

The Chemistry of Cyclopropanols

C. H. DEPUY

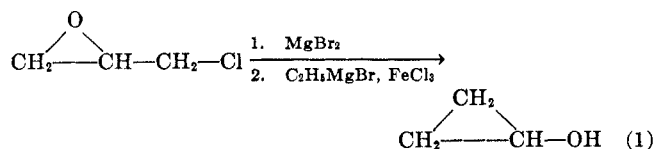
Department of Chemistry, University of Colorado, Boulder, Colorado 80302

Received June 12, 1967

Cyclopropanols have been principally synthesized by (1) reaction of epichlorohydrins with magnesium bromide followed by treatment with Grignard reagent and ferric chloride, (2) acid hydrolysis of cyclopropyl vinyl ethers, and (3) hydrolysis of cyclopropyl acetates which are available *via* the Baeyer-Villiger oxidation of methyl cyclopropyl ketones or pyrolysis of acetoxy-pyrazolines. Cleavage of a carbon-carbon bond of cyclopropanols or cyclopropyl acetates occurs upon reaction with electrophiles, leading to incorporation of the electrophile in the C₂ (or C₃) position of the original cyclopropane in the final product. Protonic acids attack *trans*-2-phenyl-1-methylcyclopropanol leading to *retention* of configuration in the product. Reaction of this same alcohol with electrophilic halogen (*t*-butyl hypohalite, N-bromosuccinimide) gives *inversion* of configuration. When *trans,trans*- or *cis,trans*-2,3-dimethyl-1-phenylcyclopropanol is cleaved with brominating agents, bromoketones are formed, also with *inversion* of configuration. In base-catalyzed cleavage of cyclopropanols, protonation occurs with *inversion* of configuration. Solvolysis of cyclopropyl tosylates and halides generally occurs with simultaneous ring opening and with the ultimate formation of allyl cations. The Woodward-Hoffmann rules, which predict a disrotatory mode of opening, are obeyed. In addition, a selection between the two allowed disrotatory modes is imposed by the relative configurational geometry of the leaving group; groups *trans* to the leaving group rotate outwardly and groups *cis* rotate inwardly. Nitrite esters of cyclopropanols rearrange spontaneously to nitroso ketones. Cyclopropanols are easily oxidized with ferric chloride, implying that homolytic cleavage of the O-X bond is exceptionally easy. Cyclopropyl acetates generally rearrange upon pyrolysis and form allyl acetates.

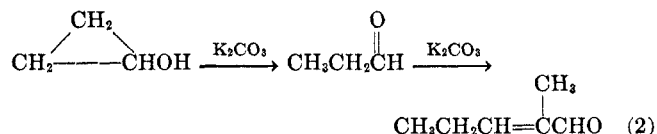
Historical

Cyclopropanol was first synthesized (accidentally) by Magrane and Cottle in 1942 by the remarkable reaction of epichlorohydrin with magnesium bromide followed by treatment with ethyl Grignard reagent.¹ In the next year attempts to reproduce the synthesis failed until it was recognized that an impure grade of magnesium was necessary for a successful reaction, or even better that small amounts of ferric chloride had to be added as a catalyst.² Under the proper conditions, yields of impure cyclopropanol of greater than 40% were realized; large amounts of ethane and ethylene were liberated as by-products.



Cyclopropanol prepared in this way was impossible to purify completely (87% maximum purity), because

upon attempted distillation it isomerized to propionaldehyde. The structure of cyclopropanol was proven by the preparation of several solid derivatives which were not identical with those of any other simple alcohols and which had correct elemental analyses. Upon standing over solid potassium carbonate, cyclopropanol was converted to the aldol condensation product of propionaldehyde.²



In 1951 Roberts and Chambers³ prepared small amounts of cyclopropanol by the oxygenation of cyclopropylmagnesium chloride and, more successfully, by the Cottle procedure described above. Again, the pure alcohol was not obtained, but a tosylate derivative was prepared and its solvolytic behavior investigated (see below). Although a few scattered references to more complex cyclopropanols appear in the earlier literature, in general the authenticity of their molecular structures remains in doubt. It seemed to us that the

(1) J. K. Magrane, Jr., and D. L. Cottle, *J. Am. Chem. Soc.*, **64**, 484 (1942).

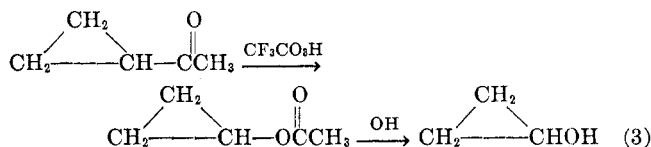
(2) G. W. Stahl and D. L. Cottle, *ibid.*, **65**, 1782 (1943).

(3) J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 3176 (1951).

chemistry of such a simple molecule deserved further investigation, especially in view of the isomerization reactions reported by Cottle, and we began several years ago a systematic study of the synthesis and reactions of what has proven to be a most remarkable group of compounds.

Synthesis of Cyclopropanols

We began by assuming (wrongly, as we shall see) that the synthesis of substituted cyclopropanols by the Cottle procedure was not likely to be fruitful. We knew that in order to investigate a variety of cyclopropanols we would need synthetic methods whose substitution patterns, both structural and stereochemical, could be controlled and determined. Not too long before our initial investigations, Emmons and Lucas⁴ showed that cyclopropyl acetate could be obtained in high yield by the Baeyer-Villiger oxidation of methyl cyclopropyl ketone (eq 3).⁵ A large variety of cyclopropyl acetates was potentially available, because methyl cyclopropyl ketones can readily be prepared from the corresponding acids, and because a large number of substituted cyclopropanecarboxylic acids are known. Therefore, we



began by investigating the possibility of hydrolyzing cyclopropyl acetates to cyclopropanols.⁶ It was shown that the hydrolysis rate of the ester is appreciably greater than the isomerization rate of the alcohol, and that it is therefore quite possible to synthesize cyclopropanol by this method. Yields are improved, however, and the isolation and purification of the alcohol is simpler, if the ester is treated with methyl lithium in



ether or, less conveniently, with lithium aluminum hydride. As prepared by this series of reactions, cyclopropanol can be purified by preparative scale gas chromatography or fractional distillation at somewhat reduced pressures. An analytically pure sample (bp 100.5–102.0°) is reasonably stable in the absence of acids or bases.

This general method of synthesis has since been extended to the preparation of a large number of substituted cyclopropanols.⁷ The synthesis of *trans*-2-phenylcyclopropanol may serve as an example. A mixture of ethyl *cis*- and *trans*-2-phenylcyclopropanecarboxylate is

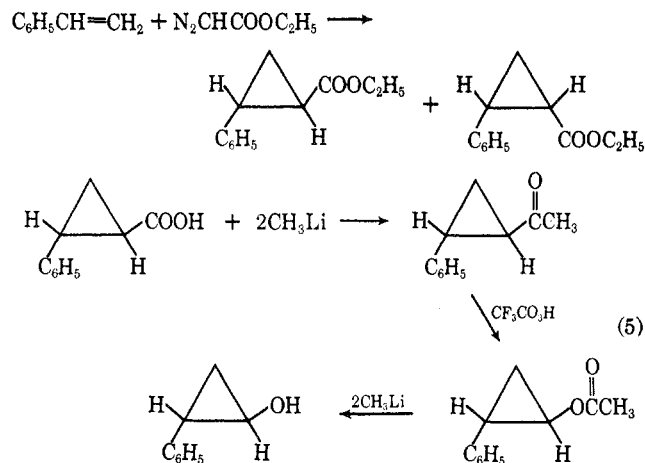
(4) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(5) Methyl cyclopropyl ketones give, on Baeyer-Villiger oxidation, cyclopropyl acetates almost exclusively. Side chains larger than methyl give mainly alkyl esters of cyclopropanecarboxylic acids [R. R. Sauers and R. W. Ubersax, *J. Org. Chem.*, **30**, 3939 (1965)].

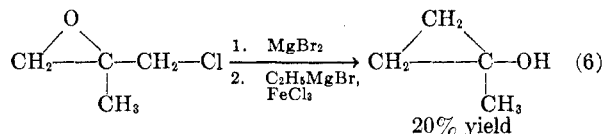
(6) C. H. DePuy and L. R. Mahoney, *J. Am. Chem. Soc.*, **86**, 2653 (1964).

(7) C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).

prepared by the thermal reaction of styrene and ethyl diazoacetate. The esters or their corresponding acids may be separated by distillation or crystallization. The *trans* acid is converted to the methyl ketone in 75% yield by reaction with methyl lithium. Oxidation with peroxytrifluoroacetic acid gives the acetate in 75–80% yield. Reaction of the acetate with two molar equivalents of methyl lithium gives, after distillation and recrystallization, the *trans* alcohol, mp 41.5–42.0°, in 79% yield. Because of the instability of cyclopropanols, they are best stored at the acetate stage and generated just before use.

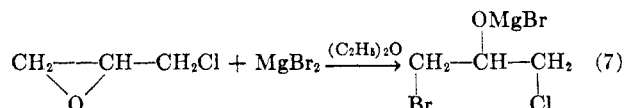


After we had gained experience in the handling and purification of cyclopropanols, we turned again to the Cottle procedure for cyclopropanol synthesis and were surprised to discover that substituted epichlorohydrins also react with ethyl Grignard and ferric chloride to produce substituted cyclopropanols. The reaction with 2-methylepichlorohydrin is typical (eq 6). Evidence



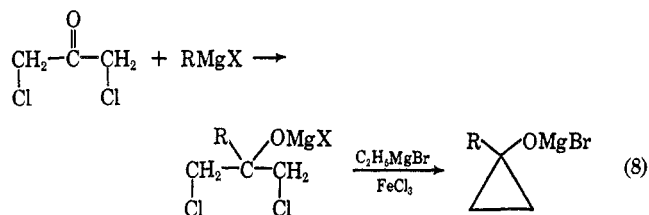
was also obtained that 1- and 2-arylcyclopropanols can be obtained in this way. In general, however, it is difficult to prepare the requisite epichlorohydrin except in the few cases where the corresponding olefin is commercially available.

Magrane and Cottle had already recognized that the first step in the transformation of epichlorohydrin to cyclopropanol involves the ring opening of the epoxide with magnesium bromide (eq 7). The corresponding



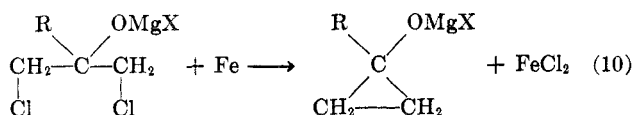
1-bromo-3-chloro-2-propanol can be isolated from this reaction upon acidification, and it, in turn, can be converted to cyclopropanol upon reaction with ethyl Grignard and ferric chloride. It occurred to us that an analogous intermediate can be generated by the reaction of the commercially available 1,3-dichloroacetone with

Grignard reagents (eq 8). In fact, this has proven to

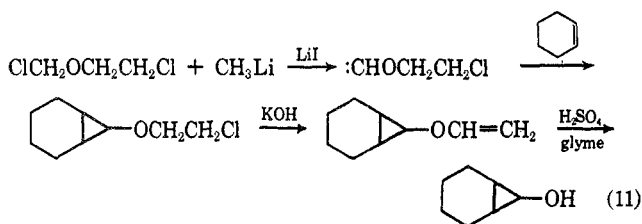


be an exceedingly convenient way of synthesizing 1-substituted cyclopropanols.⁷ For instance, if 1,3-dichloroacetone is allowed to react with phenylmagnesium bromide and then with ferric chloride and ethyl Grignard, 1-phenylcyclopropanol is obtained in 60% yield.

The steps involved in the conversion of the 1,3-dihaloalkoxide to the cyclopropanol have not been proven definitely, but a reasonable formulation is possible, based on the work of Kharasch and coworkers.⁸ Grignard reagents are known to react with ferric chloride to give intermediate, unstable organo-iron compounds. These compounds break down, forming, in the case of ethyl Grignard, ethyl radicals and, presumably, atomic iron (eq 9). Disproportionation of the ethyl radicals leads to ethane and ethylene, observed to evolve from $3\text{C}_2\text{H}_5\text{MgBr} + \text{FeCl}_3 \longrightarrow [(\text{C}_2\text{H}_5)_3\text{Fe}] \longrightarrow 3\text{C}_2\text{H}_5\cdot + \text{Fe}$ (9) the reaction mixture, while the iron dehalogenates the dihalide. In this way, the iron is recycled, and only a catalytic amount is required.

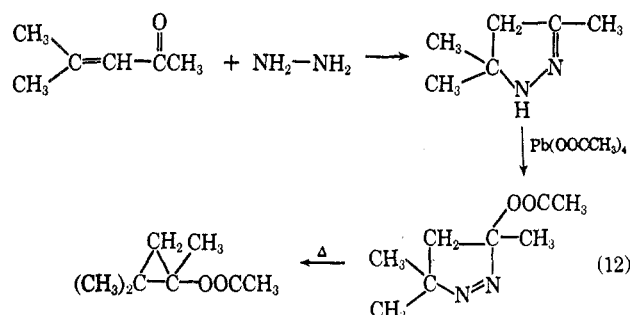


In the meantime, methods for the synthesis of cyclopropanols have been forthcoming from other laboratories. One of the more versatile methods has been devised by Schöllkopf and coworkers.⁹ In this method, a carbene generated from chloromethyl 2-chloroethyl ether is added to a double bond, forming a 2-chloroethyl ether of a cyclopropanol. Dehydrochlorination to the vinyl ether followed by mild acid hydrolysis gives the cyclopropanol.



Finally, some methods are available for the synthesis of certain types of cyclopropanols, methods which compensate in convenience for what they may lack in complete generality. Foremost among these is the method developed by Freeman,¹⁰ in which a 2-pyrazoline, formed by reaction of an α,β -unsaturated ketone

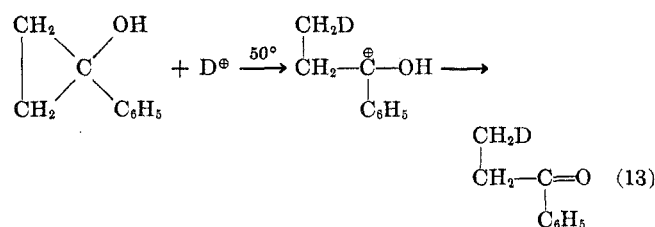
with hydrazine, is oxidized to a 3-acetoxy-1-pyrazoline by lead tetraacetate. This latter compound, upon heating, forms cyclopropyl acetate by loss of nitrogen. A large number of cyclopropyl acetates, including some stereoisomeric ones, have been prepared by this method.



Wasserman¹¹ has also prepared cyclopropanols from derivatives of cyclopropanone.

Electrophilic Reactions on Cyclopropanols

Cottle^{1,2} recognized that cyclopropanol readily tautomerizes under the influence of either acid or base, yielding propionaldehyde. The acid-promoted ring opening of cyclopropanes has, of course, been known for a long time, but the reaction is difficult to study for a number of reasons. In general, cyclopropanes open under the influence of acidic reagents so as to form the most stable carbonium ion.¹² The resulting carbonium ion may rearrange, eliminate in one of several directions, react with solvent, or give rise to any one of a number of products. Hydrogen exchange before ring opening¹³ and other complications are also being uncovered.^{14,15} Cyclopropanols, on the other hand, and especially 1-substituted cyclopropanols, share almost none of these disadvantages. The hydroxyl group, by virtue of its ability to stabilize an adjacent positive charge, controls and facilitates the ring opening so that one, or at most two, products are formed. The intermediate carbonium ion, by loss of the hydroxyl proton, is converted completely to stable ketonic products. For example, 1-phenylcyclopropanol is converted quantitatively to propiophenone in a matter of a few hours upon reaction with 1 N acid in dioxane-water at 50°. If a deuterio acid is used, a single β -deuterium atom is introduced into the ketone (eq 13). Kinetic studies have



(11) H. H. Wasserman and D. C. Clogett, *Tetrahedron Letters*, No. 7, 341 (1964).

(12) A. Bhati, *Perfumery Essent. Oil Record*, 53, 15 (1962).

(13) R. L. Baird and A. A. Aboderin, *J. Am. Chem. Soc.*, 86, 252 (1964).

(14) N. C. Deno and D. N. Lincoln, *ibid.*, 88, 5357 (1966).

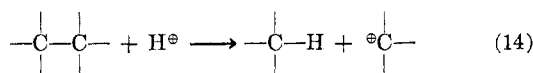
(15) H. Hart and R. H. Schlosberg, *ibid.*, 88, 5030 (1966).

(8) M. S. Kharasch, M. Weiner, W. Nudenberg, A. Bhattacharya, T. Wang, and N. C. Yang, *J. Am. Chem. Soc.*, 83, 3232 (1961).

(9) U. Schöllkopf, J. Paust, A. Al-Azrak, and H. Schumacher, *Chem. Ber.*, 99, 3391 (1966).

(10) J. P. Freeman, *J. Org. Chem.*, 29, 1379 (1964).

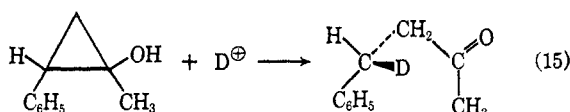
shown¹⁶ that the reaction is bimolecular, that is first order with respect to reacting alcohol and to acid. If we reduce it to its essentials, the transformation is one in which a carbon-carbon single bond is broken by a proton (eq 14). Such a reaction would be classified according to



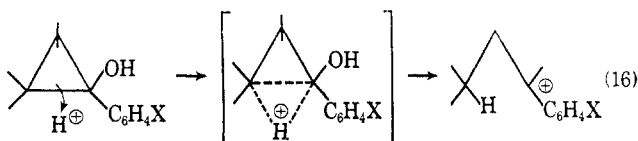
the Ingold scheme as $\text{S}_{\text{E}}2$ and has previously been investigated only among organometallic compounds.¹⁷

Stereochemistry of Ring Opening in Acid and Base

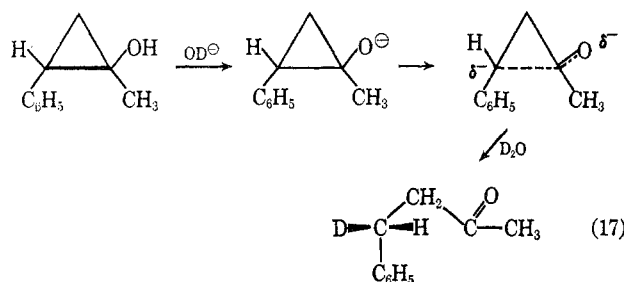
We turned first to an examination of the stereochemistry of the ring opening of cyclopropanols. As a substrate, *trans*-2-phenyl-1-methylcyclopropanol was chosen¹⁸ and was prepared in optically active form.¹⁹ Ring opening was accomplished by treatment with 1 *N* deuterium chloride (DCl) in dioxane-water at 90° . Two products are formed, the desired 4-phenyl-2-butanone and the undesired 3-phenyl-2-butanone. Racemization of the latter compound by base and careful separation of the isomers gives optically active 4-phenyl-2-butanone with *retention* of configuration (eq 15).¹⁹ Since a kinetic study of 1-arylcyclopropanols has



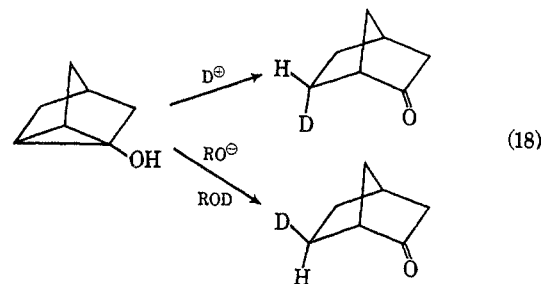
shown that appreciable positive charge develops on the 1-carbon in the transition state,¹⁶ a reasonable mechanistic picture is one in which the proton attacks the $\text{C}_1\text{-C}_2$ bonding electrons, which are postulated to bulge out around the edge of the cyclopropane ring²⁰ (eq 16).



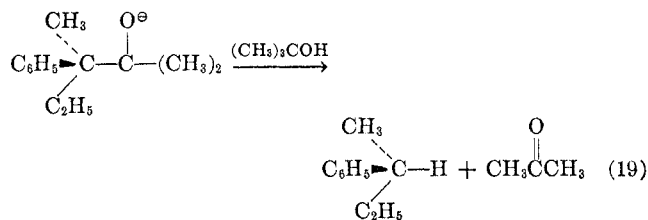
In dilute basic solution, *trans*-2-phenyl-1-methylcyclopropanol is isomerized exclusively to 4-phenyl-2-butanone. The reaction is rapid at room temperature.¹⁹ The exclusive formation of the ketone resulting from cleavage of the $\text{C}_1\text{-C}_2$ bond, plus the fact that the product arises by *inversion* of configuration at the benzylic carbon atom, led us initially to suppose that an $\text{S}_{\text{E}}1$ reaction, similar to those investigated by Cram and co-workers,²¹ was involved (eq 17). These stereochemical results (inversion in base, retention in acid) were ele-



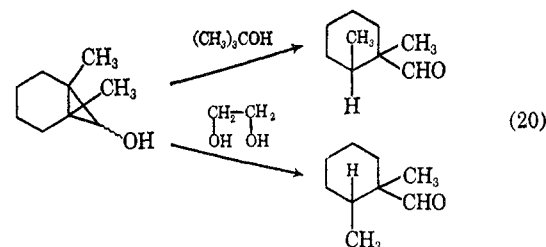
gantly demonstrated in the all-aliphatic system of Nickon²² (eq 18).



In an $\text{S}_{\text{E}}1$ reaction, a carbanion intermediate is formed in the rate-determining step. The very high degree of stereospecificity observed in these base-catalyzed openings argues against free carbanions. Besides, in the solvent-base system used by Nickon (*t*-butyl alcohol, *t*-butoxide), Cram had found predominant retention of configuration in his open-chain systems in which carbanions definitely seem to be involved (eq 19). Re-



cently Wharton and Bair²³ noted that in both *exo*- and *endo*-7-hydroxy-1,6-dimethyl[4.1.0]bicycloheptane predominant retention (90%) is observed upon opening in *t*-butyl alcohol and predominant inversion occurs in ethylene glycol (eq 20), both results being those ex-



pected on the basis of Cram's work. Additional work still remains to be done on the stereochemistry of base-catalyzed openings of cyclopropanols. The data available so far can be reconciled if it is assumed that opening of a cyclopropoxide toward a secondary or tertiary position does not occur *until* attack of a proton. When

(16) R. A. Klein, unpublished results.

(17) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter 3. See, however, H. Hogeveen and A. F. Bickel, *Chem. Commun.*, 635 (1967), for a recent report of an $\text{S}_{\text{E}}2$ reaction involving a saturated hydrocarbon.

(18) The phenyl and hydroxyl groups are *trans*.

(19) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *J. Am. Chem. Soc.*, **88**, 3347 (1966).

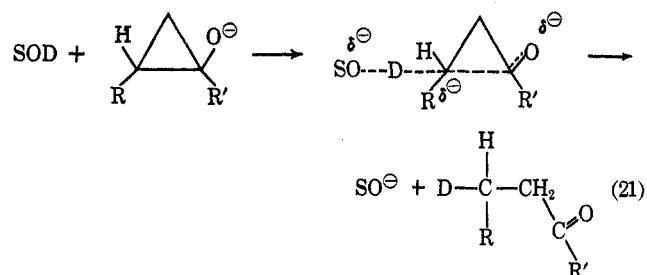
(20) C. A. Coulson and W. Moffitt, *Phil. Mag.*, **40**, 1 (1949); K. B. Wiberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, p 124.

(21) Reference 17, Chapter 4.

(22) A. Nickon, J. L. Lambert, S.J., R. O. Williams, and N. H. Westiuk, *J. Am. Chem. Soc.*, **88**, 3354 (1966).

(23) P. S. Wharton and T. I. Bair, *J. Org. Chem.*, **31**, 2480 (1966).

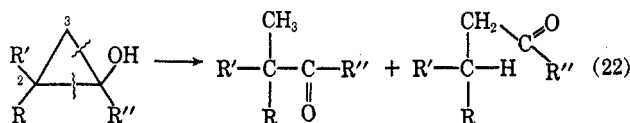
the center at which the proton must attack is quaternary, as it is in the compounds studied by Wharton and



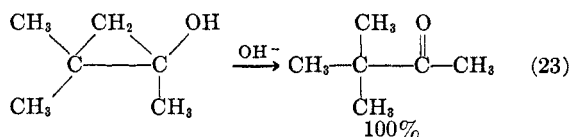
Bair, a carbanion intermediate may be involved. It is known that attack at such centers is slow relative to attack at centers containing hydrogen atoms. Alternatively, Wharton²³ has suggested that Nikon's results may not be general in that *exo* attack in the norbornyl system may be so much favored as to force inversion.

Direction of Ring Opening in Acid and Base

Additional information about the transition states in acid- and base-catalyzed ring openings may be gained from studies of the *direction* of opening in unsymmetrically substituted cyclopropanols. In every case investigated so far, base-catalyzed opening occurs more readily toward the carbon (C₂ or C₃) which can better stabilize a negative charge. As already mentioned,



2-phenyl-1-methylcyclopropanol gives exclusively 4-phenyl-2-butanone. In addition, 1,2,2-trimethylcyclopropanol gives pinacolone exclusively upon treatment with base²⁴ (eq 23).

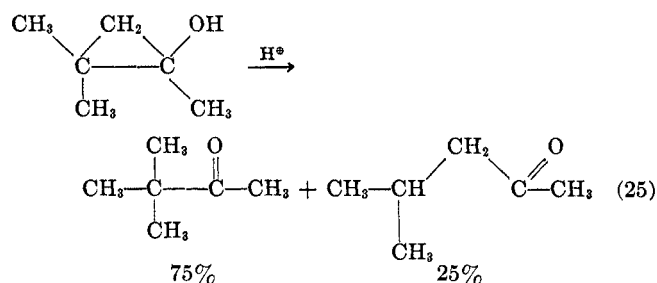
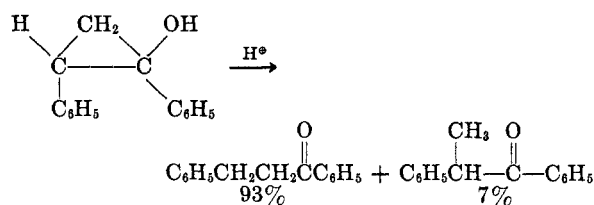
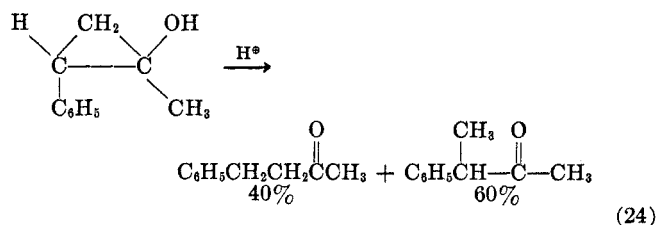


The effect of structure upon the direction of acid-catalyzed opening is not yet clear. The nature of substitution at C₁ as well as at C₂ affects the product ratio, as the following two examples show^{19,25} (eq 24). In the second example, substitution of the benzene ring at C₂ by either electron-attracting or electron-donating groups has little effect on the rate of acid-catalyzed C₁-C₂ bond breaking. Furthermore, a change in stereochemistry (making the phenyl groups *trans* to each other) also has little effect on the rate. Acid treatment of 1,2,2-trimethylcyclopropanol gives a mixture of 75% pinacolone and 25% methyl isobutyl ketone (eq 25), perhaps an indication of the operation of steric hindrance.^{24,26}

(24) C. H. DePuy, W. C. Arney, Jr., and D. H. Gibson, submitted to *J. Am. Chem. Soc.*

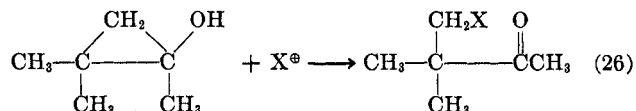
(25) J. P. Clark, unpublished results.

(26) B. R. Davis and P. D. Woodgate, *Chem. Commun.*, 65 (1966).



Ring Opening with Electrophilic Halogen

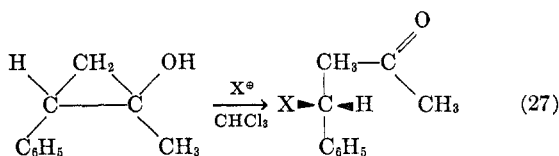
Considering their great reactivity toward protonic acids, it seemed reasonable to suppose that cyclopropanols would undergo ring opening with other electrophiles, and we have recently completed studies with several halogenating agents.²⁴ The results are extremely clear-cut, although mechanistic ambiguities still remain. 1,2,2-Trimethylcyclopropanol reacts rapidly and quantitatively with sources of positive halogen (hypochlorous acid, *t*-butyl hypochlorite, *t*-butyl hypobromite, *N*-bromosuccinimide) in a variety of solvents (water, *t*-butyl alcohol, chloroform). A single haloketone results from cleavage of the C₁-C₃ bond. Reaction at the hydroxyl bond, with either an



electrophile or a radical, should have given rise to C₁-C₂ bond cleavage (see below for the case of the cyclopropoxy radical). We assumed, therefore, that electrophilic attack was occurring. We next examined the ring opening of optically active *trans*-2-phenyl-1-methylcyclopropanol.²⁷ The results were surprising in that, in contrast to acid-catalyzed opening of the same compound, only a single bromoketone was formed, with *inversion* of configuration²⁸ and with C₁-C₂ bond breaking.

(27) W. C. Arney, Jr., unpublished results.

(28) This stereochemical conclusion must be qualified to this extent: the absolute configuration of the product has not been determined chemically and its assignment rests on close analogies in the literature and also on Brewster's rules [J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959)]. Experiments are underway to prove this point conclusively. Our present opinion is that the reaction is completely stereospecific, proceeding with 100% inversion. If this is true, this method may afford a unique and useful way of synthesizing optically active halides of known configuration.



We next turned our attention to a system in which there was not an aryl group at the 2 position. Because of the possible complications in the norbornyl system (see above), we chose to examine the 2,3-dimethyl-1-phenylcyclopropanols, compounds which could be synthesized fairly easily. If ring opening with positive halogen were to occur with *retention* of configuration, then the *trans,trans*-dimethyl alcohol would give rise to *erythro* bromoketone and the *cis,trans*-dimethyl compound to the *threo* bromoketone. If *inversion* were to occur, these results would be reversed. Although the configurational assignment to the *threo* and *erythro* bromoketones had not been made previously, it seemed possible to do so on the basis of a stereospecific *trans* elimination under mild conditions. A mixture of the two bromoketones was prepared by the zinc bromide catalyzed addition of benzoyl bromide to 2-butene and, as the nmr spectrum shows (Figure 1), the methyl doublets of the two diastereomers appear at distinctly different positions, making stereochemical analysis easy. Each isomeric bromoketone was identified by its exclusive conversion to an unsaturated ketone by base-

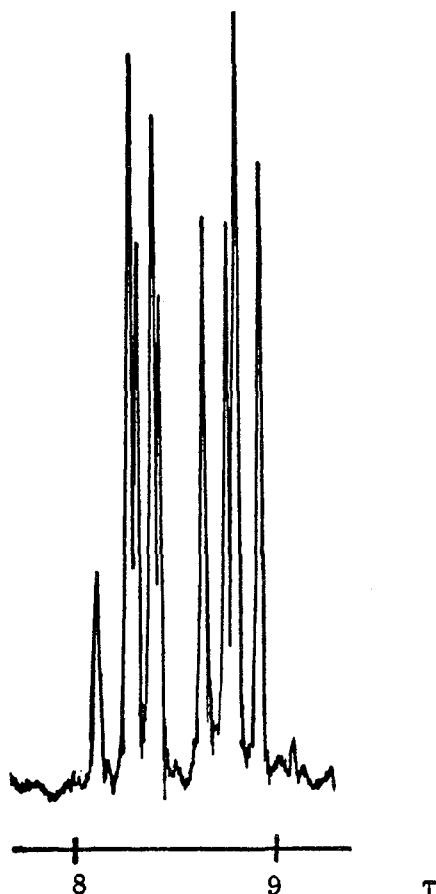
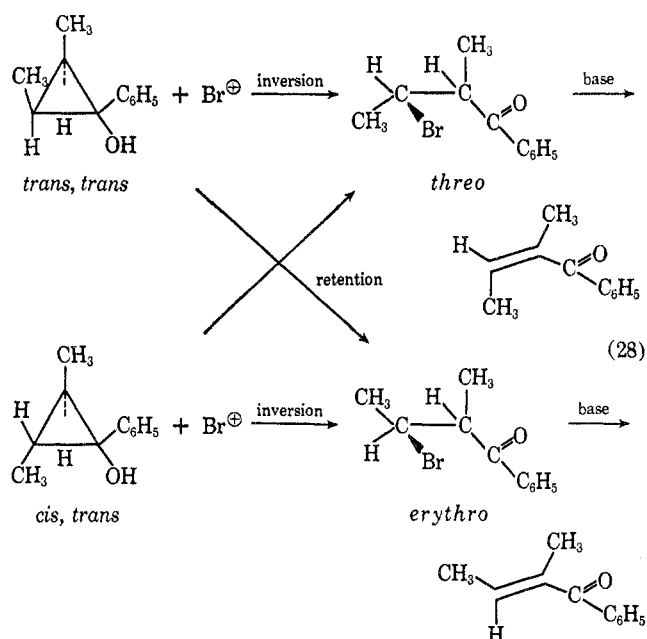


Figure 1. Methyl peaks from the nmr spectrum of a mixture of *erythro*- and *threo*- α -methyl- β -bromobutyrophenone.



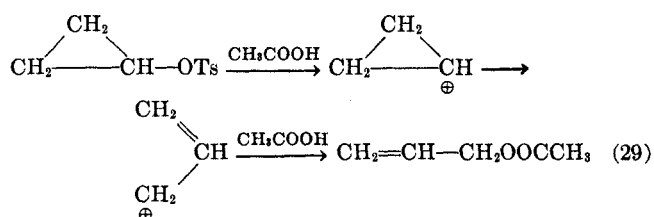
catalyzed elimination (potassium acetate or potassium hydroxide in ethanol at room temperature). The unsaturated ketones, presumed to arise *via* a *trans* elimination process, were identified by comparison of their spectral properties with those of authentic samples. The results were as follows: both the *trans,trans* and *cis,trans* isomers react with bromine in *t*-butyl alcohol or in acetic acid, with *N*-bromosuccinimide in *t*-butyl alcohol, or with *t*-butyl hypobromite in *t*-butyl alcohol exclusively with *inversion* of configuration. No trace of the isomer resulting from retention could be detected. The stereochemical results were not unique to the free alcohol, since the corresponding acetates also undergo cleavage with brominating agents exclusively with *inversion* of configuration.

It seems clear, then, that the stereochemistry of electrophilic reactions of cyclopropanols depends in some not yet understood way on the nature of the electrophile and the substrate. With bromine, inversion seems to be the rule. With hydrogen, retention is observed in acid solution, while both inversion and net retention have been observed in basic solution, depending upon the substrate used. Clearly additional work is needed before this interesting and important problem is clarified.

Solvolysis of Cyclopropyl Tosylates

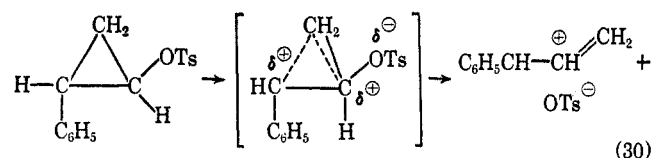
Roberts and Chambers²⁹ were the first workers to study the solvolytic behavior of cyclopropyl compounds quantitatively. They observed that cyclopropyl tosylate is extremely inert, requiring 180° for acetolysis. The product of the reaction is not cyclopropyl acetate, but rather allyl acetate. These results are consistent with the rate-determining formation of the cyclopropyl cation followed by rearrangement to the allyl cation, although, as Roberts and Chambers pointed out, this does not constitute a proof of this mechanism. The

(29) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).

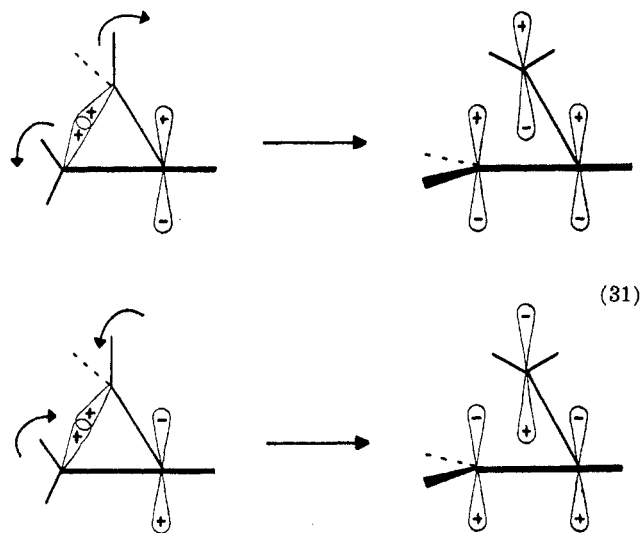


very high activation energy could be due in part to the increase in angle strain in going to the intermediate cation, as well as to possible ground-state effects.

In our own investigations³⁰ we discovered that, as expected, 1-arylcyclopropyl tosylates react much more rapidly than cyclopropyl tosylate itself. More surprising was the observation that either *cis*- or *trans*-2-arylcyclopropyl tosylate is also more readily solvolyzed than the parent compound. To accommodate these and related results we postulated that the cyclopropyl cation is not an intermediate in these solvolyses, but that ring opening occurs simultaneously with loss of tosylate, leading to a partial positive charge on the benzyl carbon atom in the transition state. In this way a 2-aryl group, either *cis* or *trans*, can stabilize the transition state and thereby enhance the solvolysis rate.³¹



The rearrangement of a cyclopropyl to an allyl cation is the simplest example of an electrocyclic transformation, and hence is susceptible to treatment by the Woodward-Hoffmann rules.³² In this case the prediction is extremely easy to make; a cyclopropyl cation is predicted to rearrange in a disrotatory fashion so as to generate the required symmetry of the lowest molecular orbital of the allyl cation (eq 31). For a cyclopropyl

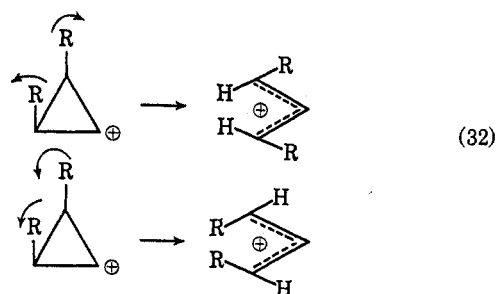


(30) C. H. DePuy, L. G. Schnack, and J. W. Hausser, *J. Am. Chem. Soc.*, **88**, 3343 (1966).

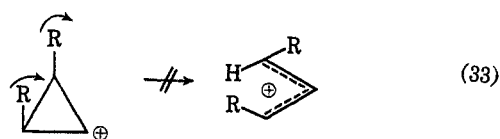
(31) Foote and Schleyer had earlier postulated, on the basis of their correlation of solvolysis rate with bond angle, that cyclopropyl compounds solvolyze with simultaneous ring opening [C. S. Foote, *ibid.*, **86**, 1853 (1964); P. von R. Schleyer, *ibid.*, **86**, 1854 (1964)].

(32) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965).

cation substituted *cis* in the 2,3 positions, two different disrotatory transformations are allowed, still observing the orbital symmetries demanded for these transformations; the two substituents may both move *outward*, leading to a *trans,trans*-allyl cation, or both *inward*, leading to a *cis,cis*-allyl cation (eq 32). It should be emphasized that *both* transformations are allowed on

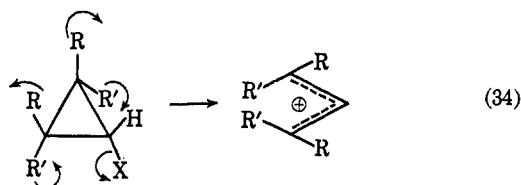


symmetry grounds; the conrotatory transformation leading to the *cis,trans*-allyl cation is disallowed by the Woodward-Hoffmann rules (eq 33). Given a free choice between the two disrotatory modes, the first

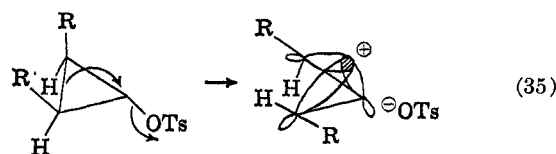


would appear to be more favorable on steric grounds.

We speculated, however, that the molecules might not have a free choice between the two disrotatory modes, but rather that the mode of rotation is dependent upon the stereochemistry of the leaving group. Calculations predicted³² and experiments showed³³ that substituents *cis* to the leaving group rotate *inwardly* and substituents *trans* to the leaving group rotate *outwardly* (eq 34). This postulate was based initially on our feel-



ing that the electrons of the C₂-C₃ bond would interact with the rear of the developing orbital on C₁. Later kinetic and stereochemical work has seemingly fully confirmed this postulate. The most extensive kinetic investigations are those of Schleyer, Schöllkopf, *et al.*^{34,35}

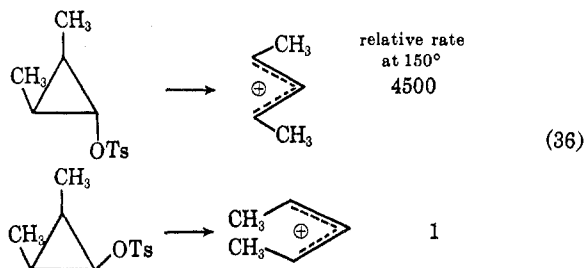


(33) S. J. Cristol, R. M. Sequeira, and C. H. DePuy, *ibid.*, **87**, 4007 (1965).

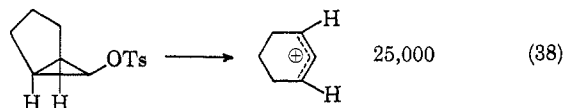
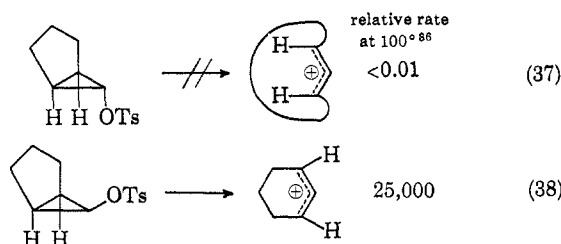
(34) P. von R. Schleyer, G. W. Van Dine, U. Schöllkopf, and J. Paust, *ibid.*, **88**, 2868 (1966).

(35) U. Schöllkopf, K. Fellenberger, M. Patsch, P. von R. Schleyer, T. Su, and G. W. van Dine, *Tetrahedron Letters*, No. 37, 3639 (1967).

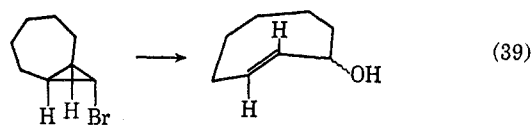
These workers showed that 2-*trans*-3-*trans*-dimethylcyclopropyl tosylate, which on the basis of the above postulate should give the stable *trans,trans*-dimethylallyl cation, undergoes acetolysis approximately 5000 times faster than its C_1 epimer, which is predicted to give rise to the *cis,cis* cation. Notice, in these cases, that it is



the isomer with the alkyl groups *trans* to the leaving group which reacts the more rapidly. This order of reactivity can be reversed by simply joining the two substituents into a ring.^{33,35} If the ring is small, a *trans,trans* allyl cation cannot be accommodated, but a *cis,cis* cation can.



The results above are kinetic, and the stereospecificity is only to be inferred from the relative rates. However, it has been shown recently that isomeric olefins are formed from the solvolysis of 8-bromobicyclo[5.1.0]octane.³⁷ The *endo* isomer reacts readily and gives rise to a *cis*-cyclooctenol. The *exo* isomer is much less reactive, but when reaction is forced the highly strained *trans*-cyclooctenol is formed.

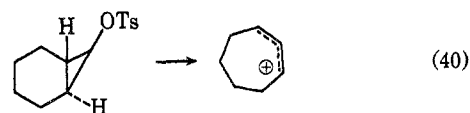


It appears then that this highly stereospecific rearrangement of cyclopropyl derivatives can profoundly influence both the reactivity of the starting material and the structure of the products. Questions concerning this reaction still exist, however. In particular, it would be interesting to know how much energy is required to carry out a solvolysis which violates the Woodward-Hoffmann rules. An example of this violation would be the solvolysis of the norcaranyl tosylate in which the six- and three-membered rings are fused *trans*. If rearrangement occurred at all, it might lead, *via* a conrotatory transformation, to the cycloheptenyl cation, rather than to a *trans* cycloheptene derivative. The

(36) Not on the same scale as above.

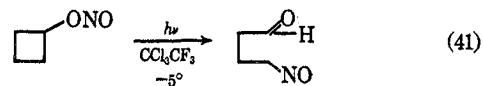
(37) G. H. Whitham and M. Wright, *Chem. Commun.*, 294 (1967).

starting tosylate does not appear to be prohibitively strained.³⁸

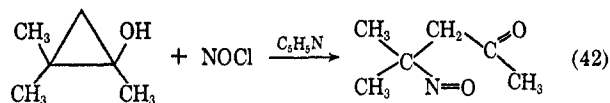


Other Reactions of Cyclopropanols

In the course of our investigations of the electrophilic and solvolytic reactions of cyclopropanols, a number of other transformations of these compounds and their derivatives have been uncovered and are currently under investigation in these and other laboratories. As mentioned earlier, we had to worry about whether cyclopropoxy radicals might be involved in the reaction of various halogenating agents with cyclopropanols. We set out to generate such radicals by photolyzing the nitrite ester of 1,2,2-trimethylcyclopropanol. Nitrite esters are customarily prepared by the reaction of alcohols with nitrosyl chloride in pyridine; the purified nitrite esters are photolyzed to give a nitroso carbonyl compound in systems in which a Barton reaction cannot occur³⁹ (eq 41). When an attempt was made to prepare



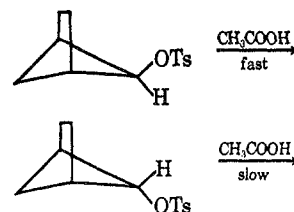
a nitrite ester of several cyclopropanols, the nitroso ketone was formed directly, even at -50° ⁴⁰ (eq 42).



Apparently the cyclopropoxy radical, or its ring-opened analog, is formed with great ease. The fact that opening occurred between C_1 and C_2 (as one would predict) is to be contrasted with the exclusive cleavage between C_1 and C_3 in the halogenative openings (eq 26).

It has also been observed⁴¹ that, in contrast to other alcohols, cyclopropanols are easily oxidized by ferric

(38) It is interesting to speculate about whether similar stereospecificity might not occur in other carbonium ion rearrangements. Specifically, the postulation that *cis* groups rotate inwardly, *trans* groups outwardly in the cyclobutyl tosylate-homoallyl cation rearrangement allows one to rationalize the enormous (10^6) *endo/exo* rate ratio observed in the acetolysis of the 5-tosylates of bicyclo[2.1.1]hexane [K. B. Wiberg and R. Feroglio, *Tetrahedron Letters*, No. 20, 1273 (1963)]. If one considers that cyclobutane is merely *homocyclopropane*, the same rules may be applied. In these cases the products are again of no help, since further transformations are involved.

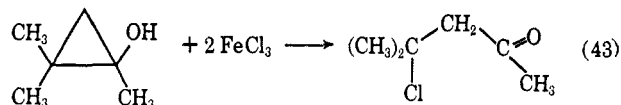


(39) P. Kabasakalian and E. R. Townley, *J. Org. Chem.*, 27, 2918 (1962); Barton reaction: D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, 82, 2640 (1960).

(40) H. L. Jones, unpublished results.

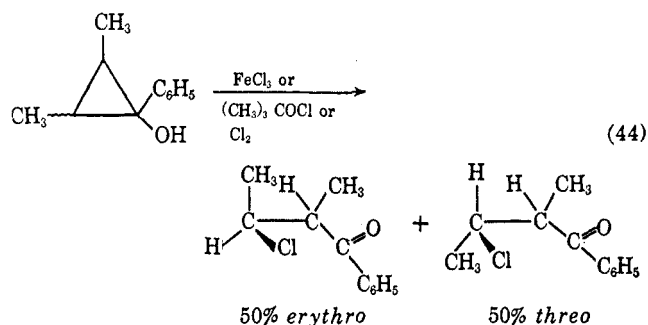
(41) S. E. Schaafsma, H. Steinberg, and Th. J. De Boer, *Rec. Trav. Chim.*, 85, 73 (1966).

chloride in ether. When this reaction is applied to 1,2,2-trimethylcyclopropanol,⁴⁰ a chloroketone is formed (eq 43). These results indicate that homolytic cleavage



of the $-\text{O}-\text{X}$ bond in cyclopropane derivatives is easily accomplished. It has not yet been determined whether the cyclopropoxy radical is an intermediate (if so, it must have some special stability, like the cyclopropylcarbinyl cation), or whether the reactions proceed readily because of ring opening in the transition state such that the activation energy is lowered by relief of ring strain. Electron spin resonance studies⁴¹ favor the latter interpretation, since ring-opened radicals have so far been the only ones detected.

These results may have a bearing on the reactions of the dimethylphenylcyclopropanols with chlorinating agents. The same mixture of *threo*- and *erythro*-chloroketones is obtained upon treatment of *trans,trans*-2,3-dimethyl-1-phenylcyclopropanol with ferric chloride and of the *cis,trans* or *trans,trans* compound with chlorinating agents (eq 44). We feel that this lack of

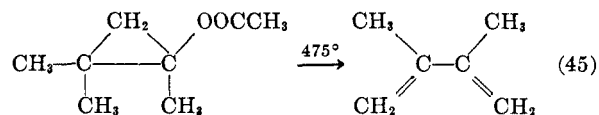


stereospecificity may be due to attack at the $-\text{O}-\text{H}$ bond, and not electrophilic attack at either $\text{C}-\text{C}$ bond.⁴²

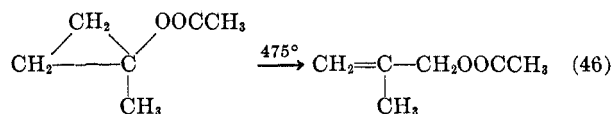
Finally, among miscellaneous reactions of cyclopropanol derivatives might be mentioned the rearrange-

(42) We at one time suggested free radical attack at the $-\text{O}-\text{H}$ bond to account for the rearrangement of cyclopropanols when heated in carbon tetrachloride solution in the presence of oxygen [C. H. DePuy, G. M. Dappen, and J. W. Hausser, *J. Am. Chem. Soc.*, **83**, 3156 (1961)]. We later withdrew this suggestion [C. H. DePuy and F. W. Breitbeil, *ibid.*, **85**, 2176 (1963)] for the cases in which we had proposed it. The results reported above on the ease of breaking of the $-\text{O}-\text{X}$ bond make it seem likely that under some as yet to be discovered conditions such a mechanism is possible.

ment of cyclopropyl acetates upon pyrolysis.⁴³ We first noticed this reaction when, in view of our earlier interest in pyrolytic eliminations,⁴⁴ we wondered if cyclopropenes could be formed in this manner. Indeed, upon pyrolysis, 1,2,2-trimethylcyclopropyl acetate smoothly eliminates a mole of acetic acid at 475°, but the product is 2,3-dimethylbutadiene (eq 45). All speculations

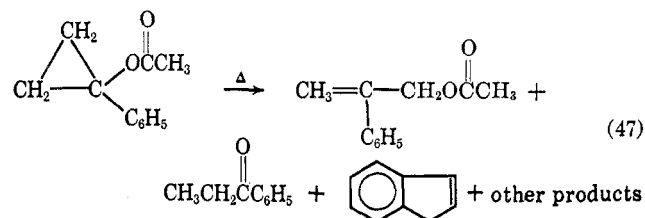


about the possibility of cyclopropene intermediates in this transformation were put to rest when it was shown that 1-methylcyclopropyl acetate rearranges exclusively to 2-methylallyl acetate under the same conditions (eq 46). In the trimethyl case such rearrangement would



lead to an acetate which would pyrolyze to dimethylbutadiene under the reaction conditions.

Initially we favored a concerted, cyclic mechanism for this rearrangement, in line with those postulated in other pyrolytic eliminations. With more extensive work, however, it appears that homolytic C_2-C_3 bond breaking in the cyclopropyl ring is the initial reaction. In agreement with this idea, 1-phenylcyclopropyl acetate (in which homolytic C_1-C_2 bond breaking would be more favored over C_2-C_3 bond breaking) gives a new set of products.



I am greatly indebted to the National Science Foundation for its generous support of this work, and to a fellowship from the Alfred P. Sloan Foundation which allowed us to initiate our studies in cyclopropane chemistry. I also wish to express my sincere appreciation to the graduate students and postdoctoral associates to whose work I have referred in this article.

(43) D. Zabel, unpublished results.

(44) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).