

(*c* 1.0, 95% ethanol). After four recrystallizations from acetone the salt had mp 193.4° dec and $[\alpha]_D^{27} +99.5^\circ$ (*c* 1.0, 95% ethanol).

*Anal.*²⁰ Calcd for $C_{30}H_{32}N_2O_6$: C, 69.75; H, 6.25; N, 5.42. Found: C, 69.52; H, 6.4; N, 5.52.

To a solution of 0.15 g of the monoquinine salt in 5 ml of 95% ethanol was added 8 ml of 3 *N* hydrochloric acid. The solution was diluted with 50 ml of water and extracted with five 15-ml portions of ether. The combined ether extracts were washed once with 4 ml of 2 *N* hydrochloric acid. The acidic solution was extracted once with ether, and the combined ether solutions were dried with sodium sulfate. The solvent was removed at reduced pressure, and the yellow solid residue was recrystallized three times from acetonitrile, yielding 12 mg of 2,4,6,8-cyclooctatetraene-1,2-dicarboxylic acid, mp 194.5° dec, $[\alpha]_D^{27} 0^\circ$.

Mono-*d*- α -methylphenethylamine (Dexedrine) Salt of 2,4,6,8-Cyclooctatetraene-1,2-dicarboxylic Acid. To 35 ml of a 10% sodium hydroxide solution was added 300 mg of Dexedrine sulfate.

(20) This analysis was obtained by combustion after mixture with copper oxide.

The mixture was shaken well and then extracted with three 25-ml portions of ether. After drying with calcium sulfate, the ether solution was filtered and concentrated to 50 ml. A 310-mg sample of 2,4,6,8-cyclooctatetraene-1,2-dicarboxylic acid in 2 ml of 95% ethanol was added to the ether solution. Upon heating, a pale yellow crystalline salt separated (477 mg, 91%) which after five recrystallizations from ethanol-ethyl acetate afforded 231 mg of the salt having mp 156.8–158.6° dec and $[\alpha]_D^{27} +4.7^\circ$ (*c* 1.0, 95% ethanol).

*Anal.*²⁰ Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.89; H, 6.39; N, 4.52.

To a cold solution of 128 mg of the salt in 3 ml of methanol, 9 ml of a dilute hydrochloric acid solution (approximately 1.5 *N*) containing cracked ice was added. The solution was diluted to 40 ml with water and extracted with five 15-ml portions of ether. The combined ether solutions were extracted once with 5 ml of 3 *N* hydrochloric acid and dried with magnesium sulfate. Removal of the solvent at reduced pressure afforded 46 mg (61%) of the dibasic acid **4**, which after one recrystallization from acetonitrile had mp 195–197° dec and $[\alpha]_D^{27} 0^\circ$.

Cycloadditions. XII. The Relative Reactivity of Carbethoxycarbene and Carbethoxynitrene in Cycloadditions with Aromatics^{1,2}

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Contribution from the W. A. Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois 61801. Received November 4, 1966

Abstract: Carbethoxycarbene and carbethoxynitrene have been generated through the thermal decomposition of ethyl diazoacetate and ethyl azidoformate at 129.6° in a solution of benzene and anisole, toluene, chlorobenzene, fluorobenzene, or trifluoromethylbenzene in an unreactive perfluorinated polyether. From the relative rates at which the aromatic substrates were consumed in the competitive situation obtaining, linear free energy correlations of carbethoxycarbene and -nitrene reactivity were established. The Hammett ρ for the carbethoxycarbene additions to monosubstituted benzenes was -0.38 ; for the carbethoxynitrene additions, ρ was -1.32 .

Carbenes^{5,6} and nitrenes⁷ are isoelectronic species which have been characterized or postulated as intermediates in various reactions. Carbon is divalent in carbenes, while nitrogen is monovalent in nitrenes; either may have two nonbonding electrons spin paired (singlet state) or spin unpaired (triplet state). In the singlet state, carbenes or nitrenes behave as electrophiles or nucleophiles, depending upon their complete structure. In the triplet state they may manifest radical character. Such diverse possibilities for chemical reactivity in a single family of species engender special theoretical and practical chemical interest.



Carbalkoxycarbenes **1** and carbalkoxynitrenes **2** are less reactive and more selective than unsubstituted carbene and nitrene in such characteristic reactions as insertions into aliphatic carbon-hydrogen bonds and additions to olefinic and aromatic carbon-carbon bonds.⁸⁻¹¹ They may also enter into 1,3 cycloadditions with reaction partners containing suitable multiple bonds,^{12,13} processes inaccessible to simpler carbenes and nitrenes. Their structural similarities and capabilities of participating in at least four distinct types of intermolecular processes make possible a wide range of comparisons of relative reactivity and selectivity, which could lead to an unusually detailed knowledge of the chemical behavior of these comparatively unstable reactive intermediates.

Quantitative data on the relative reactivity of carb-

(1) Paper XI in this series: J. E. Baldwin, M. C. McDaniel, M. G. Newton, and I. C. Paul, *Tetrahedron Letters*, 4239 (1966).

(2) Supported in part by the National Science Foundation (Grant No. GP-5226) and a Du Pont Grant-in-Aid to the Department of Chemistry and Chemical Engineering of the University of Illinois.

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(4) Archer Daniels Midland Co. Fellow, 1964-1965.

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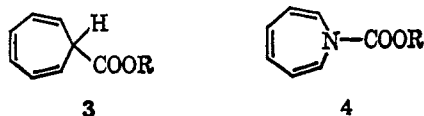
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alkoxycarbene and carbalkoxynitrenes in insertions into aliphatic carbon-hydrogen bonds, additions to olefinic¹⁴ and aromatic carbon-carbon bonds, and 1,3 cycloadditions have not been available. This paper describes a determination of the relative reactivity of carbethoxycarbene and carbethoxynitrene in their cycloadditions with aromatics.

Results and Discussion

Thermal or photochemical decomposition of alkyl diazoacetates generates carbalkoxycarbene, which may react with benzene nuclei to give 7-carbalkoxycyclohepta-1,3,5-trienes (**3**).^{5,15,16} Under similar conditions alkyl azidoformates lose nitrogen to form carbalkoxynitrenes, which may react with benzene nuclei to give N-carbalkoxyazepines (**4**).^{7,17-20} The former has provided a much traveled route to synthetic cycloheptatrienes²¹ and azulenes.²² The latter was used to create the first parent azepine ring system.¹⁷



The relative reactivity of carbethoxycarbene and carbethoxynitrene in such additions with substituted benzenes was sought in the present work.

Correlations of structure and reactivity in systems involving direct attack of a reactive species on benzene nuclei have been valuable aids to the understanding of aromatic substitution reactions.²³ However, the utility of such correlations in determining the reactivity of an intermediate which takes part in an aromatic addition reaction has been almost unexplored. The only indication that a meaningful correlation of structure and reactivity may be obtained in the latter type of reaction is found in the results of Abramovitch and co-workers.²⁴ They determined relative rates for the reaction of benzene and toluene, chlorobenzene, and anisole with methanesulfonylnitrene. A plot of the logarithm of the relative rates for the methanesulfonylnitrene cycloadditions²⁴ against the corresponding Hammett substituent constants, σ_p , reveals an excellent linear relationship.

A partially analogous approach was used to secure a quantitative measure of the relative reactivity of carbethoxycarbene and carbethoxynitrene. Generation of either reactive chemical intermediate in the presence of benzene and a suitable monosubstituted benzene in

an inert solvent creates a competitive system from which the ratio of relative rates, $k_{rel} = k_{C_6H_5X}/k_{C_6H_6}$, may be obtained by standard treatment of the kinetic data.²⁵ The required data for the calculation of k_{rel} are the initial concentration of each of the competing aromatic substrates and the concentration of each at a subsequent stage in the reaction (eq 1).²⁵ In principle these data may be determined either directly by measur-

$$k_{rel} = \frac{k_{C_6H_5X}}{k_{C_6H_6}} = \frac{\log \left(\frac{[C_6H_5X]}{[C_6H_5X]_0} \right)}{\log \left(\frac{[C_6H_6]}{[C_6H_6]_0} \right)} \quad (1)$$

ing the amount of aromatic reactant remaining or indirectly from a knowledge of the concentration of reaction products.²⁴ For reactions which may form several products the former method is preferred and was adopted here. Gas-liquid partition chromatography (glpc) was selected as the analytical method for determining the required data.

If analysis of the data according to eq 1 is to be meaningful, aromatic components must not be lost except through cycloadditions with carbethoxycarbene or -nitrene. Loss through evaporation was minimized by conducting the reactions in sealed glass tubes and performing all critical transfers within a few seconds. Attempts to carry out the reactions by photolytic generation of the reactive intermediates were abandoned when it was observed that the aromatic substrates were being decomposed by the ultraviolet light at rates comparable to those for the formation of the carbene and the nitrene.²⁶ The aromatics were found to be stable under the reaction conditions required to generate the reactive species thermally. By conducting the reactions thermally, the potential complications owing to photoexcited aromatic substrates²⁷ were also avoided.

The possibility of losing substituted benzenes through attack of the carbethoxycarbene or -nitrene at the substituent or through insertion into aromatic C-H bonds was considered and, after weighing the available evidence, was anticipated to be of negligible importance.^{5,8,16,18,28} The experimental results proved consistent with this anticipation, with one exception. In competition with benzene for both carbethoxycarbene and carbethoxynitrene under the experimental conditions employed in this study, nitrobenzene proved to be about ten times more reactive than would have been predicted from the correlations of Figure 2 below. The abnormally high relative reactivity of nitrobenzene may be caused by attack of intermediate at the nitro group itself, or by another change in mechanism.

Loss of the aromatics during the analysis occurred for reaction solutions containing ethyl diazoacetate,

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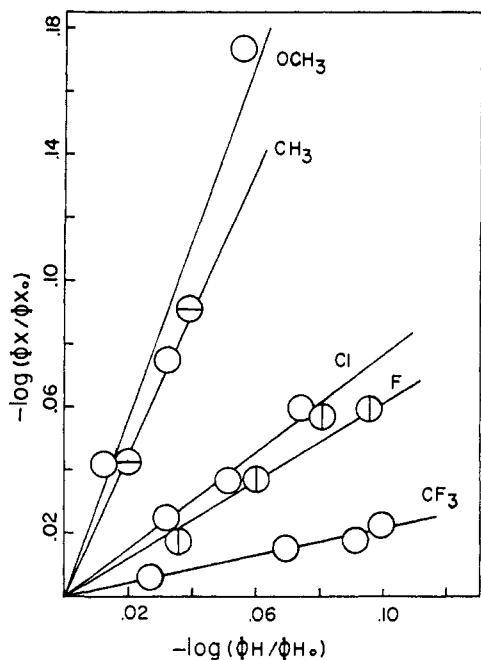


Figure 1. Relative rate data obtained at several stages of each reaction from competitions with carbethoxynitrene and monosubstituted benzenes.

but not for those containing ethyl azidoformate, probably through attack by carbethoxycarbene generated within the chromatograph. For this reason, the concentrations of the unreacted aromatics in the "carbene" runs were determined either in solutions to which ethyl diazoacetate had not been added or which had been allowed to react long enough to decompose the bulk of the ethyl diazoacetate present.

"Freon" E-4, a perfluorinated polyether (bp 193°), was selected as the solvent for the reactions because of its inertness. An unexpected advantage of the "Freon" solvent was its behavior during the analyses. It was the first component of the solutions to be eluted from the gpc column and yet did not interfere with the determination of any of the aromatics. Although the solubility of the aromatics in "Freon" E-4 was low, it was adequate for the present study. Solutions which were 0.05 M in each of the two aromatic components and 0.10 M in the carbene or nitrene precursor could be prepared, reacted, and analyzed conveniently. The mean of each set of determinations was used to compute the ratios $[C_6H_5X]/[C_6H_5X]_0$ from which the relative rates were calculated according to eq 1. The relative rate ratios determined for the additions of thermally generated carbethoxycarbene and -nitrene with five pairs of benzenes are given in Table I.

The mean standard deviation for all sets of data derived from the competition experiments was estimated to be $\pm 1.5\%$ of the set means. The best sets of data points for the "carbene" and "nitrene" runs were $\pm 0.5\%$ in standard deviation from the set means; the worst sets were ± 6.6 and $\pm 3.8\%$, respectively.

In an ideal system of homocompetitive second-order reactions, the relative rates are constants which are independent of the stage of the reaction at which they are measured.²⁵ In the reactions of carbethoxynitrene the rate ratios were found to be reasonably constant throughout. This was demonstrated by plotting the

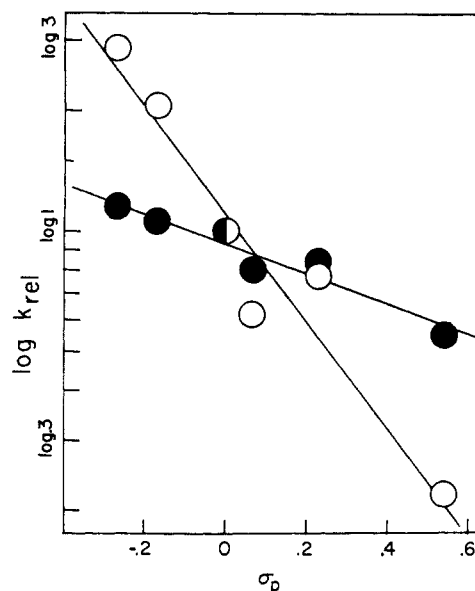


Figure 2. Correlation of relative rates with substituent constants for cycloadditions of carbethoxycarbene, ●, and carbethoxynitrene, ○, with monosubstituted benzenes.

logarithm of the fraction of the monosubstituted benzene remaining against that of benzene remaining for the competitive reactions (Figure 1). The slope of each line is the relative rate.

Table I. Relative Rate Ratios for the Reactions of Carbethoxycarbene and Carbethoxynitrene with Benzene and Monosubstituted Benzenes at 129.6°

Aromatic	Relative rate, Carbethoxy-carbene reaction	$k_{C_6H_5X}/k_{C_6H_6}$ Carbethoxy-nitrene reaction
Anisole	1.15	2.88
Toluene	1.06	2.06
Benzene	1.00	1.00
Fluorobenzene	0.80	0.62
Chlorobenzene	0.84	0.77
Trifluoromethylbenzene	0.55	0.22

The relative rates were found to correlate satisfactorily, using the Hammett equation and σ_p substituent constants²⁹ (Figure 2). The equations which gave the best linear least-squares fit of $\log k_{rel}$ with σ_p were found to be $\log k_{rel} = 0.052 - 1.32\sigma_p$ for the carbethoxynitrene additions, and $\log k_{rel} = -0.033 - 0.38\sigma_p$ for the carbethoxycarbene reactions.

Having determined the relative rates for carbethoxycarbene and -nitrene additions to benzenes under strictly analogous conditions, the relative reactivity of the two isoelectronic reactive chemical intermediates could be deduced. The carbene:nitrene relative reactivity according to the ratio of the slopes of the two Hammett plots (Figure 2) is 3.47. A plot of the logarithm of the relative rates for the "nitrene" reactions with aromatics against the logarithm of the relative rates for the "carbene" reactions is linear (Figure 3). The slope of this line represents the relative re-

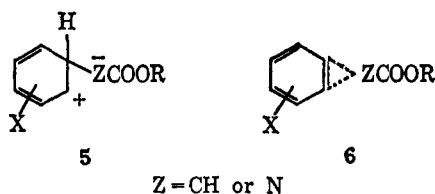
(29) The σ_p constants used were from the compilation of D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 23, 420 (1958).

activity of carbethoxynitrene and carbethoxycarbene in the electrophilic cycloaddition with aromatics. A value of 3.33 was obtained when the curve was fitted by the method of least squares.

The discrepancy between these two values for the relative reactivity is simply that between a ratio of averages and an average of ratios. The average of ratios (Figure 3) may more closely approximate the actual relative reactivity than the ratio of the independent correlations, since the former value is the result of a direct correlation of the independent reactivity data.

From the observed substituent effects ($\rho = -0.38$ for the carbethoxycarbene; $\rho = -1.32$ for the -nitrene reactions) and the plot of Figure 3 it may be concluded that both intermediates are electrophilic, and that the carbethoxycarbene is by far the more indiscriminate in its selection of substrates in a competitive situation. This noteworthy difference in reactivity may be underscored by the following comparison. The relative reactivities of one of the most reactive reagents in electrophilic aromatic substitution reactions ($C_2H_5^+ GaBr_4^-$) and of one of the least reactive (Br^+ from bromine in aqueous acetic acid) differ only by a factor of about 5.²³

A complete reaction profile for the electrophilic cycloadditions of carbalkoxynitrenes with benzenes would show, after formation of a presumed azanorcaradiene (7-azabicyclo[4.1.0]heptatriene) intermediate,³⁰ reversible electrocyclic isomerization to an N-carbalkoxyazepine and other processes, such as dimerization of the azepine^{31,32} or isomerization of the azanorcaradiene to phenylurethans, leading to more stable compounds. A largely similar reaction scheme could be constructed for the analogous system formed from a carbalkoxycarbene and an aromatic.³³



Models of the two transition-state species corresponding to stepwise **5** or concerted additions **6** of the electron-deficient intermediates with benzenes differ primarily in that the former entails a higher degree of charge separation. In the stepwise processes, direct resonance effects could operate to stabilize the positive charge on the aromatic moiety of the activated complex; in the concerted process, substituents could not. Thus large substituent effects would be anticipated for the nonconcerted additions, but not for the concerted ones. Since the reactions are observed to be much less sensitive to substituent effects than electrophilic aromatic substitution reactions, they might be considered concerted; this conclusion would imply that the reactive chemical intermediates undergoing the cycloadditions with aromatics are the singlet carbethoxycarbene and singlet carbethoxynitrene. This conclusion and its

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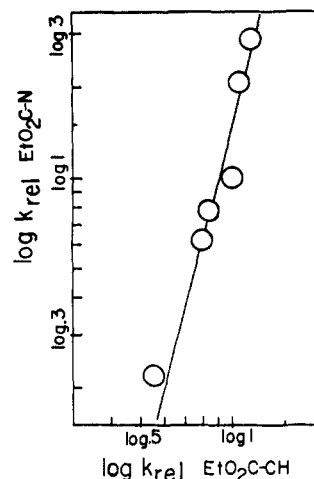


Figure 3. Linear free energy plot comparing relative reactivity of carbethoxycarbene and carbethoxynitrene in cycloadditions with monosubstituted benzenes.

direct implication could, of course, be in error if the assumptions that either **5** or **6** is a fair model for the activated complex in these reactions and that data from aromatic substitution reactions may serve as a valid gauge for what constitutes a "large" substituent effect are wrong.

Whereas the thermal decomposition of ethyl azidoformate in solution has been shown to produce carbethoxynitrene in the singlet state,⁹ the multiplicity of thermally generated carbalkoxycarbenes has not been determined.³⁴ It has been well established that the reactivity of carbenes is a function of spin state;^{36,37} the effects of orbital geometry on the reactivity of such species are beginning to receive attention.³⁸

The relative selectivity of carbalkoxycarbenes and carbalkoxynitrenes in their cycloadditions with monosubstituted benzenes, corresponding to different ratios of isomeric monosubstituted cycloheptatrienes and azepines produced through the additions and subsequent valence isomerizations, is presently an unsettled issue.^{10,39} New experimental work pertinent to the problem will be published in the near future.⁴⁰

Experimental Section

Apparatus and Materials. Reagent grade chemicals were used without further purification except where noted otherwise. "Freon" E-4, a perfluorinated polyether (bp 193°), was obtained from the Du Pont Company. Ethyl azidoformate [n_D^{20} 1.4205 (lit.⁹ n_D^{20} 1.4199)] and ethyl diazoacetate [n_D^{20} 1.4616 (lit.⁴¹ n_D^{20} 1.4616)] were prepared according to known procedures;^{9,41} their refractive indices were checked periodically, and they were redistilled as required to maintain purity. Commercial reagent anisole

(34) The reaction of ethyl diazoacetate with *trans*-stilbene at 180° has been reported to proceed stereospecifically,³⁵ but the experimental evidence was equivocal; the yield of the cyclopropyl product was low, no material balance was given, and the absence of pyrazoline formation was assumed, not demonstrated.

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(39) I. C. Paul, J. E. Baldwin, and R. A. Smith, *J. Am. Chem. Soc.*, 88, 3653 (1966).

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(41) N. E. Searle, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 424.

was dried over calcium chloride and fractionally distilled, bp 155°, n_{20}^D 1.5171 (lit.⁴² bp 155°, n_{20}^D 1.5179). Fractional distillation of fluorobenzene gave material of bp 85°, n_{20}^D 1.4654 (lit.⁴² bp 84.9°, n_{20}^D 1.4658). Trifluoromethylbenzene purified by fractional distillation had bp 102°, n_{20}^D 1.4136; less than 0.1% of impurities was detected by glpc. Reagent grade nitrobenzene was steam distilled, dried first over calcium chloride, then over phosphorus pentoxide, and fractionally distilled; bp 210°, n_{20}^D 1.5522 (lit.⁴² bp 211°, n_{20}^D 1.5529).

Reaction tubes were made from 5-mm Pyrex or 6-mm Vycor glass cut into 10-cm lengths; the glass was cleaned with chromic acid, washed in aqueous sodium hydroxide, rinsed with deionized water, dried at 110°, and stored in a desiccator over phosphorus pentoxide.

Thermal kinetic runs were carried out with an oil bath maintained to $\pm 0.03^\circ$ by a proportional controller⁴³ at $129.6 \pm 0.2^\circ$.

Ultraviolet radiation was provided by a low-pressure mercury lamp (No. RPR-2537A) in a Rayonet photochemical reactor. The reactor temperature did not rise above 45° during irradiations.

Thermal Kinetic Runs. Solutions for the "nitrene" runs were prepared by weighing benzene, a monosubstituted benzene, and ethyl azidoformate from a 50- μ l syringe into a 10-ml volumetric flask; dilution to the 10-ml mark with "Freon" E-4 produced a solution 0.050 *M* in each aromatic component and 0.100 *M* in azidoformate. Solutions for the "carbene" runs were prepared by weighing benzene and a monosubstituted benzene into a 10-ml volumetric flask; dilution to the 10-ml mark with "Freon" E-4 produced a solution 0.050 *M* in each aromatic component. Ethyl diazoacetate was weighed into a 5-ml volumetric flask and diluted to the 5-ml mark with the "Freon" E-4 solution of two aromatics to give a solution 0.100 *M* in diazoacetate and 0.0497 *M* in each aromatic component.

(42) C. D. Hodgman, Ed., "Handbook of Chemistry and Physics," 43rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1961.

(43) R. O. Anderson, *J. Chem. Educ.*, in press.

Reaction tubes were filled with about 0.38 ml of a "carbene" or "nitrene" solution and sealed. Sets of tubes were immersed in the reaction bath in wire-screen baskets. The tubes were quenched at -80° upon removal from the bath. In the "nitrene" runs, the reaction was terminated at several points within 1 hr after immersion; the "time-zero" set of tubes in these runs was removed after 5 min in the bath. In the "carbene" runs, a set of tubes containing the ethyl diazoacetate-aromatics solution was allowed to react for a minimum of 9 hr; the "time-zero" set of tubes in the "carbene" study contained only the two aromatics in "Freon" E-4 and was simply set aside until analyzed.

Analysis of the contents of each tube for benzene and the mono-substituted benzene was accomplished by glpc, carried out with a Wilkins Aerograph Model A-90-P chromatograph in conjunction with a Brown "Elektronik" recorder and disk integrator. The linearity of the thermal conductivity detector response was confirmed for the appropriate components and concentration range.

The columns used were 25% di-*n*-decyl phthalate or Apiezon L on Chromosorb W (nonacid washed) at temperatures between 85 and 145°. Each determination was carried out at least in triplicate; three reaction tubes were used for each determination. The relative rate ratios found are given in Table I.

The analyses of two "Freon" E-4 solutions of anisole, 0.050 *M*, one of which contained ethyl azidoformate, 0.10 *M*, were identical. When an analogous experiment was performed on the "carbene" system, as much as 12% of the anisole disappeared in the presence of ethyl diazoacetate.

The refractive index of each of the aromatic substrates was shown to remain unchanged after heating in sealed tubes for 12 hr at $135 \pm 25^\circ$. Irradiating "Freon" E-4 solutions of monosubstituted benzene in sealed Vycor tubes placed in a Rayonet reactor caused between 21 (anisole) and 84% (trifluoromethylbenzene) decomposition of the aromatics.

Acknowledgment. We thank Professor K. Hafner and Professor W. Lwowski for helpful suggestions.

7,12-Dihydropleiadenes. V. Transannular 1,4-Hydride Rearrangements in 1-Substituted 7-Hydroxy-12(7H)-Pleiadenones

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Contribution from the Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214. Received November 29, 1966

Abstract: 1-Chloro-7-hydroxy-12(7H)-pleiadenone (I) rearranges by intramolecular 1,4-hydride migration to 1-chloro-12-hydroxy-7(12H)-pleiadenone (IV) when treated with alkali metal *t*-butoxides in dimethyl sulfoxide. The rate-determining step is the transannular hydride rearrangement of the initially formed alkoxide and has $E_a \sim 24$ kcal/mole for the potassium salt in 95:5 DMSO-*t*-butyl alcohol. The primary deuterium isotope effect and metal cation effects on the rearrangement are also reported. The isomeric reactant and product hydroxy ketones both exhibit ring-chain tautomerism in solution.

We have recently studied several aspects of 7,12-dihydropleiadenone chemistry, including the free energy barriers for "boat-to-boat" ring inversion^{2,3} and the conformational preferences of alkyl⁴ and other⁵ substituents on the 7 position. Because of the close proximity of the 7- and 12-carbon atoms, it seemed

(1) (a) Alfred P. Sloan Foundation Fellow, 1963–1967. (b) Du Pont Predoctoral Teaching Fellow, 1966–1967.

(2) P. T. Lansbury, J. F. Bieron, and M. Klein, *J. Am. Chem. Soc.*, **88**, 1477 (1966).

(3) P. T. Lansbury and F. D. Saeva, *Tetrahedron Letters*, 5991 (1966).

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probable that transannular rearrangements involving these positions might occur. In this paper, we report on the 1,4-hydride shift that occurs when 1-chloro-7-hydroxy-12(7H)-pleiadenone (I) is converted to the alkali metal salt (IIa-d) in dimethyl sulfoxide (DMSO) which leads to the isomeric alkoxide (IIIa-d) of 1-chloro-12-hydroxy-7(12H)-pleiadenone (IV). Although other transannular hydride shifts have been investigated by deuterium labeling and product studies,⁶ no kinetic investigations have been reported from which activation parameters for the rearrangement step could

(6) For a recent review and further references, see A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev.* (London), **20**, 119 (1966).