Migration of Electronegative Substituents. I. Relative Migratory Aptitude and Migration Tendency of the Carbethoxy Group in the Dienone–Phenol Rearrangement[1]

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Abstract: The rearrangement, in trifluoroacetic acid at 38.5°, of two series of 4,4-disubstituted cyclohexadienones to give 3,4-disubstituted phenols has been studied. In the first series, a carbethoxy group is placed in intramolecular migratory competition with other common substituents (Me, Et, Ph, i-Pr, Bz). The carbethoxy group is found to migrate in preference to Me, Et, or Ph with relative rates of 1:0.45:135. In the case of the i-Pr and Bz substituted compounds, fragmentation occurs instead of rearrangement to give 4-carbethoxyphenol and the i-Pr and Bz carbonium ions, respectively. In the second series, intermolecular kinetic comparisons of a series of compounds in which the substituents migrate in a methyl-substituted framework allows one to assess the migration tendency, as defined by Stiles and Mayer, of the substituents in the dienone system. The order found is Me < COOEt < Et < Ph with relative rates of 1:14:55:260. Unlike the relative migratory aptitude, which is influenced by a number of factors, the migration tendency is believed to measure primarily the inherent ability of the substituent to migrate in this system. The reason why an electronegative substituent, such as carbethoxy, is able to migrate at all is discussed.

The intramolecular 1,2-shift (Wagner–Meerwein rearrangement) of a group R to a cationic center is a much studied process. The group undergoing the migration is commonly a substituent, such as alkyl or aryl, which can stabilize the positive charges in the transition state for the rearrangement.

A small but growing number of examples are now known in which electron-withdrawing substituents (such as keto,[3] ester,[4] thio ester,[5] amidate,[6] phosphonate,[7] and phosphinyl[8] groups) undergo such migrations with ease in certain systems.[9] Yet the atom actually undergoing the migration is itself partially positive by normal polarization within the electronegative substituent. Thus, the atom undergoing the migration should not be good in stabilizing further positive charge density in the transition state for the rearrangement, and other factors must be operating to allow such groups to migrate with relative ease.

In the rearrangement of benzoyl epoxides with BF₃,

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(3) (a) H. O. House, *J. Amer. Chem. Soc.*, 76, 1235 (1954); (b) H. O. House and D. J. Reif, *ibid.*, 77, 6525 (1955); (c) H. O. House, *ibid.*, 78, 2298 (1956); (d) H. O. House and R. L. Wasson, *ibid.*, 78, 4394 (1956); (e) *ibid.*, 79, 1488 (1957); (f) H. O. House, D. J. Reif, and R. L. Wasson, *ibid.*, 79, 2490 (1957); (g) H. O. House and D. J. Reif, *ibid.*, 79, 6491 (1957); (h) H. O. House and G. D. Ryerson, *ibid.*, 83, 979 (1961); (i) H. Hart and L. R. Lerner, *J. Org. Chem.*, 32, 2669 (1967); (j) V. Tortorella, L. Toscano, C. Vetuschi, and A. Romeo, *J. Chem. Soc.*, 2422 (1971).

(4) (a) H. Plieninger and T. Suehiro, *Ber.*, 2798 (1956); (b) E. E. Blaise and A. Courtot, *Bull. Soc. Chim. Fr.*, 35, 360, 589 (1906); (c) S. Inayama and M. Yanagita, *J. Org. Chem.*, 27, 1465 (1962); (d) D. E. McGreer and Y. Y. Wigfield, *Can. J. Chem.*, 47, 2905 (1969); (e) S. P. Singh and J. Kagan, *J. Amer. Chem. Soc.*, 91, 6198 (1969); (f) J. Kagan, D. A. Agdeppa, Jr., and S. P. Singh, *Helv. Chim. Acta*, 55, 2252 (1972).

(5) J. Wemple, *J. Amer. Chem. Soc.*, 92, 6694 (1970).

(6) L. A. Paquette, T. Kakahano, and J. F. Kelly, *J. Org. Chem.*, 36, 435 (1971).

(7) R. H. Churi and C. E. Griffin, *J. Amer. Chem. Soc.*, 88, 1824 (1966); M. Sprecher and D. Kost, *Tetrahedron Lett.*, 703 (1969); N. N. Girotra and N. L. Wendler, *ibid.*, 4647 (1969); M. Sprecher and E. Nativ, *ibid.*, 4405 (1968).

(8) P. F. Cann and S. Warren, *Chem. Commun.*, 1026 (1970); P. F. Cann, D. Howells, and S. Warren, *ibid.*, 1148 (1971).

(9) Aspects of this type of reaction have only been reviewed briefly: (a) R. N. McDonald in "Mechanisms of Molecular Migrations," B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1971; (b) R. M. Acheson, *Accounts Chem. Res.*, 4, 177 (1971).

House[3a–h] has established that the benzoyl group migrates in an intramolecular sense, that the electronic requirements of the migrating group are not large ($\rho \sim -1$ for a series of substituted benzoyl epoxides), and the relative migratory aptitudes of common groups follow the order Ph > PhCO > H > Me. Kagan[4e,f] has shown that similar relationships exist for the carbethoxy groups in the rearrangement of glycidic esters and related pinacols.

We have embarked on a program to study in more detail the migration of electronegative substituents, choosing the acid-catalyzed dienone–phenol rearrangement of 4,4-disubstituted 2,5-cyclohexadienones for this study. Two examples of this type of rearrangement in slightly more substituted dienones are known. Plieninger[4a] reported that carbethoxy migrated in preference to methyl in 3,4-dimethyl-4-carbethoxy-cyclohexadienone and Inayama and Yanagita[4c] observed carbethoxy migration in preference to ring methylene in a substituted hydronaphthalenone. No mechanistic studies were reported.

We report here the rearrangement of two series of cyclohexadienones. In one of these (I) a carbethoxy group is placed in intramolecular migratory competition with common groups (R = Me, Et, i-Pr, Ph, Bz). This allows one to determine relative migratory aptitudes in the normal manner. The other series (II) provides comparison data in which the parent


I   II
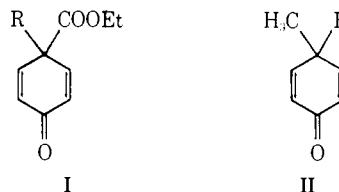
system is a methyl-substituted cyclohexadienone and only one substituent R is varied (R = Me, Et, Ph, COOEt). Since only the R group migrates (*vide infra*), this allows intermolecular kinetic comparisons among various substituents to be made, yielding values known

as migration tendencies, as defined by Stiles and Mayer.[10]

Synthesis of Cyclohexadienones. The cyclohexadienones (I) were synthesized by a Robinson annelation sequence, as depicted in Scheme I.

Scheme I

a, R = Me
b, R = Et
c, R = Ph
d, R = i-Pr
e, R = Bz
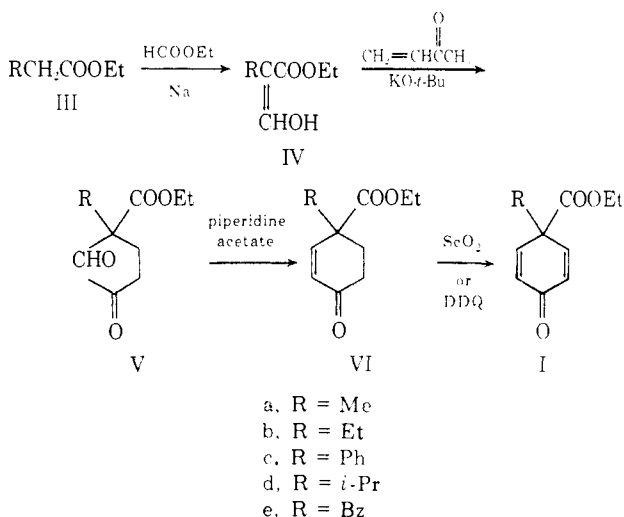
The formylation step to give IV has been reported previously[11] in all cases and proceeded in poor yield (3–25%) except for IIIc (78%). The addition of methyl vinyl ketone to give V and the subsequent cyclization to VI went in good yield. The dehydrogenation to the dienones (I) with dicyanodichloroquinone (DDQ) gave reasonable yields for the simpler members VIa and b, but gave low yields for VIc and d, and gave cleavage of the benzyl group to yield 4-carbethoxyphenol from VIe. Selenium dioxide in tert-butyl alcohol, however, gave improved yields (40–95%) in all cases.[12] In some cases, dimeric 2-substituted diselenides were formed as side products.[15] The dienones of series II are known compounds.[16–18]

Product Studies. Rearrangement of the cyclohexadienones of series I and II was carried out in trifluoroacetic acid. Compound Ia gave only 4-methyl-3-carbethoxyphenol (VIIa), the product of carbethoxy migration, as was expected.[4a] None of the product of methyl migration, 4-carbethoxy-3-methylphenol, was detected by vpc, and the nmr spectrum of the product mixture was superimposable on that of the pure compound. The structure of the product was assigned from the 60-MHz nmr spectrum in the aromatic region

(ABM pattern which appears as δ 6.79 (1 H, d, $J_{6,2}$ = 3 Hz, C-6 H), 6.86 (1 H, s, C-5 H, $J_{5,6}$ not detectable because of the similarity of the chemical shifts), 7.26 (1 H, d, $J_{2,6}$ = 3 Hz, C-2 H)). If the product were 4-carbethoxy-3-methylphenol, the C-2 and C-6 protons should be almost equivalent. Saponification of VIIa gave the known[19a,b] 4-methyl-3-carbethoxyphenol, which coincidently has almost the same melting point reported[19c] for 4-carbethoxy-3-methylphenol. However, the structural assignment was strengthened by reinvestigation[20] of the rearrangement of the closely related compound, 3,4-dimethyl-4-carbethoxycyclohexadienone, first reported by Plieninger.[4a] In this case, the product, 4,5-dimethyl-3-carbethoxyphenol, showed an identical nmr pattern for the C-2 and C-6 protons as did VIIa, thus ruling out the alternative symmetrical structure, 3,5-dimethyl-4-carbethoxyphenol.

The ethyl compound Ib rearranged smoothly with carbethoxy migration, to give only 4-ethyl-3-carbethoxyphenol (VIIb), whose structure follows from the almost identical nmr spectrum in the aromatic region to 4-methyl-3-carbethoxyphenol (VIIa).

The phenyl compound Ic rearranged very rapidly with carbethoxy migration to give only 4-phenyl-3-carbethoxyphenol (VIIc). Although the nmr spectrum was of no help in assigning the structure, saponification gave the known[21] 4-phenyl-3-carboxyphenol, further identified by sulfuric acid cyclization to 2-hydroxy-fluorenone (IX).[21] 4-Carboxy-3-phenylphenol and 3-hydroxyfluorenone, which would have resulted had the phenyl group migrated, are also known compounds[22] and have quite different melting points from our compounds. To strengthen the assignment further, the product was converted into its methyl ether (Xa), then the ester was converted into a methyl group via LiAlH$_4$ reduction to the alcohol Xc, conversion of this to the bromide Xd, and further LiAlH$_4$ reduction. The resulting product was identified as 4-phenyl-3-methylanisole (Xe), since it was clearly different from 3-methyl-4-phenylanisole (XIb), derived from rearrangement of dienone IIc (vide infra).

The isopropyl compound Id in trifluoroacetic acid gave only rapid cleavage to 4-carbethoxyphenol (XIIa) and isopropyl trifluoroacetate. Similarly, the benzyl compound Ie underwent rapid cleavage to 4-carbethoxyphenol (XIIa) (50%), benzyl trifluoroacetate (20%), polymer derived from the benzyl carbonium ion (30%), and 2-benzyl-4-carbethoxyphenol (XIIb) (50%), a product which doubtlessly arises by intermolecular recombination of the initial fragmentation products. As structure proof, compound XIIb was synthesized independently from 4-carbethoxyphenol and benzyl chloride with ZnCl$_2$.

4,4-Dimethylcyclohexadienone (IIa) gave only 3,4-dimethylphenol (VIIIa), as reported.[23] 4-Methyl-4-ethylcyclohexadienone (IIb) is reported[24] to give only 4-ethyl-3-methylphenol, the product of methyl migra-

(10) M. Stiles and R. P. Mayer, *J. Amer. Chem. Soc.*, **81**, 1497 (1959).

(11) (a) H. H. Harkins and T. B. Johnson, *J. Amer. Chem. Soc.*, **51**, 1237 (1929); (b) L. Legrande and N. Lozach, *Bull. Chem. Soc. Jap.*, **22**, 79 (1955); (c) H. Watanabe, A. Ide, N. Sugimoto, Y. Noguchi, R. Ishida, and Y. Kowa, *Yakugaku Zasshi*, **83**, 1118 (1963).

(12) Although all the details of the mechanism of dehydrogenation by these reagents are not known, the key step of DDQ oxidation probably involves hydride abstraction by the reagent[13] from the β position of the enol form of the ketone, while the SeO$_2$ reaction involves β-proton loss from an α-seleno derivative of the ketone.[14] Thus, it is reasonable to expect that DDQ would show the observed large steric effect and SeO$_2$ would not.

(13) *Cf.* B. M. Trost, *J. Amer. Chem. Soc.*, **89**, 1847 (1967).

(14) *Cf.* K. B. Wiberg and S. D. Nielson, *J. Org. Chem.*, **29**, 3353 (1964); K. B. Wiberg, "Oxidation in Organic Chemistry," Part A, Academic Press, New York, N. Y., 1965, p 105 ff.

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(20) J. N. Marx and R. L. Hartwell, unpublished observations.

(21) E. K. Huntress and M. K. Seikel, *J. Amer. Chem. Soc.*, **61**, 816 (1939).

(22) (a) G. Errara and G. G. LaSpada, *Gazz. Chim. Ital.*, **35**, II, 539 (1905); (b) F. Ullman and H. Bleier, *Ber.*, **35**, 4273 (1902).
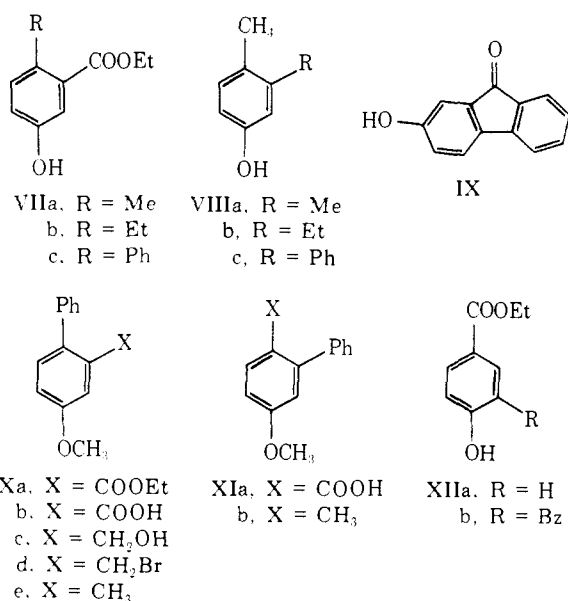
(23) V. P. Vitullo, *J. Org. Chem.*, **35**, 3976 (1970).

(24) R. H. Burnell, *J. Chem. Soc.*, 1307 (1958).

Table I. Rearrangement of 4,4-Disubstituted Cyclohexadienones in Trifluoroacetic Acid[a]

Compd	Substituents	Group migrating	$t_{1/2}$, min	$k_{obsd} \times 10^5$, sec^{-1}	$k_2 \times 10^5$, sec^{-1}[b]	$k_p \times 10^5$, sec^{-1}[c]	Migration tendency[d]
Ia	Me, COOEt	COOEt	120	9.56	19.1	19.1	14
Ib	Et, COOEt	COOEt	277	4.18	8.36	8.36	
Ic	Ph, COOEt	COOEt	1.6	1300	2600	2600	
Id	i-Pr, COOEt	Fragments	<1				
Ie	Bz, COOEt	Fragments	<1				
IIa	Me, Me	Me	648	1.75	2.80	1.40	1.00
IIb	Me, Et	Et (98%)	29	39.0	78	76.5	55
		Me (2%)				1.5	
IIc	Me, Ph	Ph	7.6	153	364	364	260

[a] Determined on 10% (w/v) solutions in CF$_3$COOH at 38.5°. [b] Corrected for the degree of protonation from the formula $k_2 = k_{obsd}[1 + ([I]/[A])]$ (see Scheme II). [c] $k_p = \alpha k_2$, where k_p = partial rate constant of the group R and α = fraction of the overall rearrangement due to R.[10] The k_p values as originally defined require corrections for the acidity of the medium. This is unnecessary here since the relative concentrations of the ions A can be determined directly by nmr spectroscopy. [d] As defined by Stiles and Mayer,[10] migration tendency $M_{CH_3} = k_p^R/k_p^{CH_3}$ (in IIa).

VIIa, R = Me
b. R = Et
c. R = Ph

VIIIa, R = Me
b, R = Et
c, R = Ph

IX

Xa, X = COOEt
b. X = COOH
c. X = CH$_2$OH
d. X = CH$_2$Br
e. X = CH$_3$

XIa, X = COOH
b, X = CH$_3$

XIIa, R = H
b, R = Bz

tion. This is contrary to the normally observed migratory order of the two groups and to the results in a naphthalenone system, where ethyl migrates exclusively.[25] We have found that the authentic sample of 4-ethyl-3-methylphenol, prepared by room temperature Fries rearrangement of m-cresol acetate[26] followed by Clemmensen reduction, is different by vpc and spectral criteria from the major product of rearrangement of IIb, even though the 3,5-dinitrobenzoate esters melt in exactly the same place and show no mixture melting point depression, as reported,[24] even though we did not obtain the reported value. Thus, the major product of the rearrangement is 4-methyl-3-ethylphenol (VIIIb), as expected, a formulation in accord with all spectral data of the compound.[26c] However, by methylation of the total product and use of Eu(fod)$_3$,[27] the presence of 2 ± 0.2% of the isomeric 4-ethyl-3-methylphenol was

(25) R. B. Carlin and K. P. Sivaramakrishnan, *J. Org. Chem.*, **35**, 3368 (1970).

(26) (a) K. W. Rosenmund and W. Schnurr, *Justus Liebigs Ann. Chem.*, **460**, 56 (1928). (b) *Cf.*, R. R. Read and J. Wood, Jr., "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 444.

(26c) NOTE ADDED IN PROOF. This conclusion has recently been independently verified: J. W. Pilkington and A. J. Waring, *Tetrahedron Lett.*, 4345 (1973). These authors report a "migratory aptitude" of ethyl over methyl in aqueous H$_2$SO$_4$ of 25. This value agrees well with our observed migration tendency of 55 in CF$_3$COOH (Table I) when the statistical and protonation corrections are taken into account.

(27) R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971).

detected by integration of the methoxy singlets in the shifted nmr spectrum.

4-Methyl-4-phenylcyclohexadienone (IIc)[18] rearranged rapidly to a single product, which was identified as 4-methyl-3-phenylphenol (VIIIc), the product of phenyl migration. Permanganate oxidation of the derived methyl ether (XIb) yielded the known[28] 4-methoxy-2-phenylbenzoic acid (XIa), whose melting point is much different from that of 5-methoxy-2-phenylbenzoic acid (Xb), which has also been synthesized by an unambiguous route.[28] This assignment is strengthened still further by a method which demonstrated the purity of the products from the rearrangement of Ic and IIc. Comparison of methyl ether XIb with Xe mentioned above revealed that all methyl signals were slightly separated by nmr spectroscopy and the shift reagent Eu(fod)$_3$[27] separated the signals well enough to show that each isomer was pure to the limit of the nmr method used (*ca.* 0.1%).

Relative Rates of Rearrangement. The rearrangement of Ia was investigated in several acidic systems. The rate was very fast in concentrated HClO$_4$ or H$_2$SO$_4$ (half-life less than 1 min), and the reaction mixture contained the rearrangement product VIIa as well as p-cresol, which arose by competing hydrolysis and decarboxylation of the ester function. Plieninger[29] has observed only decarboxylation in aqueous acid for a series of dienones I in which the R groups are derivatives of propionic or pyruvic acid. Therefore, we sought an anhydrous acid which would be strong enough to protonate the carbonyl group of the dienone but which would be nonpolar enough so that the rate of the reaction could be followed conveniently. Trifluoroacetic acid proved to be a good choice, since no decarboxylation occurred and the reaction was slowed down about two orders of magnitude.

Table I gives kinetic data for the rearrangement of the cyclohexadienones in trifluoroacetic acid at 28.5°. The reactions were carried out as 10% (w/v) solutions of the compounds in CF$_3$COOH in an nmr tube, and were monitored by nmr spectroscopy. In the case of Ia, the decrease of the methyl signal at δ 1.75 and the simultaneous increase of the methyl signal at δ 2.53 of

(28) J. R. E. Hoover, A. W. Chow, R. J. Stedman, N. M. Hall, H. S. Greenberg, M. M. Dolan, and R. I. Ferlauto, *J. Med. Chem.*, **7**, 245 (1964).

(29) (a) H. Plieninger, G. Ege, H. J. Grasshoff, G. Keilich, and W. Hoffman, *Ber.*, **94**, 2115 (1961); (b) H. Plieninger, L. Arnold, R. Fischer, and W. Hoffmann, *ibid.*, **98**, 1774, 1765 (1965).

the product were followed, as was the decrease of the vinyl doublet at 6.72 (C-3 H and C-5 H in protonated Ia). Following either signal gave comparable results, and the latter was used to determine the kinetics reported. In all cases, the reactions gave good first-order kinetics for at least 3–4 half-lives. The kinetic results are summarized in Table I.

Trifluoroacetic acid does not protonate the cyclohexadienones fully, and thus the observed rate will vary with the fraction of the dienone in the protonated form (see mechanistic discussion later, Scheme II). The degree of protonation could be estimated by nmr spectroscopy. Protonation causes a downfield shift of all signals in the nmr spectrum compared to the values in CCl_4, and the shift is related to the amount of protonation.[30–33] Complete protonation occurs in H_2SO_4[31] or "magic acid."[32] For enones or acid-stable dienones such as 4-methyl-4-trichloromethylcyclohexadienone,[33] the vinyl protons α to the carbonyl group are deshielded ca. 1.0 ppm and those β ca. 1.3 ppm. Most of the dienones in Table I rearrange in H_2SO_4 too rapidly for accurate observation of the protonated form, although IIa and more highly alkylated homologs, which rearrange slower, can be observed.[33c] However, the enone precursors VI are only protonated in H_2SO_4 and show the expected shifts of the vinyl proton signals ($\alpha = 0.92 \pm 0.03$, $\beta = 1.3 \pm 0.07$). Both the enones and the dienones of series I show almost the same amount of shift (0.45 ± 0.02 for α protons and 0.53 ± 0.04 for β protons) in trifluoroacetic acid. We conclude that the shifts of the β-proton signals are more susceptible to variation by the substituents than are the α-proton signals. Although the data for protonation in H_2SO_4 are also subject to effects of a change of medium and the uncertainty in determining shifts relative to TMS accurately,[31a] we find that almost the same shifts are observed in CF_3COOH to which a small amount of H_2SO_4 has been added. Therefore, assuming a linear relationship between the downfield shift of the α-proton signals and the amount of protonation, we calculate ca. 50% protonation in CF_3COOH. Although the assumption of linearity is probably not valid, at least the amount of shift is almost the same for all compounds of series I, so they are all protonated to about the same extent and comparisons among them are valid.

In the dialkyl series II, the amount of shift observed in CF_3COOH shows more variation: IIa, $\alpha = 0.55$, $\beta = 0.80$; IIb, $\alpha = 0.45$, $\beta = 0.64$; IIc, $\alpha = 0.39$, $\beta = 0.56$. Thus, these calculations give IIa ca. 60% protonated, IIb 50% protonated, and IIc 42% protonated. This has been taken into account in calculating k_2, the rate constant for the rearrangement step of the reaction.

Discussion

Through the years, many people have determined relative migratory aptitudes of substituents.[34,35] The general method used is to generate a carbonium ion via some method at a position adjacent to two or more substituents which potentially can migrate and to observe the ratio of products formed after the migration. This method of intramolecular comparison is complicated by many factors, such as the conformational preference of the various substituents, relative stability of the products formed, amount of charge density generated before rearrangement occurs, nature of the leaving group, and the inherent ability of the substituents to migrate.

Such complications are very difficult to sort out and will be different for each different compound. Most workers have concluded that it is impossible to assess meaningful relative migratory aptitudes to substituents which will be applicable to any other system or be a property of the migrating group. Still, in most systems, the relative order of migration of some simple substituents, as determined by product studies, still holds, e.g., Me < Et < Ph, the order expected from the ability of the substituent to stabilize positive charge.

One of the best systems known for studying rearrangement reactions appears to be the pinacol or related epoxide systems.[10,35] These have large driving force to give ketones (pinacolones). Still migratory aptitudes are a property of several complicating factors besides the inherent ability of the group to migrate. Stiles and Mayer[10] have attempted to cancel out most of these complications by studying the rearrangement of a series of glycols

$$
\begin{array}{ccc}
R & CH_3 & \\
| & | & \\
CH_3C & -C & -CH_3 \\
| & | & \\
OH & OH &
\end{array}
$$
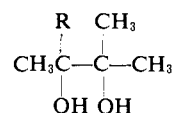
in which one group R was allowed to vary and the migration of the substituent R was determined by intermolecular comparisons of the rates with the parent compound (R = CH_3) after corrections for dehydration at the center adjacent to R. In this way, in 50% H_2SO_4, they determined an order of rearrangement of Me < Et < t-Bu with relative rates of 1:17:>4000. They have termed these intermolecular determinations "migration tendencies," a term which has gained some acceptance.[36–38]

For such migration tendencies to reflect a fundamental property of the migrating substituent in a given system, a necessary condition is that the migration occur during the rate-determining step. Stiles and Mayer[10] interpreted their data in terms of anchimeric assistance to ionization by the alkyl group, but other evidence suggests that rearrangement occurs after the rate-determining step in the pinacol rearrange-

(30) J. N. Marx, Tetrahedron Lett., 4957 (1971).

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(32) G. A. Olah, Y. Halpern, Y. K. Mo, and G. Liang, J. Amer. Chem. Soc., 94, 3554 (1972).

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(34) D. Bethell and V. Gold, "Carbonium Ions, an Introduction," Academic Press, New York, N. Y., 1967 pp 204–221.

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(37) (a) R. L. Heidke and W. H. Saunders, Jr., J. Amer. Chem. Soc., 88, 5816 (1966); (b) J. R. Owen and W. H. Saunders, Jr., ibid., 88, 5809 (1966).

(38) J. E. Dubois and P. Bauer, J. Amer. Chem. Soc., 90, 4510, 4512 (1968).

ment.[39-41] The large rate enhancement observed, at least for *tert*-butyl migration, has been ascribed primarily to relief of steric strain.[39]

The cyclohexadienone system appears to be much superior to the pinacol or any other known system for studying such rearrangements, as at least most of the complicating factors alluded to earlier should be minimized or eliminated. Thus, both substituents are held rigidly in identical steric environments in the dienone, so no migratory preference based on stereochemistry can occur, and the reaction is initiated by protonation on the carbonyl oxygen, so no complications connected with leaving groups can occur. The charge density generated at the migration terminus (C-3) by protonation can be estimated by nmr spectroscopy as *ca.* 0.15 of an electron unit.[33c] The rearrangement reaction has large driving force (aromatization), so completing reactions should be minimized or eliminated. Furthermore, the mechanism of the dienone–phenol rearrangement is now well established,[42] and it has been shown that the rearrangement step is rate determining and irreversible. This much simplifies kinetic analysis and allows one to relate kinetic results to the migration tendencies of substituents.

The data in Table I for the rearrangement of compounds Ia–e bear out the above analysis. Thus, when a carbethoxy group is placed in intramolecular competition with the common substituents Me, Et, and Ph, it is observed that *only* the carbethoxy group migrates, and that the rate is strongly influenced by the group which remains behind. This is consistent with the mechanism which has been established for the dienone–phenol rearrangement.[42] The mechanism, as it applies to the present case, is presented in Scheme II.

Scheme II
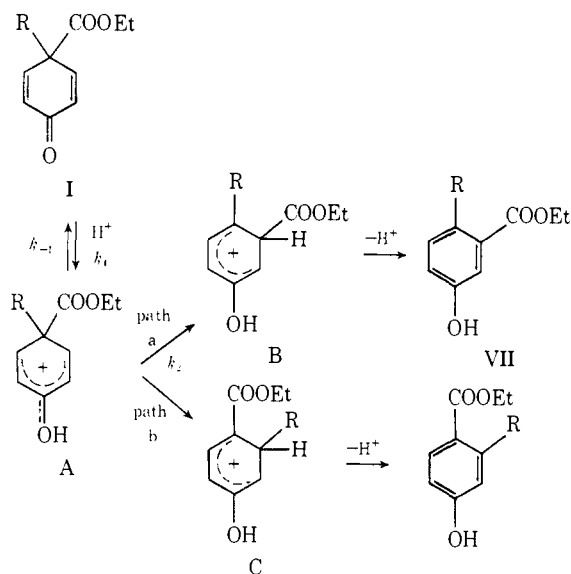
The first step is rapid and reversible, and the pro-

tonated ion A is detectable by nmr spectroscopy.[30,33] The rearrangement step is rate determining and irreversible,[42] and is followed by rapid proton loss which generates the aromatic ring. The ion A, in principle, has two rearrangement pathways open, in which either the carbethoxy group migrates to give B or the R group migrates to give C. Ion A is expected to be much more stable than B or C, since it contains the OH in resonance interaction with the charge, and B or C do not. (A resembles the Wheland intermediate for para attack on a phenol [actually, ipso attack[43]], while B or C represent Wheland intermediates for meta attack.) Thus, the rearrangement step is endothermic, but is coupled to a subsequent highly exothermic step (deprotonation). By the Hammond postulate,[44] the transition state should, therefore, more closely resemble the product ion (B or C) than A. Recent experimental evidence is in accord with this reasoning.[33a,45]

In the ion B (and thus the transition state preceding it) the group R remaining behind can stabilize the positive charge as it becomes conjugated with it. However, if R migrates to give ion C, the carbethoxy group will become conjugated with the charge. This violates Pauling's adjacent charge rule[46] and acts as a destabilizing influence. Thus, ion B is of lower energy than ion C and path a is followed.

This interpretation is in accord with the relative rates of rearrangement of compounds Ia, b, and c (Table I). Compound Ia rearranges 2.2 times faster than Ib, in accord with the fact that methyl can stabilize the developing adjacent positive charge better than ethyl. By the same token, a phenyl group would be expected to be considerably better than methyl in stabilizing this developing charge and a larger rate enhancement (135) is observed.

A more highly branched alkyl group, such as isopropyl, should be better at migrating than methyl or ethyl,[10,34] but poorer in stabilizing ion B (and the transition state leading to it). Thus, one might predict that isopropyl would migrate instead of carbethoxy and path b would be followed in this case. In fact, neither path is followed, but rather fragmentation occurs instead, as it does also when R = benzyl, a group which should stabilize ion B about as much as methyl, but which should be an even better migrating group than isopropyl. Evidently, the ion C is of too high energy to form when an alternative pathway (cleavage to a relatively stable R⁺) is open to A.

It is interesting to note that the electronegative group migrates in preference to phenyl in the dienone system but the reverse is true in the epoxide system.[3a] Using House's example, the key intermediate after the rearrangement would be D (instead of E). This places the positive charge adjacent to the benzoyl group. However, in this system, the main stabilizing influence on the positive charge doubtlessly is the adjacent oxygen atom, and the destabilizing influence of the electro-

(39) P. D. Bartlett and T. T. Tidwell, *J. Amer. Chem. Soc.*, **90**, 4421 (1968).

(40) S. Wold, *Acta Chem. Scand.*, **23**, 2978 (1969).

(41) (a) K. Matsumoto, *Tetrahedron*, **24**, 6851 (1968); (b) Y. Pocker and B. P. Ronald, *J. Amer. Chem. Soc.*, **92**, 3385 (1970).

(42) (a) V. P. Vitullo and N. Grossman, *Tetrahedron Lett.*, 1559 (1970); (b) V. P. Vitullo, *Chem. Commun.*, 688 (1970); (c) V. P. Vitullo and N. Grossman, *J. Amer. Chem. Soc.*, **94**, 3844 (1972).

(43) (a) C. L. Perrin and G. A. Skinner, *J. Amer. Chem. Soc.*, **93**, 3389 (1971); (b) C. L. Perrin, *J. Org. Chem.*, **36**, 420 (1971).

(44) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(45) Recently, V. P. Vitullo and E. A. Logue [*J. Org. Chem.*, **37**, 3338 (1972)] have shown that methyl migrates in preference to methoxy in the dienone system. Doubtlessly, other substituents capable of donating electron density through resonance would give similar results.

(46) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1948, p 199.

negative group is not nearly so important as it is in ion C of Scheme II.
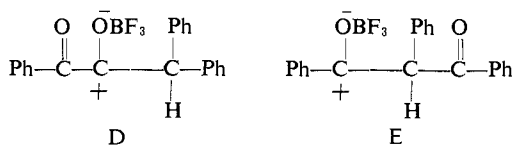
The data provided by the rearrangement of the series of dienones I allow one to assess how the carbethoxy group behaves when placed in migratory competition with other common substituents. Thus, in this system, the relative migratory aptitude of the carbethoxy group is greater than Me, Et, or Ph. But the apparent ease with which the carbethoxy group migrates is seen to be primarily an artifact, caused by the group remaining at the migration origin and thus the difference in energy between the ions B and C of Scheme II.

Recently, some attempts have been reported to determine in a systematic manner the influence the group remaining at the migration origin exerts on the migration of a substituent. These studies have compared only simple alkyl groups. Dubois and Bauer[38] have shown that the apparent relative migratory aptitudes of methyl and ethyl groups can be changed by their environment in a systematic manner in the metathetical transposition of ketones. Heidke and Saunders[37a] have been able to correlate rates of neopentyl rearrangements with the steric and electronic influence of the group not migrating, and Mazet[36] reported similar but more detailed studies in rearrangements of neopentyl-type 1,3-diols. In all these studies, however, rearrangement is apparently fairly concerted with ionization and no free carbonium ions are involved. Thus, the results are not directly applicable to the dienone system, where a large amount of positive charge density develops at the migration terminus before rearrangement takes place.[33c, 42]

In order to determine the migratory ability of substituents independently of the group remaining behind, we have studied the rearrangement of the series of dienones II (Table I), in which the group remaining behind is methyl and the migrating group is the only variable. By comparing the rates to that of 4,4-dimethylcyclohexadienone (IIa), one obtains intermolecular migration tendencies, as defined by Stiles and Mayer.[10]

Inspection of Table I reveals that in this system, ethyl migrates 55 times better than methyl under our conditions. This represents, to our knowledge, the largest migratory difference between the methyl and ethyl groups observed. Stiles and Mayer[10] report a value of 17 in the pinacol rearrangement, although this must be accepted with some reservation.[39-41] In the neopentyl rearrangements,[36-38] the order is reversed to ca. 0.5. However, this trend seems reasonable, since the difference between the two groups should increase as electronic effects become more important in a more carbonium-ion like transition state. It is reasonable, on the basis of hyperconjugative effects, to expect both that methyl should be the better remaining group to stabilize developing charge at the migration origin and ethyl should be better to stabilize the transition state for the rearrangement.

The migration tendency for the phenyl group is

260 (Table I). It seems somewhat surprising that the phenyl migrates only about five times faster than ethyl. This suggests strongly that the transition state is product-like, as expected from the Hammond postulate[44] and so the effect of the migrating group on stabilizing the transition state is not too important. The fact that the phenyl group has more rigid geometric requirements for migration may also be of some importance.[47]

An interesting correlation, from the standpoint of the present work, is the migration tendency of carbethoxy, which is found to be 14. Thus, in the intermolecular sense, carbethoxy (and by extension presumably other electronegative groups, although this is under study) is inherently a better migrating group than methyl.

The relative values of the rate constants in this series can doubtlessly be changed somewhat by the use of other reaction conditions, but we believe the order Me < COOEt < Et < Ph observed here is primarily an inherent property of the substituent[45] and should hold for any other systems in which other variables can be eliminated or minimized and the reaction involves fairly developed carbonium ion character. We are investigating this possibility at present.

It must be emphasized that the migration tendency is an empirical quantity which reflects the rate at which the group in question can migrate, independently of the other influences in the system. Thus, of necessity, it cannot be used to predict how a given group will behave when placed in migratory competition with any other group, since the other group will always exert its own influence on the migration. In this connection, it is interesting to note that in the present system, *only* one group migrates unless the two groups are very similar in their ability to act as remaining groups. In the present work only compounds IIa (groups identical) and IIb (the product of methyl migration is observed to the extent of 2%) fit this category.

It is worth considering why the carbethoxy can migrate, despite the fact that the carbon atom undergoing the migration is highly positive by polarization within the carbonyl group. The π system of the carbonyl seems to be necessary to back-donate some electron density to the transition state for the migration reaction, since the trichloromethyl group, for example, which has similar polarity to carbethoxy but which lacks π electrons, will not undergo such migrations, even under forcing conditions.[33, 48]

The present evidence does not distinguish between contributing structures for this carbonyl participation involving a phenol–acylonium ion pair and those involving a positive oxygen with a sextet of electrons, and probably both have some importance. Thus, we believe the transition state for the migration reaction in the present case should be represented as in formula F, with the migration being fairly advanced (more like product ion B than initial ion A of Scheme II).

Experimental Section

Formylation of Esters IIIa-e. A mixture of 102 g (1.0 mol) of ethyl propionate (IIIa) and 111 g (1.5 mol) of ethyl formate was

(47) *Cf.* W. E. Parham and L. J. Czuba, *J. Amer. Chem. Soc.*, **90**, 4030 (1968).
(48) M. S. Newmann, D. Pawelek, and S. Ramachandran, *J. Amer. Chem. Soc.*, **84**, 995 (1962).

F
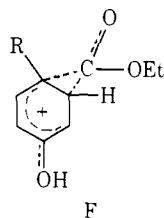
added dropwise over a 10-hr period to a large three-necked flask containing 23 g (1.0 mol) of granulated sodium suspended in 500 ml of dry ether. The mixture was stirred for 2 days, and a yellow precipitate formed as the sodium disappeared. The sodium salt was dissolved in 400 ml of H_2O and neutralized with 5% HCl. The aqueous phase was washed with two 100-ml portions of ether, and the combined organic layers were washed with aqueous NaH-CO_3 and H_2O and then dried ($MgSO_4$). Removal of the solvent followed by distillation through a short Vigreux column gave ethyl α-formyl propionate as a clear oil, 26.2 g, 23%, bp 42–45° (1.5 mm), semicarbazone mp 166–168° (EtOH).

The same procedure as above gave ethyl α-formylbutyrate (IVb), bp 38–40°, 17% yield, semicarbazone mp 173–174° (lit. bp 64–66° (16 mm), 35%;[11b] bp 71–75° (22 mm), 12.6%[11c]).

The same procedure, but using 2 equiv of Na, gave ethyl α-formyl-α-phenylacetate (IVc), bp 142–145° (4 mm), 78% yield (lit.[49b] bp 95–96° (1 mm), 48.1%).

The same procedure, except use of a fivefold excess of ethyl formate, gave ethyl α-formylhydrocinnamate (IVe), bp 107–117° (3 mm), 9% yield (lit.[11c] bp 129–132° (3 mm), 23%).

The above procedure gave a 3% yield of ethyl α-formylisovalerate (IVd). An overall yield of 20% was obtained by bromination of ethyl isovalerate, followed by Reformatsky reaction with ethyl orthoformate[49] followed by hydrolysis of the resulting acetal (5:1 acetone–concentrated HCl for 1.5 hr). The product had bp 57–59° (0.3 mm), semicarbazone 107–109° (lit.[49b] bp 68–70° (9 mm), semicarbazone mp 108°).

Reaction of Formyl Esters IVa–e with Methyl Vinyl Ketone. Ethyl α-formylpropionate (IVa) (22.8 g, 0.18 mol) and methyl vinyl ketone (12.2 g, 0.18 mol) were mixed and cooled to 0°. A solution of KO-t-Bu from 0.1 g of potassium in 20 ml of t-BuOH was added dropwise during 1 hr. The solution was allowed to warm to room temperature and stirred 24 hr, then concentrated at the aspirator. The remaining oil was taken up in ether, extracted with cold 0.5 N NaOH and H_2O, and dried over $MgSO_4$. Removal of the solvent gave 27.9 g (77%) of ethyl 2-formyl-2-methyl-5-oxocaproate (Va) homogeneous by tlc: nmr (CCl_4) δ 1.22 (3 H, s), 1.30 (3 H, t, J = 7 Hz), 2.13 (3 H, s), 1.6–2.6 (4 H, m), 4.25 (2 H, q, J = 7 Hz), 9.90 (1 H, s) (lit.[50] 66%). The material was used directly in the cyclization step.

By analogous procedures, the following compounds were prepared. IVb gave ethyl 2-formyl-2-ethyl-5-oxocapronate (Vb) (62%): nmr (CCl_4) δ 0.98 (3 H, t, J = 7 Hz), 1.28 (3 H, t, J = 7 Hz), 2.06 (3 H, s), 1.1–2.4 (6 H, m), 4.16 (2 H, q, J = 7 Hz), 9.80 (1 H, s).

IVc gave ethyl 2-formyl-2-phenyl-5-oxocapronate (Vc) (93%): nmr (CCl_4) δ 1.26 (3 H, t, J = 7 Hz), 2.00 (3 H, s), 2.33 (4 H, m), 4.22 (2 H, q, J = 7 Hz), 7.20 (5 H, m), 9.95 (1 H, s).

IVd gave ethyl 2-formyl-2-isopropyl-5-oxocapronate (Vd) (87%): nmr (CCl_4) δ 0.93, 1.03 (6 H, d of d, J = 7 Hz), 1.27 (3 H, q, J = 7 Hz), 2.07 (3 H, s), 1.7–2.6 (5 H, m), 4.35 (2 H, q, J = 7 Hz), 10.12 (1 H, s).

IVe gave ethyl 2-formyl-2-benzyl-5-oxocapronate (Ve) (67%): nmr (CCl_4) δ 1.15 (3 H, t, J = 7 Hz), 1.90 (3 H, s), 2.1–3.2 (4 H, m), 3.07 (2 H, s), 4.12 (2 H, q, J = 7 Hz), 7.20 (5 H, s), 10.00 (1 H, s).

Cyclization of Adducts Va–e to Enones VIa–e. (a) Ethyl 2-formyl-2-methyl-5-oxocapronate (Va) (27.0 g, 0.14 mol), 1.95 g (0.01 mol) of piperidine acetate, 1.95 g of glacial acetic acid, and 50 ml of benzene were refluxed into a Dean–Stark trap. After refluxing 24 hr, 2.1 ml of water (86% of theoretical) was collected. Removal of the benzene, dissolving the residue in ether and washing twice with H_2O, drying ($MgSO_4$), and removal of the ether followed by a distillation through a short Vigreux column gave 16.3 g (68%) of 4-methyl-4-carbethoxycyclohex-2-enone (VIa): bp 92–

(49) (a) K. Sestanj, Croat. Chem. Acta, 34, 211 (1962); Chem. Abstr., 59, 5012g (1963); (b) M. Miyazaki, C. Mizuno, and S. Umis, Yakugaku Zasshi, 77, 415 (1956); Chem. Abstr., 51, 12068c (1957).

(50) H. Plieninger, L. Arnold, and W. Hoffmann, Ber., 98, 1399 (1965).

97° (1 mm); nmr (CCl_4) δ 1.28 (3 H, t, J = 7 Hz), 1.42 (3 H, s), 1.8–2.6 (4 H, m), 4.21 (2 H, q, J = 7 Hz), 5.90 (1 H, d, J = 10 Hz), 6.90 (1 H, d, J = 10 Hz); semicarbazone, mp 167.5–169.5° (lit.[50] bp 135–140° (1.8 mm), mp 157°).

(b) Adduct Vb was cyclized similarly to 4-ethyl-4-carbethoxy-cyclohex-2-enone (VIb) (68%): bp 130–132° (2.5 mm); ir (film) 1730, 1695, 1620 cm^{-1}; nmr (CCl_4) δ 0.93 (3 H, t, J = 7 Hz), 1.29 (3 H, t, J = 7 Hz), 1.6–2.6 (6 H, m), 4.22 (2 H, q, J = 7 Hz); 5.93 (1 H, d, J = 10 Hz), 6.93 (1 H, d, J = 10 Hz); semicarbazone, mp 173–174°. Anal. Calcd for $C_{12}H_{19}N_3O_3$: C, 56.90; H, 7.56. Found: C, 56.82; H, 7.43.

(c) Adduct Vc was cyclized to 4-phenyl-4-carbethoxycyclohex-2-enone (VIc) (97%): bp 158–160° (1.5 mm); ir (film) 1730, 1685, 1605 cm^{-1}; nmr (CCl_4) δ 1.18 (3 H, t, J = 7 Hz), 2.2–2.8 (4 H, m), 4.14 (2 H, q, J = 7 Hz), 6.04 (1 H, d, J = 10 Hz), 7.11 (1 H, d, J = 10 Hz), 7.19 (5 H, m); semicarbazone mp 190–191°. Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.35. Found: C, 63.79; H, 6.44.

(d) Adduct Vd was cyclized to 4-isopropyl-4-carbethoxycyclo-hex-2-enone (VId) (47%): bp 132–133° (1 mm); ir (film) 1730, 1685, 1625 cm^{-1}; nmr (CCl_4) δ 0.93, 0.96 (6 H, d of d, J = 7 Hz), 1.28 (3 H, t, J = 7 Hz), 1.8–2.6 (5 H, m), 4.21 (2 H, q, J = 7 Hz), 5.94 (1 H, d, J = 10 Hz), 6.77 (1 H, d of d, J = 10 and 2 Hz); semicarbazone, mp 167–168.5°. Anal. Calcd for $C_{13}H_{21}N_3O_3$: C, 58.41; H, 7.92. Found: C, 58.10; H, 7.75.

(e) Adduct Ve was cyclized to 4-benzyl-4-carbethoxycyclohex-2-enone (VIe) (64%): bp 150–154° (0.15 mm); nmr (CCl_4) δ 1.17 (3 H, t, J = 7 Hz), 1.8–2.6 (4 H, m), 3.05 (2 H, s), 4.12 (2 H, q, J = 7 Hz), 5.92 (1 H, d, J = 10 Hz), 6.92 (1 H, d, J = 10 Hz). 7.17 (5 H, m); dinitrophenylhydrazone, mp 121.5–122° (EtOH–H_2O). Anal. Calcd for $C_{22}H_{22}N_4O_6$: C, 64.20; H, 5.73. Found: C, 64.44; H, 5.49.

Oxidation of Enones VIa–e to Dienones Ia–e. A. With DDQ. 4-Methyl-4-carbethoxy-2-cyclohexenone (VIa), 1.82 g (0.01 mol), and 2.95 g of dichlorodicyanoquinone (DDQ) were mixed and refluxed 40 hr in 50 ml of dioxane. The solution turned dark brown during the reaction. After cooling, the hydroquinone was filtered off and the dioxane removed at reduced pressure. The remaining red oil was chromatographed on a short alumina column by elution with 60% petroleum ether–40% ether. The first yellow band collected contained 1.42 g (79%) of 4-methyl-4-carbethoxy-cyclohexa-2,5-dienone (Ia): ir (film) 1740, 1670, 1640, 1615 cm^{-1}; nmr (CCl_4) δ 1.28 (3 H, t, J = 7 Hz, ester Me), 1.50 (3 H, s, C-4 Me), 4.23 (2 H, q, J = 7 Hz, ester CH_2), 6.32 (2 H, d, J = 10 Hz, C-2 and C-6 H), 7.06 (2 H, d, J = 10 Hz, C-3 and C-5 H); semicarbazone, mp 200–202°. Anal. Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37. Found: C, 54.89; H, 6.14.

Enone VIb by the same procedure gave 52% of 4-ethyl-4-carb-ethoxycyclohexa-2,5-dienone (Ib): ir (film) 1735, 1700, 1675, 1640 cm^{-1}; nmr (CCl_4) δ 0.89 (3 H, t, J = 7 Hz), 1.29 (3 H, t, J = 7 Hz), 2.01 (2 H, q, J = 7 Hz), 4.22 (2 H, q, J = Hz), 6.29 (2 H, d, J = 11 Hz), 7.01 (2 H, d, J = 11 Hz); semicarbazone mp 139–140°. Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82. Found: C, 56.60; H, 6.52.

Compound VIc gave 25% of dienone Ic: ir (film) 1730, 1665, 1630 cm^{-1}; nmr (CCl_4) δ 1.28 (3 H, t, J = 7 Hz), 4.23 (2 H, q, J = 7 Hz), 6.24 (2 H, d, J = 10 Hz), 7.12 (2 H, d, J = 10 Hz), 7.18 (5 H, s); semicarbazone, mp 184–185°. Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.73. Found: C, 64.60; H, 5.64.

Compound VId gave 15% of the dienone Id after chromatography on silica gel: nmr (CCl_4) δ 0.93 (6 H, d, J = 7 Hz), 1.29 (3 H, t, J = 7 Hz), 2.3 (1 H, m), 4.23 (2 H, q, J = 7 Hz), 6.32 (2 H, d, J = 10 Hz), 7.05 (2 H, d, J = 10 Hz). Attempted semicarbazone formation resulted in fragmentation of the compound.

Compound VIe, upon reflux with DDQ for 42 hr then chromatographic purification on silica gel, gave 4-carbethoxyphenol, mp 111–112° (CCl_4), identical with an authentic sample, as the only identifiable product. No attempt was made to determine the fate of the benzyl fragment from the compound.

B. With Selenium Dioxide. 4-Benzyl-4-carbethoxycyclohex-2-enone (VIe), 5.414 g (0.020 mol), 250 ml of t-BuOH, 3.21 ml of glacial HOAc, and 2.38 g (1.0 equiv) of SeO$_2$ were refluxed for 24 hr. An additional 2.38 g of SeO$_2$ was added and the black mixture refluxed an additional 24 hr. The mixture was filtered and worked up by the method of Wettstein.[51] Thus, the brown filtrate was concentrated in vacuo, taken up in EtOAc, washed succes-

(51) C. Meystre, H. Frey, W. Voser, and A. Wettstein, Helv. Chim. Acta, 39, 734 (1956).

sively with dilute $NaHCO_3$, water, cold dilute $(NH_4)_2S$, cold dilute NH_4OH, water, dilute HCl, and water, and then dried over $MgSO_4$. Evaporation of the solvent gave 3.38 g of yellow oil which was chromatographed over 400 g of silica gel. Elution with increasing amounts of ethyl acetate in petroleum ether gave in the 2:8 fractions 2.15 g (40%) of pure 4-benzyl-4-carbethoxycyclohexa-2,5-dienone (IIe): nmr (CCl_4) δ 1.12 (3 H, t, J = 7 Hz), 3.20 (2 H, s), 4.12 (2 H, q, J = 7 Hz), 6.22 (2 H, d, J = 10 Hz), 7.11 (2 H, d, J = 10 Hz), 7.20 (5 H, s). Attempted semicarbazone formation resulted in the formation of phenolic materials. Similar oxidation of enones VI gave dienones I with the following yields, after chromatography: Ia, 72%, Ib, 75%, Ic, 91%, Id, 83%, IIb, 70%. In the case of IIa and IIb, the crude product before distillation deposited 14% of crystalline selenium-containing compounds from CCl_4, identified as bis-2-(4,4-dimethylcyclohexa-2,5-dienoyl) diselenide, mp 155–157°, and bis-2-(4-methyl-4-ethylcyclohexa-2,5-dienonyl) diselenide, mp 141–143°, respectively.[15]

Rearrangement of 4-Methyl-4-carbethoxycyclohexa-2,5-dienone (Ia). The dienone Ia (50 mg, 0.27 mmol) was dissolved in 1 ml of trifluoroacetic acid. The nmr spectrum showed the protonated dienone: δ 1.39 (3 H, t, J = 7 Hz), 1.75 (3 H, s), 4.42 (2 H, q, J = 7 Hz), 6.72 (2 H, d, J = 10 Hz), 7.59 (2 H, d, J = 10 Hz). After ca. 2.5 hr, the signal at δ 1.73 had decreased to half its intensity and a new methyl signal at δ 2.52 had grown to half its final height. After 24 hr, the peaks for starting material were no longer detectable. After 48 hr, the mixture was diluted with water, extracted with ether, washed with 5% $NaHCO_3$ and then water, then dried ($MgSO_4$), and the ether removed. Vpc and tlc showed only 4-methyl-3-carbethoxyphenol (VIIa): nmr (CCl_4) δ 1.37 (3 H, t, J = 7 Hz, ester Me), 2.42 (3 H, s, C-4 Me), 4.25 (2 H, q, J = 7 Hz, ester CH_2), 6.79 (1 H, d, J = 3 Hz, C-6 H), 6.86 (1 H, s, C-5 H), 7.26 (1 H, d, J = 3 Hz, C-2 H). Saponification with 3 N NaOH at 50° for 1 hr gave only 4-methyl-3-carboxyphenol, mp 179–180° (benzene) (lit. 182°,[20a] 184°[20b]). 4-Carboxy-3-methylphenol has a reported[20c] mp 177–179°, but the nmr spectrum rules it out as the structure for the product.

Rearrangement of 4-Ethyl-4-carbethoxycyclohexa-2,5-dienone (Ib). A solution of 50 mg of Ib in 1 ml of trifluoroacetic acid showed the following nmr spectrum: δ 0.95 (3 H, t, J = 7 Hz), 1.40 (3 H, t, J = 7 Hz), 2.28 (2 H, q, J = 7 Hz), 4.45 (2 H, q, J = 7 Hz), 6.78 (2 H, d, J = 10 Hz), 7.63 (2 H, d, J = 10 Hz). After 3 days at room temperature, work-up gave only 4-ethyl-3-carbethoxyphenol (VIIb) (48 mg): nmr (CCl_4) δ 1.20 (3 H, t, J = 7 Hz), 1.40 (3 H, t, J = 7 Hz), 2.89 (2 H, q, J = 7 Hz), 4.38 (2 H, q, J = 7 Hz), 6.96 (1 H, d, J = 3 Hz), 7.06 (1 H, s), 7.39 (1 H, d, J = 3 Hz). Saponification gave 4-ethyl-3-carboxyphenol, mp 147–149° (ether). *Anal.* Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.27; H, 6.09 (lit.[52] mp 155°).

Rearrangement of 4-Isopropyl-4-carbethoxycyclohexa-2,5-dienone (Id). The dienone Id (50 mg) in 1 ml of trifluoroacetic acid was almost all rearranged by the end of 2 min, so the protonated form could not be observed. The nmr spectrum of the product in trifluoroacetic acid showed δ 1.4 (3 H? — overlap with other peaks, t, J = 7 Hz), 4.57 (2 H, q, J = 7 Hz), 7.09 (2 H, d, J = 9 Hz), 8.16 (2 H, d, J = 9 Hz) due to 4-carbethoxyphenol (XIIa) and δ 1.4 (6 H? — overlap with other peaks, d, J = 7 Hz) and 5.41 (1 H, sept, J = 7 Hz), due to isopropyl trifluoroacetate. The latter compound was synthesized from isopropyl alcohol and trifluoroacetic anhydride in pyridine and had an identical nmr spectrum (peak enhancement) and tlc behavior to one component of the reaction mixture. Chromatography of the reaction mixture over silica gel and elution with 10% ether in petroleum ether gave isopropyl alcohol from hydrolysis of the isopropyl trifluoroacetate. Further elution with 30% ether in petroleum ether gave 4-carbethoxyphenol (XIIa), mp and mmp 111–112°.

Rearrangement of 4-Phenyl-4-carbethoxycyclohexa-2,5-dienone (Ic). The dienone Ic (50 mg) in 1 ml of trifluoroacetic acid had the following partial nmr spectrum: δ 6.75 (2 H, d, J = 10 Hz, C-3 and C-5 H) and 7.82 (2 H, d, J = 10 Hz, C-2 and C-6 H). Rearrangement was complete within 0.5 hr. The usual work-up gave 48 mg of 4-phenyl-3-carbethoxyphenol (VIIc): nmr (CCl_4) δ 0.99 (3 H, t, J = 7 Hz) and 4.21 (2 H, q, J = 7 Hz), 7.25 (8 H, m). Saponification gave 4-phenyl-3-carboxyphenol, mp 199–200° (H_2O) (lit.[21] mp 201°). Treatment of the compound with concentrated H_2SO_4 gave 2-hydroxyfluorenone as orange crystals, mp 207–208° (EtOH–H_2O) (lit.[21] mp 206.5°). 3-Hydroxyfluorenone has a reported[22] mp 225°.

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4-Phenyl-3-carbethoxyphenol (VIIc) was converted into its methyl ether (Xa) with Me_2SO_4 and NaOH. This without purification was reduced with excess $LiAlH_4$ in ether at 25° for 15 min to give the benzyl alcohol Xc: nmr (CCl_4) δ 3.58 (3 H, s), 4.28 (2 H, s), 7.10 (5 H, s), 6.5–7.5 (3 H, m). This was dissolved in concentrated HBr containing a little $ZnBr_2$. After 10 min at 25°, the bromide Xd was isolated by ether extraction: nmr (CCl_4) δ 3.75 (3 H, s), 4.30 (2 H, s), 7.30 (5 H, s), 6.7–7.3 (3 H, m). Without purification, the bromide Xd was refluxed 26 hr with excess $LiAlH_4$. The product (Xe) was passed through a silica gel column with 5% ether in pentane to remove traces of contaminants, and had nmr (CCl_4) δ 2.22 (3 H, s), 3.88 (3 H, s), 7.27 (5 H, s), 6.7–7.6 (3 H, m). The peaks were shifted downfield when 0.1–0.3 equiv of $Eu(fod)_3$ was added, but no new peaks were detectable. The methyl signals in a synthetic mixture of Xe and XIb (*vide infra*) were well separated under these conditions, such that ca. 0.1% of XIb could have been detected in the original sample. The synthetic mixture was not separated at all under the chromatography conditions mentioned above, so no selective loss of one component could have occurred.

Rearrangement of 4-Benzyl-4-carbethoxycyclohexa-2,5-dienone (Ie). The dienone Ie (570 mg) rearranged in trifluoroacetic acid too fast to detect the protonated form. The nmr spectrum showed a mixture of products. Ether extraction gave 519 mg of product, which was chromatographed on 75 g of silica gel packed in benzene. Elution with increasing amounts of CH_2Cl_2 gave in fractions with 10% CH_2Cl_2, crude benzyl alcohol. By synthesis of benzyl trifluoroacetate from benzyl alcohol and trifluoroacetic anhydride in pyridine, a peak at δ 6.50 could be identified as due to benzyl trifluoroacetate. Elution with 30–50% CH_2Cl_2 gave crude XIIb, which was purified by rechromatography and recrystallization to give a sample, mp 129–131°, identical with the compound as prepared below. Integration of the δ 4.04 peak showed 50% yield of this compound. Elution of the column with pure CH_2Cl_2 gave pure 4-carbethoxyphenol, mp 112–114° (CCl_4). The ethyl signal in CF_3COOH at δ 1.50 was of the same intensity as the one at δ 1.46 due to XIIb, in the original spectrum, thus allowing an estimate of 50% yield. Other noncharacterized material was ascribed to polymer.

To a solution of 11.54 g of 4-carbethoxyphenol and 7.56 g of benzyl chloride in 20 ml of dried $CHCl_3$ (H_2SO_4, then $CaCl_2$) was added 2.72 g of $ZnCl_2$ which had been dried at 110°, and the solution refluxed overnight. The $CHCl_3$ solution was then washed with water, dried, and the $CHCl_3$ removed to give 13.3 g of a gum. Chromatography of 2 g of this material on 60 g of silica gel with CH_2Cl_2 in benzene gave, in the 1:4 fractions, 1.0 g of 4-carbethoxy-2-benzylphenol (XIIb): mp 129–131° (benzene–CH_2Cl_2): nmr ($CDCl_3$) δ 1.38 (3 H, t, J = 7 Hz), 4.04 (2 H, s), 4.39 (2 H, q, J = 7 Hz), 6.90 (1 H, d, J = 9 Hz), 7.31 (5 H, s), 7.8–8.1 (2 H, m).

Rearrangement of 4,4-Dimethylcyclohexa-2,5-dienone (IIa). The dienone (kindly supplied by V. P. Vitullo) had the following nmr spectrum: (CCl_4) δ 1.27 (6 H, s), 6.09 (2 H, d, J = 10 Hz), 6.75 (2 H, d, J = 10 Hz); (CF_3COOH) δ 1.42 (6 H, s), 6.66 (2 H, d, J = 10 Hz), 7.55 (2 H, d, J = 10 Hz). Rearrangement was followed on 50 mg in 1.0 ml CF_3COOH for 110 hr (ca. 5 half-lives), and worked up by ether extraction to give 3,4-dimethylphenol:[23] nmr (CCl_4) δ 2.17 (6 H, s), 6.3–7.4 (3 H, m), mp 62–64° (lit.[23] 62.5–65°).

Rearrangement of 4-Methyl-4-ethylcyclohexa-2,5-dienone (IIb). The dienone IIb (prepared by SeO_2 oxidation of 4-methyl-4-ethylcyclohexanone,[17] bp 45–48° (0.25 mm), mp 23.5–24°) showed the following nmr spectrum (CCl_4): δ 0.80 (3 H, t, J = 7 Hz), 1.28 (3 H, s), 1.70 (2 H, q, J = 7 Hz), 6.23 (2 H, d, J = 10 Hz), 6.81 (2 H, d, J = 10 Hz); (CF_3COOH) δ 0.81 (3 H, t, J = 7 Hz), 1.38 (3 H, s), 1.90 (2 H, q, J = 7 Hz), 6.68 (2 H, d, J = 10 Hz), 7.45 (2 H, d, J = 10 Hz). Rearrangement in CF_3COOH was complete within 3 hr. The product, 4-methyl-3-ethylphenol, appeared homogeneous by tlc and vpc, and had nmr ($CDCl_3$): δ 1.12 (3 H, t, J = 7 Hz), 2.19 (3 H, s), 2.52 (2 H, q, J = 7 Hz), 6.5–7.2 (3 H, m, main peak at 6.70). Its 3,5-dinitrobenzoate had mp 108.5–109.5° (lit.[24] 130°).

Methylation (Me_2SO_4 and NaOH) gave the methyl ether. Upon adding 0.1 equiv of $Eu(fod)_3$ in an nmr tube in $CDCl_3$, a set of smaller resonances, identical with those from the Fries product below, were separated from the main ones. The largest shift difference (ca. 10% greater for the Fries product) observed was for the methyl ether signal. Integration gave 2 ± 0.2% of this product in the mixture.

Fries rearrangement of *m*-cresol acetate at 25° in nitrobenzene gave 4-aceto-3-methylphenol,[26a] which upon Clemmensen reduction[26b] gave an authentic sample of 4-ethyl-3-methylphenol. Its 3,5-dinitrobenzoate ester had mp 108.5–109° (lit.[24] 130°), mmp (with

the sample above) 109–109.5°. However, the phenol was different by nmr (CDCl$_3$): δ 1.00 (3 H, s), 2.05 (3 H, s), 2.40 (2 H, q, J = 7 Hz), 6.4–7.0 (3 H, m, main peak at 6.62) and was slightly separated by vpc (SE-30 on Chromosorb G) from the rearrangement product above, and its nmr signals were well separated by Eu(fod)$_3$.

Rearrangement of 4-Methyl-4-phenylcyclohexa-2,5-dienone (IIc). The dienone IIc (kindly supplied by Dr. V. P. Vitullo) has the following nmr spectrum (CCl$_4$): δ 1.75 (3 H, s), 6.50 (2 H, d, J = 10 Hz), 7.20 (2 H, d, J = 10 Hz), 7.59 (5 H, s). After 1 hr, rearrangement was complete and the product, 4-methyl-3-phenylphenol (VIIIc), was isolated in the usual way. It had nmr (CCl$_4$): δ 2.25 (3 H, s), 6.8–7.4 (3 H, m), 7.58 (5 H, s).

Treatment of 127 mg of 4-methyl-3-phenylphenol with 150 mg of NaH and 5 ml of MeI in 30 ml of DMF and refluxing 1 hr gave the methyl ether (XIb): nmr (CCl$_4$) δ 2.16 (3 H, s), 3.73 (3 H, s), 6.7–7.3 (3 H, m), 7.32 (5 H, s). It was shown by the use of Eu(fod)$_3$ that the compound contained no detectable amount of the isomer Xe (*vide supra*). Refluxing of the crude product with 500 mg of KMnO$_4$ in 10 ml of 1 N NaOH for 4 hr followed by acidification with dilute H$_2$SO$_4$ gave white crystals which were collected by filtration to yield 20 mg of 4-methoxy-2-phenylbenzoic acid, mp 170–173° (HOAc–H$_2$O) (lit.[28] 169–173°). 3-Methoxy-6-phenylbenzoic acid has mp 136–137°.[28]

Kinetic Runs. Trifluoroacetic acid was freshly distilled from P$_2$O$_5$ and stored in an oil bath at 38.5°, the temperature of the nmr probe. The probe temperature was determined using the shift of the OH proton signal of a standard methanol sample, and by observing no breaks in the plot when two identical samples of either IIb or Ia in CF$_3$COOH were switched back and forth from the bath to the probe twice during a kinetic run. Methylene chloride (3% v/v) was added as an internal standard, and absorbed at δ 5.27. To a 50-mg sample of each dienone in a preheated nmr tube was added 0.5 ml of the trifluoroacetic acid *via* preheated syringe, the tube was sealed with a pressure cap and shaken well, and the nmr spectrum in the δ 5.2–6.6 region was scanned on a Varian A-60 nmr spectrometer. *Ca.* 0.5 min elapsed before the first scan. The tube was returned to the bath when not monitored for IIa but was left in the probe for all the other dienones. The relative peak height of the larger leg of the C-3 H and C-5 H doublet of the dienone (in the δ 6.2–6.6 region for all compounds) was normalized by comparison to the CH$_2$Cl$_2$ peak and the normalized value used in kinetic plotting. A least-squares fit of the data was obtained. All runs gave good first-order kinetics, with correlation coefficients of 0.97–0.99. The average rate constants from triplicate runs are recorded in Table I.

Cage Reactions of *tert*-Butoxy Radicals. Effects of Solvent and Viscosity[1]

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Abstract: Cage reactions of *tert*-butoxy radicals generated by the thermal decomposition of di-*tert*-butylperoxy oxalate were studied at 45°. In the solvents of similar properties, a reciprocal of probability of geminate recombination of *tert*-butoxy radicals was a linear function of a reciprocal of viscosity of the medium in agreement with Noyes' approach. The linear correlation with identical intercepts but with different slopes depending on the nature of solvents was ascribed to a specific interaction of caged *tert*-butoxy radical with surrounding solvent molecules. The extent of interaction was suggested to be in the order of aliphatic < olefinic < aromatic < polar compounds such as acetic acid and acetonitrile, which is the same with the extent of solvent effects on the β scission of *tert*-butoxy radical observed by Walling and Wagner. However, the extent of cage reaction was low and relatively insensitive to the bulk viscosity of the solutions containing polymeric compounds. The higher the molecular weight of the dissolved polymer, the lower the extent of cage reaction at constant viscosity.

W hen a pair of radicals is produced in solution from a radical initiator such as peroxides and azo compounds, it may either diffuse out of the solvent cage or recombine within the cage. This "cage" effect has been known for many years and studied widely by numerous investigators.[2] Effects of viscosity of the medium on the geminate recombination of the paired radicals have been studied by many workers and it has been shown that the extent of cage reaction increases with increasing viscosity of the medium. The quantitative treatment developed by Noyes[3] implies that the reciprocal of probability of cage recombination is a linear function of $T^{1/2}/\eta$ where T and η denote absolute temperature and viscosity, respectively. This linear correlation was observed by Szwarc and coworkers for each solvent in the photolyses of hexafluoroazomethane[4] and azomethane.[5] Bartlett, *et al.*,[6] also observed that this correlation held in the thermal decomposition of *tert*-butylperoxy-α-phenylisobutyrate. The cage recombination of *tert*-butoxy radicals was first reported by Hiatt and Traylor,[7] who found that the yield of di-*tert*-butyl peroxide in the decomposition of di-*tert*-butylperoxy oxalate (DBPO) increased with increasing viscosity of the solution. Kiefer and Traylor[8] and

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