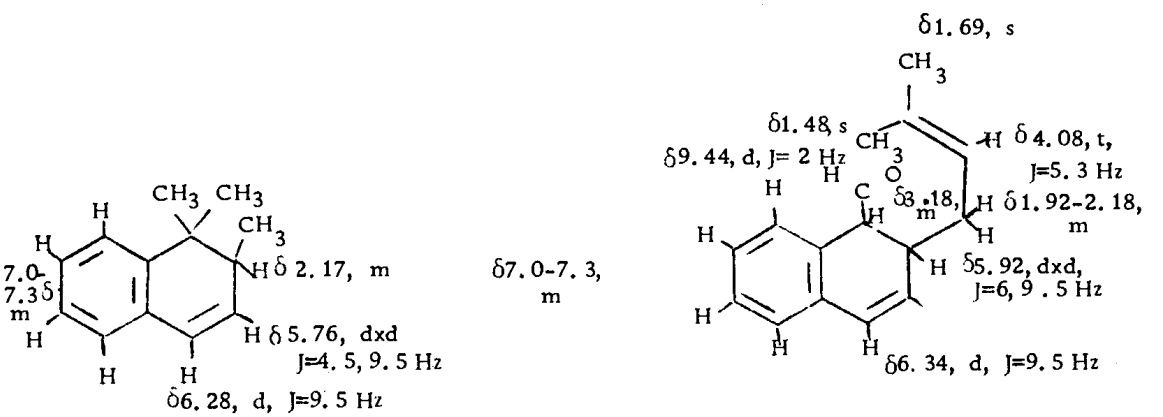
those of the siloxy-Cope ring expansions a rate enhancement of about 10^{16} to 10^{17} was found (133). No simple explanation has been proposed to account for the tremendous rate enhancement noted.

A sample of 1-naphthyl-2, 2-dimethyl-3-buten-1-ol (209) was prepared by the Grignard route and its anion was heated in HMPA. The major product was the result of a formal [1, 3] sigmatropic



209 → 210 (57%) + 211 (10%)

reaction, but the product of greatest interest was compound 211. This product, obtained pure in only 10% yield, contained an aldehyde which was not conjugated (1705 cm^{-1}) but was adjacent to a carbon bearing one hydrogen (δ = 9.44, doublet, J = 2 Hz). Comparison of

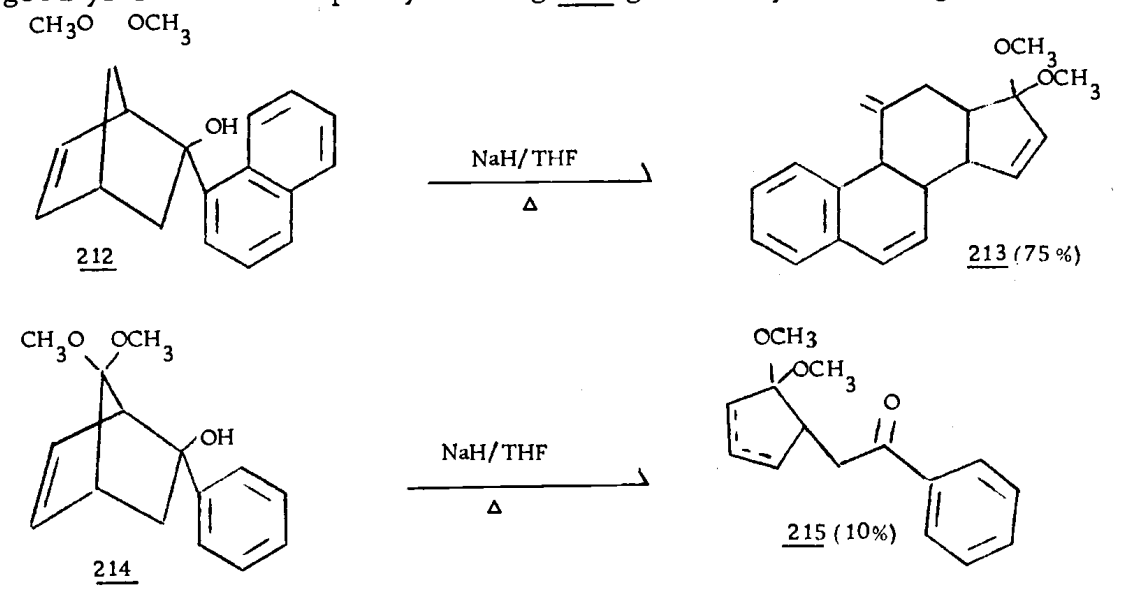


nmr spectrum with that of 1, 1, 2-trimethyl-1, 2-dihydronaphthalene

shows that 211 possesses a 1, 2-dihydronaphthalene unit (143). Finally the allyl group is still present as is indicated from the following peaks: multiplet at 1.92-2.18 δ, triplet at 5.08 δ (1H), singlet at 1.48 δ (3H), and singlet at 1.69 δ (3H).

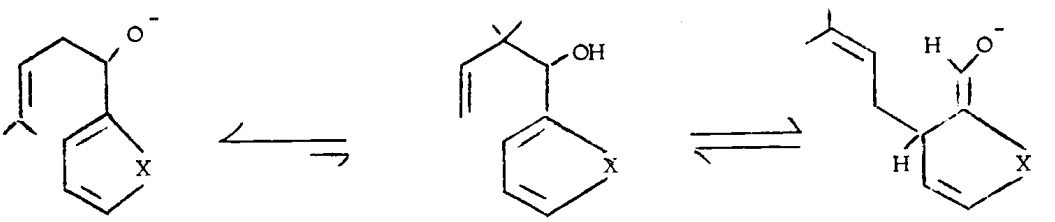
These data prove that 211 is the product of an oxy-Cope rearrangement, 2-(γ, γ-dimethylallyl)-1, 2-dihydronaphthalene-1-carboxaldehyde. This aldehyde was relatively unstable tending to rearomatize readily and was difficult to separate from the reaction mixture. However it is now apparent that the [1, 3] and [3, 3] sigmatropic reactions are at least competitive in the naphthalene system.

The recent studies of an anionic aromatic oxy-Cope rearrangement by Jung and Hudspeth are in complete agreement with our results (134). They found that compound 212 gives an oxy-Cope product in good yield while the phenyl analog 214 gives only a cleavage reaction.



The latter reaction may be related to our [1, 3] shift process because recombination in their example would lead to a four membered ring.

These data do not provide much direct evidence with respect to the rate of the anionic aromatic oxy-Cope process, since the reactions are undoubtedly equilibrium processes and at the moment we do not know whether the reactions observed were kinetically or thermodynamically controlled, but in no case would more product be produced than the equilibrium concentration. It seems very probable that at equilibrium too little 217a would be present to isolate, while with 216b the enolate (217b) might be stable enough to accumulate a measurable amount.



218 216 217

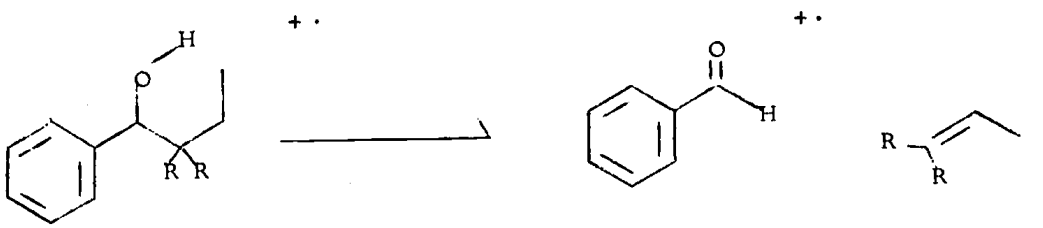
a) x = CH=CH

b) x = C_6H_4

Despite this equilibrium difficulty the fact that an anionic oxy-Cope product was found at 65° does permit an estimate of sorts to be proposed for the non-activated Aromatic Cope, certainly the reaction with 209 must be at least fast enough to give the 10% observed under

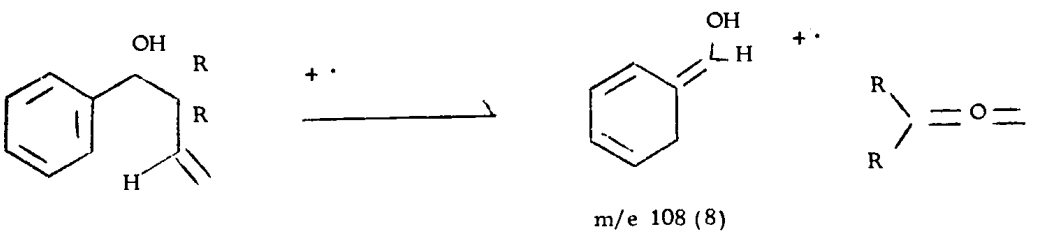
the conditions used. Thus the $\triangle G^{\ddagger}$ for the reaction must be equal to or less than 28 kcal/mole. Assuming that the rate enhancement here is the same as most of those observed by Evans and his students, i.e. 1×10^{11} and again using a $\triangle\triangle G^{\ddagger}$ between phenyl and naphthyl systems of 5 kcal/mole, we can estimate that $\triangle G^{\ddagger}$ for 4-phenyl-1-butene could be as high as 50 kcal/mole. Again the agreement with our earlier estimates is good.

The mass spectral fragmentation patterns for 196, 203, 206 and 209 show a number of similarities, and mechanisms for the major fragmentations can be proposed. These are outlined below for 196 and 206. In each case the base peak is formed by a Biemann type B

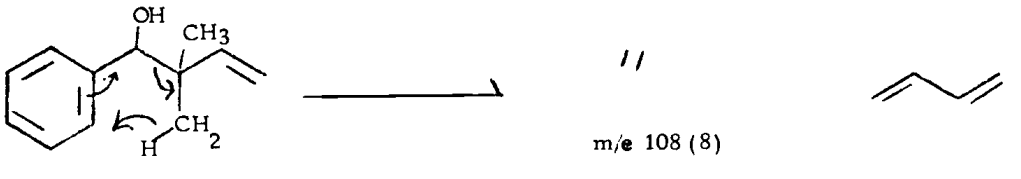


R = H, CH_3

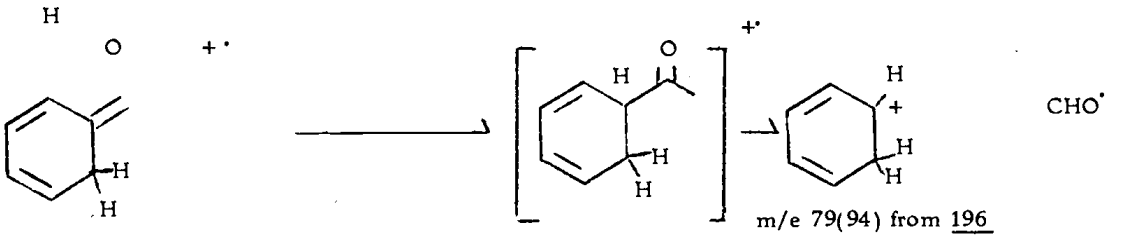
m/3 106 (2) (196 and 206)



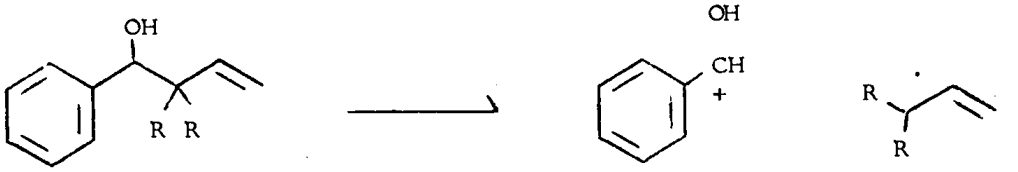
m/e 108 (8)



m/e 108 (8)



m/e 79(94) from 196
(63) from 206



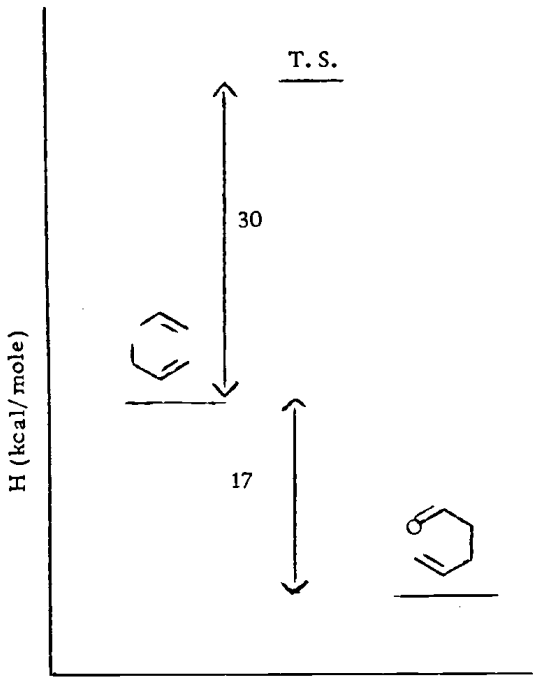
m/e 107 (100) (196 and 206)

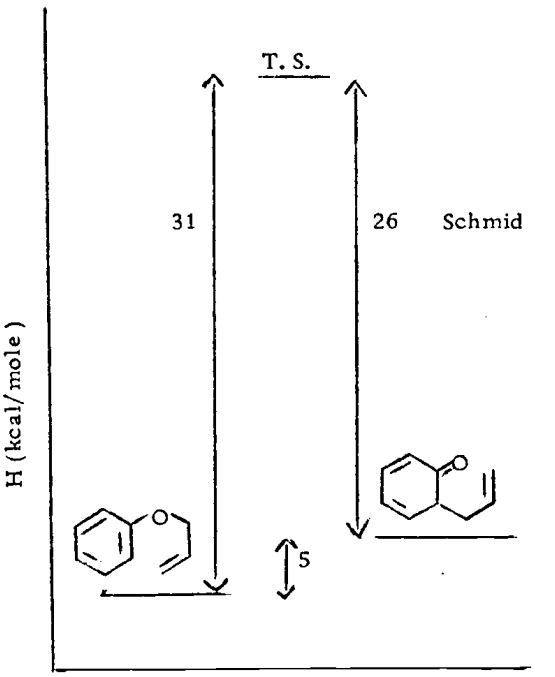
cleavage to give the highly stabilized benzyl alcohol positive ion. Most interesting is the apparent greater facility of the McLafferty rearrangement which involves a ring double bond than that which utilizes the vinyl group. While no major conclusion should be drawn from this observation, it does suggest that concerted cleavage processes leading to dearomatized products are not necessarily seriously impeded (144, 145).

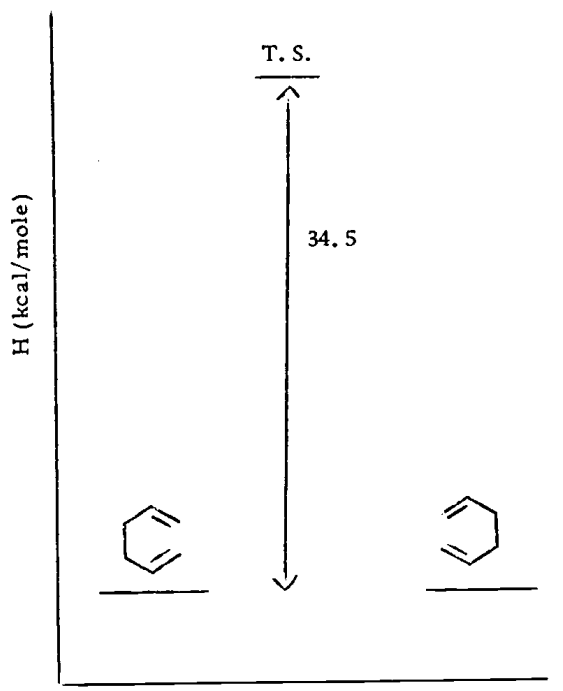
IV. Energetics-Cost for Olefinic vs. Aromatic Double Bond

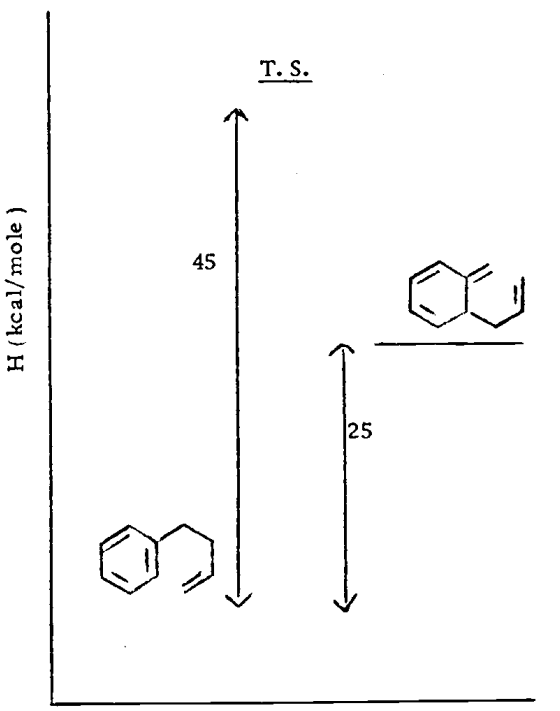
It had been established experimentally that for the Claisen rearrangement converting the vinyl double bond to a phenolic bond costs in enthalpy only about one kcal/mole. Now our experimental results and those of others from which estimates were derived show that for the Cope rearrangement the cost in enthalpy of converting one olefinic double bond to a benzene is ca. 11-12 kcal/mole. At first glance this seems very surprising and certainly deserving of explanation. Lambert has attributed the accelerating influence of the oxygen atom on the [3, 3] sigmatropic reaction to a perturbation of the frontier orbitals (149) which enhances the HOMO-LUMO interaction (122). While this may indeed account for the ca. 5 kcal difference betwen the $\triangle H^{\ddagger}$ values for Claisen and Cope rearrangements in acyclic cases, it is not immediately apparent that this perturbation is responsible for the differential cost of conversion to aromatic systems in the two reactions.

Perhaps less profound but to us more satisfying is the explanation advanced below. The use of Benson's thermochemical group equivalents permits calculation of the overall exo- or endothermicities of the four processes under consideration. Thus the acyclic Claisen is exothermic by 17 kcal/mole (146), the aromatic Claisen is endothermic by 5 kcal/mole (161-163) the acyclic Cope is


T. S.
30
17
H (kcal/mole)


T. S.
31
26
Schmid
5
H (kcal/mole)


T. S.
34. 5
H (kcal/mole)


T. S.
45
25
H (kcal/mole)

thermoneutral, and the aromatic Cope is endothermic by 25 kcal/mole. Those results alone do not necessarily account for the above mentioned differential.

Recently secondary deuterium isotope effects have been used to detail the nature of the transition states for the acyclic and aromatic Claisen rearrangements (147, 148, 151, 152, 153). These show that the exothermic acyclic reaction has an early transition state while the slightly endothermic aromatic Claisen has a transition state which is further along on the reaction coordinate. Thus the Hammond postulate is applicable to these reactions (150). As a result one can safely suggest that the transition state of the highly endothermic aromatic Cope has a strong resemblance to the product. This means that a much greater loss of the aromatic resonance energy is apparent at the transition state in this case than is true for the aromatic Claisen. In one sense this really attributes the basis for the differential energy cost between Cope and Claisen rearrangements noted above to the difference between the pi-bond strengths for C-C and C-O pi bonds. It may be noted from the enthalpy diagrams for the four reactions that reversal of the acyclic Claisen rearrangement must have a $\Delta H^{\ddagger}$ very similar to that of the aromatic Cope. The retro-Claisen in acyclic cases has rarely been observed but is known for cis-1-vinylcyclopropane-carboxaldehyde (159, 160).

CONCLUSIONS

The $\triangle H^{\ddagger}$ and $\triangle S^{\ddagger}$ for the aromatic Cope rearrangement of cis-1-(m-hydroxyphenyl)-2-vinylcyclopropane have been shown to be 26.7 ± 4.0 kcal/mole and -17.5 ± 9.8 e.u. respectively. The hydrogen migration step is rate determining in solutions of low acidity, but added acid (phenol) increases the rate of that step and at moderate acidities the Cope rearrangement step become rate determining. When cis-1-(m-methoxyphenyl)-2-vinylcyclopropane is the substrate no rearrangement is observed until an acid catalyst is added. Isolation of the single product 6, 9-dihydro-5H-benzocyclohepten-1-ol from cis-1-(m-hydroxyphenyl)-2-vinylcyclopropane is not a general result with m-substituted molecules of this type since cis-1-(m-methoxyphenyl)-2-vinylcyclopropane gives both 6, 9-dihydro-5H-benzocyclohepten-1-ol from cis-1-(m-hydroxyphenyl)-2-vinylcyclopropane is not a general result with m-substituted molecules of this type since cis-1-(m-methoxyphenyl)-2-vinylcyclopropane gives both 6, 9-dihydro-5H-benzocycloheptenyl methyl ether and 4, 7-dihydro-3H-benzocycloheptenyl methyl ether.

From our data we conclude that the aromatic Cope rearrangement of 4-phenyl-1-butene must have a $\triangle H^{\ddagger} \geq 43$ kcal/mole. The cost of conversion of a double bond to a benzene ring must be ca. 10-12 kcal/mole. This result is attributed to the highly endothermic

nature of the rearrangement and suggests that the high endothermicity must be reduced in some way before the aromatic-Cope rearrangement in 4-phenyl-1-butene systems will be obtained.

EXPERIMENTAL

General Laboratory Procedures and Conditions

Nuclear magnetic resonance (NMR) spectra were obtained on Varian EM-360 (60 MHz) and Varian HA-100 (100 MHz) spectrometers. Unless otherwise specified, tetramethylsilane was used as an internal reference, and the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet. Infrared (IR) spectra were obtained on Beckman IR-8 and Perkin-Elmer 727B infrared spectrophotometers, and polystyrene was used as a standard. Low resolution mass spectra were obtained from an Atlas CH7 instrument using a 70 eV excitation potential.

Glpc analyses were performed on either a Varian A 90-P3 with thermal conductivity detector, a Varian Aerograph Autoprep A-700 with thermal conductivity detector or an Aerograph 200 with flame ionization detector. The columns used will be referred to by the letter designations as defined below:

Column A	6' x 0.25" 20% SE-30 on Chromosorb W, acid-washed
Column B	100' x 0.01" 2147 MBMA capillary column
Column C	1' x 0.25" 9% SE-30 on Chromosorb W, acid-washed

Column D 8' x 0.25'' 3% XF-1150 on Chromosorb W, acid-washed

Column E 4' x 0.25'' 3% SF-96 on Chromosorb W, acid-washed

All analyses were performed at a detector temperature an injector temperature of ca. 200°. The integration of peak areas was determined by weighing the traces of the peaks on a Mettler balance (±0.0001 g), except for the kinetic study where the peaks were analyzed on a Hewlett-Packard model 3373B digital integrator.

Synthesis of cis-1-(m-hydroxyphenyl)-2-vinylcyclopropane (21a)

cis-1-(m-Methoxyphenyl)-2-vinylcyclopropane (181a)

m-Methoxyphenyldiazomethane (180) was prepared by the method of Closs and Moss (108). To 15.2 g (0.11 mol) of m-anisaldehyde dissolved in 50 ml of dry ether was added 5 ml (approx. 0.16 mol) of anhydrous (95%+) hydrazine, keeping the temperature below 10°. The reaction mixture was stirred for 2 hrs. at 10°, then allowed to stand at room temperature for 6 hrs. The ethereal phase was separated and was washed with water, then dried (Na_2SO_4). The dried solution was mixed with 8.0 g (0.07 mol) of anhydrous sodium sulfate and 24.0 g (0.11 mol) of mercuric oxide (yellow) and 1-2 ml of approximately 3 M (0.1 g-3 ml) methanolic potassium hydroxide solution. The reaction mixture was stirred for 2 hrs. below 10°. The cold solution (10°) was

filtered and dried (Na_2SO_4).

The m-methoxydiazomethane (180) was not isolated but was treated directly with 1, 3-butadiene using the method of Goh, Closs and Closs (109). Zinc iodide (12.0 g, 37.6 mmol) was dissolved in 100 ml of dry ether. In a 3-necked flask fitted with a dry ice condenser, an addition funnel, and approximately 50 ml (0.57 mol) of 1, 3-butadiene was condensed under nitrogen. The 1, 3-butadiene was allowed to warm up to 10° and 10 ml of the zinc iodide solution was added. The filtered solution of 180 was added dropwise so that the red color disappeared upon contact with the 1, 3-butadiene solution. When all the m-methoxyphenyldiazomethane had been added the solution was allowed to warm to room temperature. The ether and excess butadiene were evaporated and the residue was extracted twice with pentane. The pentane solution was washed with water and the pentane evaporated yielding 6.15 g (32% based on m-anisaldehyde) of a mixture containing cis- and trans-1-(m-methoxyphenyl)-2-vinylcyclopropanes (181a and 181b). Glpc analysis on column A (temp. = 1.35°, flow = 60 ml/min.) showed that the material consisted of 98% of the isomeric cyclopropanes 181a and 181b. NMR analysis of a glpc purified sample of the major component showed 85% 181a and 15% 181b: ir (CCl_4) cm^{-1} 3080, 3030 (vinyl and cyclopropyl C-H), 2995 (aromatic C-H), 1635 (vinyl), 1610, 1600, 1585, 1490 (aromatic), 1260 (aromatic C=C-O-C),

1040, 1052 (=C-O-C and cyclopropyl C-C), 985, 895 (vinyl C=C); nmr (CCl_4) δ 0.81-1.32 (m, 2.4H, gem-cyclopropyl H), 1.47-1.91 (m, 1.PH, allyl H of 181a and 181b), 2.10-2.42 (m, 0.90H, benzyl H of 181a and 181b), 3.75 (s, 3.1H, CH_3-O of both isomers), 4.70-5.22 (m, 2.6H, vinyl H's of 181a and 181b), 5.17-5.81 (m, 0.20H, vinyl H of 181b), 6.50-6.72 (m, 3.OH, phenyl), 6.91-7.20 (m, 1.1H, phenyl proton meta to -OCH_3) [Lit. (17)]

cis-1-(m-Hydroxyphenyl)-2-vinylcyclopropane (21a)

The method of Feutrill and Mirrington (110) was employed in the demethylation of a mixture of cis- and trans-1-(m-methoxyphenyl)-2 vinylcyclopropanes (21a and 21b). Sodium hydride (0.24 g, 5.6 mmol of a 56% oil dispersion) was placed in a 50 ml 3 necked round-bottomed flask followed by 10 ml of dry (CaH_2) N, N-dimethylformamide. Ethanethiol (0.50 ml, 6.8 mmol) dissolved in 10 ml of DMF was introduced into the sodium hydride solution. The mixture was stirred for 0.25 hr. at room temperature then 500 mg (2.9 mmol) of a mixture of 181a and 181b was introduced via syringe. The mixture was allowed to stand at 100° for 30 hours under a nitrogen atmosphere.

The mixture was cooled in an ice bath, acidified (3N HCl) and extracted with ether. The ether layer was washed with water and extracted with a 5% sodium hydroxide solution. The alkaline extract was

reacidified (3N HCl) and extracted with ether. This ethereal layer was washed with water, dried over anhydrous magnesium sulfate and the ether removed yielding 415 mg (90%) of a tan oil. Glpc analysis on Column A (temp = 160°, flow-60 ml/min.) indicated 16% of unreacted starting materials 181a and 181b and 84% of the 1-(m-hydroxyphenyl)-2-vinyl-cyclopropanes in the ratio of 78% 21a to 22% of 21b:[1] ir (CCl_4) cm^{-1} 3600 (sharp) and 3200-3500 broad (phenolic O-H), 3080 (vinyl C-H), 3040 (cyclopropyl C-H), 3000 (aromatic C-H), 1640 vinyl C⋯⋯), 1610, 1590, 1500 (aromatic C⋯C), 1185 (phenolic O-H), 1000, 910 (vinyl C-H), 890 (meta-substituted Ph); nmr (CCl_4) δ 0.80-1.40 (m, 2.3H, gem-cyclopropyl H), 1.62-2.01 (m, 1.5H, benzyl proton of 21b and allyl protons of both 21a and 21b), 2.13-2.57 (m, 0.78H, benzyl proton of 21a), 4.81-5.22 (m, 3.6H, vinyl H of 21a and -OH of both isomers 21a and 21b), 5.41-5.81 (m, 0.22H, vinyl H of 21b), 6.48-6.91 (m, 2.9H, Ph protons ortho- and para- to -OH), 7.02-7.23 (m, 1.0H, Ph proton meta- to -OH) [lit (17)].

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[1] This method is analogous to the one employed by Lin (15b) and based on the fact that the multiplet at 1.62 (A) corresponds to the allyl proton of 21a and both allyl and benzyl protons of 21b, whereas the multiplet at 2.13 (B) corresponds to the benzyl proton of 21a only. Thus % 21a $= \frac{B}{\frac{A-B}{2}+B} \times 100$, where A and B stand for the integration values for the respective peaks.

Pyrolytic Studies of 21a

General Conditions

Unless specified otherwise, the reactions were conducted in sealed ampoules. These ampoules were cleaned by soaking overnight in concentrated ammonium hydroxide, rinsing thoroughly with carbon dioxide-free distilled water and then drying overnight in an oven.

The samples were dissolved in anhydrous ethanol; transferred into the ampoules and degassed by freeze-thaw cycles under pre-purified nitrogen. The samples were sealed under vacuum and placed in a constant temperature bath. The product was analyzed by glpc (column A, temp 160°, flow = 60 ml/min or column B, temp = 165°, flow = 20 ml/min) using the average of three injection values.

Pyrolysis of 21a at 140°

The procedure of Lin and Marvell was employed (17). Approximately 75.0 mg (0.40 mmol) of a mixture of 21a and 21b (78% 21a to 22% 21b) was placed in a glass ampoule with 10 ml of ethanol. The ampoule was degassed, sealed under vacuum and heated at 140° for 3 hrs. in a constant temperature bath. The ethanol was removed yielding 75 mg (100%) of material. The product was analyzed by glpc on column A (temp = 160°, flow = 60 ml/min.) and showed three

peaks; (% composition, retention time), 27%, 6.6 min; 27%, 8.2 min; 46%, 8.7 min. The first peak was identified as 21b through comparison of nmr shift values as given previously. The second peak was identified as 6,9-dihydro-5H-benzocyclohepten-1-ol (22): mp 88-90° (thin needles) [lit. 17 mp 87-90° (thin needles)]; nmr (CCl_4) δ 2.22-2.61 (m, 2.0H, $ArCH_2C\underline{H}_2CH=$), 3.01 (5, 1.9H, J=6Hz, $Ar-C\underline{H}_2CH_2CH=C$), 3.41-3.72 (m, 1.7H, $Ar-C\underline{H}_2-CH=C$), 4.75 (s, 1.1H, -OH), 5.41-5.87 (m, 1.9H, $-CH_2-C\underline{H}=C\underline{H}-CH_2-$), 6.51-7.13 (m, 3.2H, H's on Ph).[2]

The third peak was identified as m-hydroxyphenyl-1,3-pentadiene (23). Since the retention times for 22 and 23 were very close, it was very difficult to obtain a pure sample of 23 by preparative glpc. The data given here are therefore of a mixture which was shown to contain 63% of 23 and 37% of 22; nmr (CCl_4) δ 1.81 (d, 3.0H, J=6Hz, $=CH\ C\underline{H}_3$ of 23, 2.25-2.45 (m, 1.4H, $-CH_2-$ of 22), 2.97 (t, 1.1H, $-CH_2-$ of 22), 3.43-3.53 (m, 1.2H, $-CH_2-$ of 22), 4.95 (br s, 1.8H, -OH of both 22 and 23), 5.50-7.28 (m, 10.7H, -CH=CH and H's on Ph of both 22 and 23) [lit (17)].

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[2] For decoupling results and peak assignments see ref. 15b.

Pyrolysis of 181a at 133.9°

A mixture consisting of 78% 181a and 22% 181b (1.0 g, 5.7 mmol) was placed in a 25 ml round-bottomed flask. To the mixture were added 0.197 g (2.09 mmol) of phenol and 25 ml of dry ethanol. The reaction mixture was placed into a heavy walled Pyrex ampoule, degassed and sealed under vacuum as described earlier. The ampoule was placed into a constant temperature bath at 133.9° for 48 hrs., cooled and the ethanol removed by rotary evaporation yielding 1.20 g (100%) of a brown oil. Glpc analysis on column E (temp = 135°, flow = 20 ml/min) showed four peaks excluding the phenol peaks: (% composition, retention time) 35.2%, 5.0 min; 27.9%, 6.7 min; 18.7%, 9.5 min; 18.2%, 12.0 min. The first peak was identified as 1-ethoxy-1-(m-methoxyphenyl)-3-pentene (188): ir(neat) cm^{-1} 3030, 2995 (aromatic and olefinic C-H), 2950, 2930, 2865 (aliphatic C-H), 1600, 1590, 1485, 1465 (aromatic C⋯⋯C), 1265 (aromatic ether), 1105 (aliphatic ether, 1085 (meta-substituted Ph), 870 (trans olefin), 790, 700 (meta-substituted Ph); nmr (CCl_4) δ 1.15 (t 3.1H, J=7Hz, $-CH_2-CH_3$), 1.63 (d, 2.9H, J=4Hz, $=CHCH_3$), 2.26 (m, 1.9H, $-CH_2-CH=$), 3.31 (dxq, 2.1H, J=2.5, 7Hz, $-OCH_2CH_3$), 3.78 (s, 3.OH, $-OCH_3$), 4.09 (dx5, 1.1H, J=2.5, 7Hz, Ph-CH), 5.38 (m, 1.9H, $-CH=CH-$), 6.66-7.24 (m, 4.OH, H's on Ph).

The second peak was identified as 6, 9-dihydro-5H-benzocycloheptenyl methyl ether (186): ir ($CHCL_3$) cm^{-1} 3050, 3020, (aromatic and olefinic C-H), 2940, 2875, 2850 (aliphatic C-H), 1600, 1590, 1475, 1460 (olefinic and aromatic C⋯⋯C), 1260 (aromatic ether), 790 (1, 2, 3-trisubstituted Ph), 660 (cis-olefin); nmr (CCl_4) δ 2.18-2.41 (m, 2.1H, Ph-CH_2-CH_2-), 2.95 (t, 1.9H, J=65Hz, Ph-CH_2-CH_2-), 3.40-3.52 (m, 2.0H, Ph-CH_2), 3.77 (s, 3.1H, -OCH_3), 5.27-5.80 (m, 2.2H, -CH=CH-), 6.54-6.74 (m, 2.1H, H's ortho- and para- to -OCH_3), 6.96 (t, 1.1H, J=7.5 Hz, H meta- to -OCH_3).

The third peak was identified as 4, 7-dihydro-3H-benzocycloheptenyl methyl ether (187): ir ($CHCl_3$) cm^{-1} 3050, 3020 (aromatic C-H), 2960, 2930, 2900, 2985 (aliphatic C-H), 1600, 1580, 1465, 1455 (aromatic and olefinic C⋯⋯C), 1250 (aromatic ether), 830 (1, 2, 4-trisubstituted Ph), 660 (cis-olefin); nmr (CCl_4) δ 2.20 (m, 2.0H, Ph-$CH_2$$CH_2$CH=), 2.89 (t, 2.0H, J=6.5 Hz, Ph-$CH_2$$CH_2$-), 3.26-3.38 (m, 2.0H, Ph-CH_2-CH=C), 3.73 (S, 3.1H, -OCH_3), 5.30-5.80 (m, 2.0H, -CH_2-CH=CH-CH_2), 6.46 (d, 1.1H, J=3Hz, H ortho- to -OCH_3), 6.58 (dxd, 1.1H, J=3, 8Hz, H ortho- to -OCH_3), 6.84 (d, 1.2H, J=8Hz, H meta- to -OCH_3).

The fourth peak was identified as 1-(m-methoxyphenyl)-1, 3-pentadiene (189): ir ($CHCl_3$) cm^{-1} 3075, 3020 (aromatic and olefinic

C-H), 2955, 2925, 2870 (aliphatic C-H), 1600, 1580, (aromatic and olefinic C$\overset{\cdot\cdot\cdot}{\text{---}}$C), 1265 (aromatic ether); nmr (CCl_4) δ 1.82 (d, 3.0H, J=6.5Hz, =CHC$\underline{H}_3$), 3.77 (s, 3.0H, -OCH_3), 5.58-6.94 (m, 7.1H, H's <u>ortho</u>- and <u>para</u>- on Ph to -OCH_3 and olefinic protons), 7.10 (t, 1.1H, J=8Hz, H <u>meta</u>- to -OCH_3).

<u>A Kinetic Study of the Aromatic Cope Rearrangement of 21a</u>

<u>Materials</u>

The sample obtained was purified by preparative glpc on column C (temp=160°, flow = 60 ml/min). The first portion of two overlapping peaks (retention time = 6.5 min) contained both isomers <u>21a</u> and <u>21b</u> in the ration of 89% <u>21a</u>: 11% <u>21b</u> as determined by glpc analysis on column B (temp = 165°, flow = 20 ml/min).

<u>n</u>-Tetradecane obtained from Analab was used as an internal standard without further purification. Ethanol (absolute) was distilled from magnesium and phthalic acid in a pre-purified nitrogen atmosphere just prior to use.

Phenol was purified by preparative glpc on column C (temp = 160°, flow = 60 ml/min) prior to use.

Preparation of Samples

Samples for each kinetic run were taken from the same stock solution. These stock solutions were prepared by weighing under pre-purified nitrogen the mixture of 21a and 21b, phenol and the n-tetra-decane into a small sealed vial. Ethanol was then added via a syringe. The quantities are listed in Table 17 below:

Table 17. Concentrations of 21, Phenol and n-Tetradecane in the Kinetic Samples.

Temperature of Kinetic Run	Quantities Used				Concentrations (M)	
	21a/21b	Phenol	$n\text{-}C_{14}H_{30}$	Ethanol	21a/21b	Phenol
121.3°C	18.8 mg	13.7 mg	10.5 mg	1.80 ml	6.52×10^{-2} M	8.12×10^{-2}
127.1	5.6	-0-	4 5	50.0	7.00×10^{-4}	-0-
127.1	21.7	3.98	8.5	1.90	7.13×10^{-2}	2.23×10^{-2}
127.1	21.7	101.2	8.5	1.90	7.13×10^{-2}	5.67×10^{-1}
127.1	21.7	430.1	8.5	1.90	7.13×10^{-2}	2.41×10^{0}
133.9	18.8	13.7	10.5	1.80	6.52×10^{-2}	8.12×10^{-2}

For the actual kinetic samples, capillary tubes (1.7x100 mm) were used. These capillary tubes were soaked overnight in concentrated ammonium hydroxide, rinsed twenty times with freshly boiled distilled water in a large test tube and then oven dried. Seventy-microliter samples were sealed in capillary tubes after degassing.

Apparatus

The constant temperature bath used consisted of a glass bath surrounded by an insulated aluminum housing. Silicon oil was used as the bath fluid and was stirred with a Lightning Model L Mixer.

The temperature was controlled using a Model 24 Precision Temperature Controller designed by Bayley Instrument Company. The controller was able to m aintain the temperature within ±0. 05° of a given temperature.

An Omega platinum resistance temperature probe coupled with a Digitec digital display platinum resistance thermometer was used to monitor the temperature through a kinetic run. At no time did the temperature vary beyond the ±0. 05° limits during a kinetic run.

Reaction Conditions and Analysis Procedure

Kinetic runs were performed at three different temperatures: 121. 3°, 127. 1°, and 133. 9°. The samples were completely submerged in a constant temperature oil bath (±0. 05°). At various time intervals a sample was removed, quenched in an ice bath and analyzed by glpc. Samples not analyzed immediately were stored in the refrigerator. Column B (temp = 165°, flow = 20 ml/min) was used in an Aerograph 204 flame ionization gas chromatograph. Each sample was analyzed three times and the integration of the peaks corresponding to the

n-tetradecane, 21a, 21b, 22 and 23 were determined and recorded by an electronic, digital integrator. The approximate retention times are shown in the table below:

Table 18. Retention Times for the Possible Rearrangement Products of 21a.

Compound	Retention Time (min)
n-tetradecane	9.2
21a	10.3
21b	11.7
22	16.0
23	17.3

Method of Calculation

The observed rate constant, k_o, is the slope from the least squares fit of the rate data treated according to the simple first order equation (Eqn 1):

$$\ln [A_o/A_n] = k_o t_n \qquad \text{(Eqn 1)}$$

where A_o and A_n are ratios of the areas for 21a and n-tetradecane. Figures 3-5 show graphically the plot of $\ln A_o/A_n$ versus t. The points shown are average values from three injections of each sample. Error analysis was determined by standard statistical analysis techniques.

The graph of ln k_o versus 1/T is given in Figure 4. The activation parameters were determined from the best straight line using the least squares method. The activation energy was calculated from the slope of the line using the following equations:

$$E_a = -(\text{slope})(R) \qquad \text{(Eqn 2)}$$

$$\triangle H^{\ddagger} = E_a - RT \qquad \text{(Eqn 3)}$$

The y-intercept of the line is calculated and from this value the Arrhenius frequency factor and the entropy of activation can be calculated.

$$y - \text{intercept} = \log A \qquad \text{(Eqn 4)}$$

$$A = e^{kt_e} \frac{\triangle S^{\ddagger}/R}{h} \qquad \text{(Eqn 5)}$$

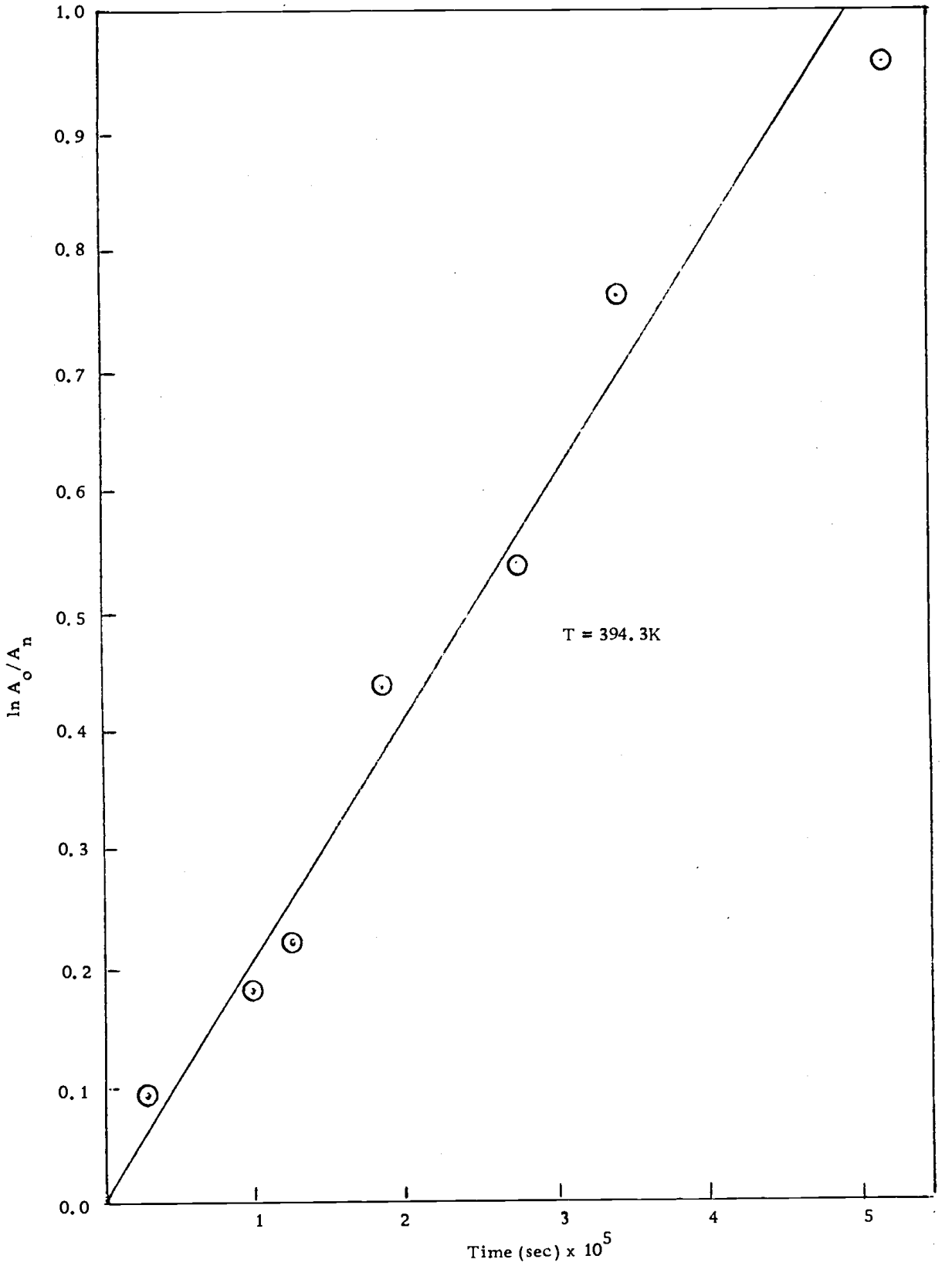

Figure 3. Plot of logarithm A_o/A_n vs time (sec) for the Aromatic Cope Rearrangement of 21a

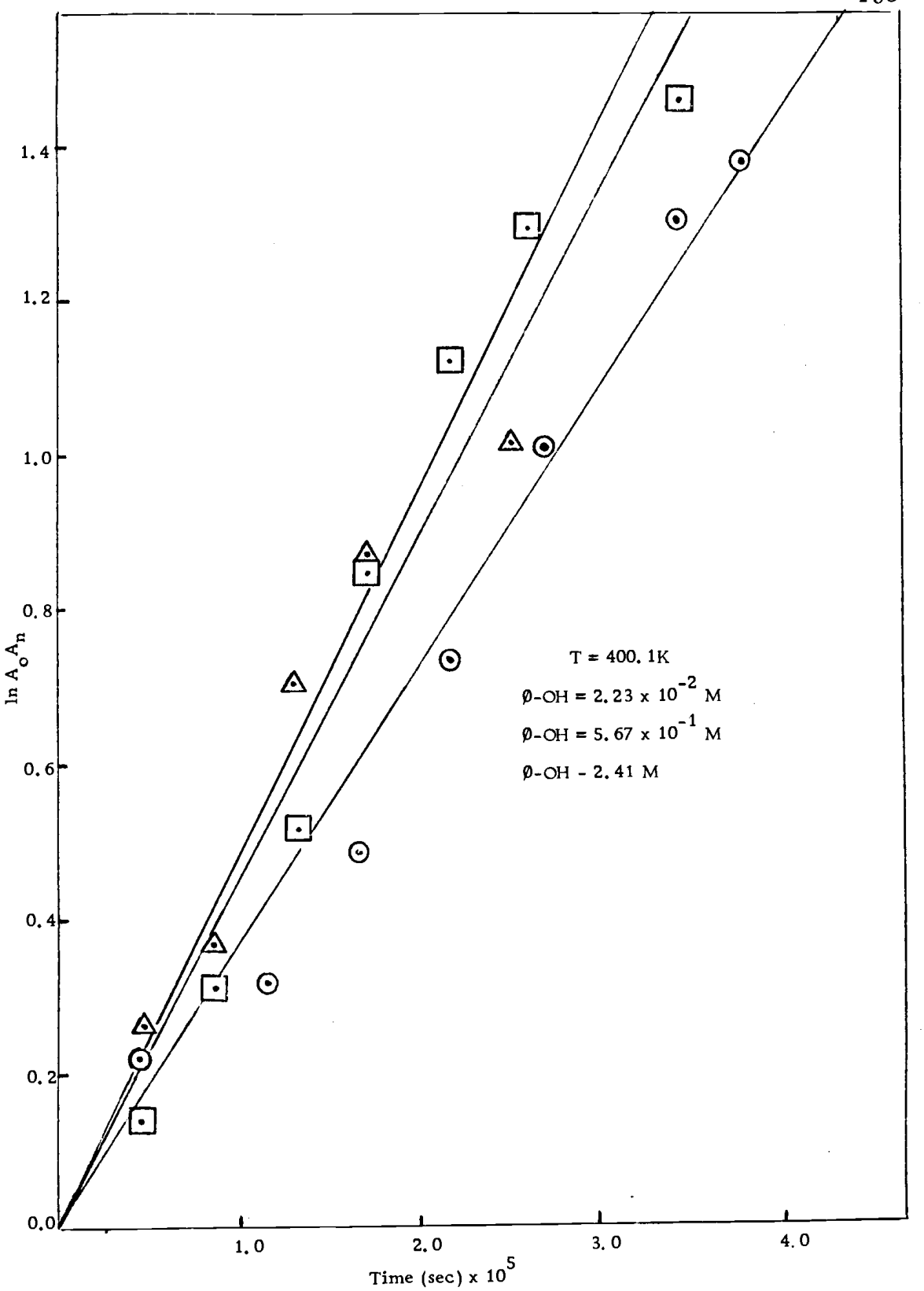

Figure 4. Plot of logarithm A_o/A_n vs time (sec) for the Aromatic Cope Rearrangement of 21a

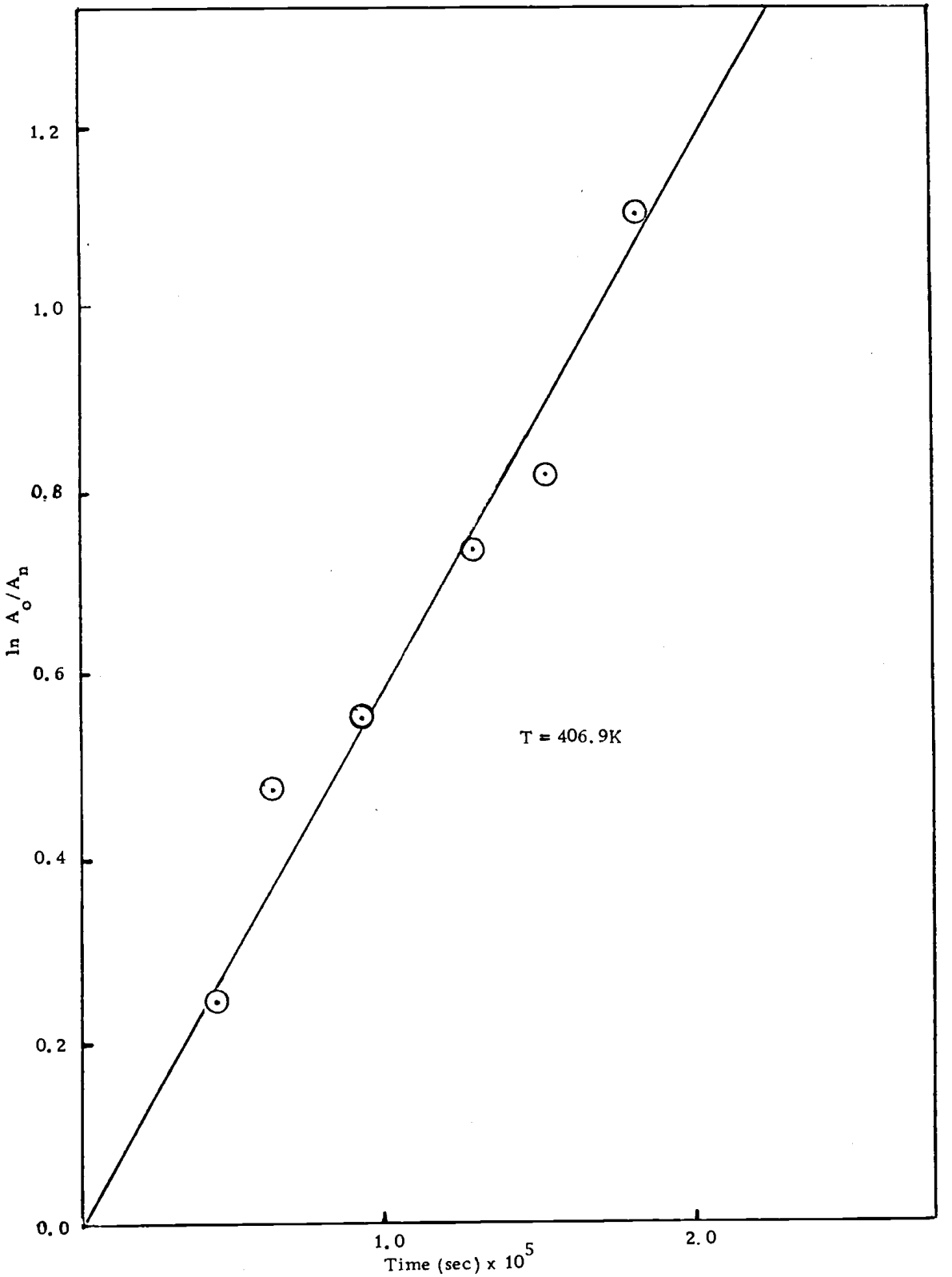

Figure 5. Plot of logarithm A_oA_n vs time (sec) for the Aromatic Cope Rearrangement of 21a

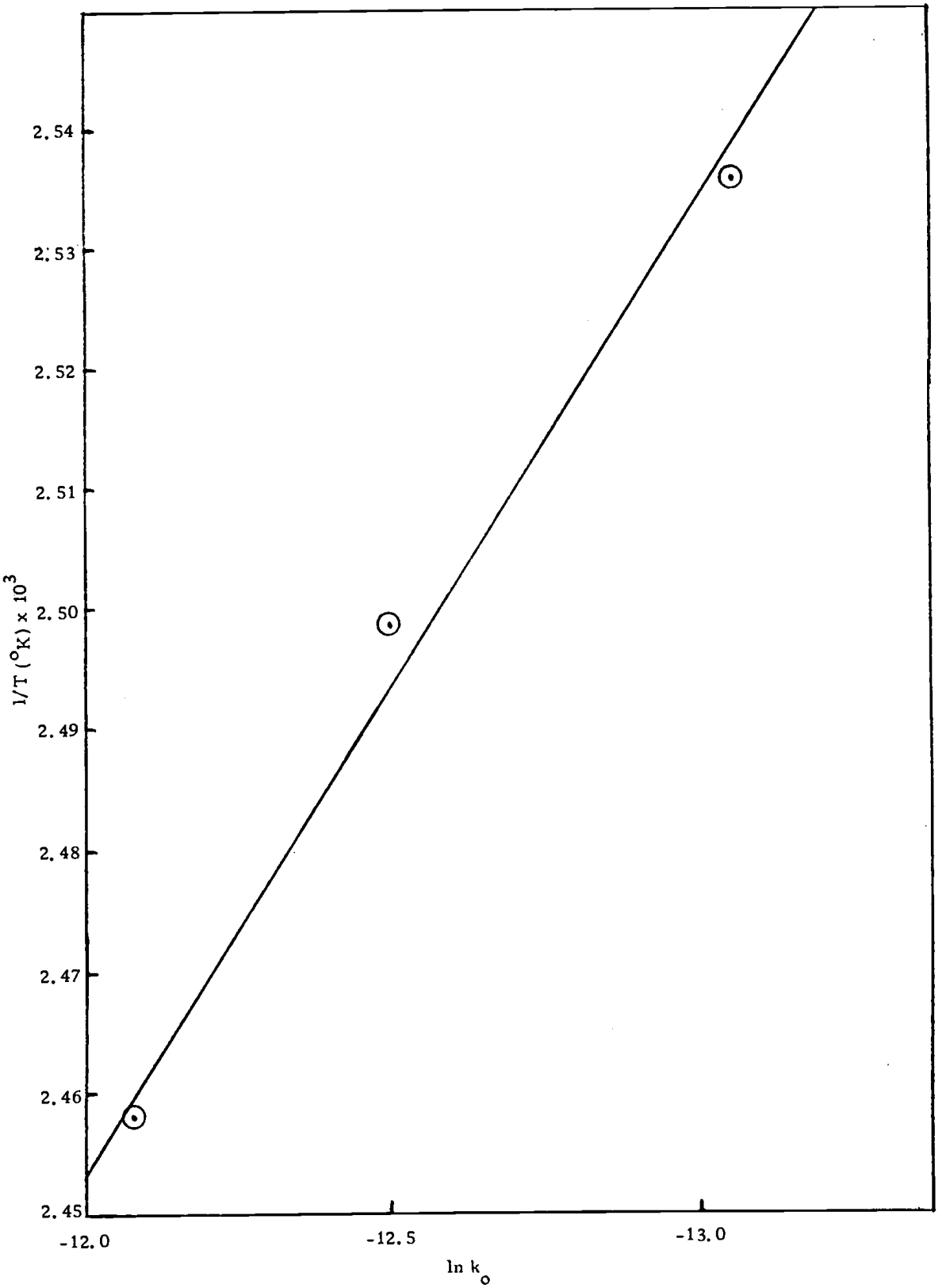

Figure 6. Plot 1/T vs $\ln k_o$ for the Aromatic Cope Rearrangement of 21a

Preparation and Pyrolysis of Diethyl phenylallylmalonate (193)

Diethyl phenylmalonate (192)

The method of Wallingford, Homeyer and Jones was used (130). Diethyl carbonate (10 ml, 117 mmol) and 2.0 (12.2 mmol) ethyl phenylacetate (191) were placed in a 50 ml round-bottomed flask fitted with an addition funnel and a fractionating column. The mixture was heated to reflux and a solution of sodium ethoxide in ethanol 0.30 g (13 mmol) of sodium in 6.7 ml of dry ethanol was added slowly while ethanol was removed by fractional distillation. The remaining material was neutralized with 3N HCl at 0° and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$) and the ether removed leaving 2.60 g (90%) of 192: ir (neat) cm^{-1} 3075, 3040, 2995 (aromatic C-H), 1735 (ester C=O), 1605, 1590, (aromatic C⋯C), 1275, 1225 (C(=O)O stretch), 795, 700 (mono-substituted Ph); nmr (CCl_4) δ 1.19 (t, 6.0H, J=7Hz, $-CH_3$), 4.13 (q, 4.1H, J=7Hz, $-C\underline{H}_2-CH_3$), 4.48 (s, 0.9H, $C\underline{H}(CO_2Et)_2$), 7.20-7.36 (m, 5.0H, H's on Ph); mass spectrum, m/z (rel intensity) 236 (59), 164 (99), 163 (100), 136 (71), 135 (68), 119 (30), 117 (18), 107 (57), 91 (67).

Diethyl phenylallylmalonate (193)

Method 1. The method of Cope, Field, MacDowell and Wright was employed (9). In a flask flushed with nitrogen were placed 0.48 g (12 mmol) of sodamide and 25 ml of ether. After the mixture had been refluxed for 3 hrs. a solution containing 2.60 g (11.0 mmol) of diethyl phenylmalonate (193) in 25 ml of ether was added. This solution was added. This solution was refluxed for an additional 2 hrs.. A solution of 1.45 g (12 mmol) of allylbromide in 25 ml of toluene was added to the reaction mixture and the solution was refluxed overnight. The reaction mixture was mixed with 50 ml of water and the layers were separated. The aqueous layer was extracted with ether and the combined ether portions were dried ($MgSO_4$). The ether was removed leaving 1.90 g of a brown oil. Preparative glpc on column C (temp = 170, flow = 60 ml/min) followed by spectral analysis showed the material to contain 55% of unreacted starting material 192 and 45% (28% yield) of 193; ir (neat) cm^{-1} 3075, 2995 (aromatic C-H), 1735 (C=O of ester), 1600, (aromatic), 1295, 1235 (C(=O)O stretch), 995, 907 (vinyl C-H), 795, 700 (mono-substituted Ph); nmr (CCl_4) δ 1.20 (t, 6.2H, J=7Hz, $-CH_2CH_3$), 2.98 (dxd, 1.9H, J=0.5, 8Hz, $C-C\underline{H}_2CH=$), 4.14 (q, 3.96H, 7=7Hz, $-O-CH_2$), 4.90-5.08 (m, 2.1H, $CH=C\underline{H}_2$), 5.52-5.93 (m, 0.9H, $C\underline{H}=CH_2$), 7.18-7.43 (m, 4.8H, H's on Ph); mass spectrum, m/z (rel. intensity 276 2), 235(5),

203 (19), 129 (100), 119 (73), 117 (81), 29 (66).

Method 2 In a 100 ml round-bottomed flask were placed 0.24 g (5.0 mmol) of sodium hydride (50% oil dispersion), 10 ml of dry ether and a solution containing 1.05 g (4.4 mmol) of 192 in 20 ml of dry ether. The solution was refluxed for 1 hr., a solution of 0.94 g (7.8 mmol) of allylbromide in 15 ml of dry ether was added, and the reaction mixture was refluxed for 48 hrs.. The mixture was cooled to 0°, acidified with 3N HCl and the aqueous layer extracted with ether. The combined ethereal solutions were washed with water, dried ($MgSO_4$) and the ether removed leaving 1.31 g of a dak oil. Glpc analysis on column C (temp = 170°, flow = 60 ml/min) showed the oil to consist of 55% of 192 and 45% (49% yield) of the desired product 193) (coinjection of authentic samples of 192 and 193).

Method 3 A take off on the methods of Wishlicensus and Goldstein (141) and Pickard and Yates (142) was utilized. A freshly prepared solution of sodium ethoxide (2.00 g of sodium in 200 ml ethanol) was cooled to 0°, a solution of 20.0 g (84.7 mmol) of 192 in ethanol was added and the reaction mixture was stirred for 20 min. Allylbromide (13.0 ml, 100 mmol) was added and the reaction mixture was refluxed for 30 min. The cooled solution was treated with water and the resultant solution was extracted with ether. The combined ether extracts were washed with water, dried ($MgSO_4$) and the ether was

removed leaving 23.0 g of residue. The residue was fractionally distilled yielding 22.1 g (95%) of 193, b.p. 112-113°/0.65 mm [lit. (142) 117-118°/1.0 mm].

Pyrolysis of 193 at 350°

In an ampoule (130 x 15 mm heavy walled pyrex) were placed 0.50 g (1.8 mmol) of 193 and 6.1 mg (0.091 mmol) of sodium ethoxide. The sample was degassed as described earlier in the pyrolysis of 21a and sealed under vacuum. The ampoule was heated to 350° for 6 hrs, allowed to cool and the contents were transferred into a separatory funnel. The reaction mixture was acidified (3N HCl), diluted with water and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$) and the ether removed by rotary evaporation yielding 0.49 g (98%) of a brown oil. Glpc analysis on column C (temp = 170, flow = 60 ml/min) showed the material to contain two major components: 90% of 193 and 10% of ethyl-2-phenyl-4-pentenoate (195): ir (neat) cm^{-1} 3050, 3020, 2995 (aromatic and vinyl C-H), 1735 (C=O of ester), 1605, (aromatic C⋯C), 1200, 1175 (ester C(=O)O stretch), 1000, 905 (vinylic C-H), 800, 705 (mono-substituted Ph); nmr (CCl_4) δ 1.15 (t, 3.1H, J=7Hz, $-CH_2\underline{CH_3}$) 2.34-2.92 (m, 1.8H, CH-$C\underline{H_2}$-CH=), 3.52 (dxd, 1.1H, J=7, 9Hz, Ph-$C\underline{H_2}$), 5.50-5.90 (m, 1.2H, -$C\underline{H}$=CH_2), 7.22 (s, 4.9H, H's on Ph); mass spectrum, m/z (rel. intensity) 203(1),

131 (51), 129 (27), 91 (97), 77 (44), 29 (100), 27 (57).

1-Phenyl-3-buten-1-ol (196)

In a 250 ml round-bottomed flask were placed 5.59 g (0.23 mol) of magnesium turnings and 50 ml of dry ether. The mixture was coole cooled to 0° and a solution containing 27.96 g (0.23 mol) of allyl bromide in 100 ml of dry ether was added at a rate which permits maintenance of the temperature below 5°. After the addition had been completed, the reaction mixture was stirred for 1 hr. at 0°.

A solution of 24.0 g (0.23 mol) of benzaldehyde in 75 ml of dry ether was then added. The magnesium salts were hydrolyzed by the addition of 25 ml of a 3N hydrochloric acid. The aqueous layer was separated and washed with two 50 ml portions of ether. The ethereal solutions were dried ($MgSO_4$) and the ether was removed by evaporation. The crude product was distilled to give 29.30 g (85%) of the alcohol 196: b.p. 73-74°/1.9 mm; ir (CCl_4) cm^{-1} 3600 (sharp) (alcoholic -OH), 3075, 3050, 3015 (vinyl C-H and Aromatic C-H), 1610, 1600 (aromatic C⋯C and vinyl C⋯C), 1005, 920 (vinyl C-H), 690 (mono-substituted Ph); nmr (CCl_4) δ 2.32 (t, 1.9H, J=7Hz, -CHOH $-C\underline{H}_2-CH=$), 3.83 (br s, 1.2H, -O$\underline{H}$), 4.48 (t, 1.1H, J=7H_3, Ph-C$\underline{H}$OH $-CH_2-$), 4.93 (dxd, 1.0H, J=2, 12H_3, C=C $\frac{H}{H}$), 4.97 (dxd, 1.0H, J=2, 15Hz, $C\diagup C=C\diagdown\frac{H}{\underline{H}}$), 5.66 (dxdxt, 1.0H, J=2, 12, 15 Hz, -CHOH-CH=CH_2),

7.16 (s, 5.4H, Ph protons); mass spectrum, m/z (rel. intensity) 148 (2), 130 (1), 108 (8), 107 (100), 106 (2), 79 (94), 78 (12), 77 (55), 51 (18.9), 39 (17).

Thermolysis of the Potassium Alkoxide of 196

A solution consisting of 2.0 g (13.5 mmol) of 1-phenyl-3-buten-1-ol, 2.41 g (15.0 mmol) of potassium hydride (97% oil dispersion) and 100 ml of HMPA was prepared as described earlier. The mixture was heated to 65% for 12 hrs. The cold acidified (5% HCl) mixture was extracted with ether. The ether extracts were washed several times with water, dried ($MgSO_4$) and the ether removed by evaporation yielding 1.57 g (79%) of crude product. The product was analyzed by glpc on column D (temp = 105°, flow = 60 ml/min) and contained two major components: (T composition, retention time), 61%, 6 min; 39%, 8 min. The second peak was identified as unreacted 1-phenyl-3-buten-1-ol 196 through coinjection of a pure sample of (196). The first peak was purified by preparative glpc on column D (temp = 105°, flow = 60 ml/min) and shown to be butyrophenone (199): ir (neat) cm^{-1} 3075, 3050, 3025 (aromatic C-H), 1685 (ketone), 1595, 1575, (aromatic C$\cdots$C), 690 (mono-substituted Ph); nmr (CCl_4) δ 0.99 (t, 2.8H, J=7Hz, $-CH_3$), 1.76 (sextet, 2.0H, J=7Hz, $-CH_2-CH_2-CH_3$), 2.88 (t, 2.0H, J=7Hz, $CO-CH_2-CH_2$), 7.35-7.49

(m, 3.0H, meta, para H's on Ph), 7.83-7.95 (m, 2.0H, ortho H's on Ph).

Addition of Methyl Iodide to the Reaction of 196→199

In a 100 ml round-bottomed flask under a nitrogen atmosphere were placed 0.54 g (3.65 mmol) of 1-phenyl-3-buten-1-ol (196), 0.77 g (4.80 mmol of potassium hydride (25% oil dispersion) and 50 ml of HMPA. The mixture was heated for 1.8 hrs. at 65°, cooled to 0° in an ice-salt bath and treated dropwise with a solution consisting of 0.517 g (3.65 mmol) of methyl iodide in 50 ml of dry ether. This mixture was acidified (3N HCl) and the total was extracted with ether. The ethereal layer was washed with water to remove all traces of HMPA and dried ($MgSO_4$). After the ether had been removed 0.50 g (93%) of crude material remained. It was analyzed by glpc on column C (temp = 140°, flow = 120 ml/min.) and was found to contain three major components: (% composition, retention time), 34.4%, 2 min; 40.9%, 4 min; 24.7%, 5.5 min. The three peaks were purified by preparative glpc on column C (temp = 140°, flow = 120 ml/min). The first peak was shown to be 1-methoxy-1-phenyl-3-butene (200): nmr (CCl_4) δ 2.13-2.69 (m, 1.95H, Ph-C<u>H</u>), 3.16 (s, 3.1H, $-OCH_3$), 4.05 (t, 1.00H, J=6.5Hz, $-C\underline{H}OCH_2$), 4.87-5.06 (2-dxd, 1.95H, J=1.5, 12Hz, J=1.5, 15.5Hz, $C=C\underline{H}_2$), 5.72 (dxdxt, 1.05H, J=7, 12, 15.5 Hz,

$-CH_2C\underline{H}=CH_2$), 7.23 (s, 4.8H, Ph protons).

The second peak was identified as 1-phenyl-2-methyl-1-butanone (201): ir (neat) cm^{-1}, 3075, 3050, 3025 (aromatic C-H), 1685 (ketone), 1600, 1580, 1470 (aromatic, C⋯C), 695 (mono-substituted Ph); nmr (CCl_4) δ 0.90 (5, 2.81H, J=7Hz, $-CH_2C\underline{H}_3$), 1.15 (d, 2.9H, J=7Hz, $-CO-CHC\underline{H}_3-CH_2-$), 1.12-1.99 (m, 2.4H, $-CHCH_3-C\underline{H}_2-CH_3$), 3.33 (sextet, 0.9H, J=7Hz, $-CO-C\underline{H}(CH_3)-CH_2-$), 7.27-7.49 (m, 3.1H, <u>meta</u>- and <u>para</u>- H's on Ph); 7.84-7.94 (m, 1.90H, <u>ortho</u>-H's on Ph).

The third peak was identified as 1-phenyl-2, 2-dimethyl-1-butenone (202): ir (neat) cm^{-1} 3075, 3045, 3020 (aromatic C-H), 1670 (Ketone), 1600, 1575 (aromatic C⋯C), 1380, 1360 (gem-dimethyl C-H), 690 (mono-substituted Ph); nmr (CCl_4) δ 0.90 (5, 3.0H, J=7.5Hz, $-CH_2-C\underline{H}_3$), 1.27 (s, 5.8H, $-CO-C(C\underline{H}_3)_2-CH_2-$), 1.80 (q, 2.1H, J=7.5Hz $-C-CH_2-CH_3-$), 7.30-7.42 (m, 3.1H, <u>meta</u>- and <u>para</u>- H's on Ph), 7.56-7.69 (m, 2.0H, <u>ortho</u>- H's on Ph).

<u>1-(α-Naphthyl)-3-buten-1-ol (203)</u>

The Grignard reaction as described earlier was used to prepare 203 starting with 11.5 g (0.737 mole) of α-naphthaldehyde. The reaction produced 14.33 g (93%) of the desired alcohol 203: ir (neat) cm^{-1} 3550 (sharp) (alcoholic O-H), 3375 (broad) (alcoholic O-H),

3000 (vinyl and aromatic C-H), 1640, 1600, 1510 (C···C aromatic and vinylic stretch), 1050 (alcoholic C-OH), 995, 920 (vinyl C-H), 780, 800 (naphthyl); nmr (CCl_4) δ 2.32-2.51 (m, 2.0 H, -CHOH-C$\underline{H}_2$CH=), 3.10 (br s, 0.99H, -O$\underline{H}$), 4.86 (dxd, 1.0H, J=1.5, 12Hz, $\overset{C}{H}$C=C$\overset{H}{\underline{H}}$), 4.96 (dxd, 1.0H, J=1.5, 16Hz, $\overset{C}{H}$C=C$\overset{H}{\underline{H}}$), 5.18 (dxd, 1.0H, J=6, 7Hz, -C$\underline{H}$OH-CH_2), 5.73 (dxdxt, 1.04, J=7, 12, 16Hz, -CH_2-C$\underline{H}$=CH_2), 7.50 (m, 7.0H, naphthyl H's); mass spectrum, m/z (rel. intensity) 198 (6), 180 (1), 158 (11), 157 (97), 156 (4), 129 (100), 128 (64), 127 (48).

Thermolysis of the Potassium Alkoxide of 203

In a round-bottomed flask under a nitrogen atmosphere were placed 1.78 g (11.1 mmol) of potassium hydride (25% oil dispersion) in 50 ml of HMPA. To this were added a solution of 2.0 g (10.1 mmol) of 1-(α-naphthyl)-3-buten-1-ol (203) in 25 ml of HMPA, dropwise, over a 35 min period. The mixture was heated to 40° for 20 hours, cooled, acidified (5% HCl), and extracted with ether. The ether extract was washed several times with water, dried ($MgSO_4$) and the ether removed by rotary evaporation yielding 1.80 g (90%) of crude product. The product was analyzed by glpc on column C (column temp = 180°, helium flow rate = 60 ml/min) and showed two major components: (% composition, retention time), 16%, 6 min; 84%,

7.3 min. The first peak was identified as unreacted 1-(α-naphthyl)-3-buten-1-ol (203) through coinjection of a pure sample of 203. The second peak was purified by preparative glpc on column C (column temp = 180°, helium flow rate = 60 ml/min) and shown to be butyronaphthone (205): ir (neat) cm^{-1} 3050 (aromatic C-H), 2950, 2900, 2850 (alkyl C-H), 1680 (ketone), 1600, 1510, 1460 (aromatic C···C), 1280, 1240, 1180 (aromatic and aliphatic ketone C-C), 800, 780 (naphthyl); nmr (CCl_4) δ 0.97 (t, 2.9H, J=7.2Hz, $-CH_2-\underline{CH_3}$), 1.76 (sextet, 2.1H, J=7.2Hz, $-CH_2-\underline{CH_2}-CH_3$), 2.87 (t, 2.0H, J=7.2Hz, $-CO-\underline{CH_2}-CH_2-$), 7.52 (m, 6.0H, naphthyl H's), 8.60 (m, 0.90H, γ -H on naphthyl ring).

2,2-Dimethyl-1-phenyl-3-buten-1-ol (206)

2,2-Dimethyl-1-phenyl-3-buten-1-ol (206) was prepared by the Grignard reaction of 5.07 g (47.8 mmole) of benzaldehyde and 3-methyl-2-butenyl magnesium chloride. The reaction produced a 4.0 g (48%) of a clear liquid, b.p. 53-54/0.1 mm. The liquid was analyzed by glpc on column C (temp = 155°, flow = 60 ml/min) and showed two major components: (% composition, retention time), 20%, 9 min; 80%, 14 min. The first peak was shown to be unreacted benzaldehyde through coinjection of an authentic sample of benzaldehyde. The second peak was purified by preparative glpc on column C

(temp = 155°, flow = 60 ml/min) and shown to be 2, 2-dimethyl-1-phenyl-3-buten-1-ol (206): ir (neat) cm^{-1} 3440 (broad, -OH), 3075, 3050, 3020 (aromatic C-H and vinyl C-H), 1600 (aromatic, C···C), 1080, 1050 (sec. -OH), 1385, 1360 (gem-dimethyl C-H), 910, 1000 (vinylic C-H), 780, 695 (mono-substituted Ph); nmr (CCl_4) δ 0.94 (s, 3.2H, $-CH_3$), 0.99 (s, 3.2H, $-CH_3$), 1.65 (br s, 0.68, -OH), 4.35 (s, 0.81H, -CHOH-), 4.98 (dxd, 0.81, J=1.5, 17 Hz, $\overset{H}{C}\!>\!C\!=\!C\!<\!\overset{H}{\underline{H}}$), 5.00 (dxd, 0.81, J=1.5, 11.5 Hz, $\overset{H}{C}\!>\!C\!=\!C\!<\!\overset{H}{H}$), 5.90 (dxd, 0.81H, J=11.5, 17Hz, $-C\underline{H}\!=\!CH_2$), 7.20 (s, 5.0H, H's on Ph); mass spectrum, m/z (rel. intensity) 108 (12.6), 107, (100), 106 (2), 79 (63), 78 (8), 77 (32).

Thermolysis of the Potassium Alkoxide of 206

In a 100 ml round-bottomed flask under a nitrogen atmosphere were placed 0.50 g (3.12 mmol) of potassium hydride (25% oil dispersion) in 25 ml of HMPA. To this was added a solution of 0.50 g (2.84 mmol) of 206 in 25 ml of HMPA, dropwise, over a 45 min. period. The reaction mixture was heated to 75° for 18 hrs., acidified with a 5% HCl solution and extracted with ether. The combined ether extracts were washed with water, dried ($MgSO_4$) and the ether was removed by rotary evaporation leaving 0.39 g (78%) of crude material. Glpc analysis on column C (temp = 145°, flow = 60 ml/min)

showed two major components: (% composition, retention time), 85%, 4 min; 15%, 5.5 min. The first peak was shown to be 4-methyl-1-phenyl-3-penten-1-ol (208): ir (neat) cm^{-1} 3375 (br, -OH), 3075, 3050, 3025 (aromatic and vinyl C-H), 1600, (aromatic C⋯C) 1080, 1050 (sec -OH), 795, 700 (mono-substituted Ph); nmr (CCl_4)δ 1.58 (s, 2.8H, $-CH_3$), 1.71 (s, 3.4H, $-CH_3$), 2.03 (br s, 1.0H, -OH), 2.37 (dxd, 1.60H, J=6.5, 7Hz, CH-C<u>H</u>$_2$-CH=), 4.57 (t, 1.0H, J=6.5 Hz, -C<u>H</u>OH-CH_2-), 5.12 (m, 0.6H, CH_2-C<u>H</u>=C), 7.24 (s, 5.0H, H's on Ph).

The second peak was unreacted 206 (comparison of spectra with an authentic sample).

1-(α-Naphthyl)-2, 2-dimethyl-3-buten-1-ol (209)

A Grignard reaction starting with 8.28 g (53.1 mmol) of α-naphthaldehyde yielded 9.10 g (76%) of a thick oil. TLC analysis on silica gel using a 50:50 mixture of diethyl ether and pet. ether (80-100°) as the eluting solvent showed two major components with R_f = 0.31 and R_f = 0.42. Column chromatography on silica gel (Activity I) using a 50:50 diethyl ether/pet. ether (80-100°) solution as the eluting solvent gave two compounds: (% composition, tlc R_f value) 27%, 0.31; 73%, 0.42. The compound with R_f = 0.31 was

shown to be 1-(α-naphthyl)-4-methyl-3-penten-1-ol (210): ir (neat) cm^{-1} 3380 (br -OH), 3055, 3050 (aromatic and vinyl C-H), 1600, (aromatic C⋯C), 1105, 1065 (α-unsaturated alcohol), 860 (tri-substituted olefin), 800, 680 (naphthyl); nmr (CCl_4) δ 1.48 (s, 3.0H, $-CH_3$), 1.65 (s, 3.0H, $-CH_3$), 2.44-2.60 (m, 2.6H, $-C\underline{H}OH-C\underline{H}_2-$), 5.14-5.28 (m, 1.8H, $-C\underline{H}OH-CH_2-C\underline{H}=$), 7.18-7.95 (m, 7.1H, H's on naphthyl).

The compound with R_f = 0.42 was shown to be 1-(α-naphthyl)-2, 2-dimethyl-3-buten-1-ol (209): ir (neat) cm^{-1} 3450 (br -OH), 3075, 3050 (aromatic and vinyl C-H), 1600, (aromatic C⋯C), 1380, 1360 (gem-dimethyl C-H), 1165, 1060 (alcohol), 990, 910 ($-CH=CH_2$), 800, 790 (naphthyl); nmr (CCl_4) δ 0.94, 0.97 (s, 6.1H, $-CH_3$'s), 2.14 (br s, 1.1H, -OH), 4.91 (dxd, 1.0H, J=1.5, 18Hz, $\overset{H}{C}C=C\underline{H}$), 4.92 (dxd, 1.0H, J=1.5, 10Hz, $\overset{H}{C}C=C\overset{H}{\underline{H}}$), 5.21 (s, 1.1H, $-C\underline{H}OH-CH_2-$), 5.87 (dxd, 1.0H, J=10, 18Hz, $C-C\underline{H}=CH_2$), 7.22-8.0H, H's on naphthyl); mass spectrum m/z (rel. intensity) 226 (1.8), 208 (0.3) 158 (14), 157 (100), 156 (23), 129 (62), 128 (32), 127 (22).

Thermolysis of the Potassium Alkoxide of 209

In a 100 ml round-bottomed flask under a nitrogen atmosphere were placed 1.32 g (8.27 mmol) of potassium hydride (25% oil dispersion) in 40 ml of HMPA. A solution of 1.70 g (7.52 mmol) of 209

in 40 ml of HMPA was added to the reaction mixture over a 45 minute period. The reaction mixture was heated to 65° for 4 hrs., cooled to 0°, acidified with a 5% HCl solution and extracted with ether. The combined ether extracts were washedwith water, dried ($MgSO_4$) and the ether removed by rotary evaporation leaving 1.68 g (99%) of a dark oil. Column chromatography on silica gel (Activity I) using a 10% solution of diethyl ether in petroleum ether (80-100°) as the eluting solvent gave two compounds A and B. Compound B was shown to be 1-(α-naphthyl)-4-methyl-3-penten-1-ol (210) by comparison of its spectral data with that of an authentic sample of (210) and isolated in a 57% yield.

Compound B which was isolated in 10% yield was shown to be 2-(γ, γ-dimethylallyl)-1, 2-dihydronaphthalene-1-carboxaldehyde (211): ir (neat) cm^{-1} 3045, 3020 (aromatic and vinyl C-H), 1705 (non-conj. aldehyde), 1600, 1510, 1490 (aromatic C⋯C), 785, 760 (1, 2-di-substituted ring); nmr (CCl_4) δ 1.48 (s, 3.0H, $-CH_3$), 1.69 (s, 3.0H, $-CH_3$), 1.92-2.18 (m, 3.0H, allylic H's), 3.28 (m, 1.0H, benzylic H), 5.08 (t, 1.1H, J=5.3Hz, $CH=C(CH_3)_2$), 5.92 (dxd, 1.0H, J=6, 9.5Hz, Ar-CH=CH-C), 6.34 (d, 1.0H, J=9.5Hz, Ar-CH=C), 7.02-7.23 (m, 4.0H, H's on Ar), 9.44 (d, 1.0H, J=2Hz, aldehydic-H).

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