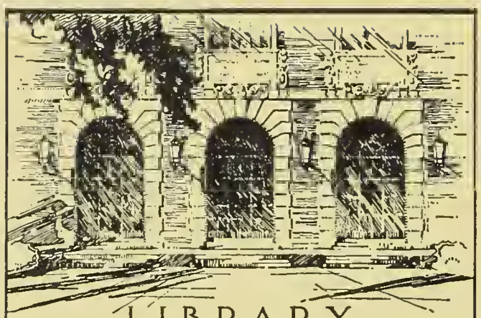

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ORGANIC SEMINAR ABSTRACTS

1966-67

Semester I

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SEMINAR TOPICS

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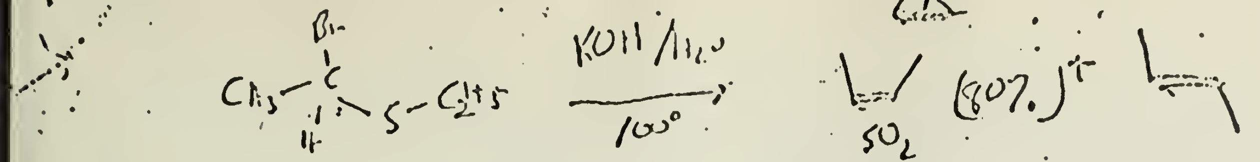


MECHANISTIC ASPECTS OF THE RAMBERG-BÄCKLUND REACTION

Reported by J. T. Lee, Jr. September 19, 1966

The conversion of α-halosulfones to olefinic products upon treatment with base, the Ramberg-Bäcklund reaction, is of current interest and in this seminar its mechanism is examined.

In the course of other work, Ramberg and Bäcklund discovered that treatment of α-bromoethyl ethyl sulfone with excess aqueous KOH at reflux gave KBr, K_2SO_3, and predominantly cis-2-butene in high yield.[1] Similarly, bis-(α-chloroethyl) sulfone gave potassium 2-butene-2-sulfonate and α-bromopropyl ethyl sulfone gave mostly cis-2-pentene.[1] The reaction appears to be generally applicable to systems containing a sulfonyl group, at least one α-halogen, and at least one α'-hydrogen atom. The sulfonyl group of the starting material is replaced by the double bond in the product. The method apparently fails when cyclobutene[2] or cyclobutadiene[3] is sought. Although the Ramberg-Bäcklund reaction has not been frequently exploited in olefin synthesis a variety of examples of its application are available and some of these are summarized in Table I.

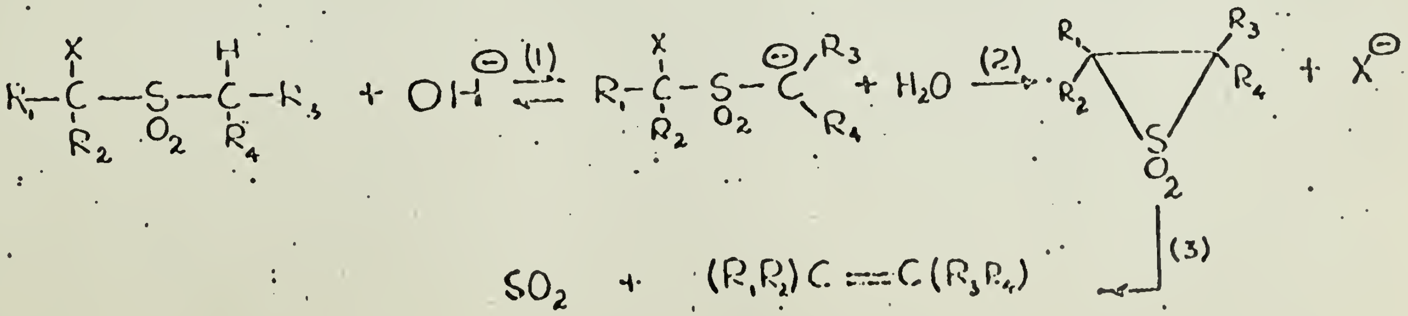
Table I. Typical Ramberg-Bäcklund Syntheses

Halosulfone	Olefin	% Yield	Reference
α-Bromoethyl Ethyl	2-Butene (80% cis-)	85	2
α-Chloropropyl Ethyl	2-Pentene (66% cis-)	74	2
α-Chlorobenzyl Benzyl	Stilbene (0% cis-)	94	2
Cyclohexyl Chloromethyl	Methylenecyclohexane	80	4
2-Bromo-Thiacyclohexane 1,1 Dioxide	Cyclopentene	82	5

The reaction of α,α- or α,α'-dihalosulfones under Ramberg-Bäcklund conditions usually affords three types of products--acetylenes, alkylidene sulfonates, and vinyl halides.[6,7,8] Although this reaction type has only recently been examined in detail[8,9] it is common practice[6,8] to regard it too as a Ramberg-Bäcklund reaction and several mechanistic arguments pertaining to the monohalosulfones have been based on results obtained in these systems. Paquette has recently described progress in the study of the dihalosulfone reactions.[6,8]

Bordwell and Cooper studied the reactions of several α-halosulfones and base. Kinetic data for the reactions of chloromethyl methyl sulfone, chlorobenzyl methyl sulfone, and chloromethyl benzyl sulfone were compatible with a second order expression for the rate of chloride release, first order in sulfone and first order in hydroxide. From data for the rate of protium-deuterium exchange in dimethyl sulfone they estimated that proton removal (1) is not rate-determining. It was suggested that closure of the α-sulfonyl carbanion to an intermediate episulfone (2)

Figure I. The Bordwell-Cooper Mechanism[10]



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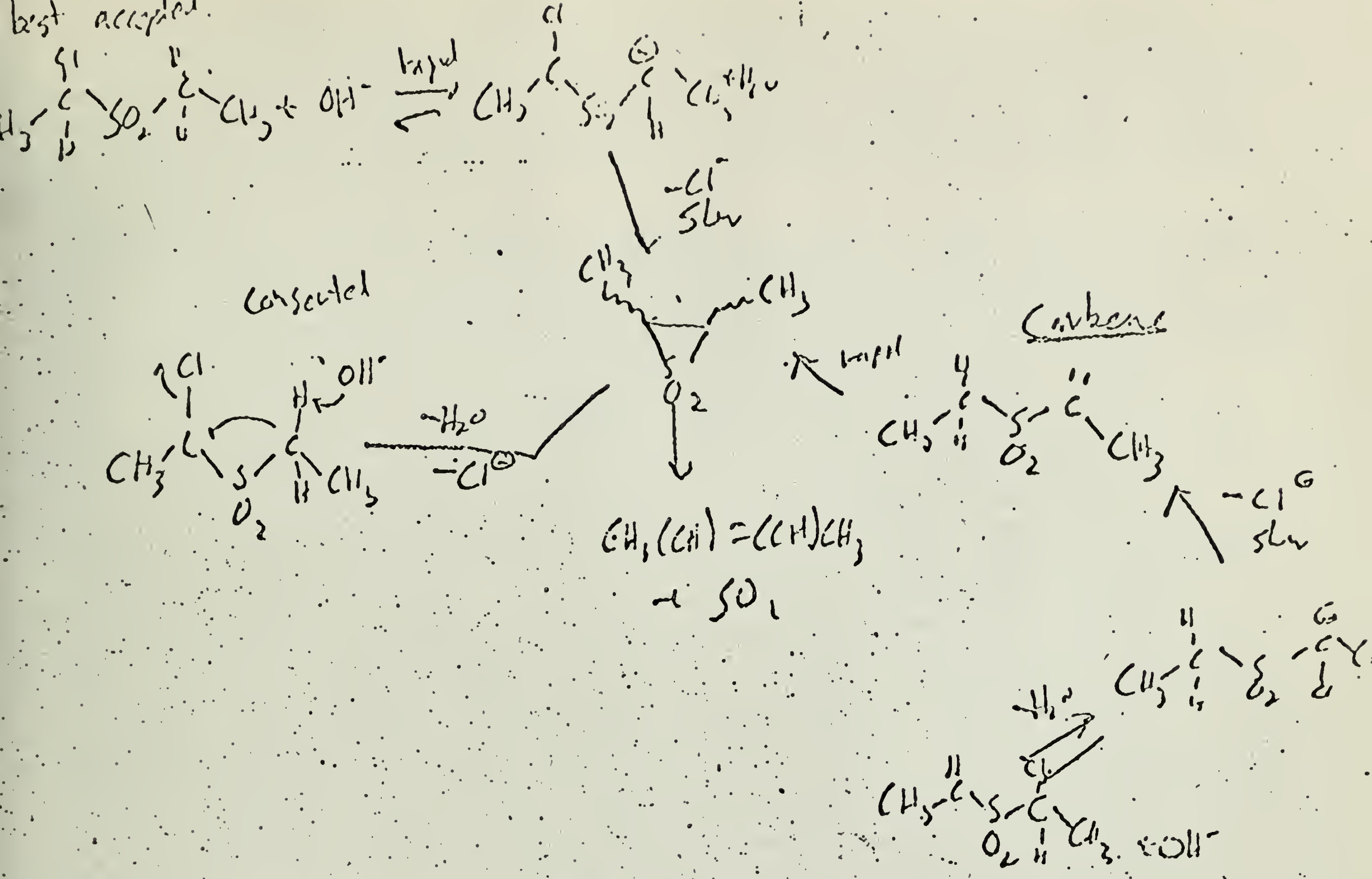


is the rate-determining step, followed by rapid loss of SO_2 and olefin formation (3). It is clear that these kinetic data cannot distinguish between concerted proton removal and discrete carbanion formation, nor can they shed light on the fast step(s) following halide loss. When all R's in Figure I are not identical an obvious feature of step (2) is the possibility of either *cis*- or *trans*-episulfone formation. Bordwell and Cooper were unable to explain the observed olefin stereochemistry in terms of this general mechanism.

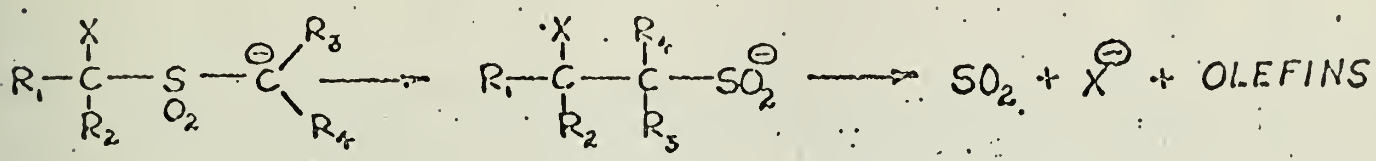
Evidence from a number of sources supports the rapid pre-equilibrium of halosulfone and α-carbanion suggested by Bordwell and Cooper. Neureiter found that treatment of α-chloroethyl ethyl sulfone with NaOD in D_2O gave 97% deuterated 2-butene-2,3-d_2[2] and Paquette showed[11] that 2-chloro-2,7-dihydro-3,4,5,6-dibenzothiepin 1,1-dioxide afforded 9,10-dideuterophenanthrene in 91.7% yield (calc. atom % excess D = 20, found = 19.97). Williams recovered completely α-deuterated starting material from the reaction of α-bromobenzyl benzyl sulfone with NaOMe in MeOD.[5] When allowed to proceed to completion this reaction produced *trans*-stilbene in 89% yield and no vinyl proton signal was observed in its NMR spectrum. This last result accommodates pre-equilibration of the sulfone and carbanions but does not conclusively establish that a carbanion is on the reaction pathway leading to olefins.[12]

Williams assumed that the subsequent reaction of the α-carbanion is episulfone formation accompanied by halide loss and reasoned that if episulfone formation is rate-determining then a leaving group effect would be detected as the halide is varied. For the reaction of α-halobenzyl benzyl sulfone with NaOMe in MeOH at 40°C the relative rates of *trans*-stilbene formation were found to be Cl:Br:I = 1:190:640. These relative rates lie in the same order as those found by Neureiter for α-haloethyl ethyl sulfones in qualitative rate measurements.[2] The influence of halide on rate was considered large in comparison to those observed in other reactions[13,14] involving formation of three-membered rings via intramolecular nucleophilic displacements. In addition it was not possible to conclusively ascribe the magnitude of the effect to the presence of the neighboring sulfonyl function even though fair analogy could be found in the reactions of other systems having a sulfonyl group adjacent to an anionic or attacking site.[15,16] It was concluded that the observed effect is probably enhanced by both the formation of a three-membered ring and the presence of the α-sulfonyl group.[5]

In kinetic studies of the reactions of α-halobenzyl benzyl sulfones with various bases Williams found large activation energies and large positive activation entropies.[5] The magnitude of the activation energy was found compatible with the formation of a strained intermediate but the entropy of activation normally expected for formation of a cyclic species was thought to be exceeded by an opposing entropy increase due to solvation changes accompanying cyclization. Significant solvent effects were observed and were interpreted as arising from differences in solvation of the incipient halide and base in the different solvent/base systems. Key assumptions here are that the transition state more nearly resembles the products than the reactants and that the assembly of solvent molecules about the "organic" portion of the ground state is essentially uncharged in the transition state. In other work the rate of proton abstraction from some halosulfones was found to increase with decreasing dielectric constant. It was concluded that the overall solvent effect on the rates of the α-halobenzyl benzyl sulfone reactions is composed of two simultaneous trends: decreasing dielectric constant and increasing base strength increase the rate of proton abstraction and decreasing dielectric constant retards the rate of ring closure. It should be noted that solvent effects on rates of ionic reactions are not generally interpretable in terms of continuum effects such as the dielectric constant.[17] Williams observed slight salt effects in several experiments but attempts to relate rate constants to ionic strength led only to a correlation involving the fifth power of ionic strength, which has no theoretical basis.[5] Variations of second order rate constants with changing α substituents were interpreted in terms of a displacement mechanism in which the transition state is very similar to the episulfone.

Efforts to establish the intermediacy of episulfones originated in the work of Bordwell and Neureiter.[18] These workers were puzzled by the stereochemistry of

2-butene formation from α-haloethyl ethyl sulfones reported by Ramberg and Bäcklund and independently verified in other laboratories.[10] It was suggested that the predominantly cis stereochemistry might also be rationalized by C-S rather than C-X cleavage upon ring closure:

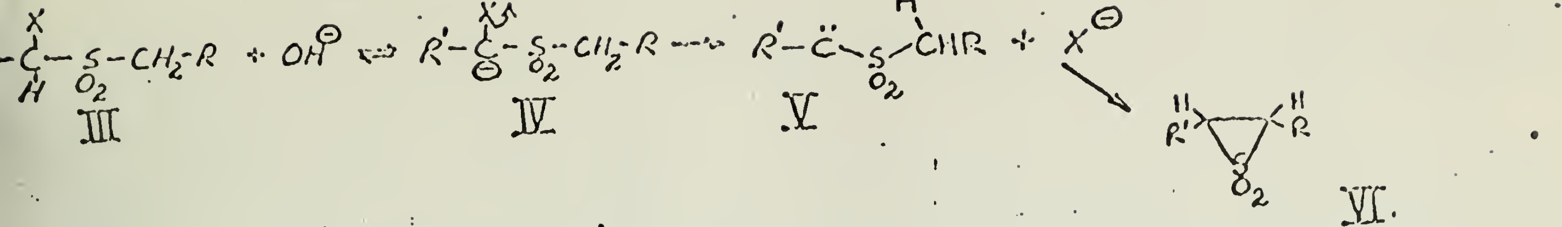


I II

If intermediate II expelled halide and SO_2, certain assumptions to reconcile the stereochemistry were said to be possible. In order to test the validity of episulfone intermediacy some presumed intermediates were synthesized and submitted to reaction conditions. Treatment of diazoethane with SO_2 in ether gave both cis- and trans-2,3-dimethylthiirane 1,1-dioxides. When the pure cis-episulfone was heated (65-85°C) either neat or in isopropyl alcohol it decomposed to SO_2 and cis-2-butene in 100% yield. The trans-episulfone, available only as a 78:22 trans/cis mixture, similarly gave a 78:22 trans/cis mixture of 2-butenes. When decomposed in various alkaline media, including Ramberg-Bäcklund conditions (aqueous KOH), the cis-episulfone gave only cis-2-butene.[18] Neureiter reasoned that the ratio of cis- to trans-olefin formed in this reaction must correspond to the ratio of cis- to trans-episulfone formed if the latter are intermediates.[2] Since episulfones generate the observed products he concluded that their intermediacy is a valid postulate. It was found that the episulfones incorporate only a slight amount of deuterium when their decompositions are conducted in $NaOD/D_2O$. Pure cis-2-butene episulfone in $NaOD/D_2O$ gave cis-2-butene in 99.5% yield with less than 5% deuteration and the 77:23 trans-episulfone/cis-episulfone mixture gave a 100% olefin yield consisting of 77% trans- and 23% cis-2-butene with an average deuterium content of about 5%.[2,18] These findings show that these episulfones generate olefins under reaction conditions more rapidly than they incorporate deuterium and clarify the labeling data which indicate the presence of carbanions prior to episulfone formation.

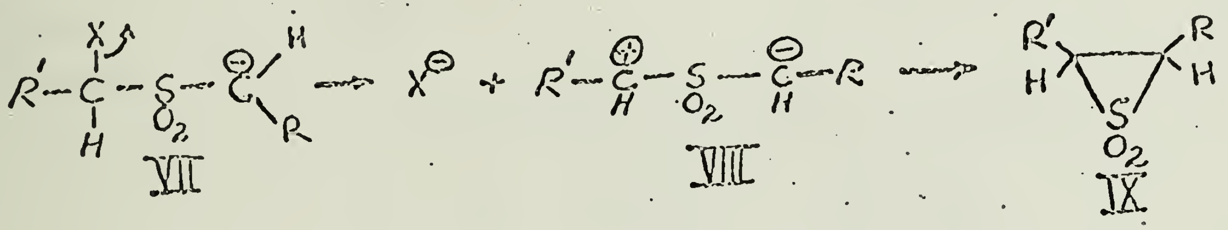
The isolation of episulfones from the reaction, an important part of establishing these species as intermediates, has not been accomplished. It is likely that this experiment is precluded by the ease of thermal decomposition of episulfones.[10,2] Williams recently presented spectral evidence for the presence of an intermediate in a dihalosulfone reaction.[5] The reaction of bis-(α-bromobenzyl) sulfone with NaOEt at 3.4°C in ethanol was monitored at 320.5 mμ, where only 2,3-diphenylthiirene 1,1-dioxide absorbs (this compound was independently synthesized and characterized). A rapid increase in absorption at 320.5 mμ during the reaction was observed and the concentration of the absorbing species first maximized and then decayed in a fashion consistent with the presence of an intermediate. Carpino and McAdams recently reported[7] the isolation of 2,3-diphenylthiirene 1,1-dioxide from what might be termed a "modified" Ramberg-Bäcklund reaction. Treatment of bis-(α-bromobenzyl) sulfone with triethylamine in methylene chloride gave in 70% yield the thiirene 1,1-dioxide. This unusually stable sulfone thermally decomposes at its melting point (116°) to diphenylacetylene and SO_2 in high yield and when treated with aqueous hydroxide provides an unsaturated sulfonate, just as does its parent α,α'-dibromosulfone.[8] These workers claim this to be the first isolation of an intermediate episulfone from a Ramberg-Bäcklund reaction.

Three modes of episulfone formation were considered by Paquette.[11] A reasonabl possibility appeared to be C-H insertion of carbene V generated by carbanion IV which might be formed by deprotonation at the halogen-bearing carbon:



However, when either chloromethyl phenyl sulfone or N,N-dimethyl chloromethanesulfonanilide was heated with strong base in cyclohexene no products derivable from carbenoid intermediates were detected and the sulfones were recovered in high yield. Further, it was pointed out that certain α,α-dihalosulfones incapable of carbene formation undergo the Ramberg-Bäcklund reaction. Paquette concluded that carbene insertion is not an acceptable postulate. Williams reached the same conclusion upon finding that t-butyl chloromethyl sulfone was recovered in 88% yield after treatment with 2N aqueous NaOH for 96 hours.[5] It was felt that the t-butyl moiety should have little effect on the ease of halide loss during carbene formation.

The second route entertained by Paquette was intervention of dipolar ion VIII according to:



Because carbon-halogen bond cleavage assistance by the α-sulfonyl carbanion was not expected and since formation of positive charge on the carbon adjacent to sulfur appeared energetically unfavorable, this possibility was abandoned. Neureiter discovered that different fractions of cis-2-pentene result from the Ramberg-Bäcklund reactions of α-chloropropyl ethyl sulfone and α-chloroethyl propyl sulfone.[2] A reproducible difference of 5.5 ± 0.3% in the cis-2-pentene contribution to total olefin yield was interpreted as evidence that the reactions do not involve common intermediates, thus excluding an electrically symmetric intermediate. The dipolar species could not be definitely ruled out but it was felt that the results were more compatible with intramolecular displacement of halide by the carbanion since the slightly different steric requirement of an ethyl group on the attacked versus the attacking center could account for a small difference in the implicit rates of episulfone formation. Williams concluded that these data rule out a dipolar species.[5]

Intramolecular nucleophilic attack of the carbanion was favored by Paquette.[11] He suggested that failures of cyclic olefin syntheses by the Ramberg-Bäcklund method may lie in the conformational restrictions in such systems which are not present in acyclic α-halosulfones. It was felt that greater rotational freedom in the latter allows the carbanion to assume a geometry favorable for backside attack at the halogen-bearing carbon. It was further stated that the conformation of the α-halosulfone required for intramolecular displacement is predicted by consideration of the sulfonyl group field effect[21,22] which is thought to result in repulsion of nucleophilic species whose approach for displacement at an α carbon brings them proximate to the sulfonyl group oxygen atoms. Paquette tested his conformational postulate in model systems chosen for their structural features, the 2-chloro-2,7-dihydro-3,4,5,6-dibenzothiepin 1,1-dioxides, and obtained data which were interpreted in terms of an intramolecular nucleophilic displacement mechanism.[11]

In all of the systems studied to date there has been no evidence that olefins isomerize under reaction conditions. The dialkyl episulfones which have been studied generate olefins stereospecifically under Ramberg-Bäcklund conditions[2,10] whereas cis-2,3-diphenylthiirane 1,1-dioxide and the α-halobenzyl benzyl sulfones under reaction conditions.[5,10] For the alkyl sulfones it

is likely that the olefin isomer ratio is kinetically controlled by the relative rates of formation of cis- and trans-episulfones. For the α-halobenzyl benzyl sulfones some other possibility must be considered. Thus attention has been directed to the influences of the α-substituents, the base/solvent system, and the halide on the stereochemistry, the reasons for an apparent preferential formation of the cis-episulfone in the alkyl sulfone reactions, and the mechanism of the episulfone-olefin transformation.

The α-haloalkyl alkyl sulfones give predominantly cis-olefins under Ramberg-Bäcklund conditions; as the size of the alkyl groups attached to the α carbon atoms increases, the cis/trans olefin ratio drops slightly as illustrated in Table II. In contrast, α-halobenzyl benzyl sulfones give only trans-stilbene.[5,8,10]

Table II. Stereochemistry of Some α-Haloalkyl Alkyl Sulfone Reactions[a,b]

Sulfone	Olefin	% Yield	Fraction cis	Fraction trans
α-Chloroethyl ethyl	2-Butene[c]	76	0.78	0.22
α-Bromoethyl ethyl	2-Butene[c]	85	0.79	0.21
α-Iodoethyl ethyl	2-Butene[c]	87	0.78	0.22
α-Chloropropyl ethyl	2-Pentene[d]	57	0.71	0.29
α-Iodopropyl propyl	3-Hexene[e]	57	0.56	0.44
α-Iodobutyl butyl	4-Octene	50	0.53	0.47

[a] Aqueous 2N KOH, 75-100°C

[b] Reference 2

Equilibrium Compositions at 100°C[23]

c	0.30 cis	0.70 trans
d	0.41 cis	0.59 trans
e	0.33 cis	0.67 trans

Neureiter found that three α-haloethyl ethyl sulfones (Table II) give similar cis/trans ratios with changing halogen atoms and concluded that the forces controlling the stereochemistry of the reaction must either be nearly independent of the halide or else affected in a compensatory fashion.[2] The difficulty of predicting the effect of halogen on the stereochemistry[24] was pointed out. He further examined the reaction of α-chloroethyl ethyl sulfone in various base/solvent combinations. In Table III is evidence indicating that the stereochemistry of this reaction is practically independent of the base/solvent system employed, with one exception. A complete reversal of stereochemistry is observed with t-BuOK/t-BuOH. Decomposition of cis-2-butene episulfone in various media gave the data gathered in Table IV. Again, the stereochemistry is reversed with t-BuOK/t-BuOH. When the decomposition of cis-2-butene episulfone was conducted in t-BuOK/t-BuOD the product was about 80% trans- and 20% cis-2-butene with an estimated (mass spectrum) deuterium content in the vinyl positions at least 94% of theoretical. Under these conditions isomerization of the olefins was not detected by control experiments. Neureiter concluded that the episulfone α-hydrogens exchange more rapidly than olefins form

Table III. Reactions of α-Chloroethyl Ethyl Sulfone in Various Media[2,18]

Base/Solvent	Temperature	2-Butene Yield	Fraction cis	Fraction trans
2N KOH/H_2O	100°C	76	0.78	0.22
2N NaOH/H_2O	100	75	0.79	0.21
1N $Ba(OH)_2/H_2O$	100	66	0.79	0.21
2N LiOH/H_2O	100	--	0.76	0.24
1M NaOBu/n-BuOH	117	74	0.75	0.25
0.75 M C_6H_5Li/C_6H_6	80	--	0.73	0.27
1.0 M t-BuOK/t-BuOH	93	82[a]	0.23	0.77
1.0 M t-BuOK/$C_6H_5CH_3$	110	--[a]	0.24	0.76

[a] 3-5% yield of iso-butene was reported.

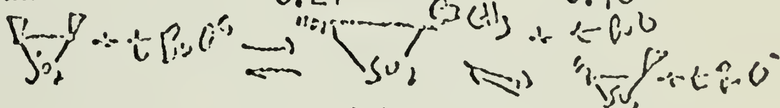


Table IV. Decompositions of cis-2-Butene Episulfone in Various Media[2]

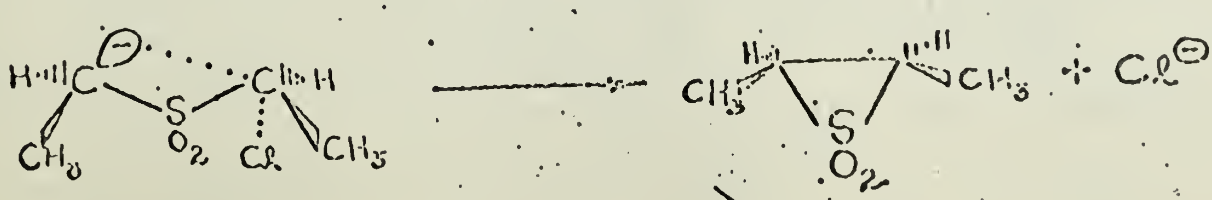
Base/Solvent	Temperature	% cis-2-Butene	% trans-2-Butene
2N KOH/H_2O	100°C	99	1
2N NaOH/H_2O	100	99.5	0.5
No Base/iso-C_3H_7OH	82	99	1
Neat	65-85	99	1
1M t-BuOK/t-BuOH	80	19.4	80.6

and that in the process of exchange the episulfone mixture equilibrates, losing SO_2 to form the olefins.[2] It is not necessary that trans-2-butene episulfone be predominant at equilibrium, as has been[2,18] suggested. Interesting results were obtained from studies of the ethyl propyl sulfones. Treatment of α-chloroethyl propyl sulfone and α-chloropropyl ethyl sulfone with excess 1M potassium t-butoxide in t-BuOH gave identical 2-pentene mixtures, 15.8% cis- and 84.2% trans-2-butene in each case, in contrast to the results obtained using NaOH/H_2O. Thus the different reactions were considered to have passed through an identical mixture of intermediate episulfones in this medium and the postulated t-butoxide-catalyzed equilibration was supported.[2]

In base/solvent systems other than t-BuOK/t-BuOH, where base-catalyzed episulfone equilibration is seemingly insignificant, the relative yields of cis- and trans-2-butene might justifiably be related to the relative amounts of cis- and trans-2-butene episulfones formed. However, the stereochemical results in t-BuOK/t-BuOH do not establish that trans-episulfone dominates the equilibrium nor do they require that cis-episulfone be formed more rapidly than trans-episulfone (or vice-versa) in the cyclization step. While a facile, t-BuO^--catalyzed equilibrium can provide a low-barrier path for transformation of either episulfone to either olefin, the position of such an equilibrium is completely irrelevant to the stereochemical fate of either episulfone isomer. The relative amounts of cis- and trans-2-butene formed in the subsequent step(s) are controlled solely by the difference in stability of the transition states leading to olefins,[25,26] assuming either a direct conversion or a step-wise process in which no equilibration of intermediate species is extant. To date there has been little inquiry into the properties of the t-BuOK/t-BuOH combination responsible for the observed stereochemistry and further understanding of this aspect of the mechanism is clearly needed.

The predominance of trans-stilbene formation in the reaction of α-halobenzyl benzyl sulfones might be interpreted as evidence of a major steric effect in the transition state leading to cis-2,3-diphenylethylene episulfone which is greatly diminished in the transition state leading to the trans intermediate. However, there is evidence that even if the cis species were produced exclusively it would isomerize rapidly to the trans-episulfone, both in NaOD/D_2O and in NaOD/D_2O-dioxane.[5,8] Thus these stereochemical results are not necessarily relevant to the very important question of why cis-episulfone is formed preferentially in the α-haloalkyl alkyl sulfone reactions. Neureiter noted that some sort of cis preference is operative in these systems, even though the cis-olefin yields diminish slightly with increasingly larger alkyl groups at the α-positions.[2]

Bordwell and Cooper envisaged transition state X in the conversion of α-chloroethyl ethyl sulfone to cis-2-butene episulfone. It was considered that the

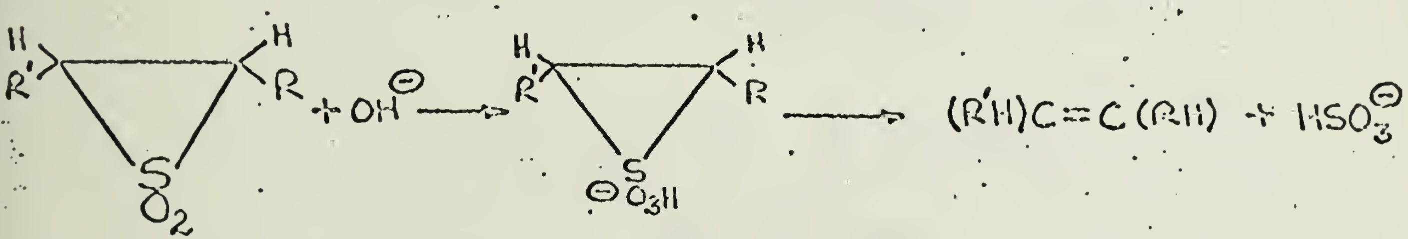


X

net methyl-methyl interaction in species X may actually be attractive.[10] Analogy was found in the case of skew butane, where the estimated difference in London and steric repulsion forces is small.[27] Calculation of the critical methyl-methyl distance in X gave no definitive value.[2]

The intriguing question of the mechanism of episulfone-olefin conversion is unanswered. It is clear that a thermal process is sufficient but not necessary.[2,10,20,28] Application of the Woodward-Hoffmann electrocyclic selection rules[29] to the eliminations of SO_2 from the *cis*- and *trans*-dialkylepisulfones indicates that a concerted thermal decomposition is symmetry-forbidden in both cases. Thus some additional postulate must be contrived to reconcile the stereospecificity of these final steps. Perhaps there is intervention of as yet unrecognized intermediates. The prospect of base-episulfone interaction must also be considered. A sequence similar to that in Figure II has been designed to rationalize the formation of alkylidene sulfonates in some dihalosulfone reactions.[6,8] The effect of base on the rates of thermal decomposition of dialkyl episulfones has not been ascertained. Williams found that the rate of decomposition of *cis*-2,3-diphenylthiirane 1,1-dioxide is accelerated by base and is very solvent-sensitive.[5] In the absence of base only *cis*-stilbene is formed but in NaOMe/MeOH only *trans*-stilbene is detected and the decomposition rate is first order in base. A control experiment, however, showed that decomposition of *trans*-episulfone is rate-limiting.

Figure II. Possible Base-Episulfone Interaction



To date the Ramberg-Bäcklund reaction has supplied some varied and interesting problems amenable to solution by physical-organic techniques. The reactions of *α*-haloalkyl alkyl sulfones appear to involve episulfone intermediates which stereospecifically decompose to olefins by processes unknown. Episulfone formation via an intermediate carbanion is accommodated by all available data but remains equivocal. The preferential formation of *cis*-episulfones has not yet been soundly explained. The stereochemical effect of the *t*-BuOK/*t*-BuOH combination has been linked to *t*-butoxide-catalyzed episulfone equilibration which disrupts the kinetic control revealed by preferential *cis*-olefin formation. The mechanism of the episulfone-olefin transformation remains obscure. A search for intermediates at this stage of the reaction is of added interest in view of recent inquiries into the course of some cycloelimination reactions.[30,31,32]

BIBLIOGRAPHY

1. L. Ramberg and B. Bäcklund, Arkiv. Kemi Mineral. Geol., 13A, No. 27 (1940).
2. N. P. Neureiter, J. Am. Chem. Soc., 88, 558 (1966).
3. J. D. Roberts and M. C. Caserio, "Supplement for Basic Principles of Organic Chemistry", W. A. Benjamin, Inc., New York, 1965, p. 271.
4. L. A. Paquette, J. Am. Chem. Soc., 86, 4383 (1964).
5. J. W. Williams, Jr., Ph.D. Thesis: Northwestern University, 1966 (privately communicated).
6. L. A. Paquette, J. Am. Chem. Soc., 86, 4089 (1964).
7. L. A. Carpino and L. V. McAdams, J. Am. Chem. Soc., 87, 5804 (1965).
8. L. A. Paquette and L. S. Wittenbrook, Chem. Comm., 471 (1966).
9. Prof. L. A. Carpino, private communication.
10. F. G. Bordwell and G. D. Cooper, J. Am. Chem. Soc., 73, 5187 (1951).
11. L. A. Paquette, J. Am. Chem. Soc., 86, 4035 (1964).
12. R. Breslow, Tetrahedron Letters, 8, 399 (1964).
13. C. L. McCabe and J. C. Warner, J. Am. Chem. Soc., 70, 4031 (1948).

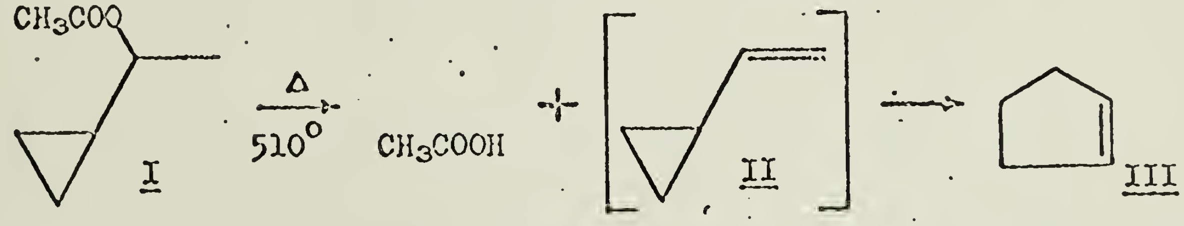
14. R. R. Frame, Ph.D. Thesis: Northwestern University, 1962, p. 49.
15. W. J. Gensler and B. A. Brooks, J. Org. Chem., 31, 568 (1966).
16. S. Ghersetti, G. Modena, P. E. Todesco, and P. Vivarelli, Gazzeta, 91, 620 (1961).
17. J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", John Wiley and Sons, Inc., New York, 1963, p. 33.
18. N. P. Neureiter and F. G. Bordwell, J. Am. Chem. Soc., 85, 1209 (1963).
19. N. Tokura, T. Nagai, and S. Matsumura, J. Org. Chem., 31, 349 (1966).
20. L. A. Paquette and L. S. Wittenbrook, J. Org. Chem., 31, 1997 (1966).
21. F. G. Bordwell and G. D. Cooper, J. Am. Chem. Soc., 73, 5184 (1951).
22. C. Y. Meyers, Tetrahedron Letters, 24, 1125 (1962).
23. "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds", API Project 44, Dec. 31, 1952, Carnegie Press, Pittsburgh, 1953, Table 8X, Parts 1 and 2.
24. W. H. Saunders, et al., J. Am. Chem. Soc., 87, 3401 (1965).
25. D. Y. Curtin, Record Chem. Progr. (Kresge-Hooker Sci. Lib.), 15, 111 (1954).
26. E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill Book Company, Inc., New York, 1962, pp. 151-53.
27. K. S. Pitzer and E. Catalano, J. Am. Chem. Soc., 78, 4844 (1956).
28. G. Opitz and K. Fischer, Angew. Chem., 77, 41 (1965).
29. R. B. Woodward and R. Hoffmann, J. Am. Chem. Soc., 87, 395 (1965).
30. Prof. J. E. Baldwin, unpublished results.
31. W. L. Mock, J. Am. Chem. Soc., 88, 2857 (1966).
32. S. D. McGregor and D. M. Lemal, J. Am. Chem. Soc., 88, 2858 (1966).

THE THERMAL ISOMERIZATION OF VINYLCYCLOPROPANES TO CYCLOPENTENES

Reported by Peter M. Harvey September 26, 1966

INTRODUCTION

In 1960 Overberger and Borchert reported that the pyrolysis of 1-cyclopropylethyl acetate (I) at 510° produces the expected vinylcyclopropane (II) in only 10% yield; the major product (60%) is cyclopentene (III).[1] In contrast, pyrolysis of the acetates of 1-cyclopentylethanol and 1-cyclohexylethanol[2] affords the corresponding vinylcycloalkanes in high yield. Furthermore, when the S-methyl xanthate of 1-cyclopropylethanol is heated at 130-230°, vinylcyclopropane is obtained in 47% yield, and no cyclopentene is detected.[3] These results suggest that cyclopentene arises by thermal isomerization of initially formed vinylcyclopropane. To verify this possibility, Overberger and Borchert pyrolized a mixture of vinylcyclopropane and acetic acid at 510° and obtained cyclopentene in 38% yield.

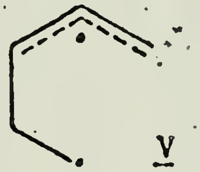


Several studies of the mechanism of the thermal isomerization of vinylcyclopropane have appeared since 1960, most of which have required interpretation of kinetic data obtained on the rearrangements of substituted vinylcyclopropanes. The early work in this field was reviewed in 1963.[4-7] In this seminar the mechanism of the thermal rearrangement of vinylcyclopropanes to cyclopentenes will be considered in the light of more recently reported results. The experimental data have been interpreted by different workers in terms of concerted and non-concerted processes. In the former case, the existence of the delocalized cyclic transition state IV has been proposed; in the latter, the diradical V has invariably been postulated as an intermediate near the "diradical transition state" of the rate determining step.

concerted

IV

diradical



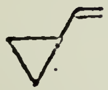
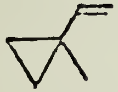
V

The absence of a suitable theoretical or experimental model for a diradical and an incomplete understanding of the transition states in reactions believed to follow concerted reaction paths have led to considerable ambiguity in the interpretation of kinetic results. In the following discussion a diradical will be regarded as a stable species with a lifetime several powers of ten longer than that of a transition state, through which a reaction is understood to pass in the order of 10^{-13} sec, the approximate period of one molecular vibration. The term "diradical transition state"[14] describes some localization of unpaired electron density in a transition state leading to a diradical (non-concerted) or directly to product (concerted), and for this discussion it will be considered to pertain to a transition state with "diradical character."

KINETICS OF THE VINYLCYCLOPROPANE REARRANGEMENT

The rates of isomerization of a large number of vinylcyclopropanes to cyclopentenes and other products in the gas phase have been measured. The activation parameters of some of these reactions as well as data on some model compounds, are compiled in Table I. Values of the transition state activation parameters $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ at 600°K were calculated from the reported Arrhenius parameters E_a and A. A transmission coefficient κ of unity was assumed for calculating $\Delta S^{\ddagger}$.

TABLE I - KINETIC DATA FOR THERMAL ISOMERIZATIONS IN THE GAS PHASE

	Reactant	Product	Temp. Range (°C)	$\Delta H^{\ddagger}_{600}$ (kcal/mole)	$\Delta S^{\ddagger}_{600}$ (eu)	$\Delta G^{\ddagger}_{600}$ (kcal/mole)	ref.
A			339-391 (4)*	48.4	0.0	48.4	8
			325-390 (5)	48.5	+0.1	48.5	9
B			313-357 (9)	48.2	+2.7	46.6	10
C			332-386 (8)	49.7	+1.6	48.7	11
D			325-368 (9)	49.3	+2.8	47.6	12
E			333-373 (9)	48.8	+1.2	48.1	13
F			350-390 (7)	53.4	+2.2	52.1	14
G			414-474	63.0	+11.4	56.1	15
		propene-d_2	414-474	$64.3^{\dagger}$	$+7.8^{\dagger}$	$58.3^{\dagger}$	15
H			380-453 (8)	58.2	+7.9	53.5	16

*The figure in parentheses is the number of temperatures studied, if reported.

†Reported Arrhenius parameters, from which these values are calculated, are not corrected for isotope effects.

The tabulated values of $\Delta S^{\ddagger}$ have not been corrected for entropy of dl mixing in reactants or transition states. The determination of such corrections requires at least a partial knowledge of the geometries of reactant and activated complex. Whereas the former can be determined, at least in principle, by direct measurements on the reactant, the geometry of the transition state can be studied only indirectly, for example, from the stereochemistry of products and from steric effects on the reaction rate. The magnitude of such corrections of $\Delta S^{\ddagger}$ will seldom be more than ±2.5 eu, so that only differences in entropies of activation of substantially larger than this figure will be considered significant.

The gas-phase kinetic studies of the isomerizations of vinylcyclopropanes were carried out in aged vessels thermostatted to ±0.2° or better; concentrations and yields were determined by gas chromatography. Formation of products and disappearance of reactants were first order in reactants for conversions of 90% or greater in most cases. The failure of the olefinic products, which are expected to be good radical traps, to lower the rate constants for product formation as their concentrations increased in the reaction mixtures suggests the absence of radical chain processes. Nine- to twenty-seven-fold variations in the surface-to-volume ratio did not affect the rate constants, indicating that the reactions have no significant heterogeneous components. In two cases, the addition of nitric oxide to vinylcyclopropane[8] and to perfluorovinylcyclopropane[17] had a negligible effect on the rate constants, and no radical trapping products were detected. Variations of the initial pressure did not alter the rate constants significantly, indicating that the kinetics were determined above the pressure fall-off region and that the isomerizations of vinylcyclopropanes are probably unimolecular processes.

ESTIMATED ACTIVATION ENERGY FOR DIRADICAL FORMATION

The understanding that the transition state may reflect the chemical character of an intermediate nearby on the reaction coordinate lies behind the postulation of diradical intermediates in reactions in which the transition state is argued to exhibit diradical character. Doering has predicted an activation energy of 42.4 kcal/mole for the isomerization of vinylcyclopropane.[5] His calculation involves the following assumptions: 1) The activation energy required to form the trimethylene diradical from cyclopropane is 64.2 kcal/mole, the Arrhenius activation energy reported by Rabinovitch, Schlag, and Wiberg for the geometrical isomerization of trans-1,2-dideuteriocyclopropane;[15] 2) The contribution of allylic resonance to the stabilization of a radical-like transition state is 21.8 kcal/mole, the difference between the dissociation energy of ethane into methyl radicals (83.3 kcal/mole[18]) and the dissociation energy of 1-butene into methyl and allyl radicals (61.5 kcal/mole[18]); 3) The additivity principle is valid and the activation energy for the vinylcyclopropane rearrangement is smaller than that for the geometrical isomerization of cyclopropane by the resonance energy of the allyl radical.

With the following qualifications, Doering's calculation can be regarded as an estimate of the activation energy for forming the diradical intermediate V from vinylcyclopropane: 1) The question of whether the geometrical and structural isomerizations of cyclopropane involve a free trimethylene diradical in the rate determining step is unsettled. The value of 64.2 kcal/mole probably represents a lower limit on the activation energy for the formation of the diradical from cyclopropane; 2) Kerr, Spencer, and Trotman-Dickenson[20] have questioned the value of 61.5 kcal/mole[18] for the activation energy for the dissociation of 1-butene. They showed that in the pressure region where this value was obtained, the rate constant shows a strong pressure dependence, and therefore the measured activation energy is lower than the high-pressure first order activation energy. If this objection is valid, the contribution of allylic resonance to stabilization of the transition state is smaller than Doering's value of 21.8 kcal/mole. Benson has studied the reaction of iodine atoms with propene[21] and with 1-butene.[22] From the activation energies for abstraction of an allylic hydrogen atom he calculates resonance energies of 10.2 and 12.6 kcal/mole for the allyl and methallyl radicals, respectively; 3) Doering's calculation does not take into account the "stabilization" of vinylcyclopropane by conjugation of the cyclopropane ring with the olefinic bond.[23] This

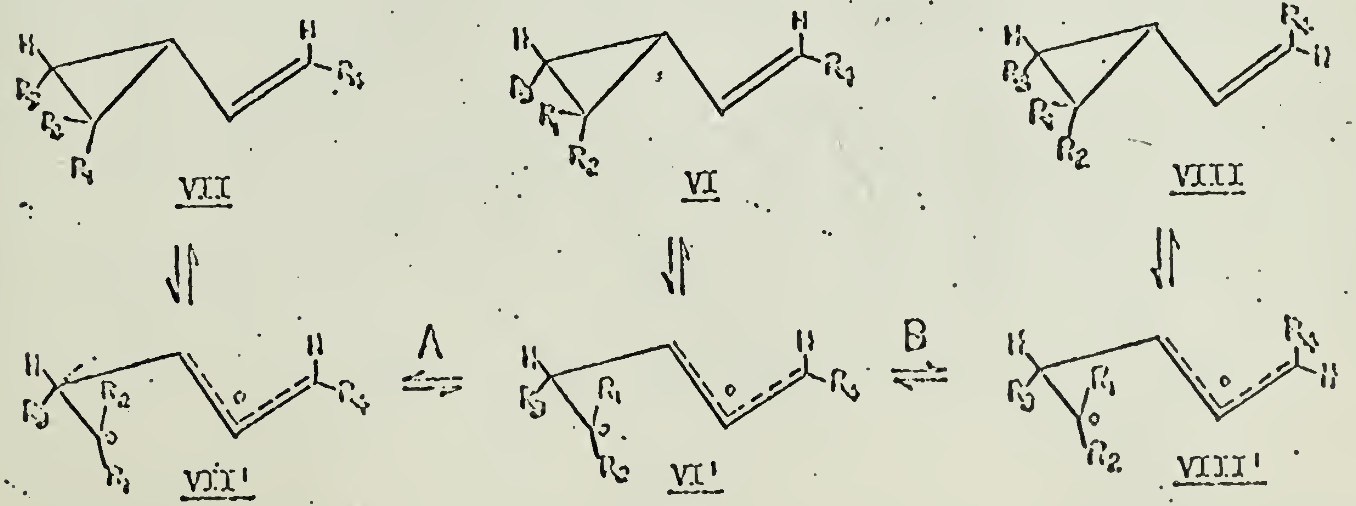
"stabilization," which must be disrupted in opening the cyclopropane ring to form the diradical V, has been estimated to be -2.1 kcal/mole, the difference between the heats of hydrogenation of vinylcyclopropane and 3-methyl-1-butene.

Using a value of 12 kcal/mole as the allylic stabilization of the transition state and -2 kcal/mole as the conjugative stabilization of vinylcyclopropane, a new minimum activation energy for the reaction I → V of 48 (62-12-2) kcal/mole may be calculated; this value corresponds to an enthalpy of activation of greater than 47 kcal/mole at 600°K. The observed activation enthalpies for the formation of cyclopentenes from vinylcyclopropane and several monoalkyl substituted vinylcyclopropanes (entries A-E in Table I) lie in the range of 48 to 50 kcal/mole. These values are sufficiently near the estimated value of 47 kcal/mole to require serious consideration of diradical V as a possible intermediate.

Ellis and Frey have noted that the contribution of cyclopropane strain release in the transition states of the isomerizations of cyclopropane and alkylcyclopropanes of about 19 kcal/mole[10] is significantly smaller than the experimentally measured cyclopropane strain energy of 27.6 kcal/mole.[24] They reason that the apparent 13 kcal/mole allylic stabilization of diradical V may similarly not represent the full resonance energy of the allyl radical and that the steric requirements of the activated complex may allow only partial delocalization in the transition state. The validity of this analogy has been questioned by Benson,[22] but the fact remains that whether or not 13 kcal/mole is the full resonance energy of the allyl radical, it represents that portion of this energy by which the transition state of a diradical process will be stabilized.

As an alternative to the diradical mechanism discussed above, a concerted reaction path in which the formation of a new carbon-carbon bond compensates for the energy required for simultaneous cleavage of the cyclopropane ring[8] can account for the low activation enthalpy of the vinylcyclopropane rearrangement relative to that of cyclopropane isomerization (entries G-H in Table I). Unlike the transition state model used for the diradical path, the cyclic model IV for the transition state in a concerted process suggests no obvious separation of the enthalpy of activation into contributions of carbon-carbon bond breaking, release of strain energy, and conjugation in reactant and transition state. Any electron delocalization in IV is a property of the transition state as a whole and cannot be ascribed to an effect analogous to allylic resonance whose magnitude can be independently estimated. Therefore the insufficiency of our models for the transition states of diradical and concerted processes makes a differentiation between the two paths on the basis of enthalpy considerations uncertain.

Frey and Marshall have proposed experiments which might be useful in demonstrating the formation of a diradical intermediate[11] provided that such an intermediate is reversibly formed. They suggest that vinylcyclopropanes with ring substituents should



VIa-VIIIa $R_2 = CH_3$, $R_1 = R_3 = R_4 = H$

VIb-VIIIb $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$

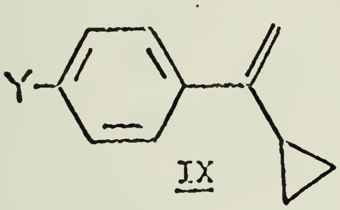
VIc-VIIIc $R_4 = CH_2CH_3$, $R_1 = R_2 = R_3 = H$

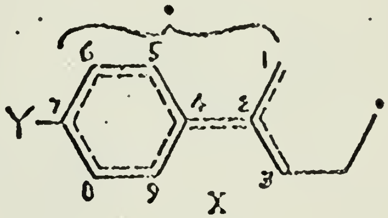
undergo cis-trans isomerizations (Path A) with activation energies smaller than those of the geometrical isomerizations of substituted cyclopropanes. Furthermore, vinylcyclopropanes with substituents on the terminal position of the olefinic bond should have lower activation energies for cis-trans isomerizations about the double bond (Path B) than ordinary olefins. The only reported tests of these proposals have given negative results. Both cis- (VIa) and trans-1-methyl-2-vinylcyclopropane (VIb) are reported to rearrange to give chiefly 1,4-hexadiene via a 1,5-hydrogen shift with no detectable products of geometrical isomerization.[25,26] trans-1-Cyclopropyl-1-butene (VIc) rearranges to 3-ethylcyclopentene without forming detectable amounts of the cis-isomer (VIIIc).[13]

STUDIES OF POLAR EFFECTS

Ketley has found that a series of 1-(p-substituted phenyl)-1-cyclopropylethylenes (IX, Y = H, CH_3, $CH(CH_3)_2$, OCH_3) rearranges to the corresponding cyclopentenes at 325° at the same rate (within experimental error).[27] The free energy of activation

Y= [illegible], CN

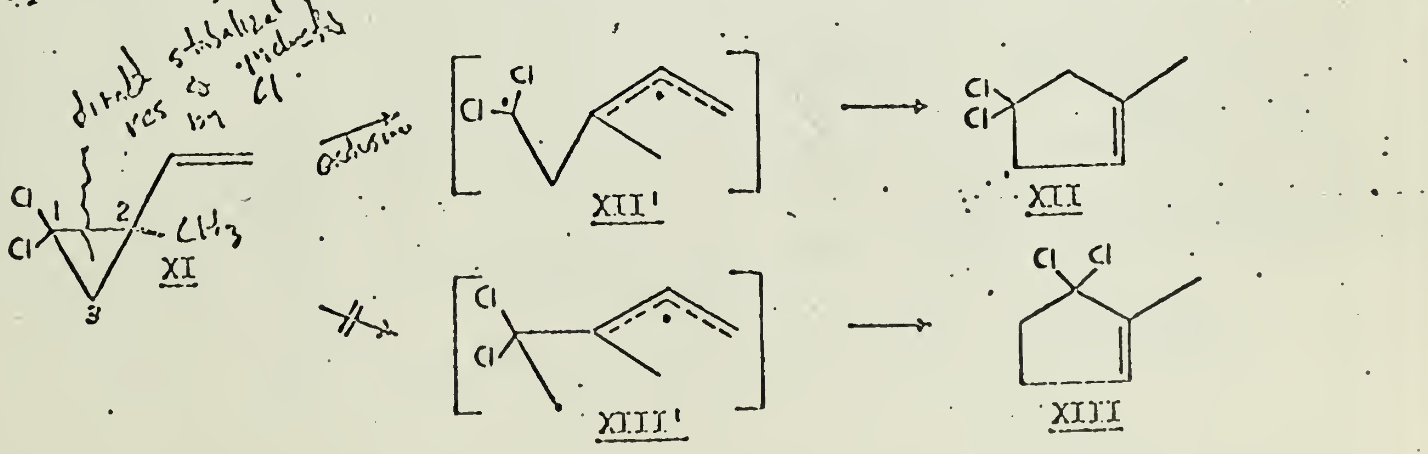

IX



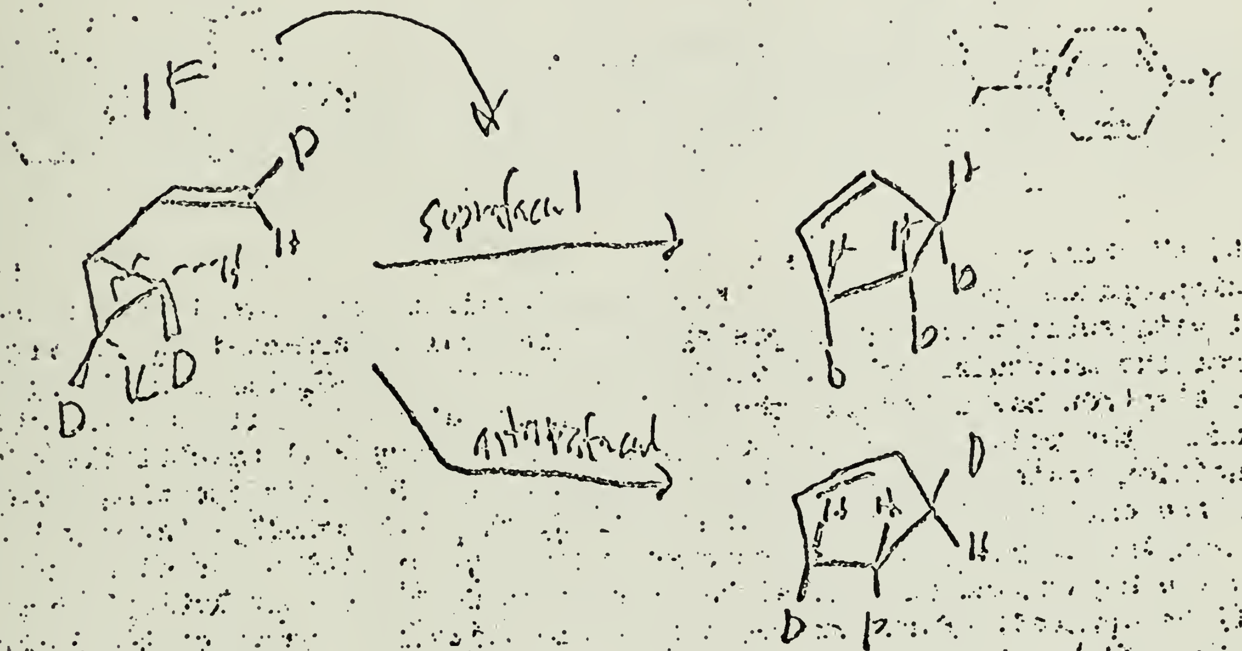
X

at 600°K, 47 kcal/mole, is close to the values obtained for alkyl substituted vinylcyclopropanes (see Table I). Ketley rationalizes the invariance of the rate constant with substituent by proposing the diradical intermediate X and arguing that since the molecular orbital of the allyl system (C_1-C_2-C_3) containing the unpaired electron has a node at the center carbon atom (C_2), it is reasonable that variation in the polarity of the substituent aryl group will have little effect on the transition state leading to the formation of X. Strictly speaking, one should consider the entire delocalized π-system of X, the 2-phenylallyl (atropyl) system, rather than the allyl system. The Hückel molecular orbital occupied by the unpaired electron the 2-phenylallyl radical has a node at C_7,[28] so that Ketley's argument can still be applied. Furthermore, the π-delocalization energy of the 2-phenylallyl radical is 0.77 β relative to styrene[29] plus a carbon 2p electron; this value is not very different from the π-delocalization energy of the allyl radical relative to ethylene plus a carbon 2p electron, 0.82 β. Therefore the fact that the transition states for the rearrangements of vinylcyclopropane and IX (Y = H) show about the same amount of stabilization is not inconsistent with a diradical process.

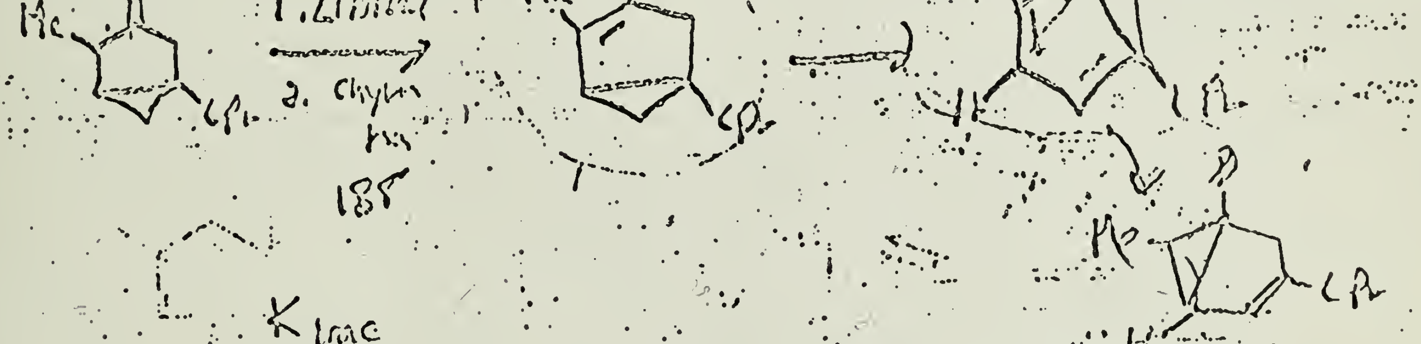
The thermal isomerization of 1,1-dichloro-2-methyl-2-vinylcyclopropane (XI) at 200-275° produces 4,4-dichloro-2-methylcyclopentene (XII) as the sole product;



no 3,3-dichloro-2-methylcyclopentene (XIII) is detected, indicating that exclusive cleavage of the 1-2 cyclopropane bond has occurred. This result has been interpreted[30] as evidence for a diradical, since the diradical XII' would be expected to be appreciably more stable than that (XIII') formed by 2-3 cleavage.[31] The enthalpy of



Dewaring —



$\frac{K_{rac}}{K_{inv}}$

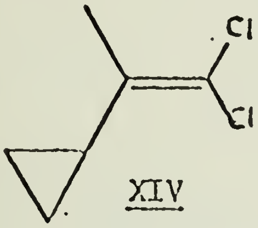
0 antarafacial — every molec that reacts yields same

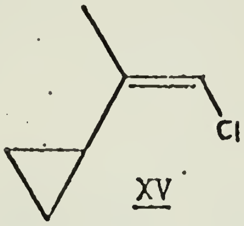
2 suprafacial — each Cis gives   Own carbon

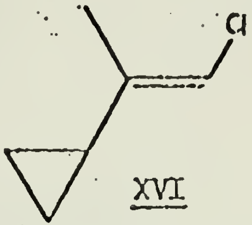
1 1:1

activation for the rearrangement of *XI* is about 19 kcal/mole lower than that for the formation of 1-methylcyclopentene from 1-methylvinylcyclopropane (entry B in Table I); this difference can be attributed to additional stabilization of the diradical-like transition state leading to XII' by two α-chlorine atoms. However, there is no evidence that the chlorine atoms could not stabilize a cyclic, non-radical transition state in a concerted process. Furthermore, the large change in the activation enthalpy accompanying the substitution of two hydrogen atoms by chlorine atoms suggests the possibility that a different mechanism is operating in this case.

1,1-Dichloro-2-cyclopropylpropene (*XIV*) does not isomerize below 400°; above 450° a mixture of sixteen liquid products and 50% of polymer is produced.[30] To


XIV


XV


XVI

test whether this inhibition of the vinylcyclopropane rearrangement is caused by steric or polar factors, the *cis* and *trans* isomers of 1-chloro-2-cyclopropylpropene (*XV* and *XVI*) were separately heated to 350° for 4 hrs; in both cases no reaction occurred. At 400° both compounds polymerized at the same rate. These results suggest that the inhibition is not a steric effect.

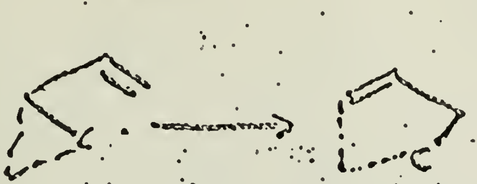
STERIC EFFECTS AND ENTROPIES OF ACTIVATION

Calculated values of entropies of activation are extremely sensitive to experimental error and to graphical error in determining the frequency factors A from the intercepts of Arrhenius plots. Consequently only large differences in values of $\Delta S^\ddagger$ may be regarded as significant. In contrast to cyclopropane isomerizations, which have entropies of activation near +10 eu, the transition states in vinylcyclopropane rearrangements have entropies of activation ranging from 0 to +3 eu (entries A-F in Table I). The large positive values for cyclopropanes have been accounted for by loosening of the molecule in a ring-expanded or ring-opened transition state.[15] Breslow regards the absence of such loosening in the case of vinylcyclopropanes, suggested by the lower entropies of activation, as evidence for a *cyclic* process in which there is simultaneous cleavage and formation of bonds.[4] On the other hand, the lowering of the entropies of activation in vinylcyclopropane rearrangements may be due to additional restriction of rotation of the vinyl group necessary to maximize allylic delocalization in a diradical-like transition state.

Ellis and Frey have predicted that if the vinylcyclopropane rearrangement involves a cyclic transition state, as would be expected for a concerted process, a vinylcyclopropane substituted on the double bond *cis* to the cyclopropyl group should undergo isomerization with an unusually high activation energy because of steric hindrance in the transition state.[13] The isomerization of 1,1-dimethyl-2-cyclopropylethylene (entry F in Table I) produces significant amounts of 5-methylhexa-1,4-diene and *cis*- and *trans*-2-methylhexa-2,4-diene in addition to the expected 3,3-dimethylcyclopentene.[14] The free energy of activation for the formation of the cyclopentene is 3 - 4 kcal/mole higher than the corresponding values for alkyl substituted vinylcyclopropanes without *cis* substituents on the double bond. This result must be correlated with Frey's prediction with some caution, since most if not all of the 3 - 4 kcal/mole difference can be accounted for by differences in enthalpies of activation. One might expect steric hindrance in a transition state to be reflected in a change in the entropy of activation; if this change is small, it might easily be missed because of the large uncertainty in $\Delta S^\ddagger$.

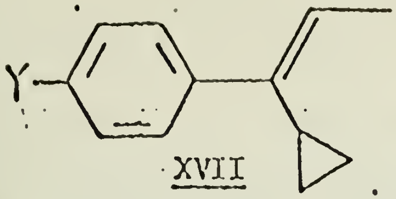
A study of the isomerization of the *cis* and *trans* isomers of 1-(*p*-substituted phenyl)-1-cyclopropylpropenes (*XVII* and *XVIII*) showed that for a number of substituents (Y = H, F, CH_3, and OCH_3) the *trans* isomer rearranges 3.3 to 3.8 times as fast as the *cis* isomer.[32] The lowering of the reaction rates observed for *cis*-substituted vinylcyclopropanes is in accord with the prediction of Ellis and Frey,

Woodward–Hoffmann ——— should predict antarafacial (??)
Calculations but correct symmetry

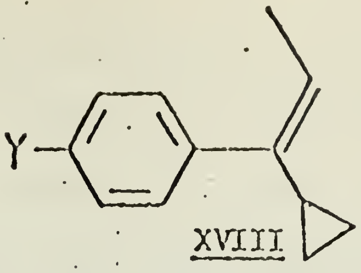


∴ Ca

Calc. - distinguish between two mechanisms



XVII



XVIII

but it does not distinguish a concerted process in which the attainment of cyclic geometry in the transition state is sterically hindered, from a non-concerted process in which steric factors increase the difficulty of achieving proper orbital alignment for maximum allylic stabilization of a diradical-like transition state.

The major problem in studying the mechanism of the thermal isomerization of vinylcyclopropanes to cyclopentenes is the lack of suitable models to which the experimental data can be compared. In some cases we can approximate these models - for example, it is possible to estimate a reasonable enthalpy of activation for the formation of a diradical intermediate - but such approximations are of little help in excluding alternative possible mechanisms. Almost every observation which has been claimed to support a diradical intermediate: the low enthalpy and entropy of activation, the effects of polar substituents, the effects of steric hindrance, can be rationalized in terms of a concerted, cyclic mechanism.

It is clear that the kind of experiments which will yield new information about the vinylcyclopropane rearrangement will take an approach different from that of the work already reported. The behavior of diradical-like species generated by the decomposition of Δ^1-pyrazolines could be compared to the behavior of proposed intermediates. In view of the stereospecific reaction path followed by many processes believed to be concerted, stereochemical studies of the isomerization products of appropriately substituted vinylcyclopropanes may provide more convincing evidence about the mechanism.

BIBLIOGRAPHY

1. C. G. Overberger and A. E. Borchert, J. Am. Chem. Soc., 82, 1007 (1960).
2. J. R. van der Bij and E. C. Kooyman, Rec. Trav. Chim., 71, 837 (1952).
3. C. G. Overberger and A. E. Borchert, J. Am. Chem. Soc., 82, 4896 (1960).
4. R. Breslow in P. de Mayo, ed., "Molecular Rearrangements," Interscience Publishers, New York, 1963, part I, p. 233.
5. W. von E. Doering and W. R. Roth, Angew. Chem., 75, 27 (1963); Angew. Chem. Intern. Ed. Engl., 2, 115 (1963).
6. G. Leadbetter, University of Illinois Organic Seminar, II Semester 1962-1963, p. 69.
7. E. Vogel, Angew. Chem. Intern. Ed. Engl., 2, 1 (1963).
8. M. C. Flowers and H. M. Frey, J. Chem. Soc., 3547 (1961).
9. C. A. Wellington, J. Phys. Chem., 66, 1671 (1962).
10. R. J. Ellis and H. M. Frey, J. Chem. Soc., 959 (1964).
11. H. M. Frey and D. C. Marshall, J. Chem. Soc., 3981 (1962).
12. C. S. Elliott and H. M. Frey, J. Chem. Soc., 4289 (1965).
13. R. J. Ellis and H. M. Frey, J. Chem. Soc., 4188 (1964).
14. C. S. Elliott and H. M. Frey, J. Chem. Soc., 345 (1965).
15. B. S. Rabinovitch, E. W. Schlag, and K. B. Wiberg, J. Chem. Phys., 28, 504 (1958).
16. M. C. Flowers and H. M. Frey, Proc. Roy. Soc. (London), Ser. A, 257, 122 (1960).
17. R. A. Mitsch and E. W. Neuvar, J. Phys. Chem., 70, 546 (1966).
18. T. L. Cottrell, "The Strengths of Chemical Bonds," Academic Press, New York, 1954, p. 201.
19. A. H. Sehon and M. Szwarc, Proc. Roy. Soc. (London), Ser. A, 202, 263 (1950).

20. J. A. Kerr, R. Spencer, and A. F. Trotman-Dickenson, J. Chem. Soc., 6652 (1965).
21. D. M. Golden, A. S. Rodgers, and S. W. Benson, J. Am. Chem. Soc., 88, 3196 (1966).
22. K. W. Eggers, D. M. Golden, and S. W. Benson, J. Am. Chem. Soc., 86, 5420 (1964).
23. P. J. C. Fierens and J. Nasielski, Bull. Soc. Chim. Belges, 71, 187 (1962).
24. Sj. Kaarsemaker and J. Coops, Rec. Trav. Chim., 71, 261 (1952).
25. R. J. Ellis and H. M. Frey, J. Chem. Soc., 5578 (1964).
26. W. R. Roth and J. König, Ann. Chem., 688, 28 (1965).
27. A. D. Ketley, Tetrahedron Letters, 1687 (1964).
28. A. Streitwieser, Jr. and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Pergamon Press, New York, 1965, vol. 1, p. 49.
29. A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, New York, 1961, p. 107.
30. A. D. Ketley, A. J. Berlin, E. Gorman, and L. P. Fisher, J. Org. Chem., 31, 305 (1966).
31. P. D. Bartlett, L. K. Montgomery, and B. Seidel, J. Am. Chem. Soc., 86, 616 (1964).
32. A. D. Ketley, A. J. Berlin, and L. P. Fisher, J. Org. Chem., 31, 2648 (1966).

FREE RADICAL ADDITIONS TO CARBONYLS

Reported by John Engelmann September 29, 1966

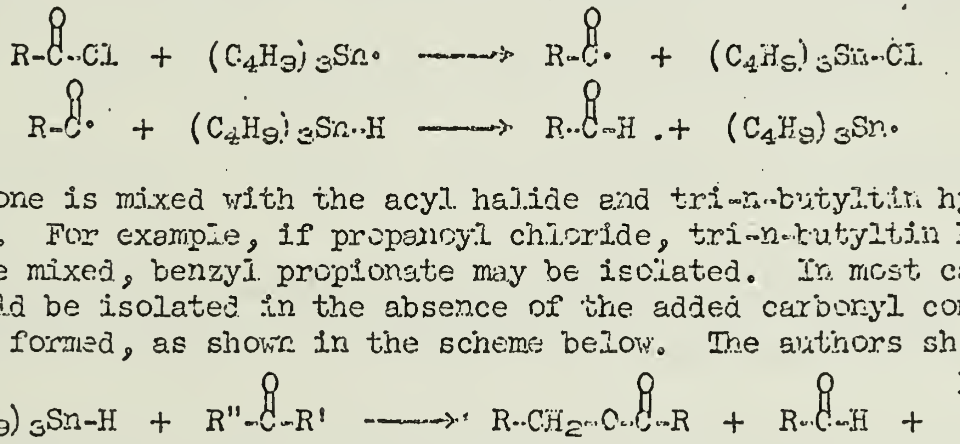
INTRODUCTION

Ionic additions to carbonyls are well known. Free radical decomposition of carbonyl compounds is also well documented. In this seminar we will consider a series of less well-known reactions, and their mechanisms, in which a radical adds to a carbonyl. We will discuss the reverse of acyl radical decomposition; that is a reaction in which radicals add to carbon monoxide to form acyl radicals.

ADDITION OF ACYL RADICALS TO CARBONYLS

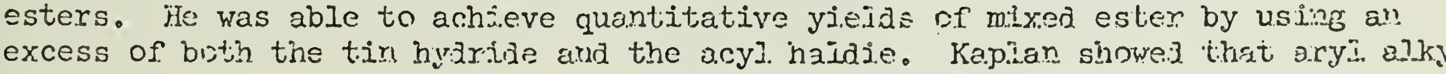
Work has been done in the case of the reduction of acyl halides by tri-alkyl or tri-aryl tin hydrides. Kerk, Noltes, and Luijten[1] isolated benzaldehyde from the reaction of triphenyltin hydride and benzoyl chloride. Later, Kupchick, and Kiesel[2] reported that benzyl benzoate was the major product in the reaction between benzoyl chloride and triphenyltin hydride. The yields of ester were about 70%. The authors could not find benzaldehyde, although they did a control experiment which showed that 2% benzaldehyde could readily be detected. Radical inhibitors such as galvinoxyl, hydroquinone, and trans stilbene inhibited the reaction, while azobisisobutyronitrile accelerated the reaction. These two facts suggest a radical mechanism for the reaction.

Kuivala and Walsh[3] investigated the reaction between tri-n-butyltin hydride and acyl halides. They demonstrated that both aldehydes and esters were produced in the reaction. The yields of ester and aldehyde depended on the acyl halide being reduced and on the reaction conditions. When the reaction was run in a solvent, the yield of aldehyde rose. As the alkyl group of the acyl halide becomes larger and more branched the yield of aldehyde increased. As before, the authors observed that a small amount of azobisisobutyronitrile accelerated the reaction. They proposed the radical mechanism shown below for the formation of aldehyde. The authors did not propose a detailed initiation step but they did suggest that radicals might be formed in a bimolecular reaction between the hydride and the acid chloride. If an aldehyde or ketone is mixed with the acyl halide and tri-n-butyltin hydride, a mixed ester is formed. For example, if propanoyl chloride, tri-n-butyltin hydride, and benzaldehyde are mixed, benzyl propionate may be isolated. In most cases both the ester which would be isolated in the absence of the added carbonyl compound, and the mixed ester are formed, as shown in the scheme below. The authors showed that the reaction proceeded with aromatic aldehydes, cyclic ketones, and aliphatic aldehydes.



$$R{-}\overset{\overset{O}{\|}}{C}{-}Cl + (C_4H_9)_3Sn\cdot \longrightarrow R{-}\overset{\overset{O}{\|}}{C}\cdot + (C_4H_9)_3Sn{-}Cl$$

$$R{-}\overset{\overset{O}{\|}}{C}\cdot + (C_4H_9)_3Sn{-}H \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}H\ . + (C_4H_9)_3Sn\cdot$$

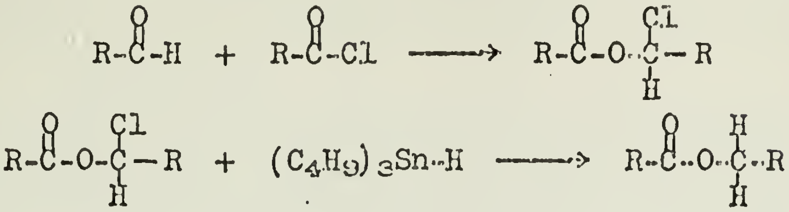


$$R{-}\overset{\overset{O}{\|}}{C}{-}Cl + (C_4H_9)_3Sn{-}H + R''{-}\overset{\overset{O}{\|}}{C}{-}R' \longrightarrow R{-}CH_2{-}O{-}\overset{\overset{O}{\|}}{C}{-}R + R{-}\overset{\overset{O}{\|}}{C}{-}H + {}^{R'}_{R''}\!>\overset{H}{C}{-}O{-}\overset{\overset{O}{\|}}{C}{-}R$$

The yields of mixed ester varied from a high of 70% in the case of propanoyl chloride and benzaldehyde, to a low of 3.2% in the case of propanoyl chloride and cyclopentanone. Kaplan[4] explored the possibility of using the reaction between triphenyltin hydride, an acyl halide, and a ketone as a synthetic route to certain esters. He was able to achieve quantitative yields of mixed ester by using an excess of both the tin hydride and the acyl haldie. Kaplan showed that aryl alkyl ketones reacted in this manner with alkyl acid chlorides, and that benzoyl chloride was a suitable acid chloride for this reaction.

Kuivala and Walsh[5] proposed four possible mechanisms for ester formation in the reaction of acyl halides with tri-n-butyltin hydride. In each case some of the acyl halide is reduced to the aldehyde by the free radical mechanism shown previously. In the first mechanism the aldehyde could react with the unreacted acyl halide to form an α chloro ester. The α chloro ester could then react with the tin hydride to

form the observed ester. To justify the formation of the α chloro ester the authors cite the work of Adams and Vollweiler.[30] This mechanism is shown in the scheme below.

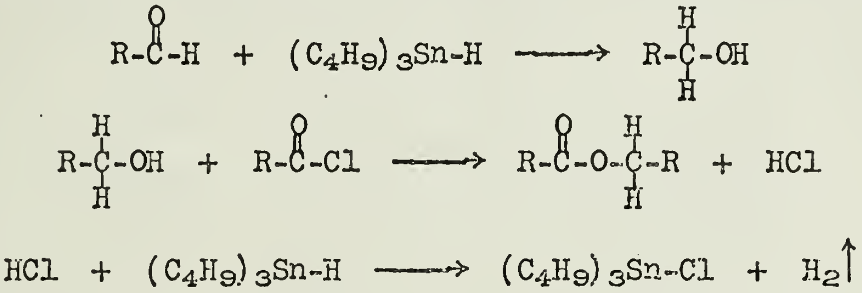


$$R-\overset{O}{\overset{\|}{C}}-H + R-\overset{O}{\overset{\|}{C}}-Cl \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-\underset{H}{\overset{Cl}{C}}-R$$

$$R-\overset{O}{\overset{\|}{C}}-O-\underset{H}{\overset{Cl}{C}}-R + (C_4H_9)_3Sn-H \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-\underset{H}{\overset{H}{C}}-R$$

The authors ruled out this mechanism by showing that the α chloro ester reacted much more slowly with the tin hydride than did the acid chloride.

The second mechanism which Kuivala proposed was that the aldehyde was reduced further to the alcohol. The alcohol could react with unreduced acyl halide to form the observed ester as shown in the equation below. The authors were able to rule out this mechanism when they observed that even though the reduction to the alcohol was catalysed by tri-n-butyltin chloride, this reaction was still slower than the reaction between the tin hydride and the acyl halide. Furthermore, if the reaction went by this mechanism, the HCl formed in the reaction between the acyl halide and the alcohol, would react with the tin hydride to form H_2. Hydrogen is not an observed product.

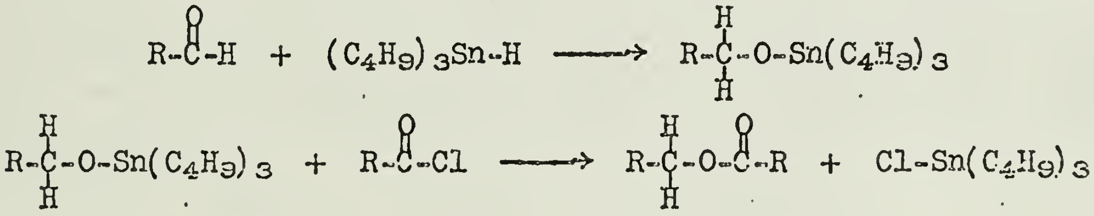


$$R-\overset{O}{\overset{\|}{C}}-H + (C_4H_9)_3Sn-H \longrightarrow R-\underset{H}{\overset{H}{C}}-OH$$

$$R-\underset{H}{\overset{H}{C}}-OH + R-\overset{O}{\overset{\|}{C}}-Cl \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-\underset{H}{\overset{H}{C}}-R + HCl$$

$$HCl + (C_4H_9)_3Sn-H \longrightarrow (C_4H_9)_3Sn-Cl + H_2\uparrow$$

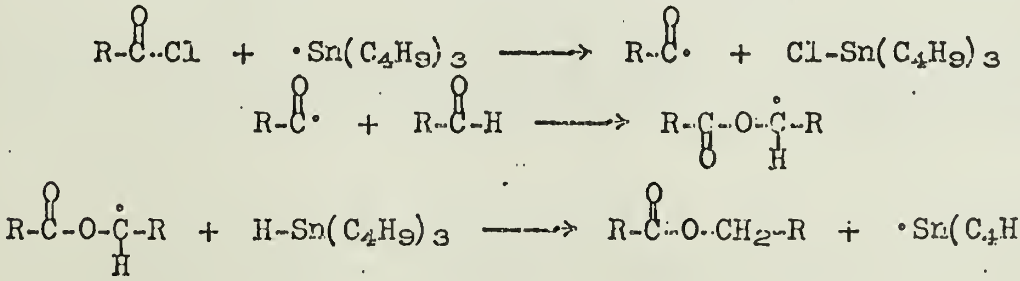
The third mechanism proposed by Kuivala was that the aldehyde is reduced to the tin alkoxide. The tin alkoxide then reacts with unreacted acyl halide. This mechanism is shown in the scheme below. This mechanism would not require hydrogen as a product. Because the reduction of the aldehyde is slower than the rate of the reaction, the authors ruled out this mechanism as a major contributor. However, they were not able to exclude the possibility that some ester was produced by this process.



$$R-\overset{O}{\overset{\|}{C}}-H + (C_4H_9)_3Sn-H \longrightarrow R-\underset{H}{\overset{H}{C}}-O-Sn(C_4H_9)_3$$

$$R-\underset{H}{\overset{H}{C}}-O-Sn(C_4H_9)_3 + R-\overset{O}{\overset{\|}{C}}-Cl \longrightarrow R-\underset{H}{\overset{H}{C}}-O-\overset{O}{\overset{\|}{C}}-R + Cl-Sn(C_4H_9)_3$$

The fourth mechanism which Kuivala and Walsh proposed was a radical mechanism in which a tin radical abstracts a halogen atom from the acyl halide, forming an acyl radical. The acyl radical then attacks the oxygen of the aldehyde forming a radical of the ester. The ester radical then abstracts a hydrogen atom from the tin hydride. The mechanism is shown in the equations below.



$$R-\overset{O}{\overset{\|}{C}}-Cl + \bullet Sn(C_4H_9)_3 \longrightarrow R-\overset{O}{\overset{\|}{C}}\bullet + Cl-Sn(C_4H_9)_3$$

$$R-\overset{O}{\overset{\|}{C}}\bullet + R-\overset{O}{\overset{\|}{C}}-H \longrightarrow R-\underset{\overset{\|}{O}}{C}-O-\underset{H}{\overset{\bullet}{C}}-R$$

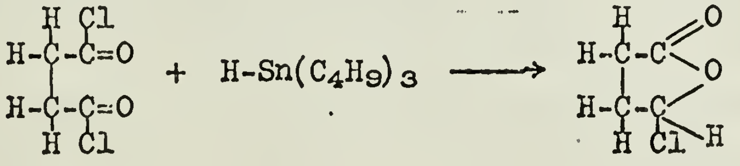
$$R-\overset{O}{\overset{\|}{C}}-O-\underset{H}{\overset{\bullet}{C}}-R + H-Sn(C_4H_9)_3 \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-CH_2-R + \bullet Sn(C_4H_9)_3$$

If acyl radicals were intermediates in the reaction, one would expect that a certain amount of decarbonylation might occur. This decarbonylation is difficult

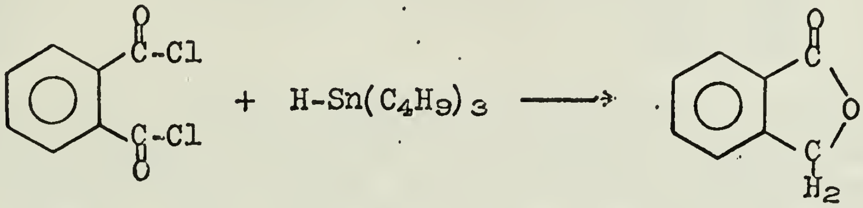
to observe because the tin hydride is an efficient hydrogen donor. Kuivala and Walsh[3] found that if tri-n-butyl tin hydride was added slowly to triphenylacetyl chloride, 10-12% carbon monoxide could be isolated. The yield of triphenylmethane was 5%. The production of carbon monoxide provides good evidence for the presence of acyl radicals as intermediates.

This mechanism readily explains all the data. For example, the fact that an increase in the branching of the alkyl group of the acyl halide increases the yield of aldehyde is explained by the increase in the activation energy for radical attack on the aldehyde with increasing steric requirements of the alkyl group. The effect of solvent in increasing the yield of aldehyde can be rationalized by postulating that the acyl radical can abstract a hydrogen from the solvent as well as from the tin hydride.

As would be expected from the preceding mechanism di-acyl halides have a tendency to form cyclic products. For example, Kuivala[6] reacted succinyl chloride (I) and phthalyl chloride (II) with tri-n-butyltin hydride. He obtained the cyclic products shown in the equations below.

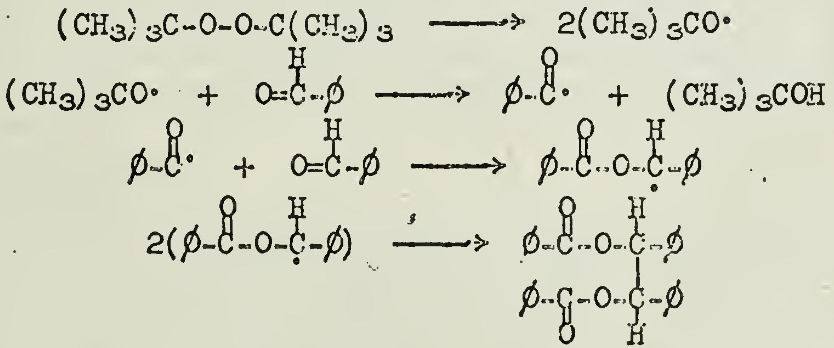


(I)



(II)

Further evidence for this mechanism is provided by a reaction in which acyl radicals generated by another reaction add to an aldehyde to form an ester. Rust, Seubold, and Vaughan[7] reacted di-t-butyl peroxide and benzaldehyde. They isolated the dibenzoate ester of 1,2 diphenyl ethanediol (III) in 85% yield. The formation of this product is readily rationalized by the scheme shown below. This scheme



(III)

seems justified since the abstraction of the aldehyde hydrogen by peroxide radicals or other radicals is a very well-documented reaction.[8-11] In addition benzyl benzoate and di-t-butyl peroxide give the same dibenzoate ester as benzaldehyde and di-t-butyl peroxide.

There is one problem which remains, however. That is the problem of substituent effects. Kupchick and Kiesel[2] studied the reaction between triphenyltin hydride and substituted benzoyl chlorides. They ran reactions for a standard amount of time and monitored the extent of the reaction by measuring the amount of triphenyltin chloride formed. The results are shown in the table below. The

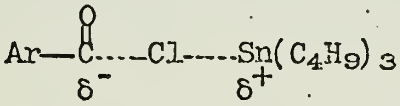
reaction was run without solvent with a 1:1 mole ratio of chloride to hydride.

para substituent	% yield	% yield with 10 mole % azobisisobutyronitrile
CH_3O	77.9	----
CH_3	70.1	----
H	32.5	----
F	0	51.9
CF_3	0	31.1
NO_2	0	0

Although the data is not expressed in the form of rates, it is clear that electron releasing groups accelerate the reaction. On the other hand, Kuivala and Walsh[3] ran competitive reactions between benzyl bromide or 2 bromooctane and substituted benzoyl chloride for a deficiency of tri-n-butyltin hydride in solution. The authors determined hydrocarbon and unreacted acid chloride. They assumed that no tin hydride was consumed in side reactions. From this data they computed relative reaction rates. The relative rates in m-xylene are shown in the table below.

substituent	rel. rate	substituent	rel. rate
H	1.00	para CF_3	38.10
para Cl	1.27	para CN	61.40
meta F	2.34	meta CH_3	0.937
meta Cl	8.20	para CH_3	0.290
meta CF_3	9.50	para OCH_3	0.166

It is clear that in this case electron releasing substituents slow the reaction, while electron withdrawing groups accelerate the reaction. Kuivala and Walsh proposed that the rate controlling step in the reaction was the abstraction of chloride by the tin radical. They suggested that the radical formation step involved a transition state with considerable charge separation. Kupchick and Kiesel

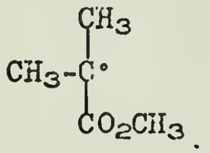


$$\mathrm{Ar{-}\overset{O}{\underset{\delta^-}{C}}\cdots Cl\cdots \underset{\delta^+}{Sn}(C_4H_9)_3}$$

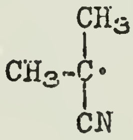
ran their reaction without solvent so that the solvent was the polar acid chloride. The difference in solvent polarity cannot be used to explain the difference in observed substituent effects because Kuivala and Walsh observed the same direction of substituent effects when they ran the reaction in an ester. In spite of this uncertainty about substituent effects, the main part of the mechanism probably does not require revision.

RADICAL REACTIONS OF QUINONES

It has been known for a long time that quinones would quench free radical polymerizations, or at least retard them.[12-17] There has been some speculation in the literature about the mechanism of this inhibition. In order to explore this reaction, Bickels and Waters[18] produced free radicals in the presence of benzoquinone. They decomposed both dimethyl α α' azoisobutyrate and α α' azoisobutyronitrile in toluene and derived the radicals shown below. These radicals were



$$\mathrm{CH_3{-}\overset{CH_3}{\underset{CO_2CH_3}{C}}\cdot}$$

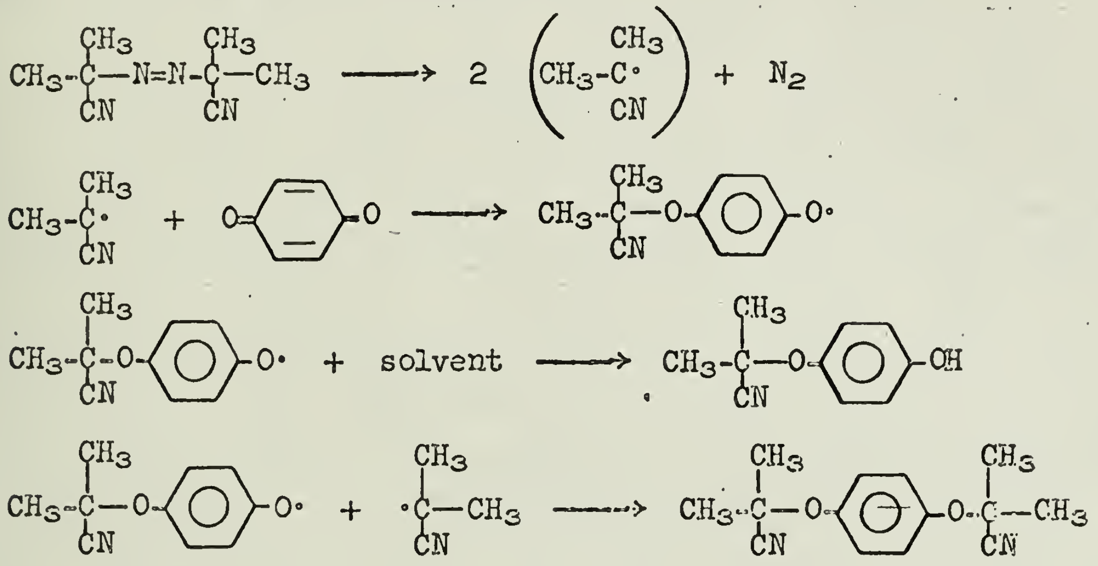


$$\mathrm{CH_3{-}\overset{CH_3}{\underset{CN}{C}}\cdot}$$

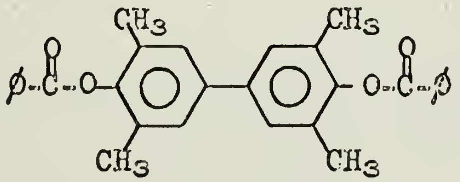
allowed to react with quinone and the nature of the products was determined. In each case the authors isolated both the mono and the di-ether of hydroquinone in the yields shown in the following table. The methyl isobutyrate radical does not react with hydroquinone. This data is consistent with a mechanism in which a

	dimethyl α α' azoisobutyrate	α α' azoisobutyronitrile
mono ether	40%	46%
di-ether	10%	27%

radical attacks the oxygen of the quinone forming a semi-quinone radical, which either abstracts a hydrogen atom from solvent or from some other molecule to form the mono ether, or reacts further with another radical to form the di-ether. This mechanism is shown in the scheme below.



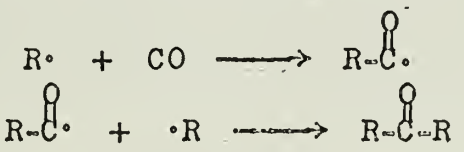
The results shown above were confirmed by Dogoplosk and Parfenova[12] when they ran the reaction between α α' azoisobutyronitrile and benzoquinone in benzene. They obtained yields of 16.8% mono ether and 38.9% di-ether. In another reaction, the benzoyl peroxide catalyzed oxidation of benzaldehyde, Moore and Waters[20] determined the effect of 3,5 3',5' tetramethyl 4,4' diphenoquinone as a retarder. They were able to isolate only one reaction product of the quinone in pure form, the di-ester shown below.



None of this evidence shows directly what the role of quinone is, when it is used to retard or inhibit polymerization reactions. In order to answer this question directly, Bevington et. al.[21] used radio carbon labeled benzoquinone as an inhibitor in the azoisobutyronitrile initiated polymerization of styrene. They found that when the induction period was over, essentially all of the quinone had been consumed. Furthermore, during the induction period a low molecular weight polymer was formed which contained quinone. In order to determine how the quinone was linked in the polymer, the authors used triflouro acetic acid to hydrolyse the polymer. The triflouro acetic acid would be expected to hydrolyse ether linkages, but would not be expected to break carbon carbon bonds. If the quinone were attached through the carbons of the ring, the polymer would not be expected to lose radio-activity on hydrolysis. The polymer activity was reduced to less than one third of its initial value by the triflouro acetic acid treatment. The authors showed that quinone could be isolated after the hydrolysis treatment. Thus the majority of the quinone seems to be bound through both oxygens rather than through the ring. All the data is consistent with a semiquinone radical mechanism in which initial attack occurs on one of the oxygens.

ADDITION OF RADICALS TO CARBON MONOXIDE

It is well known that acyl radicals can lose carbon monoxide to form alkyl radicals.[22-24] Cramer[25] pointed out that for the decomposition of the acetyl radical to carbon monoxide and methyl radical the $\Delta H = 15$ Kcal. ± 3 Kcal. In other words the loss of carbon monoxide is an endothermic reaction. This fact would lead one to expect that under suitable conditions the decarbonylation reaction could be reversed and alkyl radicals could add to carbon monoxide to form acyl radicals. Attempts have been made to observe the reaction of methyl radicals and CO. For example, Porter and Benson[26] decomposed di-t-butyl peroxide in the presence of CO at a temperature greater than 150°. The authors used radioactive CO, so that they could tell if any CO had been incorporated in the products. They could not find any radioactivity in the condensable products. Thus the authors concluded that methyl radicals had not added to CO to any measurable extent. The authors believe that the reason that they could not observe the reaction between methyl radicals and CO was that the acetyl radical was unstable at higher temperatures. This reasoning is supported by the work of Faltings[28] who obtained methyl radicals by the photolysis of ethane. For the light source he used a high intensity xenon source which he states emits wavelengths of 1470 A° and 1295 A°. He mixed 20% ethane and 80% CO and photolysed the mixture. Acetone was the major product with a quantum yield of 0.1. Formaldehyde was also present in small amounts with a quantum yield of 0.005. Cramer[25] obtained similar results using ethyl radicals derived from pyrollysis of tetraethyllead. He reacted tetraethyllead, benzene, and CO at a pressure of 1000 atmospheres in a silver lined reactor. The reaction temperature was 200°. He obtained di-ethyl ketone in a 14% yield. In addition he obtained higher boiling products which were converted to di-ethyl ketone on alkaline permanganate oxidation. The author assumed that the products which could be converted to di-ethyl ketone were actually thermal polymerization products of di-ethyl ketone. If this assumption is made, the yield of di-ethyl ketone is about 50%. The formation of ketones in the reaction between alkyl radicals and CO is readily rationalized by the scheme shown below.



$$R\cdot + CO \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}\cdot$$

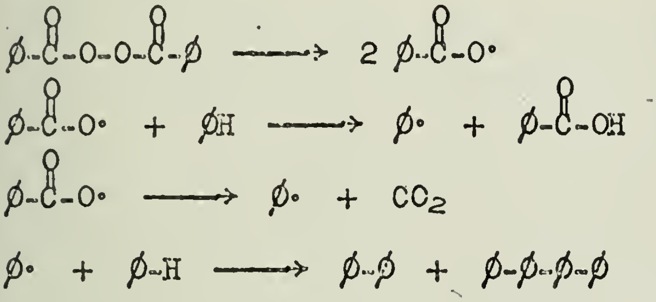
$$R\text{-}\overset{O}{\overset{\|}{C}}\cdot + \cdot R \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}\text{-}R$$

The addition of free radicals to CO can readily be observed in the radical initiated copolymerization of CO and ethylene. Brubaker et. al.[27] mixed ethylene, CO, and di-t-butyl peroxide in a silver lined reactor. They varied both the composition of the initial mixture, and the pressure of the reactants. The amount of CO incorporated in the polymer, and the molecular weight of the polymer vary as the experimental conditions are varied. But, in all cases the authors obtained polyketones. The products had sharp I.R. absorbtions at 5.8μ (1725 cm.$^{-1}$). This absorbtion is presumed to be a carbonyl absorbtion. Furthermore, the products undergo typical carbonyl reactions. For example, these compounds can readily be hydrogenated to poly-alcohols. These compounds can react with hydroxylamine and with HCN. On treatment with HNO_3, various dibasic acids are produced. This data is consistent with a structure in which carbonyl groups are separated by $-(CH_2-CH_2)_x-$units. The formation of such a polymer can readily be rationalized by a mechanism similar to that for the formation of ketone. The only difference being that in the formation of the polymer termination of the radical chain does not occur until many monomer units have been added.

There are other reactions in which radicals add to CO. For example, Walling and Savas[29] decomposed benzoyl peroxide in benzene in the presence and in the absence of carbon monoxide. In the absence of CO, the benzoyl peroxide decomposes to benzo~~yl~~ate radicals which either abstract a hydrogen atom from the solvent to form benzoic acid, or decompose to phenyl radicals. The phenyl radicals can initiate benzene polymerization. Diphenyl and the all para quaterphenyl are found. In the presence of CO a new product, benzoic anhydride, is found. The appearance of benzoic

anhydride can be rationalized in two ways. Both involve the formation of an acyl radical from a phenyl radical and CO. One possibility is that the acyl radical combines with a benzoy~~l~~ate radical to yield the observed anhydride. Since the yield of benzoic acid does not go down, the authors feel that it is more probable that the acyl radical induces decomposition of unreacted peroxide. To confirm the presence of the acyl radical the authors ran the reaction in CCl_4, and isolated the expected benzoyl chloride. These reactions are shown in the set of equations below.

without CO



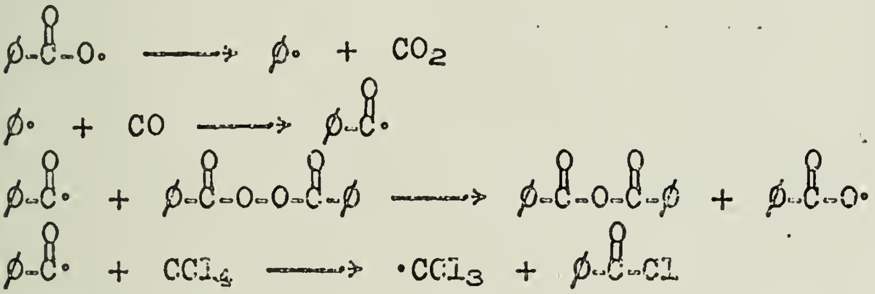
$$\phi\text{-}\overset{O}{C}\text{-O-O-}\overset{O}{C}\text{-}\phi \longrightarrow 2\ \phi\text{-}\overset{O}{C}\text{-O}\cdot$$

$$\phi\text{-}\overset{O}{C}\text{-O}\cdot + \phi H \longrightarrow \phi\cdot + \phi\text{-}\overset{O}{C}\text{-OH}$$

$$\phi\text{-}\overset{O}{C}\text{-O}\cdot \longrightarrow \phi\cdot + CO_2$$

$$\phi\cdot + \phi\text{-H} \longrightarrow \phi\text{-}\phi + \phi\text{-}\phi\text{-}\phi\text{-}\phi$$

with CO



$$\phi\text{-}\overset{O}{C}\text{-O}\cdot \longrightarrow \phi\cdot + CO_2$$

$$\phi\cdot + CO \longrightarrow \phi\text{-}\overset{O}{C}\cdot$$

$$\phi\text{-}\overset{O}{C}\cdot + \phi\text{-}\overset{O}{C}\text{-O-O-}\overset{O}{C}\text{-}\phi \longrightarrow \phi\text{-}\overset{O}{C}\text{-O-}\overset{O}{C}\text{-}\phi + \phi\text{-}\overset{O}{C}\text{-O}\cdot$$

$$\phi\text{-}\overset{O}{C}\cdot + CCl_4 \longrightarrow \cdot CCl_3 + \phi\text{-}\overset{O}{C}\text{-Cl}$$

CONCLUSION

We have shown that radical addition to carbonyl compounds is a possible reaction. Attack of the radical occurs on the oxygen in most of these reactions. Carbon monoxide undergoes bond formation on the carbon. These free radical reactions can be of synthetic importance because they provide a mild method of affecting certain transformations.

BIBLIOGRAPHY

1. G. J. M. Van der Kerk, J. G. Noltes, and J. G. A. Luijten J. Applied Chem. (London), 7, 356 (1957).
2. E. S. Kupchick and R. J. Kiesel, J. Org. Chem., 29, 3690 (1964).
3. H. G. Kuivala and E. J. Walsh, Jr., J. Am. Chem. Soc., 88, 571 (1966).
4. L. Kaplan, J. Am. Chem. Soc., 88, 1833 (1966).
5. E. J. Walsh, Jr. and H. G. Kuivala, J. Am. Chem. Soc., 88, 576 (1966).
6. H. G. Kuivala, J. Org. Chem., 25, 284 (1960).
7. F. F. Rust, F. H. Seubold, and W. E. Vaughan, J. Am. Chem. Soc., 70, 3258 (1948).
8. M. S. Karash, W. H. Urry, B. M. Kuderna, J. Org. Chem., 14, 248 (1949).
9. T. M. Patrick, Jr., J. Org. Chem., 17, 1009 (1952).
10. R. N. Brinmell, A. F. Trotman-Dickenson, J. Chem. Soc., 2059 (1960).
11. D. H. Volman and R. K. Brinton, J. Chem. Phys., 20, 1764 (1952).
12. B. A. Dolgoplosk and G. A. Parfenova, J. Gen. Chem. USSR (English transl.) 27, 2810 (1957).
13. G. Goldfinger, J. Skeist, H. Mark, J. Phys. Chem., 47, 578 (1943).
14. F. R. Mayo, R. A. Gregg, J. Am. Chem. Soc., 70, 1284 (1948).
15. S. G. Foord, J. Chem. Soc., 48 (1940).
16. F. Tüdős, J. Polymer Sci., 30, 343 (1958).
17. H. W. Melville, W. F. Watson, Trans. Faraday Soc., 44, 886 (1948).
18. A. F. Bickels and W. A. Waters, J. Chem. Soc., 1764 (1950).
19. R. F. Moore and W. A. Waters, J. Chem. Soc., 238 (1953).
20. R. F. Moore and W. A. Waters, J. Chem. Soc., 2432 (1952).

21. J. C. Bevington, N. A. Ghanen, and H. W. Melville, J. Chem. Soc., 2822 (1955).
22. S. Winstein, F. H. Seubold, Jr., J. Am. Chem. Soc., 69, 2916 (1947).
23. E. F. P. Harris and W. A. Waters, J. Chem. Soc., 3108 (1952).
24. J. G. Calvert and J. T. Gruver, J. Am. Chem. Soc., 80, 1313 (1958).
25. R. Cramer, J. Am. Chem. Soc., 79, 6215 (1957).
26. G. B. Porter, S. W. Benson, J. Am. Chem. Soc., 75, 2773 (1953).
27. M. M. Brubaker, D. D. Coffman, and H. H. Hoehn, J. Am. Chem. Soc., 74, 1509 (1952).
28. K. Faltings, Ber., 72B, 1207 (1939).
29. C. Walling and E. S. Savas, J. Am. Chem. Soc., 82, 1738 (1960).
30. R. Adams and E. H. Vollweiler, J. Am. Chem. Soc., 40, 1732 (1918).

THE ELECTRONIC NATURE OF THE REACTIVE SPECIES FROM THE THERMAL DECOMPOSITION OF ARYLDIAZONIUM SALTS

Reported by Gerald F. Koser October 3, 1966

Within the past five years there have been several suggestions in the literature that the reactive species generated from the thermal decomposition of aryldiazonium salts in aromatic and protic media may have free radical character and thus differ from the previously accepted carbonium ion intermediate.[1-3] On the other hand, there is much evidence for a cationic reactive species as indicated in an earlier review.[4] The objective of this seminar is to examine all of the available data in an effort to determine the need for a revised formalism.

The fact that the thermal decomposition of aryldiazonium salts obeys first order kinetics in protic, non-basic media has been well established by a number of workers. For example, Crossley, Kienle, and Benbrook have shown that the thermolysis of benzenediazoniumchloride in aqueous solution is first order over a concentration range from 0.044 to 23.69 molar although the yield of product phenol varies from 95.2% to 24.3%. The major side product is chlorobenzene.[5] Several studies have verified the independence of the rate constant on the nature of the anion in hydroxylic media. DeTar and Ballentine have shown that the rate constants for the thermolysis of benzenediazonium boroflouride, bisulfate, and chloride in aqueous acidic solution are nearly identical.[6] Thus, the anion does not appear to be involved in the rate determining step, a fact which argues against homolytic cleavage to radical intermediates. Pray has shown that the decomposition of aryldiazonium salts in protic media is fairly insensitive to solvent changes within a given class. Thus, although the magnitude of the rate constant may change in going from water to alcohols to carboxylic acids, the rate constants for the thermolyses in methanol, ethanol, propanol, isopropanol, butanol, and isobutanol are nearly identical. Furthermore, any anomalies appear to be due to mechanistic changes rather than solvent variations.[7] These observations tend to exclude the formation of an adduct between the solvent and the diazonium salt and may be advanced as evidence against direct solvent participation in the transition state, although this conclusion is less certain. Lewis has demonstrated that the reactive species from the thermal decomposition of benzenediazoniumboroflouride in aqueous chloride solutions to yield phenol and chlorobenzene is not nearly as selective toward chloride ion and water as are the trityl, benzhydryl, and *t*-butyl carbonium ions.[8,9] This behavior would be expected for the highly energetic phenylcarbonium ion. In conclusion, the data for the thermolysis of aryldiazonium salts in protic media strongly support a unimolecular decomposition mechanism involving the heterolytic cleavage of molecular nitrogen with subsequent formation of a cationic reactive species.

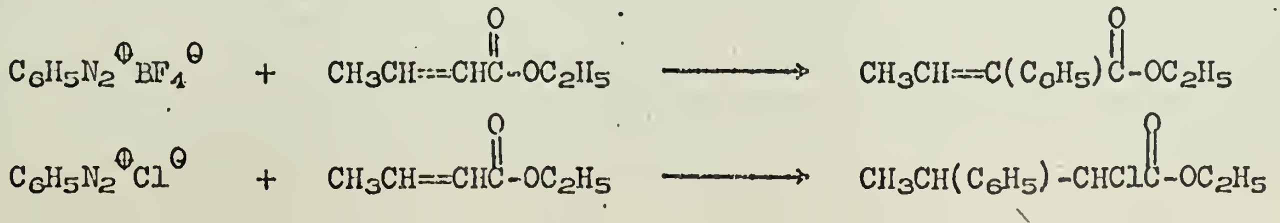
$$ArN_2^{\oplus} \xrightarrow{k_1} Ar^{\oplus} + N_2$$

$$Ar^{\oplus} \xrightarrow[k_w]{H_2O} ArOH$$

$$Ar^{\oplus} \xrightarrow[kc_1]{Cl^{\ominus}} ArCl$$

The postulate that the heterolysis step is reversible[10-12] has recently been challenged by kinetic[13] and nuclear magnetic resonance[14] studies on ^{15}N labeled diazonium salts.

Mechanistic interpretations in non-hydroxylic solvents are more complicated due to an apparent dependence of the rate constant on the propensity of the anion to form a covalent bond with the diazonium ion. For example, when benzenediazoniumboroflouride is thermally decomposed in ethylcrotonate, arylation of the α carbon is observed in accord with a carbonium ion mechanism. However, when the decomposition of benzenediazoniumchloride is carried out in the same solvent, the α-chloro-β-phenyl adduct is formed.[15]



$$C_6H_5N_2^{\oplus}BF_4^{\ominus} + CH_3CH{=}CH\overset{O}{\overset{\|}{C}}{-}OC_2H_5 \longrightarrow CH_3CH{=}C(C_6H_5)\overset{O}{\overset{\|}{C}}{-}OC_2H_5$$

$$C_6H_5N_2^{\oplus}Cl^{\ominus} + CH_3CH{=}CH\overset{O}{\overset{\|}{C}}{-}OC_2H_5 \longrightarrow CH_3CH(C_6H_5){-}CHCl\overset{O}{\overset{\|}{C}}{-}OC_2H_5$$

A second example of the inadequacy of the carbonium ion mechanism in non-hydroxylic media is afforded by the thermal polymerization of acrylonitrile in the presence of p-bromo or p-methoxy benzenediazoniumboroflcuride which is thought to proceed by a free radical mechanism.[16]

The supporting evidence for a carbonium ion intermediate when aryldiazonium salts are thermally decomposed in aromatic substrates is the apparent sensitivity of the reactive species to substituent directive effects. Thus, the major biaryl product formed from the thermolysis of benzenediazoniumboroflouride in nitrobenzene or triflouromethylbenzene arises from aromatic substitution at the meta position of the substrate.[15]

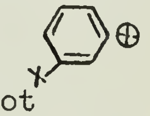
The first suggestion that the reactive species might be a "non-classical" arylcarbonium ion was made by Taft who applied a modified Hammett equation[17] to the thermal decomposition of a series of meta substituted diazonium salts.[1] An implicit assumption in the Taft proposal is the treatment of the quantity (log k/ko) for meta and para substituted benzene derivatives as the sum of an inductive effect and a resonance effect.[17] (Where k and ko are rate constants for the substituted and unsubstituted benzene derivatives under concern.) Furthermore, the meta substituents employed were members of a select group which obey precise linear free energy relationships[18] with far more generality than others and whose mean sigma values are designated as σ^{o}. The unusual degree of precision exhibited by these substituents has been rationalized by Taft[17] to arise from the fact that there is no direct conjugation between the substituent and the reaction center. Thus, the sole electrical effect attributable to x is an inductive polarization. Furthermore for other meta substituents any deviations from the Hammett relation may be attributed to an unusual resonance effect. These arguments may be mathematically summarized as follows:

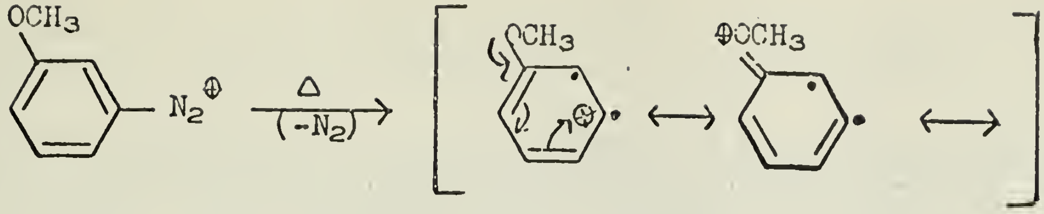
$$\log k/ko = \sigma\rho = I + R$$
$$\text{but if } R = 0, \text{ then } \sigma = \sigma^{o}$$
$$\log k/ko = \sigma^{o}\rho = I$$

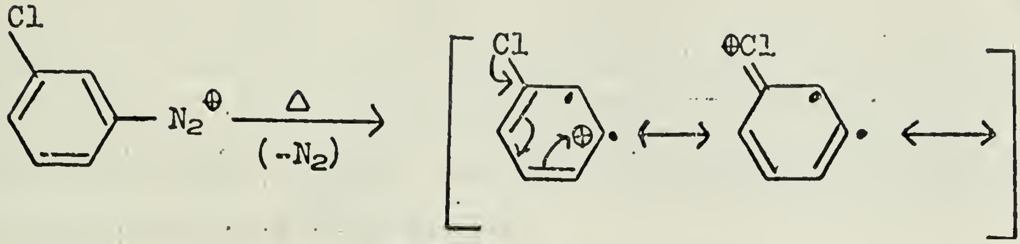
The resultant equation is a quantitative measure of the inductive effect of a given substituent on the rate constant of a specified reaction. σ^{o} is termed an inductive constant.[17] When Taft applied this relation to the reactions of meta substituted aryldiazonium salts in aqueous media, he observed that some electron donating groups in the class for which σ^{o} is defined cause rate enhancements beyond those calculated for simple inductive effects. Moreover, the magnitudes of the deviations varied with the nature of the substituent. Taft concluded that "special" resonance effects were operative ($R \neq 0$) and proceeded to calculate activation energy decreases with the following equation:[1] $\Delta(\Delta F^{\ddagger}) = -2.303\, RT(\log k/ko - \rho \log K/K_o)$ K and Ko are the respective ionization constants for benzoic acid substituted in the meta position with substituents for which σ^{o} is defined and for benzoic acid itself. The data are summarized in Table 1:

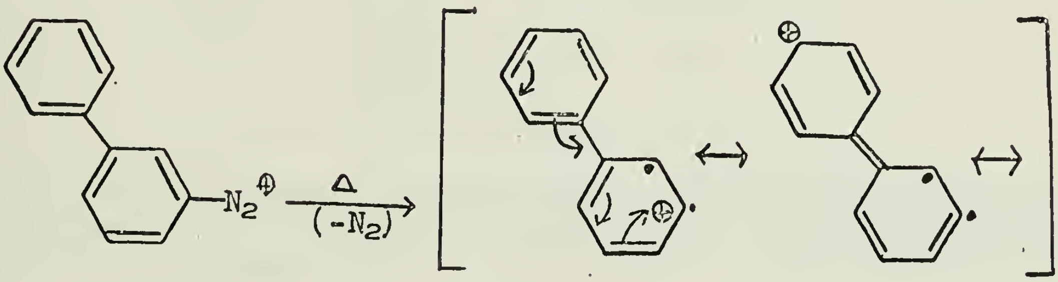
TABLE I:

Aryldiazonium Salt	$\Delta(\Delta F^{\ddagger})$ Kcal Mole^{-1}
m-OCH_3-$C_6H_4N_2^{\oplus}BF_4^{\ominus}$	-1.7
m-OH-$C_6H_4N_2^{\oplus}BF_4^{\ominus}$	-1.5
m-C_6H_5-$C_6H_4N_2^{\oplus}BF_4^{\ominus}$	-0.8
m-CH_3-$C_6H_4N_2^{\oplus}BF_4^{\ominus}$	-0.5
m-Cl-$C_6H_4N_2^{\oplus}BF_4^{\ominus}$	-0.2

Taft suggested that the data could be conveniently rationalized if the transition state formally resembled an intermediate diradical cation rather than a classical arylcarbonium ion.[1,19] Thus, for the traditional carbonium ion species , resonance structure specifically localizing the positive charge on x cannot be written and, beyond inductive polarization, a substituent effect on the energy of the transition state would not be expected. However, for a diradical cation species in which a pi electron has been placed in an sp^2 hybridized atomic orbital, resonance structures localizing the positive charge on x can be written and substituent resonance effects at least rationalized.







Although Taft's argument appears to be reasonable, caution must be exercised in accepting it as the only rationale. The treatment of log(k/ko) solely in terms of inductive and resonance effects is an approximation since steric factors and ground and transition state solvation effects may not be negligible.

The possibility that the reactive species from the thermal decomposition of aryldiazonium salts could have both free radical and carbonium ion character was extended to non-protic solvents by Abramovitch and co-workers who employed electron spin resonance techniques.[2] When benzenediazoniumboroflouride was decomposed under heterogeneous conditions in toluene or in the solid state, a symmetrical, three line e. s. r. signal with the center line more intense than the other two was observed at temperatures above 60° C. The overall width was 27 gauss and the hyperfine line width 7 gauss. Furthermore, the intensity of the signal increased with time and diminished very slowly after cooling to room temperature. The authors concluded that "the signal arose from an aromatic radical." When the decomposition of the same diazonium salt was carried out under homogeneous conditions in nitrobenzene, a symmetrical, three line (1:1:1) spectrum was observed at 42° C with a hyperfine line width of 4 gauss and a splitting constant of 9 gauss. Such a spectrum would be expected for a single electron localized on nitrogen.[20] These results were interpreted as unquestionable evidence for the intermediacy of a free radical species during the decomposition reaction and were cited as plausible support for a diradical carbonium ion.[2] However, as the authors themselves recognized, the observed radical may or may not be the reactive species. It is tempting to attribute the ~1:2:1 signal to the phenyl radical since such a spectrum would not appear to be unreasonable. However, Bennet and Thomas have shown that phenyl radicals generated from the action of sodium metal on iodobenzene give rise to a single line e. s. r. spectrum with only a hint of fine structure.[21] Moreover, the phenyl radical would be expected to have a transient existence. The possibility that the benzyl radical was generated by hydrogen atom abstraction when benzenediazoniumboroflouride was decomposed in toluene may be excluded since the benzyl radical spectrum is far more complex than that observed.[22] Similarly, the electron spin resonance spectra of the toluene,[20] nitrobenzene,[23] and benzene[20] anion radicals do not correspond to either of those recorded for the thermal decomposition of benzenediazoniumboroflouride in toluene or nitrobenzene. Finally, if the diazonium ion radical were formed, a five line (1:2:3:2:1) spectrum with a splitting constant of 9.3 gauss would be expected.[22]

At the present time, the data are not definitive enough for conclusions about the reactive species. Studies relating the kinetics of the observed radical to the rate of disappearance of starting material and the rate of appearance of products are a necessity.

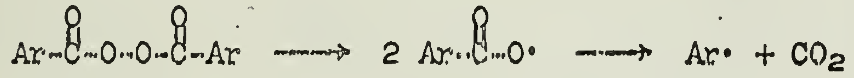
The most recent argument for a revised concept of the reactive species has been formulated from a study of the arylation of several aromatic substrates with benzenediazoniumboroflouride.[3] The collected data was compared to that of (1) homolytic aromatic substitution with aryl radicals, (2) arylation with carbene intermediates and (3) heterolytic, electrophilic aromatic substitution such as nitration. It was hoped that comparisons with the range from nucleophilic to electrophilic attacking agents would permit a more accurate characterization of the electronic nature of the reactive species from the thermal decomposition of aryldiazonium salts. The authors determined total rate ratios (${}^{C_6H_5X}_{C_6H_6}K$), isomer distributions, and partial rate factors (Fr) for ortho, meta, and para substitution.

$$(1)\ Fo = 3\ {}^{C_6H_5X}_{C_6H_6}K\ (\%\ \text{ortho isomer})$$

$$(2)\ Fm = 3\ {}^{C_6H_5X}_{C_6H_6}K\ (\%\ \text{meta isomer})$$

$$(3)\ Fp = 6\ {}^{C_6H_5X}_{C_6H_6}K\ (\%\ \text{para isomer})$$

The thermal decomposition of benzoylperoxide and its substituted analogs was chosen as a model for homolytic aromatic substitution. The accepted mechanism for this reaction is the following:[24]



$$(1)\ Ar-\overset{O}{\overset{\|}{C}}-O-O-\overset{O}{\overset{\|}{C}}-Ar \longrightarrow 2\ Ar-\overset{O}{\overset{\|}{C}}-O\cdot \longrightarrow Ar\cdot + CO_2$$

$$(2)\ Ar\cdot + Ar'H \longrightarrow [ArAr'H\cdot]\ \text{sigma complex}$$

$$(3)\ ArAr'H\cdot \xrightarrow{\text{oxidation}} ArAr'$$

$$(4)\ 2\ ArAr'H\cdot \xrightarrow{\text{dimerization}} [ArAr'H]_2$$

$$(5)\ 2\ ArAr'H\cdot \xrightarrow{\text{disproportionation}} ArAr' + ArAr'H_2$$

$$(6)\ ArAr'H_2 \xrightarrow{\text{oxidation}} ArAr'$$

The fact that no symmetrical biaryls are formed coupled with the absence of a kinetic isotope effect has been advanced as evidence for the formation of a sigma complex with the solvent in the rate determining step.[24] Although the presence or absence of oxygen and variations of the substrate ratio in competition experiments may significantly change the overall yield of biaryl products, the rate factors and isomer distributions remain unchanged. Apparently the side reactions (disproportionation, dimerization, etc.) do not selectively remove the ortho, meta, and para sigma complexes.[25]

Abramovitch and Saha have recently reported isomer distributions, total rate ratios, and partial rate factors for the thermolysis of benzenediazoniumboroflouride in toluene, anisole, nitrobenzene and bromobenzene.[3] The decomposition was run heterogeneously in all solvents but nitrobenzene, in which the diazonium salt is soluble. The major product (>90%) in all cases was flourobenzene, the expected product of the Schieman reaction, whereas the biaryl yields varied from 3% to 5%. The data are summarized in Tables 2, 3, and 4 along with the corresponding results for nitration and homolytic arylation.

The isomer distributions indicate that the reactive species from the thermal decomposition of benzenediazoniumboroflouride is more sensitive to directive effects than is the "neutral" phenyl radical and, thus, appears to be more electrophilic. This is particularly apparent with the thermolysis in nitrobenzene. On the other hand, an examination of the partial and total rate factors indicates that the $NO_2^{\oplus}$ cation is far more selective than the reactive species from benzenediazoniumboroflouride both positionally and toward competing substrates. However, it must be noted here that the nitrating species may not be a good model for the phenylcarbonium

TABLE II

Substrate	Nuclear position	% Isomer formed with $C_6H_5N_2^{\oplus}BF_4^{\ominus}$[3]	$(C_6H_5CO_2)_2$[25,26]
	ortho	57.5	66.5
$C_6H_5CH_3$	meta	20.0	19.3
	para	22.3	14.2
	ortho	56.1	56.2
C_6H_5Br	meta	19.8	27.3
	para	24.1	16.5
	ortho	57.5	69.8
$C_6H_5OCH_3$	meta	10.0	15.8
	para	32.5	15.8
	ortho	19.6	63.2
$C_6H_5NO_2$	meta	80.4	9.7
	para	----	27.1

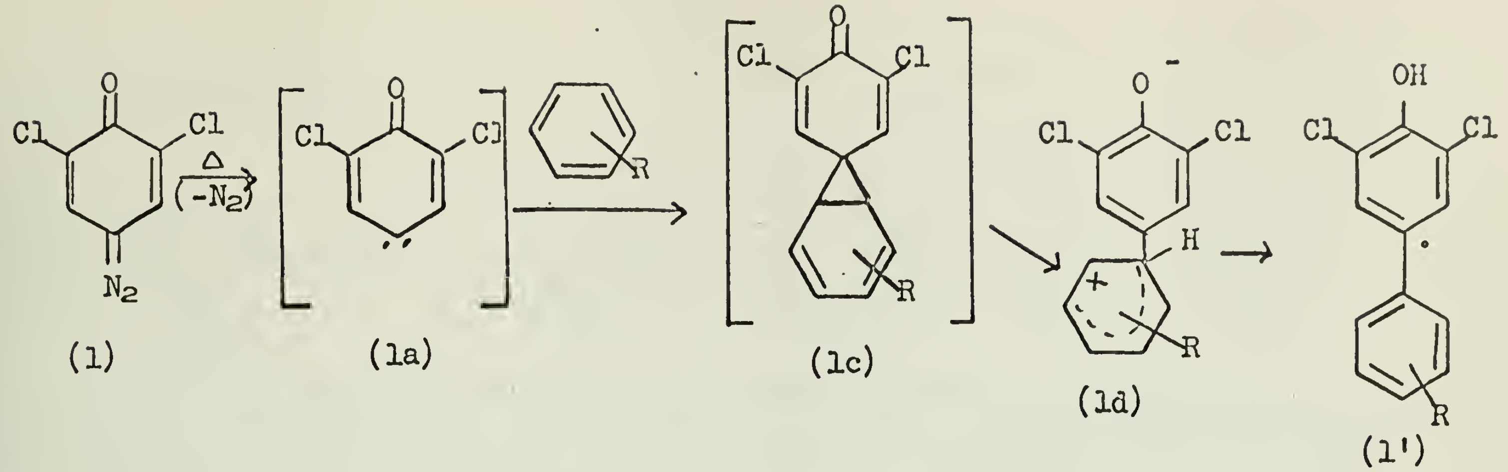
TABLE III

Substrate	$C_6H_5N_2^{\oplus}BF_4^{\ominus}$[3]	${}^{C_6H_5}_{C_6H_6}K$ Nitration[26]	$(C_6H_5CO_2)_2$[24,25]
$C_6H_5CH_3$	0.72	23.0	1.23
C_6H_5Br	0.31	0.03	1.14
$C_6H_5OCH_3$	1.445	----	2.0
$C_6H_5NO_2$	0.35	$\sim 10^{-6}$	2.94

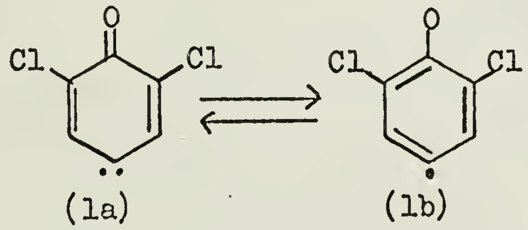
TABLE IV

Substrate	Nuclear Position	$C_6H_5N_2^{\oplus}BF_4^{\ominus}$[3]	Fr Nitration[26]	$(C_6H_5CO_2)_2$[24,25]
	ortho	1.24	40	2.5
$C_6H_5CH_3$	meta	0.43	3	0.71
	para	0.96	51	1.0
	ortho	0.52	0.037	1.9
C_6H_5Br	meta	0.18	0.000	0.93
	para	0.45	0.106	1.13
	ortho	2.49	.....	4.19
$C_6H_5OCH_3$	meta	0.43	.....	0.87
	para	2.81	.....	1.90
	ortho	0.21	0.24×10^{-6}	5.60
$C_6H_5NO_2$	meta	0.84	2.75×10^{-6}	0.86
	para	0.00	0.03×10^{-6}	4.80

ion since it is relatively stable. Abramovitch and Saha have pointed out[3] that the total rate factors, which are close to unity in all cases, are more consistent with those for arylations with electrophilic radicals such as the orthonitrophenyl radical, and for the proposed carbene intermediate from the thermolysis of 2,6-dichloro-1,4-benzenediazooxide.[27] Arylations with the latter species are thought to proceed by the following mechanism:



Analogous to a proposal made by Abramovitch, the formation of polymers incorporating solvent molecules when (I) is thermally or photolytically decomposed in halogenated aromatic substrates, is rationalized in terms of an equilibrium to between the carbene 1a and the diradical 1b.



Dewar has pointed out that (Ia) and (Ib) are not resonance structures since the wave function of (Ib) is antisymmetric for reflection through the nodal plane and the wave function for Ia is symmetric for reflection through the nodel plane.[27] Further data comparisons with benzenediazoniumboroflouride are summarized in Table 5 and 6.

TABLE V

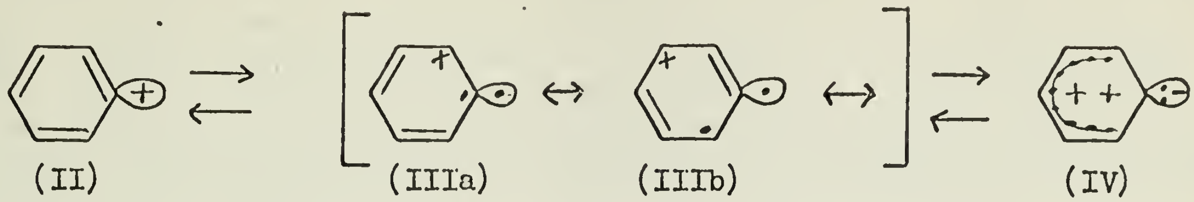
Arylating Agent	K		Fr	
	Anisole	Bromobenzene	Anisole	Bromobenzene
$^3C_6H_5N_2{}^{\oplus}BF_4{}^{\ominus}$	1.445	0.31	o 2.49	0.52
			m 0.43	0.18
			p 2.81	0.45
$^{27}C_6H_2Cl_2N_2O$ (I)	1.276	0.345	o 2.78	0.59
			m 0.00	0.00
			p 2.09	0.88

TABLE VI

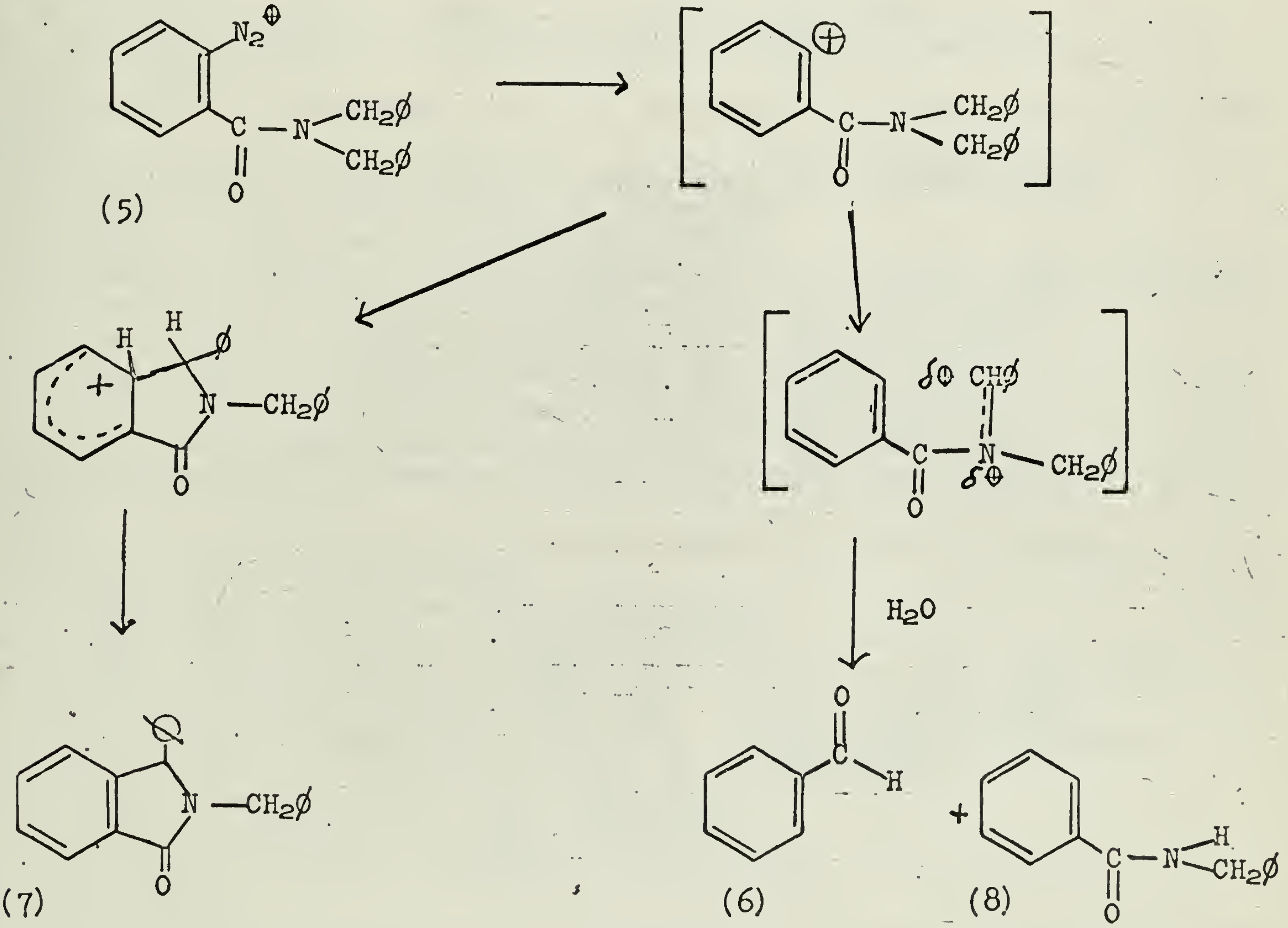
Arylating Agent	$\frac{C_6H_5NO_2}{C_6H_5}K$	$\frac{C_6H_5CH_3}{C_6H_6}K$
$(P\text{-}CH_3\text{-}\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}O)_2{}^{28}$	3.4	-----
$(\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}O)_2$	2.94	1.23
$(P\text{-}Br\text{-}\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}O)_2{}^{30}$	1.76	----
$P\text{-}NO_2\text{-}\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}O)_2{}^{29}$	0.94	2.50
$O\text{-}NO_2\text{-}\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}O)_2{}^{29}$	0.26	1.16
$^3\phi N_2{}^+BF_4{}^{-3}$	0.35	0.72

From the magnitudes of the partial and total rate factors, the authors have concluded that "such behavior is consistent with an electrophilic attack but not by a 'classical' phenyl cation." Furthermore, an equilibrium involving three

distinct carbonium ion species has been postulated to account for all characteristics of the reactive species.[3]



The relative stability of the three cationic species based on molecular orbital calculations is III > IV > II.[31] The authors suggest that such an equilibrium system could rationalize both cationic and radical behavior. Furthermore, the rationale that the products from the thermal decomposition of the diazonium salt of o-amino-N,N-dibenzylamide arise from a hydrogen transfer and carbonium ion insertion[32,33,34] would be strengthened if species III and IV exhibited some properties of singlet and triplet carbenes in addition to radical cation character.



Although the rationale of a classical arylcarbonium ion intermediate generated from the thermal decomposition of aryldiazonium salts in protic and aromatic media may leave a few observations unexplained, it is generally satisfactory. Thus, if a revised model of the reactive species proves to be necessary, its adoption must rest on more extensive experimental verification. The observation of total rate ratios close to unity is not surprising. The phenyl-carbonium ion would be a highly energetic species and attack on aromatic substrates should be quite exothermic. A high degree of selectivity is not expected when such conditions obtain. Furthermore, as the authors have pointed out, products formed under heterogeneous reaction conditions are not subject to kinetic control and the corresponding rate factors must be accepted with caution.

The suggestion that carbene character may be invoked to explain the products arising from the thermal decomposition of the diazonium salt of o-amino-N,N-dibenzylamide is questionable since a carbonium ion mechanism does not appear to be unreasonable. Further consideration must also be given to the Taft treatment. The σ^{o} values for the meta, electron donating substituents examined may not be valid for the thermal decomposition of aryldiazonium salts since the formal charge in the proposed transition state would be generated on the phenyl nucleus rather than a reactive side chain.

Future mechanistic interpretation would benefit from a comparison of the reactions of aryldiazonium salts with other possible arylcarbonium ion donors such as triaryloxonium salts.

BIBLIOGRAPHY

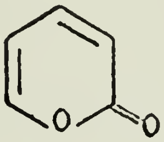
1. R. W. Taft, Jr., J. Am. Chem. Soc., 83, 3350 (1961).
2. R. A. Abramovitch, W. A. Hymers, J. B. Rajan, and R. Wilson, Tetrahedron Letters, 23, 1507 (1963).
3. R. A. Abramovitch and J. G. Saha, Can. J. Chem., 43, 3269 (1965).
4. A. L. Tveten, University of Illinois Seminars in Organic Chemistry, p. 87, Nov. 10, (1958).
5. M. L. Crossley, R. H. Kienle, and C. H. Benbrook, J. Am. Chem. Soc., 62, 1400 (1940).
6. D. F. DeTar and A. R. Ballentine, J. Am. Chem. Soc., 78, 3916 (1956).
7. H. A. Holden Pray, J. Phys. Chem., 30, 1477 (1926).
8. E. S. Lewis, J. Am. Chem. Soc., 80, 1371 (1958).
9. C. G. Swain, C. B. Scott, and K. H. Lohmann, J. Am. Chem. Soc., 75, 136 (1953).
10. E. S. Lewis and J. E. Cooper, J. Am. Chem. Soc., 84, 3847 (1962).
11. J. M. Insole and E. S. Lewis, J. Am. Chem. Soc., 85, 122 (1963).
12. E. S. Lewis and J. M. Insole, J. Am. Chem. Soc., 86, 32 (1964).
13. L. L. Brown and J. S. Drury, J. Chem. Phys., 43, 1688 (1965).
14. A. K. Bose and I. Kugajevsky, J. Am. Chem. Soc., 88, 2325 (1966).
15. A. N. Nesmeyonov, L. G. Makarova, and T. P. Tolstaya, Tetrahedron, 1, 145 (1957).
16. C. S. Marvel, H. Z. Friedlander, Sherlock Swann Jr., and H. K. Inskip, J. Am. Chem. Soc., 75, 3846 (1953).
17. R. W. Taft Jr., J. Phys. Chem., 64, 1805 (1960).
18. L. P. Hammett, Trans. Faraday Soc., 34, 156 (1938).
19. R. W. Taft, I. R. Fox, and I. C. Lewis, J. Am. Chem. Soc., 83, 3349 (1961).
20. A. Carrington, Quarterly Reviews (Chem. Soc. London), 17, 67 (1963).
21. J. E. Bennet and A. Thomas, Proc. Roy. Soc., Series A (280), 123 (1964).
22. W. T. Dixon and R. O. C. Norman, J. Chem. Soc., 4857 (1964).
23. R. L. Ward, J. Am. Chem. Soc., 83, 1296 (1961).
24. G. H. Williams, Chem. Ind. (London), 1286 (1961).
25. R. T. Morrison, J. Cazes, N. Samkoff, and C. A. Howe, J. Am. Chem. Soc., 84, 4152 (1962).
26. G. H. Williams, Homolytic Aromatic Substitution. Pergamon Press, London (1960).
27. M. J. S. Dewar and K. Narayanaswami, J. Am. Chem. Soc., 86, 2422 (1964).
28. J. K. Hambling, D. H. Hey, S. Orman, and G. H. Williams, J. Chem. Soc., 3108 (1961).
29. D. H. Hey, H. N. Moulden, and G. H. Williams, J. Chem. Soc., 3769 (1960).
30. D. F. DeTar and Kazimi, J. Am. Chem. Soc., 77, 3842 (1955).
31. Private Communication to Abramovitch from I. Absar and K. L. McEwan.
32. T. Cohen, A. H. Dinwoodie, and L. D. McKeever, J. Org. Chem., 27, 3385 (1962).
33. T. Cohen and J. Lipowitz, J. Am. Chem. Soc., 86, 2514 (1964).
34. T. Cohen and J. Lipowitz, J. Am. Chem. Soc., 86, 2515 (1964).

THE PHOTOCHEMISTRY OF 2- AND 4-PYRONES

Reported by Joseph C. Stickler October 10, 1966

INTRODUCTION

The photochemical investigation of the derivatives of 2-pyrone (I) and 4-pyrone (II) began early in this century.[1-5] Before all the structural nuances of the photoproducts were known, interest was generated because of the physiochemical activity of some photodimers which were known to cause pigmentary dermatitis.[6,7] Not until this decade, however, has the stereochemistry of the photoproducts been clearly defined and investigation of the possible mechanisms been explored. This seminar will be concerned with illustrating the progress made in determining stereochemistry and reaction pathways.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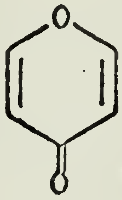
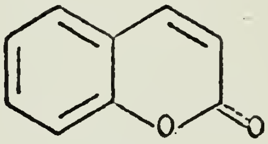
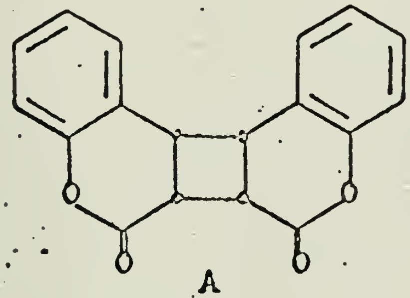
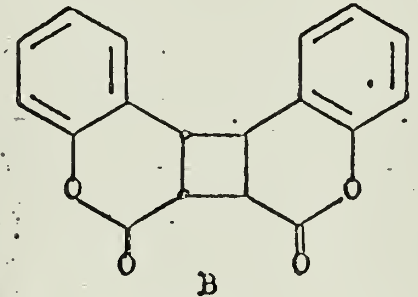

II

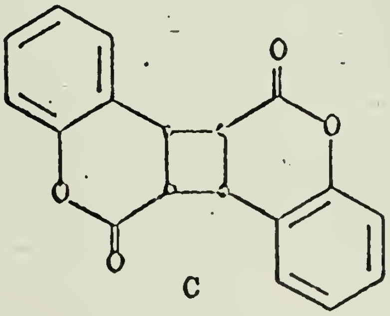
PHOTODIMERIZATION OF THE 2-PYRONES

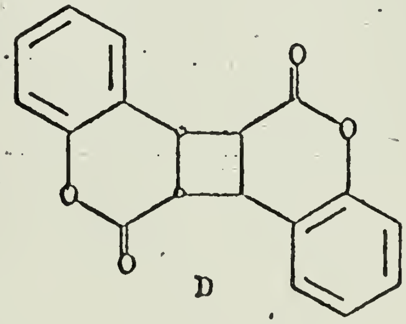
The most extensive work in this area concerns the photodimerization of coumarins (III). As early as 1902 it was known that coumarins form photodimers.[1] Assuming cis ring fusion for the dimerization with the formation of a cyclobutane ring, four structures are possible for the dimers: syn-head-to-head (A), anti-head-to-head (B), syn-head-to-tail (C), and anti-head-to-tail (D). Although structural details had accumulated prior to the 1960's,[4,8,9] it was Anet's[10] and Schenck's[11,12] detailed nmr and chemical analyses which finally confirmed the actual disposition of the atoms in the four possible dimers.


III

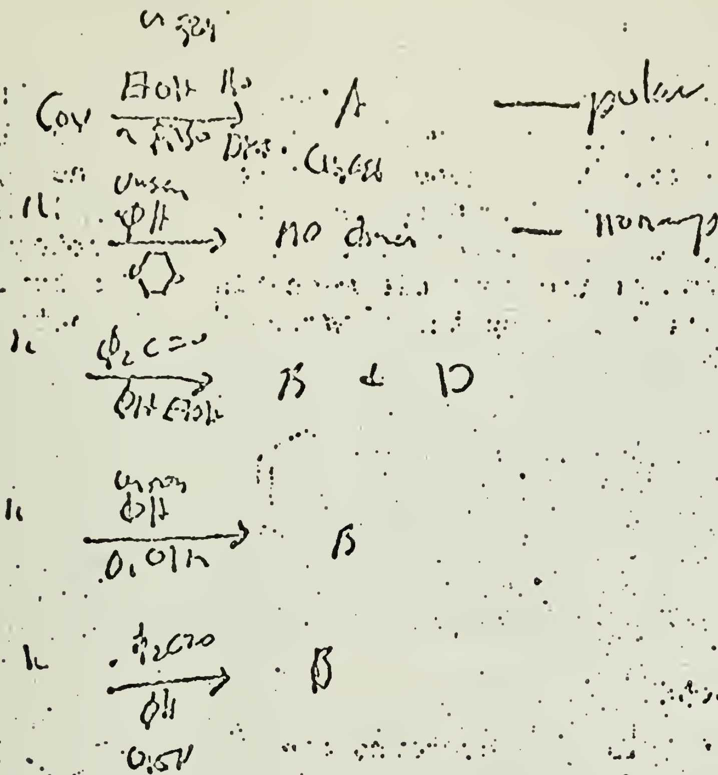

A


B


C


D

Prior to Hammond's careful mechanistic work[13] on the coumarin dimerization the following was known: (1) Unsensitized photolysis of coumarin in ethanol[1] or water[8] led to the formation of dimer A, while in benzene no dimer was formed. (2) The sensitized dimerization in benzene led mainly to dimer B with a small amount of D. The latter was not isolated when ethanol was the solvent.[11] (3) Dimer C had not been isolated. (4) Schenck noted that the sensitized and unsensitized reactions must not have a common intermediate based on the stereospecificity. He also proposed that the sensitized reaction proceeded through a short-lived biradical complex



n 324
Cov
EtOH H₂O
n EtSO
Drs
A
— polar
Cu₃Cl
II:
Unsen
ΦH
no chan
— nonpolar
II
φ₂C=O
ΦH EtOH
B & D
II
Unsen
ΦH
0.01N
B
II
φ₂C=O
ΦH
0.5N
B

between the excited sensitizer and the coumarin molecule, which may react with another coumarin molecule and decay into the ground state sensitizer and dimer. Schenck's mechanistic scheme is as follows:

$$\text{S} \xrightarrow{h\nu} \cdot\text{S}\cdot \text{ (excited, biradical state)}$$

$$\cdot\text{S}\cdot + \text{X} \longrightarrow \cdot\text{S-X}\cdot$$

$$\cdot\text{S-X}\cdot + \text{X} \longrightarrow \cdot\text{S-X-X}\cdot$$

$$\cdot\text{S-X-X}\cdot \longrightarrow \text{S} + \text{XX}$$

S = sensitizer; X = substrate

Hammond's[13] initial hypothesis is that the syn dimer A arises from an excited-state singlet and the anti dimers B and D from excited-state triplets. In order to rule out the possibility of photoisomerization of a primary product, A and B were irradiated under sensitized and unsensitized conditions for long periods of time with no change detected. It was then determined that in the sensitized irradiation, the coumarin molecules absorbed 99.15% of the incident light. The coumarin fluorescence could be quenched by the addition of benzophenone and considerable overlap existed between the emission spectrum of coumarin and the absorption spectrum of benzophenone. These facts led Hammond to the proposal of the following mechanism:

$$\text{Cou} \xrightarrow{h\nu} \text{Cou}^{*(1)} \qquad (1)$$

$$\text{Cou}^{*(1)} + \text{S} \longrightarrow \text{Cou} + \text{S}^{*(1)} \qquad (2)$$

$$\text{S}^{*(1)} \longrightarrow \text{S}^{*(3)} \qquad (3)$$

$$\text{S}^{*(3)} + \text{Cou} \longrightarrow \text{S} + \text{Cou}^{*(3)} \qquad (4)$$

$$\text{Cou}^{*(3)} + \text{Cou} \longrightarrow \text{B} + \text{D} \qquad (5)$$

Cou = coumarin S = sensitizer

The quenching of the coumarin fluorescence supported the proposal of step (2) which, at first, was believed to occur by energy transfer; but further evidence supported the trival mechanism of emission and reabsorption. Dimer A is believed to result from attack of an excited-state singlet on a ground state molecule, step (6).

$$\text{Cou}^{*(1)} + \text{Cou} \longrightarrow \text{A} \qquad (6)$$

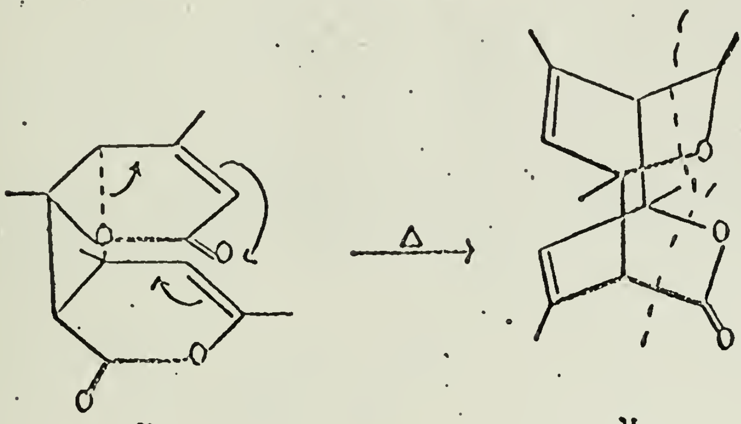
Since there was no product formed in benzene, a competing self-quenching reaction, step (7), was proposed. In a study of solvent effects on the unsensitized photo-

$$\text{Cou}^{*(1)} + \text{Cou} \longrightarrow 2\text{Cou} + \text{energy} \qquad (7)$$

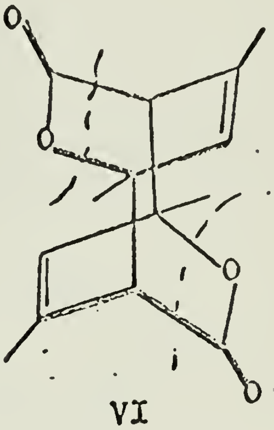
dimerization, irradiation of coumarin in polar solvents resulted in the formation of A. In non-polar solvents no dimer was formed. Hence steps (6) and (7) must be competing reactions with the bimolecular encounters being solvent dependent. Hammond stated that since the singlet is polar, such solvent effects are not unexpected. The fluorescence and phosphorescence spectra of coumarin are very similar in intensity, and it was therefore reasoned that intersystem crossing must occur to some extent. To validate this idea, a very dilute (0.01M) solution of coumarin in benzene was photolyzed and the expected dimer B, which has the proposed excited-state triplet precursor, was isolated. The dilute solution allows intersystem crossing to compete favorably with self-quenching. Although Hammond's work does not disprove the Schenck mechanism, it does show that the formation of B may proceed by another mechanism and seems to present a more acceptable mechanistic description. In a solvent study on the unsensitized photodimerization of coumarin, Morrison[14] found that of all solvents studied propyl bromide gave the largest conversion to B. If this observation implies a heavy-atom solvent effect, which would favor the formation of triplets, then it seems to lend support to the hypothesis that a triplet precursor is responsible for the formation of B. Schenck[12] has reported this year the isolation of the previously unknown syn dimer C in a study where A, B, and C were isolated from unsensitized irradiation of coumarin in several solvents. Although Schenck does not defend his original mechanistic proposal, he

states that Hammond's scheme seems to be an oversimplification. He believes that the various dimers arise due to associations of the coumarin molecules in solution, which are both solvent and concentration dependent. However this new experimental work does not seem incompatible with Hammond's mechanism.

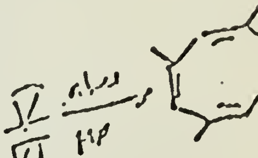
Although it was known that the 2-pyrone nitrogen analogs, 2-pyridones formed 1,4-photodimers, de Mayo was the first to report their existence in the pyrone system.[15] De Mayo irradiated 2,4-dimethyl-2-pyrone in a saturated benzene solution using a Pyrex filter and isolated three dimers to which he assigns the structures IV, V, and VI. The assignments were made on spectral data and the following observations: (1) V and VI on brief heating above their melting points led to the formation of 1,3,5,7-tetramethylcyclooctatetraene. (2) IV could be converted to V thermally at 160°, a reaction similar to the Cope rearrangement. Therefore V must be the syn-1,4-dimer leaving VI as the anti-1,4-dimer.



IV V

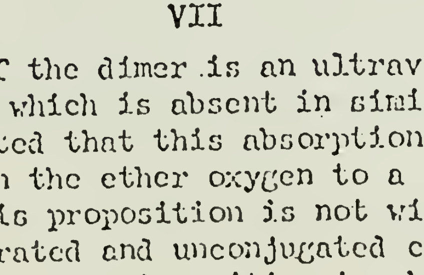


VI



PHOTODIMERIZATION OF 4-PYRONES

Since 1914 it has been known that 2,6-dimethyl-4-pyrone (Xa) formed a dimer when exposed to sunlight,[5] and in 1951 an incorrect structure was reported for this dimer.[16] Only recently has the actual structure of this dimer been fully described by Yates and Jorgenson.[17,18] These workers irradiated 2,6-dimethyl-4-pyrone in the solid state and in concentrated ethanol, benzene and acetic acid solutions with a sunlamp and found one dimer formed exclusively. The photodimer's composition was established as a head-to-tail cage structure (VII) by extensive degradative and product analyses.



VII

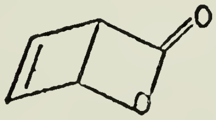
λ_{max} 233 mμ
$n_c \to \pi^*$

An interesting feature of the dimer is an ultraviolet absorption λ_{max} 233mμ (log ε 3.82) in acetonitrile, which is absent in similar cage compounds without the ether linkages. Yates suggested that this absorption was the result of a transition from a non-bonding electron on the ether oxygen to a π-antibonding orbital on the carbonyl group ($n_E \to \pi^*$). This proposition is not without analogy. Anomalous absorptions in certain unsaturated and unconjugated carbonyl compounds have been ascribed to a charge transfer $\pi \to \pi^*$ transition in which an olefinic π-electron is excited to a π-antibonding orbital of the carbonyl group.[19] One might picture this cage dimer with a perimeter of annular orbital overlap. Certain aspects of the chemistry of this photodimer contrast with that of similar compounds, such as the cage dimer of 2,6-dimethyl-p-benzoquinone. These differences have been attributed to this unusual overlap. For example, analogous compounds show a tendency to form hydrates while VII does not which Yates reported might show a stabilization of the ground state by annular overlap. Also, dimer VII underwent hydrogenolysis of the

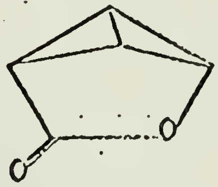
carbonyl group very easily which is reported to be suggestive of the presence of this overlap in the transition state. The exclusive formation of the head-to-tail dimer in the solid state is consistent with the X-ray crystallographic experiments which show that the molecules are arranged in a head-to-tail manner. This would facilitate the observed dimerization. However, the rationale for the formation of the head-to-tail dimer in solution is still at the speculatory stage.

PHOTOISOMERIZATION AND PHOTOFRAGMENTATIONS

A very interesting photoisomerization was discovered when unsubstituted 2-pyrone (I) was irradiated in ether above wave lengths of 250mμ at -10 to -20° forming in almost quantitative yield the isomeric bicyclo-β-lactone (VIII) by a 1-4 internal cyclization.[20] It was determined that upon standing in an inert polar solvent for six to twelve hours that VIII rearranged to the "isophotoproduct" (IX).[21] It is interesting to note that if a simple decarboxylation of VIII or IX were performed, VIII might yield the elusive cyclobutadiene and IX the intriguing tetrahedrane. As yet, these reactions have not been reported.

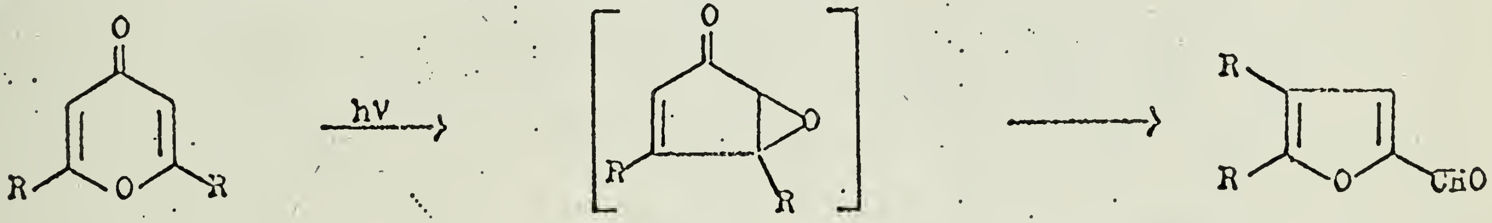


VIII



IX

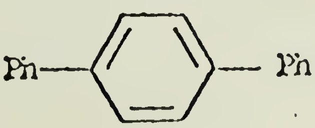
Yates[22] irradiated an aqueous 0.2% solution of 2,6-dimethyl-4-pyrone (Xa) in a quartz apparatus for 36 hours and in addition to the usual cage dimer, isolated about 1% of 4,5-dimethyl-2-furaldehyde (XIIa). Because of the structural similarity of X to the 2,5-cyclohexadienones, Yates suggested that this rearrangement might initiall proceed through the intermediacy of 3,4-dimethyl-4,5-epoxy-2-cyclopenten-1-one (XIa) which is analogous to the intermediate established by Zimmerman[23] in his mechanistic work in the photolysis of 2,5-cyclohexadienones.



X XI XII

R = Me (Xa, XIa, XIIa)
R = Ph (Xb, XIb, XIIb)

Because of his interest in the photochemistry of unsaturated epoxyketones and to establish the authenticity of Yates' proposed intermediate (XIa), Padwa and co-workers started a study of the photochemical behavior of 3,4-diphenyl-4,5-epoxy-2-cyclopenten-1-one (XIb).[24-27] When the cyclopentenone oxide (XIb) is photolyzed for 18 hours in anhydrous ether at 25° with ultraviolet light of wave lengths above 260mμ, two major components, p-terphenyl (XIII) and diphenylacetylene (XIV) are produced. Padwa has established that this reaction proceeds by a sequence of three



XIII

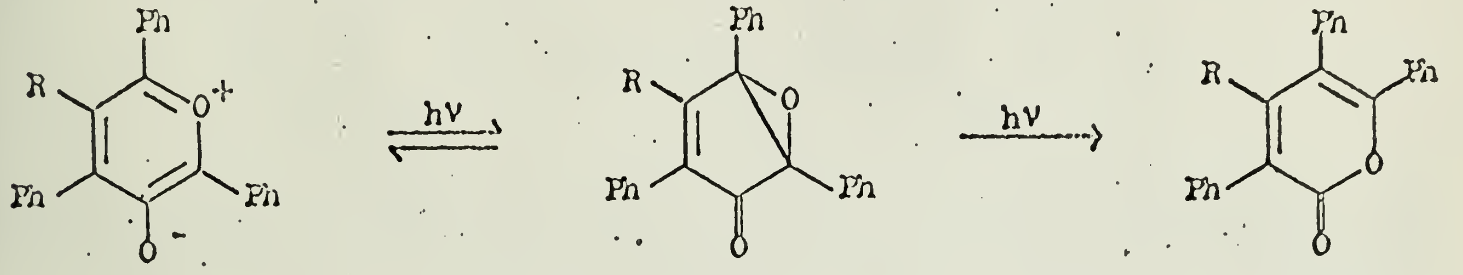
$Ph—C\equiv C—Ph$

XIV

separate photochemical reactions. This was accomplished by monitoring the transformation and detecting two intermediates by thin layer chromatography and also consideration of the product distribution as a function of time. The first intermediate isolated in this sequence was identified as 4,5-diphenyl-2-pyrone (XV). Padwa established further support for the intermediacy of XV by irradiating XV, itself, and found about the same product distribution as a function of time as when

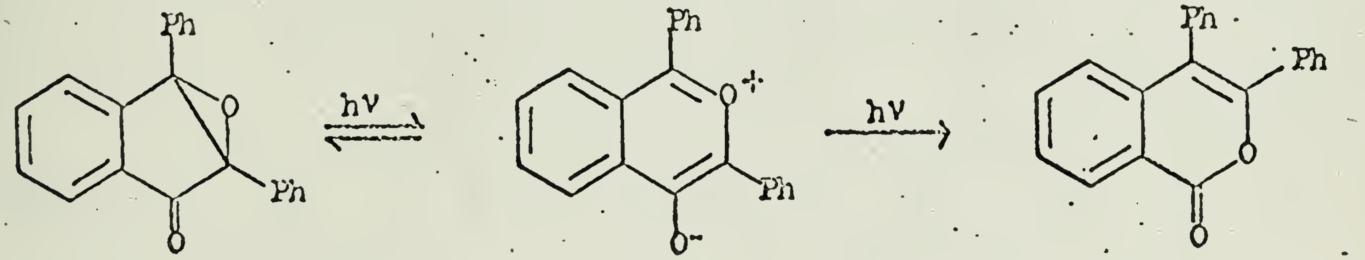
the cyclopentenone oxide (XIIb) was photolyzed.

Dunston and Yates[28] discovered that upon irradiation of 2,3,4,5-tetraphenyl-4,5-epoxy-2-cyclopenten-1-one (XVIa) in ethanol with a Pyrex filter, a photochemical valence tautomerism was established between XVIa and a pink colored species identified as 2,4,5,6-tetraphenylpyrylium-3-oxide (XVIIa) with concurrent rearrangement of XVIa to 3,4,5,6-tetraphenyl-2-pyrone (XVIIIa). The identification of XVIIa was accomplished by isolation and examination of the pyrylium oxide perchlorate salt and by comparison with Ullman's work[29,30] on the photoequilibrium between the red 2,4,6-triphenylpyrylium-3-oxide (XVIIb) and 2,4,5-triphenyl-4,5-epoxy-2-cyclopenten-1-one (XVIb). The latter rearranged to 3,5,6-triphenyl-2-pyrone (XVIIIb). In a related study by Ullman,[29-34] a photochemical valence tautomerism between 2,3-diphenylindenone oxide (XIX) and the red 1,3-diphenyl-2-benzopyrylium-4-oxide (XX) was established by irradiation in deoxygenated benzene at $365 m\mu$. Continued irradiation led to the formation of 3,4-diphenylisocoumarin (XXI) which was believed to arise from XX. Ullman has stated that the above cyclopentenone oxide - pyrylium oxide photochemical valence tautomerizations proceed by excited ground state intermediates. Since no color change was observed upon irradiation and attempts to trap a pyrylium oxide intermediate failed, Padwa concluded that the transformation did not proceed through a pyrylium oxide intermediate. The author rationalized the transformation by the following:

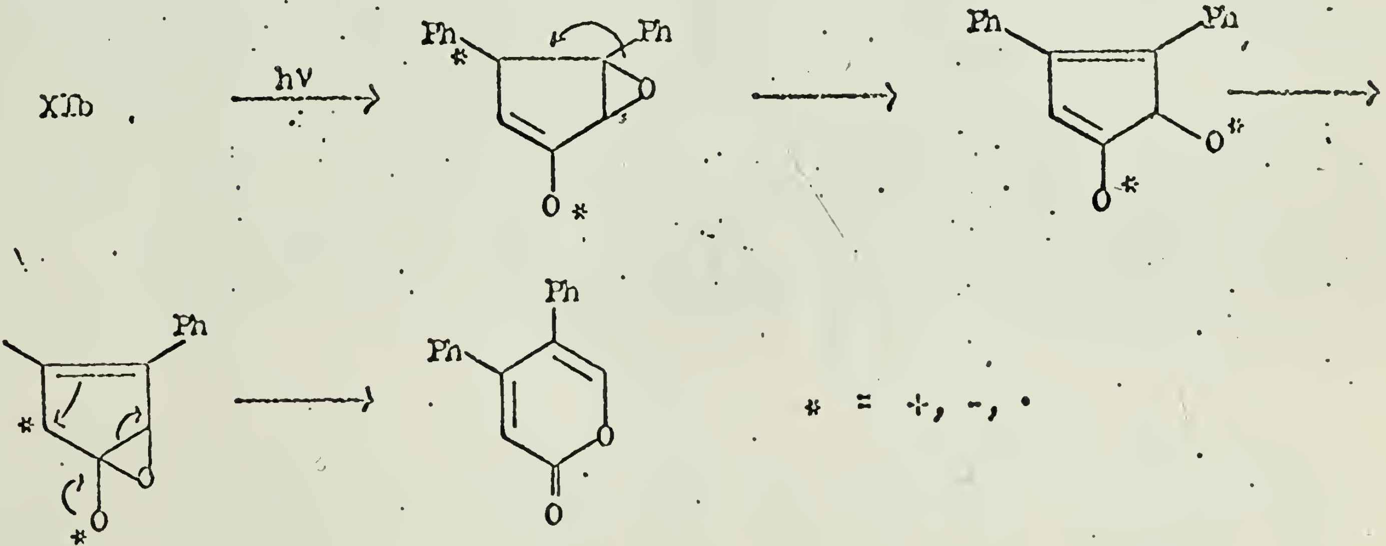


XVII XVI XVIII

R = Ph (XVIa, XVIIa, XVIIIa)
R = H (XVIb, XVIIb, XVIIIb)



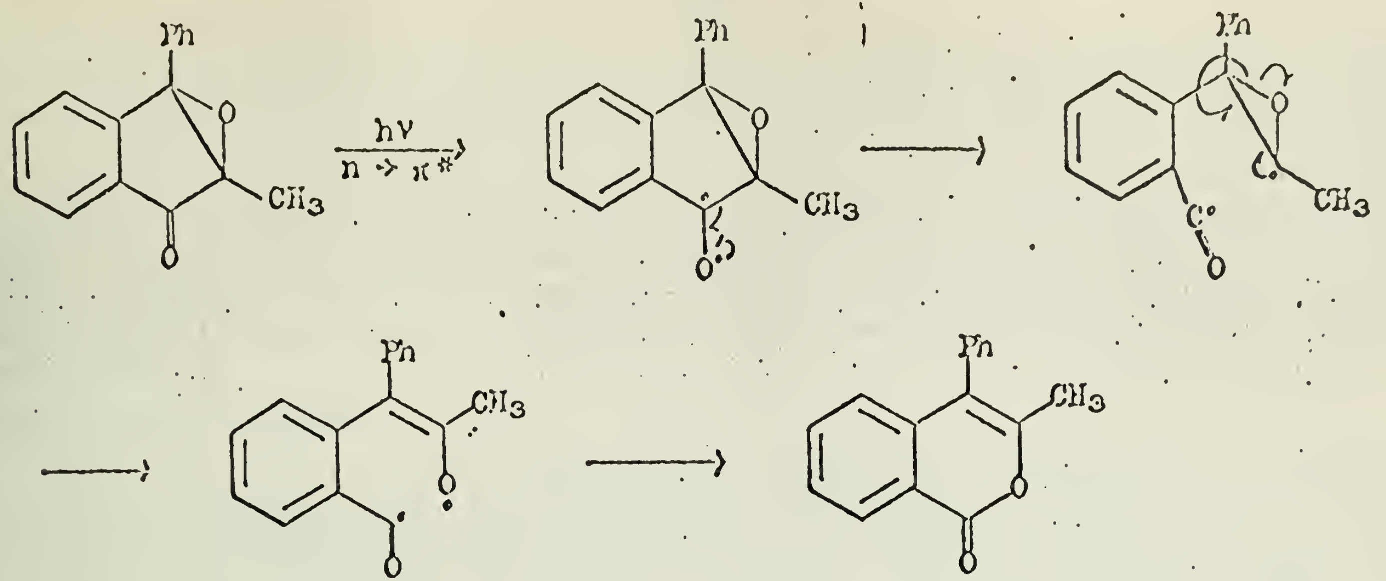
XIX XX XXI



XV

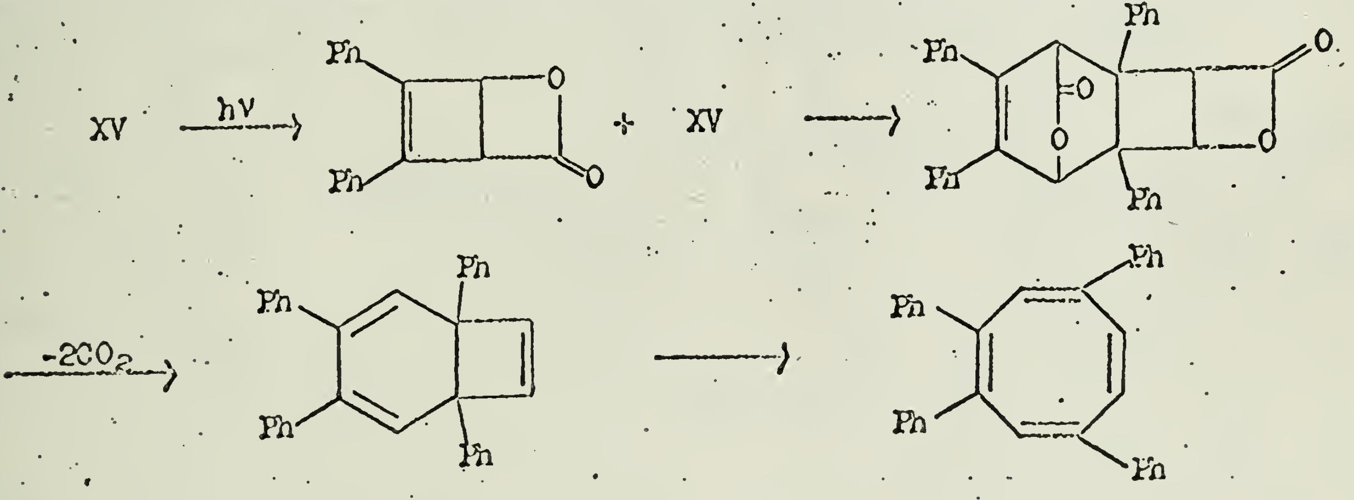
* = +, -, ·

However, Zimmerman[35] has proposed an alternative route for this type of rearrangement in a similar compound with the primary step being an $n \rightarrow \pi^*$ excitation. Ullman stated that this proposal is not compatible with his results on the indenone oxide



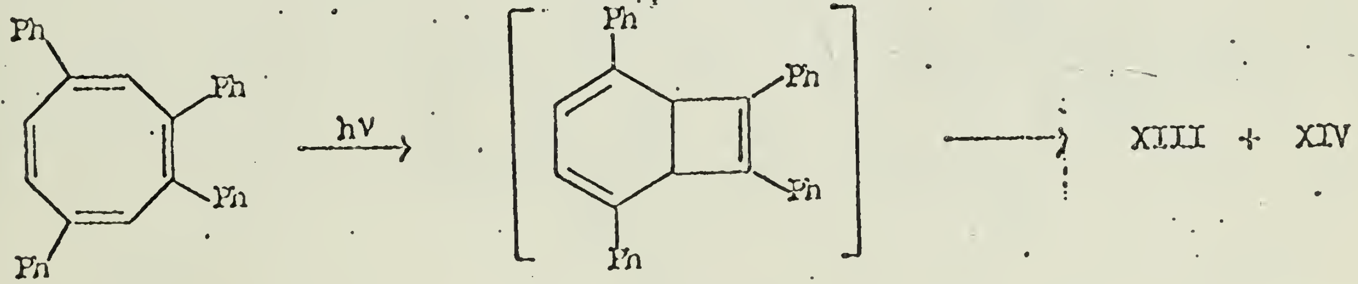
system. Evidence to confirm the exact nature of the excited state species in the rearrangement of XIb to XV is inadequate. However, since no phosphorescence from XIb was detected and 1,3-pentadiene failed to quench the reaction, Padwa believed that a triplet state is not involved.

The second intermediate in the sequence was identified as 1,2,4,7-tetraphenylcyclooctatetraene (XXII).[27] Corey's work,[20] the preparation of the β-lactone photoproduct of 2-pyrone, led Padwa to the proposal of a plausible pathway for this second step. However, experiments designed to trap the bicyclo-β-lactone failed.



XXII

The last step is the photochemical fragmentation of XXII which had already been reported by White,[30] who suggested the bicyclic intermediate XXIII which has not been isolated. Now that the three step sequence is established, work must be done to elucidate the nature of the excitation steps.



XXII

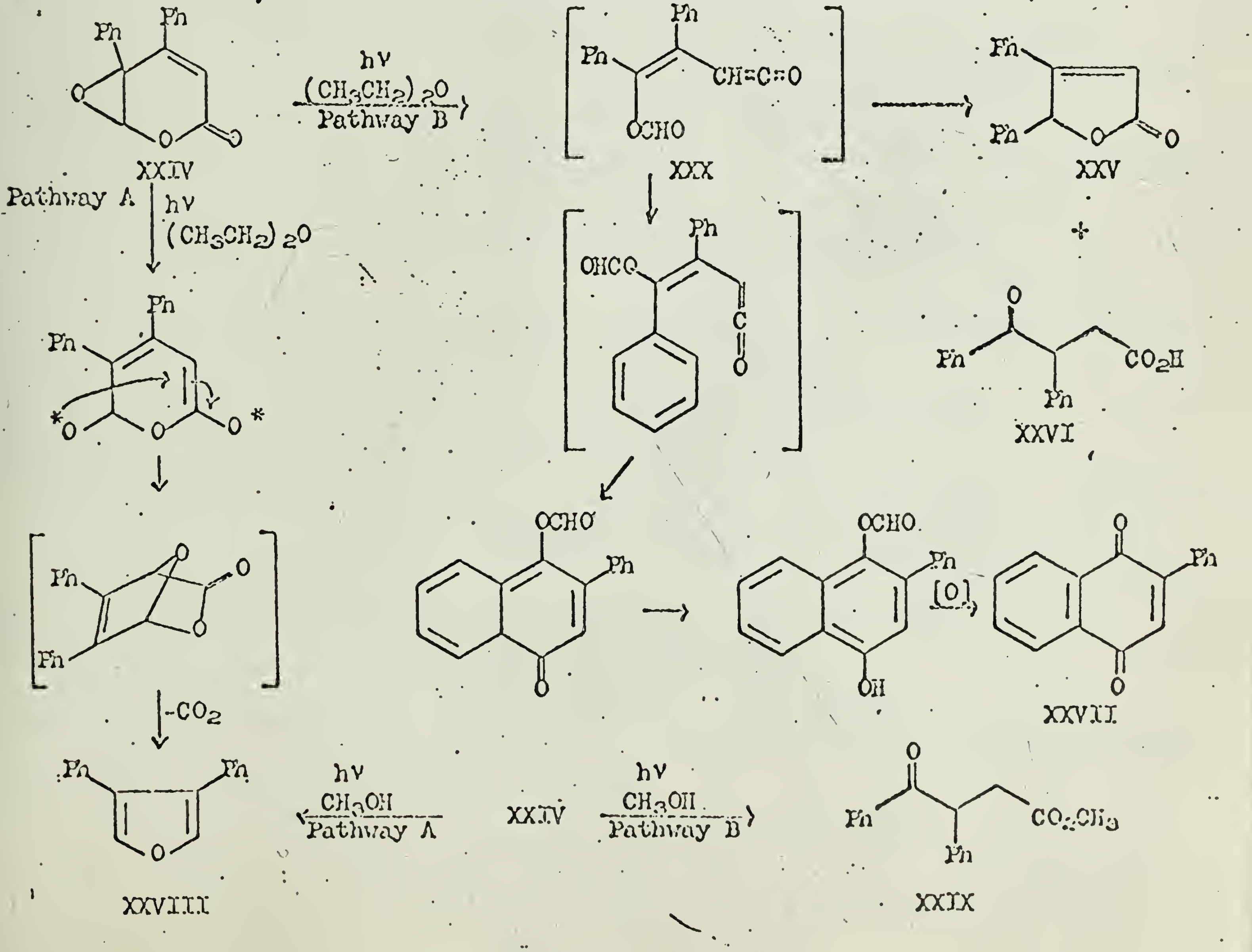
XXIII

Since the photolysis of the phenyl substituted cyclopentenone oxide did not produce any 4,5-diphenyl-2-furaldehyde (XIIb) some suspicion is cast on the cyclopentenone oxide intermediate proposed by Yates in the photolytic transformation of 2,6-dimethyl-4-pyrone (Xa) to 4,5-dimethyl-2-furaldehyde (XIIa). However, since a β phenyl substituent might effect the nature of the excitation step the photolysis of 2,6-dimethyl-4-pyrone might proceed by a different route than the related phenyl compound. The photolysis of 2,6-diphenyl-4-pyrone (Xb) in anhydrous benzene at 25°

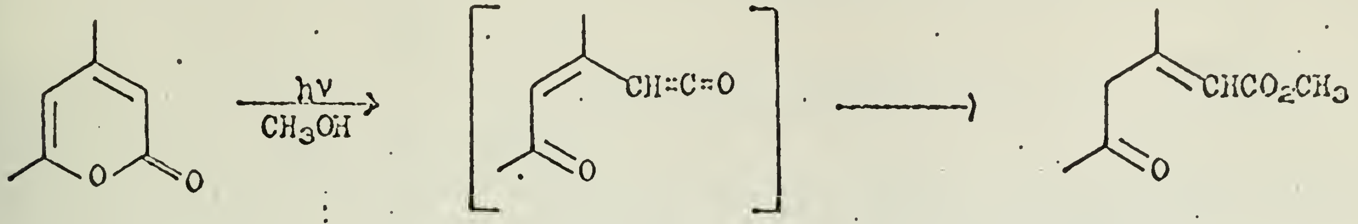
for 48 hours with ultraviolet light of wave lengths above 260mμ was run without isolation of a corresponding furan derivative. In order to determine if a ground state pathway existed for the cyclopentenone oxide rearrangement to the furaldehyde, the reaction of XIb in acidic anhydrous methanol was carried out and 4,5-diphenyl-2-furaldehyde (XIIb) was isolated in 10% yield.[37] Although this suggests that the 4,5-dimethyl-2-furaldehyde might have been produced by a competing ground state pathway, it does not eliminate the possibility of different excitation steps for the methyl and phenyl compounds. The photolysis of 3,4-dimethyl-4,5-epoxy-2-cyclopenten-1-one (XIa), using the same conditions as Yates, certainly would provide useful information.

PHOTOADDITION REACTION

The mechanism of several photoaddition reactions of 2-pyrones is plausibly rationalized by postulating the intermediacy of a ketene. However, in no cases reported has this proposed ketene been isolated. Recently, Padwa[38-40] reported that the photolysis of 5,6-epoxy-4,5-diphenyl-2-pyrone (XXIV) in anhydrous ether with wave lengths above 260mμ for 4 hours yielded four components: 4-hydroxy-3,4-diphenylcrotonic acid γ-lactone (XXV), desyl acetic acid (XXVI), 2-phenyl-1,4-napthoquinone (XXVII), and 3,4-diphenylfuran (XXVIII). Also, irradiation of XXIV in methanol led to the formation of XXVIII and methyl desylacetate (XXIX), however no XXVII could be detected. Padwa advanced the following speculatory information about the pathways that might be involved: (1) The formation of XXVIII might follow pathway A, (2) and the formation of XXV, XXVI, XXVII, and XXIX is believed to proceed through a ketene intermediate (XXX), pathway B. (3) A photoisomerization from the _cis_-ene-ketene intermediate to the _trans_-ene-ketene, followed by cyclization and air oxidation, is invoked to rationalize the formation of XXVII.



De Mayo[41] reported that in the presence of methanol the irradiation of 4,6-dimethyl-2-pyrone (XXXI) yielded methyl β-acetonylcrotonate (XXXII) of unknown stereochemistry and suggested a ketene intermediate (XXXIII).



XXXI XXXIII XXXII

CONCLUSION

Although the advances in solving the structural and stereochemical problems of the photolyses of pyrones seem impressive, the mechanistic work lags behind this progress. Some theoretical calculations reported by Malrieu[42] on the variations in bond orders in the $n - \pi^*$ and $\pi - \pi^*$ excited states of 2-pyrone led him to the conclusion that most of the photochemical reactions of 2-pyrones can best be rationalized by invoking a $\pi - \pi^*$ excited state species. However, more experimental work in identifying excited state species is necessary before these calculations can be verified.

BIBLIOGRAPHY

1. G. Ciamician and P. Silber, Ber., 35, 4128 (1902).
2. G. Ciamician and P. Silber, ibid., 36, 4266 (1903).
3. K. T. Ström, ibid., 37, 1383 (1904).
4. A. W. K. de Jong, Rec. trav. chim., 43, 316 (1924).
5. E. Paterno, G. Chieffi, and G. Perret, Gazz. chim. ital., 44, 151 (1914).
6. L. Musajo, G. Rodighiero, and G. Caporale, Chimica e industria, 35, 13 (1953).
7. G. Rodighiero and V. Cappellina, Gazz. chim. ital., 91, 103 (1961).
8. F. Von Wessely and I. Plaichinger, Ber., 75B, 971 (1942).
9. A. Schönberg, N. Latif, R. Moubasher, and W. I. Awad, J. Chem. Soc., 374 (1950).
10. R. Anet, Can. J. Chem., 40, 1249 (1962).
11. G. O. Schenck, I. v. Wilucki, and C. H. Krauch, Ber., 95, 1409 (1962).
12. C. H. Krauch, S. Farid, and G. O. Schenck, ibid., 99, 625 (1966).
13. G. S. Hammond, C. A. Stout, and A. A. Lamola, J. Am. Chem. Soc., 86, 3103 (1964).
14. H. Morrison and H. Curtis, Abstracts of the 151st A. C. S. Meeting, K55 (1966).
15. P. de Mayo and R. W. Yip, Proc. Chem. Soc., 84 (1964).
16. M. Giua and M. Civera, Gazz. chim. ital., 81, 875 (1951).
17. P. Yates and M. J. Jorgenson, J. Am. Chem. Soc., 80, 6150 (1958).
18. P. Yates and M. J. Jorgenson, ibid., 85, 2956 (1963).
19. H. Labhart and G. Wagnière, Helv. Chim. Acta, 42, 2219 (1959); C. F. Wilcox, Jr., S. Winstein, and W. G. McMilan, J. Am. Chem. Soc., 82, 5450 (1960); S. Winstein, L. de Vries, and R. Orloski, ibid., 83, 2020 (1961); R. C. Cookson and N. S. Wariyar, J. Chem. Soc., 2302 (1956); H. Birnbaum, R. C. Cookson, and N. Lewin, ibid., 1224 (1961).
20. E. J. Corey and J. Streith, J. Am. Chem. Soc., 86, 950 (1964).
21. E. J. Corey and W. H. Pirkle, private communication.
22. P. Yates and I. W. J. Still, ibid., 85, 1208 (1963).
23. H. E. Zimmerman and D. I. Schuster, ibid., 84, 4527 (1962).
24. A. Padwa and R. B. Hartman, Abstracts of the 148th A. C. S. Meeting, 25S (1964).
25. A. Padwa and R. Hartman, J. Am. Chem. Soc., 86, 4212 (1964).
26. A. Padwa, Tetrahedron Letters, 813 (1964).
27. A. Padwa and R. Hartman, J. Am. Chem. Soc., 88, 1518 (1966).
28. J. M. Dunston and P. Yates, Tetrahedron Letters, 505 (1964).
29. E. F. Ullman, J. Am. Chem. Soc., 85, 3529 (1963).
30. E. F. Ullman and W. A. Henderson, Jr., ibid., 86, 5050 (1964).
31. E. F. Ullman and J. E. Milks, ibid., 84, 1315 (1962).
32. E. F. Ullman and J. E. Milks, ibid., 86, 3814 (1964).

33. E. F. Ullman and W. A. Henderson, Jr., private communication.

34. J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley and Sons, Inc., New York, 1966, p 311ff.

35. H. E. Zimmerman and R. D. Simkin, Tetrahedron Letters, 1847 (1964).

36. E. H. White and R. L. Stern, ibid., 193 (1964).

37. A. Padwa, ibid., 1409 (1965).

38. A. Padwa and R. Hartman, Abstracts of the 151st A. C. S. Meeting, K79 (1966).

39. A. Padwa and R. Hartman, Tetrahedron Letters, 2277 (1966).

40. A. Padwa and R. Hartman, J. Am. Chem. Soc., 88, 3759 (1966).

41. P. de Mayo, Advan. Org. Chem., 2, 394 (1960).

42. J. P. Malrieu, Photochem. and Photobiol., 5, 301 (1966).

STEREOSELECTIVITY OF N-ALKYLATION IN NITROGEN HETEROCYCLES

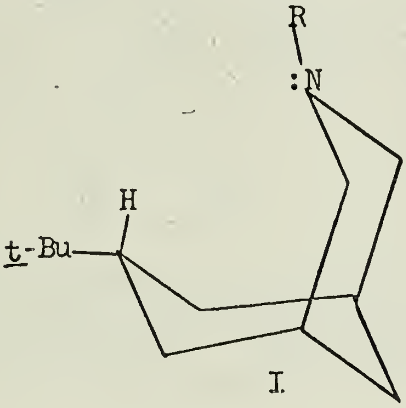
Reported by R. F. Aycock October 13, 1966

INTRODUCTION

Until recently, very little consideration has been given to the conformational equilibrium present in nitrogen heterocycles or the configuration of the products when the mobile nitrogen atom has been fixed by quaternization, although it had been noted by Fodor and co-workers that in the tropine series these quaternizations may be highly stereoselective.[1,2] The determination of the configuration of such stereoisomeric pairs is important for it would aid in determining the structural and mechanistic factors which lead to stereoselectivity in such N-alkylations and permit prediction of this stereoselectivity in future cases. This seminar will present studies on the N-alkylation of these cyclic nitrogen atoms and conformational work concerning the free base.

STERIC REQUIREMENTS OF NITROGEN NONBONDING ELECTRON PAIR

Aroney and Le Fevre[4] have reported that based upon measurements of molar Kerr constants of piperidine and N-methylpiperidine, the electron lone pair must be larger than hydrogen and, in fact, almost as large as the methyl group. "Larger" here is defined as the group which preferentially occupies the equatorial position. However, several workers disagree with these conclusions. Experimental work by Allinger and co-workers[5] using dipole moment measurements of N-methylpiperidine, piperidine, N-methylpiperazine and N,N'-dimethylpiperazine was used to calculate results indicating an equatorial preference for the methyl group of about 1.7 kcal/mole and for hydrogen of about .4 kcal/mole in benzene. Katritzky and coworkers,[6] also using dipole moments, found the equatorial isomer to be predominant for both 4-p-chlorophenylpiperidine (88%) and 4-p-chlorophenyl-1-methylpiperidine (94%) in benzene at 25°C. Pumphrey and Robinson[7] have examined the infrared spectrum of I and found absorption at 2700-2800 cm^{-1} which is characteristic of a nitrogen lone-pair which is trans to at least two axial hydrogen atoms on carbon atoms adjacent to it.[8] Thus, the lone-pair must be in the very crowded endo position and the workers conclude that the lone-pair must not require as much room as the hydrogen. This would appear, however, to be a poor model in which to study this property because of the difference in hydrogen-hydrogen interactions and hydrogen-lone-pair interactions. The absorption at 2700-2800 cm^{-1} noted is attributed to partial bonding of the lone pair with the anti-coplanar $\sigma^*(C\text{-}H_{ax})$ orbital of the α-carbon atom. Le Fèvre and co-workers have noted that this criterion is not applicable to morpholine or several substituted 4-pyridones and, in general, for rings in which deformation occurs.[9] Lambert and Keske[10] have investigated the nmr spectra of piperidine, N-methylpiperidine, and N-t-butylpiperidine; all of which had been deuterated in the β-positions to simplify the spectra. From the fact that the axial protons which are on the α-carbon atoms and are anti-coplanar to the nitrogen lone pair (the lone pair is axial) are shifted upfield,[11] it was determined that in piperidine the lone pair was equatorial and the following steric order was suggested: $CH_3 >$ lone pair $> H$. The same argument applied to explain the infrared absorption is used to rationalize this upfield shift in the nmr.

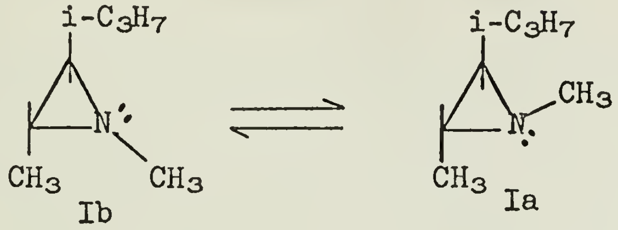


I

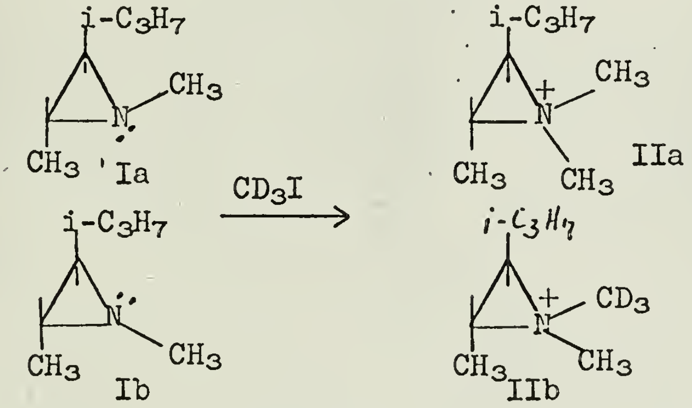
R=H, CH_3

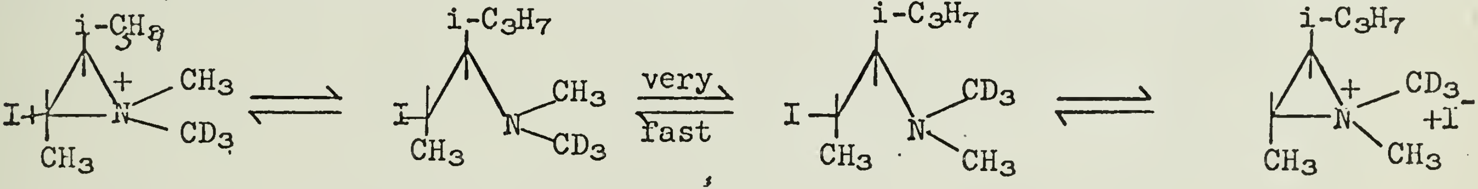
AZIRIDINIUM SYSTEMS

Bottini and co-workers[12] have determined the conformational equilibrium of trans-1,2-dimethyl-3-isopropylaziridine by nmr in a temperature range from -55.5° C to 9°C for which ratios range from 4.3 to 3.69 of Ib/Ia. This assignment is made by assuming steric requirements i-Pr > Me > electron pair. Then isomer Ib is presumed to be more stable and the larger N-methyl nmr peak at higher field is assigned to it.



Both cis- and trans-1,2-dimethyl-3-isopropylaziridine have been quaternized with methyl iodide and shown to exist as stable monomeric aziridinium iodides.[13,14] Quaternization of both compounds with methyl-d_3 iodide yielded a 50-50 mixture of the two diastereomers for each.[13] This was first rationalized by proposing that the ratio of rate constants, i.e., k_{Ia}/k_{Ib}, is very nearly equal to the equilibrium constant Ib/Ia since it might be expected that Ia will have a lower activation energy because less non-bonded interactions are introduced. However, in later work[15] the course of the reaction of trans-1,2-dimethyl-3-isopropylaziridine was followed by nmr and it was found that at 50% completion the ratio of IIb:IIa was 2.4, but upon going to completion it decreased to unity. The ratios were determined by nmr and the peak at higher field was assigned to more stable isomer and confirmed by comparing benzyl derivatives. The following equation shows the proposed explanation for the change in the ratio of products.





This is supported by the fact that quaternization with deuteriomethyl benzenesulfonate yields a reaction mixture which is 2.93:1 with IIb the predominant product, and also by the observation that there is a decrease in the ratio if one goes from a solvent medium of methanol to benzene.

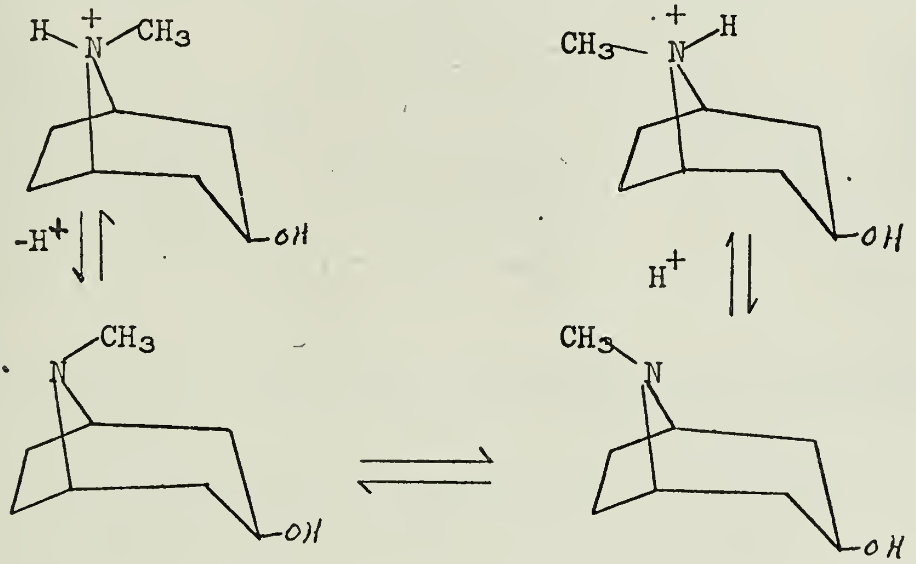
PIPERIDINE SYSTEMS

Le Fèvre and co-workers have studied the conformations of several substituted epimeric piperidine-4-ols[17] and 4-piperidones[18] by use of nmr, dipole moments and molar Kerr constants and demonstrated all exist predominantly in the chair conformation as one might expect.[19] McKenna and co-workers[20] have examined the quaternization of a number of 2-methyl- and 4-phenylpiperidine systems and House[21] and co-workers have examined the 4-t-butylpiperidine system. Both groups concluded that the preferred direction of attack was in the axial position from considerations of the

composition of the reaction products by nmr using Closs's method. Kinetic studies conducted by Katritzky's group[22] upon the quaternizations of N-alkylpiperidines and N-alkylpiperazines and comparison of these rates with the rates for quinolizidine, 2-methyl-2-aza-adamantane, and N-methyltropane led them to conclude, in contrast to the above, that 1-alkyl-4-*t*-butylpiperazines undergo predominantly equitorial alkylation except in the case of N-*t*-butyl derivatives.

AZABICYCLIC SYSTEMS CONTAINING NO BRIDGEHEAD NITROGEN

In Fodor's work[1] in the tropane system it was shown that upon quaternization the entering group assumes principally or exclusively the equatorial position to the piperidine ring and the conclusion was drawn that in the free bases the N-substituent occupied primarily the axial position. This condition it is not necessary to explain the observed results as may be seen by consideration of the Curtin-Hammett principle. Closs,[23] therefore, has examined these systems by nmr and concluded that, in general, the free base having the N-substituent in the equatorial position is the more stable one. Since this method has been used quite extensively to determine the configuration at nitrogen in several systems it will be discussed in detail for one compound, pseudotropine. Because of the fast rate of inversion of the free base, the equilibrium of the conjugate acids, (eq. 4), was examined. If one assumes the steric requirements of the lone electron pair on nitrogen resembles those of the proton, one would expect the conformation preference of the acid to be similar to that of the free base. Examination of the nmr spectra of the hydrochloride of pseudotropine at pH 1 shows one doublet at 136 and 141 cps (relative to aromatic H in toluene at 40 mc) and another much weaker doublet at 128 and 133 cps. These signals are assigned to two non-equivalent N-methyl groups. In order to assign the absorptions to axial and equatorial methyl groups, pseudotropine was ethylated which, as noted previously, should place the methyl group in the axial position. Methylation of N-ethylnorpseudotropine was assumed to result in the methyl group occupying the equatorial position. The nmr spectra of these quaternized products were then examined and the signal at higher field assigned to the equatorial isomer and the lower field signal to the axial isomer. Extrapolating these results to the deuteriochloride of pseudotropine and measuring the ratio of the areas of the N-methyl peaks, an equilibrium constant of approximately 9.8 was found favoring the equatorial isomer.

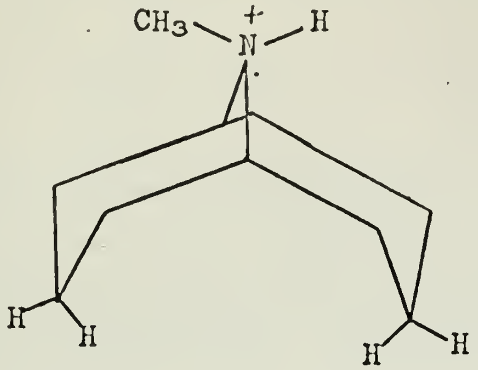


(4)

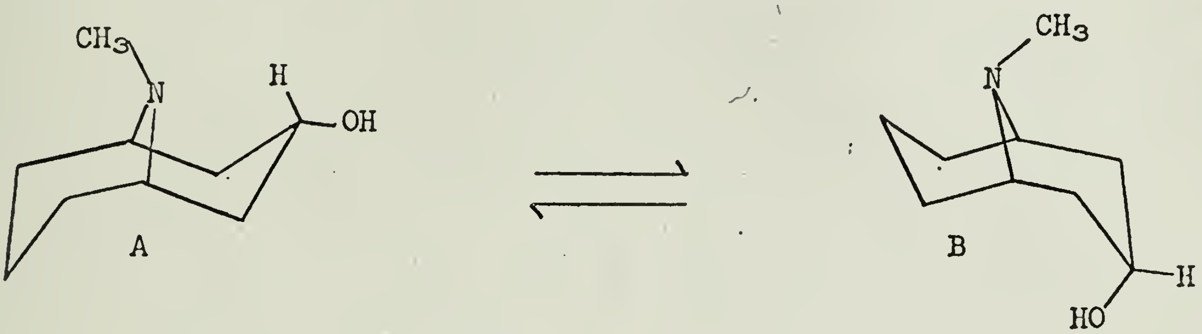
Le Fèvre and co-workers have studied 3-halogenotropanes by means of nmr[24] and dipole moment measurements and molar Kerr constants[25] and concluded that the piperidine ring occupies the chair conformation and the methyl group is in the equatorial position. Fodor and Katritzy[26] and co-workers have confirmed Closs's work but point out that the introduction of a 3-α-substituent such as the cyano group causes deformation of the piperidine ring. X-ray work has also been carried out by Fodor and MacGillavry[27] on the N-ethylnortropine methobromide. This shows the methyl group equatorial to the piperidine ring thereby further substantiating Fodor's earlier reports.

The crystal structure of 9-azabicyclo[3.3.1]nonane hydrobromide (III) has been analysed by X-ray crystallography and has been found to exist in the chair-chair conformation although the bond angles deviate somewhat from the ideal values, which is probably due to steric repulsion between the non-bonded hydrogen atoms.[28]

III



This is similar to results obtained for the analogous carbocyclic system which spectroscopic studies indicate exists as a chair-chair conformer in both solid and solution.[29] Le Fèvre and Chen have studied the 3-keto derivative[30] and its reduced products[31] by use of nmr. They concluded that the ketone existed in the chair-chair conformation but that one of the reduced products, 3-α-granatanol, existed primarily as an equilibrium between two chair-boat isomers A and B in which A predominates.

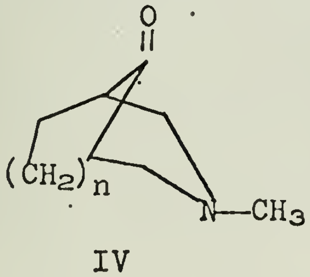


A

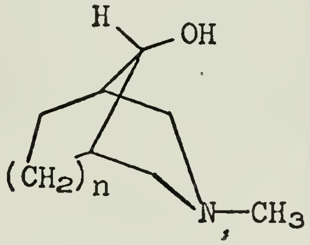
B

3-β-Granatanol, in which there exists the possibility of hydrogen bonding in the boat-chair conformation, was found to exist principally as the chair-chair conformer.

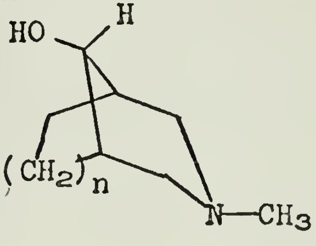
House[32] and co-workers have investigated the stereochemistry of quaternization by trideuteriomethyl p-toluenesulfonate in IV, V, and VI.



IV



V

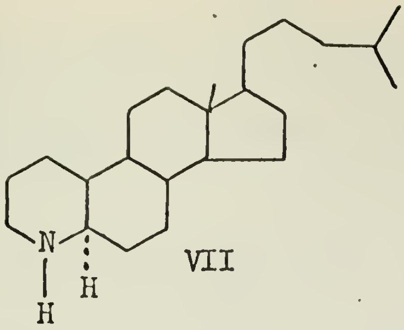


VI

n =1,2,3

Further investigations of the N-alkylations of the amino alcohols and ketones with methyl bromoacetate[33] led to the tentative assignment that the predominant direction of attack was syn to the methylene bridge for the three homologous series. There was no evidence that the nature and steric arrangement of the oxygen function exerts any control over the direction of these N-alkylations.

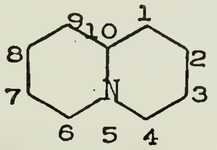
Stereoselectivity has also been observed in the quaternization of N-methyl-4-aza-5α-cholestane(VII) with alkyl iodides other than methyl and the preferred direction of attack has been shown to be equatorial.[34] However, no selectivity was shown in methylation.



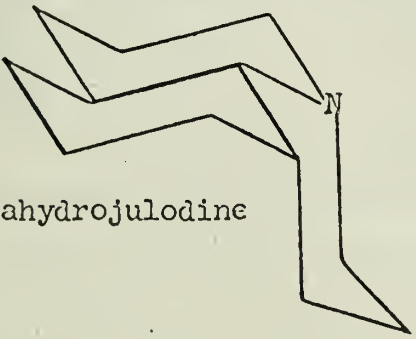
VII

FUSED SYSTEMS CONTAINING NITROGEN AT RING FUSION

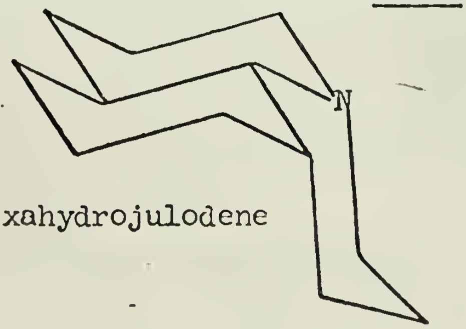
Katritzky[35] and co-workers have synthesized *c*-1-,2-,3-,4-, and *t*-1,2-,3-,4-methylquinolizidine where the *c* and *t* refer to the *cis*- and *trans*-relationship of the 10-hydrogen atom and the hydrogen on the substituted carbon atom. *Cis*- and *trans*- will indicate ring conformations. Infrared and nmr spectra of these and of quinolizidine indicate that all of these compounds exist predominantly with the ring system in the *trans*-conformation except *t*-4-methylquinolizidine which lacked the characteristic absorption at 2700-2800 cm^{-1} Bohlmann[8] had shown occurs in the *trans*-quinolizidines. *t*-4-Methylquinolizidine was assigned the *cis*-ring system on this basis. In quaternization of the free bases which have the *trans* ring structure and the methyl group in an equatorial position the methiodides are formed with retention of this configuration. Those in the *trans* ring which possesses an axial group on the same side of the molecule as the lone pair (the *c*-1- and *c*-3-isomers) form methiodides derived from the *cis* ring system and equatorial methyl group presumably due to interference of the methyl group with the entering group. *t*-2-Methylquinolizidine exists in a *trans* ring with an axial methyl group which does not directly hinder the approach of the methylating agent. However, 1,3-diaxial interactions in the methiodide are evidently enough greater than in the free base that they cause a mixture of methiodides in *trans*-fused ring/axial methyl and *cis*-fused ring/equatorial methyl configurations. It appears that approximately equal amounts of the same isomers are obtained from the *t*-4-methylquinolizidine. Kinetic studies[36] have since indicated that this isomer exists in the *trans* ring conformation. There is not explanation as to why the compound failed to absorb in the 2700-2800 cm^{-1} band characteristic of this type structure. In these studies the rates of quinolizidine and the methylquinolizidines were compared with the rates of isomers of the hexahydrojulodines which have fixed *cis*- and *trans*-fused ring systems. Otherwise, these studies confirmed the previous results. It has also been noted elsewhere that a hindered *trans*-quinolizidine system may react through the *cis*-conformation. Shamma and Moss[37] have observed that the *trans*-quinolizidine system in raunitidine must undergo conformational change before methylation with methyl iodide occurs to yield ultimately a *cis*-quinolizidine structure indicating that steric hindrance has made the transition state for the *trans*-conformer much less favorable than that for the *cis*. Mason and co-workers have



quinolizidine



c,*t*-hexahydrojulodine

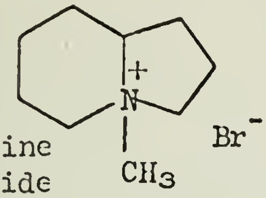


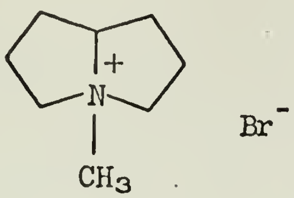
t,*t*-hexahydrojulodene

reported that (-)-1-oxoquinolizidine also exists primarily (90% at room temperature) in the *trans* ring conformation.[38]

Meyer and Sapianchiay have synthesized and examined the indolizidine and pyrrolizidine methobromides.[39]

indolizidine
methobromide





pyrrolizidine
methobromide

The methobromides formed by cyclization of N-methyl-2-(3'-bromopropyl)piperidine, -pyrrolidine, and N-methyl-2-(4'-bromobutyl)pyrrolidine yielded only the *cis* ring structure. This would indicate that the transition state for the *cis* ring system is of lower energy than that for the *trans* system since inversion at nitrogen is much faster than the rate of cyclization. It might also be mentioned that Katritzky[35] also obtained only the *cis* ring system is a similar cyclization to form quinolizidine methiodide. Methylation of indolizidine yields a 50:50 mixture of *cis*-*trans*-systems. According to the Curtin-Hammett principle, this would indicate that the *cis*-like and *trans*-like transition states are of about equal energy. The assignment of isomers was based primarily on the fact that the nmr signals occurred at the same positions Katritzky[35] observed for the quinolizidinium system.

Fodor[40] and co-workers have studied two interesting intramolecular quaternizations of two pyrrolidizine isomers; one of which is forced to occur with retention of configuration at nitrogen and the other with inversion.

FACTORS AFFECTING STEREOSELECTIVITY

McKenna[20,34] and co-workers have compiled a summary of characteristic stereoselectivities for some quaternizations (Table I) and proposed the following rationale to explain these results.

Table I

Characteristic Stereoselectivities of Quaternizations in Acetone

Base System	Characteristic Selectivity[a] N-Me + AlkI	 N-AlK + MeI	Preferred Direction of Quaternization
2-Methylpiperidine	0	+	Axial
trans-Decahydroquinoline	0	+	Axial
4-Aza-5α-cholestane	+	0	Equatorial
Camphidine	+	+++	Axial
4-Phenylpiperidine	++	++	Axial
Tropane	++	++	Equatorial

[a] 0, roughly equal proportions; +, *ca*. 2-5:1; ++, *ca*. 5-20:1

First, it is felt that the transition states for the quaternizations involves a tetrahedral nitrogen with sp^3-hybridization. If this is the case, then the relative steric demands of a fully attached R and a partly attached R' are important in the two competing transition states. With respect to this steric effect, it is felt that the incoming quaternizing primary alkyl group is effectively larger than a primary N-alkyl group present in the cyclic base. However, if the nitrogen ring is fairly flexible in the vicinity of the nitrogen, then this flexibility combined with the fairly long partial bond between the incoming group and the base in the

transition state may result in the incoming group being preferentially placed on the more hindered side of the nitrogen atom. Another steric factor which was felt to be important was diaxial interaction. It was proposed that in the quaternization of N-alkylpiperdines, including bridged- or fused-ring systems, diaxial interactions affecting alkyl groups fully or partly attached to the nitrogen atom are, in general, more important than any interactions affecting groups fully or partly attached equatorially. As an example, quaternization products of *trans*-decahydroquinoline and N-methyl-4-aza-5α-cholestane may be compared; in which N-methyl-4-aza-5α-cholestane has an angular methyl group which hinders attack on the axial nitrogen position, especially as the quaternizing agent becomes larger. However, the equatorial position will be subject to steric effects due to groups which are attached axially or equatorially to the α-carbon atoms. Such interactions might be expected to reduce stereoselectivity due principally to diaxial interacions. Table I shows this is the case. For example, the stereoselectivity of 2-methylpiperidine, *trans*-decahydroquinoline, and N-methyl-4-aza-5α-cholestane is lower than in camphidine or 4-phenylpiperidine. The abnormally high stereoselectivity of the tropane system is attributed to the rigid ring system which prohibits axial attack.

SUMMARY

Evidence has been presented that, in general, one can expect to find the piperidine ring system in the chair form with the N-alkyl group equatorial. The quaternizations of several cyclic nitrogen systems have been examined and it was determined that a number of these quaternizations were highly stereoselective. This has been rationalized by means of an sp^3-or near sp^3- hybridization for nitrogen in the transition state and by steric interactions.

BIBLIOGRAPHY

1. G. Fodor, Tetrahedron, *1*, 86 (1957).
2. G. Fodor in "The Alkaloids," Vol. 6, R.H.F. Manske, Ed., Academic Press Inc., New York, N.Y., 1960, pp. 145-177.
3. E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N.Y., 1962, p. 436.
4. M. Aroney and R. J. W. Le Fevre, J. Chem. Soc., 3002 (1958).
5. N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, J. Am. Chem. Soc., *87*, 1232 (1965).
6. R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, and A. R. Katritzky, Proc. Chem. Soc., 257 (1964).
7. N. W. J. Pumphrey and M. J. T. Robinson, Chem. Ind. (London), 1903 (1963).
8. F. Bohlmann, Chem. Ber., *91*, 2157 (1958).
9. C.-Y. Chen and R. J. W. Le Fevre, Tetrahedron Letters, *No. 21*, 1611 (1965).
10. J. B. Lambert and R. G. Keske, J. Am. Chem. Soc., *88*, 620 (1966).
11. H. P. Hamlow, S. Okuda, and N. Nakagawa, Tetrahedron Letters, *No. 37*, 2553 (1964).
12. A. T. Bottini, R. L. VanEtten, and A. J. Davidson, J. Am. Chem. Soc., *87*, 755 (1965).
13. A. T. Bottini and R. L. VanEtten, J. Org. Chem., *30*, 575 (1965).
14. G. K. Helmkamp, R. D. Clark, and J. R. Koskinen, *ibid.*, *30*, 666 (1965).
15. A. T. Bottini, B. F. Dowden, and L. Sousa, J. Am. Chem. Soc., *87*, 3249 (1965).
16. A. T. Bottini, B. F. Dowden, and R. L. VanEtten, *ibid.*, *87*, 3250 (1965).
17. C.-Y. Chen and R. J. W. Le Fevre, J. Chem. Soc., 3467 (1965).
18. M. J. Aroney, C.-Y. Chen, R. J. W. Le Fevre, and A. N. Singh, *ibid.*, (B), 98 (1966).
19. D. H. R. Barton and R. C. Cookson, Quart. Rev., *10*, 44 (1956).
20. (a) J. McKenna, J. M. McKenna, J. White, and A. Tulley, J. Chem. Soc., 1711 (1965); (b) J. K. Becconsal, R. A. Y. Jones, and J. McKenna, *ibid.*, 1726 (1965); (c) J. McKenna, J. M. McKenna, and J. White, *ibid.*, 1733 (1965).

21. H. O. House, B. A. Tefertiller, and C. G. Pitt, J. Org. Chem., 31, 1073 (1966).
22. J.-L. Imbach, A. R. Katritzky, and R. A. Kolinski, J. Chem. Soc., (B), 556 (1966).
23. G. L. Closs, J. Am. Chem. Soc., 81, 5457 (1959).
24. C.-Y. Chen and R. J. W. Le Fevre, J. Chem. Soc., 3473 (1965).
25. J. M. Eckert and R. J. W. Le Fevre, ibid., 3991 (1963).
26. R. J. Bishop, G. Fodor, A. R. Katritzky, F. Soti, L. E. Sullivan, and F. J. Swinbourne, ibid., (C), 74 (1966).
27. C. H. MacGillavry and G. Fodor, ibid., 597 (1964).
28. M. Dobler and J. D. Dunitz, Helv. Chim. Acta. 47, 695 (1964).
29. W. A. C. Brown, J. Martin, and G. A. Sim, J. Chem. Soc., 1844 (1965).
30. C.-Y. Chen and R. J. W. Le Fevre, Chem. Ind. (London), 306 (1965).
31. C.-Y. Chen and R. J. W. Le Fevre, J. Chem. Soc., (B), 539 (1966).
32. H. O. House and C. G. Pitt, J. Org. Chem., 31, 1062 (1966).
33. H. O. House and B. A. Tefertiller, ibid., 31, 1068 (1966).
34. J. McKenna, J. M. McKenna, A. Tulley, J. Chem. Soc., 5439 (1965).
35. T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, ibid., 2637 (1962).
36. C. D. Johnson, R. A. Y. Jones; A. R. Katritzky, C. R. Palmer, K. Schofield, and R. J. Wells, ibid., 6797 (1965).
37. M. Shamma and J. B. Moss, J. Am. Chem. Soc., 84, 1739 (1962).
38. S. F. Mason, K. Schofield, and R. J. Wells, Proc. Chem. Soc., 337 (1963).
39. W. L. Meyer and N. Sapianchiay, J. Am. Chem. Soc., 86, 3343 (1964).
40. G. Fodor, F. Uresch, F. Dutka, and T. Szell, Coll. Czech. Chem. Commun., 29, 274 (1964).

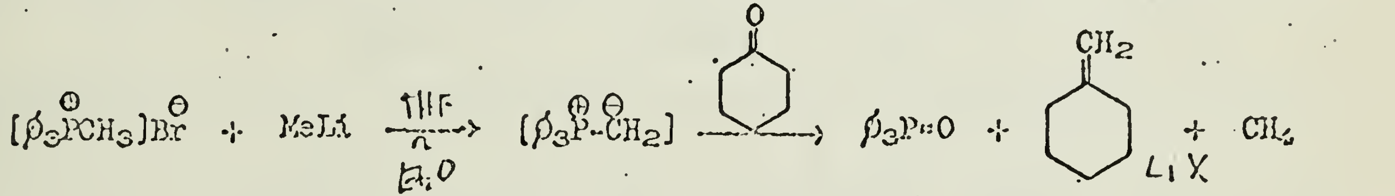
THE GENERATION OF PHOSPHINEALKYLIDENES BY ORGANOLITHIUM REAGENTS

Reported by Fred R. Scholer October 17, 1966

The general synthesis of olefins by the reaction of carbonyl compounds with phosphinealkylidenes was discovered by Wittig, Geissler, and Schollkopf.[1,2] The generation of the phosphinealkylidene reagents (equation 1) presumably proceeds by abstraction of the acidic α-hydrogen by the lithium reagent from the original phosphonium species present.[3] Seyferth, Hughes, and Heeren have recently reported that by attack of the alkyllithium reagent, displacements occur on the positively charged phosphorous atom, and this subsequently produces a different phosphinealkylidene.[4,5] The purpose of this seminar will be to examine the proposed mechanisms for the attack on the phosphorous atom, to consider the generation of the phosphinealkylidenes following the displacement attack, and to illustrate the effect of electronic and steric factors on the site of attack.

Early preparations of the Wittig reagent involved the reaction of triarylmethylphosphonium halides with strong bases such as sodium or lithium alkoxides or alkyllithium reagents.[6] In 1962 Seyferth sought to determine the mechanism of the latter reaction using methyllithium.[5] One of the first systems studied in detail was the generation of triphenylphosphinemethylene from the triphenylmethylphosphonium salt and methyllithium. However product analysis revealed that two competing reactions

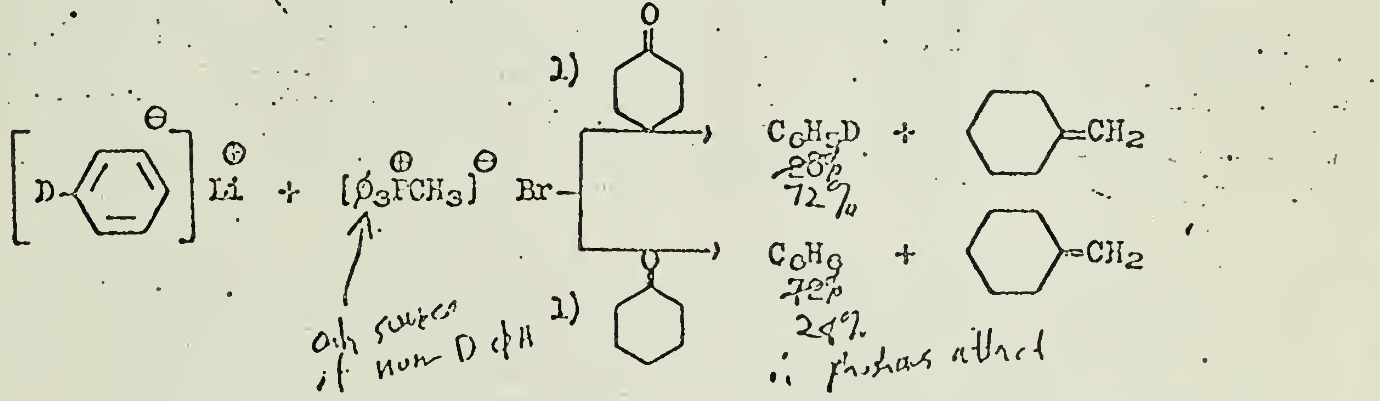
(1)



were occurring in the preparation of the Wittig reagent. If only attack at the α-hydrogen had occurred, benzene would not be expected as a product, yet a 20% yield of benzene was obtained based on the amount of methyllithium used.

In a similar manner the phosphinealkylidene developed in situ was quenched with cyclohexanone after the Gilman Color test[7] for methyllithium proved negative. Benzene was again formed in approximately 21% yield and methylenecyclohexane in 80% yield. Ethereal p-deuteriophenyllithium, 100% active, reacts with methyltriphenylphosphonium bromide to give a mixture of 28% deuterio-benzene and 78% non-deuterated benzene.[5] The 28% yield of C_6H_5D results from attack at phosphorous.

(2)



These results and previous data suggest major attack at the α-hydrogen but that significant attack also occurs at the phosphorous atom. When attack at phosphorous by the alkyllithium reagent occurs, either phenyllithium or benzene is displaced and after quenching the phosphinealkylidene intermediate with aqueous HBr, a mixture of phosphonium salts as shown in equations 3 and 4 would be expected. Attack at phosphorous by methyllithium would give dimethyldiphenylphosphonium bromide after quenching, while direct removal of the acidic α-hydrogen would regenerate the starting material after quenching. The expected ratio of the two different phosphonium salts based on the average yields of benzene obtained would be 3:1,

$$(3)\qquad [(\phi)_3\overset{\oplus}{P}CH_3]\overset{\ominus}{Br} + MeLi \longrightarrow \xrightarrow{HBr} [(\phi_3\overset{\oplus}{P}CH_3]\overset{\ominus}{Br} + CH_4 + LiBr$$

Phosphorus attack

$$(4)\qquad [(\phi)_3\overset{\oplus}{P}CH_3]\overset{\ominus}{Br} + MeLi \longrightarrow \xrightarrow{HBr} [(\phi)_2\overset{\oplus}{P}(CH_3)_2]\overset{\ominus}{Br} + \phi H + LiBr$$

$[(\phi)_3\overset{\oplus}{P}CH_3]\overset{\ominus}{Br}/[(\phi)_2\overset{\oplus}{P}(CH_3)_2]\overset{\ominus}{Br}$ assuming the rates of quenching with HBr would be much faster than equilibration.

The ratio of salts was determined quantitatively by infrared spectroscopy.[4] The infrared spectra of several mixtures of $[(\phi)_3\overset{\oplus}{P}CH_3]\overset{\ominus}{Br}$ and $[(\phi)_2\overset{\oplus}{P}(CH_3)_2]\overset{\ominus}{Br}$ obeyed Beer's Law. A comparison of authentic samples with a mixture prepared according to the previous data gave a ratio of 3.03 and a mole percent for $[(\phi)_2P(CH_3)_2]Br$ of 24%. These results show that significant attack does occur at the phosphorous atom, albeit astraction of the α-hydrogen is still the major product.

Having confirmed that two pathways are available for generation of the phosphinealkylidene and that one of the two modes involves attack on the phosphorous, Seyferth and his co-workers considered two possible mechanisms for replacement of the phenyl group on phosphorous.[4,5]

Mechanism I involves the loss of benzene from a phosphorous five coordinate intermediate.

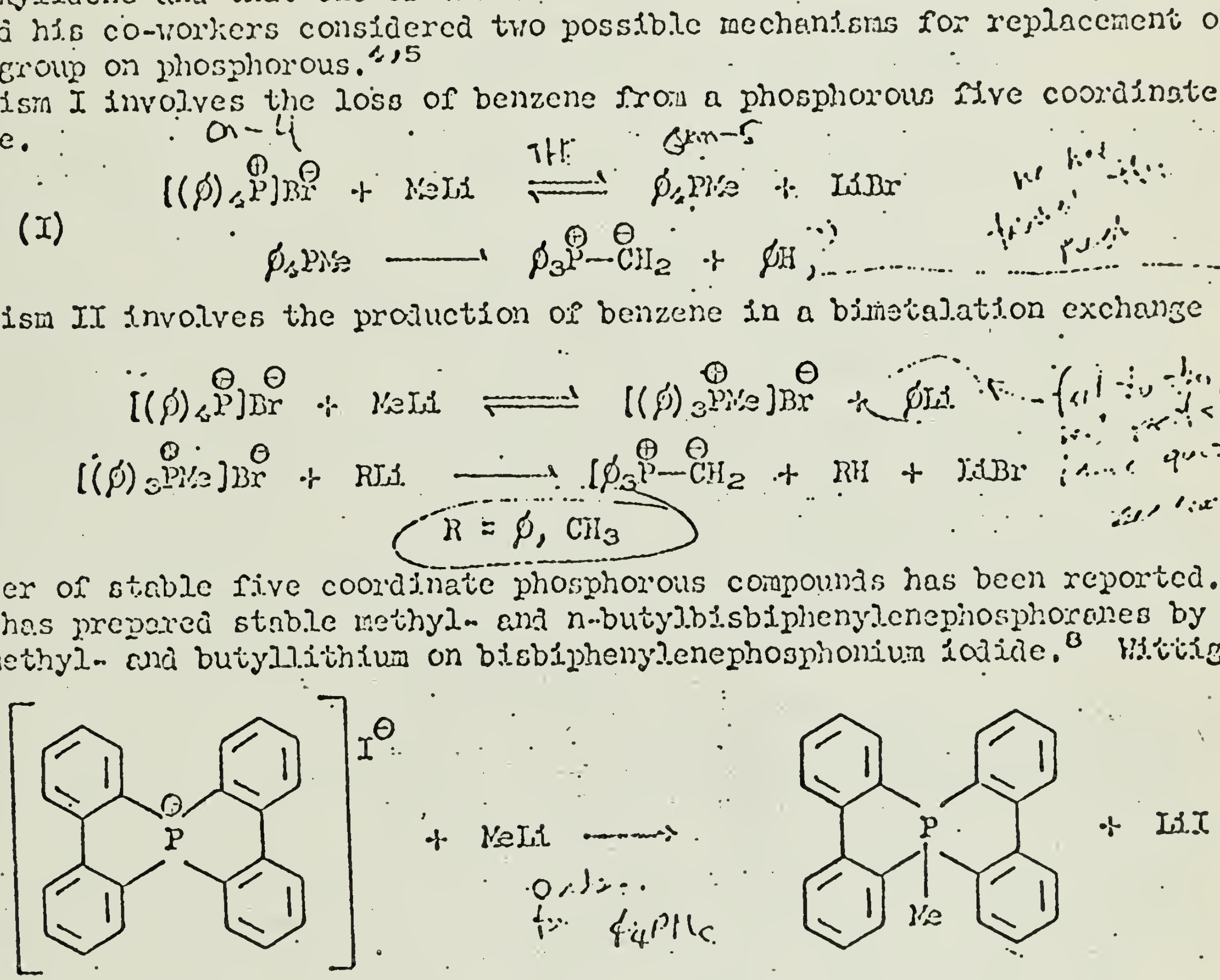
$$(I)\qquad \begin{array}{l} [(\phi)_4\overset{\oplus}{P}]\overset{\ominus}{Br} + MeLi \rightleftharpoons \phi_4PMe + LiBr \\ \phi_4PMe \longrightarrow \phi_3\overset{\oplus}{P}-\overset{\ominus}{C}H_2 + \phi H, \end{array}$$

Mechanism II involves the production of benzene in a bimetalation exchange reaction.

$$(II)\qquad \begin{array}{l} [(\phi)_4\overset{\ominus}{P}]\overset{\ominus}{Br} + MeLi \rightleftharpoons [(\phi)_3\overset{\oplus}{P}Me]\overset{\ominus}{Br} + \phi Li \\ [(\phi)_3\overset{\oplus}{P}Me]\overset{\ominus}{Br} + RLi \longrightarrow [\phi_3\overset{\oplus}{P}-\overset{\ominus}{C}H_2 + RH + LiBr \\ \qquad R = \phi,\ CH_3 \end{array}$$

A number of stable five coordinate phosphorous compounds has been reported. Hellwinkel has prepared stable methyl- and n-butylbisbiphenylenephosphoranes by the action of methyl- and butyllithium on bisbiphenylenephosphonium iodide.[8] Wittig and

(5)



Rieber have demonstrated the easy formation of pentaphenylphosphorane by the reaction of tetraphenylphosphonium bromide with phenyllithium in ether.[9] Wheatly has given added support for Seyferth's proposed mechanism I by providing X-ray crystal data on pentaphenylphosphorane,[10] which revealed that the phenyl groups are arranged about the phosphorous atom in a trigonal bipyramidal configuration. This evidence although only circumstantial has led Seyferth to favor mechanism I involving the five coordinated phosphorous intermediate.

The main difference between mechanism I and II is the production of benzene in mechanism I and of phenyllithium via mechanism II. In his earlier papers Seyferth cited his inability to trap the phenyllithium produced as evidence against mechanism II.[5] However in later experiments in which there was a very large excess of methyllithium present (10:1 ratio of methyllithium to tetraphenylphosphonium bromide), using trimethylchlorosilane as a trapping reagent for phenyllithium, as

$$(6)\qquad Me_3SiCl + \phi Li \longrightarrow Me_3Si\phi + LiCl$$

much as 31% trimethylphenylsilane was produced.[4] The yield was lowered considerably by decreasing the methyllithium present.

This could be taken as evidence for mechanism II since phenyllithium is in equilibrium with methyllithium in the first step of mechanism II. This did not provide conclusive evidence for or against either mechanism, according to Seyferth, because of the possibility of the intervention of hexaorganophosphorous intermediates. An alternative pathway for the production of phenyllithium other than mechanism II has been proposed.[5] Initially a pentaorganophosphorane may be formed, which could react with additional alkyllithium reagent to give a hexavalent anionic

$$(7)\qquad \phi_4PMe + MeLi \rightleftharpoons [\phi_4\overset{\ominus}{P}(Me)_2]\overset{\oplus}{Li}$$

species, equation 5, or could dissociate to give phenyllithium and triphenyl-

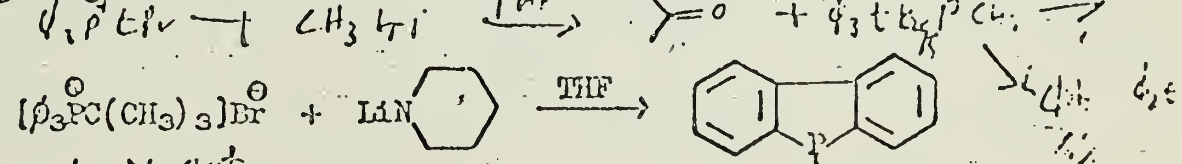
$$(8)\qquad [\phi_4\overset{\ominus}{P}(Me)_2]\overset{\oplus}{Li} \rightleftharpoons \phi Li + \phi_3PMe_2$$

dimethylphosphorane. This alternative pathway imposes an additional equilibria on mechanism I and the pentacoordinate phosphorous intermediate involved.

The present chemical evidence does not provide an answer to the mechanistic problem. However the use of P^{31} nmr may be of some help, if the reaction rate for the second step in each proposed mechanism and the rate of the reverse reaction in step two is slow enough to insure formation of a detectable amount of the intermediate species. If bimetalation exchange does occur by mechanism II the P^{31} nmr signal would show a change from the starting material $\overset{\oplus}{P}(\phi)_4$ to $\overset{\oplus}{P}(\phi)_3Me$. Whereas in mechanism I the change observed in the nmr signal would be to a five coordinate phosphorous intermediate, $P(\phi)_4Me$. The difference in chemical shifts for the neutral trigonal bipyramid and the ionic $\overset{\oplus}{P}(\phi)_3Me$ is large.[11a,b] For tetra-coordinated phosphorous compounds the range of chemical shifts with respect to orthophosphoric acid is approximately 100 ppm with the majority within 50 ppm. However large positive shifts with respect to the tetra-coordinated phosphorous atoms are found for the five substituted systems. For example, PCl_5 has a chemical shift of + 80 ± 2 ppm relative to orthophosphoric acid whereas the chemical shifts for tetra-substituted compounds are usually found at the maximum to be about 30 ppm. If detectable amounts of the intermediate are formed, the spectra should be well enough resolved to differentiate between the two possibilities.

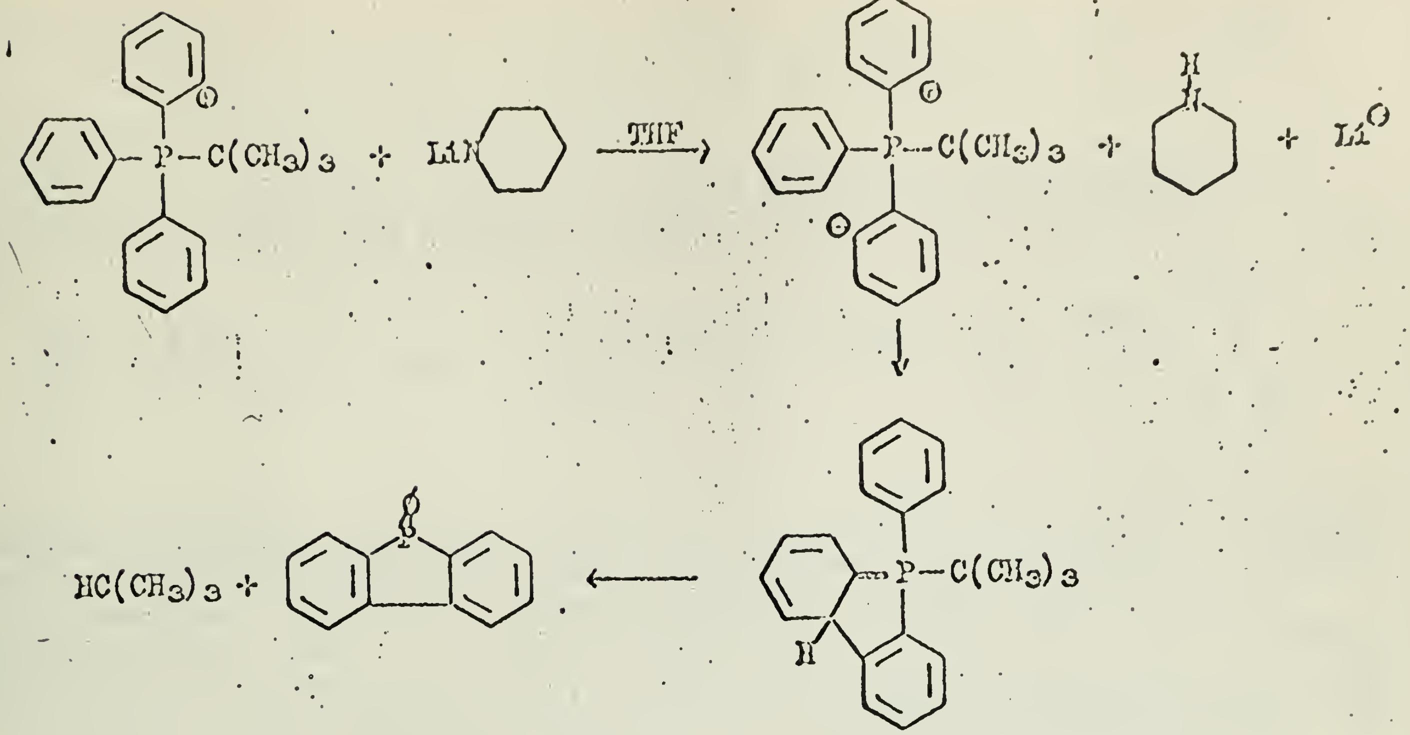
Although the sudy of the mechanisms has not been conclusive, further work into the reaction systems of phosphonium salts with organolithium reagents has been synthetically fruitful. In such systems as t-butyltriphenylphosphonium bromide attack at the α C-H linkage is no longer possible. The reactions of this compound with lithium piperidide, which could not form a phosphinealkylidene, has been reported.[12] The phosphonium salt is open to either attack at the t-butyl group with subsequent β elimination to give isobutylene or abstraction of the proton on the phenyl ring to give an ortho metalated product. The somewhat surprising

(9)



formation of 9-phenyl-9-phosphafluorene in 42.4% yield, while isobutylene was formed in 16% yield, is rationalized as proceeding by an ortho-metalated intermediate. The proposed mechanism involves the attack by the lithium reagent at the ortho proton and subsequent nucleophilic attack by the anionic center at the ortho position of an adjacent phenyl group with the loss of benzene. Thus in spite of the accessibility of the C-H linkages of the tert-butyl group and also the steric hindrance associated with the attack at the ortho position of the phenyl ring, the major product of the reaction is still the ortho-metalated product. It would appear steric factors are not a mjaor factor in determining the course of the reaction. In this connection 9-phenyl-9-phosphafluorene was also found as a by-product in the reaction of methyllithium with tetraphenylphosphonium bromide in

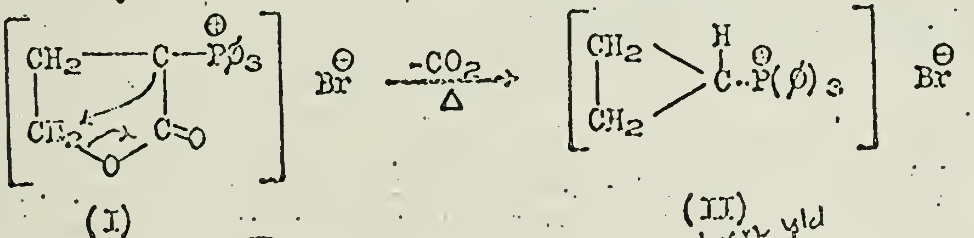
(10)



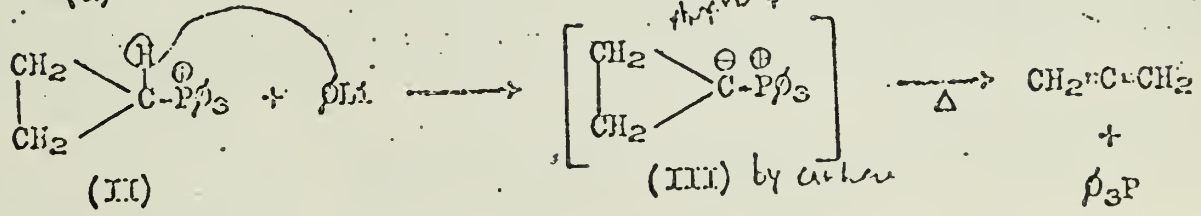
THF/ether medium[13] and also has been reported in small yields by phenylsodium metalation of triphenylphosphine.[1] Thus in systems where the arylphosphinealkyliden formation is not possible because of steric factors involved in the phosphonium salt and the lithium reagent, high yields of the ortho-metalated product may be expected.

Proton abstraction at the α position has led to numerous interesting reactions. Bestmann and Denzel have reported a novel route for the preparation of triphenylcyclopropylphosphonium bromide in good yield.[14] The synthesis is accomplished by thermal decomposition of the phosphonium salt (I). Treatment of (II) with phenyllithium leads to the triphenylphosphine-cyclopropylylid (III), which on thermal decomposition yields allene and triphenylphosphine.

(11)

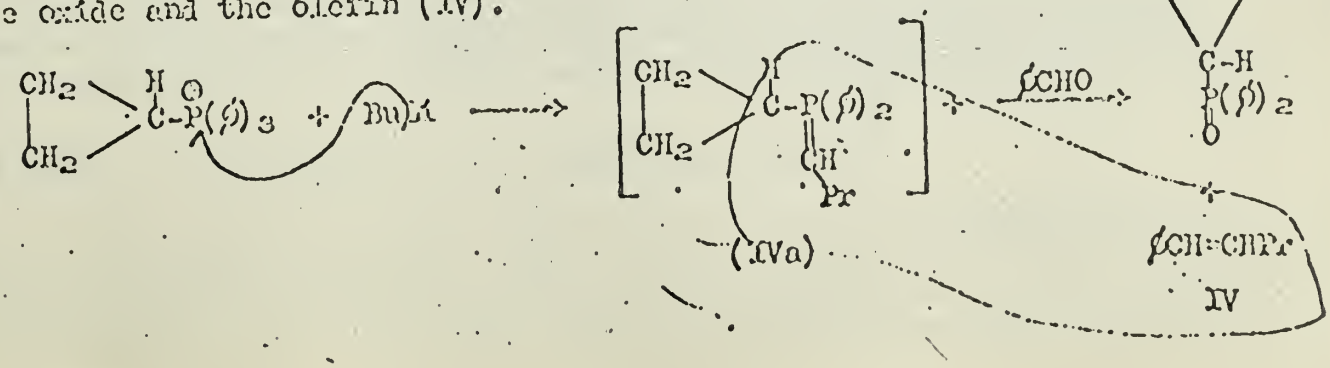


(12)



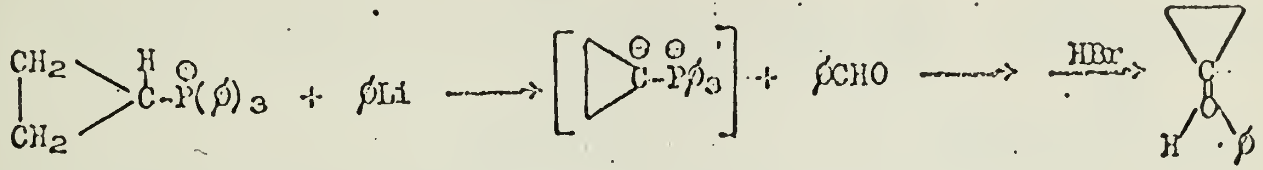
It may be noted that the same reaction with butyllithium attacks at the phosphorous with a subsequent loss of benzene to give an intermediate ylid species which undergoes the Wittig reaction with benzaldehyde to give diphenylcyclopropyl phosphine oxide and the olefin (IV).

(13)

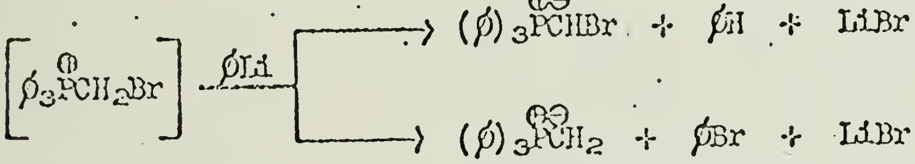


Although the two sets of data appear to be in conflict based on hydrocarbon acidities, the reactions would be consistent if the phenyllithium also attacked phosphorous. The only α-hydrogen available is on the cyclopropyl ring and therefore the product expected is the ylid III.

Bestmann has extended the reactions of the cyclopropyl ylid intermediate to prepare various derivatives, of which one is the cyclopropyl ring system (V), containing an exo-double bond structure proposed on the basis of unreported chemical shifts.

(14)

(V)

The use of phosphinealkylidene systems in preparing vinylic chloride compounds has been extended by Seyferth to include vinylic bromides and iodides.[15] To investigate the possible preparation of vinylic bromides or iodides, the action of phenyllithium on the bromo- or iodomethyltriphenylphosphonium halides was studied.[16] Quenching of the reaction mixture with cyclohexanone showed the presence of benzene 58%, bromobenzene 46%, methylenecyclohexane 46%, and bromomethylenecyclohexane 46% yield. The iodo system gave similar results but benzene and iodobenzene were

(15)

$$\left[\phi_3\overset{\oplus}{P}CH_2Br\right] \xrightarrow{\phi Li} \begin{cases} (\phi)_3\overset{\oplus\ominus}{P}CHBr + \phi H + LiBr \\ (\phi)_3\overset{\oplus\ominus}{P}CH_2 + \phi Br + LiBr \end{cases}$$

obtained in 26% and 73% yield respectively and methylenecyclohexane and (iodomethylene) cyclohexane in yields of 55% and 22% respectively. Thus, unlike the chloromethyl-system, the bromomethyl- and iodomethylphosphonium halides experience halide cation abstraction as well as proton abstraction by phenyllithium. This is in agreement with the known relative reactivities of carbon-halogen linkage toward organolithium reagents.[17] This work closely parallels the study of reactions between butyllithium and 1-halo-2-2-diphenylethylene systems, in which similar ratios of halide cation abstraction to proton abstraction were found.[18] No attempt was made to relate the proposed mechanism for the phosphinealkylidene work to the study of the ethylene system.

In order to obtain higher yields of the bromovinylic compounds, reactions were devised for generating the dihalo or monohalo-methylphosphinealkylidene <u>in situ</u> in the presence of the desired ketone. General yields up to 55% have been obtained for vinyl bromide systems. Benzaldehyde in the presence of tribromomethylphenylmercury and triphenylphosphine has produced the desired dibromo vinylic system in 50% yield. One possibility for the mechanism involves the carbene trapping by the phosphine as one discrete step and then reaction with the available carbonyl system to yield the vinylic halide. However a direct reaction of the carbonyl system with the intermediate phosphonium salt must also be considered.

(16) $$C_6H_5HgCX_2Br \longrightarrow CX_2 \xrightarrow{\phi_3P} (C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}X_2 \xrightarrow{RR'C=O} RR'C=CX_2$$

In further studies on the reactions of phosphinealkylidenes, nucleophilic displacement of halide ion from various group IV-B organometallic halides by triphenylphosphinemethylene was studied and formulated (equation 17).[19] However

(17) $$\phi_3\overset{\oplus}{P}-\overset{\ominus}{C}H_2 + (CH_3)_3SiBr \longrightarrow [\phi_3\overset{\oplus}{P}CH_2Si(CH_3)_3]Br^{\ominus}$$

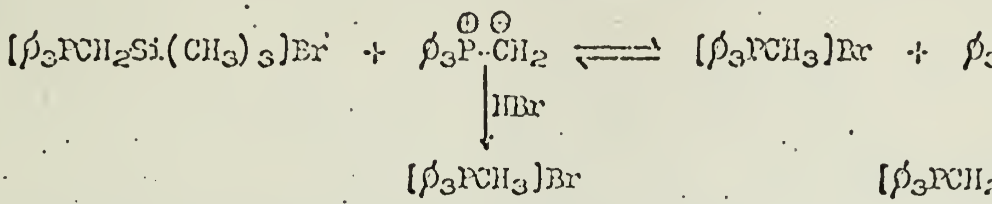
the purity of the product has always been suspect because of contamination by methyltriphenylphosphonium bromide. After Bestmann proposed that "trans-ylidation" occurs readily between a phosphinealkylidene and a phosphonium salt system,[20] Seyferth reinvestigated the triphenylphosphinetrimethylsilylmethylene system.[21]

(18) 

$$\phi_3\overset{\oplus}{P}\text{-}\overset{\ominus}{C}H_2 + [\phi_3PCH_2R]X \rightleftharpoons \phi_3\overset{\oplus\ominus}{P}CHR + [\phi_3PCH_3]X$$

R phenyl, acyl

An equilibrium involving two different phosphinealkylidene systems was shown by quenching with HBr and isolating the following products (equation 19).

(19) 

$$\begin{tikzcd}[\phi_3PCH_2Si(CH_3)_3]Br + \phi_3\overset{\oplus}{P}\text{-}\overset{\ominus}{C}H_2 \arrow[d, "HBr"] \arrow[r, shift left] & \arrow[l, shift left] [\phi_3PCH_3]Br + \phi_3\overset{\oplus\ominus}{P}CHSi(CH_3)_3 \arrow[d, "HBr"] \\ {[\phi_3PCH_3]Br} & {[\phi_3PCH_2Si(CH_3)_3]Br}\end{tikzcd}$$

Thus the original methods for the preparation of the triphenylphosphinemethylenetrimethylsilyl bromide was complicated by the competition of the unreacted trimethylbromosilane and the already formed triphenylphosphinemethylenetrimethylsilyl salt for the phosphinemethylene reagent as it was being added. The pure product was finally isolated by using a two to one excess of the phosphinemethylene reagent.

Apriori the electron withdrawing effect of the trimethylsilyl group would tend to destabilize the triphenylphosphinetrimethylsilylmethylene relative to the triphenylphosphinemethylene. One explanation of the unusual results of "transylidation" would involve Cp_π - Sid_π bonding. However Seyferth prefers to base the effect on steric and not electronic factors, since the triphenylphosphinemethylenetrimethylsilyl bromide is actually a "neopentyl" type system. The quaternary phosphorous and silicon centers should cause severe crowding of the methylene protons and thus these protons may be susceptible to removal. Two explanations were offered. One, the severe crowding may lead to elongation of the methylene C-H bond and therefore increase the acidity of the proton. The analogy cited in the literature for this "lengthening effect" was the decrease in the wave number of the N-H bond absorption in phosphoamides of the type $RR'P(=O)NHR''$,[21] as the bulk of the R'' group is increased, assuming the decrease in wave number parallels the increase in bond length. Second, any change in hybridization of the methylene carbon atom to place the electron pair in a p orbital would relieve strain by increasing the distance between the phosphine and silyl groups and also to allow the electron pair to back bond with the empty d orbitals on ~~silicon~~. phosphorus

In summary phosphinealkylidene systems provide novel routes to the synthesis of new and interesting compounds. Although the evidence for the proposed mechanisms has not proved conclusive all the observations have led to the conclusion that the type of attack the organolithium reagent choses is highly dependent on the electronic and steric factors present in the phosphonium salt as well as the organolithium base.

BIBLIOGRAPHY

1. G. Wittig and G. Geissler, Ann., 580, 44 (1953).
2. G. Wittig and U. Schollkopf, Chem. Ber., 87, 1318 (1954).
3. for reviews: S. Trippet, *Quarterly Reviews*, 17, 406 (1963); S. Trippet, "Advances in Organic Chemistry," Vol. 1; Interscience Pub., Inc., New York, 1960, pp. 83-102.
4. D. Seyferth, W. B. Hughes, and J. K. Heeren, J. Am. Chem. Soc., 87, 2848 (1965)
5. D. Seyferth, W. B. Hughes, and J. K. Heeren, J. Am. Chem. Soc., 84, 1764 (1962)
6. D. D. Coffman and C. S. Marvel, J. Am. Chem. Soc., 51, 3496 (1929).
7. W. Langham, R. Q. Brewster, and H. Gilman, J. Am. Chem. Soc., 63, 545 (1941).
8. D. Hellwinkle, Chem. Ber., 98, 576 (1965).
9. G. Wittig and M. Rieber, Ann., 562, 187 (1949).
10. P. J. Wheatly, J. Chem. Soc., 2206 (1964).
11. (a) J. R. Van Wazer, C. F. Callis, J. N. Shoolery, and R. C. Jones, J. Am. Chem. Soc., 78, 5715 (1956); (b) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press,

New York, 1966, Vol. 2, p. 1054.

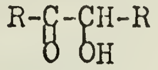
12. D. Seyferth, M. Eisert, J. K. Heeren, J. Organomet. Chem., 2, 101 (1964).
13. D. Seyferth, W. B. Hughes, and J. K. Heeren, J. Am. Chem. Soc., 87, 3467 (1965).
14. Hans-Jergen Bestmann and T. Denzel, Tetrahedron Letters, 3591 (1966).
15. D. Seyferth, S. O. Grim, and T. O. Read, J. Am. Chem. Soc., 82, 1510 (1960); 83, 1617 (1961).
16. D. Seyferth, J. K. Heeren, and G. Singh, J. Organomet. Chem., 5, 267 (1966).
17. R. G. Jones and H. Gilman, Org. Rxtns., 6, 342 (1951).
18. D. Y. Curtin and E. W. Flynn, J. Am. Chem. Soc., 81, 4714 (1959).
19. D. Seyferth and S. O. Grim, J. Am. Chem. Soc., 83, 1610 (1961).
20. Hans-Jergen Bestmann, Chem. Ber., 95, 58 (1962).
21. D. Seyferth and G. Singh, J. Am. Chem. Soc., 87, 4156 (1965).

ESR SPECTROSCOPY OF SEMIDIONES; DETERMINATION OF STRUCTURE AND CONFORMATION

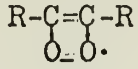
Reported by Buren Ree October 20, 1966

INTRODUCTION

Characteristic colors formed on exposure of basic solutions of aromatic acyloins (I, R=Ar) to oxygen were ascribed to semidione radical anions (II, R=Ar) by Michaelis and Fetcher.[1] In an earlier study of the oxidation of acyloins


$R-\underset{O}{\overset{}{C}}-\underset{OH}{CH}-R$

I

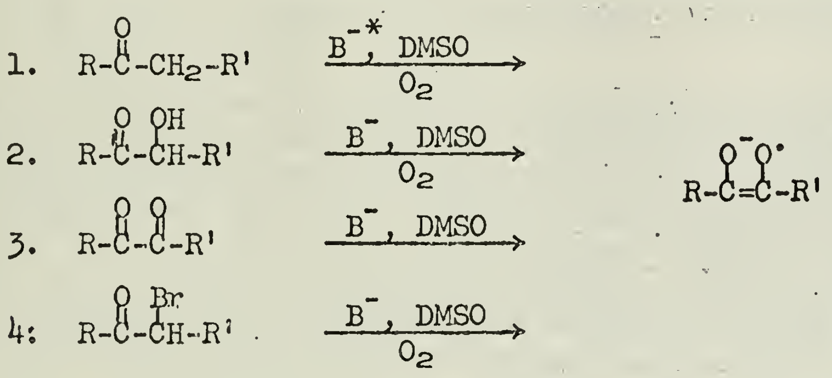

$R-\underset{O^-}{C}=\underset{O\cdot}{C}-R$

II

to their respective diketones, Weissberger and co-workers[2,3] described a similar species to be present in some of their solutions. Since then, these acylyls have received considerable study and their paramagnetic nature has been established.[4-7] The corresponding aliphatic and alicyclic radical anions have only recently been detected and identified.[8-11] This seminar will deal with the application of electron spin resonance spectroscopy to the determination of structure and conformation in some of these aliphatic and alicyclic semidiones.

ALIPHATIC SEMIDIONES

Solutions of the semidiones can be prepared by four general methods.

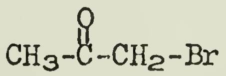


* B^- = tertiarybutoxide anion

Reaction 1 produces radicals in lower yields than any of the other three and is non-specific if there are two types of α-methylene groups. Preparation of the semidione via the α-bromoketone (reaction 4) allows the formation of radical anions from ketones that are not easily oxygenated in basic solution. For example, exposure of basic solutions of ketones or α-hydroxyketones where R is methyl (reactions 1 and 2) to oxygen usually fails to give the semidione. However, solutions of III and IV in DMSO containing an excess of potassium t-butoxide have been smoothly converted to the corresponding acylyls.[12] H. C. Heller produced


$CH_3-\overset{O}{\overset{\|}{C}}-\overset{Br}{CH}-CH_3$

III


$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-Br$

IV

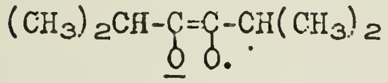
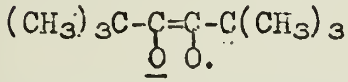
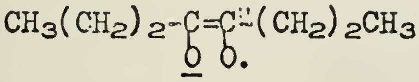
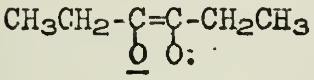
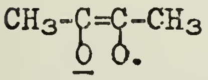
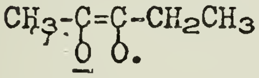
solutions of semidiones from the acyloins isobutyroin (R=R'= isopropyl) and pivaloin (R=R'= t-butyl) by irradiation of 0.5N NaOH/ethanol/water solutions.[10] Similar solutions of the non-sterically hindered butyroin (R=R'= n-propyl) readily produced octane-4,5-semidione without irradiation. G. A. Russell and co-workers found that aliphatic ketones other than methyl ketones readily oxidize under the conditions of method 1 to produce the corresponding semidiones.[11] The mechanism of formation of the semidione, while not yet established, has been proposed to involve intermediate formation of the diketone followed by electron transfer from some carbanion.[6,19]

Solutions of aliphatic semidiones are generally stable enough at room temperature that their electron spin resonance (e.s.r.) spectra can be determined at leisure. In some cases, flow techniques were utilized.[12] The observed hyperfine

splitting constants (h.f.s.c.) for several aliphatic semidiones are shown in Table 1.

Table 1

Hyperfine Splitting Constants Of Aliphatic Semidiones

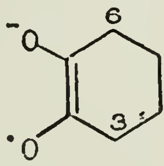
Radical	a^H (gauss)	Reference
 $(CH_3)_2CH-\underset{\underline{O}}{C}=\underset{O\cdot}{C}-CH(CH_3)_2$	2.1, α^*	10
 $(CH_3)_3C-\underset{\underline{O}}{C}=\underset{O\cdot}{C}-C(CH_3)_3$	0.28, β	10
 $CH_3(CH_2)_2-\underset{\underline{O}}{C}=\underset{O\cdot}{C}-(CH_2)_2CH_3$	4.82, α	10
 $CH_3CH_2-\underset{\underline{O}}{C}=\underset{O\cdot}{C}-CH_2CH_3$	4.68, α 0.22, β	11
 $CH_3-\underset{\underline{O}}{C}=\underset{O\cdot}{C}-CH_3$	6.06, α	11
 $CH_3-\underset{\underline{O}}{C}=\underset{O\cdot}{C}-CH_2CH_3$	5.96, CH_3 4.97, CH_2	11

* α refers to splitting by hydrogens on the carbon atom adjacent to the carbonyl carbon.

The h.f.s.c. for protons attached to a carbon atom adjacent to a carbon atom carrying a free electron are believed to satisfy the equation $a^H = B\,\rho\,\cos^2\Theta$, where Θ is the time averaged dihedral angle between the carbonyl carbon p_z orbital and the α-carbon-hydrogen bond, and ρ is the spin density on $C\pi$.[13,19] This angular dependence of h.f.s.c. has been used by Russell and co-workers to explain the differences in a^H among the aliphatic acylyls, butane-2,3-semidione (a^H=6.06 gauss), hexane-3,4-semidione (a^H=4.68), and the semidione derived from isobutyroin (a^H= 2.1).[11,19] Russell attributed the decrease in a^H to a decrease in the average value of $\cos^2\Theta$ corresponding to a preferred conformation of the alkyl substituent on the α-carbon atom in the more sterically hindered semidiones.

CYCLOHEXANONES

The electron spin resonance spectra of semidiones have found major application in the study of cyclohexanones, decalones, and related steroidal ketones. Russell and co-workers prepared cyclohexane-1,2-semidione (V) from a DMSO solution of



V

cyclohexanone and potassium t-butoxide on exposure to air and from cyclohexane-1,2-dione in the absence of oxygen. The e.s.r. spectrum of V at 25° consisted of a quintet (a^H= 9.83 gauss) with hyperfine splitting by four magnetically equivalent α-hydrogen atoms. Hyperfine splitting by β-hydrogens was not observed and must be less than 0.05 gauss under these conditions. Thus, at 25°, there is no evidence of conformational stability of the cyclohexene ring relative to e.s.r. frequency ($\sim 10^4$ M c.p.s.), corresponding to a conformational lifetime of less than 4×10^{-8} seconds. At slower rates of interconversion of axial and equatorial positions, a 1:2:1:2:4:2:1:2:1 (triplet of triplets) or 1:4:1 spectrum is expected.[14,22] The h.f.s.c. observed for a series of substituted cyclohexane-1,2-semidiones are shown in Table II. The geminally disubstituted semidiones, like the unsubstituted,

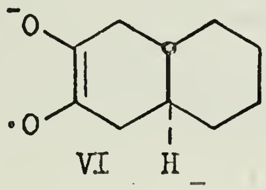
Table II

Hyperfine Splitting Constants for Substituted Cyclohexane-1,2-semidiones (gauss)

Radical	a^H, axial		a^H, equatorial
unsubsitututed		9.83	
3,3-dimethyl		9.74	
4,4-dimethyl		9.74 (C_6-H) 9.41 (C_3-H)	
4-t-butyl	13.02		6.64
4-isopropyl	12.63		7.02
4-methyl	12.33		7.34
3-methyl	11.15 (C_6-H) 10.29 (C_3-H)		8.56

show no conformational stability. 3,3-Dimethylcyclohexane-1,2-semidione gives a 1:2:1 triplet splitting by two equivalent hydrogen atoms at C_6. The 4,4-dimethyl derivative gives a five multiplet spectrum from splitting by two pairs of magnetically nearly equivalent hydrogens at C_3 and C_6.

For semidiones derived from monosubstituted cyclohexanones, the alkyl substituent should favor a quasi-equatorial position. Thus, 4-t-butylcyclohexanone gives a radical with two pairs of magnetically non-equivalent α-hydrogen atoms, two primarily quasi-axial and two quasi-equatorial. Differences in h.f.s.c. due to chemical non-equivalence of the two α-methylene groups were not resolved. From the observed h.f.s.c. for monosubstituted semidiones, Russell and co-workers have calculated conformational preferences for the alkyl substituent.[15] To do this they determined the axial and equatorial h.f.s.c. for α-hydrogen atoms in the model, trans-Δ^2-decalin semidione (VI). This acylyl has a frozen conformation



VI

and gives $a^H = 13.18$ gauss for axial hydrogens and $a^H = 6.59$ gauss for equatorial hydrogens. These values they assumed to be equal to hyperfine splittings by purely quasi-axial and quasi-equatorial α-hydrogen atoms respectively. Also inherent in the calculation are the assumptions that alkyl substituents will not affect these h.f.s.c. and that only half chair conformers are involved. The fraction of semidione existing in the conformation with quasi-equatorial alkyl substituent (x) can then be calculated from the following equations:

$$\text{observed } a^H\text{ax.} = 13.18\,(x) + 6.59\,(1-x)$$

$$\text{observed } a^H\text{eq.} = 6.59\,(x) + 13.18\,(1-x)$$

The results of this calculation are shown in Table III. The low conformational

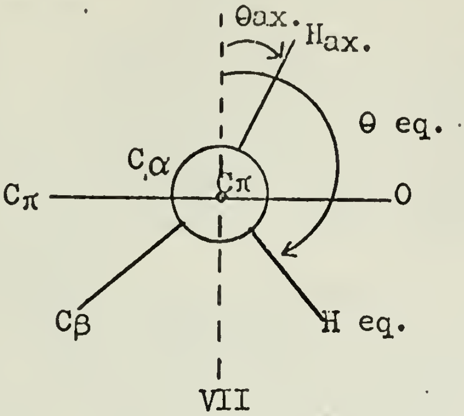
Table III

Conformational Preferences For Substituted Cyclohexane-1,2-semidiones.

Substituent	Percent of molecules with equatorial substituent 1*	2*
4-t-butyl	98	99
4-isopropyl	92	93
4-methyl	87	89
3-methyl	69	70

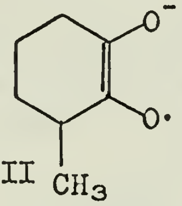
*1-Calculated from a^Haxial
2-Calculated from a^Hequat.

preference shown by the 3-methyl semidione has been attributed to eclipsing of the methyl group in the equatorial position and the oxygen atom on carbon-2.[15] This conclusion is supported by conformational studies on 1,6-disubstituted cyclohexenes.[16] The larger h.f.s.c. have been assigned to axial hydrogen atoms on a consideration of dihedral angles (fig. VII).

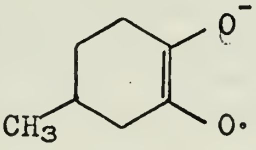


VII

The foregoing concepts have been applied by Russell and co-workers to distinguishing the three isomeric methylcyclohexanones.[15,17] 2-Methylcyclohexanone, on oxidation in DMSO containing an excess of potassium t-butoxide, gives the 3-methylcyclohexane-1,2-semidione (VIII) with an eight line spectrum due to the three non-equivalent hydrogen atoms. The 4-methyl ketone produces 4-methylcyclohexane-1,2-semidione (IX) and its spectrum consists of a 1:2:3:4:3:2:1 heptet (overlapping triplet of triplets) indicating splitting by two pairs of equivalent hydrogen atoms. 3-Methylcyclohexanone gives a mixture of the above two radical anions and its spectrum is readily distinguished as a composite spectrum of the two semidiones.



VIII



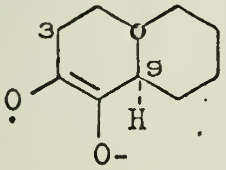
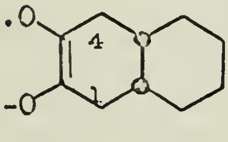
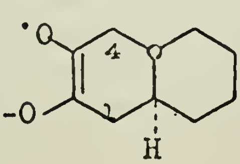
IX

DECALONES

Oxidation of cis-2-decalone and trans-2-decalone gives rise to mixtures of semidiones X and XI (ratio 1.5:1), and X and XII (1:3) respectively. Trans-2-

Table IV

Hyperfine Splitting Constants Of Semidiones From 1- And 2-Decalones

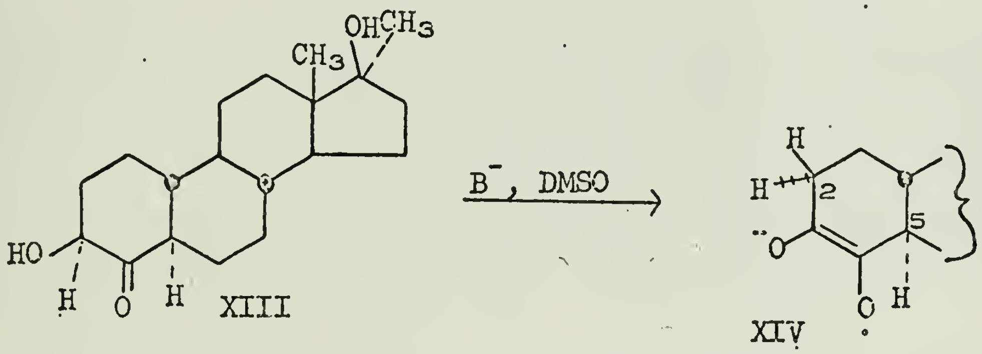
Radical	a^H (gauss)	
X 	12.66, 13.17	C_3-H_{ax} C_9-H_{ax}
	7.09	(C_3-H_{eq})
XI 	13.83, 12.72	C_1-H_{ax} C_4-H_{ax}
	7.37, 6.55	C_1-H_{eq} C_4-H_{eq}
XII 	13.18, 13.18	(C_1-H_{ax}, C_4-H_{ax})
	6.59, 6.59	(C_1-H_{eq}, C_4-H_{eq})

decalone produces a Δ^2-semidione (XII) containing two pairs of magnetically equivalent hydrogen atoms whereas cis-2-decalone produces a Δ^2-semidione (XI) with four magnetically non-equivalent hydrogens (11-16 line spectrum). Thus a distinction can be made between decalones with cis and trans ring junctures by examination of the e.s.r. spectrum of the Δ^2-semidione without reference to model compounds.[15] Semidione X has been assigned the trans structure on the basis of its production from both the cis and trans ketones and epimerization at C-9 may arise from the intermediacy of the 1,2-diketone. To further define the observed splitting in X, Russell oxidized cis-9-methyl-2-decalone to produce a Δ^1 and a Δ^2 radical anion. The Δ^1 isomer has hyperfine splitting by two different hydrogen atoms, $a^H = 12.95$ and 7.11 gauss, assigned to quasi-axial and quasi-equatorial hydrogens on C-3, respectively. This lends support to the assignment of the larger h.f.s.c. in X to the two "axial" hydrogens.

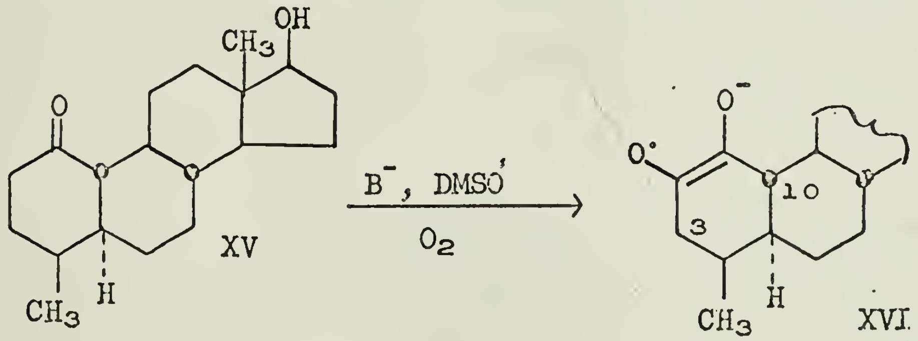
Exposure of a basic solution of cis-1-decalone in DMSO to oxygen yields a single radical anion, X, whose low resolution e.s.r. spectrum is a 1:1:2:2:1:1 sextet, corresponding to two nearly equivalent hydrogen atoms (quasi-axial at C-3, C-9) and one magnetically different hydrogen (quasi-equatorial at C-3). The h.f.s.c. observed at higher resolution are shown in Table IV.

STEROIDS

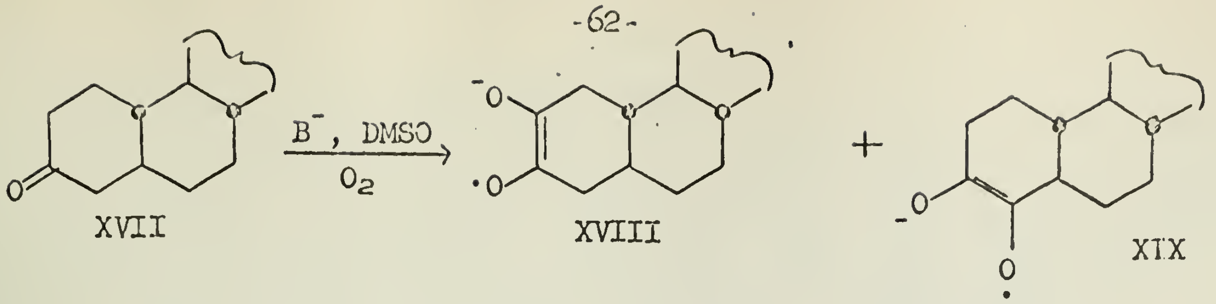
The information gleaned from studies of 1- and 2-ketodecalins can be applied to a large number of ketosteroids.[15,17,18] 1-, 4-, 15-, and 17a-ketones in the 19-nor and 18-nor-D-homo series of steroids produce a single radical anion analogous to X with hyperfine splitting by three hydrogen atoms, two of which are magnetically nearly equivalent or often equivalent. For example, 17α-methyl-19-nor-5α-androstane-3β, 17β-diol-4-one (XIII) on treatment with potassium t-butoxide in DMSO in the absence of air, produces the 3,4-semidione (XIV) which exhibits a 1:1:2:2:1:1 sextet splitting under low resolution.



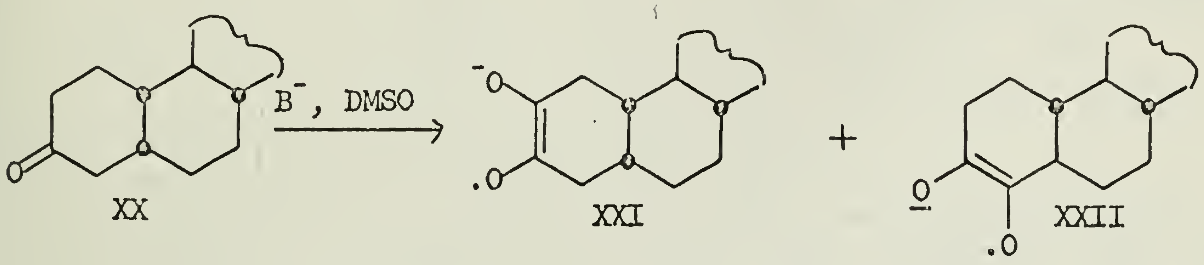
Oxidation of 4β-methyl-19-nor-5α-androstan-17β-ol-1-one (XV) produces the $\Delta^{1(2)}$ acylyl XVI whose e.s.r. spectrum indicates hyperfine splitting by three non-equivalent hydrogen atoms.

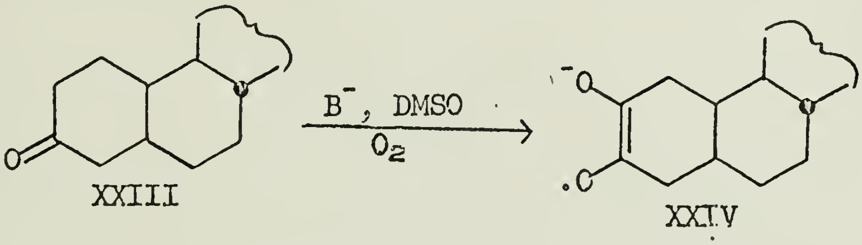


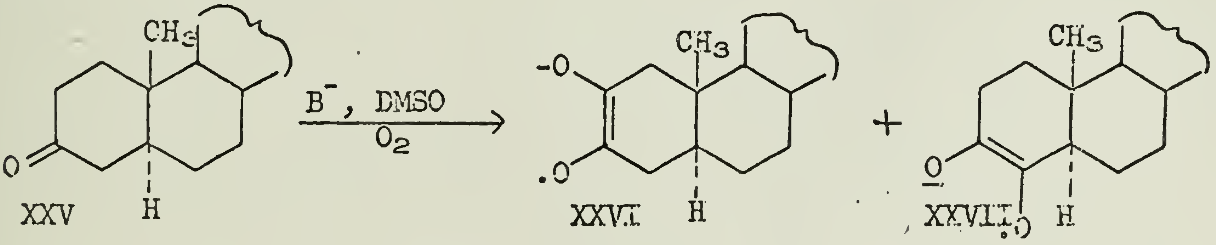
19-Nor-3-keto and 18-nor-D-homo-17-keto steroids are similarly comparable to 2-decalones. Formation of a Δ^2 (or Δ^{16}) acylyl with a triplet of triplets or heptet (due to overlap) spectrum will be characteristic of a trans A/B or C/D ring juncture whereas a 11-16 line spectrum will be characteristic of a cis ring juncture. 19-Nor-5α, 10β-androstan-17β-ol-3-one (XVII) on oxidation produces the Δ^2 and Δ^3 semidiones XVIII and XIX in a ratio of seven to one. The e.s.r. spectrum of XVIII is a 1:2:3:4:3:2:1 heptet, consistent with a trans



A/B ring juncture. 17β-Acetoxy-19-nor-5β, 10β-androstan-3-one (XX) gives rise to acylyls XXI and XXII (1:1.5). The minor radical XXI is present in sufficient quantity to identify it as an acylyl with a cis ring fusion due to the presence of 13-16 lines. 17β-Acetoxy-19-nor-5α, 10α-androstan-3-one (XXIII) gives exclusively the Δ^2 acylyl XXIV. Thus, cis-β ring junctures can be distinguished from cis-α ring junctures (e.g. XX) by the presence or absence of the Δ^3 acylyl. Certain substituent effects can be useful in assigning structures to keto steroids. For example, substitution of a 10β-methyl group in 5α-3-keto steroids increases the selectivity of oxidation at C-2 versus C-4. Oxidation of trans-2-decalones gives Δ^2 and Δ^1 acylyls in a ratio of 3:1, XVII gives Δ^2 and Δ^3 acylyls in a ratio of 7:1, and 10β-methyl-5α-3-keto steroids (XXV) give Δ^2 (XXVI) and Δ^3 (XXVII) acylyls in a ratio of 19:1.







SUMMARY

Oxidation coupled with e.s.r. spectroscopy can be used to define the position of the carbonyl function and alkyl substituents in cyclohexanones, decalones, and steroidal derivatives. It also allows establishment of the nature of ring fusions in these compounds. Russell and co-workers have utilized the angular dependence of h.f.s.c. for hydrogens on carbon atoms adjacent to the dicarbonyl system to calculate the time averaged dihedral angles for these hydrogens in a series of alicyclic semidiones.[8] Conformational preferences for certain aliphatic semidiones have been calculated from a similar analysis.[11,19] The above technique has also been used in a study of long-range e.s.r. splittings in rigid bicyclic semidiones.[20,21]

BIBLIOGRAPHY

1. L. Michaelis and E. S. Fetcher Jr., J. Am. Chem. Soc., 59, 1246 (1937).
2. A. Weissberger, E. Strasser, H. Mainz, and W. Schwarz, Ann., 478, 112 (1930).

3. A. Weissberger, Ber., 65B, 1815 (1932).
4. B. Venkataraman and G. K. Fraenkel, J. Am. Chem. Soc., 77, 2707 (1955).
5. J. L. Ihrig and R. G. Caldwell, ibid., 78, 2097 (1956).
6. G. A. Russell, E. G. Jantzen, and E. T. Strom, ibid., 84, 4155 (1962).
7. R. Dehl and G. K. Fraenkel, J. Chem. Phys., 39, 1793 (1963).
8. G. A. Russell and E. T. Strom, J. Am. Chem. Soc., 86, 744 (1964).
9. G. R. Luckhurst and L. E. Orgel, Mol. Phys., 7, 297 (1964).
10. H. C. Heller, J. Am. Chem. Soc., 86, 5346 (1964).
11. E. T. Strom, G. A. Russell, and R. D. Stephens, J. Phys. Chem., 69, 2131 (1965).
12. G. A. Russell, R. D. Stephens, and E. R. Talaty, Tetrahedron Letters, 1139 (1965).
13. C. Heller and H. M. McConnell, J. Chem. Phys., 32, 1535 (1960).
14. S. Owaga and R. W. Fessenden, ibid., 41, 994 (1964).
15. E. R. Talaty and G. A. Russell, J. Am. Chem. Soc., 87, 4867 (1965).
16. E. W. Garbish, J. Org. Chem., 27, 4249 (1962).
17. G. A. Russell and E. R. Talaty, Science, 148, 1217.
18. G. A. Russell and E. R. Talaty, J. Am. Chem. Soc., 86, 5345 (1964).
19. G. A. Russell, E. T. Strom, E. R. Talaty, and S. A. Weiner, ibid., 88, 1998 (1966).
20. G. A. Russell and K. Y. Chang, ibid., 87, 4381 (1965).
21. Ibid., 4383 (1965).
22. R. W. Fessenden and R. H. Schuler, J. Chem. Phys., 39, 2147 (1963).

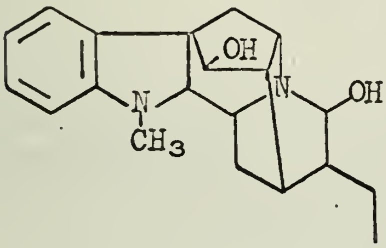
THE BIOSYNTHESIS OF INDOLE ALKALOIDS

Reported by Joel L. Kirkpatrick October 24, 1966

INTRODUCTION

The discovery of the pharmacological activity of reserpine in 1952 and the dramatic increase in efficiency of structural determination by means of infrared, nuclear magnetic resonance and mass spectroscopic analysis as well as the single crystal x-ray technique, have greatly accelerated investigations of indole alkaloid bearing plants. During the past ten years, the biosynthesis of indole alkaloids has been studied by the use of isotopically labeled precursors.

The recent interest in alkaloid biosynthesis has been shown by the relatively large number of reviews on the subject in the past five years,[1-5] with a brief summary by Taylor[6] devoted entirely to the origin of indole alkaloids. This seminar will deal with the three main classes of indole alkaloids; ajmaline (I), ajmalicine (II), and serpentine (II, ring C aromatized) from the Yohimbe family, catharanthine (III) and ibogaine (IV) from the Iboga family, and vindoline (V) and 1,2-dehydroaspidospermidine (VI) from the Aspidosperma family. Experimental evidence indicates these structurally diverse compounds are formed from common biosynthetic precursors.



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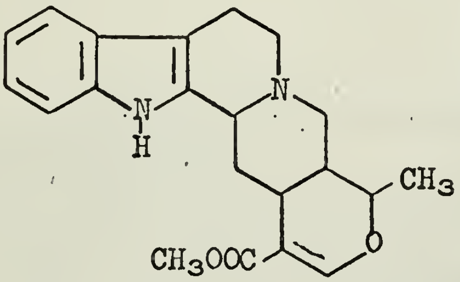

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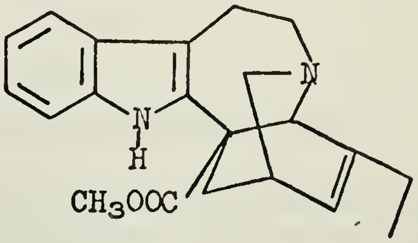

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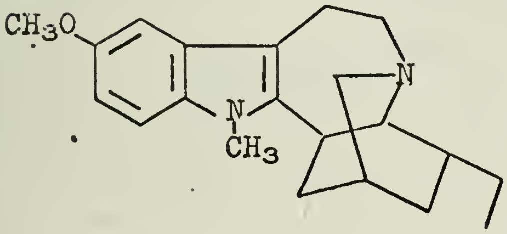

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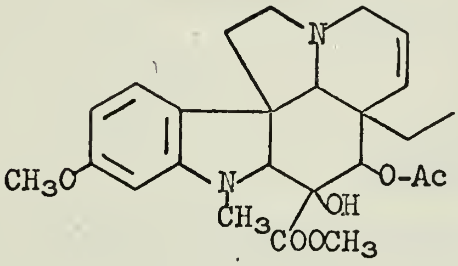

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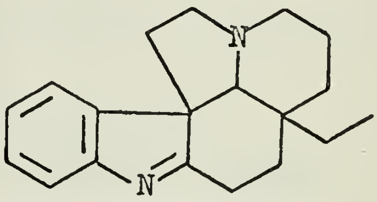
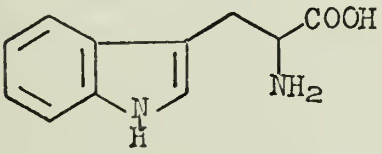


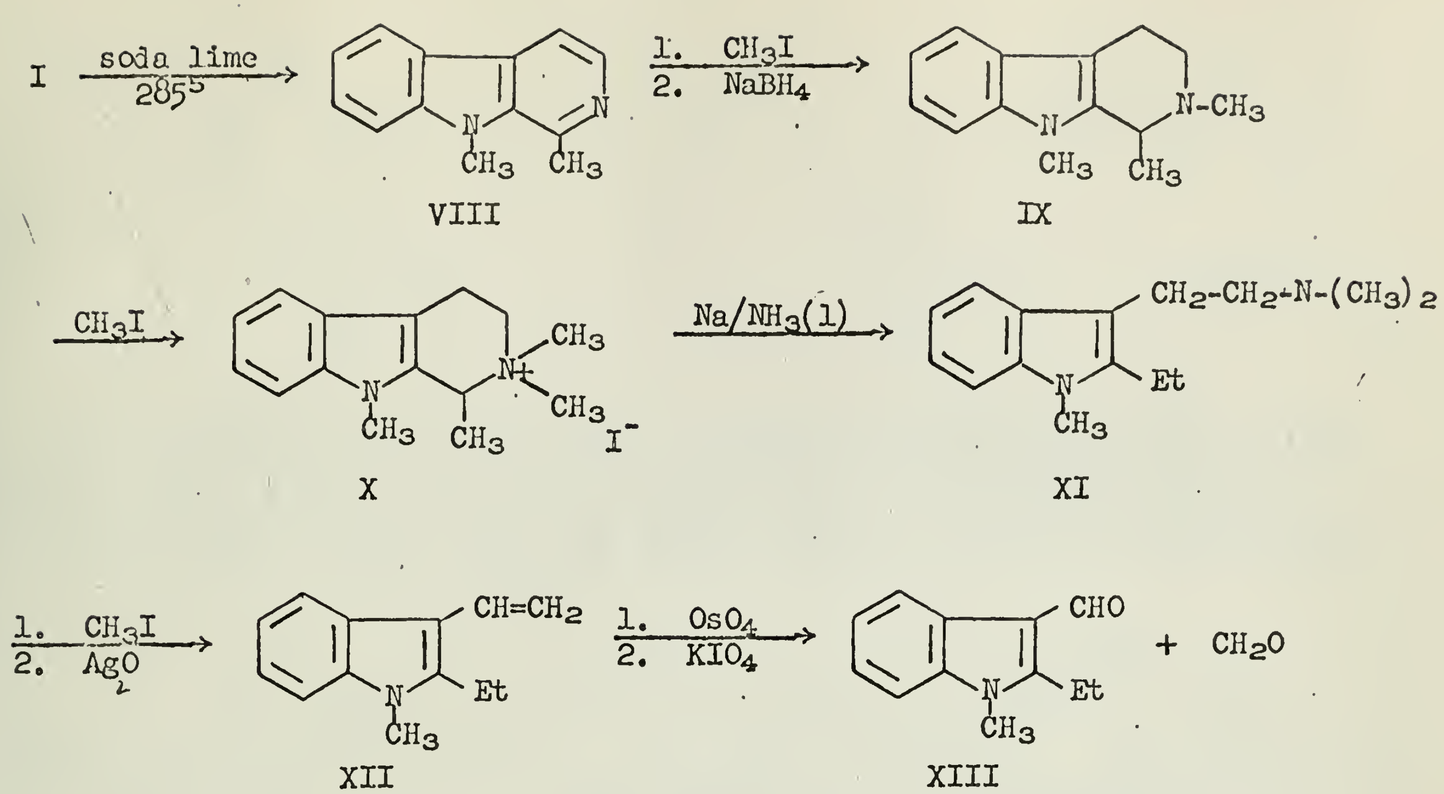
VI

THE TRYPTOPHAN DERIVED PORTION

It has long been assumed in the discussions of the biosynthesis of indole alkaloids that rings A and B and part of ring C were derived from tryptophan (VII) or its decarboxylated product, tryptamine,[7-10] but this was not substantiated by feeding experiments until 1960.[11] Leete administered tryptophan-2-^{14}C to *Rauwolfia serpentina* plants by the cotton wick method and isolated radioactive ajmaline (I) 45 days later. Degradation to locate the position of the label was carried out. I was treated with soda lime at 285° to give ind-N-methyl-harman (VIII),[12] which was treated with methyl iodide and then reduced to IX. Quaternization of IX gave X which, when subjected to Emde reduction (Na/liq. NH_3) gave XI; methylation followed by Hoffman elimination gave 1-methyl-2-ethyl-3-vinylindole, (XII). This was reacted with osmium tetraoxide and the resulting glycol was cleaved with potassium periodate to give formaldehyde, isolated as the crystalline dimedone derivative, and 1-methyl-2-ethyl-3-formylindole, (XIII).



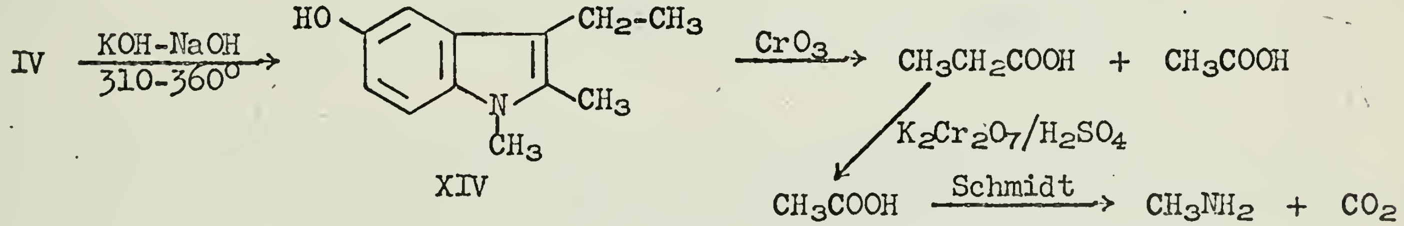
VII



Essentially 100% of the label was found in the formaldehyde derivative which corresponds to C-5 in the intact alkaloid.

In 1961 Leete showed that tryptophan-2-^{14}C was incorporated into serpentine (II, ring C aromatized)[13] and that the label was in the 5 position as expected.

DL-Tryptophan-3-^{14}C was fed to 5 month old Tabernanthe iboga plants and harvested 3 weeks later,[14] to give radioactive ibogaine (IV). Fusion with KOH-NaOH at 310-360° gave XIV in 4.2% yield.[15] Oxidation with 30% CrO_3 gave a mixture of acetic and propionic acids. After separation, the propionic acid was



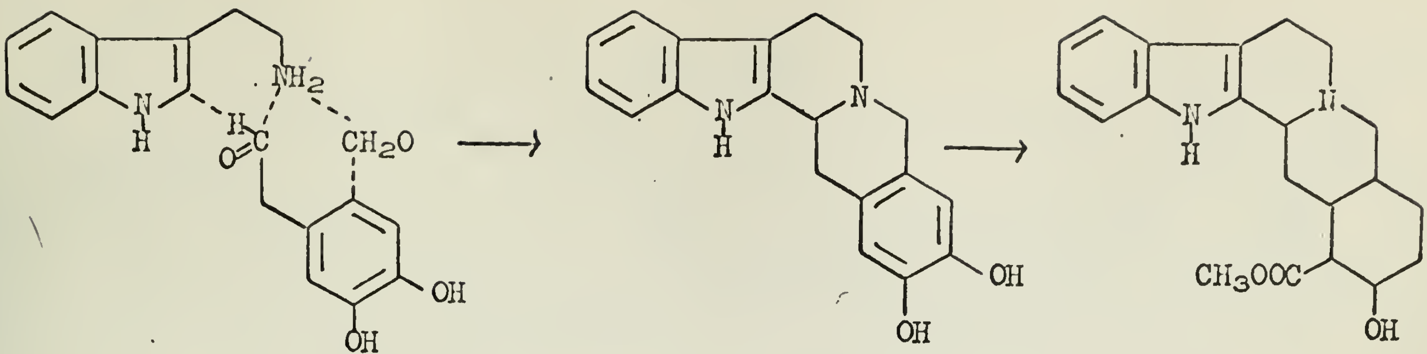
oxidized to acetic acid with $K_2Cr_2O_7$ in H_2SO_4 which was then subjected to the Schmidt reaction to give CO_2 (collected as $BaCO_3$) with 77% of the activity of ibogaine and CH_3NH_2 (isolated as the N-methylbenzamide derivative) with no activity.

The aspidospermine type alkaloid, vindoline (V), was isolated from Vinca rosea plants which were fed DL-tryptophan-2-^{14}C[16] and using the initial key step in the degradation to ind-N-methylnorharmine,[17] was shown by a route analogous to the one previously described for ajmaline, that C-10 in the intact alkaloid was derived from C-2 of tryptophan.

THE MONOTERPENE DERIVED PORTION

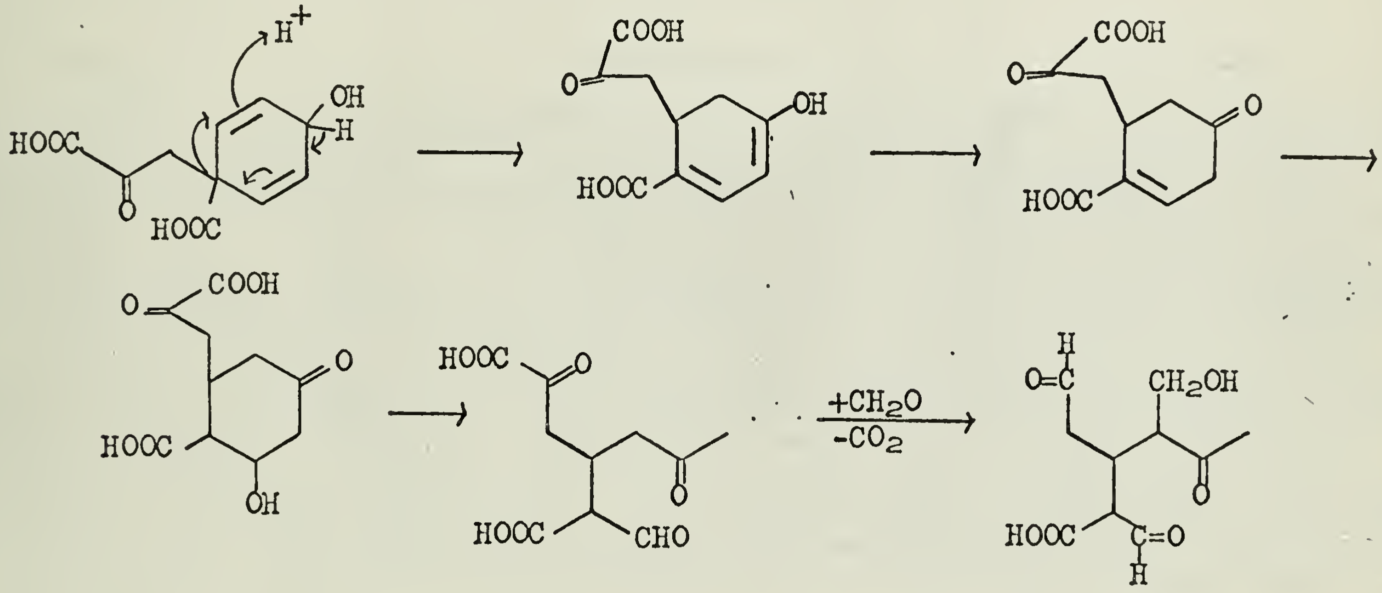
In contrast to the general agreement concerning the origin of the β-(2-aminoethyl) indole moiety in indole alkaloids, the origin of the C_{9-10} group that makes up the rest of the carbon skeleton (D and E rings) has been under considerable debate. Four major hypotheses have been offered; the Barger-Hahn theory[7,8] later modified by Woodward (Woodward fission),[18] the prephenic acid theory,[19] the acetate-formate-malonate theory,[20] and the monoterpene theory.[21,22]

In the Barger-Hahn theory, Yohimbine (XV) would be derived from tryptophan, dihydroxyphenylalanine and formaldehyde or their biological equivalents.



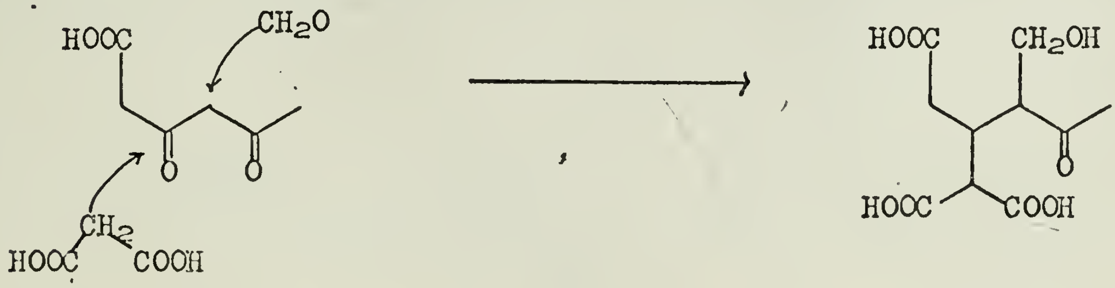
XV

In the prephenic acid theory, Wenkert suggested that prephenic acid could undergo a stereospecific rearrangement, hydration and retroaldolization to give a structural unit similar to the C_{9-10} portion found in the Yohimbe alkaloids. Addition of formate or some other one carbon fragment and loss of CO_2 would give XVI which has the formally correct structure.



XVI

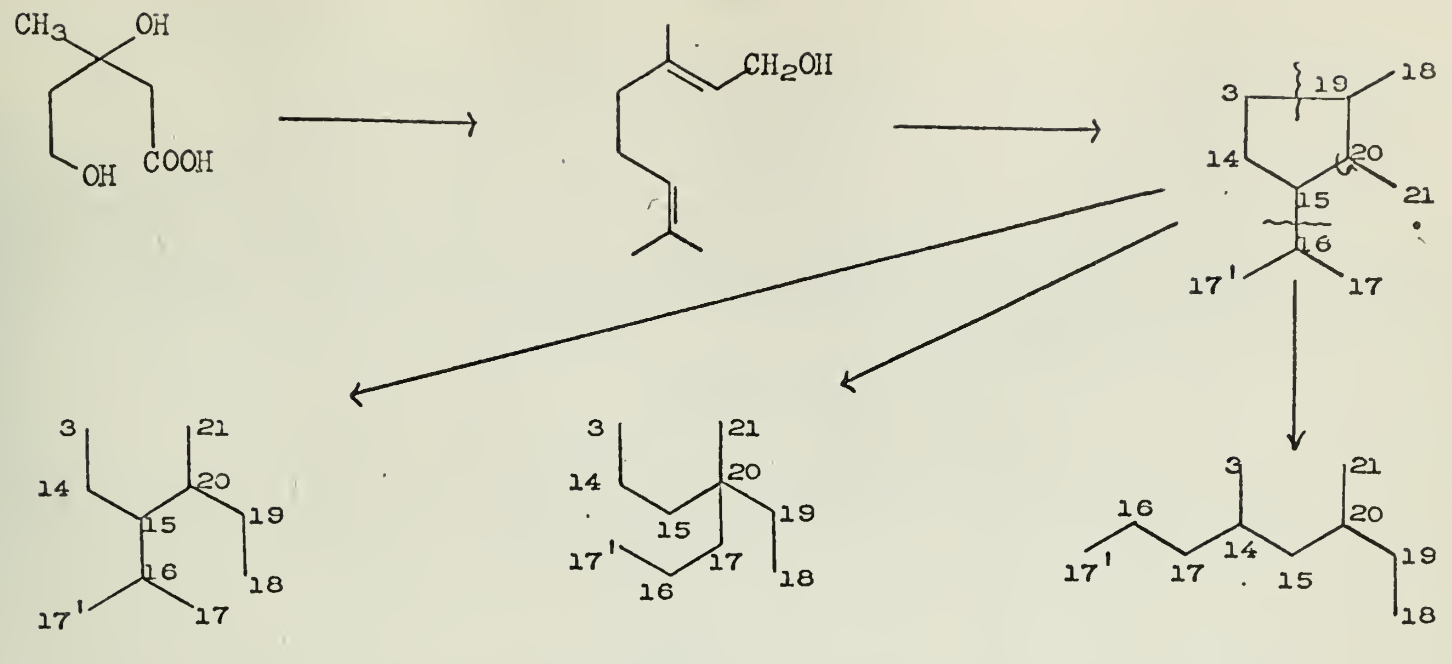
The acetate-formate-malonate theory would require three acetate units to be linked in a linear chain with the condensation of formate and malonate in the desired manner.



These three pathways require the addition of formate to complete the structure of the presumed precursor.

After some initial confusing results concerning the acetate-formate-malonate theory,[23-25] it was eliminated from consideration as a possible pathway by several groups of workers.[26-29] Other work showed that the Barger-Hahn theory was probably incorrect[29] and another cast serious doubts on the prephenic acid theory.[30]

The monoterpene theory does not depend upon formate but is derived from two units of mevalonic acid to give a monoterpene, presumably through geraniol, which could then cleave and rearrange to the C_{9-10} portion of all the indole alkaloids under consideration.

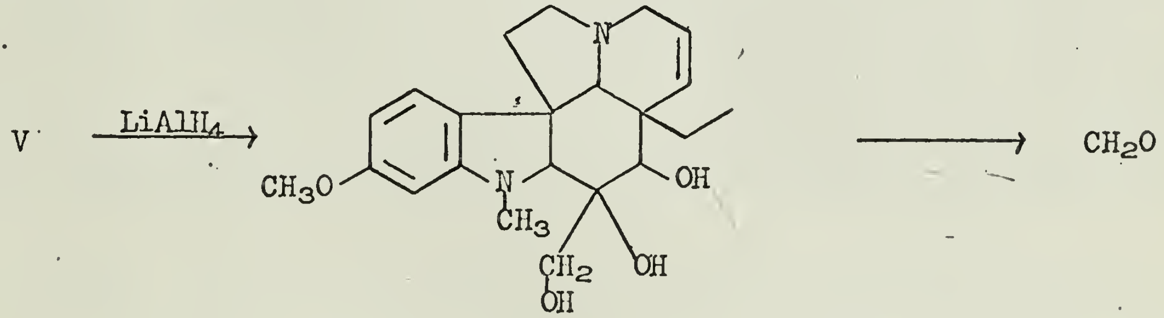


Yohimbe Aspidosperma Iboga

Evidence in favor of this pathway has been presented almost simultaneously by three groups of workers.[31a,32,33] Just prior to these disclosures, Scott and coworkers[31b] reported the incorporation of radioactivity into vindoline (V) when melvalonic acid lactone-2-^{14}C was administered hydroponically to freshly cut shoots of 3 month old V. rosea. This stands in contrast to a previous report that no label was detected in ajmaline when mevalonic acid-2-^{14}C was fed to R. serpentina.[24]

LeMen and Taylor[34] have proposed a uniform numbering system for indole alkaloids, based on biogenetic considerations, and the formation of the C_{9-10} units from mevalonic acid labeled in various positions may be considered in terms of this numbering system. If mevalonic acid-2-^{14}C is fed, 50% of the label should appear at C-3 and 25% should appear at both C-17 and C-17'. The C-2 and C-6 of one mevalonate have become equilibrated in the transformation to monoterpene and become C-17 and C-17'. This distribution of label has been observed in the biosynthesis of plumiericin.[35] If mevalonic acid-3-^{14}C is fed, half of the label should appear at C-16 and half at C-19.

When dl-mevalonic acid lactone-2-^{14}C[31a] or sodium dl-mevalonate-2-^{14}C[32] were fed to V. rosea, radioactive vindoline (V) was isolated. Hydrolysis to desacetyl vindoline showed no decrease in activity which indicated no radioactivity had been introduced into the acetate function by degradation of mevalonate. Lithium aluminium hydride reduction gave vindolinol (XVII) with the



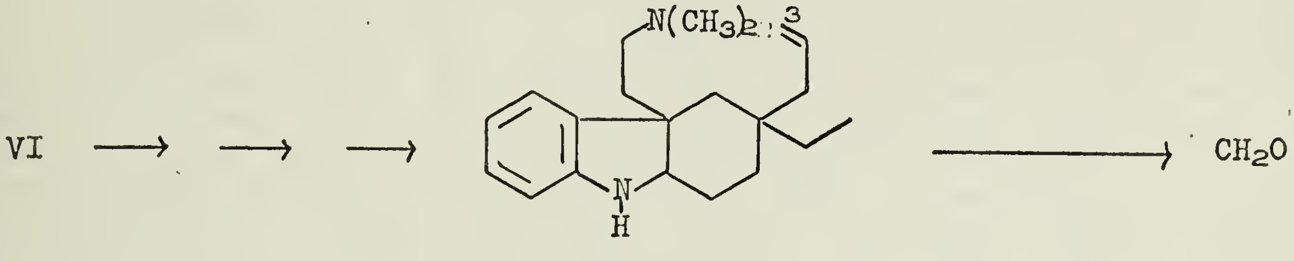
XVII

same specific activity showing there was no incorporation in the ester methyl group. Periodic acid oxidation gave formaldehyde, C-17', as its dimedone derivative that had 22% of the radioactivity which corresponds very favorably to the 25% expected if the monoterpene theory is correct.[31a]

Goeggel and Arigoni[32] reported identical results for C-17' and showed that the O-CH_3 and N-CH_3 groups isolated by Zeisel determination as well as propionic acid from Kuhn-Roth oxidation of the ethyl side chain were free of activity. These

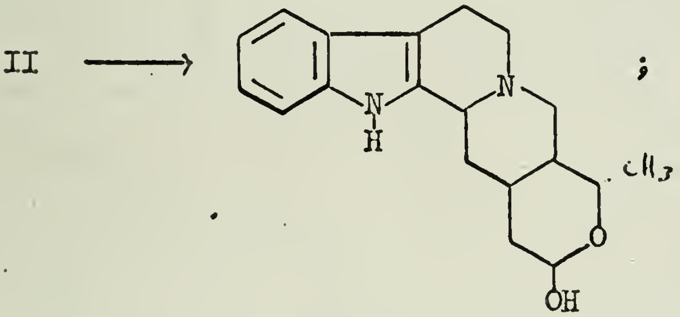
results are expected if the monoterpene theory is correct, i.e., C-18, 19, and 20 should be radioinactive.

Battersby and co-workers[33] carried out an extensive study on alkaloids of all three classes. Their results with 1,2-dehydroaspidospermidine (VI), isolated from Rhazia stricta plants fed with sodium-dl-mevalonate-2-^{14}C, were identical to those of Arigoni concerning C-18, 19, and 20 of vindoline. They extended this study by degrading the dihydro derivative of VI by Emde and Hoffman steps[36] to the base XVIII, then determining the activity at C-3 by oxidizing to formaldehyde. It was found to contain 65 ± 6% of the total activity which is very close to the expected value of 67% if there was no scrambling. (C-17' was lost during the formation of VI.)

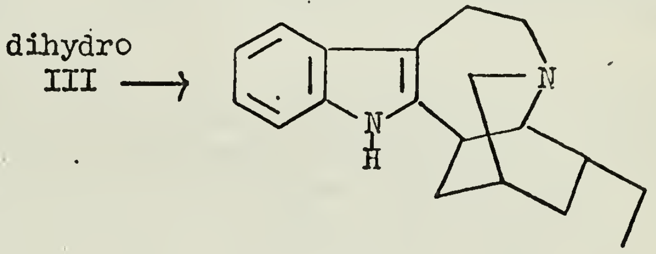


XVIII

Isolation of radioactive ajmalicine (II) and catharanthine (III), when V. rosea was fed sodium-dl-mevalonate-2-^{14}C, was followed by Zeisel determination to show that no significant label was present in the O-CH_3 groups. Elimination of the methoxycarbonyl group from II to give XIX[19b] and from the dihydro derivative of III to give XX[37] showed that C-17' of each contained 24 and 23% of the label respectively.



XIX



XX

Kuhn-Roth oxidation of III gave inactive propionic acid consistant with no label at C-18, 19, and 20. Dehydration of III over palladium[37] gave 3-ethylpyridine with 48% of the total activity, indicating that half of the activity was located at C-3, 14, 15, or 21, or a combination of locations, and that 29%, by difference, was located on C-16 or 17. These results are consistant with the monoterpene theory which requires C-17' to have 25%, C-17 to have 25% and C-3 to have 50% of the label.

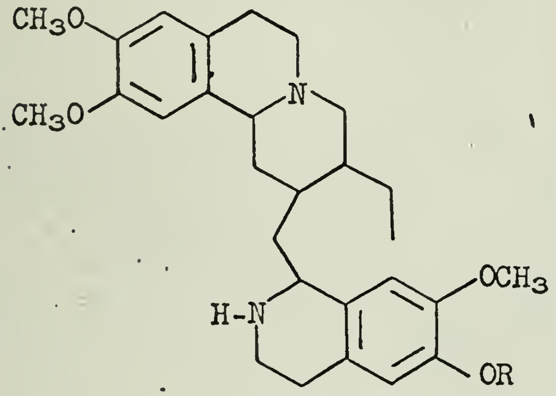
When 1,2-dehydroaspidospermidine was isolated from plants fed sodium-dl-mevalonate-3-^{14}C and was reduced, then oxidized by Kuhn-Roth method, acetic and propionic acids were isolated, each having 47% of the total activity. Schmidt reaction on acetic acid gave methylamine with no activity which would indicate C-18 and 20 to be essentially inactive and C-19 to carry one-half of the total activity. The proposed pathway predicts 50% of the activity to be on C-19 and the other 50%, on C-16.

Since mevalonic acid has been shown to be a direct precursor to the C_{9-10} unit of indole alkaloids, and geraniol is a known product of head-to-tail combination of two mevalonate units,[38] then geraniol should be the C_{10} precursor to the monoterpene unit. Three groups simultaneously published the results of feeding geraniol-2-^{14}C[39-41] to V. rosea plants. The incorporation of label was much higher than had been obtained when sodium mevalonate was fed under the same conditions. Ajmalicine (II), catharanthine (III) and vindoline (V) were isolated. Kuhn-Roth oxidation of both catharanthine and desacetyl vindoline gave mixtures of radioinactive acetic acid and propionic acid that contained nearly 100% activity. This further strengthens the monoterpene theory as being correct since it predicts all the activity to be at C-20.

Scott and co-workers[41] also fed 5-$^{2}H_2$-mevalonic acid lactone and 1-$^{2}H_2$-geraniol to V. rosea in separate experiments and studied the mass spectrum of the purified vindoline isolated from each case. They reported no enrichment of peaks known to be from tryptophan derived fragments[42] but an average of 1.6% enrichment of peaks from fragments containing portions of the C_{9-10} unit.[42] They concluded that this result was consistent with the monoterpene theory and that the low enrichment values were meaningful.

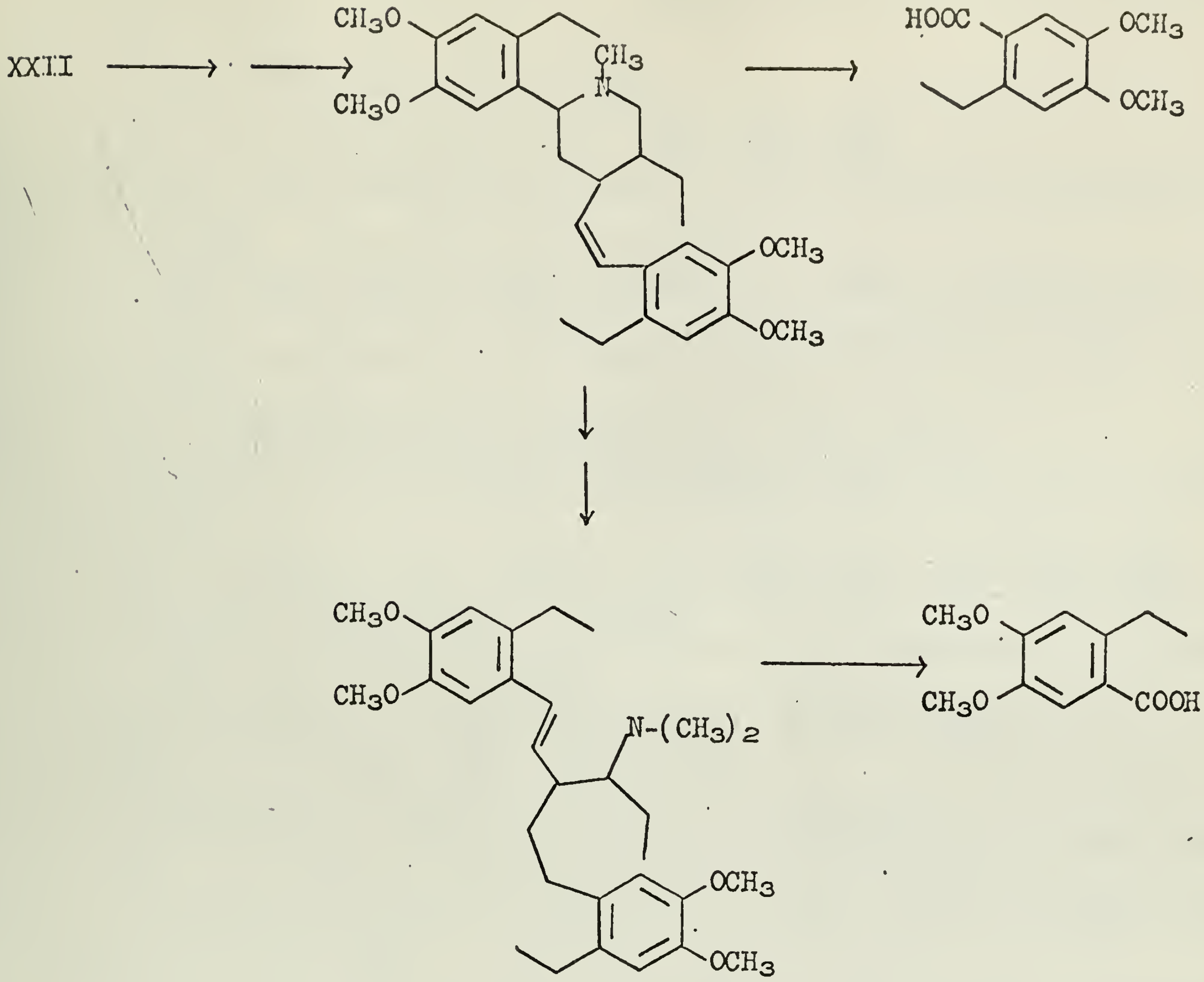
The correct pathway might have been worked out sooner except for some very convincing results supporting the acetate-formate-malonate theory. In 1961 and 1962, Leete and co-workers[23-25] published experimental results which completely verified this theory and reported no incorporation of label in ajmaline (I) isolated from R. serpentina fed with mevalonic acid-2-^{14}C.[24] They reported[23] that when sodium formate-^{14}C was fed to R. serpentina, radioactive ajmaline was isolated and on degradation that 12% of the activity was at C-21. Later,[24] sodium acetate-1-^{14}C, when fed to the same plant, gave active ajmaline. Kuhn-Roth oxidation gave radioactive acetic acid which was subjected to the Schmidt reaction and gave active CO_2, 26% of the total activity, and inactive methyl amine. This would mean C-19 was about 25% labeled. Treatment with soda lime gave active ind-N-methyl harman which gave active acetic acid after Kuhn-Roth oxidation; the acetic acid gave active CO_2, 25% of the total activity, using the Schmidt reaction. This would mean C-3 was labeled about 25%. This would eliminate mevalonate as a precursor because it should be labeled at C-14, 16, 19, and 21, and would support the acetate-formate-malonate theory. Still later[25] confirmation of these results were obtained by degrading serpentine (II, ring C aromatized) and finding radioactivity where expected. When malonic acid-1,3-^{14}C was fed R. serpentina and active serpentine isolated, Kuhn-Roth oxidation gave inactive acetic acid but Schmidt reaction on serpentine acid showed 48% of the total activity present at C-17'.

The first indication that the work described above was probably not correct came from Battersby's group,[26] when it was reported that sodium acetate-1-^{14}C was fed to R. serpentina and Cephaelic ipecacuanha, ajmaline (I) and cephaeline (XXI) were isolated respectively, and shown by Kuhn-Roth oxidation to give acetic and propionic acids with random scatter of label. It was also found when sodium formate-^{14}C, methionine-methyl-^{14}C[27] or methionine-methyl-(^{3}H)[28] were fed, most of the label went to the N-CH_3 or O-CH_3 groups, and only very low scatter or no activity was found at C-21. At this time Leete, Ahmad and Kompis[16] published results which confirmed the idea that the acetate-formate-malonate hypothesis was incorrect. They restudied the major alkaloids isolated from R. serpentina fed sodium acetate-1-^{14}C and found extensive scrambling had occurred. Kuhn-Roth oxidation of desacetyl vindoline gave acetic and propionic acids uniformly labeled, as did the same reaction with catharanthine. These results indicate the label of acetate-1-^{14}C has entered the general metabolic pool involving carbohydrates and the probable precursor of the C_{9-10} unit may be closely related to intermediates involved in carbohydrate metabolism.



XXI (R=H)
XXII (R=CH_3)

Battersby and co-workers[29] found that in cephaeline (XXI) almost uniform scattering had occurred when C. ipecacuanha was fed sodium acetate-1-^{14}C. In addition to this, they eliminated the Barger-Hahn theory by feeding tyrosine-2-^{14}C and performing the necessary degradations to locate the radioactivity. Even though cephaeline is an isoquinoline alkaloid, the similarity to the Yohimbe indole alkaloids is apparent and most of the workers in the field believe there is a common origin of the C_9 unit in both. Cephaeline was isolated and converted to emetine (XXII) with diazomethane, then degraded by known methods used in determining the structure.[43] The 6-ethylveratric acids contained about 95% of the total activity and both gave almost inactive CO_2 by the Schmidt reaction.



Kuhn-Roth oxidation, then Schmidt reaction showed all the activity to be at position 3 and 3'. The Barger-Hahn theory requires one-third of the activity to be at position 1', on the carboxyl group from the 6-ethyl-veratric acid from the F ring.

The prephenic acid theory has, in effect, already been eliminated, since it has been shown that a one carbon unit does not enter into the structure directly, i.e., C-21 in ajmaline (I). Further proof was presented by Stolle, Gröger, and Mothes[44] who fed (U-^{14}C) shikimic acid to *V. rosea* and isolated radioactive vindoline (V) and catharanthine (III). When vindoline was treated by the usual degradative procedures, no activity was found in the C_{10} portion. Over 90% of the activity was located in the aromatic part of the indole nucleus, which indicates that shikimic acid went into the shikimic-prephenic-aromatic amino acid pathway.

CONCLUSION

The evidence published to date strongly indicates that the biosynthetic formation of indole alkaloids is by a condensation of tryptophan, or its biological equivalent, with a monoterpene derived from mevalonic acid. These results are consistent with the biosynthesis of another class of indole alkaloids, the ergot group, where the precursors were shown to be tryptophan and mevalonic acid.[45] It may now be considered that the indole alkaloids are, in this respect, a new class of terpenes.

BIBLIOGRAPHY

1. A. R. Battersby, Quart. Rev. (London), 15, 259 (1961).
2. E. Leete in P. Bernfield, "Biogenesis of Natural Compounds," Pergamon Press, Oxford, 1963, p. 768.
3. K. Mothes and H. R. Schütte, Angew. Chem. internal. Edit. 2, 341, 441 (1963).

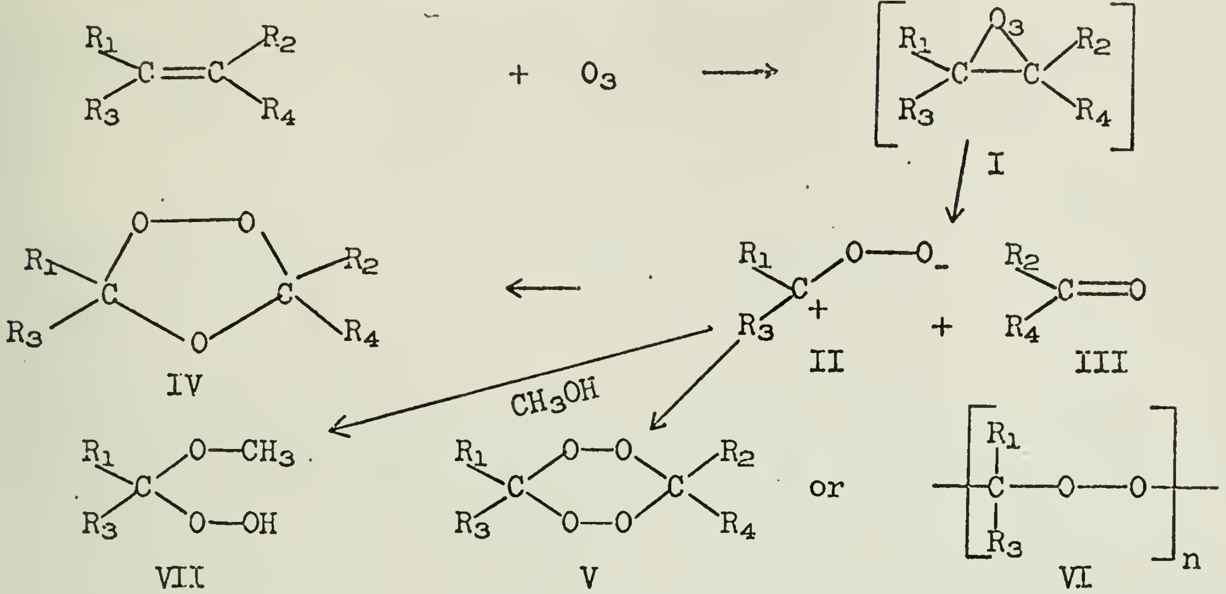
4. A. R. Battersby in "Biogenesi delle Sostanze Naturali," Accademia Nationale dei Lincei, Roma, 1964, p. 47.
5. E. Leete, Science, 147, 1000 (1965).
6. W. I. Taylor, Science, 153, 954 (1966).
7. G. Barger and C. Scholz, Helv. Chim. Acta., 16, 1343 (1933).
8. G. Hahn and H. Werner, Liebigs Ann., 520, 123 (1935).
9. R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955.
10. R. B. Woodward, Angew. Chem., 68, 13 (1956).
11. a) E. Leete, Chem. and Ind., 692 (1960); b) E. Leete, J. Am. Chem. Soc., 82, 6338 (1960).
12. F. A. Anet, D. Chakravart, R. Robinson, and E. Schlittler, J. Chem. Soc., 1242 (1954).
13. E. Leete, Tetrahedron, 14, 35 (1961).
14. M. Yamsaki and E. Leete, Tetrahedron Letters, 1499 (1964).
15. E. Schlittler, C. A. Burckhordt, and E. Gellert, Helv. Chim. Acta., 36, 1337 (1953).
16. E. Leete, A. Ahmad, and I. Kompis, J. Am. Chem. Soc., 87, 4168 (1965).
17. M. Gorman, N. Neuss, and K. Bieman, J. Am. Chem. Soc., 84, 1058 (1962).
18. R. B. Woodward, Nature, 162, 155 (1948).
19. a) E. Wenkert, Experientia, 15, 165 (1959); b) E. Wenkert and N. V. Bringi, J. Am. Chem. Soc., 81, 1474 (1959).
20. E. Schlittler and W. I. Taylor, Experientia, 16, 244 (1960).
21. R. Thomas, Tetrahedron Letters, 544 (1961).
22. E. Wenkert, J. Am. Chem. Soc., 84, 98 (1962).
23. P. N. Edwards and E. Leete, Chem. and Ind., 1666 (1961).
24. E. Leete, S. Ghosal, and P. N. Edwards, J. Am. Chem. Soc., 84, 1068 (1962).
25. E. Leete and S. Ghosal, Tetrahedron Letters, 1179 (1962).
26. A. R. Battersby, R. Binks, W. Lawrie, G. V. Parry, and B. R. Webster, Proc. Chem. Soc., 369 (1963).
27. H. Goeggel and D. Arigoni, Experientia, 21, 369 (1965).
28. D. H. R. Barton, G. W. Kirby, R. H. Prager, and E. M. Wilson, J. Chem. Soc., 3990 (1965).
29. A. R. Battersby, R. Binks, W. Lawrie, G. V. Parry, and B. R. Webster, J. Chem. Soc., 7459 (1965).
30. K. Stolle, D. Gröger, and K. Mothes, Chem. and Ind., 2065 (1965).
31. a) F. McCapra, T. Money, A. I. Scott, and I. G. Wright, Chem. Comm., 537 (1965); b) T. Money, I. G. Wright, F. McCapra, and A. I. Scott, Proc. Nat. Acad. Sci., U.S.A., 53, 901 (1965).
32. H. Goeggel and D. Arigoni, Chem. Comm., 538 (1965).
33. A. R. Battersby, R. T. Brown, R. S. Kapil, A. O. Plunkett, and J. B. Taylor, Chem. Comm., 46 (1966).
34. J. LeMen and W. I. Taylor, Experimentia, 21, 508 (1965).
35. D. A. Yeowell and H. Schmid, Experientia, 20, 250 (1964).
36. H. Conroy, P. R. Brooks, M. K. Rout, and N. Silverman, J. Am. Chem. Soc., 80, 5178 (1958).
37. N. Neuss and M. Gorman, Tetrahedron Letters, 206 (1961).
38. A. White, P. Handler, and E. Smith, "Principles of Biochemistry," McGraw-Hill Book Company, Inc., New York, 1964, p. 471.
39. A. R. Battersby, R. T. Brown, J. A. Knight, J. A. Martin, and A. O. Plunkett, Chem. Comm., 346 (1966).
40. P. Loew, H. Goeggel, and D. Arigoni, Chem. Comm., 347 (1966).
41. E. S. Hall, F. McCapra, T. Money, K. Fukumoto, J. R. Hanson, B. S. Mootoo, G. T. Phillips, and A. I. Scott, Chem. Comm., 348 (1966).
42. H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry. Vol. 1; Alkaloids," Holden-Day, San Francisco, 1964, and references found therein.
43. A. R. Battersby and H. T. Openshaw, J. Chem. Soc., 3207 (1949); and references found therein.

44. K. Stolle, D. Gröger, and K. Mothes, Chem. and Ind., 2065 (1965).
45. A. J. Birch, B. J. McLouglin, and H. Smith, Tetrahedron Letters, 1 (1960).

RECENT STUDIES CONCERNING THE MECHANISM OF THE OZONOLYSIS OF OLEFINS

Reported by J. Douglas McCullough, Jr. October 27, 1966

The Criegee mechanism[1-5] has been quite successful in explaining many aspects of the reaction of olefins with ozone. It is generally expressed as:

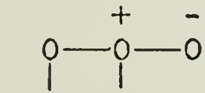


In a nucleophilic solvent such as methanol a hydroperoxide (VII) is formed. The ozonide IV is usually the main product in inert solvents if III is an aldehyde. Under the same conditions, when III is a ketone, dimers and polymers are the major products.

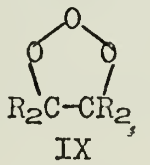
In recent years it has become increasingly apparent that the Criegee mechanism does not suffice to explain all the experimental data. The question of the nature of the first intermediate[6-16] has received much attention. Very recently, interest has been directed toward the Criegee zwitterion II. Indeed, evidence has been presented[17-25] that indicates that in some cases the zwitterion plays a minor role and an entirely different mechanistic route is the major path.

Staudinger[6] observed that a monomeric ozonide could not be converted to the polymeric ozonide and concluded that the monomer must be a secondary reaction product which arose from a primary product termed a molozonide.

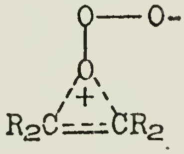
Bailey in a series of papers[7,8,9] attempted to correlate cleavage direction of the molozonide with the mode of initial attack of ozone. He considered the possible intermediates as VIII, a structure similar to that postulated by Staudinger, IX, a 1,2,3-trioxolane structure and X an activated π complex. Bailey reported that his results were not consistent with only one species.[9,10]



VIII



IX

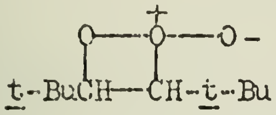


X

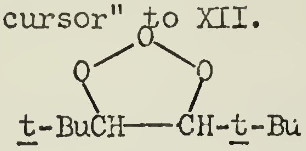
Bailey, Thompson and Shoulders[11] eliminated VIII as a structure for the molozonide of trans-1,2-di-t-butylethylene by a low temperature n.m.r. study. The ozonations were carried out in Freon 11 ($CFCl_3$) at -110° and in acetone-d_6 at -95°. The n.m.r. spectra consisted of two singlet peaks, representing the t-butyl protons and the methine protons respectively, in the expected ratio of 9:1. No observable change in spectrum occurred when the temperature was allowed to rise to about 60°. The bands characteristic of the molozonide disappeared at this temperature, and new bands characteristic of the decomposition products, trimethylacetaldehyde (XIII) and polymer of zwitterion XIV appeared.

The cold Freon 11 reaction mixture was treated with methanol in order to show the presence of the molozonide. The expected methoxy hydroperoxide (XVI) was obtained in good yield. Since the spectrum of the initial ozonide had only two bands, all the t-butyl protons were equivalent as were both methine protons. The unsymmetrical

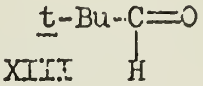
nature of XI would lead one to expect a more complex spectrum than the one obtained, so XI can be eliminated as a possible structure for the molozonide. The most reasonable structure based on these data is XII, but, according to Bailey,[11] a π complex may be a "fleeting precursor" to XII.



XI

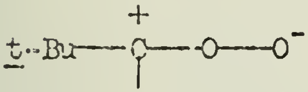


XII



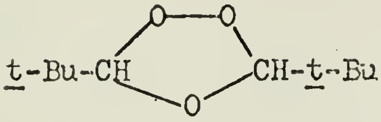
XIII

$t\text{-Bu-}\underset{H}{C}=O$

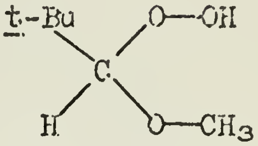


XIV

$t\text{-Bu}-\overset{+}{\underset{H}{C}}-O-O^{-}$



XV

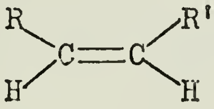


XVI

When cis-1,2-di-t-butylethylene was ozonized in Freon 11 under the same conditions as used for the trans isomer, the n.m.r. spectrum gave no indication of the presence of a molozonide. Only the bands for the mixture of true ozonides XV were observed. Evidently, as suggested by the authors, the cis isomer does not form a molozonide, or the molozonide is too unstable to be detected by n.m.r. at -110°. Since this study was performed on the highly hindered cis-1,2-di-t-butylethylene it cannot without some reservation be extrapolated to a less hindered olefin.

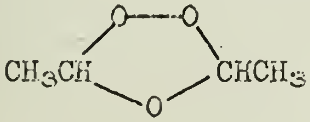
It should be mentioned that Criegee and Schroder[12] had previously obtained XVI, the methoxy hydroperoxide, from cold ozonation mixtures, and furthermore, they obtained some indication of the presence of molozonide intermediates when ozonation reaction mixtures were treated with Grignard reagents. Additional studies with Grignard reagents were carried out by Greenwood and Haske.[13-16]

With an unsymmetrical olefin (XVII), there are two zwitterions and two carbonyl compounds possible according to the Criegee mechanism.

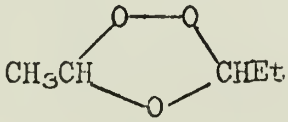


XVII

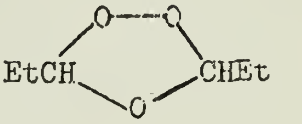
Therefore a possibility of three cis-trans pairs exists in theory. A number of workers have been able to obtain cross ozonides and thus substantiate the original Criegee mechanism.[18,19,26-29] Results indicate that the relative amounts of the different ozonides depends on factors such as zwitterion stability,[18,19] concentration in solution,[18,19] and solvent effects.[22] Story, Loan and Murray[18] reported a study in which pentene-2 was ozonized in pentane solution at a number of different concentrations in order to determine the extent of the solvent cage interaction which had been postulated by Criegee[5] for the formation of ozonide. In Figure 1, the ratio of pentene-2 ozonide (XIX) to butene-2 ozonide (XVIII) is shown as a function of pentene-2 concentration.



XVIII



XIX



XX

It can be seen that the ratio approaches the statistical value of two as solvent is removed. Similar results were found for the ratio of pentene-2 ozonide to hexene-3 ozonide (XX). The fact that the ratio never reached the value of two could be attributed to some reaction always occurring in a solvent cage, an observation that was also made by Lorenz and Parks.[19] Criegee, Blust and Zinke[5] had in earlier work found that zwitterions could be trapped from the solvent cage by adding an excess of formaldehyde. The solvent apparently plays an important role in determining the relative amounts of ozonides obtained, but, as of the present, no explanation has

been advanced, although Greenwood[22] stated that solvent nucleophilicity may be important.

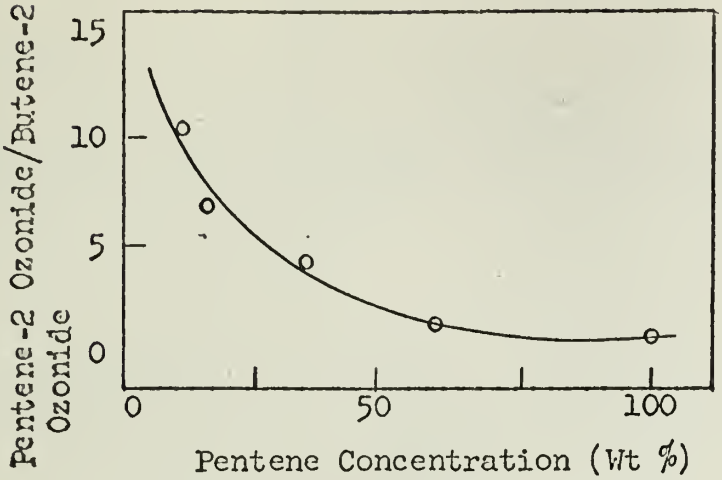


Figure 1. Effect of pentene-2 concentration on ozonide distribution.

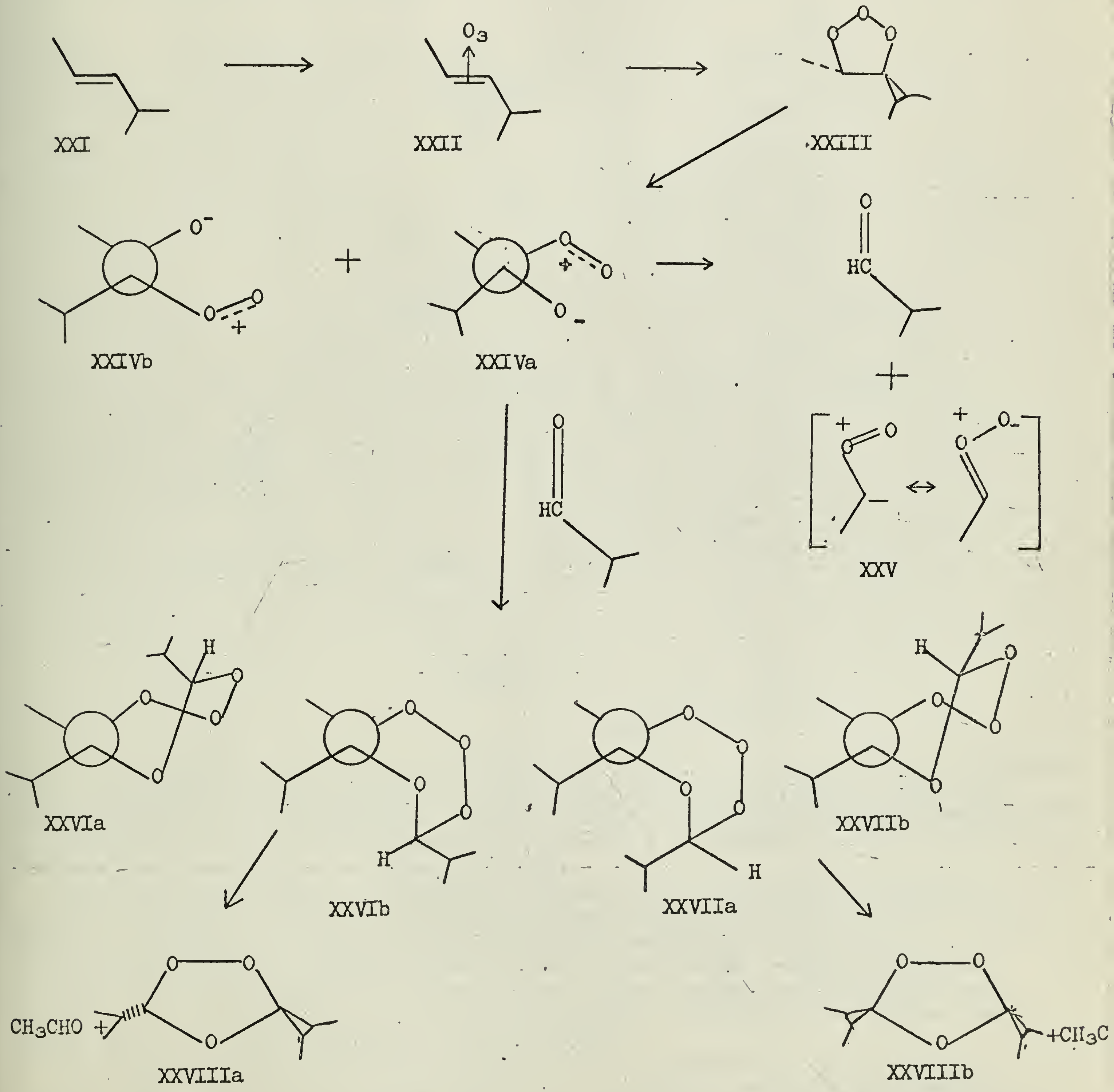
Schröder presented evidence that contradicted the Criegee zwitterion mechanism. Using v.p.c., he found that *trans*-di-*t*-butylethylene gave a single ozonide, which was formulated as the *trans* ozonide. Moreover, *cis*-di-*t*-butylethylene gave an ozonide ratio, *cis*:*trans*, of 70:30. Reasoning by the Criegee mechanism, the same *cis*:*trans* ozonide ratio would be expected irrespective of the geometry of the starting olefin. Surely this work demonstrates that the mechanism needed re-examination. After this study, other workers also found that the *cis*:*trans* ratio depended upon the parent olefin stereochemistry.[19,20,30,31]

Prior to mechanistic work it was important to be able to assign ozonide stereochemistry unequivocally. Assignment had been made by means of n.m.r., infrared spectroscopy, v.p.c. retention times and chemical reactivity data by many workers; however, these methods were not always satisfactory.[19] Using the earlier observation that ozonides react rapidly with amines, Story and co-workers[23] treated each isomer of diisopropyl ozonide with a less than stoichiometric amount of brucine at -70° in order to obtain a kinetic resolution of the *trans* isomer, which is a *d*,*l* pair. The remaining unreacted ozonides were isolated and identified by comparison with authentic samples. Subsequent investigation of optical activity using ORD curves indicated that the isomer though to be *trans* on the basis of other evidence was indeed the *trans* isomer, since it gave a strong rotation. As expected, the *cis* isomer gave no rotation.

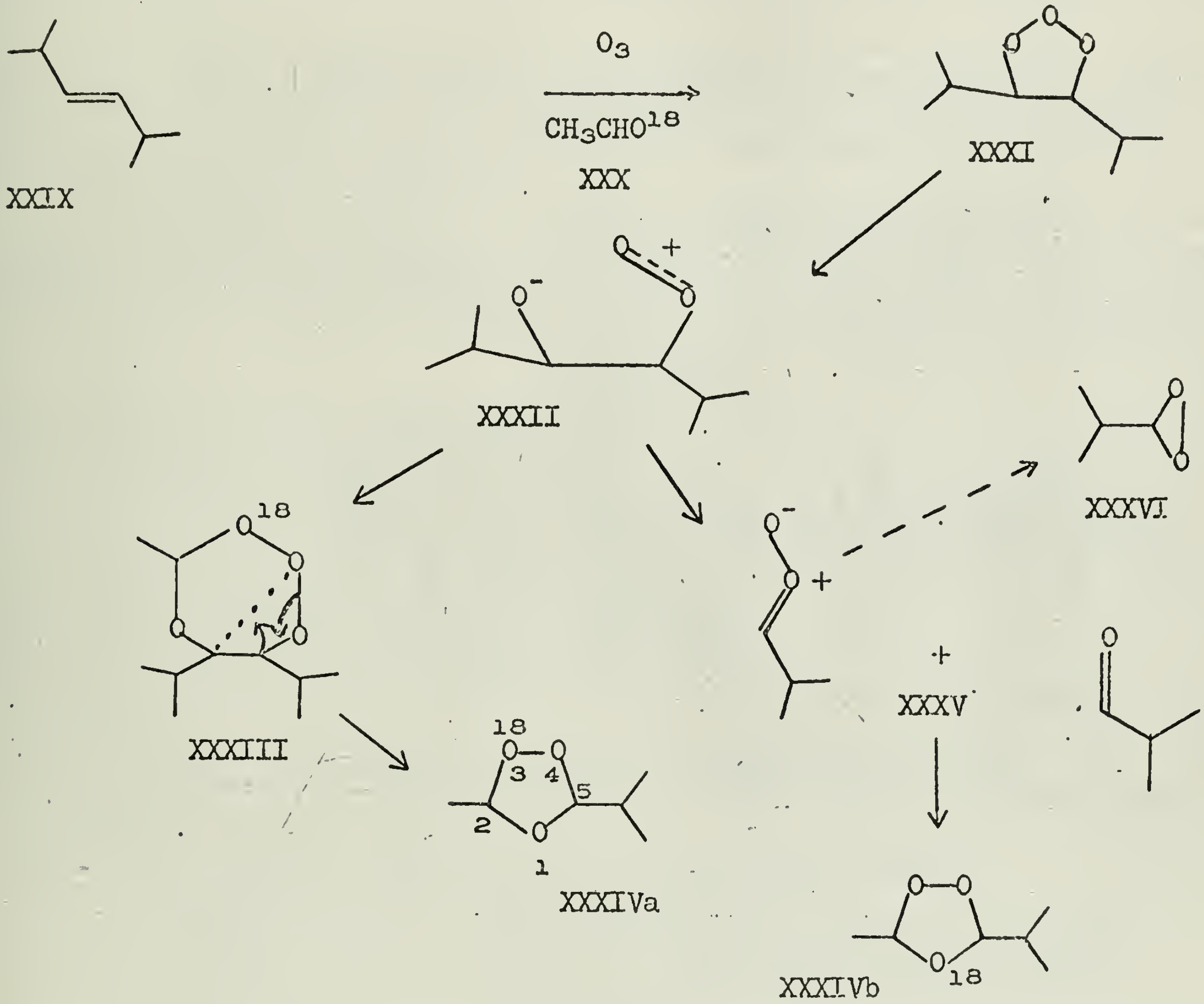
Both Story and co-workers,[18] and Lorenz and Parks,[19] suggested that stereochemically sensitive pathways may be general in ozonide formation. Furthermore, Story[20,21,24,25] in studying the *cis*:*trans* ratio of cross ozonides found that the true ozonides were at least in part formed by a mechanistic route which does not involve the Criegee zwitterion. The new mechanism is meant to apply only to *trans* and sterically unhindered *cis* olefins. They postulated that, as suggested by Bailey,[8,9] ozone and the double bond first form a *π* complex. The path which the *π* complex then takes is determined principally by the steric requirements of the double bond substituents. Their mechanism correctly accounted for the finding that *cis* olefins will generate relatively more *cis* ozonide than will the corresponding *trans* olefin.

The proposed mechanism is depicted using *trans*-4-methylpentene-2 (XXI). It should be noted that cleavage of the molozonide is represented by a structure which differs from the one usually accepted.[8,32,33] It is suggested[25] that the structure is reasonable on the grounds that this cleavage is analogous to the cleavage of alkyl hypohalites. As can be seen in the scheme for the formation of the diisopropyl ozonide (XXVIII), the mechanism also allows for the concurrent operation of the Criegee zwitterion mechanism.

By examining models of XXVI and XXVII, and the probable steric effects on transition states, the authors arrived at the conclusion that there should be little preference for *cis* or *trans* ozonide, which agrees well with the actual *cis*:*trans* ratio of 1:1. On the contrary, with the *cis* olefin, they felt that a definite preference for one species existed on the basis of smaller non-bonded interactions.[21] From this argument, a preponderance of the *cis* isomer would be predicted. The observed *cis*:*trans* ratio of 66:34 agrees with this prediction. The energy difference in the transition states which would lead to this ratio is however only about 0.3 k. cal./mole.[34]



Other support for the new mechanism was obtained from an oxygen-18 labeling experiment. Story and co-workers noted that the position of incorporation of the oxygen from the aldehyde depends on whether the Criegee or the new mechanism is operative. In their experiment, trans-1,2-diisopropylethylene (XXIX) was ozonized in the presence of acetaldehyde-O^{18} (47.8% by mass spectral analysis) at -70° in pentane solution. The methyl isopropyl ozonide (XXXIV) was isolated by means of v.p.c. in 17% yield. Any product ozonide which came by way of the Criegee mechanism should have label at position 1, while any product which followed the new mechanistic pathway should have label at position 3. The authors assumed that the zwitterion would not lead to the ozonide through 1,3 addition to the aldehyde of a species represented as XXXVI.



In such an instance, label would be incorporated at position 3 as in the new mechanism. Such a structure would not account for the dependence of the cis:trans ratio of cross ozonides on olefin geometry. However, similar structures have been postulated[32,33] as intermediates in the rearrangement of zwitterions to products such as esters, lactones, acid anhydrides and other compounds.

The label was located by reducing the ozonide with $LiAlH_4$ and subsequent mass spectral analysis of the only reduction products, ethanol and isobutyl alcohol. Several assumptions were made by the authors in interpreting their results. First, it was assumed that the reduction goes by way of the usually accepted mechanism in which one of the oxygens of the two oxygen bridge is lost, and that the loss of oxygen-3 was just as likely as loss of oxygen-4. Further, it was assumed that steric effects are not important in the reduction.

It was found that the ethanol contained 25.4% oxygen-18 and the isobutyl alcohol 7.6%. From the above assumptions, it is apparent that label in isobutyl alcohol can only be due to ozonide which was formed by way of the Criegee mechanism, and it follows that there must be an equivalent amount of label in the ethanol.

Therefore, there is 15.2% oxygen-18 in the product which was formed by the Criegee mechanism. The remaining 32.6% must be due to the new mechanism. Half of this would be lost in the reduction, so only 16.3% plus the previously mentioned 7.6% must remain in the ethanol. The calculated value of 24% checks very well with the experimental value of 25.4% in the ethanol.

The authors mention that caution should be exercised because the mechanism of hydride reduction of ozonides is not known with certainty. The numbers will be in error if any oxygen from position 1 is lost. Even so, although the detailed distribution may be in doubt, the results are consistent with a new mechanistic pathway operating concurrently with the Criegee zwitterion mechanism, and at least with the ozonide considered, 70% is produced by the new mechanism, and 30% by the Criegee route.

To account for hindered olefins, Story, Murray and Youssefyeh thought that the ozone-olefin π complex may in part collapse to a σ complex.[21] This σ complex then rearranges in a concerted stereospecific manner to the cis ozonide. The authors noted support for this hypothesis in the formation of epoxides in the ozonolysis of hindered olefins.[8]

In conclusion, questions still remain regarding the structure of the initial ozonide and the new mechanism. Story[25] indicated that experiments are in progress designed to check the possibility of structure XXXVI. Also, assuming that the new mechanism is valid, its generality and details will be an area for new research.

BIBLIOGRAPHY

1. R. Criegee and G. Wenner, Ann., 564, 9 (1949).
2. R. Criegee, Ann., 583, 1 (1953).
3. R. Criegee, G. Blust, and H. Zinke, Chem. Ber., 87, 766 (1954).
4. R. Criegee, A. Kerchow, and H. Zinke, Chem. Ber., 88, 1978 (1955).
5. R. Criegee, Record Chem. Progr. (Kresge-Hooker Sci. Lib.), 18, 111 (1957).
6. H. Staudinger, Ber., 58, 1088 (1925).
7. P. S. Bailey, Chem. and Ind., 1148 (1957).
8. P. S. Bailey, Chem. Rev., 58, 925 (1958).
9. P. S. Bailey, S. B. Mainthia, and C. J. Abshire, J. Am. Chem. Soc., 82, 6136 (1960).
10. C. J. Abshire. MIT Seminar in Organic Chemistry, May 1962.
11. P. S. Bailey, J. A. Thompson, and B. A. Shoulders, J. Am. Chem. Soc., 88, 4098 (1966).
12. R. Criegee and G. Schröder, Chem. Ber., 93, 689 (1960).
13. F. L. Greenwood, J. Org. Chem., 29, 1321 (1964).
14. F. L. Greenwood and B. J. Haske, Tetrahedron Letters, 631 (1965).
15. F. L. Greenwood and B. J. Haske, J. Org. Chem., 30, 1276 (1965).
16. F. L. Greenwood, J. Org. Chem., 30, 3108 (1965).
17. G. Schröder, Chem. Ber., 95, 733 (1962).
18. L. D. Loan, R. W. Murray, and P. R. Story, J. Am. Chem. Soc., 87, 737 (1965).
19. O. Lorenz and C. R. Parks, J. Org. Chem., 30, 1976 (1965).
20. R. W. Murray, R. D. Youssefyeh, and P. R. Story, J. Am. Chem. Soc., 88, 3143 (1966).
21. P. R. Story, R. W. Murray, and R. D. Youssefyeh, J. Am. Chem. Soc., 88, 3144 (1966).
22. F. L. Greenwood, J. Am. Chem. Soc., 88, 3146 (1966).
23. R. W. Murray, R. D. Youssefyeh, and P. R. Story, J. Am. Chem. Soc., 88, 3655 (1966).
24. P. R. Story, Abstracts 152nd. National Meeting of the American Chemical Society, New York, N. Y., Sept. 1966, p. S5.
25. P. R. Story, C. E. Bishop, J. R. Burgess, R. W. Murray, and R. D. Youssefyeh, private communication from P. R. Story.
26. O. Lorenz and C. R. Parks, J. Rubber Chem. Tech., 36, 201 (1963).
27. G. Riezebos, J. C. Grimmelikhuysen, and D. A. Van Dorp, Rec. Trav. Chim., 82, 1234 (1963).

28. O. S. Privitt and E. C. Nickell, J. Am. Oil Chemists' Soc., 40, 22 (1963).
29. O. S. Privitt and E. C. Nickell, J. Am. Oil Chemists' Soc., 41, 72 (1964).
30. R. Criegee, S. S. Bath, and B. V. Bornhaupt, Chem. Ber., 93, 2891 (1960).
31. P. Kolsaker, Acta Chem. Scand., 19, 223 (1965).
32. R. Criegee in Peroxide Reaction Mechanisms, edited by J. O. Edwards, Interscience, New York, N. Y., 1962, p. 29.
33. R. Huisgen, Angew. Chem. Intern. Ed. Engl. 2, 565 (1963).
34. E. L. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill, New York, N. Y., 1962.

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THE THERMAL AND BASE INDUCED DECOMPOSITIONS OF N-ALKYL-N-NITROSO UREAS

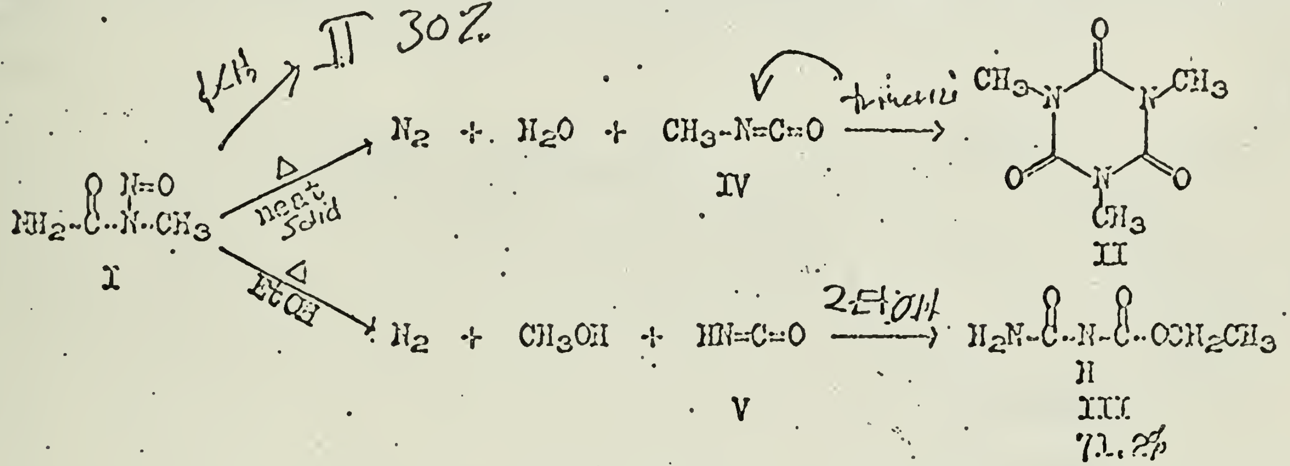
Reported by Sheldon A. Schaffer October 31, 1966

INTRODUCTION

Recently, Jones, Muck, and Tandy have proposed new mechanisms for the thermal[1] and base induced[2] decompositions of N-alkyl-N-nitroso ureas. This seminar will discuss the data pertaining to these decompositions and the evidence for the mechanisms postulated by Jones and his co-workers.

THERMAL DECOMPOSITION

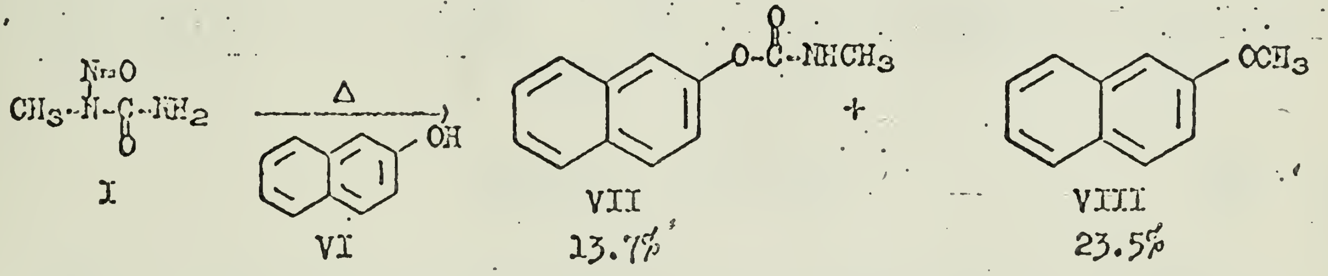
E. A. Werner[3] in 1919 thermally decomposed N-methyl-N-nitroso urea (I) both neat and in ethanolic solution. From the neat decomposition, Werner observed the formation of trimethyl isocyanurate (II), while the only product isolated from the decomposition of I in ethanol was ethyl allophanate (III). Werner postulated the



(1)

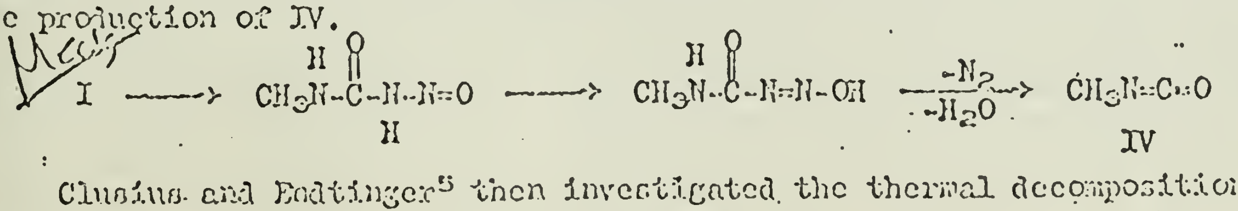
intermediacy of methyl isocyanate (IV) to explain the production of II and claimed that III was formed from the reaction of ethanol with isocyanic acid (V). The origins of IV and V were not specified.

Huisgen and Reimlinger[4] decomposed I in toluene and obtained a 30% yield of trimethyl isocyanurate (II). They, too, proposed methyl isocyanate as an intermediate leading to II, and to support this postulate they decomposed I in the presence of β-naphthol (VI). This decomposition produced a 13.7% yield of the naphthylurethane (VII) which Huisgen and Reimlinger reasoned was formed by the



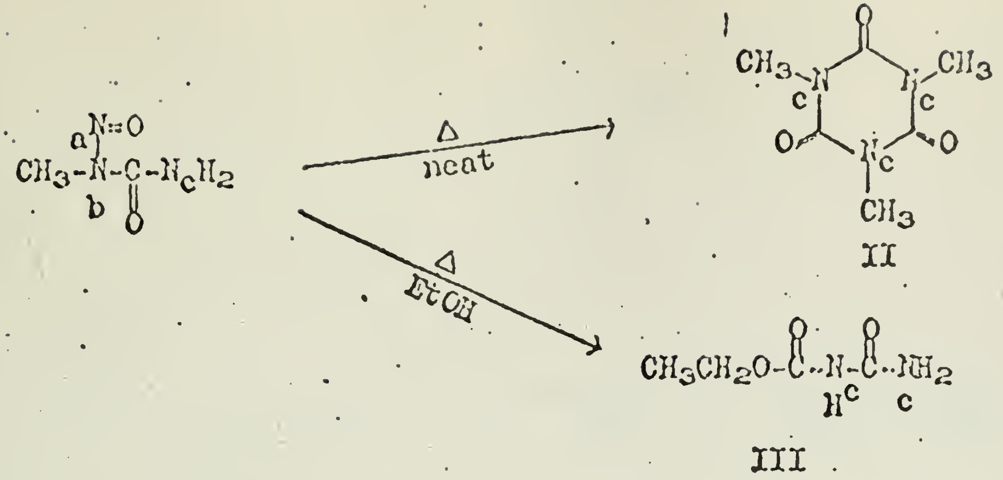
(2)

reaction of IV with β-naphthol. Also produced in this reaction was a 23.5% yield of β-methoxynaphthalene (VIII), but no explanation of its origin was offered. The mechanism in equation 3 involving a nitroso migration was postulated to rationalize the production of IV.



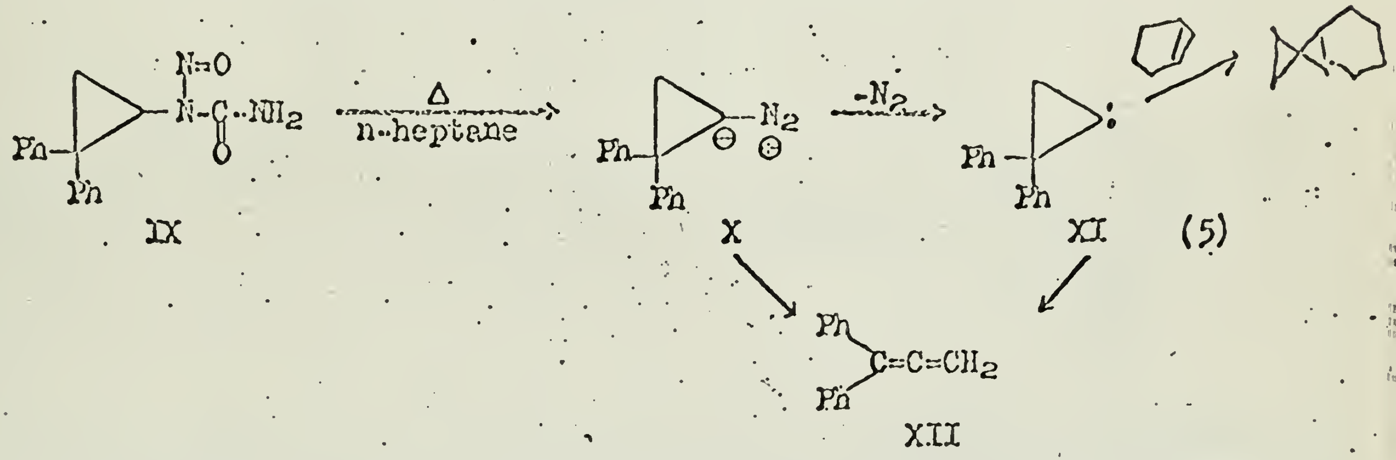
$$\text{I} \longrightarrow CH_3\overset{H}{N}-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-N=O \longrightarrow CH_3\overset{H}{N}-\overset{O}{\overset{\|}{C}}-N=N-OH \xrightarrow[-H_2O]{-N_2} \underset{\text{IV}}{CH_3N=C=O} \qquad (3)$$

Clusius and Endtinger[5] then investigated the thermal decomposition of N-methyl-N-nitroso urea using an ^{15}N labeled compound and found that from the neat decomposition all the nitrogen in the product, trimethyl isocyanurate (II), came from the NH_2 nitrogen (c) of the reactant. Similarly, when the urea was decomposed in ethanol all the nitrogen in the ethyl allophanate (III) produced came from nitrogen c.



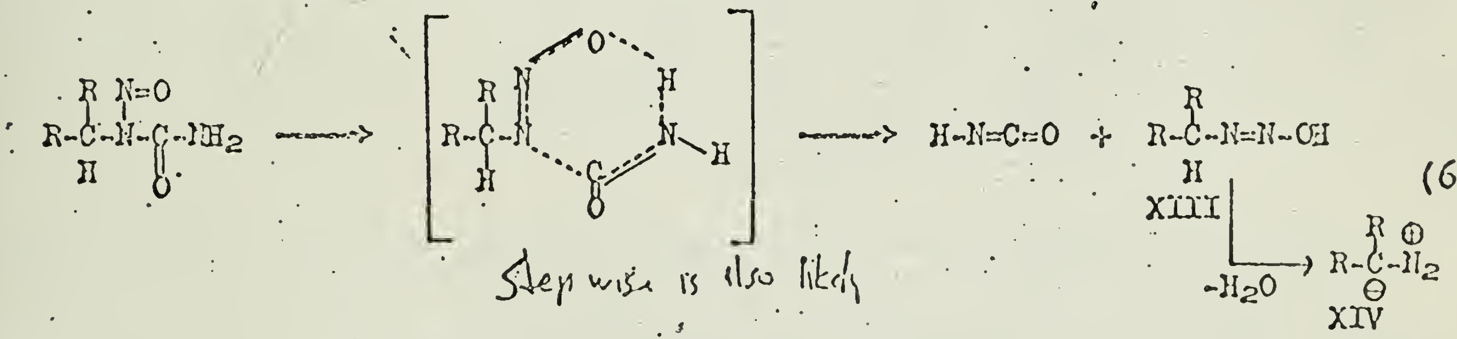
(4)

This data, plus the finding of Jones, Grasley, and Baarda[6] that the thermal decomposition of N-nitroso-N-(2,2-diphenylcyclopropyl) urea (IX) leads only to products of the diazocyclopropane (X), sheds considerable doubt on the Huisgen mechanism.



(5)

In lieu of Huisgen's mechanism, Jones and Muck[1] have proposed the mechanism in equation 6 for the thermal decomposition of N-nitroso-N-alkylureas. The authors have arbitrarily pictured the abstraction of a proton from the NH$_2$ group and the loss of isocyanic acid as a concerted process. They state that a stepwise process leading to the products shown is just as likely.



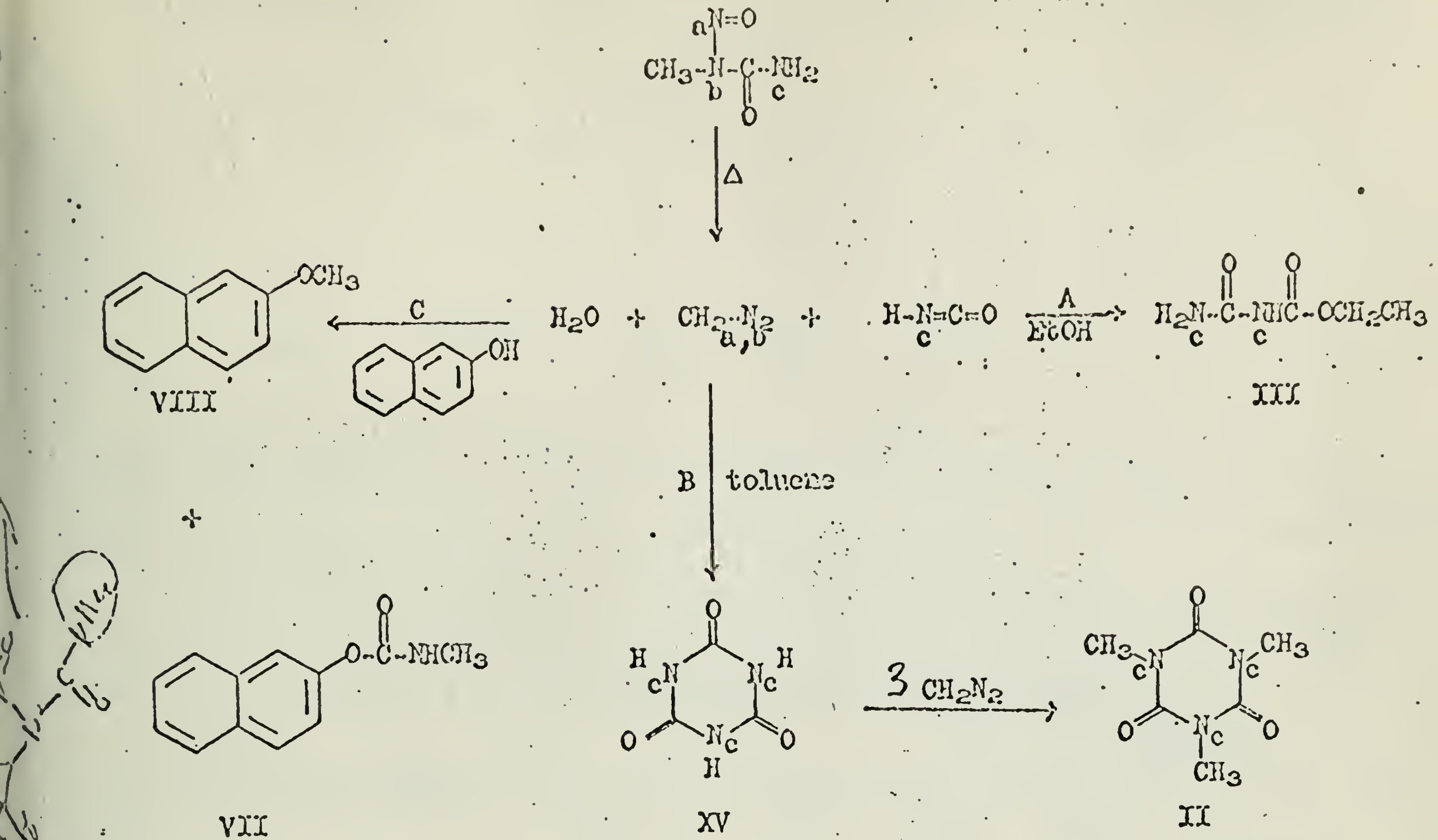
(6)

Step wise is also likely

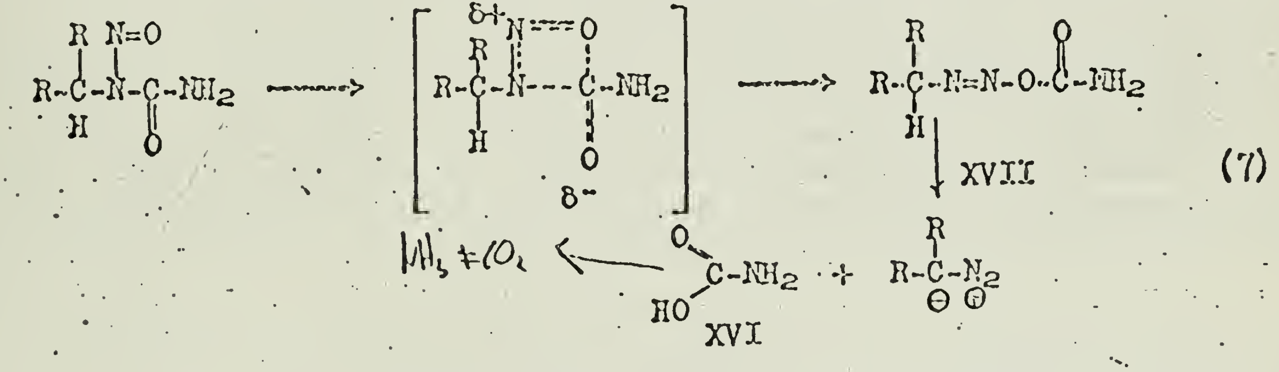
Scheme I illustrates the consistency of the Jones and Muck mechanism with the data given above for the decomposition of N-methyl-N-nitroso urea. The decomposition of I in ethanol leads to the formation of ethyl allophanate with the nitrogen labeling as found by Clusius and Endtinger,[5] which demonstrates that the nitrogen of the isocyanic acid comes from the NH$_2$ nitrogen of the urea. Path B illustrates how trimethyl isocyanurate might be formed under Huisgen and Reimlinger's conditions. Control experiments proved that diazomethane does react with cyanuric acid under the reaction conditions to give trimethyl isocyanurate. However, it was not independently determined that isocyanic acid will trimerize to cyanuric acid (XV) under these conditions. Support for path B comes from that fact that it does lead to the correct nitrogen labeling pattern.

As shown in path C, the Jones and Muck mechanism can explain the formation of β-methoxynaphthalene as well as the naphthylurethane (VII) when I is decomposed in the presence of β-naphthol.

Scheme I



As a possible alternative to the mechanism shown in equation 6, a decomposition of the nitrosourea similar to the thermal decompositions of N-nitrosoamides[7-11] was considered. In order for this mechanism to hold, carbamic acid (XVI) must dehydrate to give isocyanic acid, the observed product of the decomposition. When this dehydration was attempted by treating lithium or sodium carbamate with p-toluenesulfonic acid in refluxing benzene, the only products obtained were ammonium p-toluenesulfonate and lithium (or sodium) p-toluenesulfonate which are the products expected from the normal decomposition[12] of the carbamate.



(7)

It is also possible that the diazocarbamate XVII could decompose to give isocyanic acid and the diazohydroxide XIII. This pathway is consistent with all the data above and cannot be ruled out.

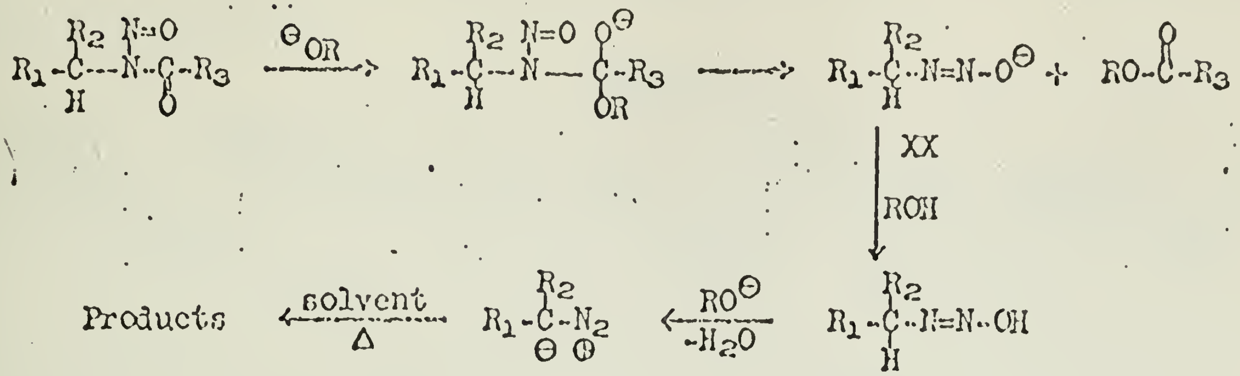
As further support for their mechanism, Jones and Mack heated N-nitroso-N-(2,2-diphenylcyclopropyl)-N',N'-dimethyl urea (XIX) under normal reaction conditions and observed no gas evolution. When heated more strongly, XIX decomposed slowly to give a gummy material which exhibited none of the characteristics of 1,1-diphenylallene, the normal decomposition product.

BASE INDUCED DECOMPOSITION

Base induced decompositions of N-nitrosoureas, amides, urethanes, and guanidines have long been used to generate diazoalkanes.[13,14] In the cases of the amides and urethanes, there is a large body of evidence[15-17] to support a mechanism (shown in Scheme II) which involves initial base attack on the carbonyl carbon of the nitroso

compound, followed by loss of ester, to give a diazotate (XX) which can then undergo further reaction to give a diazoalkane and/or products derived from diazoalkanes.

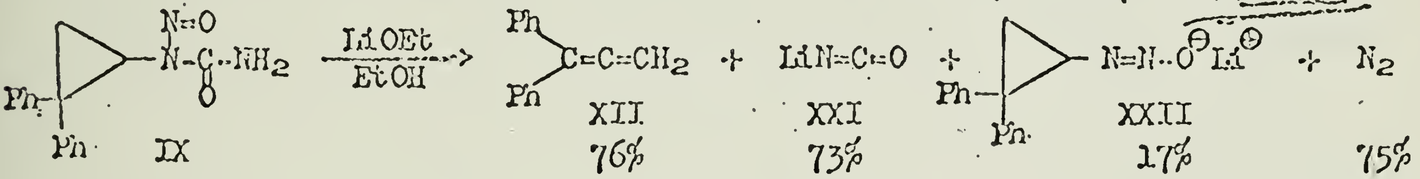
Scheme II



It had been assumed[18,19] that the ethoxide induced decomposition of N-nitrosoureas involved a similar attack by base on the carbonyl carbon, but in a study by Jones and Muck on a number of N-alkyl-N-nitrosoureas,[20] none of the expected product from such an attack, ethyl carbamate, was observed. Controls had established that ethyl carbamate was stable to the reaction conditions.

In an attempt to determine the mechanism for the base induced decomposition of N-nitrosoureas, Jones, Muck, and Tandy carried out a careful study of the lithium ethoxide decomposition of N-nitroso-N-(2,2-diphenylcyclopropyl) urea (IX).[2] The products they observed from this decomposition are shown in equation 9.

Known results were conducted

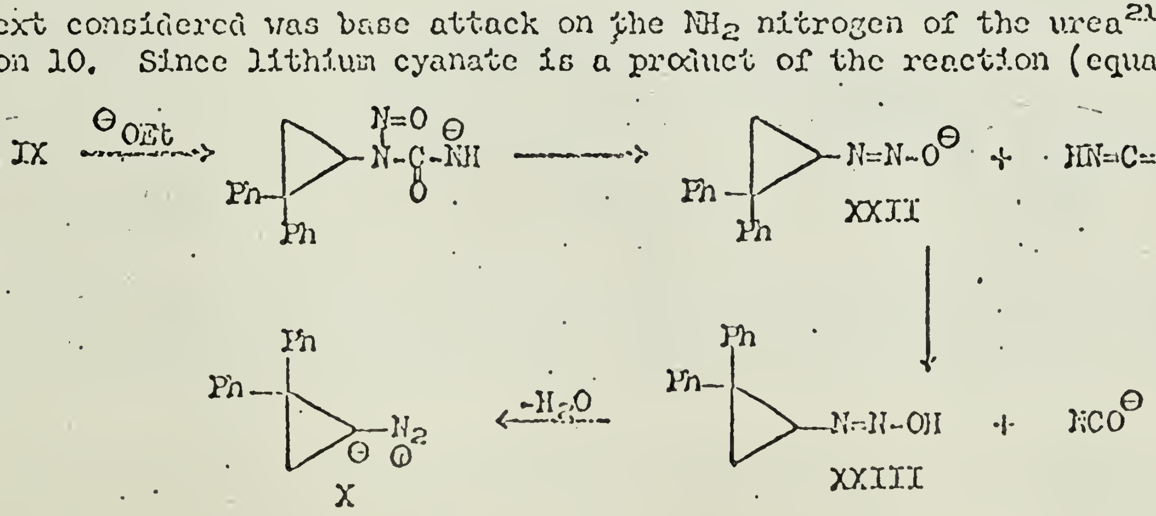


(9)

Application of the N-nitrosoamide type mechanism to the decomposition of IX would give the diazotate XXII as the initial product, but XXII should be decomposed by lithium ethoxide and ethanol to the diazocyclopropane X which itself is unstable and decomposes to 1,1-diphenylallene (XII). As shown in equation 9, the diazotate XXII was formed in the reaction, but when an independently synthesized sample of XXII was subjected to a mixture of lithium ethoxide and ethanol it was found to be unreactive. Jones and Muck did not explain how the diazotate was formed in the decomposition of IX, but, on the basis of its stability to base and ethanol, they concluded that it could not be an intermediate in the formation of the diazoalkane or allene.

Other mechanisms involving initial base attack at the carbonyl carbon were considered, but all these mechanisms involved the diazotate; and when each, in turn, was tested, they were rejected due to the stability of the diazotate to the proposed reaction conditions.

Next considered was base attack on the NH_2 nitrogen of the urea[21] as shown in equation 10. Since lithium cyanate is a product of the reaction (equation 9), this

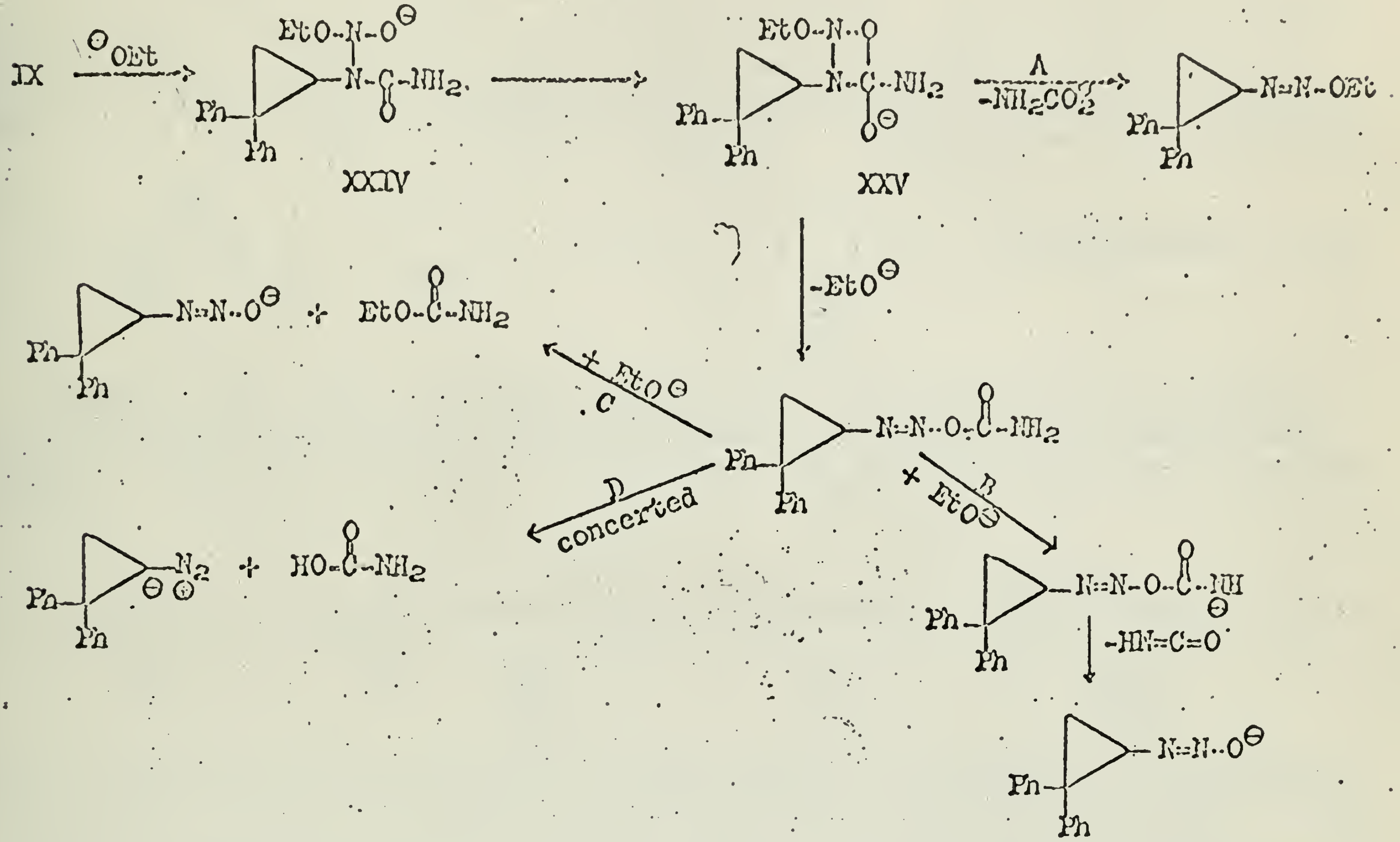


(10)

route looked promising, but it too had to be rejected when it was found that the diazotate was stable to lithium cyanate.

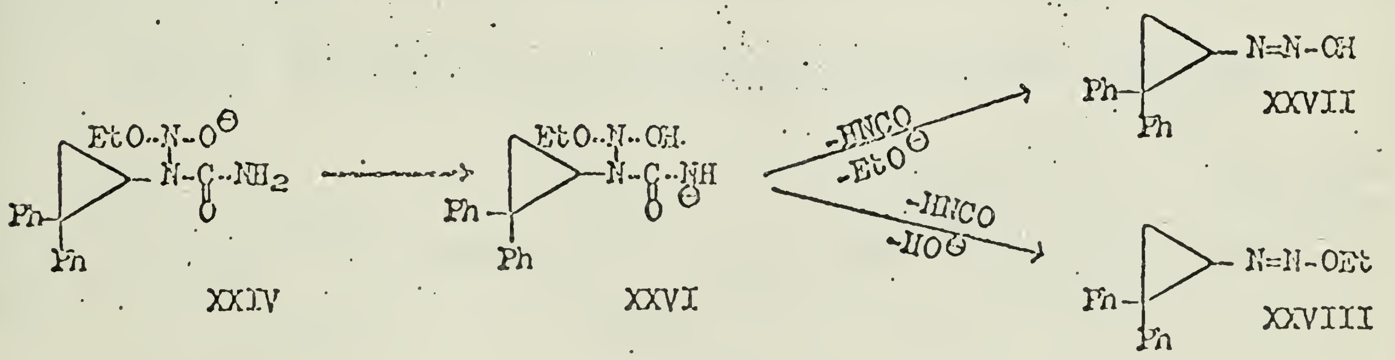
The last reasonable point of attack for the base on the nitrosourea is the nitrogen of the nitroso group. Such attack would lead to the anion XXIV which could possibly decompose through the cyclic intermediate XXV by one of the paths outlined in Scheme III.

Scheme III



All of the paths in Scheme III were eliminated for the following reasons: Paths A and C) Neither carbamic acid nor lithium carbamate were products of the reaction and neither decomposes under the reaction conditions to the observed product, lithium cyanate; Paths B and D) These paths are excluded by the previous observatio that the diazotate XXIII is stable to the reaction conditions.

As an alternative to the cyclic intermediate XXV, the oxygen of the anion XXIV could abstract a proton from the NH_2 nitrogen of the urea to give XXVI which could then lose either $^{\ominus}$OEt or $^{\ominus}$OH to give XXVII or XXVIII.



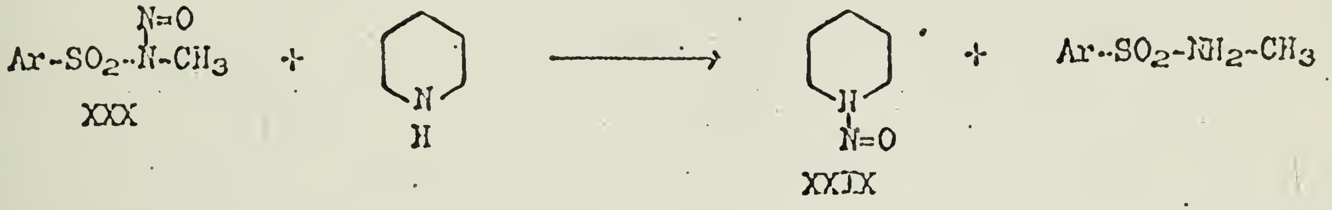
(11)

Moss[22] has shown that quenching a diazotate, such as n-C_8H_{17}-N=N-$O^{\ominus}M^{\oplus}$, with water to give the diazohydroxide leads to gas evolution and to products derived from diazoalkanes and carbonium ions. Thus, it would be expected that at least XXVII could decompose to give a diazoalkane, or in the case of IX, 1,1-diphenylallene.

Although no direct evidence has been obtained for the mechanism in equation 11 Jones, Muck, and Tandy consider it to be the best mechanism proposed, at least for the alkoxide induced decomposition of N-nitroso-N-(2,2-diphenylcyclopropyl) urea. They claim support for this mechanism on the basis of its similarity with the mechanism for the thermal decomposition of N-nitroso-N-(2,2-diphenylcyclopropyl)

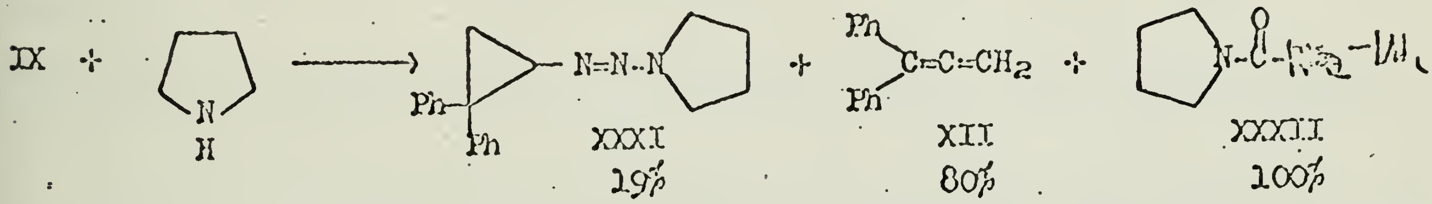
urea[1] and from the observation that N-nitroso-N-(2,2-diphenylcyclopropyl)-N',N'-dimethyl urea is stable to the reaction conditions.

The key step in the Jones, Muck, and Tandy mechanism, base attack on the nitroso nitrogen, has some precedent. Bollinger, Hayes, and Siegel[23] observed methyl nitrite and N-cyclohexylurethane as products from the reaction of ethyl N-nitroso-N-cyclohexylcarbamate with potassium carbonate in methanol. Jones and his co-workers interpret the products of this reaction as arising from attack of methoxide on the nitroso nitrogen. Furthermore, Backer and de Boer[10] obtained N-nitrosopiperidine (XXIX) from the reaction of piperidine with N-methyl-N-nitroso-p-toluenesulfonamide (XXX) which, again, apparently involves nucleophilic attack on the nitroso nitrogen.



(12)

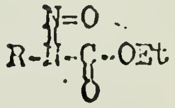
Finally, Jones, Muck, and Tandy observed that when N-nitroso-N-(2,2-diphenylcyclopropyl) urea was decomposed with pyrrolidine, up to 19% of the triazene XXXI was formed along with 80% of 1,1-diphenylallene, and 100% of N-pyrrolidylcarboxamide (XXXII).



(13)

The only source for the triazene XXXI, besides attack of pyrrolidine on the nitroso group, is the reaction of 2,2-diphenyl-diazocyclopropane (X) with pyrrolidine. This possibility was excluded when none of the triazene was formed when the diazocyclopropane (generated by the pyrolysis of pyrrolidinium 2,2-diphenylcyclopropyldiazotate) was reacted with pyrrolidine.

Jones and Muck have also reinvestigated the base induced decompositions of N-nitrosoamides and urethanes[20] to determine to what extent, if any, base attack at the nitroso group occurs in these compounds. They reason that it should be possible to separate attack on the nitroso nitrogen from attack on the carbonyl carbon by measuring the yield of ethyl carboxylate (or diethyl carbonate) produced in the reaction of the amide (or urethane) with ethoxide. A portion of their data is presented in Tables I and II.

Table I Decomposition of N-Nitroso-N-alkylurethanes 
$R-\overset{N=O}{N}-\underset{O}{\overset{\|}{C}}-OEt$

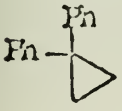
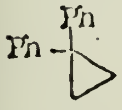
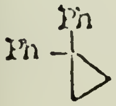
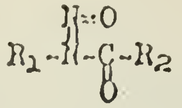
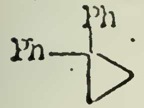
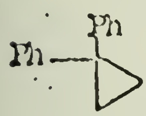
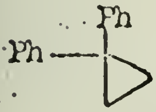
R	Solvent	Base	Gas Evolution %	Diethyl Carbonate %
	Et_2O	LiOEt	97	7
	EtOH	LiOEt	52	44
	EtOH	K_2CO_3	31	72
$C_6H_5CH_2$	Et_2O	LiOEt	52	10
$C_6H_5CH_2$	EtOH	LiOEt	46	47
$C_6H_5CH_2$	EtOH	K_2CO_3	44	52

Table II Decomposition of N-Nitroso-N-alkylamides  $R_1-\overset{N=O}{N}-\underset{O}{\overset{\|}{C}}-R_2$

R_1	R_2	Solvent	Base	Gas Evolution %^{a}	Ethyl Carboxylate^b	Alkali Carboxylate^b
	C_6H_5	Et_2O	LiOEt	96	4	80
	C_6H_5	EtOH	LiOEt	58	48	40
	C_6H_5	EtOH	K_2CO_3	47	56	37
$C_6H_5CH_2$	CH_3	Et_2O	LiOEt	50	7	86
$C_6H_5CH_2$	CH_3	EtOH	LiOEt	46	73	23
$C_6H_5CH_2$	CH_3	EtOH	K_2CO_3	47	83	9

a) Per cent of product resulting from ethoxide attack on the carbonyl carbon atom.
b) Per cent of product resulting from ethoxide attack on the nitroso nitrogen atom.

These data indicate that base attack on the carbonyl carbon varies as much as 9-90%. It is seen that attack on the carbonyl group decreases as the carbonyl substituent is changed from methyl to ethoxy (or phenyl) to amino. Jones and Muck point out that attack on the carbonyl group would be affected much more than attack on the nitroso group as the substituent at the carbonyl is varied, and the experimental data bears this out. An interpretation of the order of the decrease in attack at the carbonyl was not offered, and it is not clear what the major effect of the substituent is. In so far as the Hammett σ_p values[24] would predict the electronic and resonance contributions of the substituents in these reactions, one would expect the order of decreasing attack to be phenyl (σ_p=0.01)[25]>methyl (σ_p=-0.17)[25]>ethoxy (σ_p=-0.25)[25]>amino (σ_p=-0.66).[25] This order agrees with the experimental data except for the position of the phenyl group.

Tables I and II show two other interesting phenomena. First, there is a large solvent effect on the proportion of the reaction proceeding by initial attack at the carbonyl carbon. For the benzyl nitrourethane studied, attack on the carbonyl varied from 47% in ethanol to 10% in diethyl ether. Decomposition of the urethane in diglyme, acetone, and DMSO gave essentially the same results as decomposition in ether indicating that aprotic solvents favor attack on the nitroso group and protic solvents favor attack on the carbonyl group. Secondly, it is seen that the cation of the base used in the decomposition also affects the relative proportion of carbonyl to nitroso attack. Changing the cation from Li to K results in a decrease of attack on the nitroso group. An interpretation of these phenomena was not presented.

Bibliography

1. D. L. Muck and W. M. Jones, J. Am. Chem. Soc., 88, 74 (1966).
2. W. M. Jones, D. L. Muck, and T. K. Tandy, Jr., ibid., 88, 68 (1966).
3. E. A. Werner, J. Chem. Soc., 115, 1093 (1919).
4. R. Huisgen and H. Reimlinger, Ann., 599, 183 (1956).
5. K. Clusius and F. Endtinger, Helv. Chim. Acta., 43, 2063 (1960).
6. W. M. Jones, M. H. Grasley, and D. G. Baarda, J. Am. Chem. Soc., 86, 912 (1964).
7. E. H. White and C. A. Aufdermarsh, Jr., ibid., 83, 1174, 1179 (1961).

8. A. Streitwieser, Jr. and W. D. Schaeffer, *ibid.*, **79**, 2893 (1957).
9. K. Heyns and W. von Bebenburg, *Ber.*, **86**, 278 (1953).
10. H. J. Backer and Th. J. de Boer, *Proc. Koninkl. Ned. Akad. Wetenschap.*, **B54**, 191 (1951); *CA*, **46**:1961h.
11. E. H. White and R. J. Baumgarten, *J. Org. Chem.*, **29**, 2070 (1964).
12. J. Faurholt, *J. chim. phys.*, **22**, 1 (1925).
13. Th. J. de Boer and H. J. Backer, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, New York, N.Y., 1963, p. 250 and references found therein.
14. H. Zollinger, "Azo and Diazo Chemistry, Aliphatic and Aromatic Compounds," Interscience Publishers, Inc., New York, N.Y., 1961, Chapter 1.
15. C. D. Gutsche and H. E. Johnson, *J. Am. Chem. Soc.*, **77**, 109 (1955).
16. F. W. Bollinger, E. N. Hayes, and S. Siegel, *ibid.*, **72**, 5592 (1950).
17. R. Huisgen and J. Reinertshofer, *Ann.*, **573**, 163 (1951).
18. J. Tempé, H. Heslot, and G. Morel, *Comp. Rend.*, **258**, 5470 (1964).
19. D. E. Applequist and D. E. McGreer, *J. Am. Chem. Soc.*, **82**, 1965 (1960).
20. W. M. Jones and D. L. Muck, *ibid.*, **88**, 3798 (1966).
21. E. R. Garrett, S. Goto, and J. F. Stubbins, *J. Pharm. Sci.*, **54**, 119 (1965).
22. R. A. Moss, *J. Org. Chem.*, **31**, 1082 (1966).
23. F. W. Bollinger, F. N. Hayes, and S. Siegel, *J. Am. Chem. Soc.*, **75**, 1729 (1953).
24. E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York, N.Y., 1959, p. 220.
25. H. H. Jaffe, *Chem. Revs.*, **53**, 191 (1953).

42 min

DIRECT AROMATIC AMINATIONS

Reported by Dixon Thompson

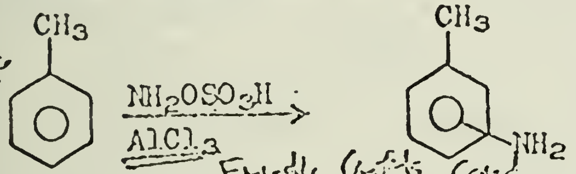
November 3, 1966

One step, or direct, displacements of hydrogen on an aromatic nucleus by ammonia, amines, or their derivatives have been carried out under a wide variety of conditions giving diverse selectivity and products. "Direct aminations" has no immediate mechanistic implications, but refers to the number of synthetic steps involved in replacing the hydrogen with the amine functional group. As these methods have only been developed to a synthetically useful stage in the last five to ten years, they are not as well known as the various multistep methods developed earlier: nitration and reduction,[1a] nucleophilic displacements of halogens,[2,3] substitution via aryne intermediates,[4,5] aminations via aryl organometallic compounds,[1b] and rearrangements.[6] Direct aminations using ammonia and high energy sources[7] or high pressure[8] will not be discussed.

Introduction

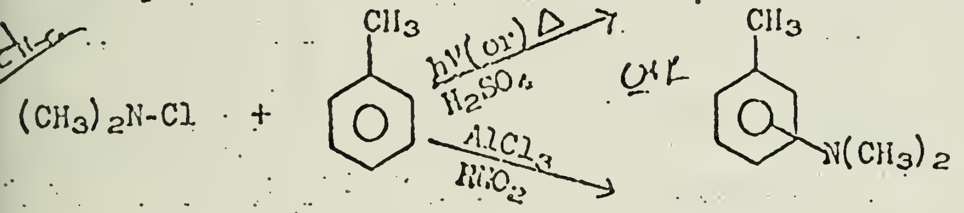
There are four general methods for carrying out direct aminations or alkylaminations. These are illustrated for toluene with the yields based on the nitrogen containing reagent.

A. Hydroxylamines, azides, and derivatives react with aromatic compounds in the presence of Lewis acids or sulfuric acid to produce aromatic amines[9-19] (reaction 1).



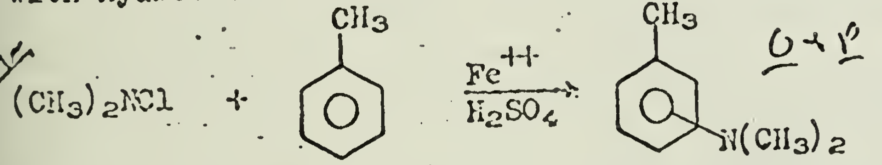
o+p		o	m	p	
	42%	51	13	36	(1)

B. N-chlorodialkylamines can be used to produce aromatic amines[20] through their thermal[21] or photolytic[22] decomposition in the presence of the aromatic hydrocarbon in sulfuric acid, or through reaction with an aromatic hydrocarbon in nitroalkanes in the presence of aluminum chloride[23] (reaction 2).



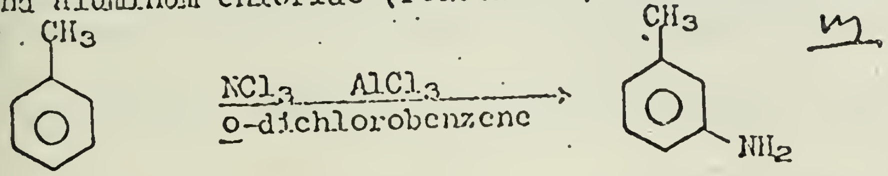
	o	m	p	
80%	9	53	38	(2)
50%	14	27	59	

C. Hydroxylamines and derivatives,[24,25,27] or N-chloramines[26,28,29,30] will react with hydrocarbon aromatic compounds in the presence of reducing metal salts (reaction 3).



	o	m	p	
11%	36	21	43	(3)

D. Aromatic hydrocarbons and haloaromatic compounds can be aminated with N-chloramine and aluminum chloride (reaction 4).



42% meta toluidine (4)

The direct aminations of hydrocarbon aromatic compounds to be discussed have been considered as examples of four different types of aromatic substitution: electrophilic substitution by a cationic species,[9] electrophilic substitution by a cation radical,[20-23] homolytic aromatic substitution,[40,41,42] and reactions which have been called sigma substitution[31,33,34,35,37,38,39] and nucleophilic sigma substitution.[32,30]

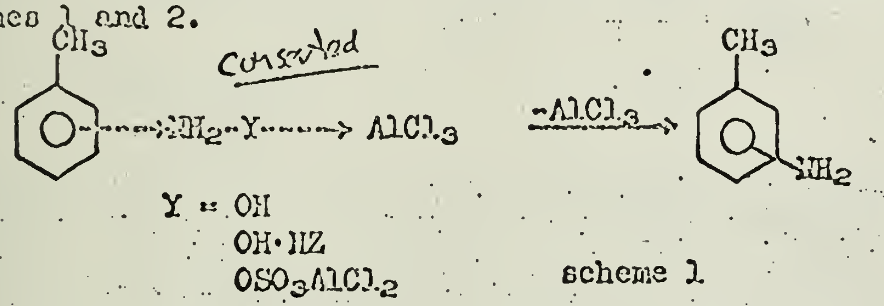
Electrophilic Aromatic Substitution

Kovacic has studied and recently reviewed[9] the direct aminations which occur

under Friedel-Crafts-like conditions, Japanese workers have done similar studies.[14] In a typical reaction the heterogeneous system of the nitrogen containing reagent (hydroxylamine, azide, or derivative) and aluminum chloride in a one molar excess is heated at 80° to 100° in excess of the aromatic substrate. The products show predominant ortho-para substitution, but compared to other electrophilic aromatic substitutions there is a relatively large amount of meta substitution, attributed to the lack of selectivity of a very reactive species. However, competitive rates for different substrates show the characteristic substrate selectivity of normal electrophilic aromatic substitution. Yields vary from 11 percent to 65 percent (based on the nitrogen source) and isomer distribution as follows: ortho 22 to 54 percent, meta 13 to 27 percent, para 31 to 60 percent. These values can be compared with those for a typical electrophilic substitution on toluene given by chlorination with aluminum chloride: ortho 68, meta 1, and para 31 percent, or for nitration of toluene: ortho 59, meta 4, and para 37 percent.

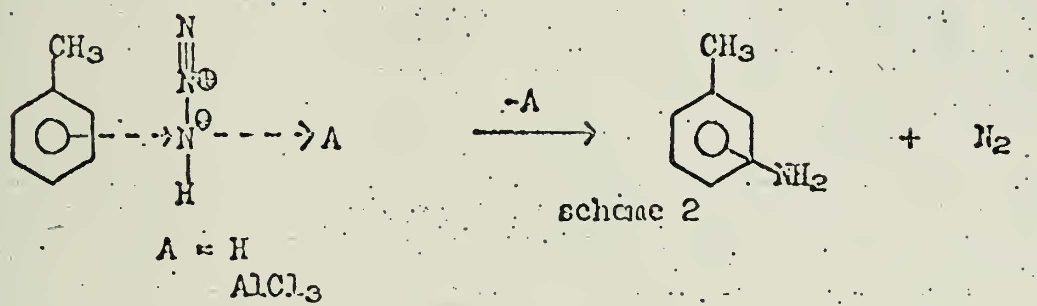
The use of azides for direct aminations has also been studied[15] and reviewed[8] by Kovacic. Hydrazoic acid reacts with toluene in the presence of aluminum chloride or concentrated sulfuric acid. The later catalyst does not generally give good yields except in the case of mesitylene,[17] which may involve a temporary sulfonation.

Although the heterogeneous systems prevent good kinetic determinations and there is very little known about the aminating species, Kovacic suggests that the mechanism for these reactions is concerted[8] and might be represented as shown in schemes 1 and 2.



scheme 1

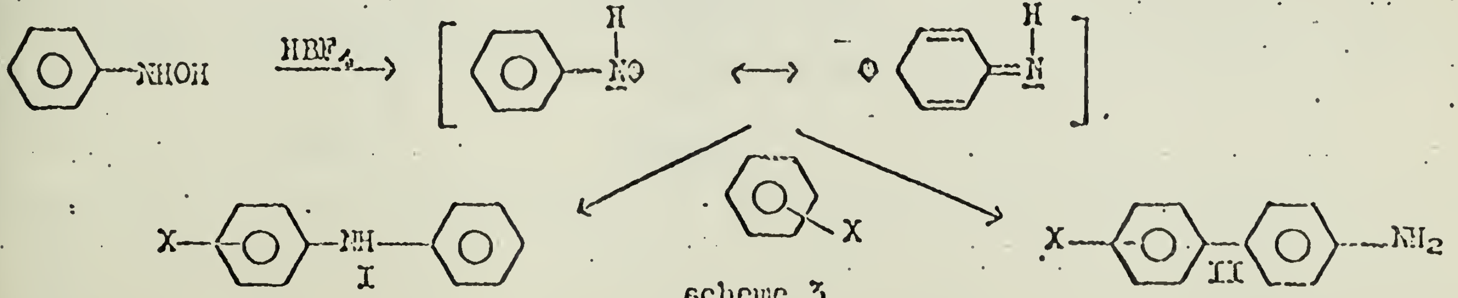
1) 11-65% yld
2) o (22-54%)
p (31-60%)
3) m (13-17)
4) rel rates (norm



scheme 2

Attempts at aminations with aluminum chloride and hydrazine, alkylhydrazines, and hydrazine salts were unsuccessful.[12]

Although Kovacic was not able to obtain aminations of alkyl benzenes using boron trifluoride and hydroxylamines,[13] Parish and Whiting[16] carried out aromatic substitutions using the highly acidic solution of boron trifluoride and hydrofluoric acid in sulfolane. When N-phenylhydroxylamine was added to this mixture followed by an aromatic compound, two types of products, I and II, resulting from substitution at nitrogen and carbon, were isolated (scheme 3).

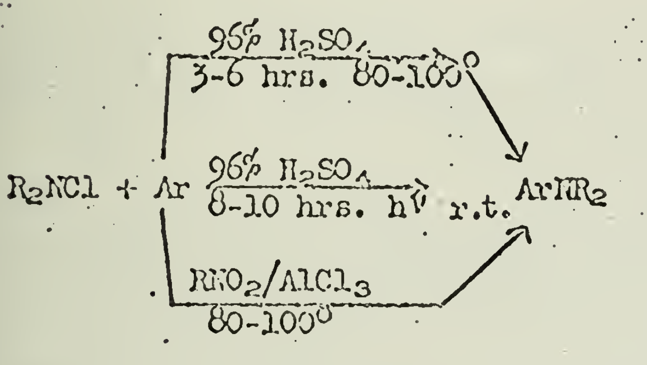


scheme 3

The phenylamination products were predominantly ortho and para, and the biphenyls produced were exclusively 2 or 4 substituted. The selectivity and directness of the reaction would make it synthetically useful.

In a communication, Kreher and Jager[18] have reported that aromatic azides will produce N-arylanilines under Friedel-Crafts conditions. It has been noted that aniline was a minor decomposition product of benzenesulfonylazides.[19,43] Lwowski and Scheiffele[43] suggested that in protic solvents the aniline arose from a Curtius-type rearrangement followed by hydrolysis. Sidhu, Thyagarajan, and Bhalerao[19] produced aromatic amines in good yields through decomposition of arylsulfonylazides in excess aromatic substrate. In this case, the product was independent of the substituents on the arylsulfonylazide which supported the proposed mechanism of electrophilic substitution followed by hydrolysis rather than an initial intramolecular rearrangement.

Early efforts to effect alkylaminations using N-chloroamines were not successful. Recently Boch and Kompa[20-23] have published details of three methods for dialkylaminations of aromatic compounds using N-chlorodialkylamines which are advantageous over other methods for the production of acid stable N,N-dialkylaromatic amines (reactions 5, 6, and 7). Yields varied from 21 to 90 percent. Competitive reactions were used to determine relative rates and these showed the characteristic intermolecular selectivity of an electrophilic aromatic substitution, as seen in Table I. However, as with Kovacic's work[9] mentioned above there was a rather high proportion of meta substitution. For example, with toluene,[20] isomer distributions for dimethylamination were as follows: 9 to 21 percent, ortho, 27 to 53 percent meta, and 33 to 59 percent para. The low amount of ortho isomer might be rationalized on the basis of steric effect, but the high meta substitution is unexplained.



(5)

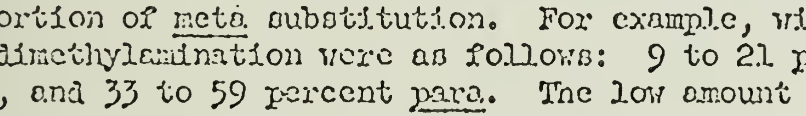
(6)

(7)

Table I-Relative Rates $\frac{k_{\text{benzenes}}}{k_{\text{toluene}}}$

Aromatic	Dimethyl-amination	Nitration	Phenylation
ΦCl	0.01	0.013	1.44
ΦH	1.0	1.0	1.0
ΦCH$_3$	9.3	10.0	1.73

Increasing the size of the alkyl groups on the N-chlorodialkylamine lowered the yields and no amination at all occurred above n-butylamines,[21,22,23] as Hoffmann-Loffler cyclization occurred exclusively. Only slight changes in reaction conditions caused chlorination to become a competing reaction. No better solvent than nitroalkanes could be found for the reaction with aluminum chloride.[23] Indeed, they were the only solvents giving practical yields. Of the specific role of the nitroalkanes it was noted that IR and dipole moment studies had showed that aluminum chloride and nitromethane produce 1:1 and 1:2 adducts probably of the nature of an aluminum chloride complex with one of the oxygens of the nitro group. The authors suggested that these species might be responsible for the success of the method.[23] Further details on the mechanism could not be obtained because the heterogeneity of the reaction mixture prevented kinetic work. However, the workers proposed a general reaction (scheme 4) for the production of a cation radical as the active species.[23] Cation radicals have been proposed in other N-cloro compound reactions:



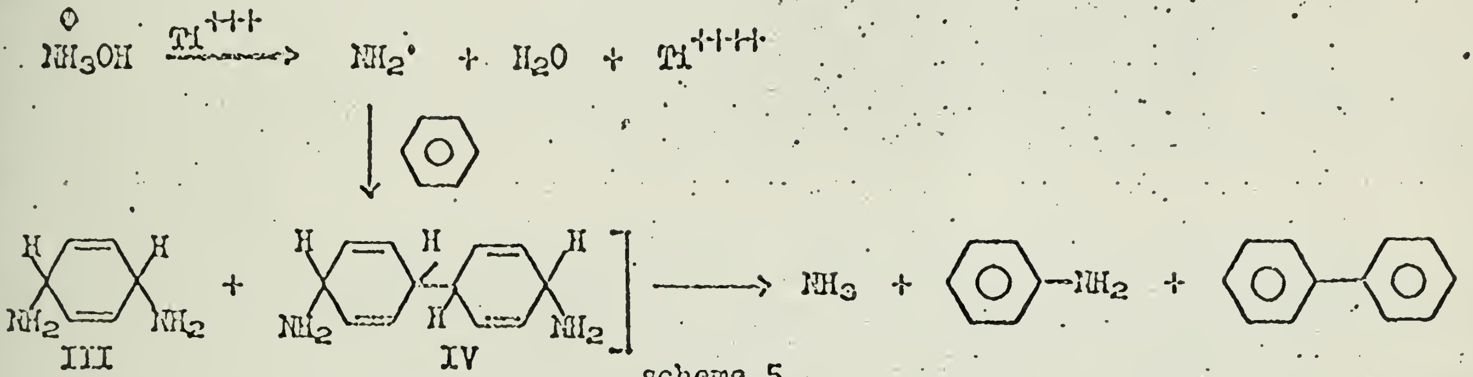
X = H or AlCl$_2^\ominus$

scheme 4

the Hoffmann-Loffler cyclization[44,45] and addition of N-chloro compounds to olefins.[4 Boch and Kompa felt that the photolytic reaction and the fact that the Hoffmann-Loffl cyclization was a competing reaction were evidence for the radical nature of the reactive species.[23] The second reaction path in scheme 4 would account for chlorination being a competing reaction. It was noted that no free radicals arise from N-chlorodialkylamines under reaction conditions.[22]

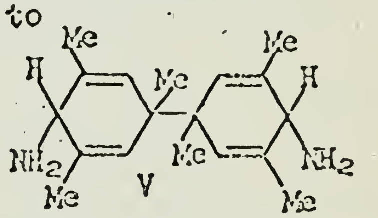
Homolytic Aromatic Substitution

Dermer and Edmison have reviewed[41] homolytic aromatic substitutions and state that prior to 1954 aminations of this type were "rare". Hydroxylamine is believed[47,48] to undergo reduction by ions of reducing metal salts such as ferrous and titanous ions to a species which behaves much as one might expect the amino radical $NH_2\cdot$ to behave; it adds to olefins and initiates vinyl polymerization.[28,47,48] In 1954 Seaman, Taylor, and Waters[47] reduced hydroxylamine with titanous ion in benzene and isolated an unstable product which decomposed to ammonia, aniline, and biphenyl on heating. They suggested a possible reaction outline (scheme 5) with III and IV as the unstable intermediates.



scheme 5

In 1959, Albisetti, Coffman, Hoover, Jenner, and Mochel[48] confirmed their results but suggested that the protonated species $\overset{\oplus}{N}H_3\cdot$ might be the active entity in scheme 5. Minisci, Galli, and Cecere[28] were able to isolate V using mesitylene as a substrate. Thus there seems to be reasonable evidence that these species add to aromatic hydrocarbons.



Cowley and Waters[49] thermally decomposed tetramethyltetrazine in liquid naphthalene and in an anisole solution of anthracine but were not able to detect any tertiary aromatic amine, dimethylamine being the principal product. The dimethylamino radical, which would be expected to be more stable that the amino radical does not react with the aromatic nucleus. Similarly, the phenylamino radical, $C_6H_5NH\cdot$, does not seem to attack alkylbenzenes.[50] If these radicals are accurate models of the amino radical, these observations suggest that simple direct radical attack on the aromatic nucleus followed by loss of a hydrogen atom to give the amine is not the reaction pathway for these systems.

Recently two groups of workers have investigated systems using reducing metal salts and hydroxylamine, hydroxylaminesulfonic acid, and N-chloroalkylamines.[24-30] Direct aminations have been obtained which they maintain are the result of the formation of free radicals as shown in reactions 8, 9, and 10.

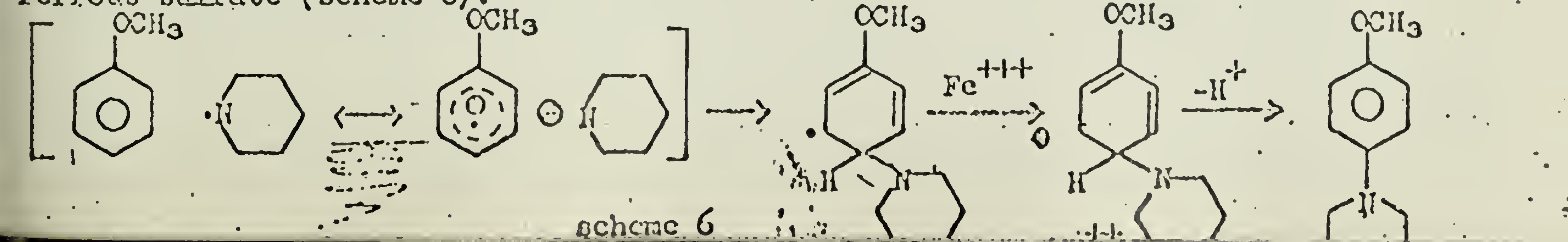
$$NH_2OSO_3H \xrightarrow{Fe^{++}} \overset{\oplus}{N}H_3\cdot + Fe^{+++} + SO_4^{=} \qquad (8)$$

$$NH_2OH\cdot HCl \xrightarrow{Fe^{++}} NH_2\cdot + Fe^{+++} + Cl^{\ominus} + H_2O \qquad (9)$$

$$R_2NCl \xrightarrow{Fe^{++}} R_2N\cdot + Fe^{+++} + Cl^{\ominus} \qquad (10)$$

Yields up to 65 percent were obtained and isomer distributions varied considerably, from complete *ortho-para* substituted products with anisole to 53 percent *meta* substitution for toluene.

Minisci and Galli[26] proposed a *charge transfer mechanism* to explain the results of the reaction of N-chloropiperidine and anisole in methanol in the presence of ferrous sulfate (scheme 6).



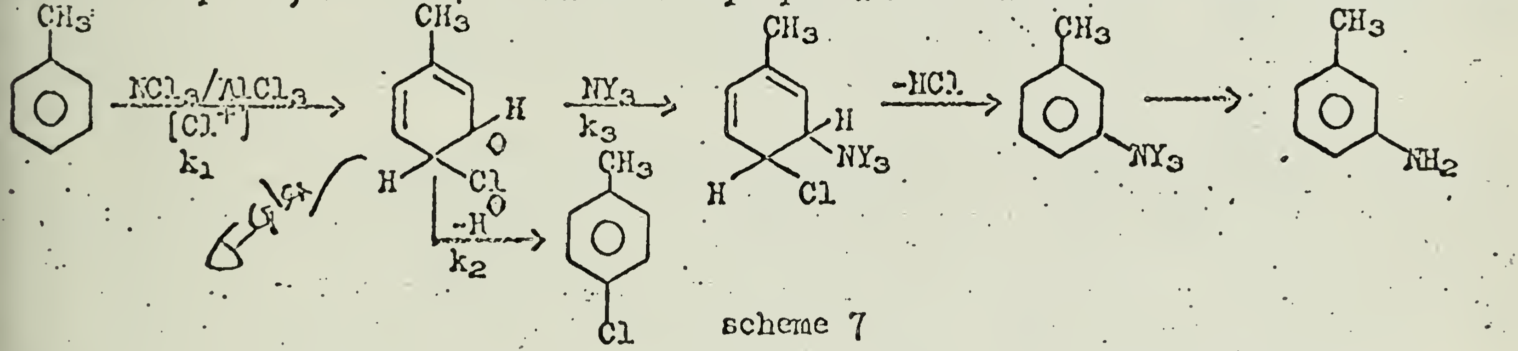
scheme 6

The synthetic values of these aminations have been pointed out by Minisci and Galli:[30] the N-cloramines are readily available, the reactions are not difficult and have been carried out in methanol,[26] water,[25] excess aromatic compound,[26] but generally in sulfuric acid.[24,26] The reaction is often selective and the yields are reasonable. As with Boch and Kompa's methods,[20-23] Hoffmann-Loffler cyclization becomes predominant when n-butyl or longer alkyl groups are involved.[30] Similarly, chlorination is a competing side reaction.[29] Indeed, good yields of benzyl chlorides can be obtained from toluene.[28]

The work of Minisci and Galli,[26-30] and Yoshida, Matsumoto, and Oda[24,25] provides evidence for the involvement of free radicals in the systems that they have worked with, however, the evidence is not conclusive. In some cases the systems show similar isomer distributions to those observed by Kovacic under Friedel-Crafts conditions.[8] Further there are similarities to the observations of Boch and Kompa, e.g. the competing chlorination and Hoffmann-Loffler cyclization.[20-23] Studies of all three systems under the same conditions are necessary for further understanding.

Sigma Substitution

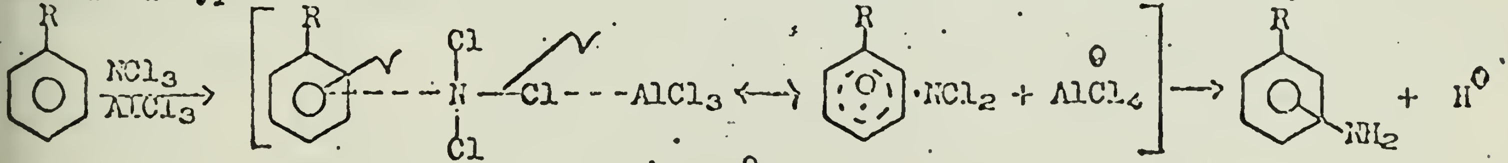
In 1964 Kovacic, Lange, Foote, Goralski, Hiller, and Levisky reported[31] that under Friedel-Crafts conditions trichloamine, dichloramine, and N-chloromethylamine produced meta substituted aromatic amines. The predominant meta substitution of the alkylbenzenes ruled out direct electrophilic amination. Relative rate studies were consistent with the formation of an arenonium ion (sigma complex) being involved in the rate determining step.[32] It was proposed that the sigma complex was formed by an electrophilic attack on the aromatic compound and that it subsequently underwent an addition-elimination. The proposal was designated as sigma substitution. In the case of toluene, using NY_3 for the aminating species and $Cl^{\oplus}$ for the electrophile, scheme 7 outlines the proposed mechanism.



scheme 7

The proposed arenonium ion intermediate could give meta amination by addition elimination, or chlorination by loss of a proton. In this scheme (7) k_1 would be rate determining, but k_2/k_3 would control the yield of amine relative to chloride.

It should be noted that Kovacic and Levisky have suggested[35] that a cation radical mechanism, (scheme 8) cannot be ruled out. This might be very close to a concerted type of mechanism with a trichloroamine-aluminum chloride complex.



scheme 8

The reaction is usually carried out by adding a solution of trichloramine in ortho-dichlorobenzene or 1,2-dichloroethane to a heterogeneous solution of aluminum chloride ($NCl_3/AlCl_3$ = 1/2) at low temperatures (-35° to 10°). After one two hours stirring the mixture is poured on a mixture of ice and hydrochloric acid and then the organic phase is collected and purified.

Yields were generally in the range of 25 to 35 percent meta-alkylaniline (based on trichloramine). When mono and dialkyl N-chloramines were used yields reached a maximum of nine percent.[37] With bibenzyl,[39] diphenylmethane,[34] cyclohexylbenzene,[34] and fluorene[39] yields of crude basic product were less than five percent. Naphthalene[39] produced approximately 30 percent naphthylamine, with the isomer distribution depending upon conditions. The use of halobenzenes as solvents was

noted to increase the yield.[31]

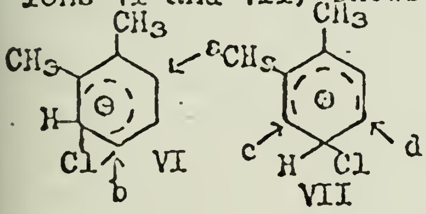
It was found that for optimum yield that the ratio of aluminum chloride to trichloramine must be two.[32] This was rationalized by noting that the basic products should be able to complex with the catalyst rendering it inert. This was given further support in that triethylamine, diethylether, and nitromethane (diluent/$AlCl_3$ = 1.5) quenched the reaction. Partially hydrolyzed aluminum chloride was apparently an effective catalyst as the yield was lowered only slightly by addition of a 1.5 molar ratio of water.[32]

With toluene as substrate a maximum yield of 42 percent meta-toluidine (based on trichloramine) was obtained. This represented only 67 to 83 percent of the basic product. Other basic products were largely 2-chloro-5-methylaniline and 3-methyl-4-chloroaniline. A large part of the neutral fraction was chlorotoluenes with an isomer distribution typical of electrophilic aromatic substitution: 68 ortho, 1 meta, 31 para. It was shown that ortho and para toluidines were stable to reaction conditions. Reaction 11 was suggested as a representation of the stoichiometry of the reaction.[34]

$$NCl_3 + 3C_6H_5CH_3 \xrightarrow{AlCl_3} \underline{m}\text{-}NH_2C_6H_4CH_3 + 2ClC_6H_4CH_3 + HCl \qquad (11)$$

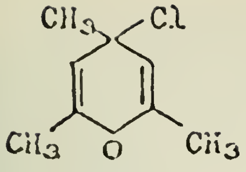
The relative reaction rates determined from competitive studies were plotted against relative rates of bromination and chlorination and against the basicities of the aromatic compounds. These showed a linear relationship which would be expected if electrophilic attack giving a sigma complex were the rate determining step.[51] However, this does not give information about the nature of the electrophile which Kovacic has suggested might arise from Cl_2 generated in situ, or from a complex of trichloramine and aluminum chloride. N-chloro compounds are known as chlorinating agents.[52] The fact that neutral and basic chlorinated products were isolated, and the production of chloro substituted aromatic amines from other haloalkylbenzenes (vide infra) tend to support a choroarenonium ion intermediate. The fact that added water did not substantially affect the yield argued against the arenonium ion arising from protonation.

Relatively little is known about the proposed nucleophile. Arguments have been advanced against trichloroamine's direct involvement. Kovacic, Levisky, and Goralski considered[34] it significant that with ortho-xylene the basic product was 57 percent 2,3-dimethylaniline and 43 percent 3,4-dimethylaniline. They noted that t-butylation of ortho-xylene gives 100 percent 3,4-dimethyl-t-butylbenzene. It was concluded that, as the more hindered isomer was produced in greater abundance in the amination, the steric requirements were smaller than those necessary for trichloroamine which would compare in size with the t-butyl group.[34] The value of this comparison may be limited as in the latter case attack occurs on the xylene producing a positive charge in the transition state whereas in the amination it is proposed that an arenonium ion is being attacked with neutralization of the ion's charge occurs during the transition state. An examination of the proposed sigma intermediates (arenonium ions VI and VII) shows that there is an alternative explanation which should be considered. In all cases the incoming group must approach a position adjacent to a chlorine, a methyl group, or both, however, only in attack at "a" on VI does the incoming nucleophile not have to approach adjacent to a chlorine. It might be this factor which give the slight preference for the more hindered isomer.



Another point cited against trichloramine being the nucleophile is the fact that the resulting N-chloroaromatic compound might undergo intramolecular chlorination. Although it has been proposed that N-chloroaromatic amines readily undergo intramolecular chlorination,[52] it is not certain that this would be the predominant reaction under the conditions used. Furthermore, ortho-chloro products have been detected in the higher boiling cut of the basic product. Also, dichloroamine and N-chloroalkylamines have been successfully used as aminating agents and methylaminating agents.[31,37] However, it must be noted that while carrying out aluminum chloride/trichloramine aminations of t-butylchloride, Kovacic and Lowery were able to isolate N,N-dichloro-t-butylamine. This points strongly to at least an N,N-dichloro aminating species.[38]

The reactions with mesitylene require comment.[34] The fact that even two percent either the arenonium ion VIII is involved, or that


VIII

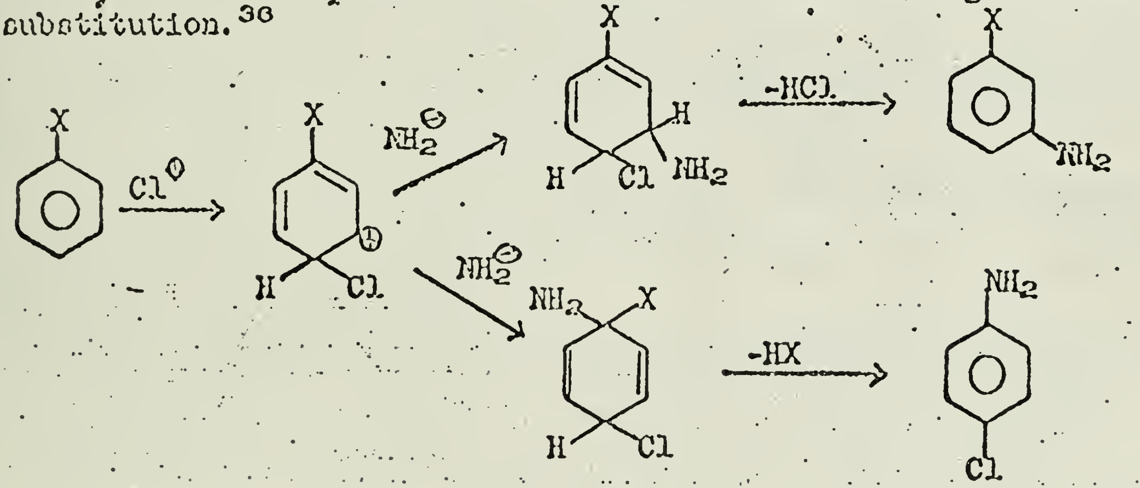
there is another reaction occurring, perhaps direct electrophilic amination.

The production of only 3-aminobiphenyl from biphenyl is noteworthy,[36] because it implies that if the proposed mechanism is correct, the attack of the aminating species occurs exclusively on the ring of the intermediate bearing the chlorine. Perhaps the overall reaction involves only one complex of trichloramine-derived entity and catalyst. This might limit the reaction to one ring of the biphenyl. Further, this would eliminate the necessity of postulating a distinct nucleophilic attack in a system containing large amounts of aluminum chloride.

Other possible mechanisms have been ruled out: direct electrophilic substitution because of the predominant meta substitution, and direct ortho-para substitution followed by rearrangement because both ortho and para toluidines are stable under reaction conditions. Orientation and relative rate studies seem to rule out free radical and nitrene reactions.

Nucleophilic Sigma Substitution

In extending their studies of the reaction of aromatic compounds with the trichloramine/aluminum chloride system, Kovacic and Gormish[36] found that with halobenzenes and anisole, a second type of reaction began to compete with the meta amination observed in other series. There compounds possessed a leaving group ortho or para to the presumed position of chlorine in the intermediate and it appeared that displacement of the halogen or methoxy group was occurring to give ortho and para-chloro aromatic amines. In fact the product of the reaction with anisole was almost exclusively ortho and para-chlorotoluidines.[33] Halotoluenes showed similar results.[36] Scheme 9 was proposed to account for the observation, and the displacement of substituent X was designated as nucleophilic sigma substitution.[36]

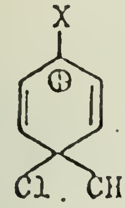


scheme 9

Conditions used were very similar to those for the other reactions;[36] a solution of trichloemine in ortho-dichlorobenzene or 1,2-dichloroethane was added to a stirred heterogeneous mixture of the aromatic compound and aluminum chloride. The procedure will be of value for the selective preparation of aromatic compounds with three substituents. Yields were in the range of 20 to 40 percent. From halotoluenes, yields of the substituted aniline with the amine group and a meta halogen were in the range of 5 to 20 percent. For example, 3-bromo-5-methylaniline was obtained in 14 percent yield from meta-bromotoluene, and 2-methyl-5-chloroaniline was obtained in 14.5 percent yield from para-chlorotoluene.[36] As strong salt and solvent effects have been observed, it may be possible that the selectivity can be tailored by alteration of conditions.

Nucleophilic displacements on NO_2 or SO_2R substituted aromatic compounds are well known.[2,3] In this case it is proposed that the displacement occurs on the arenonium ion, however, the order of ease of halogen displacement is the same in both cases: F $\gg$ Cl $>$ Br. Nucleophilic sigma substitution, for the synthesis of a substituted aniline with a para-chloro group, was most effective with fluorine compounds. Sigma substitution was most effective with bromine compounds. Reduction in the amount of sigma substitution product by meta substituents was noted for meta-halotoluenes.[36]

The reactions with para-halotoluenes produced a significant amount of para-toluidine and tar. The production of the para-toluidine would necessitate the invoking of an arenonium ion like IX.[30] This is similar to the form invoked for the reaction with mesitylene.[34] It was thought that bromo and chlorodurene might give exclusive nucleophilic sigma substitution because the meta positions are occupied. However, a mixture of products was obtained, probably through rearrangement and disproportionation.[30]



IX

Conclusion

It is interesting that a single type of reaction, direct aromatic amination, which uses similar reactants; aromatic compounds and hydroxylamine derivatives or N-chlorocompounds, would elicit such a wide variety of proposed mechanisms. If this is indeed a situation in which small changes in conditions can alter the mechanism it should deserve further attention. It is unfortunate that the systems are for the most part heterogeneous, preventing the necessary kinetic studies. A necessary first step for obtaining better data on the reactions is the finding of homogeneous systems.

The wide variety of conditions and selectivity combined with the one step nature of the reactions cannot help but attract the attention of the synthetic chemist.

BIBLIOGRAPHY

1. P. A. S. Smith, Open-chain Nitrogen Compounds, W. A. Benjamin, Inc., New York, N. Y., 1965 (a) page 116 (b) page 118.
2. J. F. Bunnett and R. E. Zahler, Chem. Rev., 49, 273 (1951).
3. J. F. Bunnett, Quart. Rev., 12, 1 (1958).
4. R. A. Larson, U. of Ill. Organic Seminars, Summer 1965, page 105
5. R. Lambert, U. of Ill. Organic Seminars, Summer 1963, page 167
6. P. A. S. Smith, Chapter 8. Molecular Rearrangements, edited by P. de Mayo, John Wiley and Sons, Inc., New York, N. Y., 1963.
7. J. R. Puig and E. Schwarz, Pro. Conf. Ind. Uses Large Radiation Sources, 1, 57 (1963) (Fr.) Chem. Abstr., 61, 5540d.
8. N. S. Koslov and L. F. Akhmetshina, J. Gen. Chem. U.S.S.K. 25, 453 (1955), Chem. Abstr. 51, 2858 (1957).
9. P. Kovacic, Chapter XLIV Friedel-Crafts and Related Reactions, edited by G. A. Olah, Vol. III, Part 2. Interscience Publishers New York, N. Y., 1964.
10. P. Kovacic and R. P. Bennett, J. Am. Chem. Soc., 83, 221 (1961).
11. P. Kovacic and J. L. Foote, J. Am. Chem. Soc., 83, 743 (1961).
12. P. Kovacic, R. P. Bennett, and J. L. Foote, J. Org. Chem. 26, 3013 (1961).
13. P. Kovacic, R. P. Bennett, and J. L. Foote, J. Am. Chem. Soc., 84, 759 (1962).
14. Z. Yoshida, T. Okushi, and R. Ola, Kogyo Kagaku Zasshi, 67, 76 (1964) Chem. Abstr. 61 5540b.
15. P. Kovacic, R. L. Russell, and R. P. Bennett, J. Am. Chem. Soc., 86, 1560 (1964).
16. J. H. Parish and M. C. Whiting, J. Chem. Soc., 4713 (1964).
17. C. M. Hoop and J. M. Tedder, J. Chem. Soc., 4685 (1961).
18. R. Kreher and G. Jager, Angew. Chemie. Inter. Ed. in English 4, (8) 706 (1965).
19. G. S. Sidhu, G. Thyagarajan, and U. T. Bhalerao, Chem. and Ind. (London) 1301 (1966).
20. H. Boch and K.-L. Kompa, Angew. Chemie Inter. Ed. in English, 4, 783 (1965).
21. H. Boch and K.-L. Kompa, Chem. Ber. 99, 1347 (1966).
22. H. Boch and K.-L. Kompa, ibid., 99, 1357 (1966).
23. H. Boch and K.-L. Kompa, ibid., 99, 1361 (1966).
24. Z. Yoshida, T. Matsumoto, and R. Oda, Kogyo Kagaku Zasshi, 65, 46 (1962) Chem. Abstr., 57, 16446i.
25. Z. Yoshida, T. Matsumoto, and R. Oda, ibid., 67, 64 (1964), Chem. Abstr., 61, 1789f.

26. F. Minisci and R. Galli, Tetrahedron Letters, (8) 433 (1965).
27. F. Minisci and R. Galli, ibid., (22) 1679 (1965).
28. F. Minisci, R. Galli, and M. Cecere, ibid., (51) 4663 (1965).
29. F. Minisci and R. Galli, ibid., (2) 699 (1966).
30. F. Minisci and R. Galli, ibid., (23) 2530 (1965).
31. P. Kovacic, R. M. Lange, J. L. Foote, C. T. Goralski, J. J. Hiller, Jr., and J. A. Levisky, J. Am. Chem. Soc., 86, 1650 (1964).
32. P. Kovacic, C. T. Goralski, J. J. Hiller, Jr., J. A. Levinsky, and R. M. Lange, J. Am. Chem. Soc., 87, 1262 (1965).
33. P. Kovacic, J. J. Hiller, Jr., J. F. Gormish, and J. A. Levisky, Chem. Comm. (22) 850 (1965).
34. P. Kovacic, J. A. Levisky, and C. T. Goralski, J. Am. Chem. Soc., 88, 100 (1966).
35. P. Kovacic and J. A. Levisky, J. Am. Chem. Soc., 88, 1000 (1966).
36. P. Kovacic and J. F. Gormish, J. Am. Chem. Soc., 88, 3819 (1966).
37. V. L. Heasley, P. Kovacic, and R. M. Lange, J. Org. Chem., 31, 3050 (1966).
38. P. Kovacic and M. K. Lowery, unpublished work.
39. P. Kovacic and A. K. Harrison, Unpublished work.
40. D. R. Augood and G. H. Williams, Chem. Rev., 49, 273 (1951).
41. O. C. Dermer and M. T. Edmison, Chem. Rev., 57, 77 (1957).
42. G. H. Williams, Homolytic Aromatic Substitution, International Series of Monographs on Organic Chemistry, Vol. 4, Pergamon Press, New York, N. Y., 1960.
43. W. Lwowski and E. Scheiffele, J. Am. Chem. Soc., 87, 4359 (1965).
44. M. E. Wolff, Chem. Rev., 63, 55 (1963).
45. R. S. Neale and M. R. Walsh, J. Am. Chem. Soc., 87, 1255 (1965).
46. R. S. Neale, J. Am. Chem. Soc., 86, 5340 (1964).
47. H. Seaman, P. J. Taylor, and W. A. Waters, J. Chem. Soc., 4690 (1954).
48. C. J. Albisetti, D. D. Coffman, F. W. Hoover, E. L. Jenner, and W. E. Mochel, J. Am. Chem. Soc., 81, 1489 (1959).
49. B. R. Cowley and W. A. Waters, J. Chem. Soc., 1228 (1961).
50. B. A. Dolgoplosk, B. L. Erusalimskii, V. A. Krol, and L. M. Romanov, Zhur. Obshchei Khim., 24, 1775 (1954), Chem. Abstr., 49, 12339c.
51. A. Streitwieser, Jr., "Molecular Orbital Theory", John Wiley and Sons, Inc., New York, N. Y., 1961 Chapter 11.
52. R. S. Neale, R. G. Schepers, and M. R. Walsh, J. Org. Chem., 29, 3390 (1964).

THE MECHANISM OF SELENIUM DIOXIDE OXIDATIONS

Reported by Bruce A. Morrison November 7, 1966

INTRODUCTION

The oxidizing ability of selenium dioxide has been known since early in this century.[1] It was not until the 1930's, however, that any systematic work on the mechanism of the reaction was begun. The major reactions of this oxidizing agent, which have been well summarized,[2,3] can be grouped into three types: the formation of α-dicarbonyls from ketones (1); dehydrogenation (2); allylic oxidation (3). Extensive data concerning the mechanism or mechanisms of these reactions has recently become available.

$$\text{-CH}_2\text{CO-} \longrightarrow \text{-COCO-} \qquad (1)$$

$$\text{-COCH}_2\text{CH}_2\text{CO-} \longrightarrow \text{-COCH=CHCO-} \qquad (2)$$

$$\text{-CH=CHCH}_2\text{-} \longrightarrow \text{-CH=CH-CH(OH)-} \qquad (3)$$

ISOLATED KETONE OXIDATION

Mel'nikov and Rokitskaya investigated the kinetics of the oxidation of ketones to α-dicarbonyl compounds.[4] They noted that the rate of this oxidation paralleled closely that for bromination of the same ketones, a reaction which was thought to proceed through the enol form of the ketone. Earlier these same workers had noted the ability of selenium dioxide to react with primary alcohols to form esters which undergo thermal decomposition to the corresponding aldehydes, selenium, and water (4).

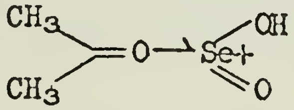
$$\text{RCH}_2\text{OH} \xrightarrow{\text{SeO}_2} \text{RCH}_2\text{OSeO}_2\text{H} \xrightarrow[300^\circ]{\text{N}_2} \text{RCHO} + \text{Se} + \text{H}_2\text{O} \qquad (4)$$

These facts led to the hypothesis of a mechanism involving enolization of the ketone followed by attack of selenous acid (the probable form of selenium dioxide in the aqueous medium) on the enol to form an ester which decomposes to products.

Duke[6] studied the oxidation of acetone to glyoxaldehyde by selenous acid and found first order dependence on added strong acid, as well as on acetone and selenous acid. The expression for the rate of selenous acid disappearance, which is the actual measured quantity, may be written as follows:

$$-d(\text{H}_2\text{SeO}_3)/dt = k(\text{acetone})(\text{H}_2\text{SeO}_3)(\text{H}^+). \qquad (5)$$

From this result Duke concludes that the rate determining step is the formation of an intermediate (I) and water from the reaction of protonated selenous acid and



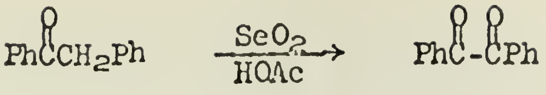
I

acetone. Subsequent rearrangement and elimination to form the observed product are said to be fast. The discovery of strong acid catalysis in addition to first order rate dependence on selenous acid precludes the possibility of a mechanism with simple enolization (whether acid catalyzed or not) as the rate determining step. The data include an inverse rate dependence on water concentration. Duke proposed two explanations: changes in the activities of the reactive species stemming from the change in solvent composition; or, the formation of the complex (I) in an equilibrium step, with the slow step occurring later. Were the latter explanation correct, the elimination of water in the formation of I would cause the rate law to be modified to (6), where K is the equilibrium constant for the reaction to

$$-\frac{d(\text{H}_2\text{SeO}_3)}{dt} = \frac{kK(\text{acetone})(\text{H}_2\text{SeO}_3)(\text{H}^+)}{(\text{H}_2\text{O})} \qquad (6)$$

form I. This possibility was not rigorously excluded.

Corey and Schaefer have carried out an extensive study of the oxidation of desoxybenzoin (II) to benzil (III) by selenium dioxide in aqueous acetic acid.



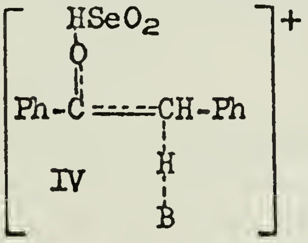
$$\underset{\text{II}}{Ph\overset{O}{\overset{\|}{C}}CH_2Ph} \xrightarrow[H_2O]{\frac{SeO_2}{HOAc}} \underset{\text{III}}{Ph\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}Ph}$$

They found a rate law (7) for the disappearance of selenous acid which agrees with that found by Duke. When the methylene protons were replaced by deuterium,

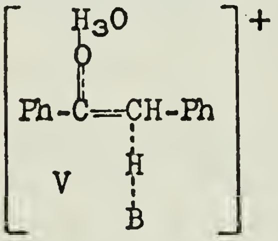
$$-d(H_2SeO_3)/dt = k(\text{ketone})(H_2SeO_3)(H^+) \qquad (7)$$

a k_H/k_D of 6.0 was observed; therefore, rapid reversible enolization cannot be occurring since this would not allow an isotope effect. Duke's mechanism is also discredited because it does not include C-H bond breaking in the rate determining step.

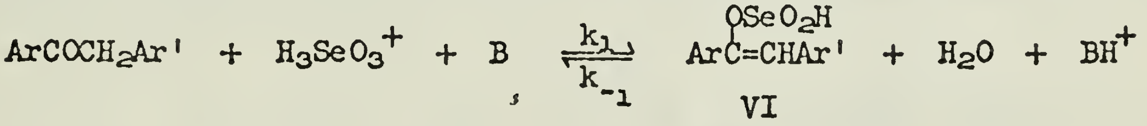
Although prior enolization may be discounted as an important process in the oxidation mechanism, the isotope effect suggests a real similarity between enolization and oxidation. Further evidence of this similarity was obtained by Corey and Schaefer from substituent effects in the acid catalyzed oxidation.[7,8] The *rho* values obtained for *para*-substitution in the benzoyl and benzyl groups using the standard Hammett *sigma* values for the substituents were $\rho_{ArCO} = -0.56$ and $\rho_{ArCH_2} = +0.25$. For enolization the corresponding values are -0.56 (determined on *p*-substituted acetophenones)[9] and +0.50 (determined on *p*-benzyl substituted desoxybenzoins).[8] Although the *p*-nitro group correlated normally for both sets of data on enolization and for oxidation in the case of benzoyl substitution, the oxidation of phenyl *p*-nitrobenzyl ketone was anomalously slow. From this general parallel between enolization and oxidation, Corey and Schaefer concluded that there is probably a strong resemblance between the transition states for these two reactions. The observed isotope effect indicated that they must involve appreciable C-H bond breaking. Acid catalysis indicated that there should be a protonated species present. The signs of the Hammett *rho* values indicated the probability of electrophilic attack at the carbonyl accompanied by nucleophilic attack on a benzyl proton. The transition state proposed, IV, is analogous to that proposed for enolization by Swain, V.[10] The base (B) can be water or added acetate ion. Assuming IV to be the transition state for selenium dioxide oxidation, Corey and Schaefer arrived at the following mechanism for the acid catalyzed reaction:



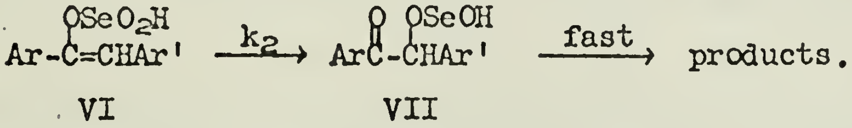
IV



V



$$ArCOCH_2Ar' + H_3SeO_3^+ + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\text{VI}}{Ar\overset{OSeO_2H}{C}{=}CHAr'} + H_2O + BH^+ \qquad (8)$$



$$\underset{\text{VI}}{Ar-\overset{OSeO_2H}{C}{=}CHAr'} \xrightarrow{k_2} \underset{\text{VII}}{Ar\overset{O}{\overset{\|}{C}}-\overset{OSeOH}{C}HAr'} \xrightarrow{\text{fast}} \text{products}. \qquad (9)$$

The observed reaction rate, v, derived from this mechanism is given by equation 10.

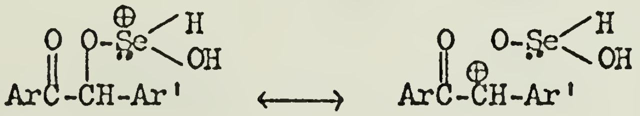
$$v = \frac{k_2k_1(H_3SeO_3^+)(ArCOCH_2Ar')(B)}{k_2 + k_{-1}(H_2O)(BH^+)} \qquad (10)$$

If the first step in (8) is taken to be the slow step, that implies that $k_2 \gg k_{-1}(H_2O)(BH^+)$. If this is the case, then the observed rate of reaction, which is the disappearance of selenous acid, is equivalent to both the rate of disappearance of ketone and the rate of formation of products. It might be noted that $H_3SeO_3^+$ is used in this mechanism on the grounds that it would be unreasonable to expect an appreciable concentration of $HSeO_2^+$ in aqueous media.

Further support for this mechanism is found in its ability to explain the anomalous rate retardation observed for the oxidation of phenyl p-nitrobenzyl ketone. This can be done if in this case $k_{-1}(H_2O)(BH^+)$ becomes important with respect to k_2. This would require that the transition state for the formation of VII from VI be destabilized by the presence of the p-nitro group. A rationale for this is provided by the further observation that the oxidation rate for phenyl p-nitrobenzyl ketone is linearly dependent on acid concentration. Since this does not follow from equation 10, a modified rate law must be derived. The rather simple hypothesis of acid catalysis for the transformation of VI to VII serves to explain both this effect and the anomalously slow oxidation rate of the nitro compound. If this assumption is true, then a modified rate law can be derived (11), where v' is the observed rate. The effect of acid catalysis of rearrangement is to

$$v' = \frac{k_2k_1(H_3SeO_3^{+})(ArCOCH_2Ar')(B)}{k_2 + k_{-1}(H_2O)} \tag{11}$$

modify the structure of VII to its conjugate acid (VIII) which would be expected to cause development of excess positive charge at the benzyl position in the transition



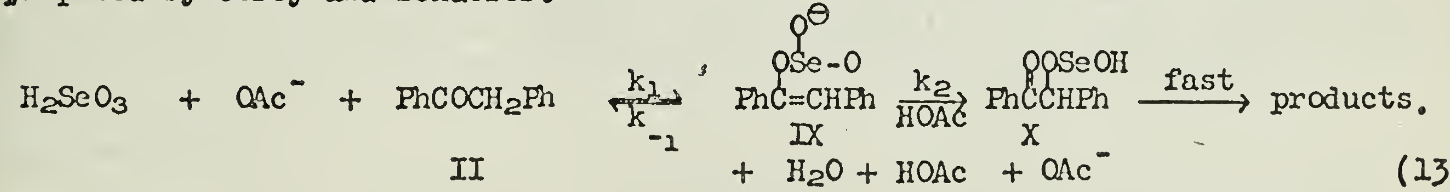
VIII VIII'

state either by an inductive effect or by participation of the canonical form VIII'. Such an effect would cause marked destabilization of this transition state by the p-nitro substituent. Although only in the case of the p-nitrobenzyl ketone is the rate of rearrangement slowed sufficiently to become a measurable reaction, it is reasonable to expect that strong acid catalysis of the rearrangement of VI to VII (in the form of VIII) is a general phenomenon for this reaction, and that equation 11 correctly describes the rate dependence.

In the same investigation, Corey and Schaefer found that the oxidation could be a base catalyzed process obeying the rate expression

$$-d(H_2SeO_3)/dt = k(H_2SeO_3)(ArCOCH_2Ar')(OAc^-). \tag{12}$$

A deuterium isotope effect ($k_H/k_D = 7.6$) once again indicated C-H bond breaking in the rate determining step. The Hammett rho value for para-benzoyl substitution ($\rho_{ArCO} = +0.77$) resembles that for enolization of acetophenones ($\rho = +0.50$).[9] Again the p-nitrobenzyl compound shows the expected enhanced enolization rate but an anomalously slow rate of oxidation. Ortho substitution on the benzoyl moiety does not retard the reaction, but ortho substitution in the benzyl group results in marked rate reduction. To explain these data, the following mechanism was proposed by Corey and Schaefer:[8]

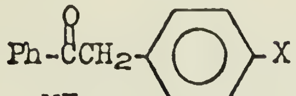


$$\underset{II}{H_2SeO_3 + OAc^- + PhCOCH_2Ph} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{IX}{PhC(OSe(O)O^{\ominus})=CHPh} \xrightarrow[HOAc]{k_2} \underset{X}{PhC(O)CH(OSeOH)Ph} \xrightarrow{fast} products. \quad + H_2O + HOAc + OAc^- \tag{13}$$

The retardation effect of the p-nitrobenzyl moiety is explained principally in terms of a decrease in the facility of rearrangement of IX to X because of the decreased acidity of the medium. This step is analogous to that rearrangement in the acid-catalyzed mechanism which was found to be dependent on strong acid concentration.

In subsequent work, Schaefer[11] has investigated further these benzyl substituent effects in the acetate ion catalyzed oxidation of desoxybenzoins. It had been observed that with unsubstituted desoxybenzoin (XIa) the addition of acetate ion increased the rate of selenium dioxide oxidation to a maximum when one equivalent had been added. Further addition of acetate ion caused a monotonic rate decrease with increasing acetate ion concentration. Schaefer studied the acetate ion catalyzed oxidation of XIa, b, and c over a large range of acetate concentrations.

He found that XIb (p-NO_2) gives the same type of increasing then decreasing rate effect as did the unsubstituted case (XIa). In the third case (XIc) the rate

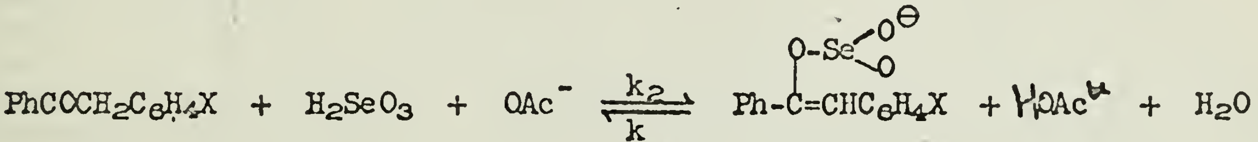


XI

a: X = H
b: X = NO_2
c: X = OCH_3

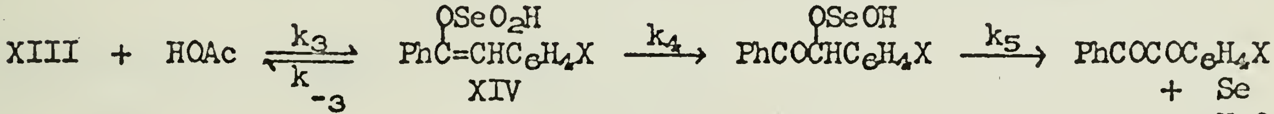
approaches a maximum value asymptotically after a rapid increase up to one equivalent of added acetate. A mechanism was proposed which explains these observations (14-16). From this formulation Schaefer derived a general rate expression (17)

$$H_2SeO_3 + OAc^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HSeO_3^- + HOAc \qquad (14)$$



$$PhCOCH_2C_6H_4X + H_2SeO_3 + OAc^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Ph\overset{O-SeO_2^{\ominus}}{C}=CHC_6H_4X + HOAc + H_2O \qquad (15)$$

XII XIII



$$XIII + HOAc \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} Ph\overset{OSeO_2H}{C}=CHC_6H_4X + OAc^- \xrightarrow{k_4} PhCO\overset{OSeOH}{C}HC_6H_4X \xrightarrow{k_5} PhCOCOC_6H_4X + Se + H_2O \qquad (16)$$

XIV XV

by application of steady-state assumptions with the slow step assumed to be the formation of XV from XIV. Schaefer claimed that if step 2 (reaction 15) becomes

$$v = a(PhCOCH_2C_6H_4X)(H_2SeO_3)_{tot.} \left[\frac{1}{\frac{b}{(OAc^-)eq} + c + d(OAc^-)eq} \right] \qquad (17)$$

rate determining, then equation 17 reduces to 18 because d becomes negligible.

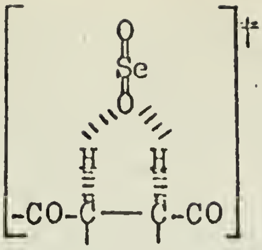
$$v' = a(PhCOCH_2C_6H_4X)(H_2SeO_3)_{tot.} \left[\frac{(OAc^-)eq}{b + c(OAc^-)eq} \right] \qquad (18)$$

These expressions can serve to explain the two types of base-dependence observed. Equation 17 corresponds to the "increase-decrease" result, whereas 18 corresponds to the "asymptotic" result. It is assumed that for the unsubstituted case (XIa) the step with constant k_4 is rate determining. Then if the rearrangement of XIV to XV is considered to involve electrophilic attack at the benzyl carbon, and if the formation of XIII is thought to include nucleophilic attack on a benzyl proton of XII, the presence of the p-nitro substituent in the benzyl group would be expected to increase k_2 and decrease k_4 relative to the unsubstituted case. The effect of p-methoxybenzyl substitution should be just the opposite. The rate data indicates that the effect is great enough to change the slow step from that measured by k_4 to that measured by k_2.

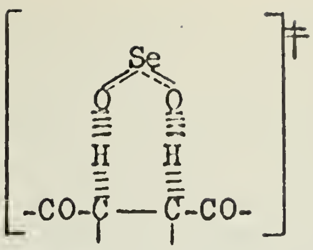
DEHYDROGENATION

Dehydrogenation of ketones to α,β-unsaturated systems by selenium dioxide is generally a competitive reaction to the formation of α-diketones. In the case of 1,4-diketones it is usually the predominant reaction to the exclusion of triketone formation.[3,12] Dehydrogenation can also be the major reaction in molecules with a single ketone function. This has been demonstrated with numerous steroid molecules.[13-17]

In 1953, Barnes and Barton[18] observed in a steroid-like system containing the 1,4-diketone moiety that dehydrogenation proceeded when the methylene protons were cis but not when they were trans. This led to the postulate of a cyclic transition state for dehydrogenation having the form XIX or XX. Later work by Banerji, Barton, and Cookson[19] demonstrated that for selenium dioxide oxidation of 1,4-diketones in dioxane-acetic acid, the reaction of compounds with cis protons was much faster than



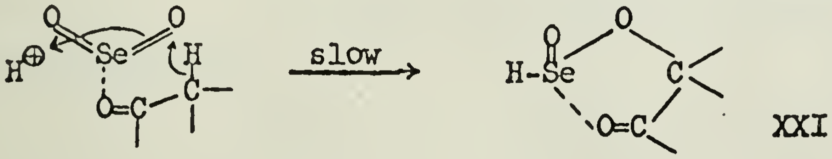
XIX



XX

that of compounds with trans protons. In the same work it was found that bromination of the same compounds in acetic acid and sodium acetate, which is thought to depend on the rate of enolization, exhibited the same favoring of cis over trans. This rather strongly suggests that the transition state might rather resemble that for enolization, and therefore, that proposed by Corey and Schaefer[7,8] for the formation of α-diketones.

Langbein studied the dehydrogenation of cortisone by selenium dioxide in t-butyl and t-amyl alcohol containing 1% acetic acid.[14] He found the reaction to be first order in both oxidizer and substrate and also to be catalyzed by strong acid. Dehydrogenation does not occur in completely aprotic media. A mechanism consistent with these data was proposed to explain both dehydrogenation and diketone formation. The slow step in each case involves the abstraction of an α-hydrogen by a protonated



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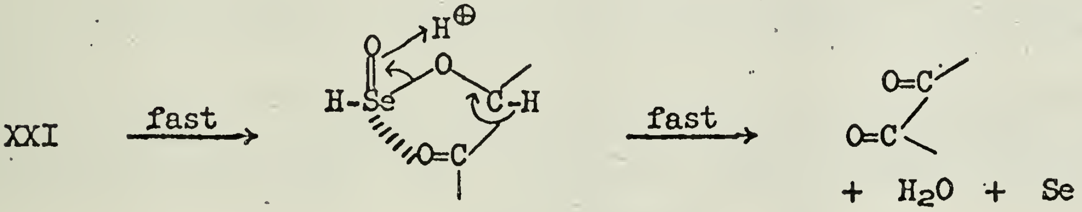

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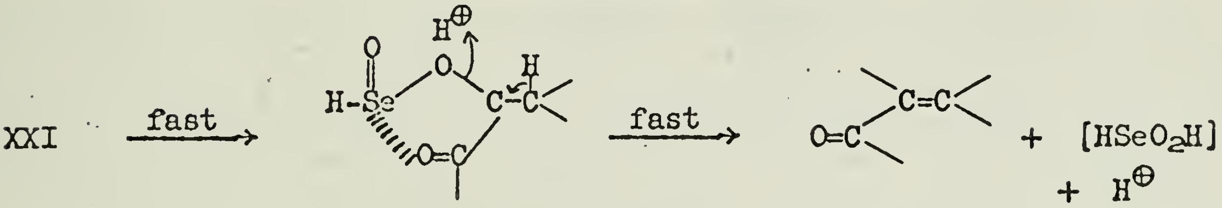


(21)

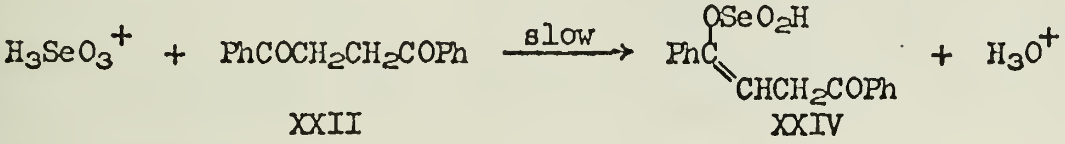
selenium dioxide molecule which is complexed with the carbonyl. It may be regarded as a combination of the Duke and the Corey and Schaefer mechanisms in which a complex is formed in an equilibrium step, and the base involved in the proton abstraction is the protonated selenium dioxide molecule. Corey and Schaefer[8] discounted a similar cyclic mechanism involving electrophilic attack by the selenium dioxide on the carbonyl and nucleophilic attack on the benzyl proton by the same species because of the linear strong acid catalysis. They reasoned that protonation could not reasonably be expected to enhance both the electrophilic and nucleophilic ability of the selenous acid. The Langbein mechanism avoids this problem by the hypothesis of electrophilic abstraction of the benzyl hydrogen. This is not in agreement with the sign of the Hammett rho value for benzyl substituents, however, which suggests nucleophilic attack at the benzyl position.

Schaefer has investigated the dehydrogenation of 1,2-dibenzoylethane (XXII) by selenous acid in 90% acetic acid.[12] He found that the rate law for disappearance of selenous acid was given by

$$-d(H_2SeO_3)/dt = k(PhCOCH_2CH_2COPh)(H_2SeO_3)^{1/2}. \qquad (22)$$

In added strong acid or acetate ion the rate dependence on selenous acid, on diketone, and on the added species each become first order. The sole product of the oxidation,

in 80-85% yield, is trans-1,2-dibenzoylethylene (XXIII). This is probably the thermodynamically favored product and it is not demonstrated in this work whether the cis product is stable under the reaction conditions. Perdeuteration of the methylene groups yielded an isotope effect ($k_H/k_D = 6.5$) which indicates C-H bond breaking in the transition state. Schaefer was unable to explain the half-order kinetics except to attribute them to a series of unspecified complicated equilibria, occurring before the rate-determining step. He then proposed the following mechanism, in which equation 23 is the slow step for acid catalyzed oxidation and 24 is the rate-determining step for the catalysis by acetate ion. This mechanism

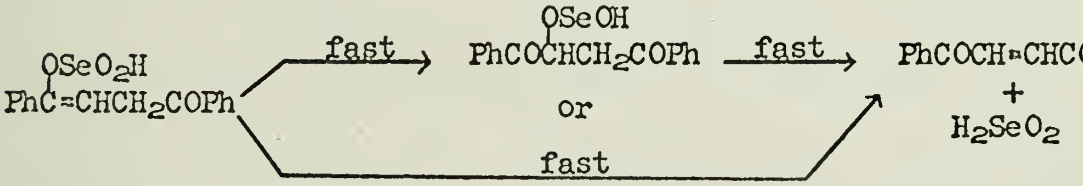


$$H_3SeO_3^+ + \underset{XXII}{PhCOCH_2CH_2COPh} \xrightarrow{slow} \underset{XXIV}{PhC(OSeO_2H){=}CHCH_2COPh} + H_3O^+$$

(23)

or

$$H_2SeO_3 + \underset{XXII}{PhCOCH_2CH_2COPh} + OAc^- \xrightarrow{slow} XXIV + H_2O + OAc^- \quad (24)$$



(25)

is such that the measured rate, which is the disappearance of selenous acid, is equal to both the rate of disappearance of diketone and that of the formation of products.

To disprove the earlier proposal of a cyclic transition state involving simultaneous removal of both the hydrogens, Schaefer synthesized 1,2-dideutero-1,2-dibenzoylethane (XXV). This compound is dehydrogenated (including some

PhCOCHDCHDCOPh XXV

dedeuteration) slower than the undeuterated compound by a factor of 1.96. From the deuterium content of the product, Schaefer calculated a k_H/k_D for the dehydrogenation of 5.4. He believed that this value is significantly lower than the 6.5 determined kinetically. Schaefer argued that if both protons were removed in the rate-determining step, the deuterium content of the product in the dideuterated case ought to give a calculated value for k_H/k_D equal to the kinetically determined value, whereas if the second proton is removed later from a high-energy intermediate, attack will be less selective, and more deuterium will be lost.

In analyzing the result of this dideuteration experiment, Schaefer assumed that C-H bond breaking occurs at the same rate in the undeuterated compound, and that C-D bond breaking occurs at the same rate as in the perdeuterated compound. This assumption neglects the possibility of secondary isotope effects which would be expected in the di- and perdeuterated cases but would not be present in the reaction of the undeuterated species. To support his assumption Schaefer calculated that the dideuterated compound should be dehydrogenated (including some dedeuteration) 2.02 times more slowly than the undeuterated compound, which agrees well with the experimental value of 1.96. However, it is not clear how this calculated value was obtained, and the fact that it suggests a rate slower then the statistical factor for reduction from four hydrogens to two is surprising.

Alternatively, the data can as well be explained if one considers the result of secondary isotope effects. A reasonable value of 10% for these effects will be assumed for illustrative purposes.[20] Were this the case, then the primary isotope effect would be 5.9 rather than 6.5, with the secondary effect of 1.1 accounting for the difference. In the dideuterated case the absence of a secondary isotope effect for deuterium removal and its presence for hydrogen removal would predict that the deuterium content value is distorted toward deuterium by 10%. Thus a primary isotope effect of 5.9 would be reasonably deduced from the experimental value of 5.4.

Two further points are important. One cannot escape the experimental rate retardation factor of 1.96 for the dideuterated dehydrogenation. Assuming once again the 10% secondary isotope effect, and assuming that attack on hydrogen and deuterium are equally probable statistically, we can derive a calculated retardation factor (26). The value of 1.87 obtained is in reasonable agreement

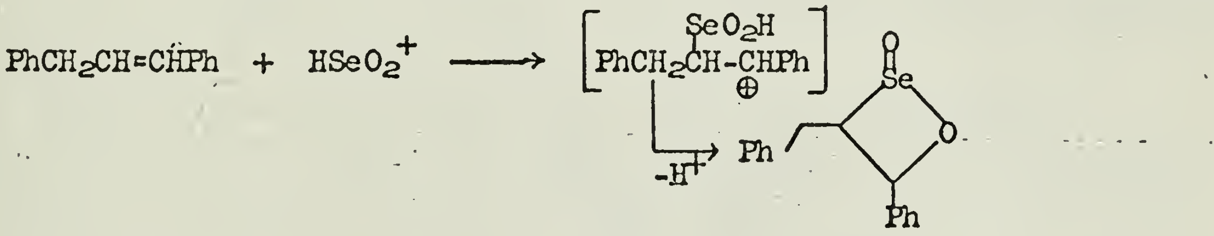
$$\text{retardation factor} = 1/\left\{1/2[1-(.1)(1)] + 1/2\left(\frac{1}{5.9}\right)\right\} = 1.87 \qquad (26)$$

with the experimental value. A secondary isotope effect of 16% would fit the experimental value exactly. Also of interest is the lack of information on the stereochemistry of the deuterium atoms in the dideuterated compound. This compound might be either meso or d,l. There is no clue to the expected stereochemistry of addition in the model reaction for this reduction.[21]

ALLYLIC OXIDATION

The subject of allylic oxidations with selenium dioxide, as well as with other oxidizing agents, has been thoroughly discussed by Wiberg and Nielson.[22] Nelson[23] presents data in support of the conclusions drawn in this review. The mechanism proposed for this oxidation in acidic media involves electrophilic attack on the double bond by protonated selenous acid, resulting in allylic rearrangement. The product arises from nucleophilic attack on the rearranged double bond (S_N2') or on the selenite ester (S_N2).

Schaefer and Horvath[24,25] studied the kinetics of the oxidation of 1,3-diarylpropenes in 99% acetic acid. Para substituent effects indicate the mechanism involves electrophilic attack on the double bond in the rate determining step with the development of slight electron defficiency at the methylene carbon in the transition state. Ortho substitution on the phenyl ring adjacent to the double bond slows the oxidation greatly. Deuterium labeling experiments were carried out to demonstrate the existence of a primary isotope effect ($k_H/k_D = 3.1$) and to show that both ends of the allylic system become equivalent during the oxidation. An S_N1 mechanism is proposed to fit these data (27-29).



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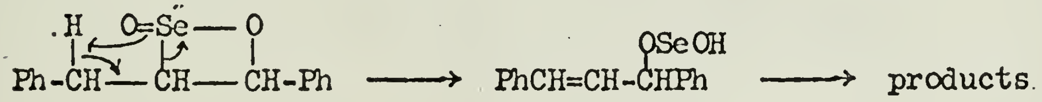

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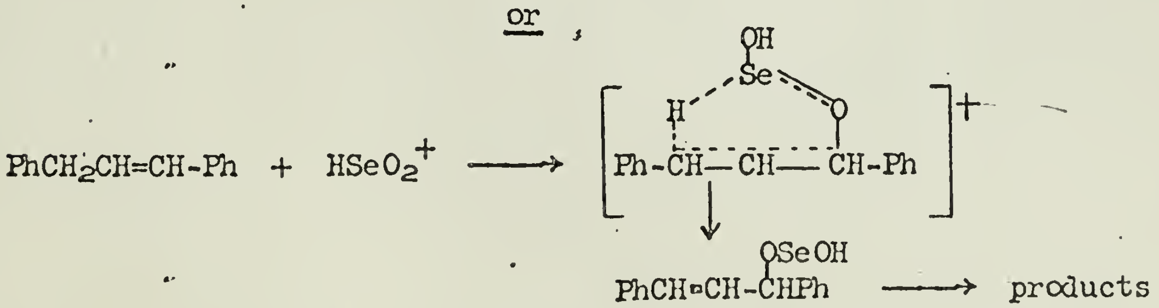
or



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A study made by Olson[26] of the oxidation of ethylene by selenous acid in acetic acid solution supports electrophilic attack on the double bond by selenous acid as the probable rate-determining step in allylic oxidations. It also gives evidence for the specific facility of this oxidation in acetic acid.

CONCLUSION

A great deal of data has been accumulated on the three major types of selenium dioxide oxidation. It is attractive to propose that all three proceed

through a rate-determining electrophilic attack on either the oxygen of a carbonyl or the least substituted end of a carbon-carbon double bond. Aside from extreme effects arising from the proximity of strongly electron-withdrawing groups (e.g., $-NO_2$), this seems a reasonable hypothesis.

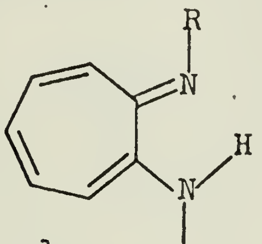
BIBLIOGRAPHY

1. L. Gmelin, "Handbuch der anorganishen Chemie," Verlag Chemie, Berlin, 1907, pp. 756, 764.
2. G. R. Waitkins and C. W. Clark, Chem. Rev., 36, 235 (1945).
3. N. Rabjohn, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, 1949, p. 331.
4. N. N. Mel'nikov and M. S. Rokitskaya, J. Gen. Chem. U.S.S.R., 15, 657 (1945) [C.A., 40, 5702 (1946)], and references therein.
5. N. N. Mel'nikov and M. S. Rokitskaya, J. Gen. Chem. U.S.S.R., 8, 1369 (1938) [C.A., 33, 4194 (1939)].
6. F. R. Duke, J. Am. Chem. Soc., 70, 419 (1948).
7. J. P. Schaefer, Ph.D. Thesis, University of Illinois, 1958.
8. E. J. Corey and J. P. Schaefer, J. Am. Chem. Soc., 82, 918 (1960).
9. D. P. Evans, V. G. Morgan, and H. B. Watson, J. Chem. Soc., 1935, 1167.
10. C. G. Swain, J. Am. Chem. Soc., 72, 4578 (1950).
11. J. P. Schaefer, J. Am. Chem. Soc., 84, 717 (1962).
12. J. P. Schaefer, J. Am. Chem. Soc., 84, 713 (1962).
13. M. Kocor and M. Tuszy-Maczka, Bull. Acad. Polon., Ser. Sci. Chim., 9, 405 (1948).
14. G. Langbein, J. Prakt. Chem., 18, 244 (1962).
15. E. Schwenk and E. Stahl, Arch. Biochem., 14, 125 (1947).
16. B. G. McKenzie, V. R. Mattox, L. L. Engel, and E. C. Kendall, J. Biol. Chem., 173, 271 (1948).
17. L. F. Fieser, S. Rajagopolan, E. Wilson, and M. Tishler, J. Am. Chem. Soc., 78, 4133 (1951).
18. C. S. Barnes and D. H. R. Barton, J. Chem. Soc., 1953, 1419.
19. J. C. Banerji, D. H. R. Barton, and R. C. Cookson, J. Chem. Soc., 1957, 5041.
20. E. A. Halevi, "Progress in Physical Organic Chemistry," Vol. I, Interscience Publishers, New York, 1963, p. 109.
21. J. P. Schaefer, J. Org. Chem., 25, 2027 (1960).
22. K. B. Wiberg and S. D. Nielson, J. Org. Chem., 29, 3353 (1964).
23. C. H. Nelson, Dissertation Abstr., 26, 1920 (1965).
24. J. P. Schaefer and B. Horvath, Tetrahedron Letters, No. 30, 2023 (1964).
25. B. Horvath, Dissertation Abstr., 25, 5560 (1965).
26. D. H. Olson, Tetrahedron Letters, No. 19, 2053 (1966).

ELECTRON DELOCALIZATION IN AMINOTROPONEIMINES

Reported by T. Gordon Scott November 10, 1966

Interest in the aminotroponeimine system centers on its exceptional electronic properties. The nature of the electronic delocalization in the parent system (1) has warranted examination for its own sake.[1-5] A natural outgrowth of that investigation, the study of the nickel (II) chelate analogs (2), has been significant in that the latter serve as probes for providing information regarding the electronic structures of the π-systems constituting the N,N'-dialkyl substituents. For example, spin densities are manifested in nuclear magnetic resonance spectra by isotropic hyperfine contact interaction shifts, which complement the spin-density distributions obtained by electron paramagnetic resonance spectroscopy.[6-13] The nickel (II) aminotroponeimineates are also of significance in nmr studies of nuclear spin-spin coupling constants.[12,14] The nmr spectra of many molecules which are of potential interest exhibit very complex spin-spin splitting patterns. But in system 2 contact shifts produced by the extensive delocalization of the electron spin onto the organic ligand are usually large compared to the nuclear spin-spin coupling constants, and the latter can be obtained readily from the resulting first-order spectra.[14] The nature of the electronic structure of system 1 and some applications of the electronic properties of system 2 in contact shift studies will be the objects of discussion in this seminar.



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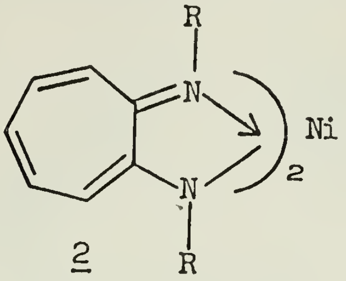
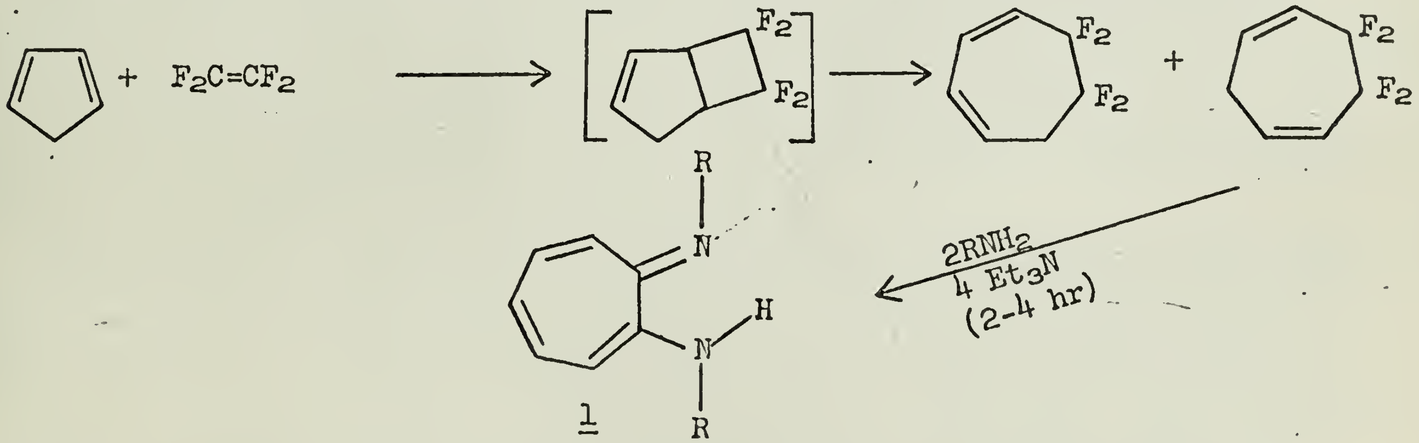


2

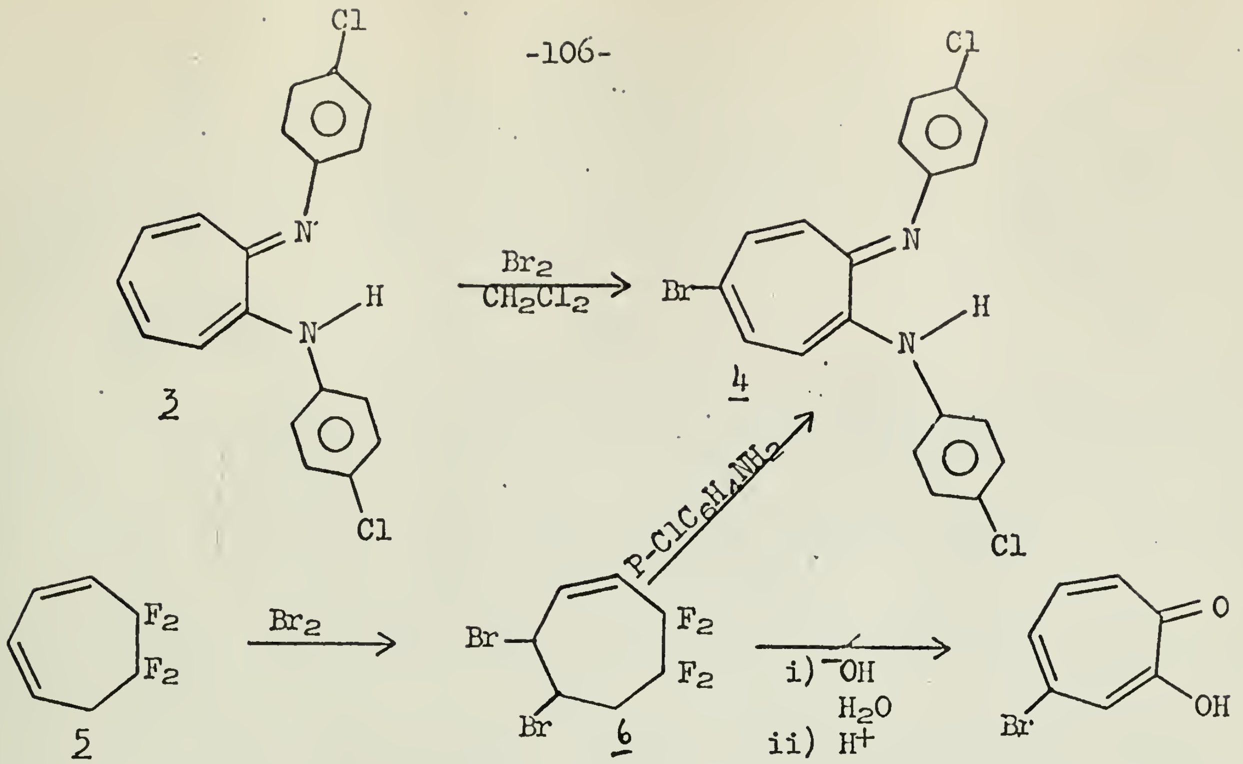
THE PREPARATION OF AMINOTROPONEIMINES

Attachment of conjugated groups to the nickel (II) aminotroponeimine system is particularly easy. In general, preparation of an aminotroponeimine with any desired group substituted on the nitrogen atoms can be achieved if a primary amine containing the group is available or can be synthesized.[4] The mixture of tetrafluorocycloheptadienes is treated with two equivalents of a primary aromatic or aliphatic amine and four equivalents of triethylamine as a hydrogen fluoride acceptor in refluxing methanol solution. The highly colored, stable products show strong infrared absorption in the 1450-1650 cm^{-1} region which was taken to be indicative of structures with electron delocalization.



THE ELECTRONIC STRUCTURE OF AMINOTROPONEIMINES

The aminotroponeimines undergo facile ring substitution by such electrophilic reactants as diazonium ion, bromine, and chlorine. For example, bromination of the p-chlorophenyl derivative (3) at 0° in methylene chloride yields a monobromo

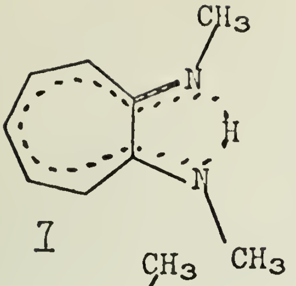


compound (4), in high yield (90%). The structure of 4 was characterized by synthesis (5→6→4) and by the first-order nmr spectrum of its nickel (II) chelate.[4] Furthermore, sulfonation and nitration are readily carried out at room temperature.

The x-ray structure of N,N'-dimethylaminotroponeimine has been determined.[15] The molecule is planar within experimental error, including both methyl carbons, and also one hydrogen of each methyl group — the methyls are staggered with respect to the nearby hydrogens on the rings. The largest deviation of any atom from the plane of the molecule is 0.02Å and most of them deviate much less than that. The amino proton appears as two distinct peaks symmetrically situated with respect to the two nitrogen atoms, about 1.1Å from each atom and about 0.5Å apart. However, these peaks are rather low (each corresponding only to a half hydrogen atom) and there is a saddle-point between them, of such height that one cannot really be sure that one does not have a single hydrogen in the center. Six of the bond distances in the ring are essentially the same as the benzenoid value; the seventh is about the same as that in butadiene, this being the C(1)-C(7) bond. The C-N distances are comparable to the aromatic distance for such a bond also, about 1.34Å.[15]

The preceding chemical and structural evidence suggested that there was appreciable electron delocalization in the aminotroponeimines. This suggestion is supported by the observation that the resonance of the ring protons (τ 3.4 - 3.8) is at significantly lower field than that of cyclic vinylic protons (~ τ 4.5) and corresponds to the <u>ortho</u>-proton resonance of aniline (τ 3.5). But it is another feature of the nmr spectra which proved to be more significant to the study of electron delocalization in the aminotroponeimines.

The electronic structure of the N,N'-dialkyl aminotroponeimines became the object of special study when nmr investigation indicated that the nitrogen atoms of the dimethylaminotroponeimine, 1 (R=CH_3) are equivalent.[3,4] Only a single methyl resonance (τ 7.0) was observed. Even when nmr studies were conducted at -80° for both the N-H and the N-D compounds in carbon tetrachloride solution, no resolvable fine structure for the methyl resonance was observed. Since the rate of deuterium exchange should be appreciably lower than that of hydrogen, this evidence supports either a symmetrical hydrogen-bonded structure (7) or an extremely rapid intramolecular hydrogen (and deuterium) exchange (8).[1,3,4] This corroborates the conclusions concerning the amino proton drawn from the x-ray study. Further support for this interpretation of an actual or time-averaged symmetrical structure comes from a comparison of the preceding nmr study with that of the same compound in trifluoroacetic acid. Under these strongly acidic conditions it is likely that 1 (R = CH_3) is converted to the symmetrical protonated derivative (9). Again only a single resonance was observed for the N-methyl protons, and, significantly, there was little change in the fine structure attributable to the ring protons.



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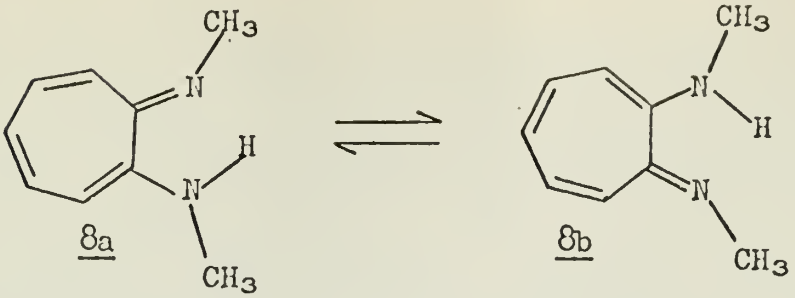

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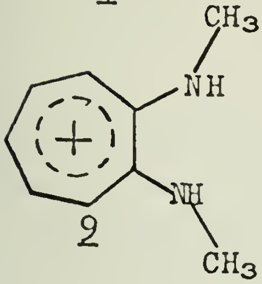
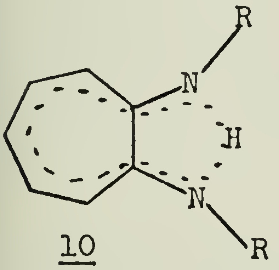


9

This close similarity of the nmr spectrum of the unprotonated system to that of the symmetrical protonated derivative (9) furnishes additional support to the hypothesis that one is dealing with either a symmetrically hydrogen-bonded product or to a fast intramolecular hydrogen exchange. The similarity was also considered to be evidence that there is electron delocalization in the unprotonated system (7 or 8). It was reasoned that if there were little delocalization in the unprotonated aminotropponeimine, it would be expected that the proton resonance of the cycloheptatriene system would be markedly altered as was found in the case of the azulene-azulenium ion system.[16] This reasoning assumes a straight-forward relationship between the observed proton chemical shifts and the π-electron delocalization of the system. This relationship was not demonstrated, in fact there is evidence that such a simple correspondence is not even to be expected;[17,18] the anisotropic magnetic susceptibility and the chemical shift of aromatic hydrocarbons generally attributed to π-electron ring currents can be represented as the sum of contributions from localized electrons of both π and σ character.

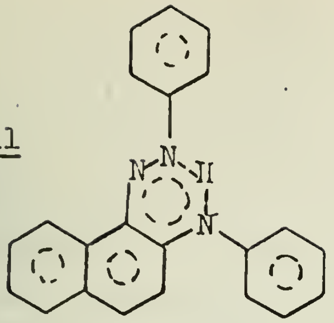
The preceding data cited for discussion refers to the N,N'-dimethylaminotroponeimine. However, single resonances for the substituents on nitrogen have been obtained for a range of groups including isobutyl, phenyl, benzyl, p-tolyl, p-dimethylaminophenyl, p-methoxyphenyl, p-nitrophenyl, and p-phenylazophenyl, and this phenomenon appears to be general.[4]

The data presented above are all well-documented and on a firm experimental basis. But it would be more satisfying if one could account for these properties in terms of a theoretical model. As Chapman has related, the whole question of whether in principle it is possible to describe these chelates as aromatic systems is an intriguing one.[19] The aminotroponeimine system contains four conjugated formal double bonds and a pair of electrons from the nitrogen of the -NHR substituent. It thus has the potential for a conjugated 10 π-electron system and would fit the Hückel formalism with n = 2. Therefore, in view of the nmr equivalence of the N-alkyl substituents, the general structure (10) was proposed.[3] Of course, the data were also compatible with the interpretation of a rapid tautomeric equilibria, but the important point with respect to structure 10 was that this alternative pictured the system in a manner amenable to treatment by an LCAO MO procedure. The dotted lines in 10 denote a peripherally conjugated 10 π-electron bicyclic system consisting of a resonance hybridization of the formally non-bonding electrons of the amino- nitrogen atom with those of the adjacent imino- nitrogen atom. However, the Hückel (4n + 2) rule was formulated in terms of a planar, monocarbocyclic system. Application of the rule to the hetero- and formally non-cyclic system is unprecedented, and its application must then be justified or, at least, rationalized.



10

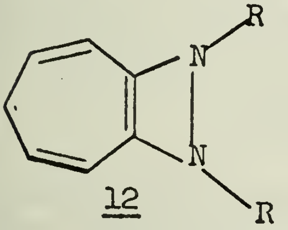
The main problem has been the electronic role of the hydrogen atom of the hydrogen bond. In a calculation on a system possessing an analogous structure (11), this hydrogen atom was regarded as an actual contributor to the π-system by means of its available $2p_z$ orbital.[20,21] This approach assumes that delocalization of the π-electrons could take place through this orbital, and one then has a theoretical rationale for the proposed structure 10 and 11. The details of the LCAO-MO calculation based on this model will not be discussed because the more important



11

question is the validity of the assumption itself. The validity of the assumption does appear doubtful, especially when one considers that the use of a higher energy orbital of hydrogen is being postulated for measurement conditions of only -80°. By way of reference, the energy difference between the quantum levels n = 1 and n = 2 for the hydrogen atom is 10.15 ev (234 kcal/mole). It has been suggested that by regarding the hydrogen bond as essentially a σ-bond in the framework and considering the π-system to be made up of only the p-orbitals of the carbon and nitrogen atoms one would have a more sensible model.[19] The model is still not problem-free, since there is now the question of whether the two nitrogen atoms are close enough to permit significant π-overlap.

This question cannot be answered unequivocally, but evidence for bonding between the nitrogen atoms has been obtained from calculations[8] based on the aminotroponeimine system. Electron spin densities at the seven-membered ring carbon atoms can be reproduced extremely well by a valence bond calculation that includes the five Kekulé structures plus the structure (12).



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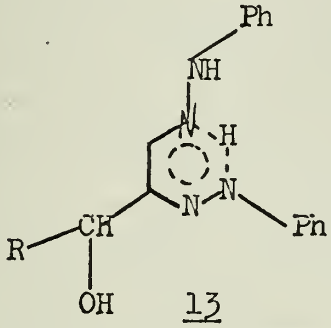
There have been two other molecules besides 1 and 11 for which π-electron delocalization has been postulated to take place in a chelate ring system. They are represented below (13[22,23] and 14[24]) in the formulation denoting the delocalization, but, as with 1, there were no observations which excluded a rapid tautomerization. However, the postulate of a substantial π-electron delocalization in 13 has been discredited by the observation that the equilibrium shown below is a more accurate description of the system.[25] In dimethyl sulfoxide solution the acyclic structure is stabilized significantly by the extra hydrogen bond to the solvent. In less strongly hydrogen bonding solvents the equilibrium shifts in favor of the chelate structure. This equilibration data show that the energy difference between 15a and 15b is small and, thus, inconsistent with any significant extra π-electron delocalization energies for 15a relative to 15b. The N,N'-dibenzylaminopenteneimine system (14), however, appears to be more strongly stabilized in the chelate form. As with the N,N'-dialkylaminotroponeimines the nmr spectrum shows the two benzyl groups to be equivalent.[24] In addition, 14 does not equilibrate with a non-chelate isomer in strong hydrogen bonding media.[19]



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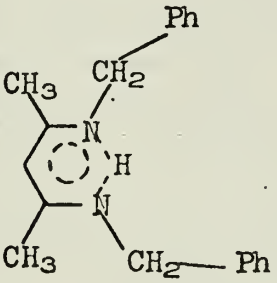

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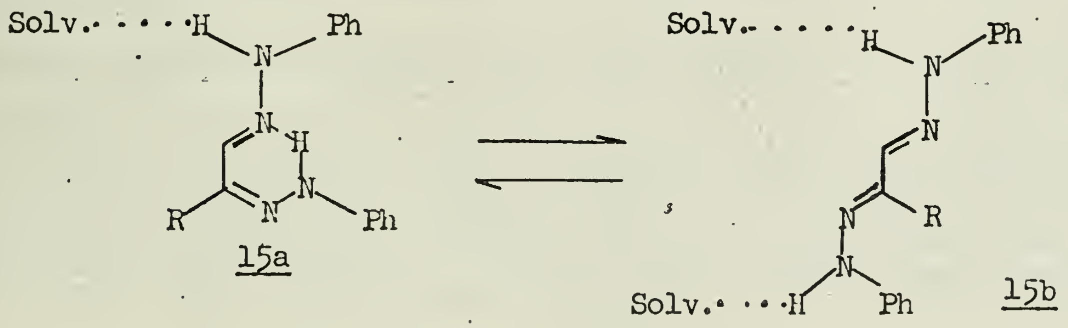


As another approach to determine the nature of the hydrogen atom of the hydrogen bond the nmr spectrum of the nickel (II) chelate of N,N'-dimethylaminotroponeimine (2, $R=CH_3$) was examined.[26] At -70° the resonances of the ring protons are very

similar to that of the unchelated product. Assuming that nickel (II) is effective for accomplishing electron delocalization in the cycloheptatriene ring, a topic which will be discussed below, this datum indicates that the N-H group is as effective as nickel (II) on the nmr time scale for effecting such electron delocalization. Studies of the transmission of spin density through the N-H group are also discussed below.

PROPERTIES OF THE NICKEL (II) AMINOTROPONEIMINEATES

The bis-nickel (II) aminotroponeimineates (2) are an exceptionally favorable system for the study of electron delocalization. Several properties are responsible for this fact. The first is that these chelates possess geometrical configurations of closely similar energies in which the environment about nickel is either approximately square planar (diamagnetic) or approximately tetrahedral (paramagnetic).[27,28] It is known that rapid intramolecular interconversion between diamagnetic and paramagnetic forms of a chelate is a mechanism for narrowing nuclear resonances of paramagnetic species.[29] In particular, it is important for observation of hyperfine contact shifts averaged over the diamagnetic and paramagnetic forms of nickel in these chelates that the equilibrium between singlet and triplet species is established in a time which is shorter than the reciprocal of the contact shift (in cps). The rate of the interconversion between the two configurations in the nickel (II) aminotroponeimineates is such that the widths of the proton resonances are usually

$$\underset{\text{(singlet)}}{\text{diamagnetic species}} \rightleftharpoons \underset{\text{(triplet)}}{\text{paramagnetic species}}$$

in the 1-2 cps range.[14] Application of this favorable property will be discussed below. Secondly, the electronic relaxation time, T_1, of the paramagnetic system and/or electronic exchange time, T_e, between paramagnetic molecules is small compared to the reciprocal of the contact-interaction constant, a_i^{-1}. Thirdly, the observed shifts are determined predominantly by a single mechanism. There is evidence that pseudo-contact contributions to the contact shifts are almost entirely absent in these chelates.[8,9] The paramagnetic form of the nickel (II) chelate possesses a d^8 configuration containing two unpaired electrons. In practice one can account for the observed shifts very well on the assumption that there is some delocalization of these unpaired electrons to the ligand, by a π-bonding interaction between the half-filled metal dπ orbitals and the filled pπ ligand orbitals. A final advantageous property of the nickel (II) aminotroponeimineates is that the ligand is a nonalternant conjugated system and that, therefore, one can observe both positive and negative spin densities giving rise to high-field and to low-field shifts respectively.[12,23]

NMR SPECTRAL ANALYSIS OF ORGANIC GROUPS USING NICKEL (II) AMINOTROPONEIMINEATES

A positive spin density is placed on the pπ orbital of nitrogen as a result of the π-interaction mentioned above. This spin density is then distributed throughout the π-system of the ligand. Spin densities on sp^2 carbon atoms to which hydrogen atoms are bonded are manifested in the nmr spectrum by large high field (positive carbon spin densities) and low field (negative carbon spin densities) shifts.[30] The contact shift of the ith proton

$$\frac{\Delta Hi}{H} = \frac{(H_{chelate} - H_{ligand})}{H} \qquad (1)$$

is produced by isotropic hyperfine contact interactions and are related to the nuclear hyperfine coupling constant, a_i, by

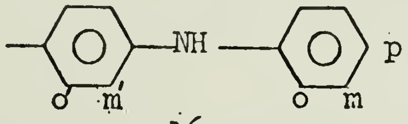
$$\frac{\Delta H_i}{H} = \frac{\Delta\nu_i}{\nu} = -\,a_i\,\frac{\gamma_e}{\gamma_H}\,\frac{g\beta S(S+1)}{S\,k\,T} \qquad (2)$$

In this equation H is the resonance field, and ν the resonance frequency of the nmr experiment, γ_e and γ_H are the magnetogyric ratios of the electron and the proton, g is the spectroscopic splitting factor for the system, and β is the Bohr magneton. The other quantities have their usual significance.[13]

Chemical shifts for protons of the substituents R in the paramagnetic nickel (II) aminotroponeimineates are up to 250 times greater than for shifts of analogous protons in the ligands themselves.[14] Since the widths of the nuclear resonances for these chelates are usually 1-2 cps, in many cases spin-spin couplings can be resolved. The large separations between the different resonances lead to simple first-order spectra from which the spin-spin couplings can be obtained directly. When the proton coupling constants for a number of simple conjugated groups observed from spectra of the chelates were compared with the values for the analogous diamagnetic compounds close agreement was found.[14] On this basis, proton coupling constants were also obtained for a number of molecules for which the direct measurement of the spin-spin coupling is impracticable. And since the sign of the spin densities alternate in these systems,[10] protons attached to adjacent carbon atoms always are shifted in opposite directions, resulting in even larger differences in resonance frequencies than if the system were alternant.[14]

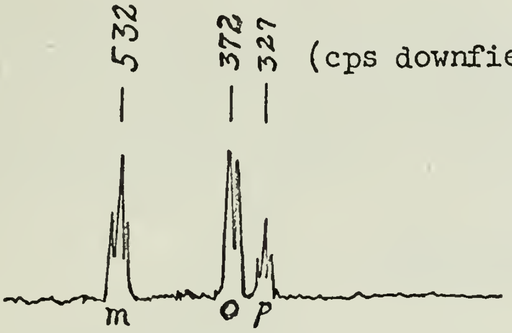
An illustration of the preceding discussion is afforded by the p-phenylaminophenyl group (16),

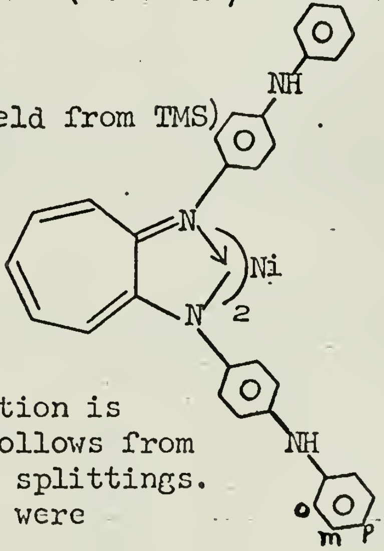
R =



16

The nmr spectra of many *ortho*- and *para*-disubstituted benzenes have been analyzed,[31,32] but the A_2B_2C pattern of a monosubstituted benzene is too complex for first-order analysis. The spectrum of the A_2M_2X system of the terminal phenyl group of N,N'-di(p-phenylaminophenyl) aminotroponeimineate (at 60 Mc/sec in CS_2) is shown below.[14]





The simplification brought about by chelation is apparent, and an unambiguous assignment follows from a consideration of the observed spin-spin splittings. The principal coupling constants obtained were

$$J_{om} = 7.7 \pm 0.2 \text{ cps} \qquad \delta/J = 20.8$$

$$J_{mp} = 7.6 \pm 0.2 \text{ cps} \qquad \delta/J = 27.0$$

Over seventy complex groups have been analyzed by this approach.[14]

SPIN DENSITY DISTRIBUTIONS FROM AMINOTROPONEIMINEATE NMR ANALYSIS

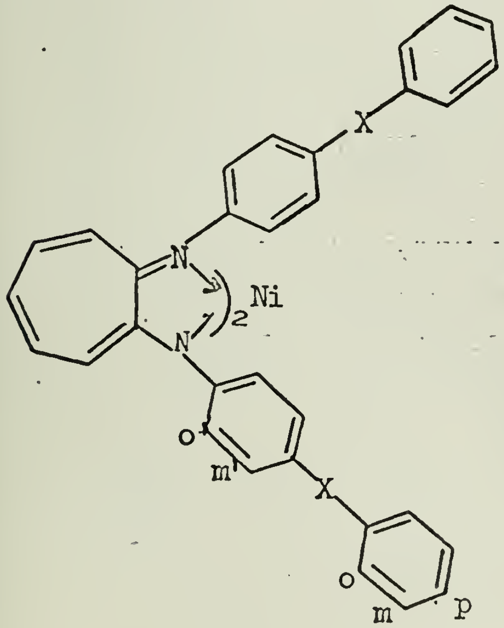
Another important application of contact shift studies in this series is the determination of spin density distributions in paramagnetic molecules. Two experimental approaches have been used for the determination of contact-interaction constants, a_i. One is by using the hyperfine splittings of electron paramagnetic resonance spectroscopy. The other approach is from the contact shifts observed in the nmr spectra of paramagnetic species.[10] In general, the conditions necessary for the observation of sharp line nmr spectra and those necessary for the observation of sharp line epr spectra are complementary. Epr requires a long electron spin relaxation time and nmr a suitably short one. It follows that where the epr spectrum has been observed at room temperature, the nmr is either not observed or is very broad. Where the epr spectrum has only been observed at liquid nitrogen temperature, the nmr lines are moderately broad. And where the epr was not observed, the nmr lines are relatively sharp. In suitable intermediate cases, however, it is perfectly possible to observe both types of resonance.[11] Certain aromatic molecules and their nickel (II) aminotroponeimineate derivatives are such cases.

Although the type of information derivable from hyperfine contact shifts parallels that obtained from epr spectra, the nmr approach, in suitable electronic systems, possesses several advantages. The synthetic flexibility and chemical stability of the nickel (II) aminotroponeimineates contrasts with the limited availability and general chemical instability of free radical species.[7] With the nmr approach negative as well as positive spin densities can be determined.[30,33] The sign of the contact interaction constant is given by the direction of the contact shift, as seen from equation (2). In the epr experiment, signs of contact interaction constants are indeterminate. Furthermore, as discussed above, the nmr approach allows an ease of spectral assignment because of relative resonance intensities and the presence of resolvable first-order spin-spin structure. As many as 12 coupling constants have been measured and uniquely assigned for a given chelate.[7] A final advantage is that very much smaller spin densities can be measured by the nmr approach, since in an epr experiment the minimum resolvable hyperfine coupling is more limited by the line widths. The latter advantage is applied in the study of the final topic to be discussed in this seminar, the transmission of spin densities through linking groups.[7,12]

The conjugative ability of various connecting groups in unsaturated systems has been evaluated by measuring the transmission of spin density through these groups.[7,13] The transmission of electronic effects through chelate metal atoms has been investigated[7] but will not be discussed in this report. Spin densities on pπ orbitals of sp^2 carbon, ρ_C, are related to contact-interaction constants by the equation[30]

$$a_i \cong Q\,\rho_C \qquad (3).$$

Some consideration of the values of Q should be given, since it is this constant which translates the experimental quantity, a_i, into the derived spin densities. From epr results, values for Q in the range -20 to -26 gauss have been reported for carbon in an sp^2 bonding situation. Some variation with small changes in bonding might be anticipated. In the results cited below spin densities have been calculated using the value -22.5 gauss obtained from the benzene negative ion.[34]



-Observed spin density distributions for three N-substituted nickel (II) aminotroponeimineates.

	observed spin densities		
	X = C≡C	X = NH	$X = \overset{O}{\overset{\|}{C}}$
α	+.0407	+.0410	+.0404
β	-.0210	-.0210	-.0210
γ	+.0566	+.0565	+.0567
o'	+.00783	+.00767	+.00769
m'	-.00825	-.00788	-.00842
o	+.00042	+.00085	<.0001
m	-.00053	-.00105	
p	+.00070	+.00146	

It is seen from these results that spin densities for the N-phenyl rings of the three chelates are similar at corresponding *ortho*'and *meta*'-positions. Spin density distributions on the second phenyl rings, however, are different. In particular, the spin densities at analogous positions of the second ring are somewhat greater for the chelate with the -NH- linking group than for the chelate with the -C≡C- group and that the carbonyl group acts virtually as an insulator. The -NH- group is roughly comparable to the -C=C- group, which has a spin density of +0.00133 at the *para*- position of the second ring.[7] Even though the function of the -NH- group is different in the present case from that in the aminotroponeimines, the observed quality of the -NH- group for transmitting spin density in aromatic systems may

lend more credibility to its postulated function as a transmitter of electron delocalization in the aminotroponeimines (1). The data also suggest the experiment in which one would insulate the electronic effect of the N-R groups from the native electron delocalization of the aminotroponeimine system by employing an N-acyl substituent.

The aminotroponeimine system remains in the category of an intriguing postulated 10π- resonance system. To date there have been no data reported which are inconsistent with the postulate,[24,35] however conclusive verification is likewise lacking. On the other hand, the nickel (II) chelates of this system have produced a substantial body of important findings. The chelates offer a promising approach for determining the spin-spin coupling constants in groups whose spectra cannot be readily analyzed by conventional methods. And the nmr spin-density determinations provide an equally promising approach to the study of conjugation in molecules containing extended π-electron systems.

BIBLIOGRAPHY

1. R. E. Benson, J. Am. Chem. Soc., 82, 5948 (1960).
2. K. N. Trueblood, U. S. Gov't. Rept., 39 (15), 144 (1964).
3. W. R. Brasen, H. E. Holmquist, and R. E. Benson, J. Am. Chem. Soc., 82, 995 (1960).
4. W. R. Brasen, H. E. Holmquist, and R. E. Benson, J. Am. Chem. Soc., 83, 3125 (1961).
5. W. R. Brasen and R. E. Benson, J. Am. Chem. Soc., 83, 3135 (1961).
6. H. M. McConnell, J. Chem. Phys., 24, 632 (1956).
7. D. R. Eaton, A. D. Josey, W. D. Phillips, and R. E. Benson, Discussions Faraday Soc., 34, 77 (1962).
8. D. R. Eaton, A. D. Josey, W. D. Phillips, and R. E. Benson, J. Chem. Phys., 37, 347 (1962).
9. D. R. Eaton and E. A. LaLancette, J. Chem. Phys., 41, 3534 (1964).
10. D. R. Eaton, A. D. Josey, W. D. Phillips, and R. E. Benson, Mol. Physics, 5, 407 (1962).
11. D. R. Eaton, J. Am. Chem. Soc., 87, 3097 (1965).
12. D. R. Eaton and W. D. Phillips, "Advances in Magnetic Resonance," Vol. 1, (J. S. Waugh, editor), Academic Press, N. Y., 1965, pp. 103-148.
13. R. E. Benson, D. R. Eaton, A. D. Josey, and W. D. Phillips, J. Am. Chem. Soc., 83, 3714 (1961).
14. D. R. Eaton, A. D. Josey, W. D. Phillips, and R. E. Benson, J. Chem. Phys., 39, 3513 (1963).
15. P. Goldstein and K. N. Trueblood, private communication from K. N. Trueblood.
16. S. S. Danyluk and W. G. Schneider, J. Am. Chem. Soc., 82, 997 (1960).
17. J. Musher, J. Chem. Phys., 43, 4081 (1965).
18. R. J. Abraham and W. A. Thomas, J. Chem. Soc., (B), 127 (1966).
19. O. L. Chapman, private communications.
20. J. Ladik, A. Messmer, J. Rédly, Acta. Chim. Hungary, 38, 393 (1963).
21. C. Shiele and G. Arnold, Tetrahedron Letters, 4103 (1966).
22. L. Mester, E. Moczur, and J. Parello, J. Am. Chem. Soc., 87, 596 (1965).
23. L. Mester, Angew. Chem., 77, 580 (1965).
24. L. C. Dorman, Tetrahedron Letters, 459 (1966).
25. O. L. Chapman, Tetrahedron Letters, 2599 (1966).
26. W. D. Phillips and R. E. Benson, J. Chem. Phys., 33, 607 (1960).
27. D. R. Eaton, A. D. Josey, R. E. Benson, W. D. Phillips, and T. L. Cairns, J. Am. Chem. Soc., 84, 4100 (1962).
28. W. C. Lin and L. E. Orgel, Mol. Physics, 7, 131 (1964).
29. D. R. Eaton, W. D. Phillips, and D. J. Caldwell, J. Am. Chem. Soc., 85, 397 (1963).
30. H. M. McConnell and D. B. Chesnut, J. Chem. Phys., 28, 107 (1958).
31. R. E. Richards and J. P. Schaefer, Trans. Faraday Soc., 54, 1280 (1958).
32. D. M. Grant, R. E. Hirst, and H. S. Gutowsky, J. Chem. Phys., 38, 470 (1963).
33. H. M. McConnell and H. H. Dearman, J. Chem. Phys., 28, 51 (1958).
34. S. I. Weissman, T. R. Tuttle, Jr., and E. de Boer, J. Phys. Chem., 61, 28 (1957).
35. L. C. Dorman, private communication.

AMINO KETONE REARRANGEMENTS

Reported by Jack E. Richman November 14, 1966

A number of α-amino ketones and α-hydroxy imines undergo thermal rearrangements with and without catalysts to isomeric α-amino ketones. Both trisubstituted and disubstituted compounds show such rearrangements.

TRISUBSTITUTED SYSTEMS--SCOPE

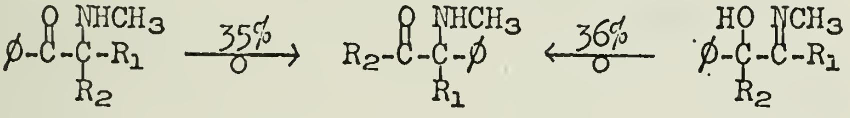
Trisubstituted α-amino ketones I have been found to equilibrate with hydroxy imines II by migration of one group and a hydrogen atom. Theoretically equilibration of six structural isomers is possible. In most cases studied, two of the substituents are the same, and the four possible isomers have been found, but I usually predominates over II. Bond energies are in agreement with this since they predict that the O=C-C-N-H system is intrinsically more stable than N=C-C-O-H by roughly 5 to 18 kcal/mole.[1]

$$R_1\overset{O}{\overset{\|}{C}}-\overset{NHX}{\overset{|}{C}}R_2R_3 \rightleftharpoons R_1R_2\overset{HO}{\overset{|}{C}}-\overset{NX}{\overset{\|}{C}}R_3$$

I II

R = Alkyl or aryl
X = Alkyl, aryl, or hydrogen

Stevens and coworkers[2,3] have studied the amino ketone rearrangement in acyclic systems. They found that α-ethyl-α-methylaminobutyrophenone (IIIa) rearranges when heated without solvent at 240° to give IVa in 35% yield. Similarly IIIb and c rearrange to IVb and c, respectively. Stevens also showed that the α-hydroxy imines Va, b, and d rearrange under similar conditions to amino ketones IV in comparable yields. In the case of Va the hydroxy imine was prepared and subjected to rearrangement. With Vb and d the imine was prepared *in situ* from methylamine and the corresponding ketol.

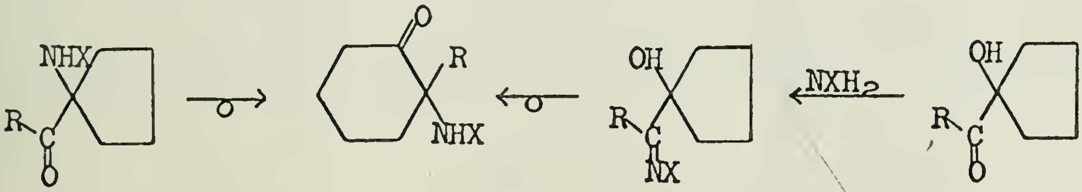


$$\phi-\overset{O}{\overset{\|}{C}}-\underset{R_2}{\overset{NHCH_3}{C}}-R_1 \xrightarrow[\Delta]{35\%} R_2-\overset{O}{\overset{\|}{C}}-\underset{R_1}{\overset{NHCH_3}{C}}-\phi \xleftarrow[\Delta]{36\%} \phi-\underset{R_2}{\overset{HO}{C}}-\overset{NCH_3}{\overset{\|}{C}}-R_1$$

III IV V

	R_1	R_2
a,	C_2H_5	C_2H_5
b,	CH_3	CH_3
c,	CH_3	C_2H_5
d,	CH_3	C_6H_5

Many rearrangements have been carried out in systems where two of the substituents are members of the same ring. Empirically, equilibration of a five- and six-membered ring can be expected to favor the six-membered ring. Stevens *et al.*[3-7] found that heating 1-aminocyclopentyl ketones VI usually produces the corresponding cyclohexyl isomer VII. Recently this reaction has been applied to D-homoannulation (ring D expansion) of steroids[8] with yields of 28 to 34%.



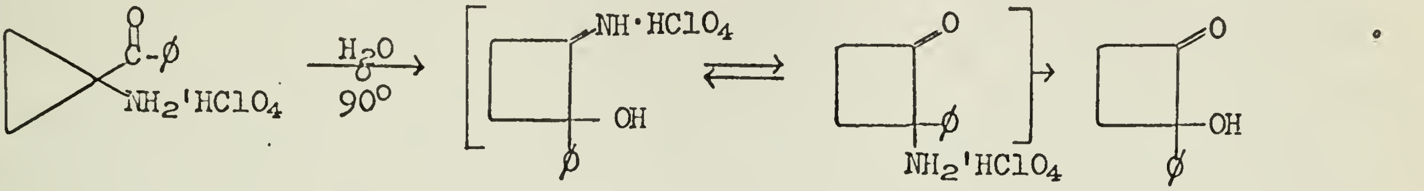
VI VII VIII IX

a, R = C_6H_5, X = CH_3
b, R = CH_3, X = CH_3
c, R = C_6H_5, X = C_6H_5
d, R = CH_3, X = C_6H_5
e, R = cycloC_6H_{11}, X = C_6H_5
f, R = o-$CH_3C_6H_4$, X = CH_3

The hydroxy imine analogues VIIIa-c also rearrange with ring expansion to VII. Thus the anil of 1-acetylcyclopentanol (VIIId) will give 2-anilino-2-methylcyclohexanone (VIId) in 44% yield.[5] Often this conversion has been accomplished by heating the α-ketol IX directly with excess amine to give the imine derivative of VII which can be readily hydrolyzed to VII. Such a procedure has been used to

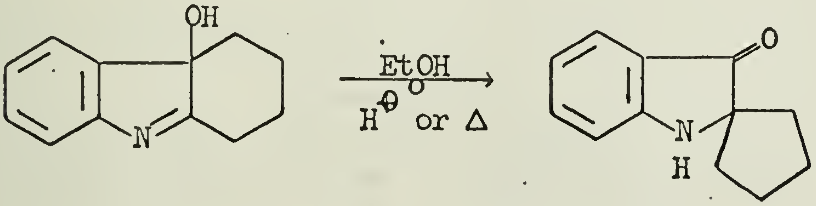
achieve D-homoannulation of steroid ketols in yields up to 84%.[9]

Expansion of the cyclopropane ring of the perchlorate salt of 1-amino-1-benzoylcyclopropane (X) proceeds in quantitative yield apparently by an amino ketone rearrangement to give 2-hydroxy-2-phenylcyclobutanone (XI).[10] This reaction is being studied in nonaqueous solvents in an attempt to isolate possible intermediates.

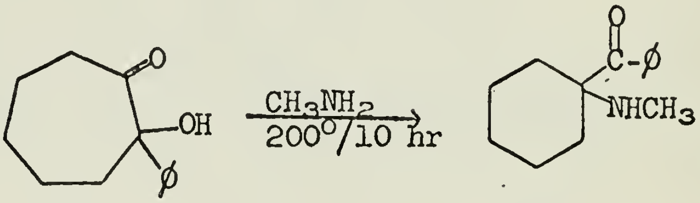


X XI

There are also examples of the amino ketone rearrangement which occur with ring contraction. Witkop and Patrick[11] report that 11-hydroxytetrahydrocarbazolenine (XII) rearranges upon warming in ethanol to spiro-[cyclopentane-1,2'-pseudo-indoxyl] (XIII). Also, this rearrangement is both acid and base catalyzed. Another example



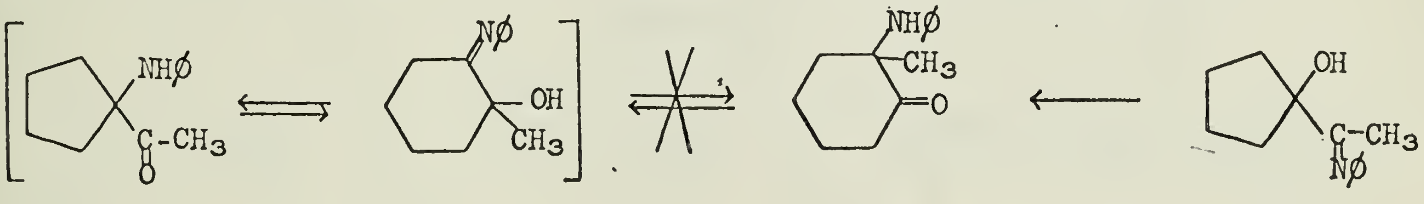
XII XIII



XIV XV

is reported by Stevens, Elliott, and Winch[3] who observed that 2-phenyl-2-hydroxycycloheptanone (XIV) undergoes ring contraction to 1-benzoyl-1-methylaminocyclohexane (XV) when treated with excess methylamine.

Although the foregoing examples demonstrate the versatility of the amino ketone rearrangement, the rearrangement does not occur in all cases. In a few instances there is a kinetic barrier to the equilibration. In particular, VId is known not to give VIId.[5] When XVI is heated it rearranges only to VId. The expected product, VIId, has been prepared by rearrangement of VIIId and is stable to further isomerization.[5] No explanation for the failure of VId and VIId to equilibrate has been advanced. It has also been shown that VIf and VIIf do not equilibrate.[6]



VId XVI VIId VIIId

In this case migration of the o-tolyl group may be sterically hindered by the ortho-methyl group. Other ortho substituents have not been examined to determine if this effect is general.

EXPERIMENTAL CONDITIONS AND CATALYSTS

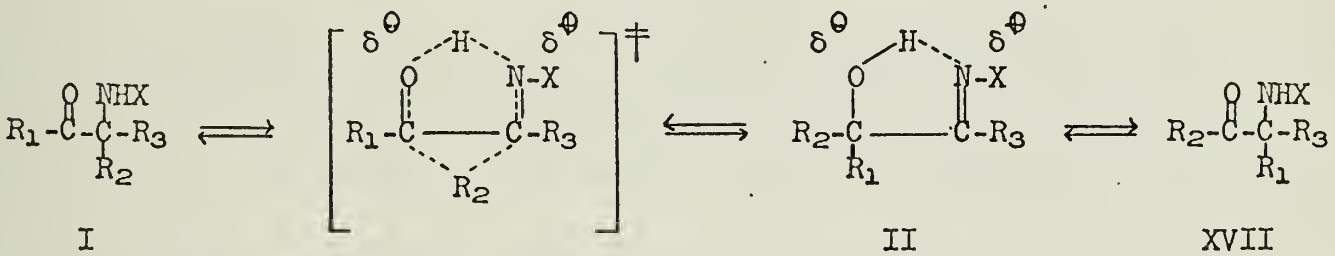
In its simplest form the amino ketone rearrangement can be accomplished by heating a sample of pure compound under a nitrogen atmosphere and, if necessary, in a sealed tube. In a few instances (XII[11] and XXIX[8]) the rearrangement can be observed near room temperature in alcoholic solvents. Ordinarily the reaction requires heating at 180° to 240° for 8 to 12 hours. Longer heating or higher

temperatures usually lead to decomposition. It has been found[5] that when an amino ketone can be prepared from both an isomeric amino ketone and an isomeric hydroxy imine, the latter usually gives higher yields of product with less vigorous conditions.

Stevens found that the addition of an equivalent of acid to α-hydroxy imines also allows less vigorous conditions and better yields.[5,7] Elphimoff-Felkin[12] found that VIIIe rearranged when heated at 100° for 5 hours in 96% formic acid. On the other hand, Morrow and coworkers[9] state that a catalytic amount of *p*-toluenesulfonic acid with steroid ketols and excess ammonia or methylamine has no effect on the reaction. This may be misleading since the large quantities of amine may tie up the acid. Witkop and Patrick[11] have done a kinetic study of the rearrangement of XII with catalysis by *p*-toluenesulfonic acid. Their results show that acid catalysis gives an overall second order reaction, first order in XII and first order in acid. The data are consistent with the reactive species for acid catalysis being the conjugate acid of XII with protonation on nitrogen. This species rearranges about 100 times faster at 30° than the neutral species at 40°.

MECHANISM

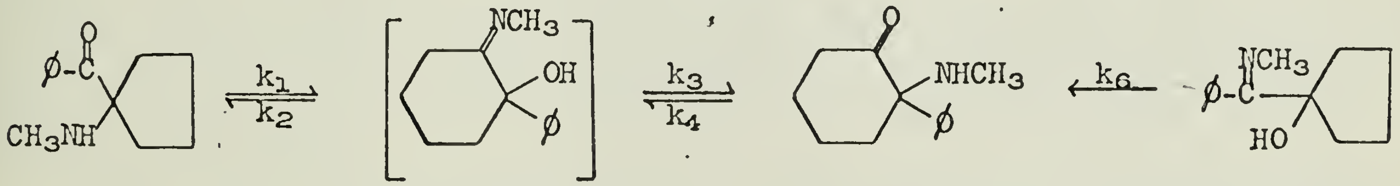
The majority of evidence on the mechanism of the amino ketone rearrangement has been reported by Stevens and coworkers in a series of papers describing the isolation of intermediates and the determination of activation parameters and substituent effects. Stevens proposes that the starting amino ketone I rearranges to the product amino ketone XVII through an intermediary hydroxy imine II. Furthermore, the equilibration of I and II supposedly proceeds by the concerted transfer of substituents R_2 and H with a slightly polar transition state.[1,4]



I II XVII

According to this mechanism the rearrangement of α-ethyl-α-methylaminobutyrophenone (IIIa) to 4-methylamino-4-phenyl-3-hexanone (IVa) should proceed through 4-methylimino-3-phenyl-3-hexanol (Va). To test this, Va was prepared and was observed to rearrange to IVa under similar conditions in comparable yield.[2,3] On the other hand, the isomeric hydroxy imine, α-ethyl-α-hydroxybutyrophenone methylimine, was ruled out as an intermediate since it gives IVa in only one fifth the yield from IIIa (7% : 35%). A second result consistent with the intermediacy of an imine is that the N,N-dimethyl derivative of IIIa is stable to rearrangement. Recently even better evidence for the intermediacy of imine XVIII in the rearrangement of VIa to VIIa has been advanced. When VIa is heated for a short time (12 min/235°)

Scheme 1



VIa XVIII VIIa VIIIa

and then the reaction mixture is reduced with sodium borohydride, the amino alcohols corresponding to VIa and XVIII can be isolated in 38 and 16% yields, respectively.[1] Only a trace of the amino alcohol from VIIa is observed, but when XVIII was independently synthesized and then rearranged both VIa and VIIa were isolated in 24 and 51% yields, respectively. Furthermore, a kinetic study of the disappearance of VIa and the appearance of VIIa indicates that there is an intermediate and that this intermediate can be XVIII. This study was done in refluxing *n*-decane (174°), decalin (190°), and *n*-tridecane (235°).[1] The concentration of VIa was determined by monitoring its ultraviolet band at 247 mμ. The appearance of VIIa was followed after

its initial build up by quantitative infrared measurements on its carbonyl band at 1740 cm^{-1}. Interference from the initially high concentration of VIa and XVIII with carbonyl and imine bands at ca 1680 cm^{-1} prohibited monitoring the 1740 cm^{-1} band throughout. The results of these determinations were used to calculate k_1, k_2, k_3, and k_4 assuming that each of these are first order rate constants. According to Stevens if k_1 had in reality been a second order constant a linear Arrhenius plot would not have resulted. A further check on the correctness of Scheme 1 was made by starting with XVIII and noting that very similar rate constants were obtained. This is the best evidence for the intermediacy of XVIII. A similar study on the nearly irreversible rearrangement of VIIIa to VIIa verified the first-order appearance of VIIa. Activation parameters from these studies are presented in Table 1 with an estimate of the accuracy of E_a.[1] The uncertainty of the analysis makes a quantitative interpretation of these results difficult; however, the large difference of entropy of activation between k_3 and k_6 probably is significant.

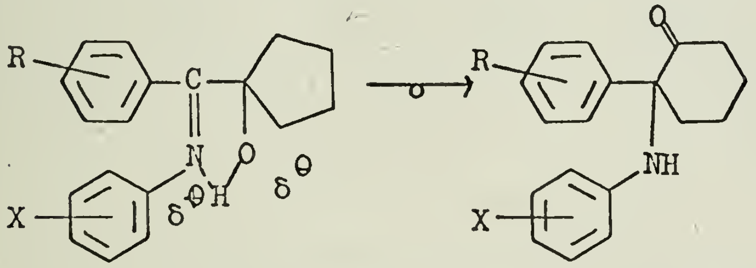
Table I

Activation Parameters for Scheme 1

Rate Constant	E_a kcal/mole	ΔS^* e u	ΔF^* kcal/mole	σ E_a, %
k_1	25.8	-23	35.8	2
k_2	22	-29	35	10
k_3	17	-43	36	14
k_6	35	-2	35	20

The small negative value of ΔS^* for k_6 has been attributed to a high degree of hydrogen bonding in the ground state of VIIIa as evidenced by the infrared spectrum. Also, there should be no loss of phenyl rotation in the transformation since phenyl is not the migrating group. The more negative value of ΔS^* for k_3 was attributed to just the opposite effects--low initial H bonding and restrictions on phenyl rotation.

Stevens has also determined substituent effects on the substituted compounds XIX reacting in decalin at 208° to give XX.[4] All exhibited clean first-order kinetics as determined by the appearance of an infrared band at ca 1715 cm^{-1} of the



XIX XX

	R	X	k_{rel}
a	H	H	1.0
b	p-OCH$_3$	H	1.3
c	p-CH$_3$	H	1.2
d	m-Cl	H	0.83
e	H	p-OCH$_3$	1.3
f	H	p-CH$_3$	1.2
g	H	m-Cl	0.81

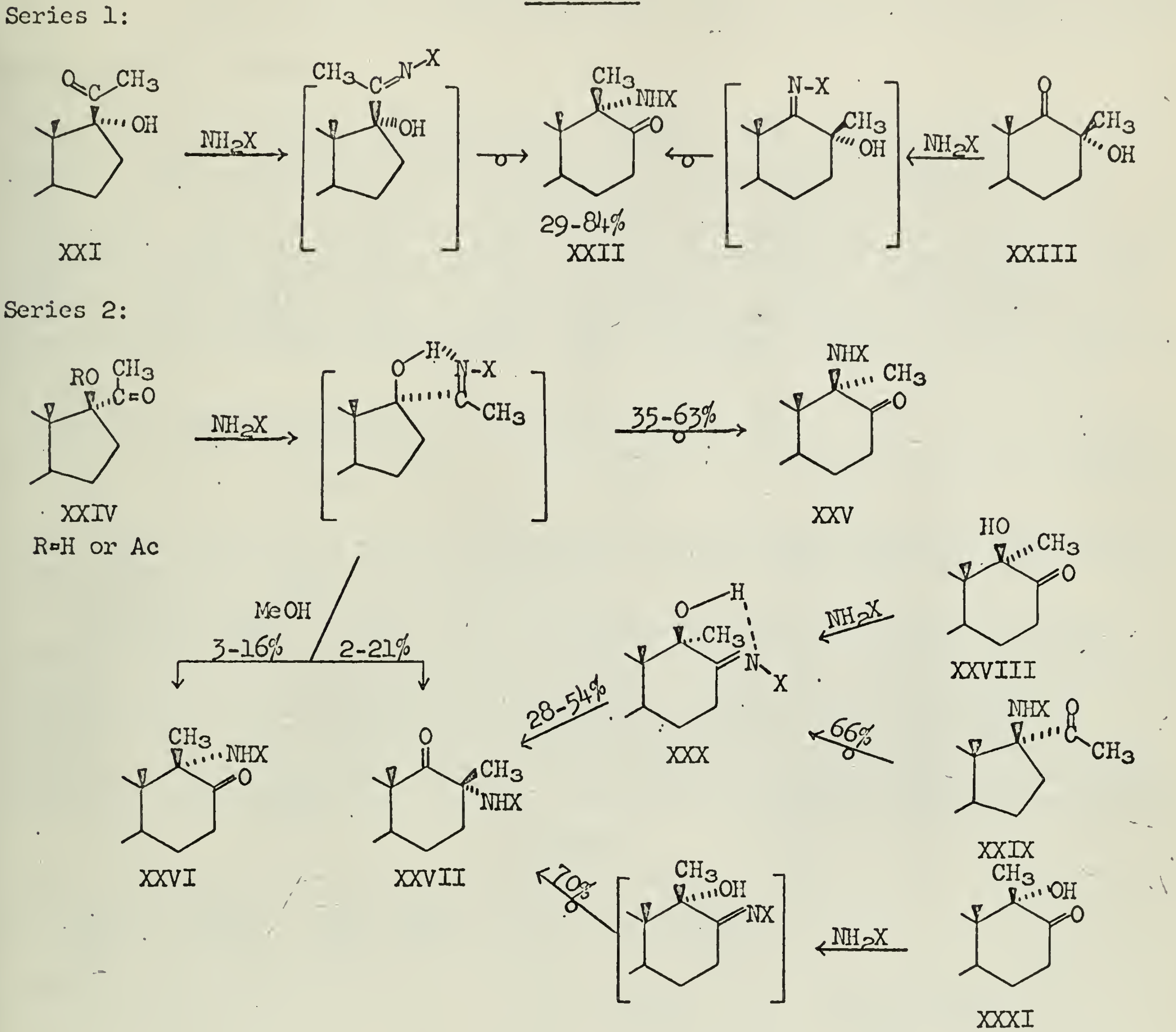
products. For both series, a Hammett plot of log k versus σ gave the same value of ρ, -0.32. Correlation was low (0.77) because of the low accuracy of the rate measurements. This value of ρ, though small in absolute value for a nonpolar solvent, probably indicates that the transition state has slightly more charge separation than the ground state.

In this same series of experiments an attempt was made to correlate relative rate to relative basicities of the hydroxy imines. Apparent pKa's were determined by potentiometric titration. There is no simple correlation since the basicities of substituted N-phenyl compounds (XIXe, f, and g) are about 1.5 times as sensitive to substituents as were compounds XIXb, c, and d; whereas, there is no significant difference in ρ in these two series. Therefore, Stevens believes that the free energy of activation for the rearrangement may have some dependence on the availability of the π electrons of the imine bond.[4]

Another important aspect of the reaction, the stereochemistry, has been determined for steroids by Morrow and coworkers.[8,9] They found that rearrangements in the D ring of steroids are fairly insensitive to differences in the A and B rings.

Most reactions were done on ketols in an excess of methylamine or ammonia by heating at 195° for 10 hours. Their results are presented in Scheme 2.

Scheme 2



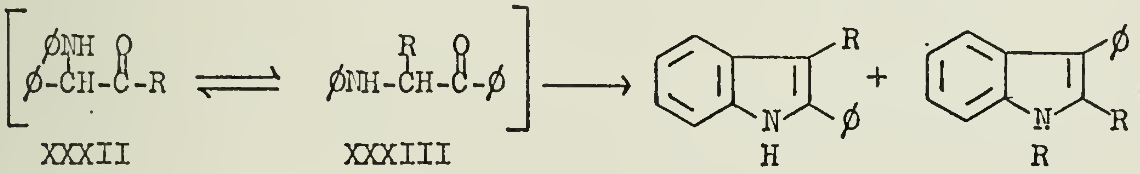
In the first series of reactions the stereochemistry is well behaved (with one exception not shown). In each case a β-hydroxyl group leads to a β-amine. The second series of reactions is much more complex. Here the products of the reactions vary with the conditions. However, it is important to note that again both of the ring enlargement reactions (i.e., XXIX → XXX and XXIV → XXV) occur so that the amino group and the hydroxyl group of the reactant and product have the same configuration with respect to the steroid ring. This behavior resembles the expansion of ring D with Lewis acid catalysis for ketol XXIV (17β-OH) which rearranges to XXVIII ($17a\beta$-OH).^{13} In this reaction the acid catalyst bonds to both the hydroxyl and carbonyl groups and thus directs the carbonyl oxygen into the same orientation (viz., α or β) as the original hydroxyl group. That the normal thermal rearrangement proceeds similarly is consistent with a hydrogen bridge between nitrogen and oxygen at the time of alkyl migration.

The anomalous cases in Series 2 can be rationalized as occurring by a base catalyzed rearrangement via a five-membered ring. Again analogy is found in the ketol series. In the presence of base, XXIV (17β-OH) rearranges to XXXI ($17a\alpha$-OH) and XXI (17α-OH) rearranges to XXVIII ($17a\beta$-OH).^{13} It would be interesting to study the rearrangement of XXX to XXVII and determine the kinetic order to see if base catalysis could be confirmed in this manner.

The kinetics and stereochemistry of the amino ketone rearrangement in the trisubstituted series are consistent with the mechanism proposed by Stevens, and he is carrying out investigations of solvent effects, steric effects, and catalytic effects. A study of migratory aptitudes (especially of substituted aromatic groups) could be especially helpful in further defining the mechanism of the rearrangement.

DISUBSTITUTED SYSTEMS

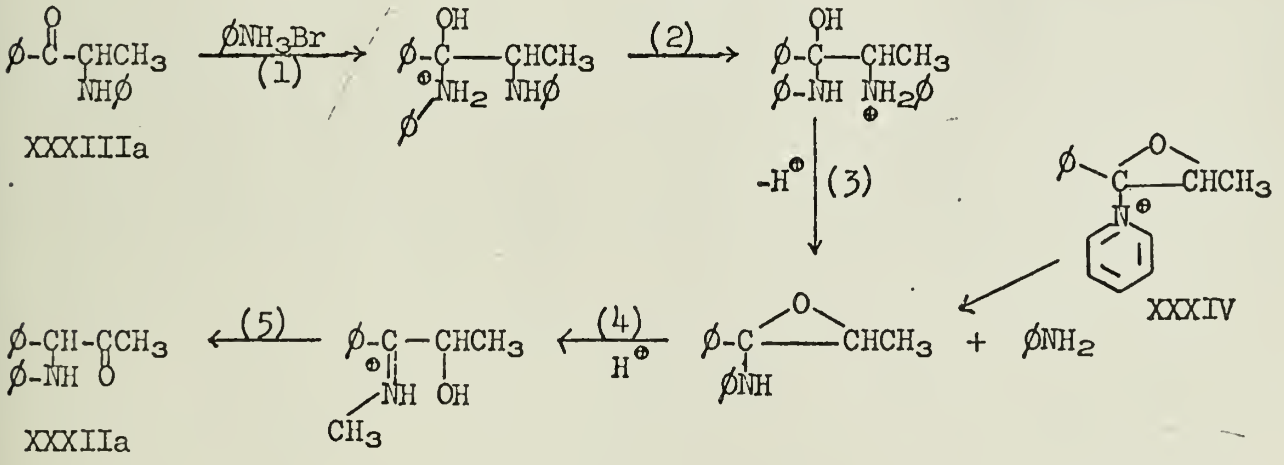
It was known in the late 19th century that phenacyl bromides when heated with derivatives of aniline at about 200° give indoles. This reaction, known as the Bischler indole synthesis, has been reviewed.[14] The precise mechanism of this transformation has been elusive, perhaps because rearrangement often accompanies the cyclization. Thus if phenacylanilines (XXXIII) are heated in the presence of anilinium bromide the products consist of both rearranged and unrearranged indoles. Indeed the rearranged products usually predominate. Julian, Meyer, Magnani, and Cole[15] in 1945 were the first to realize that phenacylanilines themselves can be rearranged to α-anilinobenzyl ketones, XXXII. Thus when XXXIIIa or b are heated as a melt with hydrochloric acid or in ethanol with anilinium bromide it rearranges to give XXXIIa or b in ca 20% yield (50% of the starting material is recovered). The rearrangement was shown to be reversible.

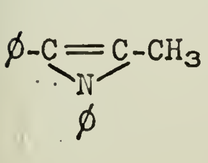


a, R = CH_3
b, R = $C_6H_5CH_2$
c, R = $\underline{p}$-$CH_3C_6H_4$

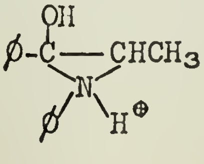
Brown and Mann[16] studied the rearrangement of XXXIIIc to XXXIIc in boiling butanol (118°). They concluded that anilinium bromide is a better catalyst than is hydrogen bromide or N-methylanilinium bromide. Thus Brown and Mann postulated a mechanism which has been modified by Nelson and Seefled[17] and is outlined in Scheme 3. The latter authors have observed that pyridinium bromide catalyzes this reaction and incorporate this into their mechanism by assuming that species XXXIV results by steps similar to 1, 2, and 3 and that it exchanges with freed aniline to give XXXIIa. As a test of their mechanism Nelson and Seefeld rearranged XXXIIIa in ethanol containing 5% water enriched in ^{18}O. Their data rule out a statistical exchange of ^{18}O into the rearranged product, although some direct exchange occurred under these conditions. Their data, according to Nelson and Seefeld, rule out the intermediacy of structures XXXV and XXXVI in which oxygen exchange would be expected. In the latter case this is questionable.

<u>Scheme 3</u>

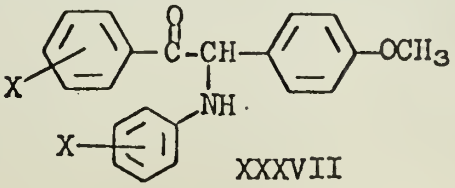




XXXV



XXXVI



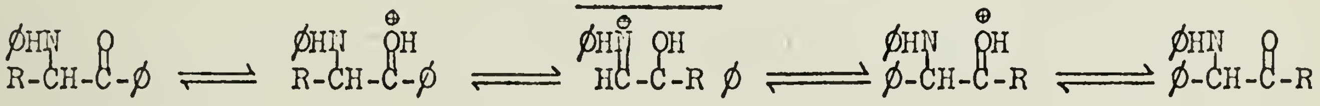
XXXVII

a, X = Cl
b, X = Br

In an attempt to further substantiate their mechanism, Nelson, Robertson, and Duvall[18] have prepared 2-(4-chloroanilino)-1-(4-chlorophenyl)-2-(4-methoxyphenyl) ethanone (XXXVIIa) and the dibromo analogue (XXXVIIb). They rearranged a 50 : 50 mixture of these compounds in ethylene glycol at 148° for 2 hours with an equivalent of picoline hydrobromide. Unfortunately the authors were unable to separate the mixture of products. They report that the mass spectrum of the reaction mixture shows that some compounds are present which contain both chlorine and bromine. No estimate of the amounts of such compounds was made. The authors believe that their data support their mechanism since anilines should mix at step 3. They did not rule out the possibility that they are observing exchange with the starting material or products. Weygand and Richter[19] have shown that phenacylaniline exchanges with aniline-^{14}C in a few minutes at 100° when a trace of anilinium bromide is added. Thus, any source of free anilines in the Nelson experiment (e.g., from $Br^{\ominus}$ displacement) would probably give the observed results regardless of the mechanism.

Obviously more mechanistic work must be done on the amino ketone rearrangement of the disubstituted type. To date none of the evidence has ruled out the possibility that this reaction occurs by migration of alkyl and aryl substituents rather than by exchange of heteroatoms. A possible alternative mechanism based on analogy to the mechanism proposed for the trisubstituted system is depicted in Scheme 4.

Scheme 4



XXXIII

XXXII

SUMMARY

The amino ketone rearrangement of trisubstituted systems has been extensively studied. The mechanism of the reaction based on kinetic and stereochemical evidence appears to be a concerted skeletal rearrangement equilibrating an amino ketone with a hydroxy imine. The mechanism of rearrangements of disubstituted amino ketones is uncertain.

BIBLIOGRAPHY

1. C. L. Stevens, H. T. Hanson, and K. G. Taylor, J. Am. Chem. Soc., 88, 2769 (1966).
2. C. L. Stevens, R. D. Elliott, B. L. Winch, and I. L. Klundt, ibid., 84, 2272 (1962).
3. C. L. Stevens, R. D. Elliott, and B. L. Winch, ibid., 85, 1464 (1963).
4. C. L. Stevens, A. Thuillier, and F. A. Daniher, J. Org. Chem., 30, 2962 (1965).
5. C. L. Stevens, I. L. Klundt, M. E. Munk, and M. D. Pillai, ibid., 30, 2967 (1965).
6. C. L. Stevens, A. Thuillier, K. G. Taylor, F. A. Daniher, J. P. Dickerson, H. T. Hanson, N. A. Nielsen, N. A. Tikotkar, R. M. Weier, ibid., 31, 2601 (1966).
7. C. L. Stevens, A. B. Ash, A. Thuillier, J. H. Amin, A. Balys, W. E. Dennis, J. P. Dickerson, R. P. Glinski, H. T. Hanson, M. D. Pillai, and J. W. Stoddard, J. Org. Chem., 31, 2593 (1966).
8. D. F. Morrow, M. E. Butler, E. C. Y. Huang, ibid., 30, 579 (1965).
9. D. F. Morrow, M. E. Brooke, G. W. Moersch, M. E. Butler, C. F. Klein, W. A. Neuklis, E. C. Huang, ibid., 30, 212 (1965).
10. C. L. Stevens, R. M. Weier, and K. G. Taylor, Abstr. Papers Am. Chem. Soc., 152nd Meeting, S101 (1966), and private communications.
11. B. Witkop and J. B. Patrick, J. Am. Chem. Soc., 73, 2188 (1951).
12. I. Elphimoff-Felkin, Bull. Soc. Chim. France, 653 (1962).
13. N. L. Wendler, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N.Y., 1964, p. 1114.
14. P. L. Julian, E. W. Meyer, H. C. Printy, "Heterocyclic Compounds," R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N.Y., 1952, Vol. 3, p. 22.

15. P. L. Julian, E. W. Meyer, A. Magnani, and W. Cole, J. Am. Chem. Soc., 67, 1203 (1945).
16. F. Brown and F. Mann, J. Chem. Soc., 858 (1948).
17. K. L. Nelson and R. L. Seefeld, J. Am. Chem. Soc., 80, 5957 (1958).
18. K. L. Nelson, J. C. Robertson, and J. J. Duvall, ibid., 86, 684 (1964).
19. F. Weygand and E. Richter, Ber., 88, 499 (1955).

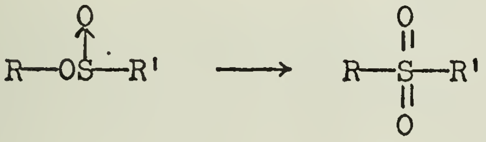
1,2 SHIFTS IN N-O, S-O, AND P-O BONDS

Reported by R. J. Basalay November 17, 1966

INTRODUCTION

The rearrangement of amine oxides to ONN-trisubstituted hydroxylamines (Meisenheimer-Rearrangement) (1); the rearrangement of sulfinates to sulphones (2), sulfoxylates to sulfinates (3) and sulfenates to sulphoxides (4); and the rearrangement of trivalent phosphorus compounds with at least one ester group to a "phosphine oxide" with one less ester group (Michaelis-Arbuzov Rearrangement) (5) will be considered. The mechanisms for these rearrangements will be discussed.

(1) 
$R-\overset{\overset{O}{\uparrow}}{\underset{R'}{N}}-R'' \longrightarrow R-\underset{R'}{N}-OR''$ R" = allyl-, benzyl-

(2) 
$R-O\overset{\overset{O}{\uparrow}}{S}-R' \longrightarrow R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-R'$

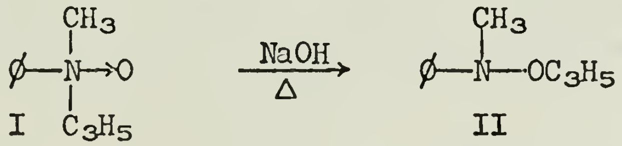
(3) 
$RO-S-OR' \longrightarrow R-\overset{\overset{O}{\uparrow}}{S}-OR'$ R = allyl-, benzyl-

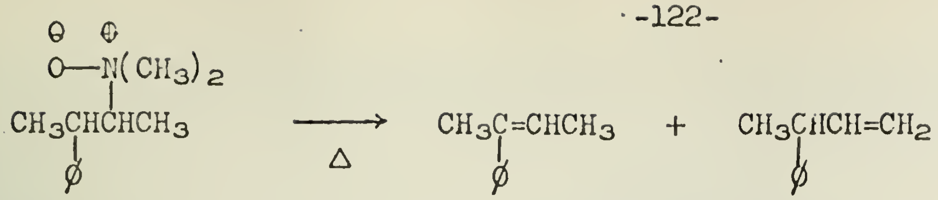
(4) 
$ROSR' \longrightarrow R-\overset{\overset{O}{\uparrow}}{S}-R'$ R' = allyl-, benzyl-

(5) 
$>POR \xrightarrow{RX} >\overset{\overset{O}{\uparrow}}{P}-R$ X = Cl, Br, I

THE MEISENHEIMER REARRANGEMENT

Meisenheimer[1] has shown that allylmethylaniline oxide (I) rearranges readily on heating with aqueous sodium hydroxide to give O-allyl-methyl-N-phenylhydroxylamine (II). Later, allylethylaniline oxide and benzylmethylaniline oxide[2] were shown to rearrange under the same conditions, but allyldimethylamine oxide and allyldiethylamine oxide did not rearrange. Cope and Towle[4] confirmed that allyl dialkylamine oxides do not rearrange in aqueous base. However, they do rearrange on heating without base after most of the water has been removed by distillation. If a driving force of the reaction is a nucleophilic attack of an unshared electron pair of oxygen on the allyl group, a possible explanation for this difference in behavior of amine oxides and aniline oxides would be a stronger solvent association with the oxygen for the amine oxides. The greater tendency of aliphatic amine oxides to hydrate, trialkylamine oxides form very hydroscopic mono- or dihydrates and aniline oxides are hydroscopic but form no definite hydrates, is in accord with this; but could reflect crystal lattice stabilization rather than solvent association. Cram and Sahyun[3] observed a large reduction in the rate of elimination with amine oxides when a hydrogen-bonding solvent such as water or methanol rather than tetrahydrofuran or dimethyl sulphoxide is used. An unreactive hydrogen-bonded amine oxide was

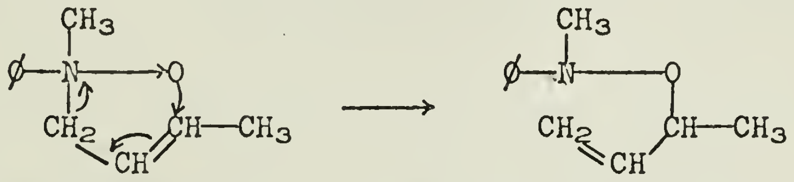

$\phi-\overset{CH_3}{\underset{C_3H_5}{N}}\rightarrow O \xrightarrow[\Delta]{NaOH} \phi-\overset{CH_3}{N}-OC_3H_5$
I II



postulated as the cause indicating a strong solvent association for trialkylamine oxides.

Kleinschmidt and Cope[5] examined the rearrangement of crotylmethyl aniline oxide (III) to o-methylvinylcarbinyl-N-methyl-N-phenylhydroxylamine (IV) with rearrangement of the crotyl group. This indicates an intramolecular, cyclic mechanism for rearrangements of allyl groups in amine oxides. Wragg, Stevens, and Ostle[6] explored this amine oxide rearrangement by simple kinetic experiments which indicated a process first order in amine oxide and independent of added base. From their results in Table 1, it can be seen that the allyl group migrates more readily than the benzyl group.

III



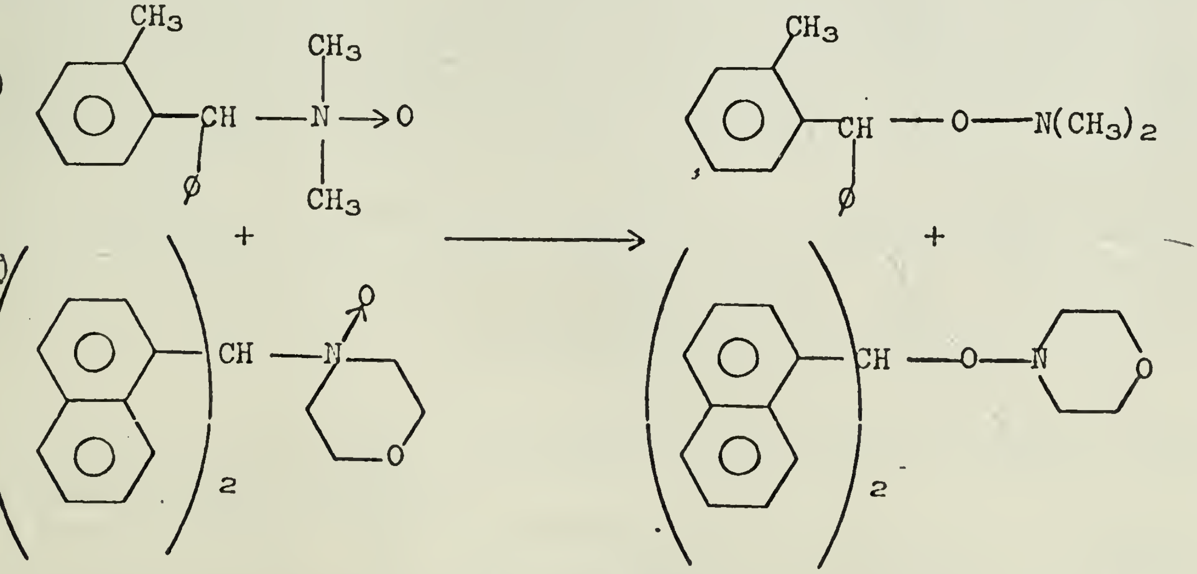
IV

Table 1

		k_{20°	k_{30°	k_{60°
1	$PhCH_2N(O)MePh$	-	-	0.0062
2	$PhCH_2N(O)MeC_6H_5Br(p)$	-	-	0.014
3	$CH_2=CHCH_2N(O)MePh$	-	0.0071	-
4	$CH_2=CHCH_2N(O)PhCH_2Ph$	0.013	0.055	-

Electron-attracting substituents in either stationary group accelerate the reaction. They may remove charge from oxygen lowering its hydrogen-bonding ability. The allyl group in case 4 of Table 1 migrates exclusively. A large rate enhancement was observed for an electron-withdrawing nitro group in diphenylmethyl migrating groups. The rearrangements of a mixture of dimethyl (phenyl-o-tolylmethyl) amine oxide (V) and N-di-α-naphthylmethylmorpholine oxide (VI) and the separation of the reaction product into N-di-α-naphthylmethoxymorpholine (VIII) and NN-dimethyl-o-(phenyl-o-tolylmethyl) hydroxylamine (VII) by steam distillation in almost quantitative yield was used as evidence for a intramolecular reaction.

(V) (VI) (VIII) (VII)



Evidence was found by Schöllkopt *et al.*[7] that the rearrangement involving benzyl groups is not concerted since optically active dimethyl-benzyl-(α-D)-amine oxide rearranges and becomes at least 61-62% racemized indicating a two-step splitting-recombination mechanism. Kinetic evidence excluded a carbonium ion intermediate

on the basis of the substituent effects on the relative rates (see Table 2). On the same basis a free radical might be eliminated since the reverse substituent effect is found for the free radical abstraction of benzylic hydrogen.[8] However, free radicals were detected by ESR-spectroscopy during the rearrangement of methyl-phenyl-benzylamine oxide, and the rearrangement occurs not only thermally but also photochemically. The substituent effects may reflect the degree of solvent association with the amine oxide. An anionic mechanism should have relative rates more sensitive to substituent effects than is found since a full charge would be developed on the anionic migrating group. Also, a positive entropy of activation (+7.9 ± 2.5 ev.)[9] was obtained for the rearrangement of benzyldimethylamine oxide. This entropy value is consistent with either an anionic or free radical mechanism. The effects of solvation and the solvent association present could be used to justify a range of entropy values in either case.

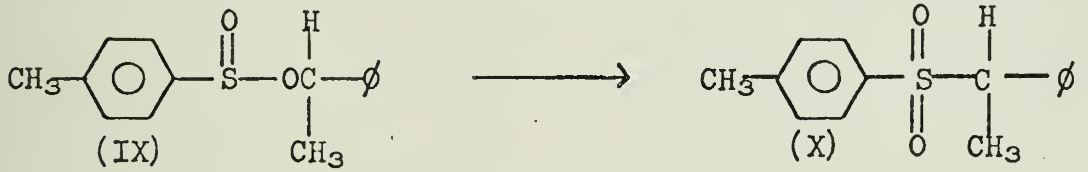
Table 2
Relative Rates
$RC_6H_4CH_2N(O)(CH_3)_2$

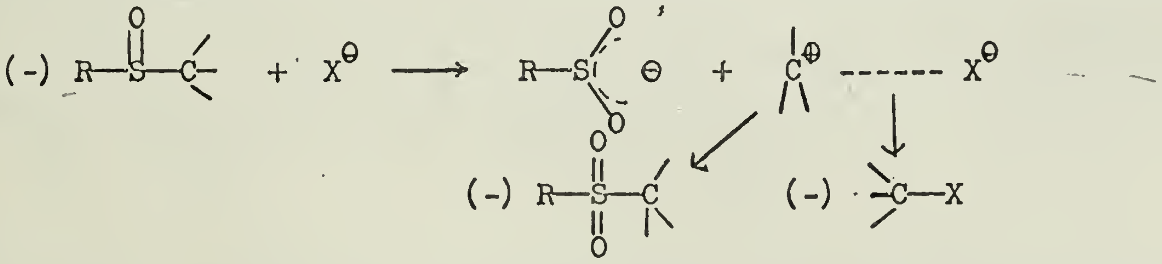
R	H	m-Cl	p-NO_2	p-C_6H_5	p-CH_3	p-OCH_3
k/k_o	1	1.1	14.8	1.95	0.32	0.24

The mechanism for the Meisenheimer Rearrangement appears to be intramolecular for allyl-migrating groups and a two-step free radical dissociation-recombination by benzyl migrating groups although an anionic mechanism cannot be ruled out.

REARRANGEMENT OF SULFINATES TO SULPHONES

Kenyon and coworkers[10,11] studied the conversion of optically active α-methylbenzyl toluene-p-sulfinate (IX) into α-methylbenzyl-p-tolyl sulphone (X), and found that the (-) sulfinate rearranges to the dl-sulphone in formic acid or neat. If sodium formate is added to the formic acid solvent, the products are (-) and dl-sulphone (10%) and (-) and dl-phenylmethylcarbinyl formate (75%). The (-)-formate has the opposite configuration of the (-)-sulphone or -sulfinate. If sodium formate and p-toluene-sulfinate are added, a high yield (62%) of formate is obtained but almost completely racemic. A mechanism for this involves the ionization of the (-)-sulfinate and then recombination to give dl-sulfinate or sulphone. In the presence of formate ions, the formate ion can react with the free cation to give dl-formate, or it can coordinate with the cation as it ionizes and either react to give (-) formate or allow the anion to recombine to give (-) sulfinate or sulfone.



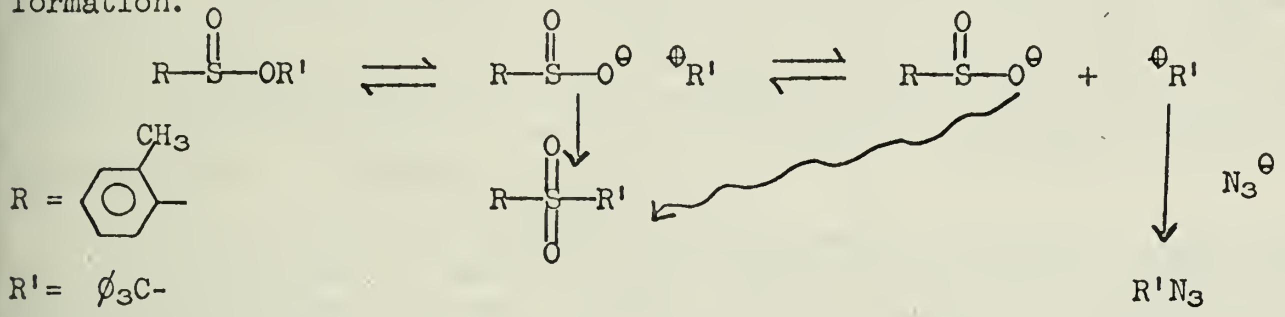


When sulfinate ion is added, it competes with formate ion and thus reduces the amount of optically active formate.

Darwish and coworkers[12,13] examined the solvolysis and rearrangement of arylsulfinate esters. They found no increase in the amount of sulphone produced when sulfinates were rearranged in the presence of sulfinate ion in water-ethanol solutions. Trityl 2-methylbenzenesulfinate

was allowed to rearrange in the presence of tetra-n-butylammonium azide in varying concentrations.

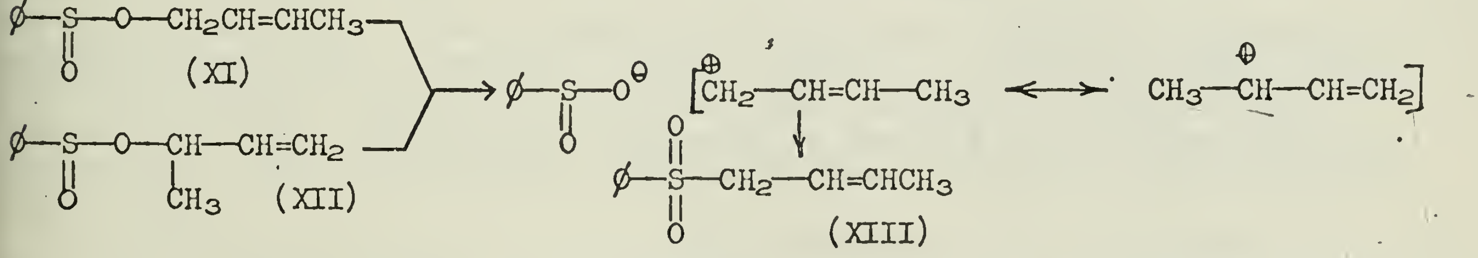
A maximum of $\sim$45% conversion of ester to azide was obtained. A competition experiment was carried out by adding trityl perchlorate (0.027M) to acetonitrile containing 0.071M tetra-n-butylammonium azide and 0.071M tetra-n-butylammonium 2-methylbenzenesulfinate. Infrared analysis indicated $\sim$45% yield of trityl azide. Trityl 2-methylbenzenesulfinate rearranges at room temperature in CCl_4, $CHCl_3$, ϕNO_2, CH_3CN, and DMSO. The first-order rate constants in the first three solvents, containing 0.03M. lutidine, are 3×10^{-6} sec.$^{-1}$, 5×10^{-4} sec.$^{-1}$ and 1.3×10^{-3} sec.$^{-1}$. respectively. A more ionizing solvent increases the rate of rearrangement. A comparison of the reaction rate of α-(p-methoxyphenyl) ethyl over α-phenylethyl 2,6-dimethylbenzenesulfinate show an enhancement of both solvolysis and sulphone formation in ethanol by approximately four powers of ten. An effect of this magnitude indicates the formation of ionic species. The evidence supports an ionic dissociation mechanism with ion pair formation.



Wragg, McTadyen, and Stevens[14] found that the availability of protons was necessary for the rearrangement of sulfinic esters. Sulphones were prepared from the related sulphinic acid and alcohol in three ways: by heating the acid and alcohol in acetic acid-hydrochloric acid solution; by heating the related sulphinic ester in the same medium; and by thermal rearrangement of the ester alone or in an inert solvent. In each case substantially the same results were given. The synthesis of sulphone from alcohol and sulfinic acid proceeded easily in acetic acid, nitromethane, acetonitrile, benzene, or toluene; but rearrangement of the ester took place only in the first two solvents. Rearrangement was observed in the remaining sovents in the presence of a little toluene-p-sulphinic acid. A mixing experiment, where diphenylmethyl toluene-p-sulfinate is heated in acetic acid containing p-chlorobenzene sulfinic acid yielding a small amount of p-chlorophenyl diphenylmethyl sulphone, indicates a intermolecular reaction.

The rearrangement of sulfinates appears to be acid or base catalyzed and proceeds through an ionic dissociation-recombination mechanism with ion-pair formation.

Cope, Morrison, and Field[15] effected the rearrangement of allyl benzenesulfinate, crotyl benzenesulfinate (XI), and α-methylallyl benzenesulfinate (XII). The latter two gave crotyl phenyl sulphone (XIII) as the major product . A possible mechanism for this was given, but the possibility of a concerted intramolecular path was not excluded, because of the possibility of interconversion of the isomeric sulfones at the temperature of the rearrangement to an equilibrium mixture of mainly the crotyl phenyl sulphone.



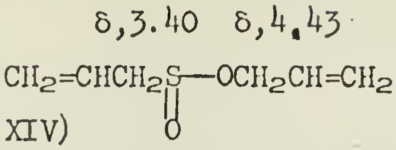
REARRANGEMENT OF SULFOXYLATES TO SULFINATES

In the course of studying the synthesis of sulfoxylates from alcohols and sulfur dichloride, Thompson[16] found that benzyl and allyl alcohols behaved abnormally and yielded sulfinate esters. Allyl alcohol and sulfur dichloride with triethylamine in methylene chloride at -95° react to give a tarry material. The pmr of a pure material has two doublets, equivalent to two protons each, at δ = 3.40 and 4.43 ppm.,

thus indicating sulfinate (XIV) rather than sulfoxylate (XV). Benzyl alcohol was treated

$(CH_2{=}CHCH_2O)_2S$

(XV)



$\delta,3.40 \quad \delta,4.43$

$CH_2{=}CHCH_2\overset{}{\underset{\underset{O}{\|}}{S}}{-}OCH_2CH{=}CH_2$

(XIV)

similarly and yielded an oil which partially crystallized on standing. The pmr spectrum of the recrystallized product shows two slightly broadened bands at δ=3.90 and 4.88 ppm. corresponding to nonequivalent benzylic methylene groups indicating a sulfinate, again. When α-methylallyl alcohol reacts, a complex mixture of esters was obtained which was not separated.

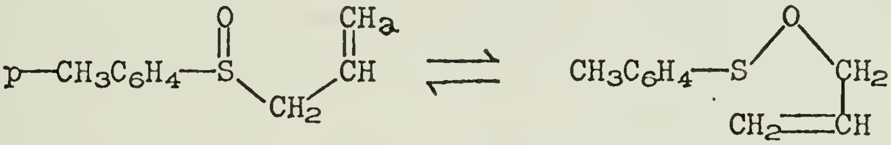
The reaction of the "α-methylallyl sulfoxylate" appears similar to the rearrangement of α-methylallyl benzenesulfinate to crotyl phenyl sulphone.[15] A complex mixture of products is obtained possibly containing crotyl and α-methylallyl sulfoxylate and sulfinate esters. The "benzyl sulfoxylate" could rearrange by an ionic mechanism considering the discussion of benzyl migrations in the rearrangement of sulfinate esters. The low temperature of the reaction probably stops the reaction at sulfinate although there is probably some sulphone present in the impure products.

REARRANGEMENT OF SULFENATES TO SULPHOXIDES

The rearrangement of sulphoxides was attempted by Cope.[15] Who expected a rearrangement similar to that of amine oxides, allylphenyl sulphoxide was heated, but no rearrangement occurred. However, it was observed[17] later that heating benzylmethyl sulphoxide to 220° for a short time produced a distillate which was benzaldehyde and a strong mercaptan smell. The result indicated the rearrangement of the sulphoxide to phenyl methyl sulfenate occurred with subsequent decomposition to benzaldehyde. Many other substituted benzyl sulphoxides reacted similarly.

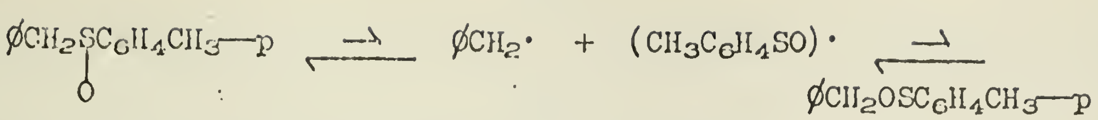
$$PhCH_2\overset{O}{\overset{\|}{S}}Me \longrightarrow Ph\underset{\underset{O}{\|}}{C}H + MeSH$$

Mislow and coworkers[18] in studying the mechanisms of thermal racemization of sulphoxides observed a ten-thousandfold increase in rate with allyl-p-tolyl sulphoxide and a thousandfold increase with benzyl p-tolyl sulphoxide over other substituted sulphoxides. The pyramidal inversion mechanism they had used to explain the general case could not be used to explain the rate enhancement. A cyclic rearrangement mechanism was introduced in which the chiral sulphoxide is in mobile equilibrium with



the achiral sulfenate. They examined the thermal rearrangement of sulfenates to sulphoxides and found it occurred easily. Reaction of p-toluenesulfenyl chloride with lithium allyl alcoholate or lithium crotyl alcoholate in ether at room temperature yielded allyl p-tolyl sulphoxide or 1-methylallyl p-tolyl sulphoxide, respectively. The rearrangement in this case would proceed by a concerted 1,3 allylic shift.

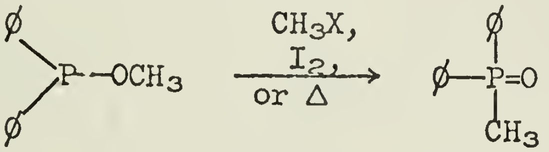
For the racemization of benzyl p-tolyl sulphoxide, $\Delta H^* = 43$ kcal/mole and $\Delta S^* + 24$ ev are found which are in accord with a homolytic dissociation mechanism. In the course of the racemization some decomposition occurs, the decomposition products could arise from the dimerization of radicals. Benzyl p-toluene-sulfenate rearranged at temperatures above 110° to give an equilibrium mixture of sulfenate (~5%) and benzyl p-tolyl sulphoxide (~95%) in less than 24 hours. Rates and equilibrium positions were measured by pmr, and $\Delta H^* = 29$ kcal/mole and $\Delta S^* = 0 \pm 2$ eu. are found. A strong esr signal is observed at 160° during the rearrangement in naphthalene. The evidence leads to a homolytic dissociation mechanism although some "leakage" <u>via</u> an intramolecular path cannot be ruled out.

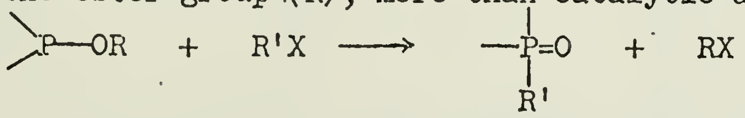


$\phi CH_2\underset{\overset{|}{O}}{S}C_6H_4CH_3\text{—}p \rightleftharpoons \phi CH_2\cdot + (CH_3C_6H_4SO)\cdot \rightleftharpoons \phi CH_2OSC_6H_4CH_3\text{—}p$

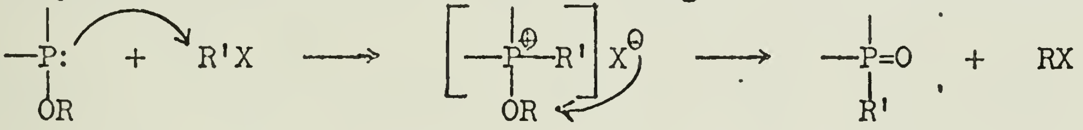
THE MICHAELIS-ARBUZOV REARRANGEMENT

The rearrangement of trivalent organic phosphorus compounds with at least one ester group is catalyzed by an organic halides with the same organic group as the ester of the phosphorus compound to give a quasi-phosphine oxide with one less ester group. Some especially reactive phosphorus esters, methyl, benzyl, or allyl diphenylphosphinites isomerize[19] on warming with a crystal of iodine or even on strong heating alone. If the organic group (R') of the halogen compound is not the same as that of the ester group (R), more than catalytic amounts of the organic halide must be used since it is consumed in a replacement reaction with the organic group on the ester.





The mechanism of this rearrangement or reaction is generally described[20] as a nucleophilic displacement of halogen by the unshared pair of electrons on phosphorus to form a quasi-phosphonium compound. The quasi-phosphonium compound is then attacked by the halide ion to eliminate an organic halide and form a quasi-phosphine oxide.



The properties of the quasi-phosphonium compounds have been examined.[21] In polar solvents the P-X bond is largely ionic and dissociated into ions as indicated by conductivity experiments. The solutions are strong electrolytes comparable to those of tetramethylammonium iodide. In solutions with non-polar solvents, the dipole moments of these compounds are considerably lower than those for ionic compounds indicating nonequivalent covalent bonds, at least one of which being strongly polar.

The reaction with CCl_4 as the halide and solvent proceeds by a free radical path.[22] The radical chain reaction produces a quasi-phosphonium compound which then decomposes. Under conditions favorable for the presence of radicals, the reaction or rearrangement can proceed by a radical chain mechanism. The research on the Michaelis-Arbuzov reaction continues by investigating exceptions to the generally accepted mechanism caused by special properties of the organic groups or reaction conditions.[23]

STRENGTH AND BOND CHARACTER OF N→O, S→O, AND P→O BONDS

The reversal in direction of the rearrangement of benzyl p-toluene sulfinate,[18] as compared with the formally analogous Meisenheimer-Rearrangement, has its source in the formation of the strong sulfur-oxygen double bond (90 kcal/mole). The strength of this bond may reside in its multiplicity[24] which in turn arises from back donation of the unshared electron pairs on oxygen into vacant d orbitals on sulfur.[25] This mechanism of bond strengthening is not available to the amine oxides because the d orbitals on nitrogen are too high in energy to be used in any significant bonding.

The multiplicity of S-O and P-O bonds has been examined and there seems to be some difference of opinion. C^{13}-H coupling constants are found proportional to the S character of the carbon AO used to form the bonding MO.[26] The hybridization of a C-H bond appears to depend on both the electronegativities of attached groups or atoms, and on the radii of the attached atoms. The investigation[24] of the C^{13}-H coupling constants of nitrogen, phosphorus, and sulfur compounds offers an ideal way to detect the amount of positive charge on N, P, or S atoms and therefore the amount of

p-d bonding in compounds with N-O, P-O, and S-O bonds. From Table 3, a large increase in the coupling constant of $(CH_3)_4N^+$ over $(CH_3)_3N$ is seen and can be attributed to the greater electronegativity of N^+ compared to $\geqslant$N:. The C^{13}-H coupling constant for $(CH_3)_3NO$ shows that the electronegativity of N in the N-oxide is nearly the same as that of N^+ in quaternary ammonium salts so that this N-O bond must be almost completely N^+-O^-. The coupling constant for $(CH_3)_3PO$ indicates that its phosphorus atom more closely resembles a neutral P rather than P^+. This is also observed for sulfur compounds. Hence, the S-O, and P-O bonds are best described as double bonds. However, Juan and Gutowsky[27] felt that unshared electron pairs on an atom bonded to carbon have a large effect on the C^{13}-H coupling constants. This would account for the change in coupling constants observed in Table 3 by the loss of an unshared pair of electrons on the atom attached to carbon. This argument was proposed to explain data such as the change in the coupling constant from 125 cps in ethane to 151 cps in methyl iodide despite carbon and iodine having similar electronegativities (Pauling, 2.5). This difference can also be attributed to the longer bond length in methyl iodide which then fits under the first explanation. The linear dependence of C^{13}-H coupling constants on electronegativity holds within any one row of the periodic table. The description of P-O bonds as double bonds is concluded in other cases.[28] The sulfur-oxygen moment in sulphoxides and sulphones has been calculated[29] which indicated that it is mainly a double covalent bond. However, Wagner[30] calculated the bond orders of symmetrically substituted phosphoryl molecules, Y_3PO, using an internally consistant LCAO-MO method, and found $(CH_3)_3PO$ to have a coordinate single P-O bond. The molecular refractions of several sulphoxides support the report of Vogel[31] that the S-O bond is best represented as a semipolar single covalent bond.

Table 3

C^{13}-H Coupling Constants

Compound	Solvent	J(cps ± 0.05 cps)
$(CH_3)_3N$	Neat	131
$(CH_3)_4N^{\oplus}Cl^{\ominus}$	D_2O or CF_3CO_2H	145
$(CH_3)_3N^{\oplus}H$	D_2O or CF_3CO_2H	143
$(CH_3)_3N$-O	H_2O	143
$(CH_3)_3P$	Neat	127
$(CH_3)_4P^{\oplus}$	D_2O	134
$(CH_3)_4P^{\oplus}H$	CF_3CO_2H	135
$(CH_3)_3P$-O	D_2O	129
$(CH_3)_2S$	Neat	138
$(CH_3)_3S^{\oplus}I^{\ominus}$	CF_3CO_2H	146
$(CH_3)_2S$-O	Neat	138
$(CH_3)_2SO_2$	D_2O	139

In the rearrangements discussed, one notes that amine oxides rearrange to hydroxylamines. However, sulfenates rearrange to an equilibrium mixture, in the case of benzyl p-tolyl sulfenate, where the major component is sulphoxide; and phosphinites rearrange to phosphine oxides. In these transformations an O-C bond is exchanged for a N, S, or P-C bond and a N→O, S→O, or P→O bond with the loss of a pair of unshared electrons on the N, S, or P atom. Since a N, S, or P-C bond is generally weaker than an O-C bond, the trend observed during the rearrangement to change the equilibrium position must be due to the N→O, S→O, or P→O bond.

$$-\ddot{X}-O-R \longrightarrow -\overset{R}{\overset{|}{X}}\rightarrow O$$

X=N, S, or P

This trend would be explained by a single ionic covalent bond in N→O and covalent double bonds in S=O and P=O. Thus these rearrangements provide additional experimental support of the multiplicity of S=O and P=O bonds.

BIBLIOGRAPHY

1. J. Meisenheimer, Ber., 52, 1667 (1919).
2. J. Meisenheimer, H. Greeske, and A. Willmerdorf, Ber., 55, 513 (1922).
3. M. R. V. Sahyun and D. J. Cram, J. Am. Chem. Soc., 85, 1263 (1963).
4. A. C. Cope and P. H. Towle, J. Am. Chem. Soc., 71, 3423 (1949).
5. R. F. Kleinschmidt and A. C. Cope, J. Am. Chem. Soc., 66, 1929 (1944).
6. A. H. Wragg, T. S. Stevens, and D. M. Ostle, J. Chem. Soc., 4057 (1958).
7. U. Schöllkopf, M. Patsch and H. Schäfer, Tetrahedron Letters, No. 36, 2515 (1964).
8. M. M. Martin and G. J. Gleicher, J. Am. Chem. Soc., 86, 233 (1964).
9. G. P. Shulman, P. Ellgen, and M. Connor, Can. J. Chem., 43, 3459 (1965).
10. J. Kenyon and H. Phillips, J. Chem. Soc., 1677 (1930).
11. C. L. Arcus, M. P. Balfe, and J. Kenyon, J. Chem. Soc., 485 (1938).
12. D. Darwish and R. McLaren, Tetrahedron Letters, No. 26, 1231 (1962).
13. D. Darwish and E. A. Preston, Tetrahedron Letters, No. 2, 113 (1964).
14. A. H. Wragg, J. S McFadyen, and T. S. Stevens, J. Chem. Soc., 3603 (1958).
15. A. C. Cope, D. E. Morrison, and Lamar Field, J. Am. Chem. Soc., 72, 59 (1950).
16. Q. E. Thompson, J. Org. Chem., 30, 2703 (1965).
17. W. Carruthers and B. J. Millard, Chem. and Ind. (London), 342 (1966).
18. E. G. Miller, P. Bickart, A. J. Gordon, and K. Mislow, J. Am. Chem. Soc., 88, 3138 (1966); E. G. Miller, D. R. Rayner, and K. Mislow, J. Am. Chem. Soc., 88, 3139 (1966).
19. A. E. Arbuzov and K. V. Niknoro, Zhur. Obshchei Khim., 18, 2008 (1948); Chem. Abstr., 43, 3802 (1949).
20. A. Y. Garner, E. C. Chapin, and P. M. Scanlon, J. Org. Chem. 24, 532 (1959).
21. B. G. Liorber and A. I. Razumov, Zhur. Obshchei Khim., 34, 1867 (1964).
22. F. M. Kharrasova and Gil'm Kamai, Zhur. Obshchei Khim., 34, 2195 (1964).
23. H. J. Harwood and D. W. Grisley, Jr., J. Am. Chem. Soc., 82, 423 (1960).
24. P. Haake, W. B. Miller, and D. A. Tyssee, J. Am. Chem. Soc., 86, 3577 (1964).
25. N. Kharasch, "Organic Sulfur Compounds", Vol. 1, Pergamon Press Inc., New York, N. Y., 1961, pp. 35, 36.
26. N. Muller and D. E. Pritchard, J. Chem. Phys., 31, 1471 (1959).
27. C. Juan and H. Gutowsky, J. Chem. Phys., 37, 2203 (1962).
28. D. P. Craig, A. Maccoll, R. S. Nyholm, L. E. Orgel, and L. E. Sutton, J. Chem. Soc., 332 (1954); J. R. VanWazer, J. Am. Chem. Soc., 78, 5709 (1956).
29. C. W. N. Cumper and S. Walker, Trans. Faraday Soc., 52, 193 (1956).
30. E. S. Wagner, J. Am. Chem. Soc., 85, 161 (1963).
31. C. C. Price and R. G. Gillis, J. Am. Chem. Soc., 75, 4750 (1953); A. I. Vogel, W. T. Cresswell, G. H. Jeffery and J. Leicester, J. Chem. Soc., 514 (1952).

SECONDARY DEUTERIUM ISOTOPE EFFECTS

Reported by David J. W. Goon November 21, 1966

INTRODUCTION

Deuterium isotope effects have come into widespread use in the study of organic reaction mechanisms over the last twenty years. Many reviews on the theory and application of these effects are available.[1] A primary effect is observed only when the C-D bond is broken in the rate determining step. Secondary deuterium isotope effects are all other isotope effects arising when deuterium is substituted for a hydrogen atom. This seminar will consider the secondary effects. Much of the work done prior to 1963 has been reviewed by Halevi,[1a] and part of the more recent literature has been briefly reviewed by Thornton.[1f] In this seminar emphasis will be placed on an understanding of the origins of secondary deuterium isotope effects.

STERIC ISOTOPE EFFECT

Bartell[2,3] has invoked nonbonded repulsions or steric hindrance as the chief cause of secondary isotope effects. In applying his postulate to solvolysis reactions,[4] Bartell stated that there would be more and stronger nonbonded repulsions in the tetrahedral reactant than in the carbonium ion considered to be a model for the transition state. If deuterium is "smaller" than protium, the trigonal transition state would then be relieved of greater nonbonded repulsions when it contains hydrogen rather than deuterium. Bartell then proceeded to quantitatively formulate his postulate. His basic principle was that the amplitude of vibration of the hydrogen atom was greater than that of deuterium by a predictable amount. Furthermore, for a given nonbonded interaction, the isotope effect would be proportional to the mean-square of the mass-sensitive component of the relevant amplitude of vibration and to the second derivative of the potential function. Another assumption was that the nonbonded interaction between a hydrogen atom and any given atom may be approximated by a potential function, V, which is dependent on the distance, r, between atoms but independent of the orientation or deformation of the remainder of the molecule to which the atoms are attached. Then by use of a perturbation method and further assumptions, Bartell derived equation 1, where ΔΔE is the isotopic

$$\Delta\Delta E \approx \Sigma\Delta\Delta E_{ij} \qquad (1)$$

difference in total energy of the entire molecule. $\Delta\Delta E_{ij}$ is the energy difference of each component of the molecule and is approximated in equation 2, where l_m^2 is

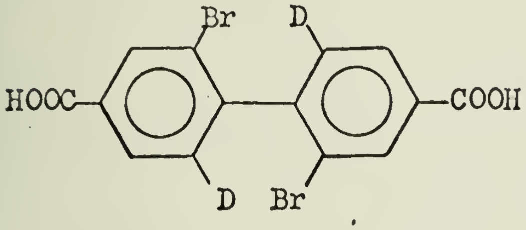
$$\Delta\Delta E_{ij} \simeq 0.13\ l_m^2(H)(1 + 15 \times 10^{16}\ l_t^2(H))_{ij}(V_{ij}''(r_g \text{ trig.}) - V_{ij}''(r_g \text{ tetr.})) \qquad (2)$$

the mass-sensitive component of the mean-square of vibration of the atom pair, l_t^2 the mean-square amplitude of vibration of the atom pair, and the last term the difference of the second derivatives of the potential functions between the transition state and the reactant with r_g the mean distance between nonbonded pairs. With these equations, the average over the lowest vibrational level of the potential energy due to H--H, C--H, and C--C nonbonding interactions in the reactant and in the product or model of the transition state was calculated. Treating the vibrations as harmonic, Bartell assigned attractive and repulsive parameters for the interactions and for the solvolysis of *t*-butyl chloride calculated an isotope effect which was approximately half of that observed for *t*-amyl chloride. The isotope effect for *t*-butyl chloride was not reported at that time, but Bartell felt that the increased bulk of the *t*-amyl group would increase the isotope effect. Thus, Bartell felt that he was able to show at least qualitatively that nonbonded interactions contribute to the isotope effect.

Shiner[5] has pointed that the isotope effect on the solvolysis of *t*-butyl chloride is approximately the same as on the solvolysis of *t*-amyl chloride. It was further noted that Bartell's calculation overestimates the isotope effect by assuming a carbonium ion transition state. Bartell's steric model has also received criticism from Wilson,[6] who pointed out that little is known about forces within a

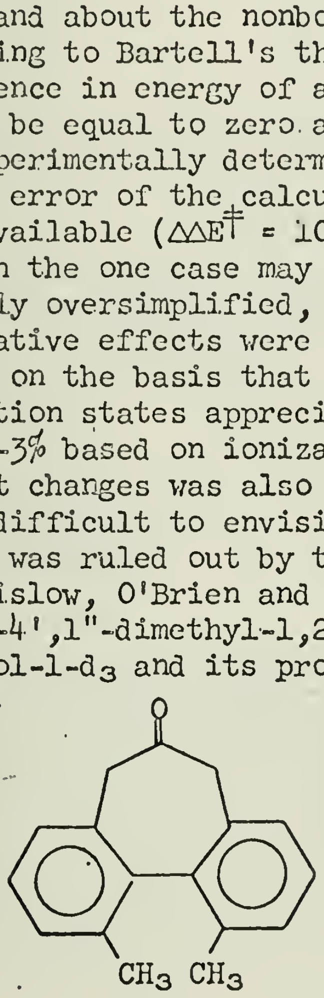
molecule let alone whether they are repulsive or attractive. It was also noted that studies of gas imperfections, compressibility of solids and quantum mechanical theory indicate steric repulsion is very dependent on distance and different substituents should have different repulsions. Criticism of the simplifying assumptions made by Bartell in his quantitative approach have been made by Halevi.[1a]

Melander and Carter[7] have used Bartell's approach to predict the isotope effect in the racemization of 2,2'-dibromo-4,4'-dicarboxybiphenyl-6,6'-d_2 (I) and determined experimentally the effect from -20° to 0° in ethanol. This compound was studied because the transition state leading to its racemization was believed to be planar. Knowledge of the transition state was considered important since it was felt that difficulties in computations like Bartell's arose from the lack of information about the detailed conformation of the transition state and about the nonbonded potentials between the different pairs of atoms. According to Bartell's theory, the entire isotope effect is assumed to be due to a difference in energy of activation. The isotopic entropy of activation difference should be equal to zero and $\Delta\Delta E^{\ddagger} = \Delta\Delta H^{\ddagger} = \Delta\Delta F^{\ddagger}$. A $\Delta\Delta F^{\ddagger}$ of 89 ± 16 cal./mole at 0° was experimentally determined for the racemization of I. This was within experimental error of the calculated $\Delta\Delta E^{\ddagger}$ for one set of potential parameters of the two sets available ($\Delta\Delta E^{\ddagger}$ = 100 or 506 cal./mole). The authors admitted that the agreement in the one case may have been fortuitous and that the calculations were probably oversimplified, but the alternative explanations of inductive or hyperconjugative effects were ruled out. The inductive effect was eliminated as a factor on the basis that it would not change the energies of the ground and transition states appreciably in this case and a maximum effect was probably less than 1-3% based on ionization in aromatic systems.[8,9] A lack of sensitivity to solvent changes was also cited as evidence against an inductive effect. Although it is difficult to envision a hyperconjugative effect in this system, hyperconjugation was ruled out by the authors on the basis of improper geometry.

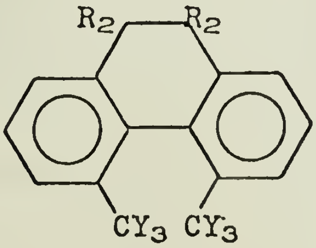


I

Mislow, O'Brien and Schaefer[10] in a study of the partial asymmetric reduction of (±)-4',1"-dimethyl-1,2,3,4-dibenzcyclohepta-1,3-diene-6-one (II) with (+)-(*S*)-2-propanol-1-d_3 and its protium analog in dioxane containing aluminum *t*-butoxide at 63° found a negligible difference (<0.1 cal./mole) in the energies for the diastereoisometric transition states. This was accounted for by the assumption that the sensitivity of the ketone was lost when the differential compressions became sufficiently small. The authors felt that a more highly crowded transition state would be required for the exhibition of a steric isotope effect. In the racemization of 9,10-dihydro-4,5-dimethylphenanthrene (III-d_0) and its d_4, d_6, and d_{10} analogs in benzene at 42°, Mislow and co-workers[11] have found isotope effects k_D/k_H of 1.05, 1.13, and 1.18 for III-d_4, -d_6, and -d_{10}, respectively. They noted that the effects appear to be additive and that the 5% of the isotope effect in III-d_4 and -d_{10} could be related to a change in the potential barrier around the 9,10-bond or to isotopic differences in the interaction between the 9,10-hydrogens and the nearest hydrogens at the 1- and 8-positions. The 13% isotope effect in III-d_6 and -d_{10}



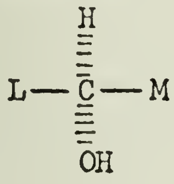
II



III

d_0 R = Y = H
d_4 R = D, Y = H
d_6 R = H, Y = D
d_{10} R = Y = D

was considered to be steric in origin. This was claimed to be the first unambiguous evidence for the operation of a steric kinetic isotope effect. However, the authors were not certain as to whether the effect arose mainly from nonbonded repulsions and to what extent other factors needed to be considered. Horeau, Nouaille, and Mislow[12] have studied secondary isotope effects in asymmetric synthesis and kinetic resolutions. They found that partial asymmetric alcoholysis of α-phenylbutyric anhydride in (+)-(S)-2-propanol-1-d_3 (IV) yields, after hydrolysis of unreacted anhydride, α-phenylbutyric acid with a detectable optical activity. It has been shown empirically by Horeau[13] that the sign of rotation of the acid is related to the absolute configuration of the inducing alcohol. This means that partial alcoholysis with alcohols of configuration (V), where L is the large group and M the medium-sized group, results in an acid containing an excess of the (+)-(S)-enantiomer. The results above indicated to the authors that the configuration (V) corresponded to the configuration of IV if and only if CH_3 is assumed to be the large group and CD_3 the medium-sized group. This result was felt to be consistent with the postulate[11] that CH_3 exceeds CD_3 in effective bulk.



V

$$L-\overset{\overset{H}{|}}{\underset{\underset{OH}{|}}{C}}-M$$

Raaen and co-workers[14] have studied secondary isotope effects in the acid-catalyzed reactions of several C^{14}-labeled ketones with 2,4-dinitrophenylhydrazine at 0°. Their results are given in Table I. The errors are the sums of the standard deviations of the rates compared. The authors felt that assuming the isotope effects had a common cause and that no change in mechanism occurred with structural changes, the cause of the isotope effect seemed to be mostly attributable to steric factors, specifically, to the decreased steric crowding when deuterium is substituted for hydrogen in the transition state which is formed by attack of hydrazine on the conjugate acid of the ketone. Raaen also felt that an inductive effect would predict that the hydrogen compound would react faster than the deuterium compound and that hyperconjugation could not rationalize the first two entries of Table I. Lansbury, Bieron, and Klein[15] have reported that low temperature nmr was not sensitive enough to detect a steric isotope effect on the inversion barrier separating the folded configurations of 7,12-dihydropleiadiene.

Table I

Isotope Effects on the Reactions of Several Ketones with 2,4-DNP at 0°.

Deuterated Ketone	k_D/k_H
$ArCOCD_3$	1.119 ± 0.005
	1.104 ± .002
$ArCOC(CH_3)(CD_3)_2$	1.046 ± .0015
$ArCOCD_2CH_3$	1.124 ± .005
$ArCOCH_2CD_3$	0.995 ± .001

$Ar = C_6H_5$

Recently, Brown[16,17] has called for a re-evaluation of isotope effects in terms of Bartell's steric model. Brown and McDonald[16] have studied the rates of reaction of methyl substituted pyridines and their deuterated methyl analogs with alkyl iodides. Their results are given in Table II. The errors given are estimates of experimental precision. From these results, Brown and McDonald concluded that deuteration of the 3- and 4-methyl groups had no effect outside of experimental error on the reaction

Table II. Kinetic Isotope Effects in the Reactions of Pyridines with Alkyl Iodides.

Pyridine	Alkyl Iodide	Temp., °C	$(k_D/k_H)_T$	$(k_D/k_H)_{25^\circ}$
4-Methyl-d_3	Methyl	25.0	1.001 ± 0.01	1.001
3-Methyl-d_3	Methyl	25.0	1.009 ± 0.01	1.009
2-Methyl-d_3	Methyl	25.0	1.030 ± 0.01	1.030
	Ethyl	75.0	1.036 ± 0.01	1.042
	Isopropyl	100.0	1.058 ± 0.03	1.073
2,6-Dimethyl-d_6	Methyl	25.0	1.095 ± 0.01	1.095
	Ethyl	75.0	1.072 ± 0.02	1.085
	Ethyl	100.0	1.070 ± 0.02	1.088
Pyridine-4-d_1	Methyl	25.0	1.012 ± 0.01	1.012
Pyridine-d_5	Methyl	25.0	1.031 ± 0.01	1.031

rate, while the 2-CD_3 definitely increases the rate relative to the protium compound. With methyl iodide, the CD_3's of 2,6-dimethyl-d_6-pyridine appear to have an effect which is more than twice that of the one CD_3 in 2-methyl-d_3-pyridine. However, with ethyl iodide, the effects in these two compounds appear to be additive. The isotope effect appears to increase with the 2-methyl-d_3-pyridine as the alkyl iodide is changed from methyl to ethyl to isopropyl, while the same trend is not obvious with 2,6-dimethyl-d_6-pyridine. It was pointed out by Brown and McDonald that a reversal in the isotope effects of the deuterated lutidine was within experimental error. Finally, it appears that deuteration of the ring in the 4-position does not seem to exhibit an isotope effect while it does in pyridine-d_5. The authors felt that these results were in complete accord with Bartell's steric model which would predict a k_D/k_H greater than unity for the 2,6- and 2- deuterated methyl pyridines but little effect for the 3- and 4-methyl-d_3-pyridines. Brown and McDonald felt that while the inductive effect would predict the same rate enhancement of the deuterium compounds, it would operate in all three ring positions. However, it would seem that the inductive effect would be a function of distance. Hyperconjugation was seen to reduce the rate of the deuterium compound relative to the hydrogen compound since in the transition state a positive charge would develop on the nitrogen which would then be stabilized by methyl groups in the 2- and 4-positions.

Secondary isotope effects on the heats of reaction of methyl pyridines with boron trifluoride and diborane have been measured by Brown and co-workers.[17] Their results are given in Table III. Although the differences are small and therefore inconclusive (they are also within experimental error), Brown felt that the similarity between this study and the previous one with the alkyl iodides gave confidence that the observed changes were due to true secondary isotope effects. Again, hyperconjugation was seen to predict opposite results while the inductive effect was expected to operate almost as efficiently from the 3- and 4-positions as from the 2-position. Brown felt that much of the literature existing on secondary isotope effects could be rationalized by a steric model and that a re-evaluation of the data and conclusions of these investigations would be fruitful. However, he did indicate that the postulate that the dominant factor in secondary isotope effects may be of steric origin was speculation. Brown also stated that he knew of only two cases in which the steric explanation was inadequate. One is that the solvolysis of p-methyl-d_3-benzhydryl chloride is 2-6% slower than the undeuterated compound,[18] and the other is that the solvolysis of dimethylpropynyl-d_3-carbinyl chloride is 8% slower than its protium analog.[19] The steric model would predict no significant difference in either case. There are other examples in which a steric explanation does not appear to provide a rationale for secondary isotope effects, and the remainder of this seminar will be devoted to discussion of these cases.

Table III. Isotope Effects on the Heats of Reaction of Pyridines with BF_3 and B_2H_6 in Nitrobenzene at 25°.

Pyridine	Ref. Acid	$\Delta H_H - \Delta H_D$ kcal./mole
4-methyl-d_3	BF_3	-0.04
3-methyl-d_3		-0.10
2-methyl-d_3		0.16
2,6-dimethyl-d_6		0.23
2,6-dimethyl-d_6	B_2H_6	-0.02

HYPERCONJUGATION AS THE ORIGIN OF ISOTOPE EFFECTS

Lewis[4b] and Shiner[4a] were the first to interpret β-deuterium isotope effects in terms of hyperconjugative interaction between the carbonium ion center and the site of isotopic substitution. It should be noted that hyperconjugation cannot rationalize α-deuterium effects. In essence, hyperconjugation has associated with it the withdrawal of electrons from C-H bonds which in turn weakens the bonds and lowers the zero-point vibration energies.[3] Since deuterium is heavier than hydrogen, the C-D bond has a lower zero-point energy initially and less zero-point energy is lost at the transition state.[20] The energy of activation is therefore greater for the deuterated molecule.

Halevi and Nussim[21] have suggested that hyperconjugation is an important effect on the stability of charge-transfer complexes between aromatic hydrocarbons and the electron acceptor chloranil. They determined spectrophotometrically that the

deuteration of the methyl group in toluene decreases the association constant by 7% and that deuteration of one methyl group in m-xylene decreases the constant by 8%. This requires that the net electron donation by the ring be reduced in the deuterated compounds. Several factors were cited which ruled out a significant contribution by a steric isotope effect in this system. (1) The inter-ring distance was thought to be so large that the short-range nonbonding interactions with the methyl hydrogen atoms would be very small, and isotopic differences in these repulsions would be negligible. (2) It was noted that in another study[9] in which a steric effect of the methyl group does seem to exist that the effect was not significantly isotope-dependent. (3) It was also noted that steric isotope effects have been ascribed to the greater vibrational amplitude of the hydrogen atom. Such an effect operating in the above system would tend to increase the association constants of the deuterated hydrocarbons. An inductive effect was considered unlikely by Halevi and Nussim as an important factor on the basis that it would be expected to affect the results in the opposite way to that which was observed.

Shiner[4a] has suggested that large secondary isotope effects caused by β-deuterium substitution are characteristic of a deuterium in a trans position to the leaving group in the transition state. The dependence of the isotope effect on the conformation of the molecule has been used as an argument against the postulate that steric isotope effects are the dominant influence on isotope effects. Shiner has done much of the work on conformation effects on secondary isotope effects in solvolysis reactions. The results of one such study are given in Table IV.[22] The standard deviation of each rate constant was about 0.01% and considered to be accurate to within less than 0.1%. The results show that the isotope effect per deuterium increases as the extent of deuteration of a methyl group increases. Also, as each methyl group is deuterated, the isotope effect remains constant within the uncertainty of deuterium analysis. Shiner felt that a strong conformational dependence of the isotope effect would mean that rate retardation caused by successive replacement of the hydrogens of a methyl group adjacent to a solvolyzing center would not be exactly cumulative. Thus the above results seemed to be evidence for this conformational dependence. Shiner felt that vibrational coupling between hydrogens attached to the same carbon atom was a negligible influence in that coupling effects lead to the largest change in zero-point energy on the first isotopic substitution. It was reasoned that the largest isotope effect would occur on the first substitution of deuterium.

Table IV. Isotope Effects on the Solvolysis of t-Butyl Chloride in 60% Aqueous Ethanol at 25°.

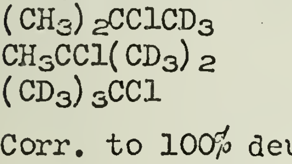
Deuterated Cpd.	k_H/k_D	k_H/k_D per D
$(CH_3)_2CClCH_2D$	1.0922	1.092
$(CH_3)_2CClCHD_2$	1.2016	1.096
$(CH_3)_2CClCD_3$	1.3303	1.100
$CH_3CCl(CD_3)_2$	1.7095	1.102
$(CD_3)_3CCl$	2.3271	1.103*

*Corr. to 100% deuteration

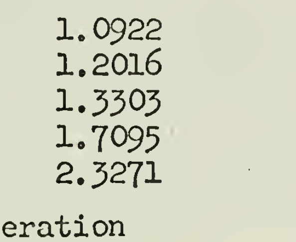
Shiner[22] then calculated the magnitude of the isotope effect by use of a simple conformational model. Two possible conformations of the transition state of t-butyl-d_1 chloride are A and B. The solvolysis rate of the undeuterated chloride is k_H and that of the deuterated chloride k_D. It was then assumed that a, the isotope effect per deuterium in the trans position (A) to the leaving group, would be given by $a = k_H / 3k_a$ while b, the isotope effect of the deuterium in the gauche position, would be $b = k_H / 3k_b$. k_a and k_b are the rates of solvolysis of conformations A and B, respectively. By giving double weight to conformation B, the isotope effect for the substitution of one deuterium would be given by equation 3. Assuming that the isotope effects of the trans and gauche

$$k_H / k_{D1} = 3ab / (b + 2a) \qquad (3)$$

deuterium are unaffected by the substitution of other deuteriums on the same carbon atom, the isotope effect of the substitution of two and three deuteriums in the methyl



A



B

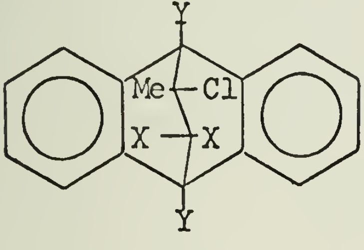
group are given by equation 4 and 5, respectively. Shiner then used the observed

$$k_H / k_{D2} = 3ab^2 / (a + 2b) \qquad (4)$$

$$k_H / k_{D3} = ab^2 \qquad (5)$$

k_H/k_{D1} and k_H/k_{D3} values to calculate a(1.3016) and b(1.0110). Then using equation 4, k_H/k_{D2} was calculated to be 1.0958 (1.096, experimental). To Shiner this quantitative correlation of experimental and calculated isotope effects showing a strong conformational effect was a strong presumptive influence for hyperconjugation. Thornton[11] has recently stated that conformational dependence does not eliminate a steric model but did not elaborate.

In a study of the solvolysis of 11-methyl-11-chloro-9,10-dihydro-9,10-ethanoanthracene (VIa) and its 12,12-d_2 (VIb) and 9,10-d_2 (VIc) analogs in 60% aqueous ethanol at 45°, Shiner and Humphrey[5] presented further evidence that the isotope effect may show angular dependence. Isotope effects of 1.14 ± 0.01 and 0.986 ± 0.01 were observed for VIb and VIc, respectively. It was postulated by the authors and shown by these results that a C-D bond orthogonal to a developing vacant orbital at an adjacent solvolytic center (VIc) should exhibit an insignificantly small isotope effect. A maximum rate retardation would then be observed when the β-C-D bond axis is parallel to the axis of the developing vacant p-orbital.[23] Shiner and Humphrey felt that a phenomenon dependent on hyperconjugation between a single bond and an adjacent p-orbital should be angular dependent.



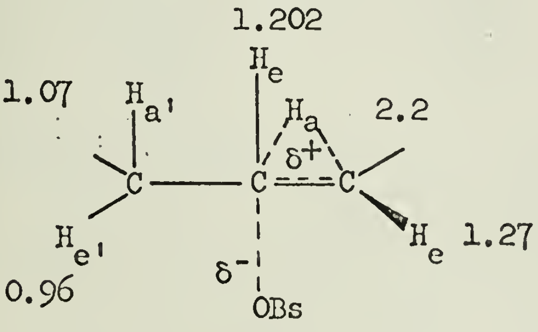
(a) X = Y = H
(b) X = D, Y = H
(c) X = H, Y = D

VI

The isotope effect for each of four β-hydrogen atoms on the rate of solvolysis of cis-4-t-butylcyclohexyl brosylate (VII) has been determined by Shiner and Jewett.[23,24] Their results are given in Table V. From these results, it appears that β-deuterium substitution at conformationally equivalent sites does not lead to cumulative isotope effects (2.565/1.096 = 2.340 > 2.062 = $(1.436)^2$). The effect of each different atom was calculated using a simple conformational model as before. The calculated values are given with structure VIII. The noncumulative behavior and large k_H/k_D associated with the axial hydrogen were thought to be in accord with the postulate of hydrogen participation in the solvolytic transition state. Shiner and Jewett felt that neighboring participation was an extreme example of a type of electronic interaction associated with hyperconjugation. They felt that the only conceivable driving force was the formation of a stabilized, bridged, nonclassical carbonium ion and that absence of extensively rearranged substituted products was indicative that the nonclassical ion was unsymmetrically hydrogen bridged. The difference between hyperconjugation and participation was thought to be that cumulative isotope effects from equivalent initial state sites would occur in hyperconjugation while there would be noncumulative contributions in participation. t-Butylcyclohexene was found to be the main product (86%) of the ethanolysis of VII and complete deuteration of the positions did not "substantially lower" the olefin fraction.[24] Thornton[11] has stated that since olefin is the major product in this solvolysis, it would be difficult to exclude competition between

Table V. Isotope Effects in the Solvolysis of VII in 50% Aqueous Ethanol at 35°.

Deuteration	k_H/k_D
α-D, e	1.202
β-D, a	1.436
β-D, e	1.096
β-D(3), a,a,e	2.565
β-D(3), a,e,e	1.784
β-D(4), a,a,e,e	2.862

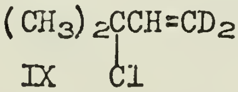


VIII

elimination involving concerted loss of β-deuterium and another reaction leading to alcohol and ether as the mechanism of the solvolysis. Furthermore, he felt that neighboring group participation was a primary effect and that the stereospecificity of the isotope effect did not eliminate a steric model as the cause of the isotope effect. Shiner and Jewett[25] have also studied the ethanolysis of trans-4-t-butylcyclohexyl p-bromosulfonate. In this case, the equatorial hydrogens were seen to have a cumulative effect while the axial β-hydrogens were nonequivalent in the transition state.

CHANGE IN HYBRIDIZATION AS A CAUSE OF α-SECONDARY ISOTOPE EFFECTS

An analysis by Streitwieser[26] based on statistical mechanics indicated that the α-deuterium isotope effect in the acetolysis of cyclopentyl-1-d_1 tosylate was predominantly affected by a change in hybridization at the solvolytic center, i.e., "to the change of a tetrahedral C-H bending vibration to an out-of-plane deformation in the transition state." Recent evidence for this postulate has been given by Belanić-Lipovac, Borčić, and Sunko[27] in an investigation of the rate of solvolysis of 1,1-dimethylallyl-3,3-d_2 chloride (IX) and 3,3-dimethylallyl-1,1-d_2 chloride (X) in ethanol. For X an isotope effect k_H/k_D of approximately 1.2 was found.


$(CH_3)_2C(Cl)CH{=}CD_2$

IX

$(CH_3)_2C{=}CHCD_2Cl$

X

There was no appreciable isotope effect for IX. It was pointed out that in IX that the C-D bonding orbitals are already sp^2 hybridized in the ground state, and assuming that with respect to positive charge the transition state of IX resembles that of X, this would mean that no rehybridization would occur in the solvolysis of IX. Since the C-D bonding orbitals in IX are orthogonal to the π-system in the transition state, a rate retardation due to hyperconjugation would not be observable. However, the authors felt that an inverse isotope effect for IX might have been expected. One reason was that electron withdrawing substituents had been found to increase the C-H out-of-plane bending frequency in ethylene. Therefore, the electron demand on the double bond in the form of stabilization of the transition state by allylic resonance should have resulted in stiffening of the C-D bonds and a subsequent rate acceleration. An inverse effect might have also been expected due to the fact deuterium has a larger electron releasing power than hydrogen. Mocek and Stewart[28] have studied the effect of α-deuteration on the ionization of 4,4'-disubstituted benzhydrols. Their results are given in Table VI. It was noted that electron withdrawing groups increase the size of the isotope effect.

Table VI. Isotope Effects on the Ionization of $(YC_6H_4)_2CDOH$ in Aqueous H_2SO_4 at 25°.

Y	K_H/K_D
H	1.29
Cl	1.35
CH_3	1.20
CH_3O	1.18
C_2H_5O	1.17
$(CH_3)_2N$	1.[illegible]

INDUCTIVE ISOTOPE EFFECT

Dipole moments, nuclear quadrupole coupling constants, nmr chemical shifts, molecular refraction and optical activity all seem to indicate that the C-D bond is more electropositive and less polarizable than the C-H bond.[1a] This means that the C-D bond is capable of greater electron release. Equilibrium studies[8,9,29] have shown that the inductive effect is a real effect on secondary isotope effects. Streitwieser[8] and Halevi[9] have attempted to elicit the extent that deuterium acts as a normal electron donating inductive substituent by determining the effect of deuteration on the pK values of several carboxylic acids. The results of Streitwieser's conductometric study are given in Table VII. These results show that deuteration lowers the acidity of the acid; a result which would be predicted by an inductive effect of deuterium. Bell and Crooks[30] have used the observed vibrational frequencies of HCOOH, DCOOH, $HCOO^-$, and $DCOO^-$ to calculate the isotope effect on formic acid and found a difference of 0.037 ± 0.002 pK units at 25°. For the solvolysis of benzhydryl chlorides, Streitwieser and Klein[31] have obtained the isotope effects given in Table VIII. The effect appears to be a

Table VII. Isotope Effects on the pK Values of Carboxylic Acids in Water at 25°.

Acid	$pK_D - pK_H$
DCOOH	0.035 ± 0.002*
CD_3COOH	0.014 ± 0.001
$(CD_3)_3CCOOH$	0.018 ± 0.001
C_6D_5COOH	0.010 ± 0.002
2,6-$C_6H_3D_2COOH$	0.003 ± 0.001

*from ref. 29.

function of ring position with *ortho* > *meta* > *para* and is approximately additive. The lesser effect of the *para*-deuterium relative to that of the *meta* could not be explained; the reverse was expected since the *para* substitution is known to have marked effects ascribed to resonance in the system. Application of Taft's F^{19} chemical shift correlation to detect isotope effects on the character of the methyl group in *meta* and *para* substituted fluorobenzenes has shown no inductive effect.[32] In the cycloaddition of diphenyl ketene to cyclohexene-1-d_1,[33] it was found that the adduct was opposite that which an inductive effect would predict.

Table VIII. Isotope Effects on the Solvolysis of Various Deuterated Benzhydyl Chlorides at 25°.

	In 80% Acetone		In 70% Acetone	
Deuteration	k_D/k_H	$100(k_D/k_H - 1)$ per D	k_D/k_H	$100(k_D/k_H - 1)$ per D
o	1.070 ± 0.003	1.8 ± 0.1	1.007 ± 0.003	1.9 ± 0.1
m	1.057 ± 0.002	1.4 ± 0.05	1.060 ± 0.003	1.5 ± 0.1
p	1.020 ± 0.003	1.0 ± 0.2	1.019 ± 0.002	1.0 ± 0.1
o,m,p	1.160 ± 0.001		1.170	
α	0.881 ± 0.005		0.880	
o,p	1.094 ± 0.004		1.095	

CONCLUSION

From the preceding examples, it is apparent that at present all observed secondary deuterium isotope effects cannot be rationalized solely by either a steric model or any of the other rationales discussed. Rather, if the rationales that have been presented are the only ones possible, it appears that many secondary isotope effects have more than one influence acting on them, this being a function of the system being investigated. The main difficulty in interpreting these effects appears to lie in differentiating and evaluating the various factors which influence the magnitude of the overall effect. As secondary deuterium effects come into wider application, a more detailed clarification of the origins of these effects will probably be necessary.

BIBLIOGRAPHY

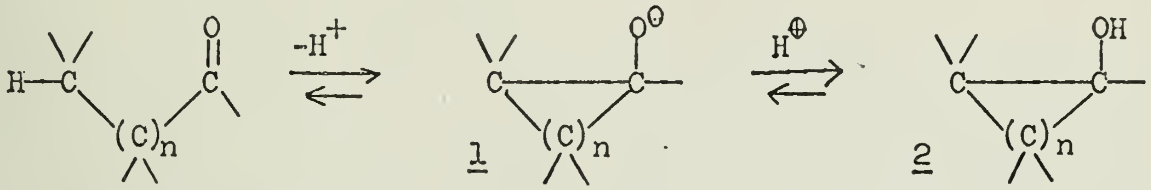
1. (a) E. S. Halevi, Prog. Phys. Org. Chem., 1, 109 (1963); (b) F. H. Westheimer, Chem. Rev., 61, 265 (1961); (c) K. B. Wiberg, Chem. Rev., 55, 713 (1955); (d) L. Melander, "Isotope Effects on Reaction Rates," The Ronald Press Co., New York, N. Y., 1960; (e) J. Bigeleisen and M. Wolfsberg, Advan. Chem. Phys., 1, 15 (1958); (f) E. R. Thornton, Ann. Rev. Phys. Chem., 17, 349 (1966).
2. L. S. Bartell, Tetrahedron Letters, No. 6, 13 (1960).
3. L. S. Bartell, J. Am. Chem. Soc., 83, 3567 (1961).
4. (a) V. J. Shiner, Jr., Tetrahedron, 5, 243 (1959); (b) E. S. Lewis, Tetrahedron, 5, 143 (1959).
5. V. J. Shiner, Jr. and J. S. Humphrey, Jr., J. Am. Chem. Soc., 85, 2416 (1963).
6. E. B. Wilson, Jr., Tetrahedron, 17, 191 (1962).
7. L. Melander and R. E. Carter, Acta Chem. Scand., 18, 1138 (1964).

8. A. Streitwieser, Jr. and H. S. Klein, J. Am. Chem. Soc., 85, 2759 (1963).
9. E. A. Halevi, M. Nussim, and A. Ron, J. Chem. Soc., 866 (1963).
10. K. Mislow, R. E. O'Brien, and H. Schaefer, J. Am. Chem. Soc., 84, 1940 (1962).
11. K. Mislow, R. Graeve, A. J. Gordon, and G. H. Wahl, Jr., J. Am. Chem. Soc., 86, 1733 (1964).
12. A. Horeau, A. Nouaille, and K. Mislow, J. Am. Chem. Soc., 87, 4957 (1965).
13. A. Horeau, Tetrahedron Letters, No. 15, 506 (1961); A. Horeau, Tetrahedron Letters, No. 21, 965 (1962); A. Horeau and H. B. Kagan, Tetrahedron, 20, 2431 (1964).
14. V. F. Raaen, T. K. Dunham, D. D. Thompson, and C. J. Collins, J. Am. Chem. Soc., 85, 3497 (1963).
15. P. T. Lansbury, J. F. Bieron, and M. Klein, J. Am. Chem. Soc., 88, 1477 (1966).
16. H. C. Brown and G. J. McDonald, J. Am. Chem. Soc., 88, 2514 (1966).
17. H. C. Brown, M. E. Azzaro, J. G. Koelling, and G. J. McDonald, J. Am. Chem. Soc., 88, 2520 (1966).
18. V. J. Shiner, Jr. and C. J. Verbanic, J. Am. Chem. Soc., 79, 373 (1957).
19. V. J. Shiner, Jr. and G. S. Kriz, Jr., J. Am. Chem. Soc., 86, 2643 (1964).
20. A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.
21. E. A. Halevi and M. Nussim, J. Chem. Soc., 876 (1963).
22. V. J. Shiner, Jr., B. L. Murr, and G. Heinemann, J. Am. Chem. Soc., 85, 2413 (1963).
23. V. J. Shiner, Jr. and J. G. Jewett, J. Am. Chem. Soc., 86, 945 (1964).
24. V. J. Shiner, Jr. and J. G. Jewett, J. Am. Chem. Soc., 87, 1382 (1965).
25. V. J. Shiner, Jr. and J. G. Jewett, J. Am. Chem. Soc., 87, 1383 (1965).
26. A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, J. Am. Chem. Soc., 80, 2326 (1958).
27. V. Belanić-Lipovac, S. Borčić, and D. E. Sunko, Croat. Chem. Acta., 37, 61 (1965).
28. M. M. Mocek and R. Stewart, Can. J. Chem., 41, 1641 (1963).
29. R. P. Bell and W. B. T. Miller, Trans. Far. Soc., 59, 1147 (1963).
30. R. P. Bell and J. E. Crooks, Trans. Far. Soc., 58, 1409 (1962).
31. A. Streitwieser, Jr. and H. S. Klein, J. Am. Chem. Soc., 86, 5170 (1964).
32. D. D. Traficante and G. E. Maciel, J. Am. Chem. Soc., 87, 4917 (1965).
33. T. J. Katz and R. Dessau, J. Am. Chem. Soc., 85, 2172 (1963).

HOMOENOLIZATION

Reported by Warren Peascoe November 28, 1966

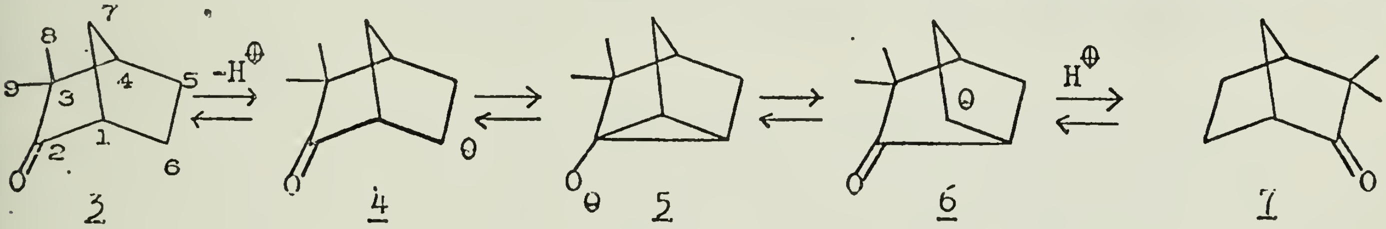
Abstraction of a proton from a carbon atom alpha to a carbonyl group produces an enolate anion. The stability of enolate anions has generally been ascribed to the delocalization of the negative charge between the carbonyl oxygen and the carbon alpha to the carbonyl.[1] Proton capture at either oxygen or carbon provides a mechanism for base-catalyzed interconversion of the keto and enol tautomers. Recent studies have shown that a nonenolizable carbonyl can activate a noncontiguous carbon sufficiently to produce an anion stabilized by homoconjugation.[2] The anion is termed a homoenolate anion 1 and the cyclic alcohol derived by protonation of the oxygen is



its corresponding homoenol 2. The evidence for the formation of homoenolate anions, their structure, and synthetic uses will be considered in this seminar.

EVIDENCE FOR THE FORMATION OF HOMOENOLATE ANIONS

Nickon and Lambert[3,4] used optically active camphenilone 3 as a substrate to provide evidence for the formation of homoenolate anions. This ketone has no enolizable alpha hydrogens, but has several beta and gamma hydrogens. If the beta hydrogen from C-6 were abstracted to produce a homoenolate anion whose charge was delocalized to the carbonyl group, a symmetric structure 5 would be expected to result. This could be detected by racemization of optically active starting material.



Camphenilone treated with a two-fold excess of potassium *t*-butoxide produced no racemization at 150° after 166 hr, whereas a five-fold excess of base produced 92% racemization at 165° after 336 hr. Higher temperatures produced significant racemization with much shorter reaction times. At 250° the racemization was complete after 4 hr. When the base was excluded and potassium perchlorate added as an inert salt to provide a medium of similar ionic character, no racemization was found even at 250° for 215 hr. Thus alkali must be present for racemization to occur.

When optically active camphenilone was reacted with *t*-butyl alcohol-O-*d* as solvent, the incorporation of deuterium was found to parallel the extent of racemization. The extent of deuterium incorporation was determined by mass spectroscopy and the combustion infrared method. Thus the process which creates the mesoid ion (or its equivalent) 5 must be the same one which introduces the deuterium. The first hydrogen exchanged must be at position 6 since exchange at any other site does not lead to a symmetric ion.

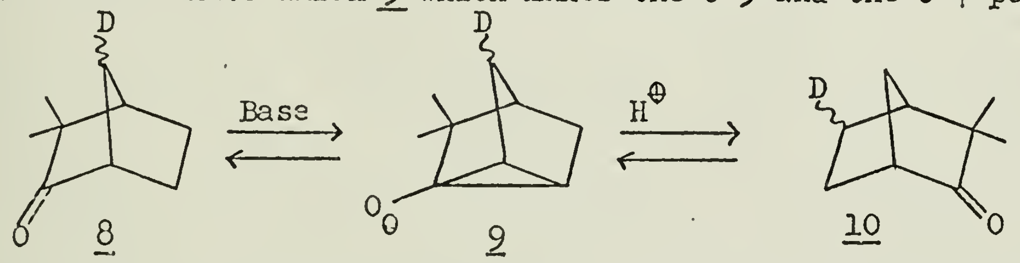
In a further study Nickon and coworkers[5] subjected camphenilone to longer reaction times and more vigorous reaction conditions to determine the extent and location of hydrogen-deuterium exchange. Camphenilone heated at 250° with a 6-fold excess of potassium *t*-butoxide for 216 hr and then recycled with fresh t-butyl alcohol-O-*d* for another 215 hr produced the following isotopic distribution: 3% 0-D, 6% 1-D, 14% 2-D, 22% 3-D, 22% 4-D, 16% 5-D, 9% 6-D, 5% 7-D, 2% 8-D, and 1% 9-D.

Nmr data was used to obtain evidence for deuterium incorporation at C-1 and on the geminal methyl groups. Camphenilone-*d* (total, 3.72 atom excess of deuterium) was converted to its *p*-toluenesulfonylhydrazone. The nmr of the hydrazone revealed substantial reduction (*ca*. 50%) in the intensity of the C-1 proton signal at δ 3.03 ppm and (*ca*. 30%) intensity reduction in the geminal methyl signals at δ 1.01 and 0.96 ppm

relative to the natural abundance derivatives with the aromatic methyl group (δ 2.41 ppm) as an internal integration standard. Quantitative analysis was precluded by overlap broadening of the signals and the noise level. These data establish that deuterium can end up at the C-1 position and that the methyl groups are homoenolizable sites.

To obtain information about the remaining sites specifically labeled camphenilone was prepared. Camphenilone-4-*d* which contained 89.5% monodeuterated and 10.5% nondeuterated molecules as determined by mass spectroscopy was heated at 185° for 200 hr in *t*-butyl alcohol containing potassium-*t*-butoxide in 8-fold excess. The recovered ketone was recycled with a 10-fold excess of base at 185° for 300 hr. Mass spectrometry indicated 89.1% monodeuterated and 10.9% nondeuterated ketone. Gas chromatography of the residue from the mass spectral analysis indicated 99% camphenilone and 1% of an unidentified impurity.

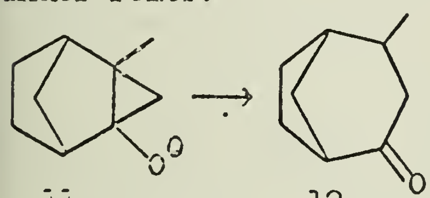
Camphenilone-7-*d* 8 (25% 2-D, 49.5% 1-D, 25.5% 0-D) was prepared. This ketone was heated at 185° with potassium t-butoxide for 98 hr and recovered. Mass analysis revealed no deuterium loss even when the ketone was recycled at 185° for an additional 200 hr at a higher base concentration. This reveals that neither C-5 nor C-7 are homoenolizable sites since the reaction conditions are more than sufficient to generate the homoenolate anion 9 which makes the C-5 and the C-7 positions equivalent.



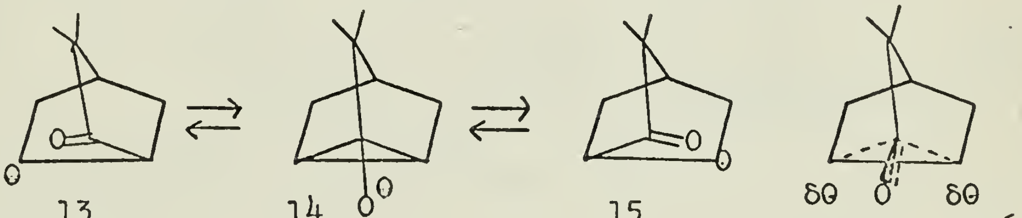
8 9 10

Camphenilane prepared by Wolff-Kishner reduction of camphenilone was treated under the reaction conditions for 250 hr at 185°. Mass spectral analysis of the recovered camphenilane indicated less than 1% each of the mono and dideuterated camphenilane species.

The fact that the methyl hydrogens are exchangeable clearly implicates a homoenolate ion such as 11. This unsymmetric ion could have undergone protonation at C-3 to give rearranged product 12 rather than regenerating camphenilone. No evidence was found for rearranged products and the general 80% yield of recovered camphenilone indicates that pathways which would transform camphenilone play only minor roles.



11 12

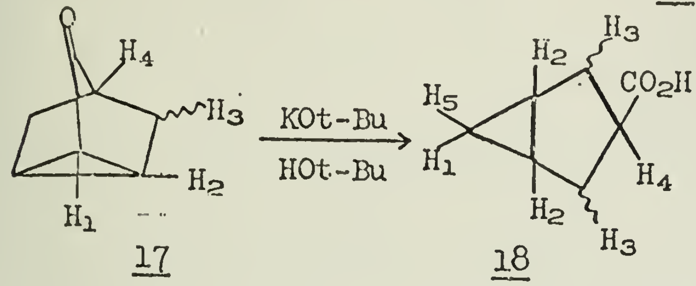


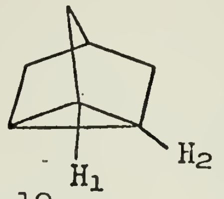
13 14 15 16

The structure of the homoenolate anion deserves some comment. Since the rate of deuterium incorporation and racemization of camphenilone are equal, the homoenolate anion has either a symmetrical structure 14 or, if asymmetrical, it rearranges to its enantiomer faster than it reverts to the ketone. The symmetrical ion may be described by the three rapidly equilibrating structures 13, 14, and 15 if each structure is a distinct entity. If the three structures 13, 14, and 15 are not distinct, the equilibrium arrows ($\rightleftarrows$) may be replaced with resonance arrows ($\longleftrightarrow$) and the resulting structure formulated as 16. The experimental distinction between mesomeric and rapidly equilibrating ions is not easy to make, and for economical representation of a homoenolate anion a single classical structure 14 with charge localized on oxygen appears adequate.

The homoenolate ion must be stabilized by orbital interaction between the homoenolic carbon and the carbonyl group. This follows from considering the preferential exchange at the C-6 position. If the ion is stabilized only by inductive effects of the carbonyl, the preference for C-6 hydrogen abstraction compared with abstraction of the methyl hydrogens leading to a primary carbanion is difficult to explain.

That the inductive effect of the carbonyl will have some influence was shown by Gassman and Zalar[6] who treated nortricyclanone 17 at *ca.* 200° for 22 hr with a two-molar excess of potassium *t*-butoxide in *t*-butyl alcohol-O-*d* and found significant hydrogen-deuterium exchange at the bridgehead positions (H_1 73%, H_2 70%, and H_4 68%). The extent and position of the H-D exchange was determined from nmr spectra of *cis*-bicyclo(4.1.0)hexane-3-carboxylic acid 18 prepared by cleavage of the ketone 17.





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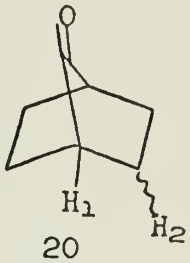

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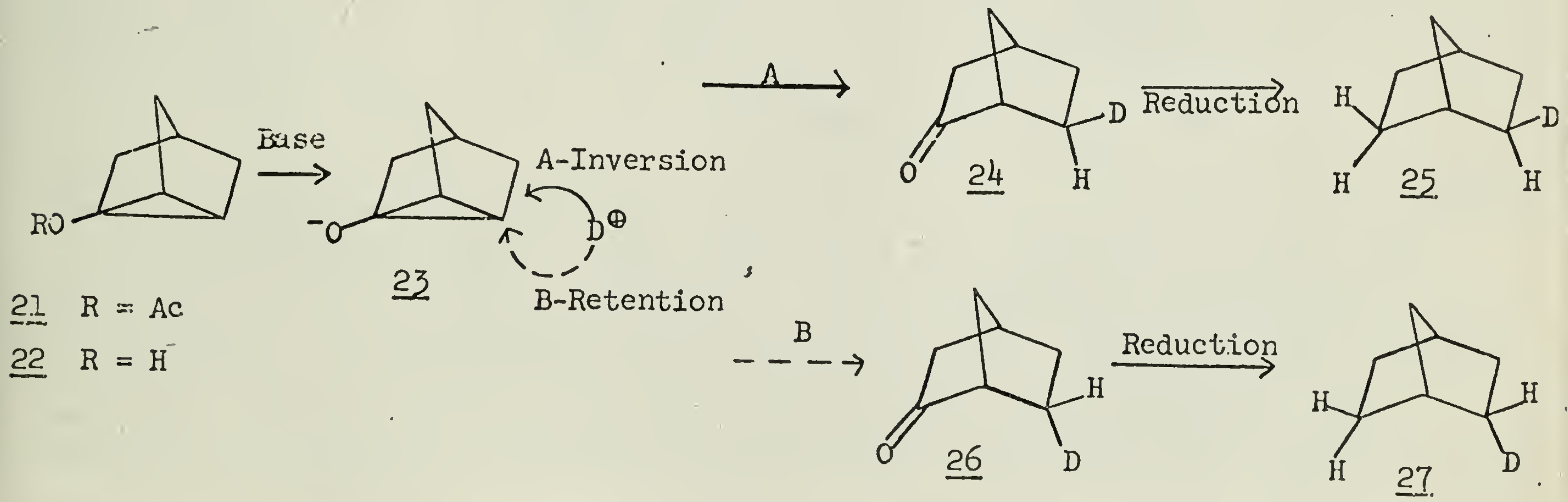
These results were compared with those obtained from treating nortricyclene 19 and 7-ketonorbornane 20 under the same conditions. After treatment for 48 hr 7-ketonorbornane exchanged only H_1 25% as determined from nmr spectra of norbornane obtained by Wolff-Kishner reduction of the ketone. Nortricyclene exchanged protons H_1 and H_2 10% each after reacting 48 hr as revealed directly by nmr. The fact that both 7-ketonorbornane and nortricyclanone show increased H-D exchange relative to their saturated analogues clearly demonstrates that a carbonyl group can provide stabilization for an adjacent carbanion by a purely inductive effect since the geometry prevents any resonance interaction with the carbonyl. Interestingly Gassman and Zalar did not observe any exchange in nortricyclanone of protons H_3 or in 7-ketonorbornane of protons H_2 as would be expected by homoenolization. Homoenolization was probably precluded by failure of the ketones to meet the geometrical requirements necessary for stabilization of the incipient anion by the carbonyl group.

STEREOCHEMISTRY OF HOMOENOLIZATION

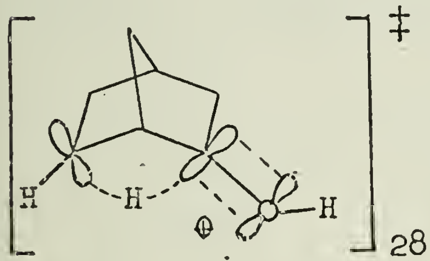
To determine the stereochemistry of the homoenolization process the reverse reaction, the opening of appropriately substituted cyclopropanols to give aldehydes or ketones, has been studied. Nickon and coworkers[7,8] examined the opening of 1-acetoxynortricyclene 21 at 27° in several solvents. In various deuterated alkaline media the homoketonization produced an *exo*- C-D bond (94.5-98%). Abstraction of the R group from 1-acetoxynortricyclene produced the corresponding homoenolate ion 23 which underwent irreversible homoketonization to norbornan-2-one by deuterium capture to yield the *exo*-deuterated ketone 24 if the electrophilic attack proceeded with inversion of configuration (path A) and the *endo*-deuterated ketone 26 if the attack proceeded with retention of configuration (path B). The low temperature (27 ± 3°) of the hydrolysis guaranteed that the homoketonization was irreversible and that the stereochemical integrity of the label at C-6 was preserved. Additional deuterium incorporated at C-3 by subsequent enolization was washed out by repeated mild



treatment with methanolic potassium hydroxide until the mass spectrum indicated that the multilabeled species were absent and that the percentage of monolabeled species was essentially constant. The 6-deuterio-norbornan-2-one was converted to the corresponding deuterated norbornane by Wolff-Kishner reduction. Mass spectral analysis of the deuterated hydrocarbon revealed that no deuterium was lost under the vigorous alkaline conditions of the Wolff-Kishner reduction. The configurational distribution of deuterium was then determined by appropriate infrared comparisons with mixtures of authentic *exo*-*d* and *endo*-*d* norbornane. The deuterium was found to be greater than 94.5% in the *exo*-configuration after treatment with potassium *t*-butoxide in *t*-butyl alcohol-O-*d*, potassium methoxide in methanol-O-*d* or in a mixture of equal weights of methanol-O-*d* and dimethyl sulfoxide, and tetramethylammonium deuterioxide in *t*-butyl alcohol-O-*d*. These results indicate that the reaction proceeded with predominant inversion of configuration. Direct evidence for the reaction proceeding with retention of configuration is presented by base-catalyzed deuterium incorporation at C-1 in camphenilone since this reaction requires retention.

Homoketonization of 1-acetoxynortricyclene with sulfuric acid-d_2 in methanol-O-*d* or acetic acid-O-*d*-deuterium oxide solvent predominantly (*ca.* 95%) formed *endo*-*d*-norbornane-2-one. Thus retention of configuration is the preferred path in electrophilic ring opening. The high stereospecificity held whether the substrate was 1-acetoxynortricyclene or 1-hydroxynortricyclene prepared by action of lithium aluminum hydride on the acetate. Either the ester is hydrolyzed to the homoenol prior to ring cleavage or the stereospecificity is independent of the nature of the oxygen function attached to the three-membered ring.

Although acid-induced homoenolizations have not yet been observed, these results indicate that if only one transition state is traversed in acid-induced homoketonization, an *endo*-hydrogen would be preferentially abstracted in homoenolization 28. Base-induced homoenolization of norbornan-2-one would then be expected to involve preferential abstraction of the *exo*-hydrogen 29. A mechanism which draws stability from simultaneous attraction of the proton to both of the equivalent electron-rich carbons to give a symmetrical species such as 30 can be ruled out for the homoenolization of optically active camphenilone since it would allow racemization without deuterium incorporation.



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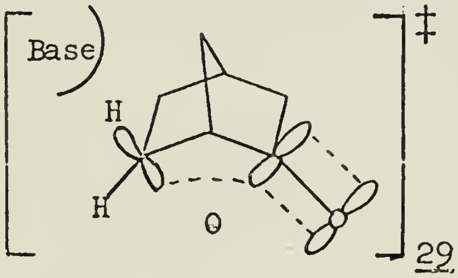

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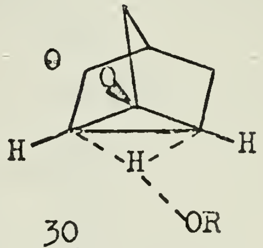

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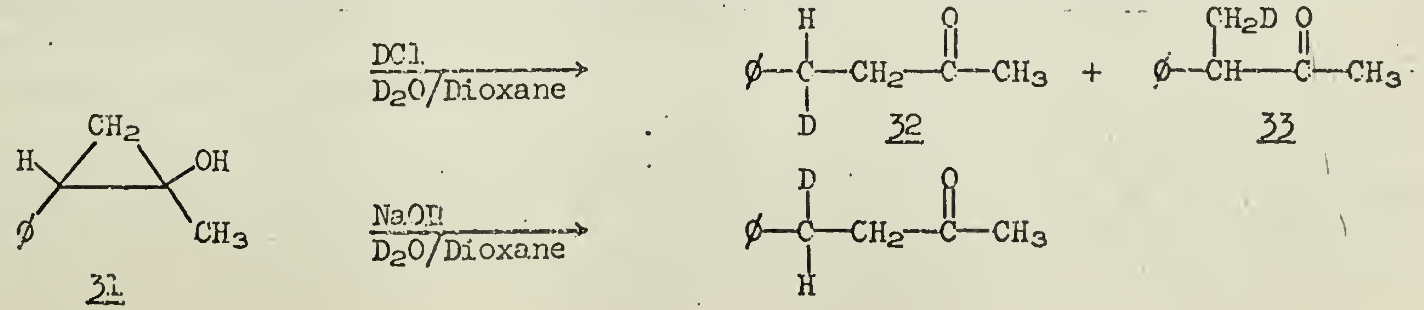
Stahl and Cottle[9] reported that cyclopropanol was opened upon treatment with anhydrous potassium carbonate to propanal. DePuy and coworkers[10] examined the stereochemistry of the reaction by investigating the acid- and base-catalyzed opening of optically active *cis*-2-phenyl-1-methylcyclopropanol 31. They found that in 1 M hydrochloric acid in a (50:50 v/v) dioxane-water solvent the cyclopropane ring was opened with nearly complete retention of configuration, whereas nearly complete inversion of configuration was observed in the same solvent with 0.1 M sodium hydroxide.

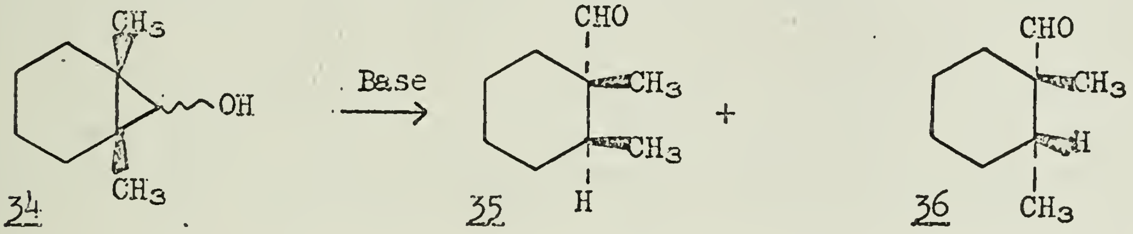


Optically active alcohol reacted with 1 N deuterium chloride for 67 hr at 90° produced two products 60% 4-phenyl-2-butanone 32 and 40% 3-phenyl-2-butanone 33. The 4-phenyl-2-butanone contained one deuterium atom on the benzyl carbon, whereas in the 3-phenyl-2-butanone the methyl group contained one deuterium atom. The ketones were treated with base to insure racemization of the 3-phenyl-2-butanone and the cleavage of any possible remaining cyclopropanol. The neat rotation of purified 4-deuterio-4-phenyl-2-butanone was measured and found to be +0.456 ± 0.014°.

Optically active alcohol cleaved with 0.1 N sodium deuterioxide at 90° for 40 hr under nitrogen produced only 4-phenyl-2-butanone with one deuterium on the benzyl carbon. The neat rotation of purified ketone was measured and found to be -0.424 ± 0.016°. Thus acid- and base-catalyzed reactions proceed with opposite stereochemical consequences.

To specify unequivocally which reaction proceeded with retention and which proceeded with inversion, optically active though not optically pure alcohol 31 and product ketone 32 of known absolute stereochemistry were synthesized. It was concluded that the acid-catalyzed reaction proceeds with net retention of configuration and that base-catalyzed reaction proceeds with net inversion. Without optically pure compounds the extent of stereospecificity of the reactions could not be determined. The same magnitude of the rotations of the products from acid- and base-catalyzed reactions was thought to indicate 100% stereospecificity of the reactions.

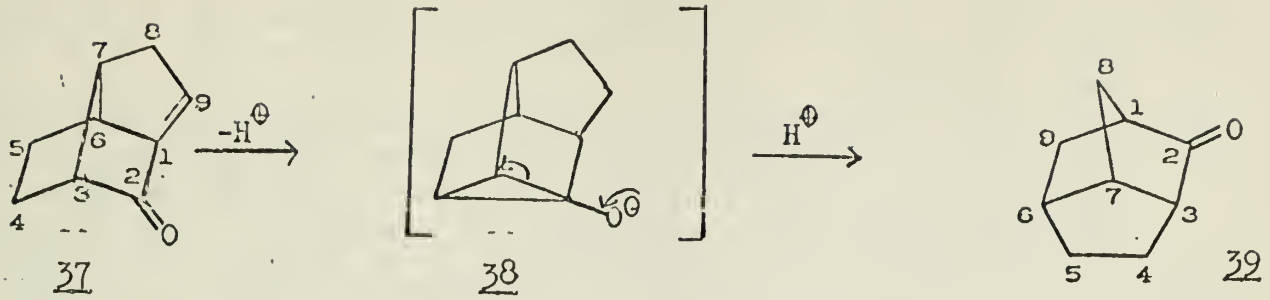
The generality of this conclusion has been questioned by Wharton and Bair who studied the stereochemistry of the opening of endo- and exo-7-hydroxy-1,6-dimethyl (4.1.0)bicycloheptane 34.[11] They found that both the exo- and endo-alcohol gave greater than 90% retention of configuration (product 35) when treated with ca. 1 M potassium t-butoxide in t-butyl alcohol under nitrogen at 57° for 60 hr. Treatment with ethylene glycol and its sodium salt ca. 1 M at 57° gave 40% and 70% inversion (product 36) for the endo- and exo-alcohols. Samples of endo- or exo-alcohol were reacted with 0.2 M hydrochloric acid in aqueous dimethoxyethane, and the reaction was found to proceed with 98% and 93% retention respectively. The products were analyzed by gas chromatography, and a mixture of the products 35 and 36 showed aldehydic peaks in the infrared. The nmr spectrum of the reactants remained constant after the reaction was essentially complete indicating stability of the system as a whole under the reaction conditions.



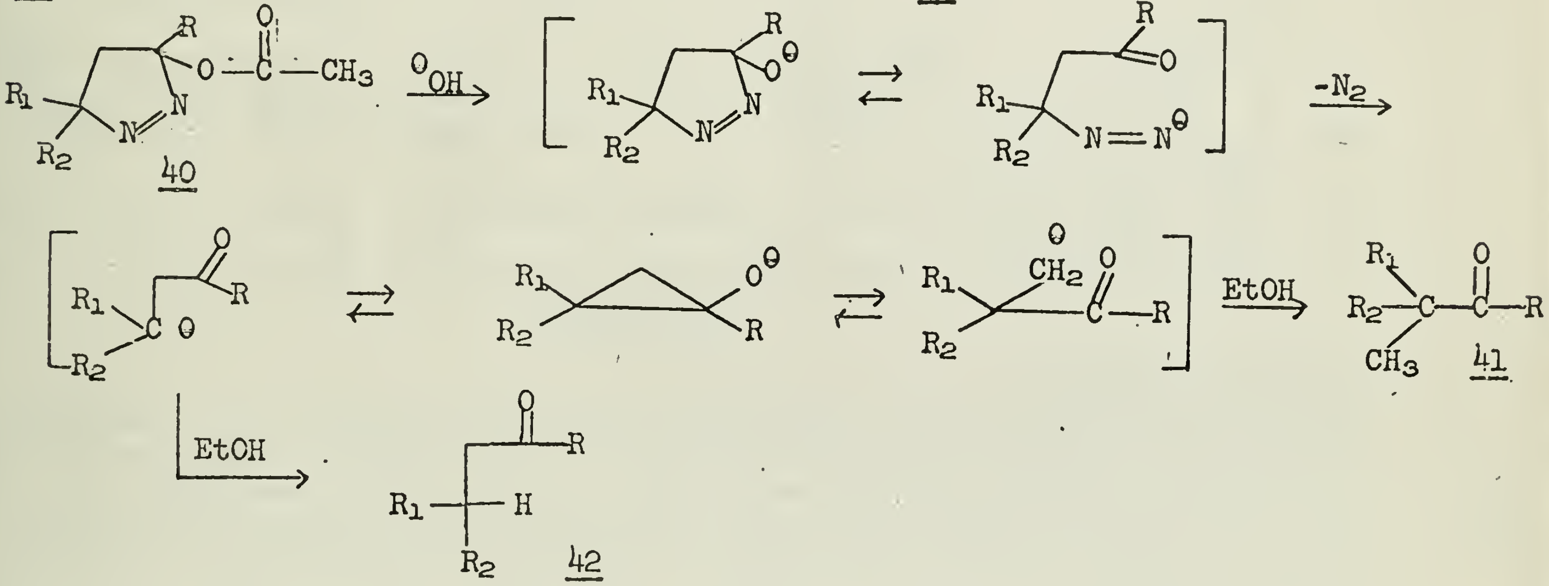
These results are in accord with Cram's over-all stereochemical pattern of electrophilic substitution at carbon,[12] predominant retention in t-butyl alcohol and substantial inversion in ethylene glycol. DePuy's results of predominant inversion of configuration in the opening of cis-2-phenyl-1-methylcyclopropanol on treatment with sodium hydroxide in dioxane-water solvent are also consistent with Cram's findings. Solvents of high dielectric constant which are good proton donors are expected to give moderately high inversion.[12] Thus the inversion observed in the ring opening of 1-hydroxynortricyclene in various solvents is not general for cyclopropanol systems.

HOMOENOLIZATION IN OTHER SYSTEMS

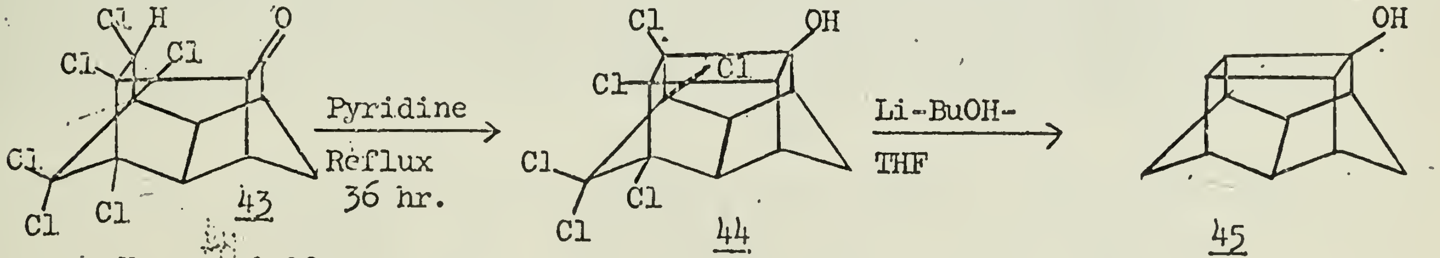
There have been several reports of other reactions which may conveniently be interpreted in terms of mechanisms involving homoenolate ions. Cram and Smith[13] found hydrogen-deuterium exchange when di-t-butyl ketone was treated with potassium t-butoxide in t-butyl alcohol-O-d. Nickon and coworkers synthesized tricyclo ($4.2.1.0^{3,7}$) nonane-2-one 39 from tricyclo ($4.3.0.0^{3,7}$) nonane-2-one 37[14,15] through a homoenolate anion.

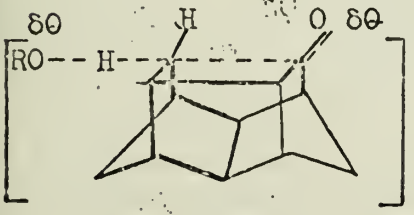


Freeman and Plonda^{16} found that the hydrolysis of 3-acetoxy-Δ^1-pyrazolines 40 produced a skeleton rearrangement that appeared to involve the intermediate formation of a homoenolate ion. This rearrangement may be interpreted in terms of the scheme below. Hydrolysis of 40 with alkyl groups in the R positions yielded 41 as a major product along with lesser amounts of 42.



The abstraction of a gamma hydrogen to form the four carbon cyclic homoenol has been observed in the "birdcage hydrocarbon" system.^{17} The first reported example was formation of the hexachloro alcohol 44. Soloway and coworkers^{18} described isolation of a material from treatment of the chlorinated half-cage ketone 43 with one equivalent of lithium aluminum hydride in dibutyl ether for which the structure 44 was proposed. They pointed out that this alcohol was an isomer of the ketone, and the term "transannular enolization" was proposed to describe its formation. Carter, Howe, and Winstein^{19} found that the ketone 43 could also be converted to the alcohol 44 by base-catalyzed homoenolization upon treatment with alcoholic sodium hydroxide or by heating in pyridine solvent.





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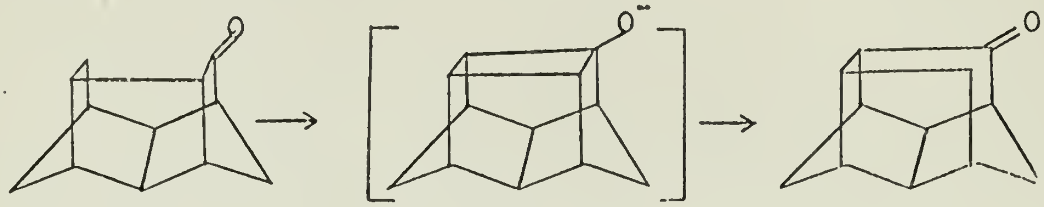
The hexachloro alcohol 44 could be successfully dechlorinated with lithium and t-butyl alcohol in boiling tetrahydrofuran without any appreciable disturbance from homoketonization. The alcohol 45 could be transformed into its brosylate which was solvolized in acetic acid. The resulting acetate was saponified with alcoholic potassium hydroxide to nearly pure unrearranged alcohol.

Howe and Winstein^{20} and also Fukunaga^{21} independently found that the half-cage ketone 47 and the alcohol 45 both isomerized completely (greater than 99% for

Winstein and Howe and 96% for Fukanaga) to the new half-cage ketone 49 with the alcohol reacting ca. 33,000 times as rapidly as the ketone at 100°. The reaction presumably proceeded through a homoenolate anion 48, and obeyed first-order kinetic at 175-200° in t-butyl alcohol 0.9 M in potassium t-butoxide. The structure of the new ketone 49 was assigned on the basis of spectral evidence and its behavior upon



47 48 49

lithium aluminum hydride reduction. There was no evidence for the stereochemistry of the homoenolization, however by analogy with base-catalyzed homoenolization-homoketonization involving cyclopropanols a transition state such as 46 was propose It depicts homoenolization proceeding with inversion of configuration at the gamma carbon, an "outside" hydrogen being removed. This process is not the only one which may occur in the homoenolization of the ketone since the conversion of the chlorinated ketone 43 to its homoenol must have involved homoenolization proceeding with retention of configuration.

CONCLUSION

Base-catalyzed homoenolization has been observed in a number of systems. The stereochemistry of the reaction seems to depend on the substrate. From homoketonization reactions of cyclic alcohols it appears that ketones with the carbonyl fixed near the site of proton abstraction homoenolize with predominant inversion of configuration whereas ketones whose geometry is not fixed homoenolize in accordance with Cram's over-all stereochemical pattern of electrophilic substitution. The detailed description of the transition state and structure of the homoenolate anior are as yet unknown.

BIBLIOGRAPHY

1. J. Hine, "Physical Organic Chemistry", McGraw-Hill Book Co., Inc., New York, 1962, Chapter 10.
2. D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, 1965, p. 114-116.
3. A. Nickon and J. L. Lambert, S. J., J. Am. Chem. Soc., 84, 4604 (1962).
4. A. Nickon and J. L. Lambert, S. J., J. Am. Chem. Soc., 88, 1905 (1966).
5. A. Nickon, J. L. Lambert, S. J., and J. E. Oliver, J. Am. Chem. Soc., 88, 2787 (1966).
6. P. G. Gassman and F. V. Zalar, J. Am. Chem. Soc., 88, 3070 (1966).
7. A. Nickon, J. L. Lambert, S. J., and R. O. Williams, J. Am. Chem. Soc., 85, 3 (1963).
8. A. Nickon, J. L. Lambert, S. J., R. O. Williams, and N. H. Werstiuk, J. Am. Chem. Soc., 88, 3354 (1966).
9. G. W. Stahl and D. L. Cottle, J. Am. Chem. Soc., 65, 1782 (1943).
10. (a) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, J. Am. Chem. Soc., 88, 3347 (1966); (b) C. H. DePuy and F. W. Breitbeil, J. Am. Chem. Soc., 85, 2176 (1963); (c) C. H. DePuy, Trans. N. Y. Acad. Sci. 28, 561 (1966).
11. P. S. Wharton and T. I. Bair, J. Org. Chem., 31, 2480 (1966).
12. D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, 1965, p. 137-154.
13. D. J. Cram and R. O. Smith, Unpublished work, see Ref. 12, p. 65.
14. A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, J. Am. Chem. Soc., 87, 1615, (1965).
15. A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, J. Am. Chem. Soc., 87, 1613 (1965).

16. J. P. Freeman and J. H. Plonka, J. Am. Chem. Soc., 88, 3662 (1966).
17. C. L. Mampacy, "Hexachlorododecane", U. of Ill. Organic Seminar, 1965-66, 2D Semester, p. 32.
18. S. B. Soloway, A. M. Damiana, J. Sims, H. Bluestone, and R. E. Lidov, J. Am. Chem. Soc., 82, 5377 (1960).
19. P. Carter, R. Howe, and S. Winstein, J. Am. Chem. Soc., 87, 914 (1965).
20. R. Howe, and S. Winstein, J. Am. Chem. Soc., 87, 915 (1965).
21. T. Fukunaga, J. Am. Chem. Soc., 87, 916 (1965).

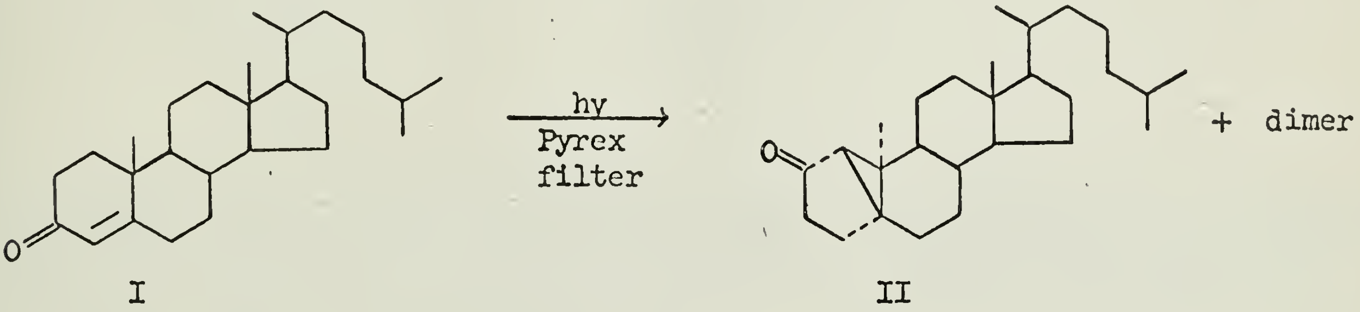
PHOTOCHEMICAL REARRANGEMENTS OF 2-CYCLOHEXENONES

Reported by James E. Shaw December 1, 1966

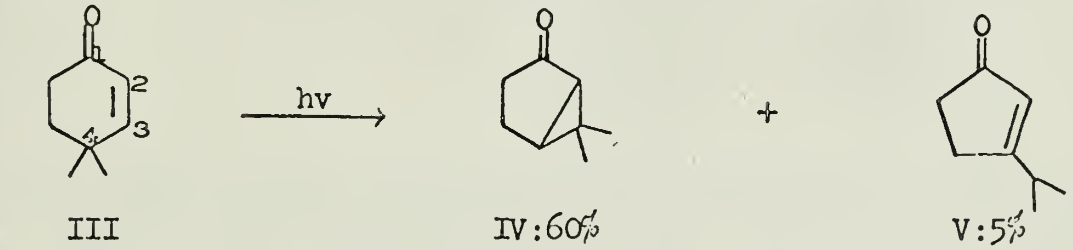
Photochemical rearrangements of conjugated cyclohexenones have been the subject of considerable interest over the past few years. Most of the compounds which have been studied are 4,4-dialkylated 2-cyclohexenones.

TYPES OF REARRANGEMENT

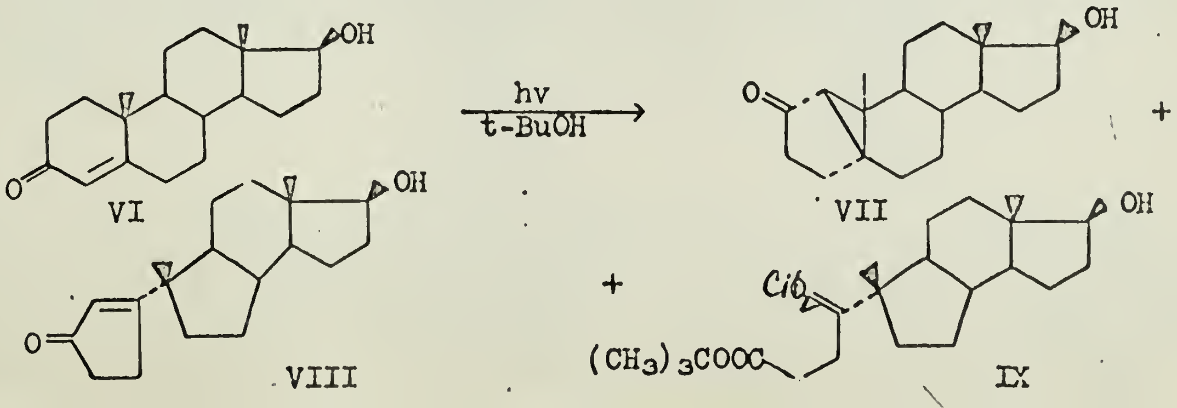
Three general types of photochemical cyclohexenone rearrangements are known. The first, termed "type A" results in a bicyclo[3.1.0]hexan-2-one structure. This rearrangement was first observed in 1962 by Gardner and co-workers who reported that ultraviolet irradiation of a 0.5% solution of 4-cholesten-3-one (I) in t-butyl alcohol resulted in stereospecific formation of lumicholestenone (1β,5-cyclo-5β,10α-cholestan-2-one, (II)) in approximately 25% yield.[1,2]



Another example of this type of rearrangement has been provided by Chapman[3,4] who irradiated a 0.5% solution of 4,4-dimethyl-2-cyclohexenone (III) in t-butyl alcohol with ultraviolet light from a Pyrex jacketed, immersion type mercury arc lamp.

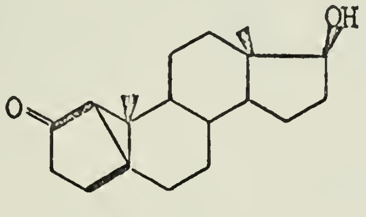


In product IV it appears that there has been an interchange of the C-3 and C-4 carbons. It was found that separate irradiation of IV in acetic acid produced only the 3-isopropylcyclopentenone V. Chapman suggested that this process is analogous to the vapor phase photoisomerization of methylcyclopropylketone to 3-penten-2-one.[5] The cyclopropyl ring would open to give a biradical which then by a hydrogen shift would give the product. "Type A" skeletal rearrangements have also been observed by Jeger[6-8] and Chapman[3] in the testosterone steroids. Upon irradiation of a 0.016 M solution of testosterone VI in t-butyl alcohol with unfiltered light from a high pressure mercury arc lamp, Jeger obtained 9% VII, 23% VIII and 2% IX along with 48% of unreacted starting material.



Separate irradiation of VII gave VIII as the main product plus small amounts of testosterone VI.[9] The formation of testosterone was taken to indicate that it may be the precursor of the cyclopentenone VIII rather than the bicyclic ketone VII as Chapman proposed. Separate irradiation of the cyclopentenone VIII gave the t-butyl ester IX.[6] On the basis of these observations Jeger proposed that the formation of the bicyclic product VII from testosterone is reversible while formation of the cyclopentenone VIII from testosterone is irreversible.[9] However, taking into account both Chapman's and Jeger's work, a decision concerning the direct precursor(s) of the cyclopentenone products needs more experimental investigation.

In the reaction mixture obtained from testosterone VI only products with the stereochemistry shown by VII and VIII were obtained. No traces of the respective diastereoisomers X and XI were found.[10,11]



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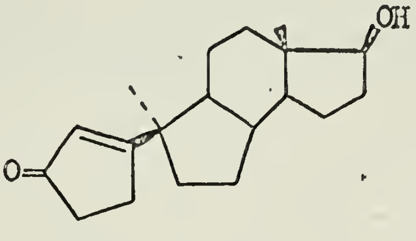
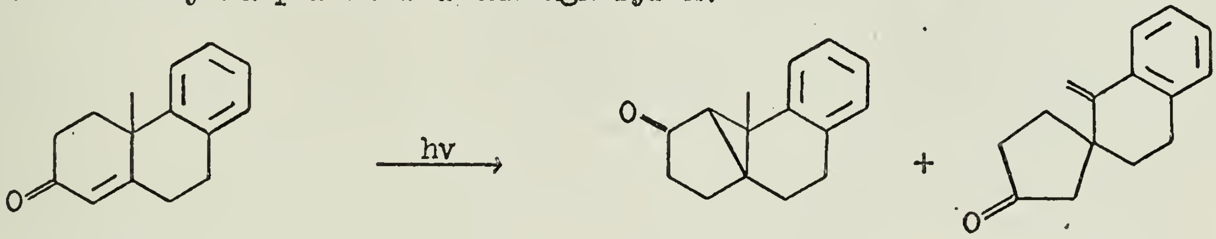


XI

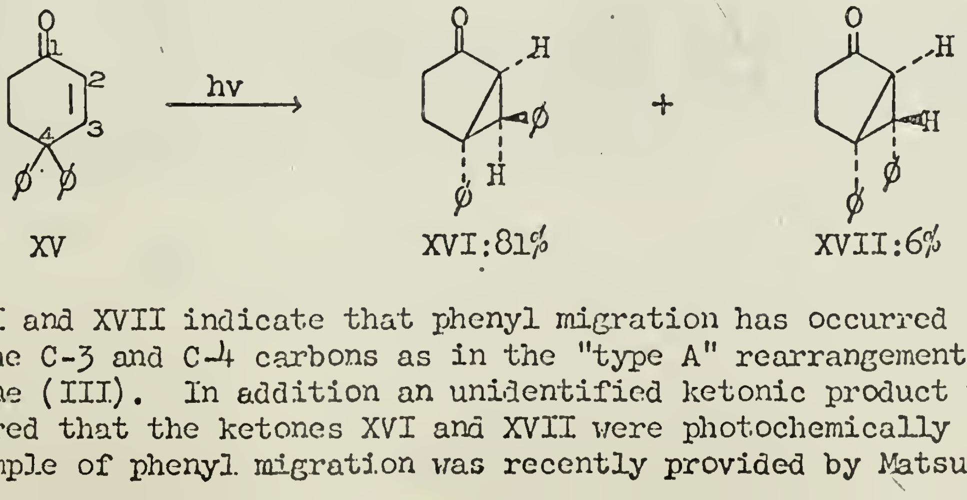
Thus the rearrangement of testosterone is stereospecific. This was also previously mentioned for the rearrangement of 4-cholesten-3-one. Another example of a compound with a rigid ring system which undergoes stereospecific "type A" rearrangement has been provided by Chapman[12] who irradiated cyclohexenone XII in t-butyl alcohol using a Hanovia mercury lamp filtered through Pyrex.



XII XIII:70% XIV:1.5%

Resolution of the racemic ketones XII and XIII was accomplished by the corresponding pyrrolidinium d-camphor-10-sulfonates.[13] The rotations of the ketones were XII, $[\alpha]_D^{27^\circ}$+332 and -332, and XIII, $[\alpha]_D^{27^\circ}$+42.5 and -42.3. Upon separate irradiation of each of the enantiomers of XII, a minimum of 95% retention of optical activity was observed. The photochemical rearrangement is thus stereospecific. It was shown that separate irradiation of XIII gave the spiro compound XIV.

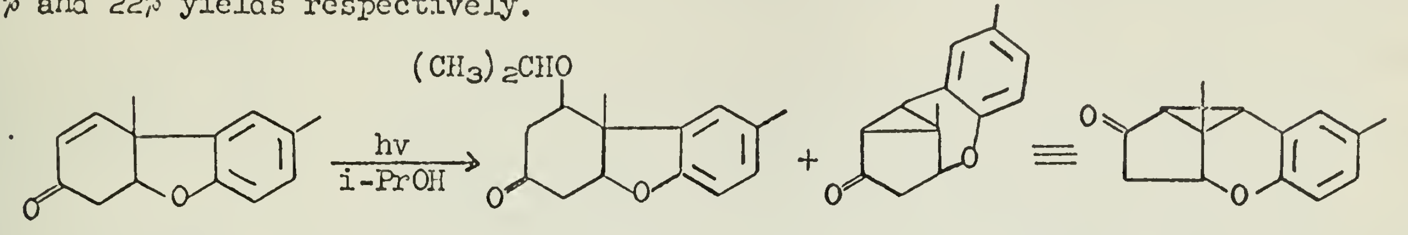
The second general type of photochemical cyclohexenone rearrangement proceeds with phenyl group migration from the C-4 to C-3 position. The earliest example of this type was provided by Zimmerman and Wilson,[14,15] who irradiated dilute benzene or 95% ethanol solutions of 4,4-diphenyl-cyclohexenone (XV) using a Hanovia lamp with a Pyrex filter.



XV XVI:81% XVII:6%

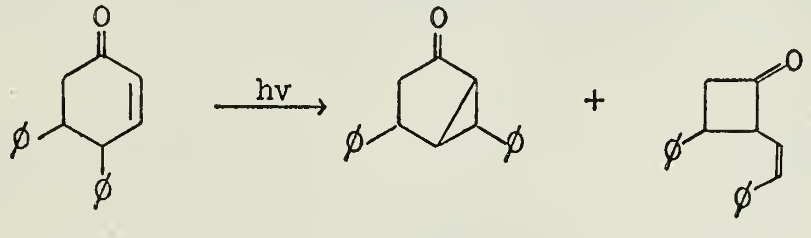
Products XVI and XVII indicate that phenyl migration has occurred rather than interchange of the C-3 and C-4 carbons as in the "type A" rearrangement of 4,4-dimethylcyclohexenone (III). In addition an unidentified ketonic product was reported. It was discovered that the ketones XVI and XVII were photochemically interconvertible. Another example of phenyl migration was recently provided by Matsuura,[16] who

irradiated a 1% solution of Plummer's ketone (XVIII) in isopropyl alcohol using a mercury vapor lamp with a Pyrex cooling jacket. Products XIX and XX were formed in 37% and 22% yields respectively.



XVIII XIX XX

The third type of photorearrangement observed with 2-cyclohexenones is cyclobutanone formation. Zimmerman^{17,18} irradiated 4,5-diphenylcyclohexenone (XXI) in t-butyl alcohol to give 40-45% of 4,6-diphenylbicyclo[3.1.0]hexane-2-one (XXII) and 8-10% of 2-(cis-styryl)-3-phenylcyclobutanone (XXIII).

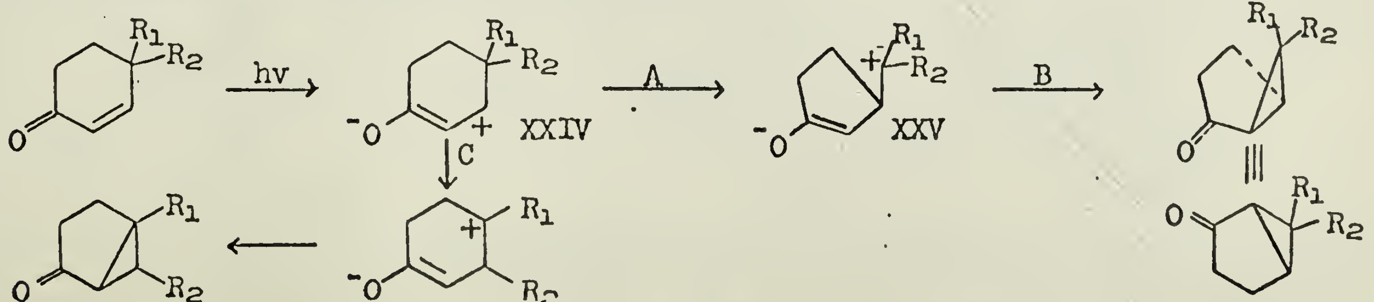


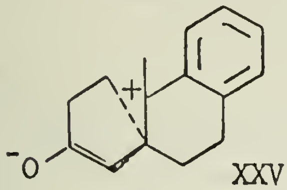
XXI XXII XXIII

It is realized that both phenyl migration from the C-4 to C-3 position in XXI and "type A" rearrangement where the C-3 and C-4 carbons of the ring interchange would result in formation of the same bicyclic product XXII. In order to determine which rearrangement was operating, Zimmerman labeled enone XXI at the C-3 position with radioactive carbon. If "type A" rearrangement occurred, the radioactivity would be found in the C-4 carbon of the bicyclic product, but if phenyl migration took place, the radioactive carbon would still be in the C-3 position. After photolysis in 95% ethanol, photoketone XXII was subjected to a degradation which disected C-3 of the six membered ring as benzaldehyde and C-4 as iodoform. The radiocarbon was found 1.39 ± 0.03% in the benzaldehyde and 98.61 ± 0.03% in the iodoform. This shows that the reaction goes mainly by the "type A" route (98.6%) and to a small extent (1.4%) by phenyl migration. Zimmerman felt that the difference in the rearrangement of 4,5-diphenylcyclohexenone compared to 4,4-diphenylcyclohexenone, where only phenyl migration was observed, was due to several factors. One of these was that phenyl migration in both compounds would lead to an intermediate where an odd electron is localized on C-4, but in the 4,4-diphenyl compound a phenyl group remaining on the 4-position could delocalize the electron. Also, there is relief of strain by migration of one of the geminal phenyl groups in 4,4-diphenylcyclohexenone. Another factor was that in the 4,4-diphenyl compound at least one phenyl group is axial and in conformation to migrate while in the 4,5 isomer the phenyl groups appear to be trans and there is no axial group.

MECHANISTIC CONSIDERATIONS

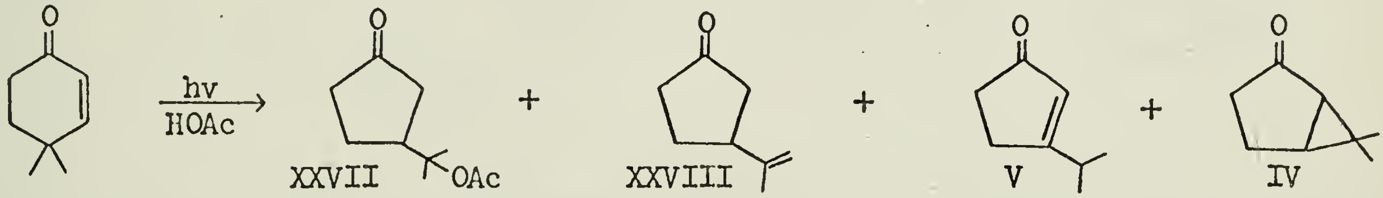
In order to explain the rearrangements of cyclohexenones Chapman^{3,19} proposed the "polar state concept" in which $n \to \pi^*$ excitation of the carbonyl group provides, by an unspecified process, an excited state with the electronic distribution of the dipolar species XXIV which reacts as shown below.





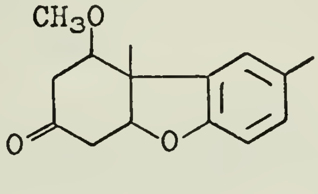
XXVI

This mechanism can account for the stereospecific results observed for the steroids, I and VI, and phenanthrone XII in the following manner. Step A could proceed by a concerted process providing steric control to give intermediate XXVI as in the case of phenanthrone XII. Formation of product XIII from this intermediate would be stereospecific due to the required cis fusion of three and six membered rings. Rotation of groups R_1 and R_2 to give racemic product can not occur in XXVI since R_2 is part of a cyclohexane ring. Step C in the mechanism which shows 1,2 migration of the group R_2 was proposed by Chapman before examples of phenyl migration were known. Chapman's proposal of this mechanism rests largely on two facts. First, cyclohexenone rearrangement products appear to be the result of successive alkyl shifts of the type expected for electron deficient systems in ground state chemistry. Second, nucleophillic solvent incorporation, which could be expected for polar intermediates, has been observed. An example of this is the photolysis of 4,4-dimethylcyclohexenone in acetic acid instead of in t-butyl alcohol as was previously presented.[3]

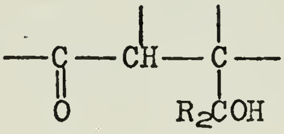


XXVII XXVIII V IV

Products XXVII and XXVIII suggest the intervention of a dipolar species of type XXV which upon addition of acetic acid or proton elimination from methyl would yield these products. As was previously mentioned separate irradiation of the bicyclic ketone IV in acetic acid gave V but none of the other photoproducts. Involvement of a polar intermediate of type XXIV is suggested by the photoadducts, XIX and XXIX, formed in the irradiation of Plummer's ketone (XVIII) in isopropyl alcohol and methanol respectively.[16]



XXIX



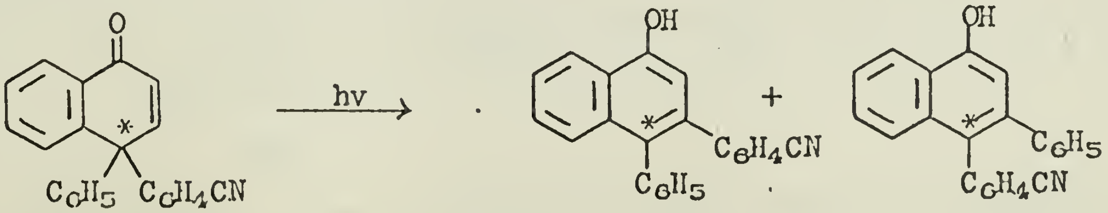
$$-\underset{\underset{O}{\|}}{C}-\overset{|}{C}H-\underset{\underset{R_2COH}{|}}{\overset{|}{C}}-$$

XXX

The formation of these products does not appear to have any parallel in the photoreactions of other α,β-unsaturated ketones in alcoholic solvents. It has been reported that irradiation of some α,β-unsaturated ketones in a primary or secondary alcohol give adducts of type XXX shown above, which are formed by a radical process.[20]

Zimmerman has presented theoretical and experimental evidence that the first dipolar excited species XXIV in Chapman's mechanism cannot be involved in all cases. From molecular orbital calculations[14,21,22] and resonance considerations[23] he predicted that the beta carbon in the n → π* excited state of cyclohexenones should be electron rich rather than electron deficient as Chapman proposed. In order to probe the β-carbon valency in the excited state, Zimmerman[14,24] irradiated a benzene solution of 4-(p-cyanophenyl)-4-phenyl-1(4H)-naphthalenone (XXXI), which was labeled in the C-4 position with radioactive carbon.

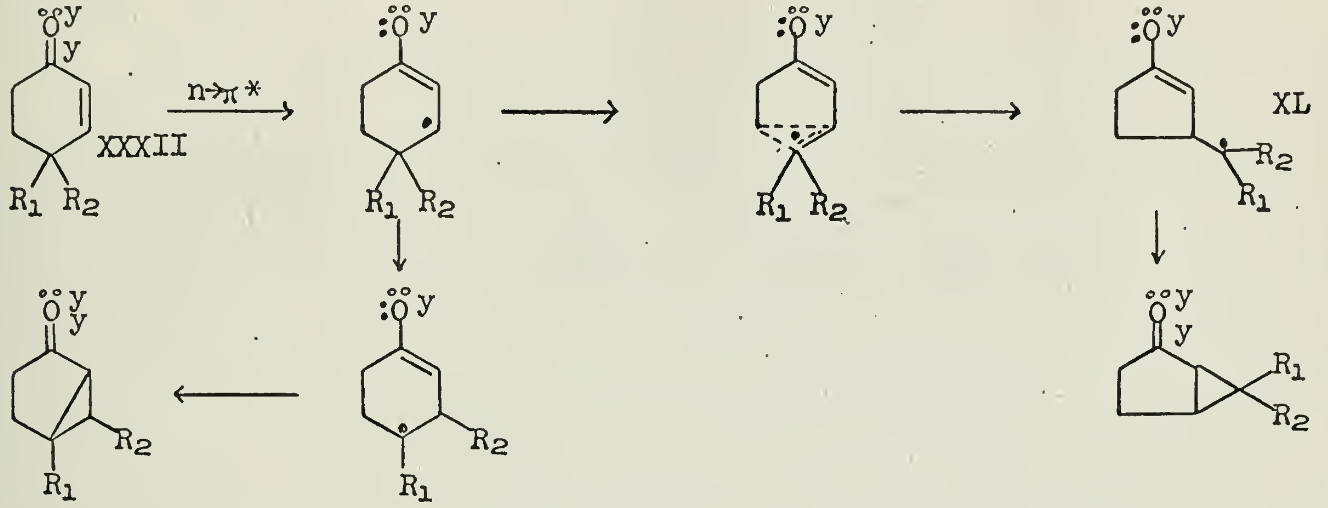
XXXI



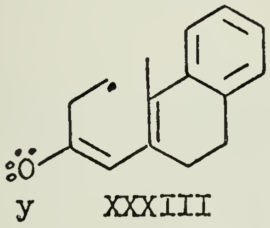
If the carbon beta to the carbonyl group is electron deficient as shown in Chapman's mechanism, one should observe migration of the phenyl rather than the p-cyanophenyl group. It was observed that p-cyanophenyl migration was preferred by a ratio of

approximately 2:1. The fact that ^{14}C remained in the C-4 position indicated that no skeletal rearrangement had occurred. In contrast, the non-photochemical, acid-catalysed rearrangement of enone XXXI, where the β-carbon does become electron deficient, gave exclusively the product of phenyl migration. This experimental work suggests that $^{+}$C-C=C-O^{-} is not a good representation of the excited state.

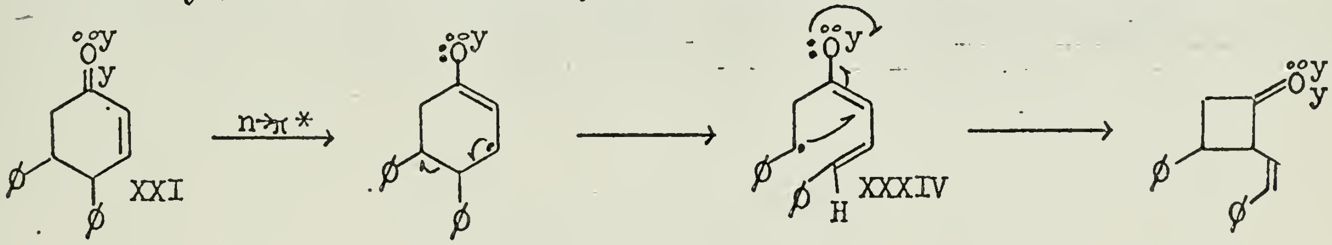
The mechanism proposed by Zimmerman[14,15,25] for the photochemical rearrangements of cyclohexenones is illustrated below.



According to Zimmerman,[23] the two unshared electrons of oxygen which are represented by small circles in enone XXXII are in a spheroidal orbital which is heavily weighted in s character. The other two unshared electrons are in a p orbital which is parallel to the y-axis of a three coordinate system and are therefore designated by the letter y. In n-π* excitation a "y electron" is promoted to an antibonding π* orbital. Application of this mechanism in the case of the steroids, I and VI, and phenanthrone XII, can also account for the stereospecific results observed in these systems. An intermediate of type XXXIII as in the case of phenanthrone XII is not possible since this would destroy the asymmetric center and should give optically inactive product.[12] The following mechanism was proposed by Zimmerman for cyclobutanone formation.[17,18]

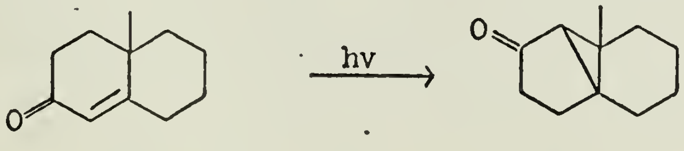


XXXIII



Zimmerman felt that it was possible but not necessary that the phenyl group at the 5-position in XXI promoted the formation of a ring-opened species XXXIV which could react as shown above.

Zimmerman has shown that the rearrangements of the phenanthrone XII and the octalone XXXV in t-butyl alcohol proceed by a triplet excited state.[25,26]



XXXV

This was demonstrated by means of sensitization and quenching experiments using acetophenone and naphthalene respectively. The quantum yield was observed to be the same in both the sensitized and unsensitized runs. In cases where acetophenone was used the conditions were such that it was absorbing virtually all the light (approximately 97%). The concentration of the enone was on the order of 7 x 10^{-3}M,

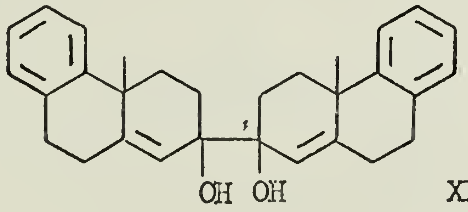
a concentration sufficiently low so that the acetophenone singlet excited state could not survive long enough to collide with enone molecules and excite these to singlet species. The concentration was, however, sufficiently large to allow acetophenone triplets to collide with enone molecules before their decay and give triplet transfer. Quenching by naphthalene showed that a triplet species was also involved in the unsensitized reaction. Chapman[12] has also shown that the reaction proceeds at a comparable rate in the presence of dibenzothiophene as sensitizer (greater than 90% of the light absorbed by dibenzothiophene) and in the absence of sensitizer. Also, the reaction was almost completely quenched by 0.03 M piperylene.

The quantum yield in the case of phenanthrone XII was only about .0085. From the fact that the quantum yield on sensitization was essentially the same as that from direct irradiation, Zimmerman[25] concluded that the low quantum efficiency of the enone rearrangement was not due to poor intersystem crossing but due to inefficient reaction of the enone triplet once formed. This was in agreement with the observation that the triplet was quenched by naphthalene at modest concentrations. The fact that the efficiency of di-t-butylnitroxide quenching was the same as that of naphthalene indicated that the quenching was probably diffusion controlled. A plot of the reciprocal of the quantum yield of phenanthrone photoproduct XIII versus quencher concentration gave a straight line. If k_r is the unimolecular rate constant for rearrangement, k_q is the bimolecular rate constant for quenching, k_d is the unimolecular rate constant for triplet decay to the ground state, E* is the enone triplet concentration, and Q is the quencher concentration, then $1/\Phi$ is given by the following expression.

$$\frac{1}{\Phi} = \frac{k_rE^* + k_dE^* + k_qQE^*}{k_rE^*} = \frac{k_r + k_d}{k_r} + \frac{k_qQ}{k_r}$$

Therefore, the slope of the plot is k_q/k_r and the y-intercept gives $(k_r + k_d)/k_r$. Thus assuming a diffusion controlled rate constant for quenching (k_q) of 2×10^9 l. mole^{-1} sec^{-1}, Zimmerman was able to calculate the rate constants for rearrangement (k_r) and decay (k_d) of the phenanthrone triplet. The values were 2.9×10^5 sec^{-1} and 3.9×10^7 sec^{-1} respectively showing that the low quantum yield of the enone rearrangement was due to a slow rate of rearrangement of the triplet relative to triplet decay.

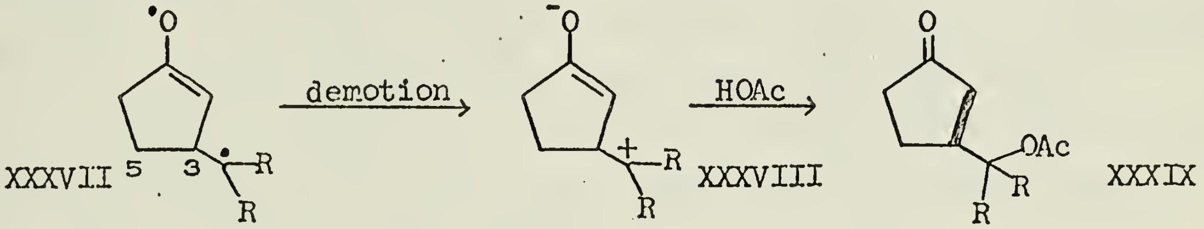
Zimmerman also investigated the question of whether the rearrangements proceed by a n-π* triplet or a π-π* triplet[14,25,26]. Irradiation of phenanthrone XII in isopropyl alcohol afforded the pinacol XXXVI in addition to the usual photoketone XIII.


XXXVI

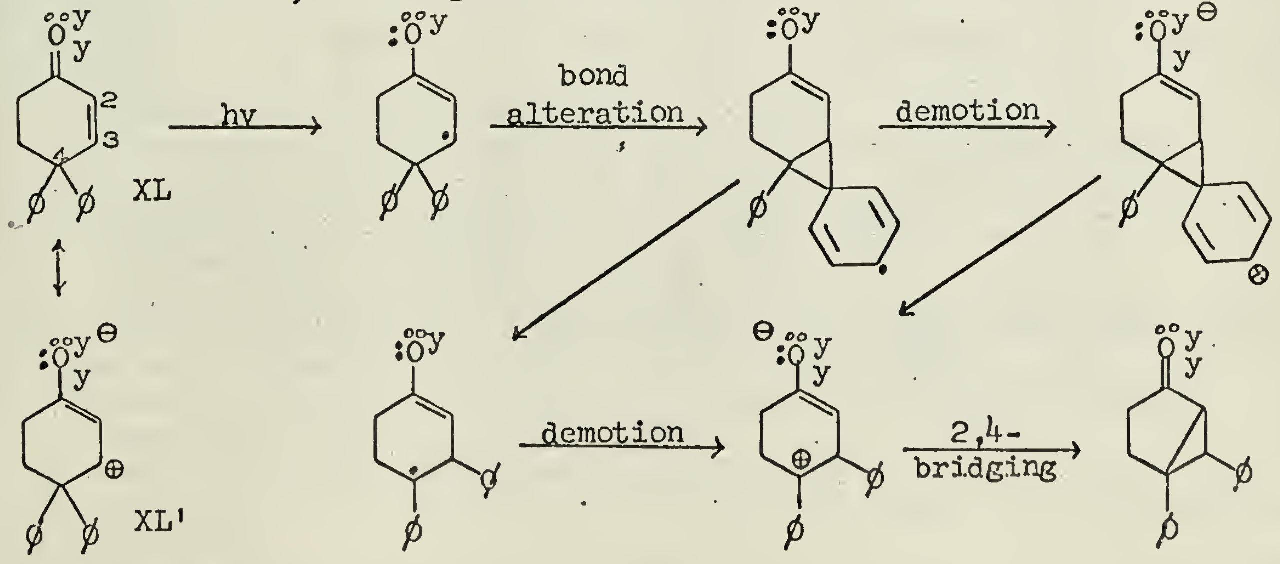
The pinacol to photoketone ratio was approximately 1:5, and in a separate experiment both products were quenched equally by naphthalene indicating that they were both probably formed from the same triplet. From this data and the previously reported rate constant for enone triplet rearrangement, Zimmerman estimated the bimolecular rate constant for hydrogen abstraction to be 3×10^3 l. mole^{-1} sec^{-1} which is over 100 times smaller than that for the n-π* triplet of acetophenone in the same solvent. Although hydrogen abstraction is characteristic of both n-π* and π-π* triplets, it has been observed[27,28] that π-π* triplet abstraction rates are lower than those for n-π* triplets. Thus, the low rate of hydrogen abstraction of the cyclohexenone triplet compared to that of the acetophenone n-π* triplet indicates that a π-π* triplet may be involved. However, it is quite possible that abstraction rates for enones are inherently lower than those for aromatic ketones and thus a comparison of the two may not be significant.

Other evidence indicates that a n-π^* triplet may be involved. It was previously mentioned that from molecular orbital calculations[14,21,22] and resonance considerations,[23] Zimmerman predicted that the β-carbon in the n-π^* excited state of cyclohexenones should be electron rich. He assumed that the triplet and singlet species had the same or very similar electron distributions. Experimentally it has been shown that in n-π^* excited carbonyl groups the electron density is reduced on the oxygen and increased on the carbon. The dipole moment of the ground state of formaldehyde was 2.34 D while that of the n-π^* excited state was 1.48 D in the same direction.[29] To the extent that the π-π^* triplet has the electron distribution approaching that of the singlet π-π^* species, the beta carbon of the π-π^* triplet might be electron deficient as is classically pictured in the literature[30] by $^{+}C-C=C-O^{-}$. As was previously mentioned, Zimmerman demonstrated that in the photolysis of 4-phenyl-4-p-cyanophenyl-1(4H)-naphthalenone (XXXI), p-cyanophenyl migration was preferred over phenyl migration by a ratio of 2:1 thus showing that the beta carbon is not electron deficient and indicating that the π-π^* triplet is not involved. Also, this reaction has been shown by benzophenone sensitization to proceed by a triplet state. The phosphorescence emission spectrum from phenanthrone XII was reported by Zimmerman[25] to be suggestive of the presence of n-π^* triplets, but no details were given. However, in earlier work on cyclohexadienones Zimmerman and Swenton[21] pointed out that similarity between the phosphorescence emission spectrum of 4,4-diphenyl cyclohexadienone and that of benzophenone indicated that the lowest energy triplet, which they presumed to be the reacting triplet, was n-π^*.

Little has been done to answer the questions concerning the demotion of the electronically excited state to the ground state. Zimmerman[14,23] has suggested that this takes place after formation of the C-3 to C-5 bond in species XXXVII in his mechanism.



A mesionic ground state species of type XXXVIII preceeding 2,4-bonding could then explain the formation of a product of type XXXIX in the photolysis of 4,4-dimethylcyclohexenone in acetic acid.[3,4] In the case of 4,4-diphenylcyclohexenone Zimmerman[15] has considered the possibilities of demotion after the beginning of phenyl migration but before 2,4-bonding as shown below.



Zimmerman felt that if demotion occurred prior to any molecular change then the electronic ground state (XL ↔ XL') would be regenerated. Calculations by Zimmerman showed that it is very unlikely that a highly vibrationally excited ground state molecule XL formed by radiationless electron demotion could rearrange by the

equivalent of a pyrolytic process. Collisional quenching by solvent would deactivate such a hot species prior to thermal rearrangement. However, it should be noted that other workers[31,32] have studied photorearrangements of different types of compounds in solution where the data suggests that it is probable or possible that the reactions are proceeding by way of a vibrationally excited ground electronic state. The preferred migration of p-cyanophenyl over phenyl in the irradiation of naphthalenone XXXI indicated that a species of type XL' is not involved before migration.

CONCLUSION

It is apparent that more work is necessary to identify the triplet state and transient intermediates involved in these reactions. Also, solvent effects should be further studied since it has been observed in previous examples[3,16] and in other cases[6,12] that different products are obtained when the reactions are carried out in solvents other than the commonly used t-butyl alcohol. Finally, it should be noted that different functional groups attached to the cyclohexenone ring such as an aldehyde group or exocyclic double bond may be a determining factor in regard to the products formed.[6,33-35] Thus, there are a multitude of compounds containing the cyclohexenone ring that remain to be studied.

BIBLIOGRAPHY

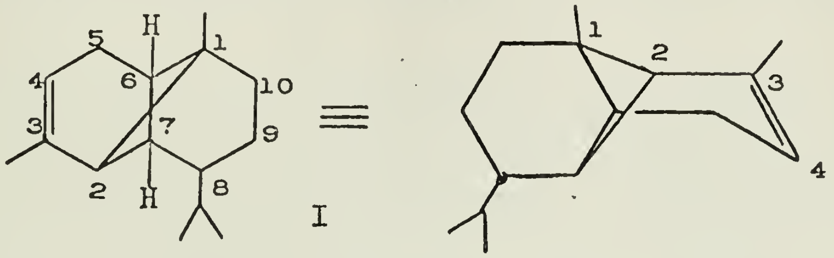
1. W. W. Kwie, B. A. Shoulders and P. D. Gardner, J. Am. Chem. Soc., 84, 2268 (1962).
2. B. A. Shoulders, W. W. Kwie, W. Klyne and P. D. Gardner, Tetrahedron, 21, 2973 (1965).
3. O. L. Chapman, T. A. Rettig, A. A. Griswold, A. I. Dutton and P. Fitton, Tetrahedron Letters, 2049 (1963).
4. O. L. Chapman, A. I. Dutton and P. Fitton, Abstracts of the 142nd Meeting of the Am. Chem. Soc., Sept., 1962, p. 88Q.
5. J. N. Pitts, Jr. and I. Norman, J. Am. Chem. Soc., 76, 4815 (1954).
6. B. Nann, D. Gravel, R. Schorta, H. Wehrli, K. Schaffner and O. Jeger, Helv. Chim. Acta, 46, 2473 (1963).
7. H. Wehrli, R. Wenger, K. Schaffner and O. Jeger, ibid., 46, 678 (1963).
8. O. Jeger, Angew. Chem., 76, 275 (1964).
9. O. Jeger and K. Schaffner, Chem. Weekblad, 60, 389 (1964).
10. J. Frei, C. Ganter, D. Kagi, K. Kocsis, M. Miljkovic, A. Siewinski, R. Wenger, K. Schaffner and O. Jeger, Helv. Chim. Acta, 49, (1966), in press.
11. B. Nann, H. Wehrli, K. Schaffner and O. Jeger, ibid., 48, 1680 (1965).
12. O. L. Chapman, J. B. Sieja and W. J. Welstead, Jr., J. Am. Chem. Soc., 88, 161 (1966).
13. W. R. Adams, O. L. Chapman, J. B. Sieja and W. R. Welstead, Jr., ibid., 88, 162 (1966).
14. H. E. Zimmerman, Pure Appl. Chem., 9, 493 (1964).
15. H. E. Zimmerman and J. W. Wilson, J. Am. Chem. Soc., 86, 4036 (1964).
16. T. Matsuura and K. Ogura, ibid., 88, 2602 (1966).
17. H. E. Zimmerman and D. J. Sam, ibid., 88, 4114 (1966).
18. H. E. Zimmerman and D. J. Sam, ibid., 88, 4095 (1966).
19. O. L. Chapman, Advan. Photochem., 1, 323 (1963).
20. (a) M. Pfau, R. Dulou and M. Vilkas, Compt. Rend., 254, 1817 (1962); (b) I. A. Williams and P. Blandon, Tetrahedron Letters, 257 (1964).
21. H. E. Zimmerman and J. S. Swenton, J. Am. Chem. Soc., 86, 1436 (1964).
22. H. E. Zimmerman, Science, 153, 837 (1966).
23. H. E. Zimmerman, Advan. Photochem., 1, 183 (1963).
24. H. E. Zimmerman, R. C. Hahn, H. Morrison and M. C. Wani, J. Am. Chem. Soc., 87, 1138 (1965).
25. H. E. Zimmerman, R. G. Lewis, J. J. McCullough, A. Padwa, S. W. Staley and M. Semmelhack, ibid., 88, 1965 (1966).
26. H. E. Zimmerman, R. G. Lewis, J. J. McCullough, A. Padwa, S. W. Staley and M. Semmelhack, ibid., 88, 159 (1966).

27. G. S. Hammond and P. A. Leermakers, ibid., 84, 207 (1962).
28. G. Porter and P. Suppan, Pure Appl. Chem., 9, 499 (1964).
29. D. E. Freeman and W. Klemperer, J. Chem. Phys., 40, 604 (1964).
30. S. F. Mason, Quart. Rev. (London), 15, 287 (1961).
31. E. F. Ullman and W. A. Henderson, Jr., J. Am. Chem. Soc., 86, 5050 (1964).
32. G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. D. Cowan, R. C. Counsell, V. Vogt and C. Dalton, ibid., 86, 3197 (1964).
33. D. E. Poel, H. Wehrli, K. Schaffner and O. Jeger, Chimia (Aarau), 20, 110 (1966).
34. P. D. Gardner and H. F. Hamil, J. Am. Chem. Soc., 83, 3531 (1961).
35. J. J. Hurst and G. H. Whitman, J. Chem. Soc., 2864 (1960).

NATURALLY OCCURRING TRICYCLO[$4.4.0.0^{2,7}$]DECANE SYSTEMS

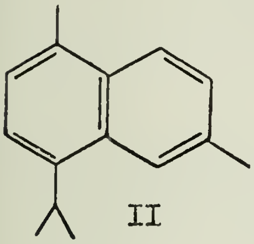
Reported by Edward F. Bertram December 5, 1966

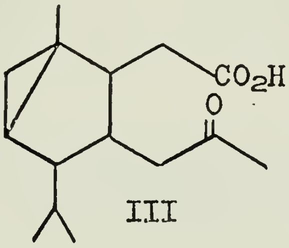
Recently, structural determinations and synthesis have shown the sesquiterpene (-)-copaene to be 1,3-dimethyl-8-anti-isopropyltricyclo[$4.4.0.0^{2,7}$]dec-3-ene (I). It has also been shown that the sesquiterpenes mustakone and ylangene possess the same tricyclo[$4.4.0.0^{2,7}$]dec-3-ene system.



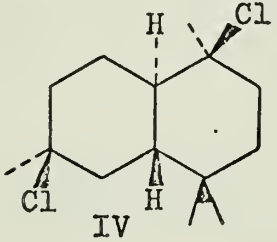
I

In 1952 Barton reviewed the work done on (-)-copaene.[1] By then it had been shown that (-)-copaene has elemental analysis of $C_{15}H_{24}$. On catalytic hydrogenation it takes up 1 mole of H_2. Dehydrogenation over S gives cadalene (II). Reaction with $KMnO_4$ gives a keto acid (proposed to be III) and reaction with HCl gives cadinene dihydrochloride (IV). The double bond was located in the 3 position of a cadalene structure by the method of Campbell and Soffer[2,3] (epoxide formation, reaction of the epoxide with methyl magnesium iodide, Se dehydrogenation of the alcohol formed and isolation of the cadalene V).

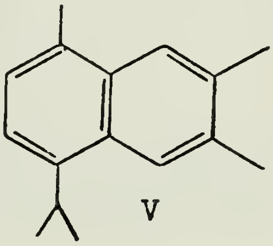

II



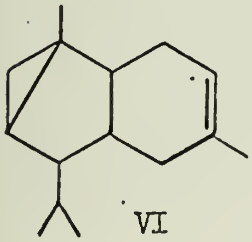
III

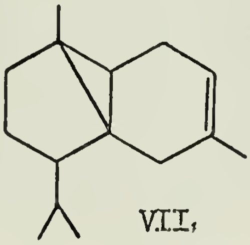


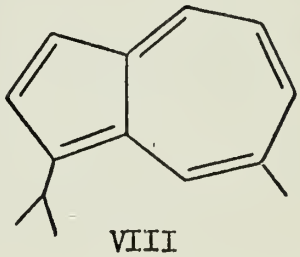
IV


V

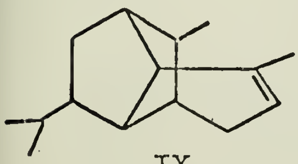
From this data, tricyclic compounds VI and VII were proposed for (-)-copaene. Structure VI was accepted as the most probable since the azulene VIII was not found in the dehydrogenation products.

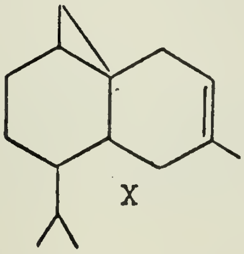

VI

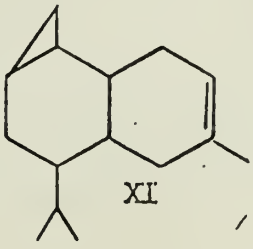

VII

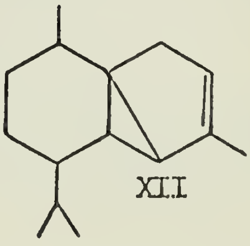

VIII

The proposed structures were criticized and alternatives proposed. Birch in 1951 suggested IX since there was no direct proof for a cyclopropane ring.[4] De Mayo in 1958 criticized the proposed non Markownikoff ring opening on the addition of HCl and suggested as possible structures X, XI, and XII.[5]


IX


X


XI

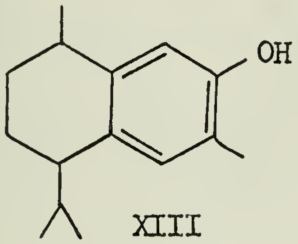

XII

In 1960, Sorm assigned a band at 3040 cm^{-1} in the infrared of (-)-copaene to a cyclopropane methylene and used this as additional evidence for VI.[6]

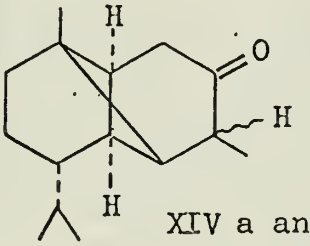
Then in 1963, with the acid labile bond much in doubt, de Mayo, Williams, Buchi and Feairheller (using essential oils from Cedrela toona Roxb. and Chloranthis spicatus of Chinese origin) and Kapadia, Nagasampagi, Naik and Dev (using Cyperus rotundus Linn.) simultaneously proposed structure I for (-)-copaene.[7,8]

An nmr of (-)-copaene showed 1 isopropyl group (6H doublet, τ 9.17, J=6 c/s) 1 quaternary methyl group (3H singlet, τ 9.21) 1 vinyl methyl group (3H doublet, τ 8.35, J=2 c/s) 1 vinyl proton (1H, τ 4.85) and no cyclopropyl methylene (no resonance above the τ 9.21). From this nmr data, all of the previously proposed structures could be ruled out.

Since there is a possibility of rearrangement in the Campbell and Soffer method, de Mayo rigorously ascertained the position of the double bond. (-)-Copaene was oxidized with OsO_4 to a diol which on further oxidation with CrO_3 in pyridine yielded a 6 membered ring ketol (IR 1718, 1408 cm^{-1}). This ketol was refluxed in formic acid, the resulting ester hydrolized and the phenol XIII was obtained. The structure of XIII was determined by infrared, nmr, ultraviolet and later by synthesis.[9] De Mayo located the double bond in still a third way by isolating two 6 membered ring ketones XIV(a and b) (infrared 1710 and 1715 cm^{-1}) obtained from the CrO_3 in pyridine oxidation of the alcohols which resulted from the hydroboration of (-)-copaene. Both ketones incorporated 3 deuteria in 1N NaOD in D_2O.



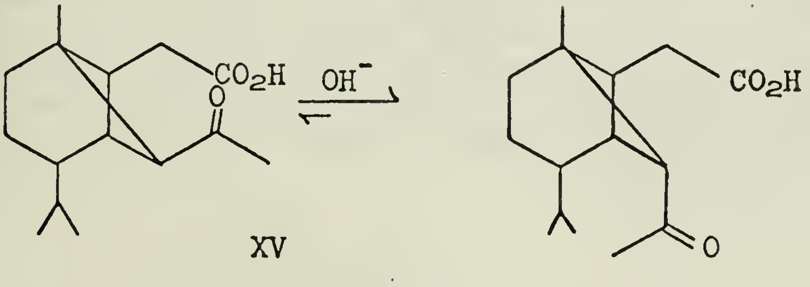
XIII



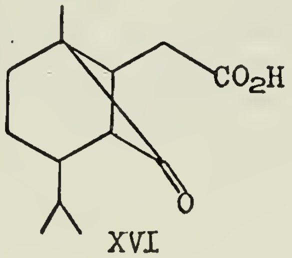
XIV a and b

Dev showed that copaene was unchanged after digestion in 98% formic acid for 4 hours at 100° C and attempted hydrogenation over PtO_2 in acetic acid containing perchloric acid. He therefore concluded that copaene did not contain a cyclopropane ring.

The nature of the labile bond was determined similarly by both groups by ozonolysis of (-)-copaene and H_2O_2 oxidation to yield a keto acid which was not the same as that from $KMnO_4$ oxidation. The keto acid obtained from ozonolysis was isomerized to the $KMnO_4$ oxidation product by refluxing in base. Thus the α position of the ketone function must be asymmetric. A Baeyer-Villiger oxidation of both keto acids and further CrO_3 pyridine oxidation of the resulting acid alcohol produced another keto acid (infrared 1780 cm^{-1}) with the ketone group being in a 4 membered ring. Thus with the epimeric carbon placed next to the double bond carbon with the methyl group and the nmr requirement of a quaternary methyl group, XV can be assigned to the first keto acid and XVI to the last one.

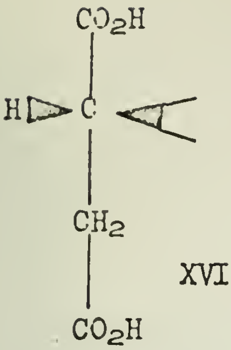


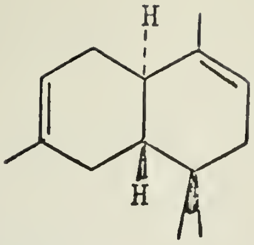
XV



XVI

From the above chemical evidence, plus the fact that (-)-copaene yields cadinene dihydrochloride, which has the assigned configuration IV (shown by X-ray analysis),[10] and the isolation of D(+)-isopropyl succinic acid (XVII)[11] from the HNO_3 oxidation of (-)-β-cadinene (XVIII) structure I represents the absolute stereochemistry of (-)-copaene.


XVII

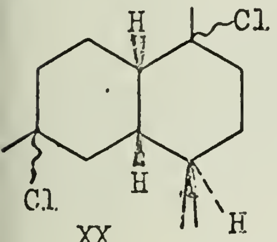

XVIII

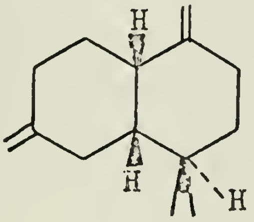
Dev proposed two possible mechanisms for the formation of cadinene dihydrochloride from (-)-copaene.[8] One suggestion was that the ion XIX may be formed by the path shown.

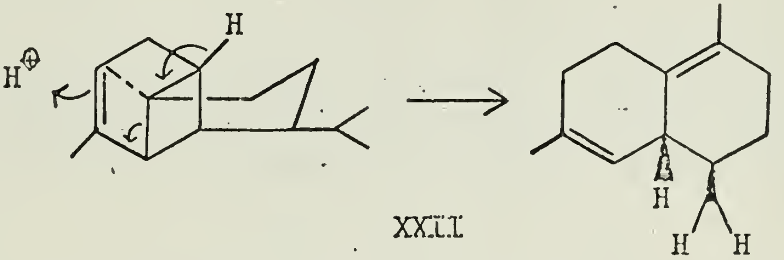

XIX

If this ion were an intermediate, the formation of (-)-muurolene dihydrochloride (XX) would be expected and Westfelt[12] did obtain a 1:6 ratio of (-)-muurolene to (-)-cadinene dihydrochlorides on HCl addition to (-)-copaene (isolated from Pinus silvestris L.). Other workers isolated only 25-60% cadinene dihydrochloride but did not identify the balance of the products. In order to get cadinene dihydrochloride, there would have to be epimerization at C_6. It would be expected that a similar ion would be present to some extent on HCl addition to (-)-muurolenes (XXI). Westfelt reported a 1:3 mixture of (-)-cadinene to (-)-muurolene dihydrochlorides[12] but Herout reported only (-)-muurolene dihydrochloride even with varied conditions.[13]

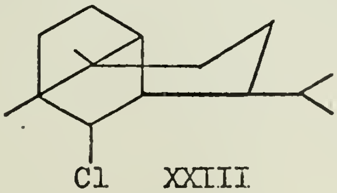
The second mechanism proposed by Dev was a concerted one with the formation of the intermediate XXII and subsequent HCl addition to give (-)-cadinene dihydrochloride. This mechanism has the preferred anti-parallel geometry and would establish epimerization at C_6.


XX


XXI

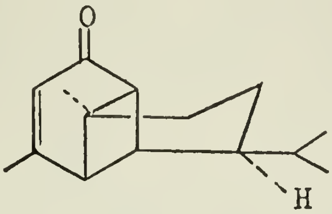

XXII

Also, if the ion XIX is an intermediate, there is the possibility of XXIII being formed by an alkyl shift (as α-pinene and α-longipinene[14] do on HCl addition). Dev searched the mother liquor by examination of the nmr but found no secondary chloride. Since no XXIII is formed, the concerted mechanism was favored. There is also the possibility that XXIII is unstable to reaction conditions and thus may go on to form the observed dihydrochloride.


XXIII

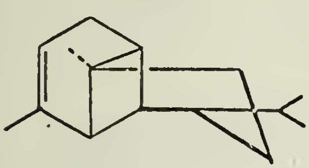
A compound which helped Dev in the assignment of structure I to (-)-copaene was mustakone, a sesquiterpene isolated from Cyperus rotundus Linn. along with copaene. This compound is an αβ-unsaturated ketone (infrared 1685 cm^{-1}, ultraviolet λ_{max} 255 mμ) which undergoes catalytic hydrogenation to a tricyclic

ketone in a 6 membered ring (infrared 1712 cm^{-1}). In addition, a Wolff-Kishner reduction converted the saturated ketone (dihydromustakone) into dihydrocopaene. From this evidence, structure XXIV was assigned to (-)-mustakone. Some additional evidence for this structure was obtained by the oxidation of (-)-copaene to (-)-mustakone with t-butyl chromate in benzene.

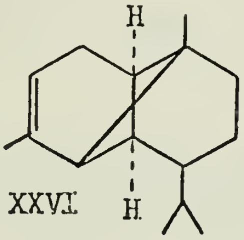


XXIV

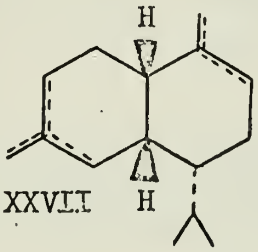
The structure of a third copaene type sesquiterpene, (-)-ylangene (XXV or its mirror image) has also been determined. It was first proposed to contain a cyclopropane ring.[15] Later Hunter and Brogden compared it to (-)-copaene by infrared, nmr, mass spectra and observed similar products from the 2 compounds from rearrangement on silica gel.[16] They also observed that (-)-copaene and ylangene gave only cadinane on strong catalytic hydrogenation (Pd/C, 240° C, 1,550, psi). These conditions ruptured the cyclobutane ring while less stringent conditions gave dihydrocopaene and dihydroylangene. The silica gel rearrangement of copaene and ylangene was compared to that of α pinene and it was suggested that they were similar reactions. Thus they proposed a ring junction isomer XXVI for ylangene and assumed that the isopropyl group had the same configuration as (-)-copaene. Sorm later assigned the difference to be in the isopropyl group configuration, partially because of the recent isolation of amorphenes (XXVII) and muurolenes (XXI) which differ from each other only in the configuration of the isopropyl group.[17] He also criticized the change in the ring junction because this would require a trans decalin precurser which would forbid the 4 membered ring closure of either copaene or ylangene. Heathcock later showed by synthesis that ylangene was indeed the C_8 epimer of (±)-copaene ((±)-8-isocopaene).



XXV

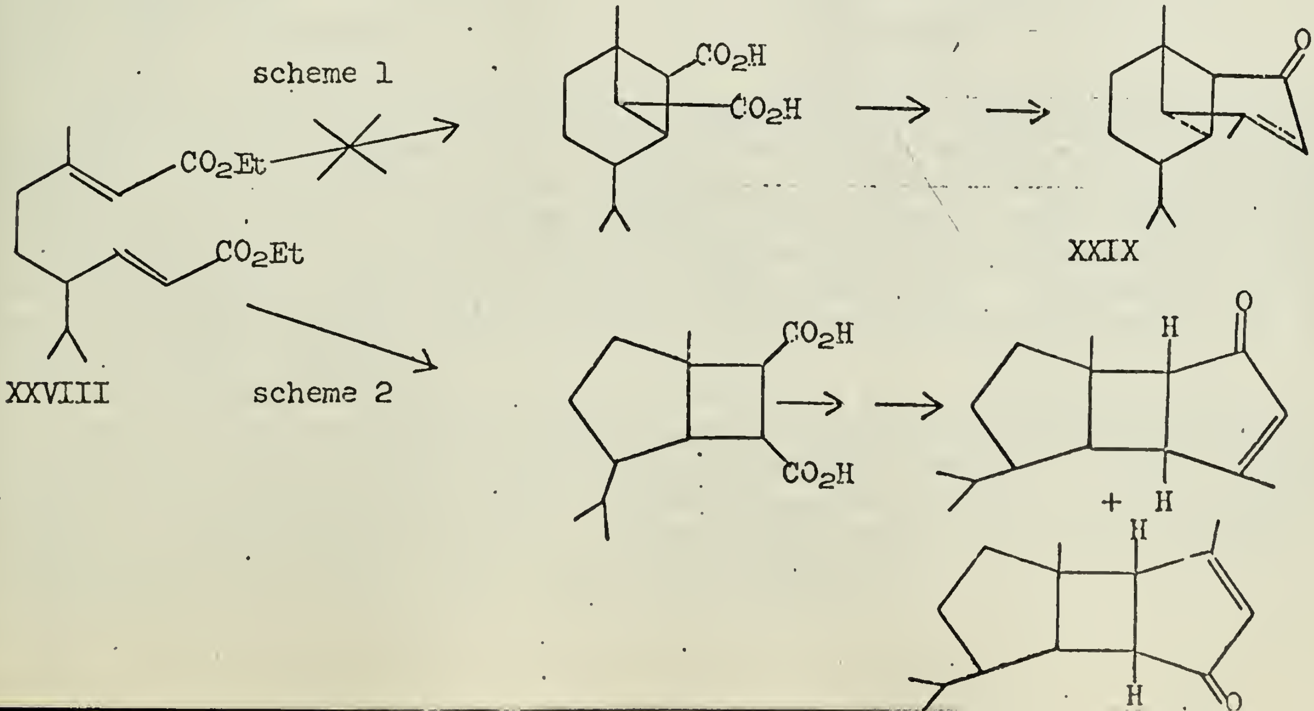


XXVI



XXVII

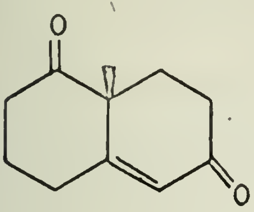
Brown attempted to synthesize copaene by photolysis of the bis-unsaturated compound XXVIII.[18] He hoped to obtain head-to-tail cyclization, then to convert the diacid formed to the diketone and subsequently to cyclize to the unsaturated ketone XXIX (scheme 1). Instead however, he obtained only head-to-head cyclization (scheme 2).



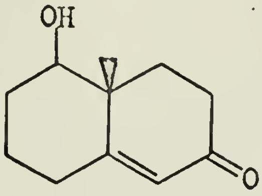
XXVIII

XXIX

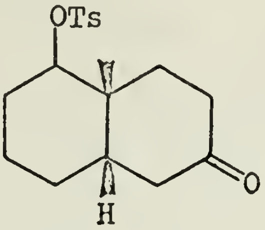
Heathcock[19] starting with the Wieland-Miescher ketone XXX, reduced it with $NaBH_4$ in ethanol to get the unsaturated ketol XXXI. This was treated with p-toluene sulfonyl chloride in pyridine to give the corresponding tosylate which, on hydrogenation over palladized strontium carbonate, yielded the cis-fused keto tosylate XXXII (55% over all yield). The cis-fused tosylate was eliminated in refluxing pyridine to give 95% of the octalone XXXIII.



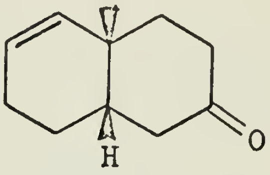
XXX



XXXI

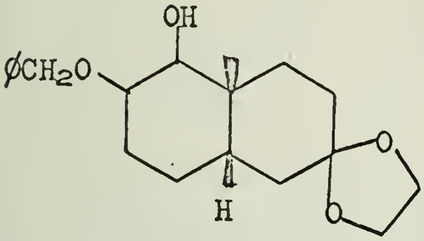


XXXII

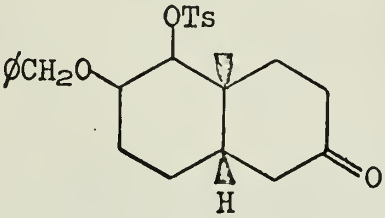


XXXIII

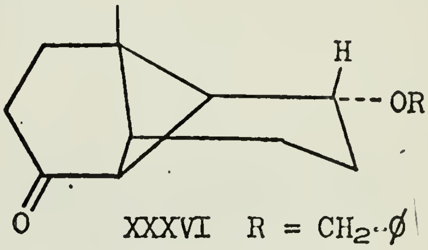
Ketalization of XXXIII, epoxidation by peracid in $CHCl_3$ of the unsaturated ketal thus formed and treatment of the epoxide in 1N sodium benzylate in benzyl alcohol at 200° C gave XXXIV, a benzyl ether. This benzyl ether was reacted with tosyl chloride and then deketalized to give the substituted octalone XXXV. This compound was then reacted with methyl sulfynyl carbanion in DMSO to give the tricyclic compound XXXVI.



XXXIV



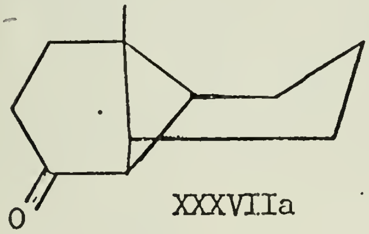
XXXV



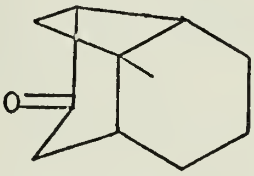
XXXVI $R = CH_2\text{-}\phi$

XL $R = \underset{\overset{\|}{O}}{C}CH_3$

This reaction had previously been worked out using the tosylate XXXII. Reaction of this tosylate with the methyl sulfynyl carbanion in DMSO gave the saturated tricyclic ketone XXXVIIa or XXXVIIb (70% yield) plus 3% of the unsaturated decalin XXXIII.



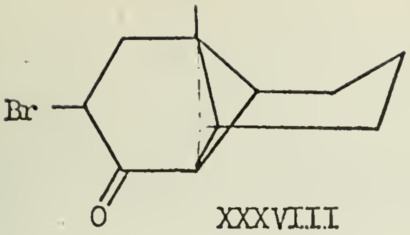
XXXVIIa



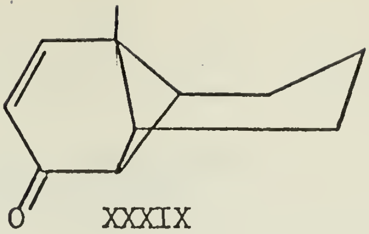
XXXVIIb

XXXVIIa was favored over XXXVIIb because the nmr shows a sharp band at τ 7.46 assigned to the bridgehead H adjacent to the carbonyl (C_7-H). The other two bridgehead H are at 90° so by the Karpus equation they should be very weakly coupled with the C_7-H. If it were XXXVIIb, the dihedral angle between bridgehead H would be 30°, 30° and 90°. Therefore appreciable coupling would be expected for the analogous bridgehead H adjacent to the carbonyl. Stereomodels of the tosylate before reaction also favored a back side carbanion attack on the tosylate giving compound XXXVIIa.

The tricyclic compound was shown chemically to be XXXVIIa by reaction with Br_2 in acetic acid to give an α-bromo ketone XXXVIII and then elimination in γ-collidine to an αβ-unsaturated ketone XXXIX (ultraviolet λ_{max} 252 mμ, ε 3,000, infrared 1695, 1660 cm^{-1}). Thus XXXVIIb can be eliminated because there is no possibility of forming an αβ-unsaturated ketone. To show that there was no rearrangement, XXXIX was hydrogenated over Pd/C to give back ketone XXXVIIa.

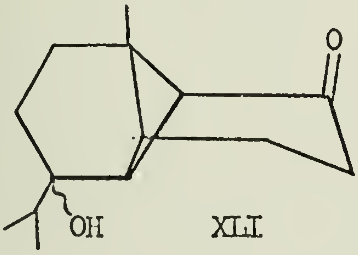


XXXVIII

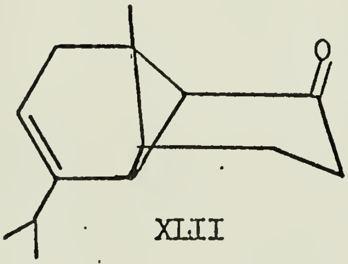


XXXIX

The tricyclic compound XXXVI was debenzylated by 1N HBr in glacial acetic acid to the keto acetate XL (nmr proton at τ 7.31 which was shown to be characteristic for tricyclic $[4.4.0.0^{2,7}]$decan-8-one (XXXVIIa, nmr τ 7.46 1H)).[20] XL was alkylated with isopropyl lithium to give the diol which on oxidation by the Jones method yielded the ketol XLI. On dehydration in pyridine with phosphorous oxychloride, XLI yielded the unsaturated ketone XLII which, on reaction with methyl lithium followed by hydrogenation over Pd/C and a second dehydration, yielded a mixture of (±)-copaene and (±)-8-isocopaene. These were separated by preparative gas chromatography.



XLI



XLII

The racemic copaene was identical by infrared, mass spectra and nmr with the natural (-)-copaene from Copaiba oil, Ylang Ylang oil and Chloranthus oil. The (±)-8-isocopaene agreed with that of ylangene isolated from Schizandria chinensis (Tucz) Baill supplied by Sorm.[15]

BIBLIOGRAPHY

1. a) J. L. Simonson and D. H. R. Barton, "The Terpenes. Vol. III," Cambridge University Press, New York, 1952, p. 88.
   b) D. H. R. Barton in E. H. Rodd, "Chemistry of Carbon Compounds. Vol. II," Elsevier, Amsterdam, 1953, p. 641.
2. W. P. Campbell and M. D. Soffer, J. Amer. Chem. Soc., 64, 417 (1942).
3. L. H. Briggs and W. I. Taylor, J. Chem. Soc., 1338 (1947).
4. A. J. Birch, Rep. Progr. Chem., 47, 195 (1951).
5. P. de Mayo, Perfum. Essent. Oil Rec., 49, 238 (1958).
6. F. Vanasack, V. Herout, and F. Sorm, Coll. Czeck. Chem. Comm., 25, 919 (1960).
7. a) P. de Mayo, R. E. Williams, G. Buchi, and S. H. Feairheller, Tetrahedron, 21, 619 (1965).
   b) G. Buchi, S. H. Feairheller, P. de Mayo, and R. E. Williams, Proc. Chem. Soc., 214 (1963).
8. a) V. H. Kapadia, B. A. Nagasampagi, V. G. Naik, and S. Dev, Tetrahedron, 21, 607 (1965).
   b) V. H. Kapadia, B. A. Nagasampagi, V. G. Naik, and S. Dev, Tetrahedron Letters, 1933 (1963).
9. W. Cocker and D. M. Sainsbury, J. Chem. Soc., 3319 (1965).
10. a) F. Hanic, Chem. Listy, 52, 165 (1958).
    b) V. Sykora, V. Herout, and F. Sorm, Coll. Czeck. Chem. Comm., 23, 2181 (1958).
11. V. Herout and V. Sykora, Chem. and Ind., 130 (1958).
12. L. Westfelt, Acta Chem. Scand., 18, 572 (1964).
13. A. Zabza, M. Romanuk, and V. Herout, Coll. Czeck. Chem. Comm., 31, 3373 (1966).
14. H. Erdtman and L. Westfelt, Acta Chem. Scand., 17, 2351 (1963).

15. O. Motl, V. G. Bucharov, V. Herout, and F. Sorm, Chem. and Ind., 1759 (1963).
16. G. L. K. Hunter and W. B. Brogden, J. Org. Chem., 29, 982 (1964).
17. O. Motl, V. Herout, and F. Sorm, Tetrahedron Letters, 451 (1965).
18. M. Brown, Chem. Comm., 340 (1965).
19. C. H. Heathcock, J. Amer. Chem. Soc., 88, 4110 (1966).
20. C. H. Heathcock, Tetrahedron Letters, 2043 (1966).

CYCLOOCTATETRAENE-METAL TRICARBONYL COMPLEXES

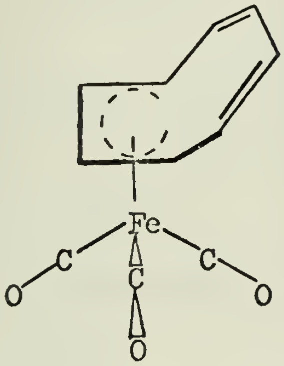
Reported by Edward F. Johnson December 8, 1966

In 1958 Hallam and Pauson[1] re-investigated the reaction between iron pentacarbonyl and butadiene and isolated a 1,3-diene iron tricarbonyl complex. An analogous complex, 1,3-cyclohexadiene-iron tricarbonyl, was prepared in a similar manner, showing that it is highly probable that the diene system adopts a *cis* arrangement of the double bonds. With the synthesis of 2,5-bicycloheptadiene-iron tricarbonyl, Pettit demonstrated that a diene need not be conjugated, but only oriented so that bonding to iron can occur.[2] Three independent research groups synthesized an iron carbonyl complex of cyclooctatetraene (COT).[3-5] Within the last year carbonyl complexes of the type COT $Mo(CO)_3$[6] and COT $Cr(CO)_3$[7] have been prepared.

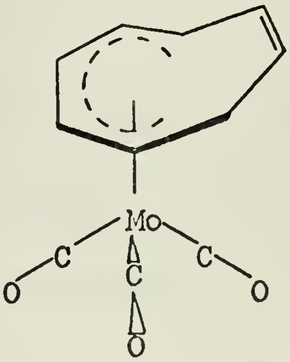
GEOMETRY OF THE RING

COT $Fe(CO)_3$ is a stable solid (mp 92°) which is soluble in most organic solvents.[3] This compound does not react with bromine in carbon tetrachloride, shows no uptake of hydrogen under normal conditions, and exhibits an unusual resistance to the formation of Diels Alder adducts. The nmr spectrum shows that all protons are equivalent. In conjuction with the chemical evidence, the presence of this single, sharp proton resonance, and the absence of a strong IR absorption attributable to an olefinic C=C stretching vibration led many of the early workers to interpret these results as strong evidence for a planar COT ring in the complex.

In 1961 Dickens and Lipscomb[8] completed a single crystal X-ray study of COT $Fe(CO)_3$ and proved all previously proposed structures to be incorrect. The X-ray study showed that the bonding of $Fe(CO)_3$ to the butadiene-like residues of the cyclooctatetraene changes the geometry of the ring, giving it a dihedral form with an angle of 139° between the two planes of the ring (I). In this structure 6 of the 8 carbon atoms on the ring are very nearly planar, and 6 of the 8 angles are within 3° of 135°--the angle for a regular octagon. Very recently McKechnie and Paul[9] completed the crystal structure of COT $Mo(CO)_3$ (II) and found the structure similar to that of COT $Fe(CO)_3$, bearing in mind the fact that molybdenum needs 6 electrons to obtain a rare gas configuration. One uncomplexed pure double bond was found with the Mo atom associated closely, but not equally, with the remaining 6 carbon atoms. Again 6 of 8 angles approach the ideal value of a regular octagon, and 6 of 8 atoms deviate only 0.16 Å from a planar conformation.



I



II

The single peak in the nmr of COT $Fe(CO)_3$ can be explained by (a) identical chemical shifts for the protons in the complex, (b) a structure in solution which is radically different from the geometry in the crystal, or (c) valence tautomerism, which would make all the protons equivalent on the nmr time scale.

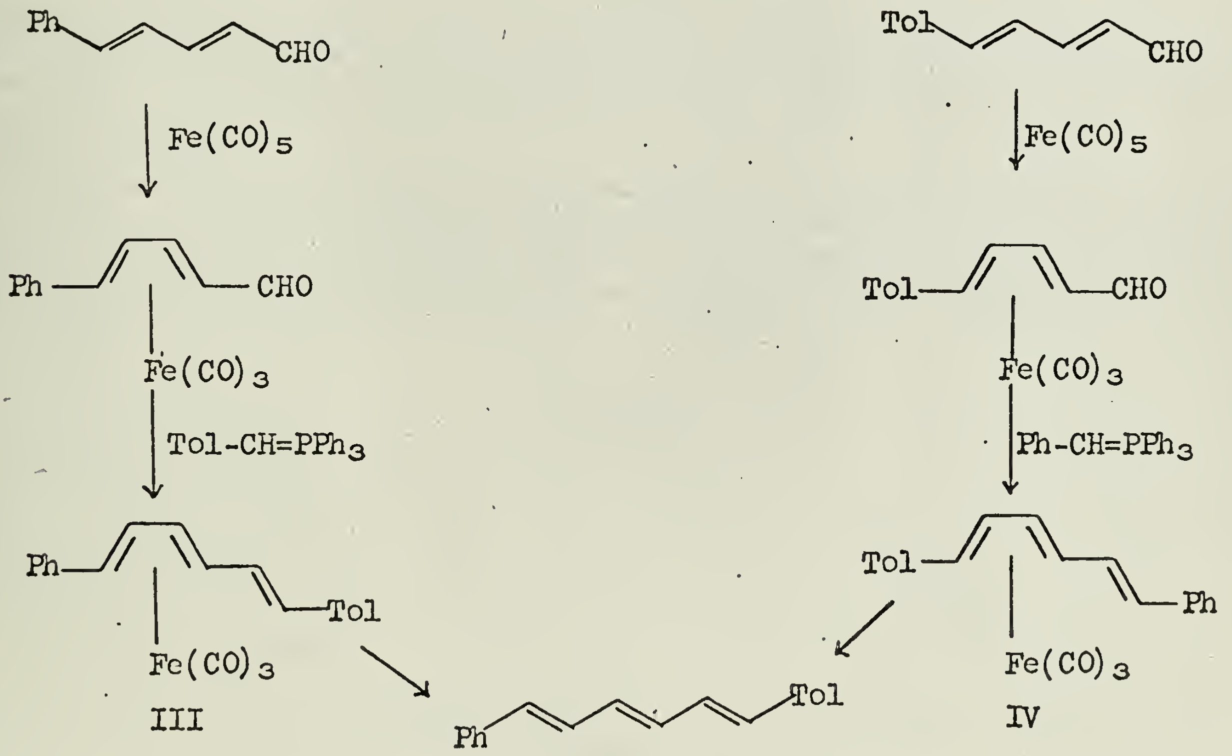
The first explanation is easily ruled out by the fact that the nmr spectra of similar complexes show distinct chemical shift differences. For example, cyclohexadiene-iron tricarbonyl shows a difference in chemical shift of 2.09 ppm between the "vinyl" protons; for 2,4-bicyclo(5.1.0)octadiene-iron tricarbonyl a chemical shift difference of 1.21 ppm is found between "vinyl" protons.[10]

An examination of the infrared and the Raman spectrums[11] led to the conclusion

that the geometry in the solid state is not radically different from that in solution. Because of the large number of observed frequencies and the coincidences between the infrared and the Raman spectrums, the complex has been shown to have low symmetry. This lack of symmetry for COT $Fe(CO)_3$ in solution would rule out any highly symmetrical planar complex in which the Fe is bonded to all the carbon atoms equally. There is also excellent agreement between the infrared spectra of the complex in the solid state and in solution. The iron complex shows no bands in the region of 1708 to 1562 cm^{-1}, a region which includes the stretching frequencies of the conjugated double bonds in cyclooctatetraene. Several bands below 1562 cm^{-1} have been attributed to the double bond stretching modes. The Mo and Cr complexes show double bond absorption at 1675 and 1668 cm^{-1} respectively.[6]

It was concluded by the investigators that the general geometry of the ring and the butadiene-like bonding between a 1,3 diene and the metal are present both in solution and in the solid state.[11] If this is the case, then the only remaining rationale to explain the nmr data is valence tautomerism--- a rapid shifting of the metal-diene bonds to make all carbon atoms equivalent. The concept of valence tautomerism has been used to explain the nmr data of similar compounds, including $C_7H_7^+$ $Fe(CO)_3$,[12] COT $Fe_2(CO)_5$,[13] COT $Mo(CO)_3$ and COT $Cr(CO)_3$.

Whitlock[14] has investigated the potential shuffling of an iron tricarbonyl residue along a polyene chain to see if this is a unique feature of cyclic structures, or a general characteristic of polyene-iron carbonyl complexes. Two 1,6 diaryl hexatriene-iron tricarbonyl (III and IV) complexes, differing only in the position of attachment of the iron tricarbonyl residue were prepared as shown. Complexes III and IV are not identical. They show different melting points, a depressed mixed melting point, and different IR absorptions. The two complexes are interconverted when heated to 120°. The first order rate constant for this reaction was found to be 9.2×10^{-4} min^{-1} at 99.6°. However, the minimum rate constant for the time averaging of COT $Fe(CO)_3$ protons can be calculated as being 2×10^4 min^{-1} at -60°. Thus, there is a large difference in rates, on the order of 10^7, without correcting for the 160° temperature difference of the two reactions.



Two reasons may be offered for the rate difference. First, the COT $Fe(CO)_3$ has a cisoid arrangement of p-orbitals which is not present in the acyclic complex. However, cycloheptatriene-iron tricarbonyl exhibits a complex nmr spectrum at room temperature.[15] Therefore, the most important factor must be the complete cyclic conjugation present in cyclooctatetraene. These two conditions are met for all complexes considered to exhibit valence tautomerism.

Kreiter, Maasbol, Anet, Kaesz, and Winstein[7] have obtained the first nmr spectrum of a complex of cyclooctatetraene whose proton magnetic resonance shows observable change from rapid to arrested valence tautomerism. The nmr spectra of COT Mo(CO)$_3$ and COT Cr(CO)$_3$ are almost identical and can readily be interpreted in terms of the structure found in the solid state by Paul for COT Mo(CO)$_3$.[9] The spectra of both complexes show a single resonance at 80° with broadening at low temperatures. At -40° the spectrum consists of four complex peaks centered at τ3.77, 4.86, 5.04, and 5.52 for the molybdenum complex and τ3.74, 4.82, 5.08, and 5.38 for COT Cr(CO)$_3$. The assignment of the protons was based on a large amount of nmr evidence which shows the internal protons to be at low field and the terminal protons at high field, separated by more than 80 cps. Additional support for the assignment was found by King[16] in an investigation of 1,3,5-cyclooctatrienemolybdenum tricarbonyl which exhibits protons at τ4.15, 4.86, and 5.31 (2:2:2). Furthermore, protons of uncoordinated double bonds (τ5.04) are shifted by approximately 0.7 ppm to higher field from their position in free cyclooctatetraene (τ4.30).[10]

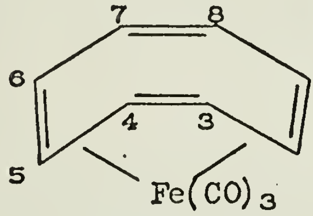
Recently, Winstein and coworkers have also undertaken low temperature nmr studies of COT Fe(CO)$_3$ and found that the single line in the nmr spectrum broadened rapidly below -100°, and separated into two bands below -118°. At -130°, the spectrum consisted of two broad peaks centered at τ4.0 and 5.5. Identical behavior was observed in dimethyl ether, acetaldehyde--deuterochloroform, and dichlorofluoromethane--trifluorobromomethane. The spectrum showed no further change when observed in Freon mixtures at -150°. This splitting is further evidence against the existence of a symmetrically bonded complex in solution. Winstein and coworkers concluded that this evidence, along with the IR evidence reported earlier, strongly favored a 1,3-diene bonded system of the same geometry found in the solid state. The model would require an $A_2B_2M_2N_2$ pattern which is consistent with the spectrum found at low temperature. The high field absorption was assigned to the four protons of the diene-iron tricarbonyl moity and the low field absorption was attributed to the four olefinic protons.

Other workers have done low temperature nmr studies on the same complex, but have offered alternate interpretations of these results. Cotton, Davison and Faller[17] observed the following spectrum for COT Fe(CO)$_3$ in a 1:1 dichlorofluoromethane-dichlorodifluoromethane mixture at about -155°. Cotton and coworkers argue that this spectrum is inconsistent with the "frozen" structure being the 1,3-diene. They point out that the generalities, which may be developed from the study of the chemical shifts of "inside" and "outside" protons in model complexes, are inconsistent with the observed chemical shifts. It is found that inner protons are located 0.5 to 1.0 ppm at higher field than the corresponding protons in the uncomplexed case; likewise, the outer protons are at higher field by 2.5 to 3.0 ppm. For example, 1,3-cyclohexadiene-iron tricarbonyl shows inside protons at τ4.77 and outside protons at τ6.86 (uncomplexed vinyl protons at τ4.22).[10] A particularly good model for a 1,3-diene iron tricarbonyl moity on the COT ring is given by COT Fe$_2$(CO)$_6$.[3-5] This di-iron complex has been shown by X-ray studies[8] to have two 1,3-diene iron tricarbonyl residues--one on each side of a chair conformation of the ring. The nmr spectrum of this complex shows peaks of equal intensities at τ4.4 and 6.9.[10] This spectrum is

Figure 1

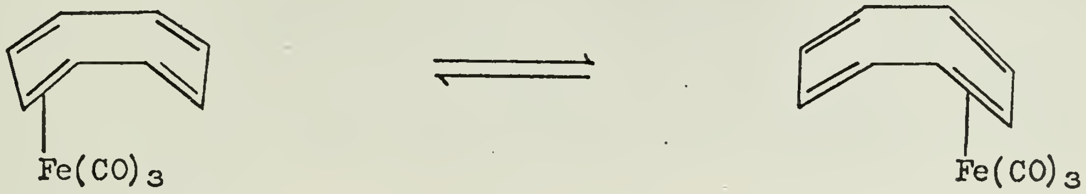
in general agreement with the assignments made previously. Therefore, for the nmr of COT $Fe(CO)_3$ in the "frozen" 1,3-diene form at -155°, one would expect one peak close to or slightly downfield from the peak for the protons of cyclooctatetraene which appears at $\tau 4.3$. A slightly higher upfield peak ($\tau 4.4$) would be expected corresponding to the inner protons of the complex; and, finally, the two outer protons would be expected at still higher field ($\tau 7.0$). With incomplete resolution, one would expect, at worst, two peaks with relative areas of 6 to 2, centered approximately at $\tau 4.4$ and 6.8. With better resolution one would expect 3 peaks with relative areas 4:2:2. This is in contrast with the experimental results shown in Figure 1.

Cotton further argues that the low temperature spectrum is what would be expected for a 1,5-diene complex of the COT in the tub form[17] (IX). The high field peak is assigned to the complexed 1,5-diene (H_1,H_2,H_5,H_6) protons and the low field peak is due to the vinyl hydrogens (H_3,H_4,H_7,H_8). Also, Cotton points out that the infrared observations are not completely similar for the complex in the solid state as in solution, especially in the C-H stretching region. The data may be consistent for a 1,3-diene complex, but it does not rule out a 1,5 complex.



IX

Pettit[18] has also examined COT $Fe(CO)_3$ by low temperature nmr. At -120° he reported a spectrum which consisted of two absorptions of equal area centered at $\tau 4.06$ and 5.44. He concluded, using the same reasoning as Cotton, that the experimental data does not correspond to the "frozen" model as shown in I. Pettit concluded that the most reasonable way to accommodate the spectrum found at -150° was to assume that the complex is undergoing the isomerization indicated by Xa $\rightleftharpoons$ Xb.



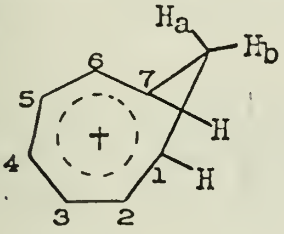
Xa Xb

If one assumes the reasonable values used previously for the "inside", "outside", and vinyl protons and an averaging of these values as they would be averaged in such an isomerization, a spectrum consisting of two absorptions with τ values of 4.1 and 5.5 would be predicted. These calculated peaks are in good general agreement with that which is actually observed. However, the fact that all protons are equivalent at higher temperature must still be explained. Therefore, at least one other process must take place to account for the valence tautomerism. These other processes are open to a great deal of discussion. Indeed, the facility of this isomerization is quite remarkable.

PROTONATION OF CYCLOOCTATETRAENE AND ITS COMPLEXES

The protonation of cyclooctatetraene has been reported to yield a stable cation,[19] the so called homotropylium ion, in $HSbCl_6$ or concentrated H_2SO_4. The hexachloroantimonate salt, when isolated, may be stored indefinitely under nitrogen in a refrigerator. This salt decomposes when exposed to a humid atmosphere, reacts immediately with water or alcohol, and is insoluble in all non-polar solvents.

When it is reacted with cycloheptatriene, tropylium hexachloroantimonate is isolated in yields of about 40%. On the basis of this chemical evidence, there can be little doubt as to the presence of a carbonium ion, but the factors contributing to its stability are less clear. Part of the stability is believed to result from the fact that a cyclopropyl ring can emulate a carbon-carbon double bond so that a "psuedoaromatic" ring somewhat analogous to tropylium is formed. Evidence supporting this argument is seen in the nmr spectrum[20] of the cation in H_2SO_4 which shows multiple peaks centered at $\tau 1.4$, 3.4, 4.8, and 10.6 (areas 5:2:1:1), attributed to the protons on carbons 2 through 6, 1 and 7, H_b, and H_a respectively as shown in XIa.



XIa

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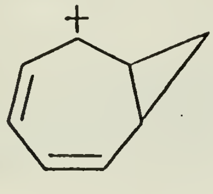

XIb

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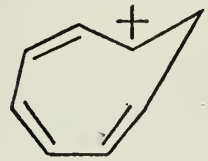
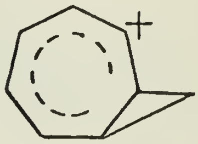


XIc

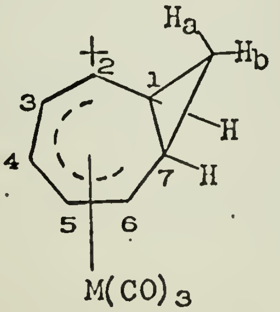


XII

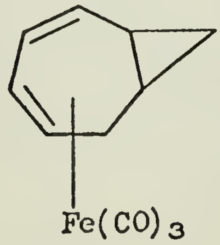
Carbons 2-6 bear most of the positive charge and therefore would be expected at low field. The two hydrogens on C_1 and C_7 give rise to the multiplet at $\tau 3.4$, an abnormally low value for cyclopropyl hydrogens, which probably indicates the extent to which C_1 and C_7 participate in the cyclic conjugation. The large difference in chemical shift (5.8 ppm) between protons H_a and H_b (the largest separation in chemical shift ever reported for two protons attached to the same carbon atom) may be rationalized on the basis of a ring current. H_a, which is over the ring, is shielded, while H_b, which is more nearly in the plane of the ring, is deshielded. Further evidence for this explanation comes from the observation of the nmr spectrum of cyclooctatetraene in D_2SO_4.[21] The spectrum shows the same chemical shifts as before, but now the areas occur in the ratio of 5:2:1/2:1/2, and expected simplification of the multiplets occurs. Also, it can be seen readily, that the protonation of cyclooctatetraene is irreversible on the nmr time scale. The system is thus presumed to have the non-classical homotropylium structure.[22]

Deno[23] has stated that properties of the cation are in accord with structure XII, and he implies that nothing more than the normal stabilization of a cation by a cyclopropane ring is operative. The following evidence has been used previously in support of the non-classical structure. (a) The chemical shifts of the four protons in the "cyclopropane" ring in tropylium ion differ by 7.2 ppm, whereas those studied by Deno and co-workers, differ, if at all, only by 0.6 ppm. (b) In homotropylium the coupling constant $J_{b,1}$ is 7.6 cps, whereas $J_{1,7}$ is close to zero. (c) No bicyclo(5.1.0)octane derivatives have been isolated when the cation was reacted with nucleophiles.

In order to obtain further evidence in the assignment of classical or non-classical character to the COT cation, the iron and molybdenum carbonyl complexes were compared to the free ion. The protonation of COT $Fe(CO)_3$ has been carried out by Wilkinson[24] in H_2SO_4 and D_2SO_4 and has been studied by nmr. The spectrum shows a quintuplet ($\tau 2.26$), and broad singlet ($\tau 4.62$), another broad singlet ($\tau 7.48$), and a multiplet ($\tau 8.56$) with relative areas 1:4:2:2.



XIII

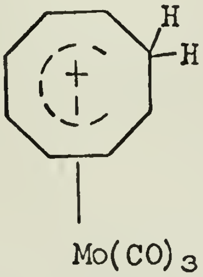


XIV

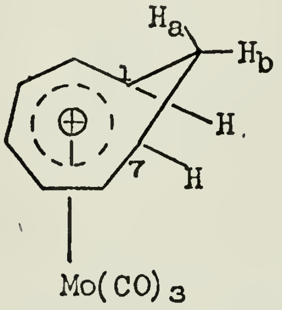
The proton on carbon 4 was assigned to the lowest peak downfield ($\tau 2.26$).

The quintuplet structure arises from approximately equal spin coupling to the four protons H_2, H_3, H_5 and H_6 and has been confirmed by proton-spin decoupling experiments. H_2, H_3, H_5, and H_6 appear to be nearly equivalent ($\tau 4.62$). The bridgehead hydrogens H_1 and H_7 were assigned to the band at $\tau 7.48$ and the high field band is assigned to the two non-equivalent methylene protons (H_a, H_b) on C_8. This last absorption is an AB pair and careful analysis shows the values $\tau 8.65$ and $\tau 8.47$ (J_{ab} 4.86 cps). This spectrum would be expected for the classical structure of the COT cation as shown in XIII (M = Fe). Further proof of the classical character of the cation was obtained from the fact that COT^+ $Fe(CO)_3$ cation, when treated with $NaBH_4$ in THF, yields the tricarbonyl bicyclo(5.1.0)octa-2,4-dieneiron (XIV).

Because of the different electron requirements of Mo compared to Fe, one would not expect the protonation of COT $Mo(CO)_3$ to give the classical structure XIII (M = Mo).[21] The 6π electronic preference of the molybdenum limits the choice of structures to the cyclooctatrienyl, XV, or homotropylium ion, XVI. . The nmr spectrum



XV



XVI

of protonated Mo carbonyl complex is very similar to the free cyclooctatetraene cation. The spectrum displays peaks centered at $\tau 3.72$, 5.73, 6.63, and 10.15 (areas 5:2:1:1). Only the homotropylium structure, XVI, would exhibit a proton at such high field. The planar cyclooctatrienyl structure, XV, may be excluded because this should have magnetically equivalent H_a and H_b methylene protons. The peaks have been assigned in the same manner as in the free ion. The large chemical shift difference between "inside" and "outside" protons of 3.52 ppm has been again attributed to a ring current in the tropylium ring.

A large part of the support for the homotropylium ion structure is based on the assumption of ring current to explain the large difference in chemical shift of protons H_a and H_b. Evidence for the validity of this assumption could be found by considering a series of related structures in which the geometry of the carbon skeleton remains fixed, but in which the two protons in question experience different shielding due to the differences in ring current. Johnson and Bovey[25] have deduced that in a constant applied magnetic field the chemical shift (δ) of a proton due to the presence of a ring current in the molecule is related in the following manner:

$$\delta \propto I \times f(x,y,z)$$

where I is the magnitude of the ring current and f(x,y,z) is a function of the coordinates of the position of the proton relative to the ring.

Pettit has reasoned,[22] by using the above equation, that, if one looks at compounds with varying amounts of ring current, there should be a linear relationship between δ, the chemical shift of one proton, and Δ, the difference in chemical shift between the two protons. The various metal carbonyl complexes of cyclooctatetraene do have the closely related carbon skeleton and, because of the difference in electronic requirements of the metals, different ring currents are expected. Such a plot of δ vs Δ for a series of protonated COT complexes is shown in Figure 2. The systems plotted are homotropylium (XI), the $C_8H_9^+$ $Mo(CO)_3$ cation (XVI), the $C_8H_9^+$ $Fe_2(CO)_6$ cation[13] (XVII), homotropone[26] (XVIII) and the $C_8H_9^+$ $Fe(CO)_3$ cation (XIII). A roughly linear plot is obtained which implies that the delocalization of

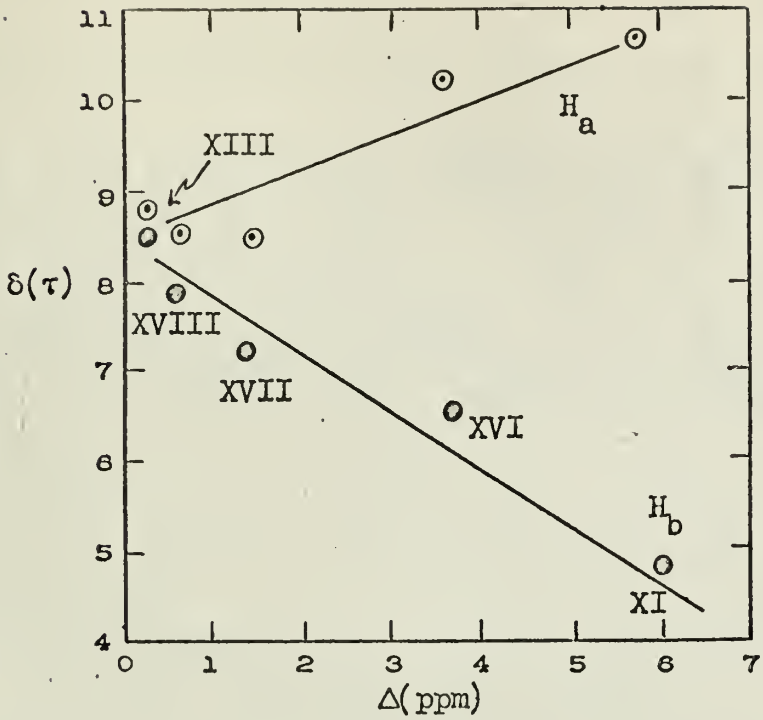
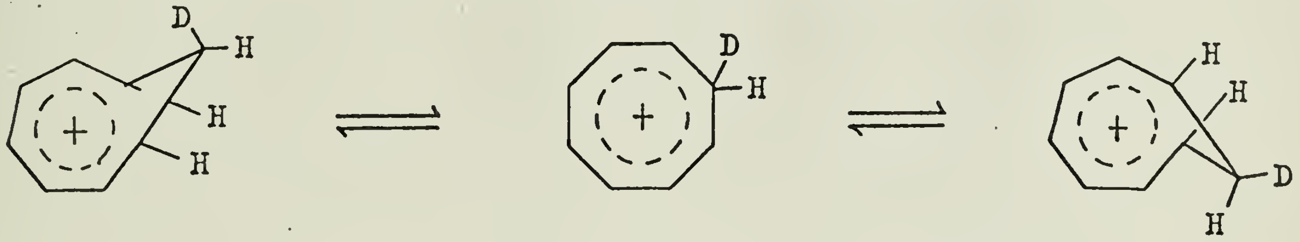


Figure 2

electrons in the free COT cation is extensive, and thereby supports the non-classical formation of the COT cation. However such a plot can be misleading because ring currents are not the only factor which cause variation in δ. The charge concentration on carbon 8 will certainly have a large effect on δ.[7]

By studying the line widths of H_a and H_b signals,[29] the first order rate constant for the ring inversion can be calculated. From the rate constant, one can calculate a minimum value of 22.3 kcal/mole for the free energy difference between the non-classical homotropylium ion (XVIIIa or XVIIIc) and classical planar cyclooctatrienyl cation (XVIIIb) assuming the equilibration is visualized to proceed through the planar form. A value of 16 kcal/mole is calculated for the protonated molybdenum complex.[21] Thus, the homotropylium structure is substantially more stable than the cyclooctatrienyl structure.



XVIIIa XVIIIb XVIIIc

BIBLIOGRAPHY

1. B. F. Hallam and P. L. Pauson, J. Chem. Soc., 642 (1958).
2. R. Pettit, J. Am. Chem. Soc., 81, 1266 (1959).
3. T. A. Manuel and F. G. A. Stone, Proc. Chem. Soc., 90 (1959); J. Am. Chem. Soc., 82, 336 (1960).
4. M. D. Rausch and G. N. Schrauzer, Chem. and Ind. (London) 957 (1959).
5. A. Nakamura and N. Hagihara, Bull. Chem. Soc. Japan, 32, 880 (1959).
6. S. Winstein, H. D. Kaesz, C. G. Kreiter, and E. C. Friedrich, J. Am. Chem. Soc., 87, 3267 (1965).
7. C. G. Kreiter, A. Maasbol, F. A. L. Anet, H. D. Kaesz, and S. Winstein, J. Am. Chem. Soc., 88, 3444 (1966).
8. B. Dickens and W. N. Lipscomb, J. Am. Chem. Soc., 83, 489 (1961); J. Am. Chem. Soc., 83, 4862 (1961); J. Chem. Phy., 37, 2084 (1962).

9. J. S. McKechnie and I. C. Paul, J. Am. Chem. Soc. to be published.
10. M. L. Maddox, S. L. Stafford, and H. D. Kaesz, Advan. Organometal. Chem., 3, 1 (1965).
11. R. T. Bailey, E. R. Lippincott, and D. Steele, J. Am. Chem. Soc., 87, 5346 (1965).
12. J. E. Mahler, D. A. K. Jones, and R. Pettit, J. Am. Chem. Soc., 86, 3589 (1964).
13. C. E. Keller, G. F. Emerson, and R. Pettit, J. Am. Chem. Soc., 88, 1388 (1966).
14. H. W. Whitlock, Jr. and Y. N. Chuah, J. Am. Chem. Soc., 86, 5030 (1964); J. Am. Chem. Soc., 87, 3605 (1965).
15. R. Burton, L. Pratt, and G. Wilkinson, J. Chem. Soc., 594 (1961).
16. R. B. King, Inorg. Chem., 2, 807 (1963).
17. F. A. Cotton, A. Davison, and J. W. Faller, J. Am. Chem. Soc., 88, 4507 (1966).
18. C. E. Keller, B. A. Shoulders, and R. Pettit, J. Am. Chem. Soc., 88, 4760 (1966).
19. J. L. von Rosenberg, Jr., J. E. Mahler, and R. Pettit, J. Am. Chem. Soc., 84, 2842 (1962).
20. C. E. Keller and R. Pettit, J. Am. Chem. Soc., 88, 604 (1966).
21. S. Winstein, H. D. Kaesz, C. G. Kreiter, and E. C. Freidrich; J. Am. Chem. Soc., 87, 3267 (1965).
22. C. E. Keller and R. Pettit, J. Am. Chem. Soc., 88, 606 (1966).
23. N. C. Deno, Prog. Phys. Org. Chem., 2, 148 (1964).
24. A. Davison, W. McFarlane, L. Pratt, and G. Wilkinson, J. Chem. Soc., 4821 (1962).
25. C. E. Johnson and R. A. Bovey, J. Chem. Phy., 29, 1012 (1958).
26. J. D. Holmes and R. Pettit, J. Am. Chem. Soc., 85, 2531 (1963).
27. S. Winstein, C. G. Kreiter, and J. I. Brauman, J. Am. Chem. Soc., 88, 2047 (1966).

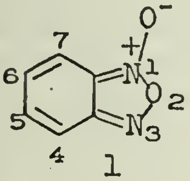
THE STRUCTURE AND REACTIONS OF BENZOFUROXANS

Reported by Robert Kalish December 12, 1966

Although furoxans have been known for over seventy years, within the last six years there has been a marked resurgence of interest in these substances. Work done prior to 1960 has been well reviewed,[1-3] and this seminar will be confined to a discussion of recent studies of the benzofuroxans, for it is here that the most definitive work has been done.

STRUCTURE OF THE BENZOFUROXANS

Since its preparation in 1894, the nature of the compound obtained from the pyrolysis of o-nitrophenylazide, the oxidation of o-benzoquinone dioxime or the alkaline hypochlorite oxidation of o-nitroaniline, and generally called benzofuroxan, has been the subject of much controversy.[1-3] Among the structures that have been proposed for this compound are the benzofurazan-N-oxide (1), o-dinitrosobenzene (2), dioxadiazine (3), and others, 4, 5 and 6.



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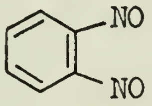

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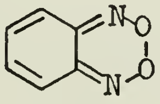

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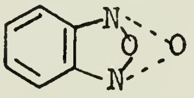

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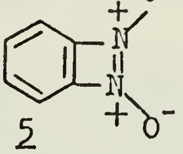

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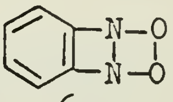

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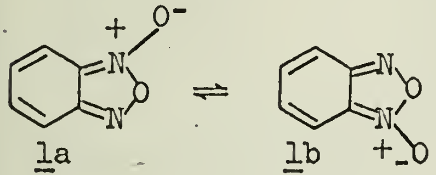
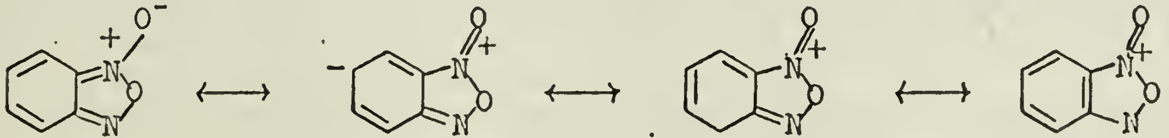
The unsymmetrical, quinoidal benzofurazan-N-oxide structure (1) is best in accord with the observed chemical and physical properties of benzofuroxan, but fails to account for the fact that only a single compound is obtained upon alkaline hypochlorite oxidation of 4- or 5- substituted 1,2-nitroanilines or pyrolysis of 4- or 5- substituted 1,2-nitrophenylazides. This absence of isomers led many early workers to favor structures 2-6, which have a symmetrical N_2O_2 grouping.[1-3] In 1933, however, Hammick proposed that a facile equilibrium of the form 1a ⇌ 1b exists between isomeric benzofuroxans thus preventing their separation.[4] This view later came into general acceptance although Boyer continued to refer to benzofuroxans as o-dinitroso compounds.[2]

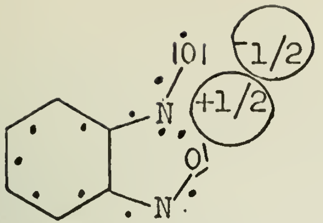


Recent variable-temperature nmr studies have confirmed that, in solution, benzofuroxans do possess the unsymmetrical benzofurazan-N-oxide nuclear configuration, and that failure to isolate isomeric benzofuroxans is due to rapid equilibration between them.[5-11] Thus at -50° benzofuroxan possesses an ABCD H^1 nmr spectrum; at about 5° the spectrum begins to collapse into an A_2B_2 spectrum which then becomes well-defined at temperatures above 60° indicating rapid equilibration on the nmr time scale ($k > \sim 10^3 sec^{-1}$).[5-10] Further evidence for an unsymmetrical structure is provided by the O^{17} nmr spectrum of benzofuroxan which at 0° shows two different types of oxygen atoms located -475 and -350 ppm away from H_2O^{17}; the two lines coalesce at 40°.[9] Similar results have been obtained for many other benzofuroxans.[5-8]

Although their nuclear configuration has been established, the ground state electronic structure of the benzofuroxans is still not well understood. A priori, benzofuroxan and its derivatives would be expected to possess a delocalized 12-π electron system, and to be a resonance-hybrid representable by canonical forms such as 7-10.



Linnett, using his double-quartet (non-pairing) theory of bonding, has recently suggested the importance of structures involving bonds containing an odd number of electrons such as 11-13[12,13] (the dots represent single electrons of unpaired spin and the formal charges are circled).



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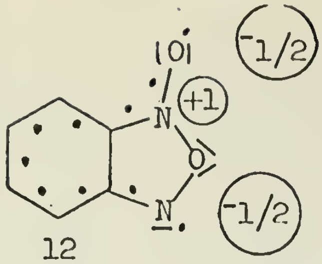

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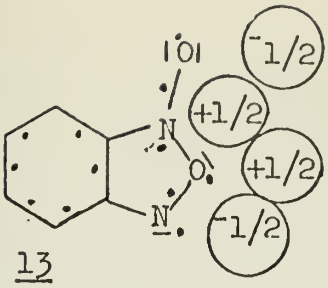

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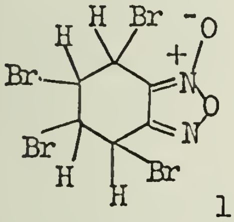
In these structures interelectronic repulsion is minimized as there is a reduction in the number of electron pairs in the same bond, perhaps explaining why the observed benzofurazan-N-oxide structure is preferred to the o-dinitrosobenzene one, in which there is benzenoid resonance energy and no formal charge separation.

From an extensive study of the chemical shifts and coupling constants in various benzofuroxans, Boulton and Katritzky have concluded that there is partial bond-fixation in the benzofuroxan molecule giving it o-quinoidal character (structure 7). For example, the ortho coupling constants across the 4-5 and 6-7 bonds are significantly larger than those across the 5-6 bonds (9.2 versus 6.4 cps in benzofuroxan); thus J is larger across the bonds of expected higher order similar to results obtained for benzofurazan and naphthalene.[14]

The reaction of benzofuroxan with bromine to yield the tetrabromo adduct 14 has been taken to indicate an o-quinoidal electronic system.[4] Little is known about the reactions of benzofuroxan with electrophilic reagents; nitration with a nitric-sulfuric acid mixture yields either 4-nitrobenzofuroxan or 4,6-dinitrobenzofuroxan,[15] and may be an example of an electrophilic aromatic substitution reaction.



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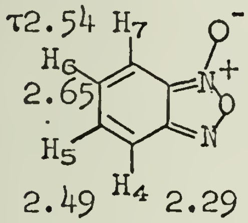
In acetone solution the ring protons of benzofuroxan absorb at a lower field than those of benzene (τ 2.69).[8] Katritzky attributes this to a combination of inductive, resonance and anisotropic effects together with an upfield shift due to a lesser ring-current in benzofuroxan than in benzene; he presents no evidence for this view, however. Furthermore, in benzofuroxan there is a greater upfield shift of the protons at the 4 and 6 positions than for the proton at the 5 position relative to the model compound benzofurazan [τ ($H_{5,6}$) 2.40; τ($H_{4,7}$) 2.04].[8] Katritzky believes that this indicates the relative importance of canonical forms 8 and 9. The magnitude of this N-oxide donation effect is surprisingly large, however, and Katritzky's reasoning assumes that the main contribution to the upfield shift is in the local diamagnetic term.



X-ray studies of benzofuroxan,[16] 5-bromobenzofuroxan[17] and 5-chlorobenzofuroxan[17] demonstrate that these compounds possess the planar benzofurazan-N-oxide configuration in the solid state. Unfortunately, no bond lengths were reported for benzofuroxan, and thermal disorder in the 5-halobenzofuroxans made the observed bond lengths too uncertain to allow meaningful conclusions to be drawn about the electronic structure of these compounds. Accurate X-ray data for benzofuroxan and its derivatives would greatly aid in the elucidation of the ground state electronic structure of these substances.

MECHANISM OF THE BENZOFUROXAN INTERCONVERSION

The benzofuroxan interconversion 1a $\rightleftharpoons$ 1b has long been assumed to involve o-dinitrosobenzene (2) either as an intermediate or as a representation of the transition state. However, other symmetrical species such as 3-6 must also be considered as possible representations of the transition state.

Variable-temperature nmr kinetic investigations have recently shed much light on the mechanism of this rearrangement.[8,11] The relevant kinetic data is presented in table 1. All of the interconversions are first-order in the benzofuroxan with no observable acid catalysis.

Table 1

Compound	k (sec^{-1})	Ea(kcal-mole^{-1})^{a}	ΔS^{*} (eu)^{b}	ΔG^{*} (kcal-mole^{-1})
benzofuroxan$^{d,8-10}$	7.7×10^{3} (45°)	17.2 ± 1.5	$+10 \pm 4$	15 ± 1
4,7-dibromobenzofuroxan^{c,11}	1.7×10^{2} (30°)	16.3 ± 0.5	+4	15.1 ± 0.5
4,7-dichlorobenzofuroxan^{c,11}	2.2×10^{2} (30°)	16.5 ± 0.5	+5	15.0 ± 0.5
5,6-dichlorobenzofuroxan^{c,11}	5.3×10^{3} (30°)	15.0 ± 0.5	+6	13.2 ± 0.5

a. $Ea = \Delta H^{*} + RT \sim \Delta H^{*}$ as $RT \sim 0.6$ kcal at room temperature.

b. Evaluated from the absolute rate theory expression $\Delta S^{*} = 4.576 \log (A/T) - 49.2$ at the temperature indicated.

c. Data obtained from the analysis of the H^{1} line shapes in the $-40°$ to $+50°$ region assuming the existence of a single, symmetrical intermediate; if no intermediate is involved the values of k are too large by a factor of 2 and those of ΔS^{*} by 1.4 eu.

d. Data obtained from variable-temperature H^{1} and O^{17} nmr studies.

Mallory suggests that the positive values obtained for ΔS^{*} indicate that the rate-determining step in the equilibration involves the formation of a ring-opened transition state resembling *o*-dinitrosobenzene.[11] Rate-determining formation of a transition state similar to species 4 or 6 would be expected to result in a negative ΔS^{*} as a bicyclic transition state is being formed from a monocyclic ground state.

The relatively small values of ΔH^{*} do not appear to be consistent with the rate-determining formation of high energy species such as 3-6, which have been calculated to have energies at least 64, 78, 20 and 100 kcal-mole^{-1} higher than 2,[18] respectively, but are consistent with the minimal strain and benzenoid stabilization of a transition state resembling an *o*-dinitrosobenzene.

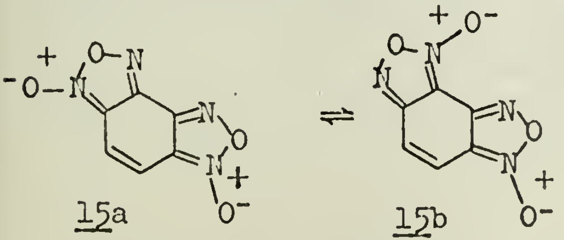
More conclusive evidence for an *o*-dinitrosobenzene-like transition state comes from an examination of the relative rates of equilibration of 4,7-dibromo-, 4,7-dichloro- and 5,6-dichlorobenzofuroxan.[11] According to Mallory, ring-opening of a benzofuroxan to such a transition state should result in an increase in the spatial requirements of the N_2O_2 group due to non-bonded interactions between the nitrogen and oxygen atoms that were bonded together in the benzofuroxan. The presence of bulky groups in the 4 and 7 positions would thus be expected to retard the rate of interconversion *via* ring-opening. This has been found to be the case (table 2).

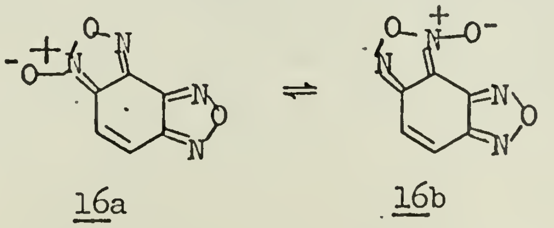
Table 2

4,7 Substituent (Compound)	k relative	van der Waals radius of substituent
Br (4,7-dibromobenzofuroxan)	1	1.95 A
Cl (4,7-dichlorobenzofuroxan)	1.3	1.80 A
H (5,6-dichlorobenzofuroxan)	31	1.2 A

These results are not compatible with rate-determining formation of a bicyclic transition state such as 4 in which the steric requirements of the N_2O_2 group should be smaller than in the ground state benzofuroxan.

Studies of the interconversions of furoxanofuroxan (15a ⇌ 15b) and furazanofuroxan (16a ⇌ 16b)[19] shed further light on the mechanism of the benzofuroxan interconversion. The free energies of activation for these two processes (21.7 ± 0.3 and 21.8-22.2 ± 2 kcal-mole^{-1}, respectively) are considerably higher than those for the simple benzofuroxan interconversion (about 15 kcal-mole^{-1}). This finding is in accord with a ring-opened transition state resembling *o*-dinitrosobenzene, assuming


15a ⇌ 15b


16a ⇌ 16b

that similar mechanisms are operative in all cases with similar entropies of activation. The benzenoid stabilization energy available to the o-dinitrosobenzene transition state for process 1a ⇌ 1b would serve to make ΔG^* ($\overline{\Delta H}^*$) lower for this rearrangement than for processes 15a ⇌ 15b and 16a ⇌ 16b in which the transition state lacks benzenoid stabilization energy. Separation of ΔG^* into ΔH^* and ΔS^* terms will be necessary to confirm this supposition, for it is conceivable that variations in ΔS^* account for the variations in ΔG^*.

The disubstituted aliphatic furoxans 17 and 18, long known to possess the furazan-N-oxide structure,[1-3] undergo interconversion upon heating by a mechanism similar to that postulated for the benzofuroxans.[18] These interconversions are slow enough to allow separation of the isomers and use of kinetic methods other than nmr. Both interconversions follow first-order kinetics with no detectable side reactions. The pertinent kinetic parameters are given in table 3.

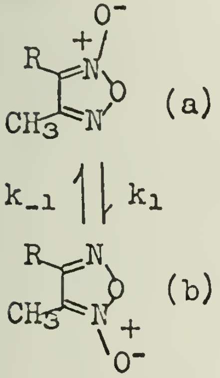
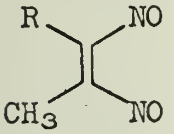


Table 3

	Reaction	$k_1 \times 10^5$ (sec^{-1})	E_a(kcal-mole^{-1})	ΔS^*(eu)
17: R=C_6H_5	17a ⇌ 17b	13.7$\pm$0.3 (140.2°)	34.2$\pm$0.3	+4$\pm$0.9
18: R=C_2H_5	18a ⇌ 18b	14.7$\pm$0.4 (140.8°)	35.3$\pm$0.4	+7$\pm$0.9

By analogy with the benzofuroxans, the most likely mechanism for these interconversions involves the rate-determining formation of a ring-opened transition state resembling a 1,2-dinitrosoalkene, 19, which can then recyclize to either isomeric furoxan. Other possible models for the transition state are 20-23. Bond energy and strain energy considerations similar to those used for the benzofuroxan interconversion eliminate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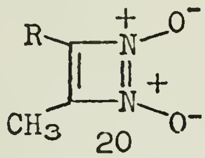
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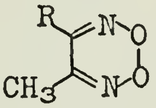
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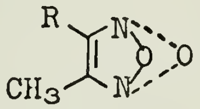
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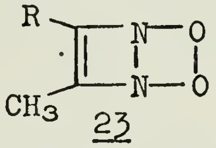
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species such as 20-23, leaving 19 as the most reasonable model for the transition state.[18] The observed positive values of ΔS^* are also in accord with a ring-opened transition state. Furthermore, the large differences in activation energy between the interconversions of the benzofuroxans and the simple furoxans is readily explicable on the basis of the postulated mechanism: whereas an o-dinitrosobenzene transition state possesses benzenoid stabilization energy relative to the benzofuroxan ground state, a 1,2-dinitrosoalkene transition state lacks such stabilization energy relative to the aliphatic furoxan ground state.

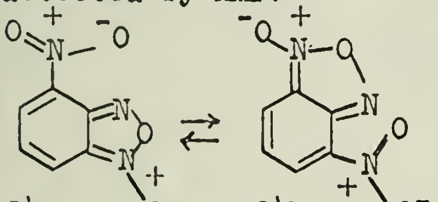
Although all of the evidence cited points to the rate-determining formation of a ring-opened transition state resembling o-dinitrosobenzene, little is known as to its exact nature. The relatively small values of ΔS^* for the benzofuroxan interconversion indicate that there may not be much more vibrational and internal rotational freedom in the transition state than in the ground state, and are in accord either with a partially ring-opened transition state resembling o-dinitrosobenzene in which N-O bond breaking is not complete, or with a transition state closely resembling o-dinitrosobenzene in which rotation of the nitroso groups is restricted. Furthermore, the effect of solvent changes on the rate of the benzofuroxan interconversion has not been determined, and the small positive entropies of activation may be due in part to a diminution of solvent ordering in the transition state as could be expected in going from a dipolar benzofuroxan to a formally neutral o-dinitrosobenzene. However, the rates of equilibration of aliphatic furoxans 17 and 18 are identical in ethylene glycol monomethyl ether, 1,1,2,2-tetrachloroethane and N,N-dimethylformamide.[18] In the absence of proper models the meaning of this finding is unclear, but may indicate that, at least for aliphatic furoxans, the charge separation in the transition state is similar to that in the ground state. A study of the rate of benzofuroxan equilibration as a function of the electronic nature of a 5 or 6 substituent (to minimize steric effects) would be useful in determining the degree of charge separation in the transition state.

Both Mallory and Katritzky believe that these interconversions involve one or more o-dinitrosobenzene intermediates.[8,11] However, all attempts to chemically trap such species by the use of reagents which normally react with nitroso groups have

failed.[10] Thus benzofuroxan is neither oxidized by nitric or peracetic acid, nor converted into an azo compound by reaction with aniline. In order to explain these results, Mallory has postulated that these bimolecular trapping reactions are too slow to successfully compete with the rapid, unimolecular recyclization of o-dinitrosobenzene to benzofuroxan.[11] It is also conceivable that intramolecular nitroso group association or other electronic properties of o-dinitrosobenzenes preclude their reaction as normal nitroso compounds. Intramolecular trapping experiments are clearly needed.

REACTIONS OF NITRO-SUBSTITUTED BENZOFUROXANS

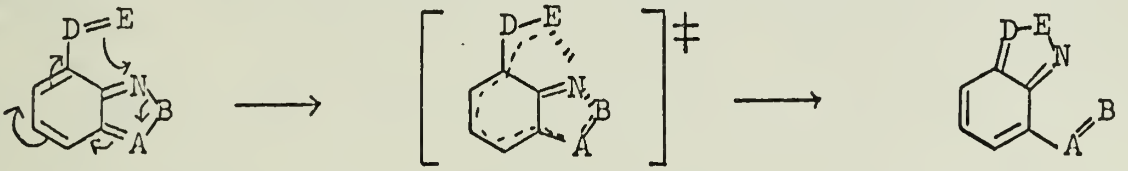
In their studies of the nitrobenzofuroxans Katritzky and Boulton discovered a new type of benzofuroxan rearrangement.[20] In addition to the 1a ⇌ 1b type of rearrangement, it might be expected that 4-nitrobenzofuroxans could undergo a degenerate rearrangement of the form 24a ⇌ 24b. However, the nmr spectrum of 4-nitrobenzofuroxan displays a single, sharp ABC pattern in the -60° to +180° region indicating that such a rearrangement does not readily occur on the nmr time scale.[8] From this data the free energy of activation for this reaction was estimated to be greater than 20 kcal-mole^{-1}. Similar results were obtained for 4,6-dinitrobenzofuroxan.[8] It is possible that these rearrangements do occur but are too slow to be detected by nmr.



24a 24b

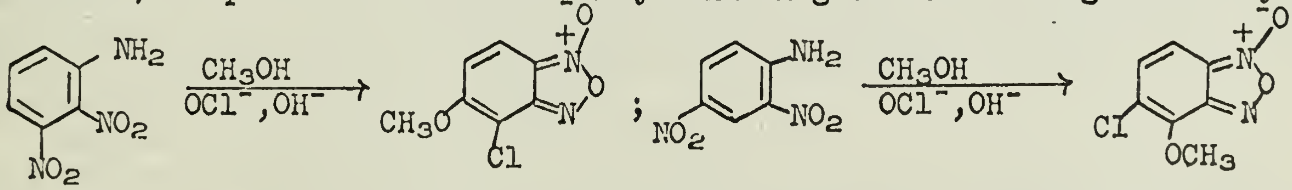
Katritzky and Boulton have found that both 5-methyl- and 5-chloro-4-nitrobenzofuroxan undergo this type of rearrangement.[20] Thus 5-methyl-4-nitrobenzofuroxan quantitatively rearranges to 7-methyl-4-nitrobenzofuroxan upon heating for two hours at 80° or for three minutes at 120°. Similarly, 5-chloro-4-nitrobenzofuroxan is completely converted into 7-chloro-4-nitrobenzofuroxan upon heating at 100° for one hour. Whether or not these latter two rearrangements are slow on the nmr time scale has not been reported.

Further work by Katritzky and co-workers has demonstrated that this rearrangement is but one example of the more general rearrangement shown in equation 1 in which A and D may be N, $N^{+}-O^{-}$ or CR, and B and E may be O, NR or CHR.[21] The mechanism shown is reasonable but, in the absence of any mechanistic studies, speculative.

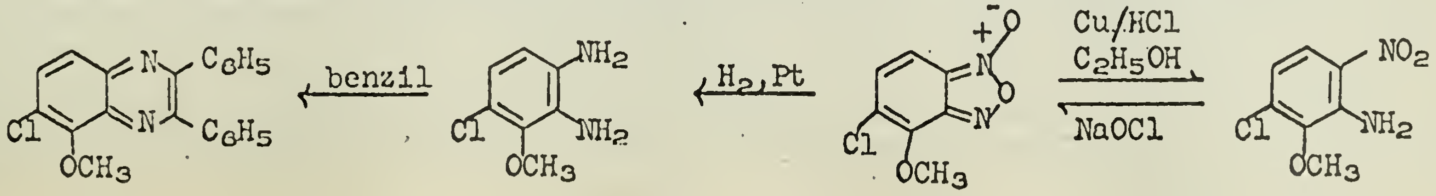
(1) 

The reactions of methanolic solutions of 2,4-dinitroaniline and 2,3-dinitroaniline with aqueous sodium hypochlorite at 50° to yield chloromethoxybenzofuroxans have recently been reinvestigated by Mallory and Varimbi,[22] who found the previous structural assignments of these products[23],[24] to be incorrect.

The product formed in 30-60 percent yield from the oxidation of 2,4-dinitroaniline was found to be 5-chloro-4-methoxybenzofuroxan, and the product formed in 20 percent yield from 2,3-dinitroaniline was identified as 4-chloro-5-methoxybenzofuroxan (equation 2). Replacement of methanol by ethanol gives the analogous ethoxy compounds. T

(2) 

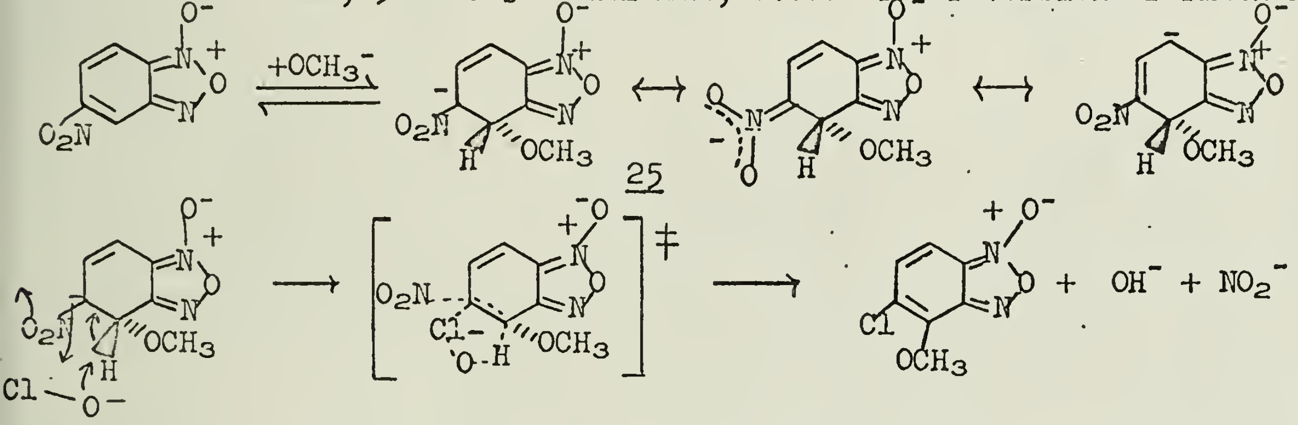
structures of these two chloromethoxybenzofuroxans were determined from their IR spectra, their nmr spectra (which in both cases show an AB pattern for the ring protons with J=9.5 cps indicative of ortho protons), and by means of a series of chemical interconversions illustrated in equation 3 for 5-chloro-4-methoxybenzofuroxan.

(3) 

The reactions leading to these chloromethoxybenzofuroxans are not those of the dinitroanilines themselves, but rather are reactions characteristic of the nitrobenzofuroxans initially formed by hypochlorite oxidation of the dinitroanilines.[22] Thus methanolic potassium hydroxide solutions of both 5-nitro- and 4-nitrobenzofuroxan are converted into 5-chloro-4-methoxybenzofuroxan and 4-chloro-5-methoxybenzofuroxan in 37 percent and 40 percent yield, respectively, upon treatment with aqueous sodium hypochlorite. Furthermore, compounds which are related to 2,4-dinitroaniline such as 2,4-dinitrophenol, 3,5-dinitroaniline and 2,4-dinitro-N-phenylaniline, but which have structural features that preclude benzofuroxan formation give no chloromethoxy products under the conditions of the reaction.

The presence of a furoxan heterocycle fused to the six-membered ring is not necessary for the haloalkoxy substitution reaction to occur; other nitrogen heterocycles can serve equally well.[22,25] Thus 5-nitro-2-phenylbenzotriazole gives a 70 percent yield of 4-methoxy-5-chloro-2-phenylbenzotriazole, and 5-nitrobenzofurazan is converted into 5-chloro-4-methoxybenzofurazan in 45 percent yield.

The mechanism postulated by Mallory for this reaction is presented for the case of 5-nitrobenzofuroxan; analogous mechanisms can be written for the reactions of 4-nitrobenzofuroxan, 5-nitrobenzofurazan, etc.. The reversible formation of adduct 25



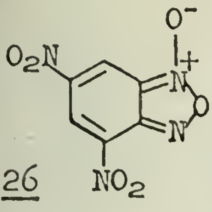
in which the negative charge is highly delocalized is reasonable by analogy to other systems,[26] and is further supported by the development of a deep red color upon dissolution of 5-nitrobenzofuroxan in alkaline methanol; this color fades rapidly upon addition of hypochlorite. The reaction of 25 with hypochlorite is postulated as occurring in a concerted fashion as shown. A stepwise mechanism involving initial attack by 25 on hypochlorous acid is also reasonable. A mechanism involving *cine*-substitution of a nitro group by a methoxy group[27] followed by chlorination *ortho* to the methoxy group is excluded by the observation that 5-methoxybenzofuroxan does not undergo chlorination under the reaction conditions. Mechanisms involving initial replacement of the nitro group by a chloro group are excluded as 5-chlorobenzofuroxan does not give 5-chloro-4-methoxybenzofuroxan when subjected to the conditions of the reaction.

Further studies by Mallory have indicated that hypobromite can be used *in lieu* of hypochlorite.[25] Attempts to use hypoiodite have been unsuccessful. Alcohols other than methanol can also be used in the reaction.[25] The use of ethanol has already been noted; reaction of 4-nitrobenzofuroxan with alkaline hypochlorite in isopropanol gives 4-chloro-5-isopropoxybenzofuroxan, albeit in only 11 percent yield. No haloalkoxy substitution reaction has yet been successfully carried out in *t*-butanol in accord with the proposed mechanism.

Isolation of adduct 25 and demonstration that it is converted by hypochlorite into 5-chloro-4-methoxybenzofuroxan at a rate no less than the overall rate of the reaction is desirable, for it is possible that formation of 25 is a reversible side reaction and that 5-nitrobenzofuroxan is converted into 5-chloro-4-methoxybenzofuroxan *via* another route.

Further indication that nitrobenzofuroxans can form Meisenheimer complexes with base comes from studies of 4,6-dinitrobenzofuroxan, 26. Ever since its preparation in 1899, the acidic character of this substance has intrigued investigators. It acts as an acid to bicarbonate solutions displacing carbon dioxide and giving stable salts, whereas π-acids of comparable or greater strength such as 1,3,5-trinitrobenzene and 5,6-dinitrobenzofuroxan do not, and it is appreciably more acidic than water.[28,29]

Possible structures for the anion formed from the reaction of 4,6-dinitrobenzofuroxan with hydroxide are 27-30. Elemental analyses of the potassium and rubidium salts are in agreement with structures 28-30.[28,29] Acidification of the potassium salt of 26 with deuterosulfuric acid regenerates 26 with no deuterium incorporation



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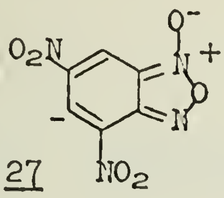

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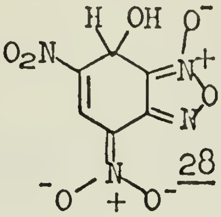

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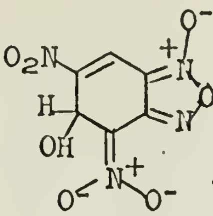

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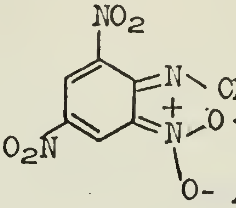

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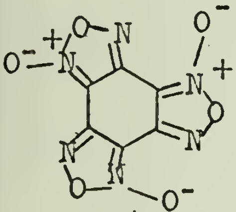
ruling out the possibility that the anion is a stable hydrate of 27.[28] Preparation of the anion in H_2O^{18} and conversion back to 26 by acidification reveals no O^{18} incorporation which would be expected from 30, which contains oxygen from the water solvent.[28]

The H^1 nmr spectrum of the anion in dimethyl sulfoxide is consistent with either structure 28 or 29 [singlet at τ 1.07 (ring vinyl H); two doublets centered at τ 3.80 ($\underline{H}$-C-OH) and τ 3.45 (-O$\underline{H}$), J=7cps].[28,29] From a consideration of the various resonance forms that can be drawn for 28 and 29, it is suggested that 28 is the more likely structure.[28,29]

Many nitrobenzofuroxans have been found to be strong π-acids giving complexes with a variety of aromatic hydrocarbons. The equilibrium constants for complex formation between some of these nitrobenzofuroxans and naphthalene in chloroform solution have been determined spectrophotometrically, and an order of increasing π-acceptor ability has been established:[30] 2,4,7-trinitrofluorenone < 5,6-dinitrobenzofuroxan < 1,3,5-trinitrobenzene < 4,6-dinitrobenzofuroxan < benzotrifuroxan. Benzotrifuroxan (31) is unique in that it forms stable complexes with over fifty aromatic hydrocarbons such as benzene, tetrahydronaphthalenes and alkyl benzenes, compounds which do not readily form solid complexes with other π-acceptors. The structures of several of these complexes,[31,32] as well as that of benzotrifuroxan itself,[33] have been determined by X-ray crystallography. In all cases the benzotrifuroxan molecule is planar and possesses the benzotrifurazan-N-oxide structure, 31. From the observed bond-lengths, bond-orders have been calculated, and these have been taken to indicate appreciable electron delocalization in benzotrifuroxan.[33]



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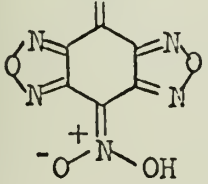
Recent studies of the reactions of benzotrifuroxan with trivalent phosphorous compounds have demonstrated that whereas the reaction of benzotrifuroxan with triethylphosphite gives deoxygenation with concurrent formation of a 1:1 adduct between benzotrifurazan and triethylphosphate,[34] the reaction of benzotrifuroxan with triphenylphosphine gives a large number of colored complexes, the structures of two of which have been shown by X-ray crystallography to be 32 and 33.[35]



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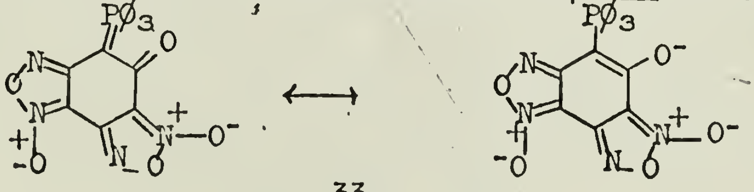

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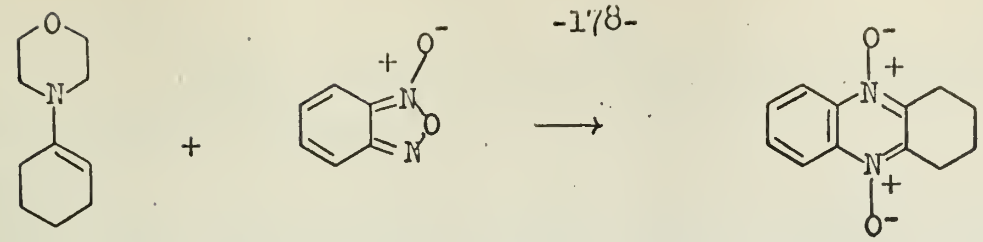
MISCELLANEOUS REACTIONS OF THE BENZOFUROXANS

Other recently reported reactions of benzofuroxan include reaction with enamines to give quinoxaline-di-N-oxides (equation 4),[36] and reaction with methyl- and benzyltrifluoromethanesulfonate to give salts of 1-hydroxybenzimidazole-3-oxides; Katritzky postulates that this reaction occurs *via* initial N-alkylation with subsequent rearrangement (equation 5).[37]

(4)



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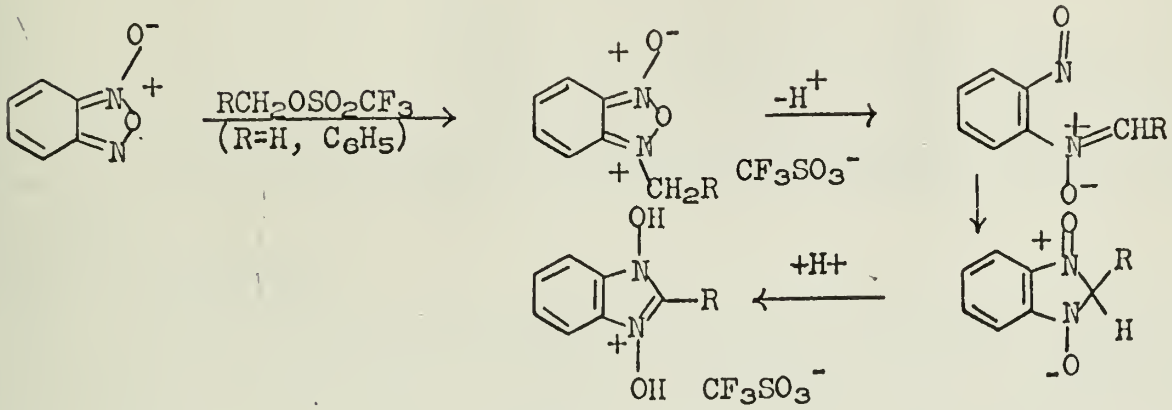


BIBLIOGRAPHY

1. J. V. R. Kaufman and J. P. Picard, Chem. Rev., 59, 429 (1959).
2. J. H. Boyer in "Heterocyclic Compounds", Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 463.
3. L. C. Behr in "The Chemistry of Heterocyclic Compounds", Vol. 17, R. H. Wiley, Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p. 295.
4. D. L. Hammick et al., J. Chem. Soc., 3308 (1931).
5. G. Englert, Z. Elektrochem., 65, 854 (1961).
6. G. Englert, Z. Naturforsch, 16b, 413 (1961).
7. G. Englert and H. Prinzbach, Z. Naturforsch, 17b, 4 (1962).
8. A. R. Katritzky et al., J. Chem. Soc., 197 (1963).
9. P. Diehl et al., Helv. Chim. Acta, 45, 504 (1962).
10. F. B. Mallory and C. S. Wood, J. Org. Chem., 27, 4109 (1962).
11. F. B. Mallory et al., J. Am. Chem. Soc., 87, 5433 (1965).
12. J. W. Linnett, "The Electronic Structure of Molecules", John Wiley and Sons, Inc., New York, N. Y., 1964.
13. J. W. Linnett and R. M. Rosenberg, Tetrahedron, 20, 53 (1964).
14. B. Dischler and G. Englert, Z. Naturforsch, 16a, 1180 (1961).
15. P. Drost, Ann., 307, 49 (1899).
16. R. Hulme, Chem. Ind. (London), 42 (1962).
17. D. Britton and W. E. Noland, J. Org. Chem., 27, 3218 (1962).
18. F. B. Mallory and A. Cammarata, J. Am. Chem. Soc., 88, 61 (1966).
19. A. J. Boulton et al., J. Chem. Soc., 5958 (1958).
20. A. J. Boulton and A. R. Katritzky, Rev. Chim. Acad. Rep. Populaire Roumaine, 17, 691 (1962).
21. A. R. Katritzky et al., Angew. Chem., 76, 816 (1964); A. R. Katritzky et al., J. Chem. Soc., in press.
22. F. B. Mallory and S. P. Varimbi, J. Org. Chem., 28, 1656 (1963).
23. A. G. Green and F. M. Rowe, J. Chem. Soc., 101, 2452 (1912).
24. L. K. Dyall and K. H. Pausacker, Australian J. Chem., 11, 491 (1958).
25. F. B. Mallory et al., J. Org. Chem., 29, 2605 (1964).
26. J. Kapecki, University of Illinois Organic Seminars, p. 154, January 6, 1966.
27. D. C. Morrison, J. Org. Chem., 27, 296 (1962).
28. W. P. Norris and J. Osmundsen, J. Org. Chem., 30, 2407 (1965).
29. A. J. Boulton and D. P. Clifford, J. Chem. Soc., 5414 (1965).
30. A. S. Bailey and J. R. Case, Tetrahedron, 3, 113 (1958).
31. B. Kamenar and C. K. Prout, J. Chem. Soc., 4838 (1965).
32. C. K. Prout and H. M. Powell, J. Chem..Soc., 4882 (1965).
33. H. H. Cady et al., Acta Cryst., 20, 336 (1966).
34. A. S. Bailey and J. M. Evans, Chem. Ind. (London), 1424 (1964).
35. A. S. Bailey et al., Chem. Commun., 664 (1966).
36. M. J. Haddadin and C. H. Issidorides, Tetrahedron Letters, No. 36, 3252 (1965).

J. Boulton et al., Chem. Commun., 741 (1966).

RECENT STUDIES OF α-HALOALKYLLITHIUM COMPOUNDS

Reported by Spencer M. Krueger December 15, 1966

INTRODUCTION

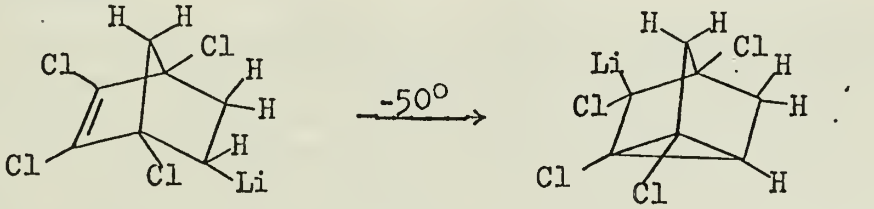
Organolithium chemistry has developed into an area of intensive research.[1,2] In particular, α-haloalkyllithiums have been of interest because of the possibility of carbene formation.[3,4,5] Carbene intermediates have recently been distinquished from carbenoid intermediates by Closs who proposed the term "carbenoid" for the description of "intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species."[6] Recent evidence for α-haloalkyllithiums as carbenoid intermediates will be discussed in this seminar.

SYNTHESIS AND STABILITY

Prior to 1964 α-haloalkyllithiums were postulated only as transient intermediates in the preparation of carbenes. Recently, however, several stable α-chloroalkyllithiums have been prepared by different routes. By the halogen-metal exchange reaction (1) of methyllithium with trichlorobromomethane in ether at -115°, Miller and Whalen prepared trichloromethyllithium.[7] From chloroform and either methyl- or n-butyllithium, Köbrich prepared the same compound, which was stable at -105° in THF.[8] Köbrich also prepared dichloromethyllithium by the hydrogen-metal interconversion (metalation) from methylene chloride and n-butyllithium in THF at -60° (2).[9] Hoeg and Lusk reported the synthesis of α,α-dichlorobenzyllithium, diphenylchloromethyllithium, trichloromethyllithium, and dichloromethyllithium in THF at -100°.[10] Recently, Schlosser has reported a unique rearrangement of a norbornene derivative to an α-chlorolithium compound (3).[11] These compounds have been identified by carbonation to the acids, by hydrolysis with hydrogen-lithium exchange, and by nucleophilic displacement on alkyl halides. The products then were identified by spectral and chemical means.

$$CH_3Li + CBrCl_3 \longrightarrow CCl_3Li + CH_3Br \qquad (1)$$

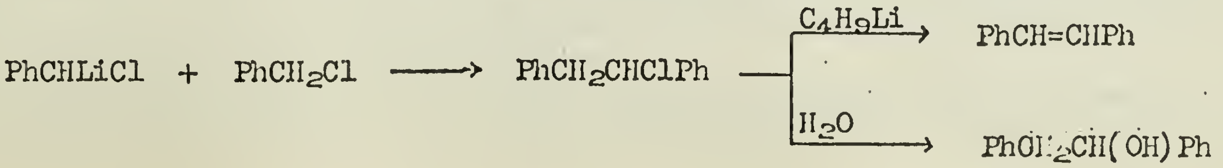
$$\underline{n}\text{-}C_4H_9Li + CH_2Cl_2 \longrightarrow CCl_2HLi + \underline{n}\text{-}C_4H_{10} \qquad (2)$$



(3)

The stability of the α-halolithium compounds is strongly dependent upon the reaction conditions.[12,13] Since the primary mode of decomposition is the formation of dimers (4), many workers have used the dimerization as evidence for a carbene intermediate.[14-16] Hoeg and Lusk have shown that in the case of the reaction of benzyl chloride with n-butyllithium in THF, the dimerization is not due to the formation of an intermediate carbene.[12] The isolation of 1,2-diphenylethanol suggested to them that α-chlorobibenzyl was a possible intermediate (5). By adjusting the stoichiometry (2 moles benzyl chloride per mole of butyllithium) and the reaction conditions, they were able to isolate α-chlorobibenzyl in over 80% yield, based on reacted benzyl chloride. A carbene mechanism, according to (6), would give a maximum yield of 50%. Hoeg did not consider a carbene reaction with insertion into either the carbon-hydrogen or carbon-chloride bond of benzyl chloride (7). Carbenes, however, could not be captured using cyclohexene as a carbene trap.

$$2PhCHClLi \longrightarrow PhCH{=}CHPh + 2LiCl \qquad (4)$$



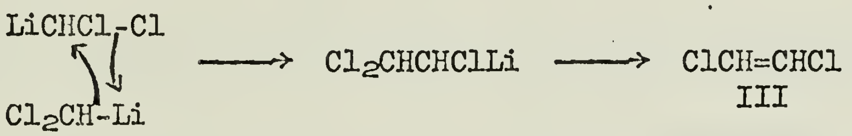
$$PhCHLiCl + PhCH_2Cl \longrightarrow PhCH_2CHClPh \begin{cases} \xrightarrow{C_4H_9Li} PhCH{=}CHPh \\ \xrightarrow{H_2O} PhCH_2CH(OH)Ph \end{cases} \qquad (5)$$

$$\begin{tikzcd}[column sep=small] \underset{(I)}{\mathrm{PhCHLiCl}} \arrow[r] & \mathrm{PhCH:} \arrow[r, "(I)"] & \mathrm{PhCHLiCHClPh} \arrow[r, "-\mathrm{LiCl}"] \arrow[dr, "\mathrm{H_2O}"'] & \mathrm{PhCH{=}CHPh} \\ & & & \mathrm{PhCH_2CH(OH)Ph} \end{tikzcd} \quad (6)$$

$$\mathrm{PhCHLiCl} \longrightarrow \mathrm{PhCH:} \xrightarrow{\mathrm{PhCH_2Cl}} \mathrm{PhCH_2CHClPh} \quad (7)$$

Köbrich investigated the decomposition of dichloromethyllithium in THF at -55°.[13] He found that at short reaction times the ratio of the number of moles of lithium chloride liberated per mole of dichloromethyllithium was larger at higher concentrations of α-haloalkyllithium. This concentration dependence suggested that the decomposition did not proceed via a free carbene as shown below (8), since such a mechanism would predict a first order decomposition. In other words, various concentrations should produce colinear curves at short reaction times. This was not observed. Köbrich argued that if the decomposition proceeds from the α-haloalkyllithium monomer, larger concentrations should decrease the rate of decomposition since the degree of association might be larger. The degree of aggregation of α-haloalkyllithiums is not known, although n-butyllithium is known to be dimeric in ether and associated into larger aggregates in hexane.[17] If, however, decomposition proceeds via a dimer (9), in which one molecule acts as a nucleophile while the other functions as an electrophile, larger concentrations should increase the ratio of moles LiCl/moles $LiCHCl_2$, as observed. A similar increase would be observed in a common second order reaction.

$$\underset{\mathrm{II}}{\mathrm{LiCHCl_2}} \xrightarrow[\mathrm{slow}]{-\mathrm{LiCl}} \mathrm{:CHCl} \xrightarrow[\mathrm{fast}]{\mathrm{II}} \mathrm{Cl_2CHCHClLi} \xrightarrow{-\mathrm{LiCl}} \mathrm{ClCH{=}CHCl} \quad (8)$$



$$\begin{matrix}\mathrm{LiCHCl{-}Cl} \\ \mathrm{Cl_2CH{-}Li}\end{matrix} \longrightarrow \mathrm{Cl_2CHCHClLi} \longrightarrow \underset{\mathrm{III}}{\mathrm{ClCH{=}CHCl}} \quad (9)$$

Köbrich also studied the decomposition of dichloromethyllithium at -74° as a function of the THF/ether ratio.[13] An outstanding stabilizing effect in THF was detected. When the THF is diluted with 80% ether decomposition is rapid. Köbrich attributed much of the decomposition which occurs at short reaction times to a temperature increase caused by the exothermic formation of lithium chloride.[9] THF stabilized the dichloromethyllithium as well as the metalation reaction, since when the reaction was initiated at 25% THF, a concentration at which the α-haloalkyllithium is stable, and then diluted to <20% THF, rapid decomposition occurred.[13] Since the lithium cation can function as a Lewis acid, Köbrich suggested that the solvation in THF would decrease the lithium cations electrophilic nature.[8] This would tend to destabilize the transition state for the decomposition reaction which could depend upon cation-assisted elimination of the halide. Since Köbrich reasoned that the dichloromethyllithium molecules would be preferentially surrounded by THF molecules, he felt that added lithium bromide should cause competition for the THF and consequently increase the rate of decomposition. This was not observed.[13]

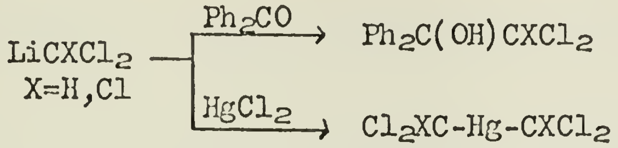
Furthermore, the rate of decomposition is dependent upon the α-haloalkyllithium. Hoeg[10] and Köbrich[18] have reported that trichloromethyllithium decomposes at a lower temperature than dichloromethyllithium. Köbrich did not expect the dichloro compound to be more stable than the trichloro compound because he felt that trichloromethyllithium should best stabilize the carbenoid state.[18]

REACTIONS OF α-HALOALKYLLITHIUM COMPOUNDS

α-Haloalkyllithiums have been found to undergo both nucleophilic and electrophilic reactions. The electrophilic reactions have, however, been explained most commonly by a carbene or by direct addition of the α-haloalkyllithium. The various reaction possibilities are discussed below.

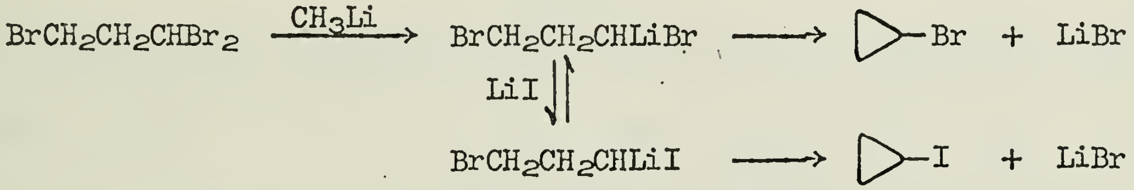
The nucleophilic reactivity of these compounds requires little comment. The α-haloalkyllithium intermediates (as typical of organolithium reagents) have often

been trapped and characterized by hydrolysis[10] and by direct carbonation to the corresponding acids.[8,10,12] Köbrich has further demonstrated the nucleophilic character of di- and trichloromethyllithium by their reaction with benzophenone and mercuric chloride (10).[18]



(10)

α-Haloalkyllithiums also can undergo displacement reactions with alkyl halides. Hoeg reported an extremely rapid displacement reaction of α,α-dichlorobenzyllithium with both methyl- and benzyl chloride at low temperatures.[11] The coupling of α-chloroalkyllithium compounds with excesses of polychloromethanes did not occur. Kirmse reported an intramolecular displacement by an α-haloalkyl carbanion.[19] The reaction of 1,1,3-tribromopropane with methyllithium (from methyl iodide) in ether at -20 to -30° produced cyclopropylbromide (50%) and cyclopropyliodide (16%)(11). The cyclopropyliodide was considered to be produced by iodide-exchange in the α-haloalkyllithium intermediate, since a control experiment with the starting tribromide and sodium iodide in acetone did not give any bromide-iodide exchange products. Iodide-bromide exchange on cyclopropylbromide in acetone is known to be slow.[20] Furthermore, the product could not result from carbene insertion into the carbon-halide bond (12) since reaction with 1,1-dibromo-3-chloropropane produced only cyclopropylbromide, whereas carbene insertion would give cyclopropylchloride.



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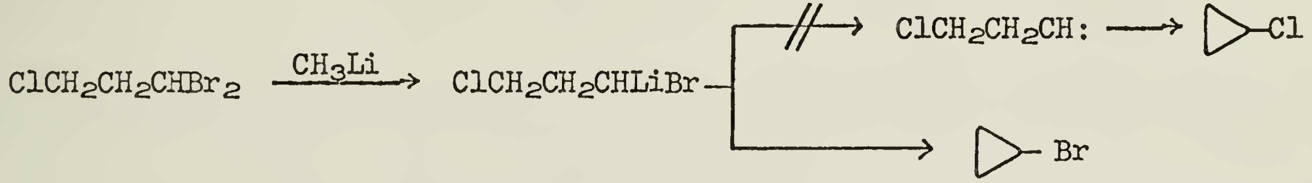
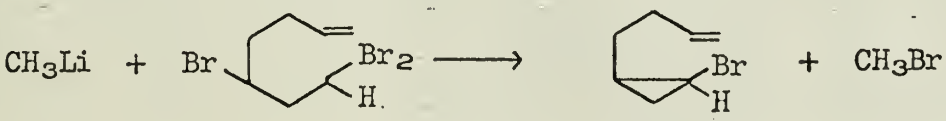


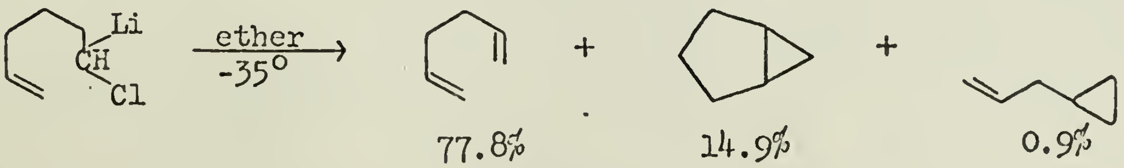
(12)

Moreover, the intramolecular nucleophilic reaction appears to be preferred to intramolecular carbenoid addition.[19] In the reaction of 5,7,7-tribromoheptene-1 with methyllithium, no addition to the olefin was detected and only IV was formed. Even with 7,7-dibromoheptene-1, in which S_N2 displacement is impossible, only 0.5% of the addition product was detected.[21] Kirmse demonstrated that, as expected, such intramolecular additions are very sensitive to chain length. In the attempted cyclization to bicyclo[n.1.0]alkanes, where n=2,3,4, only bicyclo[3.1.0]hexane was obtained in moderate yields (15%). The predominate product in each case was the diene (14). The diene could arise either from a carbene or concerted hydrogen migration involving the loss of lithium chloride.[22]



(IV)

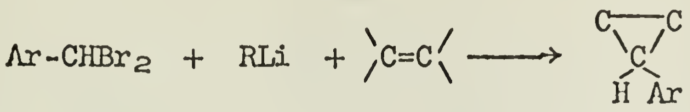
(13)



(14)

Recently, Closs and Moss have compared the results from the reaction of various α-haloalkyllithiums and olefins with those obtained via photolysis of the corresponding diazoalkanes with the olefin as a solvent (15,16).[6,23] Since evidence exists that

the photolysis of certain diazoalkanes in solution produces true divalent species,[24] a comparison with α-haloalkyllithiums should lead to a better understanding of the mechanism involved in cyclopropane formation.



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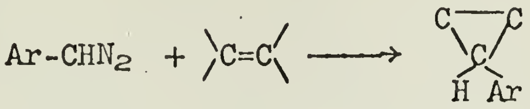


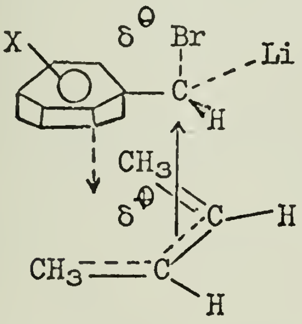
(16)

Once the configurations of the various arylcyclopropanes had been established by nmr, it was possible to examine the stereoselectivity of the addition reaction. The syn/anti ratio (where syn is defined as the configuration with the largest number of alkyl groups cis to the aryl substitutent) for the photolysis and the α-haloalkyllithium reactions were found to differ significantly (Table 1).[6] The results show that the aryl substitutents influenced the selectivity for the α-haloalkyllithiums according to the following sequence of diminishing stereoselectivity: p-OCH$_3$>p-CH$_3$>m-Cl>p-Cl>H. The syn/anti ratio for the photolysis reaction is less effected by the aryl substituents. The authors suggested that a charge separation in the transition state (V) is less severe in the syn conformation. This is based on the assumption that the positive charge in the olefin moiety will be dispersed over the alkyl groups and that the negative charge will appear in the carbene or carbenoid substitutent. Charge transfer interactions may also add to the attractive forces. Since the stereoselectivities are usually small, these effects are either weak or balanced by common steric effects. The large syn/anti ratio for p-methyl and p-methoxy groups in the α-haloalkyllithium reaction suggested that the charge transfer forces are important in these cases. The larger discriminating ability of the carbenoid as seen in the α-haloalkyllithiums, was attributed to the postulated transition state (V), which demands, according to Closs,[6] a greater proximity of the benzene ring and the olefinic alkyl substituents than in the carbene addition. This would tend to stabilize the syn transition state relative to the anti except for large steric interactions.

Table 1

Isomer Ratios (syn/anti) from Benzal Bromides (RBr$_2$) and from Aryldiazomethanes (RN$_2$) at -10° in Hydrocarbon Medium

Olefin	Phenyl Substituent									
	H		p-Cl		m-Cl		p-CH$_3$		p-OCH$_3$	
	RBr$_2$	RN$_2$	RBr$_2$	RN$_2$	RBr$_2$	RN$_2$	RBr$_2$	RN$_2$	RBr$_2$	RN$_2$
1-Butene	2.1	1.0	2.1	1.1	2.5	1.2	2.7	1.2	3.0	1.4
cis-2-Butene	2.4	1.1	2.9	1.1	3.7	1.2	4.5	1.7	8.1	2.8
2-Methyl-2-butene	1.3	1.1	1.4	1.1			1.4	1.2		



V

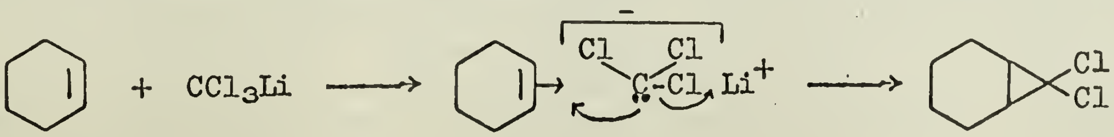
The syn/anti was, however, found to decrease with increasing size of the alkyl group in the carbenoid addition to the 1-alkylethylenes.[23] As the olefinic alkyl group increases in bulk, the energetically preferred syn addition becomes less favorable with respect to the anti in which only the hydrogen atom opposes the olefinic substitution. The syn/anti ratio also depended on the lithium halide involved, suggesting the presence of the halide in the transition state. Furthermore, the degree of substitution on the olefin affects the organolithium addition more than the photolysis reaction. For example, the organolithium intermediate reacts with trans-butene-2 much slower than with isobutene. Closs explained this result by invoking an unsymmetrical transition state for the organolithium with a large concentration of positive charge on the tertiary carbon atom of the olefin.[6]

Both the organolithium and the photolysis reactions show electrophilic behavior since the addition rate increases with increasing alkyl substitution on the olefins. However, the photolysis reaction, in contrast to the organolithium reaction, produced allylic insertion products and was not completely stereospecific in its reaction with cis-butene-2 since 3-5% of the trans product was formed. Closs attributed these two side reactions to singlet and triplet carbenes, respectively. Gaspar and Hammond preferred this explanation, although they noted that the assignment of spin states by chemical evidence is not universally accepted.[25] Closs and Moss reported that the results suggested that the same intermediate cannot be involved in both reaction types.[6,23] Both rejected the idea that photolysis produces a "hot" methylene with excess energy, whereas the organolithiums yield a methylene in thermoequilibrium with its environment for the following reasons: (a) Competition data suggested that a non-negligible activation barrier exists for the addition of methylene produced by photolysis. Therefore, Closs reasoned that the methylene probably has a long enough lifetime to reach thermoequilibrium. (b) The partial nonstereospecific addition suggested that the methylene from photolysis lives long enough to reach its triplet ground state. However, if the α-haloalkyllithium decomposed to the carbene, Closs argued that its stereospecific addition to olefins requires a higher energy singlet state. By analogy to the photolysis reaction, Closs felt that such a singlet carbene was unlikely since it should also live long enough to reach its triplet ground state, which should give a nonstereospecific addition. It is possible, however, that different preparative methods could produce a singlet carbene that could react before decaying to the triplet state.[26]

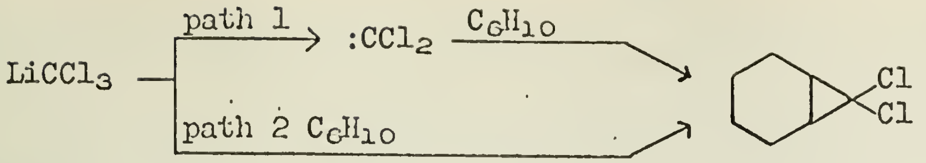
Reactions conducted in an ether-hydrocarbon solvent were considerably less stereoselective than those conducted in the pure hydrocarbon.[6,23] Closs suggested that this solvent effect was due to a lower activation energy for displacement of the bromide with increasing solvation of the lithium.[6] Closs predicted that increasing covalency of the carbon-metal bond would decrease the carbenoid reactivity. An alternative explanation was given by Moss, who suggested that the structure and reactivity of the α-haloalkyllithium could be dependent on the presence or absence of Lewis base solvents, since these species may not be monomeric.[23]

Hoeg[10] and Köbrich[8] have, however, reported results which suggest that increasing polarity of the carbon-lithium bond decreases the reactivity of the carbenoid. Tetrahydrofuran, in comparison with diethyl ether, has been shown to accelerate only nucleophilic reactions, such as carbonation and reaction with alkyl halides, and to inhibit electrophilic reactions, such as the addition to olefins.[8,27] The nucleophilic acceleration in THF is attributed to complex formation of the lithium ions with the strongly polar THF molecule.[8] The oxygen atom of the THF decreases the electrophilic character of the lithium and leaves the rest of the α-haloalkyllithium molecule with increased carbanion character. The carbenoid species in THF is less suited for complex formation with olefins. The solvated metal atom is also less helpful in the elimination of the halide both for steric and electronic reasons. In other words, THF is thought to increase the activation energy in electrophilic reactions by destabilizing the transition state and probably by somewhat stabilizing the ground state.

Miller and Whalen[7] have noted that, although trichloromethyllithium was stable in ether at -100°, addition of excess cyclohexene resulted in a 77% yield of dichloronorcarane (17). Miller,[7] Köbrich,[8] and Hoeg[10] reasoned that if the decomposition occurs via the free divalent species (path 1), the decomposition rate should be unaffected by the presence or absence of olefins; whereas if the halogenated lithium reacts directly with the olefin (path 2), the rate of decomposition should increase upon addition of olefins (18). The results are consistent with direct addition. Miller and Whalen postulated a nucleophilic attack by the olefin on the carbanion with concerted (and in ether, cation-assisted) elimination of halide.



(17)



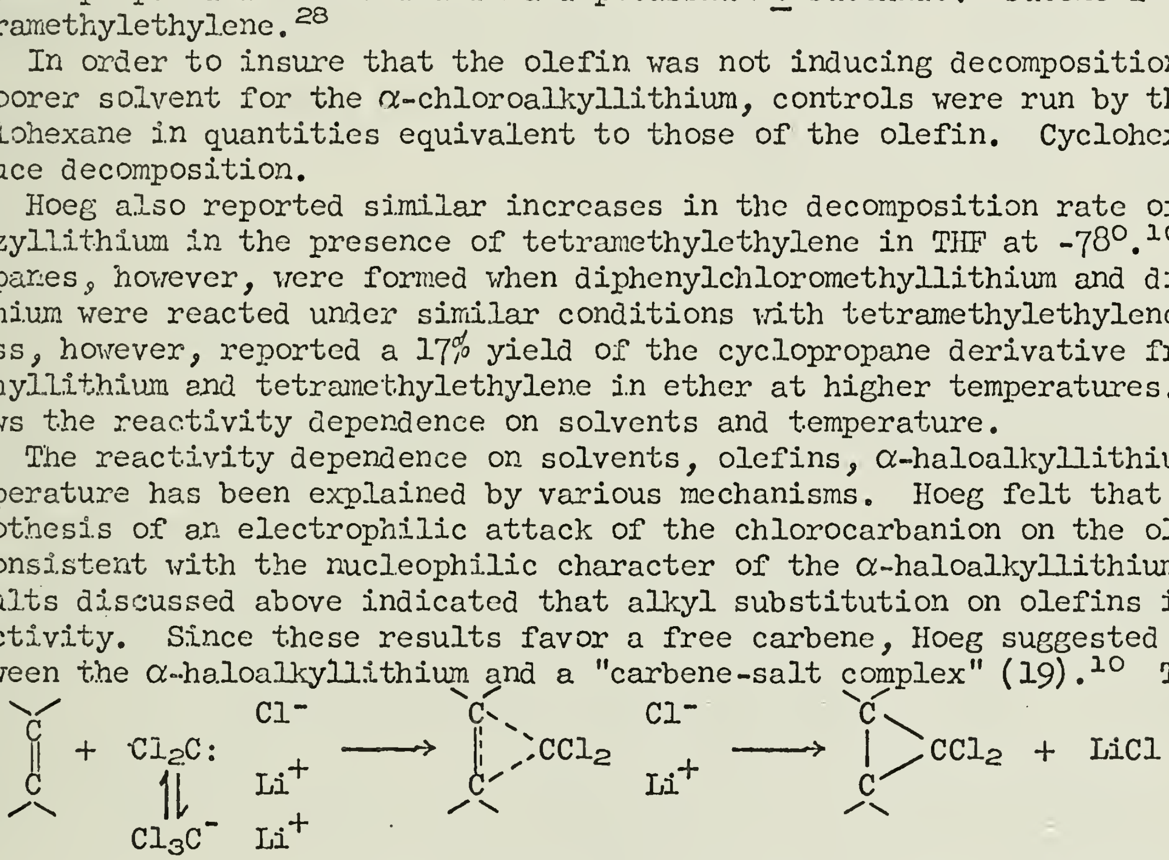
(18)

The formation of two new carbon-carbon bonds would provide, according to Miller, a large driving force for the reaction. Later, Köbrich questioned Miller's results when a large decomposition of the α-haloalkyllithium was detected even in the absence of cyclohexene.[27] Köbrich[8] and Hoeg,[10] independently, reported that although the reaction of trichloromethyllithium with cyclohexene was slow at -100° in THF, accelerated decomposition of trichloromethyllithium in the presence of olefins at higher temperature did occur. The results clearly showed that the amount of decomposition is greater upon addition of olefins. Although Hoeg's results indicated that tetramethylethylene is more reactive than cyclohexene, Köbrich stated that tetramethylethylene is less reactive. He suggested that Hoeg's results are incompatible with the electrophilic character of the α-chloroalkyllithiums.[9] Hoeg's results would, however, be predicted on steric grounds. Köbrich noted that trichloromethyllithium shows electrophilic reactivity with olefins similar to dichlorocarbene prepared from chloroform and potassium t-butoxide: butene-2 <α-methylstyrene< tetramethylethylene.[28]

In order to insure that the olefin was not inducing decomposition by acting as a poorer solvent for the α-chloroalkyllithium, controls were run by the addition of cyclohexane in quantities equivalent to those of the olefin. Cyclohexane did not induce decomposition.

Hoeg also reported similar increases in the decomposition rate of α,α-dichlorobenzyllithium in the presence of tetramethylethylene in THF at -78°.[10] No cyclopropanes, however, were formed when diphenylchloromethyllithium and dichloromethyllithium were reacted under similar conditions with tetramethylethylene at -78°. Closs, however, reported a 17% yield of the cyclopropane derivative from dichloromethyllithium and tetramethylethylene in ether at higher temperatures.[29] This again shows the reactivity dependence on solvents and temperature.

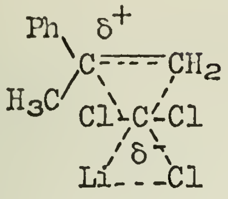
The reactivity dependence on solvents, olefins, α-haloalkyllithium, and temperature has been explained by various mechanisms. Hoeg felt that Miller's hypothesis of an electrophilic attack of the chlorocarbanion on the olefin was inconsistent with the nucleophilic character of the α-haloalkyllithiums.[10] The results discussed above indicated that alkyl substitution on olefins increases their reactivity. Since these results favor a free carbene, Hoeg suggested an equilibrium between the α-haloalkyllithium and a "carbene-salt complex" (19).[10] This carbene



(19)

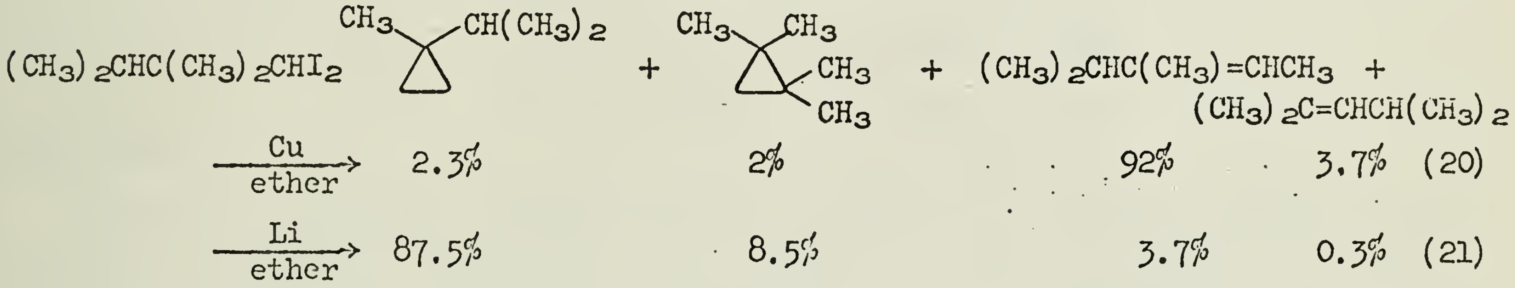
complex is the carbenoid intermediate previously suggested by Closs.[30] Hoeg suggested that below -70° the equilibrium lies on the side of the carbanion, constrained in part by the insolubility of the compound. As long as the chloride remains in the vicinity of the incipient carbene, the olefin fails to compete with it for the carbene fragment.[10] Hoeg suggested that as the temperature, and therefore also the solubility, is increased, the properties of the incipient carbene become more dominant. It is difficult, however, to comprehend how the solubility would affect the character of the reacting species, since only the α-haloalkyllithium in solution is capable of reacting. The temperature would be expected to affect the ease of breakage of the carbon-chloride bond. With more highly substituted olefins removal of the chloride ion would not have to proceed very far before bond formation to produce the cyclopropane would have started. Hoeg's mechanism appears to resemble Miller's in many respects. Apparently, the major difference between the two mechanisms is that Hoeg prefers a transition state with greater carbon-halide bond cleavage, so that the carbon atom has less carbanion character. Furthermore, Köbrich suggested that the transition state has only a partial positive charge on the

olefin carbon (VI), since he felt that α-methylstyrene should greatly stabilize a full positive charge and produce a larger yield of cyclopropane than actually observed. It is possible that the yield of the cyclopropane derivative is reduced due to greater steric strain in the transition state with α-methylstyrene than with cyclohexene to which it was compared.



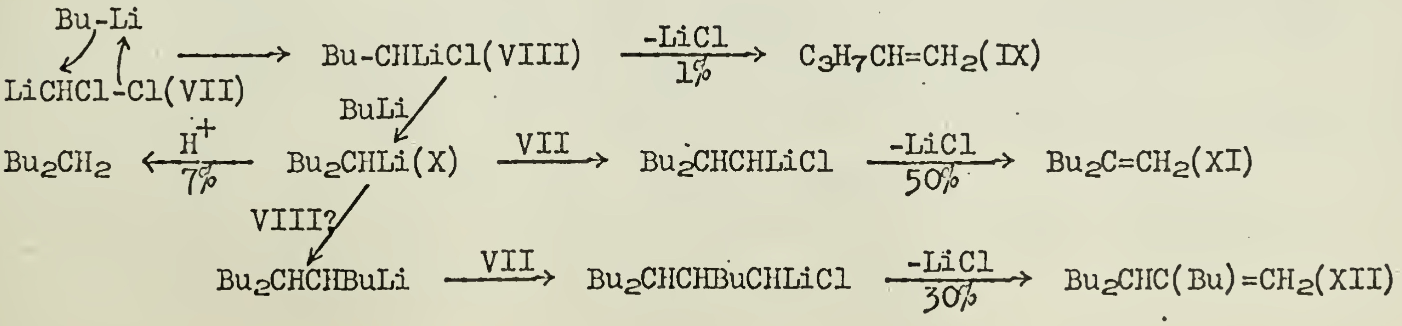
VI

Kirmse has reported evidence to show that the transition state in lithium carbenoid reactions does not have a full positive charge.[31] Kirmse constructed a molecule in which both alkyl migration and insertion into carbon-hydrogen bonds was possible. 1,1-Diiodo-2,2,3-trimethylbutane was reacted with Cu, Zn, Li, Na, and Mg in ether at room temperature. If the transition state had considerable positive charge on C-1, alkyl migration would be expected to occur. The results suggested to Kirmse that sufficient positive charge for alkyl migration was developed only with the metals, zinc and copper (Simmons-Smith reagents), since a Wagner-Meerwein rearrangement occurred with these two metals (20). The results with lithium and other alkali metals show that little rearrangement to the olefins occurred. Cyclopropane formation is the principal product (21). Sec-hydrogen migration is preferred in both cases. The α-haloalkyllithium reaction prefers primary C-H bond insertion over tertiary C-H insertion. Kirmse felt that the results favor a transition state with carbonium ion character in the Simmons-Smith reaction but not in the α-haloalkyllithium reaction. It is possible, however, that the C-H insertion reaction and the Wagner-Meerwein rearrangement do not proceed through the same transition state.



The electrophilic nature of the α-haloalkyllithium intermediate can also be demonstrated by its reaction with organolithium reagents. Köbrich has reported results which suggest that the reaction of dichloromethyllithium with n-butyllithium does not proceed via carbene insertion.[13] Although dichloromethyllithium was stable at -74° in THF, excess n-butyllithium promoted the decomposition as indicated in Scheme 1. If a carbene insertion reaction occurred, the rate of decomposition should be independent of the presence of n-butyllithium. The reaction involves nucleophilic attack of the n-butyllithium on the carbenoid carbon to give VIII. Although Köbrich attributed the high yields of XI and XII in comparison to IX to a greater tendency for tertiary β-hydrogen migration, another possible cause is that nucleophilic displacement with n-butyllithium to give X is faster than the loss of lithium chloride to give IX. Since the formation of XI and XII requires dichloromethyllithium (VII), the initial reaction of butyllithium and VII must be slow since butyllithium is present in twofold excess. If the initial reaction was very fast, XI and XII could not be formed in large yields. The n-nonane formed was attributed

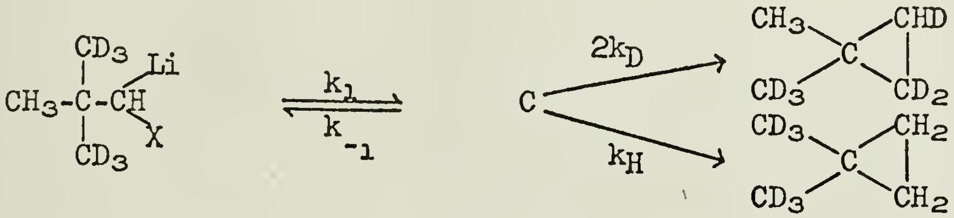
Scheme 1



to metalation of the solvent. Köbrich, however, noted that the reaction with cyclohexene and the halolithium did not take place under the reaction conditions.

Similar insertion reactions with the carbon-lithium bond in other organolithium reagents have been observed.[8,14,21,32] Nefedov has attributed the reaction of methylene chloride in excess phenyllithium in ether at -20 to +20° to insertion of chlorocarbene into the carbon-lithium bond.[14]

In addition to insertion into the carbon-metal bonds, carbon-hydrogen insertion has also been observed. Goldstein has reported results consistent with the absence of an intermediate carbene (C).[32] The insertion into primary C-H bonds proceeds directly from the α-haloalkyllithium (22), since the k_H/k_D was halide dependent, indicating that the halogen was present in the transition state for hydrogen transfer: $k_H/k_D = 2.43 \pm 0.02$ for X = iodide and $k_H/k_D = 2.06 \pm 0.10$ for X = bromide. Goldstein also recognized that the results are consistent with a fully established pre-equilibrium and with carbenes of varying energies. This is convincing proof that a carbene intermediate is not involved in the α-haloalkyllithium reactions.



(22)

CONCLUSION

There is considerable evidence for the existence for carbenoid species in many reactions. The addition to olefins and the insertion into carbon-hetero bonds no longer provide definite evidence for the existence of carbenes. Furthermore, the results have shown that the degree of carbene character is dependent upon the temperature and the solvent.

BIBLIOGRAPHY

1. D. Seyferth and R. B. King, "Annual Surveys of Organometallic Chemistry," Vol. 2, Elsevier Publishing Co., New York, 1965.
2. H. Heaney, Organometal. Chem. Rev., 1, 27 (1966).
3. J. Hine, "Divalent Carbon," The Ronald Press Co., New York, 1964.
4. W. Kirmse, "Carbene Chemistry," Academic Press, New York, 1964.
5. W. Kirmse, Angew. Chemie Inter. Ed. in Eng., 4, 1 (1965).
6. G. L. Closs and R. A. Moss, J. Am. Chem. Soc., 86, 4042 (1964).
7. W. T. Miller, Jr. and D. M. Whalen, ibid., 86, 2089 (1964).
8. G. Köbrich, K. Flory, and R. H. Fischer, Ber., 99, 1793 (1966).
9. G. Köbrich, H. R. Merkle, and H. Trapp, Tetrahedron Letters, 969 (1965).
10. D. F. Hoeg, D. I. Lusk, and A. L. Crumbliss, J. Am. Chem. Soc., 87, 4147 (1965).
11. M. Schlosser and V. Ladenberger, Angew. Chem., 78, 547 (1966).
12. D. F. Hoeg and D. I. Lusk, J. Organometal. Chem., 5, 1 (1966).
13. G. Köbrich and H. R. Merkle, Ber., 99, 1782 (1966).
14. O. M. Nefedov, V. I. Shiryaev, and A. S. Khachaturov, J. Gen. Chem. USSR, 35, 509 (1965).
15. J. V. Swisher, P. Mavrikos, and A. Cheng, J. Org. Chem., 30, 1675 (1965).
16. O. R. Pierce and G. F. Judd, J. Am. Chem. Soc., 76, 474 (1954).
17. J. F. Eastham and G. W. Gibson, ibid., 85, 2171 (1963).
18. G. Köbrich, K. Flory, and W. Drischel, Angew. Chemie Inter. Ed. in Eng., 3, 513 (1964).
19. W. Kirmse and B. G. Wedel, Ann., 676, 1 (1964).
20. A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, 1962, p. 95.
21. W. Kirmse and D. Grassman, Ber., 99, 1746 (1966).

22. G. L. Closs, J. Am. Chem. Soc., 84, 809 (1962).
23. R. A. Moss, J. Org. Chem., 30, 3261 (1965).
24. R. W. Murray, A. M. Trozzolo, E. Wasserman, and W. Y. Yager, J. Am. Chem. Soc., 84, 3213 (1962).
25. Ref. 4, p. 250ff.
26. Ref. 4, p. 270.
27. G. Köbrich, D. Flory, and H. R. Merkle, Tetrahedron Letters, 15, 973 (1965).
28. W. von E. Doering and W. A. Henderson, J. Am. Chem. Soc., 80, 5274 (1958).
29. G. L. Closs and L. E. Closs, J. Am. Chem. Soc., 81, 4996 (1959).
30. G. L. Closs and L. E. Closs, Angew. Chemie Inter. Ed. in Eng., 1, 334 (1962).
31. W. Kirmse and G. Wächterhäuser, Tetrahedron, 22, 73 (1966).
32. M. J. Goldstein and W. R. Dolbier, J. Am. Chem. Soc., 87, 2293 (1965).

THE BASIC HYDROLYSIS OF TRIFLUORO-N-METHYLACETANILIDE

Reported by Paul E. Bender December 19, 1966

INTRODUCTION

The kinetic and mechanistic investigations of the alkaline hydrolysis of amides have been limited in comparison to the numerous studies of basic ester hydrolysis.[1,2] In general the mechanistic work in the latter area has been assumed to apply to the former. This abstract will review the recent developments in amide hydrolysis by consideration of the basic hydrolysis of trifluoro-N-methylacetanilide.

RATE EQUATION AND SALT EFFECTS

In a kinetic study of the alkaline hydrolysis of trifluoroacetanilide and several acyl substituted N-methylacetanilides, Biechler and Taft[2] employed a tenfold excess of hydroxide over amide in an aqueous solution and obtained first-order kinetics where the velocity of reaction at a constant base concentration varied only in proportion to the first-order of the amide.

A change in the hydroxide ion concentration at constant ionic strength, maintained by added sodium chloride, effected k_{obs} (ie. the first-order rate constant) and $k_{obs}/(OH^-)$ for trifluoro-N-methylacetanilide as shown in table I.

Table I

Dependence of rate constant on hydroxide ion

(OH^-) (M)	$k_{obs} \times 10^3$ (min^{-1}) at $\mu = 0.011M$	$k_{obs}/(OH^-)$
0.0011	0.189	172
0.0022	0.507	230
0.0063	1.69	268
0.0111	5.00	450

It can be seen that k_{obs} is not proportional to the hydroxide concentration since $k_{obs}/(OH^-)$ doesn't remain constant. However, the values of k_{obs} fit the equation $k_{obs} = k_1 (OH^-) + k_2 (OH^-)$.[2] Similar results were found for all seven compounds in the N-methylacetanilide series studied. Plots of $k_{obs}/(OH^-)$ vs. hydroxide ion concentration gave straight lines of slopes k_2 and intercepts k_1 where the mean deviation of the k_{obs} calculated from k_1 and k_2 and the k_{obs} were ± 5%.

Variation of the ionic strength with added sodium sulfate and sodium chloride at constant hydroxide ion concentrations in the case of trifluoro-N-methylacetanilide as shown in Table II, resulted in no change in k_{obs} up to an ionic strength of 0.557M.

Table II

Dependence of rate constant upon ionic strength

(OH^-)	$k_{obs} \times 10^3$ at μ_1		$k_{obs} \times 10^3$ at μ_2	
(M)	(min^{-1})	(M)	(min^{-1})	(M)
0.0011	0.192	0.001	0.204	0.557
0.0063	1.79	0.006	1.69	0.011
0.0111	5.16	0.011	5.08	0.557

Salt effects were observed, however, at constant hydroxide ion concentration at an ionic strength of 2.60M for dimethylcyano-N-methylacetanilide. Dissection of the data in terms of k_1 and k_2 yields results shown in Table III. The data indicates that k_2 is somewhat more sensitive to a positive salt effect than k_1 in this case.

Table III

Effect of ionic strength upon derived rate constants

rate constant	μ = 0.557M	μ = 2.60M
k_1(l.-mole^{-1}-min.$^{-1}$)	0.037	0.042
k_2(l^2.-mole^{-2}-min.$^{-1}$)	0.020	0.054

An explanation of the two term rate equation, both first and second-order in hydroxide ion, in a manner which incorporates an initial equilibrium formation of an adduct, as is suggested by analogy to the H_2O^{18} exchange rates in benzamide hydrolysis,[3] is offered by Biechler and Taft in terms of the following mechanism:

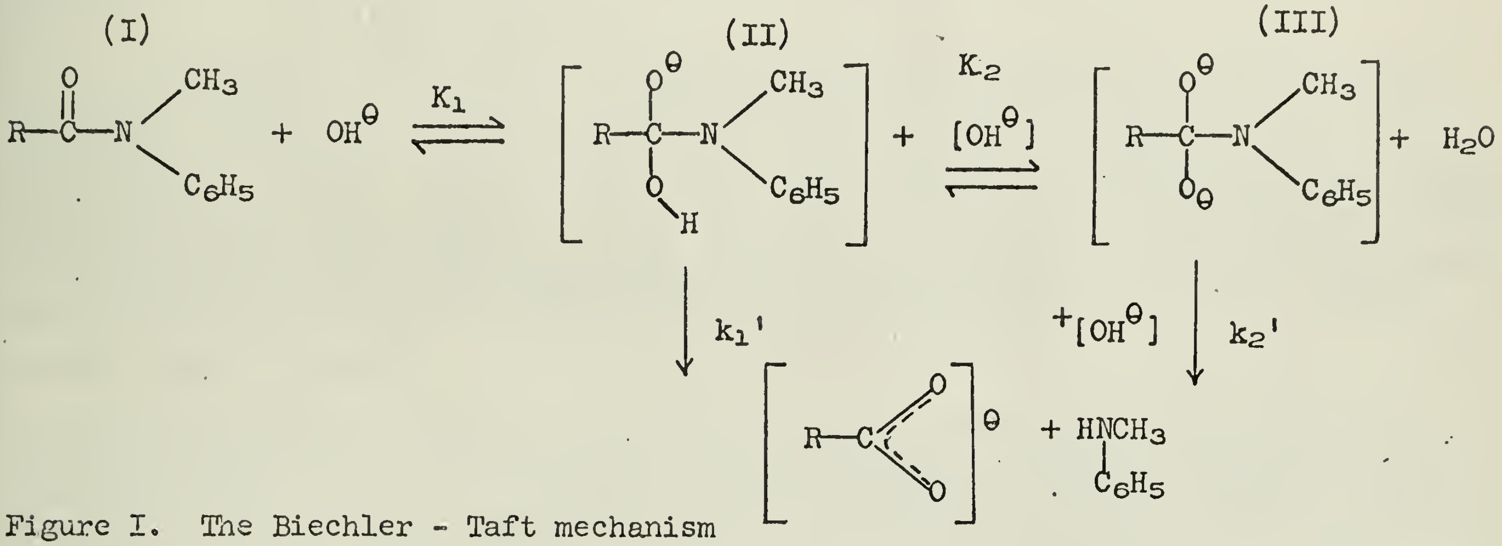


Figure I. The Biechler - Taft mechanism

Where k_1' represents the second-order overall k_1 term and is seen by the authors as a unimolecular decomposition of the adduct II to form products. The termolecular term k_2, represented by k_2', was interpreted by the authors as requiring the intermediacy of dianion III. This k_2'-step is formulated as the rate limiting step involving either the formation of III or its decomposition.

USE OF THE TAFT EQUATION

In an attempt to discriminate between the latter two mechanisms for the termolecular term, Biechler and Taft tried to fit k_1 and k_2 to the Taft equation;[4] ie. $\log(k_1/k_0) = \sigma^*\rho^* + \delta E_s$ where σ^* and E_s refer to the polar and steric substituent constants obtained from ester hydrolysis rates,[5] adjusted to account for the differences in bulk of the atoms compared. The authors did not obtain an adequately linear correlation of the data to any ρ^* and δ values and concluded that this implied a failure of the linear steric energy relationship; ie. the steric effects in anilide hydrolysis do not parallel those in ester hydrolysis.

Reasoning that the reactions represented by k_2 and k_1 differ in the presence of an additional negative charge in the transition state of k_2, Biechler and Taft plot log (k_2/k_1) vs. the polar substituent constant σ^*, but again obtained poor correlation. However, a reasonable fit was obtained to the following function: $\log(k_2/k_1) = (1.575)\,\sigma^* + (0.713)E_s + 0.43$ where ρ^* and δ were chosen to provide the best fit. There may be some doubt concerning the significance of this treatment, and the authors state that a small probability exists of coincidental fit of the data to the equation. Employing this equation, it is noted that ρ^* and δ are positive; ie. $\rho_2^* > \rho_1^*$ and $\delta_2 > \delta_1$. This means that k_2 is increased to a greater extent than k_1 by increased electron withdrawal in the transition state, and also by decreased steric bulk in the transition state. The authors argue that increased electron withdrawal should decrease k_1 more than k_2 because for the greater negatively charged transition state represented by the k_2 term, the difference in free ener between reactants and the transition state is less sensitive to decrease in negativity than in the decomposition of the monoanion. The basis for this statement was not

given, and it would seem difficult to predict or interpret the variation in k_2/k_1 in this case. However, the conclusion which the authors come to, mainly that polar effects cannot decide between the two processes may be well founded in either case.

The increased sensitivity of k_2 to steric requirements, relative to k_1, (that is $\delta_2 > \delta_1$) is taken by Biechler and Taft to indicate the operation of a rate determining proton transfer. They reason that in rate limiting proton transfer, the transition state would contain the highly solvated hydroxide ion which would give more steric crowding in the transition state than for the second-order reaction. Although they note that steric crowding might also occur from a greater solvation of the dianion transition state, relative to the monoanion transition state involved in the reaction represented as k_1, the authors believe the former argument to be more reasonable.

CONFIRMATION OF THE RATE EQUATION

In studying the first-order alkaline hydrolysis kinetics of a series of acyl substituted amides, Bruylants and Kezdy[6] obtained a two term rate law for chloroacetamide hydrolysis which was identical in form with the expression found previously by Biechler and Taft. The kinetics at 25° employing a minimum of twenty fold excess of hydroxide ion over amide in a pH range of 13 to 14 did not show proton abstraction from the amide nitrogen since the pK_a, interpolated from a plot of log $(K_i/K_{acetamide})$ vs. σ^* for acetamide, dichloroacetamide and trichloroacetamide was 14.2. This was considered too high to effect the kinetics measurably.

GENERAL BASE CATALYSIS

Schowen and coworkers[7,8] examined the alkaline hydrolysis of trifluoro-N-methylacetanilide in a pH range of 9.5 to 10.0 at 25.5 ± 0.04° in a glycine/sodium glycinate buffer series at a constant ionic strength of 0.0100M in order to study the N-disubstituted acyl amide system for general base catalysis. Mader had previously observed general base catalysis for the hydrolysis of the monosubstituted trifluoroacetanilide compound with several buffer systems.[9] For each of four ratios of glycine/glycinate employed by Schowen, the concentrations of glycine and glycinate were increased proportionately to keep the ratio and therefore the hydroxide ion concentration constant over four values of sodium glycinate concentration. Thus the first-order rate constant k_{obs} was measured as a function of glycine, glycinate, and hydroxide. A plot of k_{obs} vs. glycinate concentration is shown in figure II, where $(OH^-)^1 > (OH^-)^2 > (OH^-)^3 > (OH^-)^4$. This graph exhibits a functional dependence of the form $y(OH^-, \text{glycinate}) = b\,(OH^-) + m\,(OH^-)$ glycinate.

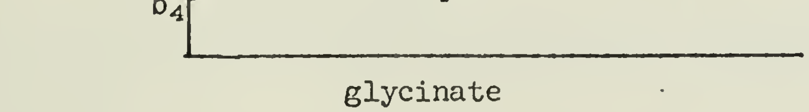


Figure II. Variation of reaction rate with buffer concentration.

This dependence satisfies the following expression:

$$-\frac{dI}{dt} = k_{obs}\,(I) = (I)\,[k_o + k_1\,(OH^-) + k_2\,(OH^-)^2 + k_3\,(OH^-)(\text{glycinate}) + k_4\,(OH^-)(\text{glycine})]$$

let $\overset{\oplus}{N}H_3\text{-}CH_2\text{-}\overset{\ominus}{CO_2} + (OH^-) \underset{}{\xrightleftharpoons{K_{eq}}} NH_2\text{-}CH_2\text{-}\overset{\ominus}{CO_2} + H_2O$ (1)

glycine glycinate

therefore $k_{obs} = [k_o + k_1 (OH^-) + k_2 (OH^-)^2] + [k_3 (OH^-) + k_4/K_{eq}]$ (glycinate) (2)

Using the slopes of two of the four lines, we can solve for k_3 and k_4, and with any three intercepts of the four lines k_o, k_1 and k_2 can be determined: eg. at glycine = glycinate = 10^{-2}M, the rate terms are as follows:

Table IV

Catalytic terms for general base catalysis

(OH^-) (M)	k_o (sec^{-1})	$k_1(OH^-)$ (sec^{-1})	$k_2(OH^-)^2$ (sec^{-1})	k_3(glycinate)(OH^-) (sec^{-1})	k_4(glycine)(OH^-) (sec^{-1})
4.5×10^{-5}	5×10^{-5}	8×10^{-5}	3.2×10^{-6}	1.3×10^{-4}	7.6×10^{-5}
10^{-2}	5×10^{-5}	2×10^{-2}	2×10^{-1}	3.3×10^{-2}	1.9×10^{-2}

The authors take the correspondence of the data to equation (2) to indicate the superimposition of general base catalysis upon specific hydroxide ion catalysis. They also state that the finding of general base catalysis excludes a rate limiting unimolecular decomposition of the dianion III in figure I. Furthermore they assert that the rate constants for oxygen to oxygen proton transfer obtained from relaxation kinetics as given by Eigen, et al.[10] preclude a simple rate limiting proton transfer. It is unlikely, according to the authors, that this rapid proton transfer to form the dianion III would be slower than the dianion decomposition to products. A Bronsted plot of log k_i vs. log K_i ($B_i + H_2O \underset{}{\overset{K_i}{\rightleftharpoons}} BH^{\oplus} + OH^-$) for i=1 to 4 yielded a slope $\beta = 0.3$ for three of the four points. Glycine was a much better catalyst than its K_i would indicate on a plot determined by the other three points. This lead the authors to suspect either bifunctional acid-base catalysis or nucleophilic catalysis as in the case of glycine. It should be noted that even the better three points did not give a perfect fit to the Bronsted equation.

The observation of general base catalysis superimposed upon ~~initial~~ specific hydroxide ion catalysis is consistent with the three mechanisms shown in Figure III below:

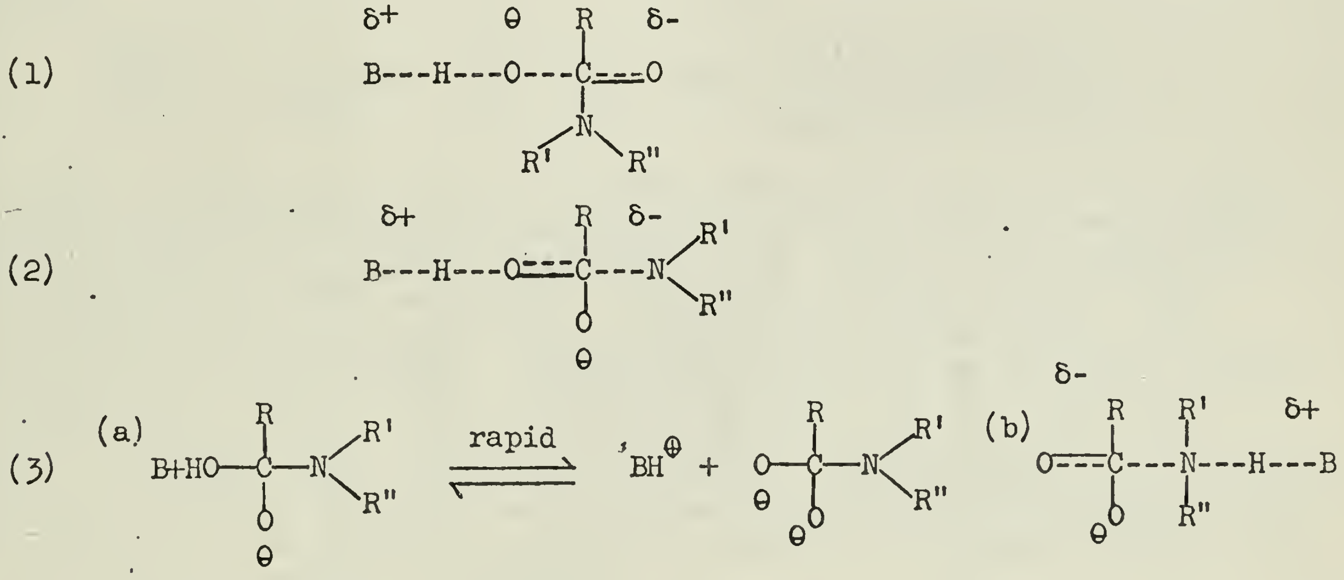


Figure III. Superimposed general base catalysis upon ~~initial~~ specific hydroxide ion catalysis.

Mechanisms (2) and (3) are kinetically equivalent, however if (3) is operating then a Bronsted plot of log k vs. log K_b will give the value of the slope β' which is equal to $1-\alpha$ where α is the Bronsted parameter for the rate limiting general acid catalysed step.[11] This renders the interpretation of β ambiguous. Further ambiguity arises from the recent work of Eigen which questions the basis of the Bronsted law.[12,13]

Although the rapid isotopic O^{18} exchange, relative to product formation in the basic hydrolysis of benzamide,[3] has been interpreted as the operation of an

additional elimination mechanism in amide hydrolysis, several workers have pointed out that the demonstration of O^{18} exchange from a substrate carbonyl group only provides evidence for a reversible formation of an intermediate, not necessarily the intermediate formed in the reaction coordinate.[14,15] An independent bimolecular displacement mechanism involving simultaneous hydroxide attack and amide ion displacement may be operating on the substrate amide while concurrent exchange is occuring by an addition elimination of hydroxide ion.

In the case of trifluoro-N-methylacetanilide, the observed first-order rate constants for basic hydrolysis at 33.9° obtained at thirteen hydroxide concentrations from pH 11.2 to 12.5 were plot against the hydroxide concentration.[16] The curve was concave upwards below approximately 9×10^{-3}M and flattened into a linear plot above this point. The authors concluded that this change from second-order kinetics at low hydroxide concentration to first-order kinetics with decreased slope at higher hydroxide concentration is a change in the rate determining step, and cannot reflect two independent single step paths, but requires a multistep reaction path. Jenks[17] had earlier proposed a similar argument for the hydroxylaminolysis of amides. Schowen and coworkers also infer from the nature of the order change that general base catalysis must be effecting the elimination and not the addition step. The mechanistic framework proposed is the following:

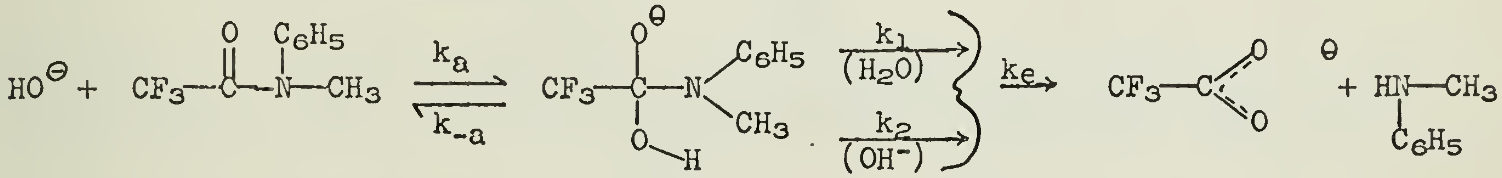


Figure IV. Site of general base catalysis upon ~~initial~~ specific hydroxide ion catalysis.

A steady state treatment of this scheme for the intermediate adduct, with the addition of a solvent catalyzed hydrolysis term (k_o) and the condition $k_e = k_1 (k_{-a}/k_a) + k_2 (k_{-a}/k_a) (OH^-)$ yields the following rate expression:

Equation (3)

$$-\frac{d[I]}{dt} = k_{obs}[I] = [I]\left\{k_o + [OH^-]\ \frac{k_a (k_1 + k_2 [OH^-])}{k_a + k_1 + k_2 [OH^-]}\right\}$$

The basic hydrolysis of trifluoro-N-methylacetanilide was studied by Schowen and coworkers at thirteen hydroxide concentrations pH 11.2 to 12.5, each at four temperatures (values of k_{obs} were reproducible to 3%) and the rate constants k_a, k_1 and k_2 calculated at each temperature. Insertion of these constants into equation (3) gave values of k_{obs} in very good agreement with the data, which demonstrates internal consistency. From equation (3) it can be seen that at low base concentrations, (pH 9.5 → 10), a k_{obs} dependency, first and second-order in hydroxide ion, indicates that the process represented by the k_e term is rate determining. At higher base concentrations, (pH 12), the reversion of the kinetics to simple first-order in hydroxide ion indicates that the addition step has become rate determining and the hydroxide catalyzed decomposition of adduct exceeds, in rate, the reversion of adduct to reactants.

Using the calculated rate constants, (uncertainties were ± 5%), the values of the activation parameters were calculated.

Table V

Activation parameters

rate constant	ΔF^*_{298}(kcal/mole)	ΔH^*(kcal/mole)	ΔS^*_{298}(e.u.)
k_a	16 ± 1	6 ± 1	-36 ± 3
k_1	17 ± 1	6 ± 1	-37 ± 3
k_2	13 ± 1	7 ± 1	-21 ± 3

To explain the low value of ΔH^* for k_1 and k_2, the authors suggest a process involving O to O or O to N proton transfer with C-N bond fission. However, it seems highly unlikely that all mechanisms involving the C-N bond fission can be ruled out solely by a low ΔH^* value. Though several mechanisms are available to justify the apparently significant $\Delta\Delta S^*$ value between k_1 and k_2, the absence of data to decide among them precludes further discussion.

Correlation can be provided for the value of the Bronsted slope β, with the extent of proton transfer in the transition state. Leffler[18] has claimed that if a plot of log k_{rate} of a reaction vs the log K_{eq} for the same reaction is linear then the slope is a parameter that measures the resemblance of the transition state to the products and the reactants. Bunnett[11] states that a high β indicates a high degree of proton transfer to the catalyzing base in the transition state, and vice versa.

To obtain a measure of the change in β as a substituent is modified the Bronsted relationship for general base catalysis by bases (1) and (2) must be considered.

$$\log k = \beta \log K + C$$

$$\text{or } \log\left(\frac{k_2}{k_1}\right) = \beta \log\left(\frac{K_2}{K_1}\right)$$

Since K_2/K_1 is a constant, independent of the substituent, the change in log (k_2/k_1) with variation in substituent is a measure of the alteration in β. Schowen and Zuorick[7] apply the data of Biechler and Taft as shown in Table VI.to this correlation

Table VI

Variation of the log of the rate constant ratio with substituent

R	$\log(k_2/k_1)$
CF_3	2.28
CHF_2	1.53
$CH_2N(CH_3)_3+$	0.75
H	0.53
CH_2Cl	0.30
$CH_2OC_6H_5$	-0.15
$C(CH_3)_2CN$	-0.30

with k_2/k_1 interpreted as the ratio of the rate of hydroxide ion to solvent catalyzed general base decomposition of the adduct. The decreasing value of log k_2/k_1 in the series CF_3, CHF_2, CH_2Cl is interpreted as a decrease in β with increasing electron donation to the carbonyl function. The authors propose that this decrease in β or in the extent of proton transfer in the transition state with electron donation is predicted by the solvation rule of Swain, Kuhn and Schowen.[19]

THE SOLVATION RULE

According to the solvation rule, the proton transfer between O or N atoms in a reaction of the type B---H---O$\underline{---}$C---L (where B is a base, H a proton and L a leaving group) involves the assignment of a proton, (closer to the more basic atom) in a stable potential well at the transition state. The rapid proton transfer occurs either before or after, but not during the transition state. Thus this rule justifies the absence of a primary isotope effect in a rate limiting process involving proton transfer. The solvation rule does not rationalize the absence of a primary isotope effect by a perturbed symmetric vibration in the transition state,[20] but rather by excluding the OHO proton from the reaction coordinate. According to Swain, Kuhn and Schowen, this makes the asymmetric stretch of the OHO system a real vibration with zero point energy in the transition state. Since the presence of an electron donating group will increase the electron density on the nitrogen and

$OD^{\ominus} + \rho H \rightleftharpoons \rho D + OH^{\ominus}$ $K_1 = 2.0$

$CH_3OH + OD^{\ominus} \rightleftharpoons CH_3OD + OH^{\ominus}$ $K_3 = 1.7$

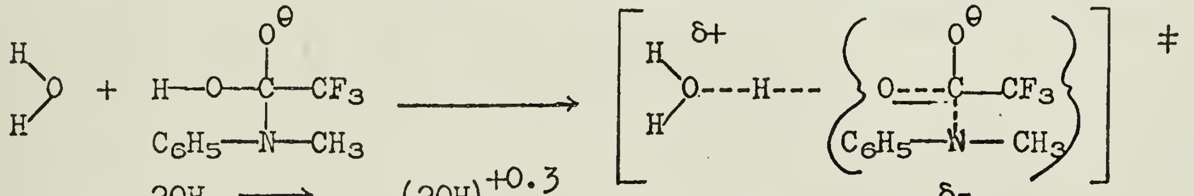
oxygen atoms of the adduct, this will render these atoms more basic. The solvation rule thus predicts that as the electron donating ability increases, the proximity of the proton to the adduct oxygen or nitrogen atom in the transition state should increase and thus β should decrease as is observed.

SOLVENT ISOTOPE EFFECTS

Schowen, Jayaraman, Kershner and Zuorick,[21] obtained the primary contribution to the observed solvent deuterium isotope effect by dividing the observed solvent deuterium isotope effect; ie. $(k_{H_2O}/k_{D_2O})_{obs}$ by the calculated secondary contribution to the solvent isotope effect; (ie. $(k^{H_2O}/k^{D_2O})_{sec}$). The latter contribution was calculated from $(k^{H_2O}/k^{D_2O})_{sec} = \prod_i K_i^{\beta}$ where each K_i corresponds to an equilibrium between protium and deuterium species, and β is the Bronsted slope, (varying between 0 and 1), which represents the extent of conversion to products. Each K_i is the maximum secondary isotope isotope contribution for process i. The values of K_1 and K_2 were derived empirically[22,23,24,25] and K_3 for the hypothetical conversion of methanol into hydroxide ion and gas phase methyl carbonium ion was calculated from the values of the isotope partition function ratios obtained from spectroscopic data.[26,27]

The secondary contributions to k_1 and k_2 were calculated by Schowen and coworkers[28] as shown in Figure V. It should be observed that in the calculation the authors

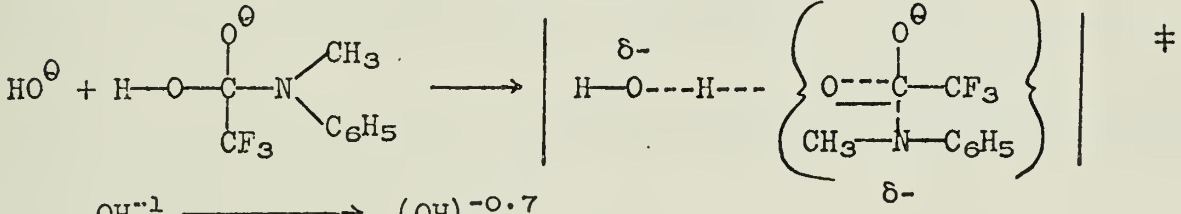
For <u>k_1</u>



$$2OH \longrightarrow (2OH)^{+0.3}_{\ddagger}$$

$$(k^{H_2O}/k^{D_2O})_{sec} = (1.5)^{2(0.3)} \left(\frac{1}{1.7}\right) = 0.75$$

For <u>k_2</u>



$$OH^{-1} \longrightarrow (OH)^{-0.7}_{\ddagger}$$

$$(k^{H_2O}/k^{D_2O})_{sec} = \left(\frac{1}{2}\right)^{0.3} \left(\frac{1}{1.7}\right) = 0.48$$

Figure V. Calculation of secondary isotope contributions

ignore solvation changes originating from C-N bond breaking by not including a $4(H_2O) + N^{\ominus}R_1R_2(D_2O)_4 \rightleftharpoons 4(D_2O) + N^{\ominus}R_1R_2(H_2O)_4$ isotope term. The values of $(k^{H_2O}/k^{D_2O})_{obs}$ in Table VII were obtained for k_a, k_1, and k_2 from equation (3) for reaction of trifluoro-N-methylacetanilide at 25.00±0.05° in water and deuterium oxide, each at thirteen concentrations of lyoxide from 1.5×10^{-3}M to 3.5×10^{-2}M. Values of the primary isotope contribution were calculated as described above.

Table VII

Primary isotope contributions

rate constant	$(k^{H_2O}/k^{D_2O})_{obs}$	$(k^{H_2O}/k^{D_2O})_{pri}$
k_a	1.0 ± 0.2	
k_1	3.3 ± 0.7	4.4 ± 1
k_2	2.2 ± 0.3	4.6 ± 1

If the calculation of the primary contribution to the solvent isotope effect is assumed correct, (the authors point out that this kind of assumption may not be

valid since no solvent isotope effect was observed for k_a where one would be expected), then this observation of sizable primary isotope effects in Table VII must eliminate the operation of the solvation rule in this system. Although the authors take the above evidence to indicate a proton transfer in the rate determining step, they choose to assume that no C-N bond breaking is occuring in the transition state.

SUMMARY

The kinetics of the basic hydrolysis of trifluoro-N-methylacetanilide was shown to be uneffected by added salt up to an ionic strength of 0.557M. The observed first-order rate constant showed a dependency on hydroxide concentration which changed form at high hydroxide concentrations. General base catalysis of adduct decomposition to products was observed to be superimposed upon specific hydroxide ion catalysis. Inapplicability of the solvation rule to the process of adduct decomposition was indicated by the finding of sizable primary isotope contributions to the solvent isotope effect.

BIBLIOGRAPHY

1. J. Hine, "Physical Organic Chemistry", McGraw-Hill, New York, N. Y. (1962).
2. S. S. Biechler and R. W. Taft Jr., J. Am. Chem. Soc., 79, 4927 (1957).
3. M. L. Bender and R. D. Ginger, J. Am. Chem. Soc., 77, 348 (1955).
4. R. W. Taft, Jr. in M. S. Newman, "Steric Effects in Organic Chemistry", J. Wiley and Sons, New York, N. Y. (1956).
5. R. W. Taft, Jr., J. Am. Chem. Soc., 75, 4231 (1953).
6. A. Bruylants and F. Kezdy, Record Chem. Prog., 21, 213 (1960).
7. R. L. Schowen and G. W. Zuorick, J. Am. Chem. Soc., 88, 1223 (1966).
8. R. L. Schowen and G. W. Zuorick, Tet. Letters, 3839 (1965).
9. P. M. Mader, J. Am. Chem. Soc., 87, 3191 (1965).
10. M. Eigen, W. Kruse, C. Maass and L. Demaeyer, Progr. Reaction Kinetics, 285 (1964).
11. J. F. Bunnett in S. L. Friess, "Investigation of Rates and Mechanisms of Reactions", vol. 8, pt 1, Interscience, New York, N. Y. (1961), pg 239.
12. Annual Reports, LX (1963), pg 49.
13. M. Eigen, Angewandte Chemie, 75, 489 (1963).
14. R. L. Schowen, H. Jayaraman and L. Kershner, Tet. Letters, 497 (1966).
15. C. G. Swain, Am. Chem. Soc., 144th Meeting, Los Angeles (1963).
16. R. L. Schowen, H. Jayaraman and L. Kershner, J. Am. Chem. Soc., 88, 3373 (1966).
17. W. P. Jenks and M. Gilchrist, J. Am. Chem. Soc., 86, 5616 (1964).
18. J. E. Leffler, Science, 117, 340 (1953).
19. C. G. Swain, D. A. Kuhn and R. L. Schowen, J. Am. Chem. Soc., 87, 1553 (1965).
20. F. H. Westheimer, Chem. Reviews, 61, 268 (1961).
21. R. L. Schowen, H. Jayaraman, L. Kershner, and G. W. Zuorick, J. Am. Chem. Soc., 88, 4008 (1966).
22. V. Gold and B. M. Lowe, Proc. Chem. Soc., 140 (1963).
23. V. Gold, Proc. Chem. Soc., 141 (1963).
24. A. J. Kresge and A. L. Allred, J. Am. Chem. Soc., 85, 1541 (1963).
25. P. Solomaa, L. L. Schaleger and F. A. Long, J. Am. Chem. Soc., 86, 1 (1964).
26. L. B. Jones, Ph.D. Thesis, Massachusetts Institute of Technology, (1964).
27. C. G. Swain, A. D. Ketley and R. F. Bader, J. Am. Chem. Soc., 81, 2353 (1959).
28. R. L. Schowen, Personal Communication, 12/5/66.

STABLE CARBONIUM ION SALTS

Reported by Jon A. Kapecki January 5, 1967

Stable carbonium ion salts have been known to chemists as far back as the beginning of the century,[1] long before carbonium ions themselves gained general acceptance as reaction intermediates. It is only in the last decade, however, that systematic research has been directed toward their preparation and structural elucidation.[2]

The carbonium ion salts isolated thus far have generally been stabilized by delocalization over pi-systems. Specifically, the positive center has either been a part of a Hückel aromatic system or has been conjugated to two or more aromatic systems. The salts are often prepared from the corresponding halides or hydrocarbons by reaction with strong Lewis acids.[3] Probably the most important characteristic of the stable carbonium ion salts is that they are amenable to more structurally definitive forms of investigation such as x-ray crystallography. These studies would be of interest not only in themselves, but also as a model for and test of our understanding of the structure of less stable carbonium ions. Such comparisons are, of course, subject to at least one important caveat--the nature of the solid state will always differ in some degree from that of the solvated system.

Carbonium ions have been the subject of several recent reviews,[4,5] including summaries of the spectroscopic studies in strong acids[6-8] and of α- and β-metallocenyl-carbonium ion systems.[9] This seminar will in general survey the literature since 1963.

STRUCTURES OF SOME MONOCARBONIUM ION SALTS

The most widely studied stable carbonium ion salts are those belonging to the triphenylmethyl system. Walden[1] reported the preparation of triphenylmethyl chlorostannate and other similar salts in 1902, while Hofmann and Kirmreuther[10] prepared the perchlorate salt seven years later. Since then many other similar salts have been prepared by various routes.[2,11]

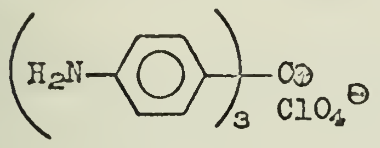
Such salts would be expected to derive their stability for the most part by a delocalization of the positive charge into the aromatic rings. This resonance interaction would be greatest for a fully planar ion with D_{3h} symmetry. It was recognized early,[12] however, that the all-planar configuration would lead to strong steric interactions between the ortho hydrogens of adjacent aromatic rings. Accordingly, a propeller-like model (D_3 symmetry) in which the aromatic rings are equivalent but slightly twisted out of the central plane by rotation about the central carbon bonds was proposed. An alternative model in which the positive charge is delocalized into only one or two of the rings has also been proposed.[13] The three rings, though presumably not all twisted out of the central plane to the same degree in this model and therefore not equivalent in the resonance hybrid, may become equivalent by a time averaging process.

Sharp and Sheppard[2] have studied the infrared spectra of a large number of triphenylmethyl salts and find that they are consistent with D_3 symmetry in the cation. The vibration frequencies of the highly symmetric anions employed in the study were also used to distinguish true ionic compounds from molecular complexes.[14] An x-ray diffraction study of tris(p-dimethylaminophenyl)methyl bromide[15] confirmed the presence of three-fold symmetry in the cation, but yielded no further details.

The first complete x-ray structure determination of a carbonium ion salt, triphenylmethyl perchlorate, was reported by Gomes de Mesquita, MacGillavry, and Eriks.[16] The salt was prepared by treatment of triphenylcarbinol with perchloric acid in acetic anhydride.[10] Above 85°, the salt crystallizes in a face-centered cubic lattice suitable for analysis. The unit cell contains 16 formula units and two types of structurally different perchlorate ions, one of which is disordered. The refinement of the structure was carried out for two models of disorder. Although these reduced the R-factor to 0.091 and 0.084, respectively, neither model was entirely satisfactory, leaving unaccounted for maxima and minima in the difference map. The results of the analysis for the cation show that all three phenyl groups are essentially equivalent and planar and that they are twisted by 31.8 ± 0.6° out of the plane defined by the trigonal central carbon and its three bonds. This corresponds to an angle (α) of 54.3° between adjacent aromatic rings.

Assuming that the distance between the *ortho* hydrogens of adjacent rings is twice the van der Waals radius for hydrogen, Deno, using various molecular parameters,[4,13] has calculated the minimum value of α to be 47, 54 or 60°. The minimum distance between hydrogen atoms of adjacent rings was found from the x-ray study to be 2.6Å, while the average distance from the central carbon atom to an attached phenyl carbon was 1.44Å. Crystals of triphenylmethyl tetrafluoroborate, investigated by the same authors in hopes of finding a well-ordered crystal which would give more reliable structural information, were found to be even more disordered at room temperature than the perchlorate salt. Data collected at 110° showed the BF_4^- salt to be isomorphous with the perchlorate.[16]

Eriks and Koh have reported the x-ray structure determination of a similar carbonium ion salt, *p*-rosaniline perchlorate (I).[17] The crystal is monoclinic and contains four molecules per unit cell. The crystallographic R-factor was reported as 0.11. As expected, the central carbon atom and its three bonds lie in a plane while the aryl groups are in the propeller form. It is highly interesting, however, that the benzene rings are not twisted equally out of the central plane; rather the angles of twist are 29, 34 and 34°. Whether this is indicative of a set of non-symmetrical isomers in which the extent of conjugation across the three aryl groups differs or whether it is merely the result of crystal packing forces is not obvious from the published data. The benzene rings are reported to be planar and to possess a "quinoid" structure[17] (Figure 1). Presumably, the bond distances given have been averaged over the three rings. It would be highly informative to find out how they differ in the rings twisted by 29 and 34°.



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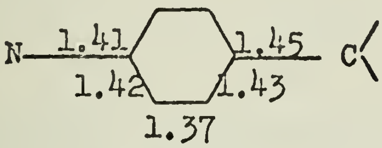


Figure 1

The cyclopropenyl carbonium ion is expected to be a stable aromatic system. As such, it has not been isolated, but in 1957 Breslow reported the first preparation of a stable derivative of this system, the *sym*-triphenylcyclopropenyl cation,[18] isolated as the mixed BF_4^--BF_3OH^- salt by treatment of 1,2,3-triphenylcyclopropenyl cyanide with boron trifluoride etherate. On the basis of van der Waal's radii interactions[19] and examination of molecular models,[20] the ion was predicted to be planar, and a pi-delocalization energy of 9.16β was calculated using simple LCAO approximations.[19,21] More recently, Breslow and co-workers have isolated a series of di- and tri-aryl and alkyl substituted cyclopropenium salts.[20,22] The stability of the alkyl salts has been explained in terms of σ-inductive electron donation by the alkyl groups to the cyclopropenium nucleus.[22] West, Sadô, and Tobey have isolated salts of the trichlorocyclopropenium ion by treatment of tetrachlorocyclopropene with $AlCl_3$, $SbCl_5$, $FeCl_3$, and $GaCl_3$. Normal co-ordinate analysis confirmed the D_{3h} symmetry expected for the cation.[23]

Sundaralingam and Jensen have recently completed an x-ray study of *sym*-triphenylcyclopropenium perchlorate.[24] The needle-like crystals belong to the monoclinic space group $P2_1/c$ with four molecules per unit cell. The structure was refined to an R-factor of 0.075 using integrated photometric data. The cyclopropenyl ring and the three carbon atoms attached to it are nearly planar, however, the phenyl rings, contrary to earlier predictions,[19,20] are twisted in a propeller-like arrangement. The angles of twist (ω) out of the plane of the three-membered ring are 7.6, 12.1, and 21.2°. It is interesting to note that the exocyclic carbon-carbon bond lengths increase with increasing angle of twist, paralleling the decrease in cyclopropenyl-phenyl conjugation that occurs with increasing twist angle (Figure 2). It is also noteworthy that the average length of these exocyclic bonds (1.436Å) is significantly shorter than a normal $C(sp^2)$-$C(sp^2)$ single bond (1.48Å). While this shortening may be due in part to increased conjugation of the phenyl groups to the positively charged central ring, it is more likely the result of the increase in s-character conferred upon orbitals pointing toward the phenyl rings by the large exocyclic bond angles (about 150°). Thus these orbitals are probably best formalized as sp^x where $2 > x > 1$.

Calculations based on the observed bond lengths and angles predict that a value

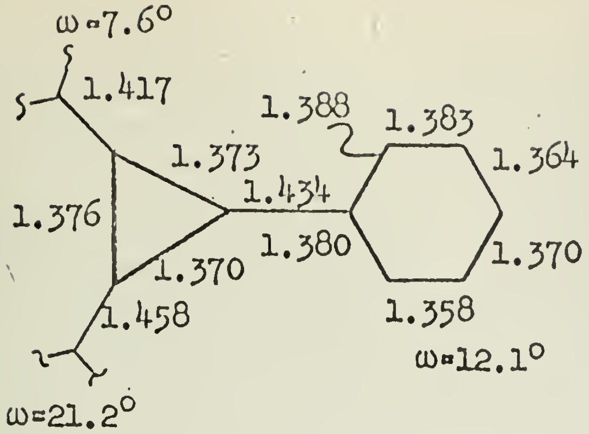


Figure 2

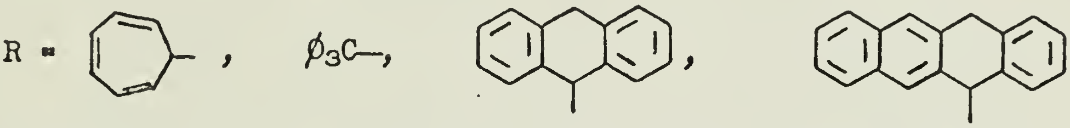
of ω = 13.6° would be sufficient to relieve *ortho* hydrogen compression. This is indeed equal to the mean value of the observed twist angles. The cyclopropenium ring is symmetrical with an average bond length of 1.373 ± 0.005Å, considerably shorter than the carbon-carbon bonds found in benzene.

RECENT PREPARATIONS OF CARBONIUM ION SALTS

Holmes and Pettit have recently prepared a series of carbonium ion salts by the reaction of antimony pentachloride with various hydrocarbons.[3] The reaction has the stoichiometry indicated in equation (1) as determined by quantitative isolation of antimony trichloride, which precludes the possibility that the compounds isolated may have been antimony pentachloride-hydrocarbon complexes.[14] In addition, the salts react smoothly with water or tropylidene to regenerate the hydrocarbons. The authors were unable to isolate a carbonium ion salt from the reaction of diphenylmethane with antimony pentachloride, though the presence of the diphenylmethyl carbonium ion in methylene chloride solution was detected by comparison of the UV-visible spectrum (λ_{max} = 451 mμ) with that of the authentic ion prepared from diphenylmethylchloride. No mechanistic studies have been carried out on these reactions, however, the simplest explanation would seem to be a direct hydride abstraction (equations 2 and 3) although the intermediacy of a charge transfer complex of the type $[RH^{+}\cdot SbCl_5^{-}]$ cannot be presently ruled out.[14] The applicability of other strong Lewis acids such as phosphorus pentachloride, stannic chloride, and the boron halides to similar reactions has not been thoroughly investigated.[25]

$$(1)\qquad RH + 2SbCl_5 \xrightarrow[\text{or}\ CS_2]{\phi H} R^{+}SbCl_6^{-} + SbCl_3 + HCl$$

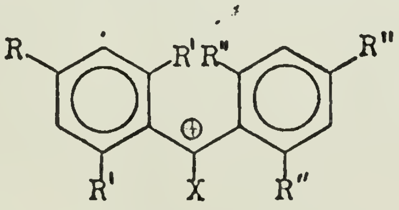
R =



$$(2)\qquad RH + SbCl_5 \longrightarrow R^{+} + HSbCl_5^{-}$$

$$(3)\qquad HSbCl_5^{-} + SbCl_5 \longrightarrow SbCl_6^{-} + SbCl_3 + HCl$$

Volz has prepared a series of diaryl carbonium ions (Table I) by treatment of the corresponding halides with antimony pentachloride in carbon tetrachloride under



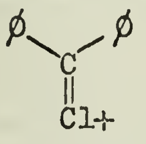
II

Table I

II	R	R'	R"	X	λ_{max}[a]	ref
a	H	H	H	H	453 (451)[b]	26,27,(3)
b	CH_3	H	H	H	459	27
c	CH_3	CH_3	H	H	465	27
d	CH_3	CH_3	CH_3	H	522	27
c	H	H	H	Cl	446 (443)[b]	28

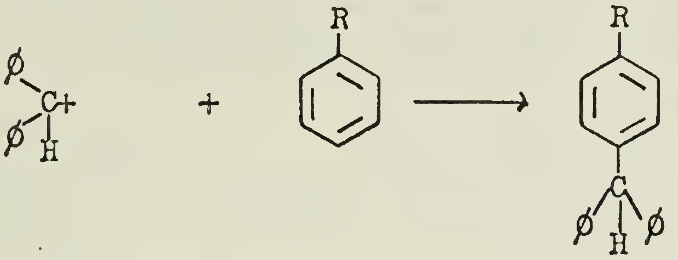
a=in CH_3NO_2, b=in CH_2Cl_2

a dry nitrogen atmosphere. The salts react smoothly with tropylidene to generate the corresponding diarylmethanes and tropylium hexachloroantimonate. An intense band at 339 cm^{-1} in the infrared spectra of the salts indicated the presence of the $SbCl_6^-$ anion. The nmr spectrum (δ units, relative to TMS) of IId is typical: 9.69 (proton X), 7.15 (ring protons), 2.50 and 2.43 ppm (methyl protons, 1:2). In IIc, the phenyl ring protons appear at 7.84-7.33 ppm. Interestingly, there are no changes in the methyl proton signals of IId over the temperature range -60 to +90°. The relative stabilities of the carbonium ions with respect to their halide precursors were determined by exchange reactions with the di- and triaryl halides and found to be in the order $\phi_3C^+ > IId > IIa \sim IIb > IIc$.[27] The significance of this order is not entirely clear, especially since the authors do not give experimental details. It might be presupposed that IId would be the least stable cation due to strong steric interactions between the ortho methyl groups which would dictate a large phenyl twist angle and hence a decrease in conjugation between the phenyl groups and the positive center. However, it is possible that the relative stabilities of the halides differ enough to strongly influence the ranking. Although salts IIa, IIb, and IIc are rapidly decomposed by moist air, IId can be kept open to the atmosphere for several hours, possibly because its ortho methyl groups effectively shield the center of positive charge. In similar exchange experiments,[28] IIe lies between the triphenylmethyl cation and IIa in stability, which was taken to indicate that the pi-conjugative effect (structure IIe') dominates over the electron withdrawing effect of the chlorine. The salt IIa reacts with ethyl triphenylmethyl ether to give benzhydryl ethyl ether and with water or 2N sodium hydroxide to yield mostly dibenzhydryl ether along with some benzhydryl chloride, benzophenone, and diphenylmethane. If the salts are suspended in benzene and shaken with water or base, IIa and IIc give mostly the diarylchloromethanes while IId yields exclusively dimesitylmethanol. Salt IIe reacts with water in 90% yield to give benzophenone. The diphenylmethyl salt acts as an alkylating agent towards the benzene nucleus (equation 4) at room temperature and with benzhydrol in benzene gives a 93% yield of triphenylmethane and 6% of a mixture containing α,α,α',α'-tetraphenyl-p-xylene, benzophenone, and diphenylmethane.



IIe'

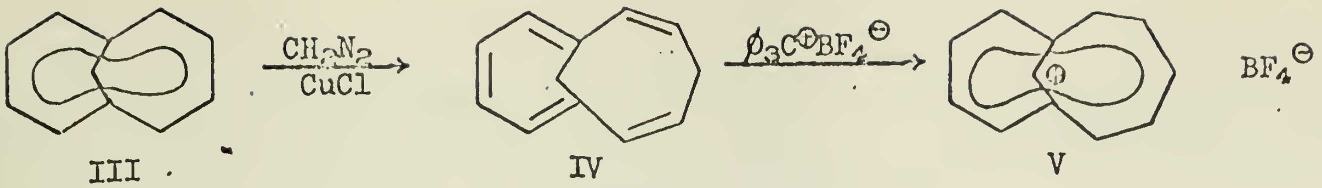
(4)



R	%yield
H	22-29%
CH_3	40-42%
OCH_3	61-65%

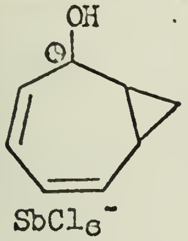
Deno and co-workers have reported the isolation of tricyclopropylmethyl hydroxytrifluoroborate as a crystalline solid from the treatment of tricyclopropyl carbinol with HBF_4.[29] The salt in 96% sulfuric acid shows one signal in the nmr at δ 2.26 ppm as does the tricyclopropylmethyl cation generated in solution. An x-ray structure determination is said to be under consideration.[29] Hexachloropropene, while unreactive towards the Lewis acids BCl_3, $SnCl_4$, and $FeCl_3$, forms 1:1 solid products with $AlCl_3$, $GaCl_3$, and $SbCl_5$.[30] The infrared spectra of these compounds are essentially identical above 500 cm^{-1} and do not exhibit the strong C=C stretching band found at 1550 cm^{-1} in the olefin. Assignment of the bands in the spectra is consistent with the presence of pentachloroallyl cation and appropriate anion. While it is not possible on the basis of present evidence to completely exclude some sort of metal halide-olefin pi-complex, the evidence seems to favor the free carbonium ion. It is interesting that all three of the compounds are highly reactive, even with such normally inert substances as ethers and saturated hydrocarbons.

Bicyclo[5.4.1]dodecapentaenyl fluoroborate (V), a carbonium ion with ten pi-electrons, has been synthesized by Vogel and co-workers according to Scheme I.[31] In the nmr spectrum, the ring protons of V appear as a complex multiplet at δ 9.6-8.3, and the highly shielded bridge protons are found at δ -0.3 and -1.8 ppm (doublets, J = 10 cps). Both IV and V on catalytic hydrogenation give the same saturated hydrocarbon $C_{12}H_{22}$, believed to be bicyclo[5.4.1]dodecane. The nmr and ultraviolet spectra

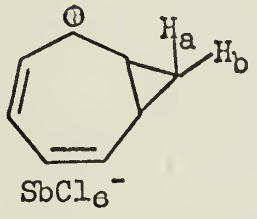


Scheme I

of V are reported to be similar to those observed for the benzotropylium cation. Pettit and co-workers have reported the isolation of two carbonium ions (VI and VII)[32] derived from the cyclooctatetraene system. In the nmr spectrum of VII, proton a appears at δ 0.6 while proton b appears at δ 5.2 ppm, indicative of the presence of a ring current.[32] Volz reports the isolation of a mixture containing pentaphenylcyclopentadienyl hexafluoroantimonate and a molecular complex of the pentaphenylcyclopentadienyl halide with antimony pentachloride.[33] Although the exchange reaction of the cation with tropylidene is reported and the ESR spectrum has been measured, there remains some doubt as to the nature of the species present.[34] Infrared spectroscopy indicates that the recently prepared triazidomethylium hexachloroantimonate, $[C(N_3)_3]^+[SbCl_6]^-$, possess C_{3v} symmetry with the three α-nitrogen atoms and the carbon atom co-planar and the azido groups bent to the same degree at the α-nitrogens.[35] Several new substituted cyclopropenyl cations have been recently prepared as intermediates in the syntheses of substituted calicenes,[36,37] and the isolation of a 1:1 crystalline molecular complex of phenothiazine and dibenzotropylium tetrafluoroborate has been reported.[38]



VI

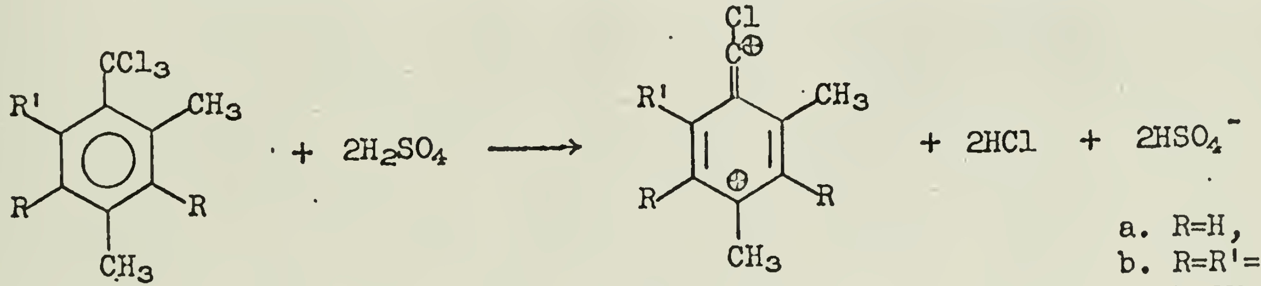


VII

DI- AND TRICARBONIUM ION SALTS

Several years ago Hart and Fish[39] reported the detection of the unusual dicarbonium ions VIIa-c derived from the ionization of α,α,α-trichloropolymethylbenzenes in 100% sulfuric acid. The authors presented as evidence the determination

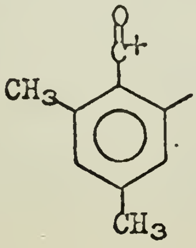
(5)



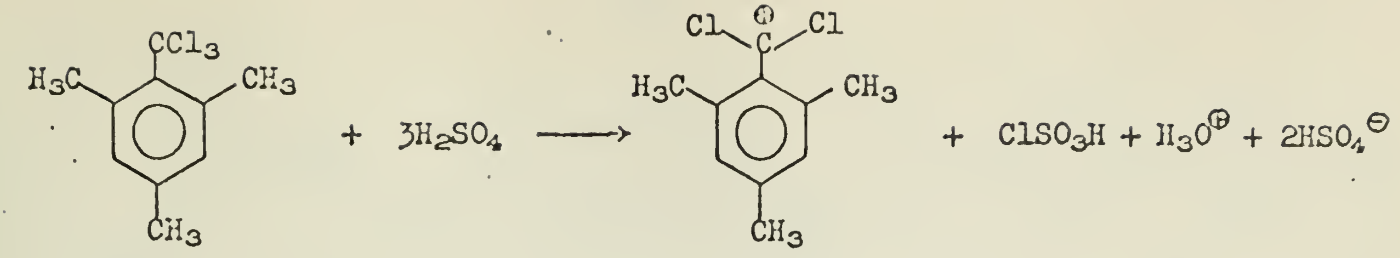
a. $R=H$, $R'=CH_3$
b. $R=R'=CH_3$
c. $R=CH_3$, $R'=H$

of the freezing point depression of the sulfuric acid solution, conductance measurements showing the formation of two hydrogen sulfate ions per atom of VI (equation 5), nmr spectra and other data. Later, Hart and Fleming reported the isolation of dicarbonium ions VIIa and b as their boron tetrahalide salts.[40] The salts exhibited nmr spectra similar to those observed for the ions generated in sulfuric acid solution [for VIIa: δ 6.96 (2H), 2.27 (6H), 2.12 (3H)] and gave satisfactory analyses for BX_4^- and chloride ion.

More recently Gillespie and Robinson have found that HCl in 100% sulfuric acid is not a non-electrolyte as represented by equation (5) but rather is nearly quantitatively ionized. In addition, the nmr and UV spectra of the ion generated from VIa in sulfuric acid have been found to be very similar to those of the mesitoyl cation (VIII) under identical conditions.[42] Furthermore, the conductivity curves for VIa and VIII in chlorosulfuric acid are virtually identical.[43] This and further evidence[42] has led several authors[41-45] to propose that reaction of VIa occurs according to equation (6) and that Hart has actually observed the mesityldichlorocarbonium ion (IX). By treatment of VIa with $SbCl_5$ in carbon tetrachloride,



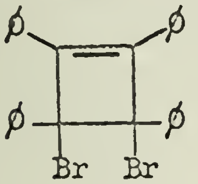
VIII

(6) 

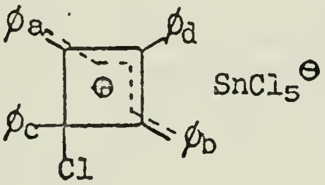
VIa IX

Volz has isolated a deep red crystalline compound whose antimony and chloride analyses are consistent with the hexachloroantimonate salt of IX.[45] The salt reacts with tropylidene to give in 85% yield α,α-dichloromethylmesitylene, and on hydrolysis yields mesitylcarboxylic acid. Volz has also been able to isolate α,α-dichlorobenzyl hexachloroantimonate as a stable salt.[45] Interpretation of the evidence is further complicated by the decomposition of IX, both in acid solution[42,44] and on exposure of the salt to moist air,[45] probably resulting in the formation of VIII or protonated mesitylcarboxylic acid. That this latter species may have been the one observed by Hart and Fish has also been proposed.[44] While the evidence seems strongly to favor the monocarbonium ion IX over the dicarbonium, the analytical results on the salts prepared by Hart[40] cannot be easily reconciled, and Hart continues to consider the species a dicarbonium ion.[46] An x-ray analysis of one of these salts would be useful in settling the structural problem.

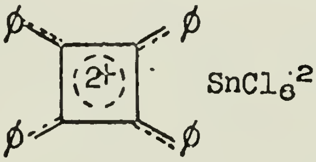
Treatment of 3,4-dibromotetraphenylcyclobutene (X) with excess tin tetrachloride gives in 75% yield a brick-red crystalline compound analyzing for $C_{28}H_{20}SnCl_6$.[47] This molecular formula is consistent with both a monocarbonium ion (XI) and dicarbonium ion salt (XII). The compound shows no nmr absorptions in the usual phenyl range



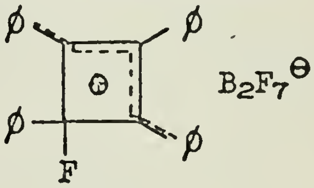
X



XI



XII



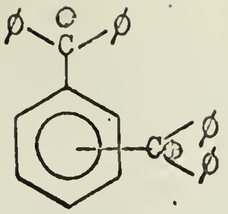
XIII

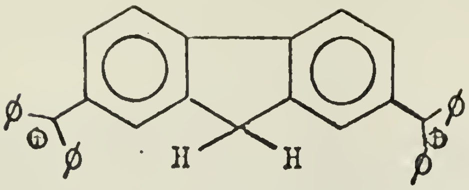
(δ 6.5-7.5), but only below 7.5 ppm. Addition of excess tropylidene converts it to 1,2,3,4-tetraphenylcyclobutene. Treatment of X in benzene or methylene chloride with two moles of a monovalent silver salt rapidly precipitates two moles of silver bromide while hydrolysis of the deep red sulfuric acid solution of X yields a mixture of bromine-free products. Application of Hückel molecular orbital theory predicts[48] that simultaneous ionization of the two bromines to give a cyclobutadienyl system conjugated to four phenyl groups is greatly favored over the ionization of only one bromine to yield a phenyl-conjugated allyl cation. Analysis of the crystalline compound by x-ray diffraction, however, reveals that, in the solid state at least, the carbonium ion salt has structure XI.[49] Phenyl rings a and b and the four-membered ring lie in a plane while phenyl rings c and d make angles of 83° and 57° to this plane. Ring d is twisted about the bond joining it to the four-membered ring, but ring c, surprisingly, shows no such twist. Thus it appears that charge delocalization takes place primarily over rings a and b.[50]

There remains the question as to what species exists in solution. In the case of the carbonium ion derived from 1,2,3,4-tetramethyl-3,4-dichlorocyclobutene, the nmr spectrum strongly indicts the monocation.[48] The F^{19} nmr spectrum of the compound prepared by treatment of X with two moles of silver tetrafluoroborate was originally interpreted as supporting the dication.[51] However, investigations in progress indicate that the species in solution is actually XIII.[52]

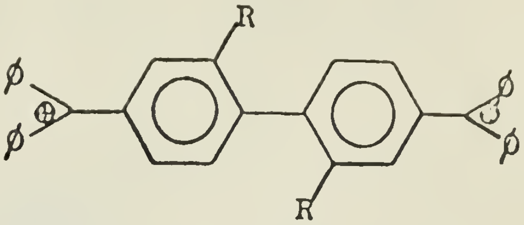
Volz and Volz de Lecea have recently prepared in good yields a highly interesting series of what appear to be di- and tricarbonium ion salts (XIV-XVII) by treatment of the corresponding di- and trihalides with $SbCl_5$ in carbon tetrachloride.[53-55] The salts react with tropylidene to give in 80 to 90% yields the corresponding hydrocarbons and exhibit nmr chemical shifts comparable to those found for similar carbonium ion salts such as the triphenylmethyl cation. Of particular interest is the series of dicarbonium ions XV, XVIa, and XVIb.[54] As the angle of twist about

XIV
a. meta
b. para

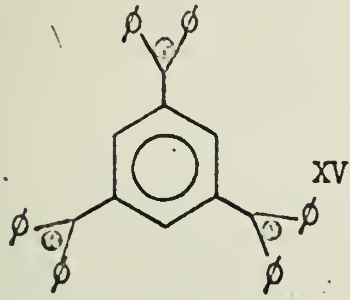




XV



XVI
a. R=H
b. R=CH_3



XVII

Compound	nmr signals in CH_3NO_2	λ_{max}
XIVa	7.27, 7.18, 6.86[a]	458
XIVb	7.35, 7.17, 6.82[a]	418
XV	7.98-8.43, 7.47	548
XVIa	7.86-8.74, 4.52	518
XVIb	7.9-8.62	456
XVII	8.06-8.6 (30 H), 7.43 (3 H)	419, 445s

[a] in SO_2

the central bond joining the two aryl groups increases, the degree of conjugation between the two positive centers is expected to decrease and the molecule begins to approximate two separate triphenylmethyl carbonium ions. Based on a series of model compounds, the angles of twist fall roughly in the range of 0°, 18-25°, and 66-75° for XV, XVIa, and XVIb respectively. The λ maxima of the cations show a corresponding decrease in wavelength (by 30 and 62 mμ respectively) with increasing twist angle, though even for the maximally twisted ion the λ_{max} is still greater by 25 mμ than that observed for the isolated triphenylmethyl cation, indicating the presence of at least some interaction between the positive centers. Molecular orbital calculations predict that the charge densities in the ortho and para positions of XV, XVIa, and XVIb are of the same order of magnitude as in the triphenylmethyl carbonium ion, and this is reflected in similar nmr chemical shifts. HMO calculations also predict carbonium ion XV to be somewhat more stable than the triphenylmethyl cation, which parallels the stabilities found by exchange experiments.

In contrast, HMO calculations for the tricarbonium ion XVII predict little interaction between the three positive centers, and as a result, XVII might be expected to resemble three isolated triphenylmethyl cations in its spectral properties. Indeed, the absorption spectrum shows only a slight shift in λ_{max} towards longer wavelengths when compared to the monocation. The nmr spectrum strongly suggests that XVII actually exists as the trication since all 30 phenyl protons appear shifted downfield. There appear to be two opposing effects acting on the protons of the central ring. One is the strong electron withdrawal by the positive centers, and the second, easily seen by means of models, is the shielding effect of the nearby phenyl groups. The appearance of a three-proton singlet at δ 7.43 ppm indicates that the latter effect is dominant. The possibility that the compounds isolated by Volz are only monocarbonium ion salts complexed with $SbCl_5$ and that the nmr spectra are the result of a time-averaged process cannot at the moment be rigorously excluded. An x-ray structure determination would not only settle this lingering question, but would also provide interesting information on the geometry in these systems.

CONCLUSION

The preliminary application of x-ray diffraction techniques to stable carbonium ion salts has led to no radical changes in our ideas about the structure of carbonium ions. The power of such techniques has been to definitively determine a specific

structure and to provide information on molecular parameters which could only be estimated by other means. In the past few years, a large number of stable mono- and possibly di- and tricarbonium ion salts have been synthesized. That many of these deserve further study seems obvious.

BIBLIOGRAPHY

1. P. Walden, Ber., 35, 2018 (1902).
2. D. W. Sharp and N. Sheppard, J. Chem. Soc., 674 (1957).
3. J. Holmes and R. Pettit, J. Org. Chem., 28, 1695 (1963).
4. N. C. Deno in Progress in Physical Organic Chemistry, Vol. 2, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, ed., Interscience Publishers, New York, 1964, p. 129.
5. K. Okamoto, Koyo Kagaku Zasshi, 69, 825 (1966).
6. J. D. Druliner, University of Illinois Organic Seminars, Summer, 1964, p. 50.
7. J. E. Gano, University of Illinois Organic Seminars, Spring, 1966, p. 40.
8. G. A. Olah and C. V. Puttman, Jr., in Advances in Physical Organic Chemistry, Vol. 4, V. Gold, ed., Academic Press, New York, 1966, p. 305.
9. M. Cais, Record Chem. Progr. (Kresge-Hooker Sci. Lib.), 27, 177 (1966).
10. K. A. Hofmann and H. Kirmreuther, Ber., 42, 4856 (1909).
11. H. J. Dauben, Jr., L. R. Honnen, and K. M. Harmon, J. Org. Chem., 25, 1442 (1960).
12. G. N. Lewis, T. T. Magel, and D. Lipkin, J. Am. Chem. Soc., 64, 1774 (1942).
13. N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, J. Org. Chem., 19, 155 (1954).
14. W. I. Aalbersberg, G. J. Hoijtink, E. L. Mackor, and W. P. Weijland, J. Chem. Soc., 3055 (1959).
15. C. Stora, C. R. Acad. Sci. Paris, 246, 1693 (1958).
16. A. H. Gomes de Mesquita, C. H. MacGillavry, and K. Eriks, Acta Cryst., 18, 437 (1965).
17. K. Eriks and L. L. Koh, Abstracts of the American Crystallographic Association Meetings, Massachusetts Institute of Technology, Cambridge, Mass., March 28-30, 1963, p. 51.
18. a) R. Breslow, J. Am. Chem. Soc., 79, 5318 (1957); b) R. Breslow and C. Yuan, J. Am. Chem. Soc., 80, 5991 (1958).
19. D. A. Bochvar, I. V. Stankevich, and A. L. Chistiakov, Russ. J. Phys. Chem., 33, 593 (1959).
20. R. Breslow and H. W. Chang, J. Am. Chem. Soc., 83, 2369 (1961).
21. D. A. Bochvar, I. V. Stankevich, and A. L. Chistiakov, Bull. Acad. Sci. USSR (English Trans.), 775 (1958).
22. a) R. Breslow, J. Lockhart, and H. W. Chang, J. Am. Chem. Soc., 83, 2375 (1961); b) R. Breslow, H. Höver, and H. W. Chang, ibid., 84, 3168 (1962).
23. R. West, A. Sadô, and S. W. Tobey, J. Am. Chem. Soc., 88, 2488 (1966).
24. M. Sundaralingam and L. H. Jensen, J. Am. Chem. Soc., 85, 3302 (1963); ibid., 88, 198 (1966).
25. a) D. N. Kursanov and M. E. Volpin, Dokl. Akad. Nauk, SSSR, 113, 339 (1957); b) D. Bryce-Smith and N. A. Perkins, J. Chem. Soc., 2320 (1961); c) ibid., 1339 (1962).
26. H. Volz, Angew. Chem. Intern. Ed. Engl., 2, 622 (1963).
27. H. Volz and H. W. Schnell, Angew. Chem. Intern. Ed. Engl., 4, 873 (1965).
28. H. Volz and W. D. Mayer, Tetrahedron Letters, 5249 (1966).
29. N. C. Deno, H. G. Richey, Jr., J. S. Liu, D. N. Lincoln, and J. O. Turner, J. Am. Chem. Soc., 87, 4533 (1965).
30. R. West and P. T. Kwitowski, J. Am. Chem. Soc., 88, 5280 (1966).
31. W. Grimme, H. Hoffmann, and E. Vogel, Angew. Chem. Intern. Ed. Engl., 4, 354 (1965).
32. a) J. L. von Rosenberg, Jr., J. E. Mahler, and R. Pettit, J. Am. Chem. Soc., 84, 2842 (1962); b) J. D. Holmes and R. Pettit, ibid., 85, 2532 (1963).
33. H. Volz, Tetrahedron Letters, 1899 (1964).
34. See also R. Breslow, H. W. Chang, and W. A. Yager, J. Am. Chem. Soc., 85, 2033 (1963); R. Breslow, R. Hill, and E. Wasserman, ibid., 86, 5349 (1964).

35. U. Müller and K. Dehnicke, Angew. Chem. Intern. Ed. Engl., 5, 841 (1966).

36. W. M. Jones and R. S. Pyron, J. Am. Chem. Soc., 87, 1608 (1965).

37. a) H. Prinzbach, D. Seip, and V. Fischer, Angew. Chem. Intern. Ed. Engl., 4, 242 (1965); b) H. Prinzbach and U. Fischer, ibid., 4, 598 (1965).

38. M. Feldman and J. A. Jackson, Tetrahedron Letters, 797 (1966).

39. H. Hart and R. W. Fish, J. Am. Chem. Soc., 80, 5894 (1958); ibid., 83, 4460 (1961).

40. H. Hart and J. S. Fleming, Tetrahedron Letters, 983 (1962).

41. R. J. Gillespie and E. A. Robinson, J. Am. Chem. Soc., 86, 5676 (1964).

42. R. J. Gillespie and E. A. Robinson, J. Am. Chem. Soc., 87, 2428 (1965).

43. E. A. Robinson and J. A. Ciruna, J. Am. Chem. Soc., 86, 5677 (1964).

44. N. C. Deno, N. Friedman, and J. Mockus, J. Am. Chem. Soc., 86, 5676 (1964).

45. H. Volz and M. J. Volz de Lecea, Tetrahedron Letters, 3413 (1965).

46. H. Hart and N. R. Roobol, J. Am. Chem. Soc., 86, 1373 (1964).

47. H. H. Freedman and A. M. Frantz, Jr., J. Am. Chem. Soc., 84, 4165 (1962).

48. T. J. Katz, J. R. Hall and W. C. Neikam, J. Am. Chem. Soc., 84, 3199 (1962).

49. R. F. Bryan, J. Am. Chem. Soc., 86, 733 (1964).

50. R. F. Bryan, private communication, November, 1966.

51. H. H. Freedman and A. E. Young, J. Am. Chem. Soc., 86, 735 (1964).

52. A. E. Young, private communication, December, 1966.

53. H. Volz and M. J. Volz de Lecea, Tetrahedron Letters, 1871 (1964).

54. H. Volz and M. J. Volz de Lecea, Tetrahedron Letters, 4675 (1966).

55. H. Volz and M. J. Volz de Lecea, Tetrahedron Letters, 4683 (1966).

MECHANISMS OF THE DIMETHYL SULFOXIDE OXIDATIONS OF ALCOHOLS, HALIDES, AND ESTERS

Reported by. Richard N. Watson January 9, 1967

INTRODUCTION

The oxidation of alcohols, halides, esters, and other compounds with dimethyl sulfoxide (DMSO) as the oxidizing agent has been used extensively in recent years. These oxidations proceed in high yields, even under mild conditions. Several synthetic successes have been obtained where other oxidizing procedures have failed. It appears that the oxygen atom of the sulfoxide group is well situated for transfer to other substrates, and this leads either directly or indirectly to a sulfoxonium salt which then decomposes to the oxidation products and dimethyl sulfide (DMS).[1]

This seminar will consider the mechanisms involved in the oxidations of alcohols, halides, and esters. Analogous oxidations of acid halides and silanes and oxidation by amine oxides are not included. Oxidations involving sulfoxides other than dimethyl sulfoxide have been reported,[2] but DMSO is by far the most commonly used. Though not specifically discussed, it is hoped that some appreciation of the diverse and general nature of these oxidations for synthesis can be gained.

OXIDATION OF ALCOHOLS BY DIMETHYL SULFOXIDE AND DICYCLOHEXYLCARBODIIMIDE

The reaction of dimethyl sulfoxide and N,N'-dicyclohexylcarbodiimide (I) with alcohols in the presence of an acid may be generalized as shown in Figure 1. The products are one equivalent each of the carbonyl, dimethyl sulfide, and N,N'-dicyclohexyl urea (II).

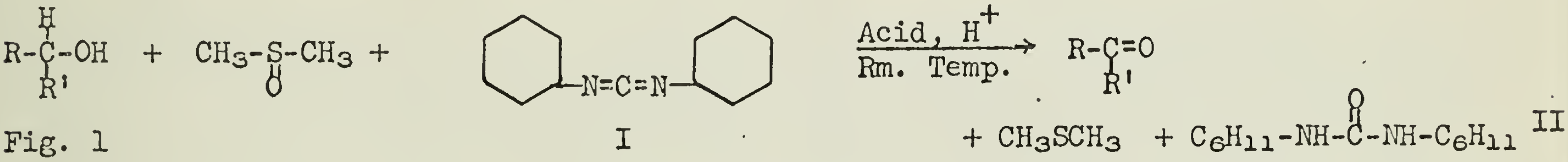


Fig. 1

Acids that may be used are anhydrous orthophosphoric or phosphorous, trifluoroacetic, and the pyridine salts of these acids or those of strong mineral acids. Strong acids and the triethylamine salts of strong acids are not effective in the reaction.[3,4]

Optimal conditions using testosterone as the alcohol were found to be: solution of the alcohol in ca. 6 molar equivalents of DMSO, or a mixture of inert solvent and DMSO, followed by addition of 3 equivalents of N,N'-dicyclohexylcarbodiimide (DCC), and 0.5 equivalents of anhydrous orthophosphoric acid or pyridinium trifluoroacetate.[3,4]

Some representative results are given in Table I, several of the compounds listed are sensitive to other oxidizing agents.

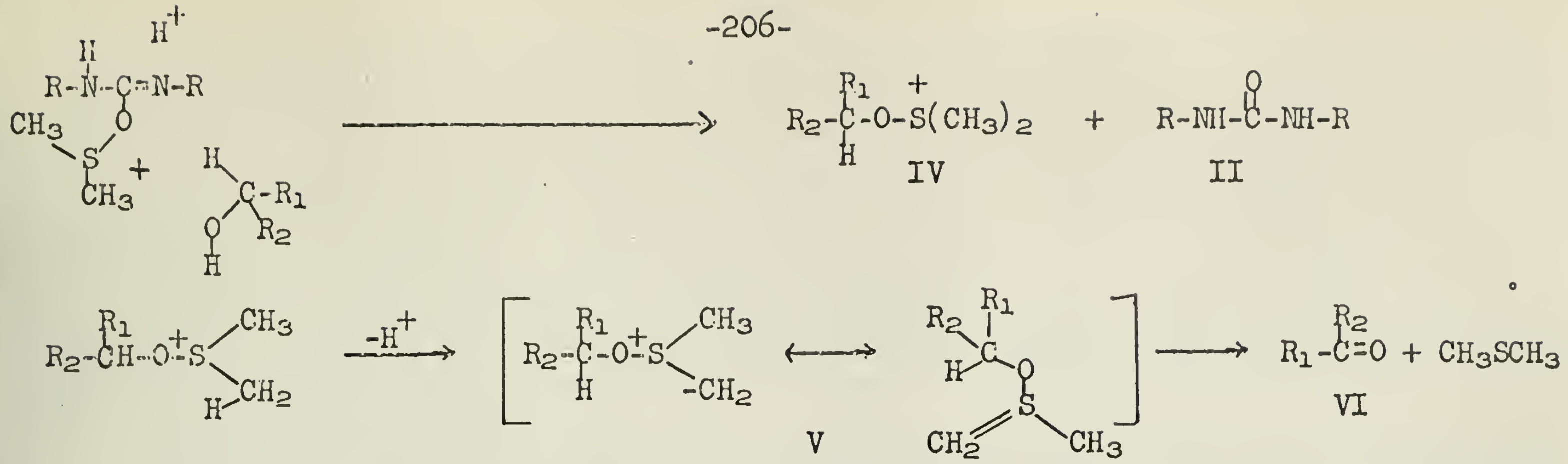
Table I. Some Representative Alcohols Oxidized By DMSO-DCC Solution.

ALCOHOL	PRODUCT	YIELD (%)	REFERENCE
testosterone	androst-4-ene-3,17-dione	87-100	4
p-nitrobenzyl alcohol	p-nitrobenzaldehyde	92	4
androst-5-en-3β-ol-17-one	Δ^5-3-ketone	90	4
yohimbine	yohimbinone	80	5
1-octanol	octylaldehyde	70	6

Pfitzer[3] and Moffatt proposed Mechanism I in which nucleophilic attack of DMSO on the carbodiimide occurs with protonation to yield the intermediate sulfonium isourea (III), which is attacked by the alcohol to form the sulfoxonium salt (IV) and insoluble N,N'-dicyclohexyl urea (II). This is followed by loss of a proton from IV giving a stabilized carbanion (V) which collapses in a concerted manner to the carbonyl (VI) and D

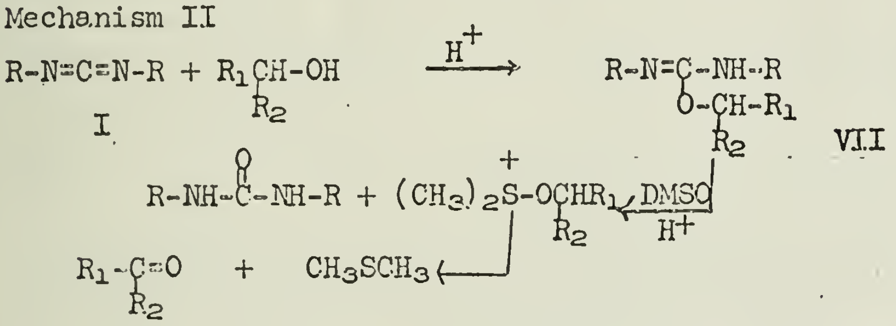
Mechanism I

III



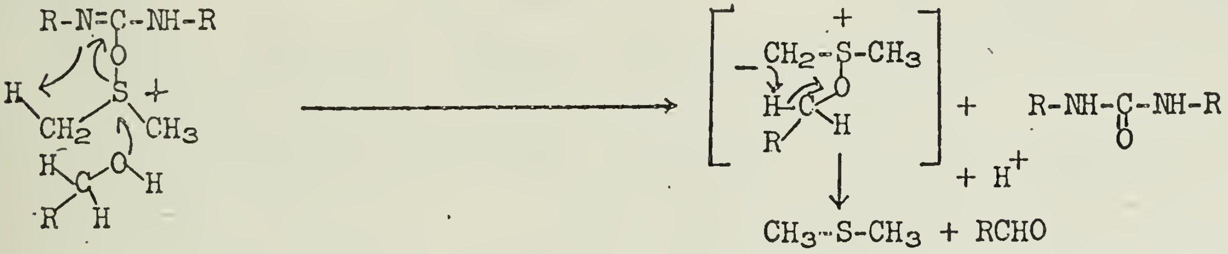
Another possible mechanism is initial formation of an alcohol -DCC adduct, pseudourea (VII), which under reaction with DMSO gives the sulfoxonium salt which decomposes into carbonyl and DMS (Mech. II).

Mechanism II



Torssell[7] believes the free sulfoxonium salt may not always be present. He circumvents the need for such an intermediate by suggesting simultaneous displacement of urea by alcohol (attacking the DMSO-DCC adduct) and abstraction of a proton from a methyl group by the urea (a strong base). The resulting ylid may then collapse to carbonyl and DMS with intramolecular transfer of an alcohol proton (Mech. III).

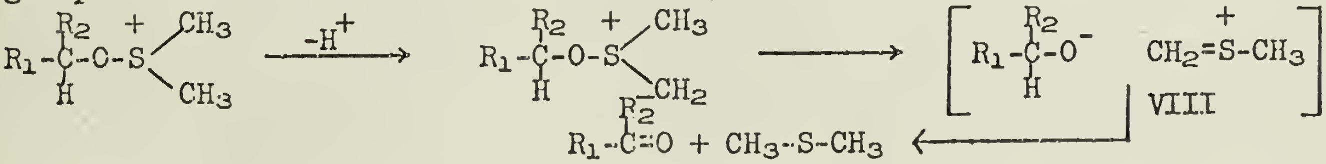
Mechanism III



Another mechanistic alternative is that the intermediate sulfoxonium ion collapses to carbonyl and DMS by the concerted loss of a proton and O-S cleavage:[7]

$$-\overset{H}{\underset{|}{C}}-O-\overset{+}{S}-(CH_3)_2 \xrightarrow{\Delta \text{ or base}} \rangle C=O + S(CH_3)_2 + H^+$$

An alternative which is not mentioned in the literature, but which can not be ruled out is the formation of ion pairs which then react within a solvent cage to form carbonyl and DMS. The ion pairs could be formed by proton abstraction from a methyl group of the sulfoxonium salt followed by elimination of the species VIII.



Analogy for the first step in mechanism I may be found in other reactions in which nucleophiles add to carbodiimides. For example the reaction of acids and alcohols with carbodiimides involves 1,2 addition.[8]

That DMSO may function as a nucleophile has been established. Smith and Winstein[9] and other workers[7,10,11] have been able to isolate sulfoxonium salts from the reaction of DMSO and simple arenesulfonates and as sulfoxonium tetraphenyloborate salts. These type products could only form by nucleophilic attack of the sulfoxide.

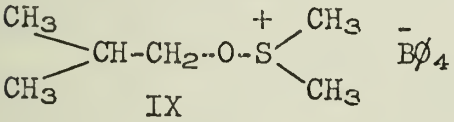
The transfer of oxygen from DMSO to the carbodiimide as required by the intermediacy of the DMSO-DCC adduct was confirmed through labeling experiments. It

was shown that p-nitrobenzyl alcohol reacts with O^{18}-DMSO, DCC, and anhydrous H_3PO_4 to produce p-nitrobenzaldehyde and O^{18}-N,N'-dicyclohexyl urea.[12] Oxidation of O^{18}-ethanol and O^{18}-benzhydrol under similar conditions gave unlabeled N,N'-dicyclohexyl urc in the case of benzhydrol, 42% of the label was found in the benzophenone.[13]

These labeling experiments rule out the possible intermediacy of a pseudourea (VII) as required by mechanism II. This conclusion is supported by the inertness of 1,3-dicyclohexyl-2-p-nitrobenzyl pseudourea when exposed to the reaction conditions.[12]

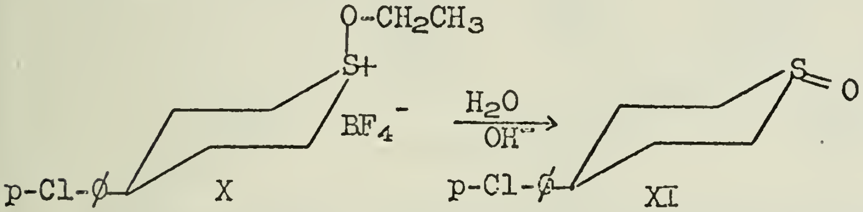
Support for the intermediate III was obtained from the acid catalyzed reaction of DMSO with ketenes and keteneimines which gives an adduct analogous to III. For exampl anhydrous HCl in a solution of diphenyl ketene-N-p-tolyimine and DMSO yields N-(p-tolyl) diphenylacetamide and DMS.[14]

Torsell's evidence for rejecting an intermediate such as III was his observation that independently prepared sulfoxonium salt IX when subjected to DMSO-DCC oxidation conditions gave ca. 10% iso-butyraldehyde and considerable amounts of iso-butanol whereas the oxidation of isobutanol by this method gave 41% aldehyde.[7] Thus, mechanism III rationalizes the occurence of the oxidation in weak acid media (in which sulfoxoniur salts are stable) and the sensitivity of the oxidation to pH. Attempts to trap the carbodiimide-DMSO adduct with sodium tetraphenyloborate were not successful.



IX

The attack of alcohol onto the DMSO-DCC adduct is similar to the known S_N2 displacement occurring in hydrolysis and alcoholysis of alkoxysulfonium salts. Thus, the solvolyses of dimethyl methoxysulfonium perchlorate in O^{18}-water yields parent sulfoxide with O^{18} incorporation,[15] and hydrolysis of optically active O-ethyl fluoroborate salt of benzyl-(p-methyl)-phenyl sulfoxide in basic conditions gives 98% inversion of configuration at sulfur.[10] Similarly, hydrolysis of cis-4-p-chlorophenyl-1-ethoxythioniacyclohexane flouroborate (X) yields 93% of the trans-thiane-1-oxide (XI).[16]



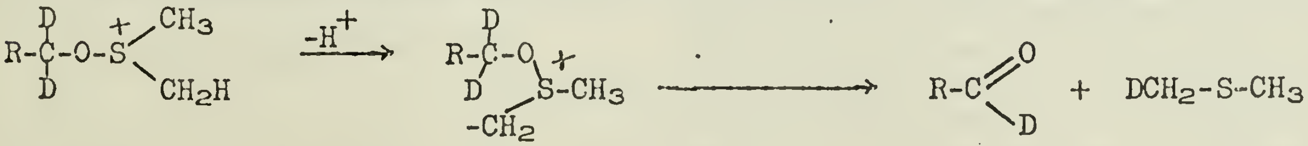
X XI

Johnson and Phillips[11] found that ~~treatment of~~ dimethyl methoxysulfonium fluoroborate, labeled with carbon-14 in the O-methyl group, reacts with NaH in DMSO to yield carbon-14 labeled formaldehyde; but when NaOMe in methanol was used, the formaldehyde had less than 1% label. Therefore, methoxy interchange with solvent occurs more rapidly than elimination to give a carbonyl compound and a sulfide.

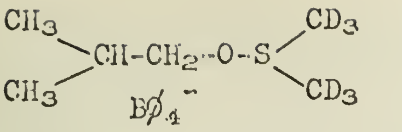
The final step of mechanism I requires abstraction of a proton from a carbon next to sulfur forming an ylid type structure, V. Since the oxidation is carried out in the presence of acid, the abstraction of a proton might not appear reasonable. However, it is known that protons of methyl groups directly attached to a sulfonium sulfur underg exchange with D_2O and the rate of this exchange is enhanced by at least several powers of ten in sulfoxonium salts.[9,12] Therefore it seems reasonable to allow proton abstracti promoted by either pyridine or the anion of phosphoric acid, to give the stabilized ylid V.[17]

The proton abstraction step is also considtent with Pfitzer and Moffatt's findings[3] that, in general, free acids of intermediate strength are required for the reaction sinc both acid and base catalyzed processes occur. For example, in strong mineral acids the reaction will not proceed. With phosphoric acid the reaction is faster than with pyridinium trifluoroacetate, but the salt gives cleaner products.

The carbanion formed by proton abstraction V can then collapse to give a carbonyl compound and DMS. Confirmation of intramolecular proton abstraction occuring here was obtained by two methods:[12] first, 1,1-dideuterobutanol-1 was oxidized with unlabeled DMSO. The mass spectrum showed one deuterium in the recovered DMS after reaction and the n.m.r. spectrum of the product aldehyde reveals that deuterium is only found on



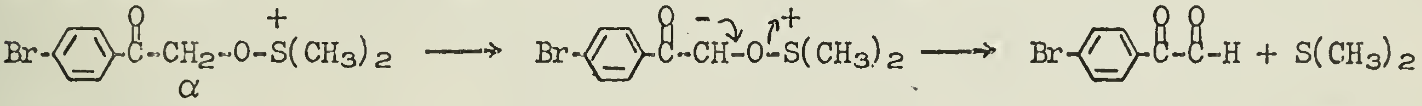
the carbonyl carbon. Secondly, unlabeled 1-butanol was oxidized by hexadeutero-dimethyl sulfoxide giving an aldehyde free of deuterium and incorporation of one hydrogen in DMS was shown by mass spectroscopy. Identical results were obtained by exposing the deuterated sulfoxonium salt XII to reaction conditions. Assuming



XII

negligible H scrambling in this ion before decomposition, intramolecular abstraction would yield CD_3-S-CD_2H detectable by n.m.r. This experiment showed that CD_3-S-CD_2H was in fact obtained.[7] The possibility that CD_3-S-CD_2H was obtained via a concerted loss of proton with elimination of DMS and a rapid exchange of deuterium with solvent was considered, but it seems unlikely that only a single deuterium would be exchanged.

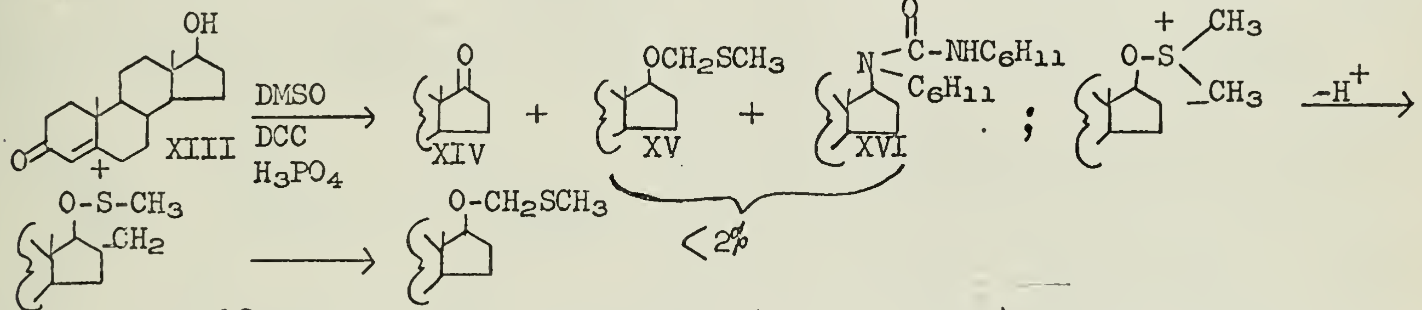
These isotope experiments rule out the possibility of any concerted loss of a proton and elimination of DMS from the sulfoxonium salt. However, with alcohols having an activated alpha proton this decomposition path is possible. An acidic alpha proton can be lost easier than an S-methyl proton. The resulting intermediate can simply eliminate DMS forming the carbonyl in a concerted process.[7] This path was tested using D_6-DMSO and p-bromophenacyl bromide; no hydrogen was found in the DMS recovered.

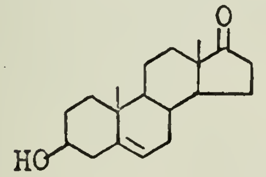


SIDE REACTIONS

In this oxidation minor side reactions occur which can be rationalized within the mechanistic framework presented above.

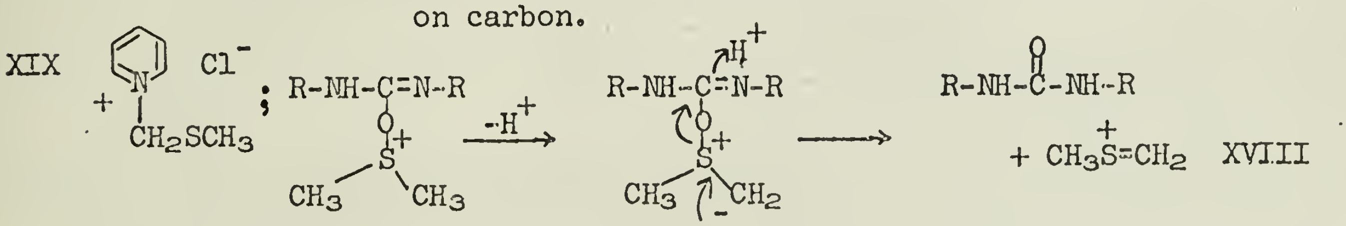
In the oxidation of testosterone (XIII) to androst-4-ene-3,17-dione (XIV) using DMSO, DCC, and orthophosphoric acid, less than 2% of the total product was identified as the compounds XV and XVI.[4] Formation of the methyl thiomethoxy derivative, XV, is thought to occur by rearrangement of an intermediate alkoxysulfonium compound. This same type of rearrangement has been observed in the oxidation of 3β-hydroxyandrost-5-en-17-one, (XVII),[18] using only one mole of DCC (little excess) and pyridinium trifluoroacetate. These conditions produced 5% of the expected ketone and 5% of the methyl thiomethoxy derivative. Jones and Wigfield believe this rearrangement to be analogous to the Stevens rearrangement. Compound XV could also be derived from a species of the form $CH_3\overset{+}{S}=CH_2$ (XVIII) if it exists in solution.



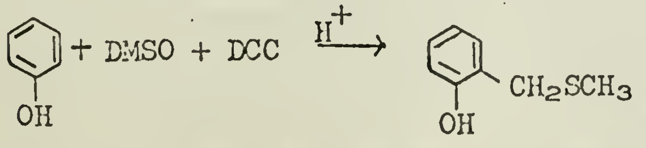


XVII

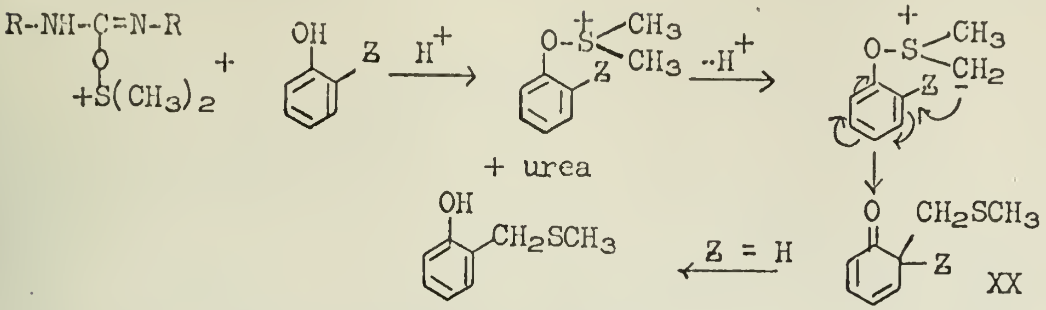
The formation of small amounts (~ 1%) of N-thiomethoxymethylpyridinium compounds, XIX, found in the oxidation of Thymidine 5'-phosphate in the presence of excess pyridine was also explained as due to the activated species XVIII.[4] Once formed XVIII is subject to nucleophilic attack by pyridine on carbon.



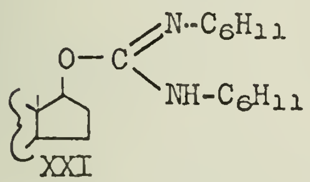
Additional information regarding the formation of thiomethoxymethyl derivatives has been obtained by observing the reactions of phenols with DMSO, DCC, and an acid.[19,2 With simple phenols the predominant reaction is the introduction of thiomethoxymethyl groups in available ortho positions. Several other types of products were also formed depending upon the nature of the phenol. With more acidic phenols, O-alkylation was observed, and phenols without a free ortho position lead to para-alkylated products. Similarly, meta-alkylation can be obtained when no ortho or para positions are available. These results were rationalized by the following scheme in which the DCC-DMSO adduct is attacked by the phenol to yield the phenoxysulfonium cation; this species loses a proton to generate the sulfonium ylid which then undergoes an intramolecular rearrangement to



the ortho position; depending on Z, the resulting dienone (XX) may be isolated, may tautomerize to the phenol (Z=H), or undergo further reactions. The meta and para alkylations are also thought to be intramolecular. This was deduced from the inability to detect any alkylation of large excesses of anisole, N,N-dimethylaniline, or furan present during para alkylation of 2,6-dimethylphenol.



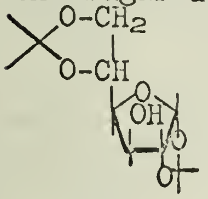
The isourea derivative XVI gotten in the testosterone oxidation could be formed by O to N migration of an isourea adduct of type XXI. The O to N migration is analogous to that encountered in the formation of N-acylureas from carboxylic acids and carbodiimides,[8] but there is no evidence that such an adduct is formed in the reaction conditions and independently synthesized isoureas show no tendency to undergo such a rearrangement in oxidation conditions.



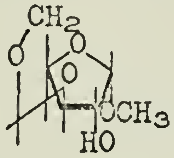
XXI

STERIC REQUIREMENTS

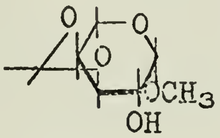
The steric requirements of the oxidation have been ascertained by studies of pairs of epimeric alcohols. With pairs of relatively unhindered alcohols, only minor differences in rates of oxidation were found.[4,6] Distinct differences in the course of the reaction can be seen with the more hindered 11-hydroxy steroids and the sugar derivatives XXII-XXIV.[21] Thus the equatorial hydroxyl in 11α-hydroxy progesterone, XXVa, was smoothly oxidized almost quantitatively, whereas the epimeric 11β-hydroxy remained completely inactive using pyridinium trifluoroacetate as the acid for the oxidation, and only 6% of the ketone was obtained using phosphoric acid.[4] Similarly the axial 11β-hydroxyl group of corticosterone-21-acetate, XXVI, was inert. This facile oxidation of equatorial 11α-hydroxyl groups and relative inertness of the axial epimers is in contrast with results obtained by chromic oxide oxidations.[4] In the DMSO-DCC oxidation the rate-limiting step could be the reaction of the alcohol with the DMSO-DCC adduct to form alkoxysulfonium salt. In this case the equatorial 11α-hydroxyl is less hindered and should react more rapidly.



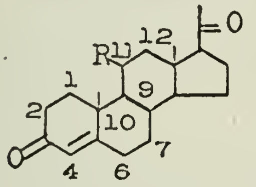
XXII



XXIII

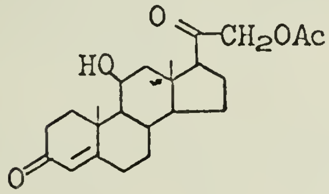


XXIV



a R = α-OH
b R = β-OH

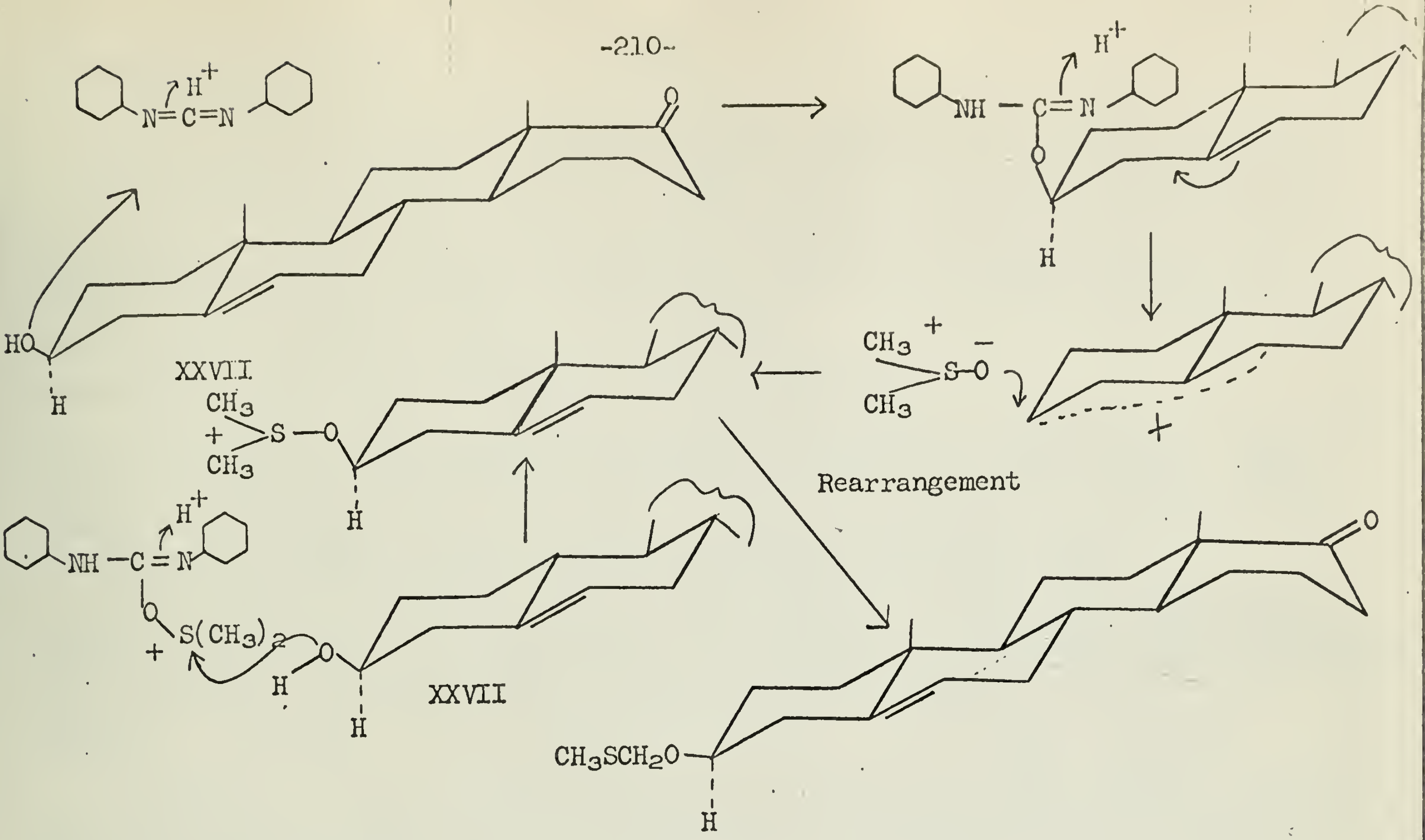
XXV



XXVI

In the case of the sugars XXII-XXIV, little oxidation took place at room temperature. In each case the hydroxyl group is flanked by ether or acetal groups which could possibly influence the rate determining step. In these cases N,N'-dicyclohexylurea forms rapidly, indicating the intermediate has formed, but oxidation involving the intermediate does not take place in these conditions.[22] These results suggest, in contrast with those of Pfitzer and Moffatt, that the rate determing step is one other than the formation of the sulfoxonium salt.

In the oxidation of 3β-hydroxyandrost-5-en-17-one (XXVII) using only one mole of DCC, the rearranged methyl thiomethoxy derivative has the same β-equatorial configuration as the starting alcohol.[18] Jones explained this observation by two possible mechanistic paths: the sulfoxonium salt intermediate may arise by activation of the 3β hydroxyl group by DCC followed by elimination with participation of the Δ^5 double bond and equatorial nucleophilic attack on the resulting carbonium ion by DMSO or the intermediate may be produced by initial attack of the DMSO-DCC adduct which preserves the configuration.[18]



DMSO-ACID ANHYDRIDE OXIDATIONS

The selective oxidation of sterically hindered hydroxyl groups to the corresponding carbonyl groups can be achieved using a DMSO-acid anhydride mixture as the oxidizing agent. Benzoic anhydride, phosphorus pentoxide and polyphosphoric acid may be used as well as the more common acetic anhydride, but trifluoroacetic anhydride is unsatisfactory. Table II contains some representative oxidations using these reagents.[13]

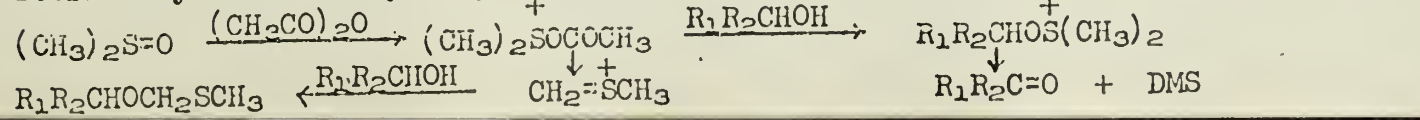
Table II. Representative Compounds Oxidized By DMSO-Acid Anhydride Mixture[13]

COMPOUND	PRODUCT	YIELD (%)
Yohimbine	Yohimbinone	80-85
β-yohimbine	Yohimbinone	-
Ajmaline	Ajmalidine	-
Testosterone	Δ^4-androstene-3,17-dione	34
11α-hydroxy progesterone	11-ketoprogesterone	13
Hydrocortisone-21-acetate	Cortisone-21-acetate	53
Methyl reserpate	methyl keto reserpate	33
p-Nitrobenzyl alcohol	p-nitrobenzaldehyde	75

The oxidation of hydrocortisone 21-acetate using this reagent (53% yield) is contrasted with the inertness of this alcohol in DMSO, DCC oxidation conditions.

Tentative suggestions for a possible mechanism were made by Albright and Goldman. Carboxylic acid anhydrides are known to react with sulfoxides to give acyloxysulfides, this rearrangement has been visualized as proceeding through acyloxysulfonium salts.[5] Nucleophilic attack of an alcohol on the sulfur of this salt with backside displacement of acetate ion could lead to an alkoxysulfonium salt which then decomposes to carbonyl and DMS by the previously mentioned mechanism.

Methyl thiomethyl ether derivatives are formed in somewhat larger amounts than in the DCC type oxidation, i.e. ~ 10% in two cases. This is thought to arise from competitive reaction involving elimination of acetic acid from the acyloxysulfonium salt to give the intermediate $CH_2{=}\overset{+}{S}CH_3$ which then reacts with the alcohol. The fact that axial alcohols give more ketone and less methyl thiomethyl ether than do equatorial alcohols is considered to result from the faster rate of oxidation of sterically hindered hydroxyl groups (analogous to chromic oxide oxidations).



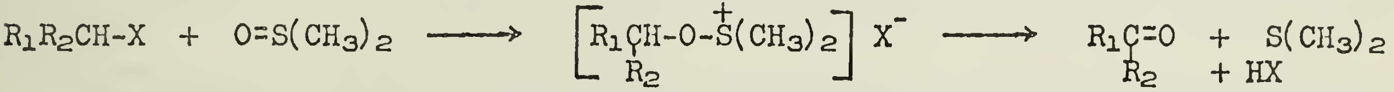
$$\begin{array}{lll} (CH_3)_2S{=}O \xrightarrow{(CH_2CO)_2O} (CH_3)_2\overset{+}{S}OCOCH_3 & \xrightarrow{R_1R_2CHOH} & R_1R_2CHO\overset{+}{S}(CH_3)_2 \\ R_1R_2CHOCH_2SCH_3 \xleftarrow{R_1R_2CHOH} \overset{\downarrow}{CH_2{=}\overset{+}{S}CH_3} & & \overset{\downarrow}{R_1R_2C{=}O} + DMS \end{array}$$

There has been one report[23] of the selective oxidation of a variety of benzyl alcohols to the corresponding aldehydes (further oxidation to the acid occuring only in 3% yield) by refluxing the alcohol in DMSO. The presence of air facilitates the reaction, but oxygen doesn't appear to be the oxidant as no oxygen uptake was found in separate experiments. Tertiary butyl peroxide catalyzes the reaction and it is suggested that electron releasing substituents para to the carbonyl enhance the reaction while electron withdrawing groups retard it. A free radical mechanism was indicated but no definite proposals were advanced.

OXIDATION OF HALIDES AND ESTERS WITH DIMETHYL SULFOXIDE

The substantial amount of work involving DMSO oxidations of alcohols is paralleled by the work done on the oxidations of halides, tosylates, and other esters. Typical reaction conditions involve solution of the ester or halide in excess DMSO, with or without an acid acceptor such as $NaHCO_3$, at temperatures between 25 and 160°. Some representative examples of this reaction are given in Table III below.

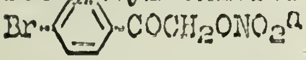
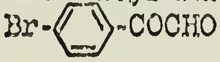
This reaction is thought to involve the intermediate sulfoxonium salts as did the above mechanisms. The first step in this mechanism is postulated to be a displacement of the halide or ester forming the sulfoxonium intermediate. This intermediate then eliminates a proton and DMS forming the carbonyl compound.[12,27,29,32]



$$R_1R_2CH\text{-}X + O{=}S(CH_3)_2 \longrightarrow \left[R_1\underset{R_2}{C}H\text{-}O\text{-}\overset{+}{S}(CH_3)_2\right]X^- \longrightarrow R_1\underset{R_2}{C}{=}O + S(CH_3)_2 + HX$$

Nucleophilic attack by DMSO is reasonable in view of the above analogies and the fact that activated alkyl halides which are known to undergo nucleophilic substitution readily are oxidized most easily.[27] Ease of oxidation increases in the halide series: chloride < bromide < iodide.[29,32]

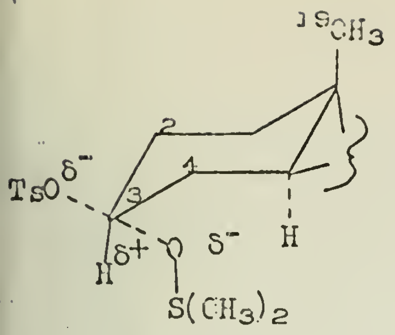
Table III. Typical Halides and Esters Oxidized by DMSO

COMPOUND	PRODUCT	TEMPERATURE (°C)	YIELD (%)	REFERENCE
1,3-diphenoxy-2-propyl tosylate	no reaction	103	0	24
" "	1,3-diphenoxy-2-propanone	150	90	24
$CH_3(CH_2)_7$-Br	$CH_3(CH_2)_6CHO$	-	74	25
$CH_3(CH_2)_7OTos$	"	150	78	25
iso-butyl benzene sulfonate	isobutyraldehyde	∽ 100	--	28
$CH_2CH(CH_2)_6I$	$CH_2CH(CH_2)_5CHO$	145-150	83	29
sec-butyl chloroformate	sec-butyraldehyde	Room	78	32
 Br-⟨⟩-$COCH_2ONO_2$[a]	 Br-⟨⟩-COCHO	25	90	33

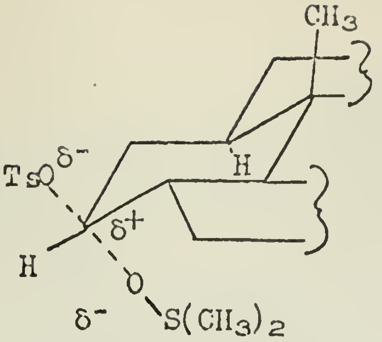
a: reaction done in presence of OAc^-

The S_N2 character of the initial step can be used to rationalize the variations in products with stereochemical variations. Thus, Jones and coworker,[27] in a study of the reactions between steroid sulphonate esters and DMSO, found that for equatorial esters the yield of ketone decreases in approximately the order expected for progressive increasing steric hindrance to development of the linear transition state for bimolecular attack by DMSO. Their results showed that the yields of ketone from the tosylate ester varied in the order: $3\beta > 7\beta > 2\alpha > 6\alpha > 11\alpha$. With 3β and 7β, compounds XXVIII and XXIX, the steric compression in the transition state would not be large, but this factor is significant in the 2α ester XXX due to interaction of the 19-methyl and DMSO. This interaction in the 6α-ester (XXXI) is expected to be even larger due to the rigidity of the B ring. Thus 5α-cholestan-6α-yl tosylate gives very little ketone and the methane sulphonate gives no reaction under the same conditions. Similar reluctance of testosterone tosylate to undergo S_N2 reactions with halide ion has been attributed to steric hindrance in the transition state by neighboring 18β-methyl and 12-methylene groups.

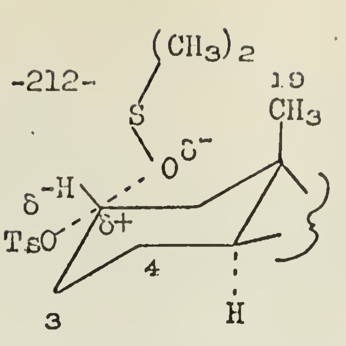
Additional evidence is obtained from the fact that 2-iodo-octane reacts with DMSO (MgO, 150°, 1 hr.) to yield 32% octan-2-one, whereas cyclohexyl iodide gives no reaction under the same conditions.[29] This is consistent with the exchange reactions of cyclohexyl iodide and 2-heptyl iodide with NaI in ethanol; the rate constant of



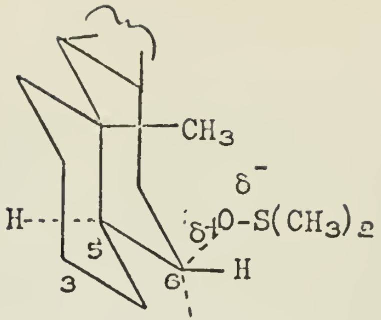
XXVIII 3β



XXIX 7β



XXX 2α



XXXI 6α

cyclohexyl iodide is approximately 0.01 times as large as that of the 2-heptyl iodide.[30] This is presumedly owing to the fixed conformation such that S_N2 attack was not favored.[29,31]

The formation and isolation of sulfoxonium salts was described above. Smith and Winstein[9] reported that DMSO served as a nucleophile to form two different 1:1 adducts with R-X molecules. The kinetically controlled O-alkyl derivatives (sulfoxonium salts) may be obtained in yields of 50-90% by quenching the reaction of methyl, ethyl, or benzyl arenesulfonates. Sulfoxonium perchlorate salts have also been isolated.[15] Also, by analogy, the N-oxides of both aliphatic and heterocyclic tertiary amines are known to react with certain halides or tosylates to form quarternary salts analogous to the sulfoxonium salts.[35]

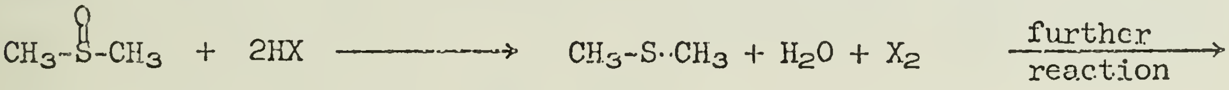
The evidence for the decomposition of the sulfoxonium salt intermediate and mechanistic path is the same as given for the identical decomposition of the sulfoxonium salt intermediate in the alcohol oxidations.

Hunsberger and Tien noticed that the oxidation of ethyl-bromoacetate to ethyl glyoxylate has a characteristic induction period, possibly indicating a free-radical mechanism. But small amounts of nitrobenzene and hydroquinone have no effect on the induction period, and they suggested an ionic mechanism is more probable.[34] Since no experimental details were given the proper analysis of these observations is difficult.

SIDE REACTIONS

The major side reaction is that of elimination of the halide or ester to form an olefin.[37,38] The proportions of elimination products versus oxidation products depends on the bases present, the structure of the halide or ester, and the temperature.[27,37,39]

Another side reaction that may occur involves the production of molecular halogen from the hydrohalide and DMSO. The halogen produced may then further react



$$CH_3-\overset{O}{\overset{\|}{S}}-CH_3 + 2HX \longrightarrow CH_3-S-CH_3 + H_2O + X_2 \xrightarrow[\text{reaction}]{\text{further}}$$

with the components of the solution. Addition of a base, sodium bicarbonate, collidine, or triethylamine, neutralizes the hydrohalide as it forms.[27,29,32,34,38,41] The base also functions as a proton acceptor in the decomposition of the sulfoxonium salt and has an effect on the ratio of elimination to substitution products. Addition of 1:2-epoxy-3-phenoxy-propane, a non-alkaline scavenger for HBr, will surpress the above reaction.[34]

Other side reactions involving the decomposition of DMSO itself may occur in this reaction medium forming methyl mercaptan, dimethyl disulfide and formaldehyde.[24] In some cases the sulfoxonium salts can also undergo hydrolysis to the corresponding alcohols.[27]

SUMMARY AND CONCLUSION

From consideration of the available evidence, it appears very likely that sulfoxide oxidations involve an ionic sulfoxonium salt as an intermediate. The sulfoxonium salts, once formed, then decompose to the observed products. This type mechanism can be extended to include the oxidation of acid halides by DMSO,[32,36,42,43,44] disproportionation reactions of sulfoxides,[45,46] and the oxidations of silanes.[47,48]

In order to make the mechanistic evidence complete, some detailed kinetic studies are needed.

BIBLIOGRAPHY

1. N. Kharasch, and B. S. Thyagarajan, Quart. Rep. Sulfur Chem., 1, 16 (1966).
2. H. R. Nace, and J. Monagle, J. Org. Chem., 24, 1792 (1959).
3. K. E. Pfitzner, and J. Moffatt, J. Am. Chem. Soc., 87, 5661 (1965).
4. Ibid., 5670 (1965).
5. J. Albright, and L. Goldman, J. Org. Chem., 30, 1107 (1965).
6. K. E. Pfitzner, and J. Moffatt, J. Am. Chem. Soc., 85, 3027 (1963).
7. K. Torssell, Tetrahedron Letters, 4445 (1966).
8. M. Smith, J. Moffatt, and H. G. Khorana, J. Am. Chem. Soc., 80, 6204 (1958).
9. S. Smith, and S. Winstein, Tetrahedron, 3, 317 (1958).
10. C. R. Johnson, and D. McCants, J. Am. Chem. Soc., 87, 5404 (1965).
11. C. R. Johnson, and W. Phillips, Tetrahedron Letters, 2101 (1965).
12. A. H. Fenselau, and J. Moffatt, J. Am. Chem. Soc., 88, 1762 (1966).
13. J. D. Albright, and L. Goldman, ibid., 87, 4214 (1965).
14. I. Lillien, J. Org. Chem., 29, 1631 (1964).
15. N. J. Leonard, and C. R. Johnson, J. Am. Chem. Soc., 84, 3701 (1962).
16. C. R. Johnson, ibid., 85, 1020 (1963).
17. W. von Doering, and A. K. Hoffman, ibid., 77, 521 (1955).
18. J. B. Jones, and D. C. Wigfield, Tetrahedron Letters, 4445 (1965).
19. M. G. Burdon, and J. Moffatt, J. Am. Chem. Soc., 87, 4656 (1965).
20. K. E. Pfitzner, J. Marino, and R. Olofson, ibid., 87, 4658 (1965).
21. B. R. Baker, and D. H. Buss, J. Org. Chem., 30, 2304 (1965).
22. Ibid., 2308 (1965).
23. V. J. Traynelis, and W. Hergenrother, J. Am. Chem. Soc., 86, 298 (1964).
24. M. M. Baizer, J. Org. Chem., 25, 670 (1960).
25. N. Kornblum, W. Jones, and G. Anderson, J. Am. Chem. Soc., 81, 4113 (1959).
26. N. Kornblum, J. Powers, G. Anderson, W. Jones, H. Larson, O. Levand, and W. Weaver, ibid., 79, 6562 (1957).
27. D. N. Jones, and M. A. Saeed, J. Chem. Soc., 4657 (1963).
28. H. R. Nace, Chem. Abst., 53, 19979c (1959).
29. A. P. Johnson, and A. Pelter, J. Chem. Soc., 520 (1964).
30. S. F. Van Straten, R. V. Nicholls, and C. A. Winkler, Can. J. Chem., 29, 372 (1951).
31. A. Streitwieser, "Solvolytic Displacement Reactions", McGraw-Hill, New York, N. Y. (1962), pg. 96.
32. D. H. Barton, B. Garnder, and P. Wightman, J. Chem. Soc., 1855 (1964).
33. N. Kornblum, and H. Frazier, J. Am. Chem. Soc., 88, 865 (1966).
34. I. M. Hunsberger, and J. Tien, Chem. and Ind. (Lon.), 88 (1959).
35. R. T. Major, and H. J. Hess, J. Org. Chem., 23, 1563 (1958).
36. R. Boyle, ibid., 31, 3880 (1966).
37. H. R. Nace, Chem. and Ind. (Lon.), 1629 (1958).
38. H. R. Nace, and R. N. Iacona, J. Org. Chem., 29, 3498 (1964).
39. R. N. Iacona, A. Rowland, and H. R. Nace, ibid., 3495 (1964).
40. H. R. Nace, J. Am. Chem. Soc., 81, 5428 (1959).
41. E. J. Moriconi, and A. J. Fritsch, J. Org. Chem., 30, 1542 (1965).
42. E. H. Amonoo-Neizer, S. K. Ray, R. A. Shaw, and B. C. Smith, J. Chem. Soc., 6250 (1965).
43. F. G. Bordwell, and B. M. Pitt, J. Am. Chem. Soc., 77, 572 (1955).
44. R. Rätz, and O. J. Sweeting, J. Org. Chem., 28, 1612 (1963).
45. W. Kenney, J. A. Walsh, and D. Davenport, J. Am. Chem. Soc., 83, 4019 (1961).
46. H. R. Davis, and D. P. Sorensen, Chem. Abst., 53, 11416i (1959).
47. R. J. Ouellette, and D. L. Marks, Tetrahedron Letters, 3449 (1964).
48. A. G. Brook, and J. B. Pierce, J. Org. Chem., 30, 2566 (1965).

THE THERMAL REARRANGEMENT OF ALKYL GROUPS FROM NITROGEN TO CARBON IN AROMATIC SYSTEMS

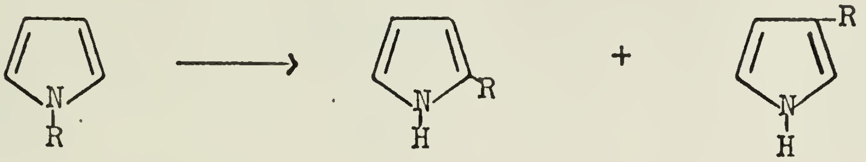
Reported by Tommy L. Chaffin

January 12, 1967

INTRODUCTION

N-Alkylpyrroles, N-alkylanilines, and N-alkylpyridinium salts rearrange at high temperatures to produce ring alkylated products. Although there is a formal similarity between them, the mechanisms of these reactions do not appear to be related.

REARRANGEMENT OF N-ALKYLPYRROLES



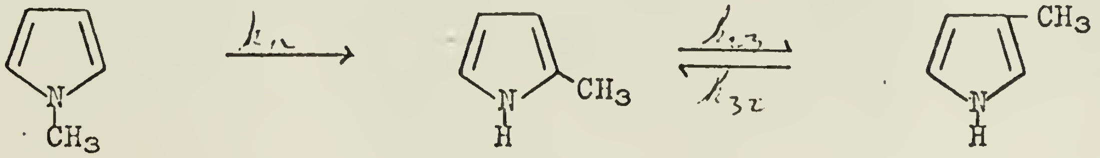
The rearrangement of N-substituted pyrroles to the 2- or 3-isomers was discovered in 1885 with N-acetyl pyrrole[1] and extended to a variety of migrating groups[2,3,4] including phenyl, pyridyl, and many alkyl groups. The rearrangement can be accomplished either in a sealed tube or by passing the vaporized compound through a glowing combustion tube. Most of the workers reported the major product to be the 2-substituted pyrrole, although a few reported some 3-substituted pyrrole, and pyridine or a 3-substituted pyridine.

Kinetic work has been done on several 1-alkylpyrroles.[5,6,7,8] Most of this work was done in a flow system through a heated vycor or quartz tube and product analysis was accomplished by comparison with authentic samples in most cases and a combination of infrared spectra, retention times from gas-liquid phase chromatography, and mass spectrometry.

The reaction was run on undiluted vapor and with nitric oxide or an inert diluent gas present and in both packed and unpacked reaction tubes. No change in the reaction rate was observed which was taken to indicate that the reaction was unimolecular, non-radical chain, and homogeneous.

The average residence times were determined by dividing the effective volume of the reaction chamber by the flow rate. The disappearance of starting material was found to be first order and activation energies were determined from Arrhenius plots.

When either 2-methyl or 3-methylpyrrole was pyrolyzed under the same conditions, a mixture of the two isomers resulted and no N-methylpyrrole was detected. Furthermore, in the rearrangement of N-methylpyrrole, no 3-methylpyrrole was detected at temperatures below 525°C. The authors felt that this indicated that the reaction involved an essentially irreversible rearrangement of the group from the 1 to the 2 position followed by a reversible rearrangement from the 2 to the 3 position:



This will rationalize the results, but does not rigorously exclude direct isomerization to the 3 position.

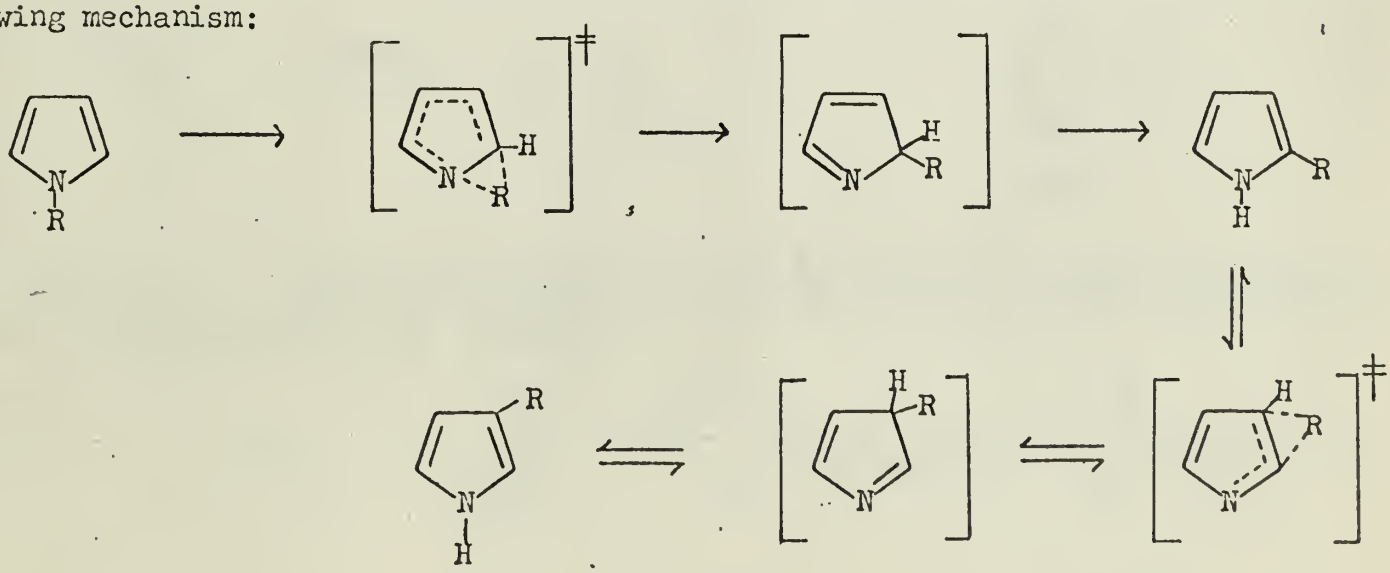
A total of nine isomerizations were studied for the methyl, n-butyl, and isopropyl rearrangements and the entropies and enthalpies of activation were obtained as shown in Table I. A plot of the entropy of activation against the enthalpy of

Table I

Reaction	ΔS^*, e.u.	ΔH^*, kcal./mole
	Methylpyrrole	
k_{12}	-1.3	56.8 ± 1.6
k_{23}	-29	34.5 ± 3.9
k_{32}	-10	48.1 ± 2.7
	n-Butylpyrrole	
k_{12}	-0.7	56.4 ± 0.2
k_{23}	-15	44.0 ± 1.5
k_{32}	-8.9	48.3 ± 1.7
	Isopropyl	
k_{12}	-2.7	54.0 ± 0.6
k_{23}	-14	44.7 ± 3.7
k_{32}	-12	45.2 ± 3.8

activation gave a straight line whose slope was considered to be the isokinetic temperature, 589°C. The authors felt that the linear relationship indicates that either the mechanism or the transition state is similar for all nine reactions,[7] according to the procedure developed by Leffler.[9,10] However Petersen[11,12,13] has criticized this type of reasoning. He points out that the entropy and enthalpy of activation are quantities derived from the same set of data and are thus insensitive to experimental error. He shows that for a true isokinetic relationship, plots of log (k/T) v.s. (1/T) for each reaction will intersect at a point corresponding to the isokinetic temperature. He has found no cases where this occurs for reactions which Leffler considered to be isokinetic. It appears that the same criticism can be made of Jacobson's conclusions since his results do not meet Petersen's criteria either.

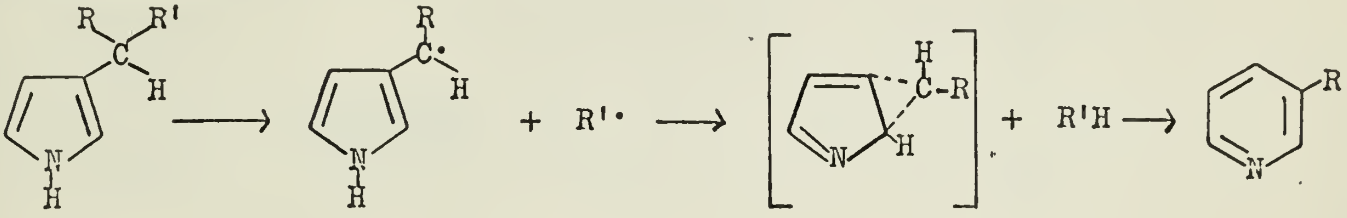
Pine[14] studied the rearrangements of para substituted benzylpyrroles. He found the products to be 2-benzyl and 3-benzylpyrroles, with some 3-phenylpyridine formed at higher temperatures. The reactions did not follow a simple Hammett plot, however the order of reactivity was the same as that reported for homolytic cleavage, $CH_3 > OCH_3 > Cl > F > H$. The entropies of activation were found to be negative. Based on this and the observed order of activation energies Pine proposed the following mechanism:



If the transition state involves simultaneous bond breaking and bond making, this mechanism would predict retention of optical activity in a migrating group with an asymmetric center attached to the nitrogen. Patterson[15] has recently investigated the rearrangement of such a system. He found 72-79% retention in the 2-substituted

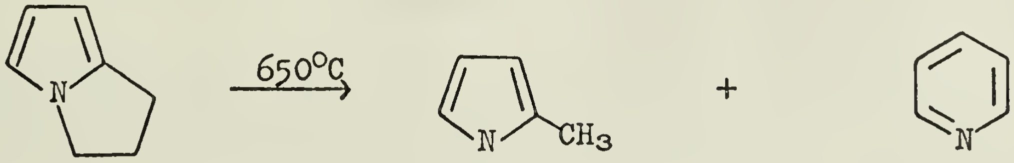
product and "nearly the same" amount[16] in the 3-substituted product for N-(sec-butyl)pyrrole or N-(1-phenylethyl)pyrrole. He interprets this in terms of Pine's mechanism even though there must be considerable radical character in the transition state. Departure from complete retention could indicate a competitive free-radical mechanism. While this mechanism is still largely speculative, a reasonable alternative has not been proposed.

When the temperature for the N-methylpyrrole rearrangement was raised above 600°C., some decomposition occurred[5] as evidenced by a gas consisting mostly of methane and hydrogen. The majority of the remaining liquid products were methyl pyrroles with traces of pyrrole, dimethyl pyrroles, indoles, benzene and pyridine. The appearance of pyridine is of interest and is postulated to result from homolytic cleavage and formation of a cyclic intermediate as shown:



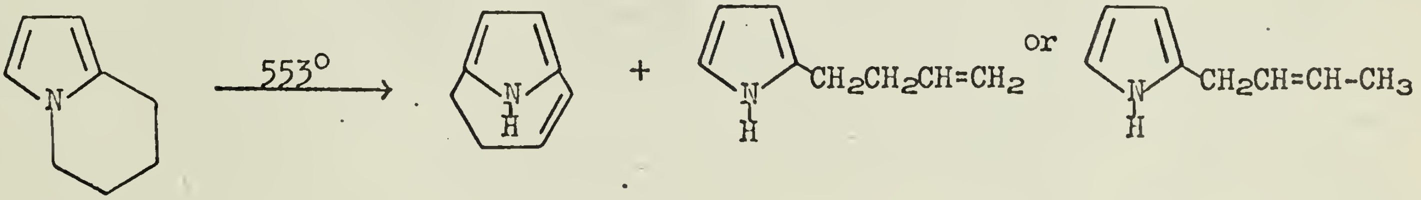
As the temperature was increased further the percentages of pyridine and pyrrole increased sharply. At 745° as much as 40% carbonization occurred[17] and the workers determined only relative yields. Under these conditions either N-methyl or 2-methylpyrrole produced 54-59% pyridine and 31-34% pyrrole. Decomposition of N-n-butylpyrrole[6] and N-isopropylpyrrole[7] produced various alkyl pyrroles, pyridine, pyrrole and hydrocarbons. No N-substituted decomposition products were found which was taken to indicate that decomposition takes place after isomerization. The relative concentrations of the decomposition products were affected by changes in the area to volume ratio and by the absence or presence of an inert gas. The presence of nitric oxide was reported to affect the decomposition of the isopropyl but not the n-butyl compound.[18] The workers felt that the decomposition was a heterogeneous, free-radical process. However, a more careful study must be made if this proposal is to be substantiated.

The pyrrole rearrangement has also been studied for some cycloalkano[α]pyrroles.[19] Pyrolysis of cyclopentano[α]pyrrole, I, at 650° produced 2-methyl pyrrole, II, and pyridine, III, as the major products.



I II III

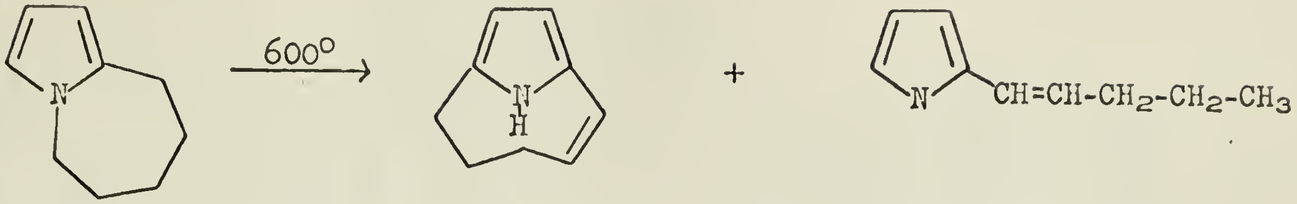
Pyrolysis of cyclohexano[α]pyrrole, IV, at 553° produced two new compounds as the major products. They were identified as 9-azabicyclo[4.2.1]nona-1,3,5-triene, V, and a 2-butenylpyrrole, VI or VII.



IV V VI VII

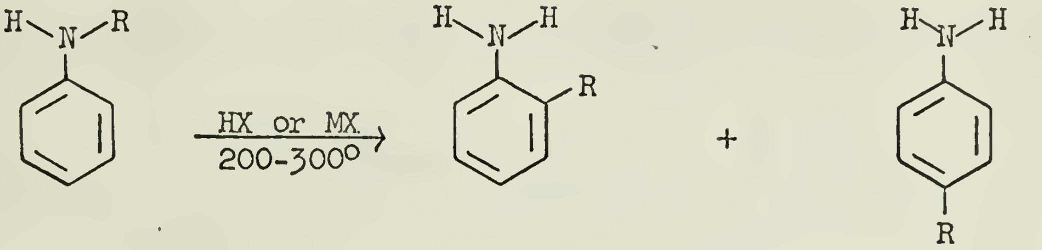
Rearrangement of cycloheptano[α]pyrrole, VIII, at 600° produced two major products which were identified as 10-azabicyclo[5.2.1]deca-1,3,5-triene, IX, and 2-(1-pentenyl)pyrrole, X. It was suggested that these products resulted from homolytic

cleavage of the carbon-nitrogen bond.



VIII IX X

REARRANGEMENT OF N-ALKYLANILINES



The rearrangement of the hydrohalides of N-alkyl~~ines~~ anilines at 200-300°C to form ortho and para-alkylanilines was first reported by Hofmann in 1871.[20,21,22] Hughes and Ingold[23,24] reviewed this reaction, known as the Hofmann-Martius rearrangement, in 1952 and proposed the mechanism shown based primarily on these facts: the products are primarily <u>para</u> if that position is unoccupied; the migrating group rearranges in a manner characteristic of carbonium ions; and olefins and alkyl halides are produced as minor products. The mechanism involves S_N2 displacement of the alkyl group to produce an alkyl halide which can then dissociate and either attack the aromatic ring or lose a proton to form an olefin.

$$\mathrm{Ph{\cdot}\overset{+}{N}H_2R} + X^- \longrightarrow \mathrm{Ph{\cdot}NH_2} + RX$$

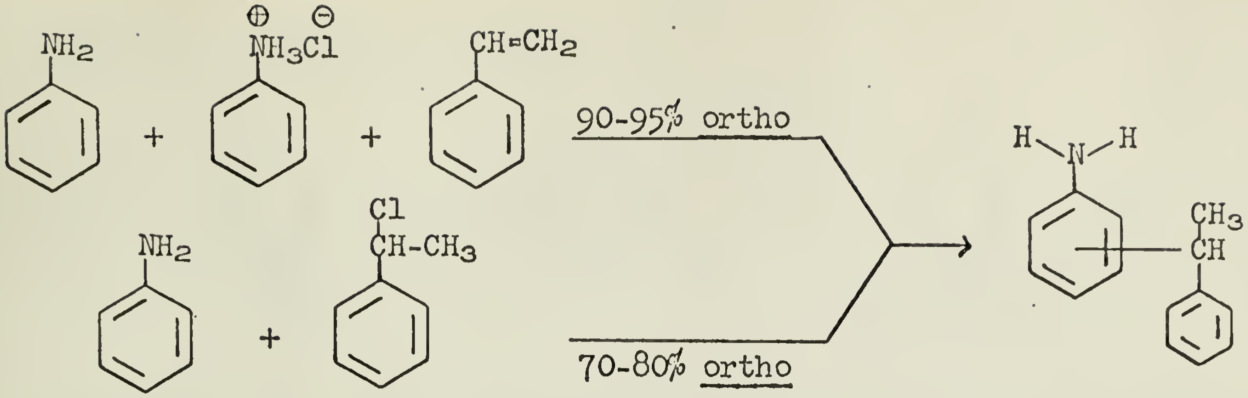
$$RX \rightleftharpoons R^+ + X^-$$

$$R^+ + \mathrm{Ph{\cdot}NH_2} \rightleftharpoons \text{Olefin} + \mathrm{Ph{\cdot}NH_3^+}$$

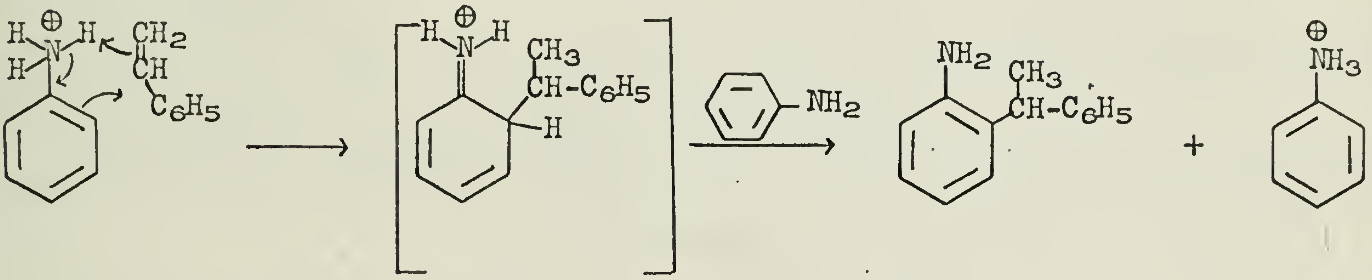
$$R^+ + \mathrm{Ph{\cdot}NH_2} \longrightarrow \text{o- and p-}R{\cdot}C_6H_4{\cdot}NH_2 + H^+$$

A great deal of the early work on this reaction was done by Hickinbottom.[25,26] He found that the rearrangement could also be catalyzed by a number of metal halides.[27] This is known as the Reilly-Hickinbottom rearrangement and it is usually thought to be an extension of Hofmann's reaction[20] although alkyl halides are not evolved and there is no rearrangement of the migrating group.

Hart and Kosak[28] reinvestigated the early work on N-α-phenylethylaniline. They showed that the hydrochloride or zinc chloride complex rearranges at 210-230°C in a sealed tube to yield <u>ortho</u> and <u>para</u>-α-phenylethylaniline and polystyrene. Zinc chloride gives higher yields and less <u>ortho</u> than the hydrochloride. Racemic products are observed when optically active N-α-phenylethylaniline is used. If the reaction is run in open vessels, the rearrangement does not occur, instead the hydrochloride sublimes, but the zinc chloride complex eliminates aniline and styrene. For this reason the alkylation of aniline by styrene[28,29,30] was studied. A mixture of aniline and its hydrochloride reacts with styrene in a sealed tube to give 64-82% <u>ortho</u> and <u>para</u>-α-phenylethylaniline of which 90-95% is the <u>ortho</u> isomer. In the absence of either aniline or its hydrochloride, no reaction occurs. Aniline and α-phenylethyl chloride react to yield 52-67% α-phenylethylaniline which is 70-80% <u>ortho</u>. This is easily explained since aniline and α-phenylethyl chloride were shown to react to form aniline hydrochloride and styrene in good yield under mild conditions.

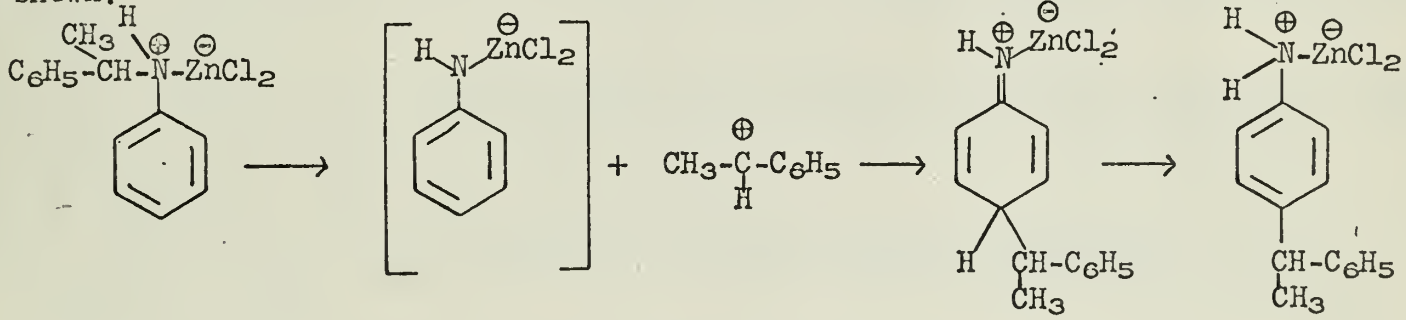


The specificity of *ortho* alkylation was rationalized by the following mechanism:



The conclusion of Hart and Kosak was that the first step of the rearrangement of N-α-phenylethylanilinium chloride cannot be dissociation to form aniline and α-phenylethyl chloride as proposed by Hughes since this would produce mainly the *ortho* product. Instead, they modify the mechanism to include the possibility of direct ionization to form the carbonium ion if it is a relatively stable one.

Regarding the differences in the zinc chloride and hydrogen chloride catalyzed reactions they propose that the mechanism of the zinc chloride catalyzed reaction is as shown:



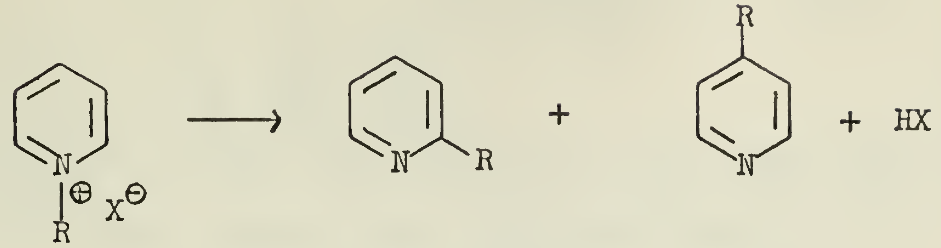
The higher yield of *para* product with zinc chloride can be rationalized by the fact that *ortho*-α-phenylethylaniline when heated in the presence of zinc chloride rearranges to give 40% *para* while the hydrochloride does not rearrange. This mechanism however, produces a carbonium ion, which is not consistent with the lack of rearrangement of the migrating group. It seems likely, therefore, that the metal halide catalyzed reaction is a good deal more complex than has been pictured.

Other workers[33] have studied the rearrangement of the hydrohalides of N-methylaniline. They found that both the *ortho*-*para* ratio and the rate of formation of the toluidines varied with the halide. This is consistent with a mechanism in which the alkylating agent is the methyl halide.

The rearrangement of trimethylphenylammonium iodide has been accomplished in the solid state.[34] The products were methyl iodide, N,N-dimethylaniline, and the *ortho* and *para* methylated derivatives. There was more *ortho* than *para* substituted product which, the author felt, was due to the lack of diffusion in the solid state.

The data presented is consistent with the proposed mechanism except for the lack of rearrangement of migrating groups for the zinc chloride catalyzed reaction. This suggests that more work should be done in order to understand the function of the metal halide. The kinetics of the system would be of particular interest.

REARRANGEMENT OF N-ALKYLPYRIDINIUM SALTS



Ladenburg[35,36] in 1883 heated N-ethylpyridinium iodide in a sealed tube and found mostly 2- and 4-ethylpyridine and some 2,4-diethylpyridine. Rearrangement of N-n-propylpyridinium iodide[37] has been reported to yield a mixture of n-propyl and isopropyl pyridines.

Chichibabin[38] found that the reaction could be catalyzed by cuprous chloride or powdered silver, magnesium, or copper. It has been shown[39] that the metal increases the relative amount of the 4-alkylated product.

Despite the formal analogy between this reaction and those previously discussed, little mechanistic evidence is available and a mechanism has not been proposed.

BIBLIOGRAPHY

1. G. Ciamician and P. Magnaghi, Ber., 18, 1828 (1885).
2. P. Crespieux and A. Pictet, Ber., 28, 1904 (1895).
3. A. Pictet, Ber., 38, 1947 (1905).
4. A. G. Oosterhuis and J. P. Wibaut, Rec. Trav. Chim., 55, 348 (1936).
5. I. A. Jacobson, Jr., H. H. Heady and G. U. Dunneen, J. Phys. Chem., 62, 1563 (1958).
6. I. A. Jacobson, Jr. and H. B. Jensen, J. Phys. Chem., 66, 1245 (1962).
7. I. A. Jacobson, Jr. and H. B. Jensen, J. Phys. Chem., 68, 3068 (1964).
8. I. A. Jacobson, Jr. and H. B. Jensen, Bureau of Mines Report of Investigations #6720, (1966).
9. J. E. Leffler, J. Org. Chem., 20, 1202 (1955).
10. J. E. Leffler and E. Grunwald, Rates and Equilibria of Organic Reactions, John Wiley and Sons, New York, (1964), p. 352.
11. R. Petersen, J. Margraf, and S. Ross, J. Am. Chem. Soc., 83, 3819 (1961).
12. R. Petersen, J. Org. Chem. 29, 3133 (1964).
13. C. Ritchie and W. Sager, Progress in Physical Organic Chemistry, Vol. 2, S. Cohen, A. Streitweiser, Jr., and R. Taft, edit., Interscience, New York, (1964), p. 356.
14. L. Pine, Ph.D. Thesis: University of Kansas, 1962.
15. J. Patterson, J. Am. Chem. Soc., 88, 3671 (1966).
16. J. Patterson, private communication, December 3, 1966.
17. J. Patterson and P. Drenchko, J. Org. Chem., 27, 1650 (1962).
18. I. A. Jacobson, Jr., private communication, December 8, 1966.
19. J. Patterson, J. Brasch, and P. Drenchko, J. Org. Chem., 27, 1652 (1962).
20. A. Hofmann and C. Martius, Ber., 4, 742 (1871).
21. A. Hofmann, Ber., 5, 704 (1872).
22. A. Hofmann, Ber., 7, 526 (1874).
23. E. D. Hughes and C. K. Ingold, Quart. Rev. (London), 6, 43 (1952).
24. C. K. Ingold, Structure and Mechanism of Organic Chemistry, Cornell University Press, Ithaca, N.Y., 1953, p. 615.
25. W. Hickinbottom, J. Chem. Soc., 1700 (1934).
26. W. Hickinbottom, J. Chem. Soc., 1119 (1937), and references cited therein.
27. J. Reilly and W. Hichinbottom, J. Chem. Soc., 117 (1920).
28. H. Hart and J. Kosak, J. Org. Chem., 27, 116 (1962).
29. W. Hickinbottom, J. Chem. Soc., 319 (1934).
30. H. Hart and J. Kosak, J. Org. Chem., 22, 1752 (1957).
31. G. Ecke, J. Napolitano, and A. Kolka, J. Org. Chem., 21, 711 (1956).

32. G. Ecke, J. Napolitano, A. Filbey, and A. Kolka, J. Org. Chem., 22, 639 (1957).
33. Y. Ogata, H. Tabuchi, and K. Yoshida, Tet., 20, 2717 (1964).
34. A. Delle Site, J. Org. Chem., 31, 3413 (1966).
35. A. Ladenburg, Ber., 16, 1410 (1883).
36. A. Ladenburg, Ber., 18, 2961 (1885).
37. A. Ladenburg, Ber., 18, 1587 (1885).
38. A. E. Chichibabin, J. Russ. Phys. Chem. Soc., 47, 1297 (1915); Chem. Abstr., 9, 3057 (1915).
39. H. Dou and B. Lynch, Comptes. Rend., 263C, 682 (1966).