71-13,786

FOSSEL, Eric Thor, 1941-
STEREOSELECTIVITY IN THE THERMAL REARRANGEMENT OF AN OPTICALLY ACTIVE METHYLENECYCLOBUTANE.

Harvard University, Ph.D., 1970
Chemistry, organic

University Microfilms, A XEROX Company, Ann Arbor, Michigan

© 1971

Eric Thor Fossel

ALL RIGHTS RESERVED

THIS DISSERTATION HAS BEEN MICROFILMED EXACTLY AS RECEIVED.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

STEREOSELECTIVITY IN THE THERMAL REARRANGEMENT OF AN OPTICALLY ACTIVE METHYLENECYCLOBUTANE

A thesis presented

by

Eric Thor Fossel

to

The Department of Chemistry

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Chemistry

Harvard University

Cambridge, Massachusetts

February 1970

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

PLEASE NOTE:

Some pages have small
and indistinct type.
Filmed as received.

University Microfilms

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

To

Holly

and

My Parents

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

also to

miss chris

and

silly wol

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

"As soon, however, as he would try to involve others in his doubt, there can easily intermingle with it an impure passion. As soon as doubt is urged upon others, an envy may be at work which finds satisfaction in depriving them of that which they regard as sure."

Soren Kierkegaard- "Shadowgraphs"
in Either/Or

"If I were to wish for anything, I should not wish for anything, I should not wish for wealth and power, but for the passionate sense of the potential, for the eye which, ever young and ardent, sees the possible. Pleasure disappoints, possibility never. And what wine is so sparkling, what so fragrant, what so intoxicating as possibility!"

Soren Kierkegaard- "Diapsalmata"
in Either/Or

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

ACKNOWLEDGEMENTS

I express my deep gratitude and sincere appreciation to Professor William von Eggers Doering. His magnificent mind conceived the problem dealt with in this dissertation and unraveled its many complexities as the work progressed. Of equal importance, his generous patience with the often slow pace of experimental progress as well as his splendid understanding of human nature and the shortcomings and limitations of his students made a significant difference in the quality of my life as a graduate student.

Many members of the Doering research group made a contribution to various phases of my education. Mega-hours of conversation, at times even on topics relevant to chemistry, with members of the group were both pleasant and beneficial. I particularly refer to Barbara Ferrier, Maitland Jones, Jr., John Gilbert, Robert Rando, Alan Krantz, Philip Shevlin, Robert Kaye, Eckhart Schmidt, Glen Beasley, David Andrews, Juris Ekmanis, Noyes Avery, and Heintz-Dieter Roth. I also thank Glen Beasley for the use of the air thermostat which he constructed and maintained. Noyes Avery is thanked for taking mass spectra.

My special thanks go to Mrs. Margaret Currier for making my transition from Yale to Harvard a smooth one and for guiding me through the red tape of the Harvard Graduate School of Arts and Sciences. Hampar Janjigian and Dr. Gerald Dudek are thanked for their assistance in my extensive NMR work.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Yale University and the Yale Chemistry Department must be given due credit for providing me with the first three years of my graduate education.

The financial assistance of a Yale University Fellowship (1964-1967), a Harvard Research Assistantship (1967-1968) and a National Institute of Health Traineeship: GM-700-08 (1969) is gratefully acknowledged.

Finally, I thank my wife, Holly, for her very special contributions, her tolerant attitude toward my eccentricities and her patient bearing of the lonely life of the wife of a chemistry graduate student.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Stereoselectivity in the Thermal Rearrangement of an Optically Active Methylenecyclobutane

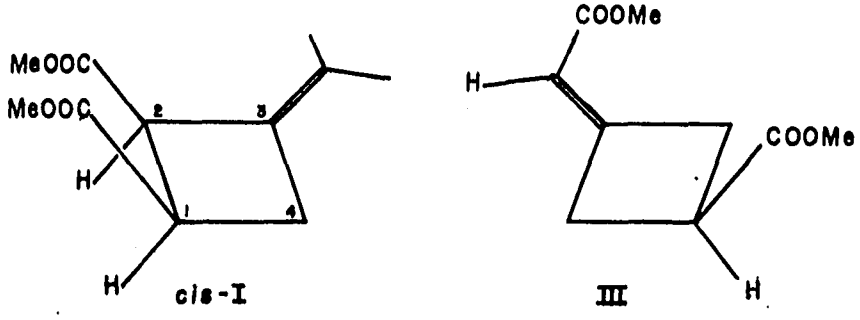
Summary

Research Director
W. von E. Doering

Eric Thor Fossel
February 1970

Optically active dimethyl *cis* and *trans* 3-methylene-cyclobutane-1,2-dicarboxylate (*cis*-I and *trans*-I) were found to rearrange to optically active methyl 3-carbomethoxycyclo-but-1-ylidene-acetate (III). The specific rotations of optically pure *cis*-I, *trans*-I and III were ascertained revealing that III from the rearrangement of *cis*-I contained 75% of the optical purity of the starting material and that III from the rearrangement of *trans*-I contained 33% of the optical purity of the starting material.

For the transformation of *cis*-I to III to occur,



it is necessary that, in the diradical intermediate, the C_2-C_3 bond rotate 90°. The C_1-C_4 bond may undergo no rotation (0°) or it may rotate 180° during the rearrangement. Examination of the NMR spectrum of the rearrangement product

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

of optically active dimethyl *cis*-3-dideuteriomethylenecyclobutane-1,2-dicarboxylate and determination of the absolute configurations of *cis*-I and III revealed that rotation of the C_2-C_3 bond always occurs in such a way as to place the carbomethoxy group *syn* to the CH_2 group which had constituted the methylene group of starting material and that 87% of the product is formed by a 0° rotation of the C_1-C_4 bond while 13% is formed by a 180° rotation.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

TABLE OF CONTENTS

Chapter I: INTRODUCTION

Diradicals-
The Trimethylene Diradical 4
The Tetramethylene Diradical 18
Transition State or Very Unstable Intermediate? 21
Sigmatropic Reactions 23

Chapter II: RESULTS AND DISCUSSION

The Degenerate Methylenecyclobutane Rearrangement 28
Preparation of Methylenecyclobutane Diesters: *cis*-I and *trans*-I 30
Thermolysis of the Methylenecyclobutane Diesters 31
Mechanistic Questions 33
Thermolysis of Optically Active Methylenecyclobutane Diesters 39
Resolution and Establishment of Optical Purity of *cis*-I, *trans*-I and III 40
Variation of Rearrangement Conditions 44
Combinations of Rotations 45
Dimethyl *cis*-3-(dideuteriomethylene)cyclobutane-1,2-dicarboxylate: *cis*-I-d_2 47
Absolute Configurations of Reactants and Product 52
The NMR Spectrum of III and III-d_2 68
Optically Active *cis*-I-d_2 and its use in distinguishing among rotational alternatives 72
Formation of *trans*-I in the thermal rearrangement of *cis*-I 82
Pressure effect on rotation specificity 84
Reversibility of the Rearrangement: conversion of III to *trans*-I 85
Points left unanswered in the conversion of *cis*-I to III 86
Conclusions 88

Chapter III: RESULTS AND DISCUSSION

Addition of Diethyl Maleate and Diethyl Fumarate to Allene 94

Chapter IV: EXPERIMENTAL 102

Appendix I: Effect of Carboxylic Ester Groups on Near-By Protons 149

Appendix II: Spectra 152

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

CHAPTER I:
INTRODUCTION

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Today's organic chemist is capable of constructing highly complex molecules through subtle and involved synthetic pathways. Yet, many of the most simple and basic questions relating to organic molecules and their behavior go unanswered and, in many cases, unasked. In some respects this is not without good cause. Many reactions, reaction media and reagents defy rational analysis because of their nearly infinite complexity and the limitations of the tools which the chemist of today can bring to the attack. In order to work on the basic questions in organic chemistry the scope and complexity of the problem attacked must be severely limited. In the field of thermal unimolecular reorganizations sufficiently simple situations can be found that the level of penetration is potentially deeper than in many other areas.

The essential features of a thermal unimolecular reorganization are the involvement of only one molecule; the absence of the requirement of solvent (indeed, the rate of the reaction is usually the same in vapor phase and in solution); and the complete absence of any sort of catalytic effect. Only the application of heat is necessary to carry out a thermal unimolecular reorganization.

Several features of the reorganization may be scrutinized by the investigator. The first, and possibly the most obvious, is the process of bond-breaking, the minimum step necessary for the initiation of many reorganizations.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

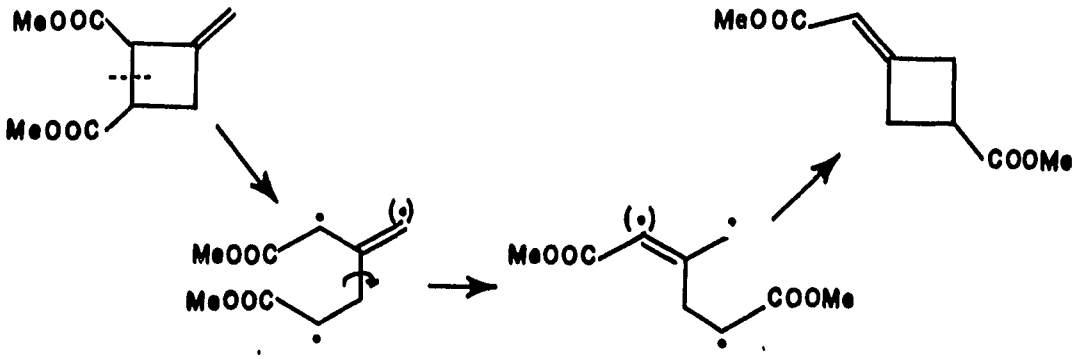
This homolytic bond rupture in a non-excited state leads to radicals of paired spins in their singlet state. The species thus formed may represent the highest energetic point or it may not. Where it does not, more energy is necessary to push the species over the energy maximum toward products. The definition of this species of sufficient energy for the reaction to proceed is studied by the kinetic determination of activation parameters. Once the molecule has received the minimum energy to effect bond-rupture, the next feature of the reaction which naturally comes to the attention of the investigator is the manner in which rebonding occurs to form product.

A description of the molecule between the time of bond-rupture and bond-formation is one of the major tasks involved in shedding light on the mechanism of the reaction. After the point of bond-rupture, reactions may be divided into two major divisions. In the first division are reactions which proceed toward products by a path in which the orbitals of the molecule interact continuously in an energetically positive sense. In the second division are the reactions which proceed along a path in which the orbitals of the broken bond and other strategic parts of the molecule are so separated from each other that there is no meaningful interaction between these portions of the molecule. This lack of interaction is not occasioned by the electrons of the broken bond being in unpaired spin states, *i.e.* in the triplet

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

state, but by distance and angle of orientation. Such an intervening species is commonly called a (singlet) diradical.

This dissertation is concerned with a reaction which is expected to fall into the second division. The specific reaction is the rearrangement of a methylenecyclobutane substituted by carbomethoxy groups and most simply is



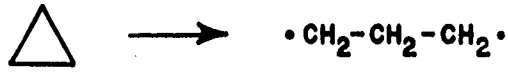
imagined to involve a diradical. In order that its qualities may be properly understood, a discussion of singlet diradicals is given.

Diradicals - The Trimethylene Diradical

A simple example of a reaction which produces two radicals is the pyrolysis of ethane. This example is not helpful in the elucidation of the properties of diradicals since the two methyl radicals are under no predictable restraint with regard to each other, either spacially or tem-

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

porally. A more useful and still simple diradical, the trimethylene diradical (I), is thought to be the intermediate in the pyrolysis of cyclopropane. The representation of I shown below makes no attempt to depict such features as geometry or orbital orientation, but simply depicts the species which has been hypothesized in the pyrolysis of *trans*-1,2-dideuteriocyclopropane[1] which leads to *cis*-1,2-dideuteriocyclopropane and propylene-d_2. The activation energies are 64 kcal/mole for geometric isomerization and 65



I

kcal/mole for propylene production. Until recently the question of providing a complete description of this hypothetical intermediate species has gone unanswered. Although "diradical" has come to refer to a species in which there is little or no interaction between the two radical centers,[2] the

---

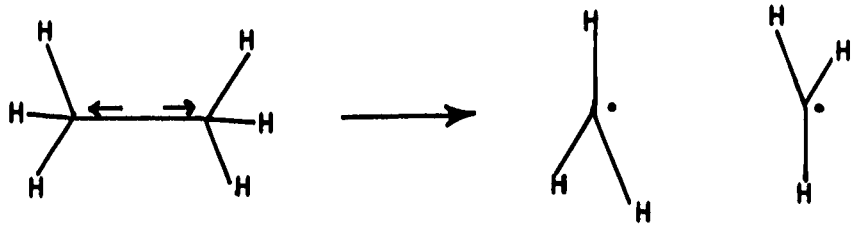
1. B. S. Rabinovitch, E. W. Schlag, and K.B. Wiberg, *J. Chem. Phys.*, 28, 504 (1958).
E. W. Schlag and B.S. Rabinovitch, *J. Am. Chem. Soc.*, 82, 5996 (1960).

2. Bartlett states, "The property of a 'biradical' which is important for the phenomena of stereoequilibration... is simply the absence of significant bonding between the carbon atoms to which 'radical' character is attributed." P. D. Bartlett, L. K. Montgomery, and B. Seidel, *J. Am. Chem. Soc.*, 86, 616 (1964).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

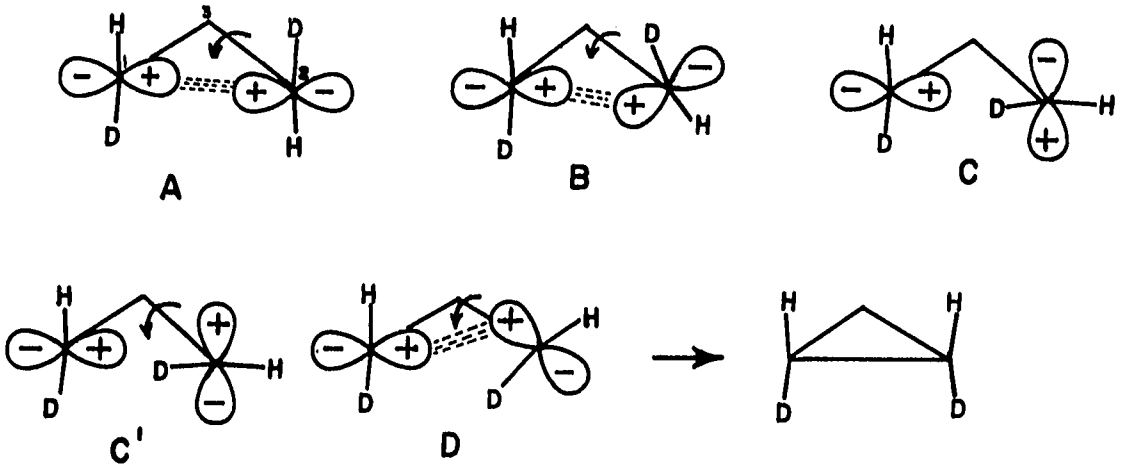
trimethylene diradical is so small and the maximum distance separating its two portions is so short that the fitness of this general definition is suspect.

The process of breaking the carbon-carbon bond in ethane might be fully described as a high magnitude stretching vibration. In cyclopropane, however, such a simple



in-plane stretching does not result in bond-rupture, since the distance between the carbon atoms remains small enough at the extremes of the vibration to retain significant overlap of the electrons. Complete removal of this residual overlap may only be effected by creating an unfavorable angular orientation of orbitals. Such orientation is achieved through rotation. As an illustration of rotation accompanying vibration, cyclopropane with its 1,2 bond stretched (A) may suffer rotation around bond 1,3 to produce B. While significant overlap (bonding) still exists between the π-orbitals on carbons 1 and 2 in B, further rotation to C would make the orbitals orthogonal. At this point all overlap and all symmetry correlations would disappear and a non-interacting diradical results. Since C and C' are indistinguishable, continued rotation of the 1,3 bond in the same

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



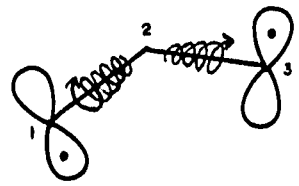
direction reestablishes symmetry correlations and overlap between the orbitals of C_1 and C_2 (D). The effect of progressing from C to D has been to invert the sign orientation of the π-orbital on C_2. Continuation of the rotation about the 1,3 bond serves to strengthen the overlap and eventually leads to the reestablishment of fully bonded cyclopropane.

From this discussion it is apparent that proper definition of the statement, "a bond is broken," is not simple. Here it implies that no effective overlap remains between the carbon atoms which had constituted the bond. The diradical produced when a bond is broken must be described in respect of its freedom of rotation, the strength of bonding between the two halves, and the requirements for recombination.

Bartlett has proposed that the observation of rotation would constitute evidence for a fully free diradical

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

with no force between the radical sites to limit rotations.[3] It would therefore be a property of a trimethylene diradical in which the two odd electrons did not influence each other that extensive rotation around the 1,2 and the 2,3 bonds could occur before recombination to cyclopropane. Certain types of initial order relating to structrual isomerism or



optical asymmetry could be destroyed by these rotations.

The relative rates of rotation and rebonding are presumably determined by the energetics of reforming a sigma bond from the two orbitals of the diradical. If there is a substantial barrier to recombination a greater opportunity for extensive rotation would exist than if the barrier were non-existent or very low. Several studies on the combination of alkyl radicals have revealed activation energies for combination of 0 kcal/mole, within experimental error. Radical combinations which have been studied include: methyl with methyl;[4,5] methyl with ethyl;[6,7]

---

3. P.D. Bartlett, L.K. Montgomery and B. Seidel, *J. Am. Chem. Soc.* 86, 625 (1964).
4. R. Gomer and G. B. Kistiakowsky, *J. Chem. Phys.* 19, 85 (1951). G. B. Kistiakowsky and E.K. Roberts, *J. Chem. Phys.*, 21, 1637 (1953).
5. M. H.J. Wijnen, *J. Chem. Phys.*, 28, 271 (1958).
6. P. Ausloos and E.W.R. Steacie, *Can. J. Chem.*, 33, 1062 (1955).
7. C. A. Heller, *J. Chem. Phys.*, 28, 1225 (1958).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

ethyl with *iso*-propyl;[8,9] *iso*-propyl with *iso*-propyl;[10] and *t*-butyl with *t*-butyl.[11] While there are important differences between the recombination of two alkyl radicals and reclosure in a diradical, it is significant that a wide variety of radicals including the two bulky *t*-butyl radicals combine with each other with zero energy of activation.

Extended Hückel calculations on the trimethylene diradical by Hoffmann[12] have indicated the absence of any minimum in the energy surface of the eclipsed trimethylene diradical (A) for C-C-C angles between 60° and 115°. Thus return of the central C-C-C bond angle toward 60° only leads to increasingly effective overlap and does not encounter a minimum corresponding to an unstable intermediate.

Further support of a low activation energy for recombination of diradicals comes from the "cage effect" which owes its very existence to an effective competition between recombination of radicals and diffusion. Examination of data on cage effects has led Bartlett[13] to the conclusion

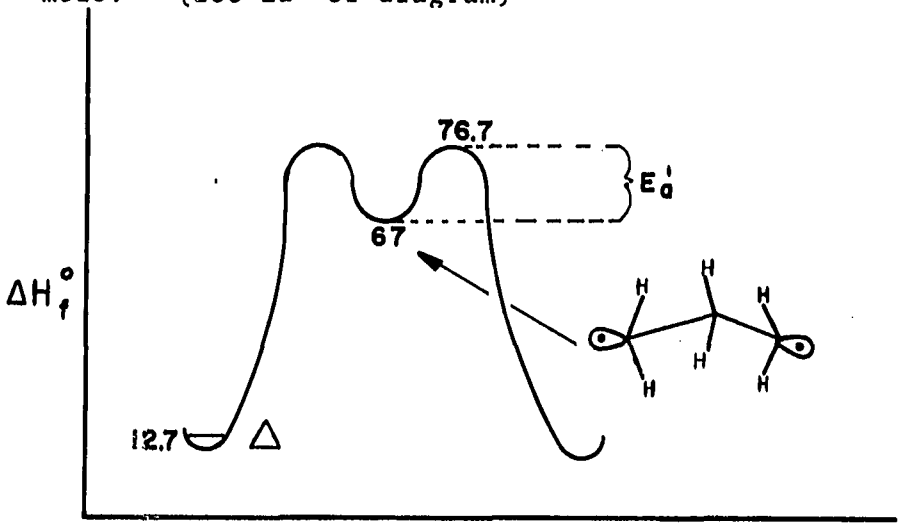
---

8. J. A. Kerr and A. F. Trottmann-Dickenson, *Trans. Farad. Soc.* 55, 572 (1959).
9. J. A. Kerr and A. F. Trottmann-Dickenson, *Trans. Farad. Soc.*, 55, 921 (1959).
10. E. L. Metcalfe and A. F. Trottmann-Dickenson, *J. Chem. Soc.*, 4620 (1962).
11. E. L. Metcalfe, *J. Chem. Soc.*, 3560 (1963).
12. R. Hoffmann, *J. Am. Chem. Soc.*, 90, 1475 (1968).
13. P. D. Bartlett and J. M. McBride, *Pure Appl. Chem.*, 89 (1967).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

that even "a resonance energy of 20-30 kcal. will not prevent a radical from coupling at a high and even diffusion-controlled rate."

Running counter to this picture of a low energy barrier to the combination of radicals or recombination within a diradical is the proposition by Benson of a barrier of 7-9 kcal/mole for the recombination of diradicals.[14] For the recombination of the trimethylene diradical he has deduced an activation energy of 9.7 kcal/mole.[15] (See Ea' of diagram)



This value is derived from a comparison of the experimental ΔH_f° for the transition state in the isomerization of

---

14. S. W. Benson and H. E. O'Neal, *J. Phys. Chem.*, 89, 1866 (1968).
15. S. W. Benson, *J. Chem. Phys.*, 34, 521 (1961).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

cyclopropane (76.7 kcal/mole) with a theoretical value (67 kcal/mole). This theoretical value can be derived at least four different ways. However, there is no direct experimental support for the existence of such a minima. Benson approaches the model intermediate from 1 -iodo-propane.

$$\underset{(\Delta H_f^\circ)\ (-6.3)}{I\text{-}CH_2\text{-}CH_2\text{-}CH_3} \longrightarrow \underset{(37.6)}{I\text{-}CH_2\text{-}CH_2\text{-}CH_2\cdot} + \underset{(52.1)}{H\cdot} + 98.0 \text{ kcal/mole}$$

$$\underset{(\Delta H_f^\circ)\ (37.6)}{I\text{-}CH_2\text{-}CH_2\text{-}CH_2\cdot} \longrightarrow \underset{(66.0)}{\cdot CH_2\text{-}CH_2\text{-}CH_2\cdot} + \underset{(25.5)}{I\cdot} + 53.9 \text{ kcal/mole}$$

Alternatively, two methyl C-H bonds of propane may be broken to give the model intermediate.

$$\underset{(\Delta H_f^\circ)\ (-24.8)}{CH_3\text{-}CH_2\text{-}CH_3} \longrightarrow \underset{(67.2)}{\cdot CH_2\text{-}CH_2\text{-}CH_2\cdot} + \underset{(2\times 52.1)}{2H\cdot} + 2\times 98.0 \text{ kcal/mole}$$

Or, three $-CH_2-$ groups from an "infinite" straight chain saturated hydrocarbon may be taken to produce the model intermediate.

$$\underset{(\Delta H_f^\circ)\ (3\times -4.9 = -14.7)}{-(CH_2)_x\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}(CH_2)_y-} \longrightarrow \underset{(67.3)}{\cdot CH_2\text{-}CH_2\text{-}CH_2\cdot} + 2\times(1/2\cdot 82) \text{ kcal/mole}$$

Finally, cyclohexane may be split into two equivalent trimethylene fragments by breaking two carbon-carbon bonds.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

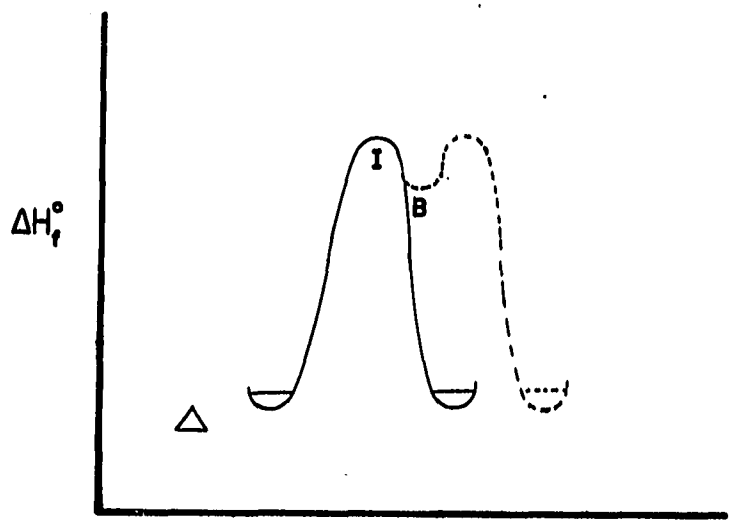
$$\longrightarrow \quad 2\cdot CH_2-CH_2-CH_2\cdot \quad + 2 \times 82.0 \text{ kcal/mole}$$

(ΔH_f°) (-29.5) (2 x 67.3)

Despite obvious flaws in each of these methods (neither the strength of the C-H or the C-C bond is known with high accuracy), the ΔH_f° of the model intermediate arrived at through these independent methods agree among each other remarkably well.

The question can be raised whether the model trimethylene diradical in actuality is equivalent to any point on the energy surface of the isomerization of *trans*-1,2-dideuteriocyclopropane. Perhaps the model intermediate represents a geometry which is inaccessible to the real molecule during isomerization. As noted earlier, the geometry of cyclopropane, or of a three carbon fragment with a sp^3 central carbon, makes it difficult for the two electrons on the terminal carbon atoms to be energetically independent of one another, an implicit assumption of the Benson trimethylene model. Thus, cyclopropane, having stretched its bonds to reach

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

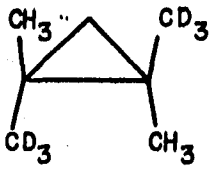


C-C' in the diagram on page 7 (point I in this figure), may begin to rebond at once and continue down the solid line. It might thereby be denied access to the Benson model intermediate (point B) and the dotted line on the energy diagram. It would probably also be denied "free" rotation since the same interaction between the odd electrons which led directly to rebonding from transition state I would also serve as an inhibition to rotation.

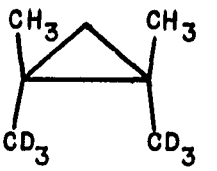
A test of the "freedom" of rotation has been reported by Berson.[16] Pyrolysis of optically active *trans*-II produced a mixture of *cis*-II and *trans*-II as well as a decrease in specific rotation of the pyrolysate. Berson defines the rate of isomerization as $k_i t = -\ln[1-(2C/T_o)]$ and the rate

16. J. A. Berson and J.M. Balquist, *J. Am. Chem. Soc.*, 90, 7343 (1968).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



trans-II



cis-II

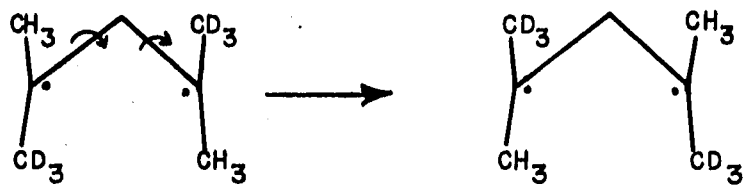
of racemization as $k_\alpha t = \ln(\alpha/\alpha_o)$. A value for the ratio of k_i/k_α of 1.74 is reported without probable limits of error. This value may be redefined in terms of the rate of *trans* to *cis* isomerization, k_{tc}, and the rate of *trans* to *trans* isomerization, k_{tt}.

$$k_i = 2\,k_{tc} \text{ and } k_\alpha = k_{tc} + 2k_{tt}$$

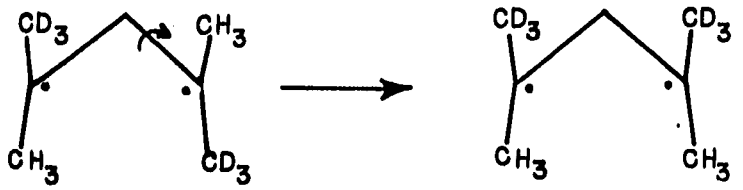
Substitution of the value of k_i/k_α of 1.74 affords a ratio of k_{tc} to k_{tt} of 14 to 1. Small errors are important, since a value of k_i/k_α of 2.0 would lead to a ratio of k_{tc} to k_{tt} of infinity. Unhappily, no error limits for k_i/k_α are reported.

The process of conversion of one enantiomer of *trans*-II to the other (k_{tt}) requires rotation of both carbon atoms of the broken bond. Such a double rotation occurs once for every fourteen times that a single rotation converts *trans*-II

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



to *cis*-II (k_{tc}).



Similar studies by Crawford[17] on *trans*-1,2-diphenylcyclopropane reveals a k_{tc}/k_{tt} of 7. Bergman has studied 1-methyl-2-ethylcyclopropane and found a value of k_{tc}/k_{tt} of 2.1.[18] "Free" rotation would require a value of k_{tc}/k_{tt} of 1.0.

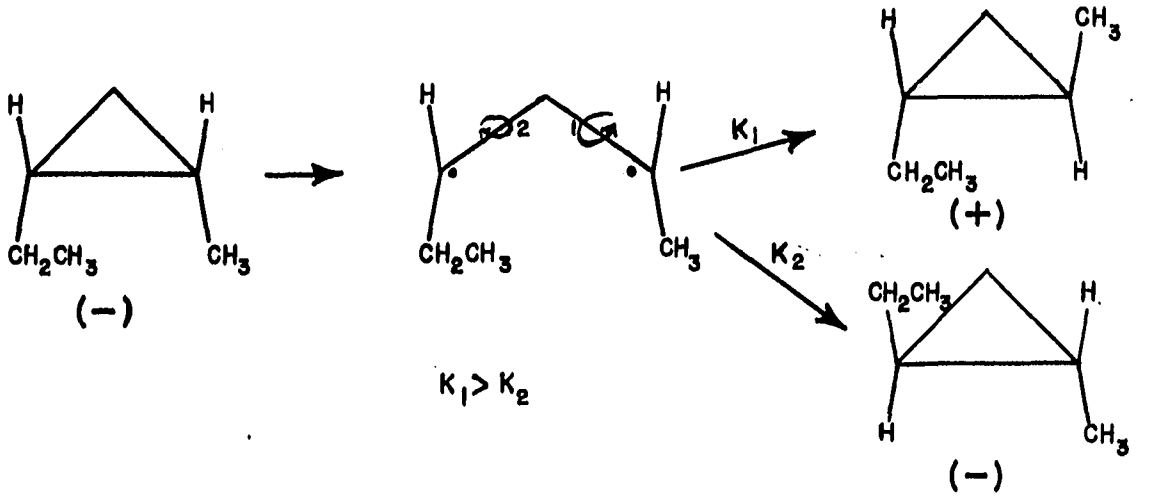
A further point of interest in Bergman's example is revealed by the unsymmetrical substitution at the carbon atoms involved in rupture. Since one carbon bears a methyl

---

17. R. J. Crawford and T. R. Lynch, *Can. J. Chem.*, 40, 1457 (1968).
18. W. L. Carter and R. G. Bergman, *J. Am. Chem. Soc.*, 90, 7344 (1968). R. G. Bergman and W. L. Carter, *J. Am. Chem. Soc.*, 91, 7411 (1969).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

group and the other bears an ethyl group, a choice must be made between them as to which carbon will rotate. This choice determines the integrity of the asymmetry of the product. If both carbon atoms rotated at equal rates racemic product would result ($k_1=k_2$).

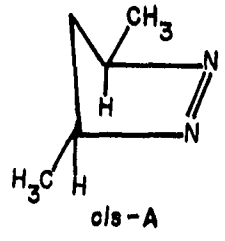


Apparently the molecule finds little difference between a methyl group and an ethyl group as only an 8% retention of optical activity is reported reflecting rotation of the methyl group 54 times for every 46 rotations of the ethyl group ($k_1>k_2$).

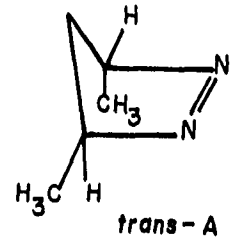
Although an exact definition of the intermediate in the thermal decomposition of pyrazolines is not available, most evidence points toward the involvement of a trimethylene diradical. Several examples of this reaction have been provided by Crawford. For example, reaction of *cis*-A gives

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

rise to 33% *cis*-1,2-dimethylcyclopropane and 66% *trans*-1,2-dimethylcyclopropane while *trans*-A gives rise to 72.6% *cis*-1,2-dimethylcyclopropane and 25.4% *trans*-1,2-dimethylcyclopropane.[19]



cis-A



trans-A

Several different approaches may be made toward understanding this result, however, it is a necessary feature of all of them that free rapid rotaion in the intermediate is disallowed. Further indication of restricted rotation is found in the fact that (+)-(1*R*:3*R*)-*trans*-A produces (+)-(1*R*:2*R*)-*trans*-1,2-dimethylcyclopropane with 24% stereoselectivity.[20]

An accurate and complete description of the trimethylene diradical has yet to appear. It is obvious rotation occurs, but it is equally obvious that the rotation is not free. Our present picture of the trimethylene

---

19. R. Moore, A. Mishra, and R. J. Crawford, *Can. J. Chem.*, 46, 3305 (1968).
20. R. J. Crawford and A. Mishra, *Can. J. Chem.*, 47, 1515 (1969).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

diradical and its properties is complicated. Since the carbon - carbon bond in cyclopropane cannot be broken by stretching alone, rotation must be an indispensible part of the bond-breaking process. However, it seems that this indispensible bond-breaking rotation does not become "free" rotation in the intermediate as in all of the examples above the ratio of k_{tc}/k_{tt} was well removed from the value expected from such "free" rotation.

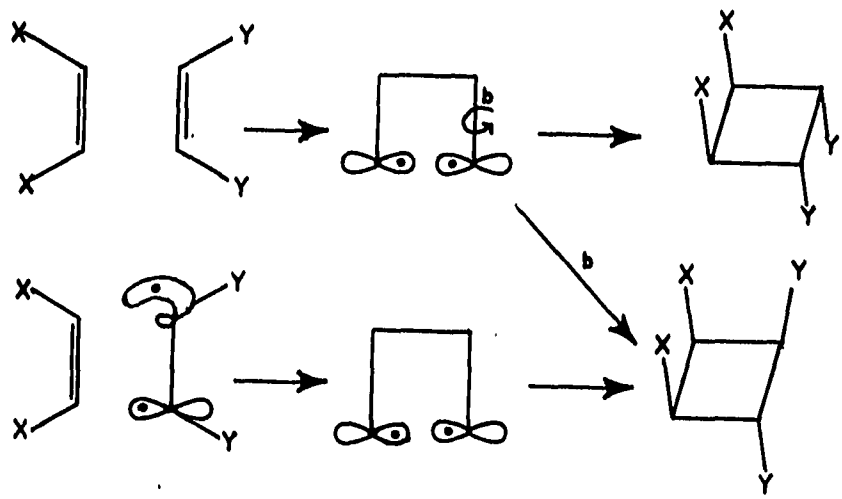
The tetramethylene diradical

Cyclobutane may rupture to the tetramethylene diradical. Since simple in-plane stretching does not represent a breaking of the carbon-carbon bond, rotation may again be necessary as a component of bond-breaking. Cleavage of the second bond may proceed through the diradical, possibly through its *transoid* configuration, or it may reclose to

cyclobutane. More extensive insight into the behavior of the tetramethylene diradical has been revealed in studies of 1,2:1,2 cycloadditions of two ethylenic molecules. According to orbital symmetry, in the addition of two double bonds to each other to form a cyclobutane ring, both bonds

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

may not be made at one time[21] unless they add in an antarafacial manner.[22] In the two-step process formation of the first bond produces a tetramethylene diradical which later closes the second bond forming a cyclobutane.



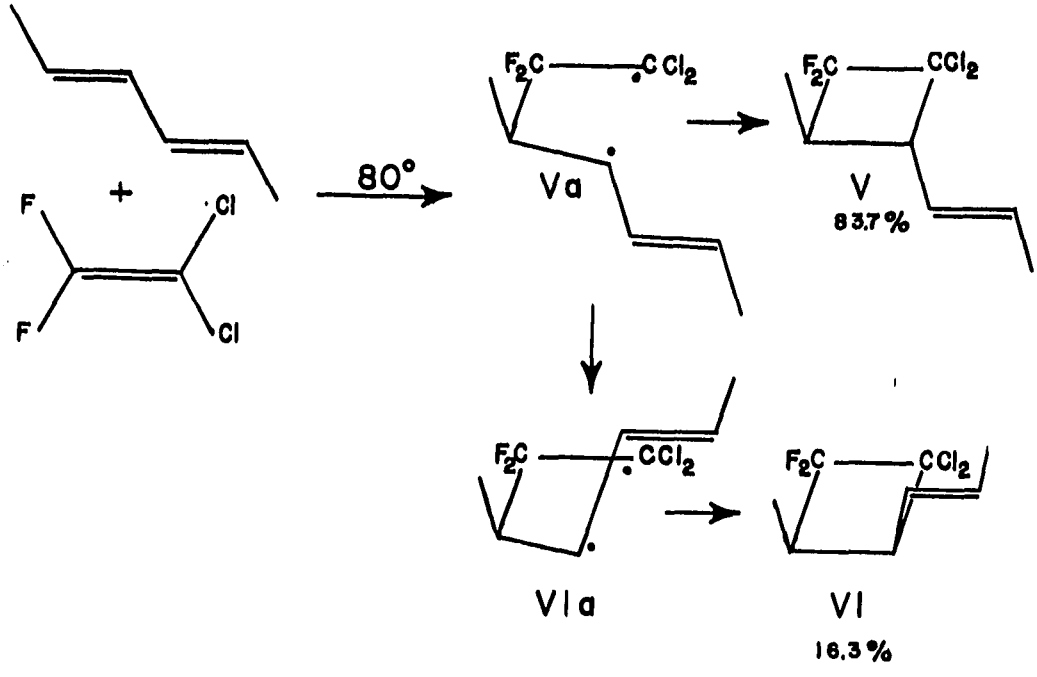
Experimental support for rotation in the tetramethylene diradical can be found in pyrolysis of *cis*-1,2-dimethylcyclobutane which gives *trans*-1,2-dimethylcyclobutane, ethylene, propylene and *cis* and *trans*-2-butene.[23] Further evidence is provided in the definitive work of Bartlett[24] and his coworkers on the addition of 1,1-dichloro-2,2-difluoro-

---

21. R. B. Woodward and R. Hoffmann, *Angew. Chem., Inter. Ed*, 8, 781 (1969).
22. Antarafacial here refers to bond-making between opposite faces of a molecule.
23. H. R. Gerberich and W. D. Walters, *J. Am. Chem. Soc.*, 83, 4884 (1961).
24. P. D. Bartlett and L. K. Montgomery, *J. Am. Chem. Soc.*, 86, 628 (1964).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

ethylene to geometrical isomers of 2,4-hexadiene. Two features indicate the intervention of a tetramethylene diradical. First, the mode of addition of dichlorodifluoroethylene is quite specific and leads to an orientation consistent with the involvement of a $\cdot CCl_2$ rather than a $\cdot CF_2$ radical. Second, the formation of two geometric isomers (V and VI) establishes that the reaction is not stereospecific. Clearly VI must result from a rotation in the diradical which converts conformation Va to conformation



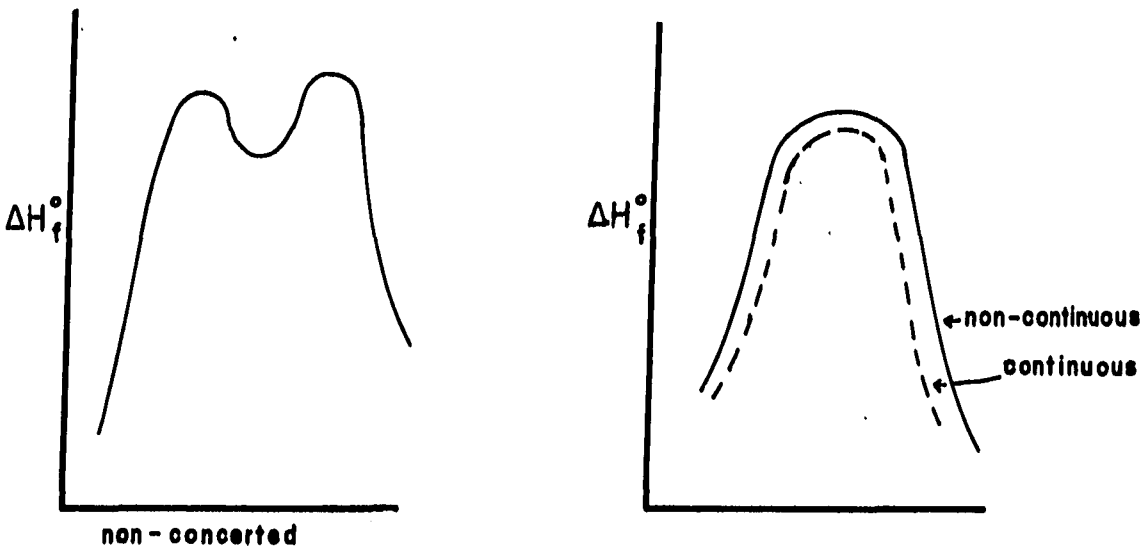
VIa. Since the major product (V) retained the geometry of the starting material, it is concluded that formation of the second bond is fast with respect to isomerization. It

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

is interesting to ponder what would have been the conclusion about the intermediacy of the diradical, had the halogen orientation been observed in the absence of any structural isomerization.

Transition state or very unstable intermediate?

An interesting question is posed by a species which is not a minimum in the energy profile and is thus not protected by energy barriers and yet does not have a structure in which orbital symmetry is conserved. Is a reaction proceeding via such a species to be considered concerted? A reaction which proceeded with continuous overlap would

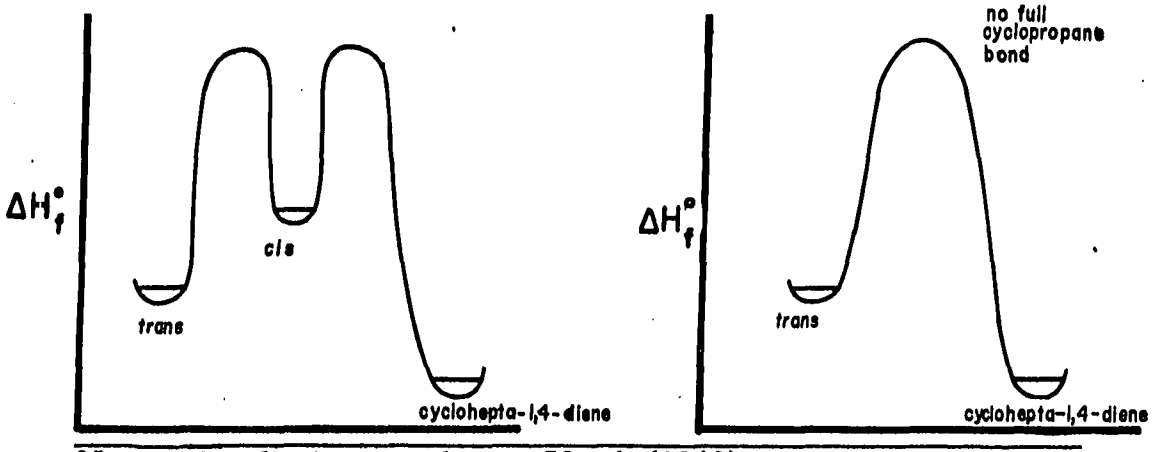


not involve an intermediate and would have a lower activation energy than a reaction which proceeded with a discontinuity

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

of overlap. If such a reaction also had no energy dips, it would have been described prior to orbital symmetry as a concerted reaction. But within the framework of conservation of orbital symmetry, such a reaction may be described as continuous but nonconcerted.

An illustrative example may be the thermal reorganization of *trans*-1,2-divinylcyclopropane to cyclohepta-1,4-diene.[25] This reaction is most easily formulated as a rearrangement to the *cis*-isomer followed by Cope rearrangement, although *cis*-1,2-divinylcyclopropane has not actually been demonstrated to be an intermediate in the reaction. The mechanism can also be formulated as proceeding from the species intermediate in the *trans* to *cis* interconversion without first reforming the cyclopropane ring. If this were the case the reaction would lack continuous orbital overlap and would proceed without a definable intermediate.



25. E. Vogel, *Angew. Chem.*, 72, 4 (1960).
E. Vogel, K. H. Ott, and K. Gajek, *Ann.*, 644, 172 (1962).

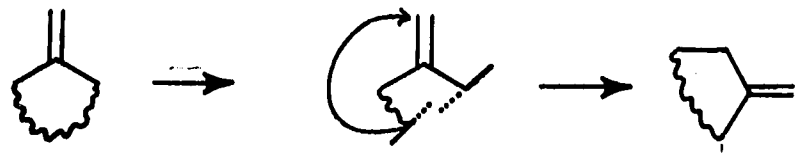
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Sigmatropic Reactions

This dissertation is concerned with a reaction defined in Woodward-Hoffmann terms as a [1,3] sigmatropic reaction.[26] The classification is useful regardless of whether or not the reaction proceeds with conservation of orbital symmetry.

In reactions of cyclic molecules, two types of [1,3] sigmatropic reactions are formally possible. In the first, both the migrating group and its anchor are attached to an end of the three carbon system. In the second, the migrating group is attached to one end of the three carbon system while its anchor is attached to the central carbon atom. [1,3] Sigmatropic rearrangements

27

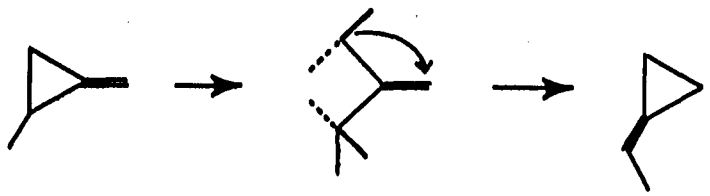


---

26. R. B. Woodward and R. Hoffman, *J. Am. Chem. Soc*, 87, 2511 (1965). "We define as a sigmatropic change of order i,j the migration of a bond, flanked by one or more π electron systems, to a new position whose termini are i-1 and j-1 atoms removed from the original bonded loci, in an uncatalyzed intramolecular process."
27. The device of using ——…… in place of ⊕⊖ to keep track of the sign orientation of orbitals is adopted.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

of either type have been relatively few in number. The reorganization of vinyl cyclopropanes to cyclopentenes is a [1,3] sigmatropic reaction of the first type. Chesick reported one of the first examples of a [1,3] sigmatropic reaction of the second type in which 2-methylmethylene-cyclopropane rearranged to ethylidenecyclopropane.[28]



The rules of orbital symmetry conservation make an explicit prediction about the stereochemistry of an orbital symmetry controlled reaction of the [1,3] sigmatropic type:[29] the carbon which migrates must suffer inversion of configuration if the migration is suprafacial. Inversion in a cyclic molecule is equivalent to a 180° rotation of a carbon-carbon bond while migrating.

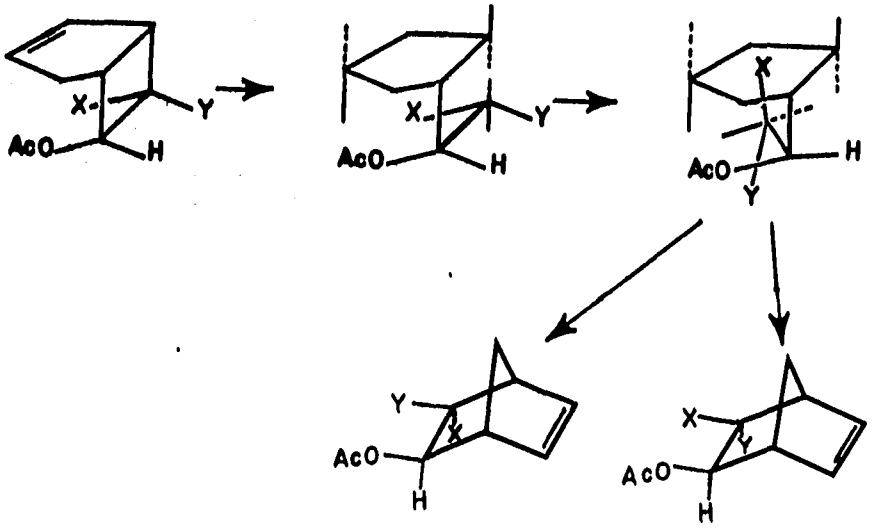
Berson has presented a [1,3] sigmatropic reaction of the first type which he advances as a rigorous test of the validity of the concept of conservation of orbital symmetry.[30]

---

28. J. P. Chesick, *J. Am. Chem. Soc.*, 85, 2720 (1963).
29. R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, 87, 2511 (1965).
30. J. A. Berson, *Accounts Chem. Res.*, 1, 152 (1968).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

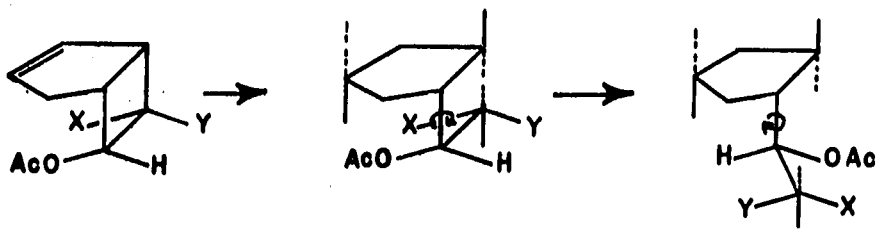
When Y=D and X=H the predicted stereochemical outcome constitutes 95% of the product. When either X or Y is methyl (*endo* and *exo* respectively) the stereoselectivity is considerably lower. Whenever a reaction can in principle be under the control of orbital symmetry but is not completely



stereospecific, two alternative explanations may be advanced. The reaction may be proceeding without continuous bonding overlap of orbitals and therefore may not be controlled by orbital symmetry; or the reaction may be proceeding by two or more paths, one of which may be under con-

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

trol of orbital symmetry and all of which lie very close in energy. In Berson's example there is insufficient evidence to permit a choice between the two possibilities. A plausible non-concerted pathway does exist however. Instead of rotating under the five membered ring the migrating group



may rotate in the opposite direction bringing it away from the five membered ring. Experimental evidence does not exclude this possibility.

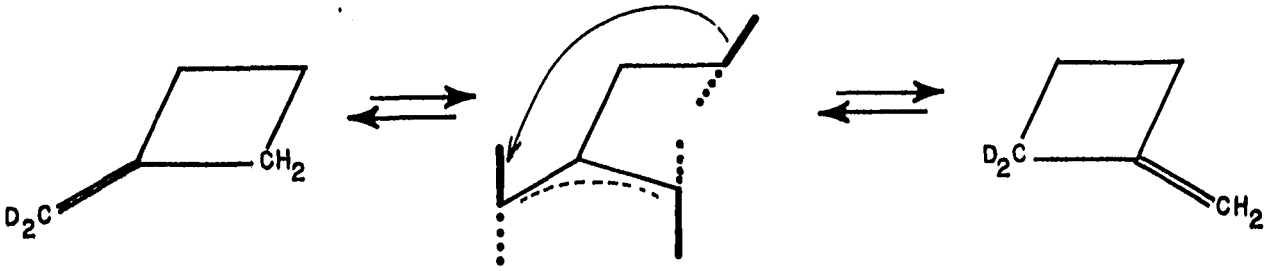
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

CHAPTER II:
RESULTS AND DISCUSSION:
THE METHYLENECYCLOBUTANE REARRANGEMENT

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

The Degenerate Methylenecyclobutane Rearrangement

The thermal reorganization of methylenecyclobutane to itself, the subject of this dissertation, was first suggested by Chesick[31] and had been conceived to involve a diradical species. He had been studying the decomposition of methylenecyclobutane to ethylene and allene and had had no opportunity to observe the hypothetical rearrangement. The reaction became observable when Doering and Gilbert,[32] following a suggestion of Chesick, prepared 1-(dideuteriomethylene)cyclobutane and found that heating caused deuterium to be incorporated into the allylic position and protium into the methylene position.



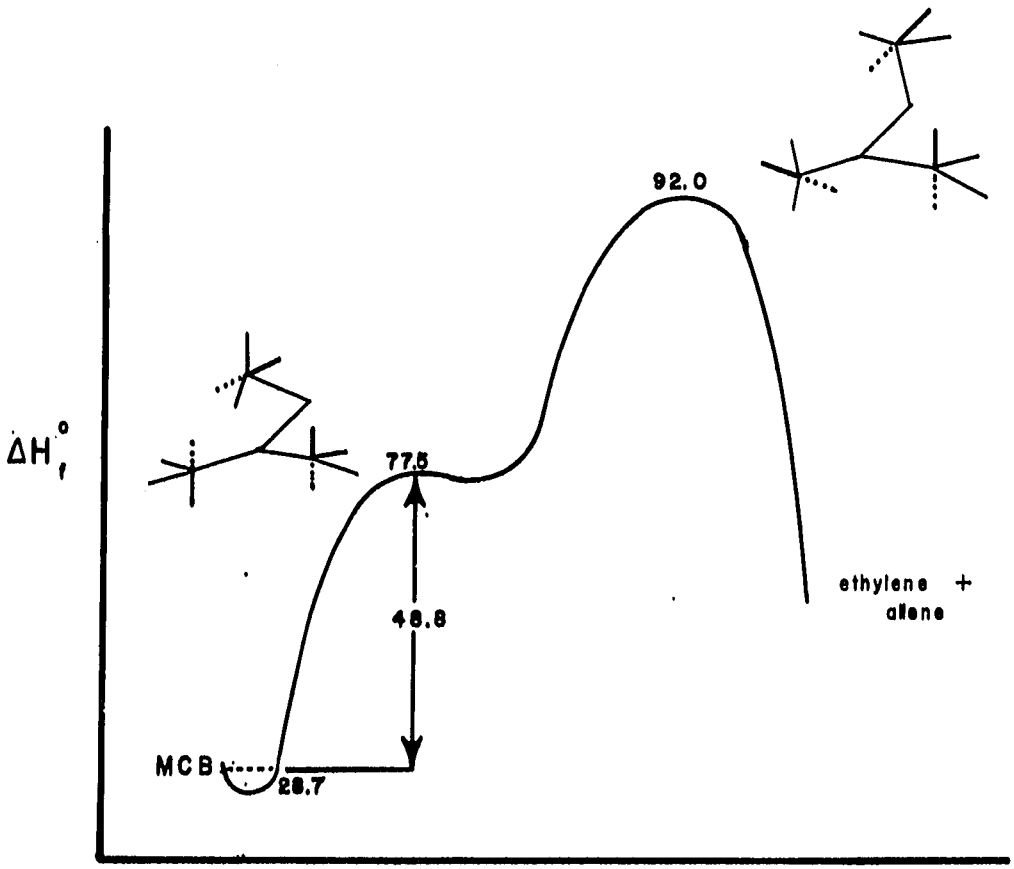
A study of the kinetics of the reaction revealed an enthalpy of activation, $\Delta H^{\ddagger}$ = +48.8±1 kcal/mole and an entropy of activation, $\Delta S^{\ddagger}$ = +5.3 e.u.

---

31. J. P. Chesick, *J. Phys. Chem.*, 65, 2170 (1961).
32. W. von E. Doering and J. C. Gilbert, *Tetrahedron*, Supplement No. 7, 397 (1967).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

The ΔH_f° of the rate-determining transition state is obtained by adding $\Delta H^\ddagger$ to ΔH_f° of starting material. Note



that the ΔH_f for the transition state in the conversion of methylenecyclobutane to ethylene and allene is 92.2 kcal/mole, 14 kcal/mole higher than ΔH_f° for the degenerate rearrangement. The value of 14 kcal/mole[33] is close to the

---

33. W. von E. Doering and G. H. Beasley in unpublished results find a value of 14.3 kcal/mole for allyl resonance energy.

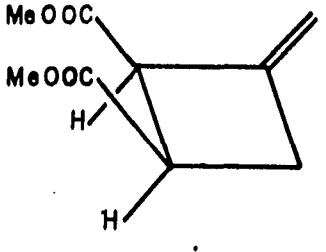
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

resonance energy of the allyl radical. It is assumed that a perpendicular, localized arrangement of the allyl portion is required for decomposition to ethylene and allene. This suggests that there is nearly full allylic delocalization in the transition state of the degenerate rearrangement. $\Delta S^{\ddagger}$ of +5.3 e.u. is suggestive of a transition state with a greater degree of disorder than that in the starting material. A diradical transition state would not be incompatible.

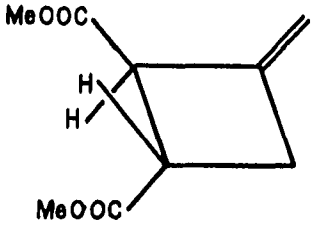
While degenerate thermal reorganizations possess a certain elegance and simplicity, they also verge on the unreal. In order to convert the degenerate methylenecyclobutane rearrangement discovered by Doering and Gilbert to a "real" reaction and possibly uncover more of the details of its mechanism, suitably substituted methylenecyclobutanes were investigated.

Preparation of Methylenecyclobutane Diesters: cis-I and trans-I

The molecules chosen for study were the dimethyl- *cis*- and *trans*-3 methylenecyclobutane-1,2-dicarboxylates. Both



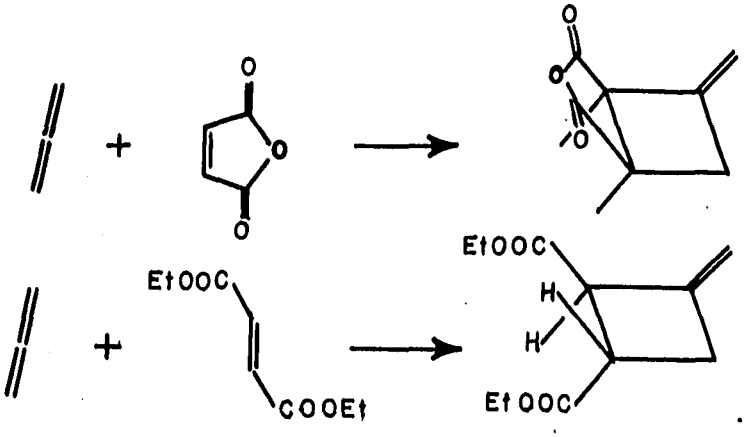
cis-I



trans-I

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

isomers had been prepared previously[34] by the reaction of allene with maleic anhydride (or diethylmaleate) and diethyl fumarate. The methods were used on a preparative scale for both isomers.



Dimethyl esters of both isomers were prepared by reaction of the corresponding diacids with diazomethane.

Thermolysis of the Methylenecyclobutane Diesters

In order to uncover the methylenecyclobutane rearrangement, dimethyl *cis*-3-methylenecyclobutane-1,2-dicarboxylate was heated in the gas-phase in the range of 225-250°. Of the two products formed, the minor one was easily identified as dimethyl *trans*-3-methylenecyclobutane-1,2-dicarboxylate. The major product, III, was unknown and more difficult to identify. The NMR spectrum showed a pseudo singlet of area

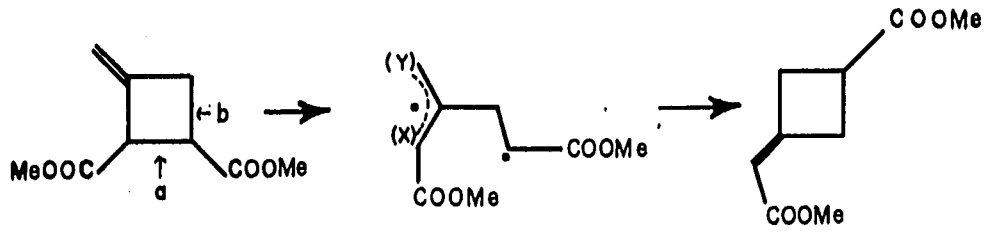
---

34. H. N. Cripps, J. K. Williams and W. H. Sharkey, *J. Am. Chem. Soc.*, 81, 2723 (1959).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

1 centered at 4.41τ, two sharp singlets at 6.35τ and 6.38τ of area 3 each, and a broad spread from 6.62τ to 7.02τ of area 5. Rearrangement has decreased the number of vinyl protons from the two in *cis*-I to one in III. In III two ester methyl resonances are no longer a singlet, but have different chemical shifts and are therefore non-equivalent. On the assumption that the mechanism proposed for the degenerate rearrangement is operating, a structure of III can be constructed. The presence of one double bond in III is confirmed by catalytic hydrogenation in which one mole of hydrogen is absorbed. When optically active III, the preparation of which is described later, is subjected to catalytic hydrogenation the product has no optical rotation. Both the chirality of III and the achirality of its dihydro derivative are consistent with the proposed structure. No other consistent structures for III come to mind.

The Chesick mechanism accounts for the gross features of the transformation of *cis*-I into III. Bond a will break more easily than the others on heating because both parts of



I III

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

the resulting diradical can be stabilized by carbomethoxy groups. If bond b were broken only an ordinary allyl radical and an α-carbomethoxy radical would result. After the hypothetical diradical has been formed, it may reclose to form *cis*-I; reorganize and close to form *trans*-I or reorganize and reclose at the opposite end of the allyl radical (point Y) to form "rearranged product" III.[35] Pyrolysis of dimethyl *trans*-3-methylenecyclobutane-1,2-dicarboxylate in the gas-phase from 235-255° afforded two products, the *cis* isomer in very small amount and again III as the major product. The realization of these non-degenerate examples of the methylenecyclobutane rearrangement opens the door to a more detailed investigation of the nature of the intermediates.

Mechanistic Questions

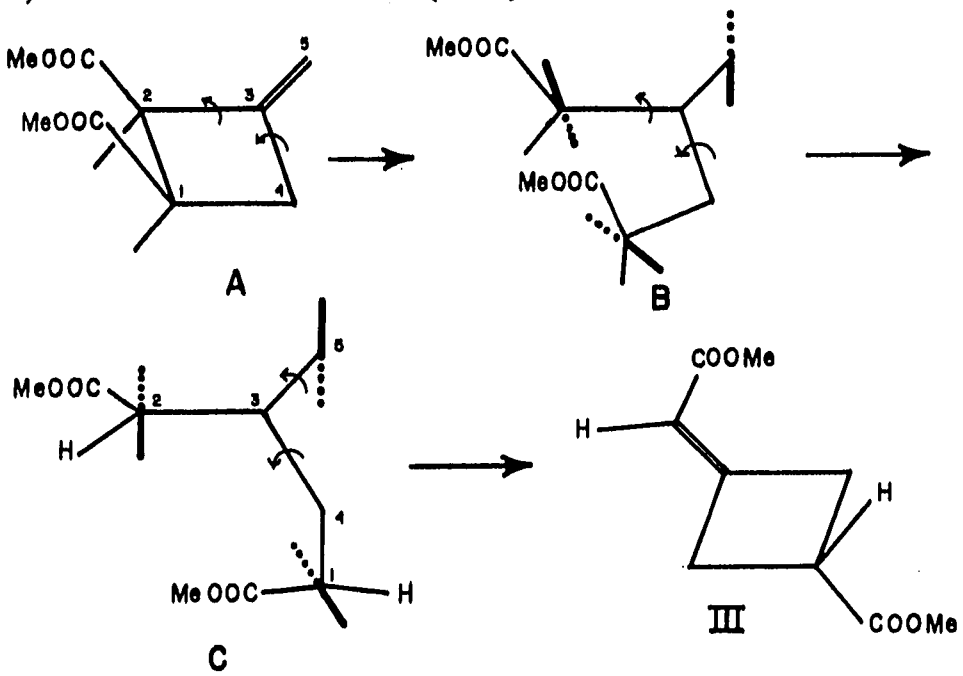
Is the reaction concerted and characterized by continuous overlap or is it mediated by a diradical characterized by lack of continuous overlap of orbitals? As previously outlined, were the intermediate species a diradical it would be expected to show free rotation. Two bonds are likely candidates for free rotation in the hypothetical intermediate.

---

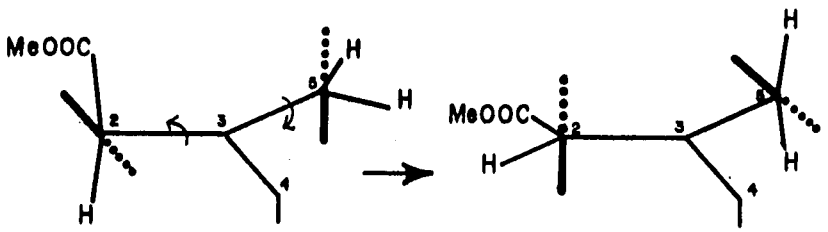
35. It is certain that what Sharkey reports to be recovered starting material from the pyrolysis of dimethyl *cis*-3-methylenecyclobutane-1,2-dicarboxylate at 600° is mostly this "rearranged product", III. [J. J. Drysdale, H. B. Stevenson and W. H. Sharkey, *J. Am. Chem. Soc.*, 81, 4908 (1959)].

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

One is the 3,4 bond. A rotation of 180° around this bond is obligatory. It serves to carry the secondary radical from one end of the allyl radical to the other (A →B →C →III). It makes no difference whether the 3,4 bond rotates 180° + n(360°) instead of 180°.

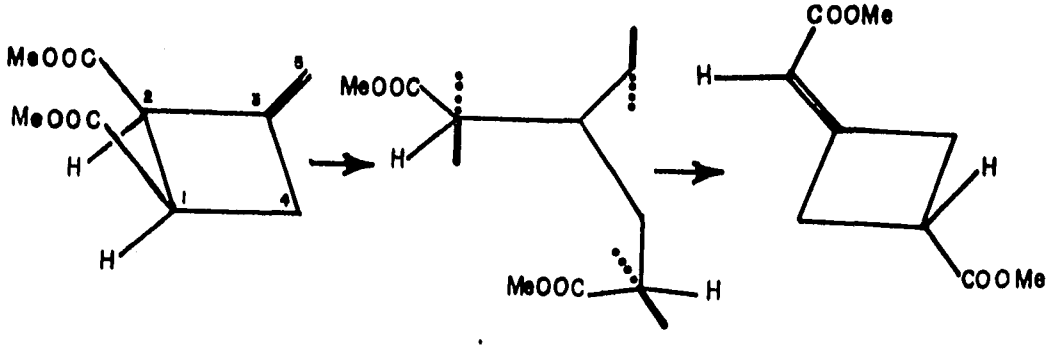


A rotation around the 2,3 bond of 90° is also obligatory if the proper allignment of the π orbital of carbon atom 2 for formation of the double bond in product III is to be achieved. Likewise a



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

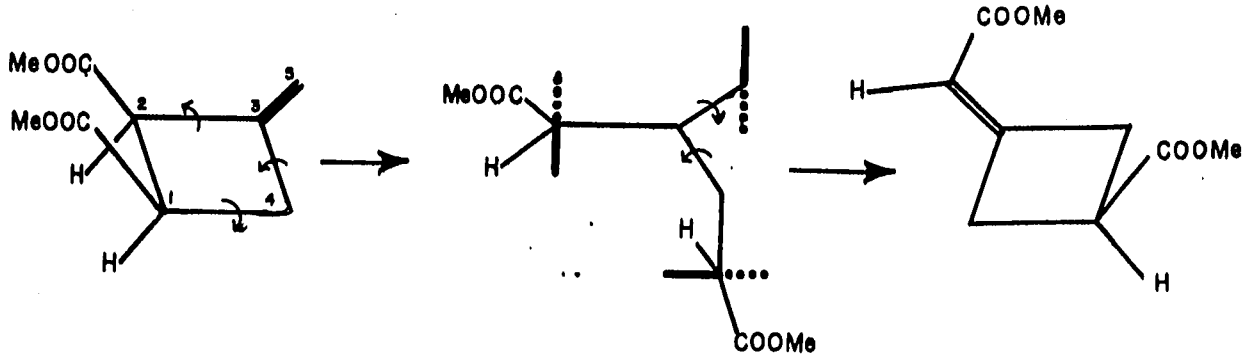
rotation of 90° is necessary to bring carbon atom 5 to a proper orientation for formation of the cyclobutane ring in III. These two rotations would not be free rotations since the allyl radical to which they lead is known to exhibit conformational stability.[36] In the earlier analysis of the energetics of the rearrangement of unsubstituted methylenecyclobutane, it was concluded that the intermediate probably contained a fully developed allyl radical. Therefore once the 2,3 bond reaches the 90° point, an allylic radical has been formed and should maintain its conformational integrity until the 3,5 bond begins its 90° rotation. The second candidate for free rotation is the 1,4 bond. Unlike the rotation of the 3,4 bond, rotation about the 1,4 bond is not required for completion of the reaction. Illustrated below in one enantiomer of *cis*-I, rotation of the 1,4 bond by 180° leads to a product in which the migrating



36. C. Walling and W. Thaler, *J. Am. Chem. Soc.*, 83, 3877 (1961).
J. K. Kochi and P. J. Krusick, *J. Am. Chem. Soc.*, 90, 7157 (1968).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

ester group is in the "down" orientation. No rotation or a 0° rotation of the 1,4 bond places the migrating ester in the "up" orientation. Although these rotations are drawn

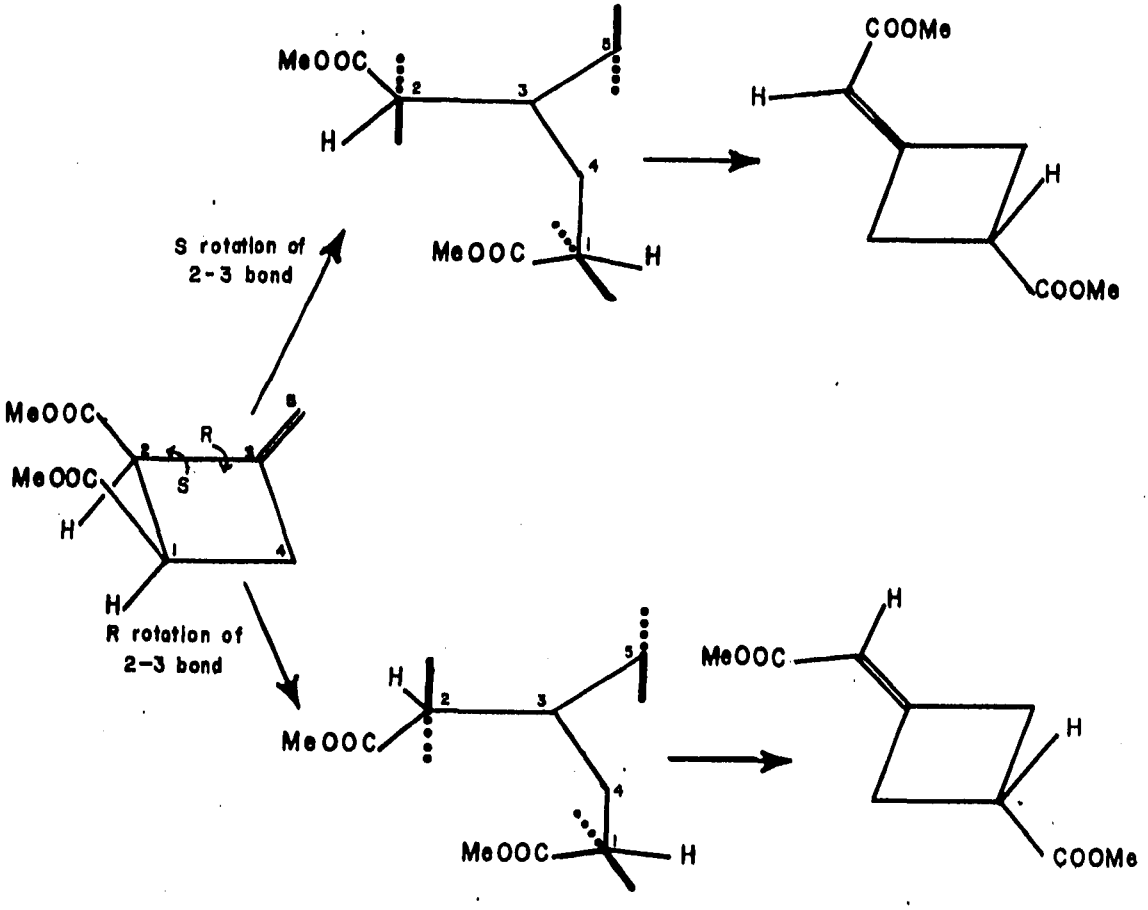


as 0° and 180°, there is no way in this molecular system of distinguishing a rotation of 0° from a rotation of 0° + n(360°) or between rotations of 180° and 180° + n(360°). If completely free rotation of the 1,4 bond prevailed, equal amounts of III resulting from 0° + n(360°) and 180° + n(360°) rotations would be formed.

The greater potential for revealing rotational freedom or its lack clearly lies in the 1,4 bond. In principle, if optically active *cis*-I afforded III containing no optical activity it might be concluded that free rotation of the 1,4 bond had occurred. If III exhibiting optical activity were produced, it would be concluded that free rotation had not occurred about the 1,4 bond during the rearrangement. The drawing of conclusions is seriously complicated by the possibility that the 2,3 bond may rotate 90° in either of

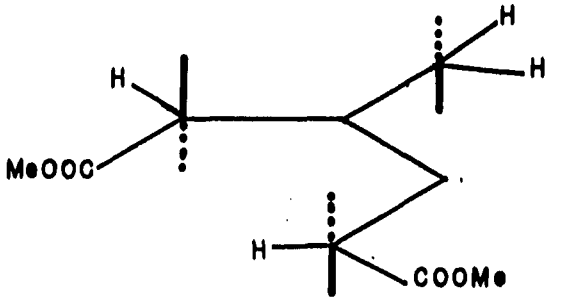
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

two directions. If rotation in each of these directions occurred equally, it would destroy any opportunity of detecting information about the 1,4 bond rotation. For example, if the reaction proceeded with only 0° rotation of the 1,4 bond, rotation of the 2,3 bond equally in both of the directions open to it would lead to racemic III and completely obscure the 100% specificity in the rotational behavior of the 1,4 bond. Equal proportion of $0^{\circ} + n(360^{\circ})$ and $180^{\circ} + n(360^{\circ})$ rotations of the 1,4 bond or an equal

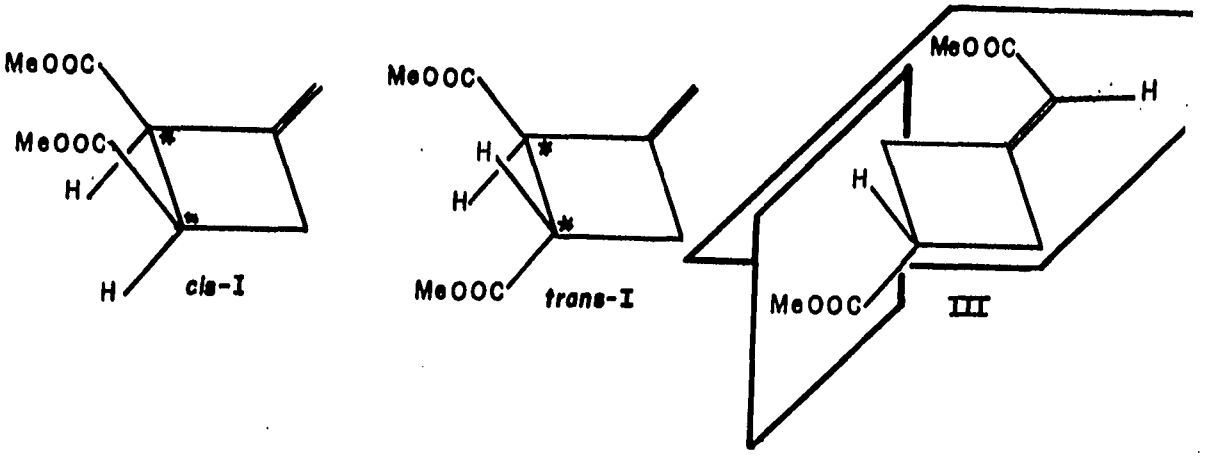


Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

proportion of the two modes of rotation of the 2,3 bond would be the equivalent of proceeding through an achiral intermediate and would lead to a totally racemic product.



Cis-I, *trans*-I and III are chiral molecules. In the first two carbon atoms 1 and 2 are asymmetric, whereas in III the molecular asymmetry is of the allenic or spirane type. Transfer of the tetrahedral asymmetry of *cis*-I and *trans*-I to the allenic asymmetry of III can only occur if



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

rotation about the 2,3 bond were not random and rotation about the 1,4 bond were not unrestricted and free.

Thermolysis of Optically Active Methylenecyclobutane Diesters

Thermal rearrangement of optically active *cis*-I and *trans*-I dimethyl esters generated III with considerable residual optical activity. To make certain that the optical activity did not originate in an optically active impurity, III (from the rearrangement of *cis*-I) was repassed through three different types of gas chromatographic columns. After each attempted purification, recovered diester exhibited an unchanged specific rotation. As noted previously, hydrogenation of optically active III afforded (of necessity) an optically inactive molecule. When III from the rearrangement of optically active *cis*-I was hydrogenated, the resulting product showed no optical rotation. This is taken as further evidence that the optical activity in the rearrangement product is associated with III and not with an impurity. It can, therefore, be safely concluded that III obtained from optically active *cis*-I consisted of unequal amounts of its two enantiomers and that free rotation had been restricted in the intermediate.

The qualitative observation of the retention of some optical activity in III produced from either *cis* or *trans*

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

optically active methylenecyclobutane dicarboxylates (*cis*-I and *trans*-I) required quantitative refinement. To determine quantitatively the transfer of optical activity from starting material to product necessitated establishment of the specific rotation of optically pure starting materials and product.

Resolution and Establishment of Optical Purity of Cis-I, Trans-I and III

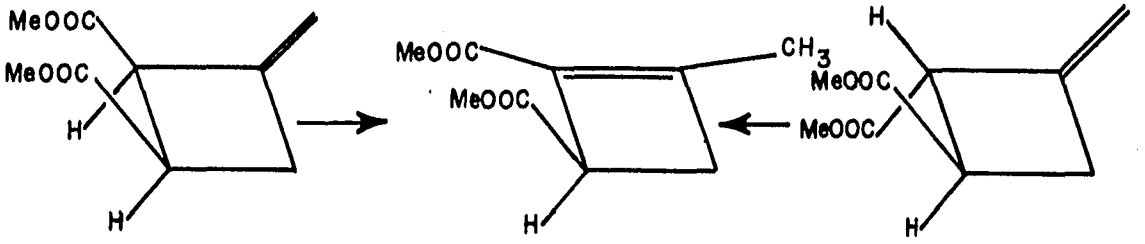
Several criteria are helpful in the establishment of optical purity. They vary in reliability and ease of application.[37] Perhaps the most reliable, but also the most difficult of execution, is dilution by radioactive isotopes.[38] Crystallization of an alkaloid salt to constant rotation is a comparatively unreliable criterion as the rotation of the salt is frequently insensitive to small changes in the optical purity of the acid. Likewise, melting point changes in salts are generally poor indicators of optical purity. That a number of substances have later been found to have larger rotations than was first reported testifies to the difficulty of achieving and establishing optical purity. *Cis*-I and III were resolved by crystallization of both enantiomers of each free diacid to constant rotation and melting point. As a

---

37. M. Raban and K. Mislow, *Advances in Stereochemistry*, 2, 199 (1968).
38. J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, 81, 4083 (1959).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

further criterion of optical purity, resolved *trans*-I and *cis*-I were both converted to II of the same specific rotation. The resolution of *trans*-I and *cis*-I had at least



reached the same level of resolution. Not improbably that level was near completion in both isomers.

Cis-3-methylenecyclobutane-1,2-dicarboxylic acid was partially resolved through the acidic quinidine salt. The first crop of crystalline salt was collected and diacid of substantial rotation was regenerated from it. On recrystallization from benzene this partially resolved acid afforded racemic material as a first crop, but, after concentration of the benzene mother liquor, yielded diacid of enhanced rotation. Three recrystallizations from benzene finally resulted in diacid which upon two further recrystallizations no longer increased in rotation or changed in melting point. Similar treatment of the mother liquor from the crystallization of the quinidine salt produced the enantiomeric diacid which had the same melting point and specific rotation at that

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

point in the fractional crystallization where two further recrystallizations produced no further improvement. It was concluded that optically pure material had been obtained.

Diacid III was resolved by repeated recrystallization of the crystalline neutral quinine salt until constant rotation was achieved. Diacid recovered from this salt melted over a narrow range and after one crystallization from dibutyl ether had a melting point and specific rotation which remained unchanged on two further recrystallizations. Diacid recovered from the mother liquor from the crystallization of the neutral quinine salt was repeatedly recrystallized from dibutyl ether and finally produced material of constant melting point and specific rotation. These values were identical to those of the enantiomeric diacid and again are believed to represent optically pure material.

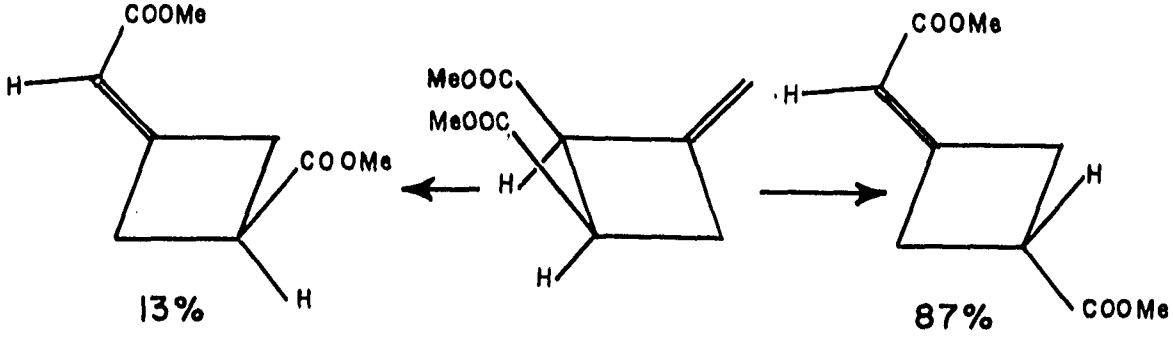
Finally, *trans*-3-methylenecyclobutane-1,2-dicarboxylic acid was resolved by crystallization of the acidic quinine salt. Diacid which was reclaimed from the crystalline salt was partially resolved. It was recrystallized from toluene repeatedly until mateiral of constant melting point was obtained.

Further support for the optical purity of the *cis* and *trans* diacids was obtained by treatment of their dimethyl esters with sodium methoxide in methanol which converted

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

them to dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate of identical specific rotation. Since they had been resolved by independent methods this identical degree of optical purity quite probably corresponds to true optical purity.

With the specific rotation of optically pure materials known it was possible to determine the efficiency of transfer of asymmetry from *cis* to *trans* I to III. Thermal rearrangements of dimethyl *cis*-3-methylenecyclobutane-1,2-dicarboxylate (*cis*-I) in both the gas and liquid phase were carried to low conversion[39] and produced III containing 75% of the possible optical activity. Thus the reaction produces 87.5% of one enantiomer and 12.5% of the other.



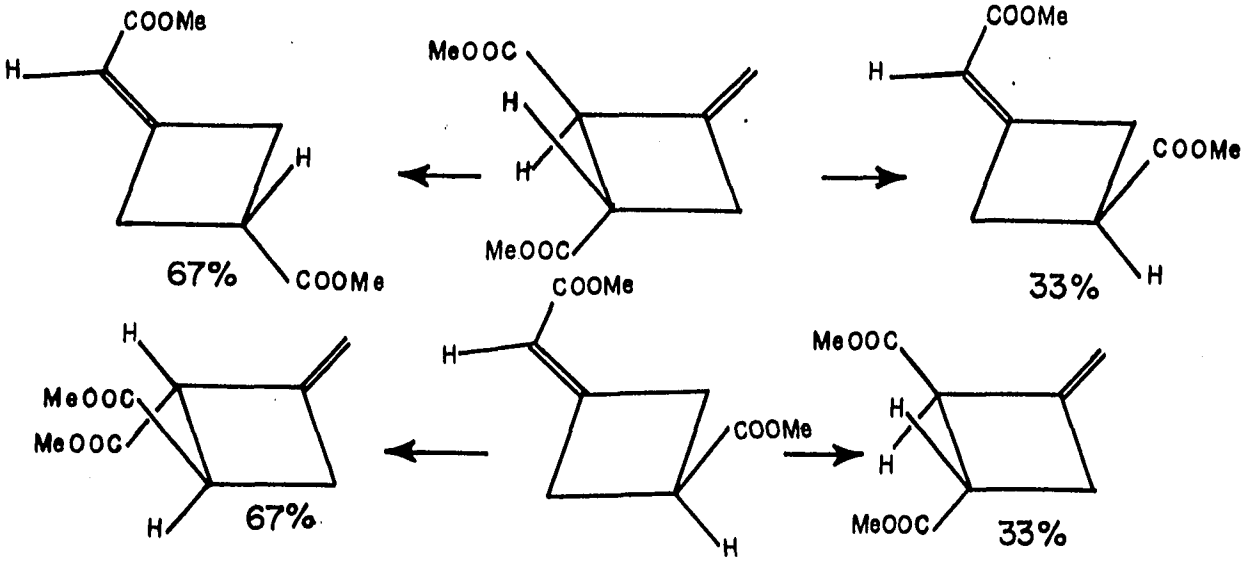
Thermal rearrangement of optically active dimethyl *trans*-3-methylenecyclobutane-1,2-dicarboxylate (*trans*-I) produced III which contained 33% of the possible optical activity and thus consisted of 67% of one enantiomer and 33% of the other.

---

39. If the reaction is carried beyond 10-12% conversion, III begins to suffer extensive racemization.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

The reaction proved to be reversible to a small extent. Thermal rearrangement of optically active III produced very small amounts of *trans*-I (∿2%) which showed 33% of the possible optical activity.



The major enantiomer in the *trans*-I had the opposite sign of rotation to that of the starting material, III, even as the major enantiomer in the III produced in the rearrangement of *trans*-I had the opposite sign of rotation to that of the starting material. Thus, the reaction proved to be microscopically reversible in all observable respects, including enantiomer relationship and enantiomer ratio.

Variation of Rearrangement Conditions

The effect of solvents and variation in pressure often

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

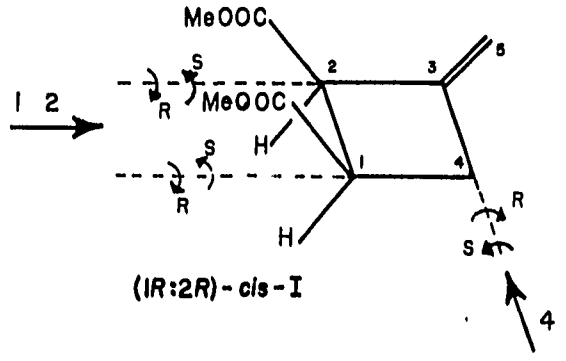
reveal information about the mechanism of a thermal rearrangement. The rearrangements described above had all been carried out in the "high pressure" range of the gas phase. "High pressure" with molecules of this size is estimated to be between 100 and 500 mm. Consistently rearrangements of optically active *cis*-I and *trans*-I carried out in benzene show no differences in product composition or enantiomer ratios. A pressure of 1 mm. has been regarded as the upper limit of the "low pressure" region in which differences may occur owing to the increased lifetime of the molecule in its excited state associated with the decrease in frequency of collisional deactivation. Rearrangements of optically active *cis*-I were carried out with minimum amounts of material in a 12-liter flask in an air thermostat at reaction pressures which were estimated to be near to 1 mm. However, the III was produced with only 45% retention of optical activity compared to 75% retention of optical activity in the "high pressure" and solution reactions. Since the thermally activated state has a longer life at "low pressure", whatever rotation or rotations are occurring may simply be more extensive at "low pressure" and thus a larger amount of minor enantiomer is produced.

Combinations of Rotations

It is recalled that none of the reactions described

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

above proceeds in a totally stereospecific manner. Each gives products which must be the result of rotational mechanistic differences. As noted earlier, operationally significant breaking of bonds in small rings is not accomplished without rotation of one or both of the carbon atoms involved in the bond being broken. In (1*R*:2*R*)-dimethyl *cis*-3-methylenecyclobutane-1,2-dicarboxylate [(1*R*:2*R*)-*cis*-I], rotation of carbon atom 2 may occur in either an *R* or an *S* manner, viewed from



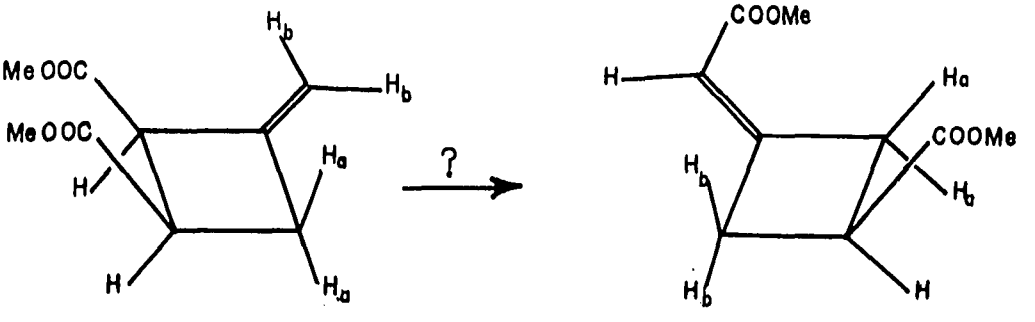
the position of the arrow 1,2 in the diagram. The consequence of an *R* rotation is to place the ester group *anti* to the *exo* carbon (C_5) of the incipient allyl radical, while that of an *S* rotation will place the ester group in a position *syn* to the *exo* carbon atom. Carbon atom 1 may rotate in either an *R* or *S* manner, either 180° [or 180° + n(360°)] or 0° [0° + n(360°)]. The molecule also has the choice of rotating around the 3,4 bond in either an *R* or an *S* manner, as viewed from arrow 4 in the diagram. A complete description of the

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

mechanism of the rearrangement must include details of direction and extent of each of these rotations. If enough internal reference points can be incorporated into the molecule and if methods for their fruitful utilization can be devised, this description may be achieved.

Dimethyl cis-3-(dideuteriomethylene)cyclobutane-1,2-dicarboxylate: cis-I-d_2

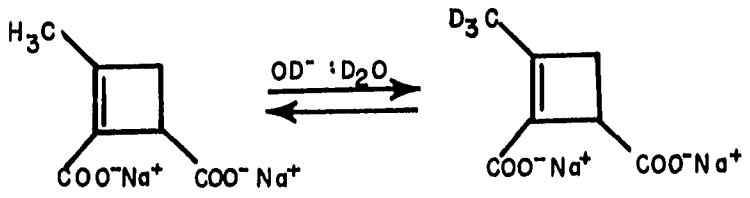
From the structural nature of the rearrangement of I, it is clear that the two methylene groups in III have a different chemical history. One had been the ring methylene group while the other had been the *exo*-methylene group in I. If replacement of hydrogen with deuterium specifically in one of these two positions could be arranged, it would be possible to identify which methylene group of III had originally been the ring methylene and which had been the *exo*-methylene of I.

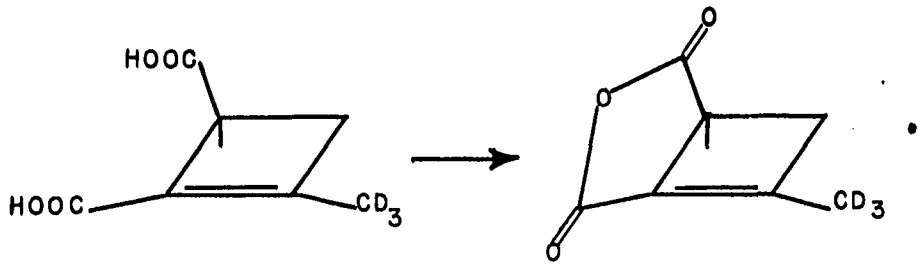


It was possible to introduce deuterium into the exocyclic

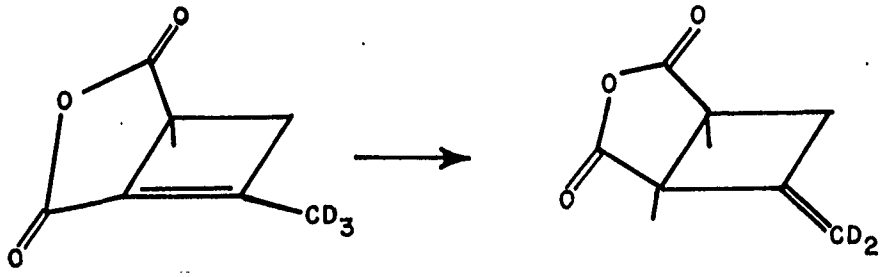
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

position by a sequence which began with the introduction of deuterium into the methyl group of disodium 1-methylcyclobutene-2,3-dicarboxylate by base catalyzed exchange in D_2O. In the second step, advantage is taken of the geometry of 1-methylcyclobutene-2,3-dicarboxylic acid which prevents the formation of an anhydride without the introduction of severe strain.





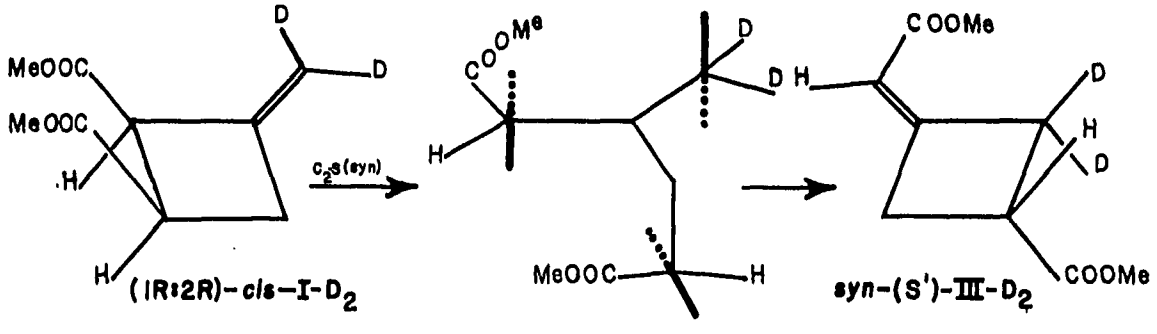
However, relief of this prohibitive strain can be accomplished by the double bond migration through a simple prototropic shift to the now exocyclic β,γ position. The resulting 3-methylenecyclobutane-1,2-dicarboxylic acid anhydride is the anhydride corresponding to *cis*-I.



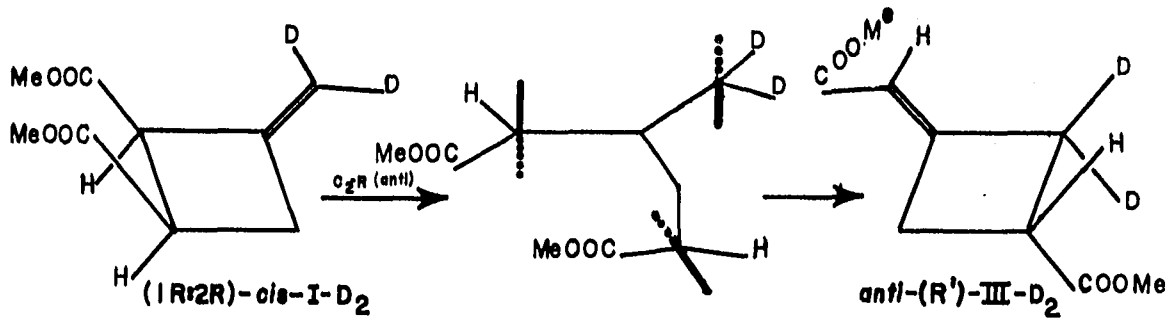
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

When trideuteriomethylcyclobutene dicarboxylic acid is treated with a mixture of acetic anhydride and pyridine the desired anhydride is formed as the major product. Hydrolysis of the mixture and crystallization of the product afforded 3-(dideuteriomethylene)cyclobutane-1,2-dicarboxylic acid. The overall yield of the process is low.

A complete analysis of the consequences of all the possible combinations of rotations of groups and atoms reveals the value of employing optically active dimethyl *cis*-3-(dideuteriomethylene)cyclobutane-1,2-dicarboxylate (*cis*-I-d_2) in the rearrangement. Thermal rearrangement of (1*R*:2*R*)-*cis*-I-d_2 in which an *R* rotation occurs at C_2 leads to a pair of products in which the CD_2 is *anti* to the carbomethoxy group on the *exo* double bond in III. An *S* rotation of C_2 in the same enantiomer leads to a pair of products with CD_2 *syn* to this ester group. The rotations at C_2 are therefore referred to as *syn* or *anti* depending on the relation of the α,β-unsaturated ester to CD_2 in the product.



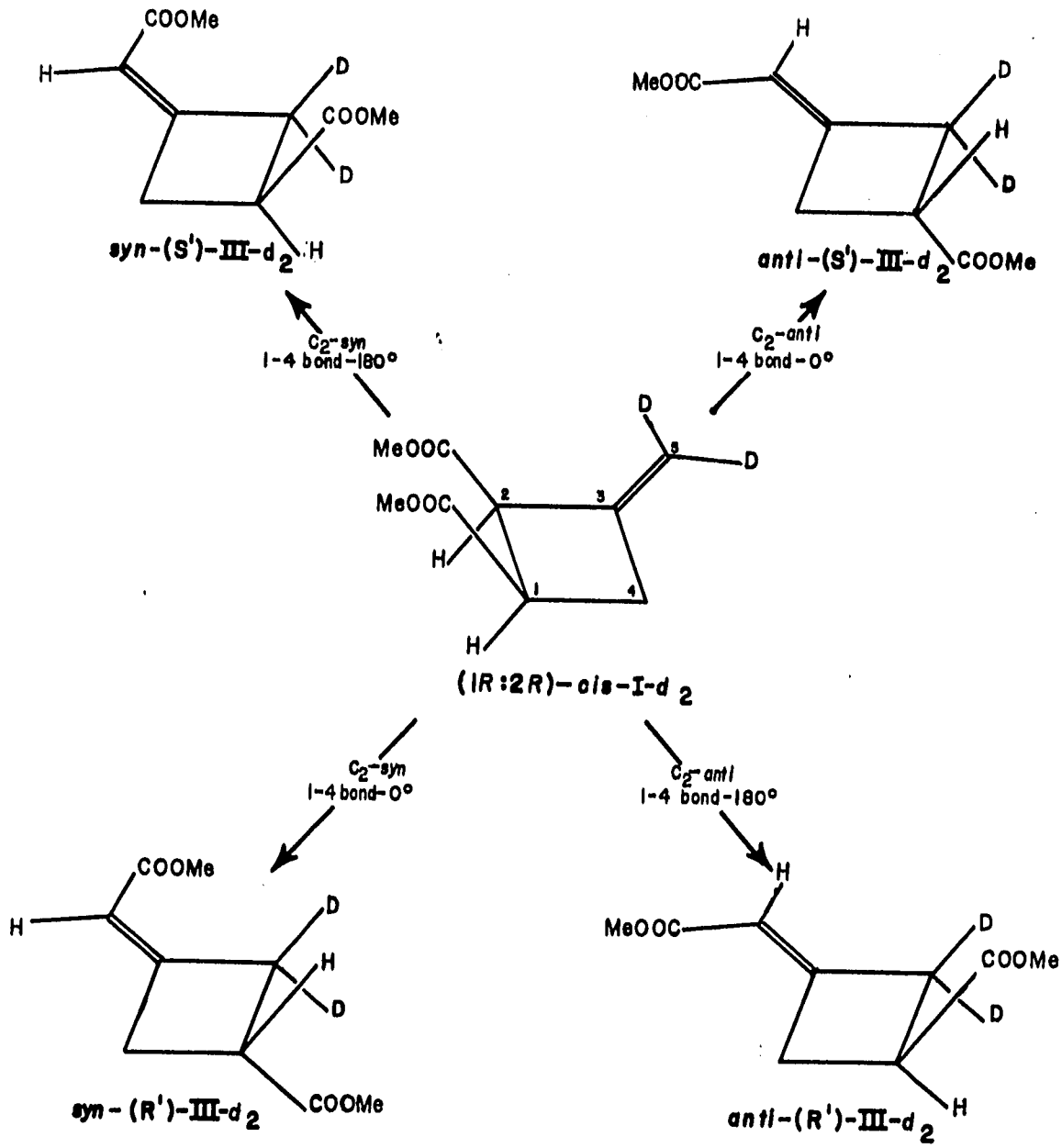
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



In the following chart the behavior of one of the enantiomers of dimethyl *cis*-3-(dideuteriomethylene)cyclobutane-1,2-dicarboxylate [(1*R*:2*R*)-*cis*-I-d_2] is shown. Four stereoisomers of III can be formed: *syn*-(*S'*)-III-d_2, *anti*-(*S'*)-III-d_2, *syn*-(*R'*)-III-d_2, and *anti*-(*R'*)-III-d_2. The stereochemistry at C_3 in III is determined by the magnitude of the C_1-C_4 rotation in I. Illustrated again with (1*R*:2*R*)-*cis*-I-d_2, a rotation of 180° or its equivalent leaves the carbomethoxy group at C_3 on the same side of the ring from which it started in (1*R*:2*R*)-*cis*-I-d_2. A 0° rotation of C_1-C_4 would place the carbomethoxy group on the opposite side. A summary of the four combinations of these two pairs of rotations is given in the diagram on page 51.

If the absolute amount of each of these four products can be determined, the relative importance of each combination of rotational processes would have been established. It is necessary to be able to distinguish *syn* from *anti* and to recognize the *R'* and *S'* configuration of III; *i.e.*,

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

to know the relative configuration of the enantiomers of *cis*-I and III. In principle the two *S'* stereoisomers of III (the two top structures in the diagram on page 51) may be physically separated from the two *R'* stereoisomers (the two bottom structures in the diagram) facilitating the determination of the absolute amount of each of these four stereoisomers produced from the reaction of (1*R*:2*R*)-*cis*-I-d_2. Completion of this determination will afford quantitative information on the rotation at C_2 and the C_1-C_4 bond. However, this molecular system clearly offers no way of distinguishing between *R* and *S* rotations of 180° about the C_1-C_4 bond. Neither does it offer the means to differentiate between an *R* or an *S* rotation of 180° about the C_3-C_4 bond.

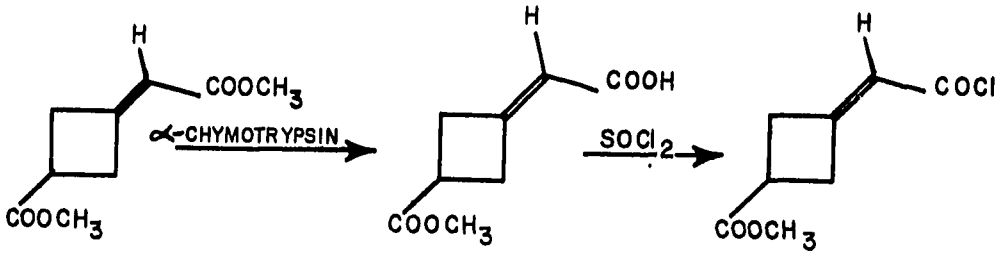
Absolute Configurations of Reactants and Product

The means of providing the two pieces of information necessary for resolution of the problem have not yet been discussed. These are the absolute configurations of *cis*-I and *trans*-I and III and the method of determining the amount of CD_2 *syn* or *anti* in a given enantiomer of III.

Absolute configurations can be established unequivocally by X-ray crystallography. To apply this method it is sufficient to prepare a derivative which possesses an asymmetric center of known absolute configuration to serve as reference.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

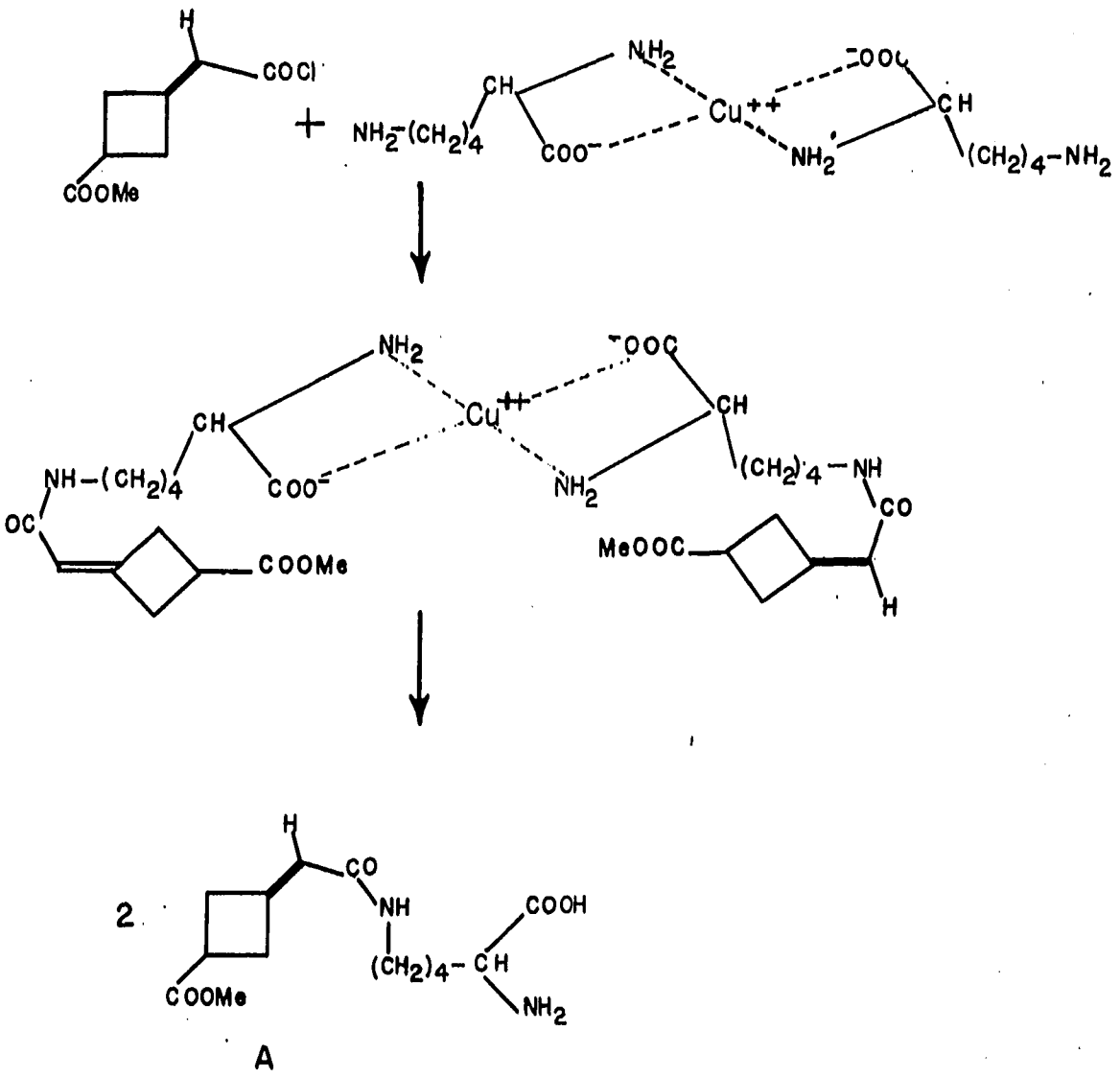
Conventional X-ray methods suffice to establish the relative configuration of atoms. In the present problem it would be most efficient if the absolute configuration of both I and III could be determined by crystallographic analysis on one crystalline substance. Such a derivative would have to consist of one molecule each of optically pure starting material, optically pure product and an asymmetric molecule of firmly established absolute configuration. If possible, it would facilitate the X-ray analysis if a heavy atom were included. A substance meeting these requirements was assembled in the following way. Optically pure (-)-III was hydrolyzed by α-chymotrypsin, an enzyme which hydrolyzes α,β-unsaturated esters substantially faster than saturated esters.[40] Examination of the NMR spectrum of the half ester obtained as product confirmed that only the α,β-unsaturated ester had been hydrolyzed. The half ester of (-)-III was reacted with thionyl chloride to produce the half acid chloride-half ester



40. S. G. Cohen, L. H. Klee, and S. Y. Weinstein, *J. Am. Chem. Soc.*, 88, 5302 (1966).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

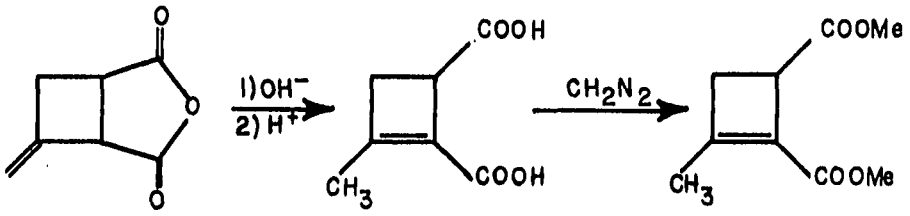
which was then treated with the copper salt of lysine. This product, A, now satisfies two of the four requirements: it contains a molecule of optically pure III and a molecule of established absolute configuration.[41]



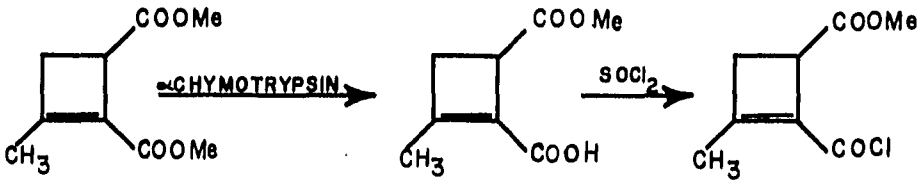
41. S. Raman, *Z. Krist.*, 111, 301 (1959).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

The starting material, *cis*-I, was incorporated in the form of its rearranged derivative, II. When optically pure 3-methylenecyclobutane-1,2-dicarboxylic anhydride is hydrolyzed with base the asymmetry of carbon 3 remains uncompromised



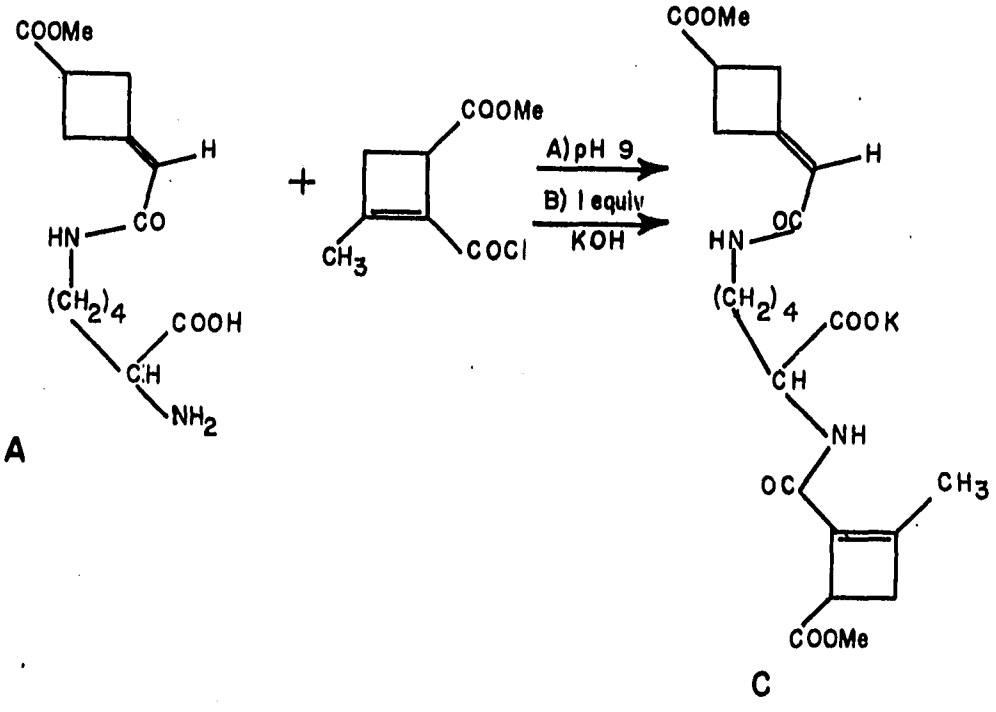
while the double bond migrates into the ring to give II. The corresponding optically pure dimethyl ester of this α,β-unsaturated acid was hydrolyzed, again by α-chymotrypsin, to provide a half ester of structure B. Reaction with thionyl chloride produced the half acid chloride-half ester which



B

was treated with the lysine derivative of (-)-III (A) in basic solution to provide (C). This molecule now contains a derivative of *cis*-I, III and natural L-lysine, a reference standard of known absolute configuration. Finally, reaction of this free acid with one equivalent of KOH introduced the necessary heavy atom.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

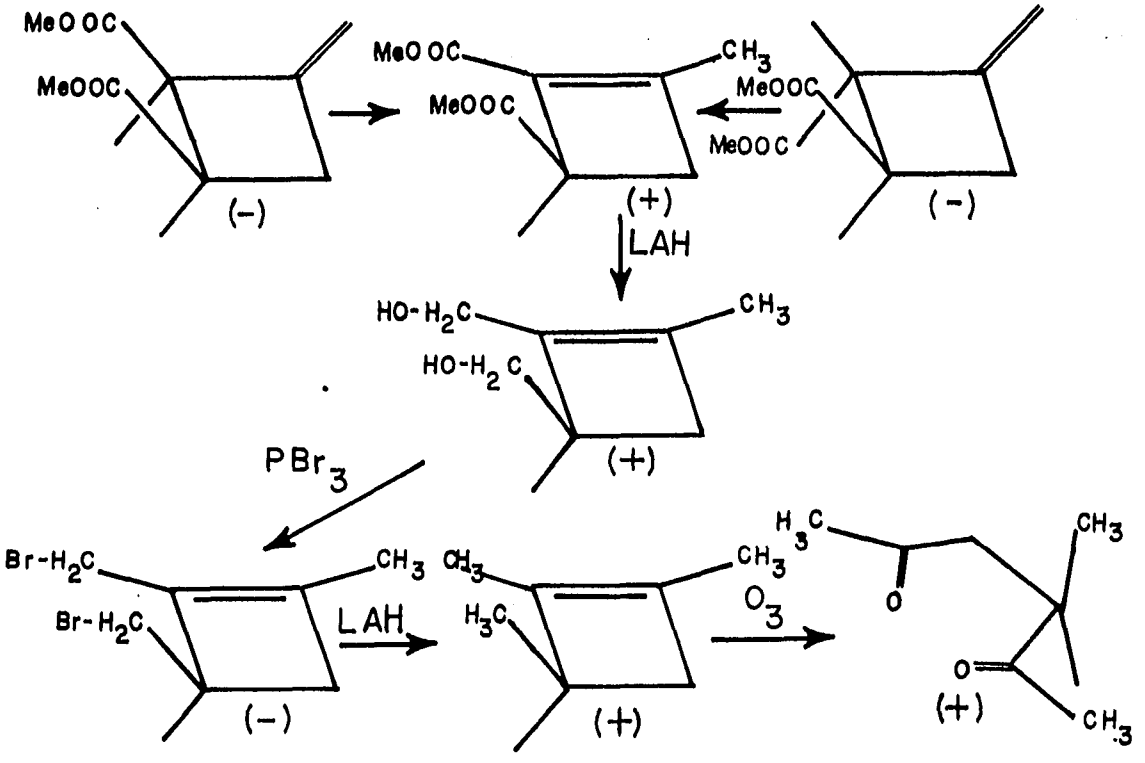


At the time of this writing the X-ray work has not been completed. Other less reliable evidence is available on which to base the absolute configurations and for the time being will have to serve.

In a thoroughly reliable chemical sequence, the configurations of *cis*-I and *trans*-I have been related to α-methyl succinic acid. The dimethyl esters [(-)-*cis*-I and (-)-*trans*-I] have been converted to (+)-dimethyl 2-methyl-2-cyclobutene-1,2-dicarboxylate [(+)-II] by treatment with sodium methoxide in methanol. Reduction of (+)-II with

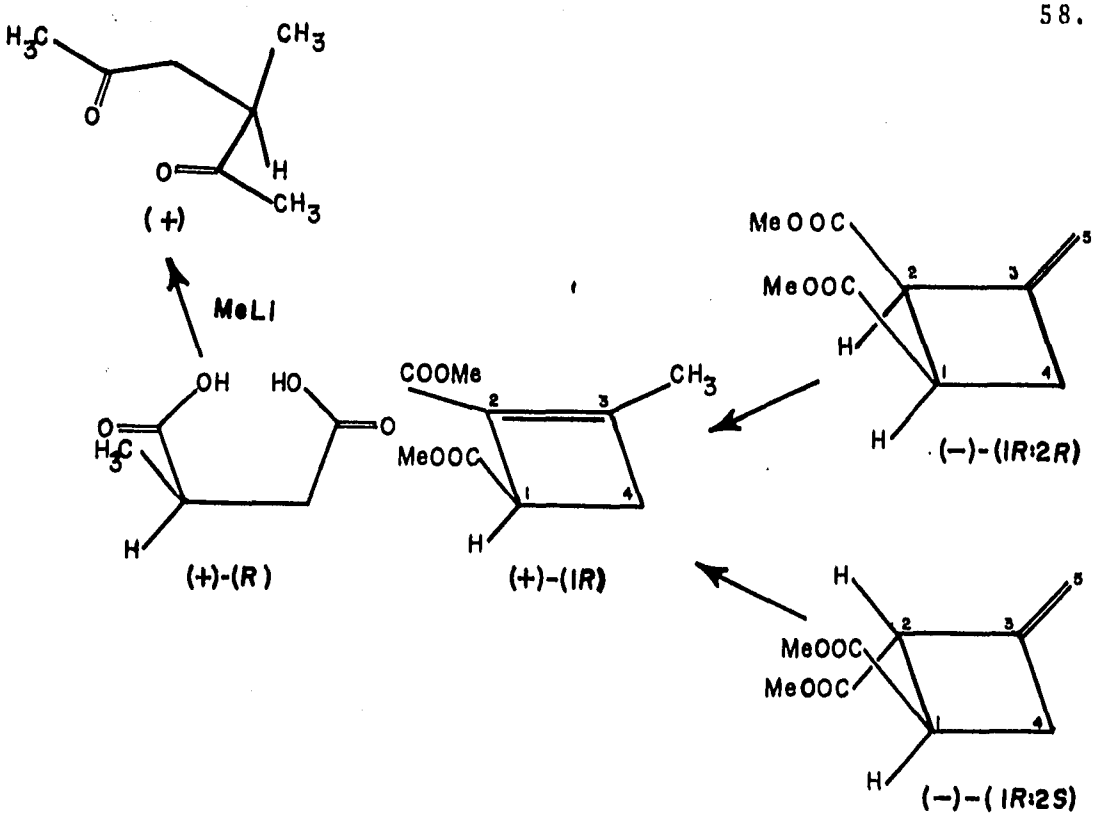
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

lithium aluminum hydride affords the corresponding (+)-diol which reacts with phosphorous tribromide to give a (-)-dibromide. Reduction of this (-)-dibromide with lithium



aluminum hydride affords (+)-1,2,3-trimethylcyclobutane, ozonolysis of which affords (+)-3-methylhexane-2,5-dione. This same material was also prepared from (+)-α-methyl succinic acid by treatment with four molar equivalents of methyl lithium and was found to be identical in v.p.c. retention time, IR spectrum and sign of rotation.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



Since (+)-α-methylsuccinic acid has been obtained by degradation of ergoflavin and the absolute configuration of ergoflavin has been determined by X-ray fluorescence,[42] (+)-α-methylsuccinic acid must be assigned to the *R* absolute configuration. It then follows that the configuration of (+)-dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate is *R* at carbon atom 1 and that the configuration of (-)-*cis*-I and (-)-*trans*-I also is *R* at carbon 1.

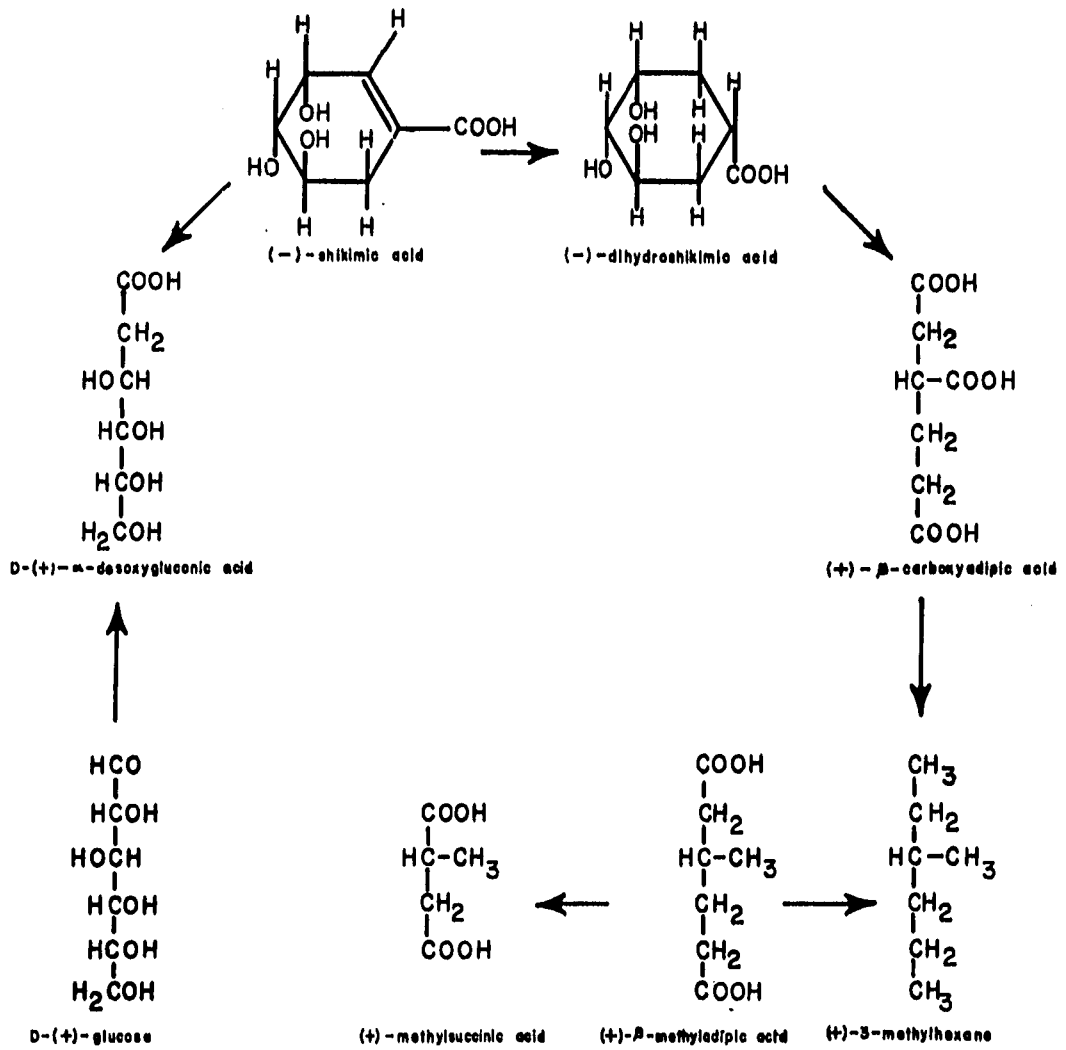
The absolute configuration of α-methylsuccinic acid has also been related to D-(+)-glucose. Both D-(+)-glucose[43]

---

42. A. T. McPhail, G. A. Simm, J. D. M. Asher, J. M. Robertson and J. V. Silverton, *J. Chem. Soc.* (B), 18 (1966).
43. M. Bergman, *Ber.*, 55, 158 (1922); *Ber.*, 56, 1052 (1922). P. A. Levene and G. Mikeska, *J. Biol. Chem.*, 88, 791 (1930).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

and D-(-)-shikimic acid[44] have been converted to D-(+)-2-desoxygluconic acid. D-(-)-shikimic acid has also been related to (+)-β-carboxyadipic acid by way of (-)-dihydroshikimic acid.[45] Both D-(+)-β-carboxyadipic acid[46] and D-(+)-



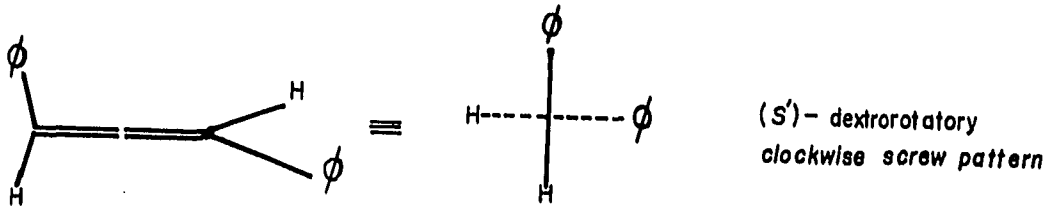
---

44. H.O.L. Fisher and G. Dangschat, *Helv. Chem. Acta*, 20, 705 (1937).
45. K. Freudenberg and J. Geiger, *Ann. Chem.*, 575, 145 (1952).
46. K. Freudenberg and W. Hohmann, *Ann. Chem.*, 584, 54 (1954).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

β-methyladipic acid[47] have been reduced to D-(+)-3-methylhexane. Finally, D-(+)-β-methyladipic acid has been converted to D-(+)-α-methylsuccinic acid.[48] This assignment of configuration to (+)-α-methylsuccinic acid is in agreement with the assignment based on ergoflavin.

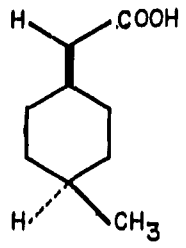
III owes its asymmetry not to an asymmetric carbon atom, but to the type of spirane or allene asymmetry. A simple method for assigning the absolute configuration of allenes has been devised by Lowe.[49] By viewing the allene along its axis a screw pattern or chirality of substituents can be defined in a clockwise or counterclockwise sense. Empiracally, clockwise chirality patterns correspond to a positive sign of rotation and counterclockwise chirality corresponds to a negative sign of rotation. This method leads to the same assignment of absolute configuration of every allene whose configuration has also been assigned by an independent method.

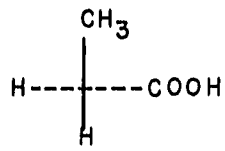


47. P. A. Levene and R. E. Marker, *J. Biol. Chem.*, 91, 77, 405, 761 (1931); 95, 53 (1932).
48. J. von Braun and F. Jostes, *Ber.*, 59, 1091, 1444 (1926).
49. G. Lowe, *Chem. Comm.*, 411 (1965).

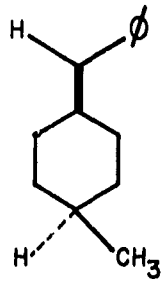
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

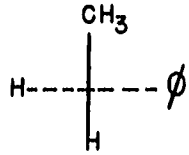
This method has been successfully extended to two alkylidene cycloalkanes, 4-methylbenzylidenecyclohexane and 4-methylcyclohexylidene acetic acid.[50] It was found that the configuration of the enantiomer associated with positive rotations had a clockwise screw pattern of substituents along its orthogonal axis.





(S)-dextrorotatory
clockwise screw pattern





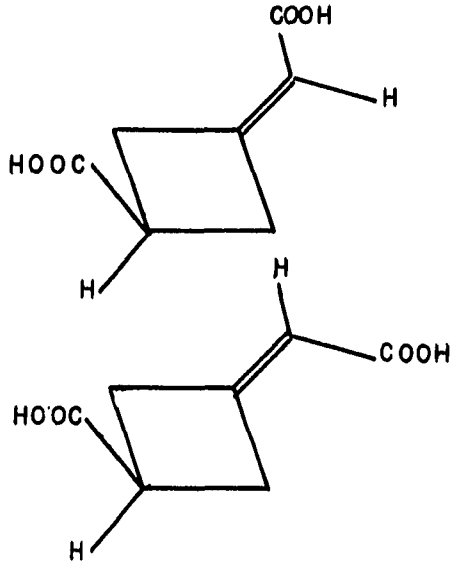
(S')-dextrorotatory
clockwise screw pattern

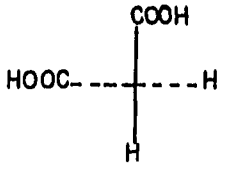
Applying this method to III leads to the conclusion that the dextrorotatory enantiomer has a clockwise chirality and the levorotatory enantiomer has a counterclockwise chirality.

---

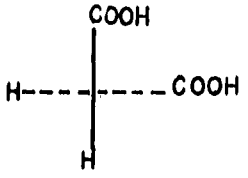
50. J. H. Brewster and J. E. Privett, *J. Am. Chem. Soc.*, 88, 1419 (1966).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



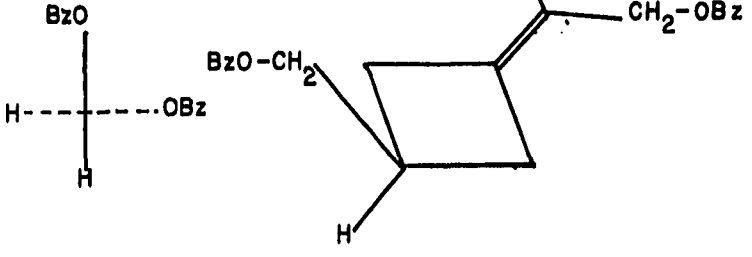


(R)-laevorotatory
counter clockwise
screw pattern



(S')-dextrorotatory
clockwise screw pattern

In a recent communication, Nakanishi[51] presents a correlation between the sign of the first Cotton effect in the circular dichroism spectra of the dibenzoate of a glycol and its absolute configuration. If the view along a line between the two benzoate groups reveals a clockwise chirality the sign of the first Cotton effect of the circular dichroism spectra will be positive and *visa versa*.



+ CD Cotton effect at 234 mμ
implies clockwise chirality

51. N. Harada and K. Nakanishi, *J. Am. Chem. Soc.*, 91, 3989 (1969).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

This method has been applied to III by reducing the dextrorotatory enantiomer with lithium aluminum hydride to the corresponding diol and converting it to the dibenzoate. The circular dichroism spectra had its first Cotton effect at 234 mμ, the same wavelength found by Nakanishi. The positive sign pointed to a clockwise chirality.

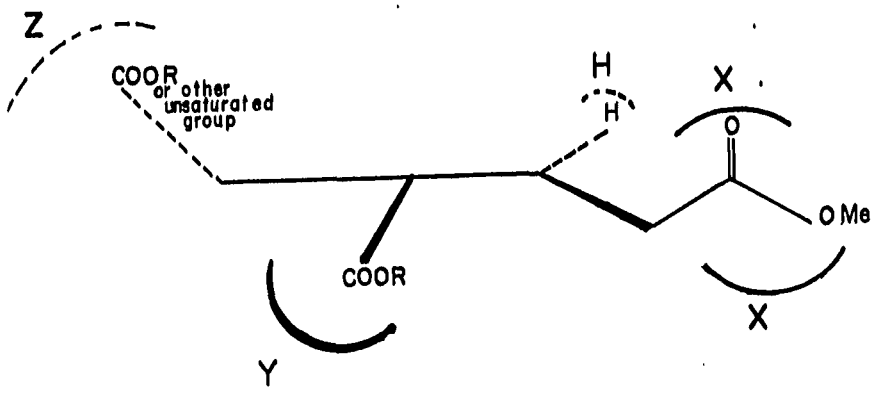
Another indication of absolute configuration is afforded by enzyme specificity. Incomplete hydrolysis of a racemic substance by α-chymotrypsin often produces optically active material because one enantiomer reacts more rapidly than the other. This phenomena is rationalized by the hypothesis that the more rapidly hydrolyzed enantiomer fits into the geometry of the active site of α-chymotrypsin the more readily.[52] Partial hydrolysis of racemic esters has previously been applied to three α,β-diesters and two β,γ diesters as well as to several other substituted esters of known absolute configuration. The results of all these hydrolyses have been generalized in terms of a description of the active site shown below. Area X binds the ester to be hydrolyzed. Area Y binds to an α carbonyl group in the molecule which is attached to the α carbon to that bound to X. H binds the H atom on this α carbon atom. Area Z binds to unsaturated and

---

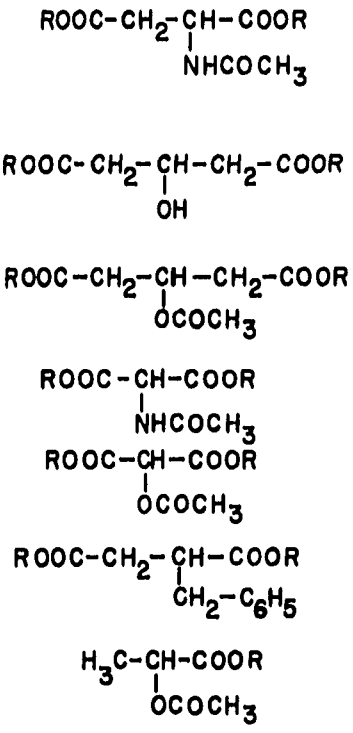
52. S. G. Cohen and A. Milovanovic, *J. Am. Chem. Soc.*, 90, 3495 (1968).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

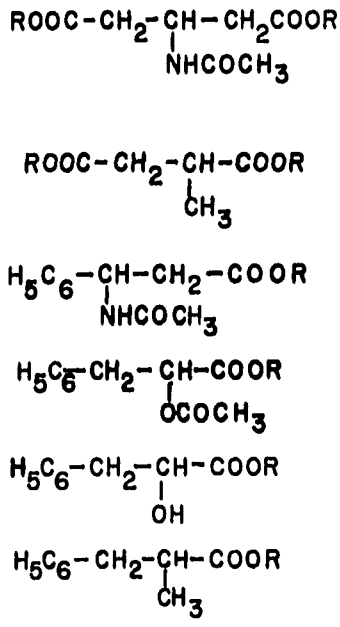
carbonyl fragments of the molecule removed by one or more carbon atom from that bound to X.



R enantiomer hydrolyzed

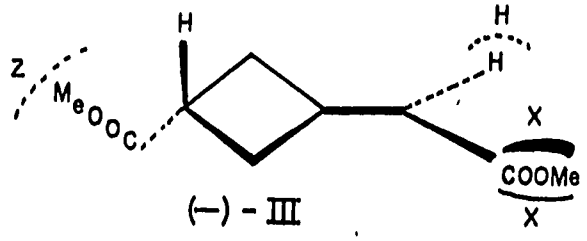


S enantiomer hydrolyzed



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Thus a choice of which enantiomer will fit the active site better, and therefore be hydrolyzed more rapidly, may be made. When III is partially hydrolyzed by α-chymotrypsin a laevorotatory half ester is produced. By application of the general hypothesis, the enantiomer which fits better into the active site, must have the *R'* configuration.



(−) - III

The application of this method confirms the deduction from the Cotton effect in assigning the *R'* configuration to the laevorotatory enantiomer. Unfortunately, dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate has no hydrogen atom attached to the carbon α to the hydrolyzed ester so no choice may be made of which enantiomer will fit the active site better.

The tabulation presented below shows that, fortunately, all of the criteria by analogy for the determination of absolute configuration lead to the same conclusion. A reasonable degree of confidence can be placed in the assignment pending the result of the X-ray determination of absolute configuration.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

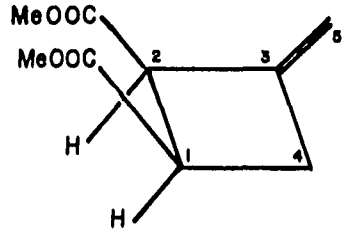
Methyl-3-carbomethoxycyclobut-1-ylidene acetate (III)

Method	*Sign of Rotation*	*Absolute Configuration*
"allene rule"	positive	*S'*
	negative	*R'*
Circular dichroism Cotton Effect of Dibenzoate	positive	*S'*
α-chymotrypsin hydrolysis	negative	*R'*

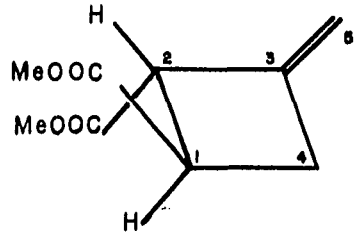
Dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate (II)

Method	*Sign of Rotation*	*Absolute Configuration*
degradation and correlation with α-methylsuccinic acid	positive	1-*R*

Since both (-)-(1*R*:2*R*)-*cis*-I and (-)-(1*R*:2*S*)-*trans*-I are convertable to (+)-(1*R*)-II, their absolute configurations are assigned:



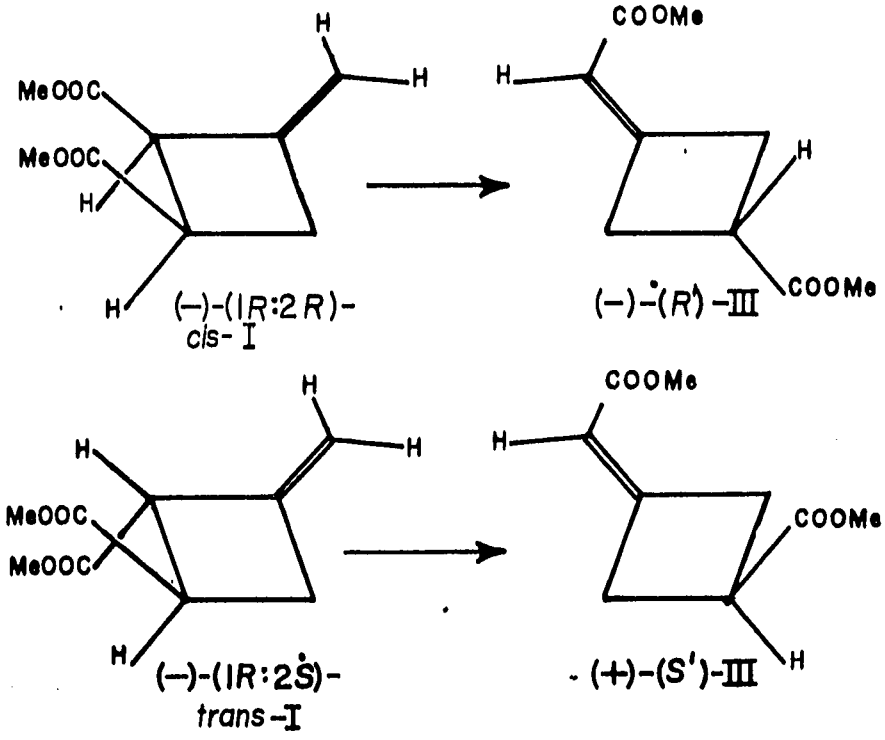
(—)-(1R:2R)-cis-I



(—)-(1R:2S)-trans-I

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

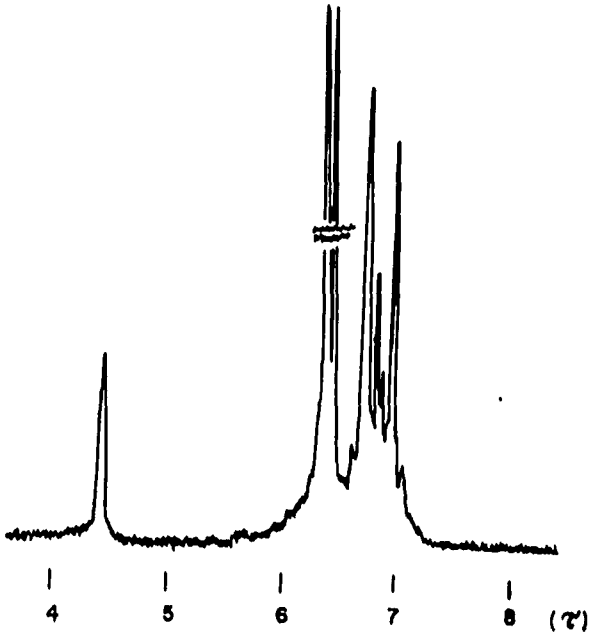
It is now possible to formulate the course of the thermal rearrangement in terms of absolute configuration of the major product. It is recalled that (-)-(1*R*:2*S*)-*trans*-I rearranges to (+)-(*S'*)-III and (-)-(1*R*:2*R*)-*cis*-I rearranges to (-)-(*R'*)-III. The gross stereochemical result can be stated in the two equations as represented below.



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

The NMR Spectrum of III and III-d_2:

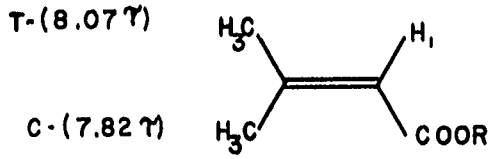
The only method available to distinguishing between *syn* and *anti* dideuteriomethylene groups in III is NMR spectroscopy. A glance at the NMR spectrum of non-deuterated III reveals an unattractive but not hopeless situation.



The assignment of the major divisions of peaks is clear: the lowfield peak of area 1 arises from the single olefinic proton; the middle peaks of area 6 represent the two non-equivalent methyl esters; and the highfield peaks of area 5 represent the five protons of the cyclobutane ring. These latter five protons are divided into two main branches of approximately equal area, but are not clearly separated. The influence of a carbonyl group on the chemical shift of nearby protons has been extensively documented (see appendix). While the theoretical analysis of this effect is not completely unam-

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

biguous, no example could be found in which a carbonyl group shifts nearby protons upfield. A typical example is that of methyl β,β-dimethylacrylate. Its two methyl groups produce signals at 7.82τ and 8.07τ. The lower field peak is assigned to the methyl group *cis* to the ester group (C) and the higher field at 8.07τ is assigned to the methyl *trans* to the ester group (T). This assignment is verified by the finding that upon irradiation at the frequency of H_1 the area of the 8.07

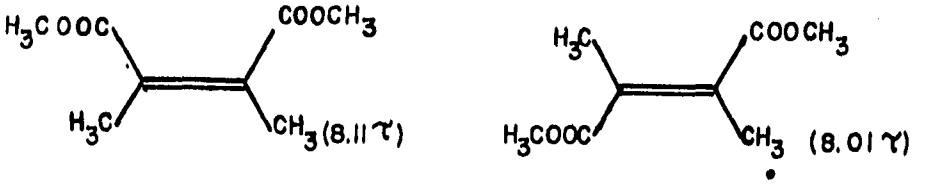


methyl group increases 17% owing to the operation of the Nuclear Overhauser Effect.[53] Since this effect is based on proximity of groups, it is concluded that the resonance of methyl group T (*cis* to H_1) increases in area. It follows that the ester group shifts the methyl group physically closest to it downfield (methyl T). Another example is the pair of isomers, dimethyl dimethylmaleate and dimethyl dimethylfumarate. The methyl groups attached to the double bond in dimethyl dimethylmaleate produce a signal at 8.11τ and are *trans* to the ester groups while the corresponding methyl groups in dimethyl dimethylfumarate

---

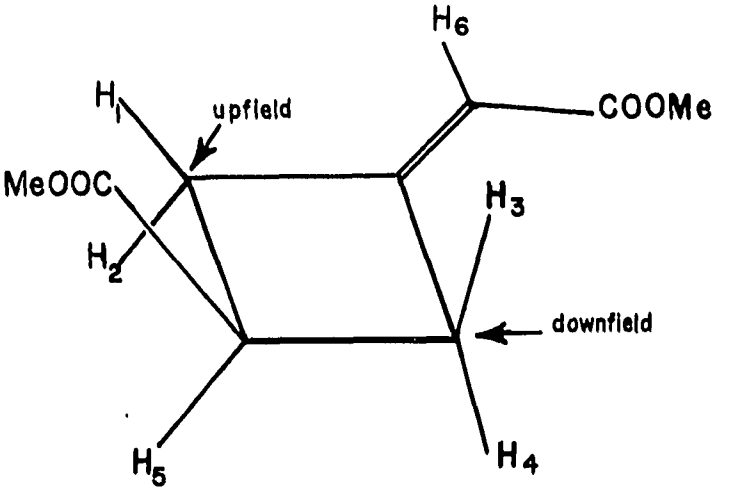
53. F. A. L. Anet and J. R. Bourn, *J. Am. Chem. Soc.*, 87, 5250 (1965).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



produce a signal at 8.01τ and are *cis* to the ester groups.[54]

The Nuclear Overhauser Effect (NOE) which has been successfully used to determine which protons are spatially closest to each other can be applied to the present problem. A recent example of the application of the NOE is the determination of the conformation of taxane derivatives.[55] Irradiation at the frequency of olefinic proton H_6 in III

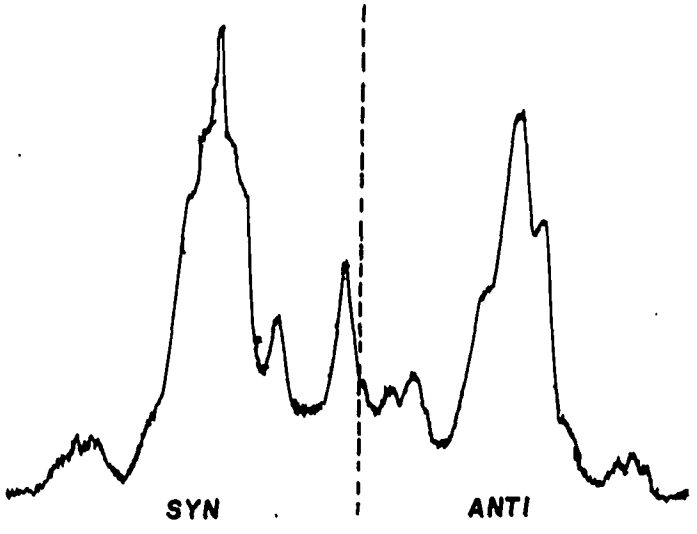


54. L. M. Jackman, *J. Chem. Soc.*, 2886 (1960).
55. M. C. Woods, H-C Chiang, Y. Nakadaira and K. Nakanishi, *J. Am. Chem. Soc.*, 90, 522 (1968).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

results in an increase in area of the upfield branch of the cluster of cyclobutane protons of approximately 14%. The upfield portion is therefore concluded to arise from the methylene group closest to H_6 and consequently *anti* to the ester. This deduction confirms the earlier assignment of the downfield branch to the *syn* methylene group. The task of estimating the relative amounts of dideuteriomethylene *syn* and *anti* to the α,β-unsaturated ester is complicated since the upfield cluster of peaks contains hydrogen 5 in addition to the four hydrogens of the methylene groups. An effort was made to increase the separation within this cluster by varying the solvent. Although solvent effects were observed, in no solvent was a spectrum produced with peaks more acceptably separated than in carbon tetrachloride.

A line drawn half-way between the mid-point of the left and the mid-point of the right branch divides the



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

cluster into segments of equal area (2.5). The assumption is therefore made that the center of the signal arising from H_5 has fallen halfway between the two multiplets associated with the *syn* and *anti* CH_2 groups. In the simplest possible case this H_5 would consist of five lines and could be considerably more complicated. The spectrum of the non-deuterated material can be divided into equal areas by a line which can then be transferred to the spectrum of the deuterated sample. The areas remaining on each side of the line after subtraction of an area equal to 0.5 protons from both should then represent the relative amounts of hydrogen *syn* and *anti* to the α,β-unsaturated ester.

Optically Active cis-I-d_2 and its use in distinguishing among rotational alternatives:

Cis-3-dideuteriomethylenecyclobutane-1,2-dicarboxylic acid (*cis*-I-d_2) was resolved by the same procedure used in the case of non-deuterated *cis*-I. The dimethyl ester of resolved diacid [(+) or (-) *cis*-I-d_2], obtained by treatment with diazomethane, was incompletely rearranged in benzene solution to methyl 3-carbomethoxycyclobut-1-ylidene-acetate-d_2 (III-d_2) in benzene solution in sealed tubes.

The object of the experiments can only be realized if the resulting deuterated enantiomers of III are both available in optically pure form for separate analysis of deuterium. Only by an examination of both enantiomers

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

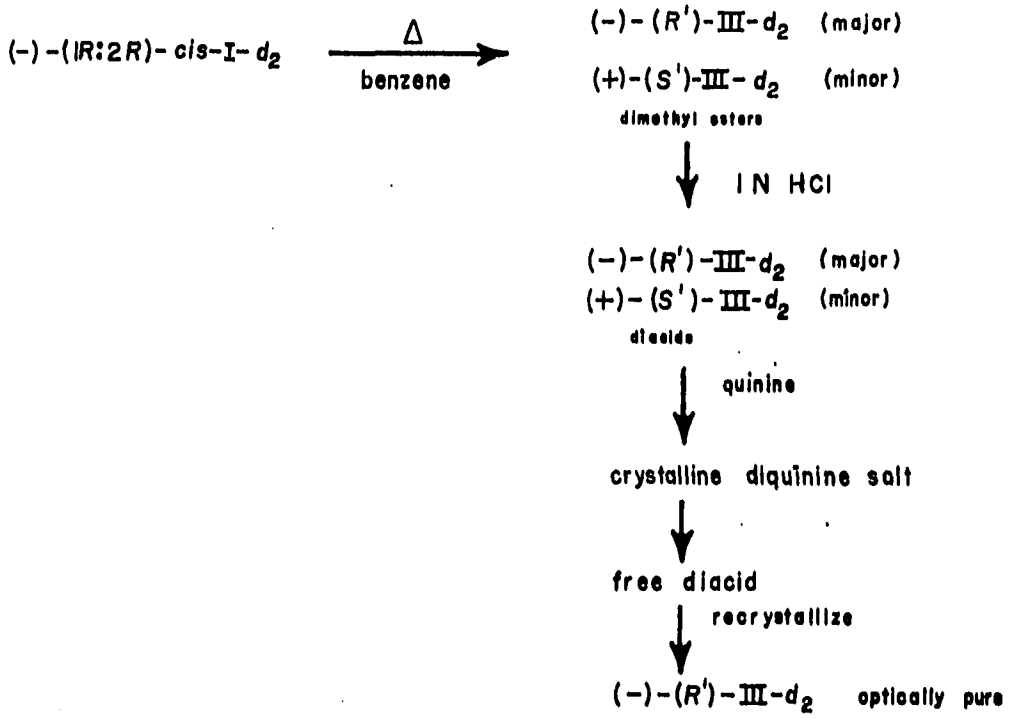
can any difference in their mechanism of formation be detected. After separation of the reaction mixture afforded pure III-d_2, the ester was hydrolyzed under mild conditions to afford III-d_2 diacid which was resolved to yield the optically pure enantiomers.

The major enantiomer from the thermal rearrangement of (-)-(1*R*:2*R*)-*cis*-I-d_2 is (-)-(*R'*)-III-d_2. The corresponding diacid was resolved by fractional recrystallization of the diquinine salt and afforded pure (-)-(*R'*)-III-d_2. No workable scheme was found for the efficient separation of the minor enantiomer (+)-(*S'*)-III-d_2. The only available method involved concentration of this enantiomer by recrystallization of the free diacid, but the amount of (+)-(*S'*)-III-d_2 obtainable was impracticably small. In order to obtain a sample of the minor enantiomer in the optically pure state, (+)-(1*S*:2*S*)-*cis*-I-$d_2$diester was prepared and rearranged. In this case (-)-(*R'*)-III-d_2 was the minor enantiomer and it could be resolved by the recrystallization of the diquinine salt. Repeated recrystallization of the mother liquor afforded the major product, (+)-(*S'*)-III-d_2, in optically pure form, although not in bounteous quantity.

Parenthetically, it can be noted that the dicarboxylic acids of III are not suited for NMR analysis of deuterium distribution. The NMR spectra of each of the optically

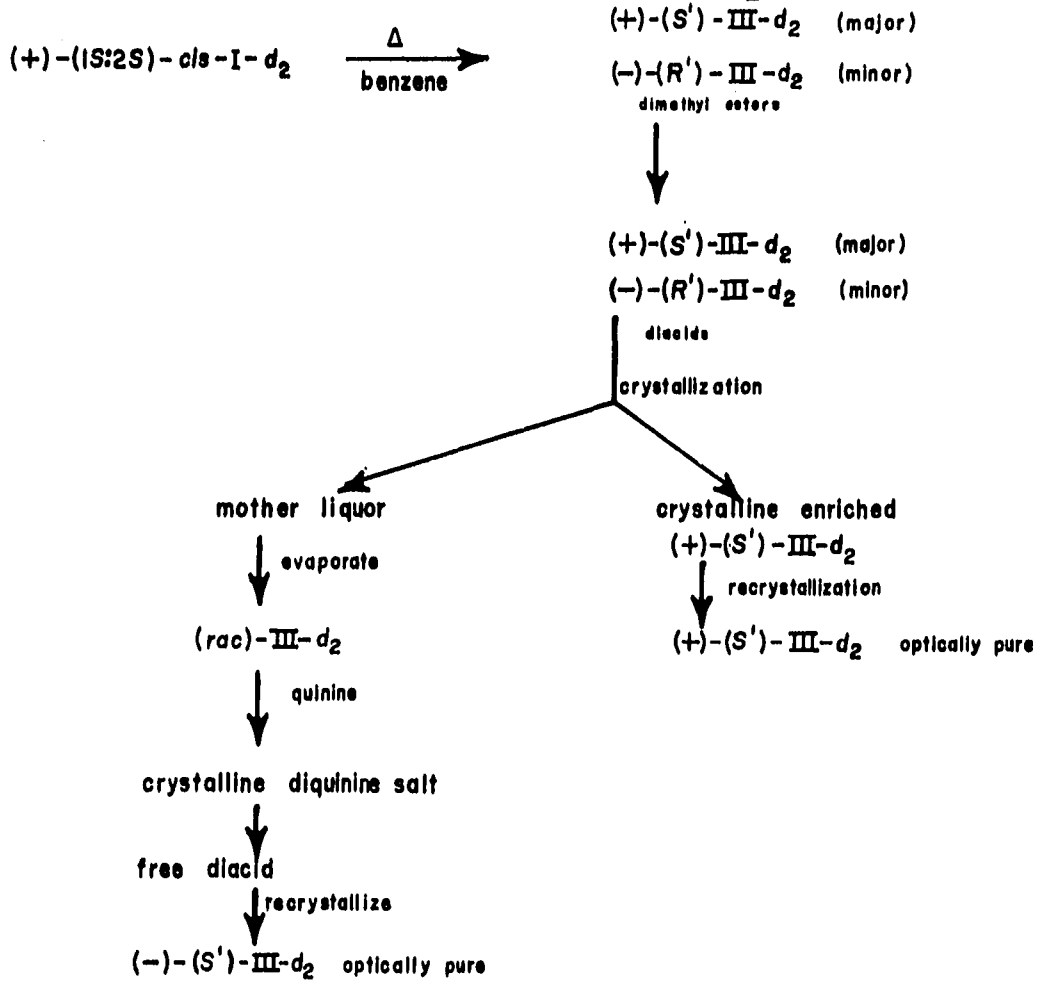
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Procedure for isolation of optically pure (-)-(R')-III-d_2 from the thermal rearrangement of (-)-(1R:2R)-cis-I-d_2



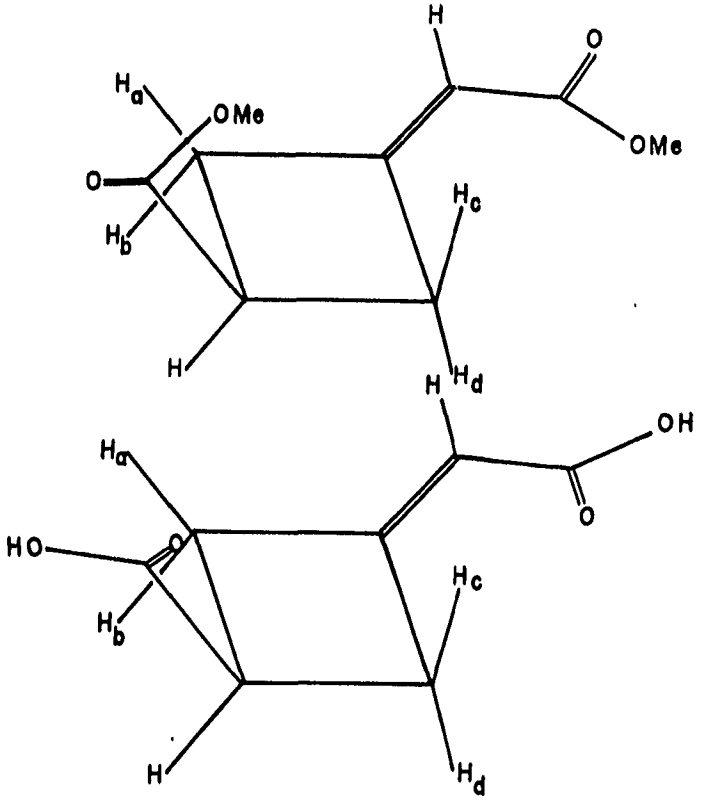
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Procedure for isolation of optically pure (+)-(S')-III-d_2 and optically pure (-)-(R')-III-d_2 from the thermal rearrangement of (+)-(1S:2S)-*cis*-I-d_2



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

pure enantiomers of III-d_2 dicarboxylic acids reveals, as expected, that the total area of the cyclobutane protons is reduced by the amount of deuterium in the molecule but it also reveals the relative areas on each side of the line supposedly dividing *syn* and *anti* to be of equal intensity. By way of explanation it is suggested that the lower field



branch in the spectrum of diacid III is made up of H_a and H_c, predominately deshielded by the carbonyl of the saturated carboxylic acid whereas, in the spectrum of the diester, the

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

lower field branch is made up of H_c and H_d predominately deshielded by the carbonyl of the α,β-unsaturated carboxylic ester.

In any case, NMR analysis of the dimethyl esters is satisfactory. The results of the rearrangement of (+)-(1*S*:2*S*)-*cis*-I-d_2 and (-)-(1*R*:2*R*)-*cis*-I-d_2 are tabulated below. The ratio of deuterium in the *syn* and *anti* positions of the pure enantiomers of III-d_2 are corrected for the hydrogen content of the *exo* methylene group of *cis*-I-d_2. The estimated limit of reliability is based on experimental errors in determining total deuterium content and in determining the *syn/anti* ratio by NMR and is presented as the actual ratios as well as a simplified ratio from which the actual ratio is indistinguishable at the 99% confidence level by the statistical *t* test.

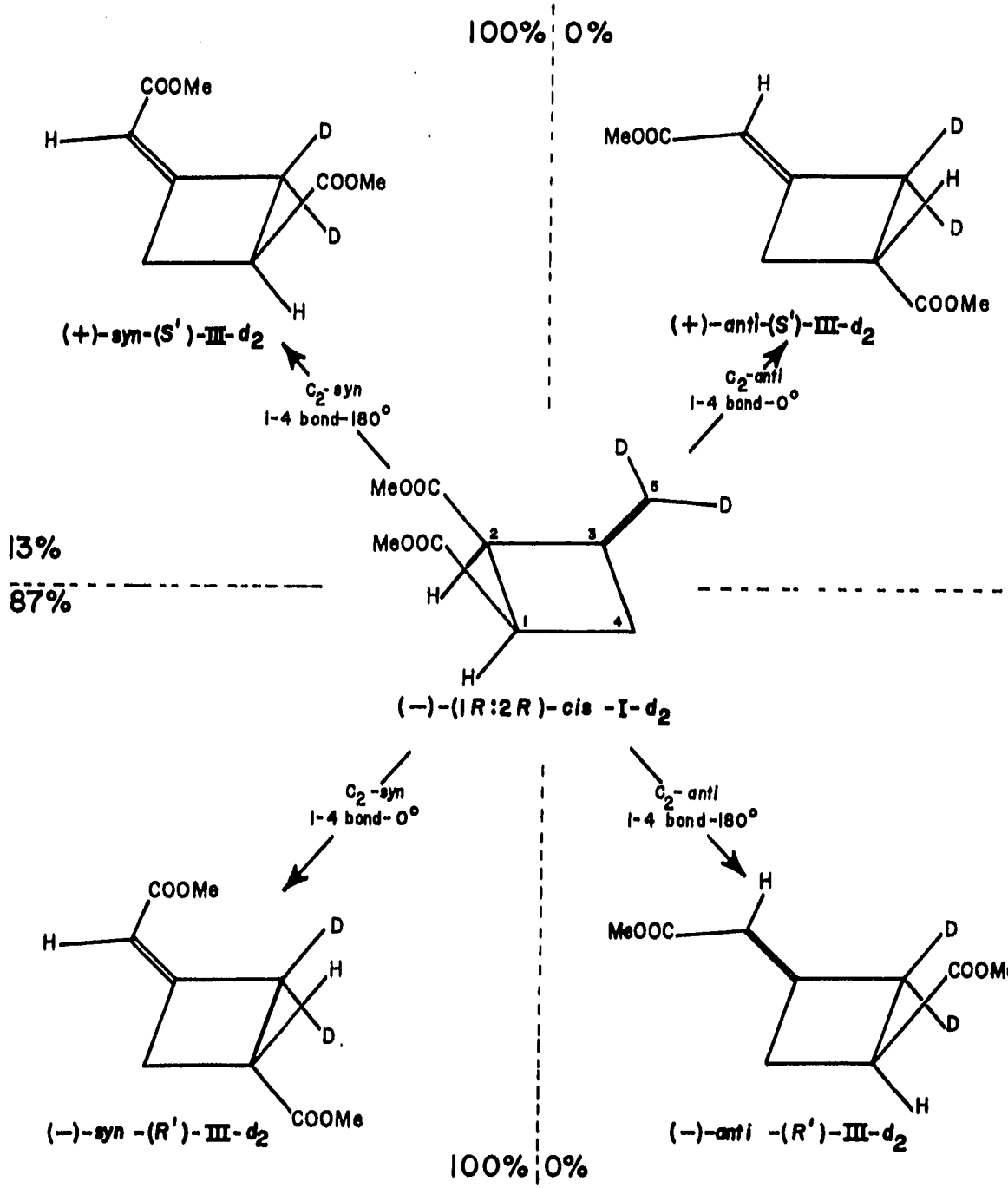
sample of III-d_2	downfield area: upfield area	indistinguishable from
(+)-(S')-III-d_2 from (+)-(1S:2S)-cis-I-d_2	−0.4% : 100.4%	0% : 100%
(−)-(R')-III-d_2 from (+)-(1S:2S)-cis-I-d_2	0.7% : 99.3%	0% : 100%
(−)-(R')-III-d_2 from (−)-(1R:2R)-cis-I-d_2	−0.8% : 100.8%	0% : 100%

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

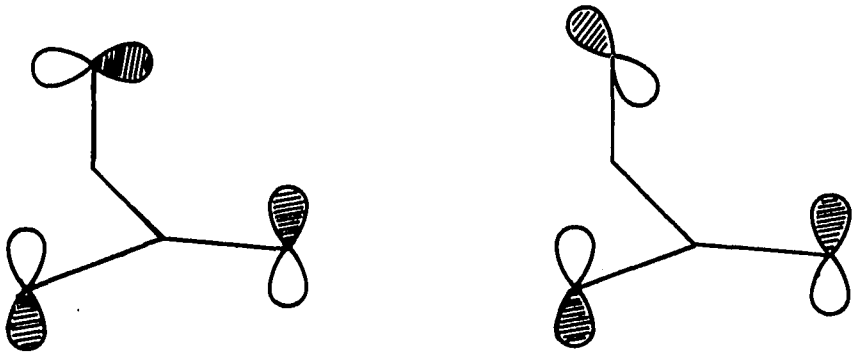
In both the major and minor enantiomer the striking result is that *syn* is markedly favored over *anti*. Rotation of C_2 is specifically *syn* while rotation about the C_1-C_4 bond is not stereospecific but strongly stereoselective. Since the absolute configurations are reasonably well established, it can be concluded that the major course of the thermal rearrangement of (-)-(1*R*:2*R*)-*cis*-I-d_2 leads to (-)-(*R'*)-III-d_2 as the major (87%) enantiomer while the minor (13%) course produces (+)-(*S'*)-III-d_2. From the diagram on the next page it can be appreciated that the major enantiomer is produced by an *S* (*syn*) rotation about C_2 and no rotation (0°) about C_1-C_4, while the minor enantiomer is produced likewise by an *S* (*syn*) rotation about C_2 but with a rotation of 180° about C_1-C_4.

These results bear on the question of control of stereochemistry by conservation of orbital symmetry. A 1,3-sigmatropic shift has two modes of orbital allignment. In the first orientation of the π orbital of the migrating carbon atom, each lobe can overlap with an end orbital of the allyl radical (A). In this orientation, the migrating carbon atom has rotated 90°. In order to complete the rearrangement it must rotate an additional 90° to complete a 180° rotation. In the second orientation, only one lobe of the migrating π orbital is directed away throughout (B). No rotation has been involved: there

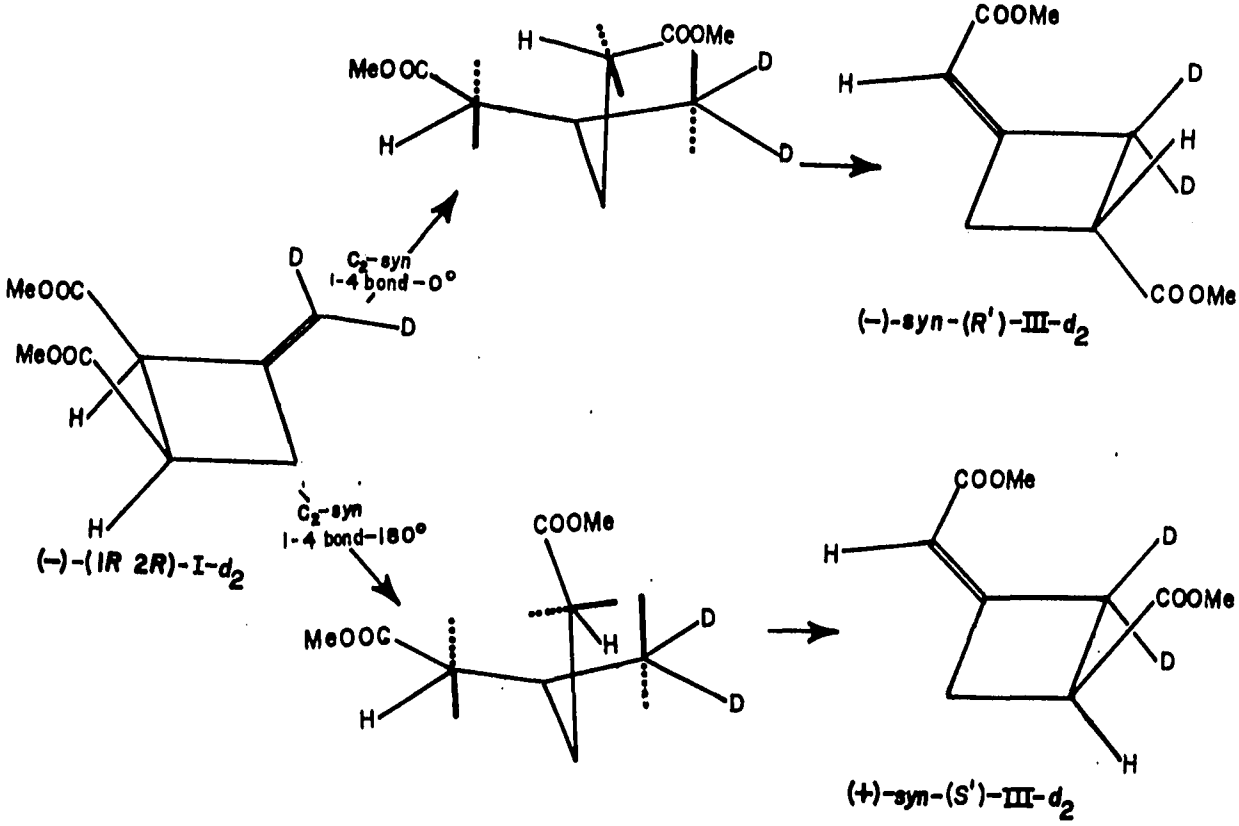
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



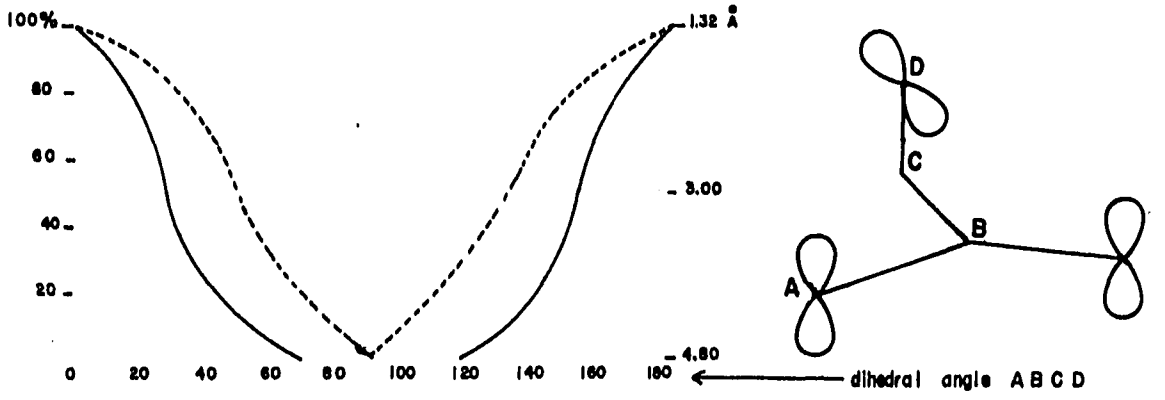
is no possibility of bonding at the mid-point; the mechanism is non-concerted. Because of the symmetry of the highest occupied orbital of the allyl radical, continuity of symmetry can be maintained only in orientation A. If path A is followed in the rearrangement of (-)-(1*R*:2*R*)-*cis*-I-d_2 to the *syn*



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

product (counterclockwise rotation at C_2), the (+)-(*S'*) enantiomer of III-d_2 is expected. In fact, the major enantiomer (87%) is (-)-*syn*-(*R'*)-III-d_2. It is not the product of the process controlled by the operation of orbital symmetry. Only the minor enantiomer may be formed by such a process. If either the identification of absolute configuration or of *syn* and *anti* methylene groups proves to be incorrect, the opposite conclusion would have to be drawn.

Since conservation of orbital symmetry requires continuous overlap throughout the reaction, it follows that the major part of the reaction proceeds through a stage in which the two portions are not bonded and electron correlation is lost. This stage is defined as a diradical regardless of



—OVERLAP[56] (left axis) as % of full sigma bond

.....DISTANCE (right axis) from D to nearest end of allyl radical

---

56. Overlap calculated by computer program "OVERLAP IV" written by Peter Offenhartz and available from QCPE at University of Indiana.

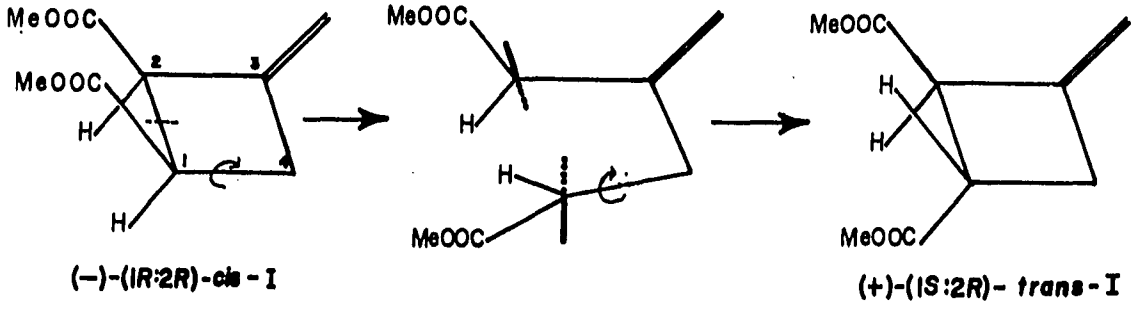
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

the operation of free rotation. Because of the presence of an insulating methylene group between the allylic and migrating portion of the system, the electrons of the allyl group and the lone π orbital are separated by such a large distance that overlap would be expected to vanish.

Formation of trans-I in the thermal rearrangement of cis-I:

We now wish to turn back to a discussion of the *trans*-I produced in the rearrangement of *cis*-I to III. When this rearrangement is effected with optically active (-)-(1*R*:2*R*)-*cis*-I the *trans*-I recovered is levorotatory and has 75% of the optical purity of the starting (-)-(1*R*:2*R*)-*cis*-I and accounts for 20% to 30% of the product based on conversion of *cis*-I.

Several mechanisms for the formation of *trans*-I are imaginable. In one mechanism, rotation about the C_1-C_4 bond may occur with no rotation about the C_2-C_3 bond prior to ring closure. The expected result, the production



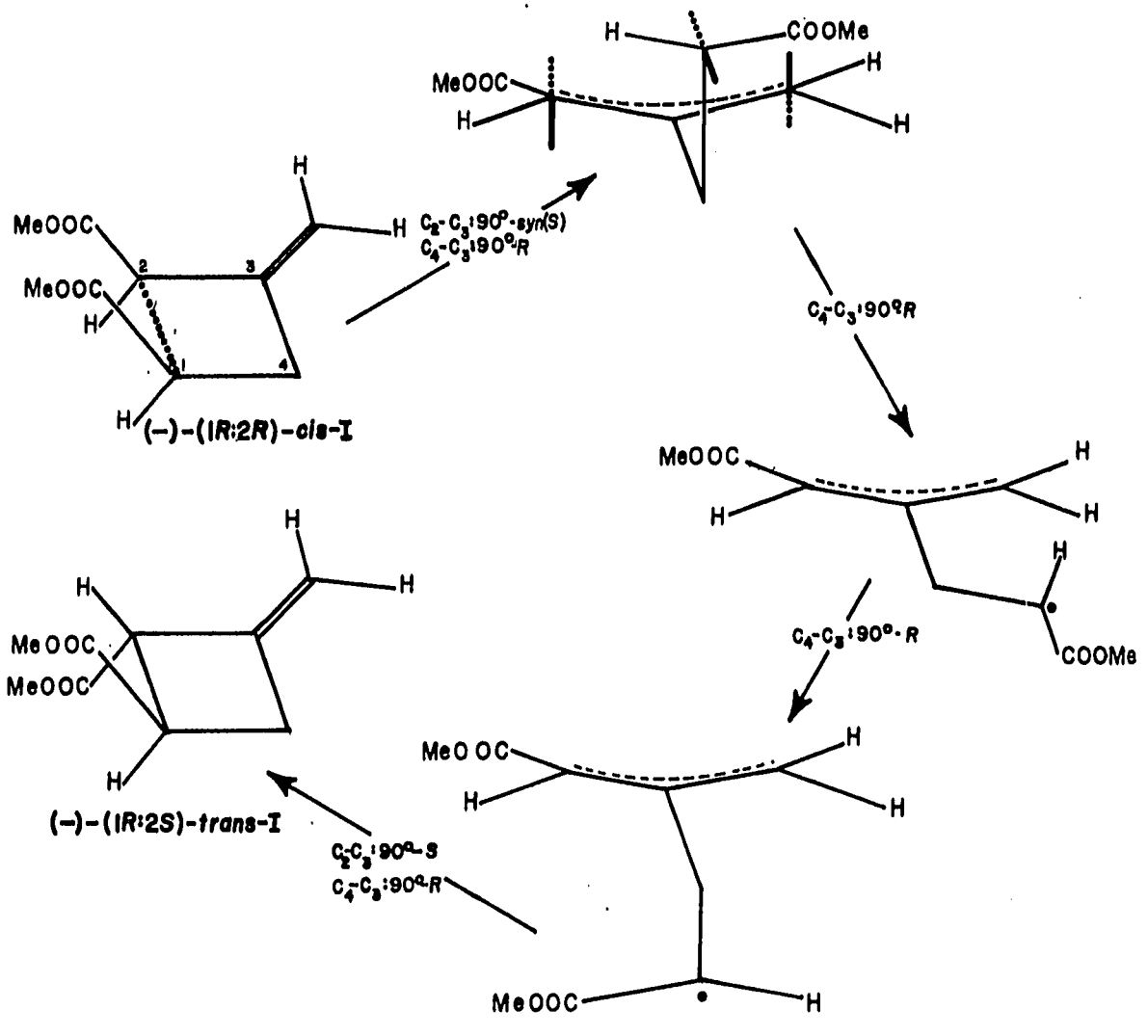
(−)-(1R:2R)-cis-I (+)-(1S:2R)- trans-I

of (+)-(1*S*:2*R*)-*trans*-I from (-)-(1*R*:2*R*)-*cis*-I is contrary

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

to the experimental result in which (-)-(1*R*:2*S*)-*trans*-I is the major product.

In an alternative mechanism, initial bond-breaking and rotation occurs as in the rearrangement to III. However, instead of bonding to form III, the migrating carbon atom



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

continues to rotate around the C_3-C_4 bond until it nears C_2 whereupon rebonding occurs. If rotation about the C_2-C_3 bond had occurred in the usual *syn* sense, rebonding would take place with the lobe of the C_2 π orbital opposite the one involved in the original C_1-C_2 bond. If there had been no rotation about C_1-C_4 during this process (the predominant path in the formation of III) retention of configuration at C_1 and inversion at C_2 would result. It should be noted that electron correlation between the tertiary radical and the allylic radical is zero after the first phase and that inversion of configuration at C_2 is occasioned by necessity of reforming the C_2-C_1 bond from the bottom. This mechanism requires that (-)-(1*R*:2*R*)-*cis*-I isomerize to (-)-(1*R*:2*S*)-*trans*-I, in agreement with the observed result.

Pressure effect on rotation specificity:

As the pressure is lowered the life time of the activated molecule before collisional deactivation increases and the opportunity for rotation might also be expected to increase.

In view of the importance assigned to rotational components, it may be speculated that the rotation at C_2 in the rearrangement of *cis*-I remains specific at low pressure. At high pressure 13% of the minor enantiomer

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

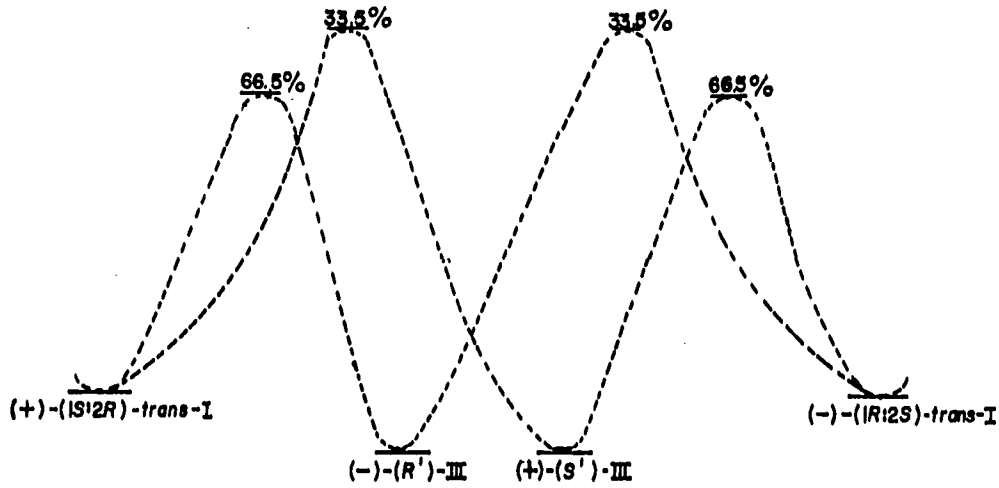
results from non-specific C_1 rotation. It was noted earlier that when the pressure is lowered to approximately one mm. in the reaction vessel the enantiomer ratio is altered from 87:13 to 72:28. At low pressure it may be reasonable to assume that this C_1 rotation, having a longer time to take place, does so to the extent of 28%.

Reversibility of the Rearrangement: conversion of III to trans-I:

All organic reactions are, in theory, governed by the law of microscopic reversibility; that is, the reverse reaction must follow exactly the same mechanistic path as the forward reaction. When optically active III is rearranged, a small amount (1%) of *trans*-I is produced in which 33% optical activity is retained; that is 67% of one enantiomer and 33% of the other is produced. The major enantiomer had the opposite sign of rotation of the starting III. This result precisely parallels that observed in the rearrangement of *trans*-I to III (see page 44). The energy diagram above reflects this microscopic reversibility. It should be noted that the absence of *cis*-I in the rearrangement of III places the transition state for the conversion of III to *cis*-I several kcal higher than either of the two transition states for the conversion of III to *trans*-I.

Unfortunately, since neither *trans*-I nor III were prepared with sufficient internal labeling the mechanism

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

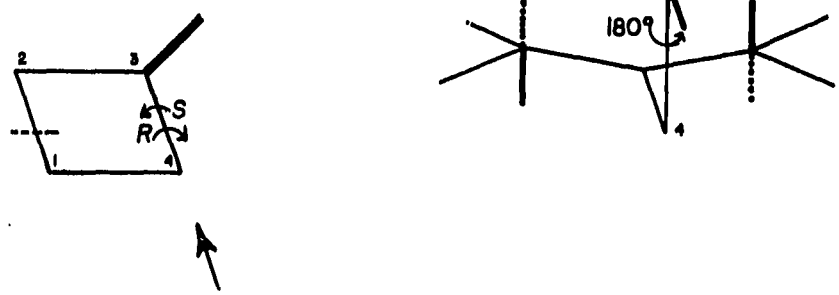


of their interconversion is not known in the same depth as the mechanism of the conversion of *cis*-I to III.

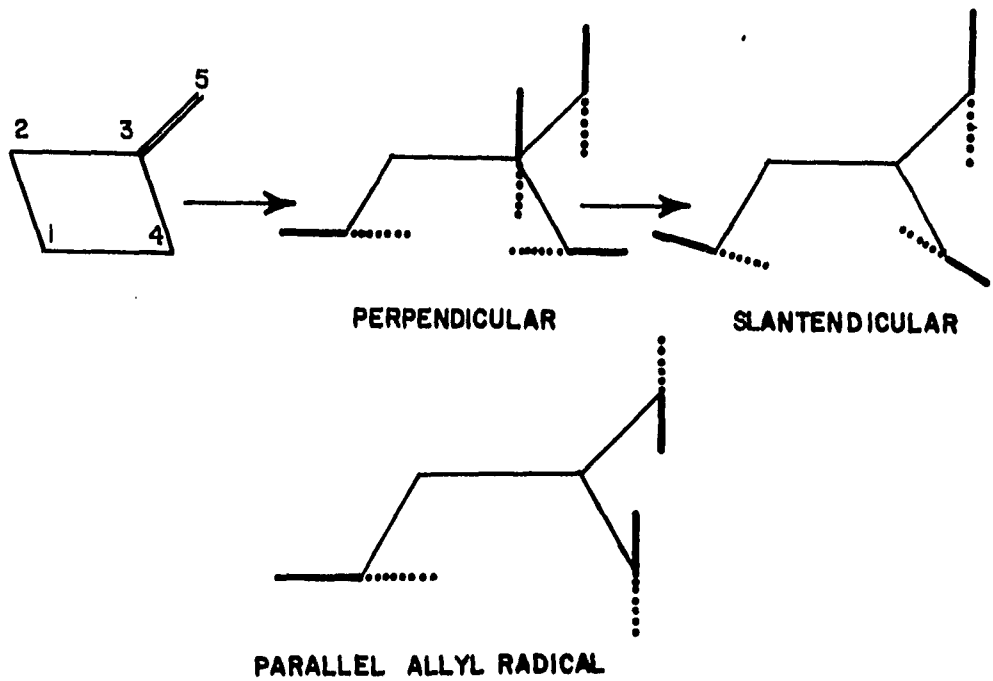
Points left unanswered in the conversion of cis-I to III:

At least three major points have been left unanswered. First, no way has been devised to differentiate between an *R* and an *S* rotation of the C_3-C_4 bond. Second, no evidence exists which differentiates between a 0° rotation and a (2n) x 180° rotation of the C_1-C_4 bond, where n is an integer; nor is it possible to differentiate between a 180° rotation and a (2n + 1) x 180° rotation of this bond. Third, nothing is known about the rotational characteristics of the C_5-C_3 bond. The relative alignment of the π orbitals of the allyl radical at various stages of the re-

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

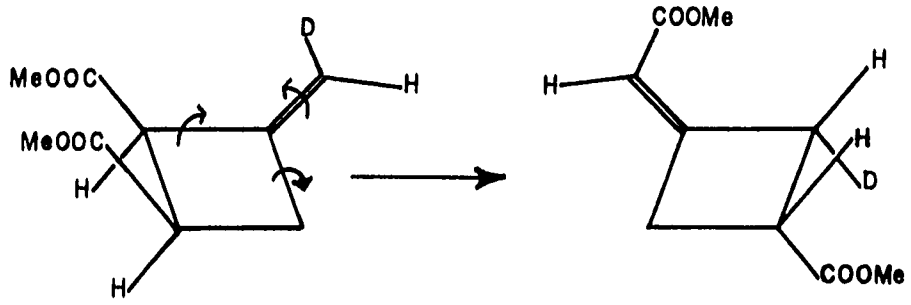


arrangement has also escaped definition. As the bond-rupture proceeds, the orbital on C_2 must proceed from a perpendicular to a slantendicular conformation. The timing of the rotation of C_5 remains undefined. It may wait for the C_2 orbital to form a parallel allylic radical, affording maximum stabilization or it may begin rotation in one direction or the other toward a slantendicular conformation before the orbital



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

on C_2 reaches completion of its required 90° rotation? A slantendicular allylic radical would represent a higher energy state than the fully parallel allylic radical. In any case, regardless of timing, the π orbital on C_5 will have the opportunity to rotate 90° *R* or *S* before reforming a cyclobutane ring. The difference between an *R* or *S* rotation may be uncovered if the methylene group in the



starting diester is unsymmetrically substituted.

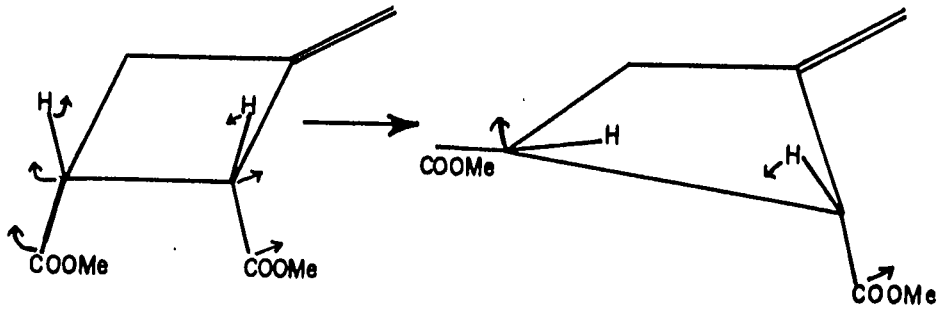
Conclusions:

The most basic conclusion from the study of the rearrangement of optically active methylenecyclobutane diesters is that the intermediate in the rearrangement is neither arrived at through random rotations nor is it rotationally equilibrated. Interpretation is not simple and requires several imperfectly elaborated chemical concepts. The task may fruitfully be broken up into three sections: description of the bond breaking process, descrip-

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

tion of qualities of the intermediate and description of the bond forming process.

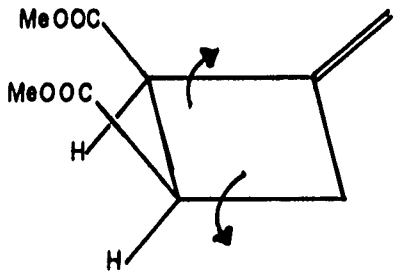
In order that rotations of bonds not be random, a directing force must operate as the atoms go through the motions necessary to carry the molecule from its starting geometry to that of the product. It was noted earlier that bonds in small rings may not be broken by simple in plane stretching. Rotation of the atoms constituting the breaking bond is necessary in order to allow the electrons, whose overlap constitute the bond, to escape from each others influence. If some of the normal modes of vibration of the molecule are allowed to continue in one direction, they become rotations. It is these twisting-vibrational modes which become bond-breaking rotational motions when sufficiently excited.



The momentum that the various portions of the molecule receive from this twisting-vibration can be imagined to cause the rotations to be directionally non-random. That the *syn* product is highly favored in both enantiomers of

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

the product from optically active *cis*-I-d_2 may be a reflection of such a momentum. If the large carbomethoxy groups *cis* to each other interfere sterically, the major vibration-twisting in bond rupture may be outward with respect to these groups and disrotatory. Such a vibration-rotation allows the molecule relief of steric crowding.

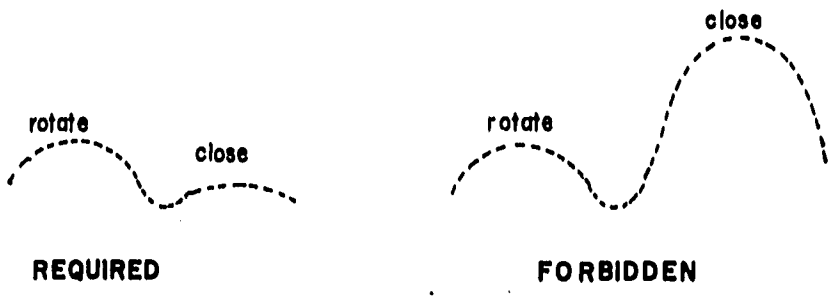


Behind the notion of free rotation in diradicals must be the assumption that, once the energy necessary to overcome rotational barriers has been supplied, groups rotate continuously through several energy barriers. The model, in ethane for example, visualizes the two methyl groups to be constantly spinning once the 3 kcal are supplied to overcome the barrier to free rotation. If this were the correct description of bond rotation it would be difficult to explain the fact that the intermediate in the methylenecyclobutane rearrangement is not rotationally equilibrated. Evidently there is some resistance within the bond itself to continuous rotation. It appears much more likely that

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

rotations proceed over one rotational energy barrier at a time and generally redistribute the energy of activation of rotation into other low lying energy levels of the molecule. A second rotation would then require new absorption of activation energy if the pressure were high or remobilization of the energy if the pressure were low.

In addition to proposing that rotation be limited to one turn at a time, it is essential that the energy barrier to bond reformation not be greater in magnitude than the barrier to bond rotation. If there were a higher barrier to reclosure than to rotation, the result would be the equivalent of free rotation in the intermediate.



The hypothesis is therefore advanced that whenever two orbitals are at proper distance and angles to each other for bonding to occur, it does occur; or more precisely, the free energy of activation for ring closure must be comparable to or less than that for rotation.

The question of concertedness which had been raised

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

earlier, has proved of little significance. In the rearrangement of optically active *cis*-I the rotation at C_2 proves to be entirely *syn*, regardless of which enantiomer of III is being formed. Rotation about the C_1-C_4 bond proves to be nonspecific to the same extent that the minor enantiomer is formed. The nature of the cause of this non-specific rotation is not clear. It may be that C_1 always begins its migration in such a manner that the major enantiomer results by 0° rotation, and that some rotation at mid course in the intermediate leads to the minor enantiomer in the equivalent of a rotation of 180°. Or it may be that there are two different types of normal modes which contribute to the bond breaking process: one which sends C_1 toward product with 0° rotation and one which sends C_1 toward product with 180° rotation.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

CHAPTER III:
RESULTS AND DISCUSSION;
CYCLOADDITION OF FUMARATE AND MALEATE TO ALLENE

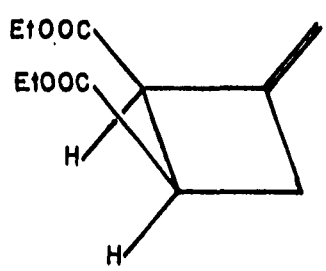
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Addition of Diethyl Maleate and Diethyl Fumarate to Allene:

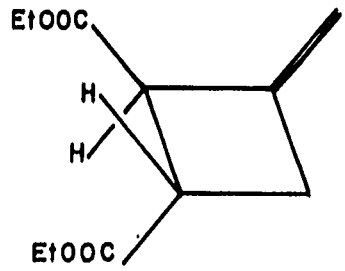
In the explorative search for synthesis of 3-methylenecyclobutane-1,2-dicarboxylates it was found that the addition of allene to diethyl fumarate affords only *trans*-diethyl 3-methylenecyclobutane-1,2-dicarboxylate (*trans*-I) but the addition to diethyl maleate affords a mixture of 85% *cis*-I and 15% *trans*-I.

Five years ago this result would have found a simple explanation, but recent theoretical developments require a consideration of more elaborate explanations.

It is a simple prediction of the principle of conservation of orbital symmetry that [2+2] cycloadditions of two ethylenic molecules may not occur in a suprafacial manner by a concerted reaction. This prediction was taken to mean that [2+2] cycloadditions would never proceed thermally in a concerted manner. However, the phrase, "in a suprafacial manner" had been overlooked by most. However, in principle there is an alternative to addition



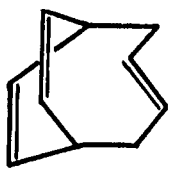
cis-I

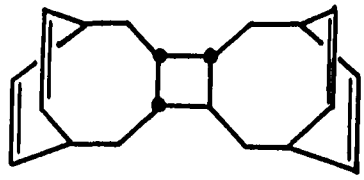


trans-I

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

"in a suprafacial manner" and that is addition in an antarafacial manner. Although antarafacial [2+2] concerted cycloaddition does violence to one's chemical intuition, this alternative must be taken seriously. In the bicyclic olefin shown dimerization occurs spontaneously[57] to give a product with *cis*, *trans* geometry. One of the olefins





appears to have added suprafacially and the other antarafacially. In Woodward-Hoffman abreviations the reaction is $[_{\pi}2_{s}+_{\pi}2_{a}]$, which is an orbital symmetrically allowed combination. For dimerization in the $[_{\pi}2_{s}+_{\pi}2_{a}]$ mode, twisting somewhat out of the planar conformation is mandatory. This analysis has led Woodward and Hoffman to predict[58] that the optically active forms, (*R+R* or *S+S*), of an olefin will dimerize <u>less</u> readily than the racemic olefin (*R+S*). Models suggest that an *R+S* fit better when twisted than do an *R+R* or *S+S* . Confirmation has been provided by Moore, Batch and Ozretich[59], who find that racemic

---

57. K. Kraft and G. Kottzenberg, *Tetrahedron Letters*, 4357, 4723 (1967).
58. R. B. Woodward and R. Hoffman, *Agnew. Chem., Inter. Ed.*, 8, 781 (1969).
59. W. R. Moore, R. D. Batch, and T. M. Ozretich, *J. Am. Chem. Soc.*, 91, 5918 (1969).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

cyclononadiene-1,2 dimerizes at a significantly faster rate than either pure enantiomer.

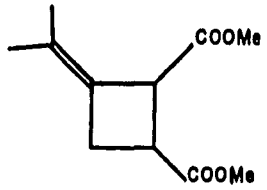
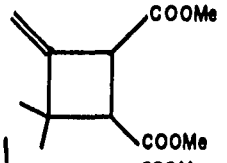
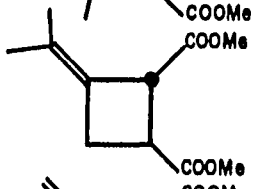
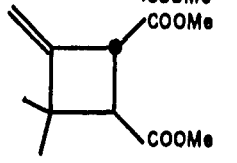
There are two further pieces of information concerning the mechanism of the reaction of allene in a [2+2] cycloaddition. Whereas the addition of 1,1-dideuterioallene to hexachlorocyclopentadiene in a concerted, $[\pi^2_s + \pi^2_s + \pi^2_s]$, Diels-Alder reaction reveals a secondary isotope effect of $K_H/K_D = 0.90$, the cycloaddition of allene to acrylonitrile reveals a secondary isotope effect of $K_H/K_D = 1.21$[60] for the [2+2] cycloaddition reaction. This difference is considered to indicate a stepwise reaction proceeding through a diradical intermediate for the cycloaddition.

In a communication entitled "Evidence for a Concerted Mechanism for Allene Cycloaddition," Kiefer and Okamura[61] examine the addition of 1,1-dimethylallene to dimethyl fumarate and dimethyl maleate. From the fumarate reaction two methylenecyclobutanes are obtained, both with *trans* configuration of the ester groups; the maleate addition affords, however, all four possible methylenecyclobutanes including approximately 10 per cent of the two *trans* methylenecyclobutane dicarboxylates.

---

60. W. B. Dolbier, Jr. and Sheng-Hong Dai, *J. Am. Chem. Soc.*, 90, 5028 (1968).
61. E. F. Kiefer and M.Y. Okamura, *J. Am. Chem. Soc.*, 90, 4187 (1968).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

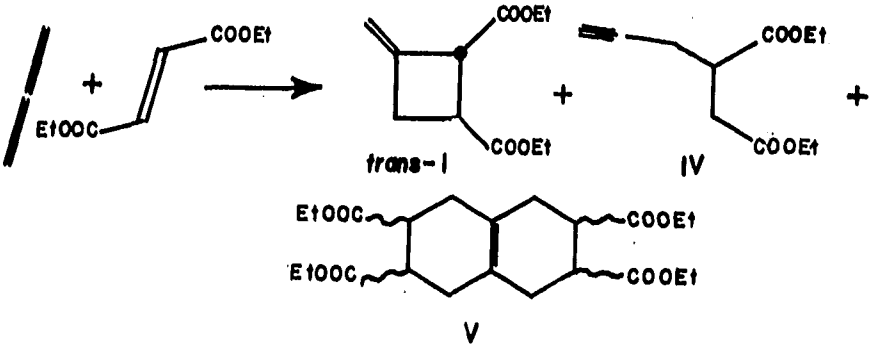
	DMA + FUMARATE	DMA + MALEATE
	0%	75%
	0%	15%
	91%	8%
	9%	2%

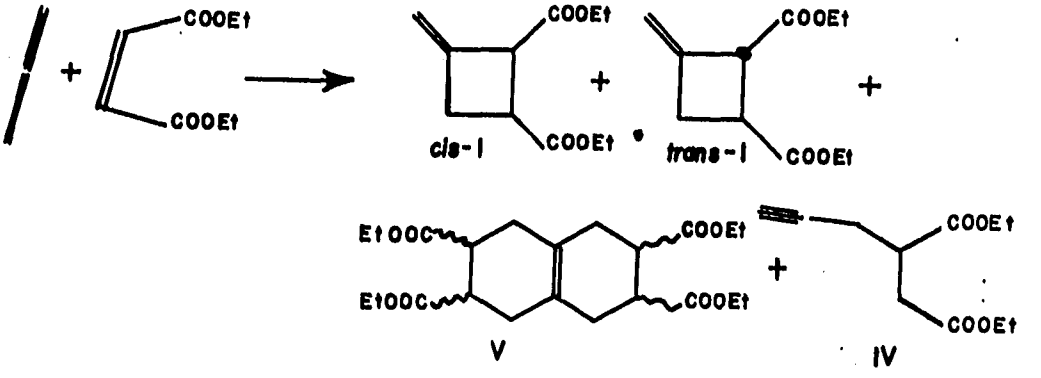
Since the *cis* products are slowly converted to the *trans* products under the reaction conditions, the exact amount of *trans* formed from maleate is uncertain, but the finding of any *trans* products makes it improbable that the reaction is completely concerted.

In this dissertation further experimental evidence on the stereochemistry of the addition of allene to diethyl maleate and diethyl fumarate is given. Pure (99.5%) diethyl fumarate and allene in benzene solution

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

in a stainless steel autoclave at 200° afforded diethyl *trans*-3-methylenecyclobutane-1,2-dicarboxylate (*trans*-I) and no *cis*-I within the limits of detection (0.2%). In addition, a product of an ene reaction (IV) and a product from reaction of allene dimer (V) are formed. However, in the reaction of diethyl maleate (99.7%) with allene under the same conditions a mixture of *cis*-I and *trans*-I are produced, in addition to IV and V. Repetition two years later in another autoclave gave the same result. Two control experiments established that *cis*-I remained unchanged

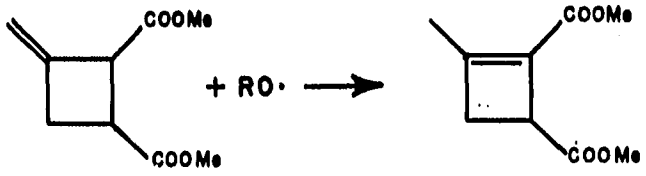




Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

stereochemically when heated at 204° for 8 hours, and that recovered maleate had the same purity as starting maleate (99.7%).

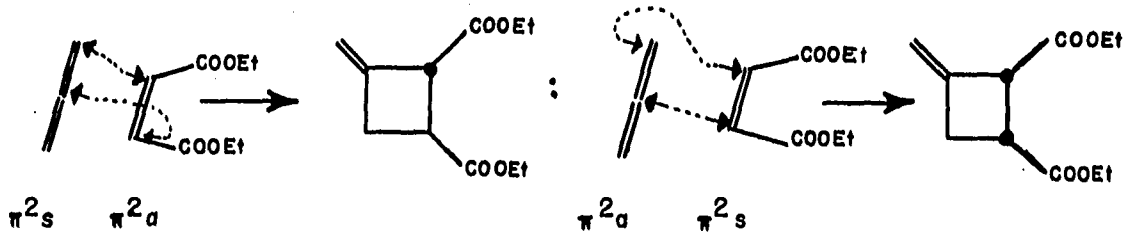
The possibility that the *trans*-I from the maleate reaction might have resulted from a radical reaction with *cis*-I was examined. Heating dimethyl *cis*-I and di-*t*-butyl



peroxide in benzene at 204° produced no detectable *trans*-I, but yielded instead as product of isomerization, dimethyl 1-methylcyclobutene-2,3-dicarboxylate. It is concluded that *trans*-I is a primary product of the reaction of allene and diethyl maleate.

For both the *cis*-I and *trans*-I to be formed by a $[\pi 2_s + \pi 2_a]$ orbital symmetrically allowed process, it is only necessary that the two components be able to act in both the $\pi 2_s$ and the $\pi 2_a$ manner. In order for *trans*-I to result, the diethyl maleate must play the role of $\pi 2_a$ (antarafacial addition) and the allene $\pi 2_s$ (suprafacial addition). *Cis* -I is then formed when allene acts as the $\pi 2_a$ component and maleate as $\pi 2_s$. Similarly in the addition of allene to diethyl fumarate, *cis*-I would result from fumarate assuming

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



the π^2_a role and allene the π^2_s role while *trans*-I would result from allene assuming the π^2_a role and fumarate the π^2_s role. The fact that no *cis*-I is detectable in the fumarate reaction is then to be explained by the assumption of a much higher energy difference between the two possible choices. The alternative explanation involves the "diradical" or stepwise mechanism. Even here, it is not clear whether the whole reaction proceeds by a diradical or whether only the 15% which produces *trans*-I proceeds in this way and the remaining 85% produces *cis*-I in a concerted manner. The results at hand do not allow one to make a choice. In the diradical mechanism, it is still necessary to explain why no *cis*-I is produced in the fumarate reaction. We propose that the driving force which would relieve strain caused by steric crowding of the *cis* ester groups is not present in the reaction of fumarate where the ester groups are already *trans* to each other and free of strain.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

CHAPTER IV: EXPERIMENTAL

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Infrared spectra were taken on Perkin-Elmer spectrophotometers model 421 and 337. NMR spectra were taken on Varian spectrometers model A-60, T-60 and HA-100. Melting points are uncorrected. Rotations were taken on a Perkin-Elmer model 141 polarimeter in an air conditioned room maintained at 25° ± 1°. Therefore all rotations were taken at the temperature of 25° ± 1°. Gas chromatographic separations and analyses were done on an Aerograph model A-90-P3. The following columns were used:

Column A: 3 m x 1/4 in. O.D.: 20% Diethyleneglycol succinate on 50/60 mesh Anakrom - acid and base washed and silanized (ABS)

Column B: 3 m x 1/4 in. O.D.: 20% General Electric methyl silicone gum rubber (SE-30) on 50/60 mesh Anakrom ABS

Column C: 4 m x 1/4 in. O.D.: 10% $AgBF_4$ and 10% carbowax 20 m on 60/80 mesh Chromosorb Pink

Column D: 1 m x 1/4 in. O.D.: 15% Cyanoethyl silicone fluid (XF-1150) on 50/60 mesh Anakrom ABS

Column E: 1 m x 1/4 in. O.D.: 15% Diethyleneglycol succinate on 50/60 mesh Anakrom ABS

Column F: 1 m x 1/4 in. O.D.: 15% General Electric methyl silicone gum rubber (SE-30) on 50/60 mesh Anakrom ABS

Unless otherwise noted, ethanol used as solvent for obtaining rotations is absolute ethanol.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Diethyl trans-3-methylenecyclobutane-1,2-dicarboxylate (trans-I):

Diethyl fumarate (Aldrich) was fractionally distilled three times through a 1 m Stedman column operated at a throughput which resulted in an efficiency of 80 plates. After these distillations no diethyl maleate was detectable by v.p.c. under conditions where 1% diethyl maleate was clearly detectable in a 1:99 synthetic mixture on Column A.

Diethyl fumarate, 645 g (3.75 m), 500 ml benzene, 100 g (2.5 m) allene and 0.5 g hydroquinone were placed in a 1-gallon stainless steel stirred autoclave (Autoclave Engineers). Heating and stirring were begun; after 2 hr 200° was reached and then maintained for 8 hr. Cooling to room temperature took 1 hr.

Benzene and excess diethyl fumarate were removed by vacuum distillation, leaving a residue which was distilled at 85-100°/1.5 mm. A second distillation afforded 64.0 g (b.p. 130-138°/15 mm) of a mixture of diethyl *trans*-3-methylenecyclobutane-1,2-dicarboxylate (*trans*-I) and diethyl 2-propynylsuccinate in a ratio of 6.1/1. (v.p.c. column A). The yield of *trans*-I was 55.0 g or 10.5% of theory based on allene. (Reported by Sharkey and Cripps[62], 10% of th.; b.p. 138-140°/22 mm).

---

62. H. N. Cripps, J. K. Williams and W. H. Sharkey, *J. Am. Chem. Soc.*, 81, 2723 (1959).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

No diethyl *cis*-3-methylenecyclobutane-1,2-dicarboxylate (*cis*-I) was detected by v. p. c. on column A under conditions where 1% could have been detected.

Diethyl cis-3-methylenecyclobutane-1,2-dicarboxylate (cis-I):

Diethyl maleate was distilled four times through the 1 m Stedman column. Thereafter no diethyl fumarate was detectable by v. p. c. on column A in the maleate, under conditions which easily detected 1% diethyl fumarate in a synthetic mixture.

To the 1-gallon stainless steel autoclave was added 750 g diethyl maleate (4.5 m), 500 ml benzene, 0.5 g hydroquinone and 120 g (3 m) allene. Over a period of 1.5 hr with stirring the temperature was raised to 200° where it was maintained for 8 hr. Cooling to room temperature took 1 hr. After removal of benzene and excess diethyl maleate by distillation at the pressure of the aspirator, the residue was distilled at 85-98°/1.5mm to give 21.5 g of a mixture which was shown by analysis by v. p. c. on column A to consist of 9.8% diethyl *trans*-3-methylenecyclobutane-1,2-dicarboxylate (*trans*-I), 63.2% *cis*-I and 27% diethyl 2-propynylsuccinate. The yield of methylenecyclobutanes was 15.3 g (2.4% of theory based on allene). The *trans*-I was identical to the product from diethyl fumarate

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

and allene. [I.R. and retention time on column A.] Repetition with 600 g diethyl maleate, 68 g allene, 500 ml benzene and 0.5 g hydroquinone afforded 15.5 g of the mixture which consisted of 10% *trans*-I, 55.5% *cis*-I and 34.5% diethyl 2-propynylsuccinate. Yield of methylenecyclobutanes is 10 g (2 . 8% of theory based on allene).

Approximately two years later and in a different autoclave of the same specifications, the reaction was repeated. A 920 g sample of carefully distilled (3x through the Stedman column) diethyl maleate (shown by v. p. c. on column A to consist of 99.83% diethyl maleate and 0.17% diethyl fumarate) 800 ml benzene, 1 g hydroquinone and 130 g allene were placed in a 1-gallon stainless steel autoclave and stirred and heated for 8 hr at 200-202°. After the reaction mixture had been removed from the autoclave and filtered, it was analyzed immediately by v. p. c. on column A to reveal the formation of 17.2 g of methylenecyclobutanes (2.5% of theory based on allene). This product consisted of 16.0% *trans*-I and 68.0% *cis*-I. The recovered diethyl maleate contained 0.24% diethyl fumarate.

Thermal stability of diethyl maleate:

Diethyl maleate (250 mg) (shown by v. p. c. on column A to consist of 99.83% diethyl maleate and 0. 17%

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

diethyl fumarate and 4.0 ml of benzene were sealed in a thick walled glass ampoule (8 ml) and heated to 204° for 10 hr. Analysis by v. p. c. of column A revealed 99.82% diethyl maleate and 0.18% diethyl fumarate.

Stability of dimethyl cis-3-methylenecyclobutane-1,2-dicarboxylate (cis-I):

a) thermal stability:

A mixture (100 mg) of 1.5% *trans*-I and 98.5% *cis*-I (v. p.c. on column A showed 1.45% *trans*-I and 98.55% *cis*-I), 4.0 ml of freshly distilled benzene and 10 mg hydroquinone were sealed in a thick walled glass ampoule (8 ml) without flushing with nitrogen. The tube was heated to 202° for 8 hr. Analysis by v. p. c. on column A revealed 1.54% *trans*-I and 98.46% *cis*-I.

b) stability in the presence of free radicals:

Pure *cis*-I (100 mg), 3.0 ml benzene and 30 mg di-*t*-butyl peroxide were sealed in a tube and heated at 204° for 8 hr. The resulting mixture, analyzed by v. p. c. on column A consisted of 13.6% dimethyl 3-methylcyclobutene-1, 2-dicarboxylate (II), 86.4% *cis*-I, but no *trans*-I. In a control experiment in which an identical tube was prepared without any peroxide and was heated the same length of time, unchanged *cis*-I was recovered.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

3-methylenecyclobutane-1, 2-carboxylic anhydride:

To a 1-gallon stainless steel, stirred autoclave was added 500 g recrystallized ($CHCl_3$) maleic anhydride, 0.5 g hydroquinone and 600 ml benzene. Allene (90 g) was introduced through a gas inlet and the mixture was heated at 200° for 7 3/4 hr. After being cooled, filtered, and freed of solvent at reduced pressure, distillation separated maleic anhydride and a fraction boiling at 85-105°/10.5 mm (108 g). Three redistillations of this fraction through an 18-in. vacuum-jacketed Vigreux column gave 62.0 g of 3-methylenecyclobutane-1,2-dicarboxylic anhydride.b.p. 96-98°/1mm; 20.3% of th. yield. This product showed no absorption at 3300 cm^{-1} in the IR spectrum, the position of a very strong peak in the IR spectrum of Propynlsuccinic anhydride.

Cis-3-methylenecyclobutane-1,2-dicarboxylic acid:

Pure 3-methylenecyclobutane-1,2-dicarboxylic anhydride (25.0 g) and 12.5 ml H_2O were stirred together in a 250-ml beaker and gradually heated. At 80° the mixture became homogeneous and an exothermic reaction set in. Heating was discontinued and the excess water was removed by drying the mixture in a desiccator under vacuum. The resulting crude product was recrystallized

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

twice from benzene (250 ml) giving 27.2 g diacid m.p. 130-131°; 96.5% of th. yield.

Trans-3-methylenecyclobutane-1,2-dicarboxylic acid:

Diethyl *trans*-3-methylenecyclobutane-1,2-dicarboxylate (15.0 g; 0.061 m) was added to 150 ml 7% aqueous HCl and refluxed until the solution became homogeneous (3.5 hr). The cooled solution was extracted with five 50-ml portions of ether. The extract was dried over $MgSO_4$ and concentrated to a residue which was crystallized from 150 ml toluene to give 7.1 g colorless crystals; m.p. 127-129°; 65% of th. yield.

Ethyl 3-carbethoxycyclobut-1-ylidene acetate (III):

A horizontal-flow pyrolysis apparatus was constructed. It consisted of a flow tube 35 cm long and 3.8 mm i. d. was filled with glass helices, heated by a suitable furnace, connected at one end through a ground-glass joint to a reservoir flask and at the other end through a ground-glass joint to a spiral condenser trap and a source of vacuum. Diethyl *trans*-3-methylenecyclobutane-1,2-dicarboxylate (8.0 g) was placed in the reservoir; the furnace was heated to approx. 550° and a vacuum of 0.5 mm was applied. A heating bath at 100-120° was placed under the reservoir

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

and the material transferred from the reservoir to the trap in approx. 45 min. The condensate contained 32% *trans*-I, 17% *cis*-I and 51% III. Distillation through a 20 cm. Vigreux column afforded two fractions: A, 3.5 g, b.p. 55-65°/0.5 mm, and B, 4.0 g, b.p. 72-75°/0.5 mm. Fraction A consisted of 55.5% *trans*-I 38% *cis*-I and 7.5% III; whereas, B consisted of 3% *trans*-I, 12% *cis*-I and 85% III. As shown by v. p. c. analysis on column A.

3-carboxycyclobut-1-ylidene acetic acid:

A 10.0-g sample of 95% pure III was added to 50 ml 5% HCl and refluxed one hour longer than required to make the solution homogeneous (4 hr). The cooled solution was extracted with five 200-ml portions of ether. Removal of the solvent at reduced pressure gave a residue which, after two recrystallizations from toluene, afforded 3-carboxycyclobut-1-ylidene acetic acid: 6.5 g; m.p. 150-151° 87% of th. yield.

3-methyl-2-cyclobutene-1,2-dicarboxylic acid:

A modification of the procedure of Sharkey and Cripps[63] was followed in which 30.0 g of 3-methylenecyclobutane-1,2-dicarboxylic anhydride was added rapidly

---

63. H. N. Cripps, J. K. Williams, V. Tullio and W. H. Sharkey, *J. Am. Chem. Soc.*, 81, 4904 (1959).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

to a stirred solution of 30.0 g NaOH in 90 ml H_2O. After 0.5 hr the mixture warmed and became homogeneous. After reacting overnight, the mixture was acidified with concentrated HCl and filtered 6 hr later. Recrystallization from 120 ml H_2O yielded 3-methyl-2-cyclobutene-1,2-dicarboxylic acid (II); 29.0 g (86% of th. yield); m.p. 180-182°.

3-Trideuteriomethyl-2-cyclobutene-1,2-dicarboxylic acid (II-d_3):[64]

A solution of 50.0 g of diacid (II), 55.0 g $NaHCO_3$, and 6.0 g NaOH in 175 ml of 70% D_2O was refluxed for 12 hr. The NMR spectrum of the reaction solution showed a ratio of CH(3.5 ppm):CH_2(2.3 to 2.7 ppm): CH_3 (2.05 ppm) protons to be 0.95:2.0:2.2. After removal of the water by vacuum distillation, 175 ml 85% D_2O and 3.0 g NaOH was added. The solution was refluxed for 14 hr, after which the proton ratio was 1.0:2.0:0.67. The procedure was repeated with 175 ml fresh 99.8% pure D_2O and 2.0 g NaOH. The mixture was refluxed for 12 hr but after the first 6 hr no further change in the NMR proton ratios was observed. The final proton ratio was 1.03:2.0:0.38. The D_2O was removed by vacuum distillation and 200 ml of 5*N* HCl added. The resulting solid was filtered and recrystallized

---

64. This preparation was patterned after the method of J. G. Atkinson, J. J. Csakvary, G. T. Herbert and R. S. Stuart, *J. Am. Chem. Soc.*, 90, 498 (1968).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

from 130 ml H_2O to yield 3-trideuteriomethyl-2-cyclobutene-1,2-dicarboxylic acid (II-d_3): 37.0 g (75% of th. yield); m. p. 179-180°.

Cis-3-dideuteriomethylenecyclobutane-1,2-dicarboxylic acid (cis-I-d_2):

Several exploratory experiments indicated that best yields were obtained with small quantities. A solution of 10.0 g of II-d_3, 100 ml acetic anhydride and 8 ml pyridine was refluxed for 40 min and then concentrated at aspirator pressure. The black residue was distilled at 0.1 mm giving between 3.5 and 4.6 g distillate per batch, b. p. 90-110°/0.5 mm. Combining the distillates from the reaction of 37 g of diacid afforded 15.5 g of crude product which was redistilled to give material (13.0 g; b.p. 92-100°/0.1 mm) which was heated with 6.5 g H_2O until the solution became homogeneous. Benzene (200 ml) was added and the mixture was distilled until excess water had been removed. The remaining benzene solution was evaporated to 75 ml and allowed to crystallize to yield 3-dideuteriomethylene-cyclobutane-1,2-dicarboxylic acid; 9.6 g (26% of theory based on 3-trideuteriomethyl-2-cyclobutene-1,2-dicarboxylic acid); m. p. 129-130°.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Resolution of cis-3-methylenecyclobutane-1,2-dicarboxylic acid (cis-I);

Attempts to resolve *cis*-3-methylenecyclobutane-1,2-dicarboxylic acid by recrystallization of alkaloid salts were complicated by considerable conversion to 3-methyl-2-cyclobutene-1,2-dicarboxylic acid apparently caused by the heating required to effect solution. The following method of resolution avoids this difficulty.

Quinidine (83.2 g; 97% of 1 equivalent) was dissolved in a stirred solution of 42.0 g *cis*-3-methylenecyclobutane-1,2-dicarboxylic acid in 600 ml absolute ethanol. On standing overnight the solution deposited a crystalline salt: 43.0 g; $[\alpha]_{546}$ +230° (c= 1.17 in 50% EtOH). This material was dissolved in 2*N* HCl and extracted with five 300-ml portions of ether. When the ether was removed by distillation, diacid was obtained: 13 g; m. p. 81-100°; $[\alpha]_{546}$ +49.9°; $[\alpha]_{578}$ +42.8°; (c= 1.13 in EtOH). This material was dissolved in 75 ml benzene by heating and allowed to crystallize overnight; 6.1 g; m. p. 122-126°; $[\alpha]_{546}$ +7.51°; $[\alpha]_{578}$ +6.05°; (c= 1.37 in EtOH). The benzene filtrate was reduced to a volume of 20 ml and allowed to crystallize in four days: 3.8 g; m.p. 96-100°; $[\alpha]_{546}$ +90.5°; $[\alpha]_{578}$ +78.2°; (c= 1.41 in EtOH). Recrystallization from 8 ml benzene (3 days) afforded diacid: 3.2 g; m.p. 98-106°; $[\alpha]_{546}$ +96.5°; $[\alpha]_{578}$ +83.6°;

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

$[\alpha]_{436}$+182.0°; (c= 1.53 in EtOH). A second recrystallization from benzene (3 days) afforded diacid: 2.8 g; m.p. 105-107°; $[\alpha]_{546}$+100.9°; $[\alpha]_{578}$+87°; $[\alpha]_{436}$+189.5° (c= 1.52 in EtOH). A third recrystallization from 8 ml benzene (2 days) yielded diacid; 2.4 g; m.p. 105-107°; $[\alpha]_{546}$+100.8°; $[\alpha]_{589}$+83.2°; $[\alpha]_{578}$+87.3°; $[\alpha]_{436}$194.8°; (c= 1.13 in EtOH). Dried at 0.2 mm, this material had m.p. 105-107°; $[\alpha]_{546}$+100.8°; $[\alpha]_{589}$+83.2°; $[\alpha]_{578}$+87.4°; $[\alpha]_{436}$+190.1°; (c= 1.17 in EtOH). The mother liquor from formation of the acid quinidine salt of *cis*-I was evaporated to dryness in a vacuum desiccator. The resulting amorphous material was dissolved in 2*N* HCl and extracted with five 300 ml portions of ether. Removal of ether afforded diacid: 27 g; $[\alpha]_{546}$-28°; (c= 2.1 in EtOH). The diacid (14 g) was recrystallized from 75 ml benzene (overnight): 8.3 g; $[\alpha]_{546}$ -3.7°. The benzene filtrate from this crystallization was concentrated to 15 ml and, after crystallization for five days, afforded diacid: 3.0 g; m.p. 94-105°; $[\alpha]_{546}$-89.0°; $[\alpha]_{578}$-76.5°; (c= 1.53 in EtOH). Further recrystallization from 25 ml benzene (3 days) afforded diacid: 2.3 g; m.p. 102-107°; $[\alpha]_{546}$-96.0°; $[\alpha]_{578}$-83.3° (c= 1.54 in EtOH). A third recrystallization from 3.0 ml benzene (3 days) afforded diacid: 1.7 g; m.p. 105-107°; $[\alpha]_{546}$-100.0°; $[\alpha]_{578}$-87.8°; $[\alpha]_{436}$-189.5° (c= 1.13 in EtOH). Further recrystallization from 4 ml benzene (two days)

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

afforded diacid which was dried at 0.1 mm: 1.7 g; m.p. 105.5-107°; $[\alpha]_{546}$-100.8°; $[\alpha]_{589}$-82.6°; $[\alpha]_{578}$-87.2°; $[\alpha]_{436}$-189.5° (c= 1.41 in EtOH).

Further recrystallization of both enantiomers failed to effect further change in rotation or melting point.

Resolution of trans-3-methylenecyclobutane-1,2-dicarboxylic acid (trans-I):

Quinine (37.0 g; 97% of one equivalent) was dissolved in a stirred solution of 17.8 g *trans*-3-methylenecyclobutane-1,2-dicarboxylic acid in 160 ml absolute ethanol. On standing for two weeks the solution deposited a crystalline salt: 10.5g; $[\alpha]_{546}$-196° (c= 1.03 in 50% EtOH). This material was dissolved in 2*N* HCl and extracted with five 100-ml portions of ether. When the ether was removed by distillation, diacid was obtained: 3.3 g; $[\alpha]_{546}$+27.2°; (c= 1.17 in EtOH). This material was dissolved in 125 ml benzene by heating and allowed to crystallize overnight: 2.0 g; $[\alpha]_{546}$+7.5° (c= 1.45 in EtOH). The benzene filtrate was reduced to a volume of 25 ml and allowed to crystallize for twelve days: 0.6 g; m.p. 87.5-91°; $[\alpha]_{546}$+68.8°; (c= 1.23 in EtOH). Recrystallization from 3 ml benzene (6 days) afforded diacid: 0.5 g; m.p. 91.5-92°; $[\alpha]_{546}$+71.1°; (c= 1.10 in EtOH). Recrystallization from 3 ml benzene (5 days) afforded diacid: 0.45 g; m.p. 91-92°; $[\alpha]_{546}$+70.8°; (c= 1.05 in EtOH).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

The mother liquor from formation of the acid quinine salt of *trans*-I was evaporated to dryness in a vacuum desiccator. The resulting amorphous material was dissolved in 2*N* HCl and extracted with five 100-ml portions of ether. Removal of ether afforded diacid: 9.9 g; $[\alpha]_{546}$ -9.3°; (c= 1.67 in EtOH).

Dimethyl <u>cis</u>-3-methylenecyclobutane-1,2-dicarboxylate (<u>cis</u>-I) - optically active:

Sufficient ethereal diazomethane to cause lingering yellow color was added to an ether (50 ml) solution of *cis*-3-methylenecyclobutane-1,2-dicarboxylic acid: 250 mg; $[\alpha]_{546}$ +98.7°; $[\alpha]_{578}$ +86.2; $[\alpha]_{589}$ +81.8; (c= 1.55 in EtOH). After sitting for one hour at room temperature, the yellow solution was extracted with three 20-ml portions of 5% $NaHCO_3$ and then three 20-ml portions of 2% HCl. The ether solution was dried over $MgSO_4$ and evaporated to a volume of 1 ml. The resulting diester was purified on v. p. c. column D: $[\alpha]_{546}$ +108.8°; $[\alpha]_{578}$ 94.2°; $[\alpha]_{589}$ 90.1°; (c= 1.22 in CCl_4).

Dimethyl <u>trans</u>-3-methylenecyclobutane-1,2-dicarboxylate (<u>trans</u>-I) - optically active:

Sufficient ethereal diazomethane to cause lingering yellow color was added to an ether (50 ml) solution of *trans*-3-methylenecyclobutane-1,2-dicarboxylic acid: 250 mg; $[\alpha]_{546}$ +56.3°; $[\alpha]_{578}$ +50.4°; $[\alpha]_{589}$ +47.7°; (c= 1.30 in EtOH).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

After sitting one hour at room temperature, the yellow solution was extracted with three 20-ml portions of 5% $NaHCO_3$ and then three 20-ml portions of 2% HCl. The ether solution was dried over $MgSO_4$ and evaporated to a volume of 1 ml. The resulting diester was purified on v. p. c. column D: $[\alpha]_{546}$ +60.1°; $[\alpha]_{578}$ +53.8°; $[\alpha]_{589}$ +51.0°; (c= 1.26 in CCl_4).

Isomerization of optically active dimethyl trans-3-methylene-cyclobutane-1,2-dicarboxylate (trans-I):

To 5 ml of a 3% solution of NaOMe in methanol was added 500 mg of *trans*-I with rotation $[\alpha]_{546}$ -49.0° (c= 4.31 in CCl_4). After one hr at room temperature, the reaction mixture was poured into 30 ml-H_2O, acidified with HCl and extracted with three 10-ml portions of ether. Analysis by v. p. c. on column B showed virtually complete conversion to dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate (II). A sample collected by v. p. c. (column B) showed $[\alpha]_{546}$ +4.12° (c= 4.61 in CCl_4). The IR spectrum was identical to that of the sample obtained from *cis*-I below.

Isomerization of optically active dimethyl cis-3-methylene-cyclobutane-1,2-dicarboxylate (cis-I):

To 3.0 ml of 3% NaOMe in methanol was added 300 mg of *cis*-I: $[\alpha]_{546}$ +86.3°; (c= 4.45 in CCl_4). After one hr the reaction mixture was poured into 18 ml H_2O, acidified with HCl and extracted with three 10-ml portions

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

of ether. Analysis by v. p. c. on column B showed virtually complete conversion to II. A sample collected by v. p. c. (column B) had a specific rotation, $[\alpha]_{546}$ -4.95°; (c= 3.95 in CCl_4) and had an IR spectrum (see appendix of spectra) identical to the sample obtained from *trans*-I. (see above)

Conversion of dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate (II) to 1,2,3-trimethyl cyclobutene:

II (6.0 g; 0.0326 mole; $[\alpha]_{546}$ +6.06°; $[\alpha]_{578}$ +4.37°; (c= 1.42 in CCl_4); 97.5% optical pure), prepared from the corresponding diacid by reaction of ethereal diazomethane, was dissolved in 50 ml dry THF and added slowly to a stirred mixture of 1.6 g LAH and 75 ml THF under nitrogen. After addition was complete, the mixture was refluxed for 2 hr. To the cooled mixture was added successively 1.6 ml H_2O, 1.6 ml 15% NaOH, and 4.8 ml H_2O. A colorless precipitate was removed by filtration. The THF solution was dried over $MgSO_4$ and distilled at atmospheric pressure to remove solvent; 1-methyl-2,3-di(hydroxymethyl)cyclobutene was distilled at 93-94°/0.25 mm giving 2.6 g; 62.5% of th. yield; $[\alpha]_{546}$ +142.5° (c= 4.15 in $CHCl_3$). IR spectrum included in appendix of spectra.

The diol above (2.6 g [0.0203 mole]) was added to 10 ml dry benzene, cooled in ice, stirred with a magnetic

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

stirrer and treated with a solution of 3.85 g (0.0139 mole) PBr_3 in 5 ml benzene. The mixture was then stirred for 2 hr at room temperature. After removal of benzene at aspirator pressure the product was distilled at 100-101°/0.5 mm to give 2.5 g (45% of th. yield) of 1-methyl-2,3-di(bromomethyl)-cyclobutene: $[\alpha]_{546}$-30.2° (c= 4.54 in CCl_4). IR spectrum is included in appendix of spectra.

The dibromide was reduced in a 150-ml, 3-necked round bottom flask fitted with a magnetic stirrer, addition funnel, nitrogen inlet reaching to the bottom of the flask, and an outlet to a spiral trap protected by a Drierite tube.

To a mixture of 3.0 g LAH (0.079 mole) and 25 ml *bis*-(2-ethoxyethyl)ether placed in the flask, there was slowly added 2.5 g (0.01 mole) of the dibromide mixed with 5.0 ml *bis*-(2-ethoxyethyl)ether. A slow stream of nitrogen was passed through the system. Thirty minutes after the addition was complete, the mixture was heated to 50° for one hr. At the end of this time, 0.87 g (98% of th. yield) of impure 1,2,3 trimethylcyclobutene was removed from the cold trap. This product proved to be approximately 96% pure by v. p. c. on column C. The specific rotation of the product was $[\alpha]_{546}$+25.0°; $[\alpha]_{578}$+21.3°; $[\alpha]_{589}$+20.2°; (c= 1.37 in CCl_4). IR and NMR spectra are included in the appendix of spectra.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

3-Methylhexane-2,5-dione:

a) from ozonolysis of 1,2,3-trimethylcyclobutene:

The above trimethylcyclobutene [0.5 g, (0.052 mole)] was added to 20 ml methanol which was cooled to and maintained at -35° in a "vacuum trap" fitted with a fritted glass inlet and a drying tube on its outlet. Ozone was produced at the rate of 1.8 g/hr and bubbled through the solution for 0.5 hr. The solution was then allowed to warm to 0° and treated with 3.0 g KI and 3.5 ml glacial acetic acid. The resulting purple color was destroyed by adding a dilute solution of thiosulfate. The cool solution was extracted with three 50-ml portions of ether; the ether extract was reduced to 3 ml and analyzed by v. p. c. (column B). The single product is presumed to be 3-methylhexane-2,5-dione and had the same retention time on column B as the main product of the reaction of 4 equivalents of methyl lithium with a α-methylsuccinic acid. This product was collected from the v. p. c. (column B) and had: $[\alpha]_{546}$ +66.2°; $[\alpha]_{578}$ +56.6°; $[\alpha]_{589}$ +53.8°; (c= 1.23 in CCl_4). Since the optical purity of the starting material for this sequence was 97.5%, a minimum rotation of optically pure diketone of $[\alpha]_{546}$ +67.8° at (c= 1.23 in CCl_4) may be calculated. The IR spectrum of the diketone was identical to that product of the reaction of α-methyl-succinic acid with methyl lithium having the same retention time on column B.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

b) from reaction of α-methylsuccinic acid with methyl lithium:

α-Methylsuccinic acid was resolved by the method of A. Ladenburg[65] using the acidic strychnine salt. One crystallization gave the (+)-enantiomer which had specific rotation: $[\alpha]_{546}$ +10.0°; $[\alpha]_{589}$ +8.44° (c= 0.9 in H_2O). To a solution of 1.0 g (0.0075 mole) of this acid in 50 ml dry ether, was slowly added 14.3 cc (0.03 mole) of an ethereal solution of commercial methyl lithium (Foote Mineral Co., 2.1 mole/liter). After being stirred for one hr, 3 ml of H_2O was added slowly followed by 10 ml H_2O. The ether layer was retained and reduced to a volume of 3 ml. V. p. c. (column D and column E and column B) showed the major peak to be identical to the product from the reaction of ozone with 1,2,3-trimethylcyclobutene. Since optically pure α-methylsuccinic acid has specific rotation: $[\alpha]_{589}$ +15.5° (H_2O), the starting material was 54.5% of optical purity. Since the diketone obtained in this reaction had specific rotation: $[\alpha]_{546}$ +30.6°; $[\alpha]_{578}$ +26.4°; $[\alpha]_{589}$ +24.7° (c= 0.59 in CCl_4), a minimum specific rotation for the optically pure diketone of $[\alpha]_{546}$ +56.1° (c= 0.59 in CCl_4) can be calculated.

---

65. A.Ladenburg, *Ber.*, 28, 1170 (1895).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Resolution of 3-carboxy-cyclobut-1-ylidene-acetic acid (III):

Two methods of resolution were effective in resolving this diacid: the first, simple resolution via recrystallization of the neutral quinine salt; the second, partial resolution of the diacid by initial formation of the neutral quinine salt followed by repeated recrystallization of the diacid to the point at which no further change occurred on further recrystallization.

I. Diacid (III) (5.0 g) and quinine (20.8 g) were dissolved in 100 ml absolute ethanol. After two days 12.5 g crystalline salt formed: $[\alpha]_{546}$ -236° (c= 1.05 in 50% EtOH) (Ia). Recrystallization from 100 ml of EtOH afforded 10.8 g salt (Ib): $[\alpha]_{546}$ -234° (c= 1.1 in 50% EtOH). The mother liquor from Ia was evaporated to 75 ml and afforded 1.9 g crystalline salt (IIb) (the mother liquor from this salt is designated mother liquor IIb): salt IIb; $[\alpha]_{546}$ -227° (c= 1.30 in 50% EtOH). The mother liquor from Ib was evaporated and used to dissolve fraction IIb. After two days 2.2 g salt had crystallized (IIc): $[\alpha]_{546}$ -231° (c= 1.30 in 50% EtOH). Ib (1.0 g) was recrystallized from 25 ml ethanol to give fraction Ic: 0.75 g; $[\alpha]_{546}$ -234° (c= 1.4 in 50% EtOH). Fraction IIc was recrystallized from 25 ml fresh ethanol to afford fraction IId: 0.5 g; $[\alpha]_{546}$ -235° (c= 1.3 in 50% EtOH). Mother liquor IIb was evaporated to 25 ml and after two days afforded

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

5.6 g salt (IIIc); $[\alpha]_{546}$ -223° (c= 1.2 in 50% EtOH).

Fractions Ib and Ic were combined, dissolved in 25 ml 2*N* HCl and extracted with five 75-ml portions of ether. Removal of solvent left 2.6 diacid (III): $[\alpha]_{546}$ -29.3° (c= 2.3 in EtOH); m.p. 180-182°. Recrystallization from 30 ml toluene afforded 2.1 g diacid: $[\alpha]_{546}$ -31.3° (c= 2.1 in EtOH); m.p. 181-182°.

II. Diacid III (6.6 g) and quinine (27.0 g) were dissolved in 200 ml EtOH and allowed to crystallize for one week. The resulting fraction Ia (17.3 g) was recrystallized from 150 ml EtOH and afforded fraction Ib (14.2 g). Concentration of the mother liquor to 100 ml afforded fraction IIb (5 g). Evaporation of the mother liquor from II to dryness in a vacuum desiccator afforded 11 g of amorphous material (fraction III).

Fraction Ib (14.2 g) was dissolved in 50 ml 2*N* HCl and extracted with seven 100-ml portions of ether. Removal of the ether yielded 2.7 g diacid III: $[\alpha]_{546}$ -22.7° (c= 2.50 in EtOH). A 1.7 g sample was crystallized (2 days) from 75 ml dibutyl ether affording 1.1 g of diacid: m.p. 170-176°; $[\alpha]_{546}$ -24.8°; $[\alpha]_{578}$ -21.7°; (c= 2.40 in EtOH). Recrystallization from 75 ml dibutyl ether (one day) afforded diacid: 0.85 g; m.p. 178-182°; $[\alpha]_{546}$ -30.1°; $[\alpha]_{578}$ -26.5°; $[\alpha]_{589}$ -25.4°; (c= 1.59 in EtOH). A second recrystallization

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

from 75 ml dibutyl ether (one day) afforded 0.75 g crystals; m.p. 181-182°; $[\alpha]_{546}$-31.4°; $[\alpha]_{578}$-27.6°; $[\alpha]_{589}$-26.6°; (c= 1.33 in EtOH). A third recrystallization from 70 ml dibutyl ether (one day) afforded 0.73 g diacid: m.p. 181-182°; $[\alpha]_{546}$-31.4°; $[\alpha]_{578}$-27.6°; $[\alpha]_{589}$-26.7°; (c= 1.26 in EtOH).

The amorphous material (fraction III) was dissolved in 50 ml 2*N* HCl and extracted with seven 100-ml portions of ether. Removal of ether left 2.0 g diacid III: $[\alpha]_{546}$+11.0° (c= 2.16 in EtOH). A 0.9 g sample was recrystallized from 25 ml dibutyl ether (two days) affording 0.6 g diacid: m.p. 157-165°; $[\alpha]_{546}$+12.0°; $[\alpha]_{578}$+9.6°; (c= 0.95 in EtOH). A second recrystallization from 35 ml dibutyl ether (two days) afforded 0.45 g diacid: m.p. 159-169°; $[\alpha]_{546}$+14.8°; $[\alpha]_{578}$+12.7°; $[\alpha]_{589}$+11.6°; (c= 1.05 in EtOH). A third recrystallization from 40 ml dibutyl ether (two days) afforded 0.21 g diacid; m.p. 169-176°; $[\alpha]_{546}$+22.1°; $[\alpha]_{578}$+19.4°; $[\alpha]_{589}$+18.8°; (c= 1.37 in EtOH). A fourth recrystallization from 55 ml dibutyl ether (two days) afforded 0.17 g diacid: m.p. 177-181°; $[\alpha]_{546}$+28.9°; $[\alpha]_{578}$+25.4°; $[\alpha]_{589}$+24.3°; (c= 1.52 in EtOH). A fifth recrystallization from 55 ml dibutyl ether (one day) afforded 0.15 g crystalline diacid: m.p. 181-182°; $[\alpha]_{546}$+31.5°; $[\alpha]_{578}$+27.5°; $[\alpha]_{589}$+26.3°; (c= 0.95 in EtOH). A final recrystallization from 55 ml dibutyl ether (one day) afforded

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

0.14 g crystalline diacid: m.p. 181-182°; $[\alpha]_{546}$ +31.4°; $[\alpha]_{578}$ +27.5°; $[\alpha]_{589}$ +26.4°; (c= 0.91 in EtOH).

Preparation of optically pure 3-methyl-2-cyclobutene-1,2-dicarboxylic acid (II):

Cis-3-methylenecyclobutane-1,2-dicarboxylic acid [(2.0 g); $[\alpha]_{546}$ +91.7°; $[\alpha]_{578}$ +78.5°; $[\alpha]_{589}$ +76.0°; (c= 1.16 in EtOH)] was boiled under reflux in 4 ml acetic anhydride for one hr. After removal of excess acetic anhydride and acetic acid by distillation at the aspirator pressure, 1.7 g product was distilled at 90-92°/0.3 mm (94% of th. yield); $[\alpha]_{546}$ +199.5°; $[\alpha]_{578}$ +172.5°; $[\alpha]_{589}$ +163.7°; (c= 1.92 in $CHCl_3$). This 1.7-g sample of anhydride was reapidly added to a stirred solution of 7.2 ml 25% aqueous NaOH. The solution became hot and, after 0.25 hr, homogeneous. After two hr, the solution was acidified with HCl to afford crystalline diacid II: 1.4 g; m.p. 156-160°; $[\alpha]_{546}$ -9.25°; $[\alpha]_{578}$ -7.32°; $[\alpha]_{589}$ -6.67°; (c= 1.60 in EtOH). Recrystallization from 10 ml H_2O (one day) afforded 1.2 g crystals; m.p. 159-161°; $[\alpha]_{546}$ -9.8°; $[\alpha]_{578}$ -7.8°; $[\alpha]_{589}$ -7.5°; (c= 1.74 in EtOH). A second recrystallization from 3 ml H_2O (one day) afforded 1.1 g diacid: m.p. 161-162°; $[\alpha]_{546}$ -10.2°; $[\alpha]_{578}$ -8.1°; $[\alpha]_{589}$ -7.9°; (c= 0.86 in EtOH). A final recrystallization from 3 ml H_2O (one day) afforded 1.05 g diacid: m.p. 161-162°; $[\alpha]_{546}$ -10.1°; $[\alpha]_{578}$ -8.14°; $[\alpha]_{589}$ -7.10°; (c= 2.04 in EtOH).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Preparation of optically active methyl 3-carbomethoxy-cyclobut-1-ylidene-acetate (III):

Sufficient ethereal diazomethane to cause lingering yellow color was added to an ether (50 ml) solution of 3-carboxy-cyclobut-1-ylidene-acetic acid (III): 250 mg; $[\alpha]_{546}$-31.4°; $[\alpha]_{578}$-27.6°; $[\alpha]_{589}$-26.6°; (c= 1.33 in EtOH). After sitting for one hour at room temperature, the yellow solution was extracted with three 20-ml portions of 5% $NaCO_3$ and then three 20-ml portions of 2% HCl. The ether solution was dried over $MgSO_4$ and evaporated to a volume of 1 ml. The resulting diester was purified on v. p. c. column D: $[\alpha]_{546}$-32.8°; $[\alpha]_{578}$-28.4°; $[\alpha]_{589}$-27.4°; (c= 2.55 in CCl_4).

"High pressure" thermal rearrangement of optically active dimethyl <u>cis</u>-3-methylenecyclobutane-1,2-dicarboxylate (<u>cis</u>-I) in the gas phase:

Cis-I diacid with specific rotation: $[\alpha]_{546}$+98.7±0.6°; $[\alpha]_{578}$+86.2 ± 0.6°; $[\alpha]_{578}$+81.9±0.6°: (c= 1.71 in EtOH), was esterified with diazomethane to afford dimethyl *cis*-I: $[\alpha]_{546}$+108.8±0.6°; $[\alpha]_{578}$+94.2±0.6°; $[\alpha]_{589}$+90.1±0.6° (C= 1.32 in CCl_4). Dimethyl *cis*-I (500 mg) and 10 mg diphenylamine was placed in a 750-ml Pyrex ampoule which had been prepared by washing successively with dil. aqueous amonium hydroxide, distilled water, and acetone, and then drying with a gas flame while blowing out the inside with

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

dry nitrogen. The ampoule was degassed on the vacuum line, sealed at 0.1 micron, and heated at 232° for 5 hr. 232° was reached 20 min after the tube was put in the furnace.

The cooled tube was opened and rinsed twice with 1 cc of ether. The combined rinses were analyzed by v. p. c. on column E and showed 12% conversion to III, 3% conversion to *trans*-I and formation of 0.5% dimethylmaleate (identified by retention time only). Relative retention times were maleate, 1; *trans*-I, 2.6; *cis*-I, 4.0; III, 7.6.

Methyl 3-carbomethoxy-cyclobut-1-ylidene-acetate (III) was collected by v. p. c. on column C: $[\alpha]_{546}$+23.2°±0.2°; $[\alpha]_{578}$+20.3°±0.2°; $[\alpha]_{589}$+19.9°±0.2°; (c= 2.92 in CCl_4).

In order to determine the percent of optical purity retained in the rearrangement it is necessary to calculate the optical purity of the starting material and product. The specific rotations of optically pure *cis*-I diacid are: $[\alpha]_{546}$+100.8°±0.5°; $[\alpha]_{578}$+87.4°±0.5°; $[\alpha]_{589}$+83.2°±0.5°: (c= 1.13 in EtOH). The diacid precursor of the dimethyl ester used in the reaction had specific rotation: $[\alpha]_{546}$+98.7° ±0.6°; $[\alpha]_{545}$+86.2°±0.6°; $[\alpha]_{578}$+81.9°±0.6°; (c= 1.72 in EtOH). The optical purities of the starting material are then at 546 mμ, 98.1%; at 578 mμ, 98.6%; and, at 589 mμ, 98.4%. The specific rotations of optically pure dimethyl ester III follow: $[\alpha]_{546}$+32.8°±0.2°; $[\alpha]_{578}$+28.4°±0.3°; $[\alpha]_{589}$+27.3°±0.3°; (c= 1.27 in CCl_4).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

From the rotations of the product of the rearrangement, calculated optical purities are obtained; at 546 mμ, 70.9%; at 578 mμ, 71.5%; at 589 mμ, 72.7%. The retention of optical activity is then 72.3% at 546 mμ; 72.5% at 578 mμ,; and 73.9% at 589 mμ. (Average is 72.9%).

After adjustment of the retention of optical purity for the amount of racemization occurring in the control reaction (below) the value becomes 74.6%.

Stability of optically active methyl 3-carbomethoxy-cyclobut-1-ylidene-acetate (III):

The reaction was carried out in a 750-ml Pyrex ampoule prepared in the manner described above. III: (100 mg; $[\alpha]_{546}$-31.6°) and 3 mg of diphenylamine were sealed in the ampoule at 0.3 micron after degassing the contents. The ampoule was heated to 233° for five hr. The product consisted of 96.3% starting III and 3.7% *trans*-I. No *cis*-I was detectable. The recovered starting material collected by v. p. c. on column D had rotation of $[\alpha]_{546}$-30.6° (c= 2.12 in CCl_4). (96.6% of the starting rotation).

Hydrogenation of optically active methyl 3-carbomethoxy-cyclobut-1-ylidene-acetate (III):

III [500 mg; $[\alpha]_{546}$+20.7° (c= 1.34 in CCl_4)] was hydrogenated in 7 ml absolute ethanol containing 100 mg 10% palladium-on-charcoal. Approx. 60 ml of hydrogen was

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

taken up. The filtered solution was concentrated to a volume of 1 ml by distillation and analyzed by v. p. c. Only one peak was found on both column E and column F. The product was collected by gas chromatography and had a specific rotation of $[\alpha]_{546}$ -0.002°±0.03 (c= 4.71 in CCl_4).

Thermal rearrangement of dimethyl cis-3-methylenecyclobutane-1,2-dicarboxylate (cis-I) in benzene solution:

Two examples of the rearrangement in benzene solution are given, the one carried to higher conversion resulted in more racemization of the product.

I. *Cis*-I: [200 mg; $[\alpha]_{546}$ -104.2°; $[\alpha]_{578}$ -90.7°; $[\alpha]_{589}$ -88.9° (c= 0.71 in CCl_4)], 20 mg hydroquinone and 3.5 ml freshly distilled benzene were placed in a clean, dry 8-ml thick-walled Pyrex tube. After nitrogen had been flushed through the solution for 15 min, the tube was cooled, sealed, and heated in the tube-furnace for 18 hr at 232°. The resulting mixture was filtered to remove hydroquinone (which had dissolved at the reaction temperature) and concentrated to a volume of 0.5 ml by distillation. Analysis by v. p. c. on column E revealed: 7.9% *trans*-I: $[\alpha]_{546}$ -33.5°; $[\alpha]_{578}$ -32.0°; $[\alpha]_{589}$ -31.2°; (c= 0.26 in CCl_4): 66.7% *cis*-I: $[\alpha]_{546}$ -104.2°; $[\alpha]_{578}$ -90.6°; $[\alpha]_{589}$ -88.9°; (c= 1.01 in CCl_4): 25.4% III: $[\alpha]_{546}$ -17.7°; $[\alpha]_{578}$ -16.5°; $[\alpha]_{589}$ -15.7°; (c= 1.30 in CCl_4). The starting material for this reaction had an optical purity at 546 mμ,

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

94.2%; at 578 mμ, 94.5%; at 589 mμ, 97.0 %. Average: 95.2%. The optical purity of *trans*-I produced in the reaction was: at 546 mμ, 44%; at 578 mμ, 47.2%; at 589 mμ, 48.3%. Average: 46.5%. The optical purity of III is: at 546 mμ, 54.3%; at 578 mμ, 58.2%; at 589 mμ, 57.2%. Average is 56.6%.

II. *Cis*-I [200 mg; $[\alpha]_{546}$-104.2°; $[\alpha]_{578}$-90.7°; $[\alpha]_{589}$-88.9° (c= 0.71 in CCl_4)] and 30 mg of hydroquinone in 4 ml freshly distilled benzene were placed in an 8-ml ampoule which had been washed and dried. After being flushed with nitrogen for 15 min, the tube was cooled, sealed, and heated at 232° for 8 hr. The resulting product mixture was 3.5% *trans*-I: $[\alpha]_{546}$-46.8°; $[\alpha]_{578}$-42.5°; $[\alpha]_{589}$-39.3°; (c= 0.41 in CCl_4): 82.5% *cis*-I with specific rotation identical to starting material: 14% III: $[\alpha]_{546}$-23.5°; $[\alpha]_{578}$-20.4°; $[\alpha]_{589}$-19.4°; (c= 0.96 in CCl_4). Optical purity of starting material was: at 546 mμ, 94.2%; at 578 mμ, 94.5%; at 589 mμ, 97.0%. Average 95.2%. The optical purity of *trans*-I produced in the reaction was: at 546 mμ, 61.2%; at 578 mμ, 62.7%; at 589 mμ, 60.8%. Average: 61.6%. The optical purity of III produced in the reaction was: at 546 mμ, 71.6%; at 578 mμ, 71.8%; at 589 mμ, 71.0%. Average: 71.4%.

Percent retention of optical activity in *trans*-I was: 64.8% at 546 mμ; 66.0% at 578 mμ; 63.2% at 589 mμ. Average: 64.6%. *Trans*-I was found to be totally optically

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

stable under the reaction conditions. Percent retention of optical activity in III was: 75.8% at 546 mμ; 76.1% at 578 mμ; 73.5% at 589 mμ (average 75.1%).

After adjustment for racemization of the III under the reaction conditions (below) the retention of optical activity was: at 546 mμ, 77.4%; at 578 mμ, 78.4%; at 589 mμ, 74.8% (average 76.8%).

Stability of optically active methyl 3-carbomethoxy-cyclobut-1-ylidene-acetate (III) in benzene solution:

III [100 mg; $[\alpha]_{546}$ +21.7°; $[\alpha]_{578}$ +19.1°; $[\alpha]_{589}$ +17.9°; (c= 1.36 in CCl_4)] and 30 mg hydroquinone in 4.0 ml benzene was placed in an 8-ml thick-walled Pyrex tube. The solution was flushed with nitrogen for 15 min. The tube was cooled, sealed and heated for 10 hr at 232°. The tube was opened, the contents filtered, and the filtrate reduced in volume to 0.5 ml by distillation. The recovered material was collected by v. p. c. on column D. Recovered material had specific rotation: $[\alpha]_{546}$ +20.8°; $[\alpha]_{578}$ +18.0°; $[\alpha]_{589}$ +17.3°; (c= 1.71 in CCl_4). Percent racemization was: at 546 mμ, 4.2%; at 578 mμ, 5.6%; at 589 mμ, 3.1% (Average: 4.3%).

"Low pressure" gas phase thermal rearrangement of optically active dimethyl cis-3-methylenecyclobutane-1,2-dicarboxylate (cis-I):

"Low pressure" reactions were carried out in a 12-liter

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

round bottom Pyrex flask in an air thermostat built by G. H. Beasley of the same design described by W. D. Clarke [Dissertation, University of Oregon, 1958]. It was estimated that, under the reaction conditions, 70 mg of *cis*-I would produce a pressure of approximately 1 mm.

The optical stability of methyl-3-carbomethoxy-cyclobut-1-ylidene-acetate (III) was confirmed at 236.5° as a control. III [50 mg; $[\alpha]_{546}$ +20.8°; $[\alpha]_{578}$ +18.0° (c= 1.57 in CCl_4)] was put into the 12-liter flask at 236.5° and allowed to react for 11.5 hr. The material was removed by vacuum transfer and purified by v. p. c. on column D. Rotation of the material purified by v. p. c. was: $[\alpha]_{546}$ +21.2°; $[\alpha]_{578}$ +17.8°; (c= 0.97 in CCl_4). This experiment was repeated at 242° for 11 hr with the same results. III [50 mg; $[\alpha]_{546}$ +20.8°; $[\alpha]_{578}$ +18.0°; $[\alpha]_{589}$ +17.1° (c= 1.57 in CCl_4)] was introduced into the 12-liter flask at 242° and allowed to remain in the flask at 242° for 11 hr. After removal and purification the specific rotation was taken. Recovered III: $[\alpha]_{546}$ +20.4°; $[\alpha]_{578}$ +17.7°; $[\alpha]_{589}$ +16.8° (c= 0.37 in CCl_4).

Three rearrangements at two temperatures are described:

I. Optically active *cis*-I [70 mg; $[\alpha]_{546}$ +94.4°; $[\alpha]_{578}$ +80.2°; $[\alpha]_{589}$ +73.6° (c= 0.33 in CCl_4)] was introduced

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

into the evacuated (0.1 micron) 12-liter flask at 235°. The material was allowed to remain in the flask at 235° for 10 hr. At the end of that time the material was removed by vacuum transfer and analyzed by v. p. c. on column D. The mixture consisted of 11.1% *trans*-I, 65.3% *cis*-I with identical specific rotation of the starting material, and 23.6% III with specific rotation: $[\alpha]_{546}$+12.8°; $[\alpha]_{578}$+11.3°; $[\alpha]_{589}$+10.6°: (c= 0.273 in CCl_4).

II. Optically active *cis*-I [70 mg; $[\alpha]_{546}$+94.4°; $[\alpha]_{578}$+81.2°; $[\alpha]_{589}$+77.6° (c= 1.02 in CCl_4)] was introduced into the evacuated 12-liter flask at 242° and allowed to react for 10 hr. Upon removal from the heating system, the mixture was found to consist of 5.5% *trans*-I, 56.0% *cis*-I with specific rotation identical to that of the starting material, and 38.4% III with specific rotation: $[\alpha]_{546}$+13.8°; $[\alpha]_{578}$+12.1°; $[\alpha]_{589}$+11.7° (c= 0.52 in CCl_4).

III. The procedure of reaction II was repeated exactly with identical material. Recovered starting material had rotations identical to starting material. Percents of *cis*-I, *trans*-I, and III were identical to those from reaction II. Specific rotation of III was: $[\alpha]_{546}$+14.5°; $[\alpha]_{578}$+12.6°; $[\alpha]_{589}$ +12.3°; (c= 0.57 in CCl_4).

Optical purity of starting *cis*-I in all three reactions was: at 546 mμ, 85.2%; at 578 mμ, 84.0%; at 589 mμ, 81.0%.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Optical purity of product (III) from reaction I is: at 546 mμ, 39.0%; at 578 mμ, 39.8%; at 589 mμ, 38.8%. retention of optical activity is: at 546 mμ, 45.7%; at 578 mμ, 47.3%; at 589 mμ, 47.2%, average is 46.7%. Optical purity of product (III) from reaction II is: at 546 mμ, 42.4%; at 578 mμ, 42.7%; at 589 mμ, 42.8%. Retention of optical activity is: at 546 mμ, 49.3%; at 578 mμ, 50.6%; at 589 mμ, 52.8%, average is 50.9%. Optical purity of product (III) from reaction III is: at 546 mμ, 44.2%; at 578 mμ, 44.2%; at 589 mμ, 44.7%. Retention of optical activity is: at 546 mμ, 51.8%; at 578 mμ, 52.6%, at 589 mμ, 55.0%, average is 53.1%.

Gas phase "High Pressure" thermal rearrangements of optically active methyl 3-carboxymethylcyclobut -1-ylidine-acetate: (III):

III [300 mg; $[\alpha]_{546}$ +21.7°; $[\alpha]_{578}$ +18.5°; $[\alpha]_{589}$ +17.7° (c= 1.60 in CCl_4)] and 10 mg diphenylamine was placed in an 800-ml Pyrex ampoule which had been washed with ammonium hydroxide, water and acetone and then flame-dried. The ampoule was degassed, sealed at 10^{-3} mm and heated at 237° for 8 hr. After the cooled tube had been opened, the contents were removed by rinsing with two 1 ml portions of ether. V. p. c. analysis on column D showed the mixture to contain 99.5% starting III: $[\alpha]_{546}$ +21.0°; $[\alpha]_{578}$ +18.2°; $[\alpha]_{589}$ +17.3°; (c= 1.48 in CCl_4): and 0.5% *trans*-I:

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

$[\alpha]_{546}$ -16.4°; $[\alpha]_{578}$ -15.0°; $[\alpha]_{589}$ -14.3° (c= 0.14 in CCl_4).

The optical purity of starting diester was 66.2% at 546 mμ, 65.2% at 578 mμ, and 65.0% at 589 mμ, the optical purity of *trans*-I produced in the reaction was: 21.5% at 546 mμ; 21.9% at 578 mμ; 22.2% at 589 mμ. Although *trans*-I is completely optically stable under the reaction conditions, correction is made for the slight racemization of starting material. This brings the optical purity of *trans*-I to: 21.8% at 546 mμ; 22.1% at 578 mμ; and 22.4% at 589 mμ. Retention of optical activity in the reaction becomes: 32.9% at 546 mμ; 33.9% at 578 mμ; 34.4% at 589 mμ (average is 33.7%).

Stability of methyl 3-carboxymethylcyclobut-1-ylidene-acetate (III) at 24° in gas phase:

III [30 mg; $[\alpha]_{546}$ -24.9°; $[\alpha]_{578}$ -21.7°; $[\alpha]_{589}$ -20.2°; (c= 1.07 in CCl_4)] and 5 mg of diphenylamine in a 500-ml Pyrex ampoule which had been soaked in ammonium hydroxide, water and acetone and flame-dried using a stream of nitrogen. The ampoule was degassed, sealed at 10^{-3} mm and heated at 240° for 5 hr. The contents were removed by rinsing with two 1-ml portions of ether and analyzed by v. p. c. on column D: 98% III $[\alpha]_{546}$ -24.2°; $[\alpha]_{578}$ -21.1°; $[\alpha]_{589}$ -19.4°; (c= 2.21 in CCl_4); and 2% *trans*-I.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

"High Pressure" gas-phase thermal rearrangement of trans-3-methylenecyclobutane-1,2-dicarboxylate (trans-I):

Trans-I [300 mg; $[\alpha]_{546}$ -41.0°; $[\alpha]_{578}$ -37.1°; $[\alpha]_{589}$ -34.6°; (c= 1.37 in CCl_4)] and 10 mg diphenylamine were placed in a 500-ml ampoule which had been soaked in ammonium hydroxide solution, water and acetone and flame-dried while flushing with nitrogen. The material was degassed and the tube was sealed at 10^{-3} mm and then heated at 240° for 5 hr. The cooled tube was opened and rinsed with two 1-ml portions of ether. V. p. c. analysis on column D showed the mixture to consist of 90% *trans*-I of unchanged rotation and 10% of III: $[\alpha]_{546}$ +5.65°; $[\alpha]_{578}$ +5.05°; $[\alpha]_{589}$ +4.95°; (c= 0.93 in CCl_4). Optical purity of the III produced in the reaction is: 16.9% at 546 mμ; 17.7% at 578 mμ; and 18.1% at 589 mμ; (average is 17.6%). After correction for racemization of III under reaction conditions (above) the optical purity of the product is: 17.1% at 546 mμ; 18.0% at 578 mμ; and 18.4% at 589 mμ; (average is 17.8%). Retention of optical activity is then calculated to be: 31.8% at 546 mμ; 33.1% at 589 mμ; and 34.1% at 589 mμ; (average is 33.0%).

Hydrolysis of (-)-methyl 3-carbomethoxycyclobut-1-ylidene-acetate, (-)-III, by α-chymotrypsin:

Preliminary experiments with racemic III established that the (-)-enantiomer is hydrolyzed more rapidly by

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

α-chymotrypsin than the (+)-enantiomer. Therefore, (-)-enantiomer was chosen for this preparation.

III [0.60 g; $[\alpha]_{546}$ -31.4°; $[\alpha]_{578}$ -28.0°; $[\alpha]_{589}$ -27.3°; (c= 3.15 in CCl_4)] was added in a single portion to a rapidly stirred solution of 75 mg α-chymotrypsin (3x recrystallized material obtained from Pierce Biochemicals, Rockford, Ill.) and 15 ml of phosphate buffer at pH 7.4. The pH was maintained at 7.4 to 7.6 by periodic addition of 1*N* NaOH solution (3.26 ml = 1 equiv.). The solution was extracted with two 100-ml portions of ether after 2.9 ml of 1*N* NaOH had been consumed, then acidified to pH 2 and extracted with five 100-ml portions of ether. This second extract afforded 495 mg of half ester upon evaporation of solvent [100% of th. yield based on 2.9 ml NaOH solution added; $[\alpha]_{546}$ -44.3°; $[\alpha]_{578}$ -38.9°; $[\alpha]_{589}$ -36.3°; (c= 1.98 in $CHCl_3$)].

Hydrolysis of (+)-dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate with α-chymotrypsin:

Dimethyl 3-methyl-2-cyclobutene-1,2-dicarboxylate [1.4 g $[\alpha]_{546}$ +5.8°; $[\alpha]_{578}$ +4.0°; (c= 1.43 in CCl_4)]; obtained by reaction of diazomethane in ether with the corresponding diacid of specific rotation: $[\alpha]_{546}$ +9.7° (c= 2.21 in EtOH) (97% of optical purity) was added to a rapidly stirred solution of 175 mg α-chymotrypsin in 28 ml of phosphate buffer (pH 7.4) and 2.0 ml acetonitrile. The pH was maintained between 7.4 and 7.6 by addition of 1*N*

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

NaOH (7.65 ml = 1 equiv.). When 7.3 ml of 1*N* NaOH had been added over a period of 9 hr, the reaction was stopped by extracting with three 10-ml portions of ether, acidifying to pH 2 with HCl, and extracting with five 10-ml portions of ether. This second extract was dried over $MgSO_4$ and concentrated to afford 1.1 g (89% of th. yield) of half ester: $[\alpha]_{546}$-11.6°; $[\alpha]_{578}$-10.6°; $[\alpha]_{589}$-10.2°; (c= 1.19 in $CHCl_3$).

3-Carbomethoxycyclobut-1-ylidene-acetyl chloride:

The proceeding sample of 3-carbomethoxycyclobut-1-ylidene-acetic acid (700 mg) was added to a solution of 20 ml dry benzene and 550 mg (1.1 equiv.) of thionyl chloride. The solution was refluxed for 4 hr and then distilled at atmospheric pressure to remove solvent and excess thionyl chloride. Distillation of product at reduced pressure afforded 690 mg 3-carbomethoxycyclobut-1-ylidene-acetyl chloride: b.p. 84°/0.2 mm; 87% of th. yield; $[\alpha]_{546}$-16.9°; $[\alpha]_{578}$-16.5°; $[\alpha]_{589}$-15.1°; (c= 1.36 in CCl_4).

Reaction of 3-carbomethoxycyclobut-1-ylidene-acetyl chloride with cupric lysinate:

To a solution of the copper salt of L-(+)-lysine (380 mg, 1.06 x 10^{-3} mole) in 1.06 ml of 2*N* NaOH prepared according to Utizino and Yoneya[66], there was slowly added

---

66. S. Utizino and T. Yonega, *Ber*, 85, 860 (1952).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

with stirring 3-carbomethoxycyclobut-1-ylidene-acetyl chloride (400 mg, 2.12×10^{-3} mole) and 1.06 ml 2*N* NaOH in such a way as to maintain a pH near 9. After the addition was complete, the solution was stirred 1 hr and the resulting bluish precipitate is filtered and washed with water, ethanol and finally with ether and dried. This precipitate is suspended in 1.5 ml water and brought into solution with the minimum amount of 2*N* HCl. Hydrogen sulfide gas was passed through the solution for 15 min. The precipitated cupric sulfide was removed by filtration and the solution was reduced to half its volume under vacuum and brought to pH 6 by addition of 25% ammonia solution. The crystalline precipitate was filtered and dried: 407 mg (66% of th. yield) $[\alpha]_{546}$ -1.01° (c= 2.12 in water at pH 5). m.p. 188-192° (dec). IR spectrum is included in the appendix of spectra.

Reaction of methyl 3-methyl-2-cyclobutene-2-carboxylate-1-carboxylic acid with thionyl chloride:

To a solution of methyl 3-methyl-2-cyclobutene-2-carboxylate-1-carboxylic acid [1.1 g, 6.47×10^{-3} mole; $[\alpha]_{546}$ -11.6°; $[\alpha]_{578}$ -10.6°; $[\alpha]_{589}$ -10.2°; (c= 1.19 in $CHCl_3$)] in 20-ml benzene there was added 770 mg (1.1 equiv.) of thionyl chloride. The reaction was refluxed for 5 hr at which time solvent and excess thionyl chloride were removed by distillation at atmospheric pressure and product was

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

distilled at 82°/0.1 mm giving 890 mg (71% of th. yield) methyl 3-methyl-2-cyclobutene-1-carboxylate-2-carboxylic acid chloride: $[\alpha]_{546}$ -11.0°; $[\alpha]_{578}$ -9.25°; $[\alpha]_{589}$ -8.67°; (c= 1.94 in CCl_4).

Reaction of methyl 3-methyl-2-cyclobutene-1-carboxylate-2-acid chloride with 3-carbomethoxycyclobut-1-ylidene -ε-N-acetyl-lysine:

The above mentioned lysine derivative composed of natural optically pure lysine and the (-)-enantiomer of the cyclobutylidene (203 mg, 6.82×10^{-3} mole) was dissolved in 1 equiv. of 3*N* NaOH plus enough to bring the solution to pH 9. To the rapidly stirred solution was slowly added methyl 3-methyl-2-cyclobutene-1-carboxylate-2-carboxylic acid chloride (141 mg) alternately with 3*N* NaOH in such a way as to maintain pH between 8 and 9. After addition was complete the solution was acidified to pH 2 with HCl. The solution was then extracted with five 10-ml portions of ether and two 10-ml portions of ethyl acetate. The organic extracts were combined, dried over $MgSO_4$ and solvent was removed leaving 161 mg. of solid. After recrystallization from acetone/pet. ether, 153 mg. of solid m.p. 81-83° was obtained $[\alpha]_{546}$ -3.48°; (c= 1.25 in EtOH).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

Thermal rearrangement of (-)-(1R;2R)-dimethyl-cis-3-dideuteriomethylenecyclobutane-1,2-dicarboxylate((-)-cis-I-d_2):

Cis-3-dideuteriomethylenecyclobutane-1,2-dicarboxylic acid was resolved in manner entirely analogous to the corresponding non-deuterated diacid. The (-)-enantiomer used in the current rearrangement was converted into dimethyl ester by treatment with diazomethane to afford (-)-*cis*-I-d_2: [910 mg; $[\alpha]_{546}$-99.8°; $[\alpha]_{578}$-86.5°; $[\alpha]_{589}$-82.7°: (c= 1.11 in CCl_4)]. The rearrangement was carried out by adding 100 mg of the diester to each of nine 8 ml thick-walled Pyrex tubes containing 4 ml freshly distilled benzene and 15 mg hydroquinone. Nitrogen was flushed through the solution in each tube for 15 min, the tubes were then sealed and heated to 232° for 8 hr. The cooled tubes were opened and the solutions filtered and combined contents were reduced to 2 ml volume by distillation of benzene. The resulting mixture consisted of 3.2% *trans*-I, 85.5% *cis*-I and 11.3% III. The specific rotation of III was $[\alpha]_{546}$-22.9°; (c= 0.87 in CCl_4). III collected from the v. p. c. (column D) [68 mg] was added to 2 ml 1*N* HCl and refluxed for 45 min. The cooled solution was extracted with ten 2-ml portions of ether. The ether extract was dried over $MgSO_4$ and evaporated to yield 52 mg of diacid (-)-III-d_2 of specific rotation $[\alpha]_{546}$-21.7° (c= 0.77 in EtOH).

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

This (-)-III-d_2 (52 mg) was added to 3 ml of absolute ethanol containing 211 mg quinine. After three days the mother liquor was removed by filtration and the salt (205 mg) was recrystallized from 3 ml absolute ethanol. The mother liquor was removed by filtration after two days and the salt (154 mg) was dissolved in 2 ml 2*N* HCl and the resulting solution was extracted with ten 2-ml portions of ether. The combined ether extracts were dried over $MgSO_4$ and upon removal of the ether (-)-III-d_2 was obtained as diacid: (14.1 mg; $[\alpha]_{546}$ -31.4°; $[\alpha]_{578}$ 27.2°; $[\alpha]_{589}$ -26.1°; (c= 1.41 in EtOH). This diacid was converted to the corresponding dimethyl ester by the exact method employed in the case of the non-deuterated diacid. The NMR spectrum of this diester, (-)-III-d_2, is included in the appendix of spectra and its details are analyzed below.

In addition, the NMR spectrum of recovered *cis*-I-d_2 showed no change in the amount of deuterium in the *exo*-methylene position indicating no detectable amount of degenerate rearrangement was proceeding *via* initial rupture of the 1,4 bond.

Thermal rearrangement of (+)-(1S:2S)-dimethyl cis-3-dideuteriomethylenecyclobutane-1,2-dicarboxylate ((+)-cis-I-d_2):

The (+)-enantiomer of *cis*-3-dideuteriomethylene-cyclobutane-1,2-dicarboxylic acid obtained through a resolution entirely analogous to that performed on the

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

non-deuterated diacid was converted into its dimethyl ester by treatment with diazomethane to afford (+)-*cis*-I-d_2: [3.9 g; $[\alpha]_{546}$+102.3°; $[\alpha]_{578}$+88.6°; $[\alpha]_{589}$+84.7°; (c= 1.02 in CCl_4)]. This material was rearranged as follows. To each of twenty-six 8-ml thick-walled Pyrex tubes containing 4 ml of freshly distilled benzene and 15 mg hydroquinone was added 150 mg (+)-*cis*-I-d_2. Nitrogen was flushed through the solution in each of the tubes for 15 min and then the tubes were sealed and heated in groups of three for 8 hr at 232°. The cooled tubes were opened, their contents filtered and reduced in volume by distillation of benzene. The combined products from all twenty-six tubes consisted of 3.7% *trans*-I-d_2, 85.5% *cis*-I-d_2 and 10.8% III-d_2 as shown by v. p. c. on column D. III collected from the v. p. c. (column D) [330 mg; $[\alpha]_{546}$+23.1° (c= 1.07 in CCl_4)] was added to 10 ml 1*N* HCl and refluxed for 1 hr. The cooled solution was extracted with ten 50-ml portions of ether, the ether extracts combined and dried over $MgSO_4$, and the ether evaporated to yield diacid: [270 mg; $[\alpha]_{546}$+22.0° (c= 0.99 in EtOH)]. This diacid (270 mg) was recrystallized from 40 ml dibutyl ether (1 day) to give diacid: 205 mg; $[\alpha]_{546}$+27.6° (c= 0.85 in EtOH) and mother liquor Ia. The diacid was recrystallized from 40 ml dibutyl ether (1 day) to give diacid: 161 mg; $[\alpha]_{546}$+30.3° $[\alpha]_{578}$ +26.1°; $[\alpha]_{589}$+25.3°; (c= 0.88 in EtOH). A third recrystallization from 40 ml dibutyl ether afforded diacid: 107 mg; $[\alpha]_{546}$

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

+31.4°; $[\alpha]_{578}$ +27.5°; $[\alpha]_{589}$ +26.5° (c= 0.86 in EtOH).

Mother liquor Ia was evaporated to dryness to yield diacid: 60 mg; $[\alpha]_{546}$ +2.0° (c= 0.51 in EtOH). The diacid (61 mg) was added to 1 ml absolute ethanol containing 246 mg of quinine. After crystallizing for three days the mother liquor was removed leaving 254 mg. of salt. Recrystallization from 3 ml absolute ethanol (2 days) afforded 97 mg of salt. Recrystallization from 2 ml absolute ethanol (2 days) afforded 68 mg of salt which was dissolved in 1 ml 1*N* HCl. The acidic solution was extracted with ten 2-ml portions of ether. The combined ether extracts were dried over $MgSO_4$ and evaporated leaving diacid: 11 mg; $[\alpha]_{546}$ -29.2°; $[\alpha]_{578}$ -25.1°; $[\alpha]_{589}$ -23.9°; (c= 1.1 in EtOH). Recrystallization from 2 ml dibutyl ether (1 day) afforded diacid: 10.4 mg; $[\alpha]_{546}$ -31.3°; $[\alpha]_{578}$ -27.7°; $[\alpha]_{589}$ -26.4°; (c= 1.04 in EtOH).

Both the optically pure (-)-III-d_2 and the optically pure (+)-III-d_2 diacids obtained above were converted to their corresponding dimethyl esters by the exact method employed in the case of non-deuterated diacid III. The NMR spectra of the optically pure dimethyl esters (-)-III-d_2 and (+)-III-d_2 are included in the appendix of spectra and their details are analyzed below.

Analysis of the NMR spectra of optically pure samples of III-d_2:

The NMR spectra of (-)-III-d_2 from (-)-*cis*-I-d_2,

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

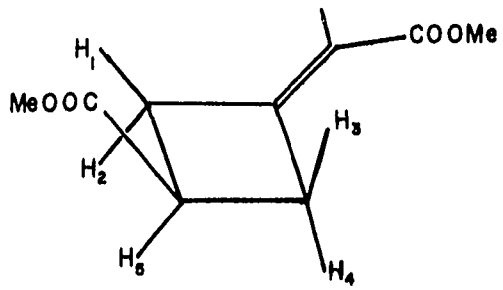
(+)-III-d_2 from (+)-*cis* -I-d_2, and (-)-III-d_2 from (+)-*cis*-I-d_2 were taken at 100 MC on a Varian-HA-100 spectrometer at sweep width of 100 cycles. The area of the spectra corresponding to the cyclobutane ring protons were Xeroxed and cut out five times each. The position of the line which divides the area corresponding to the cyclobutane ring protons in half in the spectrum of the non-deuterated III (taken under identical spectrometer settings and field) was transferred to the spectrum of deuterated sample : the peaks were divided by cutting on that line and the two segments were weighed. The standard deviation for this procedure was 0.7%. However, this is a statement only regarding the precision of the cutting weighing process, not the accuracy of the method as a whole.

The mass spectrum of *cis*-I-d_2 used in these experiments showed that 63.5% of the material contained two deuterium; 11.8% of the material contained one deuterium and that 24.7% of the material contained three deuterium. It is assumed that the material containing two deuterium had both placed in the methylene group and that the material with three deuterium had two of the three in the methylene group. In other words all of the d_2 and d_3 had two deuterium in the methylene group. The standard deviation of determining the percentage of material with two deuterium in the methylene group is 1.1%. This is confirmed by the integration of the NMR spectrum of the same material which indicated 12±2% of

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

one deuterium in the *exo* -methylene position.

Our procedure, outlined in the text on pages 70 and 71 calls for subtraction of an area equal to 0.5 proton from both the downfield and upfield branches of the cyclobutane ring proton peaks. This total area of one proton subtracted



corresponds to H_5. When this is done the following results are obtained.

sample of III-d_2	%Downfield Area	% Upfield Area
(+)-III-d_2 from (+)-*cis*-I-d_2	10.2±0.7%	89.8±0.7%
(-)-III-d_2 from (+)-*cis*-I-d_2	11.3±0.7%	88.7±-.7%
(-)-III-d_2 from (-)-*cis*-I-d_2	9.8±0.7%	90.2±0.7%

Account must now be taken of the fact that 11.8% of the material contained one hydrogen in the methylene group of the starting material and therefore there is 11.8% of one hydrogen attached to the carbon atom bearing deuterium in the products. Making correction for this factor produces the following result:

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

sample of III-d_2	% Downfield Area	% Upfield Area
(+)-III-d_2 from (+)-*cis*-I-d_2	-0.4%	100.4%
(-)-III-d_2 from (+)-*cis*-I-d_2	0.7%	99.3%
(-)-III-d_2 from (-)-*cis*-I-d_2	-0.8%	100.8%

However, application of the statistical *t* test shows that, because of the experimental uncertainty, at the 99% confidence level the results may not be distinguished from 0% downfield: 100% upfield. In fact any result where the downfield branch was less than ±2.3% could not be distinguished from 0:100 with 99% confidence.

Some discretion must be applied in the treatment of the 24% of the molecules which have a third deuterium. Should all 24% occur at one position it may influence the result. The most damaging situation would result from all 24% occurring in H_5. Even in this case the final outcome would not be changed more than 3%, *e.g.*, 3% downfield: 97% upfield.

Finally, it must be mentioned that in cutting of peaks some discretion must be applied in choosing the base-line. However, the effect of taking other choices than the one actually taken was tested and it was found that no baseline could be chosen, even the most unreasonable ones, which would change the outcome by more than 3.5%, *e.g.*, 3.5%

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

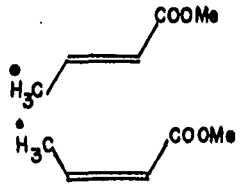
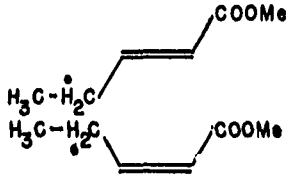
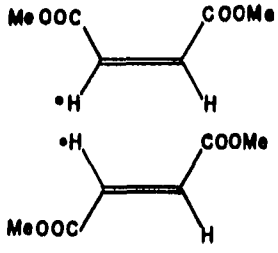
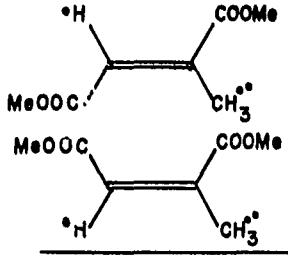
downfield: 96.5% upfield.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

APPENDIX I:

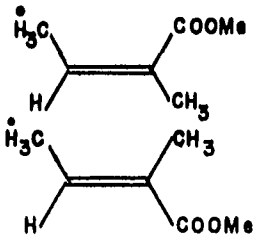
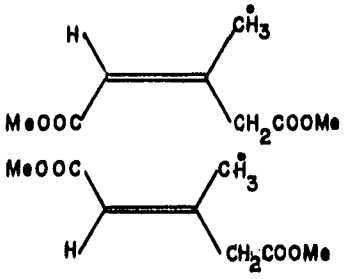
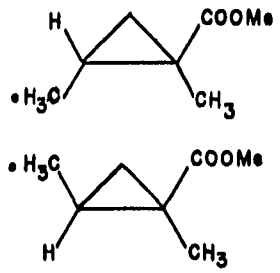
Effect of carboxylic ester groups on near-by protons

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

structural formula	chemical shift of H* (τ) and solvent	reference
	• 8.12 (CCl_4) • 7.86 (CCl_4)	67,68
	• 7.78 (CCl_4) • 7.56 (CCl_4)	67,69
	• 3.86 (CCl_4) • 3.33 (CCl_4)	68,70
	• 3.32 : 7.75 (CCl_4) • 4.23 : 7.97 (CCl_4)	67,68

67. R. R. Fraser and D. E. McGreer, *Can. J. Chem.*, 39, 505 (1961).
68. L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2886 (1960).
69. D. E. McGreer, W. Wai, and G. Carmichael, *Can. J. Chem.*, 38, 2410 (1960).
70. G. O. Schenk, E. K. von Gustorf, and M. J. Jun, *Tetrahedron Letters*, 1059 (1962)

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

	•8.05 (CCl_4) •8.25 (CCl_4)	68,71
	• 8.40 (CCl_4) • 7.80 (CCl_4)	68
	• 8.9 (CCl_4) •8.8 (CCl_4)	72

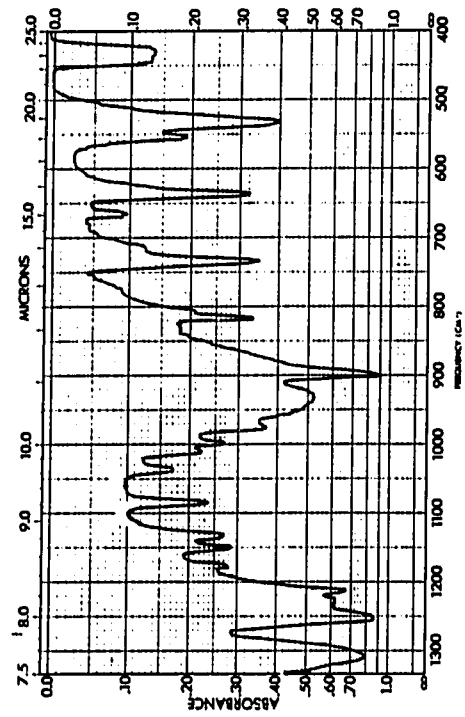
71. R. R. Fraser, *Can. J. Chem.*, 38, 549 (1960).
72. T. V. van Anken and K. L. Rinehart Jr., *J. Am. Chem. Soc.*, 84, 3736 (1962).

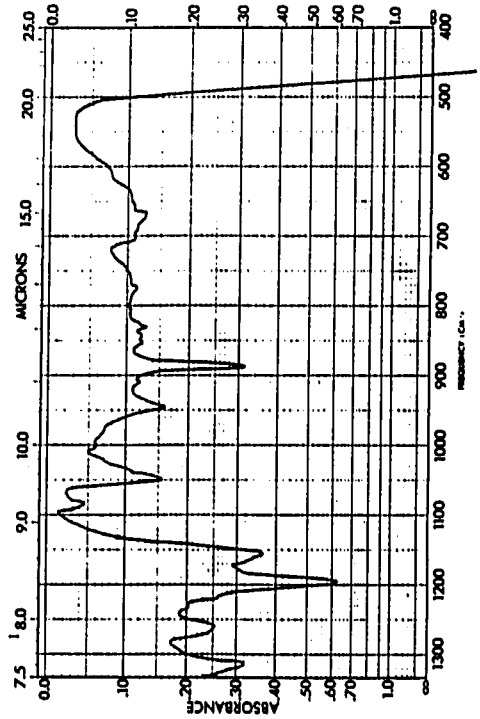
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

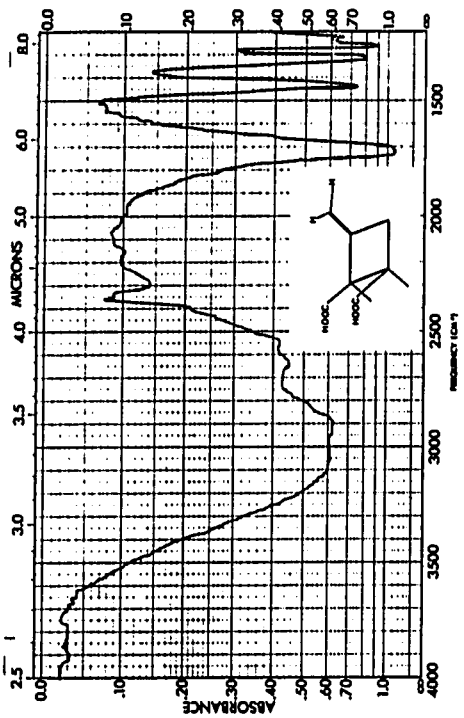
APPENDIX II:

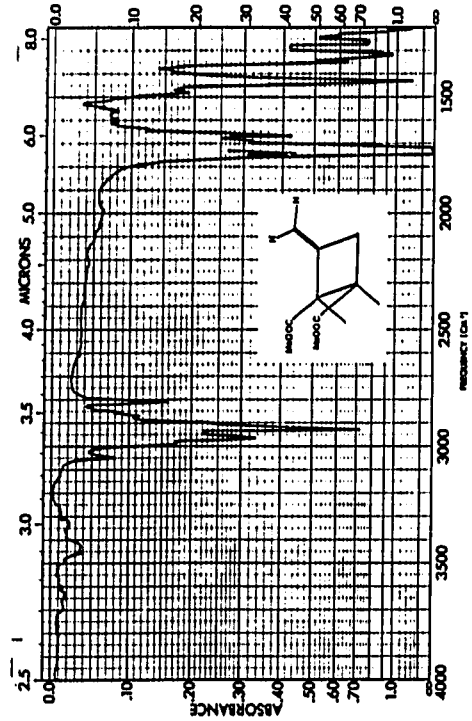
Spectra

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

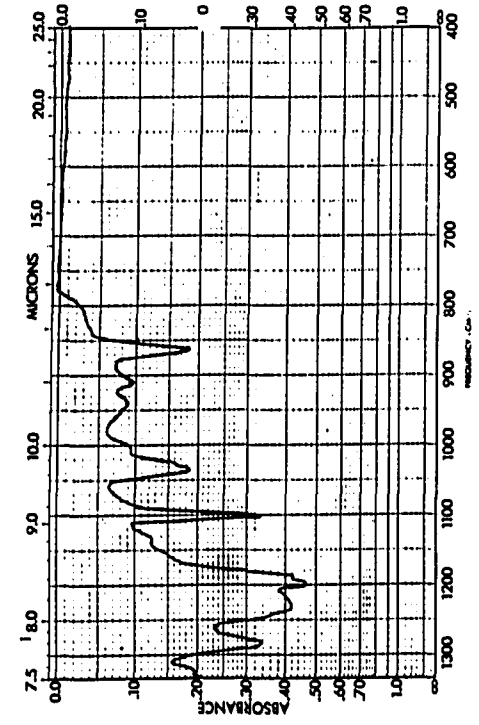


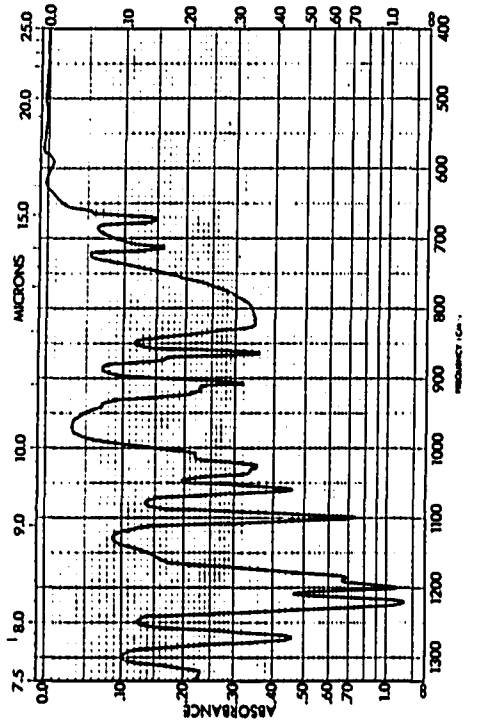


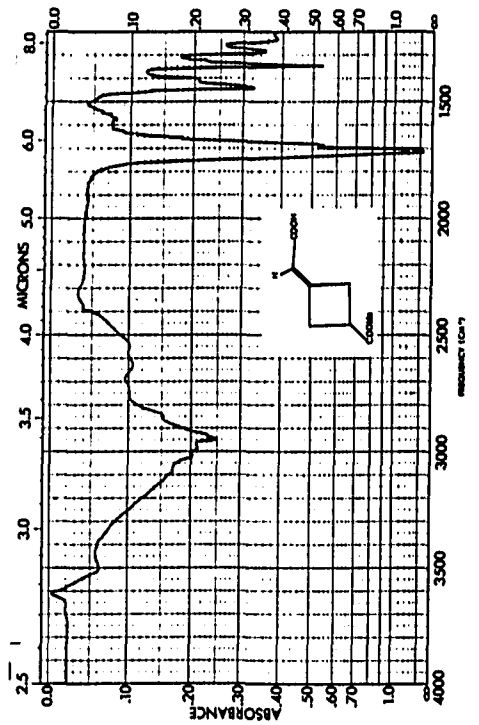


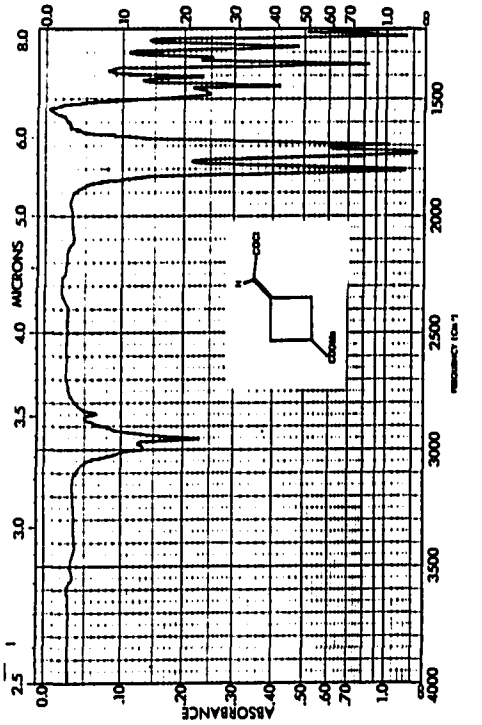


Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

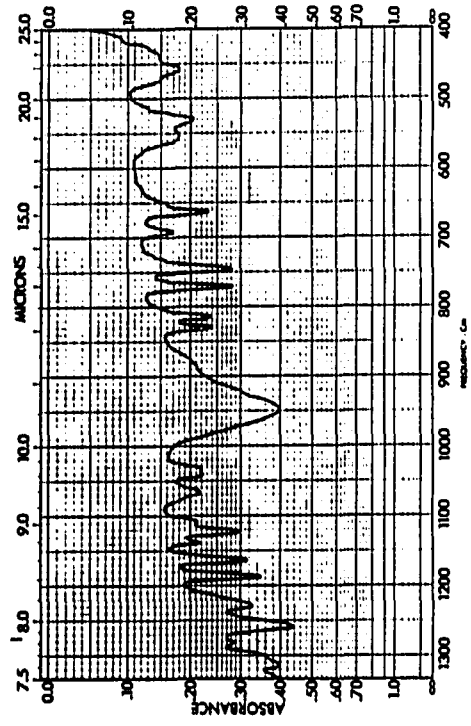


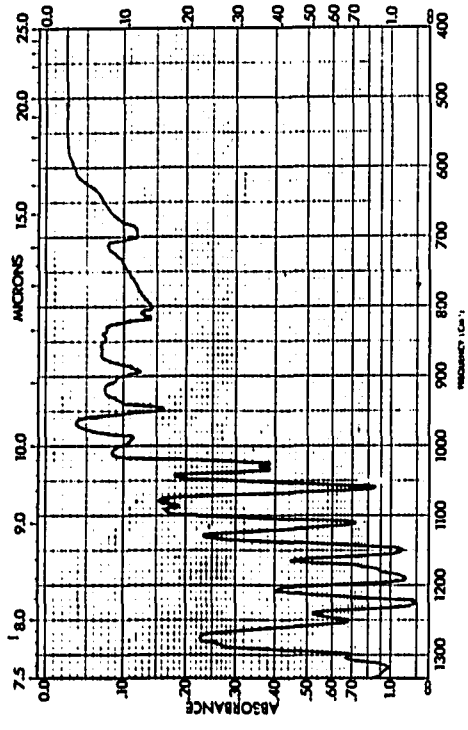


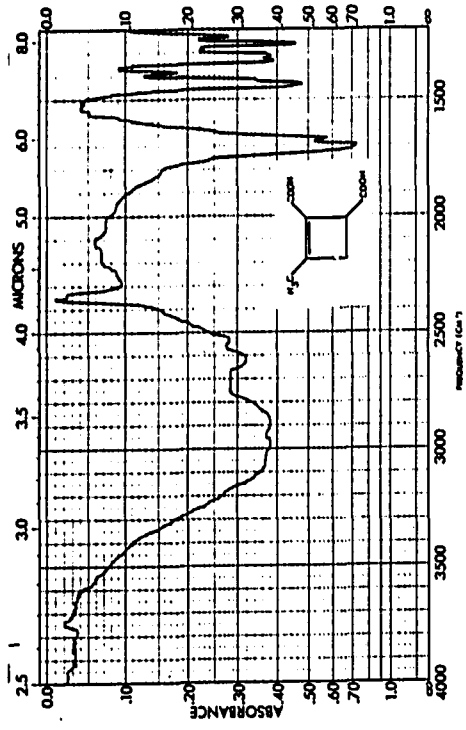


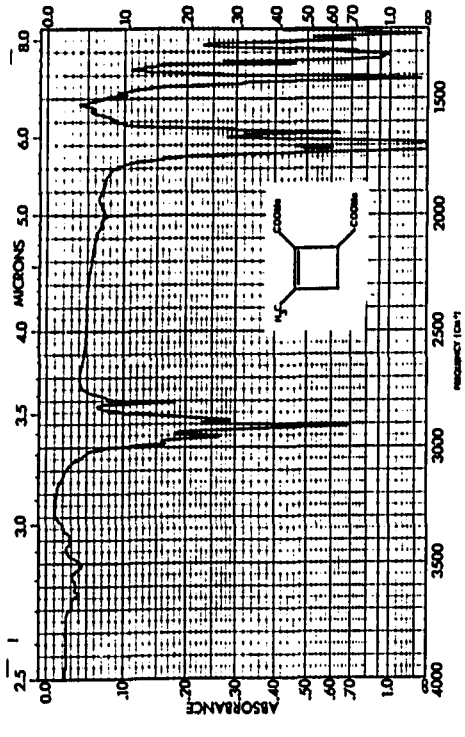


Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

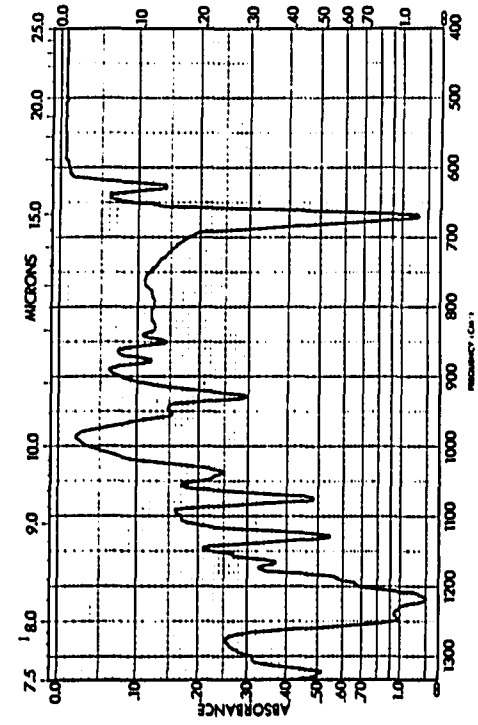


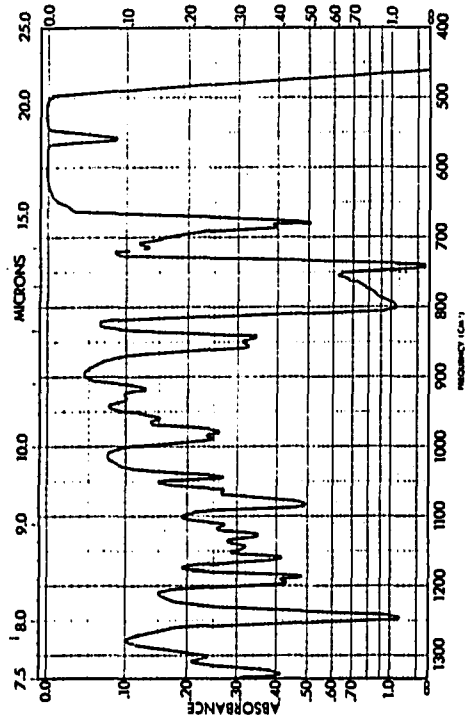


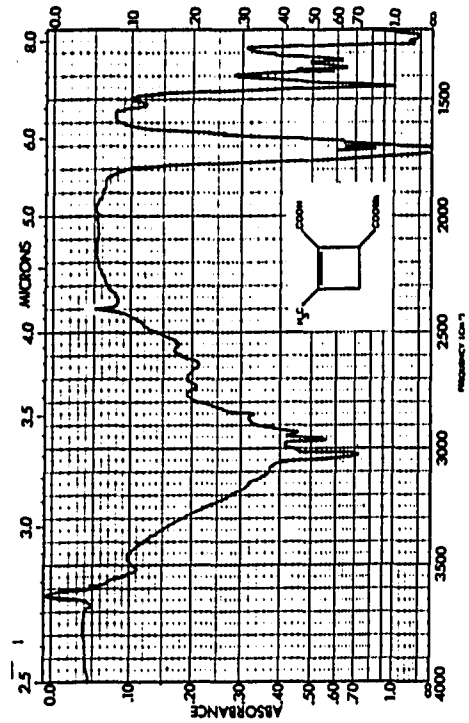


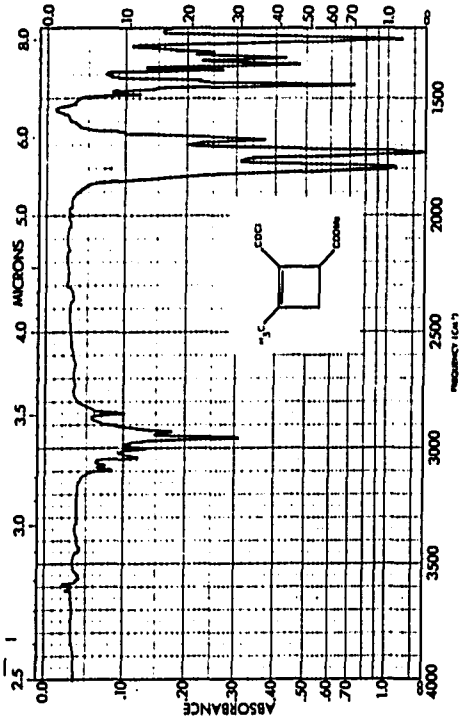


Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

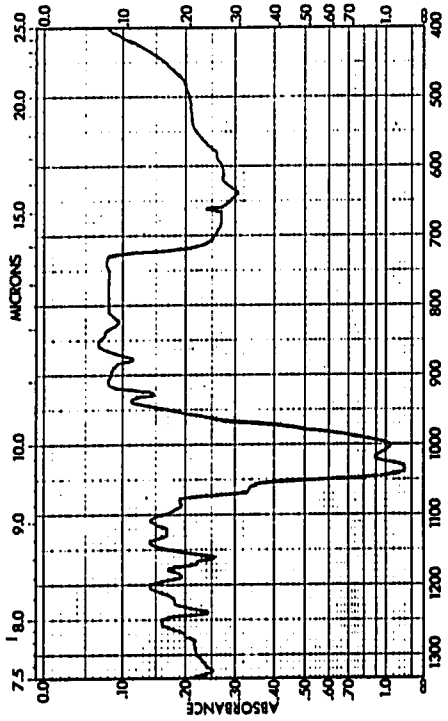


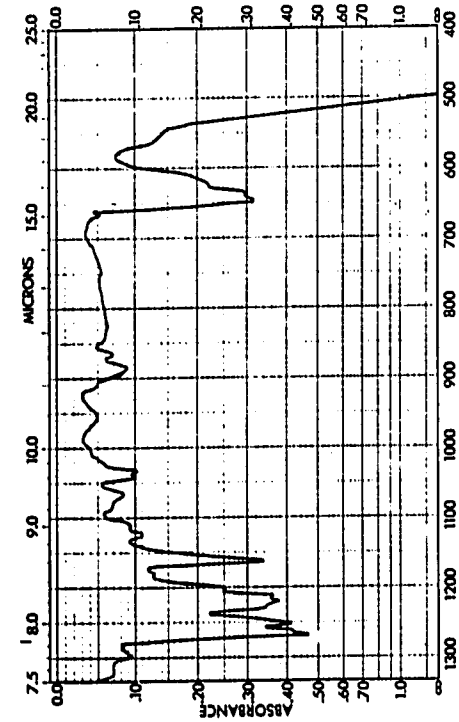


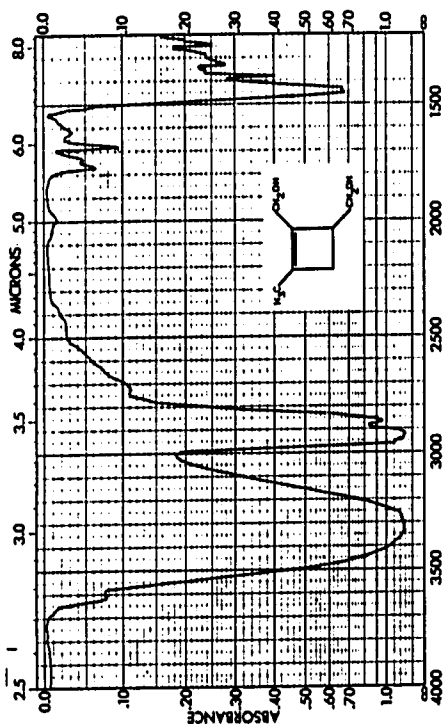


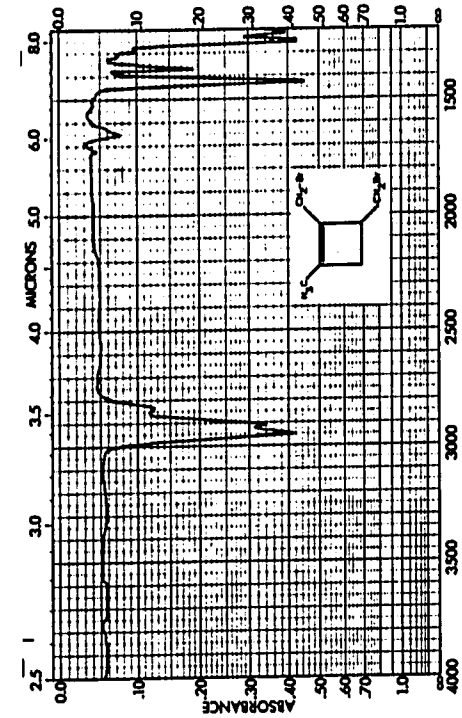


Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

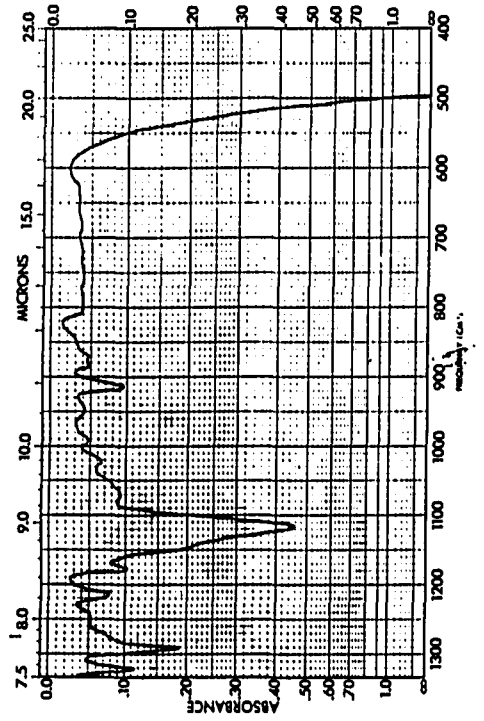


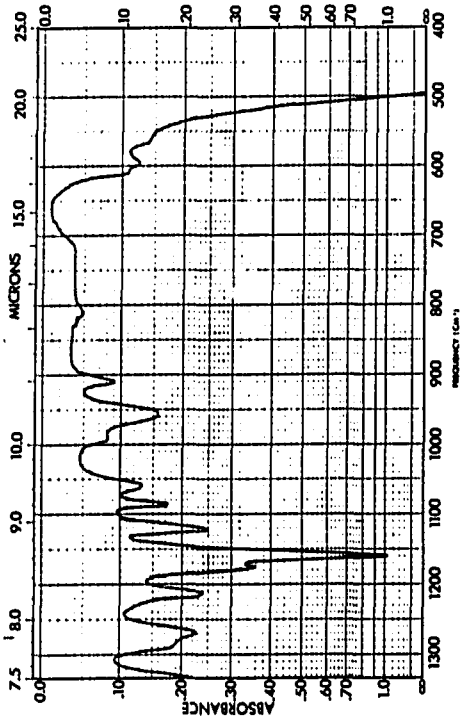


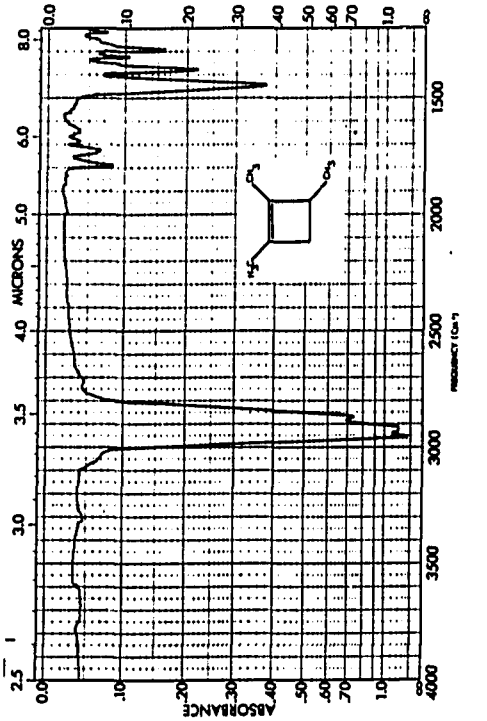


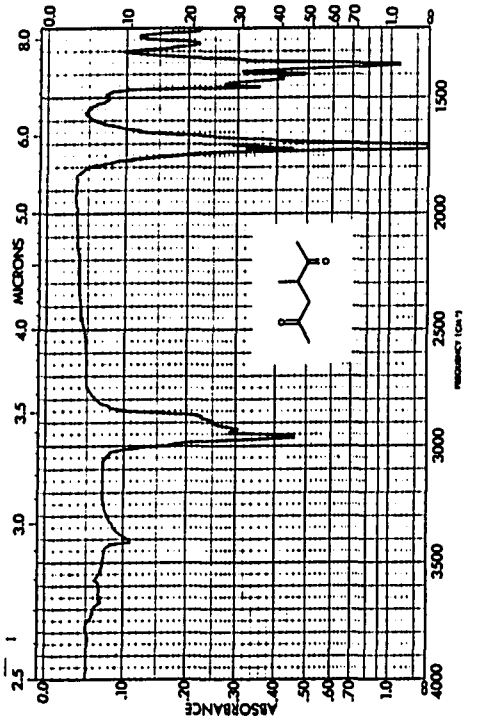


Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

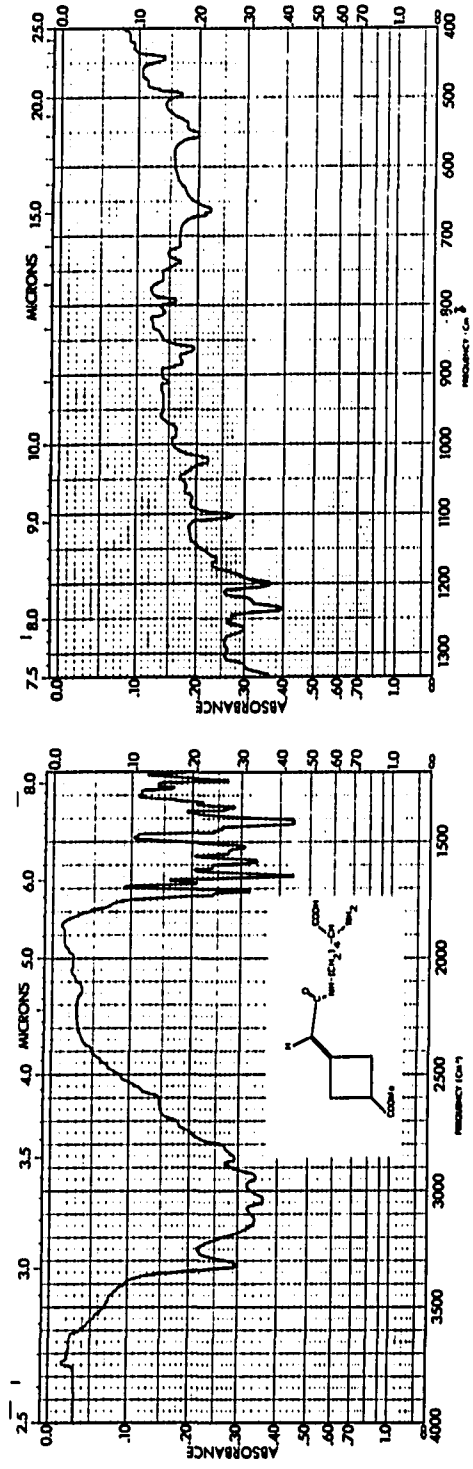




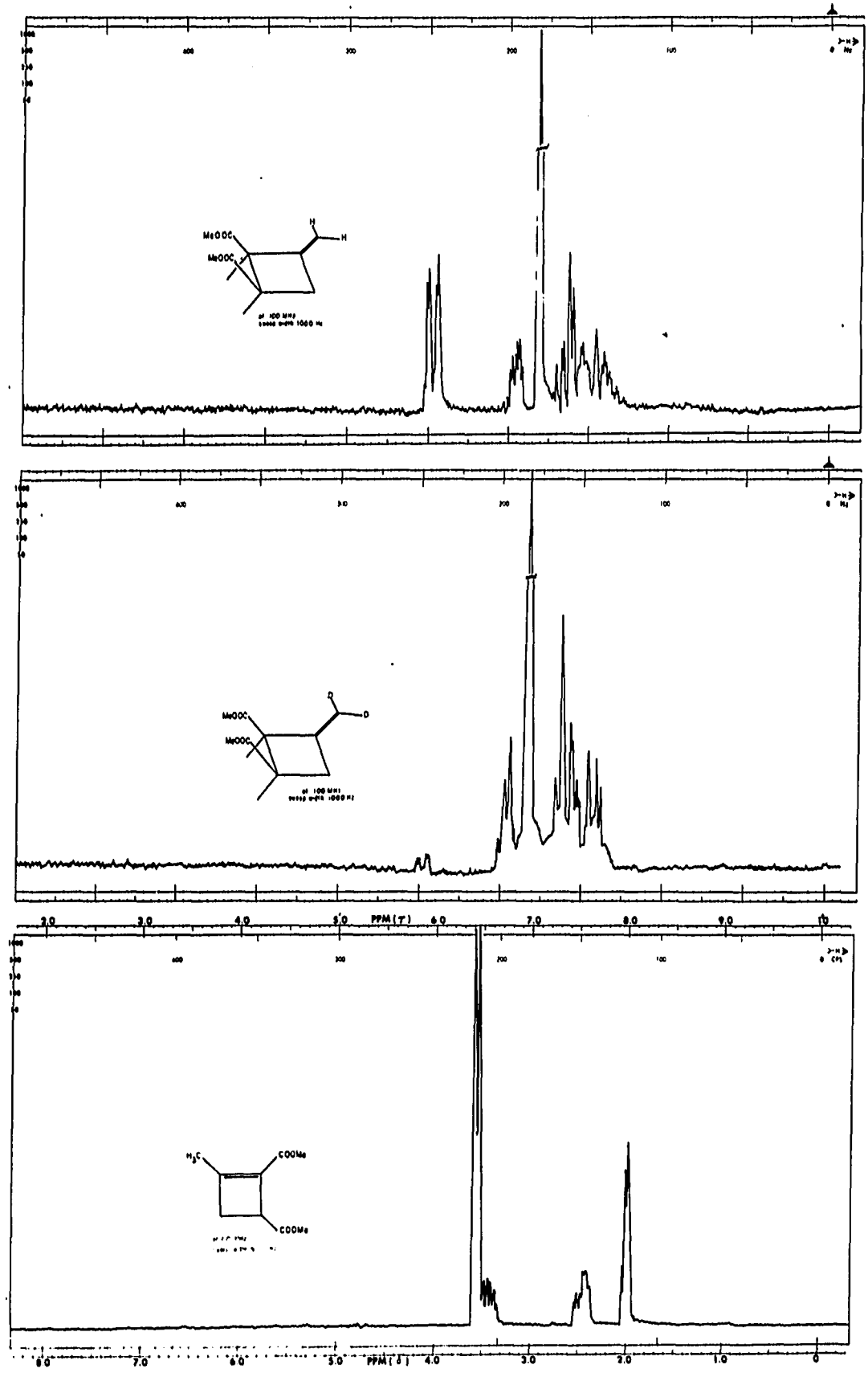




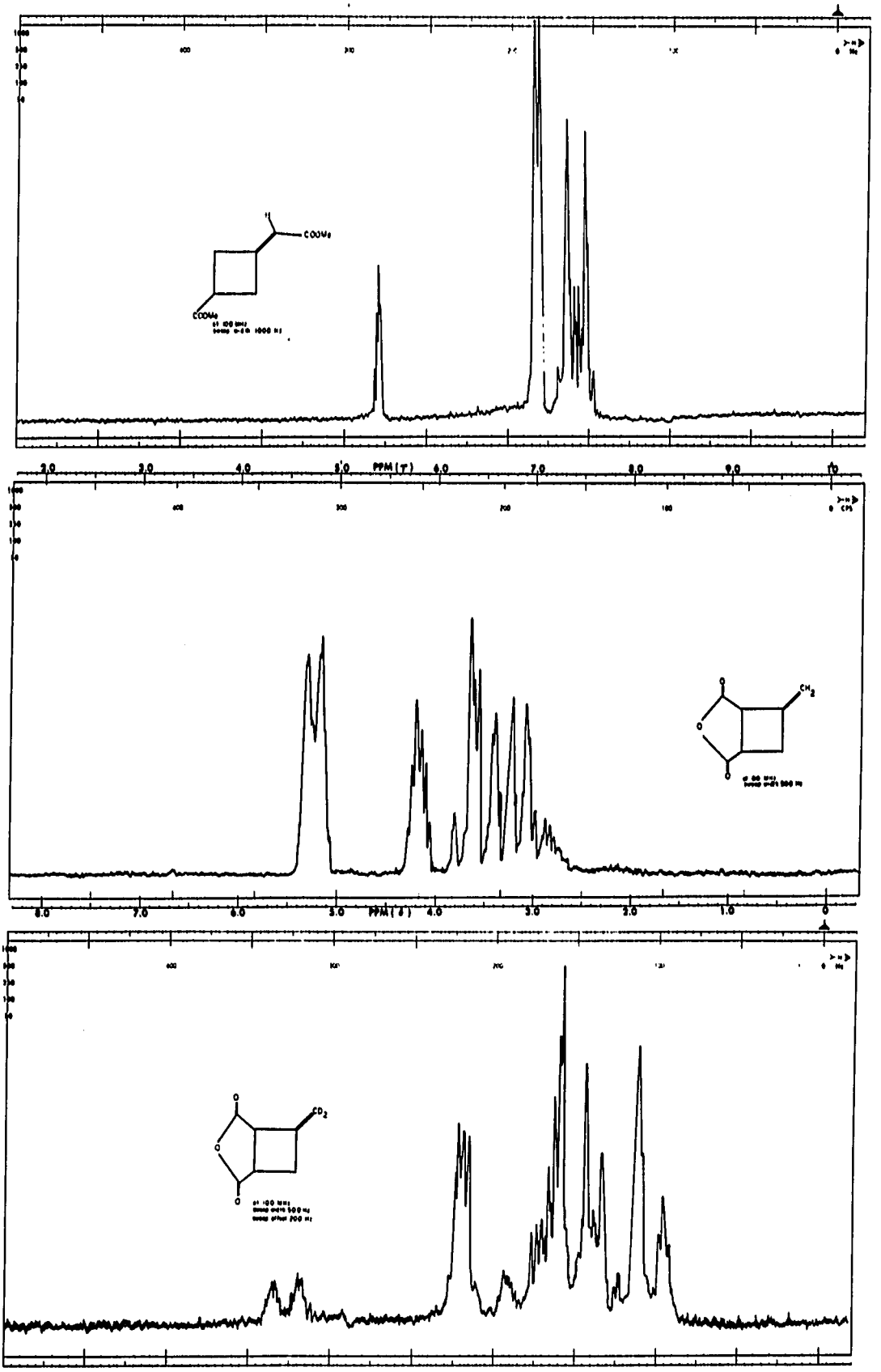
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



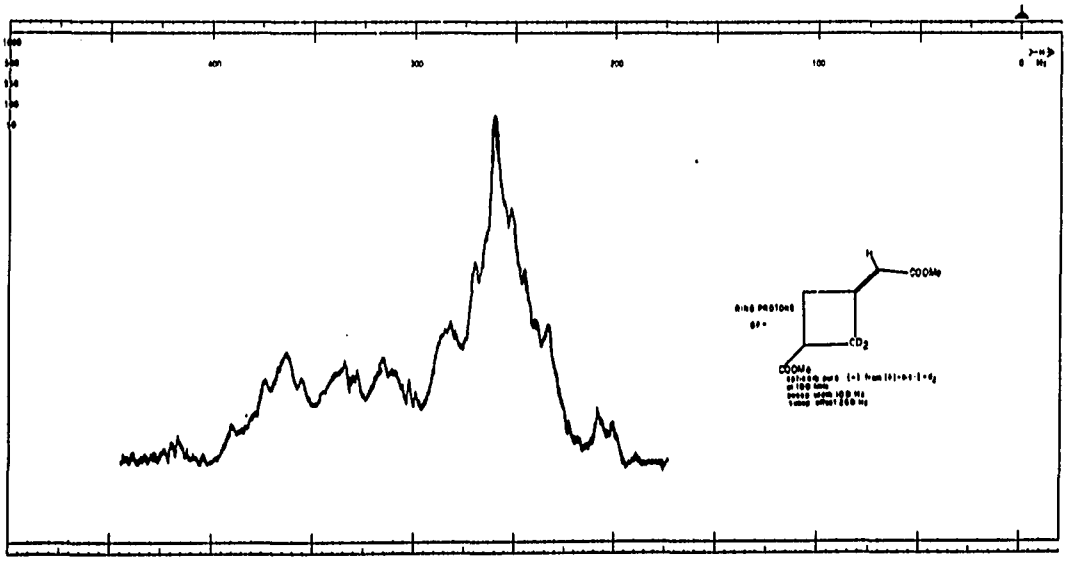
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

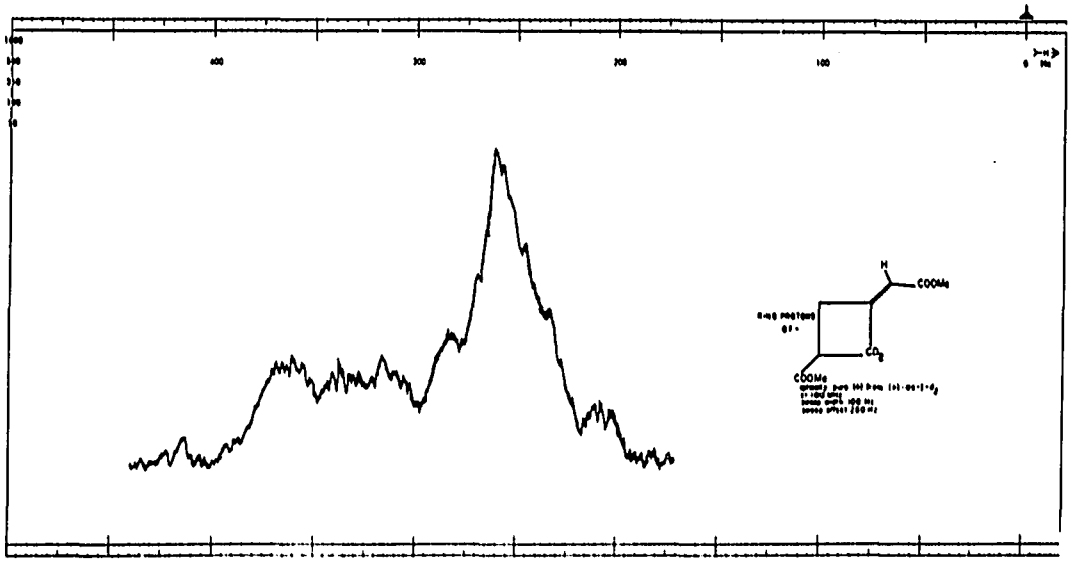


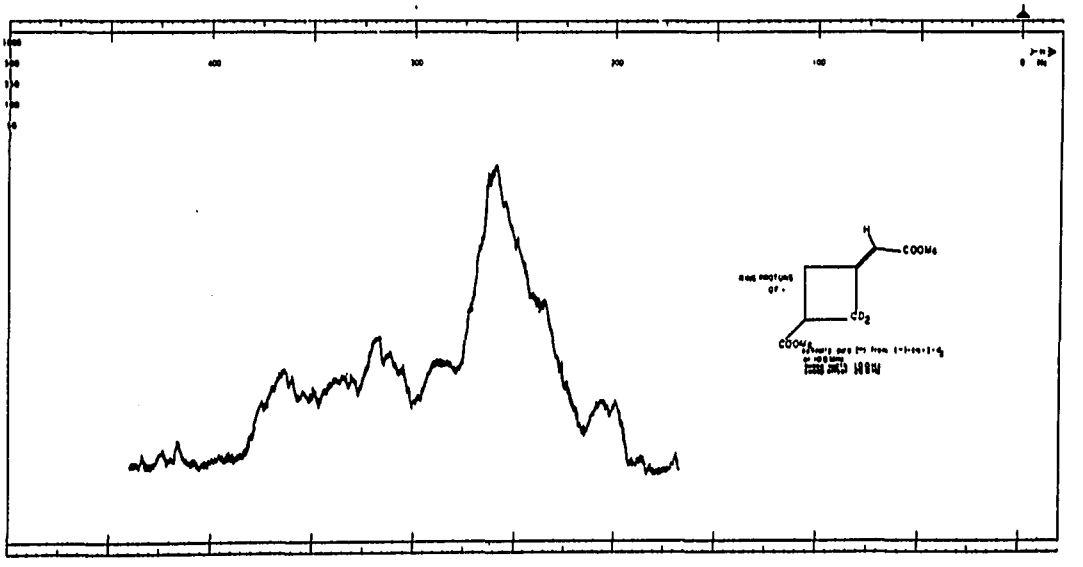
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



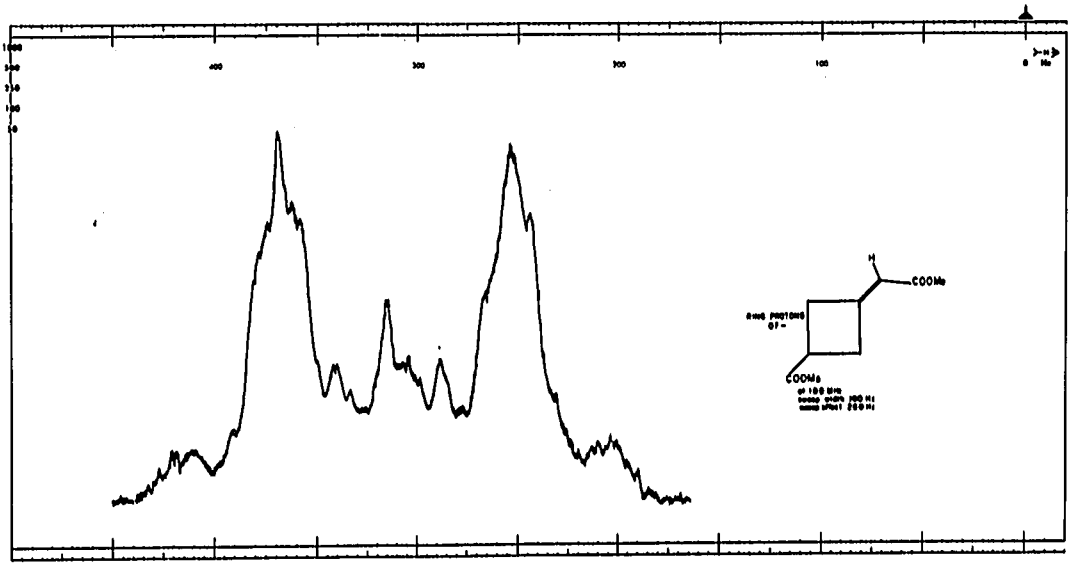
Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.







Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.



Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.