

1970

A study of the esterification of 2,2,4,4-tetramethyl-1,3-cyclobutanediol

Lewis Metzler Naylor
University of Northern Iowa

Let us know how access to this document benefits you

Copyright ©1970 Lewis Metzler Naylor

Follow this and additional works at: <https://scholarworks.uni.edu/etd>

 Part of the [Organic Chemistry Commons](#)

Recommended Citation

Naylor, Lewis Metzler, "A study of the esterification of 2,2,4,4-tetramethyl-1,3-cyclobutanediol" (1970).
Dissertations and Theses @ UNI. 1065.
<https://scholarworks.uni.edu/etd/1065>

This Open Access Thesis is brought to you for free and open access by the Student Work at UNI ScholarWorks. It has been accepted for inclusion in Dissertations and Theses @ UNI by an authorized administrator of UNI ScholarWorks. For more information, please contact scholarworks@uni.edu.

Offensive Materials Statement: Materials located in UNI ScholarWorks come from a broad range of sources and time periods. Some of these materials may contain offensive stereotypes, ideas, visuals, or language.

13

A STUDY OF THE ESTERIFICATION OF
2,2,4,4-TETRAMETHYL-1,3-CYCLOBUTANEDIOL

An Abstract of a Thesis
Submitted
In Partial Fulfillment
of the Requirements for the Degree
Master of Arts

UNIVERSITY OF NORTHERN IOWA

by
Lewis Metzler Naylor

January 1970

ABSTRACT

The purpose of this research was to prepare, identify, and characterize 2,2,4,4-tetramethyl-1,3-cyclobutanediol bischloroacetate using 2,2,4,4-tetramethyl-1,3-cyclobutanediol and monochloroacetic acid as starting materials. The synthesis of this diester has not been reported previously.

Catalyzed and uncatalyzed reactions were attempted, with the uncatalyzed having, in general, the better yield. The diester, trans-2,2,4,4-tetramethyl-1,3-cyclobutanediol bischloroacetate (mp, 103.5-104; n_D^{22} , 1.516-1.520), was isolated from a mixture of the isomers. The trans configuration of the diester was confirmed by comparing known nuclear magnetic resonance spectra to that of the diester. Infrared spectroscopy was used to confirm functional groups. Standard analytical techniques were used to determine chloride composition of the new compound.

A new method of separation of the cis diol from a mixture of the isomers is described.

A STUDY OF THE ESTERIFICATION OF
2,2,4,4-TETRAMETHYL-1,3-CYCLOBUTANEDIOL

A Thesis
Submitted
In Partial Fulfillment
of the Requirements for the Degree
Master of Arts

UNIVERSITY OF NORTHERN IOWA

by
Lewis Metzler Naylor

January 1970

This Study by: Lewis Metzler Naylor

Entitled: A STUDY OF THE ESTERIFICATION OF 2,2,4,4-TETRAETHYL-
1,3-CYCLOBUTANEDIOL

has been approved as meeting the thesis requirement for the Degree of
Master of Arts.

J. W. Kercheval

Chairman, Thesis Committee

C. S. Woo

Member, Thesis Committee

Robert J. Simpson

Member, Thesis Committee

Clifford G. McCollum

Dean of the College of Natural Sciences

Gordon J. Rhum

Dean of the Graduate College

Nov. 4, 1969

Date approved by
Dean of the Graduate College

ACKNOWLEDGEMENTS

The writer would like to acknowledge the assistance of the following men for their part in this research and preparation of the thesis. Dr. James W. Kercheval, Research Director and Thesis Committee Chairman, has provided valuable guidance enabling this work to be completed. Appreciation is expressed to Dr. Ching Woo and Dr. Robert Simpson, members of the Thesis Committee, for their cooperation and helpful suggestions.

TABLE OF CONTENTS

CHAPTER	PAGE
I. INTRODUCTION	1
Historical Background	1
Literature Search	2
Properties of 2,2,4,4-Tetramethyl-	
1,3-cyclobutanediol	5
The Statement of the Problem	8
II. A PRELIMINARY INVESTIGATION	9
Introduction	9
Preparation of a Known Compound	9
Saponification of Product I	10
III. SEPARATION OF THE <u>cis</u> AND <u>trans</u> ISOMERS OF THE DIOL	12
Introduction	12
Preparation of the Diformate Ester	13
Alcoholysis of the Diformate Ester	14
Separation of the <u>cis</u> -Diol from a Mixture	
of the Isomers	16
IV. PREPARATION, IDENTIFICATION, AND CHARACTERIZATION OF	
2,2,4,4-TETRAMETHYL-1,3-CYCLOBUTANEDIOL BISCHLOROACETATE . .	18
Introduction	18
A Summary of the Reactions	18
The Infrared Spectrum of the Chloro-diester	19
Chlorine Analysis of the Products	19

CHAPTER

Determination of the Configuration of the	
Chloro-diester	24
Conformation of the Chloro-diester	27
Experimental Work	31
Esterification of the Diol Using Zinc	
Chloride as a Catalyst	31
Esterification of the Diol Using Phosphoric	
Acid as a Catalyst	31
Esterification of the Diol Using Metallic	
Sodium as a Catalyst	33
Uncatalyzed Esterification of the Diol (I)	34
Uncatalyzed Esterification of the Diol (II)	34
V. DISCUSSION	39
Introduction	39
The Acid Catalyst	41
S_N1 or S_N2	42
Further Discussion	44
VI. CONCLUSION	47
Summary of the Study	47
Future Problems	47
BIBLIOGRAPHY	50

LIST OF TABLES

TABLE	PAGE
I. Typical Properties of 2,2,4,4-Tetramethyl- 1,3-cyclobutanediol	7
II. Saponification of Product I	11
III. Saponification of Product II	15
IV. The Correlation of the Infrared Spectrum of Product VII, the Chloro-diester	21
V. Mixture Melting Points	22
VI. Comparison of Esterification Products	23
VII. Chlorine Analysis of Product V	35
VIII. Chlorine Analysis of Product VI	35
IX. Physical Constants and Chlorine Analysis of Product VII	38

LIST OF TABLES

TABLE		PAGE
I.	Typical Properties of 2,2,4,4-Tetramethyl- 1,3-cyclobutanediol	7
II.	Saponification of Product I	11
III.	Saponification of Product II	15
IV.	The Correlation of the Infrared Spectrum of Product VII, the Chloro-diester	21
V.	Mixture Melting Points	22
VI.	Comparison of Esterification Products	23
VII.	Chlorine Analysis of Product V	35
VIII.	Chlorine Analysis of Product VI	36
IX.	Physical Constants and Chlorine Analysis of Product VII	38

LIST OF FIGURES

FIGURE	PAGE
1. Structure of 2,2,4,4-Tetramethyl-1,3-cyclobutanediol	6
2. IR Spectrum of Product VII	20
3. Structure of 2,2,4,4-Tetramethyl-1,3-cyclobutanediol bischloroacetate	25
4. NMR Spectrum of <u>trans</u> -2,2,4,4-Tetramethyl-1,3- cyclobutanediol diformate	26
5. NMR Spectrum of <u>cis</u> -2,2,4,4-Tetramethyl-1,3-cyclobutanediol . .	28
6. NMR Spectrum of <u>trans</u> -2,2,4,4-Tetramethyl-1,3- cyclobutanediol bischloroacetate	29
7. Two Possible Conformations of the Ester Linkage	30
8. Conformation of Secondary Esters as Determined by X-Ray Diffraction	30
9. Conformation of the Chloroacetate Moiety of the Chloro-diester	30
10. Molecular Structure of <u>trans</u> -2,2,4,4-Tetramethyl-1,3- cyclobutanediol bischloroacetate	32

CHAPTER I

INTRODUCTION

Historical Background

As early as 1911, an attempt was made to prepare 2,2,4,4-tetramethyl-1,3-cyclobutanediol.^{1,2} It was not, however, until 1936 that this compound was reported as being successfully prepared.³ In 1960 the diol first became available in volume quantities by Eastman Chemical Products, Inc. Experimental data obtained in their own laboratories indicate the diol has exceptional thermal and hydrolytic stability.⁴ Unusual stability of the esters of the diol prepared in their laboratories suggests their use in synthetic lubricants. In addition, many possible applications for the diol exist in the polyester field.⁵

Because esters of the diol are of current interest, preparation of a new ester should contribute to a better understanding of diol esters in general. The choice of an ester to be prepared was based on

¹E. Wedekind and M. Miller, *Ber.*, 44, 3285 (1911), cited by R. Hasek *et al.*, *J. Org. Chem.*, 26, 700 (1961).

²Henceforth the term diol may be used in place of 2,2,4,4-tetramethyl-1,3-cyclobutanediol.

³P. F. Gross, "The Structure of a Ketene Dimer," Ph.D. thesis, Cornell University, 1936, cited by R. Hasek *et al.*, *J. Org. Chem.*, 26, 700 (1961).

⁴Eastman Chemical Products, Inc., "Tetramethyl-1,3-cyclobutanediol; 2,2,4,4-tetramethyl-1,3-cyclobutanediol; Properties, Reactions," May, 1960, p. 13.

⁵Ibid.

ease of handling and identifying the new compound. A chloro-substituted ester, 2,2,4,4-tetramethyl-1,3-cyclobutanediol bischloroacetate,⁶ was chosen. The electrophilic chlorine increases the polarity of the compound, enabling crystallization to occur more readily, and, thus, the compound can be studied more easily. Standard analytical techniques for chloride are available. The chloro-ester derivative contains a known quantity of chlorine and the ester can easily be identified.

Literature Search

To assure originality of this study of the esterification of the diol to the chloro-diester, a thorough search of available literature was carried out, using the indexes of Richter; Stelzner; Beilstein; and Chemical Abstracts, 1907-1968. The search was conducted under headings: 2,2,4,4-tetramethyl-1,3-cyclobutanediol, $C_8H_{16}O_2$ and 2,2,4,4-tetramethyl-1,3-cyclobutanediol bischloroacetate, $C_{12}H_{18}O_4Cl_2$. Literature from Eastman indicates a number of esters of the diol have been prepared. However, preparation of the bischloroacetate diester of the diol has not been reported.

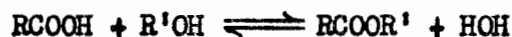
A survey of esterification procedures shows that several alternatives exist for conversion of alcohols to esters: the use of acid chlorides, anhydrides, or carboxylic acids. In general, acid chlorides esterify alcohols most readily, and carboxylic acids least readily. Because difficulty of esterification of the diol was of interest,⁷ a

⁶Henceforth the term chloro-diester may be used in place of 2,2,4,4-tetramethyl-1,3-cyclobutanediol bischloroacetate.

⁷Infra, p. 4.

carboxylic acid, monochloroacetic acid, was used in this investigation. Esterification using a carboxylic acid was first described by Fischer.⁸

The Fischer method of esterification is a reaction between a carboxylic acid and an alcohol in which an ester and water are products. A carboxylic acid and an alcohol are refluxed with 1-5% by weight of sulfuric acid which serves as a catalyst. Esterification is reversible and does not go to completion, but reaches an equilibrium state in which some acid, alcohol, ester, and water are all present.



Because esterification is reversible and reaches an equilibrium, an equilibrium constant can be expressed for the reaction:

$$K_{\text{eq}} = \frac{[\text{RCOOR}'] [\text{HOH}]}{[\text{RCOOH}] [\text{R}'\text{OH}]}$$

According to Le Chatlier's principle, more of the ester would be formed if the reaction equilibrium could be shifted to the right. An equilibrium shift can be effected in several ways. Either excess acid or alcohol can be added. This method works well, but cost or limited quantities of acid or alcohol may limit its usage. An alternative is to remove the water as it is formed. Water can be removed by using a dehydrating

⁸Fischer and Spier, *Ber.*, 28, 1150, 3252 (1895), cited by V. Migrdichian, "Organic Synthesis," Vol. 1, Rheinhold Publishing Co., New York, 1957, p. 313.

agent such as concentrated sulfuric acid, zinc chloride, or calcium chloride.⁹ Water can also be distilled off as it forms if the reaction can be carried out at a temperature greater than the boiling point of water. Another technique for water removal involves esterification in a solvent such as benzene. Water formed from the reaction and benzene from the reflux condenser are collected and separated in a Dean-Stark trap.¹⁰

An important question arises when an ester is prepared by the Fischer method: From which reactant is the oxygen eliminated--the alcohol or the carboxylic acid? Work has been done which suggests that in many cases the oxygen is eliminated from the acid. This was first indicated by the fact that a thioester is formed if a thiol is used in place of the alcohol.¹¹



Proof was later obtained using water containing isotopic oxygen for hydrolysis of an ester.¹²



⁹V. Migrdichian, "Organic Synthesis," Vol. 1, Rheinhold Publishing Co., New York, 1957, p. 315.

¹⁰F. Condon and H. Meislich, "Introduction to Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, 1960, p. 324.

¹¹E. E. Reid, Am. Chem. J., 43, 489 (1910).

¹²M. Polanyi and A. L. Szabo, Trans. Faraday Soc., 30, 508 (1934), cited by J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill Book Company, New York, 1968, p. 310.

As hydrolysis is the reverse of esterification, it is clearly evident that the oxygen is eliminated from the acid.

Further consideration of the esterification mechanism of this investigation will be considered in another part of this paper.

Properties of 2,2,4,4-Tetramethyl-1,3-Cyclobutanediol

The diol selected for esterification exists in the cis and trans geometrical isomers as shown in Figure 1. As a consequence, its molecular structure contributes several interesting characteristics. Two sets of gem-dimethyl groups offer possibilities of steric hindrance to reactivity of the diol hydroxy groups. Therefore, the difficulty of esterification should be an indication of the amount of steric hindrance. Cis and trans isomers would provide an opportunity for comparison of cis-trans isomer properties of compounds prepared.

Isomers of the diol exhibit decidedly different properties when heated with a mineral acid. The trans form is dehydrated to 2,2,4-trimethyl-3-pentenal with boiling aqueous sulfuric acid solution as dilute as 0.02N. However, the cis form is unaffected by boiling 20% aqueous sulfuric acid solution.¹³

In the work reported in this thesis, an approximate 50/50 mixture of the cis and trans isomers of the diol was used.¹⁴ Physical properties of the diol appear in Table I.

¹³R. Hasek, R. Clark, and J. Chaudet, J. Org. Chem., 26, 3130 (1961).

¹⁴The experimental sample was obtained from Eastman Chemical Products, Inc., Kingsport, Tennessee.

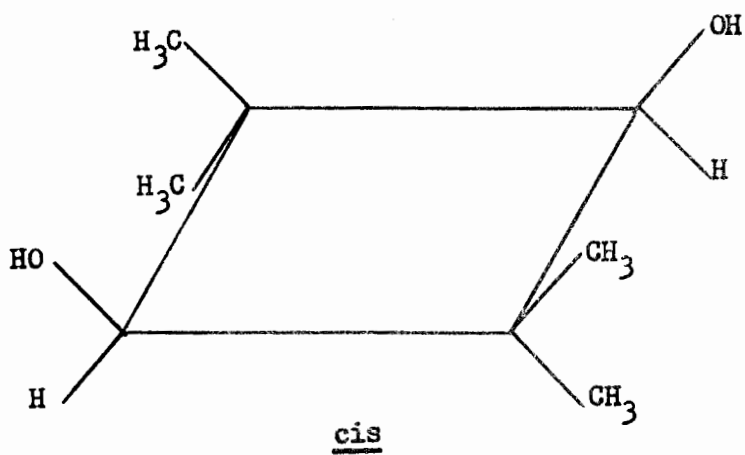
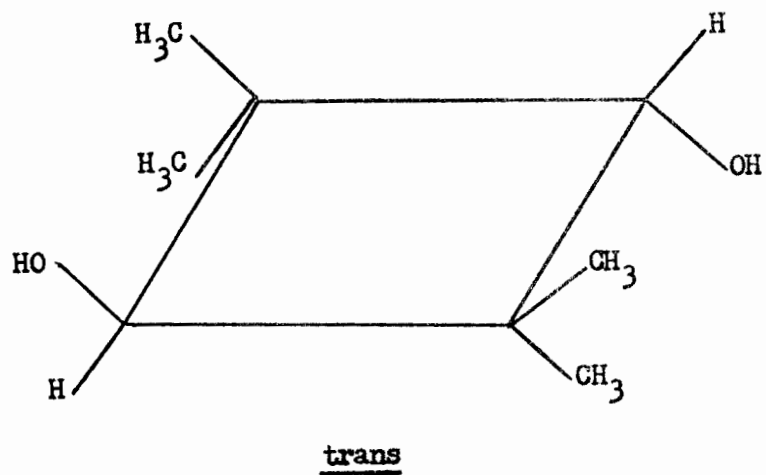


Figure 1. Structure of 2,2,4,4-Tetramethyl-1,3-cyclobutanediol

TABLE I

TYPICAL PROPERTIES OF 2,2,4,4-TETRAMETHYL-1,3-CYCLOBUTANEDIOL^{a,b}
 (Approximately 50/50 mixture of cis and trans isomers)

Formula weight (calculated)	144.2
Appearance	White crystalline solid
Purity, %	99.5
Melting point, °C	125-135 162.5-163.5 (<u>cis</u> isomer) 147-148 (<u>trans</u> isomer)
Boiling point, 760 mm, °C	222
Density, 25/25°C, gm/cm ³	1.09 (<u>cis</u> isomer) 1.02 (<u>trans</u> isomer)
Refractive index, n _D ^{20°C}	1.519 (<u>cis</u> isomer) 1.483 (<u>trans</u> isomer)
Crystal system	Tetragonal (<u>cis</u> isomer) Triclinic (<u>trans</u> isomer)
Solubility, gm/100gm solution	Water 6.0 ⁴⁰ 15.2 ⁸⁰ Toluene 2.5 ⁵⁵ 42.8 ¹⁰⁰ MeOH 47.8 ²⁵ 61.3 ⁶⁰
Crystal habitat	Slightly elongated Octahedra (<u>cis</u> isomer) Long needles (<u>trans</u> isomer)
Dipole moment ^b	2.39 (<u>cis</u> isomer) 2.10 (<u>trans</u> isomer)

^aEastman Chemical Products, Inc., op. cit., p. 14.

^bR. Hasek et al., J. Org. Chem., 26, 702 (1961).

The Statement of the Problem

The purpose of this investigation is to study the esterification of 2,2,4,4-tetramethyl-1,3-cyclobutanediol, which exists as a mixture of cis and trans geometrical isomers. The Fischer method of esterification usually involves an acid catalyst, but the trans diol is known to decompose in an acid environment.¹⁷ Therefore, esterification of the diol would probably be best carried out without the usual acid catalyst. Monochloroacetic acid is used in this esterification. Since the diol is a mixture of the cis and trans isomers, one expects that esters formed during esterification will, likewise, be a mixture of the isomers. A procedure for separation of the diester isomers will be attempted. The new compound will be identified using nuclear magnetic resonance spectroscopy, infrared spectroscopy, and standard analytical techniques. Various physical properties will be determined. Although the diol isomers have previously been separated, a simpler procedure will be sought. Data accumulated during the investigation should contribute to the mass of physical data available to all organic chemists.

¹⁷Supra, p. 5.

CHAPTER II

A PRELIMINARY INVESTIGATION

Introduction

To become familiar with the diol through actual use, 2,2,4,4-tetramethyl-1,3-cyclobutanediol diacetate was prepared as described in the Eastman technical report.¹ Physical properties of the mixture of the cis and trans isomers of the diester were compared to literature values, and the compound was identified by saponification.

Preparation of a Known Compound

A mixture of 11.2 grams (0.11 mole) acetic anhydride and 0.5 gram anhydrous zinc chloride was added to 7.21 grams (0.05 mole) of the diol. The mixture was refluxed for two hours at 125° C.² After cooling, the product remained completely liquid. Heating the liquid product under reduced pressure, a water soluble liquid having the odor of acetic acid distilled. A viscous liquid residue was washed alternately with water and aqueous sodium bicarbonate until neutral to litmus. The remaining substance solidified when chilled in an ice bath, becoming almost completely solid at 22°. When warmed slowly the solid became completely liquid at 25°. The literature melting point of the cis-trans mixture of

¹Eastman Chemical Products, Inc., "Tetramethyl-1,3-cyclobutanediol; 2,2,4,4-Tetramethyl-1,3-cyclobutanediol; Properties, Reactions," May, 1960, pp. 15-16.

²All temperatures are reported in centigrade degrees.

CHAPTER II

A PRELIMINARY INVESTIGATION

Introduction

To become familiar with the diol through actual use, 2,2,4,4-tetramethyl-1,3-cyclobutanediol diacetate was prepared as described in the Eastman technical report.¹ Physical properties of the mixture of the cis and trans isomers of the diester were compared to literature values, and the compound was identified by saponification.

Preparation of a Known Compound

A mixture of 11.2 grams (0.11 mole) acetic anhydride and 0.5 gram anhydrous zinc chloride was added to 7.21 grams (0.05 mole) of the diol. The mixture was refluxed for two hours at 125° C.² After cooling, the product remained completely liquid. Heating the liquid product under reduced pressure, a water soluble liquid having the odor of acetic acid distilled. A viscous liquid residue was washed alternately with water and aqueous sodium bicarbonate until neutral to litmus. The remaining substance solidified when chilled in an ice bath, becoming almost completely solid at 22°. When warmed slowly the solid became completely liquid at 25°. The literature melting point of the cis-trans mixture of

¹Eastman Chemical Products, Inc., "Tetramethyl-1,3-cyclobutanediol; 2,2,4,4-Tetramethyl-1,3-cyclobutanediol; Properties, Reactions," May, 1960, pp. 15-16.

²All temperatures are reported in centigrade degrees.

2,2,4,4-tetramethyl-1,3-cyclobutanediol diacetate is 22-25°. ³ At room temperature, the product was a slushy solid. This product, which will be referred to as Product I, was analyzed quantitatively by saponification.

Saponification of Product I

A known excess of standard alcoholic potassium hydroxide was added to each of three weighed samples of Product I. The solutions were refluxed over steam for thirty minutes. Alkali remaining after completion of saponification was determined by titration with standard hydrochloric acid, using phenolphthalein indicator. From the quantity of alkali unreacted, the milliequivalents of the alkali used in saponification was calculated. The saponification equivalent and the molecular weight based on two ester groups were calculated using the following formulas:

$$S. E. = \frac{\text{Weight of sample in milligrams}}{\text{Net milliequivalents of alkali used}}$$

$$M. W. = S. E. \times \text{number of ester groups}$$

Experimental results of the saponification appearing in Table II compare favorably with calculated values. Product I was assumed to be a cis-trans mixture of 2,2,4,4-tetramethyl-1,3-cyclobutanediol diacetate.

³Eastman Chemical Products, Inc., op. cit., p. 16.

TABLE II

SAPONIFICATION OF PRODUCT I

Sample	Weight of sample, mg.	Total meq. of KOH
1.	626.2	13.46
2.	623.7	13.46
3.	851.6	13.46

Sample	Meq. of KOH in excess	Meq. of KOH for saponification
1.	7.95	5.51
2.	7.97	5.49
3.	5.98	7.48

Sample	Saponification equivalent	Experimental molecular weight ^a
1.	114	228
2.	114	228
3.	114	228

^aThe theoretical molecular weight of the diester, 2,2,4,4-tetramethyl-1,3-cyclobutanediol diacetate, is 228.3.

CHAPTER III

SEPARATION OF THE cis AND trans ISOMERS OF THE DIOL

Introduction

A separation of the individual isomers of the diol may be desirable in studies involving dipole moment, nuclear magnetic resonance spectroscopy, and infrared spectroscopy. Various methods of separation of the cis and the trans forms of the diol have been reported in the literature. Miller reported separation of a sample of the mixture of the isomeric forms of the diol by vacuum sublimation.¹ He concluded two isomers melted at 127-128° and 147-148°. Hasek et al. later showed these results to be inaccurate² when they isolated and identified the cis and trans isomers of the diol, and devised a better method of separation of the diol isomers.³ Esterification of the diol using formic acid yields a mixture of the cis- and trans-diformate esters which are respectively liquid and solid at room temperature. Isomers of the diformate ester may be separated by filtration. Alcoholysis of the respective esters yields the individual cis and trans isomers of the diol.

Since esterification of the diol and subsequent alcoholysis of the ester was time consuming, a question arose concerning the possibility

¹L. L. Miller, "Structure of Some Derivatives of Dimethylketene," Ph.D. thesis, Cornell University, 1937, cited by R. Hasek et al., J. Org. Chem., 26, 700 (1961).

²R. Hasek et al., J. Org. Chem., 26, 702 (1961).

³Ibid., p. 703.

of separation of the diol by a simpler procedure. The products of the alcoholysis of the liquid portion of the diformate are described by Hasek et al. as a mixture of the diol isomers.⁴ Separation of the cis-diol from a mixture of these isomers using toluene as a recrystallization solvent is then described. Isolation of the cis-diol from the commercial sample of diol isomers should, likewise, be possible.

An attempt was then made to separate the cis isomer of the diol from the commercial sample of diol isomers, using toluene as solvent and omitting the esterification and alcoholysis steps. Similarity of the melting point to the literature value confirmed the identity of the isolated crystals as the cis-diol.

Preparation of the Diformate Ester

The diformate ester of the diol was prepared according to the procedure described by Hasek et al.⁵ A mixture of 28.8 grams (0.20 mole) of the diol, 27.0 grams (0.59 mole) of formic acid, and 18 milliliters of benzene was refluxed for five hours. The solution was cooled, a second portion of 27.0 grams of formic acid was added, and refluxing was continued for four hours. After cooling, the solution was diluted with 20 milliliters of benzene, and alternately washed with water and aqueous sodium bicarbonate until the water wash was neutral to litmus. Finally, the liquid product was dried over anhydrous sodium sulfate. After distillation to remove the solvent, the product was cooled. Upon

⁴R. Hasek et al., J. Org. Chem., 26, 703 (1961).

⁵Ibid.

standing at room temperature for thirty hours, the product separated into liquid and solid phases. The mixture was filtered, and the solid was recrystallized twice from ligroin and dried. The solid formed planar crystals which melted sharply at 67-68°. The melting point for the trans-diformate ester of the diol is 67-68°. ⁶ Saponification of these crystals (Product II) was carried out following the previous procedure. ⁷ The experimental saponification equivalent for Product II was 100. The data are given in Table III. The calculated value for the trans-diformate ester, $C_{10}H_{16}O_4$, is 100.1. Product II was assumed to be the trans-diformate ester.

Alcoholysis of the Diformate Ester

Alcoholysis of each of the separated portions of the diformate esters was carried out as described by Hasek et al. ⁸ The crystalline trans-diformate ester was dissolved in a solution of 25 milliliters of methanol and 0.2 gram of metallic sodium and allowed to stand at room temperature for twenty-four hours. One milliliter of acetic acid was added and the solution evaporated to dryness. The solid residue was dissolved in 25 milliliters of hot toluene. After filtration of the hot solution to remove insoluble solids, the solution was concentrated to a volume of about 15 milliliters and allowed to cool to room temperature. The crystals were filtered from the solution, and, after drying, melted

⁶ R. Hasek et al., J. Org. Chem., 26, 703 (1961).

⁷ Supra, p. 10.

⁸ R. Hasek et al., loc. cit.

TABLE III

SAPONIFICATION OF PRODUCT II

Sample	Weight of sample, mg.	Total meq. of KOH
1.	616.1	13.46
2.	668.3	13.46
Sample	Meq. of KOH in excess	Meq. of KOH for saponification
1.	7.33	6.13
2.	6.75	6.71
Sample	Saponification equivalent	Experimental molecular weight ^a
1.	101	202
2.	100	200

^aThe theoretical molecular weight of 2,2,4,4-tetramethyl-1,3-cyclobutanediol diformate is 200.2.

sharply at 148° . The literature melting point of the trans-diol is 148° .⁹ These crystals were assumed to be the trans-diol.

The liquid portion of the diformate ester, containing a mixture of the cis- and trans-diformate esters, was dissolved in a solution of 70 milliliters of methanol and 0.2 gram of metallic sodium and allowed to stand at room temperature for twenty-four hours. The solution was evaporated to dryness over steam and the residue dissolved in hot toluene. Filtration of this hot solution removed insoluble solids. Upon cooling, the hot toluene solution yielded a large quantity of crystals which melted at $132-154^{\circ}$. These crystals recrystallized from a second portion of toluene melted at $160-167^{\circ}$. A final recrystallization from toluene gave crystals melting at $162-164^{\circ}$. These were assumed to be the cis-diol. The literature melting point of the cis-diol is $162.5-163.5^{\circ}$.¹⁰

Separation of the cis-Diol from a Mixture of the Isomers

A preliminary investigation indicated that the cis-diol could be separated from a mixture of the isomers using toluene as the solvent. A 6.17 gram sample of the commercial cis-trans mixture of the diol was dissolved in 20 milliliters of toluene. The solution was cooled to 80° and filtered to separate the diol which had crystallized. The filtrate (I) was saved for further crystal recovery. The separated crystals melted at $158-165^{\circ}$. These were redissolved in 20 milliliters of toluene, cooled to 100° , and filtered. A final recrystallization from 10 milliliters of toluene gave 0.95 gram of the cis-diol, melting at $164-165^{\circ}$.

⁹Supra, p. 7.

¹⁰Supra, p. 7.

An unsuccessful attempt was made to separate the trans-diol from Filtrate (I). Filtrate (I) was cooled in an ice bath, and the solid diol filtered from the solution. The crystalline residue was dissolved in a second portion of hot toluene, cooled to 87°, and filtered. On standing at room temperature, the final filtrate deposited crystalline material. Separation of this material by filtration gave long tetrahedral crystals melting at 128-132°, which were probably still a mixture of the cis and trans isomers of the diol.¹¹

¹¹ Miller obtained crystals, melting point 127-128°, which Hasek et al. determined to be 30% cis-diol and 70% trans-diol, R. Hasek et al., J. Org. Chem., 26, 702 (1961).

CHAPTER IV

PREPARATION, IDENTIFICATION, AND CHARACTERIZATION OF 2,2,4,4-TETRAMETHYL-1,3-CYCLOBUTANEDIOL BISCHLOROACETATE

Introduction

Several attempts were made to prepare 2,2,4,4-tetramethyl-1,3-cyclobutanediol bischloroacetate by esterification of 2,2,4,4-tetramethyl-1,3-cyclobutanediol using monochloroacetic acid. Since esterification can be carried out in various environments, three trials were attempted using the respective catalysts: anhydrous zinc chloride, five per cent phosphoric acid, and metallic sodium. Two trials were uncatalyzed reactions: one at 108-117°, and the second at 95-105°. All esterification trials yielded a slushy solid, from which a white crystalline solid melting at about 97-100° was isolated.

A Summary of the Reactions

Considerable decomposition occurred during three of the esterification reactions: reactions having zinc chloride and phosphoric acid added as catalysts, and the 108-117° uncatalyzed reaction. Assuming the product to be the chloro-diester, yields of the crystalline product for these trials were respectively: 2%, 9%, and 18%. The trans-diol was assumed to have decomposed, rather than the cis-diol, since the former is least stable in an acid environment.¹ Because decomposition occurred

¹Supra, p. 5.

during the uncatalyzed reaction at 108-117°, a second trial was carried out at 95-105°. No decomposition occurred in the second trial; the yield was 23%. Esterification in which sodium was used as a catalyst produced a yield of 21%.

The Infrared Spectrum of the Chloro-diester

The infrared spectrum of the chloro-diester, Product VII², is shown in Figure 2. Absorptions at 5.70 μ and the shoulder at 5.85 μ represent the carbonyl group of the chloroacetate moiety. Because there is freedom of rotation for the alpha carbon, two configurations are possible: absorption occurs at 5.70 μ for the configuration in which the chlorine is nearest the carbonyl group, and at 5.85 μ for the configuration in which the chlorine is farthest from the carbonyl group.³ Twin absorptions at 7.05 μ and 7.25 μ are characteristic for gem-dimethyl groups⁴ such as the two sets substituted on the cyclobutane ring. Absorption at 8.50 μ represents the ester linkage stretch, and at 12.55 μ the carbon-chlorine stretch. The absorption of 7.60 μ is believed to be due to an impurity. A more complete description is given in Table IV.

Chlorine Analysis of the Products

The crystalline product described above, m.p. 97-100°, was not known definitely to be the chloro-diester. If the compound is the diester,

²Infra, p. 21.

³L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen and Company, Ltd., London, 1962.

⁴J. R. Dyer, "Application of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965.

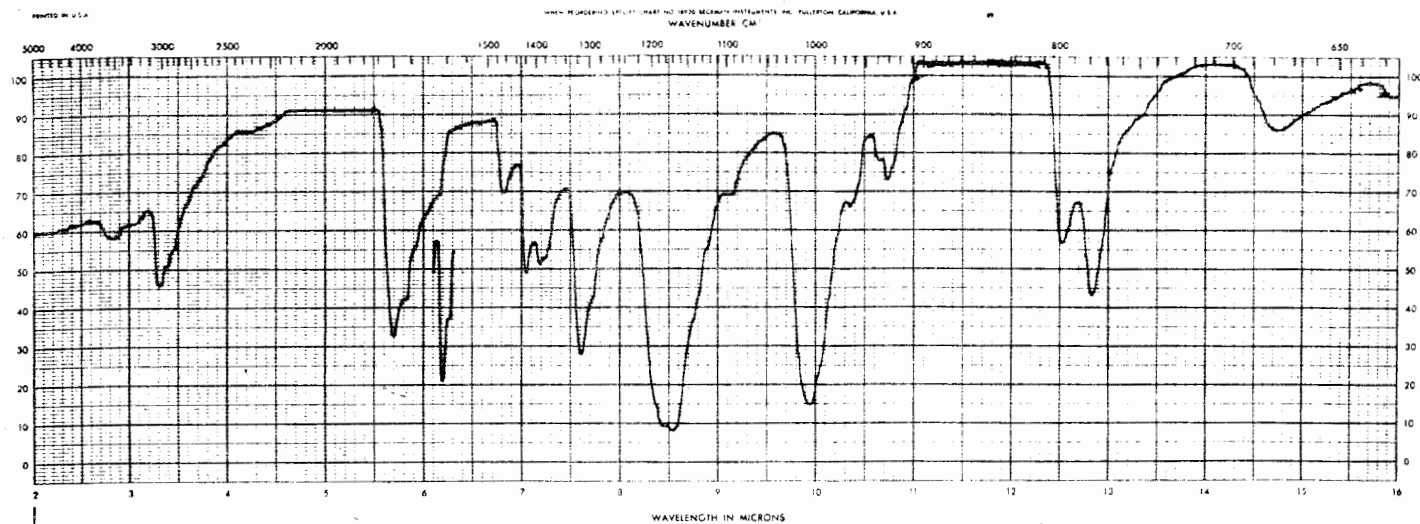


Figure 2. IR spectrum of 2,2,4,4-tetramethyl-1,3-cyclobutanediol
bischloroacetate in KBr

TABLE IV
THE CORRELATION OF THE INFRARED SPECTRUM
OF PRODUCT VII, THE CHLORO-DIESTER

Group ^a	Range μ
C-H, C-CH ₃ stretch	3.30
C=O stretch	5.70-5.82
<u>gem</u> -dimethyl asymmetric and symmetric bending	7.05-7.28
O-H bending (impurity)	7.60
C-O stretch	8.50
C-O stretch	9.95
-CH ₂ - rock	10.35-10.72
C-Cl stretch	12.55
Ring out of plane bending	12.82

^aThe absorption at 6.20 μ is a calibration peak of polystyrene at 6.24 μ .

it should have a definite amount of chlorine in the molecule and the analyzed chlorine composition would agree closely with the calculated value.

Chlorine analysis was carried out on the crystalline products from the uncatalyzed reactions, and on the crystalline product from the sodium catalyzed reaction. Chlorine in the compound was converted to inorganic chloride using a Parr bomb fusion.⁵ The Caldwell modification of the Volhard volumetric procedure⁶ was used to determine the percentage of chlorine present. Results of the chlorine analysis indicated Products V, VI, and VII, as described in Table VI, were the chloro-diester.

A lowering of the melting point of the mixture of two substances is an indication those substances are not identical.⁷ Melting points of a 50/50 mixture of various combinations of products showed no significant depression as shown in Table V.

TABLE V
MIXTURE MELTING POINTS

Products	Melting points	Melting point of a 50/50 mixture
VI, IV	99-101, 98-101	99-100
III, IV	96-100, 98-101	96-101
VII, V	101-102, 98-99	98-101
IV, V	98-101, 98-99	98-101

⁵Parr Manual Number 121, "Peroxide Bomb Apparatus and Methods," Parr Instrument Company, Moline, Illinois, 1950.

⁶J. Caldwell and H. Moyer, Ind. Eng. Chem., Anal. Ed., 7, 38-39 (1935).

⁷A. Weissberger, "Physical Methods of Organic Chemistry," Interscience Publishers, Inc., New York, 1949, p. 79.

TABLE VI

COMPARISON OF ESTERIFICATION PRODUCTS

Reaction	Product	Melting Point ^a	Per cent Chlorine ^b	Per cent Yield ^c
Catalyzed:				
Anhydrous ZnCl ₂	III	96-100	Not analyzed	2
5% H ₃ PO ₄	IV	98-101	Not analyzed	9
Metallic sodium	V	98-99	23.5	21
Uncatalyzed:				
108-117°	VI	101-102	24.5	18
95-105°	VII	101-102	23.9	23

^aThe melting points were found using an electrical heating device, the Fisher-Johns Melting Point Apparatus, Fisher Scientific Company, Pittsburgh, Pa.

^bThe theoretical percentage for C₁₂H₁₈O₄Cl₂ is 23.86.

^cBased on total diol used.

Similarity of esterification procedures, lack of depressed mixture melting points, and close agreement of melting points indicated Products III through VII, by whichever method prepared, were identical. The infrared spectrum of Product VII was used to confirm functional groups, and the nuclear magnetic resonance spectrum of Product VI confirmed the configuration. A comparison of esterification products is given in Table VI.

Determination of the Configuration of the Chloro-diester

Though the composition of the product was known to be that of the chloro-diester, the configuration, whether cis or trans, needed to be confirmed.

Nuclear magnetic resonance (NMR) was used in determining the configuration of the molecule. An NMR spectrum shows a signal or peak for each kind of proton, or hydrogen atom, in a molecule. The chloro-diester molecule contains several kinds of protons, but protons of the four methyl groups were best suited for configuration study. The environments of all methyl groups of the trans isomer are identical. (The three protons on each methyl group are equivalent.) Each methyl proton on methyl groups (a) and (b) "sees" an ester group and a lone proton on the same side of the ring, as is shown in Figure 3. The NMR spectrum would show a single peak, representing twelve methyl protons of the four equivalent methyl groups. As an example, the NMR spectrum of the trans-diformate diester is shown in Figure 4. A peak representing methyl protons appears at δ 1.1, relative to standard tetramethylsilane, TMS.

The four methyl groups of the cis isomer are not equivalent. Methyl groups (b) on the same side of the ring as the ester groups are

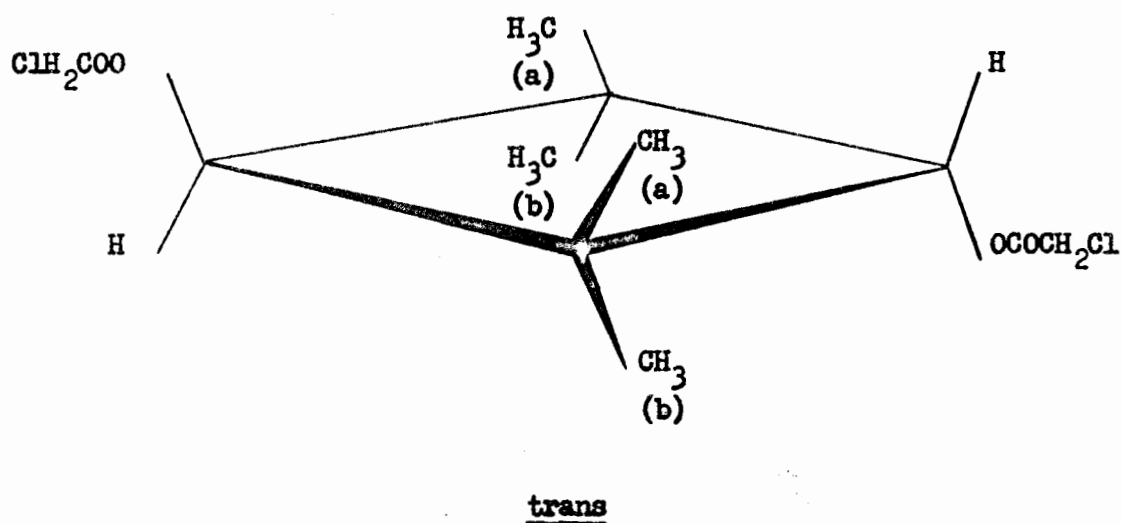
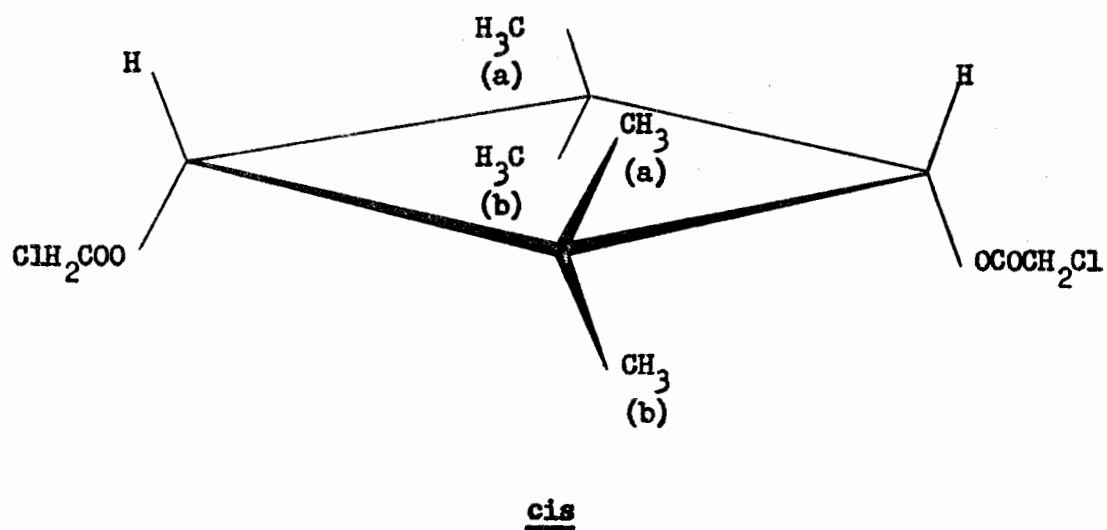


Figure 3. Structure of 2,2,4,4-tetramethyl-1,3-cyclobutanediol bischloroacetate

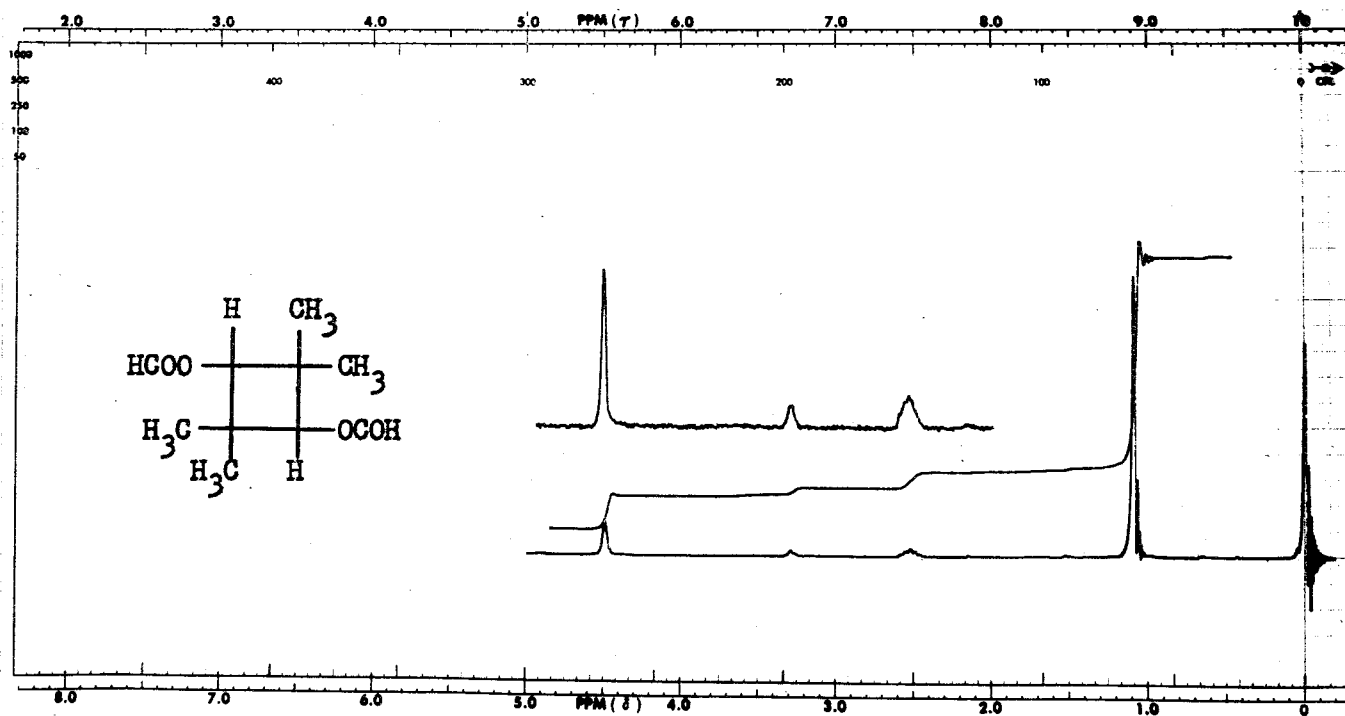


Figure 4. NMR spectrum of trans-2,2,4,4-tetramethyl-1,3-cyclobutanediol diformate in deuterated dimethylsulfoxide

equivalent. Methyl groups (a) on the opposite side of the ring are equivalent. However, each set of methyl groups "sees" a slightly different environment, as is shown in Figure 3. Thus the two sets of methyl groups are not equivalent. The NMR spectrum would show two peaks, each peak representing one set of methyl groups, or six protons. Figure 5 shows the NMR spectrum of the cis-diol as an example. The peak at δ 1.0 represents methyl protons on the same side of the ring as the hydroxy groups, and the peak at δ 0.8 represents those on the opposite side.

The NMR spectrum of the chloro-diester, Product VI, is shown in Figure 6. The single peak at δ 1.1, relative to TMS, clearly shows the product to have the trans configuration.

Alcoholysis of the chloro-diester was carried out following the same procedure as for the trans-diformate.⁸ The crystalline product, melting at 148° , was the trans-diol, further confirming the trans configuration.

Conformation of the Chloro-diester

Since the ester groups are free to rotate, a question of their most stable conformation arises. The conformation shown in Figure 7a, having a smaller dipole moment, is the favored structure. The alternative, as in Figure 7b, has a much larger moment.⁹ Crystal studies of secondary esters using X-ray analysis have shown that the conformation illustrated in

⁸Supra, p. 14.

⁹A. Liberles, "Introduction to Theoretical Organic Chemistry," Macmillan Co., New York, 1968, p. 562.

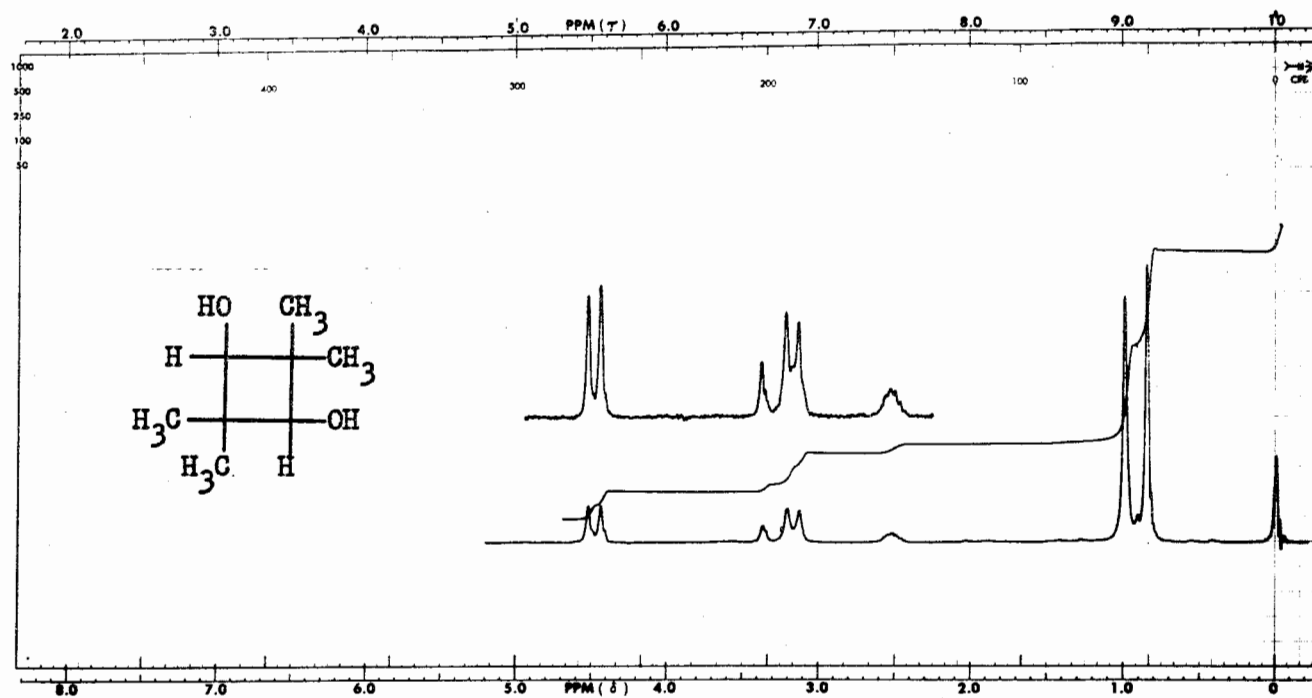


Figure 5. NMR spectrum of *cis*-2,2,4,4-tetramethyl-1,3-cyclobutanediol in deuterated dimethylsulfoxide

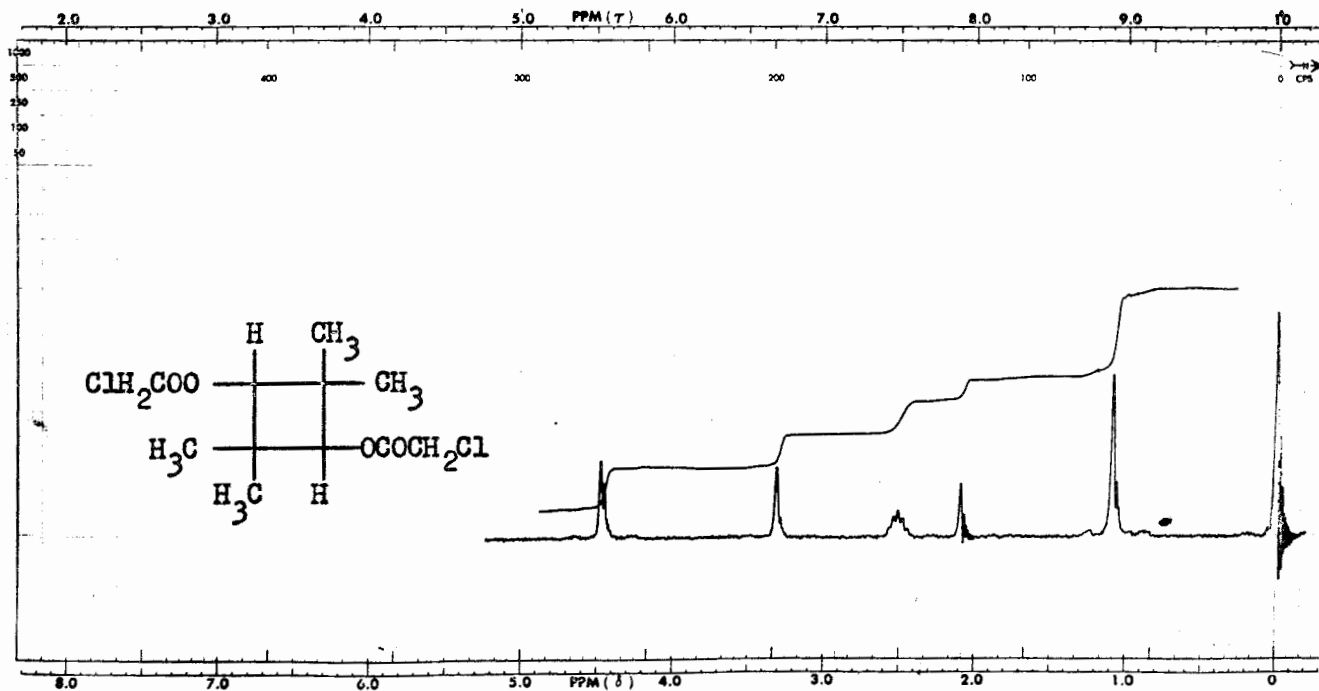


Figure 6. NMR spectrum of *trans*-2,2,4,4-tetramethyl-1,3-cyclobutanediol bischloroacetate in deuterated dimethylsulfoxide

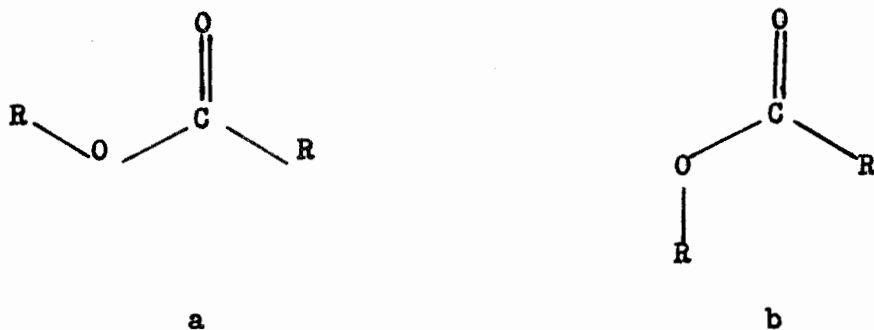


Figure 7. Two possible conformations of the ester linkage

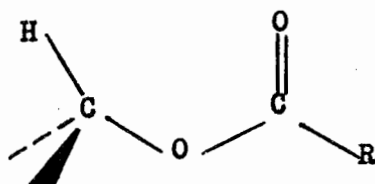


Figure 8. Conformation of secondary esters as determined by X-ray diffraction

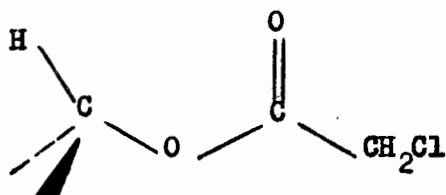


Figure 9. Conformation of the chloroacetate moiety of the chloro-diester

Figure 8 is invariably adopted.¹⁰ Conformation of the chloroacetate moiety of the diester molecule is undoubtedly as shown in Figure 9. The probable molecular structure for trans-2,2,4,4-tetramethyl-1,3-cyclobutanediol bischloroacetate is shown in Figure 10.

Experimental Work

Esterification of the Diol Using Zinc Chloride as a Catalyst.

A mixture of 7.21 grams (0.05 mole) of the diol, 10.00 grams (0.11 mole) of chloroacetic acid, and 0.28 grams of anhydrous zinc chloride was heated for two hours at 120°. The product was a black liquid, indicating considerable decomposition had occurred. After the liquid was washed alternately with water and aqueous sodium bicarbonate until the aqueous phase was no longer acidic to litmus, the product was filtered. On standing at room temperature for thirty-six hours, the liquid deposited a small portion of solid. This solid was separated by filtration and washed once with ligroin. The solid, Product III, weighed approximately 0.3 gram and melted at 96-100°.

Esterification of the Diol Using Phosphoric Acid as a Catalyst.

A mixture of 7.21 grams (0.05 mole) of the diol, 10.00 grams (0.11 mole) of monochloroacetic acid, and 0.8 gram of phosphoric acid was heated for two hours at 115°. The product, a reddish-brown liquid, had undergone considerable decomposition as was expected because of the instability of the trans-diol in an acid environment. The product became a gummy solid

¹⁰A. McL. Mathieson and J. C. Taylor, Tetrahedron, 46, 4137 (1965), cited by A. Rich and N. Davidson, eds., "Structural Chemistry and Molecular Biology," W. H. Freeman and Co., San Francisco, 1968, p. 601.

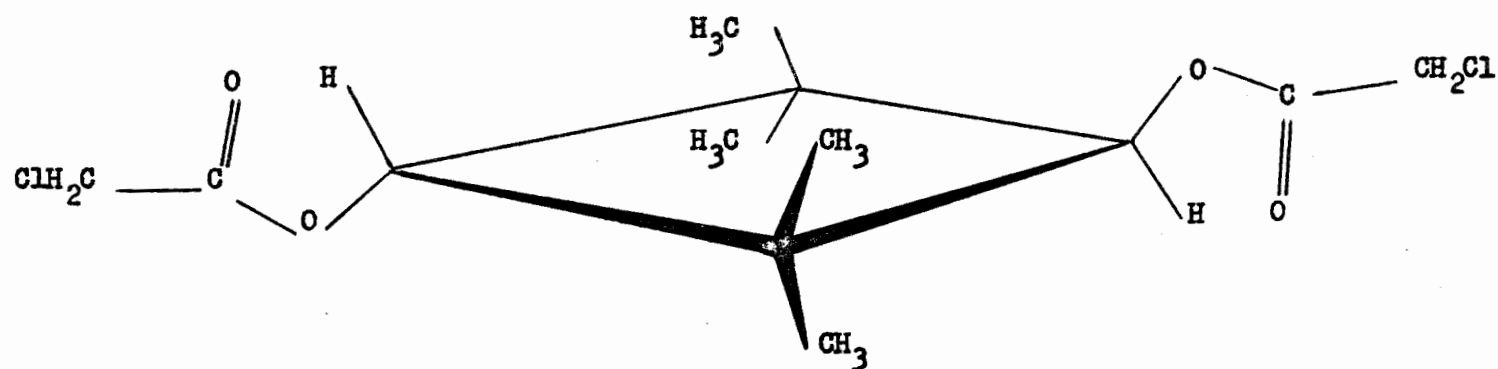


Figure 10. Molecular structure of trans-2,2,4,4-tetramethyl-1,3-cyclobutanediol bischloroacetate

after being washed alternately with water and aqueous sodium bicarbonate. This solid was washed with 50% ethanol and filtered. The residue, after drying for several hours in a vacuum desiccator weighed 0.67 gram and melted at 80-95°. After this solid was washed twice with ligroin, the crystals, Product IV, weighed 0.43 gram and melted at 98-101°. Mixture melting points of Products III and IV showed no depression, and the two products were assumed identical.

Esterification of the Diol Using Metallic Sodium as a Catalyst.

A mixture of 7.21 grams (0.05 mole) of the diol, 11.10 grams (0.12 mole) of monochloroacetic acid, and 0.1 gram (0.004 mole) of metallic sodium was heated to 125°. One milliliter of absolute ethanol was then added, forming sodium alkoxide, a powerful base. Reaction temperature was maintained at 125° for one hour. Reduced pressure distillation yielded 1.0 milliliter of water and 0.8 milliliter of a water insoluble substance thought to be ethyl chloroacetate. The odor and pH of the aqueous distillate indicated it contained dissolved monochloroacetic acid. After cooling, the residue was a white gummy solid. Drying in a vacuum desiccator for two days did not alter its physical appearance. The product was washed with 50% ethanol and filtered. The crystalline residue, Product V, weighed 3.19 grams and melted sharply at 98-99°. The filtrate from the ethanol was separated into an aqueous layer and a yellowish organic layer. After solvent removal, the organic layer weighed 6.87 grams and boiled at approximately 150° at atmospheric pressure. Further identification of the liquid was not attempted.

Product V was analyzed for chlorine. A 312.7 milligram sample of

Product V was thoroughly mixed with 150 milligrams of lactose and 15 grams of sodium peroxide. The sample mixture was placed in a Parr bomb, shaken well, and fused to convert chlorine in the compound to inorganic chloride. When cool, the melt was dissolved in distilled water, acidified with 50 milliliters of 1:1 nitric acid, and made up to 250 milliliters. One-fifth aliquots of the solution were analyzed. Chloride analysis by the Volhard method showed Product V to contain 23.5% chlorine. Experimental data for this analysis are shown in Table VII.

Uncatalyzed Esterification of the Diol (I). A mixture of 7.21 grams (0.05 mole) of the diol and 10.00 grams (0.11 mole) of monochloroacetic acid was heated for one and one-half hours at 108-117°. The reaction mixture decomposed while heating. The product became a gummy solid after being washed alternately with water and aqueous sodium bicarbonate. This solid was washed with 50% ethanol, separated by filtration, and dried. The product, brownish-white crystals, weighed 2.66 grams and melted at 99-101°. A white crystalline solid (Product VI) which melted at 101-102° resulted after the brownish-white crystals were washed once with ligroin. The Parr bomb method was used to convert the solid to inorganic chloride, and chloride analysis of aliquots by the Volhard method showed 24.5% chlorine in Product VI. Analysis data are given in Table VIII.

Uncatalyzed Esterification of the Diol (II). Because the previous esterification product had decomposed during heating, a second uncatalyzed esterification was carried out at a somewhat reduced temperature. A mixture of 14.42 grams (0.10 mole) of the diol and 20.20 grams (0.21 mole)

TABLE VII

CHLORINE ANALYSIS OF PRODUCT V

Chloride: Found		
Wt. of sample in mg. ^a	Meq. of Ag ⁺ used	Meq. of KSCN used
1. 62.54	1.520	1.102
2. 62.54	1.520	1.108
3. 62.54	1.520	1.105
Meq. of chloride in sample	Mg. of chlorine in sample	Per cent chlorine ^b
1. 0.418	14.8	23.7
2. 0.412	14.6	23.3
3. 0.415	14.7	23.5

^aThe original sample was 312.7 milligrams, and 1/5 aliquots were analyzed.

^bThe theoretical per cent chlorine for $C_{12}H_{18}O_4Cl_2$ is 23.86.

TABLE VIII

CHLORINE ANALYSIS OF PRODUCT VI

Chloride: Found		
Wt. of sample in mg. ^a	Meq. of Ag ⁺ used	Meq. of KSCN used
1. 62.54	1.508	1.078
2. 62.54	1.508	1.075
3. 62.54	1.508	1.075
4. 62.54	1.508	1.075
Meq. of chloride in sample	Mg. of chlorine in sample	Per cent chlorine ^b
1. 0.430	15.2	24.5
2. 0.433	15.3	24.5
3. 0.432	15.3	24.5
4. 0.432	15.3	24.5

^aThe original sample was 312.7 milligrams, and 1/5 aliquots were analyzed.

^bThe theoretical per cent chlorine for $C_{12}H_{18}O_4Cl_2$ is 23.86.

of monochloroacetic acid was stirred at 95-105° for three and one-half hours. The apparatus was arranged for distillation and the reaction mixture heated to 110° (25mm). During heating 2.2 milliliters of water distilled, 60% of the theoretical amount. The liquid product remaining in the flask was washed alternately with water and aqueous sodium bicarbonate to remove excess monochloroacetic acid. Standing at room temperature for two hours, the liquid product changed to a gummy solid which was washed with 50% ethanol. Filtration of this mixture gave 6.86 grams of a solid, melting at 72-84°. Recrystallization of the solid from methanol gave planar crystals (Product VII) which melted at 103.5-104°. ¹¹ The refractive index was determined by the Becke Line Method. ¹² Product VII was analyzed for chlorine using Parr bomb fusion and the Volhard procedure. Chlorine analysis showed 23.9% chlorine. Analysis data are given in Table IX.

The methanol recrystallization filtrate was chilled in an ice bath and solid particles formed in the solution. Filtration of this mixture gave a small quantity of white powder which melted at 40-50° and was thought to contain a large proportion of the cis isomer of bischloroacetate diester. No further identification was carried out.

¹¹R. Shriner, R. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, 4th edition, 1957, p. 28.

¹²A. Weissberger, "Physical Methods of Organic Chemistry," Interscience Publishers, Inc., New York, 1949, p. 933.

TABLE IX
PHYSICAL CONSTANTS AND CHLORINE
ANALYSIS OF PRODUCT VII

Chloride: Found		
Wt. of sample in mg. ^a	Meq. of Ag ⁺ used	Meq. of KSCN used
1. 62.96	1.571	1.086
2. 62.96	1.571	1.082
3. 62.96	1.571	1.083
4. 62.96	1.571	1.081
5. Blank	1.571	1.571
Meq. of chloride in sample	Mg. of chlorine in sample	Per cent chlorine ^b
1. 0.422	15.0	23.8
2. 0.426	15.1	24.0
3. 0.425	15.1	24.0
4. 0.427	15.1	24.0
5. 0		
Melting point ^c		
1. 104		
2. 103.5-104		
3. 103.5-104		
Refractive Index-Becke Line at 22°		
The index lies between 1.516-1.520 ^d		

^aThe original sample was 314.8 milligrams, and 1/5 aliquots were analyzed.

^bThe theoretical per cent chlorine for $C_{12}H_{18}O_4Cl_2$ is 23.86.

^cThe melting points were found using a calibrated electrical heating device, the Kofler Micro Hot Stage, Arthur H. Thomas Company, Philadelphia. Five melting point standards (range 44° through 174°) used in the calibration were obtained from the same company.

^dStandard liquids of known indexes, differing by 0.004, were used and were obtained from R. P. Cargille Laboratories, Inc., New York.

CHAPTER V

DISCUSSION

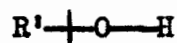
Introduction

During an investigation problems arise, many posing questions not easily answered. Often answers are buried in some obscure set of data or in seemingly unrelated bits of data. One of the problems encountered during this investigation was the reaction mechanism of the esterification of the diol by monochloroacetic acid. Unless a thorough kinetics study is carried out, the solution to the reaction mechanism must be found in reaction data.

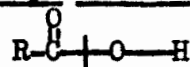
Esterification is a reversible process; the reverse reaction is known as hydrolysis. The principle of microscopic reversibility¹ states: Molecular systems participating in each step in the forward direction must be identical to the systems participating in the reverse direction. Therefore, once the mechanism for acid-hydrolysis is established, the reverse reaction, esterification, is also established.

Acid-catalyzed esterification of alcohols, or hydrolysis of esters, may be unimolecular or bimolecular, alkyl cleaved or acyl cleaved.

Alkyl Cleaved



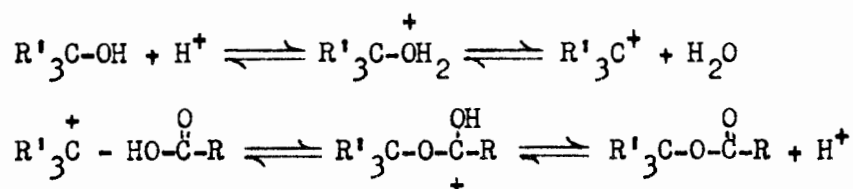
Acyl Cleaved



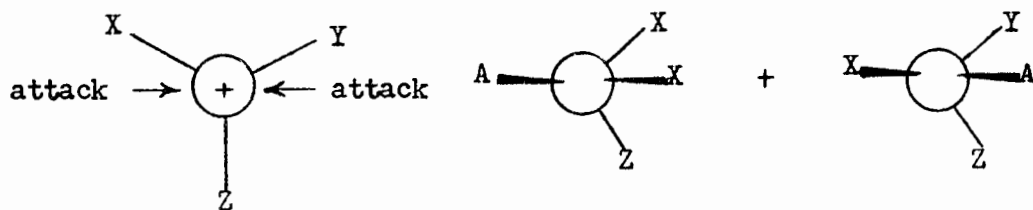
¹E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, New York, 1959, p. 319.

Unimolecular nucleophilic substitution, S_N1 , with acyl cleavage is found only where the R group of the carboxylic acid is very bulky, as is the case for mesitoic acid.²

With alkyl oxygen cleavage S_N1 esterification occurs when the R' group of the alcohol can exist as a stable carbonium ion, as is the case for tertiary alkyl, and benzyl groups.³ The mechanism is shown below:



In the carbonium ion, carbon is bonded to three other groups using sp^2 orbitals, and has a planar structure. The nucleophilic reagent may attack from either side. When this carbon is assymetric, partial racemization of products occurs:⁴

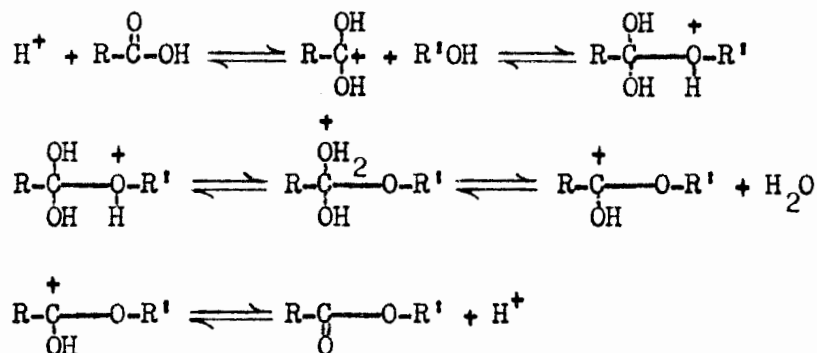


²H. P. Treffers and L. P. Hammett, J. Amer. Chem. Soc., 59, 1708 (1937).

³C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 779-782.

⁴C. A. Bunton et al., Nature, 166, 679 (1950).

Bimolecular nucleophilic substitution, S_N2 , with acyl cleavage is the most common mechanism of acid-catalyzed esterification.⁵ This mechanism has been described as follows:^{6,7}



Racemization cannot occur.

Alkyl cleaved S_N2 esterification is unknown.⁸

The Acid Catalyst

Although all esterification mechanisms described are acid-catalyzed, the hydrogen ion need not necessarily be derived from an acid added specifically for that purpose. Two factors preclude the addition of a catalyzing acid in this investigation: 1) The trans-diol decomposes in an acid

⁵E. S. Gould, op. cit., p. 318.

⁶F. E. Roberts and H. C. Urey, J. Amer. Chem. Soc., **60**, 2391 (1938).

⁷S. C. Datta, J. N. E. Day, and C. R. Ingold, J. Chem. Soc., **1939**, 838, cited by L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, 1940, p. 357.

⁸J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill Book Company, Inc., New York, 1968, p. 310.

medium, as is evidenced in the phosphoric acid-catalyzed reaction, and

2) Although substituents in the alpha position on the carboxylic acid retard the so-called uncatalyzed reaction due to steric hindrance, the exception is alpha substituted halogens which have a decided accelerating effect.⁹ Each successive halogen substituted on the alpha carbon increases the strength of the acid, as is shown below in the dissociation constants¹⁰ for acetic acid and its chlorine derivatives:

	K_a
Acetic acid	1.76×10^{-5}
Chloroacetic acid	1.40×10^{-3}
Dichloroacetic acid	3.32×10^{-2}
Trichloroacetic acid	2.00×10^{-1}

The electronegative chlorine induces an electron shift away from the carbonyl carbon stabilizing the anion and making the acid a better proton donor. Chloroacetic acid can then serve as the proton donor in the reaction often referred to as direct esterification.

S_N1 or S_N2

Alkyl cleaved S_N1 esterification is characterized by racemization. Esterification of a single diol isomer was not attempted in this investigation. However, alcoholysis, base-catalyzed, of both the trans-diformate diester and the trans-chloro-diester gave the trans-diol. Alcoholysis is

⁹V. Migrdichian, "Organic Synthesis, Vol. I," Rheinhold Publishing Corporation, New York, 1957, p. 312.

¹⁰"Handbook of Chemistry and Physics," Forty-fourth Edition, Chemical Rubber Publishing Co., Cleveland, Ohio, 1963, pp. 1753-1756.

analogous to hydrolysis: alkoxide replaces hydroxide. Although base catalyzed hydrolysis generally follows the acyl cleaved S_N2 mechanism, the alkyl cleaved S_N1 pathway is followed with alcohols which give stable carbonium ions.¹¹ Should the diol form a stable carbonium ion, the alcoholysis of a trans-diester would follow the alkyl cleaved S_N1 reaction, and racemization of products would be observed. In this investigation no racemization was observed for alcoholysis reactions, but because all esterifications were carried out using the commercial sample containing a mixture of the diol isomers, no definite conclusion can be drawn concerning the mechanism. However, an alkyl cleaved S_N1 mechanism would appear highly unlikely.

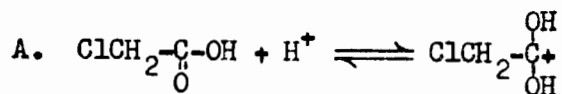
Acyl cleaved S_N1 esterification occurs only for bulky, substituted carboxylic acids. Monochloroacetic acid has no bulky substituted groups. Moreover, the inductive effect caused by the alpha-substituted chlorine would tend to form the highly unstable ion, $ClH_2\overset{O}{\underset{||}{C}}+$. This mechanism would also seem unlikely.

Tertiary alcohols generally esterify by an alkyl cleaved S_N1 mechanism. Primary alcohols follow an acyl cleaved S_N2 mechanism. Esterification of secondary alcohols may follow both mechanisms, but primarily follows the S_N2 path. Because the diol is a secondary alcohol, the S_N2 mechanism seems probable. The most common mechanism for acid-catalyzed esterification is the acyl cleaved, S_N2 type.

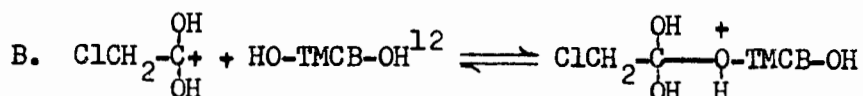
On the basis of the preceding arguments, direct esterification of the diol by monochloroacetic acid is described as an acyl cleaved,

¹¹J. March, op. cit., p. 313.

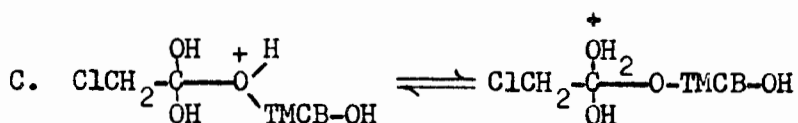
bimolecular, nucleophilic substitution. This proposed mechanism is depicted in the following series of equations:



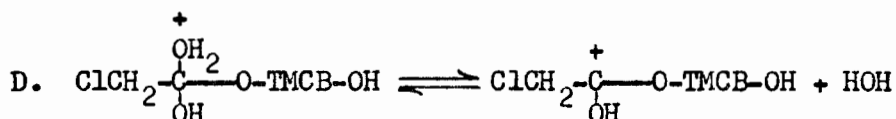
Protonation causing increased reactivity at the carbonyl carbon



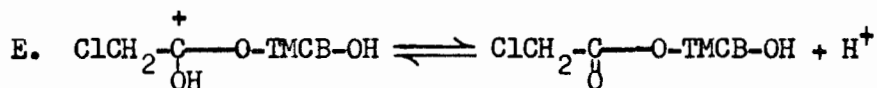
Nucleophilic attack by the diol



Proton shift forming a more stable leaving group



Departure of the leaving group



Ester formed by loss of proton

The second ester linkage is formed following the same mechanism.

Further Discussion

Considerable decomposition was noted in the esterification in which

¹²HO-TMCB-OH refers to the diol.

zinc chloride was added as a catalyst, indicating an acid medium.

G. N. Lewis first described zinc chloride and other compounds able to accept electrons and form complex ions as strong acids.¹³ The mechanism of the dehydration of the trans-diol in this reaction is beyond the scope of this paper and is not presented here.¹⁴

Probably the most unusual reaction was the esterification in which sodium was added. Gould has stated that esterification in basic media is not observed.¹⁵ The carboxylate ion, RCOO^- , is formed in a basic medium and is not subject to nucleophilic attack by alcohols. However, the above reaction gave a yield comparable to the yield of the direct esterification. An explanation of this problem would be that insufficient sodium had been added to react with all the monochloroacetic acid, and the excess acid reacted with the diol. Molar quantities of monochloroacetic acid (0.12 mole) and sodium (0.004 mole) indicated only a very small quantity of the acid would have reacted with the sodium.

Although the cis-chloro-diester is not discussed in the experimental section, this isomer is considered to be a liquid or a solid with a low melting point. The ethanol wash from the esterification in which

¹³G. N. Lewis, J. Franklin Inst., **226**, 293 (1938), cited by L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, 1940, p. 142.

¹⁴A mechanism is proposed for the dehydration of the diol in an acid medium by R. Hasek, R. Clark, and J. Chaudet, J. Org. Chem., **26**, 3130 (1961).

¹⁵E. S. Gould, op. cit., p. 315.

sodium was used as a catalyst¹⁶ is believed to contain a large proportion of the cis-chloro-diester. The liquid which boiled at approximately 150° probably is contaminated with ethanol. Even though this liquid was chilled at -18° for several weeks, no crystalline substance formed.

¹⁶Supra, p. 33.

CHAPTER VI

CONCLUSION

Summary of the Study

The diol, 2,2,4,4-tetramethyl-1,3-cyclobutanediol, was separated according to a method given in the literature.¹ A somewhat simpler method was then investigated which yielded the cis diol. Several methods of esterifying the cis and trans mixture of the diol were explored using monochloroacetic acid. Both catalyzed and uncatalyzed environments were used, with, in general, the uncatalyzed reaction having the better yield. The product isolated was the trans bischloroacetate diester of the diol which was identified by standard analytical techniques including infrared and nuclear magnetic resonance spectroscopy. The yield of about 20 per cent would indicate that considerable steric hindrance was involved in the formation of the diester. Another possibility was that some of the trans diester was mixed with the cis diester forming a liquid, from which it was difficult to isolate the trans diester product. The mechanism of this esterification is described as a bimolecular, acid-catalyzed, acyl cleavage, direct esterification of a cyclic diol.

Future Problems

During the course of this investigation many interesting problems

¹Eastman Chemical Products, Inc., "Tetramethyl-1,3-cyclobutanediol; 2,2,4,4-tetramethyl-1,3-cyclobutanediol; Properties, Reactions," May, 1960, pp. 20-21.

arose. A few of these will be listed for future consideration. Though the trans isomer of the diester was isolated, the cis isomer was not obtained pure. A better method might be devised for separation of these isomers of the diester. Esterifications of the diol using dichloroacetic acid and trichloroacetic acid should prove to be a relatively simple, but interesting, investigation. The yields of these esterifications and the properties of the diesters could be compared to those of the present investigation. X-Ray diffraction studies of the diol and its derivatives^{2,3} have shown that the cyclobutane ring is non-planar. An interesting study would be that of determining the amount of out of plane bending in the ring of the cis diester compared to that found in the trans diester. Dipole moment determination for the two isomers should, likewise, yield information concerning ring bending. Although a method has been found to separate the diol isomers,⁴ the yields are poor, and the process is time consuming. More solubility data for the individual diol isomers might lead to a better method of separating the isomers.

²J. D. Dunitz and V. Shomaker, J. Chem. Phys., 20, 1703 (1952).

³G. W. Rathjens et al., J. Amer. Chem. Soc., 75, 5637 (1953).

⁴Eastman Chemical Products, Inc., op. cit., pp. 20-21.

BIBLIOGRAPHY

BIBLIOGRAPHY

A. BOOKS

- Ayres, G. H., "Quantitative Chemical Analysis," Second Edition, Harper & Row, New York, 1968.
- Bellamy, L. J., "The Infrared Spectra of Complex Molecules," Methuen & Co., Ltd., London, 1962.
- Condon, R. E. and H. Meislich, "Introduction to Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, 1961.
- Dyer, J. R., "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood, N. J., 1965.
- Eastman Chemical Products, Inc., "Tetramethyl-1,3-cyclobutanedione; 2,2,4,4-tetramethyl-1,3-cyclobutanediol; Properties, Reactions," May, 1960.
- Fieser, L. and M. Fieser, "Advanced Organic Chemistry," Rheinhold, New York, 1961.
- Gould, E. S., "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, New York, 1959.
- Hammett, L. P., "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, 1940.
- "Handbook of Chemistry and Physics," Forty-fourth Edition, Chemical Rubber Publishing Co., Cleveland, Ohio, 1963.
- Ingold, C. K., "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York, 1953.
- Liberles, A., "Introduction to Theoretical Organic Chemistry," Macmillan Co., New York, 1968.
- March, J., "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill Book Company, New York, 1968.
- McElvain, S. M., "The Characterization of Organic Compounds," Macmillan Co., New York, 1953.
- Migrdichian, V., "Organic Synthesis," Vol. 1, Rheinhold Publishing Co., New York, 1957.

Morrison, R. T. and R. N. Boyd, "Organic Chemistry," Allyn and Bacon, Inc., Boston, 1966.

Parr Manual Number 121, "Peroxide Bomb Apparatus and Methods," Parr Instrument Company, Moline, Illinois, 1950.

Rich, A. and N. Davidson, eds., "Structural Chemistry and Molecular Biology," W. H. Freeman and Co., San Francisco, 1968.

Shriner, R., R. Fuson and D. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, 4th edition, 1957.

Silverstein, R. and G. C. Basseler, "Spectrophotometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, 1967.

Weissberger, A., "Physical Methods of Organic Chemistry," Interscience Publishers, Inc., New York, 1949.

B. PERIODICALS

Bender, M. L., J. Amer. Chem. Soc., 79, 11-16 (1957).

Bunton, C. A., et al., Nature, 166, 679 (1950).

Caldwell, J. and H. Moyer, Ind. Eng. Chem., Anal. Ed., 7, 38-39 (1935).

Dunitz, J. D. and V. Shomaker, J. Chem. Phys., 20, 1703 (1952).

Hasek, R. H., et al., J. Org. Chem., 26, 700 (1961).

Hasek, R. H., R. D. Clark, and J. H. Chaudet, J. Org. Chem., 26, 3130 (1961).

Martin, J. and K. Brannock, "U. S. Patent 3,043,791" (C1260-31.6), July 10, 1962.

Rathjens, G. W., et al., J. Amer. Chem. Soc., 75, 5637 (1953).

Reid, E. E., Am. Chem. J., 43, 489 (1910).

Roberts, F. E. and H. C. Urey, J. Amer. Chem. Soc., 60, 2391 (1938).

Treffers, H. P. and L. P. Hammett, J. Amer. Chem. Soc., 59, 1708 (1937).

Zimmerman, H. and J. Rudolph, Angew. Chem. Intern. Ed. Engl., 4, 40-49 (1965).