

AN ABSTRACT OF THE THESIS OF

RICHARD CHARLES BANKS for the DOCTOR OF PHILOSOPHY
(Name) (Degree)
in CHEMISTRY (Organic) presented on Aug. 12, 1968
(Major) (Date)

Title: I. ISOLATION OF CERTAIN TOXIC COMPONENTS OF
KRAFT MILL WASTE AND ATTEMPTS TO DETERMINE
THEIR STRUCTURE
II. STUDIES OF THE MECHANISM OF THE COPE
REARRANGEMENT OF 1, 2-DIVINYL-1, 2-CYCLO-
HEXANEDIOL

Abstract approved: [REDACTED]
Elliot N. Marvell

PART I. A chemical examination of the materials toxic to fish in kraft pulp mill wastes has been made as part of a water pollution study. Thirty gallons of "foul condensate" from a typical kraft mill gave 14 g of organic material when extracted with methylene chloride, and an additional 10 g was obtained when the residue was extracted with diethyl ether. Each extract was separated into approximately 20 fractions by column chromatography over silica gel. The fractions were tested for toxicity to guppies, and the most toxic fractions were then studied in some detail.

Four compounds were identified with certainty: guaiacol (13.2% of the total organic material), cis-terpin hydrate (1.4%), α -terpineol

(1.1%), and 4-(p-tolyl)-1-pentanol (8.0%). Two other compounds were tentatively identified as ethyl guaiacol (2.9%) and trans-sylveterpin (0.2%). The remainder of the organic material contained two major components and an extensive series of minor constituents. Both major components were relatively low in toxicity but were nevertheless examined in some detail.

A ketone, $\nu = 1720 \text{ cm}^{-1}$, constituted about 26.6% of the isolated material. It was converted to two derivatives, both oils. The suspicion that this ketone was not pure was confirmed by mass spectrometry since early scans on a sample passed to the ionizing chamber by a molecular leak differed significantly from later scans. All attempts to separate this mixture failed.

The most interesting substance was a keto-alcohol that was present to the extent of 8.7%. While not highly toxic itself, this keto-alcohol could be reduced to a diol which appears to be the most toxic compound to fish we have studied. The diol seems to be present in the waste in only minor amounts, but could account for a considerable fraction of the total toxicity. The keto-alcohol does not produce a single solid derivative. It appears to be uniform, according to all tests we could apply. It is optically active and has three CHCH_3 groups present; the composition $\text{C}_{15}\text{H}_{28}\text{O}_2$ appears most probable. Apparently it is derived from a monocyclic sesquiterpene, but to date we have not been able to degrade it to a known substance.

PART II. Thermal reaction of 1,2-divinylcyclohexane-1,2-diol was found to produce 1(7)-bicyclo[5.3.0] decen-2-one in good yield. This is the aldol product derived from 1,6-cyclodecanedione, the product expected from direct ketonization of the initial Cope rearrangement process. Since such 1,3-hydrogen shifts are forbidden in the Woodward-Hoffmann theory it seemed of some importance to learn more about the mechanism of this reaction.

Thus 1,2-dideuteroxy-1,2-divinylcyclohexane was vaporized into a nitrogen stream at low pressure and passed through a reactor at 350° C. The 1(7)-bicyclo[5.3.0] decen-2-one was trapped and purified and its deuterium content was determined by mass spectrometry. The unsaturated ketone was reduced by lithium in liquid ammonia and the saturated ketone was treated with methoxide ion in methanol. Analysis for deuterium content was again made by mass spectrometry.

The unsaturated ketone contained $29 \pm 6\%$ D_0 , $39 \pm 2\%$ D_1 , $23 \pm 3\%$ D_2 , and $7 \pm 1\%$ D_3 species. Each of these had the following percent of alpha deuterium: D_1 $3 \pm 3\%$, D_2 $14 \pm 1\%$, and D_3 $75 \pm 12\%$. We assume that the aldol condensation involves a mono-enol mono-keto form as the reactant. To account for the data obtained in this study it is necessary to postulate that a series of rapid enol-keto inter-conversions follow the initial Cope rearrangement. The series is

terminated either by the intramolecular aldol condensation or the dehydration to the unsaturated ketone.

- I. Isolation of Certain Toxic Components
of Kraft Mill Waste and Attempts to
Determine Their Structure
- II. Studies of the Mechanism of the
Cope Rearrangement of
1, 2-Divinyl-1, 2-Cyclohexanediol

by

Richard Charles Banks

A THESIS

submitted to

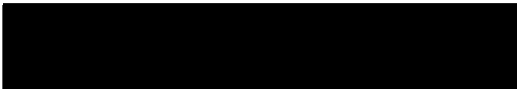
Oregon State University

in partial fulfillment of
the requirements for the
degree of

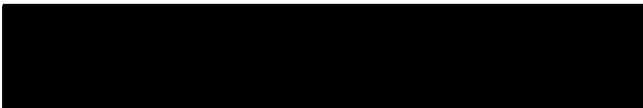
Doctor of Philosophy

June 1969

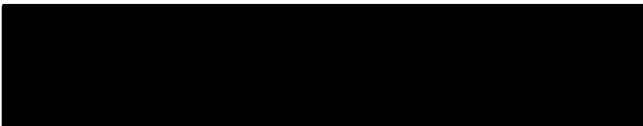
APPROVED:



Professor of Chemistry
in charge of major



Chairman of Department of Chemistry



Dean of Graduate School

Date thesis is presented Aug. 12, 1968

Typed by Gwendolyn Hansen for Richard Charles Banks

ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Dr. E. N. Marvell for his helpful guidance and discussion during the course of this work.

The enthusiasm and encouragement of the author's wife have contributed greatly to the completion of this study.

TABLE OF CONTENTS

PART I. ISOLATION OF CERTAIN TOXIC COMPONENTS OF KRAFT MILL WASTE AND ATTEMPTS TO DETERMINE THEIR STRUCTURE

	Page
INTRODUCTION	1
HISTORICAL	3
DISCUSSION	7
The Source of the Organic Material	9
Separation and Toxicity of Fractions	10
Correlation of Chromatography Fractions	11
Non-Toxic and Previously-Identified Compounds	13
Unknown 1720 Ketone	18
Unknown Keto-Alcohol B	22
EXPERIMENTAL	29
Isolation of Organic Constituents in the Mill Waste	29
Chromatographic Separations	31
a. Ether Extractives	32
b. Methylene Chloride Extractives	34
Fraction Analysis and Correlation	34
a. Thin Layer Chromatography	35
b. Gas Chromatography	36
Identification of Minor Components	36
a. Nujol	36
b. Guaiacol (<u>o</u> -Methoxyphenol)	45
c. Ethyl Guaiacol (4-Ethyl-2-methoxyphenol)	45
d. <u>α</u> -Terpineol (Δ^1 - <u>p</u> -Menthen-8-ol)	45
e. 4-(<u>p</u> -Tolyl)-1-pentanol	46
f. <u>cis</u> -Terpin Hydrate (<u>p</u> -Menthane-1,8-diol)	46
g. <u>trans</u> -Sylveterpin (<u>m</u> -Menthane-1,8-diol)	47
Unknown 1720 Ketone	48
a. 2,4-Dinitrophenylhydrazone	49
b. Oxime	50
c. Oxidation	50
Unknown Keto-Alcohol B	51
a. 2,4-Dinitrophenylhydrazone	51

	Page
b. Oxime	51
c. Acetate	52
d. Attempted Oxidation	52
e. Reduction	54
f. Toxicity of Components of MC-CC-6	54
g. 3, 5-Dinitrobenzoate of Diol	55
h. <u>p</u> -Phenylazobenzoate of Diol	55
i. Dehydrogenation of Diol	56
Spectral Data	56
Carbon-Hydrogen Analysis	57
 BIBLIOGRAPHY	 58
 PART II. STUDIES OF THE MECHANISM OF THE COPE REARRANGEMENT OF 1,2-DIVINYL- 1,2-CYCLOHEXANEDIOL	
 INTRODUCTION	 60
 HISTORICAL	 62
 DISCUSSION	 75
Introduction	75
Synthesis of 1,2-Divinyl-1,2-dideuteroxycyclohexane	76
Thermal Reactions	77
Product Identification	79
Bicyclo[5.3.0] decan-2-one	81
Results of Labeling Experiments	82
Interpretation of the Data	83
Some Mechanistic Proposals	84
 EXPERIMENTAL	 91
1,2-Cyclohexanedione	91
1,2-Divinyl-1,2-cyclohexanediol	91
1,2-Divinyl-1,2-dideuteroxycyclohexane	92
Bomb Reactions	93
Flow Reactions	93
Falling Film Flow Reactions	96
Bicyclo[5.3.0] decan-2-one	98
Mass Spectral Data	100

	Page
1,6-Cyclodecanedione	101
Spectral Data	104
Carbon-Hydrogen Analyses	104
BIBLIOGRAPHY	105

LIST OF TABLES

PART I

Table	Page
1. Positive Correlations.	14
2. Results of the Ether Extract Chromatography.	33
3. Results of the Methylene Chloride Extract Chromatography.	34
4. Gas Chromatography Conditions.	35
5. Gas Chromatography of EE-CC.	37
6. Gas Chromatography of MC-CC.	42
7. Mass Spectrum of EE-CC-6.	48
8. Mass Spectrum of Keto-Alcohol B and Its Acetate.	53
9. Toxicities of Components of MC-CC-6.	55

PART II

1. Comparison of 1(7)-Bicyclo[5.3.0] decen-2-one (A) and Bicyclo[5.3.0] decan-2-one (B).	82
2. Results of Flow Reactions.	95
3. Falling Film Flow Reactions.	98
4. Isomer Percentages.	101

LIST OF FIGURES

PART I

Figure	Page
1. Structures of complex compounds.	6
2. Liquid-liquid extractor.	30

PART II

1. Flow reaction apparatus.	94
2. Falling film molecular still.	97

PART I

ISOLATION OF CERTAIN TOXIC COMPONENTS OF KRAFT MILL WASTE AND ATTEMPTS TO DETERMINE THEIR STRUCTURE

INTRODUCTION

The problem of water pollution and the hazard which that pollution causes for wildlife is but one aspect of the general concern about man's contamination of his environment. The utilization of streams and rivers as the disposal media for industrial and even private waste products cannot help but produce ever-increasing problems for the future. The seriousness of the problem can be demonstrated by considering just one industrial source of contamination. It has been shown (17) that one kraft pulp mill alone can deposit 46,000 tons per day of chemical-contaminated water into a river or stream.

It is this special contaminant, i. e., kraft mill waste, which has been singled out for study by several groups at Oregon State University. These studies have been concerned with both the toxicity of this effluent and the identification of those compounds responsible for that toxicity. The research described in Part I of this thesis is a continuation of previous studies (11, 14, 15, 23, 24).

A few words should be included about the general kraft pulping process (10, p. 160-162). The logs are first debarked and then chipped. The chips are placed in a digester, and the cooking liquor

is added. The mixture is then cooked for a given time, during which the turpentine and volatiles distill. These are condensed and sold as crude kraft turpentine.

After the cooking period, the pulp and liquor are forced into the blow tank by pressurized steam. The pulp and black liquor are then mixed with dilute black liquor and pumped through deknotters to brown-stock washers. Here the black liquor is washed out. Following this washing, the pulp is screened and bleached.

The black liquor from the brown-stock washers, which contains about 16% solids, is partially used for dilution, and the remainder is concentrated by a series of evaporations as the first part of a recovery process. It is from these evaporations that "tall oil" is obtained. The material with which this research is concerned is the "foul condensate" or the condensed water from these evaporations. This material comes from the low vacuum stage of the black liquor evaporators and is normally used as hot water and wash water in the mill. The excess is disposed of as a large portion of the mill effluent.

HISTORICAL

The discovery of the kraft process was due to an error on the part of a digester man in Sweden. A load of chips in a digester was forced into the blow tank before the chips were fully cooked. Rather than discard the partially-cooked wood, plant officials permitted it to be processed to make a supposedly-inferior paper. The result, however, was a paper that was far stronger than any other known at that time. This paper was given the name "kraft," which is Swedish and German for "strong." From this accidental discovery came the kraft process, which continues to this day (10, p. 13).

The source of the "foul condensate" used in this study was a typical kraft mill in the Northwest. This mill pulps only Douglas fir (Pseudotsuga menziesii). Therefore only the chemical composition of Douglas fir chips is of real interest for this work. In 1962 Wiman (24) concluded that there were no references in the literature concerned with the kraft mill waste obtained from the pulping of only Douglas fir. From that date to the present no reference has been found pertaining to the same limited topic. There were some references, however, that dealt with the kraft black liquor.

Douglas fir has been shown (10) to contain 28.4% lignin, 14.1% hemicellulose, and 57.2% α-cellulose. Although the structure of lignin has not been entirely elucidated, many compounds arising from

it have been identified.

Hrutfjord (8) has reported guaiacol (o-methoxyphenol), vanillin (3-hydroxy-4-hydroxybenzaldehyde), pyrocatechol (o-hydroxyphenol), p-hydroxybenzaldehyde, and syringaldehyde (4-hydroxy-3,5-dimethoxybenzaldehyde) in the phenolic fraction of kraft black liquor. The type of wood pulped was not mentioned.

Fletcher and Harris (6), using a destructive distillation of Douglas fir lignin, found acetone, methanol, formic acid, acetic acid, phenol, o-cresol (o-hydroxytoluene), p-cresol, guaiacol, 2,4-xyleneol (2,4-dimethylphenol), methyl guaiacol (4-methyl-2-methoxyphenol), ethyl guaiacol, C_{18} - C_{22} acids, and a number of unidentified neutral compounds. McInnes (12) has isolated α-ethoxypropiovanillone (III), vanillin, and vanilloylmethylketone (IV) from the ethanolysis of Douglas fir lignin.

The volatile oil of the wood has been shown (9) to be a mixture of α-pinene (I), camphene (V), limonene (VI), α-terpineol (VII), and some unidentified compounds. Schorger (19) isolated α-pinene (I), limonene (VI), and α-terpineol (VII) from the oleoresin that collected in pockets in the heartwood. He also found α-pinene (I) and β-pinene (II) in the oleoresin that is obtained by scarification of the living sapwood. Taxifolin (VIII) was an unusual compound that was isolated from the heartwood by Pew (18).

Ashorn and Enkvist (2) have isolated and identified guaiacol,

pyrocatechol, p-methylcatechol, p-ethylcatechol, vanilloylmethylketone (IV), vanillin, protocatechualdehyde (3,4-dihydroxybenzaldehyde), p-acetopyrocatechol, and vanillic acid in the pressure-heated spent liquors. The type of wood was not indicated, but was probably not Douglas fir.

The kraft turpentine varies in composition, but normally it contains 50-60% α -pinene (I), 15-20% β -pinene (II), 10-15% monocyclic terpenes, and 10-15% sulfur-containing compounds and impurities (10). The type of wood used in the production of this turpentine was not indicated, but it is unlikely that it was Douglas fir.

Many of the compounds discussed in this thesis are given numbers (Roman numerals). These refer to the structural formulas for these compounds which have, for convenience, been gathered together in Figure 1.

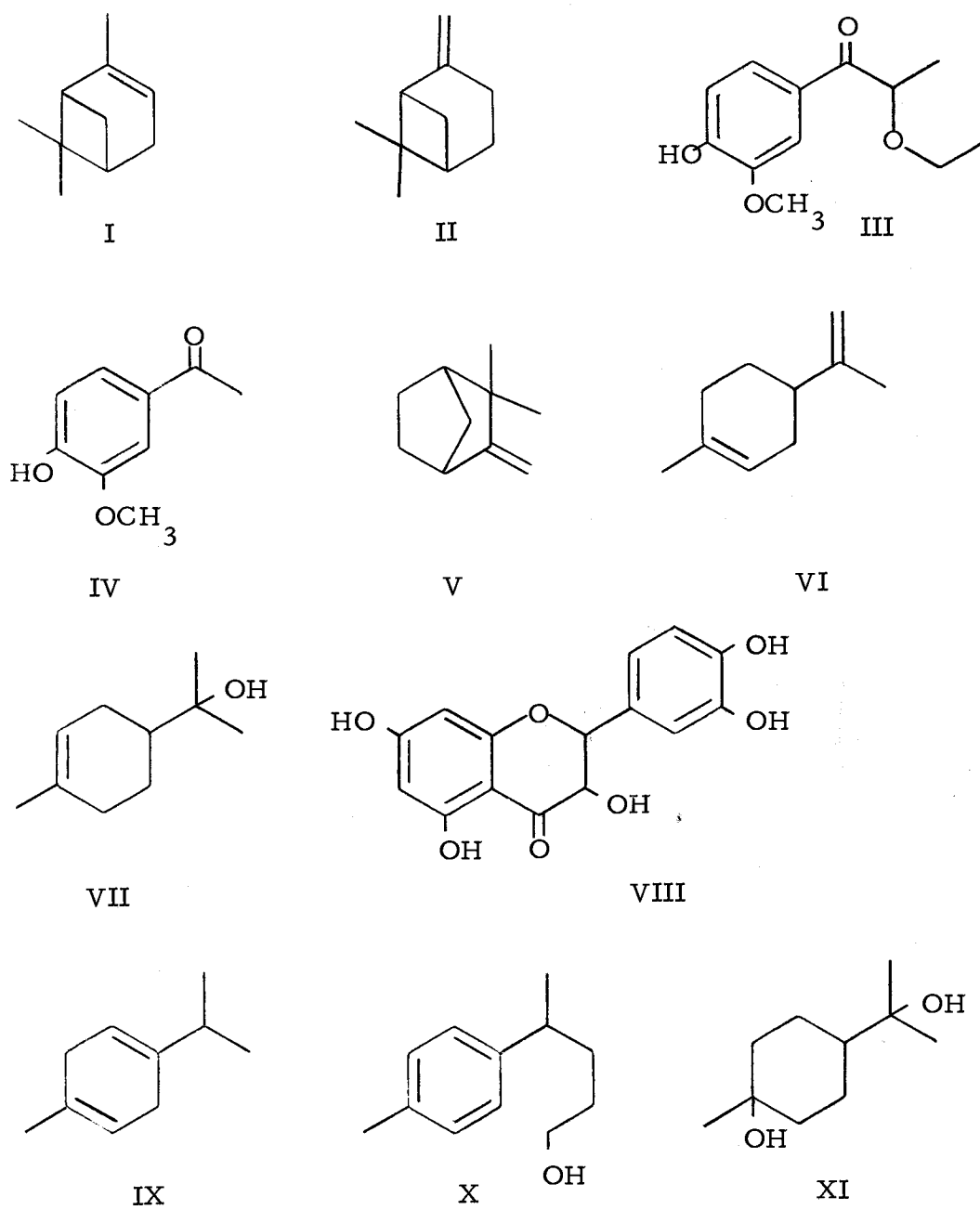


Figure 1. Structures of complex compounds.

DISCUSSION

The goal of the present work was the isolation and identification of those constituents of kraft mill waste that are toxic to fish. The toxic constituents, when identified, were to be synthesized, if necessary, so that further toxicity tests could be run on mammals.

Wiman (24) extracted 130 gallons of "foul condensate" from the Western Kraft Mill with diethyl ether and obtained 63.4 g of organic material. When this mixture was distilled, two fractions and a residual liquid were obtained. The distillable fractions were separated further by various chromatographic techniques. Gas chromatography showed that limonene (VI), γ -terpinene (IX), *p*-cymene (*p*-isopropyltoluene), and anisole (methylphenylether) were present in trace amounts. Guaiacol was shown to be present as 6.8% of the total organic material. The largest component that was isolated (11.7%) was shown by oxidative degradation, elemental analysis, spectral studies, and by synthesis of a known sample to be 4-(*p*-tolyl)-1-pentanol (X).

Shortly after Wiman left Oregon State University, the work was continued by a post-doctoral associate, Dr. Wolfgang Gänzler (14). Gänzler extracted 30 gallons of "foul condensate" with petroleum ether, a process which removed only 60% of the organic material. The aqueous residue was saturated with sodium sulfate and then

extracted with diethyl ether. This diethyl ether extract was used in the work described in the present study. When the solvent was removed, some crystals precipitated. These crystals were identified as cis-terpin hydrate (XI), a compound normally derived from α -pinene; cis-terpin hydrate is not considered to occur naturally.

Column chromatography over silica gel was used to separate the 11 g from the petroleum ether extract into 12 major fractions. These fractions are referred to as PE-CC-1-12 in the remainder of this thesis. Three of these fractions showed toxicity to fish and were consequently studied. Fraction PE-CC-10 was found to contain guaiacol; however the concentration in the waste was below the level of measurable toxicity to fish by our analysis method. This meant that another component in this fraction must have been responsible for the toxicity. Fraction PE-CC-11 contained 4-(p-tolyl)-1-pentanol, which had been previously identified by Wiman. Fraction PE-CC-12 had as a major constituent an unknown compound referred to as keto-alcohol B. The spectral data obtained will be presented later in this report. Gänzler tried to prepare a phenylhydrazone, 2,4-dinitrophenylhydrazone, semicarbazone, benzoate, p-nitrobenzoate, phenylthiourethane, and α -naphthylurethane, but in no case was a solid obtained.

The Source of the Organic Material

It has already been noted (24) that the use of the effluent from only one mill poses numerous problems. The toxicity of the waste from different mills varies significantly. The composition of kraft turpentine is known to vary with respect to changes in the cook, and such changes should also alter the composition of the effluent. Although the majority of the steam-distillable and volatile compounds has been removed from this effluent, it might be expected to contain small amounts of kraft turpentine and perhaps products from the "tall oil."

The source of the samples used in this work was the Western Kraft Mill in Albany, Oregon. This mill uses only Douglas fir, and produces unbleached pulp by using a 2.5 hour cook at 170° C in a liquor containing 7.5 pounds of sodium oxide per cubic foot and 25% sulfidity as sodium sulfide. The reason for choosing this particular mill, aside from the convenience of its location, was to obtain some uniformity of sample by using the waste from the pulping of a single species of tree. The sample was collected over an extended period of time to average out fluctuations in the pulping process.

The use of a liquid-liquid extractor with methylene chloride as a solvent gave a yield of 14 g of organic material. When the aqueous residue was checked by extraction with diethyl ether, a significant

amount of organic material was recovered. Therefore the residue was extracted with diethyl ether after the solution had been saturated with sodium sulfate.

It was found by later correlation studies that this dual extraction technique had provided no useful separation. The only exception was found with fraction EE-CC-6. This material was not extracted by petroleum ether or methylene chloride, but was readily removed with diethyl ether.

Separation and Toxicity of Fractions

The diethyl ether extracts from the present work and the work of Gänzler (14) were combined. This combined extract was separated into 22 major fractions by the use of silica gel column chromatography. The solvent was varied gradually, starting with pentane and ending with methanol. Fractions EE-CC-8, EE-CC-10, EE-CC-12, EE-CC-15, and EE-CC-16 were the only fractions that showed significant toxicity to fish. Fraction EE-CC-12 was the most toxic fraction.

A similar separation of the methylene chloride extract yielded 20 major fractions. Fractions MC-CC-3, MC-CC-5, MC-CC-6, and MC-CC-16 showed significant toxicity. Fraction MC-CC-6 was the most toxic of these.

The toxicity of the various fractions to young guppies (Poecilia

reticulata) was determined at the Oak Creek Fisheries Annex, Oregon State University. The median tolerance limits (those concentrations of tested wastes in percent by volume that are lethal to 50% of the test animals within specified exposure periods) were not determined due to the small samples available. The numbers given in the Experimental section as relative toxicity values are the number of fish of the five tested that died when exposed to a given sample for 24 hours. Each sample was made up with well water from the Annex; the amount of each fraction used for these tests was sufficient to bring the concentration of that material to its original concentration in the "foul effluent." Thus the relative toxicity value given corresponds roughly to the importance of the contribution that fraction should make to the toxicity of the original waste. During the bioassays the temperature was kept at 20° C, and the beakers containing the fish were aerated with 500 bubbles of air per minute.

Correlation of Chromatography Fractions

During the course of this and the previous work, three large column chromatographic runs were made. Numerous major fractions were collected during each run, and all of these fractions contained more than a single component.

It was, of course, very important to find some means of recognizing the common components in the various fractions. The

most successful means achieved was through the use of gas chromatography. Thin layer chromatography and infrared spectra of the crude fractions were also used in some cases. Thus it was possible to ascertain when the same compounds contributed significantly to the toxicity of the various fractions.

Thin layer chromatography (TLC) was generally found to be less helpful than might have been expected. The compounds in the fractions often tended to tail badly, and separation, in general, was not satisfactory. These faults were found to persist even with the use of polysolvent systems and techniques such as multiple elution.

The only positive correlations found via TLC were made before the methylene chloride extract was chromatographed. Therefore the MC-CC fractions were not subjected to TLC study. The TLC work showed that fractions PE-CC-10 and EE-CC-11 contained two common compounds, one of which was 4-(p-tolyl)-1-pentanol. Keto-alcohol B was present in both fractions PE-CC-12 and EE-CC-12.

Gas chromatography as a correlation technique is limited, of course, owing a) to failure of some compounds to separate, b) to possible decomposition of compounds on the column, or c) to failure of compounds that are too polar and/or too high boiling to come off the column. One simple check which shows whether the major components of a fraction have come off the column is to add an internal standard, and a second is to compare the infrared spectra of the

collected peaks with the infrared spectrum of the crude fraction.

Both procedures indicated that in our studies the compounds were eluting properly and, indeed, decomposition appeared to be minimal.

Two columns, both using the same stationary phase, were found to work very well. The results are shown in Tables 5 and 6. As others have also noted, we found that retention times tended to vary between runs. Therefore those results based solely on retention time are not as reliable as one would desire. In particular, those materials present in any fraction in such small amount that trapping and spectral examination could not be carried out fall in this class.

In several cases known samples were used for direct comparisons. When this technique was used to identify a compound, it was always found that all peaks in the infrared spectrum of the known compound could be matched with some of those in the spectrum of the crude fraction. Table 1 summarizes the most dependable results of these studies.

Non-Toxic and Previously-Identified Compounds

Eight compounds (excluding nujol) were examined; six of these were identified, i. e. , guaiacol, ethyl guaiacol, α -terpineol, 4-(p-tolyl)-1-pentanol, cis-terpin hydrate, and trans-sylveterpin. Of these, only 4-(p-tolyl)-1-pentanol had significant toxicity, and it had

been identified before (15, 24). Guaiacol and cis-terpin hydrate had also been previously identified (14, 24). The remaining three were identified during the course of this work.

Table 1. Positive Correlations.

Compound	Fractions where found
guaiacol	EE-CC-3, MC-CC-2, MC-CC-3, PE-CC-10
ethyl guaiacol	EE-CC-3, EE-CC-4, MC-CC-2
α -terpineol	MC-CC-4, MC-CC-5, MC-CC-6, MC-CC-7
1720 ketone	EE-CC-6, EE-CC-7
4-(<u>p</u> -tolyl)-1-pentanol	EE-CC-11, MC-CC-4, MC-CC-5, MC-CC-6, MC-CC-7, PE-CC-11
keto-alcohol B	EE-CC-12, MC-CC-6, MC-CC-7, MC-CC-8, PE-CC-12
<u>cis</u> -terpin hydrate	MC-CC-15, MC-CC-16

Nujol. The presence of nujol in the sample must be eyed with suspicion, if for no other reason than the fact that it appeared in the diethyl ether extract. Thus it either resisted extraction with methylene chloride or it was added to the waste after this extraction. The first possibility is highly unlikely. Since a stirrer lubricated with nujol was used during saturation of the effluent, the second possibility is the obvious answer.

Guaiacol (o-Methoxyphenol). This compound has been found in every study of kraft mill waste. It is not notably toxic to fish at the

concentration found in the waste. Its presence in EE-CC-3, MC-CC-2, and MC-CC-3 has been confirmed by both comparison gas chromatography and spectral data.

A sample of the major peak (80%) of MC-CC-2 was collected via gas chromatography. Infrared and nmr spectra from this sample were identical in all respects with the spectra of the authentic compound.

Fraction EE-CC-3 contained 5.6 mg of guaiacol. It may be assumed that half of this was from the 30 gallons of waste extracted by the methylene chloride. Fractions MC-CC-2 and MC-CC-3 contained 3.182 g. This gives the total weight of 3.184 g of guaiacol derived from this batch of waste. This is 13.2% of the total 24 g extracted by both methylene chloride and diethyl ether.

Ethyl Guaiacol (4-Ethyl-2-methoxyphenol). A peak representing about 15% of MC-CC-2 was collected from the gas chromatograph. Only enough material for spectral examination was obtained. The infrared spectrum showed a broad OH band at 3480 cm^{-1} , typical aromatic and aliphatic bands, a symmetric stretching band for C-O-C at 1035 cm^{-1} , and bands between 900 and 700 cm^{-1} indicative of a 1,2,4-trisubstituted benzene ring (16). The nmr spectrum showed a singlet due to one aromatic proton at 6.67 ppm and a multiplet at 6.58 ppm for the two other aromatic protons. A hydroxy proton appeared at 5.2 ppm, and a strong singlet representing the three

methoxy protons was found at 3.83 ppm. The ethyl group was responsible for a quartet at 2.54 ppm and a triplet at 1.2 ppm. The coupling constant for both the quartet and the triplet was 7.3 Hz (5).

This compound is present as 2.9% (632 mg) of the total waste. It is not demonstrably toxic at this concentration.

α -Terpineol (Δ^1 -p-Methen-8-ol). This compound is present in only trace amounts (256 mg) and constitutes 1.1% of the total material. No pure sample was ever collected from gas chromatography. It was therefore identified by comparison gas chromatography. Since this compound did not show a toxic reaction to our tests and was present in such small amounts, the structural assignment was not confirmed by the use of a second column. A sample of α -terpineol gave an unusual gas chromatographic peak. This same unusual peak was seen in certain fractions of the waste, and when a comparison sample was mixed with these fractions the size of the peak increased but the sharpness and the shoulder remained.

4-(p-Tolyl)-1-pentanol. This compound was originally found in the mill waste and identified by Wiman (15, 24). However, this is not the main toxic component of the waste. Its presence has been found in certain moderately toxic fractions from every sample of waste we have examined. Its identification was made by comparison gas chromatography and comparison of the infrared spectrum of the crude material with that of the authentic compound. It comprised 8.0%

(1.93 g) of the total organic material in this waste sample.

cis-Terpin Hydrate (p-Menthane-1,8-diol). When Gänzler (14) extracted the waste with diethyl ether, he found that some crystals separated when the solvent was evaporated. These were identified as cis-terpin hydrate. The same crystalline material was found in the methylene chloride extract, but this was not isolated directly. Instead it was passed through the chromatography column and appeared as a clean-cut fraction. After recrystallization it was identified as follows. The infrared and nmr spectra were identical with the spectra of the known compound, and the melting point was not depressed when some of the authentic material was added. A mixed sample on the gas chromatograph eluted as a single peak. This compound represents 1.4% (344 mg) of the waste and is not toxic via our tests at this concentration.

trans-Sylveterpin (m-Menthane-1,8-diol). A tentative structural assignment, perhaps more properly labeled an "educated guess," was made in the case of trans-sylveterpin. A small amount of crystalline material was found in a weakly toxic fraction. It was found to sublime readily and was purified in that way. The compound was isolated as colorless needles that melted at 139-141° C. The infrared spectrum was almost identical with the spectrum of cis-terpin hydrate. A literature search suggested only one reasonable possibility: namely, trans-sylveterpin (21). The problem of obtaining confirmatory

evidence for this assignment was complex. Only 43 mg of the unknown alcohol was isolated, no derivatives were listed in the literature, and no authentic sample was available. A relatively simple synthesis starting with Δ^3 -carene was published (4). This synthesis, however, gives trans-sylveterpin as a minor product, and a relatively large sample of Δ^3 -carene was needed to make isolation of this product possible. Unfortunately only a small sample was located, so the following compromise was adopted. The Δ^3 -carene was treated with hydrogen chloride gas, giving a mixture of dipentene hydrochloride and sylvestrene hydrochloride. Insufficient material was available to permit a separation of the sylvestrene hydrochloride to be made. The crude mixture was therefore treated with potassium hydroxide solution, giving trans-sylveterpin as a minor product. Gas chromatography showed that, indeed, a minor component of the synthesis product possessed the same retention time as the unknown solid. A mixed sample gave only one peak at this retention time. The evidence is thus permissive of this assignment but does not constitute a proof of the structure. This material, however, is not appreciably toxic and constitutes only 0.2% of the waste.

Unknown 1720 Ketone

An unknown compound having a carbonyl band at 1720 cm^{-1} was found to make up 26.6% (6.4 g) of the total isolated organic material.

Although it was not measurably toxic, it was present in such quantity that an examination in some detail was warranted. This unknown was not extracted by either petroleum ether or methylene chloride, and was therefore found only in the diethyl ether extract.

The spectral data, especially the mass spectrum and the UV, indicated that even the material collected from a single peak on the gas chromatograph was not pure. The ultraviolet spectrum showed two peaks, λ max 272 ($\epsilon = 320$) and 222 ($\epsilon = 1700$), which suggests that this is a substituted aromatic compound (5). The extinction coefficients indicated were calculated for a molecular weight of 320 but are lower than normal. The reason for these low values could be that the substance was impure or that the measured molecular weight is too low. The mass spectrum shows different m/e peaks when scans are taken at different times during the diffusion of the ketone into the ionization chamber. The ketone was injected directly into the liquid inlet. An early scan, as shown in the Experimental section, has no m/e peaks higher than 192. A later scan shows peaks of low intensity in the 300-500 range. Clearly, the material isolated was not a single substance. Interpretation of the mass spectrum is thus rendered difficult. One can clearly conclude, however, that an alkyl-substituted phenyl group is present, as shown by the m/e series 63, 77, 91, 105, and 133 (13).

The nmr spectrum shows an A_2B_2 pattern, which might arise

from a para disubstituted phenyl, but this interpretation is complicated by the infrared spectrum, which has bands at 785, 760, and 745 cm^{-1} , which fits better for such substitution patterns as 1,2,3 and 1,2,4 (16). The nmr spectrum shows two singlets at 4.19 and 4.11 ppm, which probably are protons next to ether oxygen. This interpretation is supported by the infrared spectrum, which shows bands at 3010, 1275, 1070, and 1040 cm^{-1} that are indicative of ether linkages. However, the nmr spectrum clearly shows that no methoxy groups are present. The carbonyl band is at 1720 cm^{-1} and probably indicates a ketone group since no aldehyde bands are present in either the nmr or the infrared spectra.

The spectral data lend themselves to the following conclusions. The compound is aromatic with evidence of para substitution. There are no methoxy groups, but ether linkages are present. If the peaks at 4.11 and 4.19 ppm are in fact a doublet, as in the grouping $\text{O}-\text{CH}_2-\text{CH}$, then the value of 5Hz for the coupling constant is too low for an open chain with free rotation by about 2Hz. Confirmation of the assumption that the carbonyl at 1720 cm^{-1} is a ketone is given by formation of derivatives.

A 2,4-dinitrophenylhydrazone was obtained using Shine's method (20). This was, however, an oil that failed to crystallize despite numerous attempts to purify it. It gave only a single spot on a thin layer chromatograph. The oil corresponds in carbon-hydrogen

analysis to $C_{36}H_{52}O_4N_4$ for the derivative or $C_{30}H_{48}O$ for the ketone if only carbonyl oxygen is present. If even one ether oxygen is present, then the analysis will fit only a compound containing over 40 carbon atoms. An oxime was prepared, but this also failed to crystallize.

An oxidation was carried out on a small sample of ketone 1720 in an attempt to obtain more information about the aromatic ring substitution. Propionic acid was identified by both thin layer and paper chromatography. No other monocarboxylic acids were found. While other acidic compounds were present they were not identified because of the complexity of the mixture and the lack of crystalline compounds. Oxidation of a larger sample was not carried out since the project was discontinued at this time.

It can be concluded that this ketone must be a relatively complex molecule of uncertain purity. It forms carbonyl derivatives readily, which suggests that the ketone is not hindered. Failure of the oxidation to give a solid aromatic acid is probably in keeping with the assumption that a phenolic ether function is present. These pieces of evidence all suggest that the ketone is a degradation product of the lignin.

Unknown Keto-Alcohol B

This compound was a liquid, first isolated by Gänzler (14), which constituted 8.7% (2.1 g) of the organic material from the present sample of the condensate. It was the most interesting component of the waste from the point of view of the objectives of the present program. Thus a considerable amount of time was devoted to a study of this compound. Much of this time was used in attempts to obtain a sample of demonstrable purity. In the process, numerous routes were explored, ranging from the formation of derivatives to structure alterations.

The spectral data accumulated from this compound have been quite complete. Gänzler (14) discovered that the substance was optically active, $[\alpha]_D^{25} + 12.5^\circ$ (CHCl_3). Its infrared spectrum showed a broad band at 3420 cm^{-1} for a hydroxyl, 1710 cm^{-1} for a saturated ketone, 1412 cm^{-1} ($\text{CH}_2\text{-C}=\text{O}$?), and bands at 1380 and 1370 cm^{-1} for C-CH_3 or possibly $\text{C}(\text{CH}_3)_2$. The ultraviolet spectrum showed a band at $283 \text{ m}\mu$ (saturated carbonyl) and one at $200 \text{ m}\mu$ which might be a trisubstituted double bond. This has been shown by the nmr spectrum and the tetranitromethane test to be an impurity. The nuclear magnetic resonance spectrum showed a doublet at 3.46 ppm, which is probably a proton on a carbon bearing a hydroxyl group, a singlet at 2.49 ppm, which moved to 2.06 ppm when the

sample was diluted (hydroxyl proton), a multiplet at 2.19 ppm which indicates the presence of protons on carbons adjacent to a carbonyl, a broad series of peaks between 1.1 and 1.9 ppm ($-\text{CH}_2-$), and three peaks between 0.81 and 1.0 ppm which are probably methyl groups. The mass spectrum showed a m/e peak at 222 which corresponds to loss of water from an alcohol with a molecular weight of 240. The fragments of m/e 43, 57, 71, and 85 suggest that a saturated isoprene unit was present as a side chain giving a normal alkyl cleavage pattern (13).

Gänzler prepared a number of derivatives, including a phenylhydrazone, 2,4-dinitrophenylhydrazone, semicarbazone, benzoate, *p*-nitrobenzoate, phenylurethane, and α -naphthylurethane, but in no case was a solid obtained. He studied chromatographic methods exhaustively in attempts to purify, and thus to obtain, any one of these derivatives in crystalline form.

A 2,4-dinitrophenylhydrazone⁴ was prepared by a new method (Shine's procedure, 20) during the course of the present work. Thin layer chromatography confirmed the formation of the derivative and suggested that it was a single compound, but it was not crystalline. An oxime was prepared but also failed to crystallize.

Oxidation by the method of Albright and Goldman (1) failed to affect the hydroxyl grouping in any way and only unreacted starting material was recovered. In view of the nmr data it seems likely

that the oxidation failed, which is not unlikely as this is a very mild oxidation procedure.

An acetate was prepared and was then purified by preparative gas chromatography. The collected liquid showed only one peak on the glc. The infrared spectrum showed no hydroxy bands and two carbonyl bands at 1740 cm^{-1} (acetate) and 1710 cm^{-1} (saturated ketone). The nmr spectrum showed a doublet at 3.96 ppm, which is probably the CH portion of a CHOAc grouping. There was a series of sharp peaks between 0.8 and 1.0 ppm which might be assigned to three methyl groups. There was a sharp singlet at 1.97 ppm which represents the methyl group of the acetate. Integration of this spectrum gave various proton counts depending on the grouping used as a reference. A proton count of 24 was found if the doublet at 3.96 ppm was used as a single proton. If the acetate group was used, then a proton count of 28 was obtained. If the peaks between 0.8 and 1.0 ppm were used as three methyl groups, the count was 30. The mass spectrum showed a molecular ion peak at 282 with the expected peak at 222 corresponding to loss of acetic acid. This corresponded to a molecular weight of 240 for the keto-alcohol. This spectrum and that of the alcohol were difficult to interpret, a result which is in keeping with the keto-alcohol nature of the molecule since neither group is particularly effective in promoting distinctive cleavage patterns. A tetranitromethane test was run on

the purified acetate to verify the absence of a tetrasubstituted double bond. If a tetrasubstituted double bond were present it should give bands between 760 and 460 $\text{m}\mu$ in this test. There was no absorption in this region (7).

A diol was prepared by the reduction of the keto-alcohol with sodium borohydride. This liquid was purified by preparative gas chromatography. The infrared spectrum showed a stronger OH band at 3350 cm^{-1} than the keto-alcohol, and the carbonyl band had virtually disappeared. There were two bands at 1040 and 1050 cm^{-1} which presumably were the C-O stretching bands for secondary alcohols, although they are lower than the normal frequency for secondary alcohols. The nmr spectrum indicated the presence of three methyl groups. It also showed a multiplet at 3.5 ppm which was due to protons on hydroxyl containing carbon, and a multiplet at 1.7 ppm for $-\text{CH}_2-$.

A 3,5-dinitrobenzoate of the diol was prepared but no crystalline material was obtained. A p-phenylazobenzoate was prepared because the color of the derivative makes chromatography more convenient. The product of this reaction gave four spots on a thin layer plate. The spots were assumed to be the di-derivative, two different mono-derivatives, and p-phenylazobenzoic acid (which did not elute). Preparative chromatography was used to separate the three derivatives. None of these compounds was a solid. A crystalline material

found in two of these spots was colorless and certainly was not the derivative. These crystals were not identified due to the small quantity present.

A portion of the diol was dehydrogenated over Pd/C, but the results were inconclusive as there was only a very small amount of product isolated. This product appeared to contain an aromatic ring, but the substitution pattern could not be determined.

The fact that none of the derivatives of the keto-alcohol or the diol could be obtained as a solid suggests that the original material was not a single compound. Until a compound or derivative of demonstrable purity can be obtained, it seems fruitless to sacrifice precious material to obtain analytical data of questionable value.

The above data do not define the structure of the keto-alcohol, but several conclusions can be drawn. The most probable molecular formula is $C_{15}H_{28}O_2$, which is based on the molecular weight of 240. The optical activity and this formula indicate that this molecule is derived from a monocyclic sesquiterpene. One problem that arises is that most sesquiterpenes have four methyl groups, and nmr data will not admit of more than three. These are probably $CHCH_3$ or CH_2CH_3 groupings as the nmr bands are not large enough or sharp enough to constitute singlets (compared with the singlet at 1.97 ppm in the acetate). The 2.1-2.4 ppm region can be assigned to protons on carbons adjacent to the carbonyl, but the integration is

not accurate enough to judge whether there are three or four alpha protons. As yet, no sample of keto-alcohol B has been obtained that is pure enough to warrant deuterium exchange to clarify this point. The doublet at 3.46 ppm for the alcohol and 3.96 ppm for the acetate shows that the hydroxyl group is almost certainly a CHOH group. If the ketone is in the ring as suggested by the mass spectra, the ring is not smaller than cyclohexane, and although certainly not conclusive the dehydrogenation suggests it may be a six-membered ring.

As Table 1 shows, keto-alcohol B was present in fractions MC-CC-6, EE-CC-12, and PE-CC-12. Thus it seemed surprising that MC-CC-6 and EE-CC-12 were the most toxic fractions from the methylene chloride and diethyl ether extracts respectively, whereas PE-CC-12 had a relatively low toxicity. The toxicity data were derived from the crude samples and therefore the results indicate that certain components of the former fractions must be exceedingly toxic and that these components must be absent from the latter fraction. The nature of the toxic components was at least partly clarified when the various components of MC-CC-6 (which is apparently identical to EE-CC-12) were collected via glc. The diol prepared from keto-alcohol B was found to be identical with a constituent responsible for a minor peak (5%) in both fractions. The diol and the keto-alcohol were tested for toxicity using the concentration of each material equal to its original concentration in the "foul condensate."

The results were quite interesting in that the keto-alcohol was not measurably toxic while the diol was exceedingly effective as a fish poison. Considering its minute concentration in the waste, the diol is certainly the most toxic material that we have isolated from the "foul condensate."

EXPERIMENTAL

Isolation of Organic Constituents in the Mill Waste

Foul condensate was obtained in 5-gal carboys from the Western Kraft Mill in Albany, Oregon. Collections were made at random intervals over a two-month period in 1964. The continuous extractor shown in Figure 2 was used to extract the condensate with methylene chloride. All samples were processed within 12 hrs after receipt to prevent further alteration of the organic material. After the extraction with methylene chloride had been carried out twice on a 5-gal sample, a test portion of the aqueous residue was saturated with sodium sulfate and extracted manually with diethyl ether. Evaporation of the solvent and weighing of the residue showed that of the total organic material extracted ca. 60% was in the methylene chloride extract and 40% in the ether extract. All of the waste was therefore submitted to the dual extraction procedure described above. From 30 gal of foul condensate, 14.01 g of organic material was recovered from the methylene chloride extracts and 10.1 g from the ether extracts.

Chromatographic Separations

The liquid mixtures recovered from the methylene chloride and the ether extracts were treated separately.

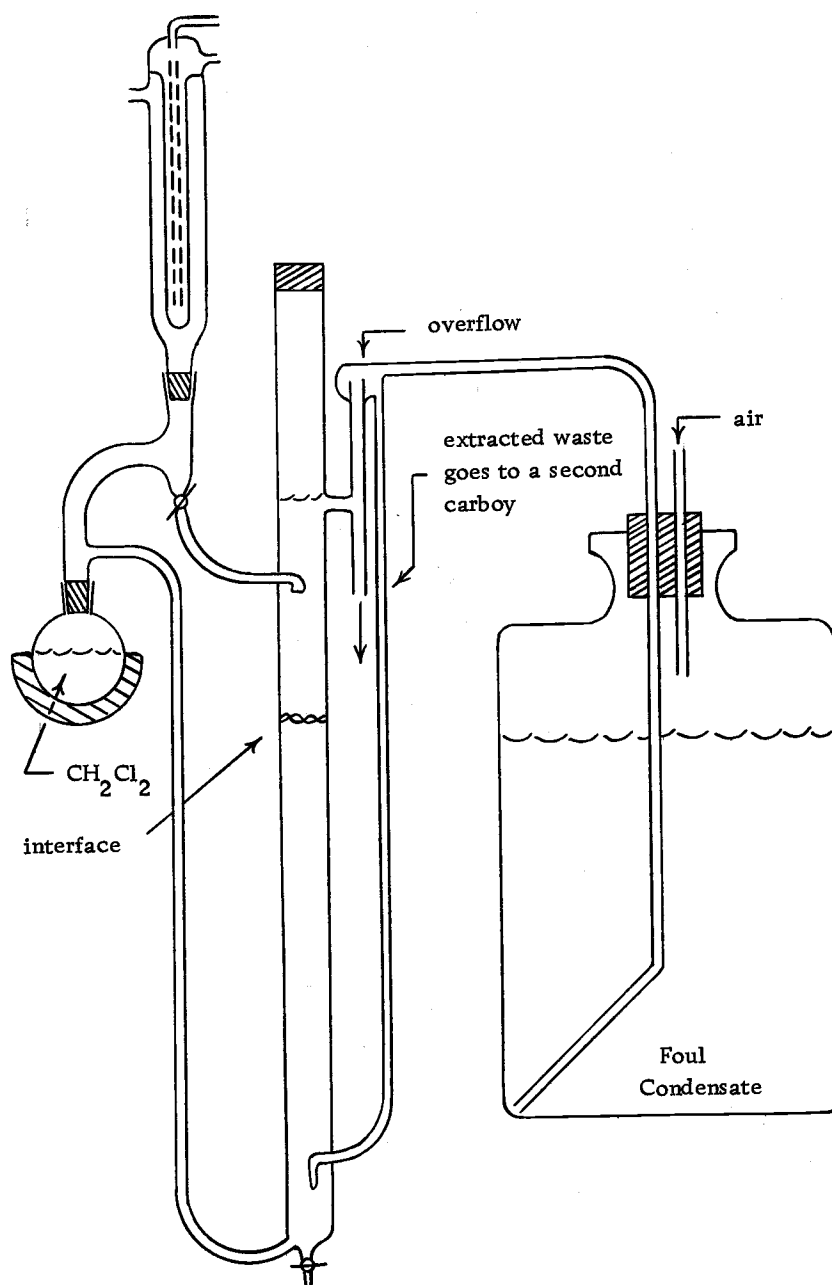


Figure 2. Liquid-liquid extractor.

a. Ether Extractives

The 10.1 g of liquid from the diethyl ether extract above was combined with 11.35 g of material recovered from a similar ether extraction of foul condensate carried out by Gänzler (14). A chromatography column 6 cm in diameter was wet packed under dry pentane with 1 kg of neutral silica gel (BDH reagent, chromatography grade). A 3.9 l. solvent-mixing chamber, stirred by a magnetic stirrer, was attached directly to the column. An upper solvent reservoir of 2.5 l. capacity was attached to the mixing chamber. The solvent reservoir was vented to the air through a drying tube filled with Drierite. The eluate was divided into 40 ml fractions and collected by means of an automatic fraction collector.

A continuous gradient elution procedure was followed, starting with pure pentane in the mixing chamber and filling the upper reservoir with 2 l. of 5% diethyl ether in pentane. When this reservoir was nearly empty 2 l. of 10% diethyl ether in pentane was added. A similar progression was made until the upper chamber contained 60% diethyl ether in pentane. The solvent was then changed to 5% acetone in diethyl ether and progressed by 5% increments to 20% acetone in diethyl ether. Finally the solvent was altered to 2.5% methanol in ether and the methanol concentration was increased stepwise until a composition of 30% methanol/70% diethyl ether was reached. The

column was then stripped with pure methanol.

A total of 584 fractions was collected. Each was stripped of solvent with a rotary evaporator under aspirator vacuum. A plot of the weight of residual material per tube vs. tube number permitted combination of these fractions into 22 major fractions. A total of 22.4 g was recovered, the small excess being accounted for by incomplete solvent removal. All fractions of sufficient size were tested for toxicity to young guppies by a procedure devised by Chadwick and Warren (23) of the Oregon State Fish and Game Department. The results of the separation and bioassays are shown in Table 2.

b. Methylene Chloride Extractives

The 14.01 g of liquid from the methylene chloride extract was chromatographed with the same apparatus described above. The column used 750 g of BDH silica gel.

Elution was started with dry distilled chloroform. After 4 l. had been collected in 200 ml fractions the lower reservoir was filled with chloroform and the upper reservoir was filled with 2% ethyl acetate/chloroform. The solvent polarity was then increased by 2.5% steps until 10% ethyl acetate/chloroform was reached. The increments were then made in 5% intervals up to 20% ethyl acetate/chloroform, and a similar progression with 10% steps was used to reach 50% ethyl acetate/chloroform. At this point, 5% methanol/ethyl

acetate was added. This was increased by 5% increments to 20% methanol/ethyl acetate. Finally methanol was used to strip the column.

Table 2. Results of the Ether Extract Chromatography

Fraction	Weight (grams)	Conc. Toxicity Sample (mg/liter)	Kill (24 hrs)
EE-CC-1	0.056		
EE-CC-2	2.238		
EE-CC-3	0.187		
EE-CC-4	0.203		
EE-CC-5	0.727		
EE-CC-6	6.943	43.9	0/5
EE-CC-7	0.522	3.2	0/5
EE-CC-8	0.814	5.2	2/5
EE-CC-9	0.917	5.1	0/5
EE-CC-10	1.354	8.0	2/5
EE-CC-11	1.916	12.1	0/5
EE-CC-12	1.903	11.9	5/5
EE-CC-13	0.851	5.6	1/5
EE-CC-14	0.856	5.5	1/5
EE-CC-15	0.744	5.5	2/5
EE-CC-16	0.579	3.8	2/5
EE-CC-17	0.097		
EE-CC-18	0.237		
EE-CC-19	0.267		
EE-CC-20	0.237		
EE-CC-21	0.307		
EE-CC-22	0.488		

There were 525 fractions collected, which were combined into 20 major fractions based on the type of plot described above. The recovery in this case was 87%. The results are shown in Table 3.

Table 3. Results of the Methylene Chloride Extract Chromatography.

Fraction	Weight (grams)	Conc. Toxicity Sample (mg/liter)	Kill (24 hrs)
MC-CC-1	0.296	3.6	0/5
MC-CC-2	3.932	52.0	0/5
MC-CC-3	0.090	2.1	2/5
MC-CC-4	1.386	18.0	1/5
MC-CC-5	0.477	5.8	3/5
MC-CC-6	1.721	22.7	5/5
MC-CC-7	0.344	4.4	0/5
MC-CC-8	1.065	13.9	0/5
MC-CC-9	0.030		
MC-CC-10	0.092		
MC-CC-11	0.116	2.0	0/5
MC-CC-12	0.022		
MC-CC-13	0.043		
MC-CC-14	0.066		
MC-CC-15	0.128		
MC-CC-16	0.241	2.9	3/5
Crystals from MC-CC-15, 16	0.8333	16.4	0/5
MC-CC-17	0.397	5.0	0/5
MC-CC-18	0.028		
MC-CC-19	0.026		
MC-CC-20	0.820		

Fraction Analysis and Correlation

a. Thin Layer Chromatography

A series of thin layer chromatographs were run using both silica gel and alumina and the following solvents: 100% pentane, 20% diethyl ether/pentane, 25% diethyl ether/pentane, 30% diethyl ether/pentane, 25% benzene/hexane, 50% benzene/hexane, 10% methanol/

pentane, 15% ethanol/cyclohexane, 30% ethyl acetate/cyclohexane, 30% ethyl acetate/benzene, and 25% ethyl acetate/benzene. The conditions that gave the best separation with minimum tailing were 25% ethyl acetate/benzene and silica gel G. PE-CC-10 and EE-CC-11 were found to contain two common components, one of which was found by comparison with an authentic sample to be 4-(*p*-tolyl)-1-pentanol. PE-CC-12 was shown to be almost identical with EE-CC-12.

b. Gas Chromatography

Two columns were prepared using Varian-Aerograph's "free fatty acid phase" (FFAP) as the liquid phase and chromosorb G as the solid support. Column A was 15 feet by 1/4 inch and contained 5% FFAP on 40/60 mesh chromosorb G. Column B was 5 feet by 3/8 inch and contained 5% FFAP on 45/60 mesh chromosorb G. The conditions used for glc are shown in Table 4.

Table 4. Gas Chromatography Conditions

Conditions	EE-CC	MC-CC
Column Temp.	200° C	200° C
Injector Temp.	220° C	220° C
Detector Temp.	220° C	220° C
Flow Rate (Helium)	33 ml/sec	2 ml/sec

Fractions were diluted with diethyl ether and approximately 20 microliters of this solution was used for each injection.

The correlations obtained in this way are compiled in Tables 5 and 6. Whenever components are assigned a structure, the assignments were checked by use of an internal standard where such standards were available.

Identification of Minor Components

a. Nujol

Fraction EE-CC-2 was obtained from the column as a colorless liquid. It solidified at 0° C, and infrared and nmr spectra showed only hydrocarbon bands.

b. Guaiacol (o-Methoxyphenol)

Guaiacol was found in EE-CC-3, MC-CC-2, and MC-CC-3. The 80% peak of MC-CC-2 was collected using column A at 200° C. The infrared spectrum was superimposable with that of a known sample (E. K., synthetic). A mixture of the two compounds gave only one peak on the glc. Ir (neat) 3480, 3050, 2990, 2860, 2830, 1610, 1605, 1590, 1513, 1365, 1260, 750 cm^{-1} .

Table 5. Gas Chromatography of EE-CC

Fraction	Peak No.	Retention Time (min)	%	Component	Column
EE-CC-1	1	0.5	5		A
0.056 g	2	0.7	3		
	3	1.0	3		
	4	1.4	5		
	5	1.6	5		
	6	1.9	5		
	7	2.3	3		
	8	2.6	10		
	9	3.6	15		
	10	5.1	15		
	11	7.1	15		
	12	9.9	15		
EE-CC-2					
2.238 g	nujol				
EE-CC-3	1-7	0.0-1.0	0.5		A
0.187 g	8	1.4	1		
	9	1.7	3		
	10	1.9	5		
	11	2.4	1		
	12	2.7	2		
	13	3.2	0.5		
	14	3.8	3	guaiacol	
	15	5.2	2		
	16	5.7	1		
	17	6.4	40	ethyl guaiacol	
	18	7.4	20		
	19	8.3	15		
	20	9.2	1		
	21	10.3	2		
	22	10.9	3		
EE-CC-4	1	6.5	5	ethyl guaiacol	A
0.203 g	2	7.4	10		
	3	8.4	30		
	4	8.7	10		
	5	11.0	15		
	6	18.2	30		

Table 5. (Continued)

Fraction	Peak No.	Retention Time (min)	%	Component	Column
EE-CC-5 0.727 g	1	2.7	1		A
	2	5.3	1		
	3	6.6	2		
	4	7.4	4		
	5	8.7	30		
	6	9.8	2		
	7	11.4	20		
	8	12.3	15		
	9	12.8	10		
	10	14.0	2		
	11	14.7	4		
	12	18.2	4		
EE-CC-6 6.943 g	1	0.5	1		B
	2	1.3	1.5		
	3	1.8	2		
	4	2.6	2		
	5	3.9	1		
	6	7.5	0.5		
	7	12.0	2		
	8	29.0	90	1720 ketone	
EE-CC-7 0.522 g	1	0.6	2		B
	2	1.3	2		
	3	1.8	2		
	4	2.7	2		
	5	6.5	40		
	6	7.5	2		
	7	29.0	50	1720 ketone	
EE-CC-8 0.814 g	1	0.2	3		B
	2	0.6	3		
	3	0.9	40		
	4	1.2	2		
	5	1.3	12		
	6	1.5	5		
	7	4.1	10		
	8	4.9	5		
	9	6.1	12		
	10	7.3	8		

Table 5. (Continued)

Fraction	Peak No.	Retention Time (min)	%	Component	Column
EE-CC-9 0.917 g	1	0.3	0.5		B
	2	0.4	0.5		
	3	0.6	90		
	4	0.8	2		
	5	0.9	2		
	6	1.4	1.5		
	7	1.6	1.5		
	8	2.0	1.5		
	9	6.9	0.5		
EE-CC-10 1.354 g	1	0.3	1		B
	2	0.4	19		
	3	0.5	5		
	4	0.8	2		
	5	1.1	2		
	6	1.2	1		
	7	1.3	2		
	8	1.6	25		
	9	2.0	18		
	10	2.3	25		
EE-CC-11 1.916 g	1	0.2	1.5		B
	2	0.3	0.5		
	3	0.4	1		
	4	0.8	4		
	5	0.9	2		
	6	1.1	1		
	7	1.4	5		
	8	1.6	15		
	9	2.4	70	4-(p-tolyl)- 1-pentanol	
EE-CC-12 1.903 g	1	0.3	1		B
	2	0.7	1		
	3	0.9	5		
	4	1.1	2		
	5	1.4	1		
	6	2.5	20		
	7	5.4	35		
	8	10.3	35	keto-alcohol B	

Table 5. (Continued)

Fraction	Peak No.	Retention Time (min)	%	Component	Column
EE-CC-13 0.851 g	1	0.2	20		B
	2	0.4	20		
	3	0.6	10		
	4	1.4	20		
	5	1.7	5		
	6	2.0	5		
	7	2.5	20		
	8	5.0	trace		
EE-CC-14 0.856 g	1	0.2	40		B
	2	0.4	25		
	3	0.9	10		
	4	1.1	5		
	5	1.4	10		
	6	1.9	2		
	7	2.5	2		
	8	3.5	1		
	9	5.0	5		
EE-CC-15 0.744 g	1	0.2	60		B
	2	0.4	25		
	3	0.6	2		
	4	0.8	2		
	5	1.0	2		
	6	1.3	2		
	7	1.6	3		
	8	2.4	2		
	9	5.0	2		
MC-CC-5 0.477 g	1	0.3	21		B
	2	0.4	5	<u>α</u> -terpineol	
	3	0.5	1		
	4	0.6	15		
	5	0.8	5		
	6	1.0	5		
	7	1.3	5		
	8	1.9	30	4-(<u>p</u> -tolyl)- 1-pentanol	

Table 5. (Continued)

Fraction	Peak No.	Retention Time (min)	%	Component	Column
MC-CC-6 1.721 g	1	0.2	1	<u>α</u> -terpineol	B
	2	0.4	2		
	3	1.1	0.5		
	4	2.0	2	4-(<u>p</u> -tolyl)- 1-pentanol	
	5	5.2	1		
	6	8.5	90	keto-alcohol	
	7	11.0	5		
MC-CC-10 0.092 g	1	1.0	45		B
	2	1.8	5		
	3	2.8	2		
	4	7.0	48		
MC-CC-15 0.128 g	1	0.3	1		B
	2	0.4	1		
	3	1.0	90	<u>cis</u> -terpin hydrate	
	4	1.4	7		
	5	1.9	0.5		
	6	3.1	0.5		

Table 6. Gas Chromatography of MC-CC.

Fraction	Peak No.	Retention Time (min)	%	Component	Column
MC-CC-1 0.296 g	1	0.5	5		A
	2	1.0	10		
	3	1.5	60		
	4	2.5	1		
	5	3.2	5		
	6	3.5	5		
	7	4.0	4		
	8	5.0	5		
MC-CC-2 3.932 g	1	1.3	1		A
	2	2.3	1		
	3	2.5	1		
	4	4.0	0.5		
	5	5.0	0.5		
	6	5.8	80	guaiacol	
	7	7.5	3		
	8	9.5	15	ethyl guaiacol	
MC-CC-3 0.090 g	1	2.5	30		A
	2	4.8	5		
	3	5.5	40	guaiacol	
	4	8.5	20		
MC-CC-4 1.386 g	1	0.3	0.5		A
	2	1.3	0.1		
	3	2.0	1		
	4	2.5	1		
	5	3.0	15	<u>α</u> -terpineol	
	6	7.5	2		
	7	12.5	3		
	8	15.8	2		
	9	18.0	78	4-(<u>p</u> -tolyl)- 1-pentanol	
MC-CC-5 0.477 g	1	2.0	18		A
	2	3.0	5	<u>α</u> -terpineol	
	3	4.3	1		
	4	5.3	15		
	5	6.5	5		
	6	7.0	5		
	7	7.5	1		
	8	8.5	5		

Table 6. (Continued)

Fraction	Peak No.	Retention Time (min)	%	Component	Column
	9	12.5	4		
	10	18.0	30	4-(<u>p</u> -tolyl) - 1-pentanol	
MC-CC-6 1.721 g	1	0.5	1	<u>α</u> -terpineol	B
	2	1.0	2		
	3	2.3	0.5		
	4	3.5	2	4-(<u>p</u> -tolyl) - 1-pentanol	
	5	10.0	1		
	6	16.3	90	keto-alcohol B	
	7	21.0	5		
MC-CC-7 0.344 g	1	0.3	2		B
	2	0.5	2	<u>α</u> -terpineol	
	3	0.8	2		
	4	1.0	5		
	5	1.3	1		
	6	2.0	1		
	7	2.5	0.5		
	8	3.5	1	4-(<u>p</u> -tolyl) - 1-pentanol	
	9	5.5	1		
	10	8.0	2		
	11	10.0	30		
	12	15.0	60	keto-alcohol B	
MC-CC-8 1.065 g	1	0.5	12		B
	2	0.8	10		
	3	1.0	5		
	4	1.3	12		
	5	1.5	2		
	6	2.0	5		
	7	3.0	55		
	8	4.0	1		
	9	5.0	1		
	10	6.5	1		
	11	7.5	1		
	12	11.5	1		
	13	14.5	1	keto-alcohol B	

Table 6. (Continued)

Fraction	Peak No.	Retention Time (min)	%	Component	Column
MC-CC-9	0.030 g	NOT RUN			
MC-CC-10	1	1.5	45	<u>trans</u> - sylveterpin	B
0.092 g	2	3.5	5		
	3	10.3	50		
MC-CC-11	1	0.3	7		B
0.116 g	2	0.5	5		
	3	1.3	5		
	4	1.8	50		
	5	2.0	5		
	6	2.8	5		
	7	3.8	7		
	8	10.5	15		
MC-CC-12	0.022 g	NOT RUN			
MC-CC-13	1	0.5	5		B
0.043 g	2	1.0	80		
	3	2.0	5		
	4	3.5	10		
MC-CC-14	0.066 g	NOT RUN			
MC-CC-15	1	0.8	1		B
0.128 g	2	1.0	1		
	3	2.0	90	<u>cis</u> -terpin hydrate	
	4	3.0	7		
	5	4.0	1		
MC-CC-16	1	1.0	2		B
0.241 g	2	2.0	95	<u>cis</u> -terpin hydrate	
	3	3.0	2		
	4	4.0	1		
MC-CC-17	1	0.8	2		B
0.397 g	2	1.0	35		
	3	1.5	3		
	4	3.0	60		

c. Ethyl Guaiacol (4-Ethyl-2-methoxyphenol)

Fractions EE-CC-3, EE-CC-4, and MC-CC-2 contain a common constituent. A sample of this material was collected via glc from column A at 200° C column temperature. The liquid material weighed 6 mg, ir (neat) 3480, 3020, 2960, 2920, 2850, 1600, 1510, 1370, 1270, 1235, 1152, 1125, 1035, 850, and 805 cm^{-1} ; nmr (CCl_4) δ 6.67 (s, 1), 6.58 (m, 2), 5.2 (s, 1), 3.83 (s, 3), 2.54 (q, 2, $J = 7.3\text{Hz}$), 1.20 (t, 3, $J = 7.3\text{Hz}$) ppm.

d. α -Terpineol (Δ^1 -p-Menthen-8-ol)

The common component of MC-CC-4, MC-CC-5, and MC-CC-6 was found by use of an internal comparison standard (MCB commercial sample) to have the same retention time on glc as α -terpineol.

e. 4-(p-Tolyl)-1-pentanol

A synthetic sample of 4-(p-tolyl)-1-pentanol (24) was used as a comparison standard for glc work. This had the same retention time as a component of fractions MC-CC-5, MC-CC-6, and EE-CC-11. The infrared spectrum of EE-CC-11 [70% of 4-(p-tolyl)-1-pentanol] was nearly identical with that of an authentic sample.

f. cis-Terpin Hydrate (p-Menthane-1,8-diol)

Crystalline material was isolated from fractions MC-CC-15 and MC-CC-16 and recrystallized from methanol/chloroform, mp 116-118° C. A mixture of this material and cis-terpin hydrate (E. K. # 439) melted at 116-118° C. Ir (nujol mull) 3535, 3410, 2925, 2890, 2820, 1460, 1448, 1370, 1175, 1105, 991, 903 cm^{-1} ; nmr (CDCl_3) δ 0.7 (m), 1.2 (m), 1.6 (m), 1.8 (m) ppm.

g. trans-Sylveterpin (m-Menthane-1,8-diol)

A solid (43 mg) was found in fraction MC-CC-10 and was purified by sublimation, mp 139-141° C (sealed capillary). Ir (nujol mull) 3420, 2925, 2890, 2820, 1460, 1375, 1260, 1240, 1130, 1080, 1020, 1000, 950, 750 cm^{-1} .

A sample of Δ^3 -carene (20 mg, 1.47×10^{-4} mole) (courtesy of Dr. E. F. Kurth, Professor, Science Research Institute, Oregon State University) was dissolved in 5 ml of dry ether, and hydrogen chloride gas was bubbled through the solution. When the reaction was complete, as indicated by the appearance of hydrogen chloride gas at the outlet, the ether was removed by evaporation. The crude mixture was converted to sylveterpin by the method of Wallach (22). The crude product was treated with 0.1 g of potassium hydroxide (1.8×10^{-3} moles) in 5 ml of water. This was heated at 80° C for 2 hrs,

neutralized with 5% hydrochloric acid solution, extracted with ether, dried (MgSO_4), and the solution was concentrated. This mixture and MC-CC-10 were compared by glc using column B. A mixed sample showed that a minor component of the reaction mixture has the same retention time as the solid from MC-CC-10.

Unknown 1720 Ketone

This material was found in fraction EE-CC-6, and a purified sample was collected by preparative gas chromatography (column B). All spectral data were obtained from the purified sample. Ir (neat) 3060 (arom H), 3010 (possibly $\text{O-CH}_2\text{-O}$), 2960, 2920, 2850, 1720 (probably ketone), 1600, 1580, 1460, 1450, 1380, 1360, 1275, 1125, 1040, 785, 760, 745 cm^{-1} ; UV (EtOH) λ_{max} 272 ($\epsilon = 320$), 222 ($\epsilon = 1700$); nmr (CCl_4) δ 7.54 (A_2B_2 aromatic, 2), 4.19(s, 1), 4.11 (s, 1), 1.97 (m, 1), 1.7 (m, 9), 0.9 (m, 6); MW 322 (osmometer). Results of mass spectral examination are shown in Table 7. A scan taken late in the sample diffusion process differs significantly from these results, showing m/e peaks in the 300-500 region. A plain ORD curve was observed, $[\alpha]_{3200}^{25} = +8.96^\circ$ (10.66 g/l., CHCl_3). A sodium fusion showed no positive test for halogens, nitrogen, or sulfur.

Table 7. Mass Spectrum of EE-CC-6^a

m/e	Rel. Abund.	m/e	Rel. Abund.	m/e	Rel. Abund.
28	52.9	69	1.3	119	21.3
29	20.6	72	1.2	121	6.2
31	29.1	77	3.8	123	0.9
32	19.4	78	2.6	127	0.7
40	2.1	79	6.6	128	1.4
41	6.8	80	5.8	129	1.0
42	7.6	81	3.9	131	1.3
43	100.0	82	5.9	132	1.3
44	6.6	83	2.0	133	2.3
47	2.5	84	3.7	134	0.6
49	2.3	85	1.5	135	0.7
50	1.3	91	4.8	145	4.6
51	2.9	92	4.0	147	6.2
52	1.4	93	3.5	149	1.4
53	2.6	94	1.7	160	0.8
55	3.2	95	1.2	161	0.5
57	2.1	96	3.9	162	3.5
58	28.7	103	1.3	163	0.4
59	1.3	104	0.9	164	0.3
63	1.5	105	2.0	165	0.4
65	2.4	107	3.0	166	0.3
66	1.4	115	1.8	167	0.2
67	2.1	117	22.9	192	0.6

^a m/e of relative abundance less than 0.5 are omitted below 160, and m/e of relative abundance less than 1.0 are omitted below 100.

a. 2,4-Dinitrophenylhydrazone

A 2,4-dinitrophenylhydrazone was prepared using Shine's method (20). Five milliliters of Shine's reagent was added to 0.1 g of EE-CC-6 in 1 ml of 95% ethanol. Three drops of concentrated hydrochloric acid were added, and the mixture was stirred for 4 hrs.

Two milliliters of water was added, and an oil separated.

A second preparation was carried out by the procedure of Cheronis and Entrikin (3, p. 318). A mixture of 2 ml of methanol, 20 mg of EE-CC-6, 20 mg of 2,4-dinitrophenylhydrazine, and two drops of concentrated hydrochloric acid was refluxed for 3 hrs. A few drops of water were added, and an oil separated.

Thin layer chromatography on alumina PF254 using 10% ethyl acetate/benzene showed both oils to be identical and not the unreacted starting material. The derivative did not crystallize.

The oils were combined and chromatographed on a column (15 x 1 cm) packed with silica gel (BDH reagent). Elution with 10% ethyl acetate/hexane gave 96 mg of oil.

Anal. Found: C, 72.0; H, 9.2.

b. Oxime

An oxime was prepared using the procedure of Cheronis and Entrikin (3, p. 319). A solution of 160 mg of EE-CC-6, 190 mg of hydroxylamine hydrochloride, 1.5 ml of 100% ethanol, and 1.2 ml of dry pyridine was heated at 70° C for 20 hours. The solvent was removed by evaporation, and the oily residue was washed with water. The resultant oil could not be induced to crystallize.

c. Oxidation

EE-CC-6 (0.3 g), potassium permanganate (1.8 g), and 25 ml of water were stirred for 6 hrs at 100° C. The mixture was filtered, acidified with 5% hydrochloric acid solution, and extracted with ether. The ether solution was dried (MgSO_4) and concentrated. Ir (neat) 3450, 2950, 2850, and 1720 cm^{-1} (carbonyl).

Thin layer chromatography of the product over silica gel PF254 using 10% ethyl acetate/benzene showed that a substance having the same R_f value as propionic acid was present. Paper chromatography on Whatman #1 paper with 95% ethanol (100 parts) and 28% ammonium hydroxide (1 part) as the solvent system showed again a substance with the same R_f value as propionic acid.

Unknown Keto-Alcohol B

This compound was found in EE-CC-12, MC-CC-6, MC-CC-7, and MC-CC-8. A sample purified by Dr. Gänzler and examined by him showed: ir (neat) 3420 (OH), 3025 ($\text{C}=\text{CH}$), 2940, 2870, 1710 (saturated ketone), 1470, 1455, 1412, 1380, 1370, 1170, 1145, 1054, 1035, 957, 930, and 895 cm^{-1} ; UV (EtOH) λ_{max} 283 ($\epsilon = 80$, based on MW of 240), λ_{max} 200 ($\epsilon = 3000$); and nmr (CCl_4) δ 3.46 (d, $J = 6.5\text{Hz}$), 2.49 (s, moves on dilution), 2.19 (m), broad series between 1.9 and 1.1, and three peaks between 0.81 and 1.0 ppm; $[\alpha]_D^{25} + 12.5^\circ$.

(CHCl₃). The spectra of fractions MC-CC-6 and EE-CC-12 were essentially the same as those reported above.

a. 2,4-Dinitrophenylhydrazone

Keto-alcohol B (0.1 g), 5 ml of Shine's reagent, 1 ml of 95% ethanol, and three drops of concentrated hydrochloric acid were stirred for 4 hrs at 60° C. Two milliliters of water was added, and a red oil separated. Thin layer chromatography over silica gel G using 25% ethyl acetate/benzene for development showed a single spot with an R_f value different from those of the starting materials. This oil failed to crystallize.

b. Oxime

Twenty milligrams of keto-alcohol B (collected via glc using column B), 20 mg of hydroxylamine hydrochloride, 1.5 ml of absolute methanol, and 1 ml of dry pyridine were heated for three days at 70° C. The solvent was evaporated, the residue was washed with water, and an oil was obtained.

A second reaction using 537 mg (purified by glc) of keto-alcohol B and a temperature of 80° C also gave an oily product. The product could not be induced to crystallize.

c. Acetate

A mixture of 0.1 g of keto-alcohol B, two drops of acetic anhydride, and one drop of pyridine was heated for 36 hrs at 80° C. A second batch was prepared from 0.3 g of keto-alcohol B, and the combined product was purified by gas chromatography using column B; ir (neat) 2960, 2920, 2870, 1740 (acetate), 1720 (ketone), 1465, 1455, 1365, 1235, 1030 cm^{-1} ; nmr (CCl_4) δ 3.96 (d, $J = 7\text{Hz}$), 2.1-2.4 (m), 1.97 (s), 1.1-1.8 (m), and a series of sharp peaks between 0.8 and 1.0 ppm. A solution containing 8 mg of acetate in 3 ml of 0.95 M tetranitromethane in CCl_4 showed no absorption between 760 and 420 $\text{m}\mu$.

Results of the mass spectra run on both keto-alcohol B and its acetate are shown in Table 8.

d. Attempted Oxidation

An oxidation was attempted using the method of Albright and Goldman (1).

Keto-alcohol B (~ 10 mg) was dissolved in 0.5 ml of dimethyl sulfoxide (DMSO) and was added to a flask containing 1 ml of acetic anhydride in 2 ml of DMSO. The flask was fitted with a drying tube containing Drierite and was stirred for 24 hrs at room temperature. One milliliter of ethanol was added, and the solution was stirred for

Table 8. Mass Spectrum of Keto-Alcohol B and Its Acetate

m/e	Relative Abundance		m/e	Relative Abundance	
	Alcohol	Acetate		Alcohol	Acetate
27	91	29.6	79	99	37.5
28	28	100.0	80		10.5
29	85	39.9	81	51	40.7
30		1.6	82		8.3
31		3.8	83		14.2
39	88	29.9	85	29	41.6
40	30	8.7	91	100	26.9
41	93	92.1	92		12.6
42	46	54.7	93	76	63.6
43	86	60.8	94		21.5
44		22.7	95	26	31.1
45		5.5	105	47	28.9
51	43	8.0	107	40	30.2
53	69	17.3	115	26	4.7
55	86	42.2	117	31	4.9
56		16.7	119	80	35.4
57	99	75.5	120	29	25.2
58		15.6	127		61.2
63	22	3.0	132	31	2.4
65	50	9.2	147		17.7
67	75	36.8	161	6	8.8
69	40	38.9	163	33	8.8
71		16.3	204		9.7
72		2.7	207		2.8
73		7.6	220	25	1.8
77	85	22.3	222	2.1	5.3
78	26	9.2	282		1.7

another hour. Several drops of water were added, and then 1 ml of concentrated ammonium hydroxide was slowly dropped in while the solution was kept at 0° C in an ice bath. The solution was extracted with ether. The ether extract was dried (MgSO_4) and concentrated. The infrared spectrum showed that only unreacted starting material was present in this reaction product.

e. Reduction

The ketone (10-100 mg) was dissolved in a few ml of dry methanol, and small portions of sodium borohydride were added at room temperature over a 1-hr period. When further additions failed to induce any reaction, water was added dropwise. The diol was extracted with diethyl ether, dried (MgSO_4), and concentrated. The product was collected from glc (column B): ir (neat) 3300 s (OH), 1720 w cm^{-1} ; nmr δ 3.5 (m), 2.7 (m), 1.4 (m), and 1.0 (d, $J = 7\text{Hz}$). Integration showed ratios of 1:1:21:3.

f. Toxicity of Components of MC-CC-6

The various components of fraction MC-CC-6 were collected via preparative gas chromatography using column B. Toxicity tests were run on the collected components using the same concentrations as they would have in the original waste. The results of these tests are shown in Table 9.

Table 9. Toxicities of Components of MC-CC-6

Sample	Conc. of Sample (mg/liter)	Kill (24 hrs)
keto-alc.	3.8	0/2
minor peaks	2.9	1/2
diol	1.3	2/2
blank		0/2

g. 3,5-Dinitrobenzoate of Diol

The procedure used was that of Cheronis and Entrikin (3, p. 249). The diol (6 mg) and 13 mg of 3,5-dinitrobenzoyl chloride were heated in three drops of dry benzene at 80° C for 36 hrs. The benzene was evaporated, and the oil was washed with bicarbonate solution and water. Crystallization was attempted from methanol/water. The derivative remained an oil.

h. *p*-Phenylazobenzoate of Diol

The diol (2 mg) and *p*-phenylazobenzoyl chloride (4 mg) were heated in dry benzene for 3.5 days at 80° C. An oil separated when water was added. This oil was washed with bicarbonate solution and then water. It was taken up in ether, dried (MgSO₄), and concentrated. Thin layer chromatography using 20% ethyl acetate/cyclohexane and silica gel PF254 gave four spots: R_f 0.0, 0.31, 0.37, and 0.63.

A second batch of derivative was prepared from 9.4 mg of diol

and separated into the three fractions by preparative thin layer, using the same solvent and support as before. The fractions were scraped off the plate and extracted with ether. The fractions of R_f values 0.63 and 0.37 both contained a colorless crystalline compound that melted at 52-53° C (hot-stage microscope). All fractions contained a highly-colored oil which would not crystallize.

i. Dehydrogenation of Diol

Approximately 10 mg of the keto-alcohol was reduced to the diol as described. The diol was mixed with Pd/C and was heated at temperatures up to 240° C for 20 hrs.

A liquid, 2.8 mg, collected on the condensing surface: ir (CCl_4) 3080, 3050, 3020, 2950, 2920, 2860, 1780, 1720, 1640, 1450, 1380, 1360, and 1000 cm^{-1} ; nmr (CCl_4) δ 7 (2 singlets, 3), 3.7 (m, 2), 2.3 (s, 2), 1.8 (m, 8), 1.3 (m and s, 7), 1 (m and 2s, 11); UV (EtOH) λ_{max} 272 ($\epsilon = 540$).

Spectral Data

The infrared spectra were taken on a Perkin Elmer Model 21 and a Beckman IR-8 infrared spectrophotometer. A Varian A-60 NMR spectrometer was used for the nmr spectra. The ultraviolet spectra were taken on Cary Model 15 and Beckman DB spectrophotometers. The mass spectral data were obtained by the use of an

Atlas CH-4 mass spectrometer (courtesy of Dr. Leonard M. Libbey, Assistant Professor of Food Science and Technology, Oregon State University).

Carbon-Hydrogen Analysis

The carbon-hydrogen analysis was run by Frank A. Lehmkuhl, Graduate Assistant, Oregon State University

BIBLIOGRAPHY

1. Albright, J. Donald and Leon Goldman. Dimethylsulfoxide-acid anhydride mixtures for the oxidation of alcohols. *Journal of the American Chemical Society* 89:2416-2423. 1967.
2. Ashorn, Theodore and Terje Enkvist. Proofs for the occurrence of homoprotocatechuic acid and some other pyrocatechol and guaiacol derivatives in pressure-heated spent liquors. *Acta Chemica Scandinavica* 16:548-552. 1962.
3. Cheronis, Nicholas D. and John B. Entrikin. Identification of organic compounds. New York, Interscience, 1963. 477 p.
4. DeMayo, Paul. Mono- and sesquiterpenoids. New York, Interscience, 1959. 320 p.
5. Dyer, John R. Applications of absorption spectroscopy of organic compounds. Englewood Cliffs, New Jersey, Prentice-Hall, 1965. 143 p.
6. Fletcher, T. L. and E. E. Harris. Destructive distillation of Douglas fir lignin. *Journal of the American Chemical Society* 69:3144-3145. 1947.
7. Heilbronner, E. Zur Tetranitromethan-Probe. *Helvetica Chimica Acta* 36:1121-1124. 1953.
8. Hrutfiord, Bjorn F. Lignin degradation product analysis by gas chromatography. *Tappi* 48:48-54. 1965.
9. Johnson, Carl H. and Russell A. Cain. The wood oil of Douglas fir. *Journal of the American Pharmaceutical Association* 26: 623-625. 1937.
10. Libby, C. Earl (ed.). Pulp and paper science and technology. Vol. I. New York, McGraw-Hill, 1962. 436 p.
11. McHugh, Robert A. Preliminary report on a study of the factors responsible for the toxicity of waste from a modern Kraft pulp and paper mill. Corvallis, Oregon State University, Dept. of Fish and Game Management, 1954. 10 numb. leaves.

12. McInnes, A. S., Einer West, Joseph L. McCarthy and Harold Hibbert. Studies on lignin and related compounds. XLIX. Occurrence of the guaiacyl and syringyl groupings in the ethanolysis products from various plants. *Journal of the American Chemical Society* 62:2803-2806. 1940.
13. McLafferty, Fred W. Interpretation of mass spectra. New York, W. A. Benjamin, 1966. 229 p.
14. Marvell, Elliot N. and Charles E. Warren. Components of Kraft mill waste and their toxicities. Corvallis, Oregon State University, Dept. of Chemistry, 1967. 45 numb. leaves.
15. Marvell, Elliot N. and Robert E. Wiman. 4-(p-Tolyl)-1-Pentanol in Douglas fir pulping product. *The Journal of Organic Chemistry* 28:1542-1545. 1963.
16. Nakanishi, Koji. Practical infrared absorption spectroscopy. San Francisco, Holden-Day, 1962. 233 p.
17. Norton, S. G. Use of sulfate turpentine as a chemical raw material. *Paper Trade Journal* 120(7):36. 1945.
18. Pew, John C. A flavanone from Douglas fir heartwood. *Journal of the American Chemical Society* 70:3031-3034. 1948.
19. Schorger, A. W. The oleoresin of Douglas fir. *Journal of the American Chemical Society* 39:1040-1044. 1917.
20. Shine, H. J. A new technique in preparing 2,4-dinitrophenylhydrazones. Use of diglyne as solvent. *The Journal of Organic Chemistry* 24:252-253. 1959.
21. Simonsen, J. L. The terpenes. Vol. I. Cambridge, Eng., University Press, 1947. 479 p.
22. Wallach, O. Zur Kenntniss der Terpene und der otherischen Öle. *Justus Liebig's Annalen der Chemie* 357:72-75. 1907.
23. Warren, Charles E. and Elliot N. Marvell. A study of constituents responsible for the toxicity of Kraft mill wastes to fish. Corvallis, Oregon State University, Dept. of Fish and Game Management, 1961. 41 numb. leaves.
24. Wiman, Robert E. Isolation and identification of certain toxic compounds in a fraction of Kraft mill waste. Ph. D. thesis. Corvallis, Oregon State University, 1962. 46 numb. leaves.

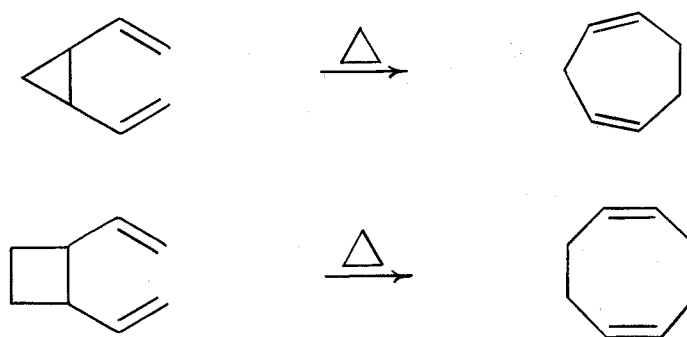
PART II

STUDIES OF THE MECHANISM OF THE COPE REARRANGEMENT OF 1,2-DIVINYL-1,2-CYCLOHEXANEDIOL

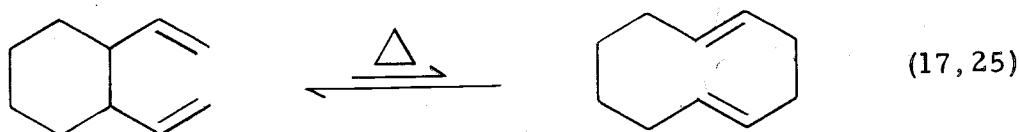
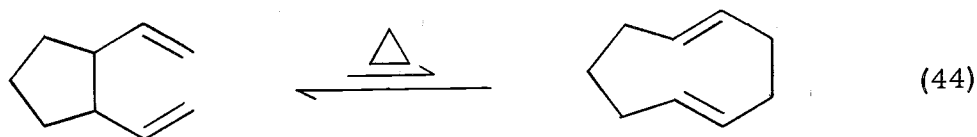
INTRODUCTION

The Cope rearrangement is one of the best known examples of the general class of concerted thermal reactions called by Woodward and Hoffmann (20, 49, 50) sigmatropic reactions. Generally these reactions show no response to acid or base catalysis, or to free radical initiators or inhibitors. They are normally stereochemically quite selective and often proceed in very high yield.

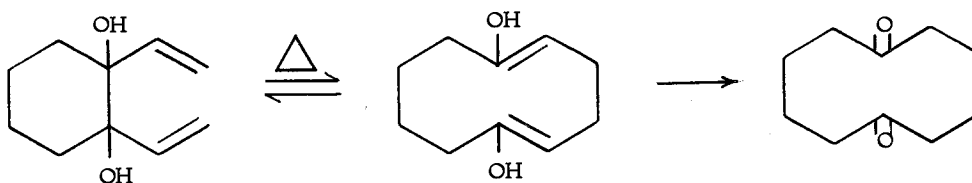
The Cope rearrangement should be a useful process for synthesis, particularly for bringing about a controlled ring expansion by four carbon atoms. It has indeed been found to proceed effectively with divinylcyclopropanes and divinylcyclobutanes (44). Unfortunately



the particularly desirable cases leading to formation of nine- and ten-membered rings fail because of an unfavorable equilibrium. An



attempt to drive the reaction in the desired direction through the use of enol-keto conversion did indeed proceed as expected, but instead of the desired 1,6-cyclodecanedione, the aldol product, 1(7)-bicyclo-[5.3.0] decen-2-one, was obtained.

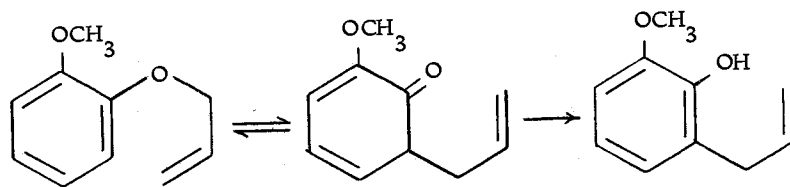


If this reaction is to serve its intended purpose for the synthesis of nine- and ten-membered rings, it will be necessary to find some means of preventing this diversion to the aldol product. With this purpose in mind, we set out to learn about the reaction scheme which leads from the 1,5-cyclodecadien-1,6-diol to the unsaturated ketone. The results of our investigation are described in this thesis.

HISTORICAL

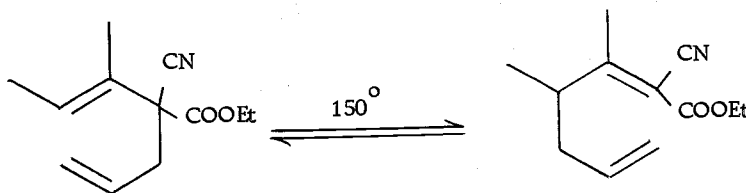
Woodward and Hoffmann have considered the Cope rearrangement as one example of a general reaction type which they have named sigmatropic reactions (20, 49, 50). They define a sigmatropic change of order $[i, j]$ as "the migration of a σ bond, flanked by one or more π electron systems, to a new position whose termini are $i-1$ and $j-1$ atoms removed from the original bonded loci, in an uncatalyzed intramolecular process" (20, p. 21). The Claisen and Cope rearrangements are sigmatropic changes of order $[3, 3]$.

The first example of a reaction of this type was found by Claisen in 1912 (8). The voluminous literature pertaining to these rearrange-



ments has been reviewed several times. It will not be considered further here. However, it should be noted that this is a general reaction of allylvinylethers, which now is named after its discoverer.

An all-carbon analog of the Claisen rearrangement was first recognized by Cope and Hardy in 1940 (9). This sigmatropic reaction



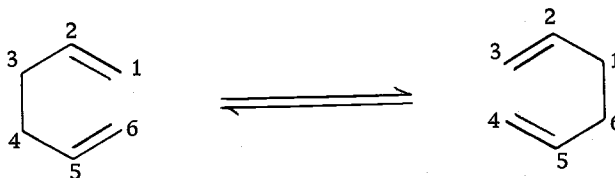
is called the Cope rearrangement. The Cope rearrangement has been extensively reviewed (12, 31, 43), and the following conclusions can be drawn (34). This reaction is insensitive to external catalytic influence. It is unresponsive to solvation effects and follows first-order kinetics. It usually proceeds as an intramolecular process. Only at rare times are any "cross-over" products found. One example was reported by Huntsman (22). He found that 2-methyl-1, 5-hexadiene gave some 1, 5-hexadiene and 2, 5-dimethyl-1, 5-hexadiene when subjected to high temperature pyrolysis (460°C). Also, Gibson and Pettit (15) found predominantly intermolecular reaction products from the thermolysis (375°C) of 5, 6-dimethyl-1, 3, 7, 9-decatetraenes. The temperature used in both cases was quite high and radical formation would not be completely unexpected.

The temperature at which measurable reaction occurs can be decreased by conjugative substituents (such as $-\text{CN}$, $-\text{COOR}$, $-\text{phenyl}$, etc.) on the central methylene carbons. The reaction is also favored by the inclusion of these central methylene carbons in a strained ring. If the two allylic groups are held in a bicyclic structure (51) the reaction is favored. Presumably the activated complex contains the two allylic systems in roughly parallel planes with the six carbons aligned in either a chair or a boat form.

This chair- or boat-form geometry is probably necessary for a concerted reaction but is not, of course, necessary for a radical

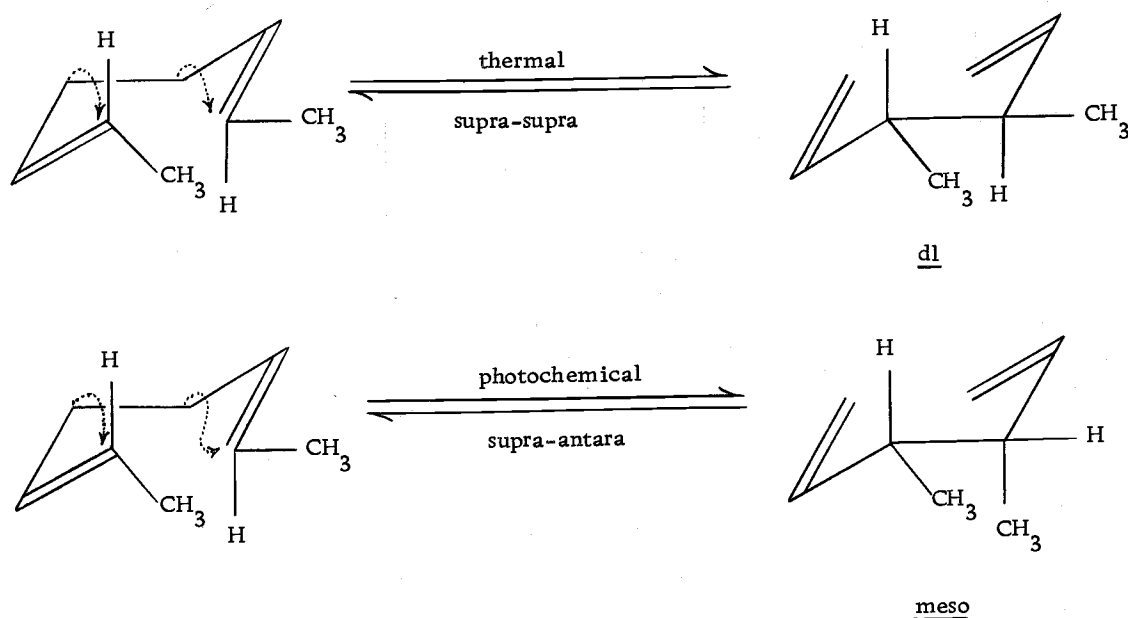
mechanism. That the latter does exist is pointed out by the work of Hammond and DeBoer (19). They have shown that cis-1,2-divinylcyclobutane reacts faster (rate = $1.39 \times 10^{-3} \text{ sec}^{-1}$) and at a lower temperature (108.5° C) than trans-1,2-divinylcyclobutane (rate = $4.66 \times 10^{-6} \text{ sec}^{-1}$ at 139.3° C). The cis compound gives cis, cis-1,5-cyclooctadiene, whereas the trans compound gives cis, cis-1,5-cyclooctadiene, 4-vinylcyclohexene, some butadiene, and some cis-1,2-divinylcyclobutane. This information shows that the energy barrier for the concerted mechanism is considerably lower than that for the radical mechanism.

A set of rules predicting the stereochemical consequences of concerted reactions has been proposed by Woodward and Hoffmann (20, 49, 50). In the Cope rearrangement the following bond migration takes place (3, 4 to 1, 6):



There are two possible ways to effect this migration. The suprafacial process is one in which the migrating bond is associated at all times with the same face of the π system. The antarafacial process is one in which the migrating bond is passed from the top face of one terminus to the bottom face of the other. By the Woodward-Hoffmann rules the Cope rearrangement is predicted to proceed in a

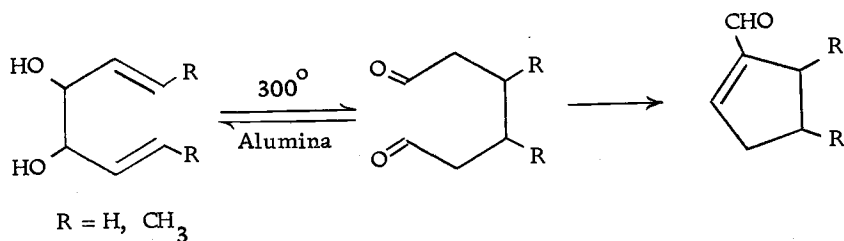
suprafacial-antarafacial manner. These are illustrated by the following figures. It simplifies the picture to imagine the pair of electrons from bond 3,4 traveling in a concerted fashion along carbons 3,2,1 and 4,5,6 respectively. In the thermal process a dl product is obtained, and a meso product results from the photochemical process if trans-2-trans-6-octadiene is the reactant (12).



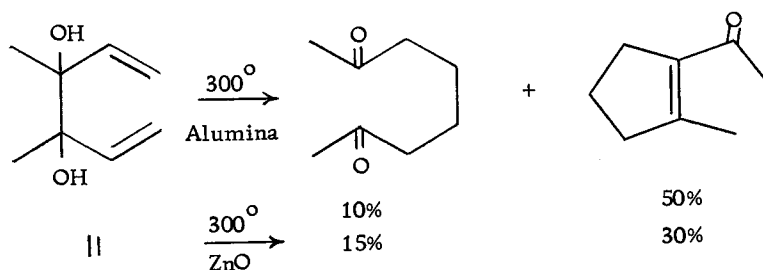
When a hydroxyl substituent is placed on one or both of the central methylene carbons the reaction adds some new terminal steps. These steps will become apparent as we review the previous work done with this particular system.

Urion (39, 40) found that divinylglycols rearranged to form aldehydes when they were heated over alumina. They did not

determine the stereochemistry of the methyl substituted product.

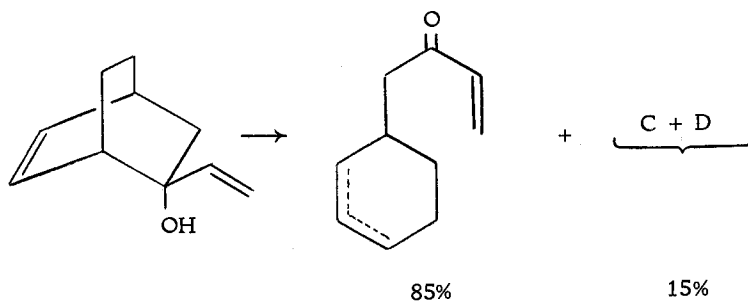
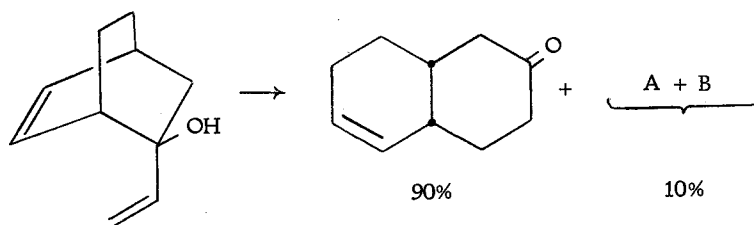


Wiemann and Thuan (38, 45, 46, 47) found similar results when they heated divinylglycols over alumina and also over zinc oxide. It has been in only the last few years that the purely thermal nature of this

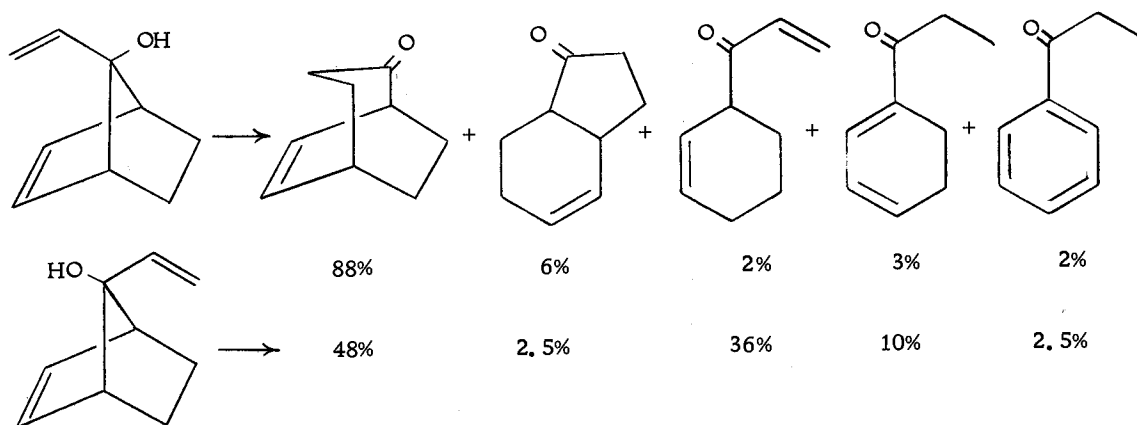


reaction has been recognized.

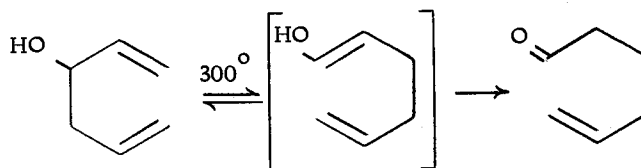
Berson and co-workers (3, 4) have run a series of thermolyses at 320° C in the vapor phase. As was shown by Hammond (19), the Cope rearrangement can proceed by a radical process when the allyl groups are not in the correct position for the concerted process. Berson found that the epimeric 6-vinyl-2-bicyclo[2.2.2] octen-6-ols gave quite different products on heating. Products A, B, C, and D were not identified.



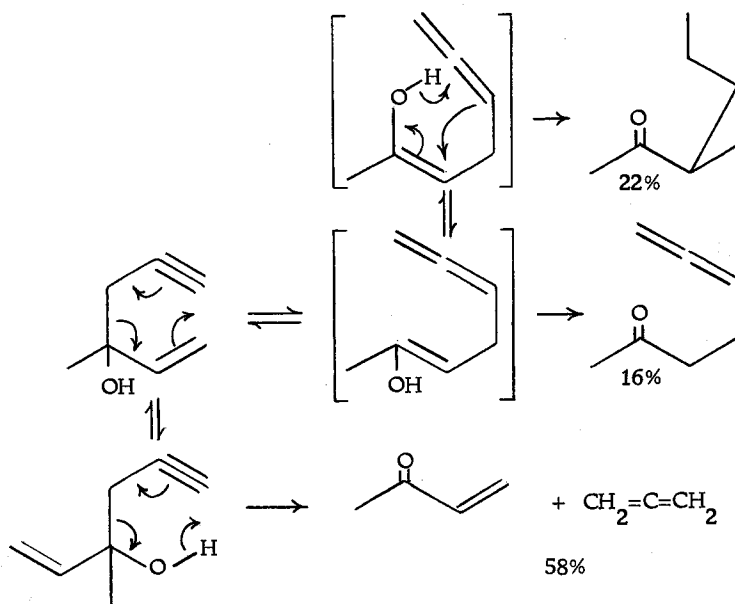
The difference in major products might suggest that the first reaction proceeds by a concerted process whereas the second proceeds via a diradical process. However, the authors feel that since the rates of both reactions are the same, a radical process is probably responsible in both cases. A second pair of epimeric molecules was also treated similarly. Again the products indicate that both isomers proceed by the same radical process.



The simplest example which can meet the conditions for this variation of the Cope rearrangement is 1,5-hexadien-3-ol. The thermolysis of this compound in the vapor-phase was carried out by Viola and Levasseur in 1965 (42). They proposed a concerted reaction scheme.

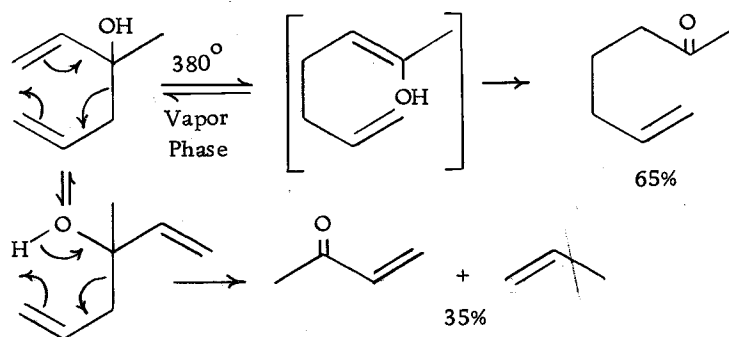


Wilson and Sherrod (48) carried out a similar rearrangement with an acetylenic analog. The mechanisms they proposed are shown in the following diagram. The 16% product is formed by a concerted



acetylenic Cope rearrangement. The 22% product is the result of an "enolene" rearrangement, and the 58% products results from an acetylenic modification of a β -hydroxyolefin cleavage. This route is supported by the fact that the propargyl radical, if formed, should have abstracted a hydrogen atom to form propyne rather than allene.

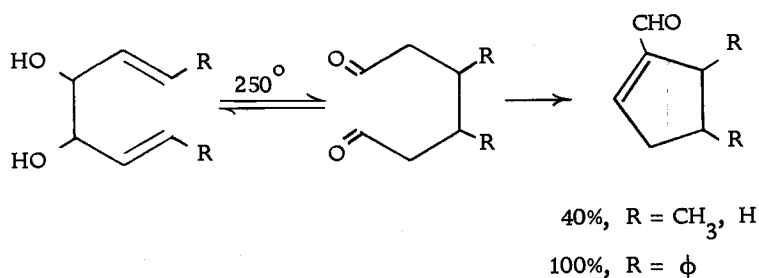
Viola and co-workers (41) have studied a series of methyl substituted 3-hydroxy-1,5-hexadienes. They found that the thermolyses resulted in rearrangement to the Δ^5 -unsaturated carbonyl compounds and in the formation of cleavage products. The formation of cleavage products predominated at higher temperatures. There were no "cross-over" products formed; therefore they feel the cleavage products resulted from concerted β -hydroxyolefin cleavages. The Δ^5 -unsaturated carbonyl compounds are the normal Cope rearrangement products. These competing concerted rearrangements are shown



for one of their reactions. Methyl substitution in the 5 position results in a larger proportion of cleavage. This substitution stabilizes

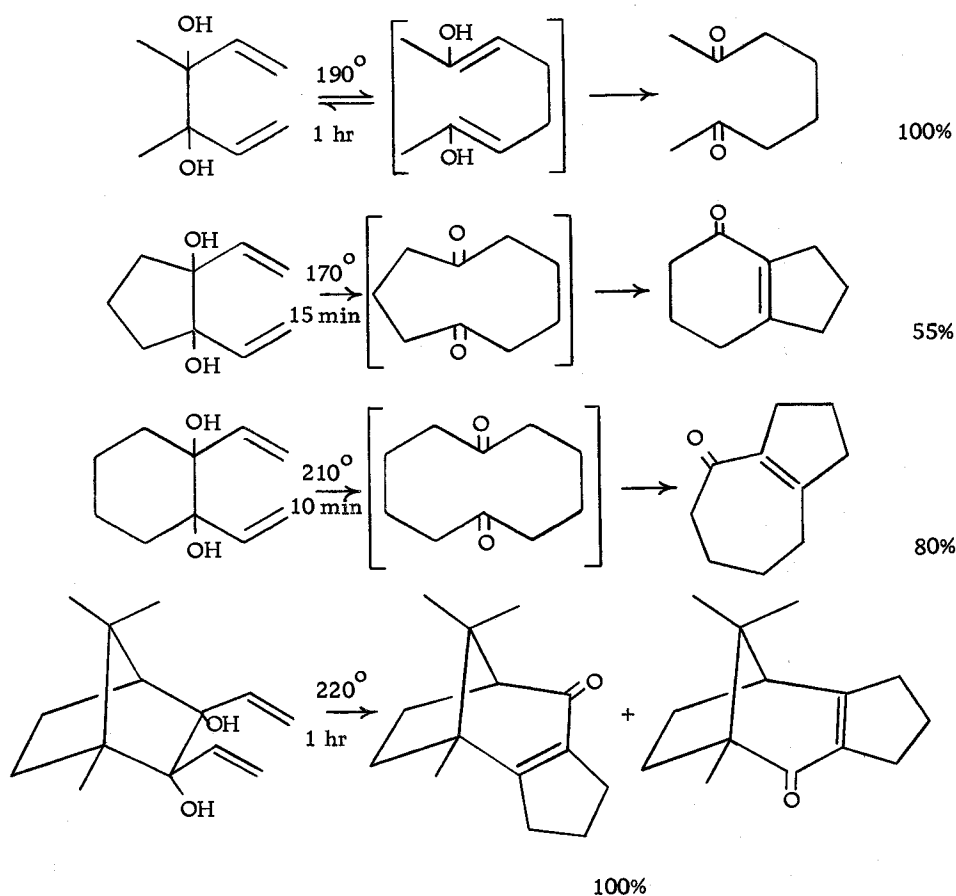
the formation of a transient positive charge, a factor favoring the more unsymmetrical transition state required by cleavage. Methyl substitution in the 3 and 4 positions changes the product ratios only slightly in favor of the Cope rearrangement product due to steric reasons. Cis substituents in the 1 position tend to favor cleavage products also for steric reasons. Trans substituents in the 1 position change the product ratio slightly in favor of cleavage products, but only by a few percent.

Chuche and Wiemann (6, 7) have carried out the thermolyses of divinylglycols substituted terminally on the vinyl groups (trans double bonds) under purely thermal conditions as opposed to some of their earlier work (38, 39, 40, 45, 46, 47). During the course of this



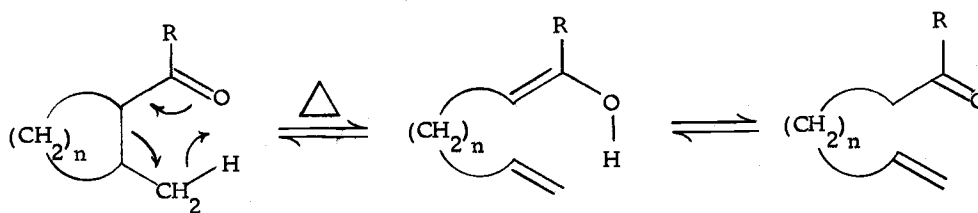
work, they found that the 4,5-dimethylformyl-1-cyclopentene was obtained as both the cis (24%) and the trans (76%) isomers. The 4,5-diphenylformyl-1-cyclopentene was formed solely as the trans isomer. The major products are thus the ones expected on the basis of the normal stereochemistry of the Cope rearrangement.

Conia and co-workers (5), in an attempt to obtain medium rings by the Cope rearrangement, tried the following divinylglycols, which they hoped would force the reaction in the desired direction by the enol-keto tautomerism. The desired diketone was formed only in the open chain example. The aldol product was the only product formed by the cyclic divinyl-diols.

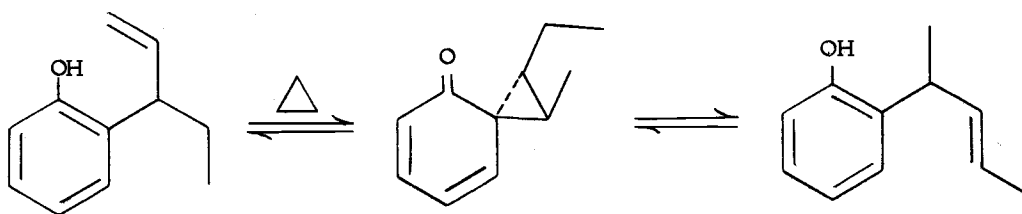


These are the only references found dealing with the so-called "oxy-Cope" rearrangement. Two reactions, the enolene rearrangement and the β -hydroxyolefin cleavage, have been mentioned as side reactions in some of the preceding examples.

The "enolene" rearrangement was discussed thoroughly by Roberts and co-workers (32). They have shown that the reaction is a general type of thermal equilibrium between acyclic enones and cycloalkyl ketones where the equilibrium is strongly dependent on

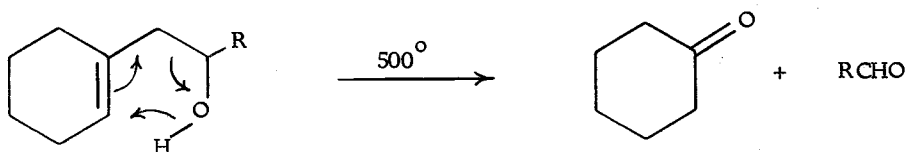


ring size. Specific examples are cited within the body of their paper. An example of an "enolene" rearrangement was found by Marvell and co-workers (26, 27) to be the second step in the "abnormal Claisen rearrangement."

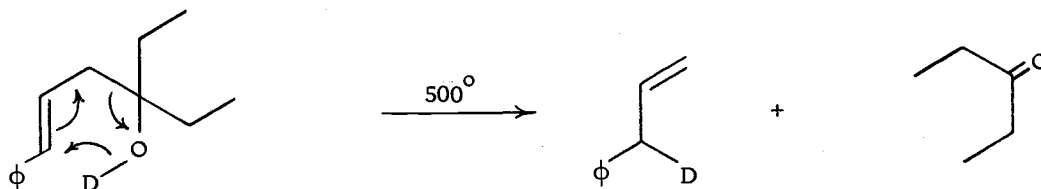


The β -hydroxyolefin cleavage was first investigated by Arnold and Smolinsky (2) to determine the mechanism of the following

pyrolysis. They (1) showed by deuterium labeling that the six center



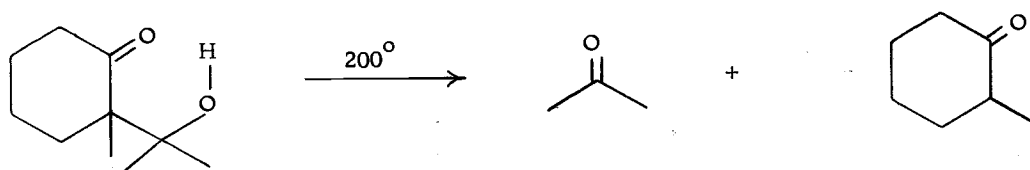
transition state was probably correct. Smith and Taylor (35) showed



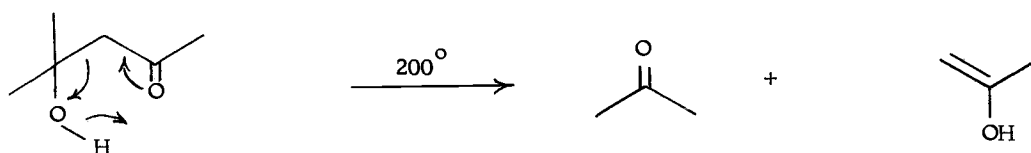
that the reaction followed first order kinetics. In a later study, Smith and Yates (37) showed that this reaction proceeds by a homogeneous, non-radical process. They based their observations on the products formed, volume-to-surface ratio changes, and inhibitor studies.

β -Hydroxy ketones (and aldehydes) are essentially the oxygen analog of the β -hydroxyolefins. It might then be expected that a cleavage of these keto-alcohols would also be observed. That this is the case is shown by studies of the thermal retrograde aldol condensation. Mole (29) realized this cleavage reaction in 1960. He found that the rate was first order and was independent of the type of glass used for the reaction bombs (silica or Pyrex), which indicates that heterogeneous catalysis was unlikely. He also found that the rate in petroleum ether was unaffected by addition of small amounts of

pyridine or acetic acid. Smith and Yates (36) also showed that the



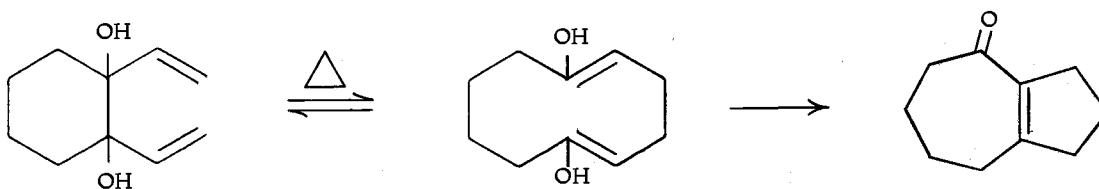
rate of this reaction was first order. They proposed a cyclic transition state for the cleavage.



DISCUSSION

Introduction

The synthetically valuable formation of cyclodecadienes from divinylcyclohexanes cannot be achieved because of an unfavorable equilibrium (17, 25). In an attempt to overcome this problem, the thermal behavior of 1,2-divinyl-1,2-cyclohexanediol was studied. The enol-keto conversion was expected to permit the isolation of 1,6-cyclodecanedione. Instead, 1(7)-bicyclo[5.3.0] decen-2-one was obtained (5, 11, 23), which suggests the Cope rearrangement was followed by an aldol condensation. Although Conia and co-

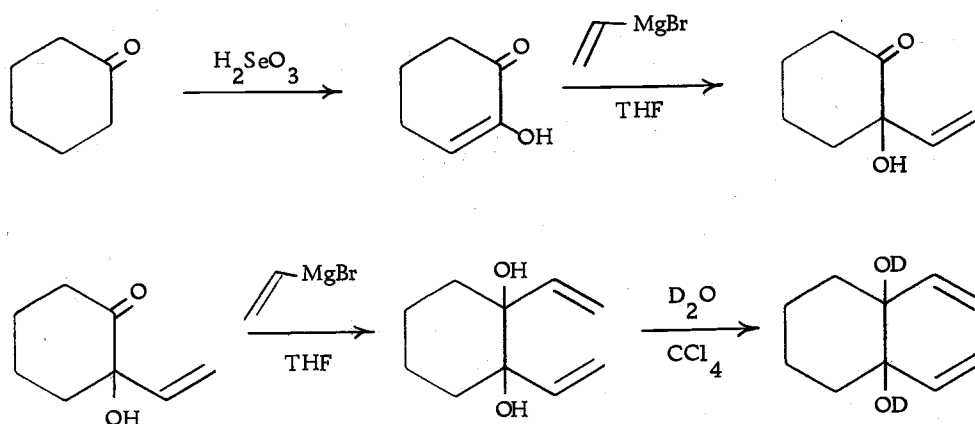


workers (5) postulated that the aldol product was formed from 1,6-cyclodecanedione, we assumed that it was formed without formation of the dione. This assumption was based on the expectation that the thermal aldol condensation can occur as a purely intramolecular process. Since the Woodward-Hoffmann theory suggests that 1,3-hydrogen shifts are stereochemically forbidden as a concerted process, the enol-keto conversion step might be expected to be either

bimolecular or a wall reaction and therefore slower than the aldol step. In order to learn more about the processes following the Cope rearrangement, we have studied the rearrangement of 1,2-divinyl-1,2-dideuteriocyclohexane.

Synthesis of 1,2-Divinyl-1,2-dideuteriocyclohexane

The route to the labeled starting material is shown by the following reaction sequence.



The 1,2-cyclohexanedione was prepared according to the procedure of Organic Syntheses (18). The infrared spectrum shows that 1,2-cyclohexanedione exists predominantly in the enol-keto form (OH band at 3400 and $\text{C}=\text{C}-\text{C}=\text{O}$ bands at 1670 and 1650 cm^{-1} , ref. 30). Thus four moles of vinyl magnesium bromide must be used to add the two vinyl groups.

Vinyl Grignard addition was made according to the procedure of

Dietz (11). The crude reaction mixture from the first addition was used directly for the second step without purification. The infrared spectrum of 1,2-divinyl-1,2-cyclohexanediol agreed in all respects with that of a sample prepared by Dietz. The spectrum shows a strong, broad OH band at 3500 cm^{-1} and the normal bands for a vinyl group at 3080, 3020, 1645, 990, and 910 cm^{-1} (30). Both the cis and trans isomers appear to be present since gas chromatographic analysis shows two partially separated bands of nearly equivalent area. The compounds were isolated by preparative glc and their infrared spectra were identical except for the heights of a few minor bands (1115, 1060, and 1020 cm^{-1}).

Deuterium exchange was carried out immediately prior to each rearrangement. The infrared spectrum of the 1,2-divinyl-1,2-dideuteriocyclohexane showed a strong, broad band at 2550 cm^{-1} for OD and no observable OH band at 3500 cm^{-1} (30).

Thermal Reactions

A first trial run was carried out by heating a 20% solution of the dideuteroxy compound in cyclohexane for 60 hours at 210° in a sealed tube. A pure sample of 1(7)-bicyclo[5.3.0] decen-2-one was isolated by preparative glc and analyzed by mass spectrometry. Unfortunately the analyst erred and used a 70 ev ionization voltage, which resulted in a cracking pattern involving the M-1 and M-2 peaks.

Thus the data are only of qualitative value. However, the terminal or dehydration step is expected to give rise to a molecule of water containing at least one hydrogen atom. Thus exposure of the starting material to this would result in exchange with the deuterioxy groups and loss of label in the starting material. Since the crude mass spectral data indicated that a large amount of the product contained no deuterium and the overall recovery of label in the product was 0.9 D/molecule, it was assumed that this mode of reaction permitted too much exchange.

To minimize the exchange process a flow reactor was designed to permit a vapor phase reaction at low concentration and short contact time. That apparatus is shown in Figure 1. Again the mass spectral data were taken under cracking conditions, but the crude results suggested that exchange was still an overly important part of the reaction. Eventually it was found that the material in the vaporization chamber was rearranging slowly before vaporization.

To eliminate this problem, a type of falling film molecular still was designed and constructed. It is depicted in Figure 2. This apparatus allowed the starting material to be vaporized at a low temperature and with a short contact time on the heated surface. It also permitted a check on the deuterium content of unvaporized starting material. No exchange or rearrangement took place during the vaporization process in any of the "falling film flow reactions." The

enone was trapped in a condensing unit and was purified via gas chromatography.

Product Identification

Only three products were isolated from these reactions. The main product under most conditions was 1(7)-bicyclo[5.3.0] decen-2-one. The other two products were obtained under milder conditions and were identified as cis and trans 7-hydroxybicyclo[5.3.0] decen-2-one.

The ultraviolet spectrum of 1(7)-bicyclo[5.3.0] decen-2-one shows an absorption at 250 $m\mu$, which corresponds to a calculated value of 254 $m\mu$ (13). The bands at 1645 and 1625 cm^{-1} in the infrared spectrum correspond to an α, β -unsaturated ketone (30). The nmr spectrum shows a multiplet at 2.5 ppm, which is due to the eight protons located on carbons 3, 6, 8, and 10. The remaining six protons (located on carbons 4, 5, and 9) appear as a multiplet at 1.85 ppm. This substance forms an oxime, mp 133-134°, which is in agreement with the melting point reported (5) for this derivative.

Two compounds found primarily in certain of the flow reactions were identified principally by spectral data as cis and trans 7-hydroxybicyclo[5.3.0] decan-2-one. The two substances could be separated via glc and samples were collected by preparative glc. The first peak gave a solid, mp 65-85° (d), while the second isomer was a

liquid. Both compounds tend to lose water on passage through the gas chromatograph. Thus ultraviolet spectral examination always disclosed contamination by unsaturated ketone. As far as can be ascertained by glc analysis, the product of the rearrangements contains about equal amounts of each isomer.

The spectra of the two isomers were essentially identical. The infrared spectra contained a broad OH band at 3490 cm^{-1} , aliphatic CH, and a ketone band at 1695 cm^{-1} (30). The nmr spectra showed a multiplet at 3.0 ppm due to the proton in the 1 position, a multiplet at 2.4 ppm corresponding to the six protons on carbons 3, 6, and 8, a multiplet at 1.75 ppm due to the eight protons on carbons 4, 5, 9, and 10, and a singlet at 2.0 ppm which shifts with concentration changes corresponding to the hydroxyl proton (13).

An oxime was prepared using the method of Hückel (21), which was identical with the oxime of 1(7)-bicyclo[5.3.0] decen-2-one. This indicates the carbon skeletons for these two isomers, and in view of the spectral data and the easy loss of water, these are assigned the indicated structures. Owing to the ease of loss of water it was not possible to obtain both isomers analytically pure. However, one sample of the liquid isomer was obtained which gave a correct analysis.

Bicyclo[5.3.0] decan-2-one

Valuable information could be obtained from the labeled 1(7)-bicyclo[5.3.0] decen-2-one if the positions occupied by the deuterium were known. Unfortunately there appears to be no simple means of ascertaining the positions of all the deuterium labels. However, a simple procedure is available for determining the amount of deuterium on C₃. Reduction of the enone to a saturated ketone would leave only the deuterium at C₃ in an enolizable, hence exchangeable, position. For this purpose a procedure designed by Djerassi (33) and shown to cause no loss of deuterium from a γ -carbon was employed. The enone was reduced with lithium in liquid ammonia, and any alcohol obtained was reoxidized with Jones reagent (14).

Bicyclo[5.3.0] decanone obtained in this fashion is expected to be predominantly the trans isomer. Both cis and trans isomers are known (10, 16) and a sample of the cis isomer was prepared by the procedure of Cope and Holzman (10). Glc analysis showed that the sample obtained in our work contained 80-85% of the trans isomer. In accord with this result the 2,4-dinitrophenylhydrazone of our product melted at 219.5-220° (10). The derivative of the cis isomer melts at 162-163° (10).

Results of Labeling Experiments

The 1(7)-bicyclo[5.3.0] decen-2-one isolated from the reactions in the gas phase flow reactor was analyzed by mass spectrometry for deuterium content. The ionizing voltage was set at a level which minimized M-1, M-2, etc., peaks. Correction for natural isotopic abundance was made in the usual fashion (24). Each sample was then reduced to the saturated ketone, the alpha deuterium was removed by treatment with methoxide ion in methanol, and the mass spectral analysis of the glc purified ketones was determined. The data for the three runs which proceeded properly are given in Table 1. All of these runs were made using the falling film vaporization technique and were shown to proceed without loss of label or rearrangement during the vaporization process.

Table 1. Comparison of 1(7)-Bicyclo[5.3.0] decen-2-one (A) and Bicyclo[5.3.0] decan-2-one (B).

Reaction	Vaporization Temp.	Pressure	Reaction Temp.	0-D	1-D	2-D	3-D
3D-A	82° C	4.0 mm	350° C	35	39	19	6
3D-B				34	51	12	1
4D-A	63° C	1.5 mm	350° C	23	41	26	8
4D-B				27	47	16	2
5D-A	63° C	1.0 mm	350° C	29	37	24	8
5D-B				35	40	16	3

Interpretation of the Data

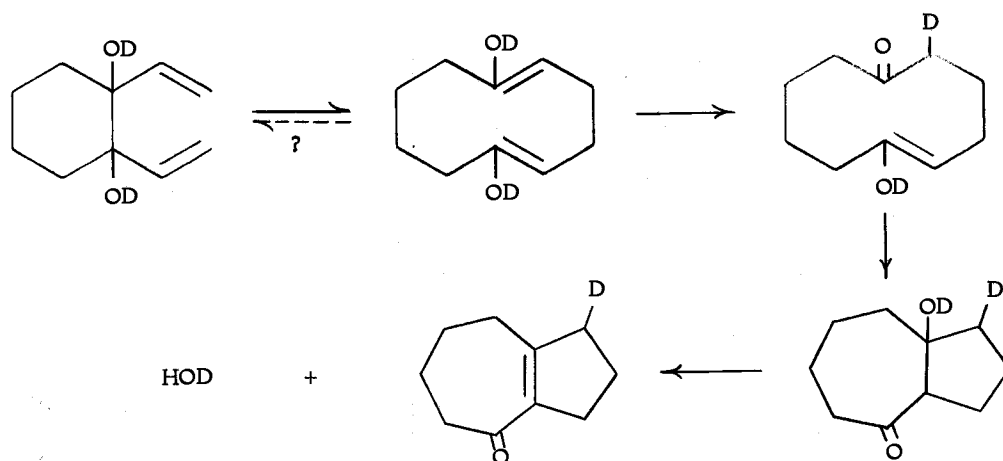
A considerable degree of caution must be used when trying to interpret these data. The extreme rapidity with which hydrogen attached to oxygen undergoes exchange means that any OH group which appears in the reaction system will dilute the amount of labeled material. The effect this will have on the deuterium content of the product will be a function of the isotope effect, which will, in turn, be a function of the mechanism. As was noted earlier, a certain amount of HOD must be formed during the reaction, so some loss of label is inevitable. Thus it is not possible to give a quantitative significance to the relations between amounts of the variously labeled species and mechanisms of their formation.

Primary attention must be given, therefore, to the fact that species with certain numbers of deuterium atoms per molecule are present in significant amounts and to the positions occupied by the labels. Thus the mechanisms proposed must account for a) the presence of monodeuterated product which contains no deuterium at C_3 , b) the dideuterated product is also present but contains ca. 55-67% of molecules having one deuterium at C_3 and ca. 33-45% having no deuterium at C_3 , and c) trideuterated molecules are present and generally contain one deuterium at C_3 .

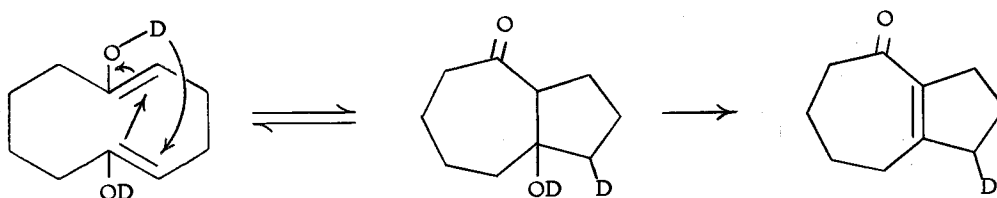
Some Mechanistic Proposals

The original impetus for this work was based on the mechanistic idea that the Cope rearrangement would be followed by one slow enol-keto rearrangement occurring as a bimolecular or wall reaction. This mono-enol mono-keto intermediate would undergo a rapid, and probably irreversible, thermal intramolecular aldol condensation, and the aldol product would lose water to form the observed product. This mono-enol mono-keto mechanism is illustrated in Scheme 1. A

Scheme 1



modification of this mechanism involves direct reaction of the bis-enol via an "enolene" rearrangement (Scheme 2). In terms of the labeling technique this is fully equivalent to mechanism 1 and need not be considered separately.

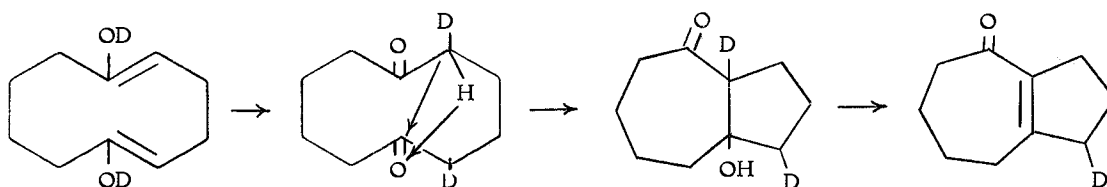
Scheme 2

As is noted in the Historical section, the previous studies of thermal aldol condensations all relate to the retrograde reaction (29, 36). In the present case, however, both forward and reverse reactions are intramolecular, and the forward direction is favored because of the instability of the cyclodecadiene ring. Similarly, the "enolene" process is moving in a direction favored thermodynamically.

Either modification of this mechanism is untenable in terms of the present results. Both are capable of accounting for the mono-deuterated product containing no deuterium at C_3 . Each could rationalize the non-deuterated product since exchange leading to loss of label would be sufficient to produce such material. However, neither can give rise to doubly- or triply-labeled product, and neither can rationalize the formation of product labeled at C_3 .

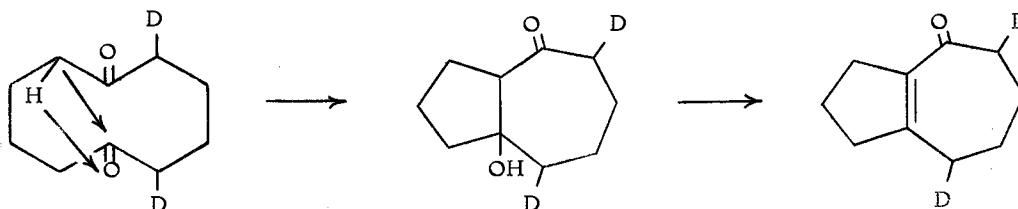
The intervention of 1, 6-cyclodecanedione as envisioned by Conia raises the question of what this proposal intends with respect to the mechanism of the step following the formation of the dione. If direct addition of the alpha carbon and an attached hydrogen to the other carbonyl group is considered (Scheme 3), it must be noted that

Scheme 3



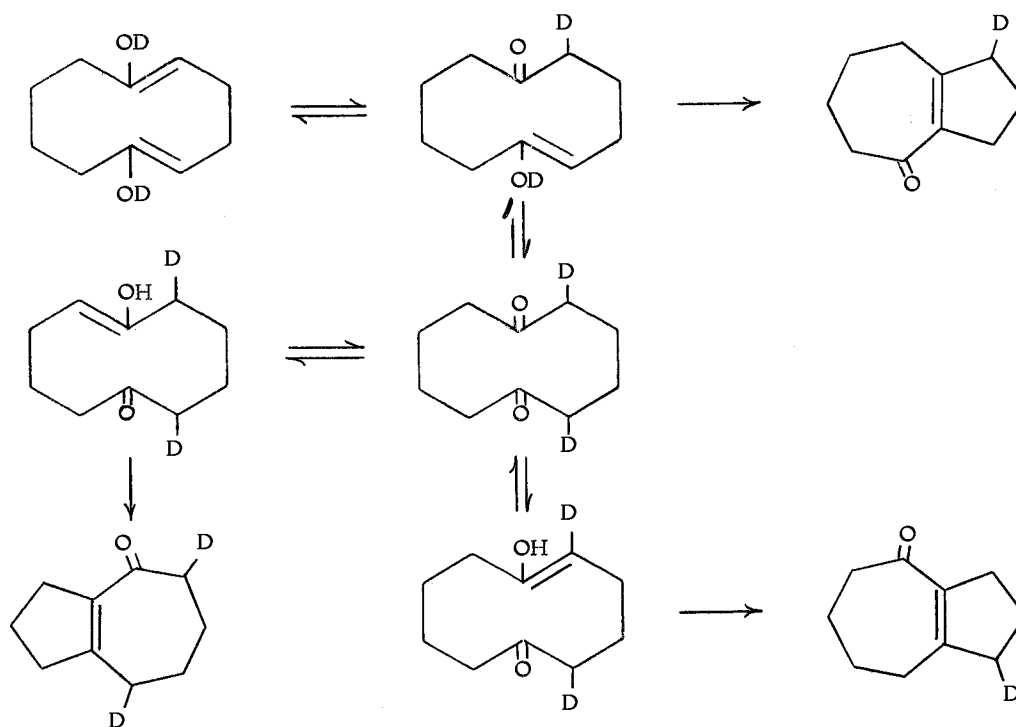
to the extent this resembles orbitally the symmetric addition of a carbon-carbon single and double bond, the concerted thermal process should be forbidden by the Woodward-Hoffmann theory (20, 49, 50). It is also rendered untenable by our data since it must lead either to the monodeuterated product (Scheme 3) or to dideuterated product exclusively labeled at the C₃ and C₆ positions (Scheme 4).

Scheme 4

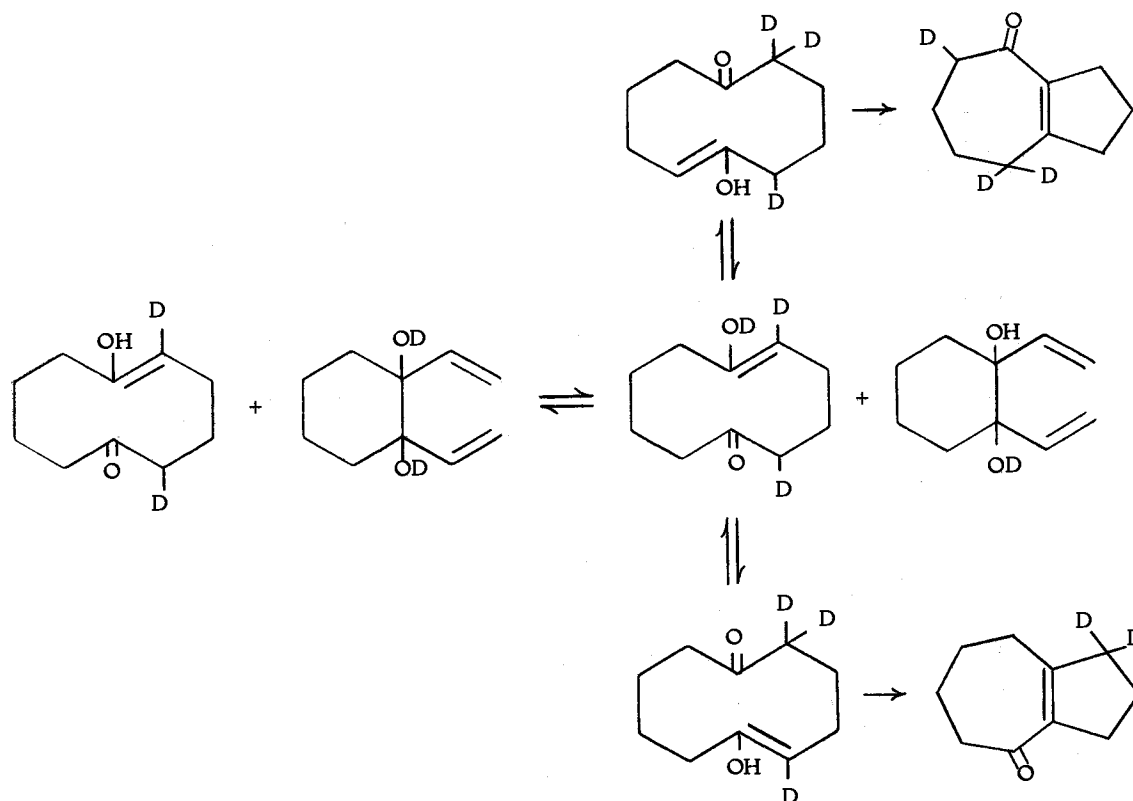


A second process relating to the dione intermediate would incorporate a reversal to the mono-enol mono-keto intermediate followed by the thermal aldol step (Scheme 5). This process is mechanistically equivalent to mechanism 1 with the addition of a reversible enol-keto tautomerism preceding the aldol reaction. On the surface it would appear to be excluded for the same reasons as was the reaction of Schemes 3 and 4. However, this is not the

Scheme 5



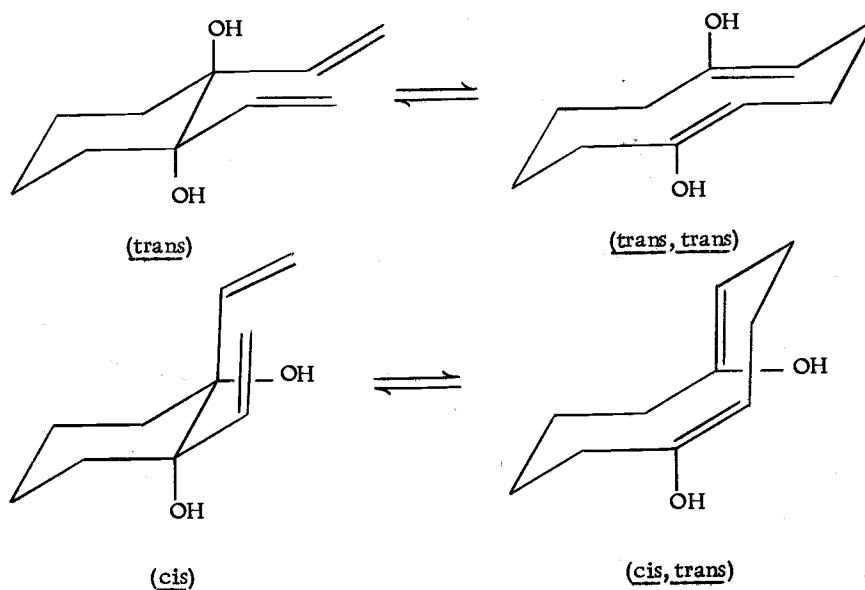
case since the rapid exchange between OH and OD species must also be considered. That this added step can accommodate the formation of both triply-labeled and doubly-labeled product with no label at C_3 is shown in Scheme 6. This appears to provide the best rationale for the data obtained in this work. Unfortunately it does not answer the question of whether the enol-keto conversion is an intramolecular concerted process or a bimolecular reaction.

Scheme 6

In the course of this work, two other observations were made which have a bearing on the mechanism of the reaction. The first of these concerns the reversibility of the Cope rearrangement step. All of the reactions were carried out with a mixture composed of nearly equal parts of the cis and trans isomers of the starting material. It was noted that these two isomers disappear at nearly equal rates. In view of the stereospecific nature of the Cope rearrangement (12), this would not be expected. The chair form transition states should be preferred and would lead in each case to different isomers of

1,5-cyclodecadien-1,6-diol, as shown in Scheme 7. Reversal should

Scheme 7

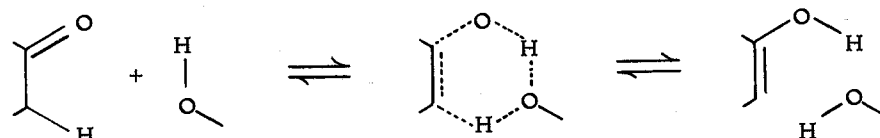


follow the same stereopath and thus no interconversion of the two isomers should be possible. However, if both bis-enols are rapidly and reversibly converted to the dione, overall equilibrium between the isomers of the starting material and dione would result in this interconversion. This would account for the result actually observed.

Finally it was found that a sample of 1,6-cyclodecanedione heated in cyclohexane solution at 210° failed to undergo any measurable conversion to 1(7)-bicyclo[5.3.0]decen-2-one. This would imply that the keto-enol interconversion is not a wall reaction and that the presence of hydroxyl groups is required for the hydrogen shift to occur. A convenient bimolecular mechanism for this catalysis of the

thermal keto-enol isomerization is shown in Scheme 8. This involves the now very familiar six-membered ring transition state.

Scheme 8



EXPERIMENTAL

1,2-Cyclohexanedione

This compound was prepared according to the procedure of Organic Syntheses (18). Selenious acid (H_2SeO_3 , 193.5 g, 1.495 moles) was dissolved in dioxane (250 ml) and water (50 ml). This solution was slowly added to 854 g of cyclohexanone (8.7 moles) at 0° . The reaction mixture was stirred for 5 hrs at 0° and then for 6 hrs at 25° . The dioxane, water, and unreacted cyclohexanone were removed by distillation. The product was distilled, bp 90° (16 mm); 98 g (10.8%); ir (CCl_4) 3600, 3400 (broad), 3020, 2920, 2850, 1720, 1670, 1650 cm^{-1} .

1,2-Divinyl-1,2-cyclohexanediol

The procedure used for this preparation was that given by Dietz (11). Magnesium turnings (18.85 g, 0.72 g atom) were placed in a 1 l. flask and covered with 100 ml of dry peroxide-free tetrahydrofuran (THF). Vinyl bromide (55 ml, 0.78 mole) was slowly added under nitrogen atmosphere over a 30-min period. The solution was kept at 0° during the addition. The mixture was allowed to warm to 25° and was stirred for 2 hrs. It was again cooled to 0° and 33.65 g (0.324 mole) of 1,2-cyclohexanedione in 100 ml of THF was added over a 30-min period. The mixture was allowed to warm

to room temperature and was stirred for 8 hrs. Most of the THF was distilled, the residual material was cooled to 0° , and saturated ammonium chloride solution and ice were added. The product was extracted with diethyl ether and dried (MgSO_4). The ether was evaporated, leaving 36.8 g (81.5%) of 2-hydroxy-2-vinylcyclohexanone; ir (neat) 3450 (broad), 3080, 3020, 1700, 1645, 990, and 910 cm^{-1} .

The crude product was used directly in the next reaction. Vinyl magnesium bromide was prepared from 18.85 g (0.72 g atom) of magnesium and 55 ml (0.78 mole) of vinyl bromide as described above. To the cold solution was added 36.8 g (0.265 mole) of 2-hydroxy-2-vinylcyclohexanone. The reaction mixture was worked up as described above, giving a crude yield of 39.5 g (89.5%). The 1,2-divinyl-1,2-cyclohexanediol was distilled, bp 120° (0.5 mm); ir (neat) 3500 (broad), 3080, 3020, 1645, 990, and 910 cm^{-1} . The spectrum is identical with that of the product obtained by Dietz (11).

1,2-Divinyl-1,2-dideuteroxycyclohexane

The dihydroxy compound (1 g, 6.3 mmoles) was dissolved in carbon tetrachloride and placed in a septum-covered flask. Deuterium oxide was added via a syringe and the flask was shaken briefly. The aqueous layer was withdrawn with a syringe. This was repeated until the carbon tetrachloride solution showed no OH bands at 3500 cm^{-1} .

in the infrared spectrum. The carbon tetrachloride was distilled and the residual 1,2-divinyl-1,2-dideuteroxycyclohexane was used immediately for the Cope rearrangements; ir (CCl_4) no OH band at 3500 cm^{-1} , strong OD band at 2550 cm^{-1} .

Bomb Reactions

A solution containing 20% of 1,2-divinyl-1,2-dideuteroxycyclohexane (0.3 g, 1.9 mmol) in cyclohexane was heated in a thick-walled Pyrex bomb for 60 hrs at 210° . Gas chromatography on a 5.5 ft (5% FFAP on Chromosorb G) column showed only one major peak. The product purified by glc showed: UV (MeOH) λ_{max} 250, $\epsilon = 3162$; ir (neat) 2920, 2840, 1640, 1625, 1430, 1380, 1350, 1335, 1265, 1050, 900 cm^{-1} ; nmr (CCl_4) δ 1.85 (m, 6), 2.5 (m, 8) ppm.

An oxime was prepared by heating 100 mg of the purified material with 200 mg of hydroxylamine hydrochloride, 3 ml of dry pyridine, and 3 ml of absolute ethanol. The solution was evaporated to dryness and the residue was washed with water. The oxime was recrystallized from methanol/water, mp $133\text{--}134^\circ$ (5).

Flow Reactions

The apparatus shown in Figure 1 was constructed. It was washed with bicarbonate solution, carbon dioxide-free distilled water, and acetone. A series of reactions was carried out under the

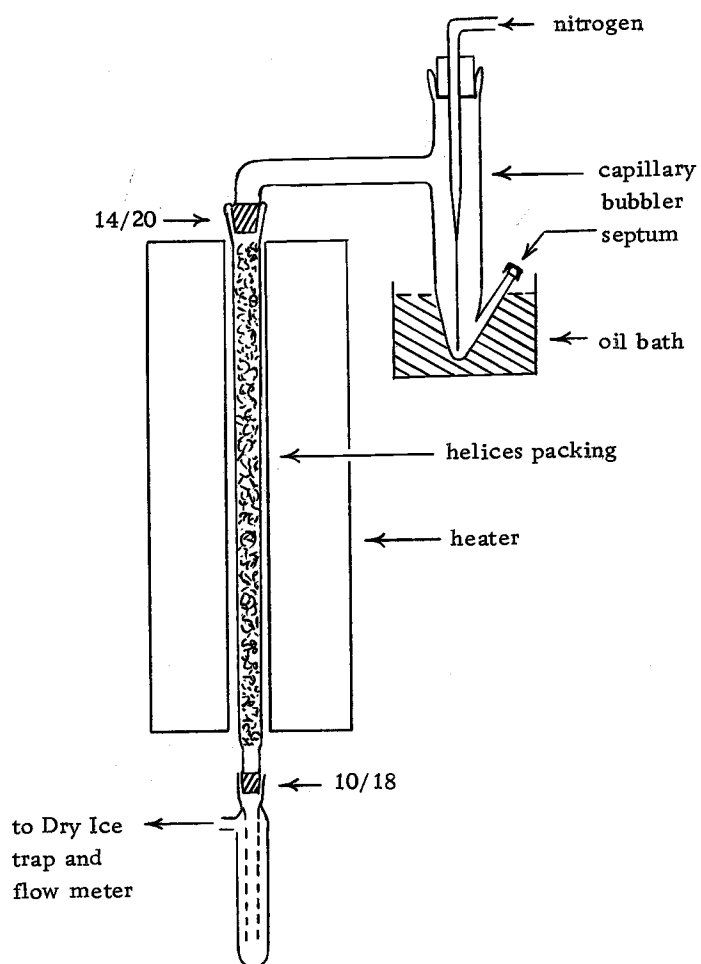


Figure 1. Flow reaction apparatus.

conditions listed in Table 2. Each reaction used 1 g (6.3 mmoles) of the divinyl-diol.

Table 2. Results of Flow Reactions.

Run	Temperature °C			Flow Rate	Conc.	Product* %		
	Bath	Connecting Arm	Heater			A	B	C
FR-1H	130	60	305	1 ml/12 sec	?	18	40	36
FR-2H	130	60	305	2 ml/3 sec	0.4 g/l.	15	52	28
FR-3H	110	60	305	10 ml/35 sec	0.2 g/l.	0	54	37
FR-4D	110	60	305	10 ml/35 sec	0.2 g/l.	-	-	-
FR-5D	110	60	305	10 ml/35 sec	0.2 g/l.	0	55	40
FR-6D	110	60	305	10 ml/35 sec	0.2 g/l.	-	-	-
FR-7D	110	60	305	10 ml/35 sec	0.2 g/l.	-	-	-
FR-8H	110	60	305	10 ml/35 sec	0.2 g/l.	5	60	30
FR-9H	110	60	305	10 ml/35 sec	0.2 g/l.	15	25	55

* Calculated from areas under glc peaks, A = cis and trans starting material, B = 1(7)-bicyclo [5.3.0]-decen-2-one, and C = cis and trans 7-hydroxybicyclo [5.3.0] decan-2-one.

The products were trapped and then separated via glc using a 15 ft (5% FFAP on chromosorb G) column. The two peaks of product C were collected together: ir (CCl_4) 3490 (broad), 2920, 2840, 1695, 1640, 1500, 1450, 1325 cm^{-1} ; nmr (CCl_4) δ 1.75 (m, 9), 2.0 (s, 1), 2.4 (m, 6), and 3.0 (m, 1) ppm. An oxime was prepared using the conditions of Hüffel (21). Approximately 5 mg (3.2×10^{-6} moles) of 7-hydroxybicyclo[5.3.0] decan-2-one was dissolved in 100 mg of methanol. Hydroxylamine hydrochloride (10 mg) and sodium acetate (12.5 mg) were dissolved in 60 mg of water and added to the methanol solution. The mixture was warmed for 5 min and then evaporated to

dryness. The residue was washed with water, leaving 3 mg of a waxy solid. Thin layer chromatography (silica gel PF254 and 20% diethyl ether/pentane) showed only one spot, which had the same R_f value as the oxime of 1(7)-bicyclo[5.3.0] decen-2-one.

A sample of each isomer of the keto-alcohol was collected via glc. Ultraviolet spectra of both isomers indicated contamination by 1(7)-bicyclo[5.3.0] decen-2-one. One isomer was a solid, mp 65-85° (d). Both isomers were analyzed but only the liquid isomer gave values in agreement with those expected.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59

Found: C, 71.40; H, 9.45

Falling Film Flow Reactions

A type of falling film molecular still was designed and constructed. It is shown in Figure 2.

The hot finger was heated by means of a constant temperature hot-water bath and pump. The apparatus was covered with asbestos in which a heating wire was embedded. In operation, the starting material was injected into the dropping funnel, and by careful control of the stopcock this material was allowed to drip slowly onto the coils.

A series of six flow reactions was run using the conditions tabulated in Table 3. All runs were started with 1 g (6.3 mmoles) of

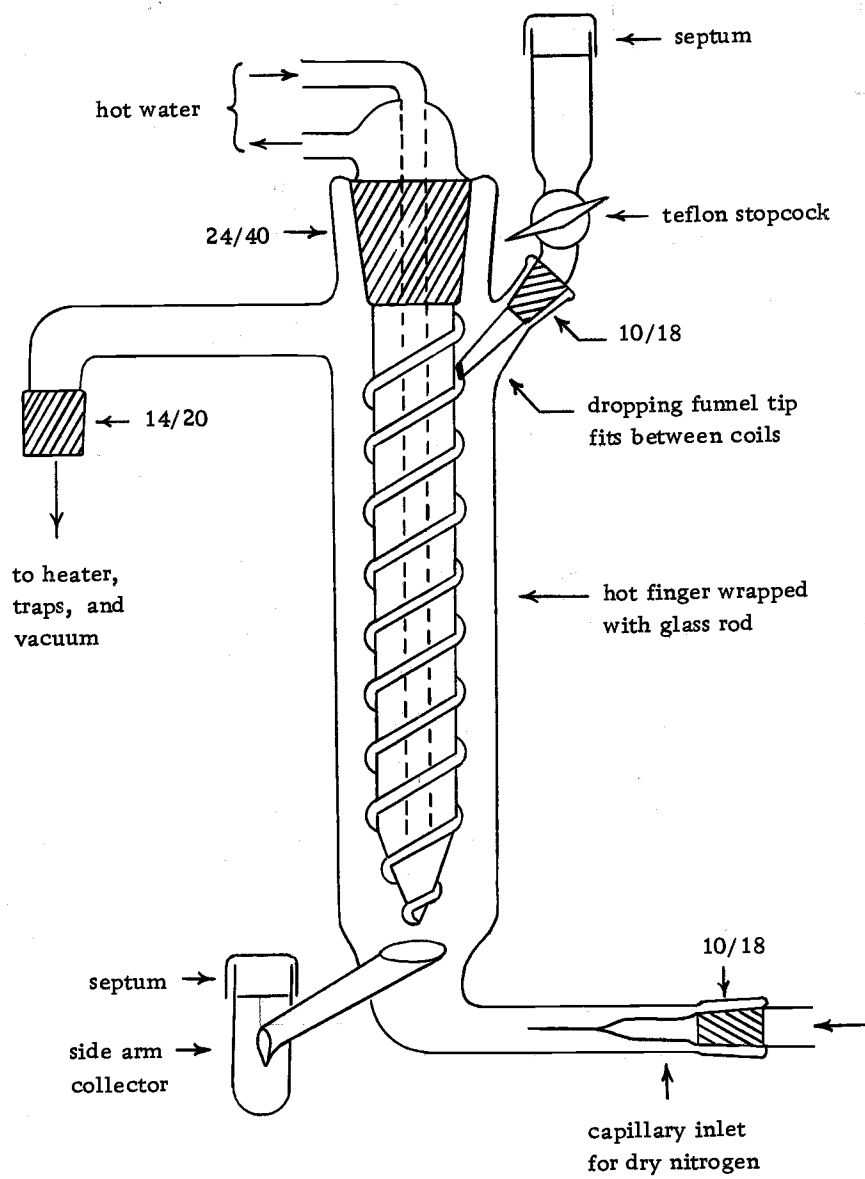


Figure 2. Falling film molecular still.

completely deuterated divinyl-diol. In all cases the jacket temperature was 70° and the reactor temperature was 350°. Product was purified by glc and analyzed via mass spectrometer.

Table 3. Falling Film Flow Reactions.

Rxn	Water Temp. for Hot Finger	Vacuum (mm)
1D	70°	2.5
2D	82°	2.0
3D	82°	4.0
4D	63°	1.3
5D	63°	1.1
6D	57°	0.4

Bicyclo[5.3.0] decan-2-one

The procedure used was adapted from that of Djerassi (33). Fifty milliliters of liquid ammonia was placed in a 100 ml flask. Lithium metal (225 mg, 0.035 g atom) was dissolved in the ammonia, the flask being cooled with a Dry Ice/acetone bath during the process. The 1(7)-bicyclo[5.3.0] decen-2-one (31 mg, 0.20 mmole) was dissolved in 20 ml of dry diethyl ether and added to the lithium/ammonia solution over a period of 20 min. The cold bath was removed and the mixture was allowed to reflux for 1.5 hrs. Ammonium chloride (3.0 g) was then added, followed by 50 ml of diethyl ether, and the ammonia was allowed to evaporate. Water was added and the ether layer was separated. The aqueous layer was extracted with diethyl

ether and the ether layers were combined. These were washed with 5% hydrochloric acid, saturated sodium bicarbonate, and finally distilled water.

The ether was evaporated and the residual material was dissolved in 30 ml of acetone. Jones reagent (14) was added to the acetone solution dropwise at 20° until an orange color persisted. The solution was stirred for 3 hrs, and the excess oxidizing agent was destroyed by the dropwise addition of isopropyl alcohol. Saturated sodium bicarbonate was added until the mixture was neutral, and the acetone was evaporated. The residual solution was extracted with ether. The ether solution was dried (MgSO_4) and concentrated.

The residue was dissolved in 20 ml of methanolic potassium hydroxide (0.05N), and the solution was refluxed for 2 hrs. Cold water (20 ml) was added and the base was neutralized with 5% hydrochloric acid. The methanol was evaporated and the residual aqueous solution was extracted with diethyl ether. The ether extract was dried (MgSO_4) and concentrated. The bicyclo[5.3.0] decan-2-one was purified via column chromatography over alumina (activity 2). The desired ketone eluted with 50% ether/pentane; 5.5 mg (17.6%); ν (CCl₄) 2920, 2860, 1705, 1480, 1350, and 1320 cm^{-1} .

A 2,4-dinitrophenylhydrazone was prepared according to the directions of Cope and Holzman (10). The ketone (9.2 mg) was added to a hot solution of 0.02 g of 2,4-dinitrophenylhydrazine in 1 ml of

glacial acetic acid. Addition of a few drops of water gave a precipitate, which was recrystallized from absolute ethanol giving orange needles, mp 219.5-220° (Thomas hot-stage microscope).

A sample of cis-bicyclo[5.3.0] decan-2-one was prepared by the method of Cope and Holzman (10). Catalytic hydrogenation of 1(7)-bicyclo[5.3.0] decen-2-one (74 mg) over Pd/C in methanol gave 61 mg of product. The ketone prepared by the lithium/ammonia reduction gave two peaks on the gas chromatograph (85-90% at 91 mm retention time and 10-15% at 85 mm). The ketone prepared by catalytic hydrogenation also gave two peaks at 91 mm (10%) and 85 mm (90%). A mixture of the two showed only the two peaks at 91 mm and 85 mm.

Mass Spectral Data

The mass spectral data from all reactions have been compiled in Table 4. Analyses of BR-3D, FR-5D, and FFFR-1D were carried out using an ionizing voltage of 70 ev and 10 μ a. The remainder were run at 10 ev and 5 μ a. Percentages were calculated from corrected peak heights (24).

Table 4. Isomer Percentages.

Reaction Product	Percentages of m/e Peak							
	149	150	151	152	153	154	155	156
BR-3D	7	34	36	18	5	1	-	-
FR-5D	7	24	49	16	3	0	-	-
FFFR-1D	7	23	44	21	5	1	-	-
FFFR-2D	2	37	43	15	4	0	-	-
FFFR-3D	0	35	39	19	6	0	-	-
FFFR-4D	1	23	41	26	8	2	-	-
FFFR-5D	1	29	37	24	8	1	-	-
FFFR-6D	2	46	30	15	5	1	-	-
Non-D	0	91	8	1	0	0	-	-
FFFR-3D-Sat.	-	-	2	34	51	12	0	0
FFFR-4D-Sat.	-	-	3	27	47	16	2	1
FFFR-5D-Sat.	-	-	3	35	40	16	3	0
Non-D-Sat.	-	-	1	95	1	0	0	0

1, 6-Cyclodecanedione

The dione was prepared according to the procedure of Cope and Holzman (10). Decalin (1 l., 6.5 moles) was heated to 130° and oxygen was introduced at the rate of 60 ml/min. Benzoyl peroxide (15 g, 0.15 mole) was added in 1 g portions every 15 min until the total amount had been added. The flask was heated for an additional 10 min after the last addition and then cooled rapidly in an ice bath. The decalin solution was washed with 10% sodium hydroxide. The red color in the decalin solution was removed by washing with ethylene glycol. Finally the colorless solution was washed with 10% sulfuric acid solution, washed with water, and dried (Na_2SO_4). The

peroxide was isolated by column chromatography (silica gel, 500 g). Decalin was eluted with hexane, and the trans-9-decalylhydroperoxide was eluted with methylene chloride. The methylene chloride was evaporated, leaving 26.8 g (1.4%, 0.15 mole) of crude peroxide.

This material was dissolved in 40 ml of pyridine and cooled to 10°. Benzoyl chloride (30 g, 0.3 mole) was added over a period of 15 min. The mixture was poured into 400 ml of cold 10% sulfuric acid, and the product was extracted with diethyl ether, giving 44 g (98%, 0.16 mole) of trans-9-decalylhydroperoxide benzoate.

The benzoate was refluxed in 5 g quantities in methanol for 1 hr. The methanol was evaporated, giving 44 g of crude product, which was dissolved in a solution containing 11.2 g of potassium hydroxide in 800 ml of methanol and 20 ml of water. The reaction mixture was refluxed for 4 hrs on a steam bath, cooled, and neutralized with 10% sulfuric acid. The methanol was evaporated, the residue was made basic and extracted with methylene chloride. The solution was dried (Na_2SO_4) and concentrated, giving 28 g (100%). The 6-hydroxycyclodecanone (14 g) was purified by column chromatography (silica gel, 50% diethyl ether/pentane). The yield of pure material was 0.6 g (4.3%), mp 68.5-70°.

The 6-hydroxycyclodecanone was oxidized by the procedure of Meinwald, Crandall, and Hymans (28). 6-Hydroxycyclodecanone (0.3 g, 1.76 mmoles) was dissolved in 2 ml of acetone and cooled to

0°. Jones reagent was added dropwise until the orange color persisted for 15 min. Sodium bisulfite was added in small portions until the orange color disappeared. The reaction mixture was extracted with pentane. The solid left after evaporation of the pentane was recrystallized from ethanol (7 mg, 2.3%), mp 99-99.5°; ir (CCl_4) 2920, 2880, 2860, 1700, 1680, 1640 (w), 1440, 1420, 1370, 1340, 1310, 1150, 1110 cm^{-1} .

Gas chromatography using either FFAP or SE-30 columns caused complete rearrangement of the dione on the column. Thin layer chromatography on silica gel and alumina also led to a rearranged product. An oxime was prepared according to the directions of Hückel (21). Two milliliters of methanol was added to the material (7 mg), and a solution containing 10 mg of hydroxylamine hydrochloride and 12.5 mg of sodium acetate in 60 mg of water was added. The material was warmed to 60° for 5 min. The mixture was cooled and a few drops of water were added. No crystals appeared, so the methanol was evaporated. A small quantity of crystals precipitated (2.8 mg, 30%). These melted at 224-226° after two recrystallizations from methanol/water (10).

A sample (7 mg) of dione was placed in a Pyrex bomb that had been washed with ammonium hydroxide, washed with carbon dioxide-free water, heated to a dull red, and cooled under dry nitrogen. One milliliter of cyclohexane was added, and the bomb was heated for

2.5 hrs at 210°. When the cyclohexane was evaporated the residue was crystalline, mp 80-90°. An infrared spectrum (pentane) showed a small band at 3400 cm^{-1} and unchanged carbonyl at 1700 cm^{-1} . An oxime was prepared as described above, mp 224-226° (10, 21).

Spectral Data

The infrared spectra were taken on a Perkin Elmer Model 21 and a Beckman IR-8 infrared spectrophotometer. A Varian A-60 NMR Spectrometer was used for the nmr spectra. The ultraviolet spectra were taken on Cary Model 15 and Beckman DB spectrophotometers. The mass spectral data were obtained by the use of an Atlas CH-4 mass spectrometer, courtesy of Dr. Leonard M. Libbey, Assistant Professor of Food Science and Technology, Oregon State University.

Carbon-Hydrogen Analyses

The carbon-hydrogen analyses were run by Frank A. Lehmkuhl, Graduate Assistant, Oregon State University.

BIBLIOGRAPHY

1. Arnold, Richard T. and Gerald Smolinsky. The mechanism of pyrolysis of β -hydroxyolefins. *The Journal of Organic Chemistry* 25:129-130. 1960.
2. Arnold, Richard T. and Gerald Smolinsky. The pyrolysis of β -hydroxyolefins. *Journal of the American Chemical Society* 81: 6443-6445. 1959.
3. Berson, Jerome A. and Joseph J. Gajewski. A synthesis of ketones by the thermal isomerization of 3-hydroxy-1,5-hexadienes. The oxy-Cope rearrangement. *Journal of the American Chemical Society* 86:5019-5021. 1964.
4. Berson, Jerome A. and Maitlan Jones, Jr. Stepwise mechanisms in the oxy-Cope rearrangement. *Journal of the American Chemical Society* 86:5017-5018. 1964.
5. Brown, Eric, Pierre Leriverend and Jean-Marie Conia. Les transpositions de Cope enologenes et bis-enologenes. *Tetrahedron Letters*, 1966, p. 6115-6119.
6. Chuche, Josselin and Joseph Wiemann. Stéréochimie de la transposition de Cope d'hexadiène-1,5-diols-3,4: étude de la jonction C₁-C₆. *Bulletin de la Société Chimique de France*, 1968, p. 1491-1497.
7. Chuche, Josselin and Joseph Wiemann. Transposition de Cope des éthane-diols α, α' -diéthyléniques du type R-CH=CH-CH(OH)-CH(OH)-CH=CH-R. *Comptes Rendus de l'Académie des Sciences (Paris)* 262:567-570. 1966.
8. Claisen, L. Über Umlagerung von Phenyl-allyl-äthern in C-Allylphenole. *Berichte* 45:3157-3166. 1912.
9. Cope, Arthur C. and Elizabeth M. Hardy. The introduction of substituted vinyl groups. V. A rearrangement involving the migration of an allyl group in a three carbon system. *Journal of the American Chemical Society* 62:441-444. 1940.

10. Cope, Arthur C. and George Holzman. Cyclic polyolefins. VIII. Reaction of 6-hydroxycyclodecanone and cyclodecan-1,6-diol p-toluenesulfonates. Journal of the American Chemical Society 72:3062-3068. 1950.
11. Dietz, Fred C. National Science Foundation Research Participant. Unpublished research on the Cope rearrangement. Corvallis, Oregon State University. 1965.
12. Doering, W. von E. and W. R. Roth. Thermal rearrangements. Angewandte Chemie, International ed. in English 2:115-122. 1963.
13. Dyer, John R. Applications of absorption spectroscopy of organic compounds. Englewood Cliffs, New Jersey, Prentice-Hall, 1965. 143 p.
14. Eisenbraun, E. J. Cyclooctanone. Organic Syntheses 45:28-32. 1965.
15. Gibson, Dorothy H. and R. Pettit. Vinylogous Cope rearrangements. The thermal isomerization of meso- and rac-5,6-dimethyl-trans,trans-1,3,7,9-decatetraene. Journal of the American Chemical Society 87:2620-2628. 1965.
16. Goering, Harlan L., Alfred C. Olsen and Herbert H. Espy. The solvolysis of 6-ketocyclodecyl p-toluenesulfonate and p-bromobenzenesulfonate. Journal of the American Chemical Society 78:5371-5374. 1956.
17. Grob, C. A. and P. Schiess. Valenzisomerisierungen bei cyclodeka-polyenen. Angewandte Chemie 70:502. 1958.
18. Hach, Clifford C., Charles V. Banks and Harvey Diehl. 1,2-Cyclohexanedione. Organic Syntheses 32:35-38. 1952.
19. Hammond, George S. and Charles D. DeBoer. Multiplicity of mechanisms in the Cope rearrangement. Journal of the American Chemical Society 86:899-902. 1964.
20. Hoffmann, Roald and R. B. Woodward. The conservation of orbital symmetry. Accounts of Chemical Research 1:17-22. 1968.
21. Hückel, Wälder, Achim Gercke and Albrecht Gross. Cyclodecan. Berichte 66:563-567. 1933.

22. Huntsman, William D. Reactions of diolefins at high temperatures. III. Reversible dissociation of 1,5-alkadienes and sensitization of cyclization by allyl bromide. *Journal of the American Chemical Society* 82:6389-6392. 1960.
23. Kinyon, Lenzie D. National Science Foundation Undergraduate Research Participant. Unpublished research on the Cope rearrangement. Corvallis, Oregon State University, 1966.
24. McLafferty, Fred W. Interpretation of mass spectra. New York, W. A. Benjamin, 1966. 229 p.
25. Marshall, James A. and Gordon L. Bundy. A new approach to medium-ring 1,5-dienes via alkylborane fragmentation. *Chemical Communications*, 1967, p. 854-855.
26. Marvell, Elliot N., D. Richard Anderson and Josephine Ong. Abnormal Claisen rearrangement. *The Journal of Organic Chemistry* 27:1109-1110. 1962.
27. Marvell, Elliot N. and Bruce Schatz. The abnormal Claisen rearrangement. II. High temperature chemistry of 1-ethyl-2-methylspiro[2.5] octa-4,6-dien-8-one. *Tetrahedron Letters*, 1967, p. 67-70.
28. Meinwald, J., J. Crandall and W. E. Hymans. Nortricyclanone. *Organic Syntheses* 45:77-79. 1965.
29. Mole, T. Thermal retro-aldol reaction. *Chemistry and Industry*, 1960, p. 1164-1165.
30. Nakanishi, Koji. Practical infrared absorption spectroscopy. San Francisco, Holden-Day, 1962. 233 p.
31. Rhoades, Sara J. Rearrangements proceeding through "no mechanism" pathways: the Claisen, Cope, and related rearrangements. In: *Molecular rearrangements*, ed. by Paul de Mayo. Vol. 1. New York, Wiley-Interscience, 1963. p. 655-706.
32. Roberts, Royston M., Robert G. Landolt, Robin N. Greene and Ernest W. Heyer. Enolene rearrangements. Relationship to the "abnormal Claisen rearrangement" and other 1,5-hydrogen shift processes. *Journal of the American Chemical Society* 89: 1404-1411. 1967.

33. Shapiro, Robert H., D. H. Williams, H. Budzikiewicz and Carl Djerassi. Mass spectrometry in structural and stereochemical problems. LIII. Fragmentation and hydrogen transfer reactions of a typical 3-keto steroid, 5 α -androstan-3-one. *Journal of the American Chemical Society* 86:2837-2845. 1964.
34. Simonetta, Massimo, Giorgio Favini, Carla Mariani and Paolo Gramaccioni. Calculated energies and geometries along the reaction path in Cope rearrangements. *Journal of the American Chemical Society* 90:1280-1289. 1968.
35. Smith, Grant Gill and R. Taylor. Kinetic evidence for the mechanism of pyrolysis of β -hydroxyolefins. *Chemistry and Industry*, 1961, p. 949-950.
36. Smith, Grant Gill and Brian L. Yates. Pyrolysis studies. XV. Thermal retrograde aldol condensation of β -hydroxy ketones. *The Journal of Organic Chemistry* 30:2067-2068. 1965.
37. Smith, Grant Gill and Brian L. Yates. Pyrolysis studies. XVI. A mechanistic study of the pyrolysis of β -hydroxyolefins. *Journal of the Chemical Society*, 1965, p. 7242-7246.
38. Thuan, Sa-Le-Thi and Joseph Wiemann. Influence des substituents α , et α , β dans la transposition pinacolique et l'isomérisation des glycols bisecondaires α , α' diéthyléniques symétriques. *Comptes Rendus de l'Académie des Sciences (Paris)* 261:1862-1865. 1965.
39. Urion, M. Décomposition catalytiques de quelques alcools complexes. *Annales de Chimie*, ser. 11, 1:5-87. 1934.
40. Urion, M. Décomposition du divinylglycol par divers catalyseurs; méthylal-1-cyclopentène-1. *Comptes Rendus de l'Académie des Sciences (Paris)* 190:1512-1514. 1930.
41. Viola, Alfred, E. James Iorio, Katherine K. Chen, George M. Glover, Ullhas Nayak and Philip J. Kocienski. The vapor-phase thermolyses of 3-hydroxy-1,5-hexadienes. II. Effects of methyl substitution. *Journal of the American Chemical Society* 89:3462-3470. 1967.
42. Viola, Alfred and Leonard A. Levasseur. The thermal vapor-phase rearrangement of 1,5-hexadien-3-ol. Preparation of 5-hexenal. *Journal of the American Chemical Society* 87:1150-1151. 1965.

43. Vogel, Emanuel. Valence isomerization in compounds with strained rings. *Angewandte Chemie, International ed. in English* 2:1-11. 1963.
44. Vogel, Emanuel, Karl-Heinz Ott and Kurt Gajek. Kleine Kohlenstoff-Ringe. VI. Valenzisomerisierungen von cis-1,2-Divinyl-cycloalkanen. *Annalen* 644:172-188. 1961.
45. Wiemann, Joseph. Problèmes de stéréochimie dans deux groupes de réactions hétérogenes. *Bulletin de la Société Chimique de France*, 1960, p. 1454-1459.
46. Wiemann, Joseph and Sa-Le-Thi Thuan. Isomérisation de l' α , α' -divinyl, α , α' -diméthylglycol. *Bulletin de la Société Chimique de France*, 1959, p. 1537-1539.
47. Wiemann, Joseph and Sa-Le-Thi Thuan. Isomérisation du mélange des α , α' -divinyl, α , α' -diméthylglycols diastéréoisomères par l'acid sulfurique ou l'alumine. *Comptes Rendus de l'Académie des Sciences (Paris)* 246:2903-2904.
48. Wilson, Joseph W. and Shelby A. Sherrod. A novel thermal rearrangement of a propargyl vinyl alcohol. *Chemical Communications*, 1968, p. 143.
49. Woodward, R. B. and Roald Hoffmann. Selection rules for sigma-tropic reactions. *Journal of the American Chemical Society* 87: 2511-2513. 1965.
50. Woodward, R. B. and Roald Hoffmann. Stereochemistry of electrocyclic reactions. *Journal of the American Chemical Society* 87:395-397. 1965.
51. Woodward, R. B. and Thomas J. Katz. The mechanism of the Diels-Alder reaction. *Tetrahedron* 5:70-89. 1959.