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Cyclobutane Ring Contractions Not Involving Carbonium Ions

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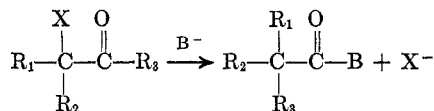
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The facile interconversions which occur among related cyclobutane, cyclopropane, and open-chain structures via carbonium ion intermediates have been extensively studied. Analogous rearrangements of small-ring compounds via carbenes or free radicals are well known, but not so widely explored.¹⁻³ A type of cyclobutane ring contraction which does not involve a carbonium ion is the base-induced skeletal rearrangement of α -halogenated cyclobutanones into cyclopropanecarboxylic acid derivatives. Such ring contractions and related rearrangements are the subject of this Account.

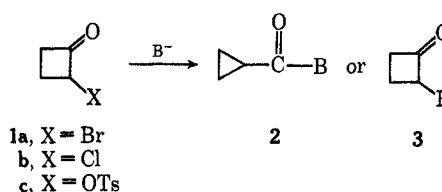
α -Halo- and α -Tosyloxycyclobutanones and Nucleophilic Reagents

In the presence of nucleophilic reagents such as hydroxides, alkoxides, or amines, α -halogenated ketones undergo skeletal rearrangement into carboxylic acid salts, esters, or amides, respectively. This reaction was



discovered by Favorskii in 1894⁴ and showed itself rapidly to be general for α -halocycloalkanones in rings of from six to ten carbon atoms.⁵ The fact that α -halocyclopentanone fails to undergo the reaction is perhaps responsible for the long reluctance to attempt such a reaction with smaller rings: *i.e.*, α -halocyclobutanones. However, α -bromocyclobutanone (**1a**) was recently reported to rearrange with high yield and stereospecificity.⁶

Mono-, di- and trihalo ketones generally undergo this rearrangement. The reaction has proven to be a reliable and important route to derivatives of highly branched acyclic carboxylic acids, to various 1-substi-



tuted cycloalkanecarboxylic acids, and for the contraction of specific rings in mono- or polycyclic and steroid systems.⁵

A survey of the literature reveals that the choice of base and solvent can profoundly affect the yield of rearranged products. Correlations have been established between the nature of the base and the products of the reaction.^{7,8} Thus, the reaction of a nucleophilic reagent with an α -halo ketone can lead to substitution product, α -ethylenic ketone, epoxide, hydroxy ketal, saturated ketone, and/or rearranged acid derivatives. The product of the reaction can be often predicted as a function of the type of nucleophile.

From 2-bromocyclobutanone (**1a**), rather specific reactions lead either to ring contraction product **2** or to substitution product **3** (see Table I^{8,9}). Reaction conditions which usually lead to an elimination product (dehydrohalogenation) did not give the expected cyclobutenone.⁶

The facility and specificity of this rearrangement, particularly with water itself, open a way to the synthesis of three-membered rings from four-membered systems (*vide infra*) which is just as useful as the interconversion of related cyclobutyl, cyclopropylcarbinyl, and homoallyl derivatives via carbonium ion reactions.¹⁰

(1) R. Breslow, "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 233.

(2) J. Jaz, *Ind. Chim. Belge*, [2] **33**, 130 (1968).

(3) K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968).

(4) A. Favorskii, *J. Russ. Chem. Soc.*, **26**, 559 (1894); *Bull. Soc. Chim. Fr.*, **14**, 1188 (1895); *J. Prakt. Chem.*, **51**, 553 (1895).

(5) A. S. Kende, *Org. React.*, **11**, 261 (1961).

(6) J. M. Conia and J. L. Ripoll, *C. R. Acad. Sci.*, **251**, 1071 (1960); **252**, 423 (1961); *Bull. Soc. Chim. Fr.*, 755 (1963).

(7) B. Tchoubar, *ibid.*, 1363 (1955).

(8) G. Stork and I. J. Borowitz, *J. Amer. Chem. Soc.*, **82**, 4307 (1960).

(9) (a) J. Salaun and J. M. Conia, *Chem. Commun.*, **20**, 1358 (1970); (b) J. Salaun and J. M. Conia, submitted for publication.

(10) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951); R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts, *ibid.*, **81**, 4390 (1959).

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Jacques Salaun obtained his Ph.D. in 1967 under the direction of Professor Conia, and continues to work with him.

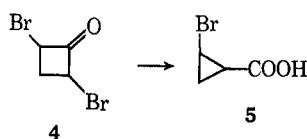
Table I
Specific Reactions of 2-Bromocyclobutanone with Various Nucleophiles^{6,9}

Ring contraction		Substitution	
Nucleophile	Yield, %	Nucleophile	Yield, %
H ₂ O	82	C ₆ H ₅ ONa, dioxane	65
C ₂ H ₅ OH	62	<i>p</i> -2-BrC ₆ H ₄ ONa, dioxane	35
NaOH, C ₂ H ₅ OH	91	(CH ₃) ₂ NH, ether	33
CO ₂ Na ₂ , H ₂ O	86	(C ₂ H ₅) ₂ NH, ether	65
NH ₄ OH	87	CH ₃ COONa, CH ₃ COOH	10
NH ₃	70	(C ₂ H ₅) ₃ N	100
C ₂ H ₅ ONa, ether	67		
LiAlH ₄ , ether	30 ^a		
CH ₃ MgI, ether	50		

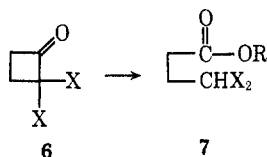
^a And 70% yield of 2-bromocyclobutanol.

While α -chloro ketones are usually preferable to bromo ketones in the Favorskii rearrangement,^{5,7} the reaction of 2-chlorocyclobutanone (**1b**) is not specific and leads mainly to substitution product (**3**).¹¹

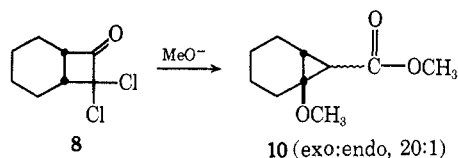
It is known that α, α' - or α, α -dihalo ketones in the presence of nucleophiles undergo rearrangement and hydrohalogenation reactions.^{4,12} Likewise, 2,4-dibromocyclobutanone (**4**) ring-contracts, giving **5** but 2,2-



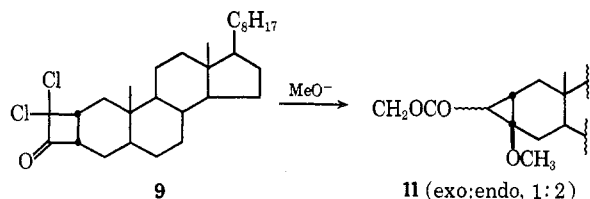
dihalocyclobutanones (**6**) undergo ring cleavage to γ, γ -dihalocarboxylic acid **7**.^{11,13} However, cis-fused



α, α -dichlorocyclobutanones **8** and (steroid) **9** undergo a



quantitative ring contraction into bifunctional cyclopropanes **10** and **11**, respectively.¹⁴ Tetrabromocyclo-



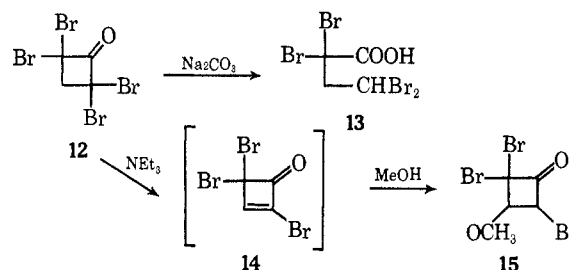
- (11) J. M. Conia and J. L. Ripoll, *Bull. Soc. Chim. Fr.*, 763 (1963).
 (12) R. B. Wagner and J. A. Moore, *J. Amer. Chem. Soc.*, **72**, 974 (1950).
 (13) L. Ghosez, R. Montaigne, and P. Mollet, *Tetrahedron Lett.*, 135 (1966); T. R. Potts and R. E. Harmon, *J. Org. Chem.*, **34**, 2792 (1969).
 (14) V. R. Fletcher and A. Hassner, *Tetrahedron Lett.*, **13**, 1071 (1970).

Table II
Ring Contractions of 2-Tosyloxycyclobutanone into Cyclopropane Derivatives^{9a,b}

Nucleophile	Yield, %
H ₂ O	100
C ₂ H ₅ OH	60
NaOH, C ₂ H ₅ OH	100
C ₂ H ₅ ONa, ether	75
LiAlH ₄ , ether	57 ^a
CH ₃ MgI, ether	60

^a And 43% of 2-tosyloxycyclobutanol.

butanone (**12**) undergoes either ring cleavage into acid **13** or dehydrobromination into cyclobutenone **14**, which is trapped by methanol to give **15**.



The reaction of α -*p*-toluenesulfonyloxy ketones with alkoxides can proceed with elimination of *p*-toluenesulfinate anion to give α -ketones.¹⁵ Data are lacking concerning the expected rearrangement of α -tosyloxycycloalkanes (for an example see ref 16). 2-Tosyloxycyclobutanone (**1c**), more readily available than other halocyclobutanones,⁹ undergoes rearrangement with nucleophilic reagents, leading to cyclopropane derivatives^{9a,b} (see Table II).

In order to determine scope, mechanism, and stereochemistry, the ring contraction of various substituted α -bromocyclobutanones, especially sterically hindered (mono- and di-*tert*-butylcyclobutanones) and strongly strained systems (one or two spiranic carbon atoms), have been investigated (*vide infra*).

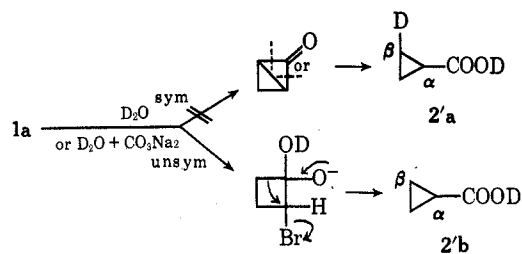
Mechanism and Stereochemistry

Considerable effort has been expended in elucidating the mechanism by which α -halo ketones are converted into carboxylic acid derivatives by nucleophilic reagents. It is now well established that the reaction can proceed by different pathways.⁵ At present, four main mechanisms have been advanced to account for the Favorskii rearrangement.^{7,17} Three *unsymmetrical* mechanisms involve either an intermediate epoxy ether (Favorskii),¹⁸ a keto carbene, and a ketene intermediate (Richard),¹⁹ or a conversion closely related to the benzylic acid rearrangement and called the semibenzilic or

- (15) R. B. Woodward and S. Levine (unpublished observation); S. Levine, Ph.D. Thesis, Harvard University, 1953.
 (16) A. W. Fort, *J. Org. Chem.*, **27**, 2625 (1962).
 (17) (a) F. G. Bordwell, R. G. Scamehour, and W. R. Springer, *J. Amer. Chem. Soc.*, **91**, 2087 (1969); (b) F. G. Bordwell and R. G. Scamehour, *ibid.*, **90**, 6751 (1968); (c) F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).
 (18) A. Favorskii, *J. Prakt. Chem.*, [2] **88**, 641 (1913).
 (19) G. Richard, *C. R. Acad. Sci.*, **197**, 1432 (1933).

quasi-Favorskii rearrangement (Tchoubar).²⁰ Finally, a *symmetrical* mechanism proceeds *via* a cyclopropanone intermediate such as proposed by Loftfield,²¹ but formed by one of six possible pathways:^{17a} by concerted α, α' elimination, by an intramolecular S_N2 -type displacement, or by other types of cyclization either from a carbonium ion formed in the solvolysis of an enolic halide,²² from a zwitterionic species, from a keto carbene intermediate giving an insertion reaction, or finally from the ionization of the α halide ion aided by the π participation of the α' carbanion.^{17b}

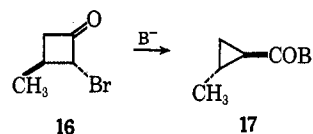
In order to distinguish between a symmetrical or unsymmetrical mechanism, the ring contraction of 2-bromocyclobutanone was studied in deuterium oxide using sodium carbonate as base (50°) or in boiling deuterium oxide only. The cyclopropane derivative resulting



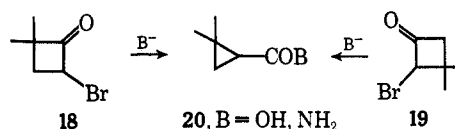
from a symmetrical mechanism would give a ratio $\beta\text{-H}/\alpha\text{-H} = 3$ (see 2'-a) and an unsymmetrical mechanism $\beta\text{-H}/\alpha\text{-H} = 4$ (see 2'-b). This ratio was readily determined by nmr, and was consistent with an unsymmetrical mechanism.^{23,24} Moreover, to take into account the fact reported later that in such a reaction the first step could be a rapid equilibrium, ketone \rightleftharpoons deuterated ketone, followed by the slow formation of the cyclopropanone intermediate,^{25,26} studies of the rearrangement effected at various temperatures by Rappe²⁷ confirm again that an *unsymmetrical mechanism is operating in the reaction*.²⁷

It is well established that the stereochemistry of the rearrangement of an α -halo ketone, occurring *via* a symmetrical mechanism, is largely dependent on the degree of solvation of the α' enolate anion by the solvent. A solvated anion (protic solvent) undergoes nonstereospecific ring contraction (inversion + retention); an unsolvated anion (aprotic solvent) undergoes stereospecific ring contraction (inversion).^{8,28} Whatever that may be, in the ring contraction of 2-bromocyclobutanone, the nature of the solvent does not seem important; *e.g.*, *trans*-2-bromo-3-methylcyclobutanone (16) undergoes

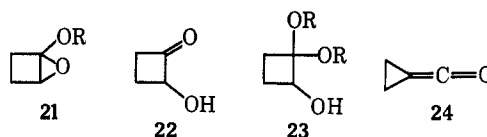
stereospecific ring contraction to form *trans*-2-methylcyclopropane derivatives 17 either using NH_3 , aqueous



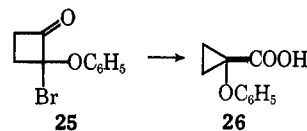
sodium carbonate, or water.^{24,29} A last argument to discard definitely a symmetrical mechanism is provided by the fact that there need be no α' hydrogen to obtain the ring contraction;³⁰ thus, 2-bromo-4,4-dimethylcyclobutanone (18) undergoes ring contraction at the same rate as 2-bromo-3,3-dimethylcyclobutanone (19) and 2-bromocyclobutanone itself.²⁴



Among the three unsymmetrical mechanisms cited above, the expected epoxy ether 21 and derivatives such as 2-hydroxycyclobutanone (22) (from 21 by hydrolysis) and 2-hydroxy ketals 23 (from subsequent reaction with alkoxide) have not been detected. The ketene mechanism,¹⁹ including simultaneous α elimination of hydrogen



halide, has been readily discarded because α -substituted α -bromocyclobutanones (*e.g.*, 25) also readily undergo the ring contraction.²⁹



The one unsymmetrical mechanism accounting for the degree of deuteration³⁴ and all other investigations in this ring contraction is the semibenzilic rearrangement;²⁰ it involves the addition of nucleophile to the carbonyl carbon atom, followed by a concerted displacement of the halide ion by the 1,2 migration of the $C_{\alpha'}-C$ carbonyl bond.

The ring contraction of 2-bromocyclobutanone with

(29) J. M. Conia and J. L. Ripoll, *Bull. Soc. Chim. Fr.*, 773 (1963).

(30) Some α -halo ketones with an α' hydrogen have been reported to rearrange by the way of the semibenzilic mechanism when this α' hydrogen is rendered relatively nonacidic; *e.g.*, cage-type α -halo ketones,³¹ α -halobicyclo[*n*.3.1] alkanones.^{32,33} Moreover, the involved pathway, symmetrical or unsymmetrical, has been shown to be depending on the base strength.³³

(31) P. E. Eaton and T. W. Cole, *J. Amer. Chem. Soc.*, **86**, 962, 3157 (1964).

(32) A. C. Cope and E. S. Graham, *J. Amer. Chem. Soc.*, **73**, 4702 (1951).

(33) E. W. Warnhoff, C. M. Wong, and W. T. Tai, *ibid.*, **90**, 514 (1968).

(34) It has been rightly argued that the formation of α' enolate ion, proved by an effective base-catalyzed deuteration, does not necessarily mean that it is on the involved reaction pathway.^{35,36}

(35) J. Hine, R. Wiesboeck, and O. B. Ransay, *J. Amer. Chem. Soc.*, **83**, 1222 (1961); R. Breslow, *Tetrahedron Lett.*, 339 (1964).

(36) F. G. Bordwell, R. R. Frame, R. G. Scamehoun, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967).

(20) B. Tchoubar and O. Sackur, *C. R. Acad. Sci.*, **208**, 1020 (1939).

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(22) W. D. Mac Phee and E. Klingsberg, *ibid.*, **66**, 1132 (1944).

(23) J. M. Conia and J. Salatin, *Tetrahedron Lett.*, 1175 (1963).

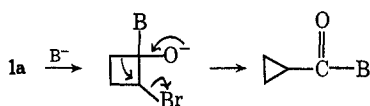
(24) J. M. Conia and J. Salatin, *Bull. Soc. Chim. Fr.*, 1957 (1964).

(25) M. Charpentier-Morize, M. Mayer, and B. Tchoubar, *Bull. Soc. Chim. Fr.*, 529 (1965).

(26) H. Ginsburg, *ibid.*, 3645 (1965).

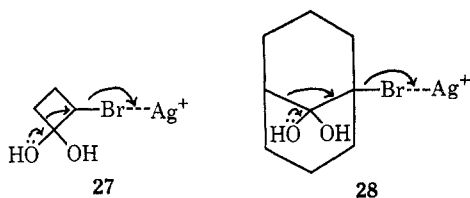
(27) C. Rappe and L. Knutsson, *Acta Chem. Scand.*, **21**, 163 (1967).

(28) N. L. Wendler, R. P. Graber, and G. G. Hazen, *Tetrahedron*, **3**, 145 (1958); H. O. House, and W. F. Gilmore, *ibid.*, **83**, 3980 (1961); C. R. Engel, G. Just, and R. Buttery, *Can. J. Chem.*, **39**, 1805 (1961); A. Gaudemer, J. Parello, A. Skrobek, and B. Tchoubar, *Bull. Soc. Chim. Fr.*, 2405 (1963); B. Tchoubar, *ibid.*, 2069 (1964); S. Skrobek and B. Tchoubar, *C. R. Acad. Sci.*, **263**, 80 (1966).



water alone is unique. The reaction, which occurs in acidic medium (HBr being produced), follows an unsymmetrical pathway (no β deuterium; cf. **2'b**), and it could be more or less related to the semibenzilic mechanism. The strain of the cyclobutanone system has been underlined by the large tendency of its carbonyl to undergo addition reactions,³⁷ e.g., the ready formation of a covalent hydrate with water. However, depending on the degree of solubility of α -bromocyclobutanone, the addition of silver ions (Ag^+) either accelerates the rate of ring contraction when the reaction medium is *heterogeneous*²⁷ (**1a** + water alone) or has no effect when the medium is *homogeneous*²⁹ (**1a** + water-dioxane, 1:1). The question is not clear yet, but it is sure that the mechanism does not involve a true carbonium ion.²⁹

A "push-pull" mechanism has been invoked here,²⁷ as suggested first by Swain concerning the termolecular kinetics of $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ displacements³⁸ and proposed by Cope and Graham³² for the silver nitrate catalyzed



rearrangement of 1-bromobicyclo[3.3.1]nonan-9-one (**28**). It must be considered, indeed, that in hydrate **27** the electron pair forming the C_{α} -C hydrate bond is in a sterically favorable position to attack the backside of the α carbon supplying the push as the bromine is pulled away. It is worth noting that the hemiketal from **1a** and ethanol also undergoes facile ring contraction⁹ resembling that of α -bromocyclobutanone hydrate. Both of these rearrangements appear closely related to the thermal ring contraction of α -bromocyclobutanone ketals (*vide infra*).

Conformationally Controlled Mechanism

To permit a high degree of participation of one bond of the ring in the solvolysis of cyclobutyl tosylates, the leaving group must occupy a pseudoequatorial position; such a cross-ring interaction, suggested by Wiberg,³⁹ was confirmed by the application of the CNDO method calculation⁴⁰ to the cyclobutyl cation.³ Cyclobutane is known to be nonplanar, with an angle between the two halves of the four-membered ring of 30–35°.⁴¹ The

bromocyclobutane ring is bent too, with a dihedral angle of approximately 29°.⁴²

We consider now the problem of the conformation of cyclobutanones (planarity or nonplanarity, mobility). There are still some discrepancies among authors, particularly between spectroscopists and other chemists. Cyclobutanone itself, from infrared investigations⁴³ and microwave spectra,⁴⁴ can be considered as planar or nearly planar with a weak barrier to inversion. Although alkyl- and halo-substituted cyclobutanones have shown presumptive evidence of nonplanarity,⁴⁵ it has been claimed, from far-infrared studies,⁴⁶ that α -bromo- and α -chlorocyclobutanones are planar. From the measurements of coupling constants of a difluorocyclobutanone, it has been suggested that the deviation from planarity in cyclobutanones is small.⁴¹

In view of the numerous reference mistakes or omissions of some authors,^{46,47} it seems necessary to recall that the nonplanarity of several substituted cyclobutanones was neither clearly established, nor rejected, from ir (shift of the carbonyl stretching frequency), uv (shift of the $n \rightarrow \pi^*$ transition),^{45b} or nmr data.^{45c} The nonplanarity was nevertheless strongly supported by dipole moment data^{45a,h} and circular dichroism measurements^{45d} (extension of the octant rule to cyclobutanones⁴⁸). Moreover, recent investigations of strongly sterically hindered monocyclic cyclobutanones^{45f} which have chemically and spectroscopically (ir, uv, nmr, X-rays⁴⁶ⁱ) evidenced their nonplanarity confirm the first deductions (existence of pseudoaxial and pseudoequatorial conformers). The subject has been reviewed;^{45j} other chemical confirmations^{45k} and CD measurements of fused cyclobutanones⁴⁷ have been recently reported.

However, the ring contraction of α -bromocyclobutanones involves the addition of the nucleophile to the carbonyl group and the conversion of the ring to a more puckered cyclobutane one; then, in most cases, *bromine is able to assume the required pseudoequatorial conformation*. For example, 2-bromo-3-*tert*-butyl- (**29**) and 2-bromo-4-*tert*-butylcyclobutanone (**30**) undergo

(42) W. G. Rothschild and B. P. Dailey, *J. Chem. Phys.*, **36**, 2931 (1962).

(43) K. Frei and Hs. H. Gunthard, *J. Mol. Spectrosc.*, **5**, 218 (1960); K. Schafer, A. Monter, E. Wolf-Mittscherlich, *Z. Elektrochem.*, **64**, 2 (1960); J. R. Durig and R. C. Lord, *J. Chem. Phys.*, **45**, 61 (1966); T. R. Borgers and H. L. Strauss, *ibid.*, **45**, 947 (1966).

(44) A. Bauder, F. Tank, and Hs. H. Gunthard, *Helv. Chim. Acta*, **46**, 1453 (1963).

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(48) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 83.

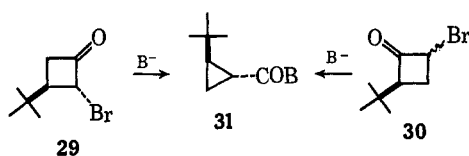
(37) A. Burger and H. H. Ong, *J. Org. Chem.*, **29**, 2588 (1964).

(38) C. G. Swain, *J. Amer. Chem. Soc.*, **70**, 1119 (1948); C. G. Swain and R. W. Eddy, *ibid.*, **70**, 2989 (1948).

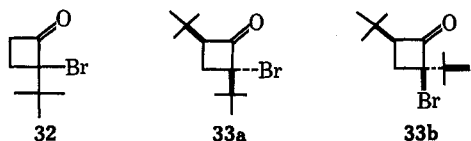
(39) K. B. Wiberg and R. Fenoglio, *Tetrahedron Lett.*, 1273 (1963); K. B. Wiberg and B. A. Hess, *J. Amer. Chem. Soc.*, **89**, 1967 (1968).

(40) J. A. Pople, D. P. Santry, and G. A. Segal, *J. Chem. Phys.*, **43**, 5129 (1965); J. A. Pople and G. A. Segal, *ibid.*, **43**, 5236 (1965); **44**, 3289 (1966).

(41) J. B. Lambert and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 3884, 3891 (1965).

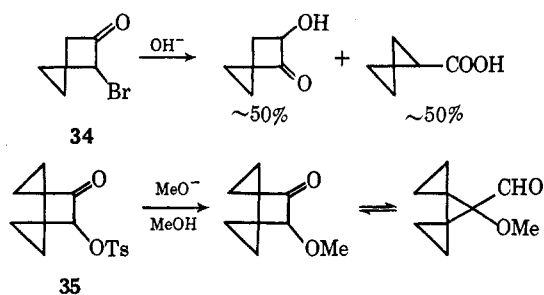


quantitative ring contractions into 2-*tert*-butylcyclopropane derivatives (**31**);^{45g} however, 2-bromo-2-*tert*-butyl- (**32**), and *cis*- and *trans*-2-bromo-2,4-di-*tert*-butylcyclobutanone (**33a** and **33b**) do not ring-contrast (they



are unreactive with nucleophiles, and Br is pulled away by Ag⁺ but without the formation of cyclopropanecarboxylic acid), probably because a real axial conformation of bromine (clearly established for **33a** by spectroscopy^{45f}) prevents the reaction course.

In the same way, a strongly favored axial conformation of the leaving group or nonexistence of the required equatorial conformation (from strained ring planarity) could explain the occurrence of substitution reactions from spirocyclobutanones **34** and **35** and OH⁻ or MeO⁻

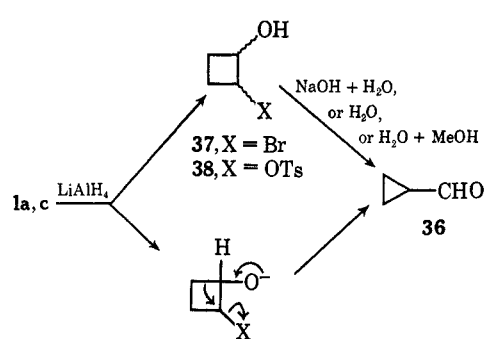


anions.⁴⁹ This conformational effect will be dealt with again in the ring contraction of inflexible, fused, nonketonic cyclobutane derivatives (*vide infra*).

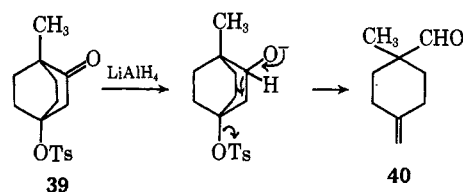
α -Halocyclobutanols and Nucleophilic Reagents

Metal hydrides and Grignard reagents are not usual as nucleophiles in the Favorskii rearrangement. From α -halocyclobutanones, the reaction provides α -halocyclobutanols which then undergo, directly or subsequently (by action of bases, boiling water or alcohols), ring contraction into corresponding cyclopropane derivatives, a rearrangement closely related to the reaction of α -halocyclobutanones with hydroxides, alkoxides, or water.

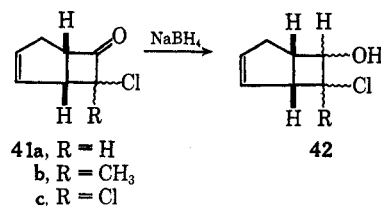
For instance, it has been established that 2-bromo- and 2-tosyloxycyclobutanone undergo the ring contraction with *lithium aluminum hydride* in ether. A mixture (quantitative yield) of cyclopropanecarboxaldehyde (**36**) and 2-bromo- (**37**) or 2-tosyloxycyclobutanol (**38**) is in fact obtained; the percentage of aldehyde (30% from **1a** and 57% from **1c** after hydrolysis with H₂O) is decreased but not suppressed by using acidic



hydrolysis; *i.e.*, whatever the pH, a significant amount of aldehyde is always detected.



This result must be compared with the reductive cleavage of β -tosyloxy ketone **39** by LiAlH₄⁵⁰ (no tosyloxy reduction occurs in both cases). Treated with aqueous base (2 M NaOH), with boiling water, or, even better, with aqueous alcohol (3:1 H₂O-CH₃OH), cyclobutanols **37** and **38** undergo a quantitative ring contraction.⁹ This reaction is comparable to the same ring contraction of *trans*-2-chlorocyclohexanol and 2-chlorocycloheptanol by boiling water and ethanol.⁵¹



Furthermore analogous rearrangements have been reported^{52,53} from 7-chloro- (**42a,b**) and 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-ols (**42c**), which were prepared without ring contraction by borohydride reduction of corresponding *endo*- and *exo*- α -chloro **41a** and **41b**, and of α,α -dichloro ketone **41c**. Such rather inflexible stereoisomeric alcohols react rapidly, stereospecifically, and in very high yields with bases (*e.g.*, aqueous KOH); however, ring contraction occurs only when the leaving group is in a *pseudo*equatorial conformation (**43**, **44a,b**) independently of the hydroxyl group conformation, while a hydride shift occurs from cyclobutanol **45** bearing a sterically favored pseudoaxial leaving group.

The utility of this stereospecific rearrangement has been recently illustrated in providing a ready route to the synthesis of *cis*- and *trans*-bicyclo[7.1.0]decan-2 one (**47a,b**); on passage through alumina the stereospecific

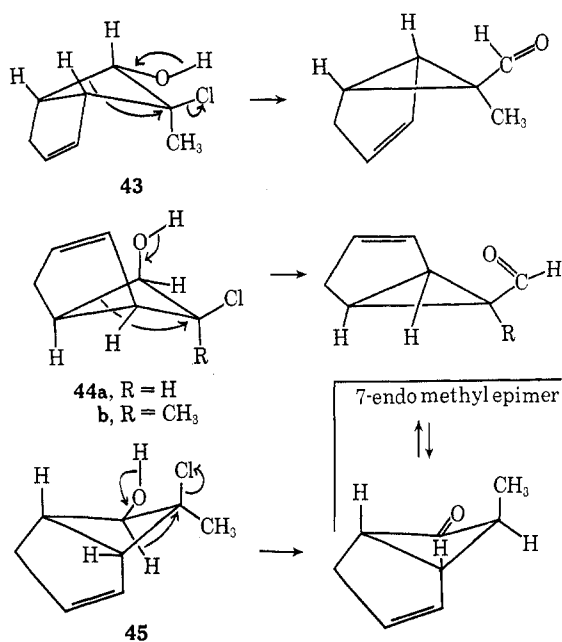
(50) W. Kraus, *Angew. Chem.*, **78**, 335 (1966); *Angew. Chem., Int. Ed. Engl.*, **5**, 316 (1966); W. Kraus, and W. Rothenwoher, *Tetrahedron Lett.*, 1013 (1968); W. Kraus and C. Chassin, *Tetrahedron*, **25**, 3681 (1969); W. Kraus and C. Chassin, *Tetrahedron Lett.*, 1003 (1970).

(51) M. Godechot, M. Mousseron, and R. Grainger, *C. R. Acad. Sci.*, **200**, 748 (1935).

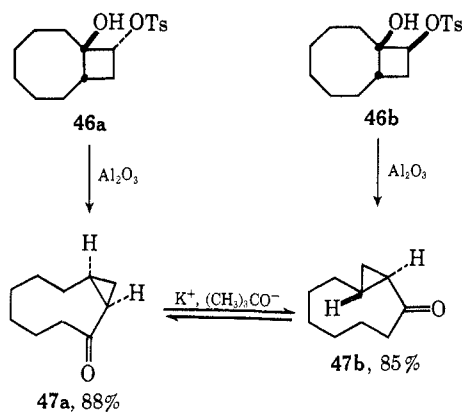
(52) P. R. Brook and A. J. Duke, *Chem. Commun.*, 652 (1970).

(53) P. R. Brook, *ibid.*, 565 (1968).

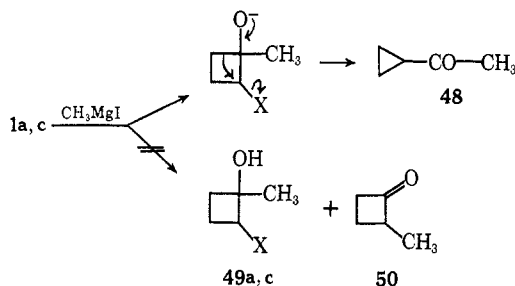
(49) (a) J. M. Conia and J. M. Denis, *Tetrahedron Lett.*, 3545 (1969); (b) J. M. Conia and J. M. Denis, *ibid.*, 2845 (1971).



ring contraction of tosyloxycyclobutanols **46a** and **46b** occurs with high yields.⁵⁴



It is known that the reactions between *Grignard reagents* and α -chlorocycloalkanones may lead to different products: halohydrins, 2-alkylcycloalkanones, and ring-contraction derivatives.⁵⁵ It has been established that the addition of methylmagnesium iodide to cyclobutanones **1a** and **1c** induces the specific ring contraction into cyclopropyl methyl ketone (**48**; respectively



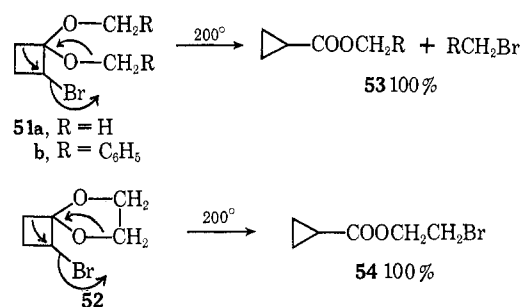
50 and 60% yield).⁹ However, if formed, cyclobutanols **49a,c** must undergo rapid ring contraction in the basic Grignard reaction medium, since no 2-methylcyclobu-

tanone (**50**), which would involve a methyl shift, is produced at the expense of ring contraction.⁹

Again, it is evident that carbonium ions cannot be involved here since such halocyclobutanols are still unaffected by silver ions⁵³ in neutral aqueous medium. However, in the base-induced reaction, the push of the cyclobutoxide ion and the pull of the halide atom supplied by any positive charge provide the driving force of the reaction.

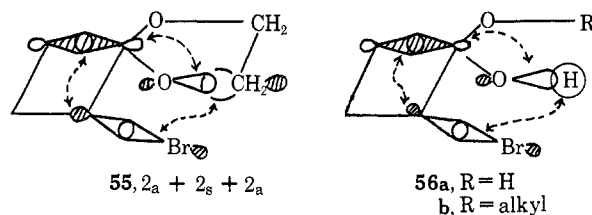
Thermal Ring Contraction of α -Substituted Cyclobutanone Ketals

On heating (*ca.* 200°), 2-bromocyclobutanone ketals **51a,b** undergo quantitative ring contraction into cyclopropanecarboxylic esters **53** and alkyl bromides; the dioxolane **52** leads to 2-bromoethyl cyclopropanecarboxylate (**54**).⁵⁶ This rearrangement is formally analogous to

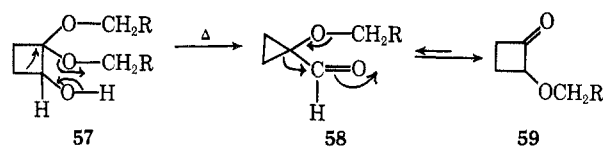


the thermal rearrangement of two dimethylnorbornadienone ketal derivatives⁵⁷ and of 2-bromotroponone ketals⁵⁸ recently reported. It must be pointed out that rearrangement does not occur from α -bromocyclopentanone and α -bromocyclohexanone ketals or from acyclic α -haloketone ketals.⁵⁶

The geometrical features of such ketals are well suited to suggest a pseudocyclic transition state including a six-electron process; thus, if concerted, the $2_s + 2_s + 2_s$ pericyclic reaction would require the retention of configuration at the ketal carbon site (*e.g.*, **55**) to be ther-



mally allowed by orbital symmetry.⁵⁹ Such a concerted pathway would be sterically favored too from hydrate **56a** and hemiketal **56b** (see ref 75a).



(56) J. Salaun and J. M. Conia, *Tetrahedron Lett.*, 4545 (1968).

(57) D. M. Lemal, E. P. Gosselink, and S. D. McGregor, *J. Amer. Chem. Soc.*, **88**, 582 (1966); D. C. F. Law and S. M. Tobey, *ibid.*, **90**, 2370 (1968).

(58) J. E. Baldwin and J. E. Gano, *Tetrahedron Lett.*, 1101 (1969).

(59) R. Hoffman and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968); *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).

(54) J. V. Paukstelis and J. Kao, *Tetrahedron Lett.*, 3691 (1970).

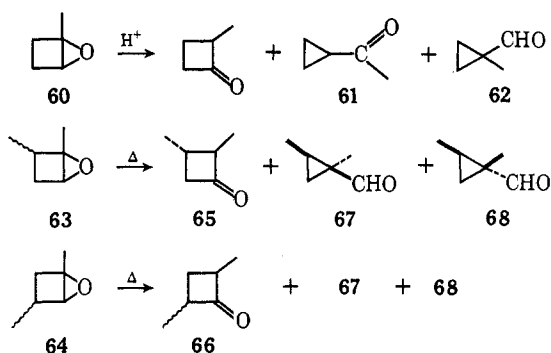
(55) L. Bouveault and C. Chereau, *C. R. Acad. Sci.*, **142**, 1986 (1906); M. Tiffeneau and B. Tchoubar, *ibid.*, **198**, 941 (1934).

In the same way, it has been established that α -hydroxy ketals **57** undergo a two-step rearrangement on heating: ring contraction into aldehyde **58** followed by ring expansion into α -alkoxycyclobutanone **59**, and not a pyrolysis providing an enol as previously suggested.⁹

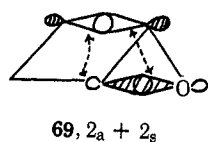
Miscellaneous Reactions

In addition to the ring contraction of cyclobutane derivatives described above, recent literature provides other examples of this reaction. Thus, cyclobutene epoxides, α -bromoaminocyclobutanes, and α,β -cyclobutanediones ring-contrast into corresponding cyclopropane derivatives by analogous pathways.

Thermal and acid-catalyzed rearrangements of epoxides are well known;^{60,61} thus cycloalkene epoxides undergo rearrangement into corresponding cycloalkanones or ring contraction into carboxaldehyde and ketone derivatives depending on the nature of the migrating groups. The acid-catalyzed rearrangement of cyclo-

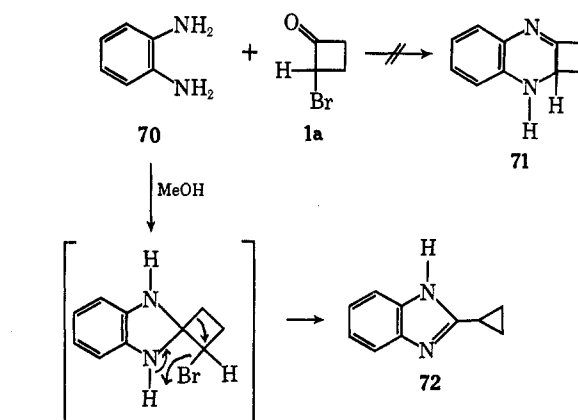


butene epoxide **60** produces ring-contraction derivatives **61** and **62** in high yields.⁶¹ However, 1,4-dimethyl- (**63**) and 1,3-dimethyl-1,2 epoxycyclobutane (**64**) rearrange spontaneously at room temperature, apparently without catalysis,⁶¹ into cyclobutanones **65** and **66** respectively and cyclopropylaldehydes **67** and **68**. This ring contraction could be considered as a $2_a + 2_s$ pericyclic reaction (see **69**), thermally allowed by orbital symmetry⁶⁹ (see ref **75b**).

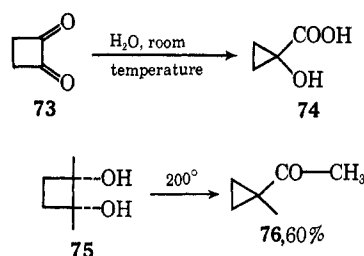


The reaction of *o*-phenylenediamine (**70**) with 2-bromocyclobutanone affords, not a fused dihydroquinoxaline derivative **71** as first claimed,⁶² but 2-cyclopropylbenzimidazole (**72**) by way of a formally similar ring contraction.⁶³

A real benzilic acid rearrangement is undergone by some 1,2-cyclobutanediones in basic medium;⁶⁴ further-



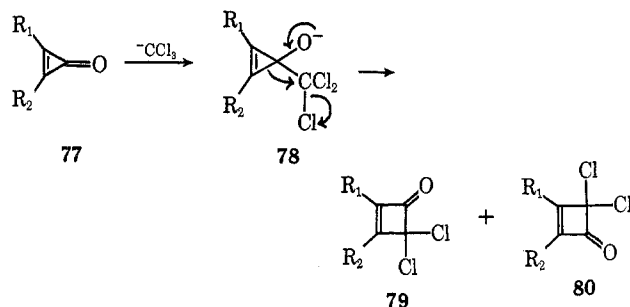
more, the readily available α -dione **73** quantitatively ring-contracts into **74** with water alone.^{49b} Likewise,



cis-1,2-cyclobutanediols (available from α -dione **73**) undergo thermal ring contraction into cyclopropane derivatives (e.g., **75** \rightarrow **76**).⁶⁵ (See also ref **66–68** and **75c**.)

Reverse Reactions. Ring Enlargements of Cyclopropane Derivatives into Cyclobutanones

The base-induced ring enlargement which occurs from 2,3-disubstituted cyclopropanones (**77**) and chloroform to yield 2,3-disubstituted 4,4-dichloro-2-cyclobutanones (**79** and **80**) was postulated⁶⁹ to involve the anionic intermediates **78**. It can be considered as the reverse reaction of the ring contraction of cyclobutane derivatives with nucleophiles.



Related ring enlargements of vinylcyclopropanol derivatives **81** were recently reported to provide, with high yields, α -substituted cyclobutanones **82**.⁷⁰ A cyclo-

(60) S. Winstein and R. B. Henderson, *Heterocycl. Compounds*, **1**, 1 (1950); R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(61) J. L. Ripoll and J. M. Conia, *Bull. Soc. Chim. Fr.*, 2755 (1965).

(62) J. H. Markgraf, W. P. Homan, R. J. Katt, and W. J. Scott, *J. Heterocycl. Chem.*, **6**, 135 (1969); C. W. Koch and J. H. Markgraf, *ibid.*, **7**, 235 (1970).

(63) R. C. De Selms, *Tetrahedron Lett.*, **34**, 3001 (1970).

(64) H. D. Scharf, W. Droste, and R. Liebig, *Angew. Chem., Int. Ed. Engl.*, **7**, 215 (1968); Ae, de Groot, D. Oudman, and H. Wynberg, *Tetrahedron Lett.*, 1529 (1969).

(65) J. M. Conia and J. P. Barnier, submitted for publication.

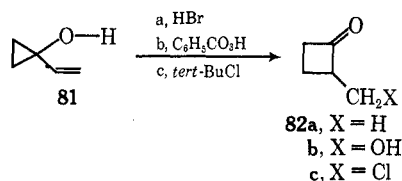
(66) I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970).

(67) L. Horner and P. V. Subramaniam, *Tetrahedron Lett.*, **2**, 101 (1965).

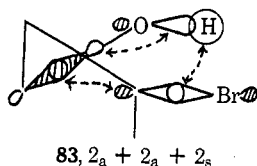
(68) W. C. Agosta and D. K. Herron, *J. Org. Chem.*, **34**, 2782 (1969).

(69) R. Breslow, L. J. Altman, A. Krebs, E. Mohacs, I. Murata, R. A. Peterson, and J. Posner, *J. Amer. Chem. Soc.*, **87**, 1326 (1965); E. V. Dehmlow, *Tetrahedron Lett.*, 4003 (1965).

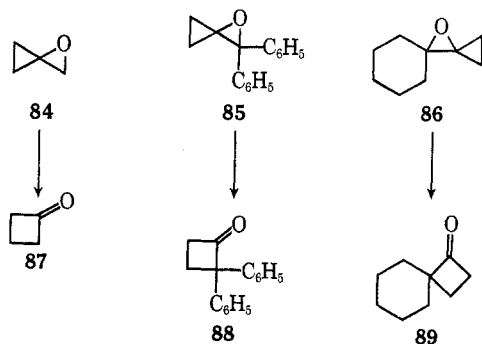
(70) H. H. Wasserman, R. E. Cochoy, and M. S. Baird, *J. Amer. Chem. Soc.*, **91**, 2375 (1969).



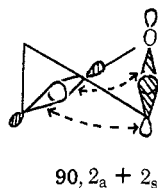
propylcarbanyl cation intermediate was suggested to be "most probably" involved in this ring enlargement, but with regard to the high specificity of the reaction, such a rearrangement could be considered as the reverse reaction of the thermal ones previously examined; if concerted, these $2_a + 2_a + 2_s$ pericyclic reactions (see **83**) would also be thermally allowed⁵⁹ (see ref 75d).



The known reverse reaction of the thermal ring contraction of cyclobutene epoxides is the ring expansion of methylenecyclopropane epoxides (**84**, **85**, and **86**) into



related cyclobutanones (**87**, **88**, and **89**).⁷¹ Such a ring enlargement could involve a $2_a + 2_s$ pericyclic thermally allowed⁵⁹ reaction (see **90**).



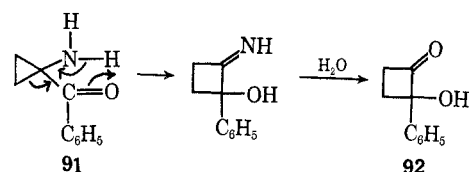
Finally, the thermolysis of 1-amino-1-benzoylcyclopropane (**91**) leading, after hydrolysis, to 2-hydroxy-2-phenylcyclobutanone (**92**)⁷² appears clearly related too.

General Conclusion

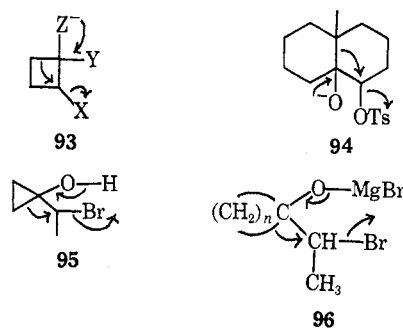
The reaction of 2-halo- (or tosyloxy-) cyclobutanones with nucleophilic reagents is not a classical Favorskii rearrangement. It involves neither a carbanion nor a carbonium ion. Actually this particularly facile ring contraction, as well as the ring contraction of 2-halo- (or

(71) P. Le Perchec and J. M. Conia, unpublished; E. V. Dehmlow, *Z. Naturforsch. B*, **24**, 1197 (1969); B. M. Trost, R. Laroche, and M. J. Bogdernowicz, *Tetrahedron Lett.*, 3449 (1970); J. R. Wiseman and K.-F. Cha, *J. Amer. Chem. Soc.*, **92**, 4750 (1970).

(72) C. L. Stevens, R. M. Weier, and K. G. Taylor, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstract No. S-101.



tosyloxy-) cyclobutanols with nucleophiles, appears to be an extension into the lower homologous series of the base-catalyzed pinacol type rearrangement of cyclic 1,2-glycol monotosylate or 1,2-halohydrin, a rearrangement known as leading to ring contraction (e.g., **94**,⁷³ compare with **93**) or to ring enlargement (e.g., **95**,⁷⁴ compare with **96**) according to the position of the leaving group in respect to the ring.



The ring contractions from 2-bromocyclobutanone hydrate, hemiketal, and ketals and from bromohydroxy-, dihydroxy- and epoxycyclobutanes, on heating, appear to be closely related. Further investigations are in progress in our laboratory in order to determine, in appropriate systems, the stereochemistry of such reactions which obviously cannot involve a true carbonium ion.⁷⁵

Part of the work discussed in this Account was performed by Professor J. Gore, Dr. J. L. Ripoll, J. M. Denis, and J. P. Barrier. We also acknowledge a discussion with Professor Nguyễn Trong Anh (Orsay, France) which helped clarify some ideas concerning orbital theory. This work was supported by the Centre National de la Recherche Scientifique.

(73) Y. Masur and M. Nussim, *J. Amer. Chem. Soc.*, **83**, 3911 (1961); C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, p 101.

(74) A. J. Sisti, *J. Org. Chem.*, **35**, 2670 (1970).

(75) NOTES ADDED IN PROOF. Since the time of submission of this paper, new results have been reported in this challenging field: (a) Concerning the thermal ring contraction of 2-bromocyclobutanone ketals, stereochemical and kinetic analyses have evidenced the occurrence of an intermolecular transfer of halogen with inversion of configuration at the migration terminus (J. Salaun and J. M. Conia, *Tetrahedron Lett.*, 1971, accepted for publication), excluding a direct control of orbital symmetry restrictions. [For attempts from analogous α -halo sulfone ketals, see: L. A. Paquette and R. W. Houser, *J. Amer. Chem. Soc.*, **93**, 944 (1971)]. (b) Concerning the cyclobutane epoxides ring contraction catalyzed by Lewis acids [D. L. Garin, *J. Org. Chem.*, **36**, 1697 (1971)] the occurrence of a cyclobutyl carbonium ion intermediate was rejected too. (c) Concerning the cyclobutanediols, it must be pointed out that *trans*-1,2-cyclobutanediol ring contracts still more easily than the *cis* isomer.⁶⁵ (d) Concerning the vinylcyclopropanols, ring enlargement into cyclobutanones occurs effectively on heating (ca. 100°) (J. Salaun and J. M. Conia, unpublished). (e) Concerning "the new(!) synthesis of cyclopropanecarboxylic acids" from some 2-halocyclobutanones and sodium methoxide recently claimed [W. T. Brady and J. P. Hieble, *J. Org. Chem.*, **36**, 2033 (1971); Abstracts of Papers, IUPAC Meeting, Boston, Mass., 1971, p 58], we expect that the present review will not be useless.