of 1 → 3. The phrase "transfer of chirality" does not by itself express the full meaning of what we intend to convey, since chirality may be taken to refer to an individual molecule, and in that case would be transferred *even in a completely nonstereospecific rearrangement.*

(4) Asymmetric induction in intramolecular transfers of chirality between sulfur and carbon has been demonstrated for allylic [2,3] sigmatropic rearrangements. (a) C → S: P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4869 (1968). (b) S → C: B. M. Trost and R. F. Hammen, *ibid.*, **95**, 962 (1973).

(5) An asymmetric induction in an intramolecular transfer of chirality from sulfur to carbon has been reported for a Pummerer rearrangement: B. Stridsberg and S. Allenmark, *Acta Chem. Scand. Ser. B*, **28**, 591 (1974); **30**, 219 (1976); T. Numata and S. Oae, *Tetrahedron Lett.*, 1337 (1977).

(6) Second-order asymmetric transformations of sulfonium salts have been previously discussed.[4b]

(7) K. K. Andersen, M. Cinquini, and N. E. Papanikolaou, *J. Org. Chem.*, **35**, 706 (1970).

(8) Racemization of a sulfonium salt is an irreversible first-order process, so that $x = a(1 - e^{-k_1 t})$, where $a$ = initial concentration, and $x$ = amount reacted. Assuming a limit of experimental error of 10% (i.e., $x = 0.10$), $k_1 = 1.38 \times 10^{-6}\ \mathrm{s}^{-1}$ and a lower limit of $\Delta G^{\ddagger}$ (20 °C) is 25.0 kcal/mol.

(9) The choice of chiral anions other than camphorsulfonate is severely limited by the sensitivity of **2** to deprotonation. For example, solutions of **2** (+)-dibenzoyl hydrogen tartrate are purple in color and show the presence of the rearrangement product, **3** (Experimental Section). The use of chiral anions of strong acids (e.g., sulfonates) is therefore an essential prerequisite for the resolution.

(10) Sulfur is the only element of chirality in the starting **2** perchlorate. Asymmetric induction by rearrangement of **2** camphorsulfonate would be ambiguous since the anion itself provides a chiral environment which could exert some influence on the direction and magnitude of the induction.

(11) Such deshielding is frequently observed in thioxanthene 10-oxides; for example, cf. S. A. Evans and A. L. Ternay, Jr., *J. Org. Chem.*, **40**, 2993 (1975), and references cited therein.

(12) Optically active 2-dimethylamino-9-methylfluorene is racemized by phenyllithium: G. Wittig, F. Vidal, and E. Bohnert, *Chem. Ber.*, **83**, 359 (1950). Although KOBu(*t*) is a somewhat weaker base, note that **3** is a triphenylmethane with vinylogous sulfur activation.

(13) *cis*- or *trans*-9-methylthioxanthene 10-oxide can be epimerized using KOBu(*t*) or sodium methoxide, but not triethylamine: L. Ens, Ph.D. Thesis, Case Western Reserve University, 1969.

(14) Since a deficiency of KOBu(*t*) was employed, 2 was present in the reaction mixtures throughout the course of the rearrangements. If proton transfer were to occur reversibly between 1 and **2** the calculated values of $k_2$ would be proportionately decreased (see Experimental Section). The $k_2$'s and energies of activation for the inversion of 1 reported in this paper are therefore the lower limits, the upper limits being $k_1$ and the energy of activation for rearrangement of 1 to **3**, respectively. In this connection, see also the related case of inversion at nitrogen in partially protonated amines: M. Saunders and F. Yamada, *J. Am. Chem. Soc.*, **85**, 1882 (1963).

(15) The absolute value of the ee is not required for the determination of $k_2$ since the reaction follows a first-order law (eq 4).

(16) The rate constant for racemization $k_{\mathrm{rac}} = 2k_2$, and therefore $\Delta G^{\ddagger}{}_{\mathrm{rac}}$ (cal/mol) = $\Delta G^{\ddagger}{}_{\mathrm{inv}} - 1.37\ T$ (K).

(17) A. Rauk, J. D. Andose, W. G. Frick, R. Tang, and K. Mislow, *J. Am. Chem. Soc.*, **93**, 6507 (1971).

(18) Although for steric reasons the 2,5-xylyl ring cannot be coplanar with the thiaanthracene framework in the transition state to inversion, the resulting attenuation of the $\pi$ overlap with the electron pair on sulfur is not expected to be severe.

(19) D. Darwish and C. E. Scott, *Can. J. Chem.*, **51**, 3647 (1973).

(20) D. Darwish and R. L. Tomilson, *J. Am. Chem. Soc.*, **90**, 5938 (1968); S. J. Campbell and D. Darwish, *Can. J. Chem.*, **52**, 2953 (1974). See also D. M. Roush and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 2337 (1977).

(21) For a detailed description of stereoisomerism in folded molecules containing a chiral center, such as **1–3**, cf. the discussion of the stereochemically correspondent 2-methyl-10-(*p*-carboxymethyl)-5,10-dihydroarsacridine: K. Mislow, A. Zimmerman, and J. T. Melillo, *J. Am. Chem. Soc.*, **85**, 594 (1963).

(22) A. K. Chandra, *Tetrahedron*, **19**, 471 (1963); J. Chickos and K. Mislow, *J. Am. Chem. Soc.*, **89**, 4815 (1967), and references cited therein; P. T. Lansbury, *Acc. Chem. Res.*, **2**, 210 (1969); D. M. Wieland and C. G. McCarty, *J. Org. Chem.*, **37**, 4285 (1972).

(23) By the Curtin–Hammett principle; cf. E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 151 ff.

(24) A. L. Ternay, Jr., L. Ens, J. Herrmann, and S. Evans, *J. Org. Chem.*, **34**, 940 (1969); A. L. Ternay, Jr., and S. A. Evans, *ibid.*, **39**, 2941 (1974).

(25) Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y. Unless otherwise noted, $^1$H NMR spectra were recorded on a Varian A-60A spectrometer and refer to ca. 10% solutions with tetramethylsilane as an internal reference. The $^{13}$C NMR and 100-MHz $^1$H NMR spectra were recorded on a Varian XL-100 spectrometer, and integrated intensities on this instrument were used to calculate values of enantiomeric excess. Infrared spectra were recorded on a Perkin-Elmer 237B spectrometer. ORD and CD measurements were recorded on a Cary Model 60 spectropolarimeter equipped with a Model 6001 circular dichroism accessory. Specific rotations at 589 and 365 nm were measured on a Perkin-Elmer 141 polarimeter; solution concentrations are given in g/100 mL. Melting points were determined on a Thomas-Hoover apparatus and are corrected. We also note that solutions (or oils and to a lesser extent the crystals) of thioxanthenium salts (**2**), of the rearrangment product (**3**), and of derivatives of **3**, **5**, and **6** used in this study are light sensitive (decomposition to a variety of highly colored products of undetermined nature was observed); all solutions, oils or crystals of the above-mentioned compounds were therefore protected from light as much as possible.

(26) D. M. Coyne, W. E. McEwen, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **78**, 3061 (1956).

(27) Procedure of N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Am. Chem. Soc.*, **81**, 4113 (1959).

(28) W. J. Pope and C. S. Gibson, *J. Chem. Soc.*, **97**, 2211 (1910).

(29) This solvent is of comparable polarity to $\mathrm{Me_2SO}$ but has the advantage of maintaining the homogeneity of the reaction mixture at lower temperatures.

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# A Study of the Mechanism of the Cope Rearrangement[1,2]

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*Received July 30, 1975*

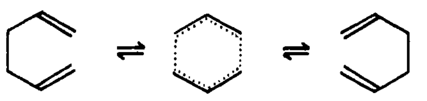
**Abstract:** Kinetic studies are reported for the Cope rearrangements of the 2-phenyl, 3-phenyl, 2-($\alpha$-naphthyl), 2-($\beta$-naphthyl), 2,4-diphenyl, and 2,5-diphenyl derivatives of 1,5-hexadiene. The results suggest that the transition state for the reaction is a biradicaloid akin to the 1,4-cyclohexylene biradical.

Although the Cope rearrangement of 1,5-hexadienes was discovered over 30 years ago,[3] and although it has been studied in detail by a number of workers,[4] its mechanism is still not completely understood.

It has been established that the reaction is normally intramolecular,[5] that it involves rearrangement of each allyl group, implying the intervention of intermediates with bonding across the 1,6 positions, and that the preferred conformation of such intermediates is analogous to the "chair" conformation of cyclohexane.[6] It is, however, possible for the reaction to take place via the alternative "boat" conformation,[6] even in the case of 1,5-hexadiene (**1**) itself,[7] and indeed the "boat" rearrangement can take place extremely easily if facilitated by relief of ring strain, as in the degenerate Cope rearrangement of semibullvalene.[8-10]

Cope[3,11] assumed that the reaction takes place in a single step via a cyclic transition state, i.e., that it is a pericyclic process in current terminology,[12] and this view has been commonly accepted. According to it the degenerate rearrangement of **1** would be represented as **1** → **2** → **3**, where **2** is the symmetrical transition state, isoconjugate with benzene and so aromatic.[13] On this basis the preferred chair conformation of **2** can be attributed to an antibonding 1,4 interaction.[13] Similar conclusions follow from orbital correlations between **2** and a pair of allyl radicals[12] or from arguments based on the frontier orbital method.[14]

Recently, however, this picture has been challenged. Doering et al.[15] have suggested that the symmetrical intermediate in the reaction may be a 1,4-cyclohexylene biradical (**4**) rather than a pericyclic transition state. They estimated the heat of formation of **4** from thermochemical data for analogous hydrocarbons and monoradicals, arriving at a value consistent with the observed activation energy for the rearrangement of **1**.



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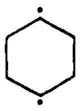

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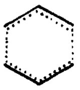
A further revision has been made necessary by the recent theoretical studies of McIver,[16] who has shown that if a symmetrical intermediate participates in the interconversion of **1** and **3**, it must be a minimum on the potential surface and not a transition state. In that case there will be two equivalent transition states, separating the stable symmetrical intermediate from **1** and **3**.

Yet a third suggestion has been made recently by Salem[17] on the basis of his theory of narcissistic reactions. He points out that the conversion of **1** to **3** may take place in a single step if the transition state is unsymmetrical (**5**). In this case there would be two equivalent but alternative reaction paths involving **5** or its mirror image **6** as transition states. The symmetrical structure would then be an energy maximum, separating the two paths.



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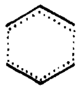

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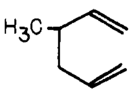
The purpose of the work described here was to try to distinguish between these various possibilities. The problem is a rather subtle one involving the detailed timing of bond-breaking and bond-forming processes during a reaction. It has been pointed out[18] that a powerful procedure in such cases is to study the changes in rate brought about by a series of ±E substituents,[18] i.e., those derived from even alternant hydrocarbons (AHs). Such substituents (e.g., vinyl, phenyl, naphthyl) exert inductive and field effects that are not only small but constant so the variations in rate are due solely to their conjugative effects. Since such conjugative interactions can be estimated very easily in the case of AHs by the PMO method,[18] it is easy to predict the pattern of rates to be expected for a given transition state structure. By comparing the observed pattern of rates with those calculated for various transition state structures, one can then distinguish between them. This approach has been used successfully in a number of cases,[18] including the Diels-Alder reaction,[19] a process commonly thought to have a pericyclic mechanism akin to that of the Cope rearrangement. We therefore decided to apply it to the rearrangement of **1** by studying the rates of rearrangement of a series of appropriate derivatives.

Relatively little work has been reported on the rearrangement of simple derivatives of **1**. One of the most thoroughly studied is that of 3-methyl-1,5-hexadiene (**7**) to *cis*- (**8**) or *trans*-1,5-heptadiene (**9**). The reactions are, as indicated, reversible, and Frey and Solly[20] have determined the values of all four rate constants over a range of temperature in the gas phase. The conversion of **7** to **9** is faster than that to **8**, due to a decrease of 1.5 kcal/mol in the activation energy. Frey and Solly pointed out that if the reaction takes place via intermediates with the preferred[6] chair conformation, these can exist in stereoisomeric forms **10** and **11**, **10** giving rise to **8** and **11** to **9**. Since the methyl group in **10** is pseudoaxial and in **11** pseudoequatorial, **11** should be favored sterically. The observed difference in activation energy (1.5 kcal/mol) for the two processes is indeed close to the difference in energy (1.9 kcal/mol) between the axial and equatorial isomers of methylcyclohexane. Perrin and Faulkner[21] have found that a similar parallel holds for all derivatives of **1** for which data are available.



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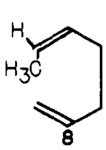

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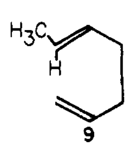

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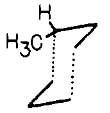

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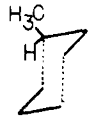

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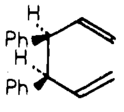
One problem in our projected work was the possibility that aryl substituents might change the mechanism of the reaction to one involving fission to a pair of allyl radicals followed by recombination (cf. ref 5). Koch[22] had in fact reported this to be the case for the rearrangement of *meso*-3,4-diphenyl-1,5-hexadiene (**12**), which, he claimed, gives a mixture of 1,4- and 1,6-diphenyl-1,5-hexadiene on rearrangement. Lutz et al.[23] have, however, shown this observation to be in error, both **12** and the corresponding *dl* isomer (**13**) giving exclusively 1,6-diphenyl-1,5-hexadiene on heating. Since the phenyl groups in **12** or **13** should be particularly effective in promoting fission to radicals, it seemed unlikely that this would happen in the cases we planned to study.



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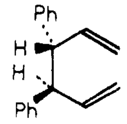

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## The Possible Mechanisms

Assuming that the Cope rearrangement is a concerted process involving a six-membered cyclic transition state, there are three main questions to be asked. First, does the reaction proceed symmetrically or unsymmetrically?[17] Second, is a stable intermediate involved? Third, what are the structures of the relevant species involved?

The intermediates can, as Woodward and Hoffmann have pointed out,[12] be regarded as arising by combination of two allyl radicals, this combination in turn being treated by perturbation theory. We can reasonably assume that the effect of combination is confined mainly to changes in the allylic $\pi$ MOs. Let us then first consider the approach of two allyl radicals to form a symmetrical ($C_{2v}$) boat- or chair-shaped structure by progressively increasing interactions between the terminal 2p AOs in their $\pi$ systems.

As the interactions between the allyl $\pi$ MOs increase, the first-order interactions between them will make their energies vary in the way indicated in Figure 1. No problems arise from the indicated orbital crossings because the orbitals differ in symmetry; their symmetries with respect to reflection in the plane of symmetry, and rotation about the twofold axis, are as indicated.

The resulting orbitals fall into three patterns, depending on the strength of the interactions between the allyl $\pi$ MOs.

(a) In the region of weak interaction, the orbital pattern is similar to that in the separated allyl radicals, two electrons occupying a MO which is only weakly bonding. The stabilizing effects of ±E substituents ($R$) should therefore run parallel

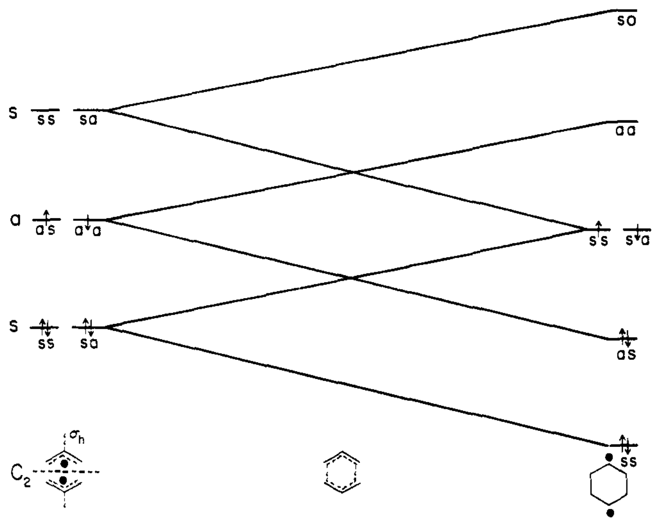


**Figure 1.** Changes in the energies of the $\pi$ MOs of a pair of allyl radicals as increasing interactions are introduced between the terminal atoms. The system has $C_{2h}$ or $C_{2v}$ symmetry as indicated in the initial formula; the symmetries of the orbitals are as indicated, the first letter referring to reflection in the plane of symmetry ($\sigma_h$ or $\sigma_v$), the second to rotation about the twofold axis.

to their effect on an allyl radical.[24] They should exert a large effect in the 1 or 3 positions and little or no effect in the 2 position. In forming such a structure from a 3-substituted 1,5-hexadiene there should of course be an additional contribution due to the change of the R-C bond from $sp^3$-$sp^2$ to $sp^2$-$sp^2$ type.[18,25] The resulting stabilization should be similar for all ±E substituents.[18d,e,25]

(b) In the central region of Figure 1, the orbital pattern is similar to that in benzene. There is one very strongly bonding MO and two that are strongly bonding and degenerate, or nearly degenerate. The structure is indeed identical with that in benzene since both delocalized systems can be derived by the interaction of two allyl moieties.[26]

Such a structure should correspond to a genuinely aromatic pericyclic transition state[13] and the effect of ±E substituents on it should be the same as on benzene, i.e., zero.[18] There should of course again be a stabilization of such a structure relative to the corresponding 3-substituted 1,5-hexadiene due to the change in the R-C bond from $sp^3$-$sp^2$ to $sp^2$-$sp^2$. Again, this should be the same for all ±E substituents.

(c) Finally, on the right-hand side of Figure 1, in the region of very strong interaction, the structure again becomes radical-like, two electrons occupying a MO which is nonbonding or weakly bonding. In the extreme case, where the perturbed antibonding allyl MO crosses the perturbed bonding one, the structure becomes a biradical with two degenerate NBMOs. Since each of these is derived from interactions between a pair of symmetric (bonding or antibonding) allyl MOs in which there is a high orbital density at the central atom,[27] the corresponding structure will be most closely represented, in classical notation, as the 1,4-cyclohexylene biradical (**4**). In this case ±E substituents will have a stabilizing effect at all positions but a much greater effect at the central allylic positions (i.e., at positions 2 or 5 in **1**) than at the terminal ones (i.e., positions 1, 3, 4, or 6 in **1**).

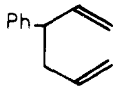
These arguments assume that the allyl moieties remain intact, as should be the case in (a) and probably a good approximation in (b). In case (c), however, where the interactions between the ends of the allyl groups are very strong, it should be advantageous to change the hybridization of the corresponding atoms so that the $\sigma$ bonds between them change from p-p to $sp^3$-$sp^3$ type. This will of course reduce the interactions between the central allylic carbon atoms and their neighbors and make the structure approximate even more closely the classical representation **4**. In the region near to the biradical (where the MOs cross), the structure will correspond to **4** with indirect (hyperconjugative) coupling between the radical carbon via the intervening C-C bonds of the type suggested by Hoffmann et al.[28] Here one would expect ±E groups in the central allylic positions to exert very large stabilizing effects while their effect in the terminal positions should be small.

Before having recourse to experiment, an obvious first step was to try to estimate just how large are the interactions between the allyl moieties in the transition state. The activation energy for rearrangement of **1** is reported[15] as 34.3 kcal/mol. We can also estimate the energy required to dissociate **1** into allyl radicals from thermochemical data for **1**[29] and allyl;[30] i.e., 62.3 kcal/mol. Thus the energy liberated when two allyl radicals combine to form the transition state is 28.0 kcal/mol. This is about half the estimated difference in $\pi$ energy between two allyl radicals and benzene (60 kcal/mol[31]), suggesting that the transition state has a structure corresponding to a point on the left half of Figure 1. Unfortunately, however, the estimate for benzene is uncertain due to uncertainties in the corrections to be made for the changes in $\sigma$ bond energy during union of allyl radicals to form benzene.

## Results and Discussion

**A. Rearrangements of 3-Aryl-1,5-hexadienes.** The first step was to study the effect of ±E substituents in the 3 position of **1**; for this should immediately distinguish between case (a) above (i.e., weakly interacting allyls) and the other two.

Preliminary studies showed that the rearrangement of 3-phenyl-1,5-hexadiene (**14**) proceeded at a convenient rate in a temperature range (190-250 °C) where its vapor pressure is considerable, leading quantitatively and irreversibly to a mixture of *trans*- (**15**) and *cis*-1-phenyl-1,5-hexadiene (**16**).



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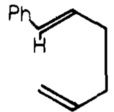

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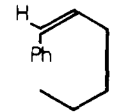


**16**

Initial erratic results were traced to the fact that the reaction, run in evacuated ampules, was taking place partly in the gas phase and partly in the liquid phase. With samples small enough to vaporize completely, very reproducible results were obtained. The reaction was entirely homogeneous, the rate being the same in packed (glass beads) and unpacked vessels. The rate constants for disappearance of **14** ($k_d$) and for formation of **15** ($k_t$) or **16** ($k_c$) were determined independently from the corresponding analytical data. The accuracy of the results (Table I) is indicated by their internal consistency, by the fact that the measured values of $k_d$ were equal to a sum of those of $k_t$ and $k_c$, and by the linearity of the corresponding Arrhenius plot. The corresponding Arrhenius parameters are also shown in Table I.

These results indicated that other 3-aryl-1,5-hexadienes should also rearrange cleanly, giving almost exclusively *trans*-1-aryl-1,5-hexadienes. This was found to be the case for the 1- (**17a**) and 2-naphthyl (**17b**) derivatives. These compounds were, however, too involatile for their rearrangements to be studied in the gas phase. Analysis of the products by GLC also proved inconvenient since rearrangement tended to take place in the column. The reactions were therefore run in *o*-dichlorobenzene (ODCB) solution and the products analyzed by NMR.

For comparison, the rearrangement of **14** was also studied in ODCB, using NMR analysis. The rates at several temperatures, and the corresponding Arrhenius parameters, are shown in Table II. It will be seen that the rate at 189.8 °C was nearly four times as great in ODCB as in the gas phase, a dif-

**Table I.** Rearrangement of 3-Phenyl-1,5-hexadiene in the Gas Phase

| Process | First-order rate constant, $s^{-1} \times 10^5$, at (°C) | | | Arrhenius parameters | |
|---|---|---|---|---|---|
| | 189.8 | 219.4 | 249.5 | $E$, kcal/mol | Log $A$ |
| Disappearance of **14** | $2.57 \pm 0.02^{a,b}$ | $21.4 \pm 0.1^{a,c}$ | $1.443 \pm 0.7^{a,c}$ | $32.461 \pm 0.006^{a}$ | $10.732 \pm 0.003^{a}$ |
| Formation of **15** | 2.52 | 20.9 | 140 | $32.376 \pm 0.008^{a}$ | $10.683 \pm 0.004^{a}$ |
| Formation of **16** | 0.0493 | 0.521 | 4.33 | $36.07 \pm 0.02^{a}$ | $10.717 \pm 0.009^{a}$ |

[a] Standard deviation. [b] Correlation coefficient 0.9997. [c] Correlation coefficient 0.9999.

**Table II.** Rearrangement of 3-Phenyl-1,5-hexadiene in ODCB

| $T^a$ | $10^5K^b$ | $T^a$ | $10^5K^b$ | $E$, kcal/mol$^c$ | Log $A^c$ |
|---|---|---|---|---|---|
| 156.3 | 1.955 | 189.8 | $1 \times 0.8$ | $29.08 \pm 0.26^d$ | $9.79 \pm 0.12^d$ |
| 170.1 | 2.78 | 200.0 | 22.9 | | |
| 180.0 | 5.72 | | | | |

[a] Temperature in °C. [b] First-order rate constant ($s^{-1}$). [c] Arrhenius parameters. [d] Standard deviation (correlation coefficient 0.9997).

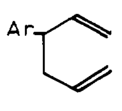
**Table III.** Rearrangements of 3-Aryl-1,5-hexadienes at 189.8 °C

| Compd | Conditions | First-order rate constant, $10^4\ s^{-1}$ | Corr coeff |
|---|---|---|---|
| **1** | Gas phase | $0.0147^a$ | |
| **14** | Gas phase | $0.254 \pm 0.02^b$ | 0.9997 |
| **14** | ODCB solution | $1.08 \pm 0.03^b$ | 0.9969 |
| **17b** | ODCB solution | $1.12 \pm 0.02^b$ | 0.9990 |
| **17a** | ODCB solution | $1.16 \pm 0.01^b$ | 0.9994 |

[a] Calculated from data of Doering et al.[15] [b] Standard deviation.

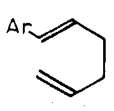
ference which seems surprising for a nonpolar reaction involving a hydrocarbon.[32] The increase in rate must be due to an increase in solvation on passing from the reactant to the transition state, as is also indicated by the simultaneous decrease in both Arrhenius parameters.[33] Since the solute is neutral and nonpolar, solvation can arise only from dipole/induced dipole interactions and dispersion forces. The increase in solvation therefore implies that the transition state is more polarizable than the reactant. The magnitude of the rate increase implies that the transition state must be highly polarizable.

Table III compares the rates of rearrangement of **14**, **17a**, and **17b** in ODCB at 189.8 °C. Within the limits of experimental error, all three are equal. Table III also shows the rate of rearrangement calculated for **1** in the gas phase at 189.8 °C from the Arrhenius parameters of Doering et al.[15] together with the corresponding gas-phase rate for **14**. Evidently **14**, **17a**, and **17b** all rearrange about 17 times as fast as **1** at this temperature.



a, Ar = 1-naphthyl
b, Ar = 2-naphthyl

17



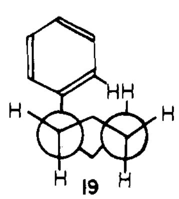
18

These results immediately eliminate transition state structures on the left side of Figure 1 because in such a structure there would be large resonance interactions with aryl groups in the 3 position and such interactions would increase in the order of ±E activity[24,34] of the groups, i.e., phenyl (0.75) < $\beta$-naphthyl (0.89) < $\alpha$-naphthyl (1.22).

This conclusion is also supported by the fact that the difference in activation energy for **14** → **15** and **14** → **16** (3.7 kcal/mol) is only a little more than the difference in energy between axial and equatorial phenylcyclohexane (3.1 kcal/mol).[35]

Since a similar parallel has been shown to hold for saturated substituents,[20,21] any conjugative effect of phenyl must be almost the same in the transition states leading to **15** or **16**. Consider now the chair transition state leading to **16**; **19** shows a Newman projection of this along the forming/breaking CC bonds. If the 3-phenyl group is to conjugate efficiently with the adjacent carbon atom, it must lie orthogonal to the (breaking) 3,4 bond. As **19** shows, there will then be a severe steric interaction between an ortho hydrogen atom of the phenyl group and the axial hydrogen at the 1 position. Since no such problems arise in the case of the transition state leading to **15**, where phenyl is equatorial, we would certainly expect the resonance interaction there to be much stronger than in **19**. Since the difference in activation energy between (**14** → **15**) and (**14** → **16**) apparently corresponds to that expected for a pure steric effect, the resonance interaction between phenyl and the 3,4 bond must indeed be small.

This argument incidentally seems to provide a distinction between the two explanations given by Lutz et al.[23] for the fact that while **13** gave exclusively *trans,trans*-1,6-diphenyl-1,5-hexadiene (**20**), as would be expected if the reaction takes place via the less hindered chair transition state, rearrangement of **12** gave only 63% of the expected *cis,trans*-diphenylhexadiene (**21**) together with 37% of **20**. Since **20** can be formed from **12** only via a boat transition state, the boat and chair transition states must here be of comparable energy. Lutz et al.[23] pointed out that in the chair transition state, one of the phenyl groups must occupy an axial position where conjugation with the 3,4 bond would be hindered; whereas in the corresponding boat transition state both phenyls can occupy equatorial positions. The differential effect of the phenyl group on the two transition states could then be due either to the greater resonance stabilization of the boat, to the increased steric repulsions in the chair, or of course to a combination of the two. Our results suggest that the steric effect predominates. A similar disturbance of the boat-chair equilibrium is also seen in the case of *trans*-1,2-diphenylcyclohexane.



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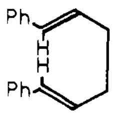

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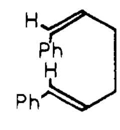


21

We have so far assumed that the transition state for the Cope rearrangement of **1** has either the symmetrical structure or one close to it; for the lack of conjugation by 3-aryl groups in the transition state could be equally well explained if the transition state occurred early in the reaction while the 3,4 bond is almost intact. If this were the case, however, it would be impossible to explain the very sizable increase in rate on introduction of an aryl substituent in the 3 position. It would also require the symmetrical intermediate to be at least comparable with **1** in stability. Now the most stable possible form of the symmetrical intermediate will be that involving the strongest possible association of two allyl radicals, i.e., 1,4-cyclohexylene (**4**) (see Figure 1). However, Doering et al.[15] have shown that **4** must be much higher in energy than **1**, being in fact comparable in this respect with the transition state. Thus the structure of the transition state must be much nearer to that of the symmetrical intermediate than to that of **1**.

**B. Rearrangements of 2-Phenyl-, 2,5-Diphenyl-, and 2,4-Diphenyl-1,5-hexadienes.** The results described above limited the mechanism of rearrangement of **1** to the center or right of Figure 1. The next step was to distinguish between these by studying the effect of a phenyl group in the 2 position.

If the reaction involves an aromatic transition state, a ±E substituent (e.g., phenyl) at the 2 position should have no effect at all upon the rate; for it is attached both initially and in the transition state to an even AH (ethylene or a benzene analogue) and the corresponding $\pi$ energies of interaction should be similar.[36] Conversely a ±E substituent at the 3 position should lead to an increase in rate because it is attached initially to a saturated carbon atom.

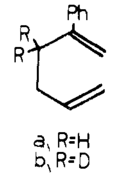
If on the other hand the transition state lies to the right side of Figure 1, approaching **4** in structure, a ±E substituent should have a large accelerating effect in the 2 position but little effect in the 3 position, for reasons indicated earlier.

The Cope rearrangement of 2-phenyl-1,5-hexadiene (**22a**) is degenerate and can therefore be followed only by deuterium labeling. The 3,3-dideuterio derivative (**22b**) was prepared according to Scheme I. It contained 97.4% dideuterated material according to NMR analysis and 96.5% according to mass spectrometry. The rearrangement of **22b** to **23** was followed by NMR, by measuring the ratio of vinylic to allylic methylene protons, allowance being made for the incomplete deuteration. Since the reaction is reversible, the measured rates of disappearance of **22b** correspond to approach to equilibrium. These rates, and the corresponding equilibrium constants, are shown for measurements of several different temperatures in Table IV. While the equilibrium constants indicate that, as expected,[37] **22b** is the more stable isomer, they show much scatter. Since they are moreover small, we decided to follow Doering et al.[15] in assuming the rate constants for the forward and backward reactions to be equal, each being equal to half the rate constant for approach to equilibrium. The results of Sunko et al.[37] indicate that the rate constants so found may be in error by ca. 5%, a negligible amount in the present connection. The corresponding Arrhenius parameters for the conversion of **22b** to **23** are then

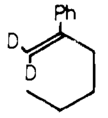
Scheme I

$$\mathrm{PhCOCH_2COOCH_2CH{=}CH_2} \xrightarrow{\Delta} \mathrm{PhCOCH_2CH_2{=}CH_2}$$

$$\xrightarrow{\mathrm{D_2O\text{-}(Et_3)N\text{-}dioxane}} \mathrm{PhCOCD_2CH_2CH{=}CH_2} \xrightarrow{\mathrm{Ph_3PCH_2}} \mathbf{22b}$$



**22**



**23**

$$E = 30.2 \pm 1.6\ \mathrm{kcal/mol};\ \log A = 10.92 \pm 0.79 \qquad (1)$$

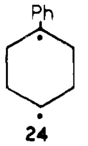
The possible errors due to our assumption are ca. 0.1 kcal/mol in $E$ and ±0.05 in log $A$.

Table IV. Rearrangements of 2-Phenyl-1,5-hexadiene in ODCB

| Temp, °C | $10^5K$,[a] $s^{-1}$ | $K$[b] |
|---|---|---|
| 150.0 | 4.02 ± 0.27 | 1.030 |
| 160.0 | 10.4 ± 0.6 | 1.030 |
| 165.0 | 13.2 ± 0.4 | 1.040 |
| 170.1 | 20.7 ± 1.2 | 1.116 |
| 170.1 | 21.6 ± 1.5 | 1.096 |

[a] First-order rate constant for approach to equilibrium. [b] Equilibrium constant, **22b** → **23**.

These parameters lead to an estimated rate of reaction at our standard temperature (189.8 °C) of $4.57 \times 10^{-4}$ mol $s^{-1}$. Comparison with Table II shows that this is four times greater than the corresponding rate of rearrangement of **14.** The transition state for rearrangement of **22b** must therefore correspond to a point well to the right of Figure 1, i.e., a structure that could be best represented in classical notation as 1-phenyl-1,4-cyclohexadienyl (**24**). Since singlet biradicals such as

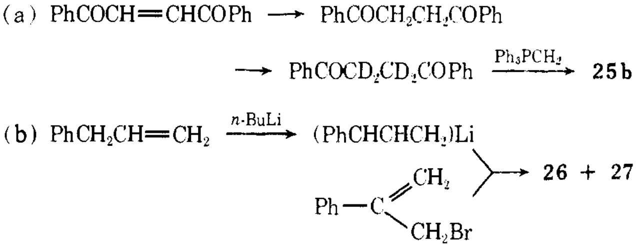


**24**

**24** are unstable, the actual structure of the transition state will be a biradicaloid derived from **24** by an appropriate distortion.[38]

In our preliminary account[2] of this work we suggested that the Cope rearrangement might have a flexible mechanism, being directed toward an aromatic pericyclic mechanism (corresponding to a point in the middle of Figure 1) by an aryl group in the 3 position and toward a "biradical" mechanism by aryl in the 2 position. To test this, we next studied the rearrangements of 2,5- (**25a**) and of 2,4-diphenyl-1,5-hexadiene (**26**). The rearrangement of **25a** is again degenerate so isotopic labeling was necessary; we used the tetradeuterio derivative (**25b**). The synthesis of this, of **26**, and of the rearrangement product (**27**) of **26** are shown in Scheme II. In this case NMR analysis indicated essentially complete deuteration in **25b**.

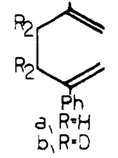
Scheme II



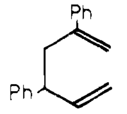
$$\text{(a)}\ \mathrm{PhCOCH{=}CHCOPh} \longrightarrow \mathrm{PhCOCH_2CH_2COPh} \longrightarrow \mathrm{PhCOCD_2CD_2COPh} \xrightarrow{\mathrm{Ph_3PCH_2}} \mathbf{25b}$$

$$\text{(b)}\ \mathrm{PhCH_2CH{=}CH_2} \xrightarrow{n\text{-BuLi}} \mathrm{(PhCHCHCH_2)Li} + \mathrm{Ph{-}C({=}CH_2)CH_2Br} \longrightarrow \mathbf{26} + \mathbf{27}$$

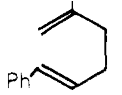
The kinetic results for the rearrangements of **25b** (to **28**) and of **26** (to **27**) are shown in Tables V and VI. The amount of **25b** was only sufficient for measurements at two temperatures; however, the results seem to be reasonably reliable since the measured equilibrium constants led to identical values for the



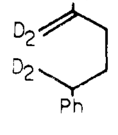
**25**



**26**



**27**



**28**

**Table V.** Rearrangement of 2,5-Diphenyl-1,5-hexadiene in ODCB

| Temp, °C | $10^5K$,[a] $s^{-1}$ | $K$[b] | $\Delta G$,[c] cal |
|---|---|---|---|
| 82.25 | 6.1 ± 0.1[d] (0.9987)[d] | 1.500 | 286 |
| 100.95 | 28.5 ± 0.8[d] (0.9965)[d] | 1.472 | 287 |

[a] First-order rate constant for approach to equilibrium. [b] Equilibrium constant. [c] Free energy of reaction. [d] Standard deviation (correlation coefficient).

free energy of reaction. The value found in this way is a little greater than that (203 cal $mol^{-1}$) reported by Sunko et al.[37] for the equilibrium between the analogous tetradeuterio derivatives of **1.** The results in Tables V and VI lead to the following Arrhenius parameters for the conversion of **25b** to **28** and of **26** to **27:**

$$\mathbf{25b} \rightarrow \mathbf{28} \qquad E = 21.91 \text{ kcal/mol}; \log A = 8.86 \tag{2}$$

$$\mathbf{26} \rightarrow \mathbf{27} \qquad E = 25.46 \pm 0.78 \text{ kcal/mol}; \log A = 9.68 \tag{3}$$

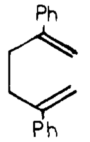
(In the case of **25b** → **28,** it was again assumed that the rate constant for the forward reaction is half that for approach to equilibrium.)

Table VII shows the rate constants for these two reactions at 189.8 °C, calculated from the parameters in eq 1 and 2. Values for the other reactions are also shown, together with an estimated value for the rearrangement of **1** under the same conditions, i.e., in ODCB solution.[39] The last column shows rates relative to **1.**

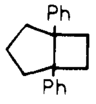
If the transition states for all these reactions are similar in structure, the effects of phenyl groups on the activation energy should be additive and their effects on the rate consequently multiplicative.[40] The values calculated in this way for the 2,4- (**25**) and 2,5-diphenyl (**26**) derivatives, using the data for the 2- (**22**) and 3-monophenyl (**14**) derivatives, are shown in parentheses in Table VII. It will be seen that the results agree quite well with experiment, given the uncertainty in the extrapolated rates for **22** and **25.** The transition states for all these reactions must therefore be similar in structure, being biradicaloids derived from biradicals analogous to **4.** This conclusion also accounts for the large solvent effect observed in the case of **14.** If the transition state is a biradicaloid, it should be highly polarizable, since it will have a very low-lying excited state.

These arguments leave open the question concerning the possible intervention of a stable intermediate. However, it seems fairly certain that if such an intermediate is formed, it must represent a very minor depression in the potential surface and so be essentially irrelevant. If this were not so, the transition state would be displaced toward **1** in structure and it would then be impossible to account for the observed changes in rate produced by phenyl substituents. Moreover, the substituents in **22** and **25** would be expected to selectively stabilize the "biradical" intermediate very strongly; if the transition state were initially displaced appreciably toward **1,** it would be displaced to an increasing extent in the series **1, 22, 25.** One would not then expect the effects of two phenyl groups to be additive.

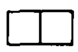
Initially we thought that the intermediate from **25** must lie in a deep well from our estimates of the heat of formation of the corresponding classical biradical **32.** In this calculation we made the usual assumption[15,41] that the energies required to break the two PhC-H bonds in 1,4-diphenylcyclohexane (**33**) are additive, the difference in energy between **32** and **33** being double that between **32** and the corresponding monoradical **34.** It has, however, recently been pointed out[42] that this procedure leads to an estimate not of the energy of the singlet biradical but of a weighted (by multiplicity) average of the singlet and triplet biradical energies. In the case of a biradical such as **4,** in which the radical centers can interact,[28] this average energy will lie below that of the singlet by $1.5K$, where $K$ is the exchange integral between the two singly occupied orbitals. In systems such as **4,** this can amount to 1-2 eV, so the conventional estimate is chemically meaningless.



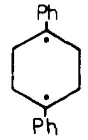
**29**



**30**

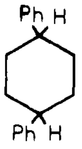


**31**

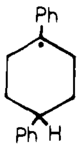


**32**

We did indeed try to trap the "biradical" intermediate (**32**) by heating **25** in the presence of hydroquinone, thiols, etc., but without success. It is interesting in this connection that Doering[43] has recently shown that the analogous diphenylheptadiene (**29**) on heating gives the diphenylbicycloheptane **30,** presumably by collapse of an intermediate biradicaloid species analogous to **32.** In the case of **1,** the corresponding product would be bicyclo[2.2.0]hexane (**31**), which is unstable at the temperatures needed to bring about the Cope rearrangement, reverting to **1.**[7]



**33**



**34**

## Experimental Section

Melting points and boiling points are uncorrected. All the compounds studied gave satisfactory elemental analyses. NMR spectra were measured in $CCl_4$ using a Varian A-60 spectrometer and the IR and UV spectra with Beckman IR8 and DH-2A spectrophotometers, respectively. Analytical GLC separations were carried out using a Wilkens C-600 instrument with flame ionization detector and a 5 ft × 0.125 in. column packed with DC 550 (20%) on Chromosorb P (NAW) (flow rates: $N_2$, 30 mL/min; $H_2$, 21 mL/min; air, 250 mL/min). Preparative GLC separations were carried out on 5 or 10 ft × 0.375 in. columns with the same packing.

**3-Phenyl-1,5-hexadiene (14) and *trans*-1-phenyl-1,5-hexadiene (15)** were prepared by a modification of the method of Cope and Levy.[44] A solution of *n*-butyllithium in hexane (37.6 mL of 2.25 N, 0.0846 mol) was evaporated, dry ether (25 mL) added, the solution cooled to −30 °C ($CO_2$-acetone), and allylbenzene (10 g, 0.0846 mol) added. The resulting red solution was taken up in a syringe and added simultaneously with one of allyl bromide (10.2 g) in dry ether (10 mL) to an initially empty flask, keeping the latter in slight excess (disappearance of red color). All these operations were carried out under

**Table VI.** Rearrangement of 2,4-Diphenyl-1,5-hexadiene in ODCB

| Temp, °C | 120.0 | 130.0 | 140.0 | 160.0 |
|---|---|---|---|---|
| $10^5K$,[a] $s^{-1}$ | 3.67 ± 0.1[b]<br>(0.9962)[b] | 7.47 ± 0.18[b]<br>(0.9973)[b] | 15.5 ± 0.2[b,c]<br>(0.9992)[b] | 73.6 ± 1.1[b]<br>(0.9990)[b] |

[a] First-order rate constant. [b] Standard deviation (correlation coefficient). [c] Value in cumene solution: 16.2 ± 0.4 (0.9965).

Table VII. Rates of Rearrangements at 189.8 °C in ODCB

| Compd | $10^4K$, s$^{-1}$ | Rel rate |
|---|---|---|
| **1** | 0.067[a] | 1 |
| **14** | 1.14 | 17 |
| **22b** | 4.57 | 69 |
| **26** | 45.7 | 690 (1170)[a] |
| **25b** | 323.0 | 4900 (4760)[a] |

[a] Calculated (see text).

nitrogen. The ether solution was washed with water, then bicarbonate solution, dried, concentrated, and distilled through an annular Teflon spinning band column (>100 plates), giving **14** (1.35 g), bp 68 °C (7 mm) (lit.[44] 78 °C (8 mm)) and **15** (4.61 g), bp 103 °C (8 mm) (lit.[44] 103 °C (8 mm)). Spectra: IR (neat liquid) **14**, 700, 750, 910, 990 cm$^{-1}$; **15**, 690, 740, 910, 960 cm$^{-1}$; NMR ($\delta$) **14**, 2.45 (t, 2 H), 3.30 (q, 1 H), 5.00 (m, 4 H), 5.80 (m, 1 H), 7.14 (5, 5 H); **15**, 2.23 (t, 4 H), 5.00 (m, 2 H), 5.75 (m, 1 H), 6.25 (d, 2 H), 7.18 (s, 5 H).

***cis*-1-Phenyl-1,5-hexadiene (15).** A solution of **14** (0.617 g) in hexane (spectroscopic grade) was irradiated in a water-jacketed Pyrex cell with a medium pressure mercury arc. Concentration and preparative GLC gave **15** (0.175 g, 28%): IR (neat liquid) 695, 765, 910 cm$^{-1}$; NMR $\delta$ 2.27 (m, 4 H), 4.95 (m, 2 H), 6.42 (d of t, 1 H), 7.18 (s, 5 H).

**3-(1-Naphthyl)-1,5-hexadiene (17a) and *trans*-1-(1-Naphthyl)-1,5-hexadiene (18a).** These were prepared in the same way as **14** and **15**, replacing the allylbenzene by an equivalent amount of 1-allylnaphthalene, and separated by preparative GLC. The structures were assigned on the basis of mass spectra (parent peak at *m/e* 208; base peak, 167, loss of allyl) and NMR and IR spectra; IR (neat liquid) **17a**, 775, 795, 910, 990 cm$^{-1}$; **18a**, 772, 790 (s), 910, 965 cm$^{-1}$; NMR $\delta$ **17a**, 2.64 (t, 2 H), 4.15 (q, 1 H), 5.00 (triplet with further splitting, 4 H), 5.92 (m, 2 H), 7.5 (m, 7 H); **18a**, 2.32 (m, 4 H), 5.00 (triplet with further splitting, 2 H), 6.0 (m, 2 H), 6.95 (s) + 7.5 (m) (8 H).

**3-(2-Naphthyl)-1,5-hexadiene (17b) and *trans*-1-(2-Naphthyl)-1,5-Hexadiene (18b).** Prepared as above, the structures were again assigned on the basis of their mass spectra (parent peak *m/e* 208, base peak 167) and NMR and IR spectra; IR (neat liquid) **17b**, 750, 810, 850, 910, 990 cm$^{-1}$; **18b**, 742, 808, 858, 910, 960 cm$^{-1}$; NMR $\delta$ **17b**, 2.57 (t, 2 H), 3.50 (q, 1 H), 5.06 (m, 4 H), 5.7 (m, 2 H), 7.5 (m, 7 H); **18b**, 2.30 (4 H), 5.0 (m, 2 H), 5.5–6.5 (m, 3 H, sharp peaks at 6.34 and 6.43), 7.5 (m, 7 H).

**2-Phenyl-3,3-dideuterio-1,5-hexadiene (22b).** Allylacetophenone[45] was deuterated with $D_2O$/dioxane/triethylamine to 2,2-dideuterio-4-pentenophenone (>98% $D_2$ by NMR). A solution of this (1 g) in dry ether (20 mL) was added to a Wittig reagent (prepared from methyltriphenylphosphonium iodide (5 g) in dry ether (60 mL) by adding *n*-butyllithium in hexane (10 mL of 1.6 N), standing for 2.5 h, and then cooling to 5 °C), dry ether (30 mL) added, and the mixture boiled under reflux. The resulting solution was filtered, washed (2 × 20 mL) with saturated $NaHCO_3$, and concentrated and the residue extracted with pentane and subjected to preparative GLC, giving **22b** (0.224 g, 23%) with the same retention time as authentic **22a**.[46] Analysis by NMR indicated the presence of 97.4% dideuterated material while mass spectral analysis gave 96.5%. IR (neat liquid) **22a**, 700, 785, 895, 910, 2920 cm$^{-1}$; **22b**, 700, 785, 905, 2100, 2200, 2920 cm$^{-1}$; NMR $\delta$ **22a**, 2.25 (m, 2 H), 2.57 (m, 2 H), 5.05 (m, 4 H), 5.80 (m, 1 H), 7.28 (m, 5 H); **22b**, 2.25 (d, 2 H), 5.05 (m, 4 H), 5.80 (m, 1 H), 7.28 (m, 5 H). The IR and NMR spectra of **22a** and **22b** were almost identical apart from those bands corresponding to the olefinic region.

**2,4-Diphenyl-1,5-hexadiene (26) and 1,5-Diphenyl-1,5-hexadiene (27).** Prepared in the same way as **14**, using 2-phenylallyl bromide in place of allyl bromide, **26** and **27** were separated by column chromatography, using a 33 × 2.5 cm column packed with silver nitrate (20%) on alumina. The column was eluted with ether (3.87 L), and then with a 1% solution of ethanol in ether. **2,4-Diphenyl-1,5-hexadiene (26)** was a liquid: IR (neat) 700, 755, 775, 895, 910 cm$^{-1}$; NMR $\delta$ 2.67 (d, 2 H), 3.30 (q, 1 H), 4.86 (multiplet, four main groupings, 4 H), 5.86 (m, 1 H), 7.04 (m, 10 H, sharp peaks at 6.98, 7.10). **1,5-Diphenyl-1,5-hexadiene (27)** (presumably trans) was also a liquid: IR (neat) 690, 700 (s), 740, 775, 895, 960 cm$^{-1}$; NMR $\delta$ 2.28 (m, 4 H), 4.95 (d, 1 H), 5.15 (d, 1 H), 6.1 (m, 3 H), 7.15 (m, 10 H); mass spectrum *m/e* 234 (parent peak), 117 (base peak, fission of 3,4 bonds).

**2,5-Diphenyl-3,3,4,4-tetradeuterio-1,5-hexadiene (25b).** 1,2-Dibenzoylethane (3.93 g) was dissolved in a mixture of dry 1,2-dimethoxyethane (350 mL) and $D_2O$ (40 mL). Lithium wire (0.25 g) was added and the mixture boiled under reflux for 1 h. The solution must remain yellow if the deuteration is to be successful. If necessary, add more lithium to maintain the yellow color. Chloroform (30 mL) was added, the organic layer dried ($MgSO_4$) and concentrated, and the deuteration repeated with dimethoxyethane (200 mL), $D_2O$ (30 mL), and lithium wire (0.25 g). Dry ether (100 mL) was then added and the organic layer separated, dried, and concentrated. Crystallization of the residue from anhydrous ethanol gave **1,2-dibenzoyltetradeuterioethane**, mp 146 °C. This was converted to **2,5-diphenyl-3,3,4,4-tetradeuterio-1,5-hexadiene (25b)** by the method used by Marvel and Gall[47] for **25a**, mp 48–49 °C (lit.[47] for **25a**, 48–49 °C) after chromatography on silica gel (97% $D_4$ by mass spectral analysis).

**Kinetic Measurements.** The reactions were carried out with degassed samples in sealed, evacuated ampules or NMR tubes in a large thermostated bath. Temperatures were measured with thermometers calibrated against NBS standard thermometers. The reactions all followed first-order kinetics accurately and were studied over at least 2 half-lives. The rate constants, together with standard deviations and correlation coefficients, were calculated by standard methods using the CDC 6400/6600 digital computer at the University of Texas Computation Center. Allowance was made for the time taken by samples to heat up after immersion in the bath by monitoring the temperature change in a dummy sample containing a thermocouple. The samples were generally analyzed by standard NMR techniques. In the case of reactions of **14** in the gas phase, the analysis was carried out by GLC, using a Wilkens Model 600-C (Hy-Fy) chromatograph equipped with a flame ionization detector and a 5 ft × 0.125 in. column packed with 20% DC550 on Chromosorb P (not acid washed). The spectrograph was calibrated with pure samples over a wide range of concentrations; the response was accurately linear. Comparison runs with **14** and **17a** showed that the rate constants found from NMR data and GLC data were the same within the limits of experimental error. All GLC analyses were repeated at least three times.

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# Photosensitized Oxygenation of $N_b$-Methoxycarbonyltryptamines. A New Pathway to Kynurenine Derivatives

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**Abstract:** Photosensitized oxygenation of $N_b$-methoxycarbonyltryptamine (**1a**) has been found to give 3a-hydroperoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole(**4a**) which then undergoes rearrangement to formylkynurenamine (**6a**) and $N_b$-formylkynurenamine (**7**) accompanied by the reduction product **5a**, showing that participation of the ethylamino side chain in **3** predominates over the hydroperoxy group. This suggests a new reaction pathway for the oxygenation of tryptophan to kynurenine other than the well-known hypothetical dioxetane pathway. $N_b$-Methoxycarbonyl-$N_b$-methyltryptamine (**1b**) under the same conditions, however, was converted to formylkynurenine derivative **6b**, demonstrating that the hydroperoxy group participates to form the dioxetane **9** when the ethylamino side chain is prevented from participation. In the case of $N_a$-methyl-$N_b$-methoxycarbonyltryptamine (**1c**), moreover, there is clearly a temperature dependence with regard to participation of the two neighboring groups: at about −70 °C **4c** was exclusively formed while at 5–10 °C the predominant product was **6c.** In contrast to **4a, 4c,** rearranged neither to compound **6c** nor **7.** On the other hand, **4** underwent an acid-catalyzed rearrangement to give the 1,4-benzoxazine derivative **14.**

Although the photosensitized oxygenation of tryptophan[1] and related compounds[2] has been extensively studied, the dynamic chemistry of these photoproducts in organic solvents was not well known. Prior to our preliminary publication[3] of part of this work, the only detailed study of the photosensitized oxygenation of tryptophan in nonaqueous solvent had been that of Scoffone and co-workers,[4] who showed that proflavine-sensitized photooxygenation of tryptophan derivatives in an acidic solvent, such as formic or acetic acid, results in high yields of the corresponding kynurenine derivatives, but the mechanism remained to be identified. More recent work has demonstrated that singlet oxygen is indeed involved in the methylene blue sensitized photooxygenation of tryptophan,[5] although it is probable that non-singlet-oxygen reaction becomes more important in certain conditions.[6]

The reaction of singlet oxygen with enamines having an NH hydrogen has been shown to give the azomethine hydroperoxide, RN=CCOOH,[7] whereas tertiary enamines undergo, 1,2-cycloaddition to give dioxetanes which readily decompose to carbonyl fragments.[8] The photosensitized oxygenation of tryptophan to kynurenine, therefore, seems to proceed via the dioxetane pathway as has been suggested,[2a,8c-e,9] i.e., the primary 3-hydroperoxyindolenine **3** collapses to the formylkynurenine via the dioxetane intermediate **9**, for which there is no direct evidence so far.

Recently, we have succeeded in isolating tricyclic hydroperoxides, such as **4a** and **10b** which show the existence of the intermediate **3** in the photosensitized oxygenation of tryptamine derivatives.[3,10] As a continuation of our work, we investigated the rose bengal sensitized oxygenation of $N_b$-methoxycarbonyltryptamines in various organic solvents. We have now found a new class of reactions in the oxygenation of tryptamine derivatives to kynurenine derivatives involving a tricyclic hydroperoxide, instead of a dioxetane.

## Results and Discussion

When $N_b$-methoxycarbonyltryptamine (**1a**) was irradiated in thoroughly $O_2$-saturated anhydrous benzene with a 200-W halogen lamp for 20 h in the presence of rose bengal under ice cooling (the reaction temperature was 5–10 °C) followed by