for 20 min. more, then was allowed to cool gradually over a period of 1 hour. The reaction mixture was diluted with water and the crude, tan α-hydroxydibenzyl ketone product was collected by filtration, washed with water, and air-dried; 4.22 g. (93%), m.p. 111–115°. Recrystallization from methanol then from cyclohexane gave 3.51 g. of almost colorless product, m.p. 114.5–116.5° (lit.[23] m.p. 115–116°).

The oxime of α-hydroxydibenzyl ketone was recrystallized twice from methanol–water; m.p. 91–92°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.82; H, 6.54; N, 5.51.

The 2,4-dinitrophenylosazone of α-hydroxydibenzyl ketone was recrystallized from ethyl acetate; m.p. 250–251°.

Anal. Calcd. for $C_{27}H_{20}N_8O_8$: C, 55.48; H, 3.45; N, 19.17. Found: C, 55.75; H, 3.65; N, 19.16.

In a control experiment, 4.14 g. of VII in 80 ml. of methanol was boiled under reflux for 1 hour, then the mixture was allowed to stand at room temperature for 24 hours. The mixture was cooled and VII was collected by filtration; 3.19 g. (77% recovery).

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[23] M. Tiffeneau and J. Lévy, *Bull. soc. chim. France*, [4] **37**, 1247 (1925).

[Contribution from the Department of Chemistry, University of Kentucky, Lexington, Ky.]

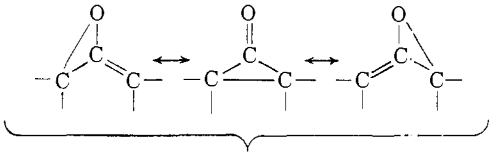
Evidence for a Delocalized Intermediate in the Favorskii Rearrangement. The Reaction of 6-Tosyloxyisophorone with Sodium Methoxide in Methanol[1]

By Arthur W. Fort

Received July 28, 1961

The reaction of 6-tosyloxyisophorone (II) with excess sodium methoxide in methanol gave a mixture of 2- and 6-methoxyisophorones (III and IV) and methyl trimethylcyclopentenecarboxylates (VIII and X). At very low methoxide ion concentration only traces of Favorskii rearrangement products (VIII and X) were produced, and the yield of 6-methoxyisophorone (IV) was increased accordingly. A common delocalized intermediate (VII) is proposed for the four reaction products.

Several reported examples of the Favorskii rearrangement seem to proceed through a delocalized intermediate.[2] Hybrid structure I, involving delocalization of four p-electrons among four parallel p-orbitals, is one possible way of representing the proposed intermediate.[2c] Structure I differs from the zwitterionic representation[2a,b] mainly in that I suggests the likelihood of some π-overlap between the radial atoms of the proposed delocalized system.



I

Previously reported work indicated that, in the absence of strong, nucleophilic base, I reacts with hydroxylic solvent to produce α-substituted ketone products instead of Favorskii rearrangement products.[2c] The present work is devoted to further study of this possible reaction path.

According to the above interpretation of the Favorskii rearrangement, the formation of Favorskii rearrangement products can be suppressed, and α-substituted ketones will be produced instead, if alkali is added slowly to a solution of the α-haloketone or related compound at such a rate that the alkali is consumed as rapidly as it is added, and the concentration of alkali in the reaction mixture remains very low throughout the reaction. In order to test this possibility, the reaction of 6-tosyloxyisophorone (II) with sodium methoxide in methanol has been examined.

6-Tosyloxyisophorone (II) possesses several desirable features for present purposes: it is a stable, crystalline compound, prepared from an α-ketol of known structure[3]; it is a derivative of an unsymmetrical ketone, a feature that makes possible easy detection of substitution with rearrangement, if it occurs; and a *gem*-dimethyl group is favorably located to hinder direct nucleophilic displacement of the tosyloxy group by methoxide ion.

Results and Discussion

The addition of a methanol solution of 6-tosyloxyisophorone (II) to a solution of five equivalents of sodium methoxide in methanol gave a 66% yield of a distilled mixture of neutral $C_{10}H_{16}O_2$ products. Gas chromatography revealed the presence of four components in the product mixture. The compounds eluted first in gas chromatography were a pair of methyl trimethylcyclopentenecarboxylates; the last compounds eluted were a pair of methoxyisophorones (see below). The yield of methoxyisophorones was approximately equal to the yield of methyl esters in this reaction (Fig. 1, run A).

The proportion of sodium methoxide was decreased to 1.1 equivalents and the reaction with 6-tosyloxyisophorone was repeated. The yield of methoxyisophorones in this run was approximately twice the yield of methyl esters, but the total yield of the four products remained unchanged (Fig. 1, run B).

In a third reaction, 1.1 equivalents of methanolic sodium methoxide was added dropwise over a period of six hours to a methanol solution of 6-tosyloxyisophorone. Under these conditions, only a trace of esters was produced (Fig. 1, run C), but the total yield of methoxyisophorones and methyl esters in this small-scale reaction was comparable (54%) to those of the reactions above.

The product that was eluted last in gas chromatography was identified as 2-methoxyisophorone

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[1] (a) Presented at the Organic Division, A.C.S. Meeting, Chicago, Ill., September, 1961; abstracts, p. 19Q. (b) Supported in part by the American Academy of Arts and Sciences.

[2] (a) J. G. Burr, Jr., and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954); (b) H. O. House and W. F. Gilmore, *J. Am. Chem. Soc.*, **83**, 3972, 3980 (1961); (c) A. W. Fort, *ibid.*, **84**, 2620 (1962).

[3] A. W. Fort, *J. Org. Chem.*, **26**, 332 (1961).

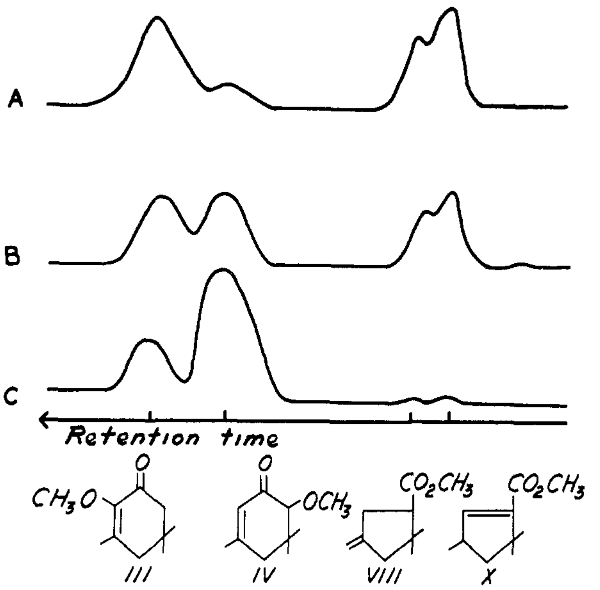
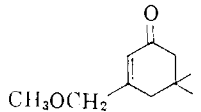


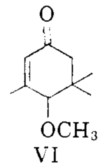
Fig. 1.—Elution peaks in gas chromatography, approximately to scale, for the products of the reaction of 6-tosyloxyisophorone with sodium methoxide in methanol: run A, 5 equivalents of sodium methoxide; run B, 1.1 equivalents of sodium methoxide; run C, 1.1 equivalents, inverse addition.

(III) by its retention time in gas chromatography, its infrared spectrum, the melting point of its 2,4-dinitrophenylhydrazone derivative, and by hydrolysis to 2-hydroxyisophorone.

The third product of the above reactions to be eluted in gas chromatography gave an analysis corresponding to $CH_3OC_9H_{13}O$. This compound was converted readily into 3,4,5-trimethylphenol by heating with concentrated hydrochloric acid[4]; it had an infrared spectrum like that of III in the region 5.9–6.1 μ (conjugated cyclohexenone) and it had an ultraviolet spectrum very similar to that of isophorone. Of the three structures, IV, V and VI, that are compatible with these observations, V can be eliminated as a possible structure on the basis of



V



VI

the n.m.r. spectrum, which showed the presence of a vinyl methyl group. A comparison of the n.m.r. spectrum of the new methoxyisophorone with that of 6-acetoxyisophorone[3] indicated that IV is the correct structure of this product.[5]

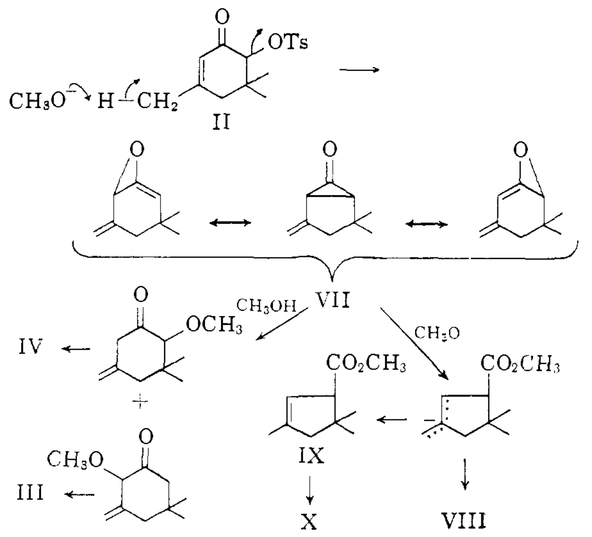


CHART I.

A possible interpretation of the present results, based on a common intermediate for all four products, is outlined in Chart I. Compound II is resistant to direct nucleophilic displacement of tosylate ion (see below) and, in the absence of catalysts, it is stable toward methanolysis.[3] Consequently, it seems probable that the present reactions are initiated by methoxide ion, acting as a base. For steric reasons, base attack should occur more readily at the vinyl methyl group than at the C-4 methylene group of II, and it is to be expected that elimination of a proton and a tosylate ion will occur predominately C-6–C–methyl, to give an intermediate which may be represented by the delocalized structure VII.[6] The decreased yield of esters that was observed to accompany decreased methoxide ion concentration in the present reactions can be understood readily on the basis of a rapid reaction of methoxide ion with VII to give esters, in competition with a slower reaction of VII with solvent to give methoxyketones. In run C, in which the concentration of methoxide ion was low throughout the reaction, practically all of the proposed intermediate VII reacted with solvent, and only a trace of esters was obtained. The variation in the ratio of 2-methoxyisophorone (III) to 6-methoxyisophorone (IV) observed in the present reactions (Fig. 1) shows that this interpretation is somewhat oversimplified. The variation in the relative amounts of the two methoxyisophorone products can be understood readily if it is assumed that VII can react with methoxide ion to give rise to methoxyketones[7] along with the Favorskii rearrangement products VIII and X, and that

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[4] 6-Tosyloxyisophorone (II) also gives 3,4,5-trimethylphenol when treated with hydrochloric acid; see ref. 3.

[5] A methoxyl group at C-4 would be expected to cause at least a small shift in the vinyl methyl peak, but this peak occurs at the same position in the n.m.r. spectrum of this product as in those of isophorone and 6-acetoxyisophorone. The methylene protons of this product, like those of 6-acetoxyisophorone, are split into a quartet of somewhat broadened peaks. The broadening of the methylene peaks indicates coupling of the methylene protons with the vinyl proton, an effect that is compatible with structure IV, but not with structure VI. The peak corresponding to –CH–O in the n.m.r. spectrum of this product is a sharp singlet, similar to the corresponding peak in 6-acetoxyisophorone. A broadening of the $-\underset{|}{\mathrm{C}}\mathrm{H}-\mathrm{O}$ peak, owing to coupling with the vinyl proton, would be anticipated if the methoxyl group were located at C-4. For these n.m.r. spectra and interpretations the author is indebted to Professor C. H. DePuy of Iowa State University.

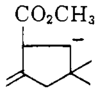
[6] A model of VII shows the *exo*-methylene group to be slightly out of the plane defined by the four atoms of the delocalized system. Consequently, the *exo* double bond is probably not strongly conjugated with the delocalized system.

[7] The reaction of 3α,20-dibenzoyloxy-9α-bromo-5β-pregnan-11-one with potassium hydroxide in methanol to give the 12α-methoxy-11-ketosteroid may occur by a similar reaction path; J. S. G. Cox, *J. Chem. Soc.*, 4508 (1960).

methoxide ion attack on VII gives more 2-methoxyisophorone than 6-methoxyisophorone. It appears from the results obtained in run C, that the major product of reaction of the proposed intermediate VII with methanol is 6-methoxyisophorone (IV).

In certain alkali-promoted reactions of α-haloketones, the formation of rearranged products corresponding to III has been attributed to S_N2' displacement on the enol form by methoxide ion,[7] or to isomerization of the parent α-haloketone followed by direct nucleophilic displacement,[8] and the formation of products corresponding to IV has been attributed to direct nucleophilic displacement on the parent α-haloketone.[8] Although these alternative reaction paths cannot be excluded, the interpretation offered above has the advantage of simplicity, particularly in accounting for the changes in relative yields of products that occurred with changing base concentration. The simpler interpretation, based on a common intermediate for all four products of the present reactions, is also compatible with the results of related work.[2c]

The structures (VIII) and (X) assigned to ester products were based on the following considerations. The intermediate VII will be cleaved by alkali preferentially in the direction that produces the more stable carbanion,[9] an allylic carbanion rather than the localized secondary carbanion XI is to be expected.



XI

The allylic carbanion will be protonated to give, initially, a mixture of the two unsaturated esters VIII and IX. However, under prolonged contact with methanolic sodium methoxide, IX will be isomerized to the conjugated unsaturated ester X. The mixture of esters obtained by fractional distillation of the product mixture A gave two elution peaks in gas chromatography and a carbonyl absorption peak at 5.77 μ. The ultraviolet spectrum of the mixture indicated that the major component was the α,β-unsaturated ester. Catalytic hydrogenation of the mixture gave a saturated ester having a single elution peak in gas chromatography.

Because of the *gem*-dimethyl group at C-5, 6-tosyloxyisophorone (II) was expected to be unreactive toward direct nucleophilic displacement of the tosyloxy group. In accordance with this expectation, II was found to be inert toward sodium iodide in acetone. Consequently, it seems unlikely that much of the 6-methoxyisophorone product of the present reactions could have arisen by direct displacement of tosylate ion from II by methoxide ion.

Experimental

Melting points are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford, Eng., and Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

6-Tosyloxyisophorone (II) with Sodium Iodide.—A solution of 1.03 g. of II,[3] m.p. 133° dec., and 1.5 g. of sodium iodide in 12 ml. of acetone was allowed to stand at room temperature. No precipitate was produced in the course of 7 days. The mixture was diluted with a little water and cooled, and recovered II was washed with water and dried; 1.02 g., m.p. 135–136° dec.

2-Methoxyisophorone (III) was prepared from isophorone oxide[10] according to the procedure of Treibs.[11] Two distillations gave a product having b.p. 109° (15 mm.) (lit.[11] b.p. 221–223°), n^{24}D 1.4740, single elution peak in gas chromatography.

The 2,4-dinitrophenylhydrazone derivative was recrystallized from ethanol–ethyl acetate; m.p. 191.5–193° dec.

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.78; N, 16.08. Found: C, 55.00; H, 6.03; N, 16.08.

The Reaction of 6-Tosyloxyisophorone (II) with Sodium Methoxide in Methanol. A.—A warm solution of 18.5 g. (0.060 mole) of II in 500 ml. of anhydrous methanol was added dropwise over a period of 45 minutes to a stirred solution of 16.2 g. (0.30 mole) of sodium methoxide in 100 ml. of anhydrous methanol with slight cooling. Stirring was continued for 30 minutes more (until all II had redissolved), then the mixture was allowed to stand at room temperature for 45 minutes. Ice and a slight excess of hydrochloric acid were added, and the mixture was neutralized with sodium bicarbonate. Most of the methanol (400 ml.) was removed by distillation, the mixture was then diluted with water, made alkaline with sodium hydroxide, and extracted with three large portions of pentane. The combined pentane extracts were washed with water, dried, and the solvent was removed by distillation. Distillation at reduced pressure gave 6.6 g. (66%) of a mixture of $C_{10}H_{16}O_2$ products which had four elution peaks in gas chromatography (Fig. 1). The yield of the pair of higher boiling products (methoxyisophorones) was approximately equal to the yield of the lower boiling pair of products (methyl trimethylcyclopentenecarboxylates), judging from the areas under elution peaks.

B.—A warm solution of 18.5 g. (0.060 mole) of II in 500 ml. of anhydrous methanol was added dropwise over a period of 2 hours to a stirred solution of 3.56 g. (0.066 mole) of sodium methoxide in 100 ml. of anhydrous methanol with slight cooling, and the mixture was allowed to stand overnight at room temperature. The reaction mixture was neutralized with acetic acid and most of the methanol (450 ml.) was removed by distillation. Workup of the mixture was completed as in reaction A. The distilled product mixture, 6.6 g. (66%), showed the same elution peaks in gas chromatography that were observed in the preceeding section, but the area under methoxyisophorone elution peaks was approximately twice the area under ester elution peaks.

C.—A solution of 0.86 g. (0.016 mole) of sodium methoxide in 250 ml. of anhydrous methanol was added dropwise over a period of 6 hours to a stirred solution of 4.4 g. (0.014 mole) of II in 300 ml. of methanol at 32 ± 2°. This reaction mixture was allowed to stand overnight at room temperature, then treated like the preceding mixture. Distillation at reduced pressure gave 1.27 g. (54%) of $C_{10}H_{16}O_2$ products. The composition of the product mixture, estimated by comparing areas under elution peaks in gas chromatography, was 74 ± 2 mole % 6-methoxyisophorone, 24 ± 2 mole % 2-methoxyisophorone and 2 ± 1 mole % of methyl trimethylcyclopentenecarboxylates.

A semi-micro column packed with glass helices was used to strip the low-boiling esters from product mixture A. The ratio of conjugated ester to unconjugated ester was estimated to be approximately 4:1 by comparing the areas under elution peaks in gas chromatography; λ_{max} near 215 mμ, ε 4,800 (ethanol); intense carbonyl absorption at 5.77 μ; n^{24}D 1.4516.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; sapon. equiv., 168. Found: C, 71.28; H, 9.26; sapon. equiv., 272, 191.[12]

Reduction of 0.80 g. of the unsaturated ester mixture in acetic acid solution under a low pressure of hydrogen in the presence of palladium–charcoal gave, after distillation, 0.50 g. of saturated ester having a single elution peak in gas

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[8] See the review by A. S. Kende for references, *Org. Reactions*, **11**, 261 (1960).

[9] See, for example, ref. 8, p. 267.

[10] H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957).

[11] W. Treibs, *Ber.*, **66**, 1483 (1933).

[12] These values for saponification equivalent seem reasonable for structures VIII and X, owing to steric hindrance to saponification.

chromatography; $\epsilon < 100$ in the region 220–300 mμ; intense carbonyl absorption at 5.78 μ; n^{24}D 1.4341.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.51; H, 10.79.

The last elution peak shown by each of the above product mixtures in gas chromatography (Fig. 1) corresponded in retention time to that of authentic 2-methoxyisophorone. A mixture of the pair of methoxyisophorones obtained in the present reactions was warmed on a steam-bath for 30 minutes with concentrated hydrochloric acid. This treatment converted the lower-boiling methoxyisophorone component into 3,4,5-trimethylphenol, m.p. 108.5° (lit.[3] m.p. 108.5°), but left 2-methoxyisophorone largely unchanged. A sample of 2-methoxyisophorone recovered from the hydrochloric acid treatment gave a single elution peak in gas chromatography, and gave a 2,4-dinitrophenylhydrazone derivative, m.p. 190–191.5° dec. after recrystallization from ethanol. The structure of this product was confirmed by hydrolysis[11] to 2-hydroxyisophorone, m.p. 91–93° (lit.[11] m.p. 92–93°).

From the product mixture of run C, a sample of **6-methoxyisophorone** was obtained by distillation, b.p. 101–103° (12.5 mm.), n^{25}D 1.4735, λ_{max} 236 mμ (ethanol). Gas chromatography revealed the presence of a few mole % of 2-methoxyisophorone as the only impurity.

Anal. Calcd. for $CH_3OC_9H_{13}O$: C, 71.39; H, 9.59; OCH_3, 18.45. Found: C, 71.55; H, 9.88; OCH_3, 18.94.

The 2,4-dinitrophenylhydrazone derivative of 6-methoxyisophorone was recrystallized from ethanol; m.p. 129.5–130.5°.

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.78; N, 16.08. Found: C, 55.08; H, 6.08; N, 16.17.

In control experiments, known mixtures of the methoxyisophorone products and of the methyl trimethylcyclopentenecarboxylate products of the above reactions were treated with methanolic potassium hydroxide for 3 hours at room temperature. Products recovered from the alkaline solutions were examined by means of gas chromatography, and in neither mixture was any change in composition found to have resulted from the treatment with alkali.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY, NEW YORK 27, N. Y.]

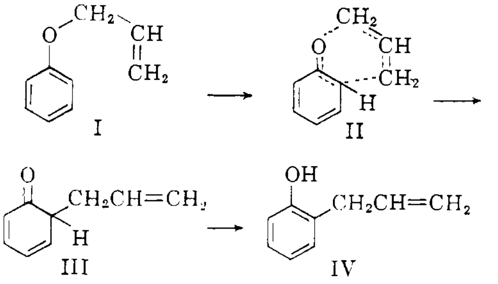
Organic Reactions under High Pressure. VI. Some Claisen and Cope Rearrangements[1]

BY CHEVES WALLING AND MICHAEL NAIMAN[2]

RECEIVED JANUARY 27, 1962

Measurements are reported on the effect of pressures up to 6000 kg./cm.^{2} on the rates of rearrangements of allyl phenyl ether (I) at 160° and ethyl (1-ethylpropenyl)-allylcyanoacetate (VIII) at 119°, each in several solvents. Both reactions are pressure-accelerated, ΔV^{*}'s being generally -6 to -7 cc./mole between 1000–6000 kg./cm.^{2} and essentially solvent independent. Extrapolations to atmospheric pressure are less certain, but indicate ΔV^{*}'s of -10 to -15 cc./mole, again with no obvious solvent dependence. These results are interpreted as consistent with rather tightly bonded cyclic transition states in which new bond formation has proceeded farther than bond breaking, rather than with transition states which are essentially ion-pairs, or in which homolytic bond cleavage has been extensive.

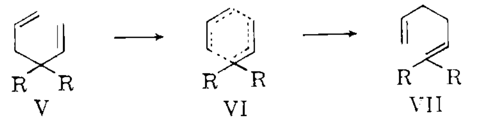
Although there is a general agreement[3] that the mechanism of the Claisen rearrangement is represented by a sequence such as



(1)

the detailed structure of the transition state II remains ill-defined. Several recent studies have attempted to establish more precisely the degree of bond breaking and bond forming, amount of ionic character and exact geometry which is involved through investigation of the effects of solvents,[4,5] and substituents[4-6] on reaction rates, and of the stereochemical course[7,8] and geometric requirements[9,10] of the rearrangement.

A similar situation arises in connection with the Cope rearrangement of 1,4-dienes, usually activated by cyano, carbethoxy or similar substituents on carbon 3.[11] Here the reaction has been shown to be intramolecular[12] and to possess a large negative entropy of activation,[13] so that it may be considered a close analog of the Claisen rearrangement, occurring in an all-carbon chain system.[11]



(2)

It seemed to us that a study of the effect of high pressures of the rates of some typical Claisen and Cope rearrangements would provide further information on the nature of the transition states involved, and our results are described here. Since our work was completed, Brower[14] has reported a study on the effect of pressure on three Claisen rearrangements leading to conclusions which are in qualitative agreement with our own.

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(1) Taken from the Ph.D. Dissertation of Michael Naiman, 1961. Support of this research by a grant from the Petroleum Research Fund of the American Chemical Society is gratefully acknowledged.

(2) Columbia University Fellow, 1959-1960.

(3) For recent reviews, *cf.* (a) D. J. Cram and M. S. Newman "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York. N. Y., 1956, pp. 295–303; (b) E. S. Gould "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, pp. 644–649.

(4) W. N. White, D. G. Wynn, R. Schlitt, C. Girard and W. Fife, *J. Am. Chem. Soc.*, **80**, 3271 (1958).

(5) H. L. Goering and R. R. Jacobson, *ibid.*, **80**, 3277 (1958).

(6) W. N. White and W. K. Fife, *ibid.*, **83**, 3346 (1961); W. N. White, C. D. Slater and W. K. Fife, *J. Org. Chem.*, **27**, 627 (1961).

(7) E. N. Marvel and J. L. Stephenson, *ibid.*, **25**, 676 (1960).

(8) A. W. Burgstahler, *J. Am. Chem. Soc.*, **82**, 4681 (1960).

(9) L. D. Huestis and L. J. Andrews, *ibid.*, **83**, 1963 (1961).

(10) W. N. White and B. E. Norcross, *ibid.*, **83**, 1968, 3265 (1961).

(11) A. C. Cope and E. M. Hardy, *ibid.*, **62**, 441 (1940).

(12) D. E. White and A. C. Cope, *ibid.*, **65**, 1999 (1943).

(13) E. G. Foster, A. C. Cope and F. Daniels, *ibid.*, **69**, 1893 (1947).

(14) K. R. Brower, *ibid.*, **83**, 4370 (1961).