I: THE ACID CATALYZED REACTIONS OF CERTAIN
       1,5-EPOXYOLEFINS

II: THE ALKYLATIVE CYCLIZATION OF 1,5-HEXADIENE

III: THE ACID CATALYZED CYCLIZATION OF
       cis,cis- AND trans,trans-2,6-OCTADIENE

IV: THE INFRARED SPECTRA OF CYCLOBUTANE COMPOUNDS

Thesis by

Harris E. Ulery

In Partial Fulfillment of the Requirements

For the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1963

ACKNOWLEDGEMENTS

There is always one person who has been of singular importance in the career of a graduate student. In my case that distinction can only be claimed by my faculty research advisor, Dr. J. H. Richards. The debt I owe Dr. Richards is not readily assessable. Suffice it to say that he has been a continuing source of stimulation and inspiration, which have given both meaning and perspective to the last four years. In addition I am particularly beholden to him as a teacher for having awakened in me an immensely rewarding interest in the chemistry of natural products.

It has been my good fortune to have been in fruitful association with nearly all of the Chemistry Faculty at one time or another in the course of my graduate work. In particular I am grateful to Professors R. M. Badger and J. Waser. In addition to giving so generously of his time in many discussion sessions over these years, Dr. Badger's valuable criticisms were an asset in the preparation of Part IV of this thesis. Two years as a Teaching Assistant to Dr. Waser has left me with a deep and secure appreciation of the merit in executing only the highest standards in teaching.

In this growing list I must include Professors Danforth, Nevill, and Oelke of Grinnell College who played determining roles in my early academic development, and who have maintained a reassuring interest in my achievements these past four years.

In recognition of the hopeless task of acknowledging all those who have contributed directly or indirectly to the work recorded here, I beg to mention only a few specifically:

My very good friend John R. McClenon with whom I collaborated in the preparation of Part IV of this thesis.

Joseph P. Fearey and the members of his group at J. P. L. as well as Dr. R. A. Sparks at U. C. L. A. for technical assistance in the writing of the computor programs used throughout this thesis.

The California Institute of Technology for supplying me with Teaching Assistantships and Summer Fellowships.

The United States Rubber Company for a terminal year Fellowship.

More deserving of recognition than all these is my wife Dana. She not only has given me the strength and comfort needed to meet this task, but has helped considerably at every stage in the development of this thesis. She has assumed the responsibility for providing the major share of the family income in addition to the responsibilities of motherhood. In return for her devotion I can only offer this thesis and my love.

ABSTRACT

I.   THE ACID CATALYZED REACTIONS OF CERTAIN 1,5-EPOXYOLEFINS

The monoxides of a number of 1,5-dienes were prepared and treated with a variety of acidic reagents known to induce cyclization of the parent diolefins. In all cases the major reaction observed was the isomerization of the epoxide to a carbonyl function. No cyclic products were observed. These results are discussed in terms of the general requirements for cyclization.

II.   THE ALKYLATIVE CYCLIZATION OF 1,5-HEXADIENE

The alkylation of 1,5-hexadiene with t-butyl chloride in the presence of aluminum trichloride was studied. The major monomeric reaction products were cyclic, and both the t-butylcyclohexane and neopentylcyclopentane skeletons were identified among them. Formation of the latter ring system appeared to be slightly favored over formation of the six-membered ring. This preference is undoubtedly due to both steric and electronic factors.

III.   THE ACID CATALYZED CYCLIZATIONS OF cis,cis- AND trans,trans-2,6-OCTADIENE

Both cis,cis- and trans,trans-2,6-octadiene were cyclized in a mixture of formic and sulfuric acids. While the cis,cis-diene gave both $2^t,3^c$-dimethylcyclohexyl^c formate and its C-1 epimer in a ratio

of approximately 15:1, the trans, trans-diene yielded only the former epimer. When cyclization was induced in deuterated acid, the trans, trans-diene gave $2^t, 3^c$-dimethyl-4^t-deuterocyclohexyl^c formate, while the cis, cis-isomer produced the C-4 epimer. These results indicate the existence of a sterically controlled reaction pathway. In the cyclization of the cis, cis-diene, this control is partially lost due to highly unfavorable conformational effects. Further, these results show unambiguously that the diene has assumed the quasi-chair conformation at the time of ring closure.

Incidental to this work the isomers of 2, 3-dimethylcyclohexanol and 2, 3-dimethylcyclohexanone were identified and characterized.

IV. THE INFRARED SPECTRA OF CYCLOBUTANE COMPOUNDS

In an attempt to locate possible characteristic frequencies of the C_4-ring, the infrared spectra of 191 cyclobutane derivatives have been examined. The most useful correlations appear to be a band near 1235 cm.$^{-1}$ for cyclobutane compounds with at least one ring methylene group, and a band near 915 cm.$^{-1}$ for mono- and 1, 1-disubstituted cyclobutanes. Less frequently a band is found close to 750 cm.$^{-1}$

In addition, a novel application of a computor technique is proposed, which may be of some value in the analysis of large numbers of spectra.

TABLE OF CONTENTS

TABLE OF CONTENTS (cont'd) (2)

TABLE OF CONTENTS (cont'd) (3)

TABLE OF CONTENTS (cont'd) (4)

TABLE OF CONTENTS (cont'd) (5)

HISTORICAL BACKGROUND

"It is probable that from the beginning of his history,
man has been interested in the diverse and fragrant
odours associated with certain plants. From such a
time, then, he may be said to have taken an interest in
terpenoid chemistry."

P. de Mayo

Organic chemistry in its earliest stages is, historically speaking,
nearly synonymous with terpenoid chemistry. This vast area of
chemical endeavor derives from the early discovery that the fragrant
principals responsible for the odors of plants could be won by a crude
process of distillation. With the development of the later technique
of steam distillation, the manufacture of these so-called "essential
oils" had made rapid progress by the sixteenth century. At this time
the chief demand for essential oils was for medicinal purposes.
According to P. de Mayo (1), as many as sixty oils were included
in the Dispensatorium Valeri Cordi of 1592.

Early Investigations

However, it wasn't until the first half of the nineteenth century
that any significant chemical investigations were possible in this
area. At this time M. J. Dumas (2) undertook a study of the more
volatile fractions of some essential oils. He found that these were

mixtures of isomers with the empirical formula, $C_{10}H_{16}$. These compounds were then given the general name of "terpenes," derived from the German word for turpentine (terpentine). The term "terpenoid" has more recently come into preferred usage in order to include the oxygenated derivatives, which occur widely in nature. Upon examination of the higher boiling essential oil fractions, compounds containing fifteen and twenty carbon atoms were discovered. The classifications now recognized are the mono-, sesqui-, di-, tri-, and tetraterpenoids. A large number of reviews and collected works dealing with these classes of compounds have been published (3-9).

Ruzicka's Biogenetic Isoprene Rule

Undoubtedly the most striking feature of the thousands of terpenoids known is the structural diversity that they enjoy. In fact, until 1922, the only relationship observed among the various groups was that they all possessed carbon skeletons, which contained a simple multiple of five carbon atoms. This relationship was first formalized by L. Ruzicka (10) in terms of the now famous "isoprene rule." According to this rule, all but a very few of the known terpenoids could be thought of structurally as low polymers of isoprene units; these generally, but not always, were joined together in a head-to-tail fashion. Isoprene itself has not been found to occur naturally, but it is readily obtained from the destructive distillation of natural rubber (11) and the pyrolysis of limonene (12).*

* The biologically active species Δ^3-isopentenylpyrophosphate has only recently been isolated (156).

Exceptions to the Isoprene Rule

When displayed against the background of its tremendous success
of bringing some unity into the broad and complex area of terpenoid
chemistry, the shortcomings of the isoprene rule, as first proposed,
were of only minor importance. As long as interest centered on the
lower terpenoids, very few examples were known of compounds whose
structures deviated "inexplicably" from the isoprene rule. In fact,
until a few years ago, the sesquiterpenoid, eremophilone (I), which
cannot be divided into isoprene units, was the only known exception to
the rule (13). Sir Robert Robinson (14) at London's Imperial College,
on the other hand, proposed that this compound was derived from a
"normal" terpenoid, which had undergone a Wagner-Meerwein 1,2-
methyl migration.

I
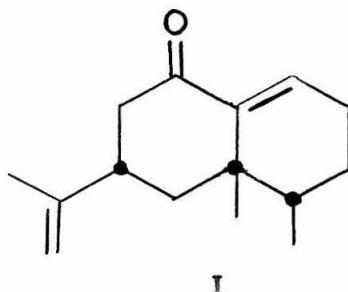
The inability of the isoprene rule to correctly predict the struc-
tures of higher terpenoids began to manifest itself when research
efforts were turned to the structural elucidation of several polycyclic
triterpenoids. In 1952, Ruzicka's E.T.H. group (15) uncovered a
second exception to the rule upon publication of the last stages in the

structure determination of lanosterol. At about this same time (1949-1955), a large number of papers, due by and large to Ruzicka's group in Zürich and D. H. R. Barton's London group at the Imperial College, appeared concerning the structures of several polycyclic triterpenoids. Representative of these, which were found to violate the simple isoprene rule (see Fig. 1), are: ursolic acid (16), taraxasterol (17), lupeol (18), phyllanthol (19), germanicol (20), α-amyrin (21), friedellin (22), taraxerol (23), and the epimers euphol (24) and tirucallol (25).

Modification of the Biogenetic Isoprene Rule

The biogenetic isoprene rule, however, had proven itself far too useful during the intervening three decades to be abandoned because of a few failures. Although the face of organic chemistry had changed considerably during this time, no basic modification of the isoprene rule had been necessary since its inception. In light of these recent results, Ruzicka, collaborating with A. Eschenmoser, O. Jeger, and D. Arigoni, was able to publish in 1955 a detailed theory of the cyclization process (26). This theory constitutes a remarkable refinement of the original isoprene rule. With this step it seemed at last possible to rationalize the complete structural and configurational details of the basic representatives of most terpenoid groups, and in particular, of all the cyclic triterpenoid groups, which are thought to be derived from the acyclic triterpenoid, squalene (27).

Ursolic acid   Taraxasterol   Lupeol

Phyllanthol   Germanicol   α - Amyrin

Friedelin   Taraxerol   Tirucallol
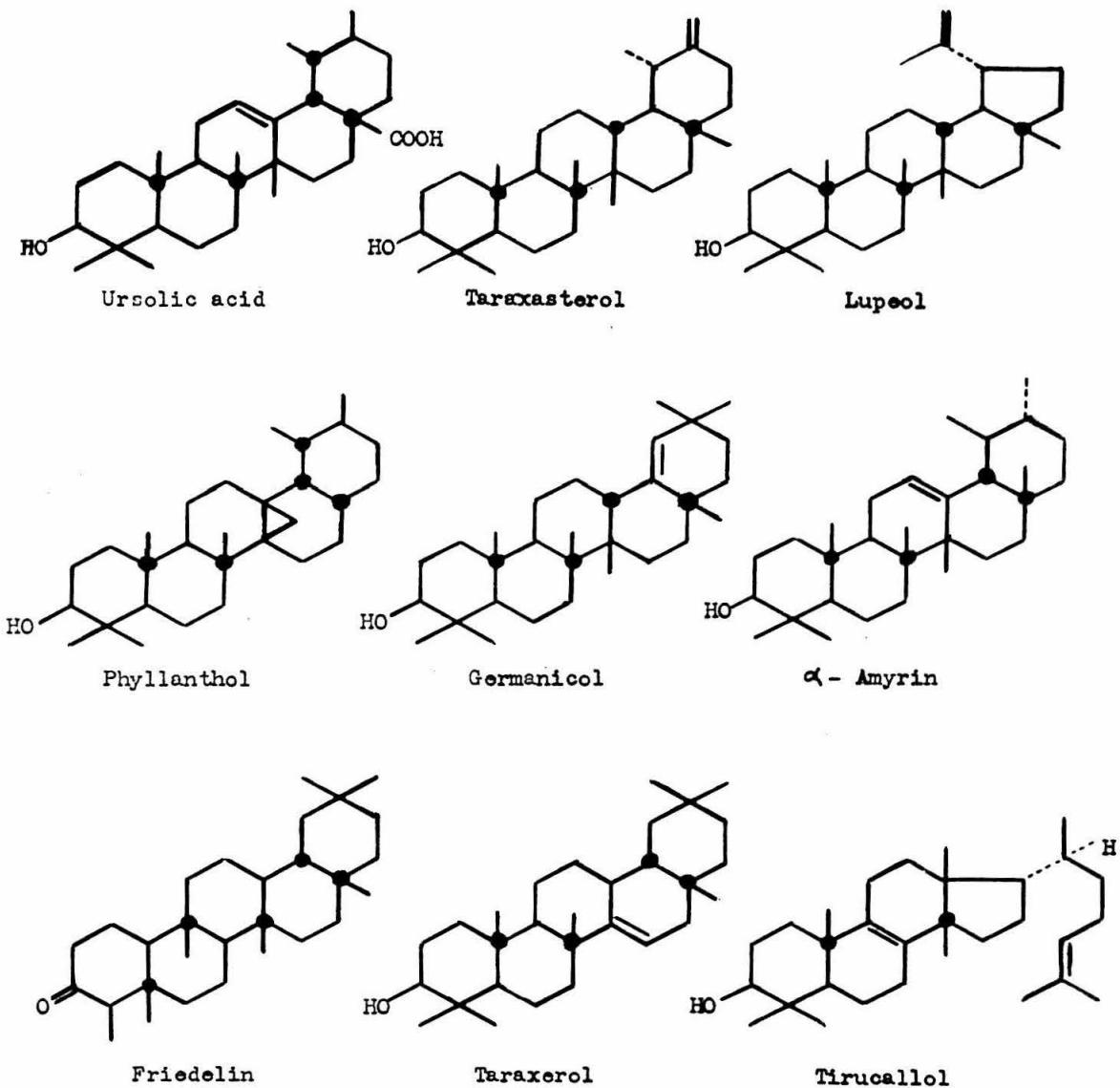
Fig. 1

Basic representatives of the polycyclic triterpenoid groups which deviate from the simple isoprene rule. Each of these groups is hypothetically derivable from the acyclic triterpene, squalene.

The set of three postulates upon which this new theory rests is as follows:

1) When acyclic terpenoids undergo electrophilically catalyzed cyclization, all double bonds are saturated by a process of trans-addition. (This process is variously referred to as antiplanar or anti-parallel addition.)

2) Wagner-Meerwein type alkyl and methyl 1,2-shifts, as well as internal hydride transfers, are facile, stereospecific processes, when optimal stereochemical requirements are satisfied. These processes always result in a Walden-like inversion at the center to which migration has occurred.

3) The course of the reaction is completely concerted (i.e. non-stop), such that no classical carbonium ion intercedes, nor does any stable intermediate, which could arise, for example, by the loss of a proton to give the corresponding unsaturated compound.

The evidence governing the choice of these postulates, and their consequences in terms of the biogenesis of the cyclic terpenoids will now be discussed:

The Postulate of trans-Addition. A period of about two decades elapsed after the original proposal of the isoprene rule before the concept of "trans-addition" achieved general popularity as a means of describing the stereochemistry of addition reactions of double bonds.

The term usually refers to the addition of two species "Y" and "Z" to a double bond in such a manner that "Y" adds from one side of the plane of the olefin and "Z" from the other. That such a restriction may at least formally be placed on the course of certain addition reactions can often be realized by examining the character of the products. The now classic examples of the electrophilic addition of bromine to maleic and fumaric acids (28) serve splendidly to illustrate that, at least under some conditions, the addition of both of the moieties, "Y" and "Z", to the same side of the double bond is highly disfavored. The mechanisms of trans-additions have been discussed quite extensively by a number of authors (29), and need not be detailed here. For the purpose of discussing the role of trans-addition in the electrophilic cyclization of terpenoids, it is sufficient to outline the essential stereochemistry of the addition reaction as follows:

IIa   IIb   IIc
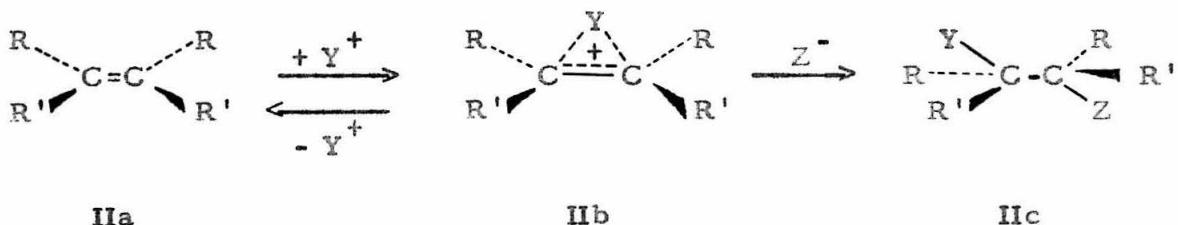
In this scheme, the initial step of the addition is an electrophilic out-of-plane attack by Y^+, which may be either a positive ion or the positive end of a dipolar species. The out-of-plane attack is quite plausible, in that this path is less sterically hindered than any of the other conceivable

in-plane approaches. The resulting cyclic or bridged ion (IIb) is expected to be more stable than a classical, trigonally hybridized carbonium ion, in which the charge density on carbon is much higher (vide infra). This non-classical ion may then suffer collapse as a result of another out-of-plane attack by an available nucleophile, Z^-. While again an out-of-plane attack is probably preferred for steric reasons, the attack must now occur on the opposite side of the plane of the molecule (as defined by the original olefin). Attack by Z^- at carbon on the same side of the plane is reasoned to be highly inefficient, due to steric shielding by the co-ordinated Y-group and is most likely to result in abstraction of the electrophile, Y^+, to regenerate the olefin (i.e. IIb→IIa).

Recently (30) it has been pointed out that steric control may not be the only important factor in determining the trans-orientation of entering groups. A quantum mechanical argument by Hammond and Collins suggests that the trans-configuration is determined by the symmetry of the antibonding orbital of the olefin, into which the pair of electrons on Z^- are introduced in order to minimize electron-electron repulsions during the course of the reaction.

The application of the trans-addition mechanism to the cyclization of terpenoids will be discussed in more detail in the section dealing with Ruzicka's third postulate.

The Postulate of Wagner-Meerwein Migrations. As was the case with the postulate of trans-addition, the empirical basis for the second postulate is found largely in the results of experiments with non-terpenoid compounds. In 1952, when Robinson (14) proposed the idea of internal methyl and hydride migrations to account for the structures of certain anomalous terpenoids, 1,2-methyl shifts were known   . (Wagner and Meerwein (31)), while hydride transfers were recognized primarily as intermolecular processes (32). Since then several internal 1,2-hydride migrations have been observed or suspected (33). Although no 1,n-methyl shifts for n greater than 2 seem to be known, internal 1,n-hydride transfers have been observed or hypothesized for all values of n up to and including 6 (34).

Inasmuch as the migration of a methyl group or a hydride "ion" involves the transfer of a pair of electrons, causing an oxidation and reduction of the donating and accepting centers respectively, it is a requirement of this process that the migration terminus, if it is a first row element, must have an actual or potential open sextet of electrons. Moreover, since such an acceptor center is created by the protonation of an unsaturated system, it is often observed that such transfer processes are acid catalyzed (33a). In these reactions, the driving force is often provided by the conversion of the relatively unstable carbonium ion into a species with a completed octet. If a new carbonium ion is formed as a result of such a migration, it is frequently

more stable. This greater stability is generally due to one or a combination of resonance, hyperconjugative, polar and steric effects (35). It is clear that acid catalyzed cyclizations of terpenoids are reactions in which these conditions may well be fulfilled. The fact that the driving force for certain hypothesized methyl and hydride migrations may derive from relief of strain through conformational reorganization in the cyclic transition state (36) will be considered in detail later with a specific example. It should be pointed out that in such rearrangements, the migrating groups act as the nucleophile in an anti-planar addition process, and hence, amount to a sterically ordered process in which a Walden-type inversion occurs at each migration terminus.

The Postulate of a Concerted Process. This postulate is designed to weld the first two postulates into a powerful theoretical instrument for predicting the stereochemistries of most terpenoid groups. Unlike the first two, it rests heavily on the results gleaned from the study of acid catalyzed polyene cyclizations.

It has been known for over half a century (37) that certain 1,5-dienes undergo cyclization in the presence of strong acids. Although the reaction has been used extensively in the study of terpenoid chemistry, comparatively little work has been directed toward discovering the mechanism involved. An early advance in this direction is due to a suggestion by Bloomfield (38) in 1943. He indicated that the acid

catalyzed cyclization of polyolefins proceeded via an intramolecular carbonium ion mechanism analogous to the polymerization of olefins (39). The first step in Bloomfield's mechanism was the rapid and reversible addition of a proton to one double bond of the polyene. The second and rate determining step in the reaction sequence was the essentially irreversible ring closure, which gave rise to a new carbonium ion. This species could then decompose by the loss of a proton in perhaps several ways to yield a cyclic olefin.

Since that time, Bloomfield's mechanism has been generalized (40) to explain the acid catalyzed cyclizations of a number of other compounds with one or more basic sites in the molecule other than carbon-carbon double bonds. A specific example of the more general scheme is given by the conversion of neral (IIIa) to racemic 4-isopropylidenyl-cyclohexen-3-ol (IIId) (41).

| IIIa | IIIb | IIIc | IIId |
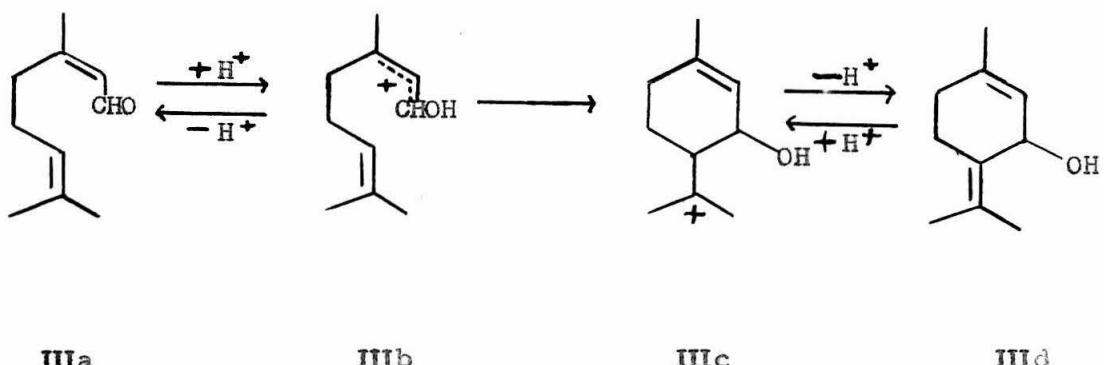
However, it is clear that in some reactions a "free" carbonium ion such as IIIc is not formed. This is quite evident, for example, in

the conversion of optically active linaloöl (IVa), in acid media, to

optically active α-terpineol (IVb) (42). The reaction has been formulated

by Robinson (43) and Swain (44) as proceeding by a concerted mechanism,

which is shown schematically below:

IVa   IVb
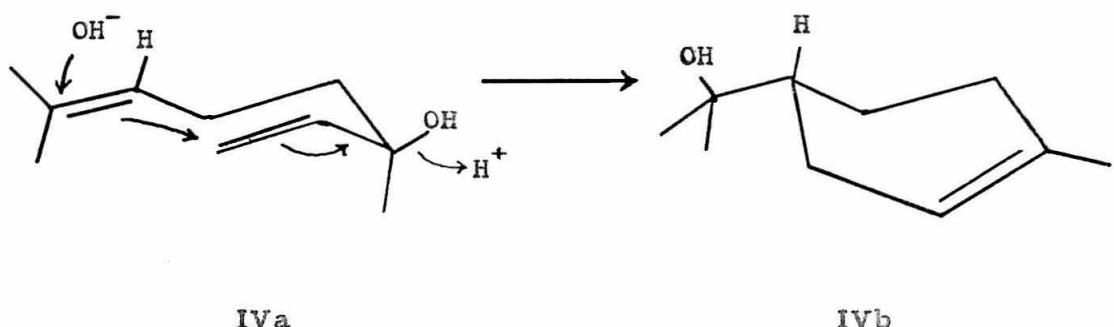
This mechanism allows that the new asymmetric center be in the process

of formation before the old one is completely destroyed. Winstein (45)

has examined the solvolysis of linaloöl p-nitrobenzoate in 70% acetone

and found evidence for a mechanism involving the collapse of an intimate

ion-pair. This topic has been discussed in considerable detail by

Ruzicka (40).

Today the over-all structural course of acid catalyzed cyclizations

of polyenes is fairly well understood. Much of our information is largely

due to the exhaustive investigations carried out over the last decade

by H. Schinz and co-workers (46). These investigators have shown,

for example. that the cyclizations of apogeranic acid (Va,b) and aponeroic

acid (VIa,b) are strictly stereospecific, leading to the _trans-_ (Vc,d)

and cis- (VIc,d) 2,2-dimethylcyclohexan-6-ol carboxylic acids

respectively. Unfortunately, due to the symmetry of the isopropylidene

end group, a knowledge of the stereochemistry of both the starting

materials and products is not enough, in this instance, to define the

geometry of the reaction, nor is it possible to determine anything about

the nature of the primary cationic species arising from the protonation

of the isopropylidene double bond. Since the reaction was carried out

in concentrated formic acid, it might well be expected that trans-

addition to the isopropylidene double bond would not occur, since the

classical carbonium ion, which could form, should be stabilized by

extensive solvation.

As it turns out, we still have very little information about those

factors which define the over-all stereochemistry of terpenoid reac-

tions. This is illustrated by a consideration of a few mechanistic

possibilities, which seem to be in harmony with the available data on

the cylization of apogeranic and aponeroic acids (Fig. 2). a) One

possibility is a completely concerted, "push-pull" mechanism (such

as the one proposed above for the cyclization of linalool) involving the

synchronous protonation of the isopropylidene double bond, ring

closure, and attack on the conjugated double bond by a nucleophile.

This process would be expected to occur while the diolefinic chain is

folded in a conformation analogous to the thermodynamically favorable

chair form of cyclohexane (cf. Va and VIa) (47,48). The nature of the
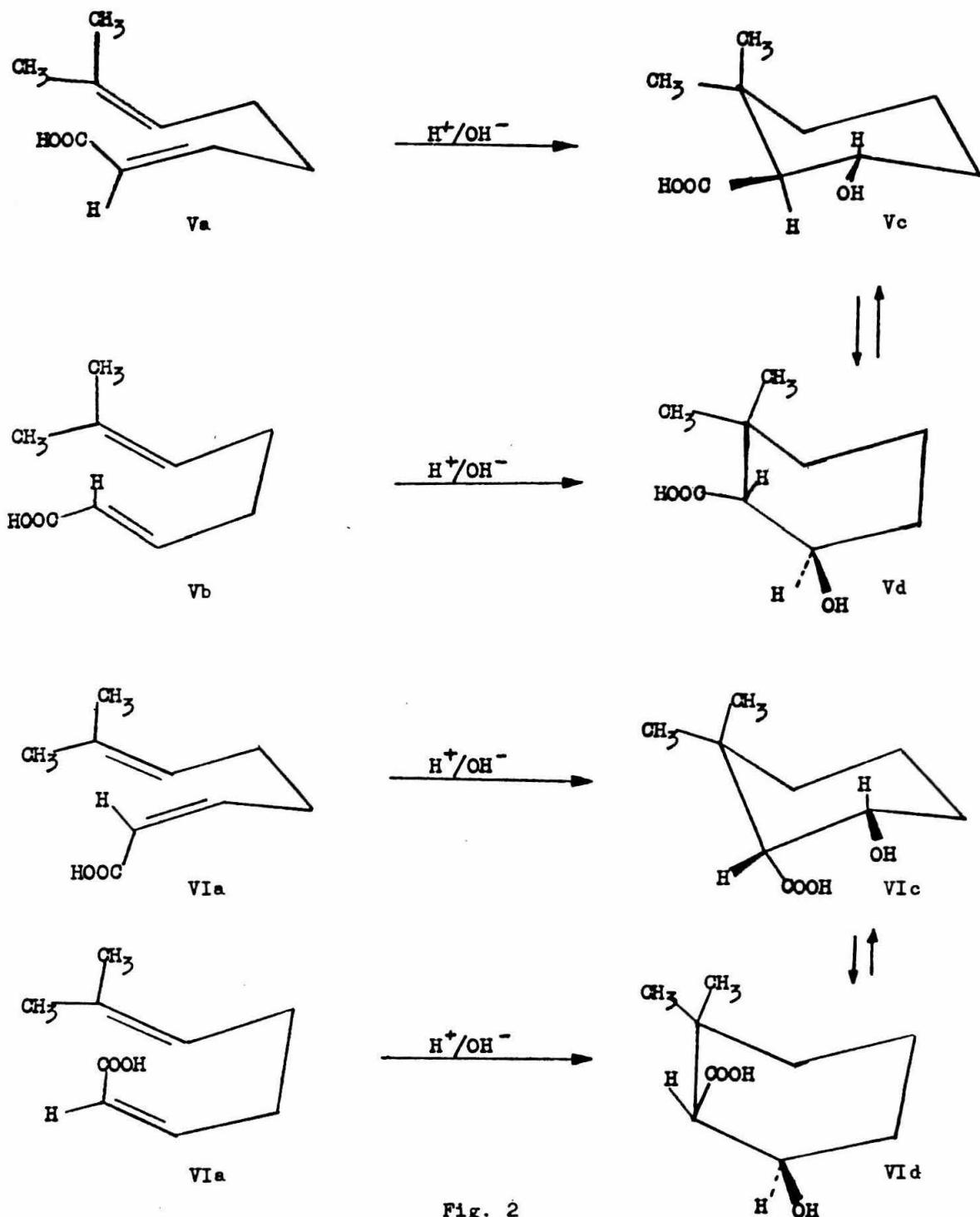
Fig. 2

Acid catalyzed cyclizations of apogeranic acid and aponeroic
acid. (Schinz and coworkers, 1952-1956)

products (Vc,d and VIc,d), however, does not demand that the diolefin
be in a chair-like conformation; indeed, the same products would result
if the initial conformation of the chain had been that of a boat (Vb and
VIb). b) A mechanism which represents the opposite extreme, with
respect to timing, is one in which each of the above processes occurs
in well defined steps, to give classical intermediates with appreciable
lifetimes. If the attack on a classical ion, such as VIIa or VIIb, is
considered, it must be assumed that it occurs before these species
are able to equilibrate conformationally (47).* c) Somewhat intermediate

VIIa   VIIb
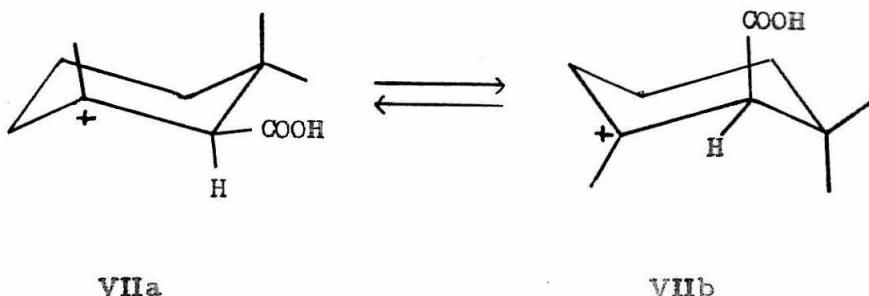
between the two types of mechanisms already suggested is a third
one, in which the rate determining step of the reaction involves the

---

* Although conceptually mechanism b is different from mech-
anism a in that the course of the reaction may be divided into discrete
stages involving classical ions, the imposed time scale for the
reaction is so contracted that these ions do not behave as such.
The result is that for all practical purposes, mechanisms a and b
are identical.

formation of a non-classical, bridged cation such as VIIIa or VIIIb.*

A trans-attack (i.e. an attack from the unhindered side of the plane

of the complexed double bond) by a nucleophile, would be expected to

lead to the observed products (in this case Vc, d). The assumption of

the intervening bridged cation allows that 1) the geometry of the product

is still determined by the geometry of the starting material and

2) that the reaction may proceed in a series of stages, each of which is

sterically controlled, such that the result is the same as for a concerted

process.
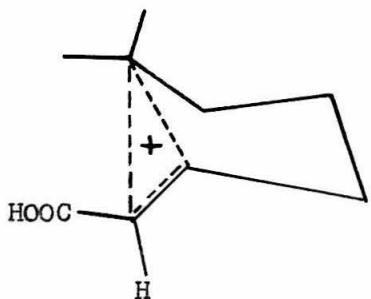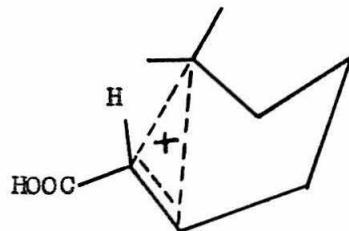
VIIIa   VIIIb

Evidence for the formation of such bridged ions, and their effect

on the stereochemical course of the addition reaction of simple systems

was alluded to earlier. There is, however, both diverse and abundant

evidence (49, 50) for the formation of bridged systems in which the

---

* The barrier to interconversion of VIIIa and VIIIb would be much
greater than that which exists between the chair and boat forms of
cyclohexane, since rotation about the C_1-C_2 and C_5-C_6 bonds is
severely restricted. Consequently, equilibration of these ions is not
anticipated.

electrophile itself is a carbonium ion. Also of interest in this regard is the large volume of stereochemical data on non-classical ionic systems formed during solvolysis reactions of certain tailored systems (51). The bridged cation may be expected to be especially readily formed, since it is in many respects similar to cyclopropenium cation; i.e. it is a three carbon, $4n + 2$ electron system, which should be highly resonance stabilized under conditions of optimum orbital overlap (52). Similar systems are formed during the 1,2-migrations discussed above.

A final observation as regards the cyclic products derived from apogeranic and aponeroic acids is that the equatorial position of the hydroxyl group in Vc and VIc is, for steric reasons, the position of preferred attack by a base, and hence is compatible with all of the above mechanistic possibilities (47, 53).

Eschenmoser and his students (54) have continued the work initiated by Schinz on more complicated sesquiterpenoids and diterpenoids in an attempt to help elucidate the conformational ambiguity which exists here. The results obtained from these systems are decidedly more difficult to interpret, and the conclusions are meager. In general, however, these reactions are relatively non-stereospecific. Eschenmoser suggests that in part the difficulty lies in the fact that these reactions begin from a conformational equilibrium of linear and

folded polyene chains in which the former predominate strongly (vide

infra). The high proton activities required for in vitro reaction lead

to the formation of high concentrations of cationic intermediates, which

encourage non-selective side reactions.

Herein lies the question of what features may be common to the

enzymic and acid catalyzed mechanisms of terpenoid cyclizations.

Indeed, in the extreme case, a requirement for antiplanar addition,

as set forth in the first postulate of the Ruzicka theory, is that the

polyene chain be appropriately folded prior to the synchronous process

in which the new bonds are developed, and that little or no conformational

reorganization occurs during the ring forming process. Such strict

control is visualized as a function of the enzyme (55). In fact, this is

the only function demanded of the enzyme by this theory (except perhaps

in certain instances when concomitant oxidation also is observed; e.g.

sterol formation). Especially in the case of the higher terpenoids

does this become important, since it is expected that increments in

the reaction energy barrier should appear chiefly in the activation

entropy term as the length of the polyolefin is increased (56). An

interesting experiment by Eschenmoser's group (27b), in which the

rates of cyclization of several alkyl substituted citronellal compounds

were measured, lends support to this belief. In non-enzymic systems

one would anticipate that the chair folding (e.g. Va and VIa) would be

the energetically preferred conformation of the polyene for the cycliza-
tion process, but there is no direct experimental support of this to date.

As D. H. R. Barton (57) points out, stereospecificity is not
necessarily a consequence of theory, but may actually be a trivial
characteristic. The same results could also obtain from a process
which does not involve antiplanar addition. Such an example would be
given by mechanism (b) cited above for the cyclization of apogeranic
and aponeroic acids. Here addition to the conjugated double bond was
not accompanied by conformational fixation; however, addition of the
nucleophile occurred more rapidly than rotations around single bonds,
and hence, stereoselectivity resulted.

The third postulate of Ruzicka's theory, then, by demanding that
no stable intermediates be formed during the course of the biogenetic
reaction, limits the total number of mechanistic pathways to the final
steric result to just those which can arise out of the several different
foldings, which can be hypothesized for a given polyene (vide infra).
The third postulate, although arbitrary, does reflect the small amount
of evidence we have at present on certain biological reactions (58).
In any case, with this postulate, the refined isoprene rule is self-
contained, allowing the structural rationalization of all the major
terpenoid groups (59) with the introduction of only a minimum of ad hoc
prerequisites.

Significance of the Revised Isoprene Rule

The great current popularity of the Ruzicka proposal lies largely in its ability to explain not only the gross structural features of sundry terpenoid groups, but also their precise stereochemistries. Another improvement over the original isoprene rule, which has thus far been neglected, is that this theory can be used to correctly predict the sites of oxidation in many terpenoid compounds (e.g. eremophilone, I, and the polycyclic alcohols in Fig. 1) (40). It should be noted, however, that this system of postulates is arbitrary, in that we have very little knowledge of the intimate processes which occur in the enzyme-substrate complex. Consequently, this theory undoubtedly effects an over-simplification of the biogenetic mechanism of cyclization processes. Nevertheless, a schematic understanding of the biogenesis of sterols and other natural products is invaluable in laying the foundation necessary for a more detailed study of these biochemical conversions. Herein lies the potential utility of the Ruzicka theory; its beauty is due to its striking simplicity.

To date the greatest test of this theory has been its ability to adequately account for the biogenetic relationship between squalene and the sterols (60). Some bicyclic sesquiterpenoids with structures related to guaiazulene are known, which stand out as exceptions to this theory. These have been discussed briefly by Arigoni (55).

NON-ENZYMIC TERPENOID CYCLIZATIONS

In order to obtain a better understanding of the enzymic cycliza-
tions that take place during the biosyntheses of higher polycyclic ter-
penoids, it would seem that one must first understand more thoroughly
those rules which govern the cyclizations of simpler systems. In
particular, a great deal is yet to be learned about the non-enzymic
cyclizations of monoterpenoids.

The Problem of Polyene Conformation

The efficiency of biosynthetic processes is frequently attributed
to enzymic control. In the formation of the higher polycyclic ter-
penoids, it is felt by many investigators that the chief function of the
enzyme is to fold the polyene in a specific conformation, necessitated
by the nature of the end product; the enzyme may or may not be
responsible for initiating the cyclization itself by supplying the ap-
propriate electrophile. Acid catalyzed, non-enzymic cyclizations,
on the other hand, while they may show stereoselectivity in the case of
some monoterpenoids (e.g. linalo͠ol to α-terpineol), are notoriously
non-stereospecific for the sesqui- and higher terpenoids (62). How
much of this lack of stereospecificity may be attributed to the absence
of the enzyme and how much to other differences in reaction conditions
is not known.

Linear vs. Folded Conformations. It has been suggested by Eschenmoser (27b) that the inefficiency of non-enzymic cyclization reactions may stem in part from the fact that a conformation equilibrium exists between folded and extended polyene chains, in which the latter conformer greatly predominates. Protonation of the two kinds of species could then presumably lead to different products. There have been no studies made which have been directed toward shedding light on this hypothesis. There seems to be no reason to assume a priori that the linear conformation of such an equilibrium should be more highly populated than the folded one. In fact, it might be expected that a mutual interaction of the double bonds of a 1,5-diene might enhance the formation of the folded conformer (vide infra). A number of physical parameters might be used to determine whether or not an unusually large proportion of folded conformers was present in a given solution. Some of these are discussed below.

Standard Formation Entropies. A number of methods are available (63) for the calculation of standard molecular entropies of formation for either the liquid or for the gaseous state, and in some cases the agreement with experimentally observed values is quite good. The method of Otozai, Kume, and Fukushima (63a) was used here to calculate the standard molecular entropies of a number of alkanes, alkenes, and alkadienes in the gaseous state at 25° C. In Table I a

Table I

No.	Compound	S° calc. (e.u.)[a]	S° obs. (e.u.)[b]	ΔS°(e.u.)[c]	Mol. Vol.[d] (ml./mol.)	Mol.Ref.[d]
	ALKANES					
I-1	n-Pentane	83.0	83.4	-0.4	116.104	25.286
I-2	n-Hexane	92.2	92.5	-0.3	131.598	29.928
I-3	n-Heptane	101.4	101.6	-0.2	147.456	34.565
I-4	n-Octane	110.6	110.8	-0.2	163.530	39.209
I-5	n-Nonane	119.8	120.0	-0.2	179.670	43.855
I-6	n-Decane	129.0	129.2	-0.2	195.905	48.503
	CYCLOALKANES					
I-7	Cyclopentane	83.3	70.7	12.6	94.713	23.144
I-8	Cyclohexane	92.2	71.3	20.9[e]	108.744	27.722
I-9	1,1-Dimethyl-cyclohexane	103.6	87.2	16.4	144.455	37.060
	ALKENES					
II-1	1-Pentene	82.3[f]	82.65	-0.3[f]	110.384	24.868
II-2	1-Hexene	91.6	91.93	-0.3	125.892	29.504
II-3	2-Hexene (cis-)	91.5	92.37	-0.9	123.34	29.56
II-4	2-Hexene (trans-)	91.5	90.97	+0.5	124.90	29.65
II-5	2-Methyl-1-pentene	89.9	91.34	-1.4	124.33	29.36

33

Table I (cont.)

No.	Compound	S° calc. (e.u.)[a]	S° obs. (e.u.)[b]	ΔS° (e.u.)[c]	Mol. Vol.[d] (ml./mol.)	Mol. Ref.[d]
	ALKENES (cont.)					
II-6	3-Methyl-1-pentene	89.9	90.06	-0.2	126.97	29.51
II-7	1-Heptene	100.7	101.24	-0.5	141.744	34.144
II-8	3-Heptene (cis-)	100.7	-----	-----	140.52	34.30
II-9	3-Heptene (trans-)	100.7	-----	-----	141.51	34.43
II-10	1-Octene	109.9	110.55	-0.7	157.85	38.79
II-11	4-Octene (cis-)	109.9	-----	-----	156.50	38.97
II-12	4-Octene (trans-)	109.9	-----	-----	158.06	39.10
II-13	1-Nonene[g]	119.1	119.86	-0.8	174.041	43.429
II-14	4-Nonene[h]	119.1	-----	-----	-----	43.75[i]
II-15	2-Methyl-2-octene	117.5	-----	-----	-----	43.67[k]
II-16	1-Decene	128.3	129.17	-0.9	190.330	48.078
	CYCLOALKENES					
II-17	Cyclopentene	82.5	69.2	13.3	88.860	22.459
II-18	Cyclohexene	91.5	74.27	17.2	101.899	27.055

Table I (cont.)

No.	Compound	S° calc. (e.u.)[a]	S° obs. (e.u.)[b]	ΔS° (e.u.)[c]	Mol. Vol. (ml./mol.)[d]	Mol. Ref.[d]
	1,3-ALKADIENES[m]					
III-1	1,3-Butadiene	72.0	66.62	5.4	87.96[n]	----
III-2	2-Methyl-1,3-butadiene	79.6	75.4	4.4	100.780	25.425
III-3	1,3-Pentadiene (cis-)	81.2	77.5	3.7	99.303	25.790
III-4	1,3-Pentadiene (trans-)	81.2	76.4	4.8	101.508	26.032
III-5	1,3-Hexadiene[p]	89.9	-----	-----	117.3[p]	30.6[p]
III-6	2,4-Hexadiene[p]	69.9	-----	----	114.9[p]	30.7[p]
	1,4-ALKADIENES					
III-7	1,4-Pentadiene	81.2	76.4	4.8	103.878	24.367
III-8	1,4-Hexadiene[q]	89.9	-----	-----	118.2[r]	29.4[s]
III-9	2-Methyl-1,4-pentadiene	89.2	-----	-----	119.2	29.0
III-10	3-Methyl-1,4-pentadiene	89.2	-----	-----	119.0	29.0
III-11	1,4-Heptadiene[u]	100.0	-----	-----	-----	33.84[v]
III-12	1,4-Octadiene[u]	109.2	-----	-----	-----	38.45[w]
III-13	1,4-Nonadiene[u]	118.4	-----	-----	-----	43.11[x]

Table I (cont.)

No.	Compound	S° calc. (e.u.)[a]	S° obs. (e.u.)[b]	ΔS° (e.u.)[b]	Mol. Vol.[d] (ml./mol.)	Mol. Ref.[d]
	1,5-ALKADIENES					
III-14	1,5-Hexadiene	90.6	-----	-----	119.42	29.01
III-15	3,7-Decadiene[y]	127.6	-----	-----	-----	-----
	1,6-ALKADIENES					
III-16	1,6-Heptadiene[z]	100.0	-----	-----	-----	33.66[aa]
III-17	7-Methyl-1,6-octadiene[bb]	116.8	-----	-----	-----	43.19[cc]
III-18	2,7-Nonadiene[z] (cis,cis-)	118.4	-----	-----	-----	42.90[aa]
III-19	2,7-Nonadiene[z] (trans,trans-)	118.4	-----	-----	-----	43.25[aa]
	1,n-ALKADIENES					
III-20	1,7-Octadiene[dd]	109.2	-----	-----	-----	38.35[ee]
III-21	1,8-Nonadiene[dd]	118.4	-----	-----	169.85[ff]	43.18[ff]
III-22	1,9-Decadiene[gg]	127.6	-----	-----	184.719	47.72

Note: Footnotes to Table I appear on Page 27.

92

FOOTNOTES TO TABLE I

(a) Calculated by the method of Otozai, Kume, and Fukushima (1); values are for standard molecular entropies in the gaseous state at 25°C. (b) Observed standard molecular entropies for the gaseous state at 25°C. Unless otherwise indicated, these values are taken from the tables of the American Petroleum Institute Research Project-44 (2), which appear to be the most reliable data to date.

(c) $S°_{calc.} - S°_{obs.}$. (d) From measurements made at 25°C. unless otherwise indicated. (e) Cf. ref. (3).

(f) The method of McCullough et al. (4) may be used to obtain calculated values of standard molecular entropies of 1-alkenes in the liquid state, which differ from experimental quantities by only 0.04%.

(g) Cf. ref. (5). (h) Mixture of cis- and trans-isomers (6). (i) At 18°C. (6). (j) Probable mixture of isomers (7). (k) At 16°C. (7). (l) Maslov (8) presents an alternative method of calculating S° for either the gaseous or the liquid state of alkadienes. (n) At saturation pressure. (p) Approximate values for a mixture of cis- and trans-forms. (q) Cis- and trans-mixture; also undoubtedly contaminated with 1,3-isomer (14, cf. 15). (r) Probably low, see footnote q. (s) Probably quite high (see footnotes q and r); the value calculated from group refractivities is 28.9. (t) Purity uncertain (16).

(u) Cis- and trans-mixture (9). (v) At 11°C. (9). (w) At 15°C. (9). (x) At 21°C. (9). (y) See ref. (11). (z) See ref. (11). (aa) At 20°C. (11). (bb) See ref. (12). (cc) At 20°C. (12).

(dd) Possibly contaminated with saturated material (13). (ee) At 21.4°C. (13). (ff) At 24.4°C. (13).

(gg) The identity of this compound is still in doubt.

comparison is made between the calculated and the observed values.
For the acyclic alkanes and alkenes, this method predicts entropies
which are quite close to the observed values, but consistently low by
0.2-1.4 e.u.; the majority of cases show disagreements of substanti-
ally less than 1.0 e.u. The one exception falls in the case of trans-2-
hexene, in which instance the calculated entropy is high by 0.5 e.u.

The method of Otozai, Kume, and Fukushima, however, does
not attempt to evaluate the effect of cycle formation or conjugation of
multiple bonds on the overall entropy. Consequently, the differences
between the calculated and the observed values for the entropies of the
cyclic systems and of the 1,3-alkadienes may be taken as approximations
to the corresponding entropies of cyclization and of conjugation in a
given system. According to the values in Table I, then, the loss in
entropy due to the formation of a formal six membered ring is about
17-21 e.u., while restriction of rotation around a conjugated "single"
bond of acyclic 1,3-alkadienes leads to an entropy loss of 4-5 e.u.

Unfortunately, entropy data for unconjugated alkadienes are
almost non-existent at present. In fact, the only diene in this category,
whose entropy of formation has been determined, is 1,4-pentadiene.
It is exceedingly interesting that the observed entropy of this compound
is lower than the Otozai, Kume, and Fukushima prediction by 4.8 e.u.
This value is 36-38% of the maximum loss of entropy expected for the

formation of a true ring with five members. The paucity of data requires some restraint in attempting to interpret this value. Upon consideration of the magnitude and direction of error in the calculated entropies, however, the discrepancy of 4.8 e.u. in this case must surely represent a significant restriction in the molecular motions of 1,4-pentadiene. The extent of this restriction is quantitatively similar to the degree of restriction to rotation, which exists about the "single" bond of conjugated dienes. It is impossible, however, on the basis of the entropy data alone, to determine qualitatively the nature of this restricted motion. Since there is no evidence for intermolecular association of the alkenes (i.e. all the deviations from the predicted entropy values are negative), there is no reason to assume that 1,4-pentadiene should possess to any great extent a polymeric gas structure. It is likely, therefore, the restriction to motion is an internal one.

Two models which might account for the observed low entropy of 1,4-pentadiene can be suggested. The first of these is based on the familiar homoallylic system (64). In this model, the C-2 and C-4 atoms of the linear diene (IXa) are considered to be slightly closer to one another than is the case in the corresponding saturated or partially saturated chain. It is presumed that the loss in entropy in this model would be balanced by a gain in resonance energy afforded by overlap of the p-orbitals on C-2 and C-4. Due to the presence of the vinyl hydrogens at C-2 and C-4, conformation IXa,b would be expected to

be twisted somewhat from planarity in order to optimize the resonance and repulsive interactions.
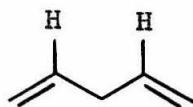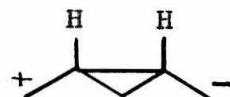
IXa   IXb

The second model assumes that the cyclic conformation is itself somehow stabilized relative to the extended conformer by an interaction between the double bonds. Fixation of the folded conformer might be attributed to either a charge transfer mechanism, resulting in a coulombic attraction between the double bonds (X), or a delocalization mechanism (XIa, b c) not unlike the one described for the first model. Of these, the latter mechanism appears to be the more reasonable. The terminal hydrogens of XI would require that the double bonds be in approximately parallel planes rather than in the same plane in order that their mutual overlap be appreciable. Resonance of the type XIa should be more important than that of XIc on the basis of overlap alone. Both of these mechanisms will be considered more quantitatively for the particular case of a 1,5-diene in a later section.

X

XIa   XIb   XIc
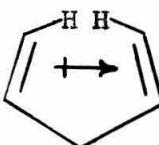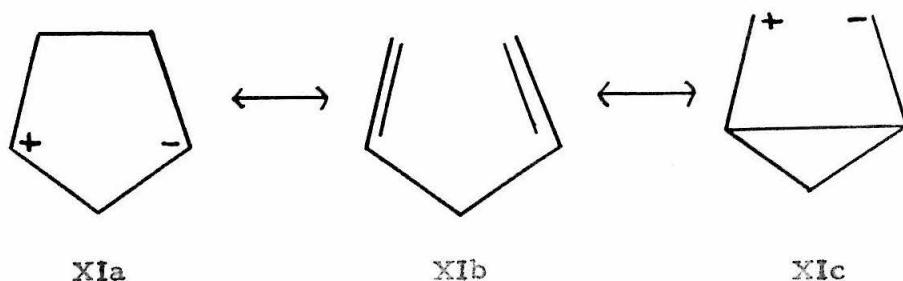
It should be emphasized that the entropy data of Table I are for the gaseous state,* and consequently, do not give any information on the condition of molecules in the liquid phase. The higher dielectric constant usually associated with the condensed phase would, however, be expected to be more conducive to formation of more polar species such as IX, X, and XI.

Molecular Volumes. The extended conformation of a hydrocarbon chain will possess a greater molecular volume than any folded species (e.g. compare the isomers cyclopentane and 1-pentene in Table I). This simple fact suggests a second means of determining the presence of folded conformers in solutions of alkadienes. The average molecular volumes of a number of hydrocarbons are given in Table I. The first section of Table II draws a comparison between the molecular volumes of some normal alkanes and the corresponding 1-alkenes. It is seen that the introduction of a terminal double bond decreases the molecular volume by about 5.7 ml./mole, but that this

---

* Data for the liquid state under comparable conditions was not available in many cases of interest.

Table II

	Olefin[a]	Reference Compound[b]	Δ(Mol. Vol.)[c]	Δ(Mol. Ref.)[c]
1	II-1	I-1	5.720	0.418
2	II-2	I-2	5.706	0.424
3	II-7	I-3	5.712	0.421
4	II-10	I-4	5.68	0.42
5	II-13	I-5	5.629	0.426
6	II-16	I-6	5.575	0.425
		mean	5.670	mean 0.422
7	III-7	II-1	6.506	0.501
8	III-9[d]	II-5	5.1	0.4
9	III-10	II-6	7.97	0.51
10	III-8[d]	II-3	6.04	0.16
11	III-8[d]	II-4	7.60	0.25
12	III-11[d]	II-8	----	0.46
13	III-11[d]	II-9	----	0.59
14	III-12[d]	II-11	----	0.52
15	III-12[d]	II-12	----	0.65
16	III-13[d]	II-14[d]	----	0.64
		mean	6.64	

Table II (cont.)

	Olefin[a]	Reference Compound[b]	Δ(Mol. Vol.)[c]	Δ(Mol. Ref.)[c]
17		II-2	6.472	0.494
18	III-16	II-7	-----	0.484
19	III-17	II-5	-----	0.480
20	III-18[e]	II-14[f]	-----	(0.85)[g]
21	III-19[e]	II-14[f]	-----	(0.50)[g]
22	III-20[d]	II-10	-----	0.44
23	III-21[d]	II-13	-----	0.25
24	III-22[d]	II-16	5.611	0.36

Footnotes to Table II: (a) Numbers refer to the compounds listed in Table I; (b) The reference compound is chosen, except where noted, to differ from the olefin in the first column only by the absence of the terminal double bond; (c) Δ = Ref. Cpd. - Olefin (i.e. decrements due to the presence of the new double bond are given as positive values); (d) See footnotes appropriate to the compound or its constants given in Table I; (e) No terminal double bond; (f) Data for 2-nonene (5) suggest it is too impure to use for comparison (Mol. Ref. calc. 43.30, found 44.78); (g) This value is included for completeness, although it is not possible to assess its significance with much certainty. A decrement of more than 0.69 in the molar refractivity is probably meaningful in the case of a cis-configuration, while the value of 0.58 seems to be a reasonable upper limit in trans-systems (see ref. 2).

REFERENCES FOR TABLES I AND II

1. K. Otozai, S. Kume, and S. Fukushima, Bull. Chem. Soc. Jap., 25, 302 (1952).

2. F. D. Rossini et al., "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," American Petroleum Institute Research Project-44, Carnegie Press, Pittsburgh, Penn., 1953.

3. J. G. M. Brenner and G. D. Thomas, Trans. Faraday Soc., 43, 779 (1947).

4. J. P. McCullough et al., J. Phys. Chem., 61, 289 (1957).

5. M. Bourguel, Bull. soc. chim. Fr., (4), 41, 1475 (1927).

6. M. V. Cox, Bull. soc. chim. Fr., (4), 37, 1551 (1925).

7. A. Kirrmann, Compt. rend., 184, 1463 (1927); ibid., Ann. chim. (10), 11, 277 (1929).

8. P. G. Maslov, Zhur. Fiz. Khim., 31, 1242 (1957).

9. O. Riobe, Ann. chim., (12), 4, 593 (1949); Chem. Abstr., 44, 2984c (1950).

10. D. D. Coffman and E. L. Jenner, J. Am. Chem. Soc., 80, 2872 (1958).

11. A. L. Henne and K. W. Greenlee, J. Am. Chem. Soc., 65, 2020 (1943).

12. H. Pines and N. E. Hoffman, J. Am. Chem. Soc., 76, 4417 (1954).

13. J. L. Everett and G. A. R. Kon, J. Chem. Soc., 3131 (1950).

14. B. H. Shoemaker and C. E. Boord, J. Am. Chem., 53, 1505 (1931).

15. C. Prevost, Bull. soc. chim. Fr., (5), 8, 89 (1941).

16. G. Wiest, Ph. D. Thesis, Ohio State University, Columbus, Ohio (1940).

value decreases as the length of the chain increases. Presumably
the introduction of a second terminal double bond should bring about
a similar reduction in molecular size, if no other changes occur.
In 1,4-alkadienes, however, the inclusion of a second double bond in
the terminal position results in an average molecular volume decrease
of 6.6 ml./mole, which is 17% greater than anticipated. The one
exception is found in the case of 2-methyl-1,4-pentadiene. The purity
of the compound upon which the measurement was made is uncertain
in this instance. The second double bond of 1,5-hexadiene produces
a 14% larger volume decrement than does the first. The decrease
associated with each of the bonds of 1,9-decadiene is the same, sug-
gesting that no special conformation advantage is provided by the
presence of the second multiple bond in the longer chain.*

The data available do not allow the calculation of the molecular
volumes of all the dienes at the same temperature. However, molar
refractivities, which are temperature independent, may be obtained
for all the hydrocarbons of Table I. The introduction of a double bond
produces a net decrease in the molar refractivity, since the two
hydrogen atoms removed have a slightly larger refractivity than the
carbon-carbon double bond. The change associated with the

---

* It should be noted that the volume contractions observed may
simply reflect increased intermolecular attractive forces which
accompany an increase in molecular polarities. If this were the case,
then longer chains should also show slight deviations.

incorporation of one terminal double bond is about 0.42. In almost all of the 1,4-, 1,5-, and 1,6-alkadienes of Table I, the change in molar refractivity is significantly larger than this value. This is indicative of an abnormal change in the polarizability of the dienes, relative to the 1-alkenes, which might possibly be related to a shift in the conformational equilibrium in favor of the folded conformer.

Viscosities. Viscosity measurements may be used to obtain the kinetic theory collision area of a molecule in the gas or liquid phase (65). Since the collision area depends on the conformation of the molecule, viscosity data for the hydrocarbons of Table I would be expected to be very useful in establishing the conformational nature of alkadienes. Although the viscosities of a large number of hydrocarbons have been measured, the alkadienes have been almost completely ignored. Cummings, McCoubrey and Ubbelohde (66), however, have measured the viscosities of n-hexane, 1-hexene, and 1,5-hexadiene in the gas phase, and have concluded that the proportion of folded conformers increases in the order mentioned at a given temperature.

More data are needed before it will be possible to make any useful generalizations about the conformation of alkadienes. At present, however, there is a strong suggestion that certain diolefins may show a greater preference for the more compact, folded conformations than do their partially or totally saturated analogues. It is likely

that the phenomenon may be explained in part by the fact that the introduction of a terminal double bond has the effect of lowering the energy barrier to rotation about the adjacent C-C bond relative to the paraffin (67). The concomitant increase in rotational freedom, however, should lead to a relative increase in the molecular entropy, which is not observed (see Table I). Also, it is difficult to see why the longer chain alkadienes (e.g. 1,9-decadiene) are not more folded relative to the parent paraffins, if more facile rotations around C-C bonds were the only important conformational effects associated with the introduction of double bonds. It was proposed, therefore, that another mechanism(s), involving an electronic interaction of the double bonds, might be important in determining the conformation of diolefinic chains of intermediate length.

Resonance and Conformation in Non-Conjugated Alkadienes

It has been suggested (pp. 29-31) that the folded conformation of certain non-conjugated alkadienes might be stabilized by an electron delocalization mechanism arising from a non-zero overlap of the classically isolated π-systems. The nature of the overlap would differ for the chair (Fig. 3) and boat (Fig. 5) folding of the diene.

Chair Conformer. In the chair conformation of a 1,5-alkadiene, only overlap between the p-orbitals on C-1 and C-6 (Fig. 3) is extensive. These orbitals are almost coaxial, and can be made exactly so with only

a very small deformation (less than 5°) of the C-C-C bond angle at C-3 or C-4. In this configuration of the diene, the approach of C-1 and C-6 is favored by the fact that there is no mutual eclipsing of the hydrogen atoms at these centers. However, folding of the chain in this fashion produces two eclipsed interactions, which are avoided in a linear conformer; namely, the vinyl hydrogens at C-2 and C-5 are brought into opposition with their neighbors on C-3 and C-4, producing a relatively weak repulsive interaction due to the 120° angle at the double bond.

In order to assess the importance of the p-p overlap in stabilizing the chair conformer, simple molecular orbital calculations based on the Hückel approximation were carried out for a number of rotameric forms leading to the limiting chair configuration. These forms are obtained from the conformer of Figure 3 by simple rotations of C-5 around the C_3-C_4 bond in either a clockwise or a counterclockwise manner. Rotation in either direction by 180° will give a particular linear conformation of the diene. Precise measurements of angles and distances were made from accurately scaled (Dreiding) molecular models. These parameters were used to obtain values for the σ- and π-overlap integrals from standard tables (68), which in turn were used to calculate the required resonance integrals (69). The resulting resonance energy (R.E.) of these rotamers is given in Figure 4 as a function of the C_1-C_6 internuclear distance.
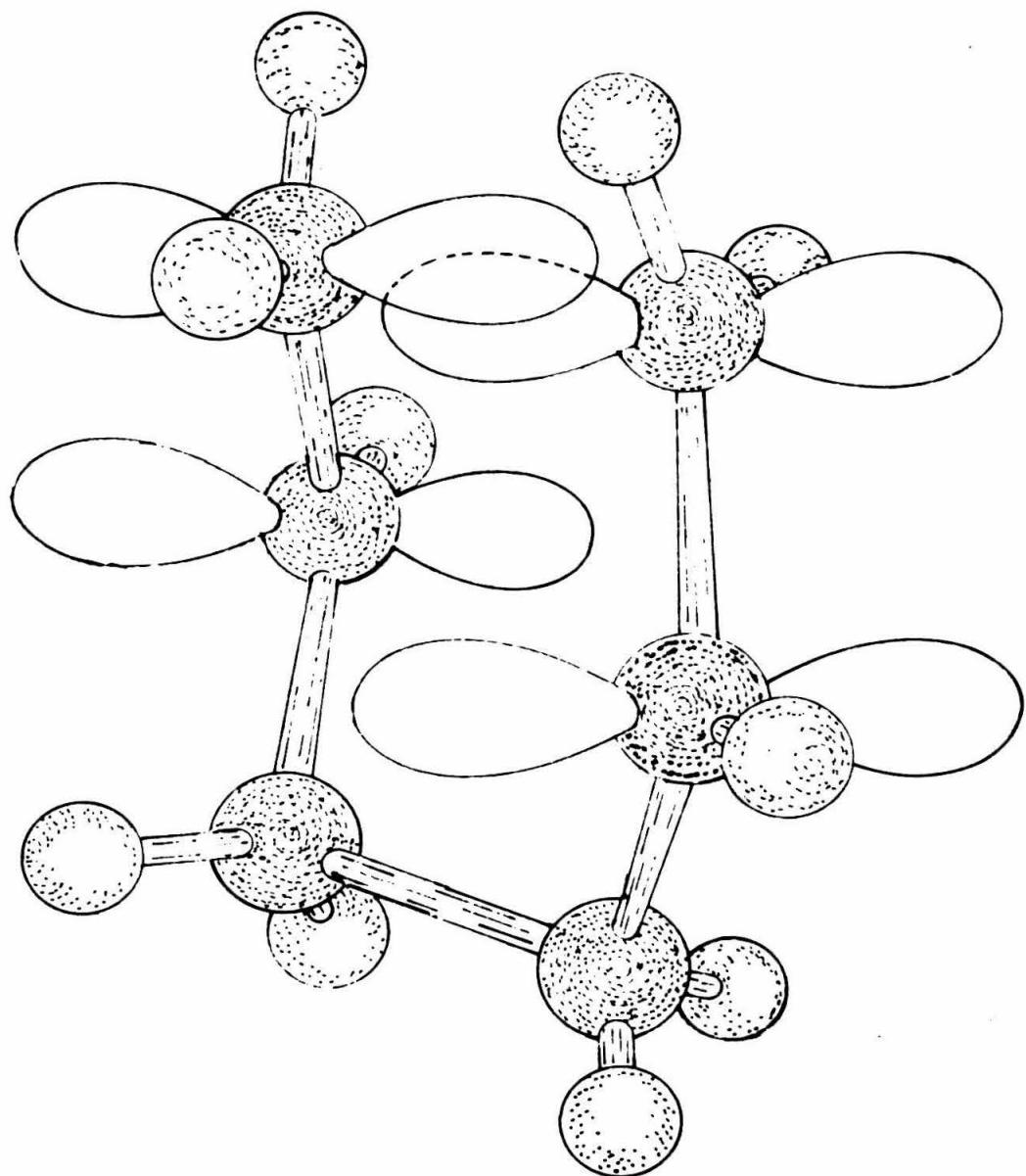
Fig. 3
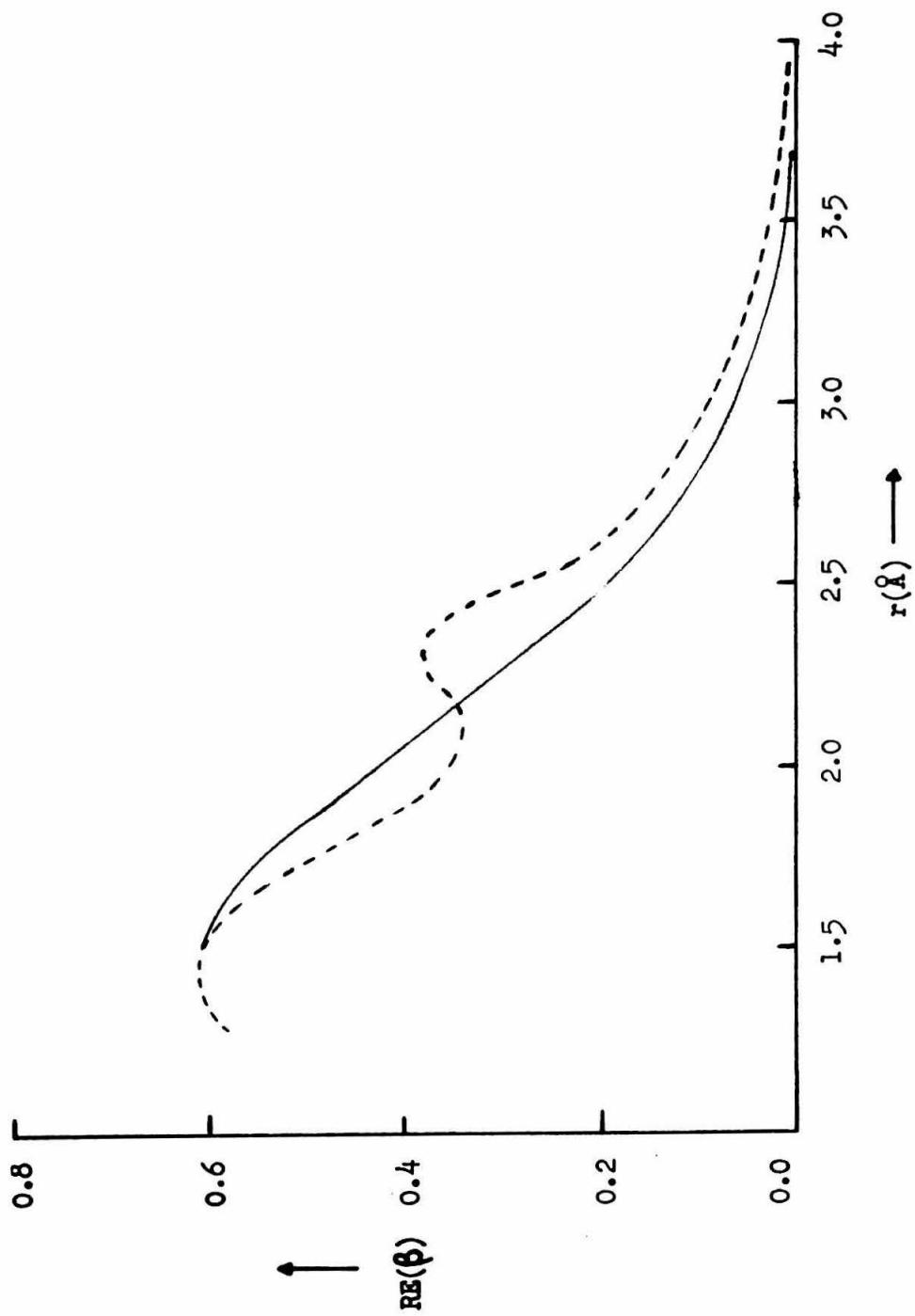
Fig. 4

Resonance energies calculated for rotameric conformations of 1,5-hexadiene
related to the chair form shown in Fig. 3 (see text).

The secular equation associated with the conformation shown in Figure 3 and with those arising from a counterclockwise rotation of the residue at C-5 resembles that of 1,3-butadiene, and consequently the small resonance energy is expected (solid line). The function is maximized when the C_1-C_6 distance corresponds roughly to that of a C-C single bond, since the overlap is primarily σ in character.

If the rotation is performed in the clockwise sense, the p-orbital at C-5 begins to overlap increasingly with that of C-1, while the orbital on C-6 becomes less involved in overlap. The relative stabilization (dotted line, Fig. 4) decreases sharply due to the appearance of a nodal plane between C-1 and C-5 in the highest bonding molecular orbital; the resonance energy reaches a minimum when the overlap of C-5 and C-6 with C-1 are about equal (ca. 2.1 Å.). As rotation in this direction is continued, bonding between C-1 and C-5 becomes more important and antibonding between C-1 and C-6 becomes less important, resulting in an increase in the delocalization energy. A second maximum is reached at a distance of about 2.4 Å., which corresponds to a C_1-C_5 internuclear separation of about 1.9 Å. The resonance energy associated with this maximum may be increased by allowing for some angle deformation in the model, but the total energy of the five membered ring conformation would still be less than that of the unstrained six membered ring. It may also be pointed out that when the overlap between C-1 and C-5 is maximized, the

conformation of the chain is analogous to the "envelope" form of cyclopentane, and the C-3 and C-4 methylene groups are eclipsed as also are the groups on C-1 and C-5. These considerations are in agreement with the fact that rings with five members are usually minor products when 1,5-dienes are cyclized (vide infra).

Boat Conformer. Molecular models of the boat conformation of a 1,5-diene indicate that σ-overlap between the p-orbitals on C-2 and C-5 is almost as extensive as that between C-1 and C-6 (Fig. 5). As long as the overlap between these pairs of centers is equal, the resonance energy predicted by the simple Hückel-type treatment is zero; that is, the bonding orbitals of the ethylene units are symmetrically split, such that there is no net increase in the delocalization energy.* However, the boat folding of a 1,5-diene is fully eclipsed, and for this reason alone would not be expected to be a stable conformation. Rotations in either sense around the C_3-C_4 axis should relieve the steric compressions due to the eclipsed groups, and at the same time would change the nature of the overlap in the system.

For very small counterclockwise rotations the σ overlap between the pairs of centers remains essentially equal, and there is no gain in delocalization energy. For larger rotations (solid line, Fig. 6),

---

* For the special case when all resonance integrals for neighboring atoms are equal to unity, the secular determinant is the same as that obtained for cyclobutadiene, and there is only one bonding orbital; the other orbital having become non-bonding and degenerate.

Fig. 5

44
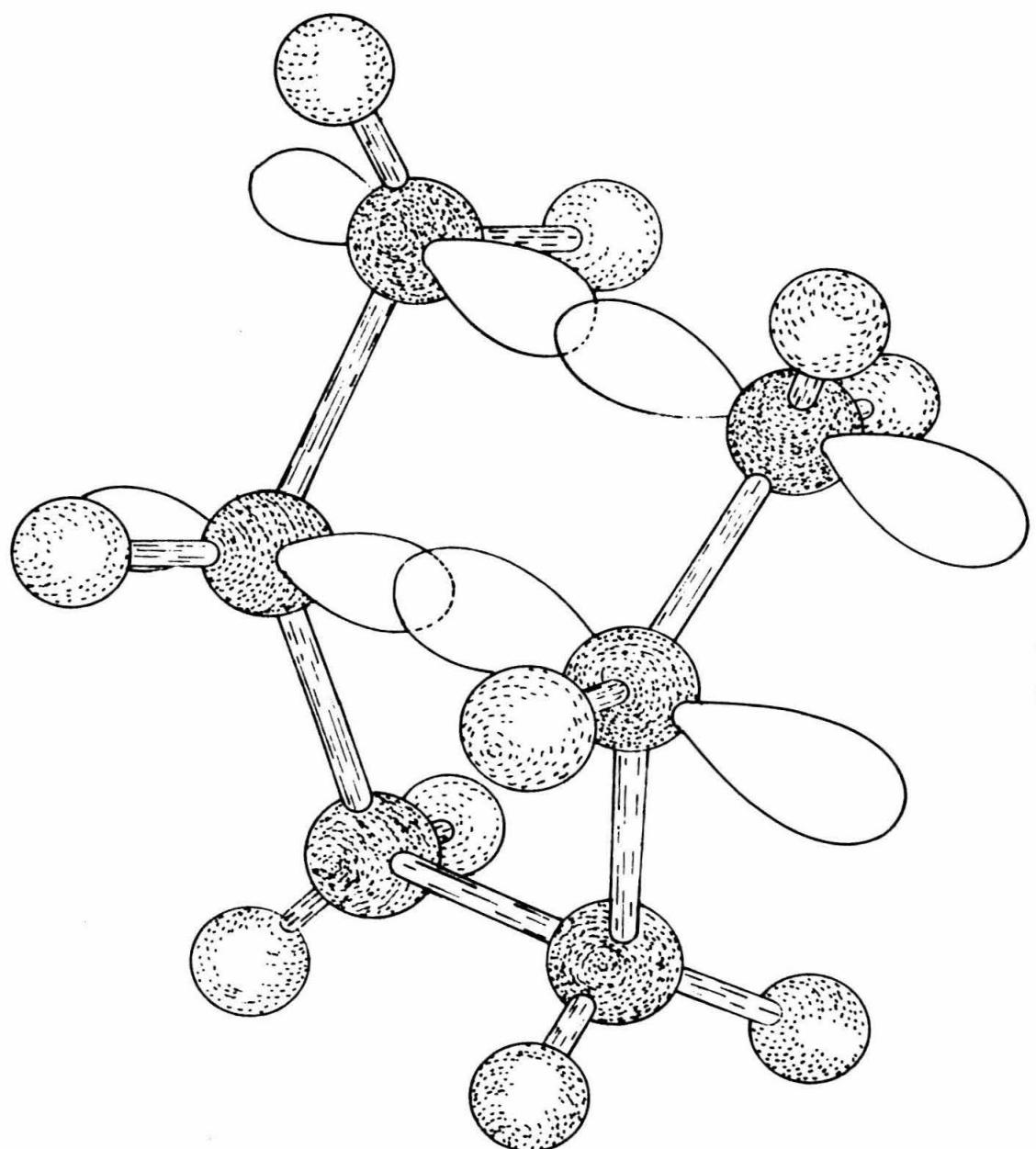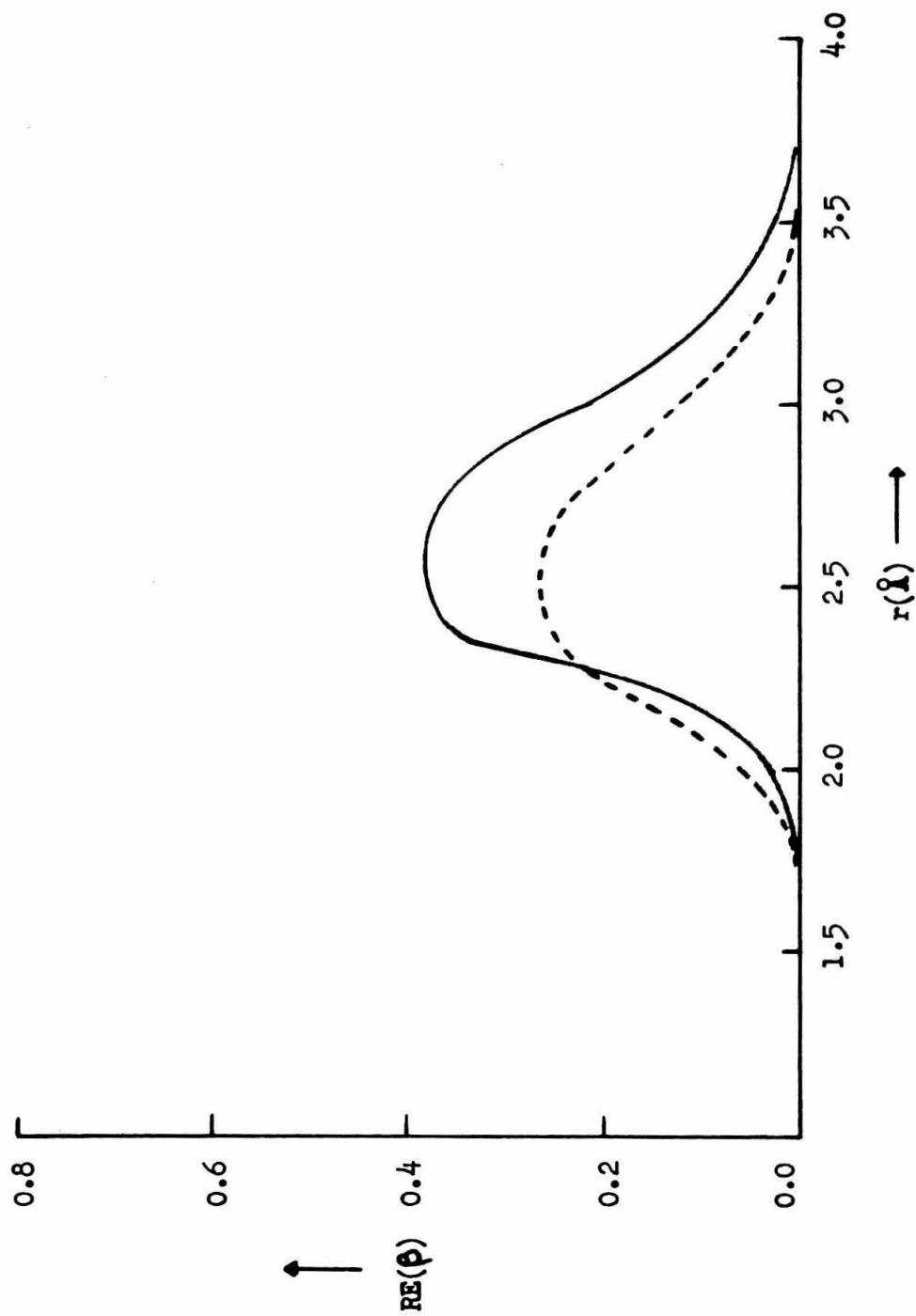
Fig. 6

Resonance energies calculated for rotameric conformations of 1,5-hexadiene related to the boat form shown in Fig. 5 (see text).

however, the p-orbitals at C-1 and C-2 both overlap extensively with that of C-6 as also do those at C-5 and C-6 with the orbital on C-2. The resulting secular determinant resembles that obtained for bicyclobutadiene. Larger increases in resonance energy are predicted as overlap between C-2 and C-6 predominates. Continued rotation diminishes the overlap and the opportunity for electron delocalization, and the resonance energy returns to zero when C-1 and C-6 are separated by about 3.7 Å. This is illustrated by the solid line in Figure 6.

Much the same behavior is observed when clockwise rotations are considered (dotted line in Fig. 6). The broadness of the curves in Figure 6 is due to the fact that small rotations, which do not result in large changes in the overlap values, give rise to relatively large separation between C-1 and C-6.

The Possibility of Intramolecular Complex Formation. That otherwise stable species, when suitably paired, give rise to molecular complexes is a widely studied phenomenon, which has been comprehensively reviewed by a number of authors (70). A variety of mechanisms for complex formation have been proposed, with the Mullikin theory of donor-acceptor interaction (71) appearing at present to be the most widely accepted. In view of this, mention should be made of the possibility for conformational fixation via a mutual (i.e. intramolecular) complexing of the olefinic centers of the 1,5-diene. If

both double bonds were similar, the resulting system would be anal-
ogous to an alkene self-complex, no examples of which are presently
known. Self-complexes, however, have been observed for a few
compounds (72), including benzene * (73). On the other hand, the
double bonds of many 1,5-dienes, especially those derived from natural
sources, are sometimes quite different; often one double bond is
conjugated with a carbonyl function, while the other one is isolated.
In such an instance, the conjugated system may possess an unfilled
orbital, which is sufficiently low lying that a charge transfer process
might provide significant stabilization in the ground state of the complex.
In order that this process be important, the conformation of the diene
must be such as to maximize the overlap between the orbitals involved,
a condition which is obviously met only in the cyclic conformers.

Resonance and Conformation in Non-Classical Ion Intermediates

The non-classical carbonium ions postulated as intermediates
in the acid catalyzed ring closure reactions of 1,5-dienes (p. 16)
are depicted in detail in Figures 7 and 8; these correspond respec-
tively to the chair and boat conformations. The geometry of these
ions is such that the three carbon p-orbitals are not coplanar, and
instead a dihedral exists between the planes containing the orbitals of

---

* The available evidence that benzene forms self-complexes
is not altogether convincing. For a discussion of this see ref. 71.
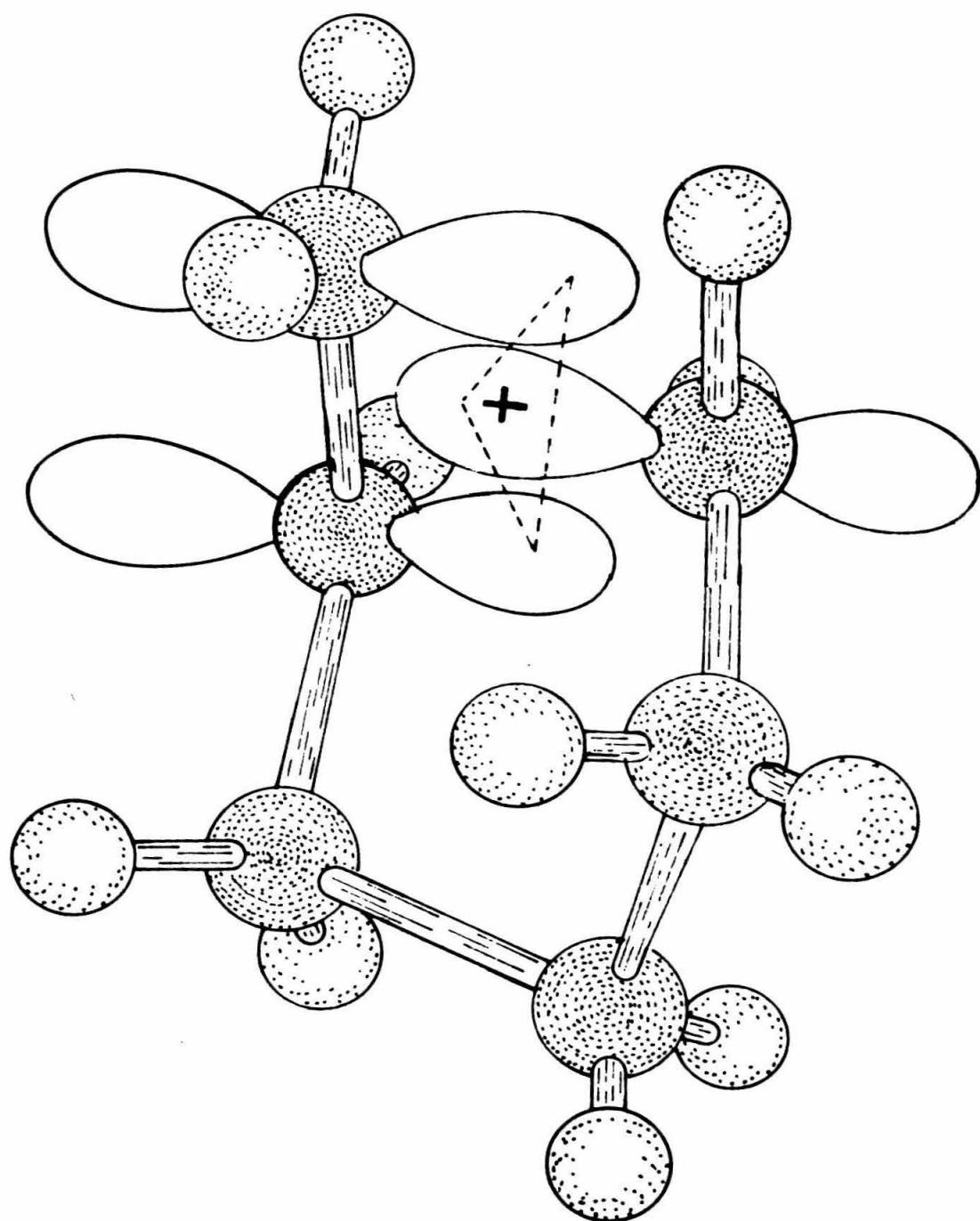
Fig. 7
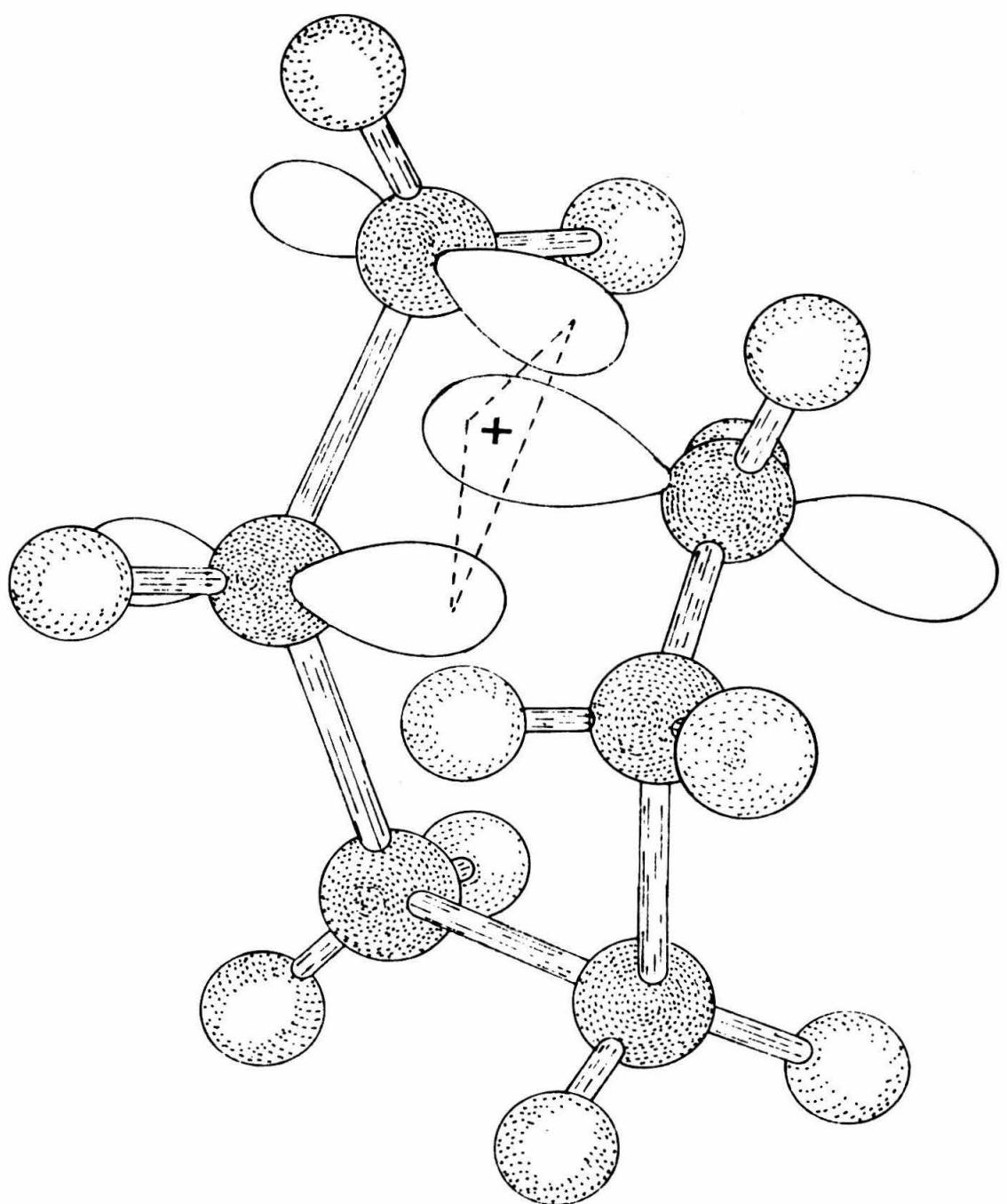
Fig. 8

the C-1 atom and the C-5 and C-6 atoms. The magnitude of this dihedral is about $3/4 \pi$, and is approximately the same for both the chair and boat conformers. The effect of this dihedral is to decrease the total overlap at a given internuclear distance relative to the planar configuration (cf. A and B, Fig. 13, Appendix). This results in decreasing the σ-character of the association, along with a concomitant increase in the π-bonding between C-1 and C-5 or C-6. Since the extent of overlap between C-1 and C-5 or C-6, when symmetrical, is determined by the distance between the C-1 position and the axis between C-5 and C-6, it is possible, assuming no change in hybridization at any center, to give the resonance energy as a function of the average separation distance. The resulting function is shown in Figure 15; the molecular orbital method used in obtaining this plot is described in the Appendix.

Figure 15 indicates a maximum stability of 2.67β occurring when the average separation is about 1.35 Å., although a significant stability is predicted for these ions with separations of up to 3 Å. The value of 1.35 Å. corresponds to a C_1-C_6 internuclear distance of 1.56 Å., indicating that the bond making process would be nearly complete. Differences in the energies of the chair and boat cations would derive largely from conformational differences in the repulsive interactions of the C-H bonds. These will be approximately the same as those described for the diene conformers, except for the altered geometry at C-2, where the proton was introduced.

Geometry of the Cyclization Reaction

General Considerations. The ambiguity concerning the con-
formation of the 1,5-diene during the cyclization process can, in
theory, be easily resolved for a perfectly general case, provided that
a process of trans-addition occurs during which there is maintained
at all times a strict stereochemical control over the course of the
reaction. The requirement for antiplanar addition restricts the number
of conformations which the polyene can assume, if it is to cyclize
according to the Ruzicka scheme. Of all the possible conformations,
only the quasi-chair (Fig. 3) and the quasi-boat (Fig. 5) foldings
satisfy these requirements. Once these conformations have been fixed,
the number of possible stereoisomeric products is reduced from eight
to two. Figure 9 shows that if the cyclization of a molecule such as
XII proceeds stereospecifically with the concomitant antiplanar addition
of the groups A and B, the configuration of the product is determined
by the conformation assumed by the hydrocarbon chain at the time the
ring is closed. The chair folding (XIIa) is anticipated to lead to a
trans-anti-trans configuration (XIIIa), while the boat conformation
(XIIb) should give rise to the trans-syn-trans configuration (XIIIb).
An important observation here is that due to the relative orientations
of R and R' (or of A and B), information concerning the conformational
course of the reaction may be obtained from less general systems.
For example, if A = H, differentiation between the two hypothesized
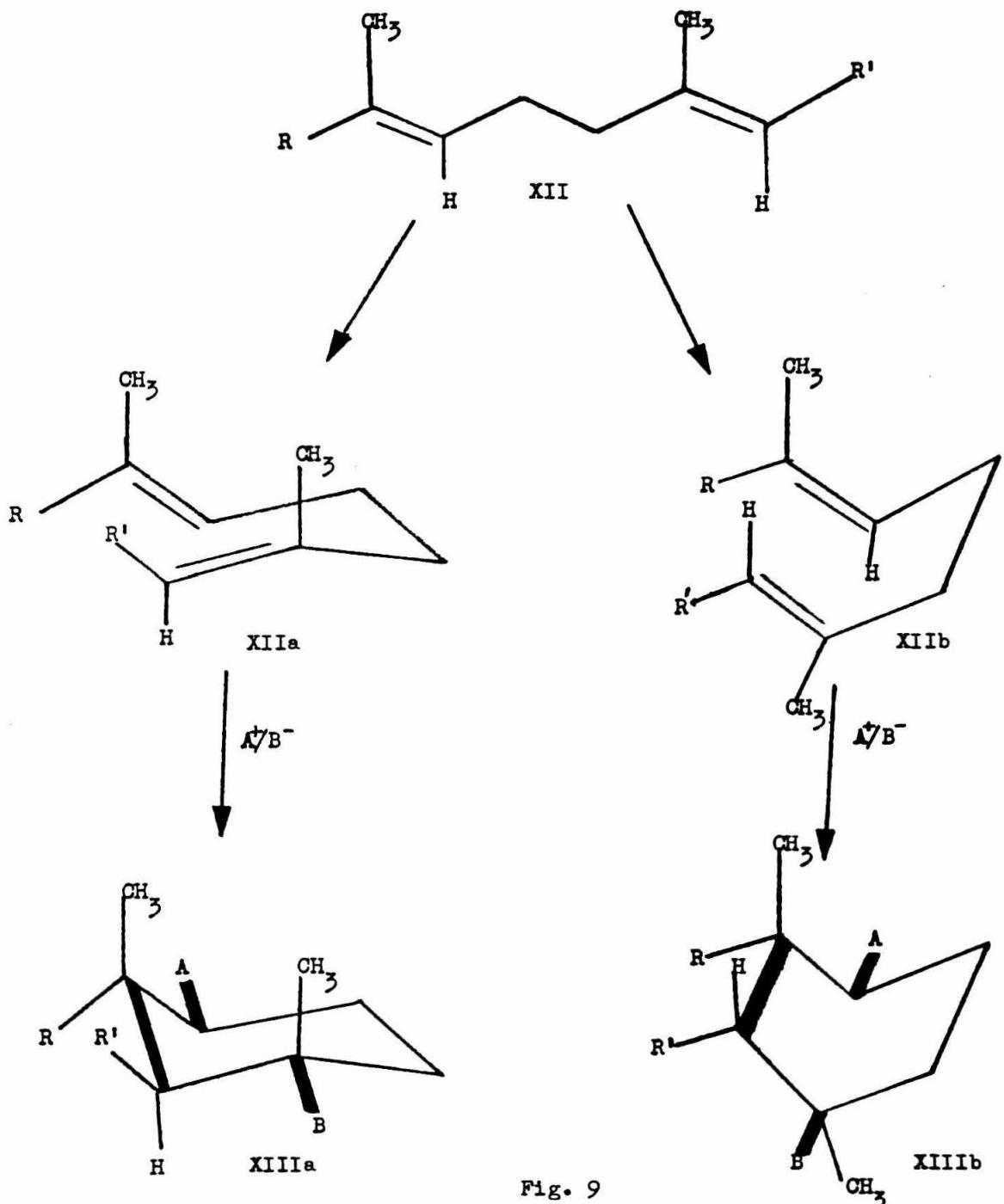
Fig. 9

Conformational and configurational relationships in the
acid catalyzed cyclization of a diisoprenic molecule. The chair
folding leads to a trans-anti-trans configuration, while the
boat folding leads to the trans-syn-trans configuration. (27b)
Note that all of the new bonds formed are nearly parallel.

pathways is possible, since the products will still differ in the ways
in which R and R' are disposed. Even if R' = H, a distinction may be
made, since a 1,3-trans relationship between R and B exists in XIIIa,
while this is a cis relationship in XIIIb. Similarly, if R = CH_3, dif-
ferent products will result, providing, of course, that A ≠ H. (Note
that with R = CH_3 and with A = H, the products XIIIa and XIIIb, as
written, are optical antipodes. However, since the initial attack by
proton can occur from either side of the plane of RCH_3=CH-, a
racemic product results.) Since most compounds of interest to the
terpenoid chemist come already equipped with R = CH_3 (the higher
terpenoids are exceptions), it is a necessary and sufficient condition
that A ≠ H, if any information concerning the conformational course
of the reaction is to be derived from a determination of the stereo-
chemistry of the system in Figure 9.

In terms of the relevancy to the biogenesis of cyclic terpenoids,
this restriction is severely limiting, because of the dearth of electro-
philic species, A^+, that initiate cyclization processes. Indeed, a
good experiment would be to repeat the cyclizations of apogeranic (VI)
and aponeroic (VIII) acids using deuterium or tritium labeled acid.

Proposed Value of Epoxides. Another interesting possibility
for the choice of A is based on the fact that certain biogenetic cycliza-
tions (e.g. squalene to lanosterol) proceed with the concomitant acqui-
sition of one atom of oxygen (74). The oxygen is incorporated into the

molecule at the position believed to be the site of initial electrophilic attack (75). In order to achieve an analogous oxidation-cyclization, it has been proposed that the monoxides of apogeranic (XIVa,b) and aponeroic (XVa,b) be prepared, and an attempt be made to cyclize these molecules stereospecifically with opening of the epoxide function to give the alcohol; the products which might be expected are shown in Figure 10. Each conformational possibility is expected to lead unambiguously to a specific configuration in the cyclic product if the mechanism involves the concerted antiplanar addition described above.

Further, it is frequently the case that in vitro acid cataly ed cyclizations of polyolefins give rise to a large number of products. This is due in part to the fact that initial protonation may occur at any one of a number of basic sites in the molecule. In view of this, it was hoped that the epoxide function would have the additional advantage of providing a specific site for acid attack, and hence, result in subsequent selective cyclization.
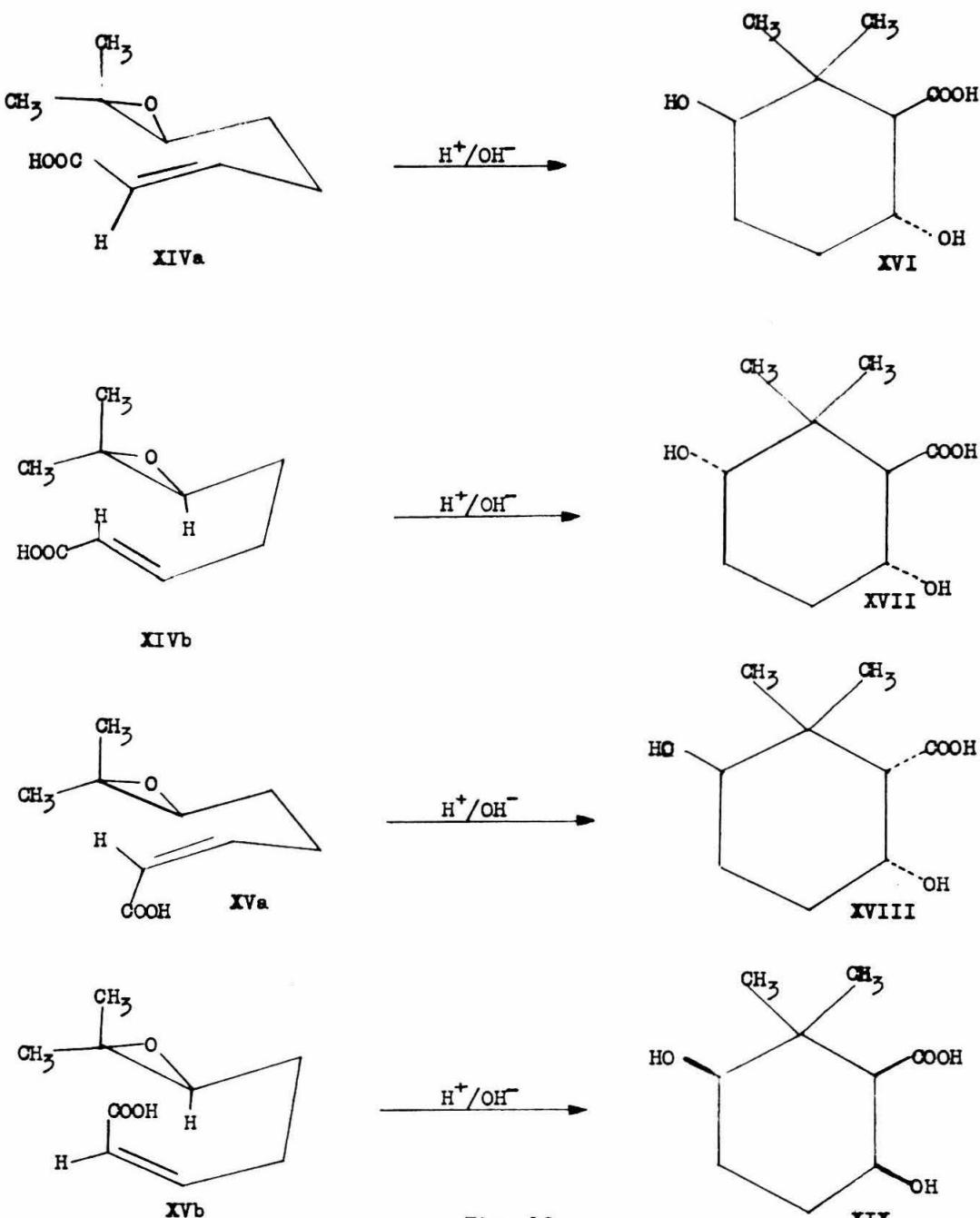
Fig. 10

Anticipated conformational and configurational relationships in the hypothetical acid-catalyzed cyclizations of epoxyapogeranic and epoxyaponeroic acids.

RESULTS

The accessibility of derivatives of geranic acid in comparison
with the relatively long synthetic routes to the apo-acid derivatives
made the former the likely starting point for investigating the acid
catalyzed reactions of 1,5-epoxyolefins (epoxenes). Methyl 6,7-
epoxygeranate (trans-isomer, XX) was prepared and treated with a
mixture of concentrated formic and sulfuric acids, under the same
conditions used by Helg and Schinz (46b) to cyclize apogeranic acid.
There was isolated from the reaction a mixture of keto-acids (50%)
and a mixture of glycolic acids (19%). The keto-acids (XXIa) were
shown* to correspond to those expected for the simple acid catalyzed
isomerization of the epoxide function, accompanied by some isomer-
ization of the position and (possibly) the geometry of the carboxyl
conjugated double bond. There was no evidence for the occurrence of
a skeletal rearrangement during the isomerization process. The gly-
colic acids (XXXIb) similarly represented a mixture of the correspond-
ing epoxide hydrolysis products, and in fact, could be converted to
the keto-acids by treatment with sulfuric acid. Attempts to obtain a
cyclic product from the non-distillable fraction of the reaction mixture
by column chromatography were unsuccessful.

---

* The evidence leading to the structural conclusions given here
is presented in a later section (pp. 63-76).
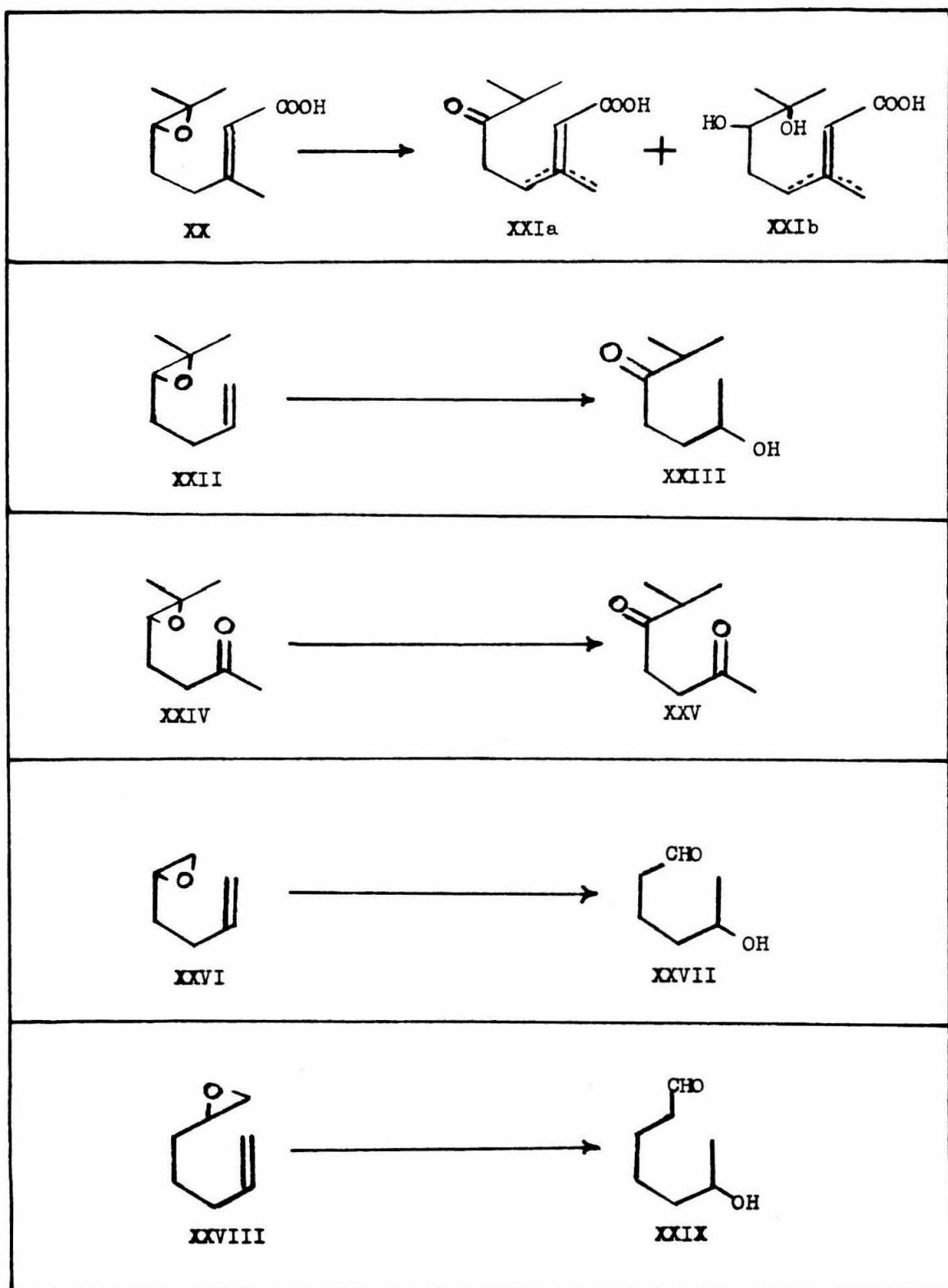
Fig. 11

A number of other methods of acid catalysis were employed in
an attempt to induce cyclization, but in no case could it be shown that
a cyclic product obtained.   Use of concentrated sulfuric acid gave
the keto-acids (XXIa) in 59% yield; considerable tarring occurred and
no glycolic product was found. The use of 85% phosphoric acid gave
only the keto-acids, but in 76% yield. A methanolic solution of p-
toluene sulfonic acid monohydrate gave a low yield (23%) of keto-acids;
the major, and higher boiling point, was not obtained in a pure form,
but its infrared spectrum suggested that it might be the monomethyl
ether of the glycolic acid. Finally, treatment of XX with boron tri-
fluoride in ether solution gave a mixture of carbonyl compounds, which
were not the keto-acids (XXIa) obtained by the other methods. These
were not investigated further, since it did not appear that cyclization
had occurred.

A number of additional epoxenes were prepared and treated
with formic and sulfuric acids. In each case, the major product
represented the isomerization of the epoxide to the carbonyl function
without concomitant skeletal rearrangement. The following reactions
(Fig. 11) were observed: 5,6-epoxy-6-methyl-1-heptene (XXII) to
6-hydroxy-2-methyl-3-heptanone (XXIII) (46%), 5,6-epoxy-6-methyl-
2-heptanone (XXIV) to 6-methyl-2,5-heptadiene (XXV), (65%), 5,6-
epoxy-1-hexene (XXVI) to 5-hydroxy-1-hexal (XXVII) (39%), and 6,7-
epoxy-1-heptene (XXVIII) to 6-hydroxy-1-heptal (XXIX). The low

yields in some of the above cases reflect in part difficulties encountered in distillations of small quantities, and do not necessarily imply an inefficient conversion to the carbonyl compound. In general, all other reaction products were considerably higher boiling than those cited, and hence, probably were not the simple cyclic structures sought, although these were not examined in detail in all cases. Only starting material was recovered when XXIV was treated with an acid exchange resin (Amberlite IR-120) for varying periods up to one week at room temperature.

DISCUSSION

The earliest known attempt to cyclize epoxyolefins was made by Kofron (76). In his work with 6,7-epoxygeranyl acetate, it was found that this compound gave the corresponding acyclic ketone as the major product when treated with concentrated sulfuric acid (23% yield*) and boron trifluoride etherate in ether (36% yield). When this epoxide was treated with 85% phosphoric acid, it was claimed that the desired cyclic alcohol, 6-hydroxy-α-cyclogeranyl acetate was obtained in a 14% yield. The latter results were considered suspect (77) and never published. That this epoxide does not cyclize in boron trifluoride etherate nor under the influence of p-toluenesulfonic acid was later substantiated by Mousseron-Canet and Levallois (78).

When each of the above conditions of catalysis was applied to methyl 6,7-epoxygeranate (XX), no cyclic alcohol was obtained.** In fact, the attempted acid-catalyzed cyclization of epoxyolefins leads in all cases studied either to ketones, to aldehydes, or to glycols derived from the epoxide function. Even when the carbon-carbon

---

* The low yields are presumably due in part to the fact that the labile ester group of both the original epoxide and the ketonic product may be displaced to give rise to a number of additional but unidentified products derived from the allylic cation. In addition, evidence obtained in these laboratories indicates that the material employed in these experiments was perhaps only 65-80% 6,7-epoxygeranyl acetate.

** Independent work by Eschenmoser and coworkers (See discussion, p. 229 , ref. 27b) has similarly shown that no cyclization of 6,7-epoxygeranic acid occurs, although the conditions employed were not specified.

double bond is replaced by the potentially more nucleophilic keto group (XXIV), no cyclization is observed, although the ketoolefin from which the epoxide is derived undergoes facile cyclization to the dihydropyran in dilute mineral acid. It would seem, therefore, that under the conditions specified, hydride migration, elimination of a proton, or nucleophilic attack are overwhelmingly more favorable reaction pathways for protonated epoxides than attack by a double bond located elsewhere on a flexible chain.

Since glycolic products were obtained only when the epoxide was treated with formic acid, it is quite likely that they resulted by way of the largely irreversible formation of the monoformate (79, cf. 46b), and thence to the diformate, possibly via the resonance stabilized orthoformoxyl ion, for which there appears to be ample precedence (80). The appearance of glycolic products may indeed reflect important solvent demands by the protonated oxirane, which cannot be adequately met by the electrons of the isolated double bond (vide infra).

The ketonic and aldehydic products, which represent the major yield in most cases studied, are presumed to arise via a hydride transfer mechanism or less likely via a mechanism involving proton elimination to give the enol. The relative merits of these two constructs have been discussed by Collins (81). As in the "pinacol"

rearrangement, studies on the mechanisms of the epoxide transformation have been complicated by the multiplicity of accessible reaction pathways. The possibility that epoxides may be intermediates in the pinacol rearrangement is not well supported by the available evidence; this topic has also been discussed by Collins (81). Since the epoxide isomerization reaction has been extensively reviewed by various authors (79, 82), it will not be included here.

Inasmuch as pyrethrosin (83) does cyclize readily when treated with acid, it would seem that conformational effects are all important in determining the course of acid induced reactions of epoxyolefins. Here, back side attack by solvent is virtually impossible, due to the presence of the transannular ring carbons. Similarly, hydride migration is probably highly disfavored, since this process would pass through an intermediate configuration in which there would be considerable crowding of groups inside the ring. The fortuitous location of the double bond allows that the new carbon-carbon bond can be formed with a minimum of conformational reorganization.

In contrast to the results so far indicated for acyclic epoxyolefins, Goldsmith (84) has only recently reported that a cyclic alcohol may be obtained as a minor (8-11% of the total) product of the reaction of 5,6-epoxygeraniolene with boron trifluoride etherate in ether. In this work it was found that ketone formation was largely suppressed such that the major product (42-86%) was the fluorohydrin; in fact,

the ketone which did form was produced apparently at the expense of the fluorohydrin. Use of boron trifluoride etherate in benzene was found to enhance cyclization, giving rise also to 1,3,3-trimethyl-1,4-endoxycyclohexane.* Goldsmith suggests that the cyclization process may involve opening of the complexed epoxide ring with olefin participation, since qualitative experiments show that the rate of disappearance of the epoxyolefin in benzene is greater than the corresponding rate for the saturated epoxide. Indeed, one would suspect that the isolated double bond could compete more successfully with benzene for the positive charge than with a more nucleophilic solvent such as ether, assuming no important differences in the activation entropies exist for the two solvent systems. That methyl 6,7-epoxygeranate (XX) and 6,7-epoxygeranyl acetate do not give observable yields of cyclic products is consistent with the lesser degree of nucleophilic character of the conjugated double bonds in these molecules. This lower nucleophilicity may also be exaggerated by complex formation between the ester function and the boron trifluoride. Such a rationale would also account for the fact that methyl heptenone oxide (XXIV) does not cyclize under these conditions.

---

* The formation of this bicyclic ether in benzene is thought to result from the fact that this solvent is not basic enough to remove

$$F_3\bar{B}-\ddot{\underset{..}{O}}$$

(i)
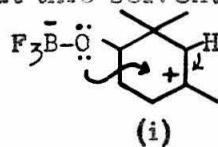
the α-hydrogen of the intermediate carbonium ion (i), which, therefore, seeks out the oxygen electrons.

MATERIALS

Preparative Schemes and Evidence of Structure

Due to the fact that a large number of products are usually
obtained when terpenoids are treated with strong acid (84), it was
desirable that the epoxides used in these experiments be of as high
purity as conveniently possible. To achieve this, it was occasionally
necessary to resort to purification of liquids by vapor phase chro-
matographic techniques on a preparative scale. In so doing there was
always the danger that rearrangements may have occurred in some
terpenoid systems. This danger was minimized, so far as possible,
by using acid-free column materials and moderate temperatures
(50-100°C.).

In many cases, the identification of reaction products was made
largely on the basis of their infrared absorption spectra. In some
instances, independent synthesis was used to confirm the identity of a
given compound. The pertinent data are discussed in detail below.

Methyl 6, 7-Epoxygeranate

Pure geranial (trans-3, 7-dimethyl-2, 6-octadienal) was obtained
from commercial citral by forming the sodium bisulfite addition com-
pound (85) and removing the non-aldehydic contaminants by ether
extraction. The cis-isomer (neral) was largely removed by fractional
distillation. Oxidation of the aldehyde with basic silver oxide (86)

gave geranic acid (trans-3,7-dimethyl-2,6-octadienoic acid). The contaminating neroic acid was readily removed by fractional distillation.

Peracid oxidation of geranic acid led to a mixture of oxidized and unoxidized material, which could not be separated by fractional distillation. Selective epoxidation of methyl geranate, however, with perbenzoic acid or peracetic acid gave good yields of methyl 6,7-epoxygeranate (methyl trans-3,7-dimethyl-6,7-oxido-2-octenoate). The latter was identified as a 1,2-epoxide by the characteristic absorption in the infrared at 876 cm.$^{-1}$ (87), which is thought to be associated with the out-of-plane deformation mode of the oxirane C-H bond (88). Another band at 1250 cm.$^{-1}$ was present, which has been attributed to the epoxide C-O bond (89), though evidence for such an assignment is quite scant. Concomitant loss of the band at 820 cm.$^{-1}$, character-istic of terpenoids with an isopropylidene end-group (also a C-H out-of-plane deformation) (90), was also observed. That the conjugated double bond was not touched is evident by the presence of bands at 1720 cm.$^{-1}$ and 1651 cm.$^{-1}$, indicative of a conjugated ester carbonyl group and a carbon-carbon double bond respectively. This is consistent with the generally observed inertness of a conjugated double bond toward epoxidation in acid media (91).

Finally, hydrolysis of the epoxyester followed by cleavage of the glycol with periodic acid (92) afforded acetone, which was identified by its 2,4-dinitrophenylhydrazone (m.p. 127°C.).

6-Keto-6,7-dihydrogeranic Acid

Fractional distillation of the complex mixture of acids obtained
by treating methyl 6,7-epoxygeranate with formic, sulfuric, or phos-
phoric acid gave a low boiling fraction (b. p. 88-95°C./0.5 mm.),
which gave an elemental analysis for $C_{10}H_{16}O_3$. Analysis by gas phase
chromatography indicated that this material was a mixture of five
acids, three of which amounted to 98% of the total; attempts to resolve
these acids by chromatography on silicic acid were not successful.
Of the mixture of three acids, one component predominated to the
extent of 80%, and has been identified as 6-keto-6,7-dihydrogeranic
acid. The remaining material is quite likely the α- and/or the β-
isomers (cis- or trans-6-oxo-3,7-dimethyl-3-octenoic acid and 6-oxo-
3-methylene-7-methyloctanoic acid). The data leading to these con-
clusions are presented below.

The infrared spectrum of a 5% solution of the three acid
mixture in carbon tetrachloride possessed a complicated absorption
pattern in the region 1600-1800 cm. $^{-1}$ By taking the spectrum of this
material in p-dioxane, which effectively reduces the concentration of
acid dimers in solution (93), it was possible to make, with reasonable
certainty, the assignments shown in Table III. The band at 1650 cm. $^{-1}$
corresponds in position and intensity to the absorption observed in the
spectra of geranic acid, 6,7-dihydrogeranic acid, and several other
trans-acids used in this study; in neroic acid this band is shifted to

Table III

Neat	CCl$_4$	Dioxane	Chromosphore
***	1788 (m)	1780 (m-s)	C=O (unconj'd acid monomer)
***	1755 (s)	1750 (vs)	C=O (conj'd acid monomer)
***	1715 (s)	1712 (w)	C=O (unconj'd acid dimer)
***	***	1699 (m)	C=O (conj'd acid dimer)
1650 (m)	1650 (m)	1650 (m)	C=C (C=O conj'd, trans-acid)
1612 (w)	1610 (w)	1610 (w)	C=C (enol)
935 (m)	935 (m)	***	C-H (conj'd, trans-acid?)
890 (vw)	890 (vw)	***	C-H (C=CH$_2$ of β-acid)
820 (w)	820 (w)	***	C-H (C=CHMe of α-acid)

1643 cm.$^{-1}$ (101). The absorption uncovered in dioxane solution at 1699 cm.$^{-1}$ is most probably due to the carboxyl carbonyl group in the conjugated acid dimer of 6-keto-6,7-dihydrogeranic acid, since a band at 1697 cm.$^{-1}$ is observed for geranic acid in dioxane, while no corresponding absorption is present in the same solvent solution of the unconjugated α-cyclogeranic acid (2,6,6-trimethyl-2-cyclohexene-1-carboxylic acid). The remaining carbonyl absorptions were assigned on the basis of the change in their intensities on going from carbon tetrachloride to the more polar solvent dioxane, and by comparison with the spectral behavior of geranic and α-cyclogeranic acids under the same conditions.

Additional evidence for the trans-configuration of the major
component of the three acid mixture is based on the gross similarity
of the region 650-1000 cm.$^{-1}$ in the spectra of the mixture and of
geranic acid itself. The spectrum of the mixture differs only in that
it contains a number of additional weak bands. Two of these absorptions
may possibly be attributed to the presence of small quantities of the
α- and β-isomers. No argument can be made for the presence of
neroic acid derivatives on the basis of the infrared spectrum, but the
possibility of the presence of small amounts of the cis-material cannot
be discounted.

The infrared spectrum of the sodium salt (nujol) possessed a
somewhat broad band centered at 1705 cm.$^{-1}$, which clearly could
not be due to the carboxyl function. This was assigned to a ketonic
carbonyl group, which assignment was substantiated by the greatly
enhanced intensity of the band at 1610 cm.$^{-1}$ and the appearance of a
very intense band at 2360 cm.$^{-1}$ A band of comparable intensity in
this region has been observed by Cardwell, Dunitz, and Orgel (94)
in the spectrum of potassium monoacid maleate. They have assigned
it to the O-H stretching in the hydrogen-bonded monoacid maleate
anion. A band near 1610 cm.$^{-1}$ has been observed in several systems,
which contain the grouping C=C-O- such as enols, enol acetates, and
vinyl ethers (95). The heightened intensity of this band in the spectrum

of the sodium salt is interpreted as indicating that in the anion, the
enol tautomer predominates, and it is strongly and very likely internally
hydrogen-bonded to the negative carboxyl group (Fig. 12). This is
further supported by the relatively low intensity of the ketonic carbonyl
band observed with the sodium salt. A weak absorption at 3612 cm.$^{-1}$
in the spectrum of the free acid was subsequently attributed to the
enolic O-H bond.
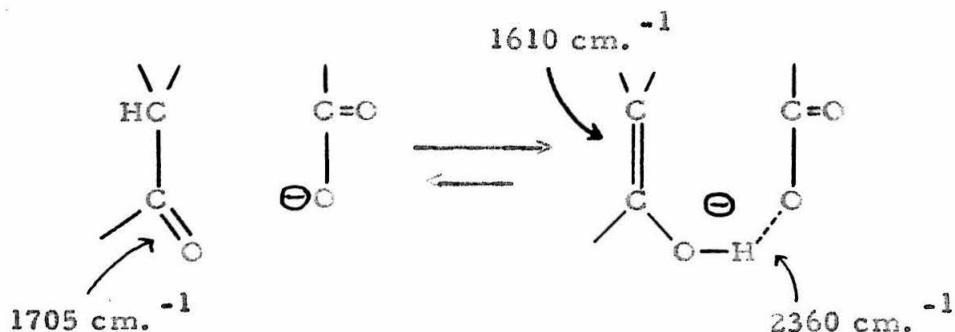
Fig. 12

Chemical confirmation that this material was a mixture of
keto-acids was obtained through the formation of a mixture of 2,4-
dinitrophenylhydrazones, which could be partially resolved chromato-
graphically on alumina; the original mixture did not reduce Tollen's
reagent. The infrared spectrum of the 2,4-dinitrophenylhydrazone of
the methyl ester of the major constituent in the reaction product
mixture showed clearly that it was an α,β-unsaturated ester, and hence,
a derivative of 6-keto-6,7-dihydrogeranic acid (or less likely the cis-
isomer).

Hydrogenation of the acid mixture gave rise to a single saturated acid, which was identical to the product obtained when the saturated epoxide, methyl 6,7-epoxy-2,3-dihydrogeranate, was treated with acid. This keto-acid gave a negative iodoform test. It was obvious, therefore, that no skeletal rearrangement was associated with the isomerization of the epoxide to the ketone.

Treatment of the acid mixture with hot concentrated base (96) and regeneration of the acid gave rise to a mixture containing 88% of 6-keto-6,7-dihydrogeranic acid and 11% of a second conjugated carboxylic acid, which may or may not have been present in the original five acid mixture. This second acid may be the cis-isomer, or 6-keto-6,7-dihydroneroic acid, since it gives the same saturated acid on hydrogenation as does the former. These results are in reasonable agreement with the observations of Linstead (97) on the alkali-catalyzed α,β-β,γ-equilibria of similar unsaturated acids. The nature of this equilibrium has been discussed in detail by a number of authors (98).

The presence of the α-isomer is suggested by the presence of a weak band in the infrared spectrum of the three acid mixture (Table III) near 820 cm.$^{-1}$, which has been considered to be due to the C-H out-of-plane deformation of the RR'C=CHR" group, and which is not present in carbonyl conjugated systems (90b). In a similar manner, the occurrence of a very weak band near 890 cm.$^{-1}$ (terminal methylene C-H deformation) (90a, c) provides evidence for the presence of the β-isomer.

6,7-Dihydroxy-6,7-dihydrogeranic Acid

A high boiling fraction (b.p. 118-124°C./0.5 mm.) was also obtained from the distillation of the product derived from the treatment of methyl 6,7-epoxygeranate with formic-sulfuric acid. This material has been identified as principally 6,7-dihydroxy-6,7-dihydrogeranic acid (trans-6,7-dihydroxy-3,7-dimethyl-2-octenoic acid).

An elemental analysis and molecular weight determination (Rast) of this material indicated its empirical formula was $C_{10}H_{18}O_4$. This fraction was, however, too viscous to be analyzed by vapor phase chromatography in the pure state, and tractable solutions prepared in chloroform, ether, and ethanol showed signs of decomposition on silicone rubber, when using a temperature (175°C.) high enough to provide reasonable retention times. However, the methyl ester, prepared by titrating the acid with diazomethane in ether, was successfully chromatographed in the gas phase at 140°C. The resulting chromatogram indicated a complex mixture in which three major components represented about 90% of the whole.

The infrared spectrum of this material in carbon tetrachloride possessed three distinct bands in the region of the free O-H stretchings: two non-equivalent alcoholic O-H groups were indicated by bands at 3602 cm.$^{-1}$ (tertiary?) and 3626 cm.$^{-1}$ (secondary?) (99); the third band, arising from the carboxyl O-H stretching mode occurred at

3547 cm.$^{-1}$. A much weaker absorption at 3690 cm.$^{-1}$ could not be identified.

The above data strongly implicated a glycolic acid. Catalytic hydrogenation of this mixture of acids over finely divided platinum gave essentially a single acid, which was identical with the 6,7-dihydroxytetrahydrogeranic acid prepared by basic hydrolysis of methyl 6,7-epoxy-2,3-dihydrogeranate and subsequent hydrogenation. Oxidative cleavage of the glycol with periodic acid and potassium permanganate led to the isolation of acetone (as its 2,4-dinitrophenylhydrazone and β-methyladipic acid, m.p. 90-92° C. (100), proving that no skeletal rearrangement had occurred in the original glycolic acid.

5,6-Epoxy-6-methyl-2-heptanone

The 5,6-epoxy-6-methyl-2-heptanone used in these experiments was prepared from natural methyl heptanone via the chlorohydrin and also by direct oxidation with monoperphthalic acid. The product in both cases was identical to the material prepared by Prilezhaev (101), as evidenced by the formation of 5,6-dihydroxy-6-methyl-2-heptanone, m.p. 65-66°C., upon basic hydrolysis. The infrared spectrum of the epoxide possessed the characteristic band at 872 cm.$^{-1}$ (87), while bands at 1680 cm.$^{-1}$ and 812 cm.$^{-1}$, associated with the isopropylidene group of methyl heptenone were absent.

The infrared spectrum of the diol displayed a somewhat unusual

absorption pattern in the carbonyl region: a strong band at 1684 cm.$^{-1}$ and a relatively weak one at 1740 cm.$^{-1}$ indicated that the carbonyl oxygen was extensively hydrogen-bonded (in carbon tetrachloride solution) to one or both of the glycol oxygen atoms. This kind of interaction seems to have been largely neglected in the literature. The spectra of beta-diketones (104), beta-keto esters and beta-keto acids (103) often possess one or more carbonyl absorptions, which have been attributed to hydrogen-bonding in the enolic species. The splittings reported are of the order of 10-15 cm.$^{-1}$ Recently Hill (104) has observed two carbonyl absorptions in the spectrum of 1'-carbomethoxyferrocinyl-methylcarbinol. In this case the bands were separated by 19 cm.$^{-1}$, and the separation was attributed to hydrogen-bonding between the alcoholic and ketonic functions. The splitting of 36 cm.$^{-1}$ observed for 5,6-dihydroxy-6-methyl-2-heptanone, therefore, would seem to be unusually large, and approaches the value found in the spectra of carboxylic acid dimers (105).

6-Methyl-2,5-heptadione

When either 5,6-epoxy-6-methyl-2-heptanone or 5,6-dihydroxy-6-methyl-2-heptanone was treated with strong acid, the only isolable product was 6-methyl-2,5-heptadione. This dione was readily identified by the formation of the known (101) monosemicarbazone, m.p. 197-198°C.

5,6-Epoxy-2,2,6-trimethyl-2,3-dihydropyran

That the major product arising from the treatment of natural methyl heptenone with peracetic acid in chloroform was indeed 5,6-epoxy-2,2,6-trimethyl-2,3-dihydropyran was demonstrated by the independent synthesis of this epoxypyran from the known 2,2,6-trimethyl-2,3-dihydropyran (106) by epoxidation with peracetic acid, and comparison of their infrared absorption spectra. Analysis by V.P.C. indicated that the dihydropyran and the resulting epoxide material were contaminated to the extent of 25-30% with what appeared to be the exo-cyclic isomers.

The infrared spectrum of the epoxide mixture possessed a complicated band structure over the region 800-1100 cm.$^{-1}$ made up of twelve sharp, well-defined absorptions, of which five were quite intense (845, 870, 955, 995, and 1005 cm.$^{-1}$). Of these, the most intense was the epoxide band at 870 cm.$^{-1}$ (87). In addition, the band at 1616 cm.$^{-1}$, which is specific for the C=C-O grouping in dihydropyran systems (107), was not present in the spectrum of the epoxide. The band at 1268 cm.$^{-1}$ in the spectrum of the dihydropyran has been identified as the C-O stretching frequency for the vinyl ether group (108), and has been replaced by a doublet at 1147 cm.$^{-1}$ and 1158 cm.$^{-1}$, which may be characteristic of unsymmetrical ethers (109). The appearance of a band at 1239 cm.$^{-1}$ may also be attributed to the oxirane group (110).

5,6-Epoxy-6-methyl-1-heptyne

Known (111) 6-methyl-5-hepten-1-yne was epoxidized with peracetic acid to give 5,6-epoxy-6-methyl-1-heptyne. The epoxide was identified on the basis of its elemental analysis and its infrared spectrum. Bands attributed to the epoxide function were found at 871 cm.$^{-1}$ and 1260 cm.$^{-1}$, and there was no evidence for a double bond. The characteristic hydrogenic stretching vibration of terminal acetylenes (112) was observed at 3300 cm.$^{-1}$

5,6-Epoxy-6-methyl-1-heptene

This epoxene was prepared by selectively hydrogenating 5,6-epoxy-6-methyl-1-heptyne with a palladium on calcium carbonate catalyst (111, 113). The infrared spectrum of this material possessed a sharp band at 870 cm.$^{-1}$ and a weak band at 1648 cm.$^{-1}$, indicative of the epoxide ring and the terminal double bond respectively.

6-Hydroxy-2-methyl-3-heptanone

The chief product obtained from the treatment of 5,6-epoxy-6-methyl-1-heptene with strong acid gave an elemental analysis for $C_7H_{16}O_2$. The infrared spectrum of this molecule possessed two carbonyl absorptions at 1719 cm.$^{-1}$ (s) and 1702 cm.$^{-1}$ (w) in carbon tetrachloride and a broad band in the O-H region indicative of hydrogen bonding. This evidence suggests that, in addition to the isomerization of the epoxide, the double bond had been hydrated to give presumably

the secondary alcohol. Since the material did not reduce Tollen's reagent, the compound was assigned the structure of 6-hydroxy-2-methyl-3-heptanone, which has not been reported.

5,6-Epoxy-1-hexene

Treatment of a large excess of 1,5-hexadiene with peracetic acid yielded a mixture of mono- and dioxidized material, which was resolved chromatographically. The infrared spectrum possessed a band at 915 cm.$^{-1}$ (C-H deformation of terminal double bond), whose intensity was less than that of 1,5-hexadiene itself. The epoxide band at ca. 870 cm.$^{-1}$ was unusually sharp. Basic hydrolysis of this material gave rise to 5,6-dihydroxy-1-hexene, which was readily identified on the basis of its elemental analysis and infrared spectrum.

5-Hydroxy-1-hexal

Treatment of both 5,6-epoxy-1-hexene and 5,6-dihydroxy-1-hexene with strong acid afforded an aldehyde (positive Tollen's test) with the empirical formula, $C_6H_{12}O_2$. The material appeared to be the same as the 5-hydroxy-1-hexal reported in the literature (114).

6,7-Epoxy-1-heptene

This epoxide was prepared similarly to 5,6-epoxy-1-hexene. Though never obtained in pure form, basic hydrolysis led to the isolation of 6,7-dihydroxy-1-heptene, which was identified on the basis of its elemental analysis and its infrared spectrum.

6-Hydroxy-1-heptal

Treatment of crude 6,7-epoxy-1-heptene with strong acid led to a mixture of aldehydes (positive Tollen's test), the infrared spectrum of which was very similar to that of 5-hydroxy-1-hexal. By analogy the product was assumed to be 6-hydroxy-1-heptal, and was not investigated any further.

EXPERIMENTAL

Use of the physical constants, boiling points, refractive indices, densities, and molar refractivities was made in the characterization of liquid products, when quantities of materials obtained were sufficient for such measurements. Melting points were taken on an Eimer-Amend apparatus (Fischer Co.) and are uncorrected. Analyses were performed by Dr. Adelbert Elek (E), Los Angeles, California, by Schwartzkopf Microanalytical Laboratory (Sch), Woodside, New York, and by Spang Microanalytical Laboratory (Sp), Ann Arbor, Michigan.

Chromatographic Techniques

Both column absorption and vapor phase chromatographic (V.P.C.) techniques have been employed in this work, the details of which are given here.

A. _Alumina:_ A dry-packed column prepared from basic alumina (Merk & Co.) and a wet-packed column prepared from base or acid washed alumina in n-hexane or benzene were used to purify small quantities of high boiling materials and certain 2,4-dinitrophenylhydrazones. In order of increasing polarity, the vehicles used were n-hexane, petroleum ether (30-60°), benzene, chloroform, and ether.

B. _Silicic Acid:_ The following modification of the Ramsey-Patterson column (115) was found to be a convenient expedient for the separation of mixtures of carboxylic acids. A mixture of 100-mesh

silicic acid (454 g., Mallinkrodt Laboratories) and Johns-Mansville Celite-545 (181 g.) are carefully blended in a large mortar. To this is added with careful blending an indicator solution, which is prepared from 34 ml. of a methanolic solution of bromocresol green (0.80 g./100 ml.), 215 ml. of absolute methanol, 46 ml. of water, and 39 drops of freshly prepared 1 N. ammonium hydroxide solution. The material should be bluish-green in color, and may be stored in a tightly capped, paraffin-sealed bottle for a period of several weeks, or indefinitely as a slurry with n-hexane. A column is prepared from the slurry. Petroleum ether and more polar solvents may not be used as vehicles, since they leach the column of indicator. Petroleum ether may be used if it is first purified by washing with sulfuric acid. Wet solvents should be avoided, since they alter the specific hydration of the silicic acid.

C. Vapor Phase Chromatography: Two commercial gas phase chromatographs have been employed for product analysis and purity control. They are: 1) The Vapor-Fractometer, Model 154-C, made by the Perkin-Elmer Corporation of Norwalk, Connecticut. There are several columns available from the manufacturer which can be used with this machine, and they are alphabetically labeled. Those used in this research were "A" (didodecyl phthalate) and "B" (di-2-ethyl-hexyl sebacate). The helium flow rate employed was 60 ml./min.

This instrument is equipped with a fraction collector. 2) The Programmed Temperature Gas Chromatograph, Model 202-A, produced by the F. & M. Scientific Corporation of New Castle, Delaware. This model has a silicone rubber column. Optimal helium flow rate was 20 ml./min.

In a few instances preparative scale gas chromatography was required to obtain pure materials. The instrument available for this purpose was the Megachrom 639-A, produced by Beckman Instruments, Inc., of Fullerton, California.

Chromatographic Analysis of Commercial Citral

A sample of commercial citral (Matheson, Coleman & Bell) was subjected to chromatographic analysis (F. & M.) at varying temperatures between 100-190°C. In all, seven constituents were found. The two principal peaks accounted for an average of about 87% (by measurement of peak areas) of the total sample, being 37% and 50% each. These were identified as neral (cis-isomer) and geranial (trans-isomer), respectively, by making comparisons with the chromatograms of known material, obtained from the corresponding alcohols (K. & K. Laboratories) by the method of Semmler (116). This method, however, was not satisfactory for preparative work.

Preparation of Geranial by Purification of Citral

Non-aldehydic and trace impurities may be removed from

commercial citral via formation of the sodium bisulfite addition compound (117), leaving upon regeneration a mixture of geranial (citral a) and neral (citral b) (118).

In a two liter, thick-walled bottle was placed 410 ml. of water, 410 g. of crushed ice, 180 g. (1.43 mole) of anhydrous sodium bisulfite, and 130 g. (1.55 mole) of sodium bicarbonate. To this was added 110 g. (0.725 mole) of the commercial citral described above. A tightly fitting stopper was wired in place, and the bottle was shaken thoroughly for six hours. The solution, containing very little unchanged citral, is extracted twice with 300 ml. portions of ether.

The aqueous phase is then placed along with 800 ml. of ether in a three liter Erlenmeyer flask fitted with a two-hole stopper. A 500 ml. separatory funnel is attached so as to lead into one hole of the rubber stopper, and the entire apparatus is placed securely on an automatic shaker. In the separatory funnel is placed 325 ml. of a 10% solution of sodium hydroxide. The sodium hydroxide is allowed to trickle into the sulfite solution slowly over a period of an hour, while the contents of the flask are vigorously shaken. The rapid polymerization of citral, which occurs on contact with sodium hydroxide, is prevented by providing an intimate mixture of aqueous solution with the ether. The aldehyde is immediately extracted, and consequently prolonged contact is avoided. After separation of the layers, the aqueous layer is shaken with an additional 170 ml. of 10% sodium

hydroxide solution, and extracted immediately with two 150 ml. portions of ether. The combined extracts are dried over anhydrous sodium sulfate.

The ether is then removed under reduced pressure, and the residual oil is fractionated through a 100 cm. column packed with Pyrex glass helices (1/8" outside diameter). Altogether, the material distilled over the range 83-90° C./2.4 mm., and amounted to 82 g. (yield 75%) of nearly colorless liquid. The highest boiling fraction, 88-90°C./2.44 mm., was refractionated to give 17.5 g. (16%) of 98% pure geranial, b. p. 89.0-89.5°C./2.4 mm., and $n_D^{20.0}$ 1.4878. Additional refraction of the unclaimed material increased the yield to 34%.

The semicarbazone was prepared according to the method of Cheronis and Entrikin (119) and recrystallized from absolute methanol, m. p. 164.0-164.3°C. (lit. 164°C.). The 2,4-dinitrophenylhydrazone was recrystallized from 95% ethanol and had m. p. 109.5-111.0°C. (lit. 110°C.).

Geranic Acid

Geranic acid has been prepared by the mild oxidation of geranial with basic silver oxide (120). Geranial (100 g., 0.66 mole) and 245 g. (1.05 mole) of silver oxide were suspended in 540 ml. of distilled water containing 54 ml. of ethanol; the mixture is chilled to 0°C. A solution

of sodium hydroxide, containing 109 g. (2.72 moles) of solid in 218 ml. of water, was added slowly in small portions over a period of eight hours. The temperature of the mixture was kept below 25°C. The contents of the flask were then shaken for a period of five days. The interior of the vessel was covered with a silver mirror at the end of this time.

The material was filtered in a large Büchner funnel, and the residue of silver and silver oxide was washed abundantly with hot water. The filtrate and washings were combined and acidified with 2 N. sulfuric acid to a pH of about two. This solution was then extracted with five 100 ml. portions of ether. An excess of 2 N. sodium hydroxide was added, and the layers were shaken and separated. The aqueous layer was extracted with three 100 ml. portions of ether to remove any unconverted geranial. Again the aqueous solution was acidified and extracted with five 100 ml. portions of ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate.

The ether was stripped at reduced pressure, and the remaining oil was fractionated through a 40 cm. column packed with glass helices and heated to 115°C. After a small forerun consisting primarily of neroic acid (b. p. 112-122°C./2.4 mm.), a principal fraction distilled at 122-124°C./2.4 mm., and had n_D^{22} 1.4860 (lit. d_D^{20} 1.4869). The yield was 81.4 g. or 74%. This material compared favorably with synthetic homogeranic acid prepared by Barnard and Bateman (121).

The dibromo-derivative was prepared by titrating 0.614 g. (3.64 mmoles) of geranic acid with a solution of bromine in carbon tetrachloride containing 0.85 mmoles/ml. An end-point was achieved when 3.61 mmoles of bromine had been added. Evaporation of the solvent left a viscous colorless oil, which crystallized after several weeks. The unreported 6,7-dibromogeranic acid melted at 82-84.5°C.; recrystallization twice from petroleum ether, m.p. 86.5-87.0°C. This material was readily identified by its infrared spectrum, which was very similar to that of geranic acid itself, indicating that the conjugated double bond had not been saturated, and that no ring had been formed.

Methyl Geranate

A one liter, three-necked, round-bottom flask was equipped with a 125 ml. dropping funnel, a stopper, and a side arm distilling head, which attached to an adapter and led into a one liter receiving flask; the adapter dipped below the surface of 500 ml. of absolute ether containing 25 g. (0.149 mole) of geranic acid. In the three-necked flask were placed 30 g. (0.226 mole) of N-methyl-N-nitroso urea (122) and 500 ml. of ether. A solution of 50% sodium hydroxide (100 ml.) was placed in the dropping funnel and allowed to enter the flask slowly over a period of thirty minutes. After the generation of the diazo-methane subsided, the reaction mixture was warmed gently with a water

bath at 50°C. until the ether solution in the receiving flask became distinctly yellow from an excess of diazomethane. The receiving flask was then allowed to stand at room temperature for about thirty minutes. The ether solution was next washed successively with an excess of 10% sodium bicarbonate solution and with a saturated solution of sodium sulfate.

The ether was removed under reduced pressure, and the crude methyl geranate was fractionated through a 40 cm. column packed with glass helices as described above. Excessive frothing occurred during this distillation, which can be suitably tamed by adding a small amount of 2-octanol, which does not contaminate the distillate. The principal fraction, b.p. 86.0-87.5°C./0.8 mm., n_D^{20} 1.4712 (lit. $n_D^{19.1}$ 1.47143) amounted to 23.6 g. (88%) (123). Nearly quantitative yields of 97% pure methyl geranate were obtained by simply removing the ether from the dried reaction mixture.

α-Cyclogeranic Acid

Cyclization of Geranic Acid: Geranic acid was cyclized in formic acid according to the procedure of Bernhauer and Forester (120a). Recrystallization of the product from petroleum ether gave small colorless prisms, m.p. 105.5-106.5°C.

Cyclization of Methyl Geranate: Methyl geranate was cyclized by the same procedure (124) used in isomerizing geranic acid. Varying

the temperature and the time during which the ester remained in contact with the acid had little effect on the overall yield of the reaction, but it did change the relative amounts of α-cyclogeranic acid and methyl α-cyclogeranate isolated from the reaction mixture. Products here were identified by comparison of both the infrared and nuclear magnetic resonance spectra. Total yield was about 45-55%.

Methyl α-Cyclogeranate

α-Cyclogeranic acid (500 mg., 2.96 mmoles) was titrated with a stock solution of diazomethane (124) in ether. The ether solution was then washed with a 10% solution of sodium bicarbonate and finally with water; the ether was dried over anhydrous sodium sulfate.

The ether was removed under reduced pressure, and the material remaining was distilled to give 422 mg. (80%) of the desired ester, b.p. 47-48°C./2 mm., n_D^{24} 1.4599.

Analysis (E & Sch). Calculated for $C_{11}H_{18}O_2$: C, 72.49%; H, 9.96%. Found: C, 72.15%; H, 9.91%.

Methyl Dihydrocyclogeranate

Methyl α-cyclogeranate (466 mg., 2.8 mmoles) was dissolved in 10 ml. of absolute methanol in a 25 ml. semimicro hydrogenation flask. To this was added 138 mg. of 85% platinum dioxide (Englehard Co.) taking the precaution of not igniting the alcohol. The material was then allowed to absorb one equivalent of hydrogen at room temperature

and pressure. At the end of this time the solution was filtered carefully through a fine grade scintered-glass funnel to remove all traces of catalyst. The solvent was allowed to evaporate. The residue was taken up in a few milliliters of spectrograde carbon tetrachloride, and the solution was carefully fractionated through a 4 cm. Vigreux column. The removal of alcohol is aided by the formation of a carbon tetrachloride-ethanol azeotrope (82.4: 15.8%), which distills at 62-64°C. (125). The saturated ester had b.p. 68-71°C./10 mm., n_D^{23} 1.4715, d_4^{26} 1.2030.

Molar Refractivity. Calculated for $C_{11}H_{20}O_2$: 42.45. Found: 42.03.

Methyl 6,7-Epoxygeranate

Peracetic Acid Oxidation (126): A 500 ml. Erlenmeyer flask was fitted with a Y-tube. A mechanical stirrer was attached, passing through the vertical branch of the Y-tube, while a 125 ml. dropping funnel was placed on the side branch. The Erlenmeyer flask was placed in a one-half gallon Dewar bottle. The Dewar bottle was partially filled with acetone, and enough dry ice was added to bring the temperature of the mixture to -50°C. A solution of 20.0 g. (0.111 mole) of freshly distilled methyl geranate in 150 ml. of technical grade chloroform was placed in the flask and stirred vigorously. To this was added dropwise, over a period of one and one-half hours, 20 ml. (0.128 mole)

of an approximately 40% commercial peracetic acid (Becco Chemical Division) solution containing 0.485 g./ml. of active peracid as determined by titration with potassium iodide and sodium thiosulfate. The peracetic acid was buffered with 1.3 g. (0.0158 mole) of anhydrous sodium acetate. The reaction mixture was not allowed to attain a temperature above -40°C. during the addition. After all of the per-acid had been added, the mixture was allowed to stir at -50°C. to -40°C. for an additional three hours.

An ice cold solution of 28 g. (0.30 mole) of potassium hydroxide in 75 ml. of distilled water was then added with the temperature being maintained below -20°C. The organic layer was separated, and the aqueous phase was extracted three times with 50 ml. portions of chloroform. The chloroform solutions were combined and washed with 50 ml. portions for a saturated solution of ferrous sulfate and a saturated solution of sodium sulfate. The dried chloroform solution was filtered and the solvent was removed under reduced pressure. The crude epoxide was distilled through a 20 cm. vacuum jacketed column packed with glass helices. After a small forerun of unoxidized methyl ester, 12.8 g. of methyl 6,7-epoxygeranate was obtained, b.p. 100-101°C./2.7 mm., n_D^{26} 1.4580-1.4585, d_4^{26} 1.02384.

<u>Molar Refractivity</u>: Calculated for $C_{11}H_{18}O_3$: 52.67. Found: 53.06.

If the recovered methyl geranate is taken into account (1.81 g., b.p. 94-100° C./2.7 mm., n_D^{32} 1.4625-1.4628), the yield was 59% with a 53% conversion. The analytical sample had, $n^{26.0}$ 1.4603.

Analysis (E).   Calculated for $C_{11}H_{18}O_3$:   C, 66.64%; H, 9.15%.
Found: C, 66.74%; H, 9.15%.

Perbenzoic Acid Oxidation (126c, 127):   Freshly distilled methyl
geranate (13.2 g., 0.0725 mole) was dissolved in 250 ml. of technical
grade chloroform and cooled to -45°C. in the apparatus described
above.   To this was added dropwise, over a period of three hours,
240 ml. of a chloroform solution containing 10 g. (0.0695 mole) of
sodium benzoate and 13,5 g. (0.080 mole, 10% excess) of perbenzoic
acid (128) as determined by iodometric titration.   The mixture was
allowed to stand with stirring for an additional three hours.   After-
wards, an ice cold solution of 40 g. (1.0 mole) of sodium hydroxide in
200 ml. of water was added.   The organic layer was removed, and the
aqueous phase was extracted with three 100 ml. portions of chloroform.
The chloroform solution was washed as above.   After removal of the
solvent, most of the material (9.0 g., 64%) distilled at 66-79°C./0.6
mm. and had n_D^{27} 1.4618-1.4630.   Analysis by V.P.C. indicated that
this material was about 90% epoxide and 8% starting material.   Refrac-
tionation gave 6.97 g. (49%) of 96% pure methyl 6,7-epoxygeranate,
b.p. 66-68°C./0.6 mm, $n_D^{27.3}$ 1.4626, which was readily identified
by comparison of its infrared spectrum with that of the known epoxide.

Methyl 6,7-Epoxy-2,3-dihydrogeranate

Methyl 6,7-epoxygeranate, 0.75 g. (3.8 mmoles) was dissolved

in 10 ml. of absolute methanol. To this was added 150 mg. of 85% platinum dioxide. The solution was stirred under hydrogen at room temperature and pressure until no further absorption occurred. The catalyst was then removed by filtering through a fine grade scintered-glass funnel. Distillation over a short path at reduced pressure gave 0.61 g. (81%) of colorless liquid, b.p. 72-73°C./1.1 mm., n_D^{27} 1.4359, and d_4^{26} 0.9063.

Molar Refractivity: Calculated for $C_{11}H_{20}O_3$: 53.87. Found: 55.98. Analysis by V.P.C. indicated the presence of an impurity to the extent of 2-3% as well as a small amount of ethanol; consequently, no carbon-hydrogen analyses were obtained. However, the material was identified as principally saturated epoxyester on the basis of its infrared absorption spectrum, which possessed bands at 1741 cm.$^{-1}$ (saturated ester carbonyl group) and 872 cm.$^{-1}$ (oxirane group).

6,7-Dihydroxy-6,7-dihydrogeranic Acid

Methyl 6,7-epoxygeranate (1.00 g., 5 mmoles) was placed in a 25 ml. hard glass test tube along with 10 ml. of an approximately 30% solution of sodium hydroxide. The test tube was equipped with a micro reflux condenser, and the mixture was refluxed for one hour. The cooled, homogeneous solution was then extracted with three 10 ml. portions of ether, which were discarded. The pH of the solution was then brought down to about two by adding 6 N. hydrochloric acid. This aqueous solution was then extracted continuously with ether for

twenty-four hours. The ethereal extract was washed with 5 ml. of a saturated solution of sodium sulfate, and the aqueous layer was extracted twice with 10 ml. portions of ether, which were combined with the original extract. This material was dried over anhydrous sodium sulfate. The solvent was stripped from the filtered solution, and the viscous residue was distilled through a 4 cm. Vigreux column to give 0.70 g. (70%) of diolic acid, b.p. 108-113°C. 2.5 mm.

The analytical sample had b.p. 111-113° C. 2.5 mm., $n_D^{23.6}$ 1.4950 and d_4^{18} 1.0453.

Molar Refractivity. Calculated for $C_{10}H_{18}O_4$: 52.66. Found: 56.21.

Analysis (E): Calculated for $C_{10}H_{18}O_4$: C, 59.38%; H, 8.97%. Found: C, 59.65%; H, 8.88%.

Methyl 6,7-Dihydroxy-6,7-dihydrogeranate

A stock solution of diazomethane in ether (124) was used to titrate a 500 mg. (2.5 mmoles) sample of 6,7-dihydroxy-6,7-dihydrogeranic acid. After reaching an endpoint, the ether was removed under reduced pressure. The oily residue was then distilled simply to give after a small forerun, 440 mg. (85%) of methyl 6,7-dihydroxy-6,7-dihydrogeranate, b.p. 80-90° C. 0.6 mm., n_D^{24} 1.4763. This material appeared to contain traces of unreacted acid; however, no attempt was made to further purify it.

6,7-Dihydroxytetrahydrogeranic Acid

Methyl 6,7-epoxy-2,3-dihydrogeranate (0.58 g., 2.9 mmoles) was mixed with 10 ml. of a 30% solution of sodium hydroxide and allowed to reflux for one hour in a 25 ml. hard glass test tube equipped with a micro reflux condensor. The solution was cooled and extracted with two 10 ml. portions of ether, which were discarded. The solution was made acid to blue litmus paper with 6 N. hydrochloric acid, and the aqueous solution was extracted continuously with ether for twenty-four hours. The extract was then washed with 5 ml. of a saturated solution of sodium sulfate, which in turn was extracted with two 10 ml. portions of ether. The combined extracts were dried over anhydrous sodium sulfate. Removal of the ether, followed by simple distillation, gave 0.23 g. (40%) of the saturated diolic acid, b.p. 98-106°C./2 mm., n_D^{26} 1.4911.

Analysis (E). Calculated for $C_{10}H_{20}O_4$: C, 58.80%; H, 9.87%. Found: 58.98%; H, 9.21%.

Methyl 6,7-Dihydroxytetrahydrogeranate

6,7-Dihydroxytetrahydrogeranic acid (100 mg., 0.5 mmole) was titrated with a stock solution of diazomethane in ether (124). Evaporation of the solvent gave 94 mg. (88%) of crude glycolic ester with n_D^{26} 1.4856.

6-Keto-6,7-dihydrogeranic Acid

Formic Acid Isomerization: In a typical run, a mixture of 2.20 ml. of 98-100% formic and 0.12 ml. of concentrated sulfuric acid (120) was added slowly to 1.00 g. (5.0 mmoles) of methyl 6,7-epoxy-geranate in a 10 ml. round bottomed flask. The material was not allowed to warm above 40°C. during the addition. The reaction flask, protected from moisture with a calcium chloride drying tube, was then placed in an oil bath at 35°C. for a period of four days.

At the end of this time, the formic acid was removed under reduced pressure at room temperature. The dark residue was taken up in 30 ml. of 2 N. sodium hydroxide solution, which was then heated on a steam bath for one hour to insure the hydrolysis of all remaining ester. The aqueous solution was extracted with two 30 ml. portions of ether, which were discarded. The basic solution was then made acid to blue litmus paper by adding 2 N. sulfuric acid. The resulting solution was extracted continuously with ether for twenty-four hours. The ethereal extract was then dried over anhydrous sodium sulfate.

The ether was then removed from the filtered solution under reduced pressure. The residue was distilled through a 4 cm. Vigreux column. The isomeric mixture of 6-keto-6,7-dihydrogeranic acids distilled at 88-95°C./0.7 mm., and had n_D^{24} 1.4758-1.4784; the yield was 0.40 g. If the recovered 6,7-dihydroxy-6,7-dihydrogeranic acid

(0.19 g., 19% b. p. 118-124°C./0.5 mm., n_D^{22} 1.4956) is taken into account, the yield of keto acids is 50% with a conversion of 43%.

An alternative procedure for obtaining pure keto acid is to chromatograph the dried residue on either neutral alumina with chloroform or preferably on the Ramsey-Patterson column (115) with n-hexane. In either case, the diolic acid remains immobile at the top of the column, and may be removed by extraction of the upper section of the column packing in a Soxlet apparatus.

<u>Analysis</u> (E). Calculated for $C_{10}H_{16}O_3$: C, 65.19%; H, 8.75%. Found: C, 65.75%; H, 8.69%.

A 129 mg. (0.70 mmole) sample of the above mixture of keto-acids was dissolved in 4 ml. of 95% ethanol and titrated with 2.8 ml. (0.70 mmole) of an approximately 0.25 M. solution of Johnson's reagent (129). The 2,4-dinitrophenyl hydrazone crystallized out almost immediately, m.p. 91-94° C. The derivative was chromatographed on neutral alumina. The first band was recrystallized from a 50:50 mixture of petroleum ether (30-60°) and ethanol, m.p. 171.5-173.0°C., 70 mg. (28%). The infrared spectrum indicated that this was the carboxyl conjugated derivative. A second band amounting to 25 mg. (10%) could not be crystallized.

The isomeric keto-acids isolated in the above procedure could be largely converted to the carboxyl conjugated material by treatment with base (130). A sample of 100 mg. (0.53 mmole) of the keto-acid

mixture was taken up in 10 ml. of 50% sodium hydroxide solution.

The resulting mixture was refluxed for thirty minutes in a 25 ml. hard

glass test tube, equipped with a micro reflux condenser. The solution

was then cooled and acidified with 6 N. sulfuric acid to a pH of about

two. This aqueous solution was extracted completely with five 20 ml.

portions of ether. The ether was dried over anhydrous sodium sulfate.

The solvent was removed from the filtered solution by evaporation,

leaving 86 mg. (86%) of crude conjugated material with n_D^{24} 1.4788.

The material could be further purified without distilling by refluxing with

a small amount of decolorizing charcoal in ether. The material thus

obtained was nearly colorless with n_D^{24} 1.4773. The 2,4-dinitrophenyl-

hydrazone melted at 172-173° C., while that of the corresponding

methyl ester melted at 109-111° C. Neither melting point was depressed

when mixed with known material (vide infra).

Sulfuric Acid Isomerization: A mixture of 2.50 ml. of concen-

trated sulfuric acid and 0.25 ml. of distilled water was cooled to 0° C.

in an ice bath. To this was added 500 mg. (2.52 mmoles) of methyl

6,7-epoxygeranate. The material was allowed to stand in an oil bath

at 35° C. for two days. The darkened solution was then poured onto

ice, and the aqueous mixture was extracted continuously with ether for

twenty-four hours. The ether solution was dried over anhydrous sodium

sulfate, after which time the solvent was removed under reduced pressure.

The dark oil was taken up in benzene and placed on a column of

neutral alumina. After 100 ml. of benzene had passed into the column, the contents were carefully extruded. The dark region at the top of the packing was dissevered, and the remainder was dried and extracted thoroughly with ether. Removal of the ether by evaporation afforded 274 mg. (59%) of essentially pure 6-keto-6,7-dihydrogeranic acid, which was identified on the basis of its infrared spectrum. The 2,4-dinitro-phenylhydrazone of the methyl ester melted at 110.0-112.5°C., and showed no depression when mixed with authentic material.

Phosphoric Acid Isomerization: A mixture of 2.50 ml. of 85% phosphoric acid and 500 mg. (2.52 mmoles) of methyl 6,7-epoxygeranate was prepared by slowly adding the ester to the cold acid. The material was allowed to stand for three days in an oil bath at 35° C. At the end of this time, the material was diluted with 5 ml. of ice water and added cautiously to 10 ml. of a 50% sodium hydroxide solution. The basic solution, which was not homogeneous, was refluxed for one hour to insure hydrolysis of all the ester. The cooled solution was diluted to twice the original volume with distilled water, and the resulting solution was extracted completely with ether; the extract was discarded. The aqueous phase was made acid to blue litmus paper with 6 N. sulfuric acid, and extracted continuously for twenty-four hours with ether. The yellow extract was then dried over anhydrous sodium sulfate.

After removal of the solvent the material remaining distilled to give 0.36 g. (76%) of carboxyl conjugated 6-keto-6,7-dihydrogeranic

acid, with b.p. 81-91°C./0.5 mm. and n_D^{25} 1.4767. Analysis by V.P.C. indicated that the product was about 95% homogeneous. The 2,4-dinitrophenylhydrazone of the methyl ester had m.p. 109-112°C. and showed no depression when mixed with known material.

Isomerization with p-Toluenesulfonic Acid: A saturated solution of methanol and p-toluenesulfonic acid monohydrate (10 ml.) was added to 500 mg. (2.52 mmoles) of methyl 6,7-epoxygeranate and the mixture was allowed to stand for three days in an oil bath at 35° C. The solution was then diluted to 25 ml. with distilled water, and extracted with three 10 ml. portions of ether. The extract was shaken with 20 ml. of 2 N. sodium hydroxide solution, which was saved, and then with 10 ml. of water. Drying of the extract followed by distillation produced 156 mg. of material with b.p. 102-131° C./2mm., and n_D^{23} 1.4781. Analysis by V.P.C. indicated that this material was mostly starting material with some methyl 6-keto-6,7-dihydrogeranate. Some of the material was too high boiling to pass through the column. The infrared spectrum showed the presence of some alcoholic material which displayed extensive intramolecular bond (bonding unaffected by concentration changes), and is presumed to be the monomethyl glycolic ether.

The aqueous phase was acidified with 6 N. sulfuric acid and extracted with four 10 ml. portions of ether, which were washed with 10 ml. of water and dried. This was titrated with a stock solution of diazomethane in ether (124). The oil (112 mg., 23%) recovered after

removal of the solvent yielded a 2,4-dinitrophenylhydrazone which melted at 76-91° C. Several recrystallizations from a petroleum ether and ethanol mixture gave a derivative with m.p. 109.5-111.5° C., which was not depressed upon admixture with the 2,4-dinitrophenyl-hydrazone of methyl 6-keto-6,7-dihydrogeranate.

Isomerization with Boron Trifluoride: A one gram sample (5 mmoles) of methyl 6,7-epoxygeranate was dissolved in 25 ml. of absolute ether. To this was added 5 ml. of freshly distilled boron trifluoride etherate (131), and the system was refluxed for one day. The ether solution was washed twice with 10 ml. portions of water. The ether solution was dried and the solvent removed under reduced pressure. The residue gave a positive test for a carbonyl compound with 2,4-dinitrophenylhydrazine reagent, but the derivative would not crystallize. The derivative was chromatographed on alumina with benzene as the vehicle, and two principal bands were obtained. The first gave a crystalline material with m.p. 121-122°, while the second band material could not be crystallized.

Isomerization of 6,7-Dihydroxy-6,7-dihydrogeranic Acid: One gram (5 mmoles) of 6,7-dihydroxy-6,7-dihydrogeranic acid was added to a mixture of 2.1 ml. of 98-100% formic acid and 0.15 ml. of concentrated sulfuric acid. The liquid turned reddish-brown after a few moments with slight warming from the exothermic process. It was allowed to stand at room temperature until the following day. To the

mixture was added 1 ml. of water, and the formic acid was removed under reduced pressure at room temperature. The dark residue was made basic with 2 N. sodium hydroxide solution, and the resulting system was extracted with ether. The pH of the aqueous layer was brought to about two with 6 N. hydrochloric acid. An organic layer formed, which was extracted continuously into ether for twenty-four hours. The extract was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave a residue, which was shown to be primarily 6-keto-6,7-dihydrogeranic acid by V.P.C. analysis.

The ketone was isolated as the methyl ester by the procedure already described. The crude ester was chromatographed on alumina using n-hexane as a carrier. This afforded 412 mg. (41%) of methyl 6-keto-6,7-dihydrogeranate with n_D^{24} 1.4693. Analysis by V.P.C. indicated that the methyl ester comprised about 90% of the isolated material.

Methyl 6-Keto-6,7-dihydrogeranate

A stock solution of diazomethane in ether (124) was used to titrate 0.29 g. (1.58 mmole) of 6-keto-6,7-dihydrogeranic acid. The ether was removed by evaporation, and the oil that remained was distilled, b.p. 87-89° C./1 mm., n_D^{24} 1.4690. The yield was 188 mg. (60%).

Analysis (E). Calculated for $C_{11}H_{18}O_3$: C, 66.64%; H, 9.15%. Found: C, 66.58%; H, 9.2%.

The 2,4-dinitrophenylhydrazone was prepared by the method of Cheronis and Entrikin (119) from 163 mg. (0.82 mmole) of the ester. The crude derivative was placed on a column of alumina and eluted with n-hexane. Two bands formed, which gave in order of elution: A, 120 mg. (41%) and B 70 mg. (23%). After several recrystallizations from petroleum ether (30-60° C.), A yielded yellow prisms, m.p. 110.5-112.0° C., and was identified as the derivative of the carboxyl conjugated ester on the basis of its infrared spectrum in carbon tetrachloride. Similarly, B gave with considerable difficulty a few small crystals, m.p. 87-96°, and was identified as the derivative of the unconjugated ester.

The analytical sample of A showed no further change in melting point on additional recrystallizations from petroleum ether.

Analysis (E). Calculated for $C_{17}H_{22}N_4O_6$: C, 53.96%; H, 5.86%. Found: C, 53.83%; H, 5.80%.

6-Ketotetrahydrogeranic Acid

Hydrogenation of 6-Keto-6,7-dihydrogeranic Acid: In a 25 ml. hydrogenation flask was placed 10 ml. of absolute ethanol containing 0.68 g. (3.7 mmoles) of an isomeric mixture of 6-keto-6,7-dihydrogeranic acids. To this was added cautiously, so as not to ignite the ethanol, 150 mg. of 85% platinum dioxide. The contents of the flask were stirred under hydrogen at room temperature and pressure. The hydrogen uptake ceased after about one equivalent of hydrogen had

been absorbed. After removal of the catalyst by filtration through a fine grade scintered-glass funnel, the solvent was removed by evaporation. The residual oil was fractionated through a 4 cm. Vigreux column. A center cut, b. p. 85-95° C./0.5 mm., had n_D^{25} 1.4570-1.4578, and afforded 0.50 g. (73%) of the saturated acid.

For analysis, the above material was redistilled to give a fraction with b. p. 85-88° C./0.5 mm. and n_D^{25} 1.4571.

Analysis (E). Calculated for $C_{10}H_{18}O_3$: C, 64.69%; H, 9.74%. Found: C, 64.58%; H, 10.06%.

A 36 mg. (0.19 mmole) sample of 6-ketotetrahydrogeranic acid was taken up in five drops of absolute ethanol, and titrated with 0.78 ml. (0.19 mmole) of 0.25 M. Johnson's 2,4-dinitrophenylhydrazine reagent (127). A few drops of water were added to complete the precipitation, and the mixture was cooled to 0° C. The curdy material was recrystallized from a large volume of petroleum ether (30-60°) giving 22 mg. (32%) of short yellow needles. Several additional recrystallizations from a solution of 5% chloroform in petroleum ether yielded a derivative with m.p. 153.5-156.0° C.

Isomerization of Methyl 6,7-Epoxy-2,3-dihydrogeranate: One hundred milligrams (0.5 mmole) of methyl 6,7-epoxy-2,3-dihydro-geranate was mixed with 0.22 ml. of 98-100% formic acid and 0.001 ml. of concentrated sulfuric acid in a test tube, and was allowed to stand stoppered in an oil bath at 35° C. for three days. The formic acid was

removed under reduced pressure at room temperature, and 5 ml. of 6 N. sodium hydroxide solution was added. The mixture was heated for 30 minutes on a steam bath. The solution was then acidified with 6 N. sulfuric acid, and the contents were extracted completely with several small portions of ether. The combined extracts were dried over anhydrous sodium sulfate.

The ether was removed by evaporation, and the residue was chromatographed on a modified Ramsey-Patterson (115) column of silicic acid and celite, using n-hexane as a carrier. One band was eluted, which gave 38 mg. (41%) of 6-ketotetrahydrogeranic acid. This material was identified by comparison of its infrared spectrum with that of the known saturated keto-acid. The 2,4-dinitrophenyl-hydrazone was prepared and melted at 150-152° C., after one recrystallization from chloroform and petroleum ether.

Methyl 6-ketotetrahydrogeranate

A 145 mg. (0.75 mmole) portion of methyl 6-keto-6,7-dihydrogeranate was dissolved in 6 ml. of absolute ethanol in a 15 ml. hydrogenation flask, and to this was carefully added 29 mg. of 85% platinum dioxide catalyst. After one equivalent of hydrogen had been absorbed at room temperature and pressure, the gas uptake ceased. The catalyst was removed by filtration, and the solvent was removed by evaporation. This afforded 107 mg. (73%) of saturated ester with

$n_D^{23.2}$ 1.4499. Analysis by V.P.C. indicated that the material was about 95% pure.

The 2,4-dinitrophenylhydrazone of methyl 6-ketotetrahydro-geranate was prepared according to the procedure of Cheronis and Entrikin (119). The oily derivative was chromatographed on a column of acid-washed alumina with benzene. After several recrystallizations from petroleum ether (30-60°), 4 mg. (15%) of yellow prisms were obtained, which had m.p. 114-116° C.

6-Hydroxy-6,7-dihydrogeranic Acid

6-Keto-6,7-dihydroxygeranic acid (1.0 g., 5.4 mmoles) was dissolved in 15 ml. of absolute methanol. This was added to 50 ml. of absolute methanol containing 1 g. (28 mmoles) of sodium borohydride (Metal Hydrides, Inc.). The mixture was allowed to stand overnight at room temperature. Glacial acetic acid (15 ml.) was added to the solution and allowed to stand for an additional one hour.

The methanol was evaporated on a steam bath, and the residue was taken up in 75 ml. of water, and acidified to a pH of about two with 2 N. sulfuric acid. The aqueous solution was extracted continuously with ether for twenty-four hours, and the extract was dried over anhydrous sodium sulfate. Removal of the solvent and simple distillation gave 0.69 g. (68%) of product with b.p. 119-142° C./0.5 mm., and n_D^{23} 1.4845.

The analytical sample was redistilled and had b.p. 126-133° C./ 0.5 mm. and n_D^{24} 1.4841.

Analysis (E) Calculated for $C_{10}H_{18}O_3$: C, 64.49%; H, 9.74%. Found: C, 64.21%; H, 9.88%.

Methyl 6-Hydroxy-6,7-dihydrogeranate

Titration of 0.4 g. of 6-hydroxy-6,7-dihydrogeranate (2.2 mmoles) with a stock solution of diazomethane in ether (10) gave, upon evaporation of the solvent, an oil which distilled at 92-96° C./0.5 mm. and had n_D^{25} 1.4773. The yield was 0.34 g. (78%).

Analysis (E). Calculated for $C_{11}H_{20}O_3$: C, 65.97%; H, 10.07%. Found: C, 66.14%; H, 10.14%.

6-Hydroxytetrahydrogeranic Acid

Absolute methanol (6 ml.) was used to dissolve 0.40 g. (2.14 mmoles) of 6-ketotetrahydrogeranic acid, and this was added to an additional 50 ml. of absolute methanol containing 0.31 g. (8.6 mmoles) of sodium borohydride. The mixture was allowed to stand for four hours, after which time it was refluxed for an additional one hour. At the end of this period, 5 ml. of glacial acetic acid was added, and the solution was allowed to stand overnight.

The solution was evaporated on a steam bath at reduced pressure to remove most of the methanol. The white solid residue was dissolved in 50 ml. of water. The resulting aqueous solution was acidified to a

pH of about two with 2 N. sulfuric acid, and the solution was extracted continuously in a modified Soxlet apparatus for twenty-four hours. The extract was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was distilled simply over a short path to give a major fraction of 0.24 g. (60%) with b.p. 110-136° C./0.5 mm., n_D^{25} 1.4803.

For analysis a few drops of this material was redistilled in an Emich tube (132) at 0.4 mm.

Analysis (E). Calculated for $C_{10}H_{20}O_3$: C, 63.79%; H, 10.71%. Found: C, 63.60%; H, 10.24%.

Methyl 6-Hydroxytetrahydrogeranate

Approximately 100 mg. (0.53 mmoles) of 6-hydroxytetrahydro-geranic acid was titrated with a stock solution of diazomethane in ether (124). The ether was removed by evaporation leaving an oil with n_D^{24} 1.4719. A few drops of this material was distilled in an Emich tube (132) at 0.4 mm. to provide the analytical sample.

Analysis (E). Calculated for $C_{11}H_{20}O_3$: C, 65.31%; H, 10.96%. Found: C, 65.09%; H, 10.44%.

5,6-Epoxy-6-methyl-5-hepten-2-one

The following oxidation with monoperphthalic acid (133) is based on available procedures for the oxidation of naturally occurring ketones (126c, 134).

A solution of 38 g. (0.30 mole) of freshly distilled 6-methyl-5-hepten-2-one (natural methyl heptenone, Trubek Labs.) in 100 ml. of absolute ether was chilled to 0° C. To this was added dropwise, over a period of thirty minutes, 625 ml. (0.36 mole) of an ether solution containing 0.108 g./ml. of active monoperphthalic acid, which was also at 0° C. The mixture was allowed to stand in a refrigerator at -5° C. for a period of five days. At the end of this time a standard iodometric titration indicated that about 85% of the peracid had been consumed.

The solution was filtered to remove the precipitate of phthalic acid. The dissolved acid was removed by washing with 300 ml. of a 1 M. solution of sodium carbonate. This was followed by washing with a saturated solution of sodium sulfate, and the ether layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the resulting oil was distilled to give 28.9 g. (68%) of the epoxide, b.p. 74-76° C./54 mm., and n_D^{20} 1.4308 (135).

Analysis (E). Calculated for $C_8H_{14}O_2$: C, 67.57%; H, 9.93%. Found: C, 67.53%; H, 10.03%.

The 2,4-dinitrophenylhydrazone was prepared according to the method of Cheronis and Entrikin (119); tiny yellow prisms from carbon tetrachloride, m.p. 123.5-125.5° C.

5-Chloro-6-Hydroxy-6-methyl-2-heptanone

To a five liter flask containing 800 g. of cracked ice, there was added a solution of 25 g. of mercuric chloride in 500 ml. of water.

A cold solution of 190 g. of sodium hydroxide in 500 ml. of water was added and a rapid stream of chlorine gas was passed into the mixture, which was maintained at 0° to 5° C. This was continued until all of the yellow mercuric oxide disappeared. Finally, 1600 ml. of cold 1.5 N. nitric acid was added slowly with stirring. The concentration of the hypochlorous acid in this solution is about 3.5%.

Freshly distilled natural methyl heptenone (50 g., 0.396 mole) was placed in a two liter separatory funnel. To this was added 400 ml. of the above solution of hypochlorous acid. This was shaken vigorously by hand with occasional cooling in an ice bath to maintain a temperature of 15° C. or less. The shaking was continued until a 1 ml. test portion gave no yellow color when treated with a few drops of a solution of potassium iodide. The process was repeated until no more hypochlorous acid was consumed.

The resulting solution was saturated with sodium chloride and steam distilled. About six liters of distillate was collected, which was also saturated with sodium chloride and then extracted with five 500 ml. portions of ether. The combined extracts were dried over anhydrous sodium sulfate. Removal of the solvent left a dark, acrid-smelling oil, which upon distillation gave 16.3-19.8 g. (23-28%) of the chlorohydrin, b.p. 60-66° C./1 mm., n_D^{22} 1.4641. Since the material decomposed very quickly with loss of HCl, a good analysis could not be obtained.

The 2,4-dinitrophenylhydrazone (119) was prepared and chromatographed on neutral alumina with benzene as the vehicle. One band was obtained, which upon recrystallization from 50:50 acetone-methanol gave fine yellow crystals with m.p. 142.5-143.5° C. This material also decomposed slowly on standing.

Analysis (E). Calculated for $C_{14}H_{19}N_4O_5Cl$: C, 46.86; H, 5.34; N, 15.61; Cl, 9.88. Found: C, 46.95%; H, 5.00%; N, 15.07%; Cl, 10.16%.

5,6-Epoxy-6-methyl-2-heptanone

A saturated solution of sodium carbonate was diluted to twice its volume to give an approximately 15% solution. A 20 ml. portion of this was placed in a 50 ml. round-bottomed flask containing 1.7 g. (9.5 mmoles) of 5-chloro-6-hydroxy-6-methyl-2-heptanone and heated on a steam bath for one hour with stirring. The solution was cooled, saturated with sodium chloride, and extracted with ether. This was washed once with a small amount of water. The ether was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the oily residue was distilled. The crude epoxyketone was collected at 72-76° C./50 mm. (94-98° C./100 mm.) and had n_D^{21} 1.4302. The yield was 0.78 g. (58%); however, the purity of the product was much lower than the material obtained by oxidation of the ketone with monoperphthalic acid.

5,6-Dihydroxy-6-methyl-2-heptanone

In a 50 ml. round-bottomed flask, equipped with a reflux con-
densor, was placed 30 ml. of a 30% sodium hydroxide solution and 0.92
g. (6.3 mmoles) of 5,6-epoxy-6-methyl-2-heptanone. The two phase
system was refluxed for two hours, and then allowed to stand overnight
with continued stirring. The solution was diluted with 50 ml. of water
and extracted in a Kutscher-Steudel apparatus with ether for twenty-
four hours. The resulting ether solution was washed with a saturated
solution of sodium sulfate, and dried over anhydrous sodium sulfate.
The solvent was removed under reduced pressure, and the viscous
residue was distilled to yield 0.91 g. (88%) of the glycol, b. p. 78-81°
C./2 mm., which solidified slowly on standing to give crystals with
m. p. 64-66° C. (135).

6-Methyl-2-5 -heptadione

Isomerization of 5,6-Epoxy-6-methyl-2-heptanone: A 3.0 g.
(21 mmoles) portion of 5,6-epoxy-6-methyl-2-heptanone was added to
50 ml. of 6 F. sulfuric acid and allowed to stand without heating for
twenty-four hours. The acid solution was extracted with three 30 ml.
portions of ether, which was washed with a 50 ml. portion of 2 F.
sodium carbonate and with water; the ether was dried over anhydrous
sodium sulfate. Most of the residue distilled over the range 87-98°C.
and had n_D^{22} 1.4351. The yield was 1.95 g. or 65%.

The monosemicarbazone (135) was prepared by the method of Cheronis and Entrikin (119) and recrystallized several times from a 3:1 mixture of methanol and water, m.p. 196-198° C.

Isomerization of 5,6-Dihydroxy-6-methyl-2-heptanone: A mixture of 2.9 g. (18 mmoles) of 5,6-dihydroxy-6-methyl-2-heptanone and 50 ml. of 6 F. sulfuric acid was allowed to stand overnight at room temperature with stirring. The dione was isolated exactly as described above, and amounted to 1.80 g. (70%) with b.p. 93-85° C./15 mm., n_D^{22} 1.4346.

The monosemicarbazone melted at 196-198° C., and showed no depression when mixed with authentic material.

5,6-Epoxy-2,2,6-trimethyl-2,3-dihydropyran

Oxidation-Cyclization of 6-Methyl-5-hepten-2-one: Freshly distilled natural methyl heptenone (75 ml., 64.5 g., 0.51 mole) was diluted with 50 ml. of technical grade chloroform and cooled to -50° C. in a 500 ml. Morton (creased) flask which was suspended in a one-half gallon Dewar flask partially filled with dry ice and acetone. The reaction flask was equipped with a high speed, air-cooled, mechanical stirrer. To the reaction flask was added dropwise with stirring, over a period of about fifteen minutes, 50 ml. of ca. 40% peracetic acid containing 1.0 g. of anhydrous sodium acetate. The material was allowed to stand overnight with stirring. A second 50 ml. portion of

peracetic acid was added as before and again the mixture was allowed to stand overnight. Finally, 10 ml. of peracetic acid was added and the mixture was allowed to stand for an additional seven hours. The total active peracid added was 53.5 g. (0.71 mole, 40% excess).

The emulsion was poured into an excess of 2 N. sodium hydroxide solution containing chopped ice and was stirred vigorously. When the decomposition of the excess peracid ceased, the layers were separated, and the aqueous base was extracted with four 50 ml. portions of chloroform. The combined chloroform solution was washed with 150 ml. of a ferrous sulfate solution; the aqueous layer was itself extracted with two 25 ml. portions of chloroform. The chloroform solution was washed with 200 ml. of a saturated solution of sodium sulfate, and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled to yield 37 g. (51%) of isomeric epoxide, b.p. 57-63° C./28.7 mm., n_D^{23} 1.4750-1.4771. Analysis by V.P.C. indicated the presence of 25-30% of the exocyclic epoxide 6-(1'6-epoxy)-methylene-2,2-dimethyltetrahydropyran.

The analytical sample distilled at 57° C./28.7 mm. and had $n_D^{25.2}$ 1.4742 and d_4^{24} 1.0144.

Molar Refractivity. Calculated for $C_8H_{14}O_2$: 39.72. Found: 38.73.

Analysis (E). Calculated for $C_8H_{14}O_2$: C, 67.57%; H, 9.93%. Found: C, 67.50%; H, 10.09%.

Epoxide Determination (Pyridinium Chloride-Pyridine Method (136)). This reaction was very slow, giving a titration value of 54% (theoretical, 100%).

The infrared spectra of the epoxide material gave no evidence for the presence of Baeyer-Villiger (137) products.

2,2,6-Trimethyl-2,3-dihydropyran

Freshly distilled natural methyl heptenone (25 g., 0.198 mole) was added slowly to a mixture of 2.6 ml. of concentrated sulfuric acid and 47.4 ml. of 98-100% formic acid in such a fashion that the temperature did not rise above 40° C. The solution became violet in color within a few minutes. This mixture was allowed to stand for three days at room temperature protected from moisture with a calcium chloride drying tube.

The reaction mixture was poured into an excess of 6 N. sodium hydroxide solution and warmed on a steam bath for thirty minutes. The cooled basic solution was then extracted with six 30 ml. portions of ether. The combined extracts were then washed with water, and the aqueous phase was also extracted with two 50 ml. portions of ether. The combined ether solutions were dried over anhydrous sodium sulfate.

The ether was removed by distillation, and the product was fractionated through a 30 cm. column packed with glass helices; 13.9 g. (56%) of cyclic material was collected boiling at 115-129° C., and it had n_D^{25} 1.4708. V.P.C. analysis indicated that about 30% of this was

the exo-methylene isomer (6-methylene-2,2-dimethyltetrahydropyran).
This material was identified by comparison of its infrared spectrum
with that of authentic material prepared by the method of Verly (106).
The two major components of the mixture were resolved by further
fractionation: 2,2,6-trimethyl-2,3-dihydropyran, 8.4 g. (33%), b.p.
118-124° C., n_D^{25} 1.4703; 6-methylene-2,2-dimethyltetrahydropyran,
4.6 g. (18%), b.p. 124-129° C., n_D^{25} 1.4716.

5,6-Epoxy-2,2,6-trimethyl-2,3-dihydropyran

The oxidation of 5 g. (40 mmoles) of 2,2,6-trimethyl-2,3-
dihydropyran was accomplished with 7 ml. of ca. 40% peracetic acid
(6 g., 48 mmoles) in 50 ml. of chloroform at -40° C. The product
was worked up as indicated previously. The material obtained, 2.5 g.
(44%), b.p. 88-91° C./100 mm., n_D^{25} 1.4756, was identified as 5,6-
epoxy-2,2,6-trimethyl-2,3-dihydropyran on the basis of its gas phase
retention time, which was the same as that of known material.

4-Methyl-1,4-pentadiol

The procedure of Gamboni, Schinz, and Eschenmoser (138) was
used to prepare 4-methyl-1,4-pentadiol. From 75 g. (0.875 mole) of
γ-butyrolactone (Matheson, Coleman & Bell) and 800 ml. of ca. 3 M.
methylmagnesium bromide (Arapahoe Chem.) in ether solution, there
was obtained 73.5 g. (72%) of diol with b.p. 97.0-97.5° C./2.5 mm.
(122-123° C./11 mm.) and n_D^{22} 1.4470 (lit. n_D^{17} 1.4489).

1,4-Dibromo-4-methylpentane

Using the procedure of Willimann and Schinz (139), 1,4-dibromo-4-methylpentane was prepared from the corresponding diol. Treatment of 20 g. (0.171 mole) of the diol in pyridine with 36.5 g. (0.134 mole) of phosphorous tribromide yielded 30.8 g. (80%) of the dibromide, b.p. 55-60° C./1 mm., contaminated with a trace of pyridine. This material was used without further purification.

1-Bromo-4-methyl-3-pentene

According to the method of Willimann and Schinz (139), 30.6 g. (0.142 mole) of 1,4-dibromo-4-methylpentane was taken up in 11 g. (0.137 mole) of pyridine and heated at 90° C. in an oil bath under aspirator vacuum. After two hours the temperature was raised to 100° C. for another fifteen minutes. The material isolated distilled at 49-51° C./1 mm. and had n_D^{22} 1.4731 (lit. n_D^{16} 1.4758). The yield was 18.7 g. or 85%.

6-Methyl-5-hepten-1-yne

Treatment of 1-bromo-4-methyl-3-pentene (17.7 g., 0.124 mole) with sodium acetylide (from 3.0 g. sodium, 0.130 g. atom) in liquid ammonia according to the procedure of Gamboni, Schinz, and Eschenmoser (138) led to the production of 2.8 g. (21%) of 6-methyl-5-hepten-1-yne. The product distilled over 66-72° C./85 mm. and had n_D^{22} 1.4401-1.4404 (lit. n_D^{19} 1.4418).

5,6-Epoxy-6-methyl-1-heptyne

A solution of 2.8 g. (26 mmoles) of 6-methyl-5-hepten-1-yne in 200 ml. of chloroform was cooled to -50° C. in dry ice and acetone. To this was added dropwise over ten minutes 5 ml. of ca. 40% peracetic acid (2.43 g. of active peracid, 32 mmoles; 22% excess) solution containing 0.1 g. of anhydrous sodium acetate. The solution was stirred in a Morton (creased) flask with a high-speed stirrer for approximately fifty hours.

The chloroform solution was shaken successively with 100 ml. 2 N. sodium hydroxide solution, 50 ml. of saturated ferrous sulfate solution, and 100 ml. of water; after each washing the aqueous phase was extracted with a small amount of chloroform. The chloroform was dried over anhydrous sodium sulfate, and then removed by fractionating through a 112 cm. column packed with glass helices. The residue was fractionated through a 4 cm. Vigreux column, and afforded 1.4 g. (45%) of 5,6-epoxy-6-methyl-1-heptyne, b.p. 76-81° C./85 mm., n_D^{22} 1.4426, d_4^{21} 0.8839.

Molar Refractivity. Calculated for $C_8H_{12}O$: 36.58. Found: 37.21.

Analysis (E). Calculated for $C_8H_{12}O$: C, 79.37%; H, 9.7%. Found: C, 79.84%; H, 9.79%.

5,6-Epoxy-6-methyl-1-heptene

Two hundred milligrams of $Pd(OH)_2/CaCO_3$ catalyst (138, 140) were suspended in 15 ml. of absolute methanol in a 25 ml. semimicro

hydrogenation flask, and stirred under hydrogen until no gas was absorbed. To this was added 1.25 g. (10 mmoles) of 5,6-epoxy-6-methyl-1-heptyne, and the mixture was stirred under hydrogen at room temperature and pressure until 250 ml. (10 mmoles, at 23° C./739 mm.) of hydrogen had been absorbed.

The solution was filtered, and the filtrate was carefully distilled at room temperature to remove the alcohol. The residue distilled to give after a small forerun, 1.03 g. (82%) of 5,6-epoxy-6-methyl-1-heptene, b.p. 93-96° C./150 mm., n_D^{23} 1.4361.

The analytical sample had b.p. 92-95° C./150 mm., n_D^{22} 1.4366, d_4^{21} 0.8599.

Molar Refractivity. Calculated for $C_8H_{14}O$: 38.12. Found: 38.44.

Analysis (E). Calculated for $C_8H_{14}O$: C, 76.14%; H, 11.18%. Found: C, 76.40%; H, 11.05%.

6-Hydroxy-2-methyl-3-heptanone

A 0.90 g. (7.1 mmoles) sample of 5,6-epoxy-6-methyl-1-heptene was mixed with 1.9 ml. of 98-100% formic acid and 0.12 ml. of concentrated sulfuric acid and allowed to stand for two days at 35° C. The reaction mixture was then diluted to approximately 5 ml. with water and made basic with 2 N. sodium hydroxide solution. The basic material was extracted with ether for fourteen hours in a modified

Soxlet apparatus; the extract was shaken with a saturated solution of sodium sulfate, and then dried over anhydrous sodium sulfate. Distillation afforded 0.47 g. (46%) of 6-hydroxy-2-methyl-3-heptanone with b.p. 91-93° C./12 mm., n_D^{21} 1.4587, d_4^{21} 0.9488.

<u>Molar Refractivity</u>. Calculated for $C_8H_{16}O_2$: 40.68. Found: 41.52.

<u>Analysis</u> (E). Calculated for $C_8H_{16}O_2$: C, 66.63%; H, 11.18%. Found: C, 66.77%; H, 11.14%.

The 2,4-dinitrophenylhydrazone was prepared from Johnson's reagent (129) as described previously. The derivative was recrystallized twice from methanol, m.p. 107-116° C., and then chromatographed on alumina, m.p. 116.5-118.0° C.

5,6-Epoxy-1-hexene

A solution of peracetic acid was prepared by slowly adding 5 ml. of cold 30% hydrogen peroxide to 25 ml. of cold acetic anhydride containing 1 g. of powdered, anhydrous sodium acetate. After the reaction was complete, the cold solution was mixed with 300 ml. of absolute ether. This solution contained about 0.087 mmoles/ml. of active peracid as determined by iodometric titration. This was filtered to remove the excess sodium acetate.

The peracid solution (300 ml., 26 mmoles of peracetic acid) was cooled to -5° C. and mixed with 7 g. (82 mmoles, 210% excess) of

1,5-hexadiene (Columbia Organic Chemicals). The mixture was refrigerated at this temperature for a period of three days. The ether was then washed with three 75 ml. portions of 2 N. sodium hydroxide solution, 50 ml. of saturated ferrous sulfate solution, and twice with 50 ml. portions of water. The ether was dried over anhydrous sodium sulfate. Removal of the ether by fractional distillation was followed by simple distillation of the residue. The 5,6-epoxy-1-hexene was obtained by means of preparative V.P.C. (Megachrom, 40° C.). The material thus obtained had n_D^{21} 1.3866, d_4^{21} 0.8331. The boiling point was found to be approximately 91-93° C. by the semimicro method of Cheronis and Entrikin (119).

Molar Refractivity. Calculated for $C_6H_{10}O$: 27.15. Found: 27.80.

Analysis (E). Calculated for $C_6H_{10}O$: C, 73.43%; H, 10.27%. Found: C, 73.95%; H, 10.47%.

5,6-Dihydroxy-1-hexene

Thirty milliliters of a 30% solution of sodium hydroxide were mixed with a solution of 500 mg. of 5,6-epoxy-1-hexene in 10 ml. of methanol, and refluxed for four hours. The basic solution was extracted with five 20 ml. portions of ether, and the combined extracts were washed with 25 ml. of water; the aqueous layer was itself extracted with three 20 ml. portions of ether, which were combined with the original extract, and dried over anhydrous sodium sulfate. The ether

was removed, and the pale yellow oil was distilled to give 0.31 g.

(53%) of 5,6-dihydroxy-1-hexene, b.p. 64-66° C./6 mm., $n_D^{22.5}$ 1.4568.

The analytical sample was redistilled and had b.p. 62-64° C./5 mm., $n_D^{22.0}$ 1.4572, d_4^{21} 0.9923.

Molar Refractivity. Calculated for $C_6H_{12}O_2$: 31.33. Found: 31.94.

Analysis (E). Calculated for $C_6H_{12}O_2$: C, 62.04%; H, 10.41%. Found: C, 61.76%; H, 10.39%.

The preparation of 5,6-dihydroxy-1-hexene via the partial hydroxylation of 1,5-hexadiene with potassium permanganate has been reported by Böeseken (141), but no physical constants were given.

5-Hydroxy-1-hexal

A mixture of 1.6 ml. of 98-100% formic acid and 0.10 ml. of concentrated sulfuric acid was added to 0.75 g. (7.7 mmoles) of 5,6-epoxy-1-hexene, and allowed to stand for two days at 35° C. After this period the mixture was diluted to 5 ml. with water and neutralized with 2 N. sodium hydroxide solution. The aqueous solution was thoroughly extracted with ether, which was washed with a small amount of a saturated solution of sodium sulfate. The ether was dried over anhydrous sodium sulfate, and removed under reduced pressure. The resulting oil was distilled to give 0.29 g. (39%) of 5-hydroxy-1-hexal with b.p. 81-88° C./10 mm. and n_D^{20} 1.4444.

Analysis (E). Calculated for $C_6H_{12}O_2$: C, 62.04%; H, 10.41%. Found: C, 62.28%; H, 10.03%.

This material appears to be the same as the 5-hydroxy-1-hexal reported in the literature (142), although the reported 4-bromophenyl-hydrazone (m. p. 85° C.) was not prepared. Instead the 2,4-dinitro-phenylhydrazone was prepared and recrystallized from methanol, m. p. 103-105° C.

6,7-Epoxy-1-heptene

A solution of 23 g. (0.24 mole) of 1,6-heptadiene (143) in 300 ml. of technical grade chloroform was chilled to -50° C. in a mixture of dry ice and acetone. To this was added with stirring, over a period of fifteen minutes, 46 ml. (0.30 mole) of ca. 40% peracetic acid. The mixture was stirred with a high-speed stirrer for two days. The chloroform solution was washed with an excess of 2 N. sodium hydroxide solution, followed by a saturated solution of ferrous sulfate, and then with water. The chloroform was dried over anhydrous sodium sulfate.

The chloroform was removed by fractional distillation. The residue distilled over 70-87° C. Analysis by V.F.C. indicated that it contained about 47% of the monoxide and 40% of the dioxide.

6,7-Dihydroxy-1-heptene

A solution of 3 g. of the above mixture of oxides and 20 ml. of methanol was added to 25 ml. of a 30% solution of sodium hydroxide

and refluxed for two hours. The cooled basic solution was then extracted
with five 20 ml. portions of ether, which was washed with 20 ml. of
water, and then dried. Removal of the very viscous residue afforded
0.61 g. of the unsaturated diol with b.p. 95-101° C./8 mm. and
n_D^{21} 1.4697. Based on the presence of 47% of the monoxide in the
starting material, the yield was 33%.

The analytical sample was redistilled and had b.p. 93-96° C./8
mm. and n_D^{22} 1.4688.

Analysis (E). Calculated for $C_7H_{14}O_2$: C, 64.57%; H, 10.84%.
Found: C, 64.39%; H, 10.63%.

6-Hydroxy-1-heptal

A mixture of 0.60 ml. of 98-100% formic acid and 0.03 ml. of
concentrated sulfuric acid was added to 345 mg. (2.64 mmoles) of
6,7-dihydroxy-1-heptene and allowed to stand stoppered for two days.
The reaction mixture was made slightly basic with 2 N. sodium hydroxide
solution and warmed for a few minutes on a steam bath before extracting
with ether. The ether was dried over anhydrous sodium sulfate, and
then removed by evaporation. The residue was taken up in chloroform
and passed through 2 cm. of alumina. When the chloroform was
removed, the residue had n_D^{21} 1.4417.

The 2,4-dinitrophenylhydrazone was prepared from Johnson's
reagent (129) and recrystallized from methanol, m.p. 157-162° C.

3-Methylcyclohexyl Formate

A mixture of 1.6 ml. of concentrated sulfuric acid and 29.0 ml. of 98-100% formic acid was added slowly to 4.7 g. (49 mmoles) of 1,6-heptadiene (Columbia Organic Chemicals) in a 50 ml. round-bottomed flask. The flask was fitted with a calcium chloride drying tube, and the two phase system was stirred magnetically for three cays at approximately 35° C. During this time, as solution of the two layers was effected, the reaction mixture became deep violet in color.

The acid solution was then neutralized by adding it dropwise to an excess of 2 N. sodium hydroxide. This was extracted completely with ether. The ether extract was washed with a small amount of water. The resulting solution was dried over anhydrous sodium sulfate. After removal of ether from the filtered solution, the material was fractionated through a 4 cm. Vigreux column under reduced pressure; the product distilled at 71-75° C./0.5 mm. and had n_D^{22} 1.4305 and amounted to 3.4 g. (58%).

3-Methylcyclohexanol

A 3.0 g. sample (27 mmoles) of 3-methylcyclohexyl formate was refluxed for one hour with 25 ml. of a 10% solution of sodium hydroxide. At the end of this time the cooled solution was extracted with ether continuously for twenty-four hours. Removal of the solvent and distillation of the residue afforded 2.0 g. (89%) of the cis- and trans-alcohols, b.p. 81-84° C./20 mm., n_D^{21} 1.4577.

Analysis by V.P.C. indicated that about 72% of the material was the cis-isomer and 28% the trans-isomer. Resolution of the mixture by means of preparative V.P.C. (F. & M., "B") led to two fractions: 1) 94% cis-3-methylcyclohexanol, n_D^{24} 1.4565, whose 3,5-dinitro-benzoate melted at 110.0-111.5° C.; 2) trans-3-methylcyclohexanol, n_D^{24} 1.4559, whose 3,5-dinitrobenzoate melted at 97.5-99.5° C. (144).

APPENDIX

Molecular Orbital Treatment of Three-Center Non-Classical Ions

General Secular Equation

If overlap integrals are neglected, the linear combination of atomic orbitals (L.A.C.O.) solution of the general three-center problem is based on the solutions of the following secular determinant:

$$\begin{vmatrix} \alpha_1 - e & \beta_{12} & \beta_{13} \\ \beta_{21} & \alpha_2 - e & \beta_{23} \\ \beta_{31} & \beta_{32} & \alpha_3 - e \end{vmatrix} = 0 \tag{1}$$

If the substitutions $x + c_i = (\alpha_i - e)/\beta$ and $k_{ij} = \beta_{ij}/\beta$, then the above problem reduces to finding the roots of the general 3rd-order equation:

$$x^3 + (c_1 + c_2 + c_3)x^2 + (c_1 c_2 + c_1 c_3 + c_2 c_3 - k_{12}^2 - k_{13}^2 - k_{23}^2)x$$

$$+ (c_1 c_2 c_3 + 2k_{12}k_{13}k_{23} - c_1 k_{23}^2 - c_2 k_{13}^2 - c_3 k_{12}^2) = 0 \tag{2}$$

In this equation the c_i represent the changes in the Coulomb integrals in units of β relative to the standard values, α. The c_i in general will be non-zero if the system contains heteroatoms or shows a large distribution of charge. The k_{ij} are proportionality constants, which relate the resonance integral, β_{ij}, to the standard resonance integral usually taken as β in benzene. By appropriate selection of these constants, the roots of equation 2 will render the eigenvalues of the desired three-center system.

The Cyclopropenium Cation

Hückel's familiar $4n + 2$ rule (145) may be stated as follows: "Those monocyclic coplanar systems of trigonally hybridized atoms which contain $4n + 2$ π-electrons will possess relative stability." The simplest system which conforms completely with the restrictions of this rule is the two-electron, three-center system.* An example of such a system is the still hypothetical cyclopropenium cation. Simple Hückel Molecular Orbital Theory predicts that this molecule will have a total resonance energy of $2\beta(c_i = 0, k_{ij} = 1)$.

It is possible to modify the Hückel treatment by considering the effect of the system's positive charge on the Coulomb integrals (146). Since the positive charge has the effect of increasing the electro-negativity of each carbon, the magnitude of the Coulomb integrals may be increased in proportion to the amount of charge the center carries (152). If the Coulomb integrals are taken to be $\alpha + 0.33\beta$ (147), the resonance energy of the system is found to be 2.67β. Inasmuch as simple molecular orbital theory will generally indicate that the stability of a system will increase as the ability of the system to delocalize the electrons increases, the cyclopropenium cation should represent the most stable all-carbon, three center, two-electron system, since it meets the requirements for maximum orbital overlap. Other non-classical ions in which two electrons are delocalized over three carbon

---

* Since electronic stabilities are measured relative to that of the isolated double bond, this two-electron, two-center system is excluded from the $4n + 2$ rule on the basis of its not being cyclic.

p-orbitals may be viewed to a first approximation as distortions of the cyclopropenium cation.

Bridged Non-Classical Carbonium Ions

It is important to note that the 4n + 2 rule is developed from the simple Hückel theory, which considers the π-electron system to be independent of the underlying σ-framework. Consequently, distortions in the σ-bonding of molecules are, to a first approximation, important only insofar as they are associated with changes in the π-electron system itself. This can only be valid as long as the σ- and π-bonding remain distinct from one another. Such a distinction cannot be profitably made in the case of a number of non-classical carbonium ions (148).

It will be useful to consider certain types of non-classical ions as distortions of the cyclopropenium cation. The kinds of distortions which will be of interest in this discussion fall into two categories: 1) Distortions resulting in changes in the internuclear distances, which cause commensurate changes in the overlap and resonance integrals (e.g. the homoallylic cation (149)) and 2) deviations in the orientations of the carbon p-orbitals, which similarly result in changes in the values of the necessary integrals (e.g. intermediates hypothesized for 1,2-rearrangements in carbonium ions (150)). As long as the distortions are small, the electronic stabilities of these (4n + 2) systems should not be altered greatly, although it would no longer be possible to

write the molecular orbitals in analytic form. For larger distortions, however, it is not possible to come to any general conclusions concerning the relative stability of the system or the form of the molecular orbitals, and the problem should be investigated individually.

One important "distortion" of the cyclopropenium cation has been mentioned before. This is the postulated non-classical ion which results from the anti-planar addition of a carbonium ion to a double bond, and which may bear a formal relationship to the non-classical intermediate in the Wagner-Meerwein alkyl rearrangements. If only the p-orbitals of carbon are considered, this system may be derived from the cyclopropenium ion by rotation of one carbon atom 90° around the opposite internuclear axis, while maintaining its p-orbital parallel to those of the remaining two carbons (Fig. 13-B). The distance between the C-1 atom and the opposite internuclear axis may be considered arbitrary. It will be observed that in this configuration the bonding between C-1 and C-2 and between C-1 and C-3 is almost exclusively σ in character, especially at large separations, while C-2 and C-3 are still mostly π-bonded. The formation of σ-bonds to C-1 would require some rehybridization about C-2 and C-3 in order to maximize the overlap of their orbitals with that of C-1. Such rehybridization would be expected to introduce some σ-character into the bond between C-2 and C-3.

Approximate Molecular Orbital Methods

Equation 2 was used to determine the resonance energies expected for the interaction of a double bond with the empty p-orbital of a carbonium ion. The energies were calculated over a range of configurations described by bringing a carbonium ion from infinite distance up to the double bond, and along some direct path lying in the plane containing the empty p-orbital and bisecting perpendicularly the axis of the double bond. In all four different methods of approximation were used. These are described below.

Method #1. The first approach is quite analogous to the simple Hückel treatment. Equation 2 was solved by assuming that all the c_i were zero and that $k_{23} = 1$; $k_{12} = k_{13}$ was allowed to take on a series of values ranging from zero to one. Curve #1 of Figure 14 indicates the resulting relationship between the resonance energy of the system as a function of the composite π-σ overlap between C-1 and C-2 or C-3.

Method #2. It would be expected that as overlap with the empty p-orbital of C-1 becomes more important, electron density would be drained away from the π-system of the double bond; this would result in a concomitant weakening of this linkage. This effect has been approximated by allowing k_{23} to diminish from 1.0 to 0.8, while k_{12} and k_{13} are increased from zero to 0.8. The value 0.8β is the resonance integral for a bond with a length intermediate between those of a single

and double bond. The choice of this value is completely arbitrary, though probably conservative. This method gives a set of energies which are slightly lower than those obtained by Method #1; this is consistent with the idea of forming a somewhat looser complex.

Method #3. The above methods are expected to give reasonable energy values when the system possesses no net charge, as perhaps in the case of a non-classical radical. In general, however, treatments which give consideration to the distribution of charge within a molecule yield better energy values than do the simpler treatments which neglect charge (151). A method already mentioned attempts to improve upon this situation by adjusting the Coulomb integrals, such that their values reflect the "effective electronegativities" of the various centers relative to uncharged carbon (152). Although it is yet without sound theoretical support, it seems reasonable to assume that the Coulomb integral should be increased by $1\,\beta$ to $1.5\,\beta$ for a positively charged core (153). Since augmenting the core potential has the effect of increasing the stabilization energy obtained for the system, the more conservative value of $\alpha + \beta$ was employed in this approximation. The adjusted core potentials appear in the selection of the c_i of equation 2. In the limiting case of no interaction between the double bond and the carbonium ion, the Coulomb integrals for C-2 and C-3 are the customary values, α, while that of C-1 will be $\alpha + \beta$; that is, $c_2 = c_3 = 0$ and $c_1 = 1$. As the carbonium ion is allowed to interact with the double bond at shorter

separations, cores C-2 and C-3 will begin to accept part of the charge; the core potential at C-1 will decrease in an amount which reflects the degree to which the charge has been transferred. At the extreme of total involvement, the charge is envisioned as being more or less equally distributed among the three centers, and hence, $c_1 = c_2 = c_3 = 0.33$. Curve #3 shows what effect this distribution of charge has on the resonance energy of the system, assuming that there is no change in the extent of overlap of the bond between C-2 and C-3 (i.e. $k_{23} = 1$).

Method #4. This last method is analogous to Method #2, and allows for the expected weakening of the $C_2=C_3$ bond as electrons are drained into the C-1 orbital. This results in partially cancelling the constriction which arises from the introduction of charge into the system and, as before, tends to decrease the stabilization energy to a small extent (Curve #4). It is interesting that this last treatment shows a nearly linear relationship between resonance energy and C_1-C_2 (or C_1-C_3) overlap integrals. This relation may be expressed approximately by

$$R.E. = 8.94\, S_{12}$$

where the resonance energy (R.E.) is given in units of β.

Of the four methods, this one appears to be the best suited for the simple description of positively charged systems. When the abscissa of Figure 14 is converted to measure the separation between C-1 and the C_2-C_3 axis, then Curve #4 transforms as is shown in Figure 15.
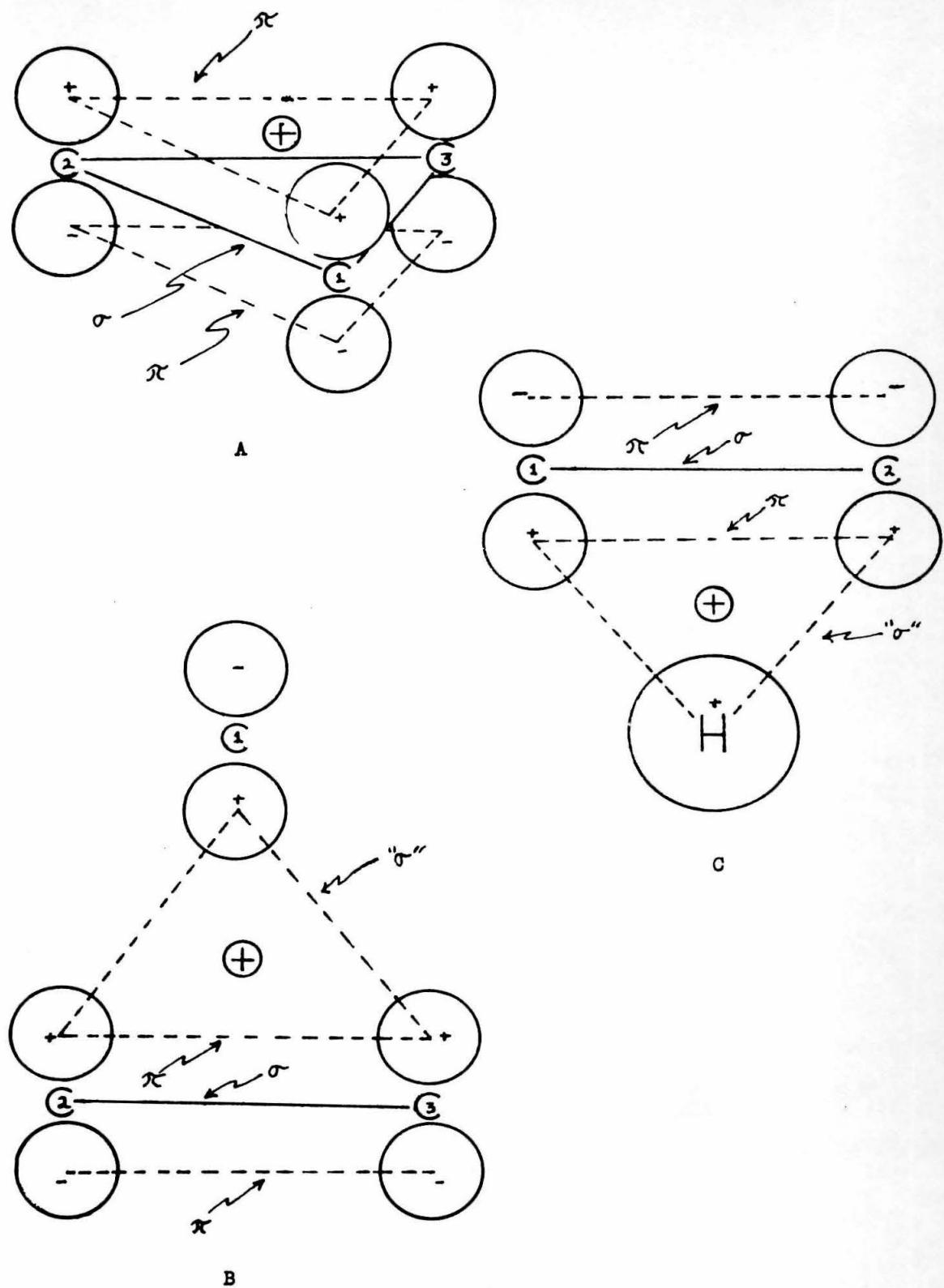
Fig. 13
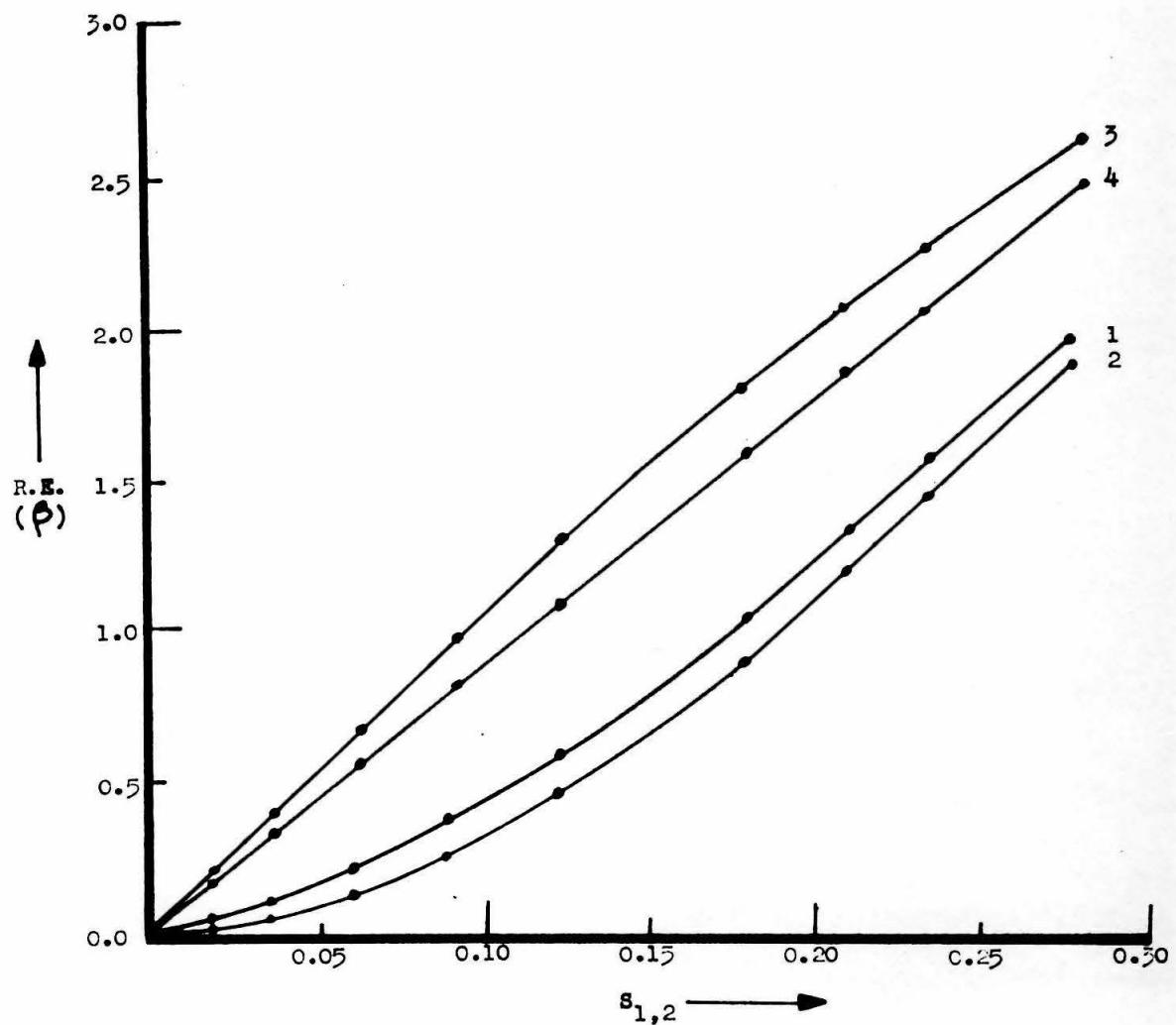
Fig. 14
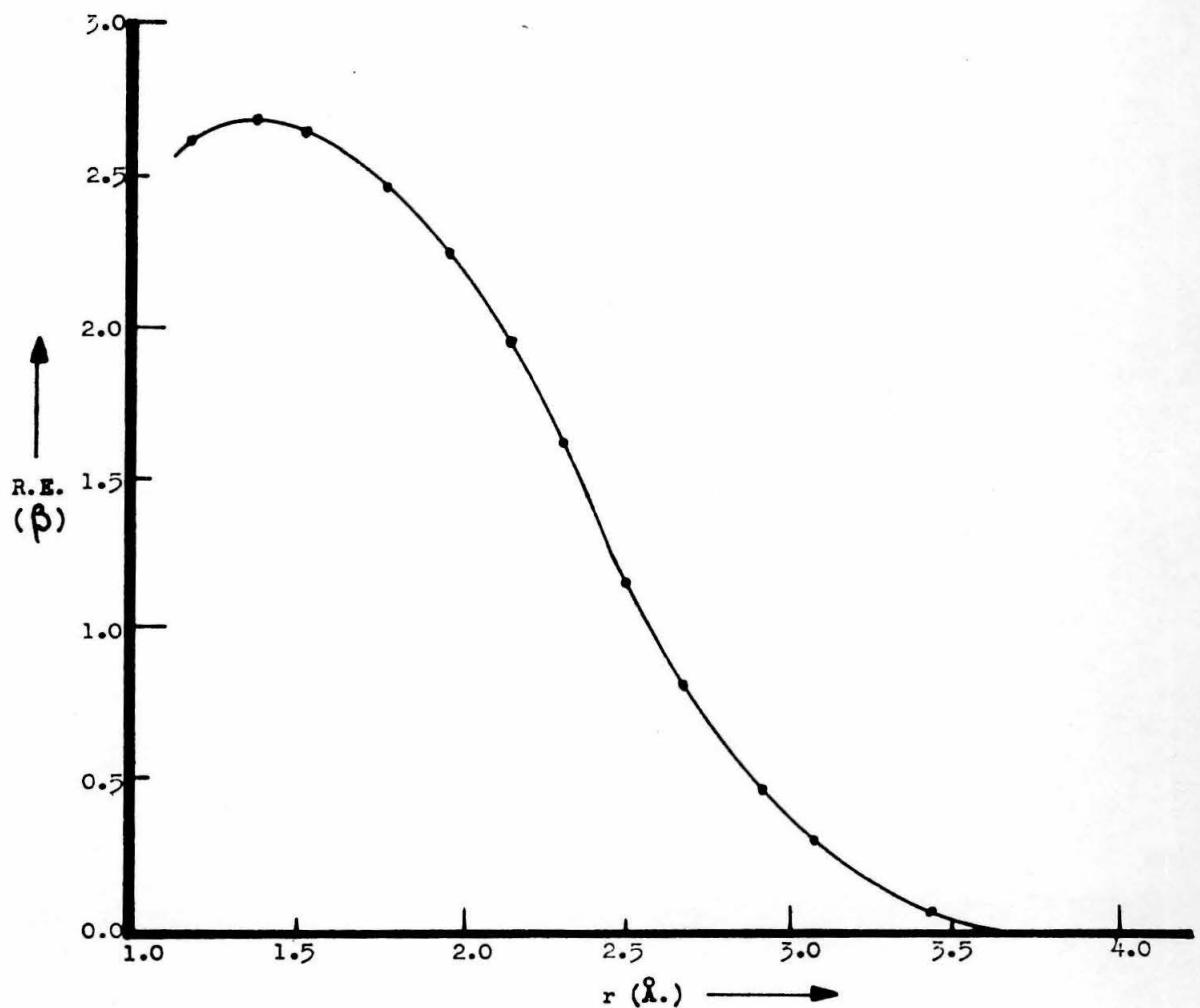
Fig. 15

Methyl Substituted Three-Center Carbonium Ions

The L.C.A.O. model which gave rise to the curves of Figure
14 involved the interaction of a carbonium ion with a double bond,
both of which were presumed to be unsubstituted. It is of some interest
to know how various alkyl substituents would affect the overall stabiliza-
tion energy of the non-classical ion. Some insight to this question
might be obtained by considering the hyperconjugative and inductive ef-
fects of methyl groups attached to the fundamental three-carbon ion.
It has been shown by Wheland and Pauling (154) that the effects of
methyl substituents can be reasonably accounted for on the basis of a
simple inductive model in which appropriately modified Coulomb
integrals are used; conjugation itself is then neglected. Though very
little data are available at present, it appears that Coulomb integrals
should be decremented by about 0.5β for each methyl group present
(155).

There are twenty-four different non-classical ions which may
be conceived of as arising from the symmetrical interaction of four
prototypical alkonium ions with the six corresponding ethylene systems.
If the k_{ij} are all taken as equal, a set of sixteen secular equations is
obtained which differ only in the assignments of the Coulomb integrals.
Table IV gives the resonance energies and relative stabilities of each
of these systems obtained by setting $k_{ij} = 0.8$ (Method #4 above), and

$c_i = 0.33 - 0.5 \times n_i \beta$, where n_i is the number of methyl groups at-
tached to the ith carbon.

The results of these calculations indicate that, as the number
of alkyl substituents on the component cation and olefin increases, the
amount of delocalization energy to be gained upon formation of a non-
classical carbonium ion decreases. Further, for systems with the
same total number of substituent methyl groups, the non-classical ion
with the most polysubstituted centers will be the most stable (e.g. the
ions of the 1,1-dimethylethylene series are consistently predicted to
be more stable than the corresponding ions of the 1,2-dimethylethylene
series). Since the resonance energies obtained are quite sensitive to
the nature of the model chosen as a basis for these calculations, as
well as being subject to the general limitations of the L.C.A.O. method, the
significance attached to these values can only be questionable. The
order of relative stabilities, however, may well be instructive, in that
it suggests which kinds of systems might be expected to favor the
formation of non-classical intermediate ions due to a gain in resonance
stabilization. Systems represented in the lower right corner of Table IV,
on the other hand, may be expected to exhibit little tendency toward
formation of non-classical ions.

The treatment undoubtedly suffers greatly from the assumption
that all the non-classical systems would be symmetrical; that is, that
all k_{ij} are equal. The less symmetrical systems would require that

electrons be placed in the more localized σ-bond, which is being formed at the expense of the original π-bond of the olefin. This would result in a corresponding decrease in delocalization energy. Hence, the interaction of t-butyl cation with 1,1-dimethylethylene is predicted to have a resonance energy of about 0.42 β on the basis of the symmetrical model. Non-bonded repulsions between the methyl groups of the cation and of the olefin, however, would be expected to favor the formation of an unsymmetrical species of somewhat lower stability. Since the same cation and 1,2-dimethylethylene, on the other hand, would be more likely to form a symmetrical intermediate, the order of stabilities of these two systems might well be reversed.

Table IV

Calculated Molecular Orbital Resonance Energies

of Non-Classical Carbonium Ions

Resulting from the Alkylation of Olefins[a]

Alkylating Ion:	$^+CH_3$	$^+CH_2Me$	$^+CHMe_2$	$^+CMe_3$
Olefin Prototype:				
Ethylene	1.86[b] (1.00)[c]	1.57 (0.84)	1.35 (0.72)	1.18 (0.63)
Methylethylene	1.57 (0.84)	1.24 (0.67)	1.00 (0.54)	0.82 (0.44)
1,1-Dimethylethylene	1.35 (0.72)	1.00 (0.54)	0.72 (0.39)	0.42 (0.23)
1,2-Dimethylethylene	1.24 (0.67)	0.86 (0.46)	0.56 (0.30)	0.36 (0.19)
Trimethylethylene	1.00 (0.54)	0.56 (0.30)	0.24 (0.13)	-0.48[d] (-0.26)[d]
Tetramethylethylene	0.72 (0.39)	0.24 (0.13)	-0.15 (-0.08)	-1.52 (-0.82)

FOOTNOTES TO TABLE IV:

a) Eigenvalues obtained from equation 2, assuming k_{ii} = 0.8 and c_i = 0.33- 0.5 $n_i\beta$. Resonance energies may be adjusted to any other value of the resonance integral, $K\beta$, by adding the quantity $4(K-k_{ii})\beta$; e.g. the H.M.O. (K = 1) R.E. is obtained by adding 0.8β to each of the above values. b) Resonance energy in units of β. c) Parentheses contain stabilities relative to the ethylene-methonium cation. d) Negative values indicate total delocalization energy is less than 3(α + β), but still positive; i.e. lowest (occupied) M.O. is still bonding.

References to Part I

1. "The Chemistry of Natural Products," K. W. Bently (ed).,
   Vol. II, Interscience Publishers, Inc., New York, p. 1, 1959.

2. a) M. J. Dumas, Ann. chim., (ii) 50, 223 (1832).

   b) M. J. Dumas, Annalen, 6, 252 (1833); see also other papers
   in this series.

3. "The Chemistry of Natural Products," K. W. Bently (ed),
   loc. cit., Vols. II and III.

4. L. Zechmeister, Fortschrt. Chem. Org. Naturst., 18, 223
   (1960).

5. "The Terpenes," J. L. Simonsen, 2nd ed., Vols. I-V, Cambridge University Press, 1947.

6. "The Essential Oils," E. Guenther, Vols. I-VI, Nostrand
   Publishing Co., New York, 1948-1952.

7. "Dio Aetherischen Öle," E. Gildemeister and F. Hoffmann,
   3rd ed., Miltitz Verlag, Leipzig, 1928-1931.

8. "Natural Products Related to Phenanthrene," L. F. Fieser and
   M. Fieser, 3rd ed., Rheinhold Publishing Corp., New York,
   1949.

9. "Steroids," L. F. Fieser and M. Fieser, Rheinhold Publishing
   Corp., New York, 1959.

10. a) L. Ruzicka, J. Meyer, and M. Mingazzini, Helv. Chim.
    Acta, 5, 345 (1922).

138

b) L. Ruzicka, Z. Angew. Chem., 51, 5 (1938).

c) L. Ruzicka, A. Eschenmoser, and H. Heusser,
   Experientia, 9, 357 (1953).

11.   "The Chemistry of Natural Products," K. W. Bently (ed.),
      loc. cit., Vol. I, p. 4.

12.   "The Terpenes," J. L. Simonsen, loc. cit., Vol. I, p. 143.

13.   a) A. E. Bradfield et al., J. Chem. Soc., 1744 (1932).

      b) A. E. Bradfield et al., ibid., 767 (1938).

      c) F. C. Cope and J. L. Simonsen, ibid., 415 (1940).

      d) A. E. Gillman et al., ibid., 60 (1941).

      e) T. Geissman, J. Am. Chem. Soc., 75, 4008 (1953).

      f) E. Kyburz et al., Helv. Chim. Acta, 36, 1891 (1953).

14.   R. Robinson in "The Terpenes," J. L. Simoensen and D.H.R.
      Barton, 2nd ed., Vol. III, University Press, Cambridge,
      p. 221, 1952.

15.   W. Voser et al., Helv. Chim. Acta, 35, 2414 (1952).

16.   D. Arigoni et al., Helv. Chim. Acta, 37, 2173 (1954).

17.   a) T. R. Ames et al., J. Chem. Soc., 1905 (1954).

      b) P. Dietrich and O. Jeger, Helv. Chim. Acta, 33, 711 (1950).

18.   T. R. Ames, T. G. Halsall and E. R. H. Jones, J. Chem. Soc.,
      450 (1951).

19.   A. Zurcher et al., Helv. Chim. Acta, 37, 2145 (1954).

20.   D. H. R. Barton and C. J. W. Brooks, J. Chem. Soc., 257
      (1951).

b) S. David, Bull. Soc. chim. Fr., 155 (1949).

21.   B. Bischof, O. Jeger, and L. Ruzicka, Helv. Chim. Acta, 32, 1911 (1949).

22.   a) E. J. Corey and J. J. Orsprung, J. Am. Chem. Soc., 77, 3667, 3668 (1955).

      b) H. Dutler, O. Jeger, and L. Ruzicka, Helv. Chim. Acta, 38, 1268 (1955).

      c) G. Ourisson and T. Takahashi, J. Chem. Ind., 1155 (1955).

      d) G. Brownlie et al., J. Soc. Chem. Ind., 686, 1156 (1955).

23.   a) J. M. Beston et al., J. Chem. Soc., 2131 (1955).

      b) E. Koller et al., Helv. Chim. Acta, 33, 1050 (1950).

24.   a) D. Arigoni et al., Helv. Chim. Acta, 37, 2306 (1954).

      b) K. Christen et al., loc. cit., 35, 1756 (1952).

      c) D. H. R. Barton et al., J. Soc. Chem. Ind., 1325 (1954).

      d) D. H. R. Barton et al., J. Chem. Soc., 876 (1955).

25.   a) D. Arigoni et al., Helv. Chim. Acta, 38, 222 (1955).

      b) E. Menard et al., loc. cit., 38, 1517 (1955).

      c) D. Arigoni et al., loc. cit., 37, 1553 (1954).

      d) D. W. Haines and F. L. Warren, J. Chem. Soc., 2554 (1949).

26.   A. Eschenmoser et al., Helv. Chim. Acta, 38, 1890 (1955).

27.   a) K. Bloch, Vitam and Horm., 15, 119 (1957).

      b) A. Eschenmoser in "The Biosynthesis of Terpenes and Sterols," G. E. W. Wolstenholme and M. O'Conner (eds.), A CIBA Foundation Symposium, J. and A. Churchill, Ltd., London, p. 217, 1959.

28. a) A. McKenzie, Proc. Chem. Soc., <u>27</u>, 150 (1911).

b) P. F. Frankland, J. Chem. Soc., 101, 673 (1912).

c) <u>inter al.</u>, J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, pp. 202-3, 1956.

29. For example see: a) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, pp. 514 ff., 1959.

b) G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, New York, pp. 391 ff., 3rd ed., 1960.

30. G. S. Hammond and C. H. Collins, J. Am. Chem. Soc., <u>82</u>, 4323 (1960).

31. a) H. Meerwein and K. van Emster, Ber., <u>55</u>, 2500 (1922).

b) H. Meerwein <u>et al.</u>, Annalen, <u>453</u>, 16 (1927).

c) F. C. Whitmore <u>et al.</u>, J. Am. Chem. Soc., <u>54</u>, 3431 (1932).

d) F. C. Whitmore <u>et al.</u>, <u>loc. cit.</u>, <u>61</u>, 1586 (1939).

e) I. Dostrovsky and E. D. Hughes, J. Chem. Soc., 157, 164, 166, 169, and 171 (1946).

32. a) E. Staple and E. C. Wagner, J. Org. Chem., <u>14</u>, 559 (1949).

b) D. S. Noyce and F. W. Bachelor, J. Am. Chem. Soc., <u>74</u>, 4577 (1952).

c) F. S. Crossley and M. L. Moore, J. Org. Chem., <u>9</u>, 529 (1944).

d) A. F. Rekasheva and C. P. Miklukhin, Zhur. Obshchei. Khim., <u>24</u>, 96 (1954).

e) P. D. Bartlett <u>et al.</u>, J. Am. Chem. Soc., <u>66</u>, 1531 (1944).

f) H. Pines et al., J. Am. Chem. Soc., 70, 3859 (1948);

H. Pines et al., ibid., 71, 3534 (1949); H. Pines et al., ibid.,

72, 1563, 5521 (1950); H. Pines and J. T. Arrigo, ibid., 80,

4369 (1958).

g) H. S. Mosher and E. La Combe, J. Am. Chem. Soc., 72, 3994;

4991 (1950).

h) R. B. Woodward et al., J. Am. Chem. Soc., 67, 1425

(1945); see also: E. D. Williams et al., loc. cit., 75, 2404

(1953); G. E. Dunn and J. Warkentin, Can. J. Chem., 34,

75 (1956).

i) C. R. Hauser et al., J. Org. Chem., 21, 260 (1956); cf.

H. Fredenhagen and K. F. Bonhoeffer, Z. Phys. Chem., A-181,

379 (1938).

j) J. Meinwald and S. L. Emerman, J. Am. Chem. Soc., 78,

5087 (1956).

k) W. E. Doering and T. C. Aschner, J. Am. Chem. Soc., 75,

393 (1953).

l) H. S. Mosher et al., J. Am. Chem. Soc., 78, 4374, 4959

(1956).

m) Y. Sprinzak, J. Am. Chem. Soc., 78, 466 (1956).

33. For recent reviews, see: a) N. C. Deno et al., Chem. Revs.,

60, 7 (1960).

b) H. E. Ulery, "Hydride Transfer Processes," Organic Chemistry

Seminar delivered at the California Institute of Technology on

March 31, 1961.

c) M. E. Vol'pin, Russ. Chem. Revs., 29, 129 (1960).

d) See also: J. S. Clovis, "Proximity Effects," Organic Chemistry Seminar delivered at the California Institute of Technology on April 7, 1961.

34. a) A. C. Cope et al., J. Am. Chem. Soc., 78, 5599 (1956); A. C. Cope et al., Chem. and Ind., 823 (1956); A. C. Cope et al., J. Am. Chem. Soc., 74, 5885 (1952).

b) V. Prelog et al., Helv. Chim. Acta, 36, 471 (1953).

c) R. L. Letsinger and P. T. Lansbury, J. Am. Chem. Soc., 81, 935 (1959).

d) S. Uyeo et al., J. Am. Chem. Soc., 80, 2590 (1958).

e) E. J. Corey and R. W. White, J. Am. Chem. Soc., 80, 6686 (1958).

f) P. D. Bartlett and B. T. Storey, J. Am. Chem. Soc., 80, 4954 (1958).

g) R. K. Callow and P. N. Massy-Beresford, J. Chem. Soc., 2645 (1958).

h) R. B. Woodward et al., J. Am. Chem. Soc., 80, 6693 (1958).

i) D. Dvornik and O. E. Edwards, Proc. Chem. Soc., 280 (1958).

j) T. Cohen et al., J. Org. Chem., 26, 1 (1961).

k) V. Prelog and W. Küng, Helv. Chim. Acta, 39, 1395 (1956); R. Crigee, Ber., 77, 22, 722 (1944).

35.   a) E. R. Alexander, "Principles of Ionic Organic Reactions,"

John Wiley and Sons, Inc., New York, pp. 41 ff., 1950.

b) E. S. Gould, "Mechanism and Structure in Organic

Chemistry," loc. cit., pp. 303 ff.

c) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry,"

M. S. Newman (ed.), John Wiley and Sons, Inc., pp. 556 ff.,

1956.

36.   a) J. S. E. Holker et al., J. Chem. Soc., 2987 (1958).

b) R. M. Carmen, G. Hassen, and R. B. Johns, J. Chem. Soc.,

130 (1959).

c) A. D. Cross, Quart. Revs., 14, 317 (1960).

37.   T. Tiemann and Fr. W. Semmler, Ber., 26, 2727 (1893).

38.   G. F. Bloomfield, J. Chem. Soc., 289 (1943).

39.   G. M. Kline, Mod. Plastics, 34, No. 5, 149 (1957).

40.   L. Ruzicka in "Perspectives in Organic Chemistry," A. Todd

(ed.), Interscience Publishers, New York, pp. 256 ff., 1956.

41.   a) C. C. Price and M. L. Dickman, Ind. Eng. Chem., 40,

257 (1948).

b) A. Verley, Bull. Soc. chim. Fr., (iii), 21, 408 (1899).

c) O. Zeitshel and H. Smidt, J. pr. Chem., (ii) 133, 370 (1932).

42.   See reference 37 and later papers.

43.   a) R. Robinson, Ann. Repts. on Progr. Chem., 117 (1923).

b) R. Robinson, "Versuch einer Electronentheorie Organish-Chemischer Reaktionen," Ferdinand Enke Verlag, Stuttgart, 1932.

44. C. G. Swain, J. Am. Chem. Soc., 72, 2794 (1950); see also earlier papers.

45. L. Ruzicka in "Perspectives in Organic Chemistry," A. Todd (ed.), loc. cit., reference 112 therin.

46. a) G. Gamboni, H. Schinz, and A. Eschenmoser, Helv. Chim. Acta, 37, 964 (1954).

b) R. Helg and H. Schinz, Helv. Chim. Acta, 35, 2406 (1952).

c) R. Helg et al., Helv. Chim. Acta, 39, 1269 (1956).

47. a) A. Eschenmoser et al., in "The Biosynthesis of Terpenes and Sterols," G. E. W. Wolstenholme and M. O'Conner (eds.), loc. cit., p. 217.

b) A. McKenzie, Proc. Chem. Soc., 27, 150 (1911).

48. See: W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," M. S. Newman (ed.), loc. cit., p. 1.

49. a) J. Hine, "Physical Organic Chemistry," loc. cit., p. 202.

b) G. W. Wheland, "Advanced Organic Chemistry," loc. cit., pp. 391 ff., 1960.

c) A. Hill, "Mechanism of Olefin-Alcohol Interchange," Organic Chemistry Seminar delivered at the California Institute of Technology on April 1, 1960.

d) E. S. Gould, "Mechanism and Structure in Organic Chemistry," loc. cit., pp. 514 ff.

e) W. J. Gensler and H. H. Schlein, J. Am. Chem. Soc., 77, 4846 (1955); cf. D. J. Cram and G. S. Hammond, "Organic Chemistry," McGraw-Hill Book Co., New York, p. 342, 1959; G. W. Wheland, "Advanced Organic Chemistry," loc. cit., pp. 403-406.

50.   a) P. F. Frankland, J. Chem. Soc., 101, 675 (1912).

b) M. J. S. Dewar, J. Chem. Soc., 407 (1946).

c) G. S. Hammond and C. H. Collins, J. Am. Chem. Soc., 82, 4523 (1960).

d) G. S. Hammond and T. D. Nevitt, J. Am. Chem. Soc., 76, 4121 (1954).

e) E. L. Purlee and R. W. Taft, J. Am. Chem. Soc., 78, 3807 (1956).

f) P. L. Southwich and J. E. Anderson, J. Am. Chem. Soc., 79, 6222 (1957).

51.   a) A. J. Streitwieser, Jr., Chem. Revs., 56, 571 (1956).

b) See also the complimentary review by R. H. Dewclf and W. G. Young, Chem. Revs., 56, 753 (1956).

52.   M. E. Vol'pin, Russ. Chem. Revs., 29, 129 (1960).

53.   A. Streitwieser, Jr., J. Org. Chem., 22, 861 (1957).

54.   a) P. A. Stadler et al., Helv. Chim. Acta, 40, 1373, 2191 (1957).

b) G. Stork and A. W. Burgstahler, J. Am. Chem. Soc., 77, 5068 (1955).

c) G. Stork and H. Conroy, J. Am. Chem. Soc., 73, 4748 (1951).

d) R. A. Barnes and A. D. Olin, J. Am. Chem. Soc., 78, 3830 (1956).

55. D. Arigoni in "Steric Aspects of the Chemistry and Biochemistry of Natural Products," J. K. Grant and W. Klyne (eds.), Biochemical Society Symposium No. 19, Cambridge University Press, pp. 32ff, 1960.

56. A. Eschenmoser et al., Helv. Chim. Acta, 38, 1890 (1955).

57. D. H. R. Barton in Discussions in "The Biosynthesis of Terpenes and Sterols," G. E. W. Wolstenholme and M. O'Conner (eds.), loc. cit., p. 228.

58. T. T. Tchen and K. Bloch, J. Biol. Chem., 226, 921, 931 (1957).

59. J. B. Hendrickson, Tetrahedron, 7, 82 (1959).

60. a) G. Popjak and J. W. Cornforth, Adv. in Enzymol., 22, 231 (1960).

b) "Steroids," L. F. Fieser and M. Fieser, loc. cit., pp. 403-420.

c) "Sterol Biosynthesis," J. H. Richards, unpublished.

61. a) L. Dolejs et al., Chem. and Ind., 566 (1959).

b) A. J. Birch et al., Tetrahedron Letters, 3, 15 (1959).

62.   a) P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschen-
moser, Helv. Chim. Acta., 40, 1373 (1957).

b) A. Caliezi and H. Schinz, Helv. Chim. Acta, 32, 2556 (1949);
ibid., 33, 1129 (1950); ibid., 35, 1637 (1952).

c) G. Stork and A. W. Burgstahler, J. Am. Chem. Soc., 77,
5068 (1955).

63.   a) K. Otozai, S. Kume, and S. Fukushima, Bull. Chem. Soc.,
Jap., 25, 302 (1952).

b) P. G. Maslov, Zhur. Fiz. Khim., 31, 1242 (1957).

c) G. Geiseler, Z. Physik. Chem., 202, 424 (1954).

d) M. Kh. Karapet'yantz, Khur. Fiz. Khim., 27, 775 (1953).

e) G. Hood, J. Am. Chem. Soc., 75, 2257 (1953).

f) M. K. Brachman, Phys. Rev., 84, 1263 (1951).

g) J. C. McCoubrey, J. N. McCrea, and A. R. Ubbelohde,
J. Chem. Soc., 1961 (1951).

h) F. D. Rossini, J. Wash. Acad. Sci., 39, 249 (1949).

i) G. S. Parks et al., J. Am. Chem. Soc., 71, 3386 (1949).

j) N. Tcherkezoff, Rev. inst. fr. petr. et Ann. combust. liq.,
1, 50 (1946).

64.   a) M. Simonetta and S. Winstein, J. Am. Chem. Soc., 76,
18 (1954).

b) C. W. Shopee, J. Chem. Soc., 1138 (1946).

c) S. Winstein, H. M. Walborsky, and K. C. Schreiber, J.
Am. Chem. Soc., 72, 5795 (1959).

65.   a) J. R. Partington, "An Advanced Treatise on Physical Chemistry--The Properties of Liquids," 2nd ed., Longmans, Green and Co., New York, 1955.

b) J. O. Hirschfelder, C. F. Curtiss, and R. B. Bird, "Molecular Theory of Gases and Liquids," John Wiley and Sons, Inc., New York, 1954.

c) See also: C. Truesdell, Z. Physik, **131**, 273 (1952).

d) K. Altenburg, Z. Phys. Chem., **199**, 69 (1952).

66.   G. A. McD. Cummings, J. C. McCoubrey, and A. R. Ubbelohde, J. Chem. Soc., 2725 (1952).

67.   a) J. C. McCoubrey, J. N. McCrea, and A. R. Ubbelohde, J. Chem. Soc., 1961 (1951); ibid., Disc. Faraday Soc., **10**, 94 (1951).

b) A. R. Ubbelohde and I. Woodward, Trans. Faraday Soc., **48**, 113 (1952).

c) J. C. McCoubrey and A. R. Ubbelohde, Quart. Revs., **5**, 364 (1951).

68.   H. J. Kopineck, Z. Naturforsch., **5-A**, 420 (1950).

69.   R. S. Mullikin et al., J. Chem. Phys., **17**, 1248 (1949).

70.   a) For reviews before 1958 see: S. P. McGlynn, Chem. Revs., **58**, 1113 (1958).

b) For reviews since 1950 see: R. S. Mullikin and W. B. Person, Ann. Rev. of Phys. Chem., **13**, 107 (1962).

c) In particular see also: G. Briegleb, "Electronen-Donator-Acceptor-Komplexe," Springer Verlag, Berlin-Göttingen-Heidelberg, 1961.

71.   R. S. Mullikin, J. Am. Chem. Soc., 72, 600, 4493 (1950); see later papers in this series.

72.   a) S. C. Abraham, J. Am. Chem. Soc., 74, 2693 (1952).

       b) H. McConnell, J. Chem. Phys., 22, 760 (1954).

       c) K. H. Hausser and J. N. Murrell, J. Chem. Phys., 27, 500 (1957).

73.   a) K. E. Shuler, J. Chem. Phys., 20, 1865 (1952).

       b) K. E. Shuler, J. Chem. Phys., 21, 765 (1953).

       c) R. S. Mullikin, J. Am. Chem. Soc., 74, 811 (1952).

       d) H. Murakami, Bull. Chem. Soc. Jap., 26, 446 (1953).

       e) C. A. Coulson and P. L. Davies, Trans. Faraday Soc., 48, 777 (1952).

74.   a) T. T. Tchen and K. Bloch, Abstrs. 130th Meeting of the Am. Chem. Soc., Atlantic City, p. 56-C, Sept., 1956.

       b) H. S. Mason, Adv. in Enzymol., 19, 79 (1957).

75.   L. Ruzicka, A. Eschenmoser, and H. Heusser, Experientia, 9, 357 (1953).

76.   a) J. T. Kofron, Jr., Ph. D. Thesis, Massachusetts Institute of Technology, 1952.

b) cf. G. Büchi, "The Relationship Between the Cyclization of Polyolefins and the Biosynthesis of Alicyclic Compounds," Organic Chemistry Seminar delivered at the Massachusetts Institute of Technology on March 7th, 1951.

77. Private communication from G. Büchi, 1960.

78. M. Mousseron-Canet and C. Levallois, Bull. soc. chim. France, 443 (1961).

79. R. E. Parker and N. S. Isaacs, Chem. Revs., 59, 737 (1959).

80. A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, p. 115, 1962; cf. A. Streitwieser, Chem. Revs., 56, 573 (1956).

81. C. J. Collins, Quart. Revs., 14, 357 (1960).

82. a) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," R. C. Elderfield (ed.), Vol. I, p. 1, John Wiley and Sons, Inc., New York, 1950.

b) E. L. Eliel, "Steric Effects in Organic Chemistry," M. S. Newman (ed.), loc. cit., p. 106.

c) A. D. Cross, Quart. Revs., 14, 317 (1960).

d) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, 1962.

83. a) D. H. R. Barton, O. C. Beckman, and P. de Mayo, J. Chem. Soc., 2263 (1960).

b) For a related cyclization of caryophyllene epoxide, see: W. Triebs, Chem. Ber., 80, 56 (1947).

84.   a) G. Büchi, "The Relationship Between the Cyclization of

Polyolefins and the Biosynthesis of Alicyclic Compounds,"

Organic Chemistry Seminar delivered at Massachusetts Institute

of Technology on March 7th, 1951.

b) See also: J. L. Simonsen, "The Terpenes," 2nd ed., Vols.

I-V, Cambridge University Press, 1953.

85.   A. Russell and R. L. Kenyon, Org. Syn., 23, 78 (1943).

86.   K. Bernhauer and R. Forester, J. pr. Chem., 147, 199 (1936).

87.   a) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules,"

2nd ed., John Wiley and Sons, Inc., New York, p. 118, 1959.

b) G. Herzberg, "Infra-red and Raman Spectra of Polyatomic

Molecules," Van Nostrand Publishers, p. 340, 1945.

88.   J. E. Field, J. O. Cole, and D. E. Woodford, J. Chem. Phys.,

18, 1298 (1950).

89.   a) L. G. Bonner, J. Chem. Phys., 5, 704 (1957).

b) R. Lord and B. Nolin, J. Chem. Phys., 24, 656 (1956)

c) H. W. Thompson and W. T. Cave, Trans. Faraday Soc.,

47, 946 (1951).

90.   a) N. Sheppard and G. B. B. M. Sutherland, J. Chem. Soc.,

1540 (1947).

b) N. W. Thompson and D. H. Whiffen, J. Chem. Soc., 1412

(1948).

c) D. Barnard et al., J. Chem. Soc., 915 (1950).

d) H. Gonthard and L. Ruzicka, Helv. Chim. Acta, 32, 2125 (1949).

91.   D. Swern, Org. Reacs., 7, 378 (1953).

92.   a) L. Malaprade, Bull. soc. chim., (iv), 43, 683 (1928).

b) L. Malaprade, ibid., (v), 1, 833 (1934).

c) E. L. Jackson, Org. Reacs., 2, 341 (1944).

d) See also: W. J. Hickinbottom, "Reactions of Organic Compounds," 3rd ed., Longmans, Green and Co., New York, p. 146 (1957).

93.   a) M. St. C. Fett, J. Chem. Soc., 962 (1951).

b) G. Fraenkel, R. L. Belford, P. E. Yankwich, J. Am. Chem. Soc., 76, 15 (1954).

c) P. J. Corish and W. H. T. Davidson, J. Chem. Soc., 2431 (1955).

94.   H. E. M. Cardwell, J. D. Dunitz, and L. E. Orgel, J. Chem. Soc., 3740 (1953).

95.   a) F. E. Bader, Helv. Chim. Acta, 36, 215 (1953).

b) W. A. Patterson, Anal. Chem., 26, 823 (1954).

c) See also: R. N. Jones and C. Sandorfy in "Chemical Applications of Spectroscopy," W. West (ed.), Interscience Publishers, Inc., New York, p. 494, 1956.

96.   H. Adkins in "Organic Chemistry," H. Gilman (ed.), John
       Wiley and Sons, Inc., New York, pp. 1041-3, 1943; see
       references cited therein.

97.   a) R. P. Linstead and J. T. W. Mann, J. Chem. Soc., 2064
       (1930).

       b) G. Armand et al., ibid., 1411 (1931).

       c) R. A. Letch and R. P. Linstead, ibid., 443 (1932).

       d) R. Kon, R. P. Linstead, and G. W. G. Maclennan, ibid.,
       2452 (1932).

98.   a) E. R. Alexander, "Principles of Ionic Reactions," John
       Wiley and Sons, Inc., New York, p. 281, 1950.

       b) B. Eistert, "Tautomerie und Mesomerie," Ferdinand Enke
       Verlag, Stuttgart, pp. 51-6, 1938.

       c) J. W. Baker, "Tautomerism," George Routledge and Sons,
       Ltd., London, p. 154, 1934.

99.   a) A. R. N. Cole and P. R. Jefferies, J. Chem. Soc., 4391
       (1956).

       b) M. I. Batuev and A. D. Matvoeva, Izvest. Akad. Nauk,
       S. S. S. R. Otdel. Khim. Nauk, 448 (1951); Chem. Abstr. 46,
       826-h (1952).

       c) J. J. Fox and A. E. Martin, Proc. Roy. Soc., A-162, 419
       (1937).

       d) See also: R. N. Jones and C. Sandorfy, loc. cit., p. 417.

100.   G. Wagner, Ber., 27, 1636 (1894).

101.   Cf. E. A. Braude and E. S. Waight, Prog. in Stereochem., 1, 126 (1954).

102.   a) K. W. F. Kohlrausch and A. Pongratz, Ber., 67, 976, 1465 (1934).

        b) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, J.Am. Chem. Soc., 71, 1068 (1949).

        c) I. M. Hunsberger, ibid., 72, 5626 (1950).

        d) H. L. Hergert and E. F. Kurth, ibid., 75, 1622 (1953).

103.   a) R. J. W. Le Fevre, J. Chem. Soc., 2230 (1949).

        b) N. J. Leonard et al., J. Am. Chem. Soc., 74, 4070 (1952).

104.   E. A. Hill, Ph. D. Thesis, California Institute of Technology, Pasadena, California, p. 134, 1961.

105.   L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, p. 165, 1959.

106.   P. Verley, Bull. soc. chim., France, (iii) 17, 185 (1894); Beilstein, 17, 22.

107.   F. E. Bader, Helv. Chim. Acta, 36, 215 (1953).

108.   W. A. Patterson, Anal. Chem., 26, 823 (1954).

109.   R. Barnes et al., "Infra-red Spectroscopy," Reinhold Publishers, New York, 1944.

110.   a) L. G. Bonner, J. Chem. Phys., 5, 704 (1937).

        b) R. Lord and B. Nolin, ibid., 24, 656 (1956).

c) H. W. Thompson and W. T. Cave, Trans. Faraday Soc., 47, 946 (1951).

111. G. Gamboni, H. Schinz, and A. Eschenmoser, Helv. Chim. Acta, 37, 964 (1954).

112. N. Sheppard and D. M. Simpson, Quart. Revs., 6, 1 (1952).

113. a) M. Busch and Stove, Ber., 49, 1063 (1916).

b) R. A. Raphael and F. Sondheimer, J. Chem. Soc., 2693 (1951).

c) Cf. H. Lindlar, Helv. Chim. Acta, 35, 446 (1952).

114. a) B. Helfrich and T. Malkomes, Ber., 55, 702 (1922).

b) K. von Auwers, Ber., 56, 1672 (1923).

115. a) L. L. Ramsey and W. I. Patterson, Official Agri. Chem., 28, 644 (1945).

b) L. L. Ramsey and W. I. Patterson, ibid., 31, 139, 164, 441 (1948).

c) W. A. Nevill, Ph. D. Thesis, California Institute of Technology, 1954.

116. F. W. Semmler, Ber., 23, 2965 (1890).

117. A. Russell and R. L. Kenyon, Org. Syn., Coll. Vol. III, 747 (1960).

118. J. L. Simonsen, "The Terpenes," Vol. I, 2nd ed., Cambridge University Press, p. 83, 1953.

119. N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed., Interscience Publishers, Inc., New York, p. 393, 1957.

120. a) K. Bernhauer and R. Forester, J. pr. Chem., 147, 199 (1936).

b) Cf. R. Helg and H. Schinz, Helv. Chim. Acta, 35, 2406 (1952).

121. D. Barnard and L. Bateman, J. Chem. Soc., 926 (1950).

122. F. Arndt, Org. Syn., Col. Vol. II, 461 (1959).

123. K. Auwers and F. Eisenlohr, J. pr. Chem., (ii), 84, 25 (1911).

124. F. Arndt, Org. Syn., Coll. Vol. II, 165 (1959).

125. N. A. Lange, "Handbook of Chemistry," 9th ed., Handbook Publishers, Inc., Sandusky, Ohio, p. 1487, 1956.

126. a) J. T. Kofron, Jr., Ph. D. Thesis, Massachusetts Institute of Technology, 1952.

b) B. A. Arbusow and B. A. Michailow, J. pr. Chem., 127, 1, 92 (1930).

c) For a review of this subject, see: D. Swern, Org. Reacs., 7, 378 (1953).

127. N. Prileschajew, Ber., 42, 4811 (1909).

128. G. Braun, Org. Syn., Coll. Vol. I, 431 (1958).

129. G. A. Johnson, J. Am. Chem. Soc., 73, 5888 (1951).

130. For discussion and leading references, see: E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, pp. 281 ff., 1950.

131. G. Zweifel and H. C. Brown, "Hydration of Olefins, Dienes, and Acetylenes Via Hydroboration," a Research Report from the Department of Chemistry of Purdue University (to be published), Lafayette, Indiana.

132. a) F. Emich and F. Schneider, "Microchemical Laboratory Manual," John Wiley and Sons, Inc., New York, p. 34, 1932.

b) F. Schneider, "Organic Qualitative Microanalysis," John Wiley and Sons, Inc., New York, p. 29, 1946.

c) N. D. Cheronis, "Micro and Semimicro Methods," Interscience Publishers, Inc., New York, p. 70, 1954.

133. H. Böhme, Org. Syn., Coll. Vol. III, 619 (1960).

134. a) P. Karrer and H. Stürzinger, Helv. Chim. Acta, 29, 1829 (1946).

b) M. Stoll, P. Bolle, and L. Ruzicka, ibid., 33, 1502 (1950).

c) M. Stoll and M. Hinder, ibid., 34, 334 (1951).

135. N. Prileschajew, J. Russ. Phys. Chem. Soc., 43, 609 (1911); Chem. Abstr., 6, 348 (1912).

136. K. G. Stone, "Determination of Organic Compounds," McGraw-Hill Book Co., Inc., New York, p. 210, 1956.

137. a) A. Baeyer and Villiger, Ber., 32, 3625 (1899).

b) C. H. Hassall, Org. Reacs., 9, 73 (1957).

138. G. Gamboni, H. Schinz, and A. Eschenmoser, Helv. Chim. Acta, 37, 964 (1954).

139. L. Willimann and H. Schinz, Helv. Chim. Acta, 35, 2401 (1952).

140. a) M. Busch and H. Stöve, Ber., 49, 1063 (1916).

   b) R. A. Raphael and F. Sondheimer, J. Chem. Soc., 2693 (1951).

   c) Cf. H. Lindlar, Helv. Chim. Acta, 35, 446 (1952).

141. J. Böeseken, Rec. trav. Chim., 45, 838 (1926).

142. a) B. Helfrich and T. Malkomes, Ber., 55, 702 (1922).

   b) K. von Auwers, Ber., 56, 1672 (1923).

143. For preparation, see: a) A. L. Henne and K. W. Greenlee, J. Am. Chem. Soc., 65, 2020 (1943).

   b) L. Everett and G. A. R. Kon, J. Chem. Soc., 3131 (1950).

144. a) E. L. Eliel and R. G. Haber, J. Org. Chem., 25, 2041 (1958).

   b) E. G. Peppiatt and R. J. Wicker, J. Chem. Soc., 3122 (1955).

   c) A. K. Macbeth and J. A. Mills, ibid., 709 (1945).

   d) G. A. C. Gough, H. Hunter, and J. Kenyon, ibid., 2052 (1926).

145. E. Hückel, Z. Physik., 70, 204 (1931).

146. A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, 454 ff., 1961.

147. A. Streitwieser, Jr., ibid., pp. 97 ff.

148. M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949.

149. See, for example, J. D. Roberts and V. C. Chambers, J. Am. Chem. Soc., 73, 5034 (1951); C. W. Shoppee, J. Chem. Soc., 1138 (1946).

150. H. E. Zimmerman and A. Zweig, J. Am. Chem. Soc., 83, (1961).

151. R. S. Hush, J. Chem. Phys., 27, 612 (1957); G. Dallinga, A. A. V. Stuart, and E. L. Mackor, J. Chem. Phys., 27, 826 (1957).

152. R. D. Brown and M. L. Heffernan, Trans. Faraday Soc., 54, 757 (1958).

153. A. Streitwieser, Jr., loc. cit., pp. 110 ff.

154. a) G. W. Wheland and L. Pauling, J. Am. Chem. Soc., 57, 2086 (1935).

b) Cf. H. C. Longuet-Higgins, J. Chem. Phys., 18, 283 (1950); idem., Proc. Roy. Soc., 207, 121 (1951).

155. a) E. L. Mackor, et al., Rec. trav. Chim., 75, 836 (1956).

b) E. L. Mackor, A. Hofstra, and J. H. van der Waals, Trans. Faraday Soc., 186 (1958).

c) A. Streitwieser, Jr., and P. M. Nair, Tetrahedron, 5, 149 (1959).

156. a) S. Chaykin et al., Proc. Nat. Acad. Sci., U.S., 44, 998 (1958).

b) F. Lynen et al., Angew. Chem., 70, 738 (1958).

PART II

THE ALKYLATIVE-CYCLIZATION

OF 1,5-HEXADIENE

INTRODUCTION

Although a great body of literature has accumulated on the
subject of acid catalyzed cyclizations of 1,5-dienes, the study of
cyclizations initiated by other electrophilic reagents has been largely
neglected. Since carbonium ions generated internally (i. e. within
the cyclizing molecule) are presumed to initiate ring closures in the
cases of certain higher terpenoids (1), we decided to study the pos-
sible use of externally generated carbonium ions as cyclizing agents.
The system chosen was the reaction between 1,5-hexadiene and
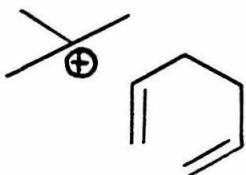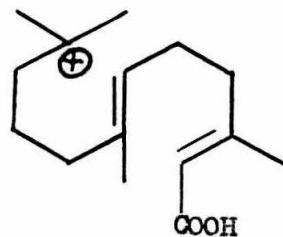
"External" Ion   "Internal" Ion

Fig. 16

t-butyl chloride in the presence of aluminum chloride. In Figure 16
a comparison is made between this system and a postulated inter-
mediate in the acid catalyzed cyclization of farnesic acid (1).

RESULTS

The t-butonium ion used to effect the alkylative cyclization
of 1,5-hexadiene in this study was generated from t-butyl chloride in
the presence of aluminum chloride in n-pentane solvent. The reaction
proceeded smoothly and to completion in one hour at 0° to 10° C.,
while no reaction was detectable in that length of time at -60° C. In
order to inhibit the formation of polymeric material, the diolefin
concentration was kept low by adding slowly a dilute solution of it in
n-pentane to a large excess of the t-butyl chloride solution. The
amount and nature of the polymer which did form was dependent on
the temperature, the concentration of the 1,5-hexadiene, and the
efficiency with which the solution was stirred. Minimum amounts of
polymer were obtained by using a high-speed (10,000 r.p.m.) stirrer;
less efficient stirring resulted in the aluminum chloride catalyst
being coated with polymer, and hence, inhibited further alkylation.
No attempt was made to collect nor to identify the gaseous or liquid
products with boiling points below that of t-butyl chloride (50° C.),
since these most certainly would represent decomposition rather
than cyclization products.

The product distributions were determined by the use of vapor
phase chromatography (V.P.C.). Peak areas were determined auto-
matically by a digital integrator. Best separations were achieved

on diisodecylphthalate and polyethylene glycol (Carbowax-1500) at 100°-150° C.; the latter column material was most efficient in separating the isomeric cycloalkyl chlorides.

Particular attention was directed to the determination of the nature of the C_6 and C_{10} products. The identification of these compounds was based largely on a comparison of the V.P.C. retention times with those of known material, and on infrared absorption data, when it was possible to obtain a reasonably pure sample of one component. The results of these experiments are summarized in Table V. The data presented for the t-butylcyclohexyl systems are more complete for two reasons: 1) the former chlorides are quite accessible, and have been previously identified; 2) chromatographic separation of the t-butylcyclohexyl chlorides in the gas phase showed far better resolution than in the case of the higher boiling neopentylcyclopentyl chlorides. In some instances it was possible to estimate the relative proportions of the cis- and trans-isomers (Table VI) on the basis of the known extinction coefficients of the axial (a) and the equatorial (e) carbon-chlorine absorption bands in the infrared.

Each of the three ring-positional isomers of neopentylcyclopentyl chloride and 4-t-butylcyclohexyl chloride were equilibrated with aluminum chloride for one hour at 0° C. Longer equilibration periods were not practicable due to the formation of polymer. Relatively large amounts of low boiling, unidentified material were also

TABLE V

ALKYLATIVE CYCLIZATION PRODUCTS

Product	0° C.		10° C.	
	2.16 M.[a,b]	0.65 M.[c]	2.16 M.[b]	0.65 M.[c]
C_6-Compounds				
Cyclohexene	trace	trace	trace	ca. 1%
Cyclohexyl chloride	trace	trace	trace	ca. 1%
C_{10}-Compounds				
t-Butylcyclohexenes	12%	2%	9%	3%
1-t-Butylcyclohexyl chloride	trace	trace	trace	trace
3-t-Butylcyclohexyl chloride	9%	10%	6%	12%
4-t-Butylcyclohexyl chloride	9%	9%	6%	5%
Neopentylcyclopentenes[d]	4%	7%	8%	14%
2- and 3-Neopentyl-cyclopentyl chloride	26%	33%	15%	25%
1-Neopentylcyclopentyl chloride	trace	trace	trace	trace
C_{14}-Compounds[e]				
Di-t-butylcyclohexenes	3%	7%	9%	8%
Di-t-butylcyclohexyl chlorides	trace	3%	3%	1%
Other[f]	26%	20%	4%	6%
Polymer	7%	3%	16%	10%

FOOTNOTES TO TABLE V: a) Concentration of t-butyl chloride in n-pentane; b) 7.3% of $AlCl_3$; c) 7.7% of $AlCl_3$; d) possibly some neopentylidenylcyclopentane; e) structure assignments tentative; f) C_{16}- and higher distillable compounds.

TABLE VI

DISTRIBUTION OF cis- AND trans-ISOMERS OF 3- AND
4-t-BUTYLCYCLOHEXYL CHLORIDES

Product	% cis-Isomer	% trans-Isomer
3-t-Butylcyclohexyl chloride[a]	70-85% (e, e)	15-30% (a, e)
3-t-Butylcyclohexyl chloride[b]	81% (e, e)	19% (a, e)
4-t-Butylcyclohexyl chloride[a]	46% (a, e)[c]	54% (e, e)

FOOTNOTES TO TABLE VI: a) Cyclization product; b) from alkylation of cyclohexene; c) only a single measurement was made on this isomer.

formed, some of which would not have appeared in Table V due to the method of work-up. The equilibration results are collected in Table VII.

Identification and Discussion of Reaction Products

$\underline{C}_6$-Products

The C_6-compounds, cyclohexene, cyclohexyl chloride, cyclohexane, 1-methylcyclopentene, and methylcyclopentane were available in these laboratories. Of these, V.P.C. analysis indicated that only the first two were among the products of the alkylative cyclization of 1,5-hexadiene. These products undoubtedly arise from the hydrogen chloride catalyzed cyclization reaction. Inasmuch as the reaction generates large quantities of hydrogen chloride, it is likely that the amount of cyclohexene produced by this mechanism is much greater than indicated in Table V, but that once it is formed, it itself, in the presence of t-butyl chloride, is alkylated to give a mixture of t-butylcyclohexyl chlorides (2).

$\underline{C}_{10}$-Products

t-BUTYLCYCLOHEXENES. 4-t-butylcyclohexene is readily obtained by the pyrolysis of 4-t-butylcyclohexyl acetate (3) or by dehydration of 4-t-butylcyclohexanol with thionyl chloride (see Experimental Section). This olefin was identified among the alkylation

TABLE VII

EQUILIBRATION PRODUCTS[a]

Reactants	4-t-Butyl-cyclohexyl chloride	x-Neopentylcyclopentyl chloride		
		x = 1-	2-[b]	3-[c]
Products				
t-Butylcyclohexenes	7%	2.5%	trace	1.5%
1-t-Butylcyclohexyl chloride	-	-	-	-
3-t-Butylcyclohexyl chloride	11%	2%	-	trace
Neopentylcyclopentenes	-	6%	2%	4%
1-Neopentylcyclopentyl chloride	-	trace	-	-
2- and 3-Neopentylcyclo-pentyl chloride	-	9%	18%	16%
Other	9%[d]	19%	31%[d]	10%
Polymer[e]	37%	61%	49%	68%

FOOTNOTES TO TABLE VII: a) Equilibrated solutions were 0.56 molar in isomeric chloride and contained 8.2 mole percent of $AlCl_3$; b) starting material was 92% pure; c) starting material was 87% pure; d) largely hydrocarbon material; e) includes higher distillates.

products. Treatment of this olefin with perchloric-acetic acid gave a mixture of compounds with similar retention times, some of which were also products of the alkylation reaction. These compounds are probably double bond and skeletal rearrangement isomers.

t-BUTYLCYCLOHEXYL CHLORIDES. Schmerling (2) has reported that the alkylation of cyclohexene with t-butyl chloride in the presence of aluminum chloride gives exclusively a mixture of 1- and 3-t-butylcyclohexyl chlorides. Both of these chlorides could be identified among the products of the alkylation of 1,5-hexadiene. 4-t-Butylcyclohexyl chloride, also found in the reaction mixture, was identified by comparison with the material obtained by the treatment of 4-t-butylcyclohexanol with thionyl chloride. No evidence could be provided for the presence or absence of 2-t-butylcyclohexyl chloride.

Within the last ten years it has become possible to assign with reasonable certainty the axial and equatorial C-Cl stretching absorptions in the infrared spectra of chlorinated six-membered rings (4). The band due to absorption by the equatorial group is found at 724-746 cm.$^{-1}$, while the axial group absorbs in the range 639-696 cm.$^{-1}$ Barton and co-workers (5) have measured the extinction coefficients for these absorptions. Using the value of 1.4 for the ratio of the coefficients (e: a), the distribution of the 3- and 4-t-butylcyclohexyl chlorides between the cis- and trans-isomers was determined. These

values are shown in Table VI along with the corresponding distribution

of geometrical isomers obtained from the Schmerling reaction. In all

cases the most stable, diequatorial isomer predominates, although

significant amounts of the less stable ones were also detected.*

NEOPENTYLCYCLOPENTENE. Neopentylcyclopentene was

detected in small quantities in the reaction mixture. The authentic

sample used for comparison was obtained from the dehydration of

1-neopentylcyclopentanol. Treatment of this olefin with perchloric-

acetic acid gave, among other products, a relatively large amount

of t-butylcyclohexene.

NEOPENTYLCYCLOPENTYL CHLORIDES. Each of the three

ring-positional isomers of neopentylcyclopentyl chloride was identified

in the alkylation product mixture. Although these isomers could not

be obtained in pure form from the reaction mixture, they were pre-

pared independently, and identified on the basis of gas phase analysis.

The 1-isomer was observed in only trace quantities; it was well

resolved chromatographically, however, so that there appeared to

be no doubt in its identification. The retention times of the 2- and 3-

isomers, on the other hand, were overlapping, and therefore it was

---

* Assuming that the t-butyl group is always in the equatorial
position, free energy differences between the two possible orientations
of the chlorine atom (6) predict that the diequatorial isomer should
predominate by 60-70% at equilibrium. The values given in Table VI
may reflect measurement errors of about 10%.

impossible to estimate the relative proportions of the two. Nothing could be said of the cis- and trans- character of these components, since the geometrical isomers appeared to be unresolved, and the analogous spectroscopic data for C_5-ring systems are lacking.

The three neopentylcyclopentyl chlorides were prepared from the corresponding alcohols. The alcohols were prepared as follows: a) the 1-isomer was obtained directly via the addition of neopentyl-magnesium chloride to cyclopentanone; b) the 2-isomer was obtained by the hydroboration of 1-neopentylcyclopentene, as well as by the alkylation of cyclopentene oxide with dineopentylmagnesium or with neopentyl lithium. Presumably these methods would lead to different geometrical isomers, but no attempt was made to isolate them in pure form; c) the 3-isomer was finally obtained by the conjugate alkylation of 2-cyclopentenone with dineopentylcadmium, followed by reduction with sodium borohydride. This scheme should produce a mixture of the cis- and trans-3-neopentylcyclopentanols. These preparations are outlined in Figure 17.

C_{14}-Products

Treatment of 4-t-butylcyclohexene with t-butyl chloride and aluminum chloride gave rise to a mixture of C_{14}-compounds, hydro-carbons and mono-chlorohydrocarbons , which were presumed to be di-t-butylcyclohexenes and di-t-butylcyclohexyl chlorides. These

171
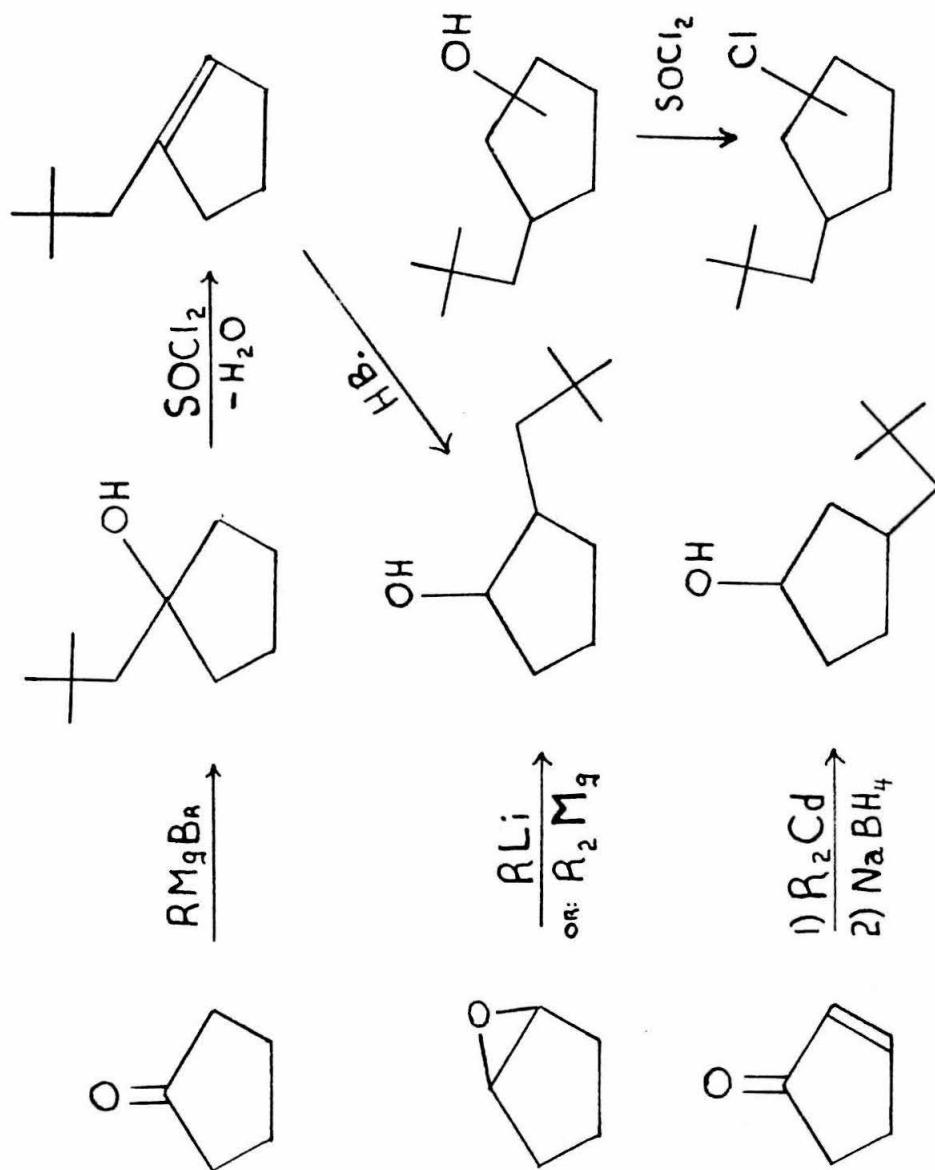
Fig. 17. Preparation of the isomeric neopentyl-cyclopentyl chlorides.

compounds had retention times similar to those of components of a

higher boiling fraction from the alkylative cyclization reaction.

Since chromatographic resolution of the higher boiling components was

poor, identification was uncertain; however, the physical constants

and infrared spectra were in reasonable agreement with what one would

expect for the hypothesized structures.

An even higher boiling liquid fraction could not be conveniently

chromatographed in the gas phase on the same column material without

serious decomposition, and hence it was not investigated. It is

assumed that it is composed of C_{16} and higher materials, although

the possibility of polychlorinated materials with fewer carbon atoms can-

not be excluded.

Polymer

The polymer formed in this reaction at 0° C. was a white

rubbery material, which was 30-40% soluble in benzene, and which

melted at 96-111° C. The polymer was observed to be partially un-

saturated as evidenced by its infrared spectrum in carbon tetrachloride.

A semi-quantitative comparison of the absorptions of the carbon-carbon

double bond (1648 cm.$^{-1}$) and the vinyl carbon-hydrogen bond out-of-

plane deformation (911 cm.$^{-1}$) of both the polymer and 1,5-hexadiene

indicated that the unsaturation amounted to about 10% (7). The polymer,

which formed at 10° C., was a dark red, gummy material, which was about 70% soluble in benzene. This material melted at 78-87° C.; it was found to be about 18% unsaturated.

Recently, Marvel and Stille (7) have polymerized 1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene, and 1,6-heptadiene with Ziegler-type catalysts to obtain chains with cyclic repeating units. These polymers bear a superficial resemblance to those obtained in this work, being 3-13% unsaturated and having low melting points. The structure proposed by Marvel and Stille as most likely for the polymer obtained from 1,5-hexadiene contained 1,3-methylenylcyclopentyl as the recurring group; this structural unit was preferred on the basis of the supposed anionic nature of the reaction. E. I. du Pont has taken out a British patent on a Ziegler process polymerization of 1,5-hexadiene (8), but gives no information on the structure of the polymer.

Arguments on the basis of a cationic, intramolecular-intermolecular mechanism for the concatanation of 1,5-hexadiene similarly lead to 1,3-methylenylcyclopentyl as the most likely repeating unit for the aluminum chloride catalyzed polymerization. However, in view of the immense proclivity for the formation of six-membered rings in the electrophilic cyclizations of 1,5-dienes, the 1,4-cyclohexanyl group must also be considered as a possibility. In fact, both units may occur extensively. The sites of unsaturation are presumed to arise from an occasional defect in the intramolecular step of the sequence.

Polymers which undoubtedly possess a polycyclohexyl structure have been obtained from the treatment of cyclohexene with hydrogen chloride and/or aluminum chloride under a variety of conditions, which are similar to those used in this work (9). However, Waterman, Leendertse, and Ter Poorten (10) found that when cyclohexene was treated with hydrogen chloride and aluminum chloride in n-pentane solution, the polymerization reaction was unusually slow, and that high temperatures (70° C.) and long reaction periods (several hours) were necessary to obtain appreciably large yields of polymer. It would not seem likely, therefore, that in the present case the cyclo-hexene by-products of the reaction of 1,5-hexadiene play more than a casual role in the formation of this polymer.

On the other hand, pure saturated hydrocarbons are known to react with aluminum chloride, especially if hydrogen chloride is not rigorously excluded from the system, to give polymers. In particular, n-pentane itself may be rapidly decomposed with the formation of varying amounts of polymer, if the aluminum chloride is not carefully purified beforehand (11); this was not done in the present work. That butenes and pentenes are notorious decomposition products of hydro-carbons which have been treated with aluminum chloride and which are found to polymerize quite rapidly, is well known (12); the polymeric products, however, tend to be tarry and ill-defined. Copolymerization

of this type may well be responsible for the "poor" quality of the polymers obtained at higher temperatures.

The reaction of hydrocarbons in the presence of aluminum chloride has been reviewed in detail by Egloff et al. (13), and more recently by Stille (14).

Mechanistic Considerations

At present there is, of course, little hope of detailing the mechanisms of olefin alkylation in the presence of boron or aluminum halides. Entrance into this area of understanding is hampered by the lack of kinetic data on these exceedingly fast reactions, and at present the techniques for obtaining this information are largely inadequate. In addition, the multiplicity of reaction pathways which must exist, as evidenced by the variety of products observed, can only compound the problem. At best then, a discussion of the butylation of 1,5-hexadiene must remain qualitative.

Alkylative Cylization of 1,5-Hexadiene. Although the literature contains numerous examples (15) of cyclopentane systems derived from the action of acid on 1,5-diolefins,* these represent what have usually been referred to as "abnormal" cyclic products.

---

* A few naturally occurring cyclopentanoid terpenes are also known (16), which undoubtedly descend from acyclic terpenoid precursors.

The more frequent observation is that such dienes give rise predominantly to cyclohexane skeletons, presumably due to their greater thermochemical stability relative to the alternative five-membered rings,* even though Markownikov's rule is often violated in so doing. It is of interest, therefore, to inquire into what factors may be responsible for the preferred formation of the neopentylcyclopentane system in the present study.

Initially it should be observed that the relative stabilities of t-butylcyclohexane and neopentylcyclopentane may not parallel those of other five- and six-membered ring systems. For example, the methyl hydrogens of the former may be sufficiently crowded by the adjacent ring hydrogens to introduce significant angle strain. In neopentylcyclopentane, on the other hand, the interposition of the methylene group between the ring and the t-butyl moiety would be expected to relieve these hydrogen-hydrogen interactions. The equilibrium data of Table VII, however, would seem to indicate that the t-butylcyclohexyl derivatives are nonetheless slightly favored, and hence, no inversion of the order of stabilities can be claimed.

One possible explanation for the preferred formation of five-membered ring products in the present reaction may lie in the different steric requirements for the two modes of addition of the t-butyl cation

---

* This topic has been given a quantitative treatment (17). It is quite interesting that 1,4-dienes do not appear to cyclize unless rearrangement to a 1,5-diene is possible, in which case the cyclohexane derivative is formed (18).

to the double bond. Reference to Figure 18 indicates that anti-planar addition to the penultimate center, which would lead to the cyclohexane derivative, requires at best two staggered methyl-alkyl interactions. In contrast, if the terminal carbon is the point of attack, only a single and somewhat longer ranged methyl-alkyl interaction results. The latter process would produce the five-membered ring products.

Although the steric requirements of the bulky t-butyl cation are undoubtedly very important, the possibility that electronic factors may play a significant role in determining the orientation of the incoming t-butyl group should not be dismissed. In particular, there is the question of whether or not a non-classical ion might be formed whose geometry would be somewhere between the extremes depicted in Figure 18. Simple molecular orbital theory (Appendix, Part I, Table IV) predicts that the resonance stability of a non-classical ion formed by the association of a carbonium ion and a double bond should decrease as the degree of alkyl substitution on the ion-complex is increased. In other words, as the opportunity for electron delocalization by a hyperconjugative or inductive mechanism increases, the less dependent is the ion upon stabilization gained by resonance within in the p-orbital system of the three carbon atoms. Consequently, a high energy species such as methonium ion would be able to loose more energy by complexing with a given olefin to produce the non-classical system than would the lower energy species, t-butonium ion.
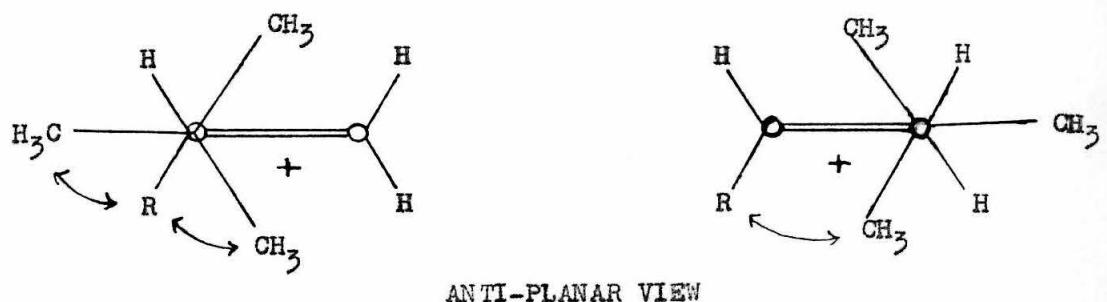
ANTI-PLANAR VIEW

IN-PLANE VIEW
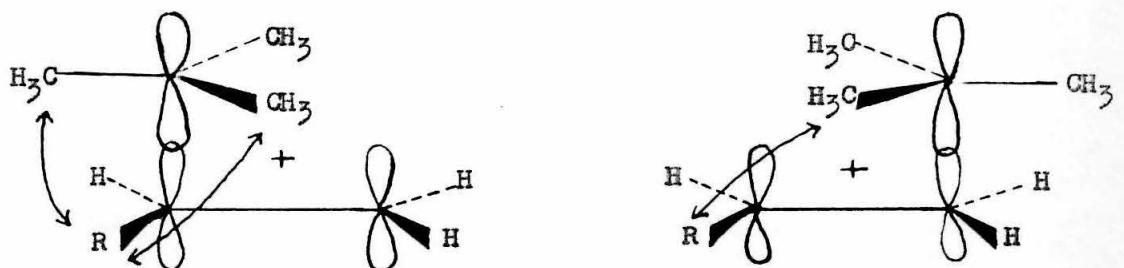
Fig. 18

In choosing a reaction path with minimum energy requirements, the more stable initiator electrophile may discover that one or more classical carbonium ions are of lower total energy that the alternative non-classical ion.[*] In the case at hand, the t-butyl cation may add to the first olefinic linkage of 1,5-hexadiene to give rise preferentially to the classical secondary ion, from which the five membered ring is formed by attack of the second double bond.

The fact that appreciable quantities of 4-t-butylcyclohexyl chloride are also formed is not adequately explained by assuming that this compound is a thermodynamically favored rearrangement product of the initially formed neopentylcyclopentane system, since only small amounts of this material were obtained from the equilibration of the three neopentylcyclopentyl chlorides. Moreover, this material is not observed when the by-product cyclohexene is alkylated under the same conditions (2). This compound could possibly derive from either the addition to give the classical primary cation (anti-Markownikov) or reasonably via a non-classical ion also produced in the reaction which might be in equilibrium with the classical secondary ion (Fig. 19).

When the flexible chain of the non-classical ion has assumed the chair (or boat) conformation necessary for ring closure, the

---

[*] The formation of cyclic non-classical ions must be expected to be accompanied by appreciable steric strain due to bond angle deformation, compression of groups, etc. (19).
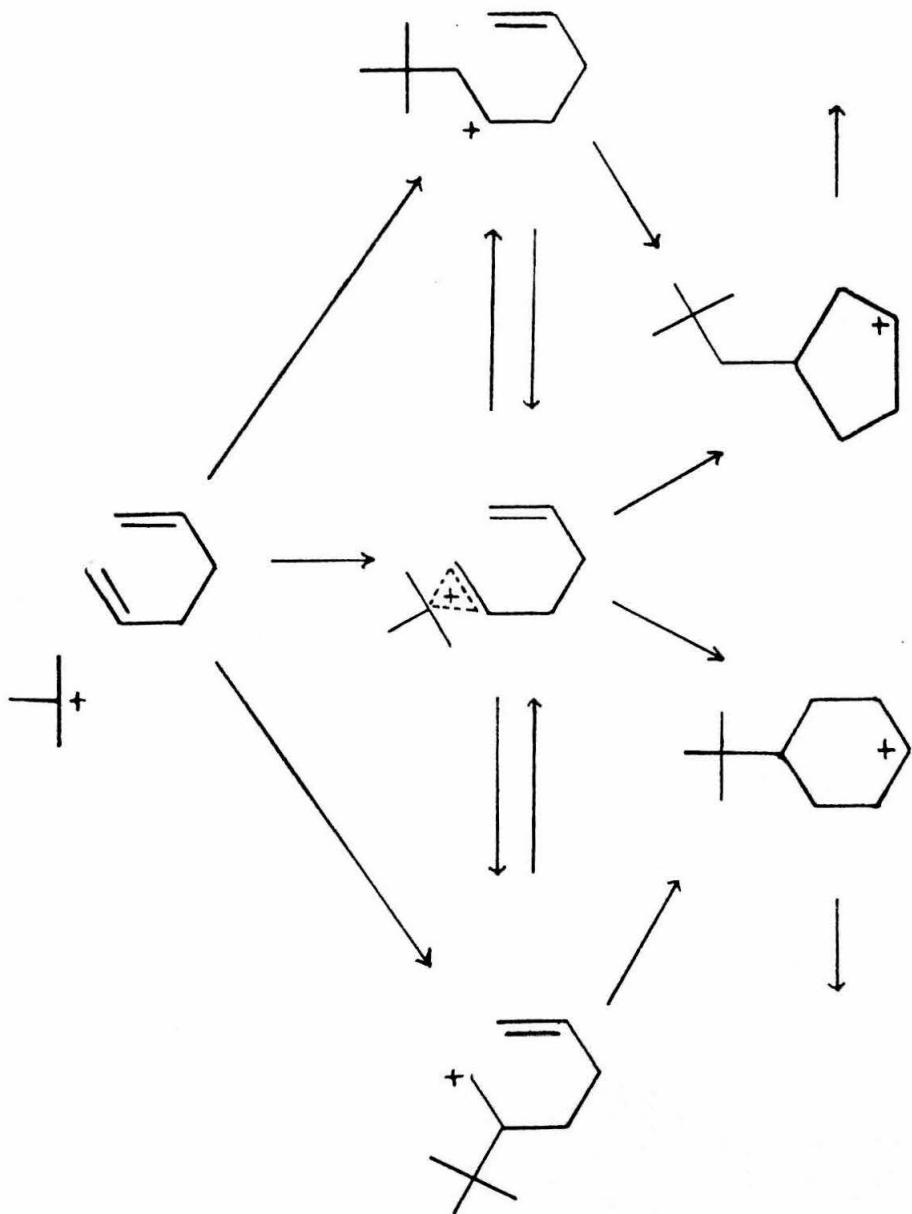
Fig. 19

terminal (C-6) carbon of the olefin would be more or less symmetric-
ally disposed with respect to the two centers (C-1 and C-2) of positive
charge. The amount of reorganization necessary to produce the five-
and six-membered rings would be approximately the same. As a
consequence, the direction of subsequent bond development would be
controlled by the competing influences of steric factors and electrical
asymmetries. If the latter are sufficiently small, the kinetically
favored product would also be the thermodynamically favored cyclo-
hexane ring. These possibilities are depicted in Figure 19.

An initial attempt to test this hypothesis by examining the
relative proportions of five- and six-membered ring products obtained
from the similar treatment of 1,5-hexadiene with methyl and ethyl
chloride was not successful. These reactions resulted mainly in the
production of polymer and recovery of the alkyl chloride; a very small
amount of cyclohexene was also obtained along with some cyclohexyl
chloride.

Alkylation of Cyclohexene. Schmerling (2) has reported that
1- and 3-t-butylcyclohexyl chloride are the only alkylation products
obtained when cyclohexene is treated with t-butyl chloride in the
presence of catalytic amounts of aluminum chloride. These same
isomeric chlorides appear in a similar ratio as cyclic products of
the alkylation of 1,5-hexadiene, and it is possible that they too arise

from the butylation of cyclohexene. It is, perhaps, somewhat sur-
prising that none of the expected 2-t-butylcyclohexyl chloride is
observed in either case. It has further been reported by Simmons
and Meunier (20) that the addition of t-butyl chloride to cyclohexene at
0° C. in the presence of hydrogen fluoride gives only the 1-chloro-
isomer.

The most obvious reason why the expected isomer does not
form is that the t-butyl group interacts sterically with an adjacent
group. Since the bulky group will assume an equatorial position pre-
dominantly, and since the chair form of cyclohexane possesses a
totally staggered configuration of bonds, the t-butyl group will inter-
fere equally with both the cis- and the trans-isomers at the C-2
position. The formation of the 1- and 3-isomers may consequently
arise from proton elimination followed by reverse addition of hydrogen
chloride (2). Inasmuch as these processes are highly reversible
(13, 14), it would be expected that cis-3-t-butylcyclohexyl chloride
would preponderate as equilibrium was approached. It is interesting
that no t-butylcyclohexenes were observed among the cyclohexene
alkylation products; also, no 4-t-butylcyclohexyl chloride was found,
which might be expected if 4-t-butylcyclohexene had enjoyed a short
existence in the reaction mixture.

A second possible mechanism involves a rearrangement of the cationic precursor of the 2-chloro-isomer (Fig. 20). This cation, instead of suffering external nucleophile attack by chloride, may possibly accept the slightly smaller hydride ion donated by a neighboring carbon. Examination of molecular models shows that, if it is assumed that the t-butyl group, in spite of its bulk, initially takes an axial position in the ring, then a transfer of hydrogen from C-3 requires that the non-bonded repulsions between the hydrogen and the t-butyl group be decreased slightly. On the other hand, if the original cation is sufficiently long-lived, it may well undergo conformational inversion giving the t-butyl group the opportunity to assume the more stable equatorial orientation. Hydrogens on both the C-1 and C-3 atoms are now properly positioned for a 1,2-hydride shift. Donation of a hydrogen by C-3 would allow the t-butyl group to pass from a pseudo-equatorial to a true equatorial position with some relief in steric strain. Donation of hydrogen by C-1 is possibly less favorable. Although t-butyl groups are known to hyperconjugate weakly with electron deficient centers(21), rehybridization about C-1 would bring the bulky group into a configuration in which the adjacent pseudo-equatorial hydrogens are fully eclipsed.

An alternative explanation is necessary if it is assumed that the entering t-butyl cation forms a non-classical ion (Fig. 21) which
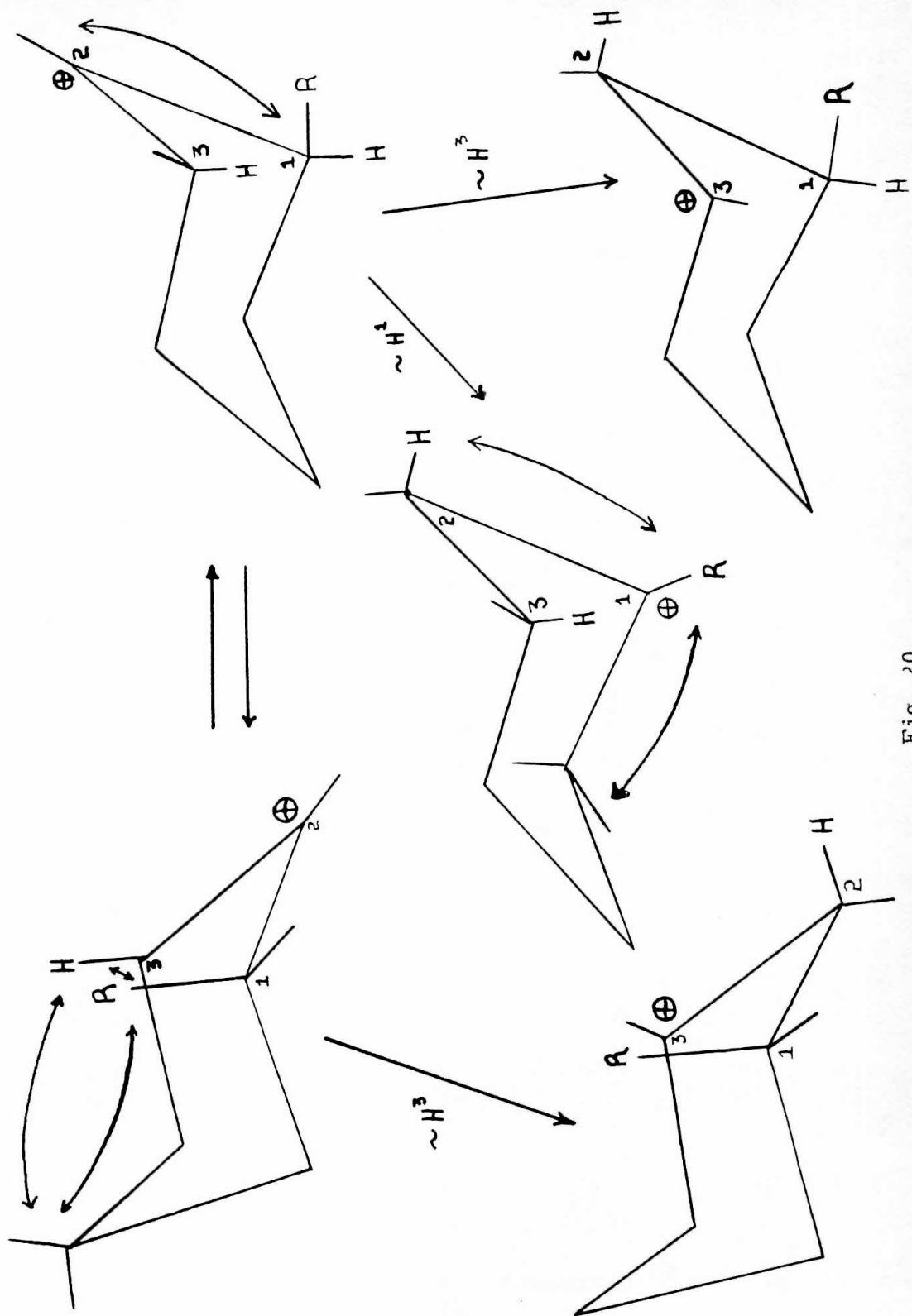
Fig. 20
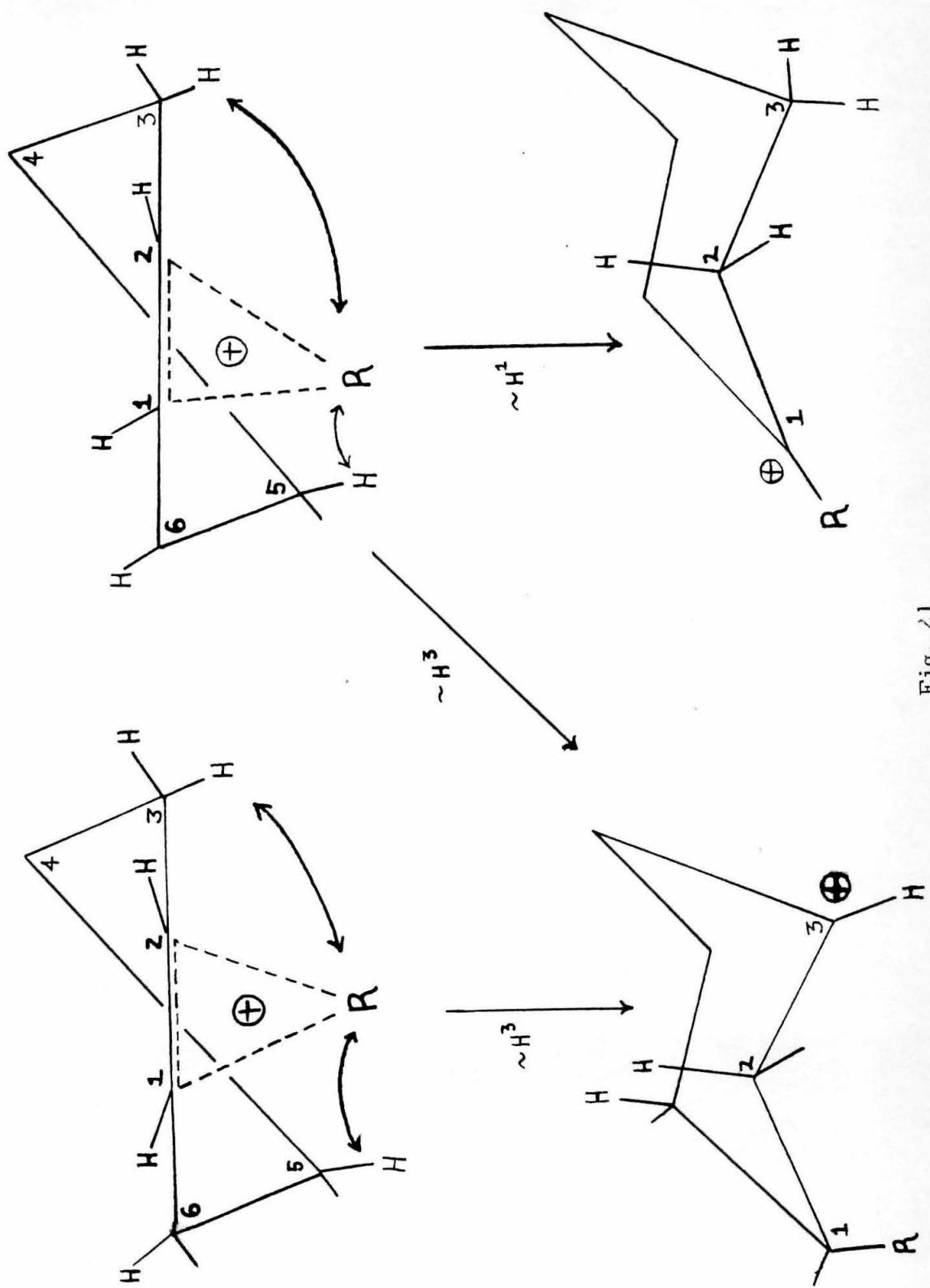
Fig. 21

experiences hydrogen migration without first opening to give the classical trigonal ion. The structure of the non-classical ion would presumably be similar to that of cyclohexene oxide (22). The trans-hydrogens at either C-3 or C-6 are oriented for migration to C-2 or C-1, respectively, with concomitant opening of the three-membered ring. The classical ion which would result could then add a chloride directly to give the trans-3-t-butylcyclohexyl chloride, or undergo ring inversion to give upon attack by nucleophile the more stable cis-isomer. Alternatively, the C-1 hydrogen would migrate to C-2 at the same time that the bond between C-1 and the t-butyl group was becoming fully developed.* The lack of symmetry in the arrangement of groups around the three carbon non-classical ion suggests a preferred direction for hydride migration in this system; thus, the t-butyl group is closer to the pseudo-axial C-3 hydrogen than it is to the one at C-5, and this distance would be further shortened if the t-butyl group were to form a full bond to C-2. These same geometrical factors would be expected to encourage the formation of an unsymmetrical non-classical carbonium ion (Fig. 21) in which the bond to C-1 is more fully matured. Also, in such an ion, migration of hydrogen from C-1 to C-2 would be accompanied by less reorganization than if the C-2 hydrogen were transferred.

---

* This type of stereocontrolled process would not be unlike known rearrangements about the backbone of certain polycyclic triterpenes (23).

EXPERIMENTAL

I. Alkylative Cyclization of 1,5-Hexadiene

The n-pentane used in this experiment was purified before use by shaking with three portions of concentrated sulfuric acid, and then washing with water until no acid could be detected with Universal Indicator Paper. The pentane was then dried over anhydrous sodium sulfate and distilled.

In a typical run a solution of 200 ml. of pure n-pentane and 40 g. (0.432 mole) of freshly distilled t-butyl chloride was cooled to -60° C. in a 500 ml. Morton (creased) flask equipped with a very high-speed stirrer. To this was added 4.2 g. (0.029 mole) of anhydrous aluminum chloride. The solution was allowed to warm to 0° C., and a solution of 30 g. (0.348 mole) of 1,5-hexadiene in 25 ml. of n-pentane was added dropwise at a rate of 50 drops/min. over a period of one and one-half hours.

At the end of this time the contents of the flask were recooled to -60° C., and the pentane solution was decanted from the catalyst and polymer. This solution was then washed with three 50 ml. portions of 1% potassium carbonate and then with five 50 ml. portions of water; the organic layer was finally dried over anhydrous sodium sulfate. The filtered solution was carefully fractionated to remove everything boiling below 35° C. The residual oil was chromatographed in the vapor

phase at 100° and 112° C. on didodecylphthalate and Carbowax-1500 to determine its composition. Distillation of this material gave a forerun of principally t-butylcyclohexene(s), 10.8 g., b.p. 81-109° C./35.5 mm. The mixture of $C_{10}H_{19}Cl$ isomers was obtained at b.p. 109-112° C./35.5 mm. and had $n_D^{23.5}$ 1.4683 and d_4^{24} 0.9788 and amounted to 14.2 g.

Molar Refractivity. Calculated for $C_{10}H_{19}Cl$: 51.05; found: 49.62.

Analysis (E). Calculated for $C_{10}H_{19}Cl$: C, 68.74%; H, 10.96%; Cl, 20.30%. Found: C, 69.16%; H, 11.18%; Cl, 19.80%.

Another 13.9 g. of higher boiling material was obtained at b.p. 60-97° C./2.5 mm. with $n_D^{22.2}$ 1.4649. Analysis (Sp., C, 74.23%; H, 11.52%; Cl, 14.15%) indicated that it was probably a mixture of C_{14}- and C_{16}-monochlorides.

II. Syntheses of Alkylation Products with Neopentylcyclopentane Skeleton Neopentylmagnesium Chloride

The preparation of the Grignard reagent derived from neopentyl chloride has been reported by only one group of workers (24), who have also commented on the general inert character of neopentyl chloride, which fails to undergo many of the usual alkyl halide reactions. The following modification of their procedure was found to give excellent yields of uncontaminated neopentyl Grignard reagent.

A 500 ml. round-bottom, three-necked flask was equipped with a reflux condensor topped with a calcium chloride drying tube, a 250 ml. dropping funnel with pressure equalizing side arm, and a gas inlet tube with a cut-off valve. In the flask was placed 5.0 g. (0.208 g-atom) of magnesium metal turnings, which had been finely splintered in a mortar. The flask and its contents were carefully flame-dried and flushed with dry nitrogen. The turnings were then covered with 100 ml. of commercial anhydrous ether, which was allowed to stand over sodium sand. To this was added one-third of a mixture of 20.0 g. (0.189 mole) of freshly distilled neopentyl chloride (b.p. 83.4° C.) and 1.0 g. of 1,2-dibromoethane. The mixture was stirred vigorously with a magnetic stirrer to avoid local heating and to suppress the concomitant coupling reaction. The remaining two-thirds of the halide mixture was diluted to 250 ml. with dry ether and added dropwise at such a rate as to maintain a mild reaction. The system was flushed with nitrogen at short intervals. Continuous delivery of nitrogen had the disadvantage of evaporating the ether and cooling the contents to the point that all visible reaction had ceased. When all of the halide-ether solution had been added, stirring was continued about three hours, at which time most of the magnesium had been consumed.

Titration with standard 0.1 N hydrochloric acid (24d) indicated that the yield was 90-95%. The reagent was stable for several hours,

and could even be stored overnight with only moderate decomposition.

1-Neopentylcyclopentanol

A 500 ml. round bottom, three-necked flask was equipped with a heating mantle, magnetic stirrer, reflux condensor capped with a calcium chloride drying tube, a 250 ml. dropping funnel, and a gas inlet tube. After the system was properly dried and flushed with nitrogen, a Grignard reagent was prepared as described above from 9.0 g. (0.38 g-atom) of magnesium turnings and 40 g. (0.375 mole) of neopentyl chloride. After the formation of the Grignard reagent was complete, the contents of the flask were allowed to cool to room temperature, and 30 g. (0.358 mole) of cyclopentanone in 200 ml. of anhydrous ether was added dropwise at a rate sufficient to maintain reflux. When the addition was complete (ca. one-half hour), the system was refluxed for an additional hour.

At the end of this time the contents of the flask were poured into a 1500 ml. beaker containing a solution of 60 g. of ammonium chloride in 200 ml. of distilled water and 400 g. of crushed ice. The layers were separated, and the aqueous phase was extracted with four 50 ml. portions of ether. The combined ether solution was washed with water and dried over anhydrous potassium carbonate. The solvent was removed from the filtered solution under reduced pressure, and the residual oil was distilled to give 34 g. (61%) of 1-neopentylcyclo-pentanol, b.p. 80-81° C./10 mm. (99-100° C./30 mm.), n_D^{24} 1.4563.

This material solidified to form long prismatic needles with a very strong menthol odor, m.p. 36-37° C. Recrystallization several times from petroleum ether (30-60° C.) does not change the melting point.

Analysis (E). Calculated for $C_{10}H_{20}O$: C, 76.86%; H, 12.90%. Found: C, 76.86%; H, 12.88%.

1-Chloroneopentylcyclopentane

The following is based on the procedure of Norris and Olmstead (25): Concentrated hydrochloric acid (sp. gr. 1.19; 5 ml., 60 mmoles) and 2.5 g. (16 mmoles) of 1-neopentylcyclopentanol were placed in a 25 ml. separatory funnel and shaken thoroughly for five minutes. To this was then added 0.1 g. of anhydrous calcium chloride, and the mixture was shaken again. The layers were allowed to separate, and the aqueous phase was removed. The organic material was then washed with two 5 ml. portions of a 5% solution of sodium bicarbonate, and dried over a small amount of powdered anhydrous calcium chloride.

Distillation gives 0.82 g. (37%) of 1-neopentylcyclopentene, b.p. 47-48° C. at 7 mm., n_D^{24} 1.4478, and 1.17 g. (42%) of 1-chloro-neopentylcyclopentane, b.p. 78-81° C./7 mm., n_D^{24} 1.4786.

Analysis (E). Calculated for $C_{10}H_{19}Cl$: C, 68.74%; H, 10.96%; Cl, 20.30%. Found: C, 69.02%; H, 11.05%; Cl, 19.96%.

Cyclopentene Oxide

Using the high-speed stirring apparatus described earlier, 90 g. (1.33 mole) of cyclopentene (27) in one pound of anhydrous ether was oxidized at 0° C. with 270 ml. of ca. 40% peracetic acid (1.75 mole active acid) containing 10 g. of anhydrous sodium acetate. After three hours the reaction was warmed to room temperature and allowed to stand for another eight hours.

The ether solution was washed with an excess of 2 N. sodium hydroxide, 200 ml. water, 200 ml. saturated ferrous sulfate, and two 200 ml. portions of water. After drying over anhydrous sodium sulfate and removal of solvent, distillation afforded 77 g. (72%) of oxide, b.p. 96-98° C., n_D^{22} 1.4399 (28).

Neopentylmercuric Chloride

The method of Whitmore, Whittle and Harriman (24a) was used to prepare neopentylmercuric chloride from the corresponding Grignard reagent. Using 50 g. (0.470 mole) of neopentyl chloride and 12 g. (0.50 g. atom) of magnesium in 400 ml. of absolute ether, the resulting Grignard reagent was decomposed with 135 g. (0.515 mole) of mercuric chloride. The alkyl mercuric chloride was recrystallized from hot 95% ethanol, yielding a total of 120 g. (85%) of white solid, m.p. 117.5-118.5° C.

Neopentyl Iodide

The method of Whitmore and co-workers (24a) was modified as follows: To a suspension of 120 g. (0.39 mole) of neopentylmercuric chloride in one liter of distilled water was added a solution of 150 g. (0.59 mole) of iodine and 200 g. (1.20 mole) in 400 ml. of water. The mixture was shaken vigorously for twenty-four hours.

The reaction mixture was then stirred with 250 ml. of a 12% solution of sodium thiosulfate and the organic (lower) layer was removed. The aqueous phase was then extracted with two 100 ml. portions of ether. The ether was combined with the crude alkyl iodide and washed with 100 ml. of salt water. The ether solution was then dried over anhydrous potassium carbonate. Removal of the ether and distillation gave without a forerun 72.2 g. (94%) of neopentyl iodide with n_D^{23} 1.4877.

2-Neopentylcyclopentanol

A. From Cyclopentene Oxide and Dineopentylmagnesium

Treatment of cyclopentene oxide with neopentylmagnesium chloride according to the method of Godschot and Bedos (29a) yielded primarily trans-2-chlorocyclopentanol (30) and little, if any, of the desired alkylation product. Use of the dialkylmagnesium compound, however, resulted in an increased yield of the desired alcohol with the following procedure (31). Neopentylmagnesium chloride was

prepared from 25 g. (0.236 mole) of neopentyl chloride and 6.0 g.
(0.25 g. atom) of magnesium turnings in 250 ml. of absolute ether.
To this was added 25 ml. of dioxane in 25 ml. of ether to precipitate
the magnesium halide. The suspension was refluxed with stirring for
two hours and then centrifuged. The ether solution was collected and
added to 200 ml. of xylene. Most of the ether was distilled from the
solution, to which was then added 15 g. (0.178 mole) of cyclopentene
oxide. The mixture was then refluxed for six hours. At the end of
this time most of the solvent was removed under reduced pressure.
The residue was then mixed with 200 ml. of ice water containing 20 ml.
of concentrated hydrochloric acid. This was extracted with three 35
ml. portions of ether. The ether extract was washed with water and
dried over anhydrous sodium sulfate. When the solvent was removed,
an oil with the odor of menthol remained. Distillation gave 9.3 g.
(34%) of a colorless liquid, b.p. 60-70° C./50 mm., n_D^{24} 1.4511.
V.P.C. showed the presence of impurities to the extent of about 12%.

The sodium salt, obtained by treating the alcohol with metallic
sodium, was used to prepare the p-nitrobenzyl ether derivative,
m.p. 89-92° C. from ethanol.

B. From Cyclopentene Oxide and Neopentyllithium

Using the procedure of Gilman and Van Eso (32a), neopentyl-
lithium was prepared from neopentyl iodide as follows. A 500 ml.
Morton (creased) three-necked flask was equipped with a high-speed

stirrer, a gas inlet valve, a low temperature reading thermometer, and a 50 ml. dropping funnel with pressure equalizing side arm. The latter possessed a pressure equalizing side arm, and was protected with a calcium chloride drying tube, which served as a gas outlet. The apparatus was flame dried and flushed thoroughly with dry nitrogen freed or both oxygen and carbon dioxide. Very dry ether (200 ml.) was poured into the flask. The thermometer was removed, and a heavy flow of nitrogen was introduced through the inlet valve. Freshly cleaned lithium wire (2.0 g., 0.286 g. atom) was added by cutting it into small pieces (ca. 0.5 cm.) and allowing them to fall into the nitrogen stream. The contents of the flask were then cooled to about 10° C. with an acetone and dry-ice bath, and the dropwise addition of 26 g. (0.131 mole) of freshly distilled neopentyl iodide was started along with mild stirring. As soon as the reaction had begun (as evidenced by the clouding of the ether), the temperature was lowered to 0° C., and the contents were stirred vigorously. When the addition was complete (ca. 30 minutes), the contents of the flask were cooled to -10° C. and allowed to stand with stirring and occasional flushing with nitrogen until the reaction was complete (two to three hours). At the end of this time, the thermometer was removed and replaced by a siphon tube, which led into a 250 ml. side arm dropping funnel. Nitrogen was used to force the solution out of the flask.

The dropping funnel was then attached to a three-necked, round bottom flask, which was equipped with the following items: a heating mantle, magnetic stirrer, gas inlet valve, and reflux condensor carrying a calcium chloride drying tube. The flask contained 10 g. (0.119 mole) of cyclopentene oxide in 100 ml. of absolute ether. The neopentyllithium solution was added as quickly as possible, and allowed to stand at reflux for twenty-four hours.

The contents were then cooled and poured into 250 ml. of 5% hydrochloric acid. The layers were separated, and the aqueous phase was extracted with 100 ml. of ether. The combined ether layers were washed with 10% sodium bicarbonate and then with water. After drying over anhydrous sodium sulfate, the ether was removed, and the residue was chromatographed on 500 g. of basic alumina. After elution of a hydrocarbon fraction (probably dineopentyl) with petroleum ether, the column was stripped with ether. Thus, 5.7 g. (31% based on cyclopentene oxide) of crude alcohol was obtained having n_D^{22} 1.4598. Distillation afforded 4.8 g. of material with b.p. 60-62° C./50 mm. and n_D^{22} 1.4609.

Analysis (Sp). Calculated for $C_{10}H_{20}O$: C, 76.86%; H, 12.90%. Found: C, 76.68%; H, 12.93%.

1-Neopentylcyclopentene

A mixture of 2.0 g. (12.8 mmoles) of 1-neopentylcyclopentanol and 3.5 g. (18.4 mmoles) of p-toluenesulfonic acid monohydrate was

heated to 130° C. in an oil bath for one hour (33). The cooled material was then poured into 25 ml. of cold water containing 1 g. of sodium hydroxide. The aqueous solution was then placed in a separatory funnel along with 20 ml. of ether and shaken. The layers were separated, and the aqueous phase was extracted with another 20 ml. of ether. The combined ether solution was washed with a few milliliters of water, and then dried over anhydrous sodium sulfate. The ether was removed, and the dark acrid liquid was distilled to give 0.83 g. (47%) of 1-neo-pentylcyclopentene, b.p. 81-84° C./40 mm., $n_D^{24.2}$ 1.4484.

Neopentylcyclopentane

One gram (7.25 mmole) of neopentylcyclopentene was taken up in 10 ml. of pentane and hydrogenated over 100 mg. of platinum di-oxide at room temperature and pressure. After the hydrogen uptake had ceased, the catalyst was filtered from the solution, and the solvent was removed. Distillation gave 0.77 g. (76%) of neopentylcyclopentane with b.p. 166-168° C. (89-92° C./4 mm.) and n_D^{27} 1.4365.

2-Neopentylcyclopentanol

An alternative route to 2-neopentylcyclopentanol involves hydroboration of 1-neopentylcyclopentene followed by oxidative cleavage with basic hydrogen peroxide (34). The procedure used here requires diglyme that has been dried over calcium hydride for several days and

then distilled from lithium aluminum hydride.

In a 100 ml. flask were placed 21 ml. of a 1 M. solution of sodium borohydride in dry diglyme and 6.9 g. (50 mmoles) of 1-neopentylcyclopentene. The flask was set in a water bath at 20° C. To this was added dropwise, with magnetic stirring, 3.5 ml. of freshly distilled boron trifluoride etherate. The contents of the flask were maintained at 20° C. for one hour. At the end of this time the excess hydride was decomposed by carefully adding dropwise 5 ml. of water. The temperature of the bath was raised to 50° C. and 6 ml. of 3 N. sodium hydroxide solution was added at once, followed by the dropwise addition of 6 ml. of a 30% hydrogen peroxide solution. The reaction mixture was allowed to stand overnight at room temperature.

The reaction mixture was extracted with two 20 ml. portions of ether, and the ether was washed with five 8 ml. portions of water to remove the diglyme. The ether solution was then dried over anhydrous sodium sulfate. Removal of the solvent and distillation gave 4.4 g. (55%) of material with b.p. 66-74° C./50 mm. and n_D^{22} 1.4640. Gas phase chromatographic analysis indicated that this material was about 80% 2-neopentylcyclopentanol, with 1-neopentylcyclopentanol constituting the major contaminant.

2-Chloroneopentylcyclopentane

Five grams (32 mmoles) of 2-neopentylcyclopentanol was placed in a 50 ml. flask containing 25 ml. of petroleum ether (60-70° C.).

To this was added in small portions 5 g. (ca. 3 ml., 42 mmoles) of thionyl chloride. Care must be taken not to lose product as a result of excessive foaming. The reaction complete, the petroleum ether was evaporated on a steam bath to remove the excess thionyl chloride. Another 25 ml. of petroleum ether was added and again evaporated. The residue was washed with 5 ml. of 2 N. sodium hydroxide solution and extracted with three 10 ml. portions of pentane. The pentane extracts were combined and dried over anhydrous potassium carbonate. Distillation gave 0.93 g. (21%) of neopentylcyclopentene, b.p. 78-86° C./40 mm., n_D^{30} 1.4461, and 2.11 g. (38%) of 2-chloroneopentylcyclo-pentane, b.p. 93-99° C./10 mm., n_D^{30} 1.4773.

3-Neopentylcyclopentanone

Treatment of 2-cyclopentenone with neopentylmagnesium chloride gave only the allylic alcohol. The 1,4-addition was enhanced by using dineopentylcadmium, prepared by Cason's (35) method, in conjunction with catalytic amounts of cuprous chloride,* which is known to suppress the 1,2-mode of addition (36).

Neopentylmagnesium chloride was prepared from 4.0 g. (0.166 g. atom) of magnesium turnings and 17.0 g. (0.160 mole) of neopentyl chloride. The Grignard reagent was then cooled to 0° C.

---

* Since this work was completed, Birch and Smith (41) have reported a greatly improved method of inducing conjugate addition via copper salt catalysis.

in a 500 ml. round-bottom, three-necked flask equipped with a mercury
sealed Hershberg stirrer, a reflux condensor carrying a calcium
chloride drying tube, and a heating mantle. Next, 15 g. (0.082 mole)
of cadmium chloride was added in small portions, and the solution
was stirred under reflux for one-half hour. The flask was then fixed
for distillation, and the most of the ether was removed from the mix-
ture. The contents were then diluted with 50 ml. of dry benzene, and
the distillation was continued until half of the benzene had been re-
covered. A fresh 100 ml. portion of benzene was added, and the
mixture was brought to a boil. A small amount of cuprous chloride
(0.25 g.) was added. Without further external heating, 10 g. (0.122
mole) of 2-cyclopentenone* (Aldrich Chem. Co.), in 50 ml. of
benzene was added over five minutes. The material was stirred
under continued reflux for one hour, and then allowed to stand over-
night at room temperature.

The contents of the flask were decomposed with an excess of
5% hydrochloric acid. The layers were separated, and the aqueous
phase was extracted with three 50 ml. portions of ether; the extracts
were combined with the benzene layer. The solvent was removed by
evaporation on a steam bath, leaving a very viscous and strong
smelling residue.

---

* The unreported 2,4-dinitrophenylhydrazone of 2-cyclo-
pentenone was prepared and recrystallized from acetone, deep red
prisms, m.p. 171.0-172.5° C.

To this residue was added a solution of 12 g. of Girard's "T" reagent (37) in 75 ml. of 95% ethanol containing 5 ml. of glacial acetic acid. This solution was refluxed for one hour on a steam bath. The resulting mixture was diluted with 300 ml. of water and extracted with three 100 ml. portions of ether which were discarded. The deep orange solution was heated on a steam bath with 15 ml. of concentrated hydrochloric acid for a period of one-half hour. The layers which formed were separated, and the aqueous phase was extracted with four 50 ml. portions of ether. The ether was removed by evaporation, and the residue which contained some tarry material was taken up in a few milliliters of benzene. This was chromatographed on basic alumina using benzene as the vehicle. Removal of the benzene left 6.9 g. (36%) of nearly colorless ketone.

Analysis (Sp.). Calculated for $C_{10}H_{18}O$: C, 75.86%; H, 11.76%. Found: C, 75.88%; H, 11.82%.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized from 95% ethanol; orange amorphous powder which melts with decomposition over 112-116° C.

Analysis (Sp.). Calculated for $C_{16}H_{22}N_4O_4$: C, 57.47%; H, 6.63%; N, 16.76%. Found: C, 57.44%; H, 6.74%; N, 16.82%.

3-Neopentylcyclopentanol

Five grams (32.5 mmoles) of 3-neopentylcyclopentanone was taken up in 50 ml. of absolute ethanol containing 0.75 g. (21 mmoles) of sodium borohydride (Metal Hydrides, Inc.) and allowed to stand for six hours at room temperature. This was followed by refluxing for an additional one hour. The solution was cooled to 0° C. and 10 ml. of glacial acetic acid was added, and the mixture was allowed to stand overnight.

The solvent was removed under reduced pressure on a steam bath, and the solid was dissolved in 50 ml. of water. This was acidified to a pH of about 2 with 2 N. sulfuric acid, and then extracted with five 20 ml. portions of ether. The extracts were combined and washed with 20 ml. of salt water, then dried over anhydrous sodium sulfate. The solvent was removed from the filtered solution, and the crude alcohol was distilled to give 3.6 g. (72%) of 3-neopentylcyclo-pentanol, b.p. 83-89° C./50 mm., and $n_D^{27.4}$ 1.4604. This material possessed a sweet-menthol odor.

Analysis (Sp.). Calculated for $C_{10}H_{20}O$: C, 76.86%; H, 12.90%. Found: C, 76.59%; H, 12.78%.

3-Chloroneopentylcyclopentane

To a solution of 2.0 g. (12.8 mmoles) of 3-neopentylcyclopentanol in 20 ml. of petroleum ether (60-70° C.) was added dropwise with

swirling 2.0 g. (1.2 ml., 17 mmoles) of thionyl chloride. The solution

was allowed to stand for about thirty minutes before evaporating the

ether on a steam bath. A fresh 25 ml. of petroleum ether was added

and again removed by evaporation. The residue was washed with 5 ml.

of 2 N. sodium hydroxide solution, followed by extraction with three

5 ml. portions of pentane. The extract was dried over anhydrous

potassium carbonate. After removal of the pentane, there was obtained

a forerun of olefinic material and 0.64 g. (29%) of 3-chloroneopentyl-

cyclopentane, b.p. 97-104° C./10 mm., n_D^{26} 1.4799. This material

was only about 88% pure according to analysis by V. P. C.

III.   Syntheses of alkylation Products with tert-Butylcyclohexane

Skeleton 4-tert-Butylcyclohexene

The pyrolysis of 4-acetoxy - tert-butylcyclohexane (38) has been

used previously to obtain 4-tert-butylcyclohexene; however, the following

procedure was found to be more convenient for the preparation of the

small quantities needed for the purpose of chromatographic comparison.

A 100 ml. Erlenmeyer flask containing 5.0 g. (32 mmoles) of 4-tert-

butylcyclohexanol was heated to 50° C. in an oil bath, and 10 ml. of

thionyl chloride was added dropwise, while the flask was swirled to

obtain a good mixing. The flask was then allowed to stand for one hour

at this temperature. To this was added 50 ml. of n-hexane, and the

solution was boiled gently on a steam bath for an additional fifteen minutes. The hexane solution was then cautiously poured onto 100 g. of crushed ice. The layers were separated, and the organic phase was washed with 20 ml. of a 5% sodium bicarbonate solution, and then with 20 ml. of water. The hexane was dried over potassium carbonate. Distillation gives 2.9 g. (66%) of 4-tert-butylcyclohexene, b.p. 72-76° C./30 mm., and n_D^{24} 1.4577. The physical constants and infrared spectrum of this material were identical with those of known material.

Oxidation of 4-tert-butylcyclohexene with 1 N. potassium permanganate solution gave 3-tert-butylhexanedioic acid; recrystallized from methanol-water, m.p. 112-113.5° C. (39).

4-Chloro-tert-butylcyclohexane

Thionyl chloride (5.0 g., 42 mmoles, ca. 3 ml.) was added dropwise to a solution of 5.0 g. (32 mmoles) of 85% trans-4-tert-butylcyclohexanol (Matheson) in 50 ml. of petroleum ether (60-70° C.), which was cooled to 0° C. After the reaction was complete, the petroleum ether was removed by evaporation on a steam bath. Another 25 ml. of petroleum ether was added, and the evaporation was repeated. The residue was washed successively with 5 ml. portions of 10% sodium carbonate and water, and extracted each time with 20 ml. of pentane. After drying there was obtained a forerun of 4-tert-butylcyclohexene, and 2.84 g. (51%) of 4-chloro-tert-butylcyclohexane, b.p. 72-84° C./2.5 mm., $n_D^{24.3}$ 1.4692, d_4^{24} 0.9914. Infrared analysis indicated that this material was about 80% trans-isomer.

Molar Refractivity. Calculated for $C_{10}H_{19}Cl$: 51.05. Found: 48.97.

Analysis (E): Calculated for $C_{10}H_{19}Cl$: C, 68.74; H, 10.96; Cl, 20.30. Found: C, 68.86; H, 11.12; Cl, 19.99.

The alkylmercuric chloride was prepared via the Grignard reagent and recrystallized from methanol-water; tiny colorless plate-lets, m.p. 116-118.5° C.

3-Chloro-tert-butylcyclohexane

A solution of 300 ml. of pure pentane and 12 g. (0.130 mole) of freshly distilled tert-butyl chloride was cooled to -60° C. in a Morton (creased) flask. To this was added 1.3 g. (9 mmoles) of anhydrous aluminum chloride. The temperature was allowed to rise to 0° C. A solution of 10 g. (0.116 mole) of cyclohexene in 50 ml. of pentane was added dropwise over a period of fifteen minutes, while stirring with a very high-speed stirrer. The solution became a bright yellow as polymer began to form. The system was stirred for an additional one-half hour. The contents of the flask were then cooled to -60° C., and the pentane solution was decanted from the catalyst and polymer. The essentially colorless solution was washed with three 50 ml. portions of a 1% solution of potassium carbonate, and with three 50 ml. portions of water, and finally dried over anhydrous sodium sulfate.

Removal of the pentane left 18.8 g. (93%) of slightly impure alkyl chloride. Distillation afforded 15.6 g. (77%) of high purity 3-chloro-tert-butylcyclohexane, b.p. 96-98° C./20 mm., n_D^{25} 1.4661 (40).

The alkylmercuric chloride was prepared in very low yield from the Grignard reagent; colorless crystals, m.p. 131.0-131.5° C. from methanol-water.

Addition of Hydrogen Chloride to 4-tert-Butylcyclohexene

A solution of 2.0 g. (14.5 mmoles) of 4-tert-butylcyclohexene in 25 ml. of n-pentane was cooled to -40° C. in a dry-ice bath and saturated with hydrogen chloride gas. The flask was stoppered tightly and secured with wire. The flask was placed in a shatter-proof safety container and allowed to warm to room temperature. After standing for one day, the flask was again cooled and charged with hydrogen chloride gas and allowed to stand for one day. The process was repeated for a third time. The total amount of hydrogen chloride absorbed was 0.6 g. (16 mmoles).

The pentane solution was washed with three 10 ml. portions of a 1% solution of potassium carbonate, and with two 15 ml. portions of water. The pentane was then dried over anhydrous sodium sulfate. Removal of the solvent and distillation gave 1.9 g. (77%) of a mixture of 3- and 4-tert-butylcyclohexyl chlorides, b.p. 88-98° C./25 mm., n_D^{23} 1.4678.

References to Part II

1. See, e.g., G. Stork and W. Burgstahler, J. Am. Chem. Soc., 77, 5068 (1955); also see references cited therein.

2. L. Schmerling, J. Am. Chem. Soc., 69, 1121 (1947).

3. D. C. Garwood, Ph. D. Thesis, California Institute of Technology, Pasadena, California, 1962.

4. a) G. H. Alt and D. H. R. Barton, J. Chem. Soc., 4284 (1954).

   b) K. Kozima, K. Sakashita, and S. Maeda, J. Am. Chem. Soc., 76, 1965 (1954).

   c) D. H. R. Barton and E. Miller, J. Am. Chem. Soc., 72, 370 (1950).

   d) P. Klaeboe, J. J. Lothe, and K. Lunde, Acta Chem. Scand., 11, 1677 (1957).

   e) K. Kozima and T. Yoshino, J. Am. Chem. Soc., 75, 166 (1953).

5. D. H. R. Barton, J. E. Page, and C. W. Shoppe, J. Chem. Soc., 331 (1956).

6. a) L. W. Reeves and K. O. Strømme, Can. J. Chem., 38, 1241 (1960).

   b) A. J. Berlin and F. R. Jensen, Chem. and Ind. (London), 998 (1960).

   c) G. Chiurdoglu et al., Bull. soc. chim., Belges, 69, 143 (1960).

7. C. S. Marvel and J. K. Stille, J. Am. Chem. Soc., __80__, 1740 (1958).

8. E. I. du Pont de Nemours and Co., British Patent 776,326 (1957).

9. a) F. W. Sullivan, Jr., _et al._, Ind. Eng. Chem., __23__, 604 (1931).

   b) See also ref. 2.

10. H. I. Waterman, J. J. Leendertse, and A. C. Ter Poorten, Rec. trav. chim., __54__, 245 (1935).

11. A. L. Glassbrook, N. E. Phillips, and W. G. Lovell, J. Am. Chem. Soc., __58__, 1944 (1936).

12. a) H. I. Waterman, J. J. Leendertse, and W. M. Klazinga, Rec. trav. chim., __54__, 79 (1935).

    b) J. J. Leendertse, A. J. Tulleners, and H. I. Waterman, Rec. trav. chim., __53__, 715 (1934).

    c) H. I. Waterman, J. Over, and A. J. Tulleners, Rec. trav. chim., __53__, 699 (1934).

13. G. Egloff, _et al._, Chem. Revs., __20__, 345 (1937).

14. J. K. Stille, Chem. Revs., __58__, 541 (1958).

15. a) G. Ciamician and P. Silber, Ber., __41__, 1928 (1908).

    b) C. Daessle, H. Favre, and H. Schinz, Helv. Chim. Acta, __40__, 2278 (1957).

    c) A. Eschenmoser and H. Gunthard, Helv. Chim. Acta, __34__, 2338 (1951); cf. A Lutz and E. Reid, J. Chem. Soc., 2264 (1954).

d) V. N. Ipatieff, et al., J. Org. Chem., 12, 34 (1947); idem, 17, 272 (1952).

e) I. Cononge and P. Dumont, Compt. rend., 220, 500 (1945); idem., Bull. soc. chim., France, 38 (1947).

f) Y. R. Naves, P. Ardizio, and B. Wolk, Bull. soc. chim., France, 1213 (1957); W. Kimel, et al., J. Org. Chem., 23, 153 (1958); G. Saucy, et al., Helv. Chim. Acta, 41, 160 (1958); cf. G. I. Samochavalov, Zhur. Obshch. Khim., 27, 2501 (1957).

16.   G. W. K. Cavill, Revs. Pure and Applied Chem., 10, 169 (1960).

17.   a) R. M. Gascoigne, J. Chem. Soc., 876 (1958).

b) cf. M. Sanders, Jr., C. S. Mathews, and C. O. Hurd, Ind. Eng. Chem., 41, 1048 (1949).

18.   L. Hibbit and R. Linstead, J. Chem. Soc., 470 (1936).

19.   For discussion, see M. Howden, Ph. D. Thesis, California Institute of Technology, 1961.

20.   J. H. Simmons and A. C. Meunier, J. Am. Chem. Soc., 65, 1269 (1943).

21.   L. M. Stock and J. Suzuki, Proc. Chem. Soc. (London), 136 (1962).

22.   B. Ottar, Acta Chem. Scand., 1, 283 (1947).

23.   a) E. J. Corey and J. J. Ursprung, J. Am. Chem. Soc., 77, 3667 (1955).

b) H. Dutler, O. Jeger, and L. Ruzicka, Helv. Chim. Acta, **38**, 1268 (1955).

c) G. Brownlie, et al., Chem. and Ind. (London), 686, 1156 (1955).

d) D. Arigoni, et al., Helv. Chim. Acta, 37, 2306 (1954).

e) D. H. R. Barton, et al., Chem. and Ind. (London), 1325 (1954).

24. a) F. C. Whitmore, E. L. Whittle, and B. R. Harriman, J. Am. Chem. Soc., **61**, 1585 (1939).

   b) F. C. Whitmore, et al., ibid., 63, 643 (1941).

   c) F. C. Whitmore and R. S. George, ibid., 64, 1239 (1942).

   d) See also: M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, Inc., New York, 1954.

25. J. F. Norris and A. W. Olmstead, Org. Syn., Coll. Vol. I, 144 (1941).

26. N. J. Demjanow and L. L. Luschinow, Zhur. Obshchei, Khim., **35**, 30 (1903).

27. O. Grummett and J. R. Johnson, Org. Syn., Coll. Vol. I, 153 (1959).

28. a) B. A. Arbusow and B. A. Michailow, J. pr. Chem., (2) **127**, 92 (1930).

   b) J. Böeseken and G. C. C. C. Schneider, J. pr. Chem., (2) **131**, 285 (1931).

c) W. D. Emmons and A. S. Pagano, J. Am. Chem. Soc., <u>77</u>, 89 (1955).

29. a) M. Godshot and P. Bedos, Compt. rend., <u>182</u>, 393 (1926).

b) cf. G. Chavanne and L. de Vogel, Bull. soc. chim. Belg., <u>37</u>, 141 (1928).

30. H. B. Donahoe and C. A. Vandenwerf, Org. Syn., <u>30</u>, 24 (1950).

31. See, for example: a) A. Cope, J. Am. Chem. Soc., <u>60</u>, 2215 (1938).

b) W. Schlenk, Ber., <u>64-B</u>, 736 (1931).

c) C. R. Noller and W. R. White, J. Am. Chem. Soc., <u>59</u>, 1354 (1937).

d) C. R. Noller and D. C. Raney, ibid., <u>62</u>, 1749 (1940).

e) R. C. Huston and A. H. Agett, J. Org. Chem., <u>6</u>, 123 (1941).

32. a) H. Gilman and P. R. Van Eso, J. Am. Chem. Soc., <u>55</u>, 1258 (1933).

b) This topic has been reviewed by R. G. Jones and H. Gilman, Org. Reac., <u>7</u>, 339 (1951).

33. J. M. Harris, Jr., J. Am. Chem. Soc., <u>51</u>, 2591 (1929).

34. G. Zweifel and H. C. Brown, "Hydration of Olefins, Dienes, and Acetylenes via Hydroboration," a Research Report from the Department of Chemistry of Purdue University (to be published), Lafayette, Indiana.

35. J. Cason, J. Am. Chem. Soc., $\underline{68}$, 2078 (1946).

36. See reference 24d, pp. 219 ff.

37. a) For preparation of Girard's reagent, see: A. Girard, Org. Syn., Coll. Vol. II, 85 (1959).

    b) For a review on the properties and uses of Girard's reagents, see: O. H. Wheeler, Chem. Revs., $\underline{62}$, 205 (1962).

38. D. Garwood, Ph. D. Thesis, California Institute of Technology, 1962.

39. J. H. Simmons and A. C. Meunier, J. Am. Chem. Soc., $\underline{65}$, 1269 (1943).

40. L. Schmerling, J. Am. Chem. Soc., $\underline{69}$, 1121 (1947).

41. A. J. Birch and M. Smith, Proc. Chem. Soc., 356 (1962).

PART III

THE ACID CATALYZED CYCLIZATIONS OF

cis,cis- AND trans,trans-2,6-OCTADIENE

INTRODUCTION

In order to elucidate the overall geometry of the acid catalyzed cyclization of acyclic 1,5-dienes, it is necessary to 1) define the changes in geometry which occur at each of the four olefinic carbon atoms, and 2) establish the conformation of the molecular chain during the ring closure process (cf. pp. 50-53). Failure of previous investigations to obtain an adequate solution to this problem lies in the unsatisfactory choice of the dienic system. We hope to overcome this difficulty by using as our model system the trans,trans- and the cis,cis- isomers of 2,6-octadiene. These hydrocarbons have no trisubstituted centers which might favor the formation of classical tertiary carbonium ions.* Furthermore, they have the advantageous feature of being symmetrical around the C_4-C_5 bond; consequently, proton attack at either end of the chain will lead to the same products.

---

* The selection of apogeranic and aponeroic acids (Fig. 2, p. 14) by Schinz and coworkers (ref. 46, Part I) was made in recognition of the fact that natural terpenoid systems with the trisubstituted double bond (i.e., with the C-5 methyl group) invariably undergo elimination instead of or subsequent to nucleophile attack. This not only interferes with the stereochemistry at C-5, but also frequently with that at C-6. Use of the apo-acids allowed these workers to follow the stereochemistry of only the C-5 and C-6 centers (i.e., the carboxyl conjugated olefinic carbons). The presence of the gem-dimethyl group at C-1, however, makes it impossible to conclude anything about the nature of the process occurring at this center, and hence, to specify the conformation of the chain during the formation of the bond between C-1 and C-6 (see pp. 12-17 and 50-53). Note that the numbering used here refers to the unsubstituted 1,5-hexadiene portion of the molecule.

RESULTS

Preparation and Identification of the Isomeric 2,3-Dimethylcyclohexanols and the 2,3-Dimethylcyclohexanones.

In order to identify the reaction products of the cyclization of 2,6-octadiene, it was desirable to characterize the four possible geometrical isomers of 2,3-dimethylcyclohexanol. Three of these isomers and the two derived 2,3-dimethylcyclohexanones were completely characterized by determination of their physical constants and by preparation of a number of solid derivatives. The fourth alcoholic isomer was less accessible and was not isolated in pure form. The results of this work are summarized in Tables VIII-XI.

The low pressure hydrogenation of 2,3-dimethylphenol over finely divided platinum metal in glacial acetic acid produced an isomeric mixture of 2,3-dimethylcyclohexanols (Fig. 22), which was readily analyzed by gas chromatography using a Carbowax-1500 column. In order of increasing retention times, these isomers were: A (9%), B (6%), C (3%), and D (82%). Hydrogenation under these conditions is known to involve predominantly cis-addition, such that the all cis product preponderates (1). That the similar reductions of 2,4-dimethylphenol (2) and 3,5-dimethylphenol (3) give the all cis compound as the major product is good evidence for the belief that the D-alcohol has the $2^c, 3^c\text{-ol}^c$ configuration (Fig. 22).
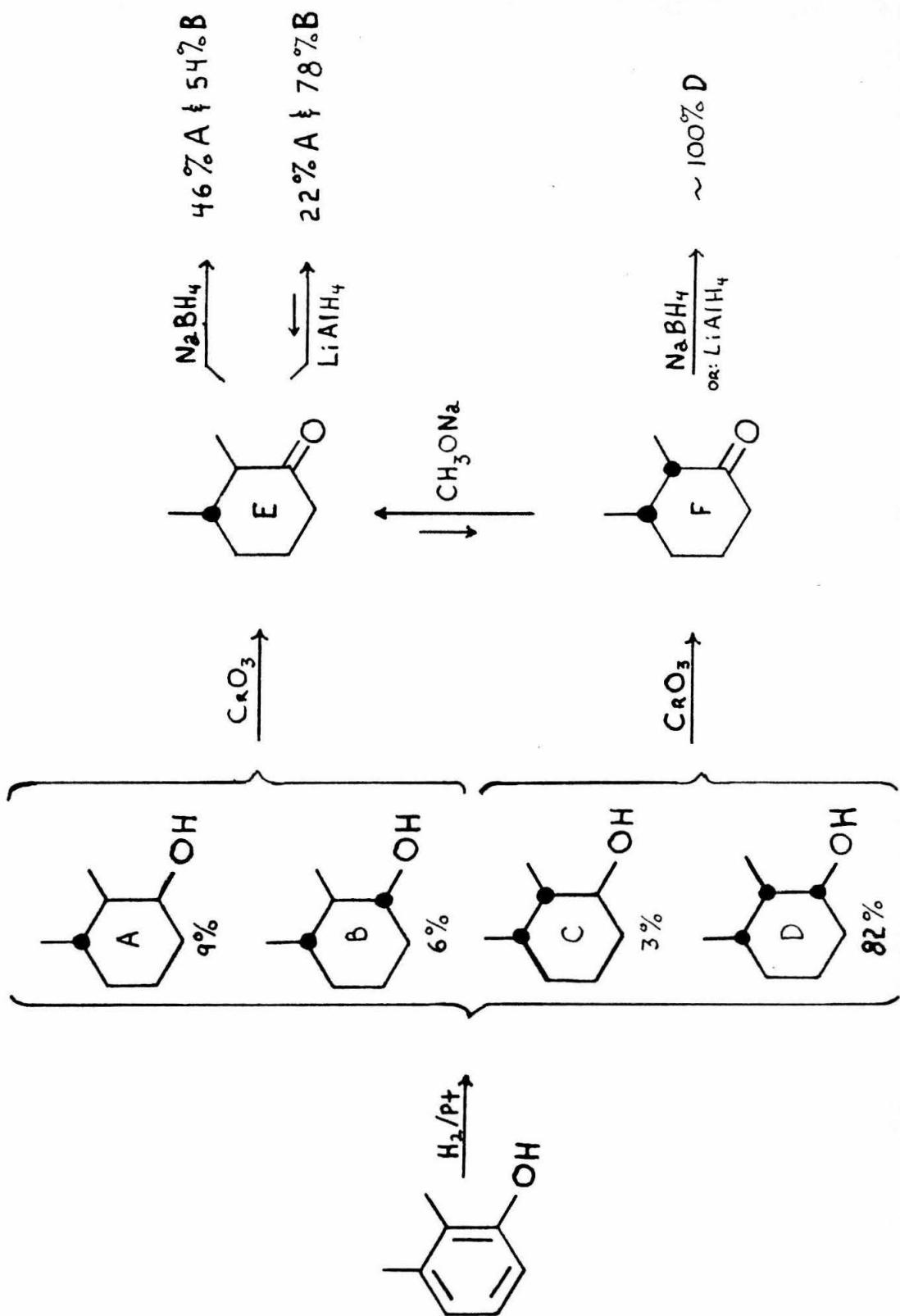
Fig. 22

If one considers the more stable of the two possible chair conformations of each of the 2,3-dimethylcyclohexanols, the all cis isomer (whose most populated conformation should be 2[a],3⌈e⌉-ol⌈e⌉) is predicted to have the highest dipole moment, and hence is in qualitative agreement with the long retention time of the D-alcohol. In consideration of the foregoing, the D-alcohol may be tentatively assigned the $2^c,3^c$-ol^c or cis-cis configuration. Later evidence will support this conclusion.

Oxidation of the above mixture of isomeric alcohols under non-isomerizing conditions (2a) gave two ketones (Fig. 22), which were designated E (15%) and F (85%) in order of their vapor phase retention times. Oxidation of pure D-alcohol gave only the F-ketone. Evidently, the C- and D-alcohols must be the C-OH epimers leading to ketone F, and the A- and B-alcohols an epimeric pair related to the E-ketone. Assuming that no isomerization did occur during the oxidation, the trans-cis or $2^c,3^c$-ol^t configuration may then be tentatively assigned to the C-alcohol.

The oxidation of the D-alcohol to ketone F requires that the geometry of the methyl groups be the same in both of these compounds if isomerization did not occur, and therefore, the F-ketone should be cis-2,3-dimethylcyclohexanone. Since the cis-ketone would have both an axial and an equatorial methyl group, it should be convertible to the more stable diequatorial trans-isomer upon treatment with base (4).

When the F-ketone is allowed to stand in contact with a dilute solution of sodium methoxide in methanol for periods up to several days, an equilibrium mixture of about 88% ketone E and 12% ketone F is obtained,* confirming that the E-ketone is the more stable of the two, and thus, is properly assigned the trans configuration. That no isomerization occurs during the oxidation reaction was later evidenced by the specific conversion of both the A- and the B-alcohols to ketone E. The physical properties of these two ketones are compared in Table VIII; in Table IX are collected the melting points of their solid derivatives.

Reduction of ketone E with methanolic sodium borohydride gives only alcohols A (46%) and B (54%), proving that they are the C-OH epimers with the trans orientation of the methyl groups. While sodium borohydride reductions generally lead to kinetically controlled products,**

---

* The free energy difference (25° C.) between an axial and equatorial methyl group in cyclohexane is about 1.5-1.9 kcal/mole (5), but should be somewhat smaller for a 3-methylcyclohexanone (6), or about 1 kcal/mole, since there is one less methyl-hydrogen interaction. The value of 1.2 kcal/mole is obtained from the equilibrium data for the 2,3-dimethylcyclohexanones. For a discussion of the 3-alkyl-ketone effect, see ref. 1a, p. 240.

** In the case of trans-2,3-dimethylcyclohexanone, molecular models indicate that both sides of the molecular plane are more or less equally susceptible to reagent attack. Hence, the epimers $2^t, 3^c$-ol^t and $2^t, 3^c$-ol^c should be about equally favored by a process under kinetic control.

TABLE VIII

Physical Constants of the cis- and trans-2,3-Dimethylcyclohexanones

Ketone Isomer	E (trans-)	F (cis-)
B. P. / 57 mm.	95.5°	99°
n_D^{25}	1.4475[a]	1.4523
n_D^{50}	1.4367[a]	1.4420
d_4^{25} ($\pm$ 0.0008)	0.9079[a,c]	0.9208
Mol. Vol. (ml./mole)	138.958	137.011
Mol. Ref. (Calc'd: 36.786)	37.164	36.982
Rel. V.P.C. Retention Times[b]	1.00	1.23

FOOTNOTES TO TABLE VIII: a) Extrapolated from data on isomeric mixtures with ketone-E present to the extent of 88.13% and 98.29%, as determined by automatic integration of completely resolved chromatograms; b) Retention times are for a Carbowax-1500 column heated to 115° C. using helium as the carrier gas; c) This extrapolated value is probably somewhat low.

TABLE IX

Melting Points of Derivatives of the Isomeric 2,3-Dimethylcyclohexanones

Ketone Isomer	E (trans-)	F (cis-)
DERIVATIVES:	MELTING POINTS:	
Oxime	113.5-114.5°	liquid
Semicarbazone	205.5-206.0°	174.5-175.5°
Thiosemicarbazone	170.5-171.0°	142.5-143.0°
Phenylhydrazone	oil	oil
p-Nitrophenylhydrazone	157.5-158.0°	149.0-150.2° (decomp.)[a]
m-Nitrophenylhydrazone	127.0-128.5°[b]	126.5-127.5°[b]
2,4-Dinitrophenylhydrazone	153.5-154.5°	109.5-111.0° (decomp.)

FOOTNOTES TO TABLE IX: a) This derivative appeared to possess a polymorphic crystalline form with m.p. 154.0-154.5° C.; b) The melting point of a 50:50 mixture of the cis- and trans-derivatives was depressed to 120-124° C.

reduction with lithium aluminum hydride is sufficiently reversible to give the thermodynamically favored product (7). When ketone E is stirred under reflux with a large excess of lithium aluminum hydride for two days, the alcoholic product obtained was found to be 78% B and 22% A.* Consequently, the B-alcohol must be assigned the all equatorial trans-trans configuration $(2^t, 3^c\text{-ol}^c)$, while alcohol A must be the cis-trans $(2^t, 3^c\text{-ol}^t)$ isomer. Again, this conclusion is in qualitative agreement with assignments predicted on the basis of the V.P.C. retention times.

Reduction of the F-ketone with either sodium borohydride or with lithium aluminum hydride gave only alcohol D, which must be kinetically favored. Since attack by reagent on the molecular face opposite the axial methyl group of the cis-ketone is highly preferred, alcohol D must correspond to the configuration previously assigned.**

It was possible to obtain reasonably pure isomeric alcohols by analytic fractional distillation. The alcoholic isomers A and B were also resolved by fractional crystallization of their p-nitrobenzoate esters. This was not found to be convenient, however, since the saponification of these esters was achieved only with some difficulty.

---

* This equilibrium (assumed) distribution of isomers corresponds roughly to a free energy difference of 0.75 kcal/mole between the axial and equatorial position of the -OH group, if only the most stable chair conformation of each epimer is considered. The tabulated value is 0.4-0.9 kcal/mole (8).

** This conclusion is independent of the conformation of the F-ketone.

The C-alcohol was never obtained in a pure form, but conceivably it may be prepared by a reaction scheme involving a single inversion at the C-1 position.

The physical properties of the 2,3-dimethylcyclohexanols are compared in Table X. It should be pointed out that the von Auwers-Skita (conformational) rule (9), which says that the isomer* with the highest enthalpy will have the highest density and refractive index (i.e., the smallest molecular volume),** is in good agreement with the assigned configurations. The ketone assignments are also supported by this rule. Table XI compares the melting points of a number of solid derivatives of the isomeric alcohols.

Some mention should be made of previous work reported on this series of compounds. Capon et al. (11) have reported that the high temperature reduction of 2,3-dimethyl-2-cyclohexenone gives a material with physical constants in agreement with those obtained from an equilibrium mixture of ketones E and F; the melting points of the reported oxime and semicarbazone are those reported here for the predominant trans-isomer. When this ketone is reduced (11, 12) with sodium in ethanol, the product alcohol gives no phenylurethane but gives a 3,5-dinitrobenzoate with melting point 118-118.5° C.; reduction

---

* Strictly speaking, the epimers should have the same dipole moment.

** Although boiling point is sometimes included in this rule, the rule is frequently found to fail for this parameter (10).

TABLE X

Physical Constants of the Isomeric 2,3-Dimethylcyclohexanols

Alcohol Isomer	A ($2^t,3^c$-ol^t)	B ($2^t,3^c$-ol^c)	C ($2^c,3^c$-ol^t)	D ($2^c,3^c$-ol^c)
B.P./38 mm.	92.5-93° C.	95-96° C.	100-102° C.[f]	103° C.
B.P./14 mm.	75.5-76° C.	78.5-80.0° C.	82-84° C.[f]	85° C.
n_D^{25}	1.4583[a]	1.4561	1.4659[d]	1.4675
n_D^{50}	1.4476[a]	1.4456	---	1.4565
d_4^{25} ($\pm$ 0.0004)	0.9113[a,c]	0.9098[b,c]	---	0.9480
Mol. Vol. (ml./mole)	140.656	140.888	---	138.125
Mol. Ref. (Calc'd: 38.303)	38.399	38.307	---	38.361
Rel. V.P.C. Retention Times[e]	1.00	1.14	1.46	1.66

FOOTNOTES TO TABLE X: a) Extrapolated from data for isomeric mixture containing 5.77% of B; b) Extrapolated from data for isomeric mixture containing 15.28% of A; c) Extrapolated value is probably slightly low; d) Value doubtful; extrapolated from data for mixture containing 13.19% of C, the remainder was alcohol D; e) Retention times are for a Carbowax-1500 column at 115° C., using helium as the carrier gas; f) Estimated from distillation curve and V.P.C. retention times.

TABLE XI

Melting Points[a] of Derivatives of the Isomeric 2,3-Dimethylcyclohexanols

Alcohol Isomer	A ($2^t,3^c$-ol^t)	B ($2^t,3^c$-ol^c)	C ($2^c,3^c$-ol^t)	D ($2^c,3^c$-ol^c)
Phenylurethane	95.0-96.0	oil	---	113.0-113.5
α-Naphthylurethane	154.0-153.0[b]	156.0-156.3[b]	---	116.5
p-Nitrobenzoate	83.0-83.5	61.0-61.5[c]	---	62.5-63.0[c]
m-Nitrobenzoate	---	111.0-112.5	---	---
3,5-Dinitrobenzoate	118.5-119.5[d]	118.0-118.8[d]	---	57.5-58.5
Monoacid Phthalate	---	---	---	165-167[e]

FOOTNOTES TO TABLE XI: a) Uncorrected; b) Mixed m.p. was 133-145° C.; c) Mixed m.p. was 47-54° C.; d) Mixed m.p. was 96-111° C.; e) Possibly contaminated.

over platinum black produces material whose phenylurethane melts at
98° C. and which gives a different 3,5-dinitrobenzoate with a melting
point of 119-119.5° C. These results would appear to be consistent
with the assignments made for the B- and A-alcohols, respectively.
Colonge, Dreux, and Thiers (13) report the preparation of a ketone
which, upon reduction with sodium in ethanol, gives an alcohol whose
α-naphthylurethane melts at 140° C. This ketone was prepared by their
method and subjected to gas chromatographic analysis; it was found to
contain only 7-8 percent total of ketones E and F , although the semi-
carbazone did melt at 204° C. Farmer and Sutton (14) report that the
high temperature hydrogenation of 2,3-dimethylphenol over nickel
catalyst gave a material whose α-naphthylurethane melted at 138-140° C.
Presumably this corresponds to the C-alcohol derivative.

Preparation of the trans,trans- and cis,cis-2,6-octadienes

Coupling of crotyl chloride (XXX) with nickel tetracarbonyl (15)
gives rise to a mixture of 2,6-octadiene (XXXI) and 3-methyl-1,5-
heptadiene (XXXII) in which the former predominates by about 3:1.
The 2,6-octadiene may be obtained in pure form by analytic fractional

XXX   XXXI   XXXII
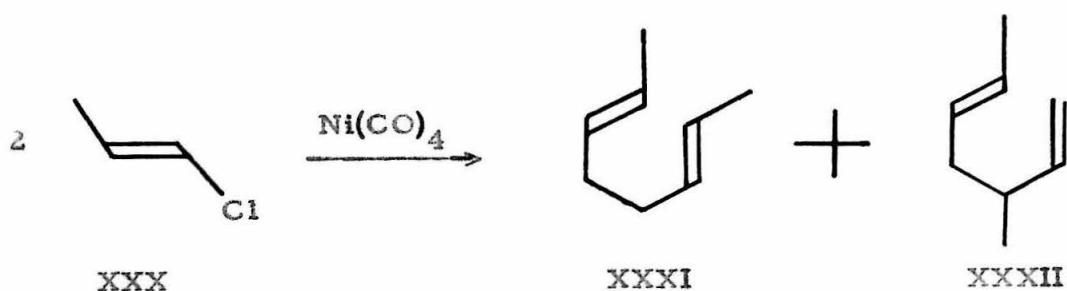
distillation; this material was found to be better than 99% homogeneous on the basis of gas chromatographic analysis using a variety of column materials. The infrared spectrum of XXXI (neat) possessed a strong band at 963 cm.$^{-1}$, which is characteristic of a _trans_-olefin (16); the spectrum was devoid of activity near 1650 cm.$^{-1}$, which may also be expected of a double bond with a center of symmetry. The spectrum presented no evidence of a _cis_-olefin. The diolefin was concluded, therefore, to be _trans,trans_-2,6-octadiene. The physical constants of this hydrocarbon are summarized in Table XII.

Partial hydrogenation of 2,6-octadiyne (XXXIII) to _cis,cis_-2,6-octadiene (XXXIV) was accomplished over Lindler's Pd:Pb/CaCO$_3$ catalyst (17); the selectivity of the catalyst was enhanced by heavily poisoning it with quinoline. The material obtained after analytic fractional distillation was at least 99 percent homogeneous according to gas analysis. The infrared spectrum of this material (neat) contained a very strong band at 713 cm.$^{-1}$ and a medium intensity at 1658 cm.$^{-1}$;
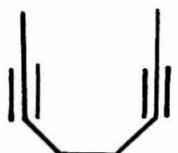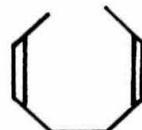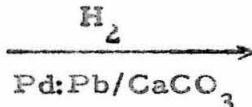
XXXIII $\xrightarrow[\text{Pd:Pb/CaCO}_3]{\text{H}_2}$ XXXIV

TABLE XII

Physical Constants of the cis,cis- and trans,trans-2,6-Octadienes

Diene Isomer	trans,trans-	cis,cis-
B.P./744 mm.	121.8-122.5° C.	124.0-124.2° C.
$n_D^{23.5}$	1.4284	1.4351
$d_4^{23.5}$ (± 0.0004)	0.7493	0.7475
Mol. Vol. (ml./mole)	147.057	147.411
Mol. Ref. (Calc'd: 37.964)	37.864	38.473
Rel. V.P.C. Retention Times[a]	1.00	1.19
Infrared Activity[b]: $>$C=C$<$	---	1658 cm.$^{-1}$
-CH=CH-	963 cm.$^{-1}$	713 cm.$^{-1}$

FOOTNOTES TO TABLE XII: a) Retention times are for a Carbowax-1500 column heated to 70° C. using helium as the carrier gas; b) Samples were neat; sodium chloride plates.

both of these bands are characteristic of the cis-disubstituted double bond (16). No evidence for the presence of trans-olefin could be obtained from the spectrum. The physical constants of the cis, cis- and trans, trans-isomers are compared in Table XII.

Cyclization of trans, trans-2, 6-Octadiene

When trans, trans-2, 6-octadiene was treated with a mixture of concentrated formic and sulfuric acids, there was obtained a 37-40 percent yield of $2^t, 3^c$-dimethylcyclohexyl^c formate (undeuterated XXXVII) which was 100.0 ± 0.1 % isomerically pure. This material was identified by 1) comparison of its gas chromatographic retention time with that of known formate prepared by an independent method, 2) comparison of the retention time of the derived alcohol with that of the B-alcohol (Fig. 22), 3) preparation of the α-naphthylurethane (m.p. = 156.5 - 157.0° C.) whose melting point was not depressed when mixed with the corresponding derivative of the B-alcohol, 4) comparison of the infrared spectra of the formate and derived alcohol with those of the B-alcohol and its formate, and 5) elemental analysis of both the formate and the derived alcohol.

A second and higher boiling fraction (50-52%) was obtained, which contained a mixture of three formate isomers that analyzed for $C_{10}H_{18}O_4$. Oxidation with chromic acid led to a mixture of three ketones whose infrared spectrum possessed a single carbonyl absorption at 1715 cm.$^{-1}$. In order of the V.P.C. retention times, the isomer

distribution was approximately 1:2:1. The nuclear magnetic resonance spectrum displayed a methyl singlet at 2.23 p.p.m. relative to tetramethylsilane (the acetone singlet appears at 2.17) and a methyl triplet centered at 1.14 p.p.m. ($J_{ppm} = 0.10$). These data are consistent with the belief that the second reaction product was a mixture of 2,7-, 2,6-, and 3,6-octadiyl diformates.

It may be added that if the cyclization reaction was interrupted before completion, no other products were obtained. Further, there was no indication that any of the unreacted 2,6-octadiene had isomerized, since the recovered olefin remained chromatographically pure. The isomeric formates were also found to be stable to the conditions of the reaction (19).

When the reaction was carried out in formic acid-d (HCOOD) and deuterium sulfate, the formate possessed a C-D absorption at 2171 ± 4 cm.$^{-1}$, which is approximately 9 percent as intense as the maximum C-H absorption (2934 cm.$^{-1}$). It has been reported (16,18) that in monodeuterocyclohexane the axial C-D stretching band appears at 2146 cm.$^{-1}$, while the equatorial C-D absorption appears at 2174 cm.$^{-1}$ Consequently, it may be concluded that the acquired deuterium occupies an equatorial position such that the product of this reaction is $2^t,3^c$-dimethyl-4^t-deuterocyclohexyl^c formate, the trans-anti-trans-isomer (XXXVII).

Cyclization of cis,cis-2,6-Octadiene

When cis,cis-2,6-octadiene was treated with concentrated formic and sulfuric acids at room temperature, the mixture became homogeneous within one hour as compared with the several hours required for the trans,trans-isomer; this rapid reaction was noticeably exothermic, causing a temperature rise of about 30° C. Under these conditions, the yield of 2,3-dimethylcyclohexyl formate was less than 3 percent. When the reaction was conducted at 0° C., several days were required to obtain a homogeneous system, and the yield of 2,3-dimethylcyclohexyl formate was increased to about 11 percent. An additional 23 percent of isomeric formate was also produced, which was not identified.* The major product of the reaction (41%) was the same isomeric mixture of acyclic octadiyl diformates obtained previously. Approximately 94 percent of the 2,3-dimethylcyclohexyl formate was the $2^t,3^c$-yl^c isomer, while the remaining 6 percent was the $2^t,3^c$-yl^t epimer (related to alcohols B and A, respectively; Fig. 22).

Although no new products were obtained if the reaction was interrupted, the unreacted diene was found to contain 1.5 percent of two new components, neither of which was the trans,trans-isomer.

---

* The infrared spectrum of this material contained none of the bands characteristic of an olefin, and hence, may well be cyclic. V.P.C. analysis shows the material to be a mixture of at least four components, all of whose retention times were shorter than those of the 2,3-dimethylcyclohexyl formates. Attempts at the independent synthesis of 1-(2'-methylcyclopentyl)-ethyl formate were not successful.

After carrying the reaction out in deuterated acid, it was possible to isolate a sample of the $2^t, 3^c$-dimethylcyclohexyl^c formate by gas chromatography. The infrared spectrum of this material possessed a band at 2142 ± 8 cm.$^{-1}$, which was assigned to an axial C-D stretching motion. The product, therefore, was apparently the trans-anti-cis isomer, $2^t, 3^c$-dimethyl-4^c-deuterocyclohexyl^c formate.

DISCUSSION

The general features of the cyclizations of 1,5-dienes have been discussed in detail in Part I of this dissertation. It was pointed out that in order to account for the stereochemistry of a large number of cyclic terpenoid compounds, a simple hypothesis has evolved. In its simplest form, this hypothesis requires that the diene, folded in either the quasi-chair (XIIa) or the quasi-boat (XIIb) conformation, undergo a pair of trans-addition processes to give products with the respective geometries indicated by XIIIa and XIIIb (p. 51). For non-enzymic reactions, the chair folding of the diene is preferred for thermodynamic reasons. This simple proposal makes no attempt to differentiate between a concerted process in which all new bonds are formed more or less synchronously and a stepwise process in which "steric control" over the products is maintained in some way by the nature of the reaction intermediates. For non-enzymic systems, the stepwise process would appear to be the more reasonable, since it does not demand the high degree of organization of both the diene and the bifunctional solvent required by the concerted mechanism.

Our present purpose, then, is to decide how well the results on the reaction of cis,cis- and trans,trans-2,6-octadiene are explained by this simple model for polyene cyclization.

Mechanism of the Cyclization of trans, trans-2, 6-Octadiene

The cyclization of trans, trans-2, 6-octadiene (XXXI) is exceedingly stereospecific--only one isomer of 2, 3-dimethylcyclohexyl formate was observed by a chromatographic method sensitive to one part per thousand. Although the infrared analysis of the orientation of deuterium was far less sensitive, this stereospecificity appears also to apply to the C-4 center of the product. The reaction of the trans, trans-diene to give $2^t, 3^c$-dimethyl-4^t-deuterocyclohexyl^c formate (XXXVII) is precisely the result anticipated by the proposed model for diene cyclization outlined above.

There remains the question of whether the observed product of this reaction may result from a non-controlled process. In this case, the answer is "yes," because the product predicted on the basis of the simple cyclization proposal is also the thermodynamically stable isomer. Consequently, if the reaction gave rise to a classical intermediate such as XXXVIb, the observed product XXXVII would be expected as a result of the thermodynamically preferred equatorial attack by solvent (20). In order to clarify this point, the mechanistic possibilities consistent with the selective formation of the all-equatorial product, XXXVII, from the trans, trans-diene are outlined below.

The first step in this reaction is the transfer of a proton (or deuterium) to one double bond of the diene (XXXI) to give either the π-complex, XXXVa, or the classical secondary carbonium ion, XXXVb

(Fig. 23). While there is some evidence from other addition reactions

(21) that a proton may be transferred to an olefin to give rise directly

to a tertiary carbonium ion, the intermediate formation of a π-complex

is generally preferred when there is no tertiary center. The production

of XXXVb, whether proceeding directly from the olefin or indirectly

via the π-complex, might be expected to result in loss of steric control

at C-3 due to the rapid reversible formation of the rotamer, XXXVc.

The difference in free energy between these two rotamers is expected

to be small, such that an appreciable concentration of both forms should

exist at equilibrium.* Presumably the cyclization of XXXVb and XXXVc

would lead to different epimers at C-3. Since the epimer derived from

XXXVc is not observed, this may be taken to indicate that the classical

ion, XXXVc, is not formed to any discernible extent, and consequently,

neither is the rotameric ion, XXXVb.**

---

* Although XXXVb and XXXVc are not the most favorable rotameric forms of this carbonium ion, they are the only ones which would be expected to give a cyclic product by antiplanar addition to the second double bond.

** This argument has, of course, a very important structural defect. Namely, it assumes that XXXVc, if formed, would cyclize as readily as XXXVb. This assumption is without good testimony. In fact, it can be argued that the transition state between XXXVc and cyclic product will be of higher energy than that which separates XXXVb from the C-3 epimer. This difference may be attributed to the additional energy required to overcome the 1,3-axial methyl-hydrogen interaction produced during the cyclization of XXXVc. Consequently, rotamer XXXVc, even though present in appreciable equilibrium concentrations, might not react fast enough with the double bond to compete with the cyclization of XXXVb. On the other hand, unless important differences in solvation exist, it is not likely that the transition state energies leading from XXXVb and XXXVc to analogous cyclic products should differ by a value large enough
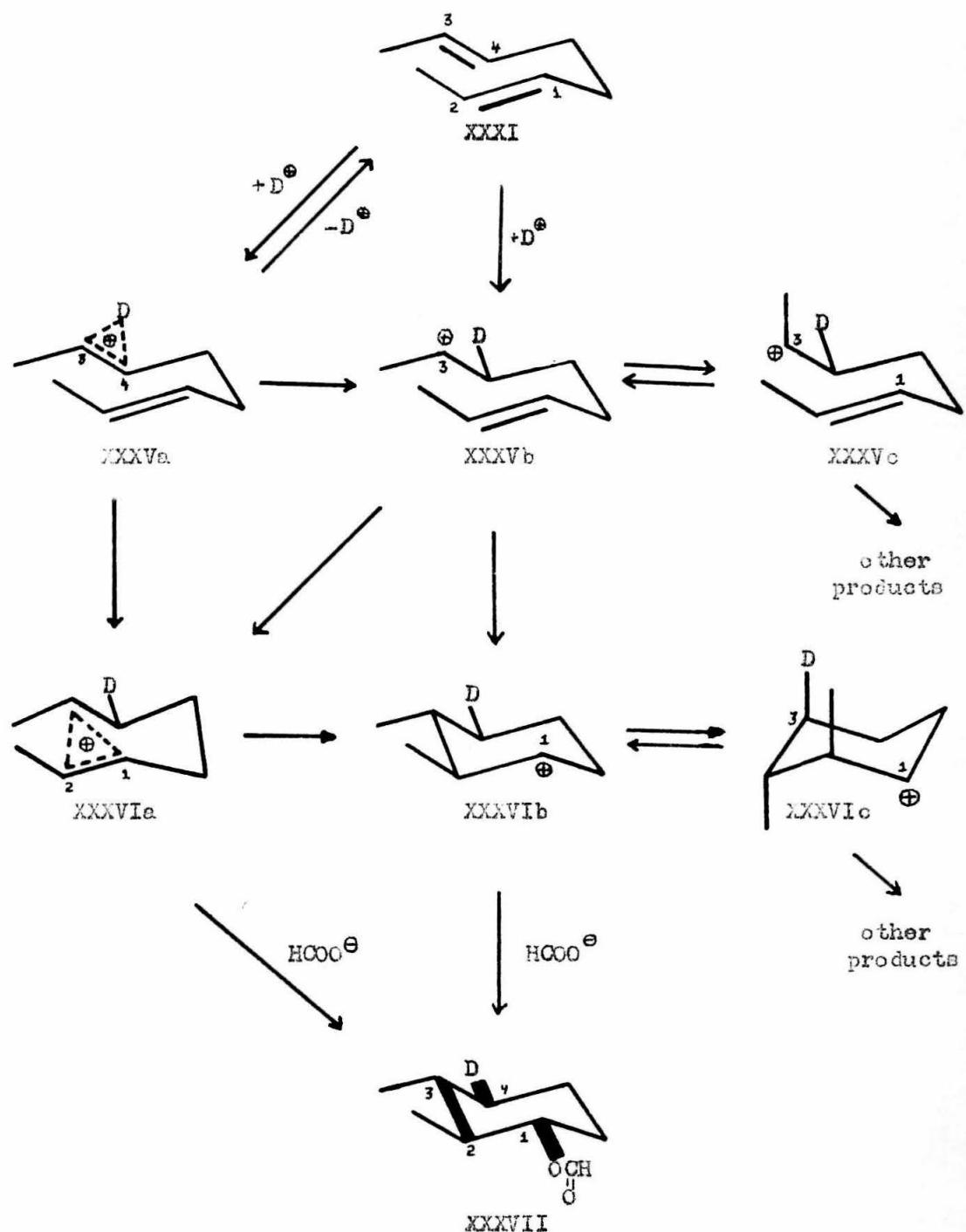
Fig. 23

The first stage of this reaction, then, may reasonably be con-
sidered as the formation of the resonance stabilized π-complex inter-
mediate XXXVa, or as progress to a transition state species for a
process in which protonation is concerted with ring closure. For the
latter, the required transition state, if we limit our attention to the
chair conformation, may be roughly indicated by XXXVIII or XXXIX,
depending on whether or not an external nucleophile is involved in the
concerted process. Either of these two modes of reaction will be con-
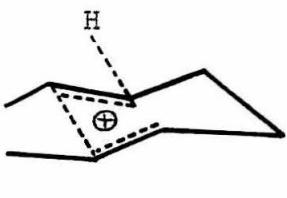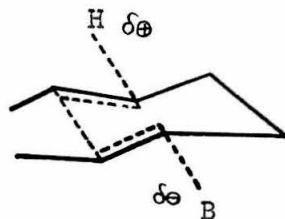
| XXXVIII | XXXIX |

sistent with the observed stereochemical outcome that the C-3 methyl
group and the C-4 deuterium are trans to one another. Both of these
reaction pathways imply strict control of the stereochemistry at C-3 and
C-4, and hence, both are compatible with the proposed model of diene
cyclization.

---

to prevent the detection of one part per thousand of the minor product
(ca. 4 kcal./mole).

A second and more reasonable assumption which was made was
that XXXVb could undergo rotamerization to XXXVc more quickly than
attack by double bond to give a cyclic species. If indeed addition to the
second double bond is the faster reaction, then XXXVb is not a classical
carbonium ion intermediate, but rather akin to the transition state for
double bond participation in a concerted process leading from either the
diene or the π-complex to a cyclic system.

The ring closure process, i.e., the transfer of electrons from the second double bond to the electron deficient center at C-3 fixes the geometry at C-3 and develops the potential stereochemistry of C-2 and possibly of C-1. For the non-concerted process, we may again entertain the likelihood of producing two types of cyclic cations: the bridged, resonance stabilized ion, XXXVIa, which is analogous to XXXVa, or another classical secondary ion, XXXVIb. Antiplanar attack by formate at C-1 of XXXVIa would give the observed product, XXXVII.* This material would also be obtained if XXXVIb suffered equatorial attack by the nucleophile. Axial attack on conformer XXXVIc, though highly disfavored for thermodynamic reasons (20), would also give XXXVII. However, to a first approximation, the diequatorial ion is expected to be favored by at least 2.5 - 3.1 kcal./mole,** which corresponds to an equilibrium concentration of 0.5 - 1.5% of conformer

---

* The heavy lines of XXXVII (Fig. 23) and of XLII (Fig. 24) are to emphasize the fact that all of the newly formed bonds are coaxial and approximately coplanar. This is a necessary consequence of a sequential antiplanar addition process.

** This value is based on the assumption that conformers XXXVIb and XXXVIc, which possess a trigonal carbon, can be likened to the two conformations of trans-2,3-dimethylcyclohexanone, whose equilibrium constant can be predicted (see footnote, p. 218). This assumption, however, is undoubtedly a rather poor one, since it neglects the very important effects of solvation. For example, it is conceivable that for conformer XXXVIb a more tightly solvated, hence more stable, species obtains than in the case of XXXVIc, whose axial methyl groups may interact sterically with solvent molecules. Preferred solvation of this type might reduce the equilibrium concentration of XXXVIc to an imperceptible value. At the same time, it may be argued that the relative rates at which XXXVIb and XXXVIc capture a solvent molecule to form a neutral product should parallel the relative solvation efficiencies.

XXXVIc. Assuming to the same degree of approximation that both con-
formeric ions react equally well with an external nucleophile, the minor
constituent, the C-1 epimer of XXXVII, should be detectable by the method
of analysis employed. On the other hand, if XXXVIb is more highly
favored in the equilibrium and/or the reaction of this intermediate with
nucleophile is more rapid than is that of XXXVIc, the epimeric product
might escape detection. In this latter case the observed stereoselectivity
would be a trivial consequence of these simple conformational factors.

Although the results of the cyclization of trans, trans-2,6-octa-
diene alone do not allow us to distinguish unambiguously between a
sterically controlled process involving configurationally constrained
species such as XXXVa and XXXVIa and a pathway embracing classical
intermediates such as XXXVb and XXXVIb, knowing the geometry of
each asymmetric center does permit us to specify the conformation of
the diene during ring formation. The product expected from the cycliza-
tion of the boat conformer of XXXI via a pair of antiplanar additions
would have the trans-syn-trans configuration (p. 51). Cyclization of
this same conformer to produce the observed trans-anti-trans config-
uration of XXXVII would have to proceed via a mechanism which
accomplishes the specific, sequential reversal of the configuration of
both centers of one double bond. Such a process is topologically tanta-
mount to cyclizing the chair conformer and appears to be without
chemical precedence. Even though small amounts of the C-4 epimer

of XXXVII might have gone undetected, it is clear, then, that the primary

mode of cyclization of trans, trans-2, 6-octadiene involves ring closure

in the quasi-chair conformation. This conclusion is in keeping with the

expectation that the energy of the transition state leading to a boat con-

former of cyclohexane will be greater than that leading to the more stable

chair conformation.

Mechanism of the Cyclization of cis, cis-2, 6-Octadiene

While the major identified cyclic product from the acid catalyzed

reaction of cis, cis-2, 6-octadiene was the same triequatorial isomer of

2, 3-dimethylcyclohexyl formate obtained from the trans, trans-diene,

the corresponding deuterated material (XLIII) was in fact epimeric at

C-4. This result is indicative of a partially controlled cyclization.

The fact that some of the predicted isomer was also observed reveals

that a completely controlled process is also occurring. The validity of

these conclusions will be evident from the following discussion.

It is reasonable to expect the protonation of cis, cis-2, 6-octadiene

(XXXIV) to produce an intermediate species analogous to that obtaining

from the di-trans-isomer under similar conditions. Hence, we suppose

that either the π-complex, XLa, or the secondary ion, XLb, is formed.*

---

* In either case, since loosening of the double bond in XLa (or
its complete dissolution in XLb) should be accompanied by relief of at
least part of the strain associated with the cis-linkage (ca. 1 kcal./mole
(22)), the protonation of XXXIV should occur more readily than proton-
ation of XXXI. Although there seems to be little precedence for this
belief, it would accord with the observation that XXXIV reacts 3-5 times
faster than XXXI at room temperature. Other factors, such as the possible
greater solubility of XXXIV in formic acid due to its higher dipole moment,
might also account for the difference in reaction rates in this hetero-
geneous system.

As before, however, neither of the epimers expected from the cyclization of XLc was observed. Since XLc is expected to cyclize more readily than its rotamer XLb,* it is surprising that only products relatable to XLa or XLb are detected. This being the case, we have a substantially stronger argument that the reaction proceeds along some pathway which <u>requires</u> the preservation of the stereochemistry of the initially protonated double bond. Hence, the mechanism does not involve an intermediate like XLb which displays classical behavior. Again, whether this means the intercession of a species such as XLa or participation by the second double bond to give a cyclic system directly is not certain.

In the event that XLa is an intermediate, the process of <u>trans</u>-addition to the first double bond is completed by the nucleophilic attack by the second double bond to give XLIa or possibly XLIb. If formed, XLIb should rapidly invert to the far more stable conformation, XLIc, which now possesses an axial deuterium. Neutralization of the latter equatorially by solvent would give the observed major isomer XLIII, the C-4 epimer of XXXVII. Decomposition of XLIa by anti-planar attack by formate or of XLIb by equatorial attack would give the minor product in its least stable conformation (XLIIa).**

---

*The argument here parallels that given for the cyclizations of XXXVb and XXXVc. Namely, the transition state leading from XLc to cyclic product possesses a single axial methyl group, while the development of two axial groups in the cyclization of XLb should lead to a transition state of higher energy.

**This scheme predicts, then, that the minor product should possess a predominantly axial deuterium (XLIIb). Unfortunately, because the overall yield of this material was so small (ca. 0.4%), it was not possible to determine the orientation of the deuterium.
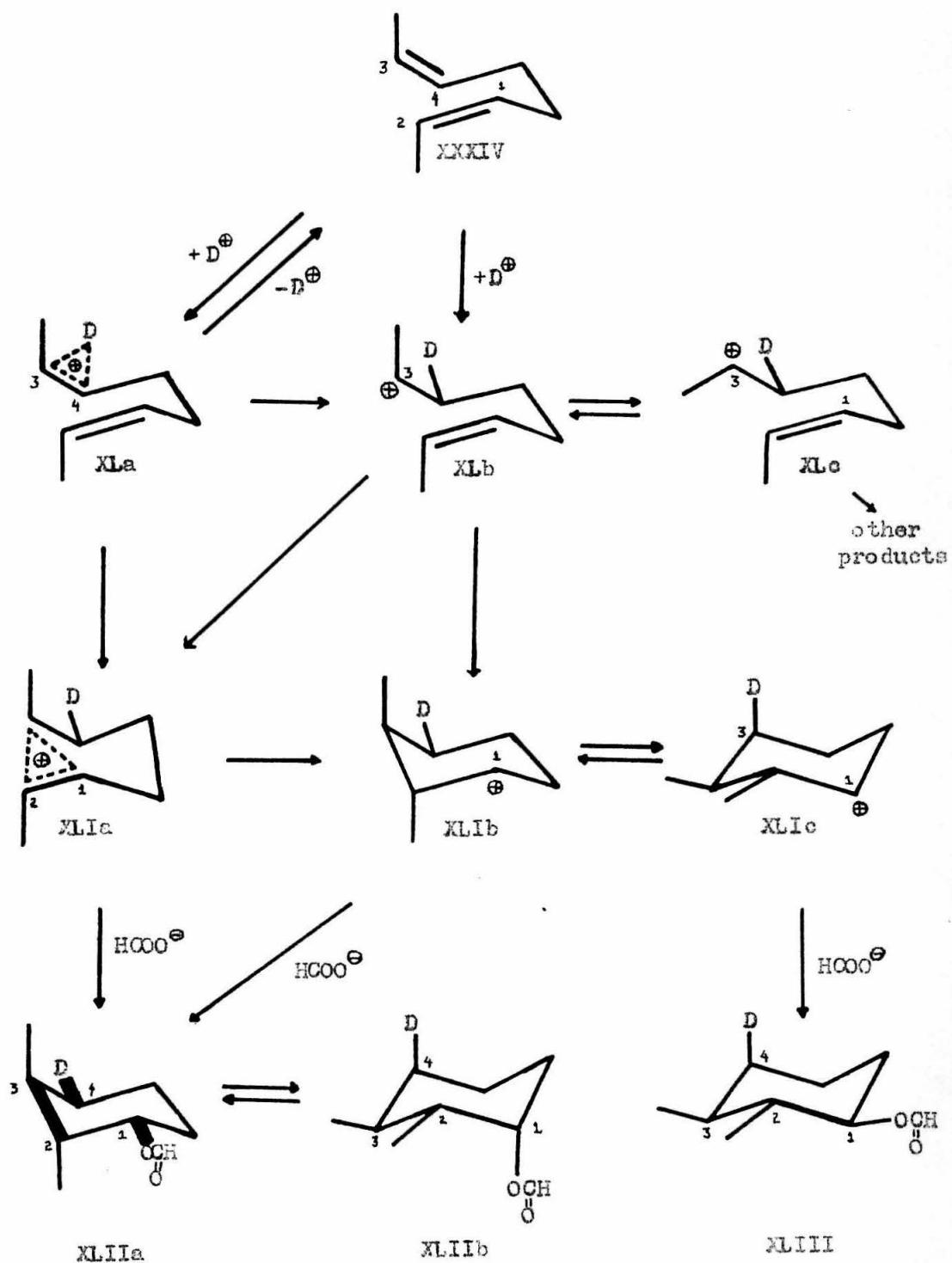
Fig. 24

That XLIb should live long enough to be neutralized by solvent is tantamount to a concerted process. If XLIIa originates from XLIa, then this too is a process which shows steric control. The only other source of this material is via axial neutralization of XLIc. This process is unlikely, however, inasmuch as no axial attack products were observed from the equivalent equilibrium conformer XXXVIb.

The fact that the major product may be traced to the classical ion XLIc would appear to demand the preevolution of XLIb. It is not very convincing, however, that the equilibrium, XLIb ⇌ XLIc, should result in 6 percent of XLIIa, while presumably in the same equilibrium, XXXVIb ⇌ XXXVIc (deuterium position disregarded), there is no product stemming from XXXVIc. For this reason, XLIb must contribute only insignificantly to the product XLIIa, which, therefore, must descend either directly from diene via double bond participation or from the bridged ion XLIa.

Taken together, the above evidence overwhelmingly supports the intermediacy of a sterically defined species such as XXXVIa and XLIa in the cyclization of the two symmetrical isomers of 2,6-octadiene. In the case of the cis,cis-diene, the data suggest that XLIa is a common intermediate for both of the observed isomeric products, and that the major yield of XLIII is the result of the decay of XLIa to the classical invertible ion XLIb.

Formation of Octadiyl Diformate

If it is the case that only one conformation of the highly flexible diene chain results in participation of the second double bond to yield cyclic products, it is perhaps not surprising that the major reaction product from both octadienes is material derived from the independent reactions of the isolated double bonds. Consideration of the origin of the octadiyl diformates may shed light on the requirements of the cyclization process itself. One likely source of diformate would be the addition of formate to a diprotonated diene. It was to discourage just such a reaction that the proton activities were kept minimal. The genesis of diformate would also result from the unsuccessful competition of the double bond with solvent for the positive charge of a monoprotonated diene. The conformation of such a species in this case is expected to play a major role in dictating the success or failure of the competition (cf. p. 22). Presumably, the need for solvation of the resonance stabilized π-complex (XXXVa or XLa) might be less than that of the classical carbonium ion (XXXVb or XLb) with its higher charge density. This might give rise to a more loosely constructed solvent shell which would enhance the opportunity for penetration by the double bond. In addition, the longer lifetime of the more stable intermediate should promote cyclization, since an acyclic ion might then have the time necessary to assume the required chair conformation. Finally, in order to account for the formation of the 3,6-octadiyl diformate, it is

possible that protonation may produce the alternative secondary ion, XLIV.
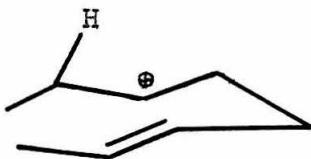

XLIV

Formation of Other Cyclic Products

The comparable yields of octadiyl diformate from both cis, cis- and trans, trans-2, 6-o tadiene indicate that the unidentified cyclic products from the former isomer were formed largely at the expense of the 2, 3-dimethylcyclohexyl formate. This would seem to imply that the reaction goes astray after the initiation of ring closure. In view of the steric strain in XLIa stemming from the four 1, 3-axial methyl-hydrogen interactions, its exigent conversion to XLIb and thence to XLIc is not an unabridged surprise.* Still another means of relieving the strain inherent in XLIa would be via the maturation of a bond between C-1 and C-3. This would give XLV, which upon neutralization would give the isomeric cyclopentane system. In fact, since the formation of

---

* If we can neglect the effects of solvation, the free energy difference between the conformers VIIa and VIIb (p. 15), which are possible intermediates in the cyclizations of apogeranic and aponeroic acid, is only of the order of 1.5 kcal./mole (23). The corresponding bridged ion derived from the aponeroic acid (the cis-isomer), therefore, does not experience as great an impress to undergo conformational inversion, and consequently, only the product resulting from its direct neutralization by solvent is observed.

XLV is, for the same reason, possible favored relative to that of XLIb, products from the former would be expected to predominate. More importantly, the same product would be obtained if XLIa suffered solvent attack at C-2. Since electronic asymmetries in XLIa are possibly small,

XLV   XLVI
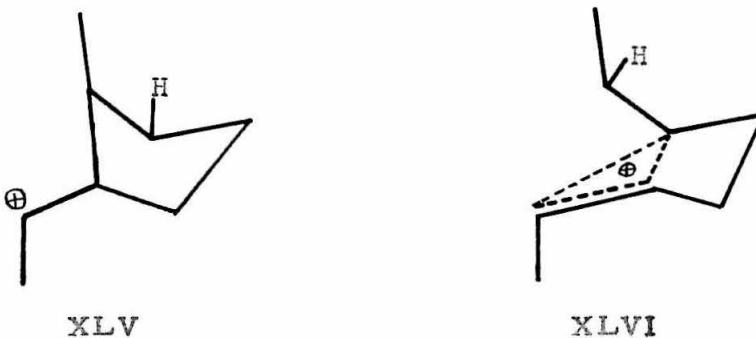
attack at C-1 or C-2 would probably be governed by the difference in strain energies of the two transition states. The process just described is also sterically controlled, and differs from the one already established merely in the final orientation of the external nucleophile.

Appreciable strain associated with XLIa could mean that its formation was disfavored relative to some other cyclic intermediate, for example, XLVI. Destruction of XLVI or of a derived classical ion by solvent would lead to other isomeric material. Finally, relief of strain in XLIa through the rearrangement of the carbon skeleton might also account for some of the observed isomeric material.

Accordingly, when the conformational characteristics of the cyclization of cis, cis- and trans, trans-2, 6-octadiene are compared, there is sound reason to expect the reduced yield of 2, 3-dimethylcyclo-hexyl formate in the case of the latter diolefin.

Conclusions

Although the appearance of a single isomer of 2,3-dimethylcyclo-hexyl formate from the cyclization of <u>trans, trans</u>-2,6-octadiene might result from either a sterically controlled (possibly concerted) reaction pathway or one involving discrete classical ions, the observed isomers from the cyclization of the <u>cis, cis</u>-diene are only explained by a process that exhibits definite steric control over the products. That steric control is observed in the latter case, when conformational factors are so un-favorable, renders it highly implausible that the cyclization of the <u>trans, trans</u>-isomer proceeds by other than a sterically regulated mechanism. In each case this control appears to derive from the characteristic geometry of bridged intermediates which occur at two stages in a step-wise reaction. It is far less likely that control stems from a concerted process in which all three new bonds are formed synchronously, although it is not possible to rule out a concerted ring closure via participation of the second double bond.

Lastly, the results of the cyclization of both diene isomers are reconciled most efficiently by assuming that the diolefin exists in the quasi-chair conformation at the time of actual ring formation.

EXPERIMENTAL

$2^C, 3^C$-Dimethylcyclohexanol^C (Alcohol D)

To a mixture of 25.0 g. (0.204 mole) of 2,3-xylenol (m.p. 72.5-74.5° C.; Aldrich Chemical Co.) in 150 ml. of glacial acetic acid was added 0.500 g. of 85% platinum dioxide. This mixture was hydrogenated at 30-35 lbs. pressure in a modified Paar apparatus until the gas uptake ceased (ca. 4-5 hrs.). The suspension was then filtered through a fine grade scintered glass funnel, and the filtrate was diluted with 200 ml. of water. This was chilled to 0° C. in an ice bath and neutralized with a cold solution of 110 g. of sodium hydroxide in 350 ml. of water. The two layers were separated, and the aqueous phase was extracted completely with six 100 ml. portions of ether. The organic layers were combined and dried over anhydrous potassium carbonate. Removal of the solvent left 30.5 g. of crude alcohol. V.P.C. analysis of this material indicated that the alcohol was a mixture of the four isomers of 2,3-dimethylcyclohexanol whose relative percentages in order of their respective retention times are as follows: A, 9%; B, 6%; C, 3%; D, 82%.

The above procedure was repeated and the products were combined and fractionally distilled through a 56 cm. stainless steel spinning band column at 30 mm. using a reflux ratio of 70:1. The early fraction had b.p. 96-103° C. and amounted to 24.7 g. (48%). The final fraction,

18.7 g. (36%), had b.p. 103° C. and according to V.P.C. analysis
was 97% D-isomer and 3% C-isomer. This fraction had the following
constants: n_D^{25} 1.4675, n_D^{50} 1.4565, d_4^{25} 0.9280.

Mol. Ref. Calculated for $C_8H_{16}O$: 38.303; Found: 38.361.

Analysis (Sp). Calculated for $C_8H_{16}O$: C, 74.94%; H, 12.58%.
Found: C, 74.84%; H, 12.51%.

The following derivatives were prepared: The p-nitrobenzoate,
colorless crystals from absolute methanol, m.p. 62.5-63.0° C.; the
acid phthalate ester, fluffy beige material from absolute methanol and
possibly contaminated with phthalic anhydride, m.p. 165-167° C.; the
m-nitrobenzoate ester was recrystallized several times from a 50:50
mixture of chloroform and hexane, and appeared to undergo rapid
decomposition, m.p. 142.5-143.0° C.; the 1-napthylurethane was
recrystallized from absolute methanol, colorless product, m.p.
116.5° C. (very sharp); the phenylurethane crystallized from the same
solvent, colorless material, m.p. 113.0-113.5° C.

$2^t, 3^c$-Dimethylcyclohexanol^t (Alcohol A)

A total of 8.0 g. (0.21 mole) of sodium borohydride was added
to a solution of 25.2 g. (0.20 mole) of trans-2,3-dimethylcyclohexanone
in 100 ml. of absolute methanol in 1 g. portions at ten minute intervals.
The mixture was cooled in an ice bath to control the vigorous reaction.
After all of the sodium borohydride had been added, the reaction mixture

was allowed to stand at room temperature for four hours. The bulk of the methanol was evaporated slowly on a steam bath, during which time the excess hydride was largely decomposed. The alcohol was regenerated by adding 700 ml. of 1 M. ammonium sulfate and extracted with two 100 ml. portions of ether. The extracts were combined, washed with 50 ml. of water, and dried over anhydrous potassium carbonate.

Removal of the solvent left 23.8 g. (93%) of crude alcohol containing 46% of isomer A and 54% of isomer B. Fractional distillation through a 56 cm., stainless-steel spinning-band column yielded 7.1 g. (28%) of material with b.p. 92.5-93.0° C./38 mm., n_D^{25} 1.4578, n_D^{50} 1.4471, d_4^{25} 0.9102. Gas analysis indicated the presence of 82.85% isomer A and 17.15% isomer B.

Mol. Ref. Calculated for $C_8H_{16}O$: 38.303; Found: 38.383.

Analysis (Sp). Calculated for $C_8H_{16}O$: C, 74.94%; H, 12.58%. Found: C, 74.87%; H, 12.57%.

Redistillation gave material which was 94.23% isomer A and 5.77% isomer B, b.p. 92.5-93.0° C., n_D^{25} 1.4581. This amounted to 4.3 g. or 17%.

The following solid derivatives of alcohol A were prepared: the α-naphthylurethane, short colorless needles from absolute methanol, m.p. 152.0-153.0° C. (A 50:50 mixture of this material with the corresponding derivative of isomer B had m.p. 133-145° C.); the phenylurethane, colorless prisms from petroleum ether (30-60° C.), m.p. 95.0-96.0° C.; the 3,5-dinitrobenzoate, colorless crystals from

absolute methanol, m.p. 118.5-119.5° C. (A 50:50 mixture with the corresponding derivative of alcohol B had m.p. 96-111° C.); the p-nitrobenzoate, colorless prisms from absolute methanol, m.p. 83.0-83.5° C.

$2^t, 3^c$-Dimethylcyclohexanol^c (Alcohol B)

A three-necked, round-bottom flask (500 ml.) was equipped with a reflux condensor carrying a calcium chloride drying tube, a 125 ml. dropping funnel, a heating mantle, and a magnetic stirrer. The flask was charged with 300 ml. of absolute ether and 4 g. (0.1 mole) of lithium aluminum hydride. A solution of 12.6 g. (0.10 mole) of trans-2,3-dimethylcyclohexanone in 50 ml. of absolute ether was added dropwise over one hour; the reaction mixture was then refluxed for forty-eight hours.

At the end of this time, the excess hydride was destroyed by adding water to the cooled (0° C.) ethereal suspension. This material was then acidified (pH $\approx$ 4) with cold 6 N. sulfuric acid. The resulting layers were separated, and the aqueous residue was extracted with two 50 ml. portions of ether. The ether solutions were combined and washed with 100 ml. of 2 N. sodium carbonate solution. After drying over anhydrous potassium carbonate and removal of the solvent, 11.2 g. (89%) of crude alcohol was obtained, which was found to have the following isomeric composition: A, 19%; B, 67%; C, 0-1%; and D, 14%. Fractional

distillation through a 56 cm. stainless-steel, spinning-band column afforded a principal cut of 9.1 g. (72%), which was ca. 79% isomer B, b.p. 95-96° C., n_D^{25} 1.4600, n_D^{50} 1.4490, d_4^{25} 0.9110.

Mol. Ref. Calculated for $C_8H_{16}O$: 38.303; Found: 38.538.

Analysis (Sp). Calculated for $C_8H_{16}O$: C, 74.94%; H, 12.58%. Found: C, 74.81%; H, 12.42%.

Redistillation gave material which was 84.72% isomer B and 15.28% isomer A, b.p. 95-96.5° C., n_D^{25} 1.4588.

The following solid derivatives of isomer B were prepared: the p-nitrobenzoate, nearly colorless prisms from absolute methanol with m.p. 61.0-61.5° C.

cis-2,3-Dimethylcyclohexanone (Ketone F)

The following method was used to oxidize 2^C, 3^C-dimethylcyclohexanol^C without isomerization (2a). A saturated solution of 3.75 g. (0.0375 mole) of chromium trioxide in 7 ml. of water was added dropwise over one-half hour to 6.5 g. (0.051 mole) of the D-isomer alcohol in 15 ml. of glacial acetic acid. The temperature was not allowed to rise above 35° C. The mixture was allowed to stand for two and one-half hours at room temperature, and then at 50° C. for an additional one-half hour.

The reaction mixture was poured into 100 ml. of water and extracted with five 10 ml. portions of ether. The extracts were combined and washed with 25 ml. of 6 N. sodium carbonate solution, and

finally with 25 ml. of water. After drying over anhydrous sodium carbonate, the solvent was removed, leaving 5.8 g. (89%) of crude ketone.

The above procedure was done in triplicate, and the combined product was distilled in a 56 cm. stainless-steel, spinning-band column. The pure cis-ketone was obtained boiling at 99° C./57 mm., and amounted to 16.9 g. or 87%. Its other constants were n_D^{25} 1.4523, n_D^{50} 1.4420, d_4^{25} 0.9208.

Mol. Ref. Calculated for $C_8H_{14}O$: 36.786; Found: 36.982.

Analysis (Sp). Calculated for $C_8H_{14}O$: C, 76.14%; H, 11.18%. Found: C, 75.86%; H, 11.28%.

The following solid derivatives were prepared: Semicarbazone recrystallized from 50:50 aqueous methanol gave tiny colorless crystals, m.p. 174.5-175.5° C.; the thiosemicarbazone, tiny colorless needle clusters from aqueous methanol, m.p. 142.5-143.0° C.; the 2,4-dinitrophenylhydrazone was prepared from Johnson's reagent and recrystallized from 95% ethanol, glistening orange flakes with m.p. 109.5-111.0° C. (decomp.); the p-nitrophenylhydrazone crystallized from 80% methanol in tiny clusters of deep yellow needles with two polymorphic forms, m.p. 149.0-150.2° C. and 154.0-154.5° C.; the m-nitrophenylhydrazone gave small orange clusters from 80% methanol with m.p. 126.5-127.5° C. The oxime and phenylhydrazone could not be obtained as solids.

trans-2,3-Dimethylcyclohexanone (Ketone E)

A mixture of 10 g. (0.08 mole) of the cis-ketone was added to 50 ml. of a 0.025 M. sodium methoxide solution and allowed to stand for periods of eight hours to three days at room temperature. The mixture was diluted with 300 ml. of water and extracted with three 50 ml. portions of ether. The combined extracts were washed with 100 ml. of water and dried over anhydrous sodium sulfate. The colorless oil that remained after removal of the ether was distilled to give a principal fraction boiling at 95.5° C./57 mm., which had n_D^{25} 1.4481. The yield was 8.8 g. or 88%. V.P.C. analysis (Carbowax-1500) indicated that the material was 88% trans-ketone with 12% of the cis-isomer.

Fractional distillation through a spinning-band column gave a small amount of material which was 98% trans-isomer. This material had n_D^{25} 1.4474, n_D^{50} 1.4467, d_4^{25} 0.9076.

Mol. Ref. Calculated for $C_8H_{14}C$: 36.786; Found: 37.164.

Analysis (Sp). Calculated for $C_8H_{14}O$: C, 76.14%; H, 11.18%. Found: C, 75.89%; H, 11.18%.

The following solid derivatives were prepared: The oxime was recrystallized from 50:50 aqueous methanol, colorless needles, m.p. 113.5-114.5° C.; the semicarbazone from 50:50 aqueous methanol, colorless, m.p. 205.5-206.0° C.; the thiosemicarbazone from 50:50 aqueous methanol, long flat, colorless prisms, m.p. 170.5-171.0° C.; the p-nitrophenylhydrazone from absolute methanol, bright yellow prisms,

m.p. 157.5-158.0° C.; the m-nitrophenylhydrazone from methanol, orange needles, m.p. 127.0-128.5° C., which on admixture with the cis-isomer derivative melted at 121-124° C.; the 2,4-dinitrophenyl-hydrazone was prepared from Johnson's reagent and obtained crystalline from 95% ethanol, bright yellow needles, m.p. 153.5-154.5° C. The phenylhydrazone was not obtained in solid form.

trans,trans-2,6-Octadiene

The following procedure is based on the method reported by Webb and Borcherdt (15a):

A one liter, three-necked, round-bottom flask was equipped with a magnetic stirrer, a 250 ml. side-arm dropping funnel, and a large dry-ice condensor packed with rock salt and ice. The condensor take-off was connected to two ice-traps in series; the first was cooled with rock salt and ice, while the second was immersed in a dry-ice and acetone mixture.

The flask was filled with 140 ml. of absolute methanol and 125 g. (1.4 moles) of crotyl chloride (K. & K. Labs.). The system was flushed with a mild stream of carbon monoxide introduced via the outlet valve of the terminal dry-ice trap (the gas was allowed to escape through the opening of the dropping funnel), and 100 ml. (132 g., 0.76 mole) of nickel tetracarbonyl was introduced directly into the dropping funnel from the one pound lecture bottle (Matheson). The stream of carbon monoxide prevented the possible spontaneous ignition of the nickel

carbonyl, which frequently occurs on contact with air. The gas flow was discontinued, and dropping funnel was tightly stoppered. The nickel carbonyl was introduced to the reaction flask dropwise with stirring at 25° C. over a period of four hours. The solution turned yellow immediately as a result of complex formation, and a moderate evolution of carbon monoxide occurred. The off-gas condensate was returned to the reaction flask, and the mixture was allowed to stand with stirring overnight.

The reaction mixture, which had largely solidified, was readily decomposed with 300 ml. of water. The green aqueous layer was removed and the hydrocarbon was washed with another 300 ml. of warm (35-40° C.) water. Traces of nickel carbonyl were removed under reduced pressure at 10° C. leaving 61 g. (79%) of hydrocarbon. Fractional distillation through a 56 cm. stainless-steel, spinning-band column afforded 11.3 g. (15%) of material which was largely 3-methyl-1,5-heptadiene, b.p. 92-121° C., and 48.1 g. (62%) of pure trans, trans-2,6-octadiene, b.p. 121-122.5° C., n_D^{25} 1.4278. Although the refractive index is lower than reported (Lit.: n_D^{23} 1.4300), gas analysis showed this material to be 99% homogeneous.

The infrared spectrum of this material (neat) possessed a strong band at 963 cm.$^{-1}$ for a trans-disubstituted olefinic linkage (16); there was no absorption at all between 1500-2000 cm.$^{-1}$

cis, cis-2, 6-Octadiene

A solution of 20 g. (0.189 mole) of 2,6-octadiyne (Farchan Chem. Co.) in 50 ml. of cyclohexane containing 0.8 g. of 90% quinoline (Eastman, Pract. Grade) was hydrogenated over 2.0 g. of Lindlar's catalyst (17a) at 5 lbs./sq. in. and room temperature in a modified Paar apparatus. Gas uptake virtually ceased after seven hours when two mole equivalents had been absorbed. The catalyst was removed by filtering through a fine grade scintered glass funnel. The solvent was removed by distillation.

The residue was fractionated through a 56 cm. stainless-steel, spinning-band column, using a reflux ratio of 100:1. The yield of di-olefin was 18.5 g. (89%); its constants were: b.p. 124.0-124.2/744 mm., n_D^{25} 1.4347, $d_4^{23.5}$ 0.7475.

Mol. Ref. Calculated for C_8H_{14}: 37.964. Found: 38.473.

Analysis (Sp). Calculated for C_8H_{14}: C, 87.20%; H, 12.80%. Found: C, 87.18%; H, 12.88%.

This material was identified as cis, cis-2, 6-octadiene on the basis of its infrared spectrum (neat) which possessed a strong band at 713 cm.$^{-1}$ and a medium one at 1658 cm.$^{-1}$

Acid Catalyzed Cyclization of trans, trans-2, 6-Octadiene

A solution of 20 ml. of 98-100% formic acid and 1.2 ml. of concentrated sulfuric acid was added to 10.0 g. (.091 mole) of trans, trans-2, 6-octadiene, and the two phase system was stirred for thirty-six

hours. At the end of this time the reaction mixture was homogeneous and deep violet in color.

The mixture was poured into 300 ml. of water containing 50 g. of sodium carbonate and 200 g. of crushed ice. The yellow basic solution was extracted with five 50 ml. portions of ether while still quite cold. The combined extracts were washed with 100 ml. of water and dried over anhydrous sodium sulfate. Removal of the solvent left 14.1 g. of dark oil, which was fractionally distilled to give 5.2 g. (37%) of $2^t, 3^c$-dimethylcyclohexyl^c formate, b.p. 90-93° C./34 mm., n_D^{25} 1.4389.

Analysis (Sp). Calculated for $C_9H_{16}O_2$: C, 69.17%; H, 10.30%. Found: C, 68.99%; H, 10.22%.

A second fraction, 7.4 g. (52%) of an isomeric mixture of octadiyl diformates was obtained with b.p. 142-146° C./30 mm., n_D^{25} 1.4300.

Analysis (Sp). Calculated for $C_{10}H_{18}O_4$: C, 59.38%; H, 8.97%. Found: C, 59.31%; H, 8.99%.

Acid Catalyzed Cyclization of cis, cis-2, 6-Octadiene

A solution of 20 ml. of 98-100% formic acid and 1.2 ml. of concentrated sulfuric acid was stirred with 10.0 g. of cis, cis-2, 6-octadiene for four days at 0° C. The reaction mixture was worked up in the same manner as for the di-trans-isomer. Distillation gave a mixture of cyclic monoformates, 4.8 g., b.p. 46-61° C./5 mm., which contained 11% of 2, 3-dimethylcyclohexyl formate according to gas analysis. Of this,

94% was $2^t, 3^c$-dimethylcyclohexyl^c formate while the remaining 6% was the C-1 epimer, $2^t, 3^c$-dimethylcyclohexyl^t formate.

Analysis (Sp). Calculated for $C_9H_{16}O_2$: C, 69.17%; H, 10.30%. Found: C, 68.88%; H, 10.19%.

A higher boiling fraction, b.p. 94-97° C./5 mm., $n_D^{21.2}$ 1.4306, afforded 7.5 g. (41%) of isomeric octadiyl diformates.

Cleavage of $2^t, 3^c$-Dimethylcyclohexyl^c Formate with Lithium Aluminum Hydride

To a mixture of 100 mg. (27 mmoles) of lithium aluminum hydride in 50 ml. of absolute ether was added dropwise 1.0 g. (6.4 mmoles) of $2^t, 3^c$-dimethylcyclohexyl^c formate. The mixture was allowed to stand for an hour, and the excess hydride was decomposed by dropwise addition of 20 ml. of a saturated ammonium sulfate solution. The ether layer was washed with 10 ml. of water and dried over anhydrous sodium sulfate. Removal of the ether left 0.71 g. (86%) of colorless oil, n_D^{25} 1.4562, which was shown by gas analysis to be entirely $2^t, 3^c$-dimethylcyclohexanol^c. Distillation gave 0.63 g. (76%) of pure alcohol B, b.p. 55° C./6 mm., n_D^{25} 1.4561.

Analysis (Sp). Calculated for $C_8H_{16}O$: C, 74.94%; H, 12.58%. Found: C, 74.69%; H, 12.61%.

The α-napthylurethane was prepared and recrystallized from absolute methanol: m.p. 156.5-157.0° C. A 50:50 mixture with authentic

material had m.p. 156.0-157.0° C.

The alcohol did not crystallize upon standing for one week at -5° C.

$2^t, 3^c$-Dimethylcyclohexyl^c Formate

A mixture of 60 ml. of pyridine, 6 g. (0.13 mole) of 98-100% formic acid, and 3 g. (0.023 mole) of $2^t, 3^c$-dimethylcyclohexanol^c was cooled to -35° C. in a dry-ice and acetone bath. Phosgene (5 g., 0.05 mole) was condensed in a small Schlenk tube immersed in the dry-ice mixture. The Schlenk tube was then inverted and the phosgene was added dropwise to the reaction mixture over a period of thirty to forty minutes. The contents were stirred vigorously by hand. After all the phosgene had reacted, the mixture was stored in a refrigerator at -10° C. for twelve hours. (Caution: if all the phosgene has not been consumed, the reaction may become violently exothermic upon removal from the dry-ice bath; this is best avoided by not overcooling the mixture during the addition of phosgene.)

The semisolid material was poured into an excess of 6 N. sulfuric acid containing crushed ice. The acid solution was extracted immediately with three 50 ml. portions of ether. The combined extracts were washed with 2 N. sodium carbonate solution, and then dried over anhydrous sodium sulfate. Removal of the solvent left a pale yellow oil, which upon distillation gave 2.56 g. (71%) of $2^t, 3^c$-dimethylcyclohexyl^c formate with b.p. 86-88° C./30 mm., and n_D^{25} 1.4381.

Analysis (Sp).   Calculated for $C_9H_{16}O_2$:   C, 69.17%; H, 10.30%.
Found: C, 68.91%; H, 10.16%.

$2^t,3^c$-Dimethyl-4^t-deuterocyclohexyl^c Formate

A solution of 2.5 g. of 100% formic acid-d (Merck) and 0.20 ml.
of concentrated deuterium sulfate was stirred with 0.75 g. (6.8 mmoles)
of trans, trans-2, 6-octadiene for two days at room temperature.   The
material was worked up as previously described.   Distillation gave 0.36
g. (34%) of $2^t,3^c$-dimethyl-4^t-deuterocyclohexyl^c formate, b.p. 46-47°C./
8 mm., n_D^{25} 1.4383, and 0.63 g. (46%) of isomeric dideuteroöctadiyl di-
formates, b.p. 65-80°/8 mm., n_D^{25} 1.4298.

The infrared spectrum (CCl_4) of the former possessed an equa-
torial C-D absorption at 2171 ± 4 cm.$^{-1}$ (16, 18).

$2^t,3^c$-Dimethyl-4^c-deuterocyclohexyl^c Formate

The cyclization of cis, cis-2, 6-octadiene in formic acid-d was
carried out as described above, except that the reaction mixture was
stirred for seven days at 0° C.   After the work-up there was obtained,
following a small forerun, 0.18 g. of isomeric formates, b.p. 48-53° C./
8 mm., n_D^{25} 1.4376.   A small amount of $2^t,3^c$-dimethyl-4^c-deutero-
cyclohexyl^c formate was recovered from this sample by use of gas
chromatography (Carbowax-1500 column, 115° C.).   The infrared
spectrum of this material showed an axial C-D absorption at 2142 ± 8
cm.$^{-1}$ (16, 18).

The dideuteroöctadiyl diformate mixture was obtained as a higher boiling fraction, b.p. 61-76° C./8 mm., n_D^{25} 1.4295, and amounted to 0.56 g. (41%).

References to Part III

1. For a discussion and leading references, see:

   a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, pp. 350 ff., 1962.

   b) E. H. Rodd, "Chemistry of Carbon Compounds," Elsevier Publishing Co., New York, Vol. II-A, pp. 124 ff., 1953.

2. a) W. Hückel and M. G. E. Ibrahim, Ber., 91, 1970 (1958).

   b) W. Hückel, et al., Ann., 624, 142-255 (1959).

   c) W. Hückel and H. Feltkamp, Ber., 92, 2851 (1959).

   d) W. Hückel, H. Feltkamp, and S. Geiger, Ann., 637, 1 (1960); et seq.

3. a) J. von Braun and E. Anton, Ber., 60, 2438 (1927).

   b) A. Skita and W. Faust, Ber., 72, 1127 (1939).

4. E. L. Eliel, "Stereochemistry of Carbon Compounds," loc. cit., pp. 239 ff.

5. a) C. W. Beckett, K. S. Pitzer, and R. Spitzer, J. Am. Chem. Soc., 69, 2488 (1947).

   b) E. L. Eliel and M. Rerick, J. Am. Chem. Soc., 82, 1367 (1960).

   c) D. S. Noyce and L. J. Dolby, J. Org. Chem., 26, 3619 (1961).

6. a) P. A. Robins and J. Walker, Chem. and Ind. (London), 772 (1955).

b) P. A. Robins and J. Walker, J. Chem. Soc., 1789 (1955).

c) W. Klyne, Experientia, 12, 119 (1956).

7. a) D. H. R. Barton, J. Chem. Soc., 1027 (1953).

b) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956.

8. E. L. Eliel, J. Chem. Educ., 37, 126 (1960).

9. a) K. von Auwers, Ann., 420, 84 (1920).

b) A. Skita, Ber., 56, 1014 (1923).

c) N. L. Allinger, J. Am. Chem. Soc., 79, 3443 (1957).

d) E. L. Eliel, "Stereochemistry of Carbon Compounds," loc. cit., p. 216.

e) E. H. Rodd., "Chemistry of Carbon Compounds," loc. cit., p. 10.

10. H. van Bekkum, et al., Rec. trav. chim., 80, 1310 (1961).

11. D. Capon, et al., Bull. soc. chim., France, 837 (1958).

12. M. M. Claudon, et al., Bull. soc. chim., France, 843 (1958).

13. a) J. Colonge, J. Dreux, and M. Thiers, Compt. rend., 243, 1425 (1956).

b) J. Colonge, J. Dreux, and M. Thiers, Bull. soc. chim., France, 450 (1959).

14. H. Farmer and D. A. Sutton, J. Chem. Soc., 10 (1946).

15. a) I. D. Webb and G. T. Borcherdt, J. Am. Chem. Soc., 73, 2654 (1951).

b) cf. I. G. Farbenindustrie, Patent (Belgium) 448,884 (1943);

Chem. Abstr., 41, 6576a (1947).

16.   E. A. Braude and E. S. Waight, Prog. in Stereochem., 1,

126 (1954).

17.   a) H. Lindlar, Helv. Chim. Acta, 35, 446 (1952).

b) R. A. Raphael, "Acetylenic Compounds in Organic Synthesis,"

Butterworths, Ltd., London, pp. 22 ff., 1955.

c) R. L. Burwell, Chem. Revs., 57, 895 (1957).

d) P. H. Emmett (ed.), "Catalysis," Reinhold Publishing Co.,

Inc., New York, Vol. III, pp. 49ff., 413 ff., 1955.

e) N. A. Dobson, et al., Tetrahedron, 16, 16 (1961).

f) M. Svoboda and J. Sicher, Chem. and Ind., 290 (1959).

g) B. Loev and C. R. Dawson, J. Org. Chem., 24, 981 (1959).

18.   M. Larnaudie, Compt. rend., 235, 154 (1952).

19.   cf. H. B. Knight, R. E. Koos, and D. Swern, J. Am. Chem. Soc.,

75, 6212 (1953).

20.   a) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, J. Am.

Chem. Soc., 76, 4420 (1954).

b) A. Streitwieser, Jr., J. Org. Chem., 22, 861 (1957).

21.   a) See A. Hill, "Mechanism of the Olefin-Alcohol Interchange,"

an Organic Chemistry Seminar delivered at the California Institute

of Technology (Pasadena) on April 1, 1960.

b) cf. P. Riesz, R. W. Taft, Jr., and R. A. Boyd, J. Am. Chem. Soc., 79, 3724 (1957).

22. a) F. D. Rossini, et al., "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds, "Carnegie Press, Pittsburgh, Pa., p. 475, 1953.

b) G. B. Kistiakowsky, et al., J. Am. Chem. Soc., 57, 876 (1935).

c) R. B. Turner, D. E. Nettleton, and M. Perelman, J. Am. Chem. Soc., 80, 1430 (1958).

23. R. D. Stolow, J. Am. Chem. Soc., 81, 5806 (1959).

PART IV

THE INFRARED SPECTRA

OF CYCLOBUTANE COMPOUNDS

INTRODUCTION

To the practicing organic chemist, one of the important problems in the area of infrared spectroscopy has been the search for characteristic frequencies of typical organic ring systems. In the case of the saturated carbocyclic molecules, moderate success has been achieved in the correlation of the spectra of cyclopropane derivatives, although the number of compounds whose spectra have been studied has been relatively small (1). Investigation of the spectra of four-, five-, and six-membered rings has at best yielded only tentative results. In view of the enhanced interest recently in the chemistry of small rings, identification of such systems by infrared means has become even more desirable. The following contains the results of our examination of the spectra of 191 cyclobutane derivatives. In addition, we would like to propose a novel application of a computer technique, which we feel will be of considerable aid in the analysis of large numbers of spectra.

Previous studies in the correlation of the spectra of cyclobutane compounds have been discussed by Bellamy (2).

METHOD

Spectra Sources. --The spectra used in this investigation were
available from the infrared files of these Laboratories.   These files
consist in part of approximately 36,000 published spectra, which
include the following compilations: Sadtler Standard Spectra, Index of
the American Petroleum Institute, Index of the National Research
Council-National Bureau of Standards, Index of the American Society
for Testing Materials, Documentation of Molecular Spectroscopy,
and the Coblentz Spectra (3).   At U. C. L. A. these spectra have been
stored on magnetic tape with the following restrictions: all absorptions
which have intensities at least 1/10th of the maximum intensity are
retained, the rest are eliminated; resolution is 0.1 micron over the
range 1.0-25.0 microns.   Particular spectra are made available by
means of a search routine programmed on an I. B. M. 1401 com-
puter.   A total of 96 non-fused cyclobutane and cyclobutene spectra
were obtained in this manner.   In addition, another 131 unpublished
spectra of cyclobutane derivatives were courteously made available
from the files of Dr. J. D. Roberts' research group at Caltech.*

---

* The preparation of many of these compounds has been
described by J. D. Roberts and C. M. Sharts (4).

Elimination of duplications and of spectra taken in the gas phase left a total of 122 spectra of cyclobutane compounds and 69 of cyclobutene compounds.

Composite Spectra. --To a first approximation, the vibrational spectrum of a molecule $R - Z_i$ may be considered as a superimposition of the individual spectra of the groups $R -$ and $Z_i -$, plus additional absorptions produced by the presence of the $R - Z_i$ bond(s). Some combinational tones may also be expected. The problem of discovering the characteristic frequencies of $R -$ can then be thought of as one of detecting the R-signal in the presence of the noise spectrum produced by the presence of $Z_i -$. If $R -$ and $Z_i -$ are both typical organic residues, the signal-to-noise ratio should be of the order of unity, and the signal is indistinguishable from the background activity. Further data are required to extract the desired information. One method of increasing the signal-to-noise ratio is to treat the noise as a random component, and simply average the spectra of several $R - Z_i$. Such a procedure can be expected to provide an efficient separation of noise and signal, only if the data can be taken as representative of a truly stochastic process.* In the case at hand, neither the choice of the groups Z_i nor the vibrations that these groups possess can be considered to be strictly random; that is, Z_i is biased to the extent that it is representative

---

* For an excellent discussion of the mathematical method and further refinements, see reference 5. For examples of other applications of this method, see reference 6.

of the particularly common organic linkages, such as C-H, C-N, C=O, etc. Nevertheless, the occurrence of combination bands, coupling effects, and frequency shifts due to differences in bond strengths will tend to augment the random behavior of this component.

Our experience indicates that about 2^4 to 2^5 spectra are needed to produce a composite (average) spectrum with sufficient reduction of the noise level to be of interpretive value. Certain prominent features of the composite spectrum may be detectable with fewer spectra, however.

In order to illustrate this technique, the Sadtler files were searched to obtain the spectra of all monosubstituted benzene compounds, except those containing a substituted or fused-ring aromatic group. A total of 1074 (ca. 2^{10}) different spectra were obtained. These were averaged by an I. B. M. 1401 computer, using the intensity maxima in 0.1 micron "windows" across the spectrum from 1.0-15.0 microns. The resulting composite spectrum is shown in Figure 1.* Since the ordinate axis is best interpreted as a measure of the relative probability of finding a band at a given frequency, the trace has been inverted as is customary in the presentation of power spectra. Of the 14 principal peaks, nine of these have been considered typically present in monosubstituted benzene systems (2). The remaining

---

* The error in the position of the maxima in Figures 1-5 is $\pm$ 0.05 μ.

Fig. 1

Monosubstituted Benzenes
(1074 compounds)

Wavelength (In Microns)

Fig. 2
Alkanes
(44 compounds)

272

Fig. 3

Cyclopentanes
(41 compounds)

Wavelength (In Microns)

Fig. 4

Cyclobutanes
(81 compounds)

Fig. 5

Cyclopropanes
(105 compounds)
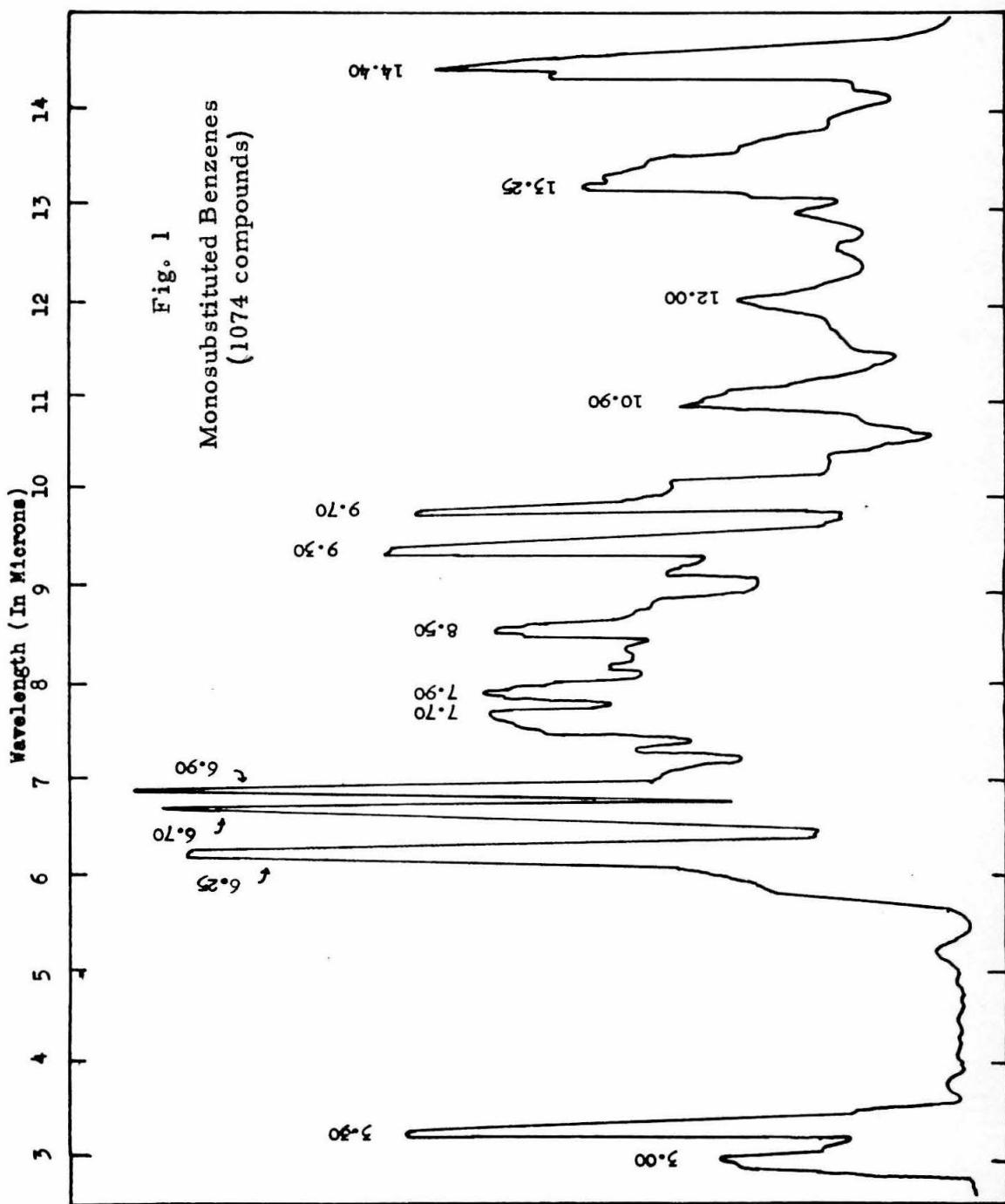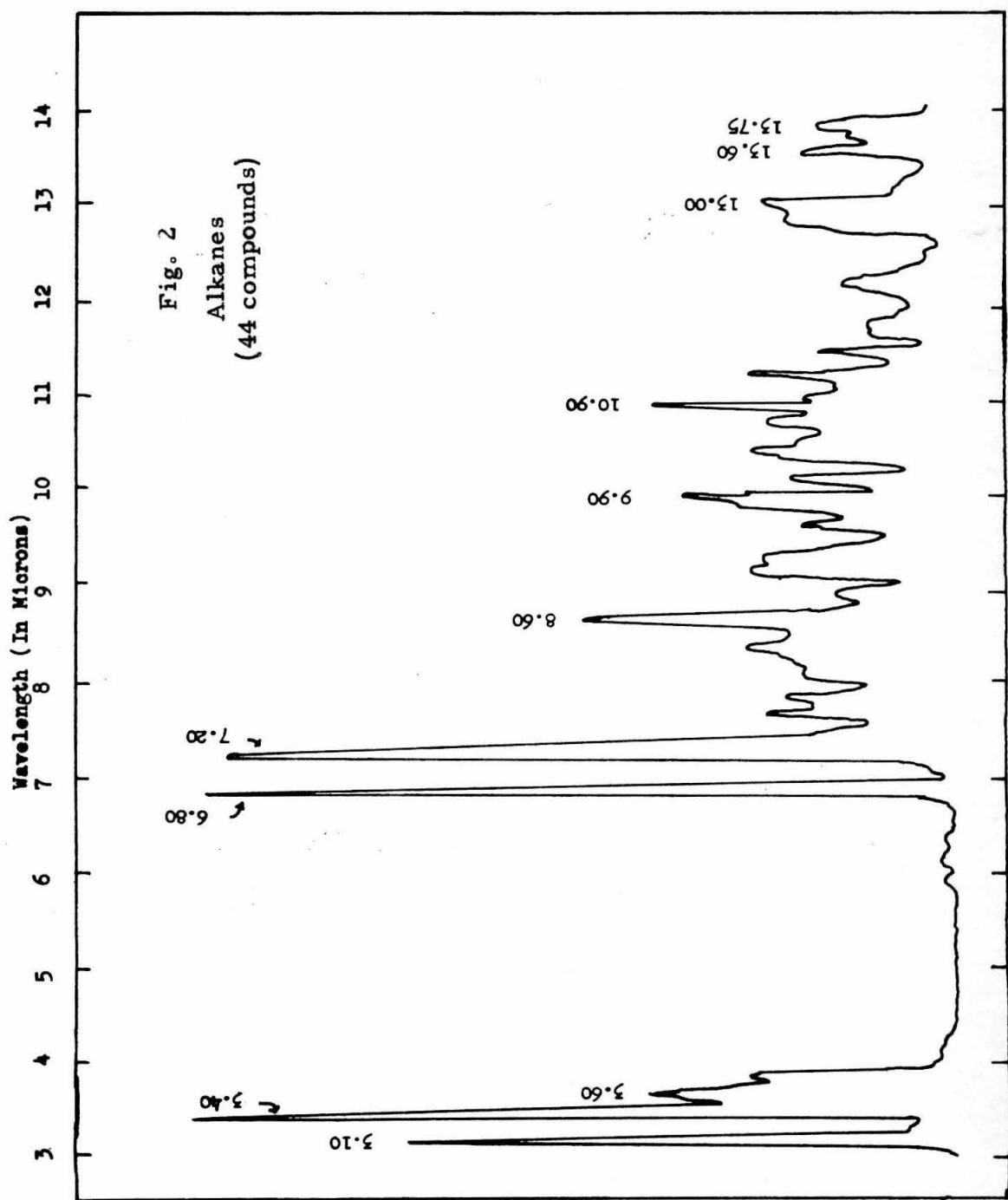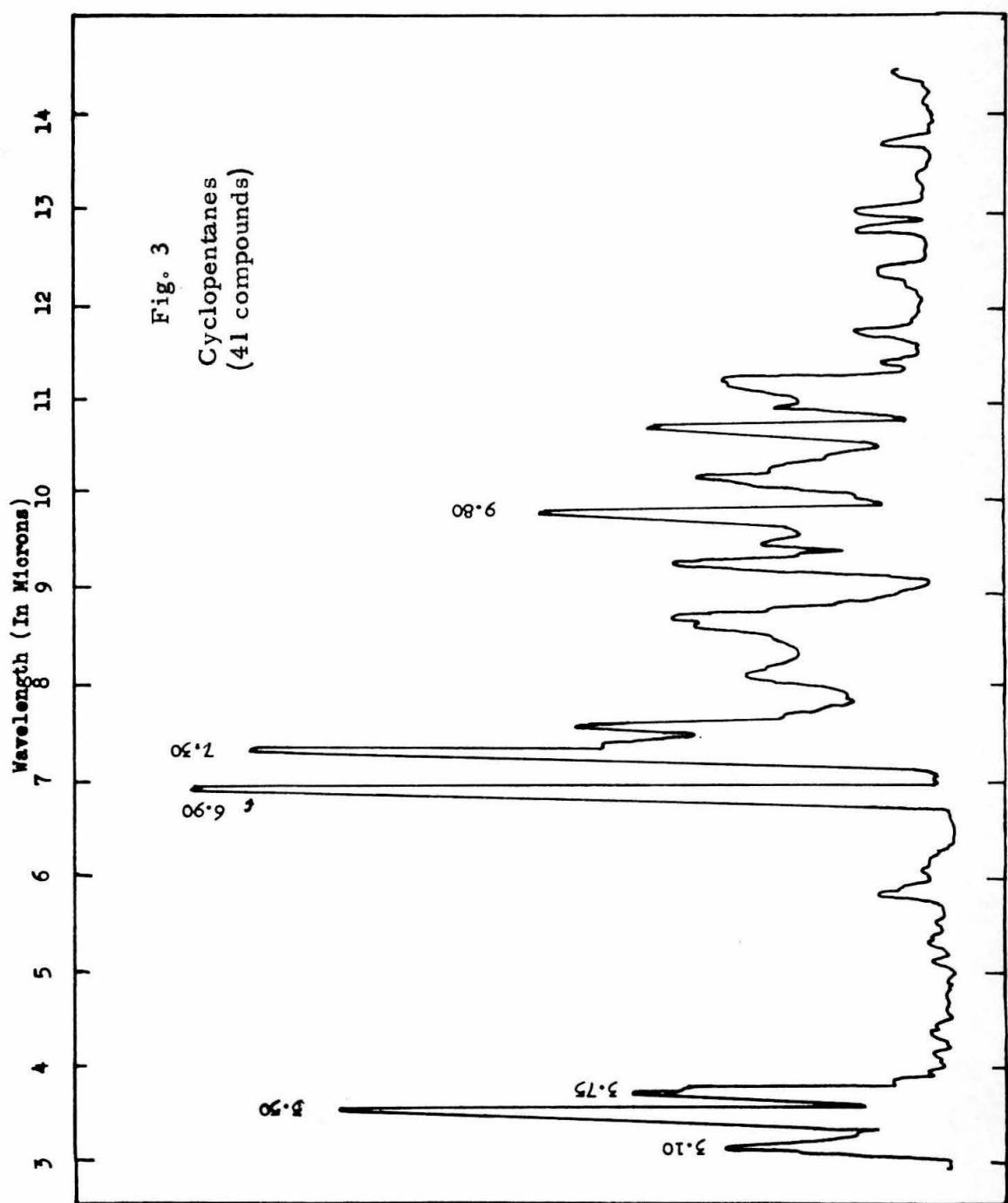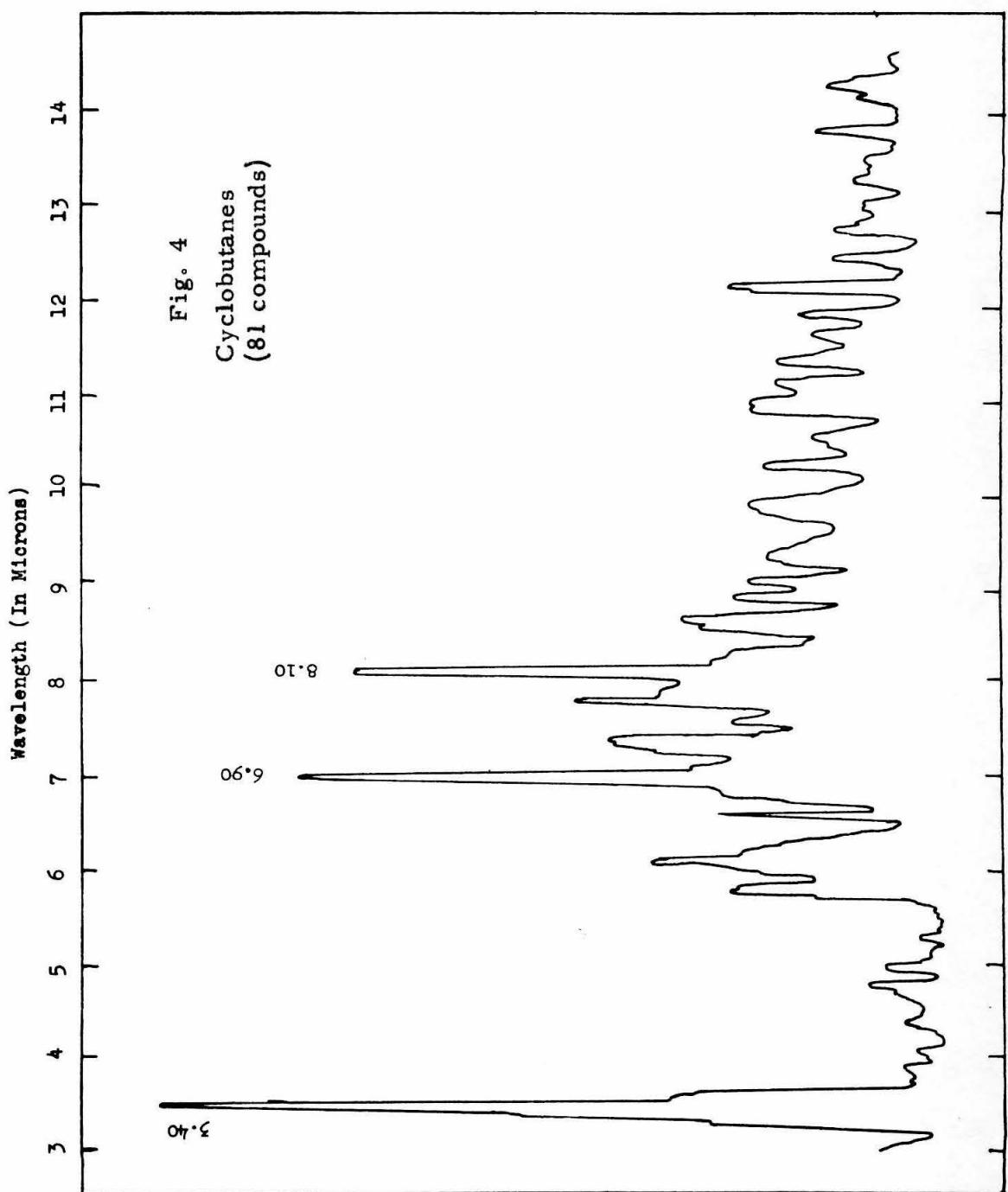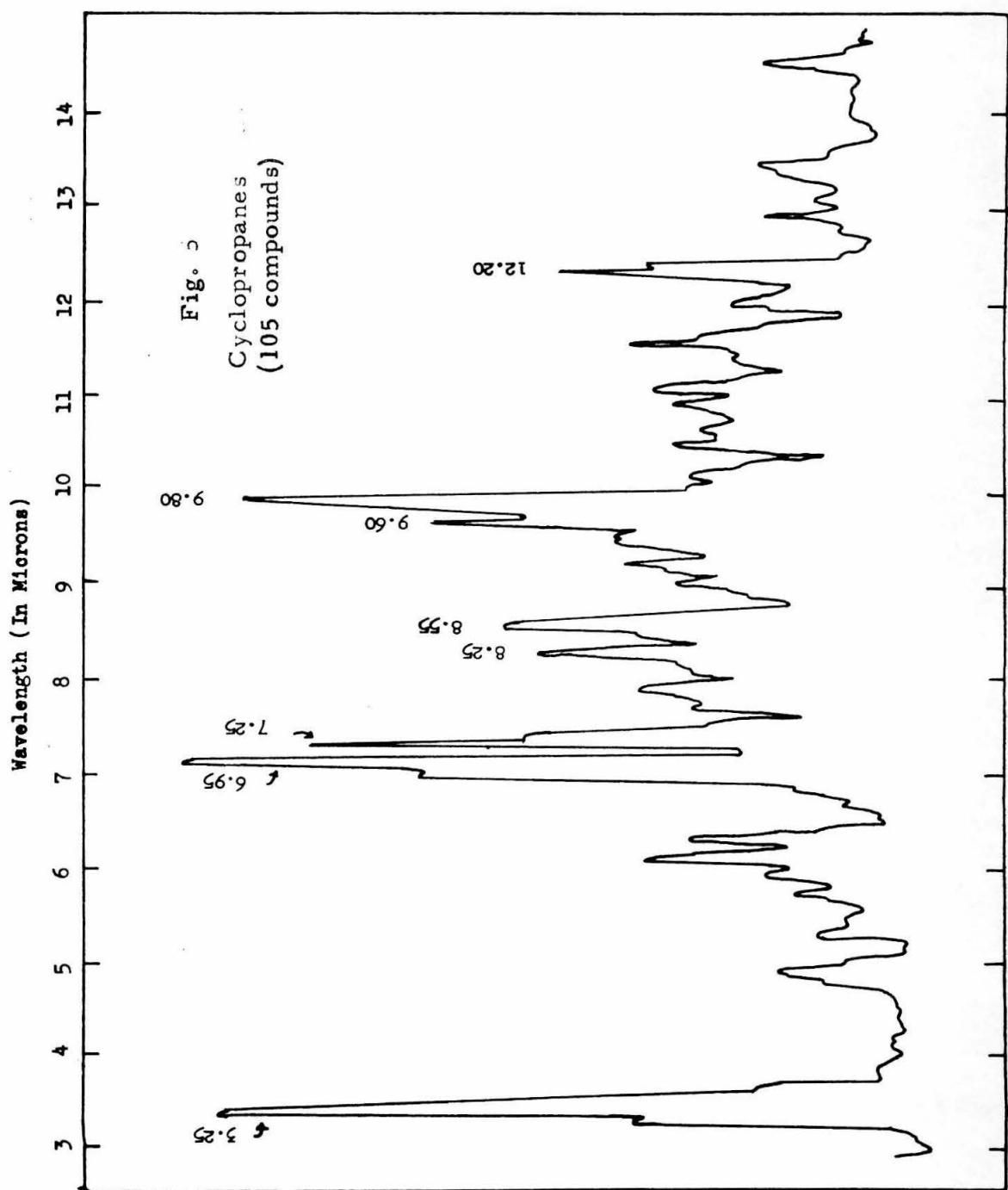
bands (3.00, 7.70, 7.90, 10.90, and 12.00 μ) are less prominent and may not rise sufficiently above the general noise level to be of much interpretive value (see Appendix).

The spectrum of cyclobutane (7) itself indicates that, in addition to specific ring motions, the motions of the ring methylene groups should be important in characterizing the spectra of cyclobutane derivatives (vide infra). In view of this, the composite spectrum of the cyclobutane system was prepared from 81 spectra of cyclobutane derivatives, which met the following restrictions: all contained at least one ring methylene group, and none possessed a fused-ring or spirane structure; no cyclopropyl nor cyclopentyl group could be present in the molecule; no cyclobutene compounds were included. The resultant spectrum is shown in Figure 4. For comparison purposes the corresponding spectra of 105 cyclopropane derivatives (Fig. 5), 41 cyclopentane compounds (Fig. 3), and 44 open chain alkanes (Fig. 2) were prepared.

It cannot be overemphasized that one should not try to extract more information from Figures 1-5 than the data from which they were constructed permit. The published spectra used in this study were prepared on numerous instruments, under various conditions, using samples (both neat and in solution) of undetermined purity. Consequently, the primary purpose served by the composite spectrum was to indicate where, if anywhere, in the spectra of cyclobutane compounds a characteristic

absorption might be found. The discussion below was based then on the examination of the individual spectra, many of which were not used to construct Figure 4.

General Distribution of Absorption Maxima. --It was suggested to us by Dr. R. M. Badger that in order to evaluate the significance of the findings discussed below, it would be useful to know the probability of finding an absorption at a particular wavelength in the spectrum of a randomly chosen compound, which does not contain the group in question, i.e., the cyclobutane ring. To obtain a measure of these probability values, the positions of all the maxima (each at least 1/10th as strong as the most intense absorption) of the spectra in the Sadtler organic index were tallied, and the relative occurrence frequencies were computed for each 0.1 μ (Table I). Since the compounds in the Sadtler index may be considered to be approximately representative of organic compounds in general, the relative frequencies will be approximately equal to the "actual" probability values. The accuracy of the approximation will depend on the extent to which the Sadtler index may be biased in its sampling. Although the spectra of cyclobutane compounds were included in this tally, their deletion could not change any probability value by more than about 0.6 percent.

Table I. Relative Occurrence Frequencies for Infrared Absorption Bands Over the Region 2.0-14.9 μ Based on 17,345 Spectra in the Sadtler (Organic) Index.

0. Y $\pm$ 0.05 μ

X.0 μ	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
2.0	<.001	<.001	.004	.006	.003	<.001	.001	.001	.016	.144
3.0	.183	.107	.095	.155	.413	.166	.035	.026	.047	.028
4.0	.016	.010	.006	.006	.006	.014	.005	.007	.005	.003
5.0	.002	.005	.008	.009	.006	.008	.018	.047	.148	.147
6.0	.149	.175	.362	.285	.138	.099	.199	.255	.294	.396
7.0	.220	.215	.230	.303	.228	.211	.238	.258	.252	.265
8.0	.246	.202	.213	.176	.206	.202	.226	.188	.182	.181
9.0	.193	.174	.173	.184	.168	.119	.151	.193	.195	.145
10.0	.122	.093	.099	.096	.110	.087	.095	.092	.108	.113
11.0	.109	.089	.090	.086	.089	.089	.099	.102	.107	.104
12.0	.114	.100	.110	.099	.097	.080	.084	.079	.084	.087
13.0	.118	.110	.144	.131	.125	.093	.082	.073	.087	.080
14.0	.061	.059	.066	.089	.108	.082	.065	.040	.033	.026

RESULTS AND DISCUSSION

Cyclobutane.--The spectrum of cyclobutane itself has been examined in detail by Rathjens et al. (7). It is reported to be complicated by the fact that the barrier to internal rotation about the C-C bond appears small enough to allow an equilibrium to exist between the planar (D_{4h}) and bent (D_{2d}) conformations, both symmetry forms being sufficiently populated at ambient temperatures to be spectroscopically active.* The most characteristic vibration, the ring breathing motion of the planar constellation, is unfortunately only Raman active (9), appearing at 970 cm^{-1} (10.30 μ). This signal is expected to be weak at most in substituted ring systems. For cyclobutane molecules with D_{2d} symmetry, there is an infrared band at 750 cm^{-1}. (13.33 μ), which has been assigned to an in-plane ring bending motion (7). This absorption should be important in the spectra of substituted cyclobutanes in which bulk and torsional effects tend to favor the non-planar conformation. Another pair of motions, which might be expected to be characteristic of cyclobutane derivatives, also appears in the spectrum of the parent compound. One is the methylene ($-CH_2-$) twisting movement. This mode is silent in the infrared for molecules with D_{4h} symmetry, but is active for the lower symmetry form and appears at 1220 cm^{-1}

---

* Recent evidence from electron diffraction studies gives support to D_{2d} as the average symmetry species (8a; cf. 8b). High resolution Raman studies also favor this species (8c).

(8. 20 μ). Rocking of the methylene group produces a band at 901 cm.$^{-1}$ (11.10 μ). In open chain hydrocarbons, the corresponding frequencies are near 1305 cm.$^{-1}$ (7. 66 μ) and 720 cm.$^{-1}$ (13.88 μ) (10).

Region Near 3000 cm.$^{-1}$ (3. 4 μ). -- In cyclobutane (7) the C-H stretching motions give rise to strong bands at 2974 cm.$^{-1}$ and 2896 cm.$^{-1}$ Conclusions to be drawn from several previous investigations (2) suggest that for cyclobutane derivatives these motions appear at lower frequencies, namely at 2926 ± 10 cm.$^{-1}$ and 2853 ± 10 cm.$^{-1}$. Our investigation of this region was hampered by the lack of good resolution here of many spectra. After an examination of the spectra of 18 cyclobutane compounds possessing a relatively simple band structure in this region, we found that it was possible to identify two bands at 2915-2950 cm.$^{-1}$ and 2855-2875 cm.$^{-1}$ Three of the spectra were of the pure liquids and the rest were of carbon tetrachloride solutions. The latter interval coincides with the one reported by Wiberley (11).

Cyclobutene compounds usually gave rise to very weak absorptions near 3000 cm.$^{-1}$, and we were unable to obtain much information about them. It appears that the stretching frequencies of the vinyl C-H units are not significantly shifted by the effects of ring strain. A more detailed study of this region, however, should be made.

Region Near 1450 cm.$^{-1}$ (6.9 μ). --The methylene group of saturated hydrocarbons is responsible for a remarkably constant band at

1468 cm.$^{-1}$ This absorption is due to the bending deformation of the H-C-H angle. This so-called "scissoring" motion* is readily identified in hydrocarbon spectra, since it is usually the only strong intensity between 1400 and 1500 cm.$^{-1}$ When the polymethylene chain forms a ring, this absorption is shifted to longer wavelengths. Thus, in carbon tetrachloride, the corresponding band of cyclohexane undergoes a significant displacement (12), falling to 1454 cm.$^{-1}$ In cyclopentane no further shift is observed, and the band appears at 1453 cm.$^{-1}$ The spectrum of liquid cyclobutane (7), at ambient temperatures, possesses a doublet at 1453 cm.$^{-1}$ and 1450 cm.$^{-1}$ In cyclopropane (13) the methylene deformation falls sharply to 1434 cm.$^{-1}$ The corresponding in-plane deformation of terminal alkenes (2)(cycloethanes) is found near 1415 cm.$^{-1}$ The cause of this shift to lower frequencies may, as in the case of C-H stretching vibrations, be due to a combination of effects arising from a decrease in ring size. Such factors include bond angle strain, compression of the C-C bond, changes in the state of aggregation of the methylene groups, and changes in the electronegativity of carbon due to differences in bond hybridization.

Except for the case of terminal alkenes, very little use has been made of the position of the methylene deformation in the infrared

---

* When the proportion of methyl groups present in the molecule is large, the asymmetrical vibration near 1460 cm.$^{-1}$ may become more conspicuous; however, it usually provides no more than a shoulder on the more intense methylene absorption under typical resolution. See reference 2.

identification of cycloparaffinic structures. Recently (10, 12), however, careful analysis of the spectra of certain steroids has shown that the methylene groups of the D-ring can be distinguished from those of the side-chain and of the six-membered rings. The fact that the position and the intensity of this absorption are strongly influenced by the presence of electronegative substituents has tended to obscure its usefulness in problems of structure identification. This is due largely to the lack of sufficient data on the spectral shifts involved, though other deterrents can also be blamed (vide infra). In cyclobutane compounds, this change in position is illustrated by the following series of mono- and 1, 1-disubstituted derivatives: methyl- (1459 cm. $^{-1}$), hydroxy- (1453 cm. $^{-1}$), bromo- (1453 cm. $^{-1}$), amino- (1451 cm. $^{-1}$), phenyl- (1449 cm. $^{-1}$), chloro- (1448 cm. $^{-1}$), 1-chloro-1-carboxy- (1418 cm. $^{-1}$), 1-fluoro-1-carboxy- (1406 cm. $^{-1}$), and oxo- (1396 cm. $^{-1}$). The shifts are seen to parallel group electronegativities very well. Although the shifts noted here are quite large, it is still often possible to observe the effects of ring size on this absorption within an homologous series of cycloalkyl derivatives. For example, Nolin and Jones (14) have shown that the C-H bending of the α-methylene groups of ketones is displaced down to 1430-1410 cm. $^{-1}$. The values of the corresponding cyclic systems are 1422 cm. $^{-1}$, 1404 cm. $^{-1}$, and 1396 cm. $^{-1}$ for neat cyclohexanone, cyclopentanone, and cyclobutanone*, respectively.

_____

* A higher value of 1402 cm. $^{-1}$ has been reported for cyclobutanone (15).

A similar trend is observed in the analogous exo-cyclic methylene derivatives (1457 cm.$^{-1}$, 1447 cm.$^{-1}$, and 1428 cm.$^{-1}$; neat). This shift to longer wavelengths is further illustrated in the spectra of the cycloaklyl bromides and chlorides published by Roberts and Chambers (16), as well as in the A. P. I. spectra (17) of mono- and 1,1-dialkyl-cycloalkanes.* The spectra of the cycloalkylbenzenes and the cyclo-alkyl carboxylic acids do not follow the usual trend. The observed deviations may be due to a coupling of the scissoring mode with the 1450 cm.$^{-1}$ skeletal motion of the aromatic ring, and with a C-O motion near 1440 cm.$^{-1}$, respectively. Although coupling of this kind should be weak, this belief is strengthened by the fact that the proper order is restored when the benzene ring is partially hydrogenated and when the carboxyl group is reduced to an aldehyde function.

Examination of this region of the spectrum showed that 93 percent (26/28) of the cyclopentane structures absorbed over 1460-1430 cm.$^{-1}$, 76 percent (84/111) of the cyclobutanes over 1450-1420 cm.$^{-1}$, while 80 percent (84/105) of the cyclopropane derivatives displayed bands in the region 1430-1390 cm.$^{-1}$ Nevertheless, except within a series of analogously substituted cycloalkanes, the position of the methylene deformation is not sufficiently characteristic of ring size to be used as a means of identification.

We have observed, however, that in the monosubstituted cyclo-propane spectra, the methylene scissoring band is invariably split by

* This shift may be easily seen in Figures 2-5 and Figures 7-10.

about 10-15 cm.$^{-1}$, while in monosubstituted cyclobutane spectra, splitting appears in about 2/3 of the cases. Cyclopentane compounds less frequently (ca. 1/3 of the time) possess a sharp absorption with a shoulder on the higher frequency slope, but seldom have the well-defined doublet structure found in the smaller rings. Six-membered rings and open chain systems possess a single band as long as the methylene groups are not rendered greatly unequivalent by the presence of strong electron-withdrawing groups. Inasmuch as the cyclopropane ring structure can usually be identified by reference to bands near 1020 cm.$^{-1}$ (9.8 μ) and 3050 cm.$^{-1}$ (3.27 μ), the absence of these bands along with the 10-15 cm.$^{-1}$ splitting of the methylene band may be evidence for the cyclobutane ring. Since the cause of this splitting is not clear, such interpretations should be made with caution, and one should be aware, insofar as possible, of those structural features which are likely to complicate the analysis of this region of the spectrum. In this connection, it may be mentioned that the presence of one or more fluorine atoms on the cyclobutane ring may give rise to a band between 1430 cm.$^{-1}$ and 1330 cm.$^{-1}$ Bands of similar contour and intensity below 1350 cm.$^{-1}$ have been observed by Thompson and co-workers (18) in a variety of fluorinated substances, although the group motions responsible for them have not yet been determined.

In addition, 31 spectra of cyclobutene compounds containing the ring methylene group were examined. An absorption was invariably

found below 1445 cm.$^{-1}$ It was not always clear whether this band was due to the ring methylene unit or to some other group.

Region Near 1235 cm.$^{-1}$ (8.10 μ).--According to the composite spectrum of 81 cyclobutane compounds (Fig. 4), an absorption occurs near 1235 cm.$^{-1}$ frequently enough to merit consideration as a possible characteristic vibration. No absorption is noted here for the cyclopropane and cyclopentane compounds examined. Since this band is very likely associated with the methylene twisting motion on the four-membered ring (7), the spectra of derivatives containing this group were examined in detail in this region. A medium to strong signal appeared in 55 percent (61/111) of the cases at 1235 ± 10 cm.$^{-1}$ In 87 percent (96/111) of the spectra, a band was found over 1235 ± 20 cm.$^{-1}$, while the interval 1200-1260 cm.$^{-1}$ contained a band in 93 percent (103/111) of the cases. Polysubstituted cyclobutanes generally represented the exceptions. Some caution must be exercised in interpreting these figures, however, since this is a region of high spectral activity (Table I). It may be that some of the observed absorptions should be ascribed to strong C-O motions. Nevertheless, the relative constancy of the 1235 cm.$^{-1}$ band in a large number of compounds indicates that it should be very useful in identifying the cyclobutane ring.

This band is not seen in the spectra of perdeuterocyclobutane and nine other cyclobutane compounds in which the ring methylene units are missing. On the other hand, cyclobutane and cyclobutene systems

which contain fluorine attached to the ring, e.g., perfluorocyclobutane itself, are quite likely to possess a strong absorption near 1235 cm.$^{-1}$

It is interesting that all of fourteen compounds containing one **exo**-cyclic double bond attached to the ring (either $=CR_2$ or $=O$) presented an absorption near 1235 cm.$^{-1}$, while as a rule cyclobutene derivatives did not. Some exceptions were noted. In particular, eleven derivatives of 1-phenylcyclobutene absorbed near 1240 cm.$^{-1}$ In simple systems, it appears that the 1235 cm.$^{-1}$ band may be of some value in distinguishing between **endo**- and **exo**-cyclic double bonds, if the presence of the C_4-ring has already been established.

Region Near 900 cm.$^{-1}$ (11 μ).--Earlier investigators have observed a band at 910-920 cm.$^{-1}$ in a number of cyclobutane spectra, and they have identified it with a methylene rocking mode (19). Our investigation revealed that this band occurs frequently (82 percent, 40/49) in the spectra of mono- and 1,1-disubstituted cyclobutanes over the interval 910-925 cm.$^{-1}$ It is, however, comparatively rare (22 percent, 16/73) in the spectra of cyclobutane compounds which possess a different substitution pattern, but which still retain at least one ring methylene group. It should be pointed out that the behavior of the methylene rocking motion, unlike the other bending modes of the methylene group, is in general considerably more susceptible to the influence of neighboring groups (10). The incidence of absorptions over the range 890-925 cm.$^{-1}$ was 53 percent (39/73). Cyclopentane

compounds have been reported (20) to absorb near 890 cm.$^{-1}$ as well as near 930 cm.$^{-1}$ Figure 3 displays bands near these values (11.2 μ and 10.8 μ).

We are not able to concur with Marrison (21) that a characteristic signal appears at 960-1000 cm.$^{-1}$ for cyclobutane systems. We observed an absorption in this interval only 31 percent (38/122) of the time; many of these were very weak bands. It may be significant that eleven of these compounds contained fluorine, although the C-F bond usually produces peaks at frequencies above 1000 cm.$^{-1}$ (2).

Deformation of the C-H bond of the terminal methylene group of alkenes produces a band at 890 ± 5 cm.$^{-1}$ In methylenecyclobutane compounds, this band appears to be shifted to slightly longer wavelengths. For non-conjugated methylene groups, the band shifts to 875 ± 5 cm.$^{-1}$ (six compounds), while for conjugated systems, the peak is at 845-850 cm.$^{-1}$ (nine compounds). As examples: methylenecyclobutane (879 cm.$^{-1}$), 3-methyl-1-methylenecyclobutane (876 cm.$^{-1}$), 1,3-dimethylenecyclobutane (870 cm.$^{-1}$); 3,4-dimethylenecyclobutene (848 cm.$^{-1}$), 1-phenyl-3,4-dimethylenecyclobutene (847 cm.$^{-1}$), 2-chloro-1-phenyl-3,4-dimethylenecyclobutene (846 cm.$^{-1}$), and 1-phenyl-3-methylenecyclobutene (850 cm.$^{-1}$). In allenes (22) (methylenecycloethanes), this band is near 860 cm.$^{-1}$

Region Near 750 cm.$^{-1}$ (13.3 μ).--Use of solvents blocked out the region near 750 cm.$^{-1}$ in most of the spectra available to us.

However, a band at 745 ± 5 cm.$^{-1}$ was observed in 70 percent (19/27) of the cases. This may result from the low frequency in-plane bending of the four-membered ring (7).

APPENDIX

The composite spectra of Figures 1-5 present an interesting but difficult problem in objective analysis. As pointed out, the Z_i- and their associated absorptions do not in fact behave completely randomly; consequently noise, i.e., absorptions not specific to the moiety R-, do appear in the composite spectrum of R-Z_i. For example, non-specific activity is anticipated near 3.5 μ and 7 μ where carbon-hydrogen motions are normally detected, since the C-H bond is expected to be an important (non-random) component of the Z_i-. A completely satisfactory analysis should be able to distinguish all such non-characteristic absorptions. Examination of Figures 2 and 3 brings to bear the question: Are the more intense bands between 8 μ and 12 μ any more or less important than certain weaker or even hidden bands in the same region? And finally, which of the bands of a given composite spectrum are most useful in establishing the presence or absence of R- in the spectrum of an unknown compound?

The chief obstacle to finding answers to the above questions lies in the fact that the "signal-to-noise" ratio is not a constant value over the entire frequency range. Further, the level to which the noise rises on a given frequency interval in a particular composite spectrum is not known. Therefore, characteristic absorptions with low extinction co-efficients may not be as prominent as less characteristic absorptions

with higher extinctions. This is particularly so if the latter fall on an interval of generally high spectral activity (Table I).

The above considerations may be taken as some specific demerits of the composite spectrum as an investigative tool. Nonetheless, an attempt to remove some of the guesswork attendant to the analysis of these spectra has been made with partial success. The method, which is adaptable to use with high-speed computers, involves elementary information theory and is outlined below.

$$*\qquad*\qquad*$$

The theory of information (23) has found increasingly wide application during the past few years. Basic to this theory is the statistical definition of information expressed by equation 1. Here P relates to

$$I = K'lnP \tag{1}$$

the probability of an event (e. g., the occurrence of a given symbol), while K' is simply a constant; I, then, is the information* to be derived from the event or the information content of the event.

For an event with a priori probability p_j, the information content may be given alternatively by equation 2:

$$I_j = -K p_j \ln p_j \tag{2}$$

---

*This definition makes no distinction between useful and useless information. Information is, however, distinct from knowledge. It is defined in terms of the "novelty" of an event. The more rare an event, the more informative it is. The human value placed on this information, however, is of no concern in this theory.

The information content of a group of N events, each with a priori probability p_j, is the sum of the information associated with the individual events, and is given by

$$I = -K \sum_{j=1}^{N} p_j \ln p_j \qquad (3)$$

where

$$\sum_{j=1}^{N} p_j = 1 \qquad (4)$$

Equation 3 is due to Shannon (24). The minus sign is introduced to make I a positive quantity. Since information is usually considered a dimensionless value, K is given no dimensions, but is used as a scaling factor. It is conventional to give I in a unit system based on binary digits (bits), in which case K has the value 3.32192 when $\log_{10} p_j$ is employed.

If the data of Table I are normalized over the interval 2.0-14.9 μ, a new table of probabilities, P_λ, may be constructed (Table II) which conform to equation 4. These represent the a priori probability of the occurrence of an absorption in a particular frequency cell, λ. The amount of information contained in such an event would be given by

$$I_\lambda = -3.32192\, P_\lambda \log P_\lambda \qquad (5)$$

Table II. Relative Occurrence Probabilities, P_λ, for Infrared Absorption Bands Over the Region 2.0-14.9 μ Based on 17,345 Spectra in the Sadtler (Organic) Index.

0.Y ± 0.05 μ

X.0 μ	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
2.0	<.0001	<.0001	.0002	.0004	.0002	<.0001	<.0001	<.0001	.0011	.0096
3.0	.0122	.0071	.0064	.0104	.0276	.0111	.0024	.0018	.0031	.0019
4.0	.0011	.0007	.0004	.0004	.0004	.0009	.0003	.0005	.0003	.0002
5.0	.0001	.0004	.0005	.0006	.0004	.0005	.0012	.0031	.0099	.0098
6.0	.0098	.0117	.0242	.0190	.0092	.0066	.0133	.0170	.0195	.0264
7.0	.0147	.0144	.0154	.0202	.0152	.0140	.0159	.0172	.0168	.0177
8.0	.0164	.0135	.0142	.0118	.0137	.0135	.0151	.0126	.0122	.0121
9.0	.0148	.0116	.0115	.0123	.0112	.0080	.0101	.0129	.0130	.0097
10.0	.0087	.0062	.0066	.0064	.0073	.0058	.0064	.0061	.0072	.0075
11.0	.0073	.0059	.0060	.0057	.0059	.0059	.0066	.0068	.0072	.0070
12.0	.0076	.0067	.0073	.0066	.0065	.0054	.0056	.0053	.0056	.0058
13.0	.0079	.0074	.0096	.0087	.0083	.0062	.0055	.0048	.0058	.0053
14.0	.0041	.0039	.0044	.0060	.0072	.0055	.0043	.0027	.0022	.0018

Plotting the I_λ versus λ would produce a distribution or spectrum of information values similar to the probability distribution obtained by plotting the P_λ against λ. This information spectrum should approximately characterize the non-specific behavior of the "noise" attributable to the Z_i in a precise system of units.

In a like manner, we may obtain a set of probability values, Q_λ, corresponding to any subclass of compounds, $R-Z_i$, and compute the related information elements,

$$I'_\lambda = -3.34194 \; Q_\lambda \; \log Q_\lambda \tag{6}$$

The I'_λ now give rise to a particular information spectrum, not unlike Figures 1-5, in which the information signal characteristic of $R-$ is superimposed on the non-specific (noise) signal due to the Z_i-. Each element, I'_λ, may be thought of as composed of two parts:

$$I'_\lambda = I^R_\lambda + I^Z_\lambda \tag{7}$$

where

$$I^R_\lambda = -K \; P^R_\lambda \; \log P^R_\lambda \tag{8}$$

and

$$I^Z_\lambda = -K \; P^Z_\lambda \; \log P^Z_\lambda \tag{9}$$

The P^R_λ of equation 8 are the probabilities that the moiety R will give rise to an absorption at λ; the P^Z_λ of equation 9 are the probabilities that the Z_i will absorb at λ. Presumably, if the Z_i are generally

representative structures, then the P_λ^Z may be estimated by the P_λ of equation 6. Consequently, we may set $I_\lambda^Z \approx I_\lambda$, and make the following approximation for I_λ^R :

$$I_\lambda^R \approx I'_\lambda - I_\lambda = \Delta I_\lambda \tag{10}$$

where the ΔI_λ may in practice be either positive or negative. The goodness of this approximation will depend upon the number and choice of the Z_i in the R-Z_i. If the Z_i are not truly representative of the population defined (in this case) by the Sadtler files, then the P_λ will not be proper estimates for the P_λ^Z.*

The ΔI_λ may now be plotted versus λ to obtain a differential information spectrum. Figures 6-10 show the differential information spectra, in histogram form, corresponding to the spectra of Figures 1-5, respectively. In the ideal situation, the positive peaks of the differential spectra correspond to the specific infrared behavior of the R-group; the intensities of these peaks are a measure of the relative amount of information to be gained from examining a given region of the spectrum for a particular class of compounds after the "noise" has been removed.

It may be mentioned in passing that since the intensities of a given differential spectrum do not depend on variable extinction coefficients

---

* It may be possible for a given system to obtain better estimates of P_λ^Z by properly defining the population described by the P_λ .
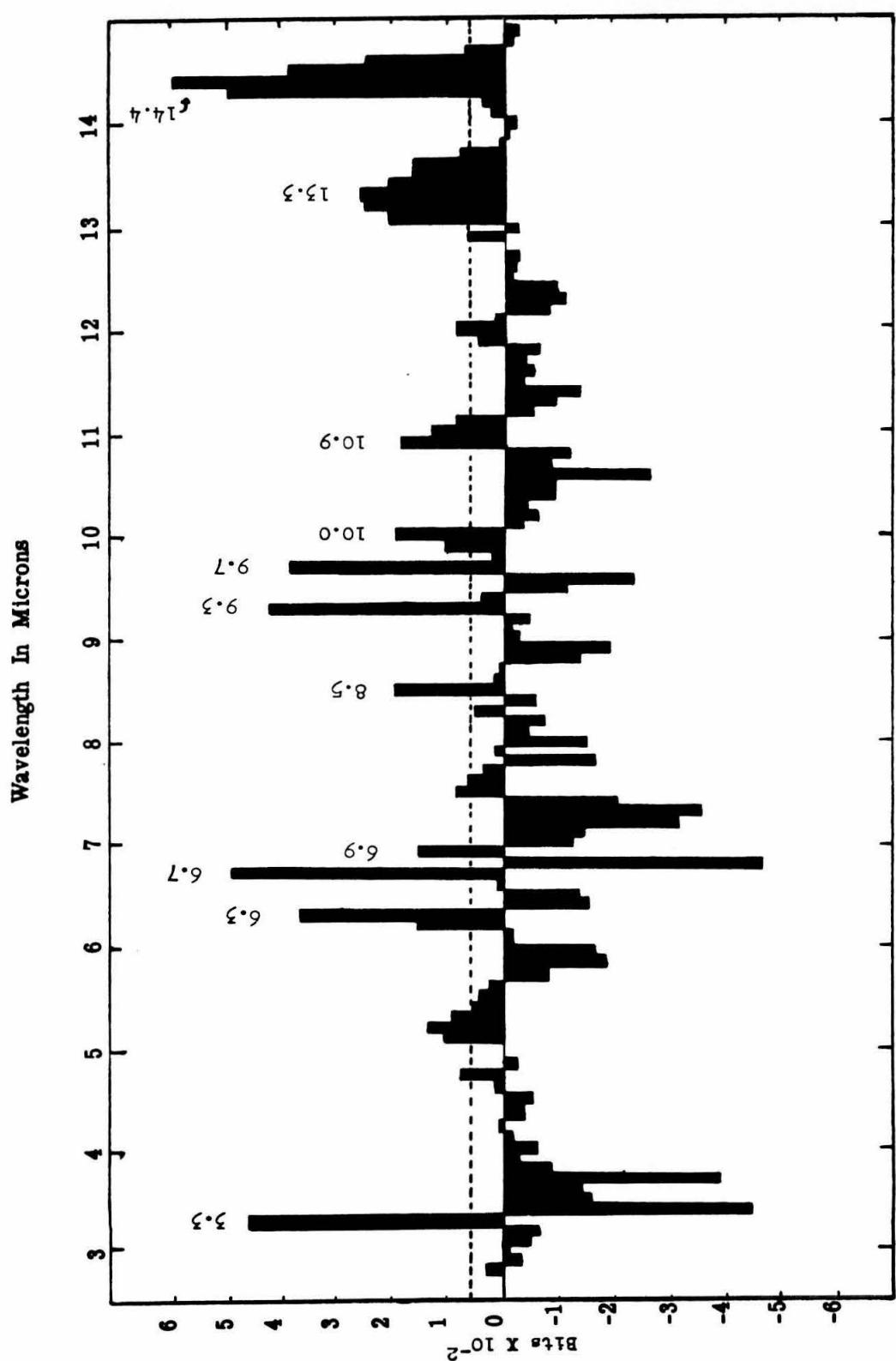
Fig. 6

Differential Information Spectrum

MONOSUBSTITUTED BENZENES
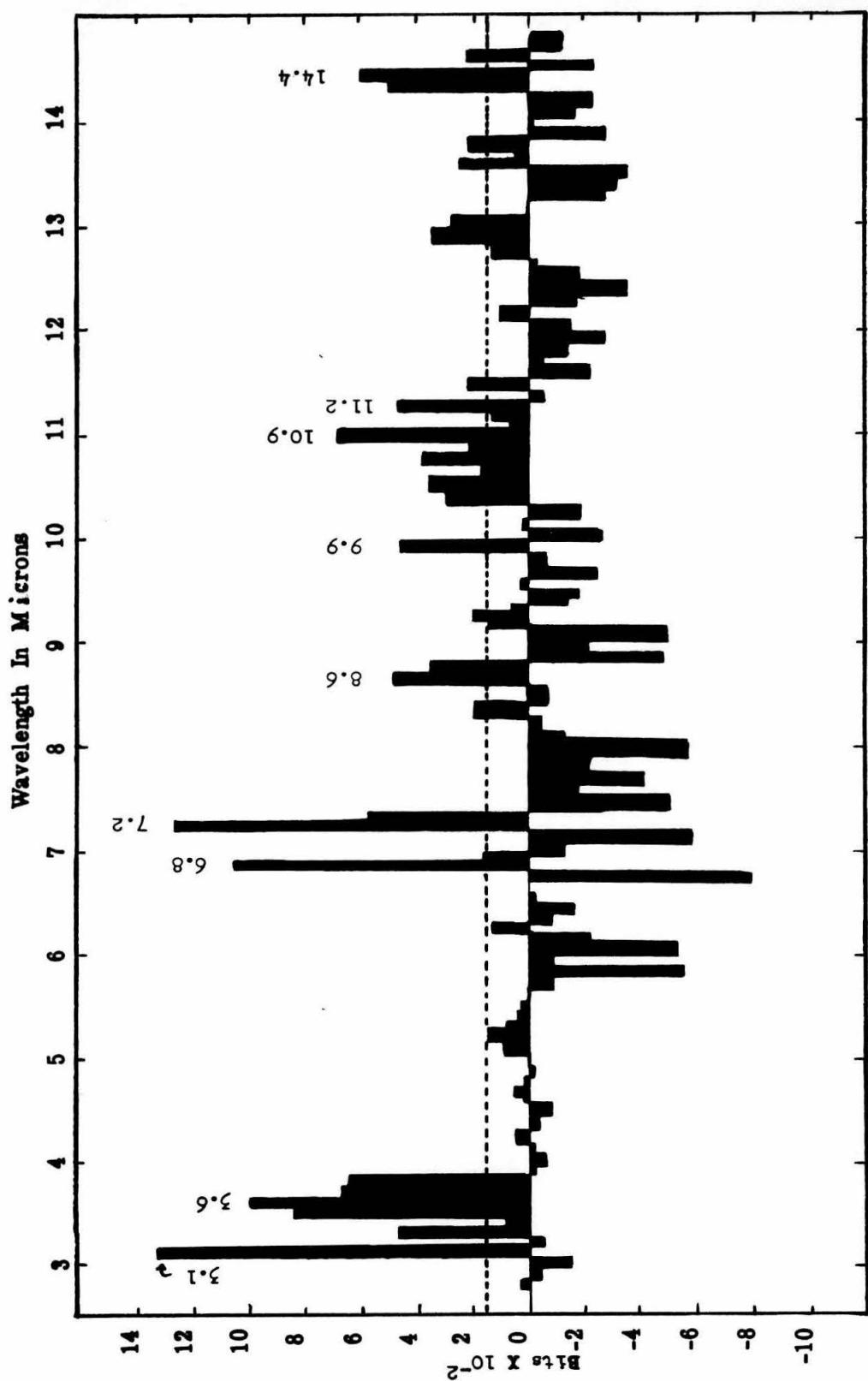
Fig. 7
Differential Information Spectrum
ALKANES
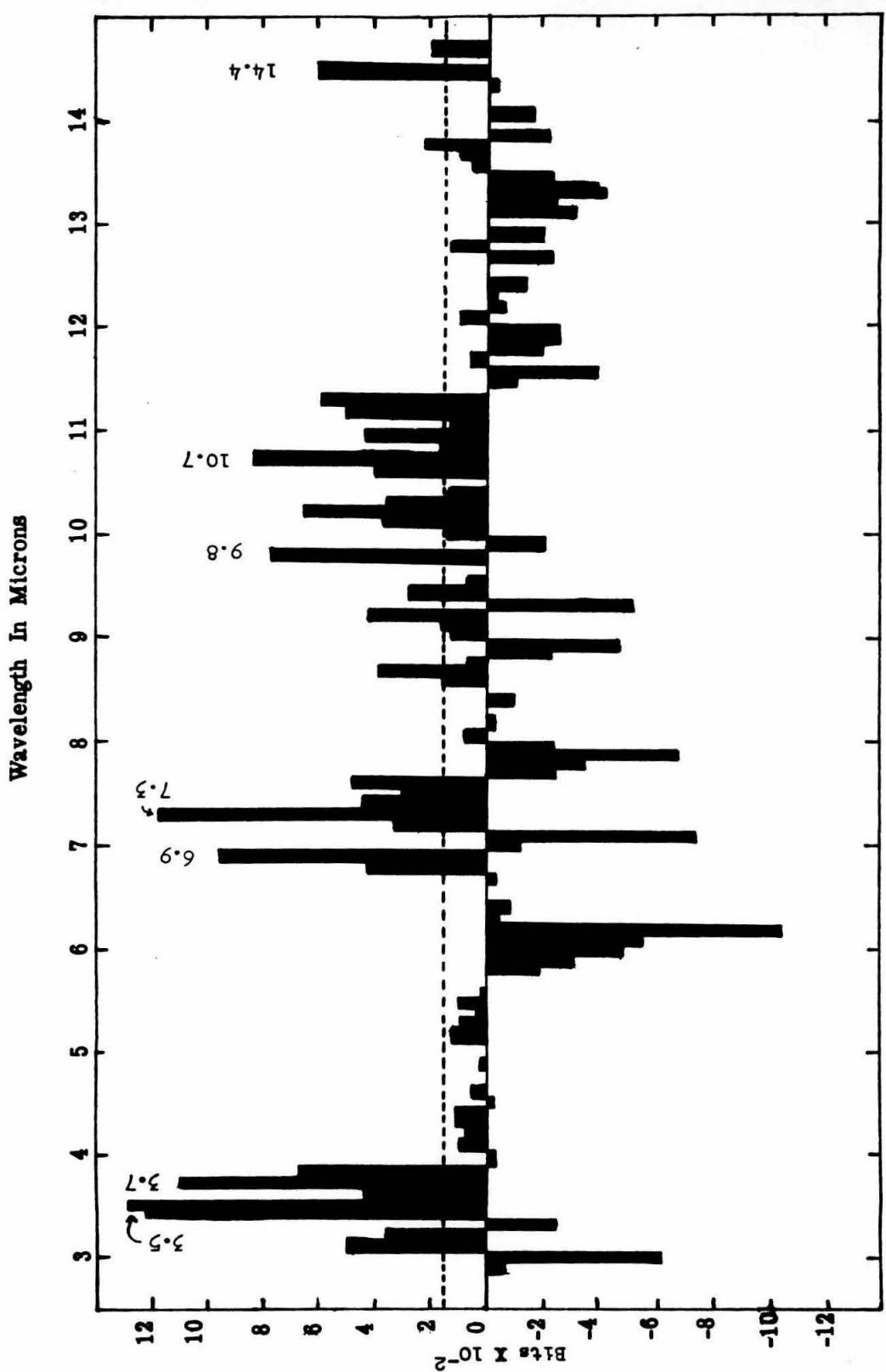
Fig. 8
Differential Information Spectrum
CYCLOPENTANES
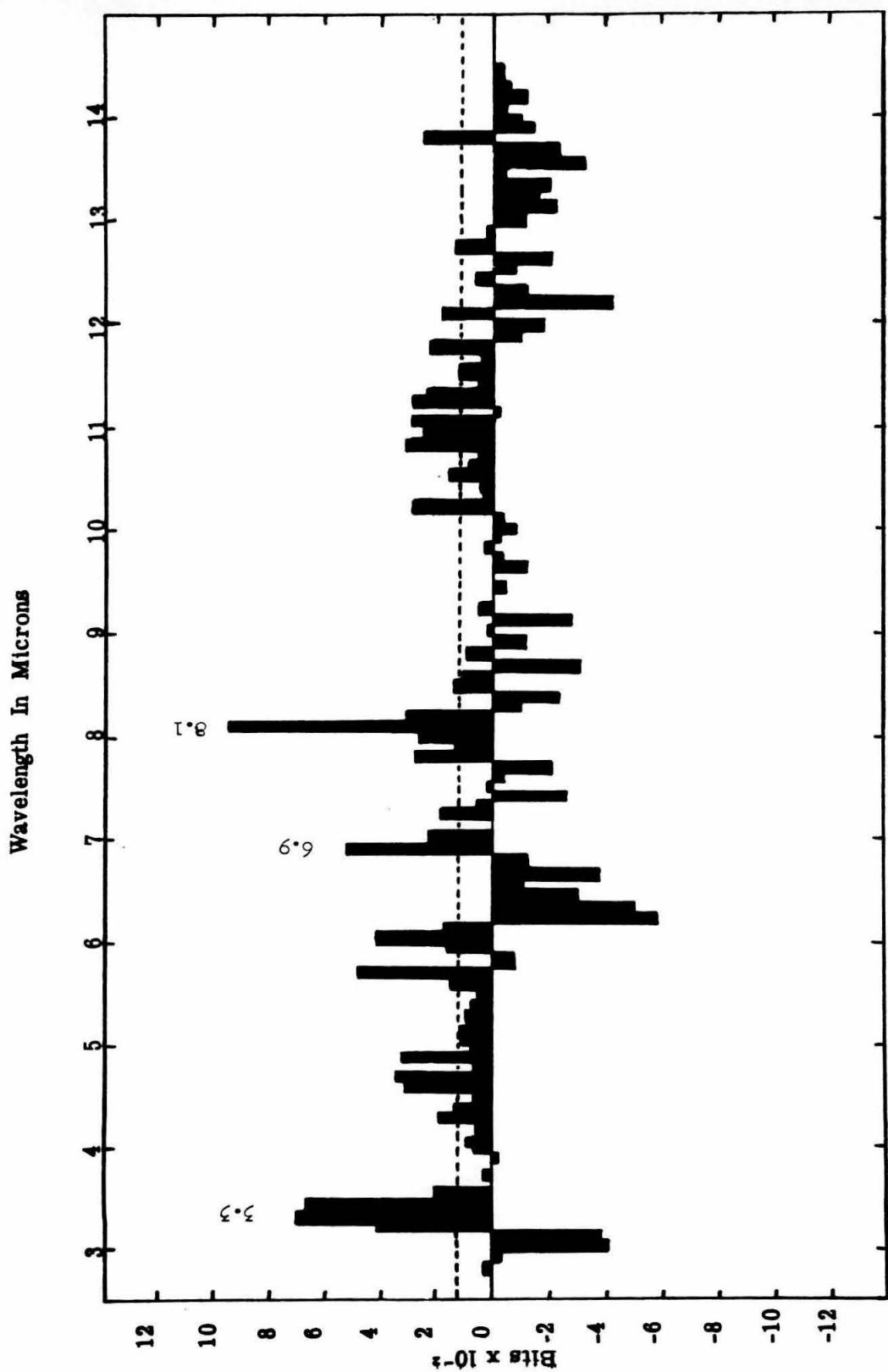
Fig. 9
Differential Information Spectrum
CYCLOBUTANES
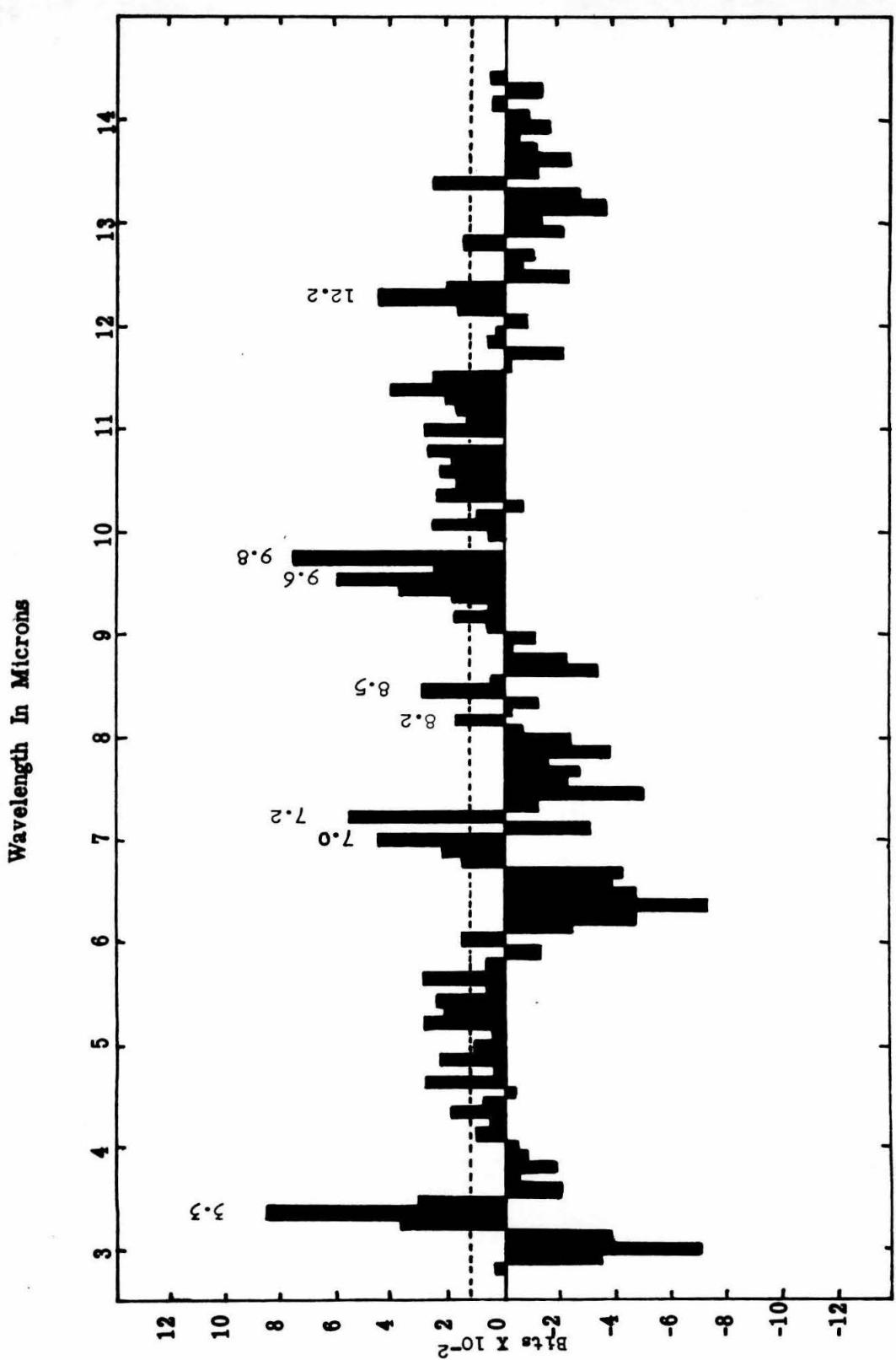
Fig. 10
Differential Information Spectrum
CYCLOPROPANES

as do those of the composite spectrum, it is possible to determine an average signal level which is independent of λ. In Figures 6-10 this value is indicated by the dotted line.

Examination of Figures 6-10 shows that this treatment still leaves something to be desired. Nonetheless, certain simplifications are obtained. In particular, the differential information spectrum of monosubstituted benzenes (Fig. 6) is seen to consist of a number of prominent information peaks with very little background noise. Of the five peaks present in Figure 1, but not generally considered indicative of the phenyl ring (p. 269), only the one at 10.9 μ remains; its information value is seen to be relatively low. A new band of low value at 10.0 μ occurs in the differential information spectrum, but appeared only as a shoulder on the 9.7 μ band in Figure 1. Of some significance is the reduced intensity of the peak at 6.9 μ. Although a skeletal motion of the phenyl ring appears to produce an absorption near here (2), so does the scissoring mode of a simple acyclic methylene group (p. 279). The relative low information content associated with this band in Figure 6 reflects the uncertainty in the origin of this absorption for an unknown compound.

According to Figure 8, the band near 10.7 μ contains about as much information as the band at 9.8 μ for the identification of the cyclo-pentane ring, although this is not obvious from Figure 3; the same is true for the bands at 10.2 μ and 11.2 μ. The 10.2 μ band (977 cm.$^{-1}$)

has been observed by Marrison (21), while the peaks at 10.7 µ (930 cm.$^{-1}$) and 11.2 µ (890 cm.$^{-1}$) have been reported by Sheppard (20).

The most important band of Figure 9 is at 8.1 µ. The peak at 6.9 µ has a much lower information value, as anticipated by our earlier discussion (pp.279-284). It is clear that the region near 10 µ contains little information on the presence of the cyclobutane ring, in spite of the earlier claim by Marrison (21).

References to Part IV

1. a) J. D. Bartleson, R. E. Burk, and H. P. Lankelma, J. Am.
    Chem. Soc., 68, 2513 (1946).

    b) V. A. Slabey, J. Am. Chem. Soc., 74, 4928, 4930 (1952).

    c) V. A. Slabey, J. Am. Chem. Soc., 76, 3604 (1954).

2. L. J. Bellamy, "The Infra-red Spectra of Complex Molecules,"
    John Wiley and Sons, Inc., New York, 1959.

3. Wyandotte--American Society for Testing Materials, Infra-red
    Spectral Absorption Data, Philadelphia, Pa.

4. J. D. Roberts and C. M. Sharts, Org. Reactions, 12, 1 (1962).

5. a) W. O. Ash and J. E. Freund, "Randomized Estimates in
    Power Spectral Analysis," Technical Report No. 31, Dept. of
    Statistics, Virginia Polytechnic Institute, Blacksburg, Va.
    (Aug. 1957).

    b) cf. H. Cramér, "Mathematical Methods of Statistics,"
    Princeton University Press, Princeton, N. J., 1957.

6. a) L. B. C. Cunningham and W. R. B. Hynd, J. Royal Stat. Soc.,
    (Supplement), 8 (1), 62 (1946).

    b) H. Press, J. Am. Stat. Soc., 50, 1022 (1955).

    c) H. Press and J. C. Houbolt, J. Aeronaut. Sci., 22, Jan.
    1954.

    d) M. A. B. Brazier, Sci. Amer., 206 (6), 142 (1962).

7. G. W. Rathjens, Jr., et al., J. Am. Chem. Soc., 75, 5634 (1953).

8. a) O. Bastiansen and P. N. Skancke, Acta Chem. Scand., 15, 711 (1961).

    b) cf., J. D. Dunitz and V. Schomaker, J. Chem. Phys., 20, 1703 (1952).

    c) R. C. Lord and B. P. Stoicheff, Can. J. Phys., 40, 725 (1962).

9. M. I. Batuev, Izvest. Akad. Nauk. S. S. S. R. Otdel. Khim. Nauk., No. 1, 3 (1947); Chem. Abstr., 42, 4463 (1948).

10. R. N. Jones and C. Sandorfy in "Chemical Applications of Spectroscopy," W. West (ed.), Interscience Publishers, Inc., New York, 1956, pp. 359 ff.

11. S. E. Wiberley, S. C. Bunce, and W. H. Bauer, Anal. Chem., 32, 210 (1960).

12. a) R. N. Jones and A. R. H. Cole, J. Am. Chem. Soc., 74, 5648 (1952).

    b) R. N. Jones, A. R. H. Cole, and B. Nolin, J. Am. Chem. Soc., 74, 5664 (1952).

13. A. W. Baker and R. C. Lord, J. Chem. Phys., 23, 1636 (1955).

14. B. Nolin and R. N. Jones, J. Am. Chem. Soc., 75, 5626 (1953).

15. Von Kl. Schäffer, et al., Zeit. für Electrochem., 65, 2 (1961).

16. J. D. Roberts and V. C. Chambers, J. Am. Chem. Soc., 73, 5031 (1951).

17. American Petroleum Institute, Index of Infra-red Absorption Data, published by the A. P. I. Research Project 44 and the Manufacturing Chemists Association, National Bureau of Standards.

18. a) P. Torkington and H. W. Thompson, Trans. Faraday Soc., 41, 236 (1945).

     b) H. W. Thompson and R. B. Temple, J. Chem. Soc., 1948, 1422.

19. a) T. P. Wilson, J. Chem. Phys., 11, 369 (1943).

     b) J. M. Derfer, et al., J. Am. Chem. Soc., 71, 2482 (1949).

     c) E. B. Reid and M. Sack, J. Am. Chem. Soc., 73, 1985 (1951).

20. N. Sheppard, J. Inst. Pet., 37, 95 (1951).

21. L. W. Marrison, J. Chem. Soc., 1951, 1614.

22. R. S. Rasmussen and R. Brattain, J. Chem. Phys., 15, 131 (1947).

23. L. Brillouin, "Science and Information Theory," 2d ed., Academic Press Inc., New York (1962).

24. See, for example: C. E. Shannon and W. Weaver, "The Mathematical Theory of Communication," University of Illinois Press, Urbana, Ill., 1949.

PROPOSITIONS

PROPOSITION I

Compound I, for which the name "paracycloquaterphenyl"
is suggested, would be expected to possess a significant degree of
aromatic character. Consequently, the molecule should be useful for
studying the general chemistry and spectral properties of a uniquely
non-planar, "classically" conjugated system. In particular, the excep-
tionally large "hole" in this molecule with its symmetrical environment
of pi-orbitals should provide an intriguing example for the study of
molecular complexes such as with iodine, benzene, or some of the
transition metals.

A synthetic route to this compound is proposed, and a simple
Molecular Orbital treatment is presented which corroborates the
anticipated stability of this molecule.

DISCUSSION

Cram and Dewhirst (1) have prepared the (4.4)-paracyclophane
tetraene, II. The ultraviolet absorption spectrum of II indicates that
the diolefinic side chains are not conjugated to a significant extent with
the aromatic nuclei. This would be anticipated, since these chains
cannot approach coplanarity with the benzene rings. Molecular scale
models indicate further that this compound is sterically open to attack
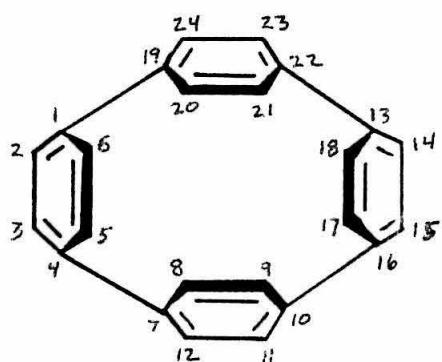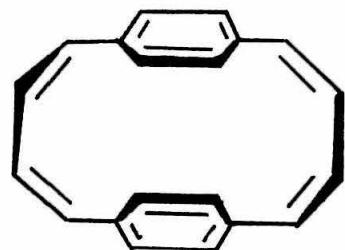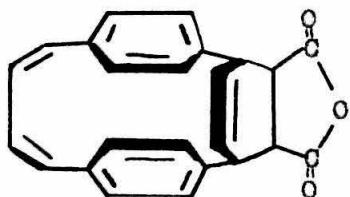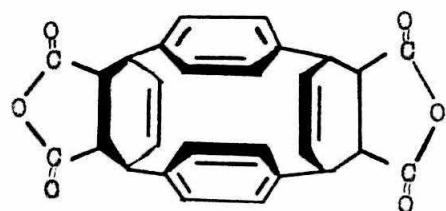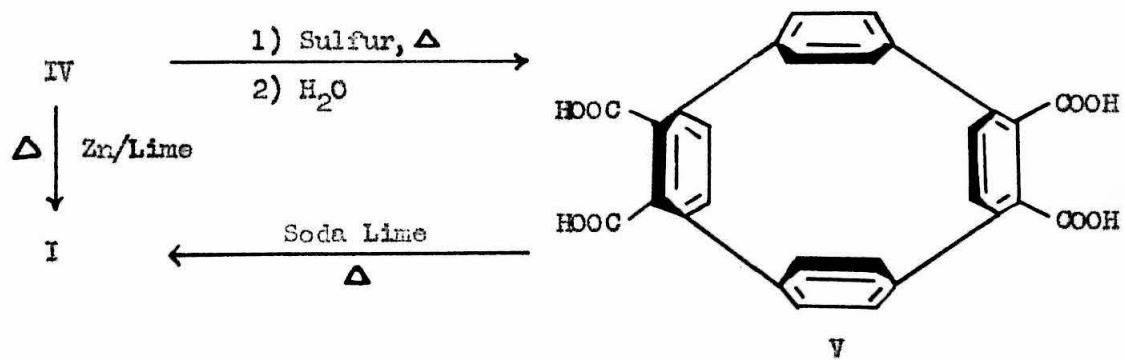
Fig. 1

by a dienophile such as maleic anhydride. Such a Diels-Alder condensation could lead to a mixture of products containing the d, l-forms of III and meso-IV*, neither of which should be as strained as other known members of the paracyclophane series. By suitable decarboxylation and/or dehydrogenation (2, 3), it should be possible to isolate at least small quantities of I or its tetracarboxylic acid derivative, V (see Fig. 1).

On the basis of known interatomic distances in benzene and linear polyphenyl systems (4), it is possible to construct an approximation to the geometry of paracycloquaterphenyl; the model for this approximation is shown in Figure 2. Of particular concern here is the out-of-plane distortions imposed on the benzene rings. Distortions of this type need not necessarily be prohibitive, especially if the system has a large reserve of resonance stabilization upon which to draw. Molecular deformation in 3: 4, 5: 6-dibenzophenanthrene is an example of how easy it is to build up quite large displacements in aromatic molecules by a series of small distortions around each of the carbon atoms of the molecular framework; the terminal rings of the latter are displaced 2.7 Å. from the planar configuration (5). In order to form a macro-ring system from quaterphenyl by joining the terminal para-

* Migration of the cyclohexene double bond into conjugation with a benzene ring in III and IV, which finds analogy in some planar systems (2), would not be favored here, for obvious steric reasons.
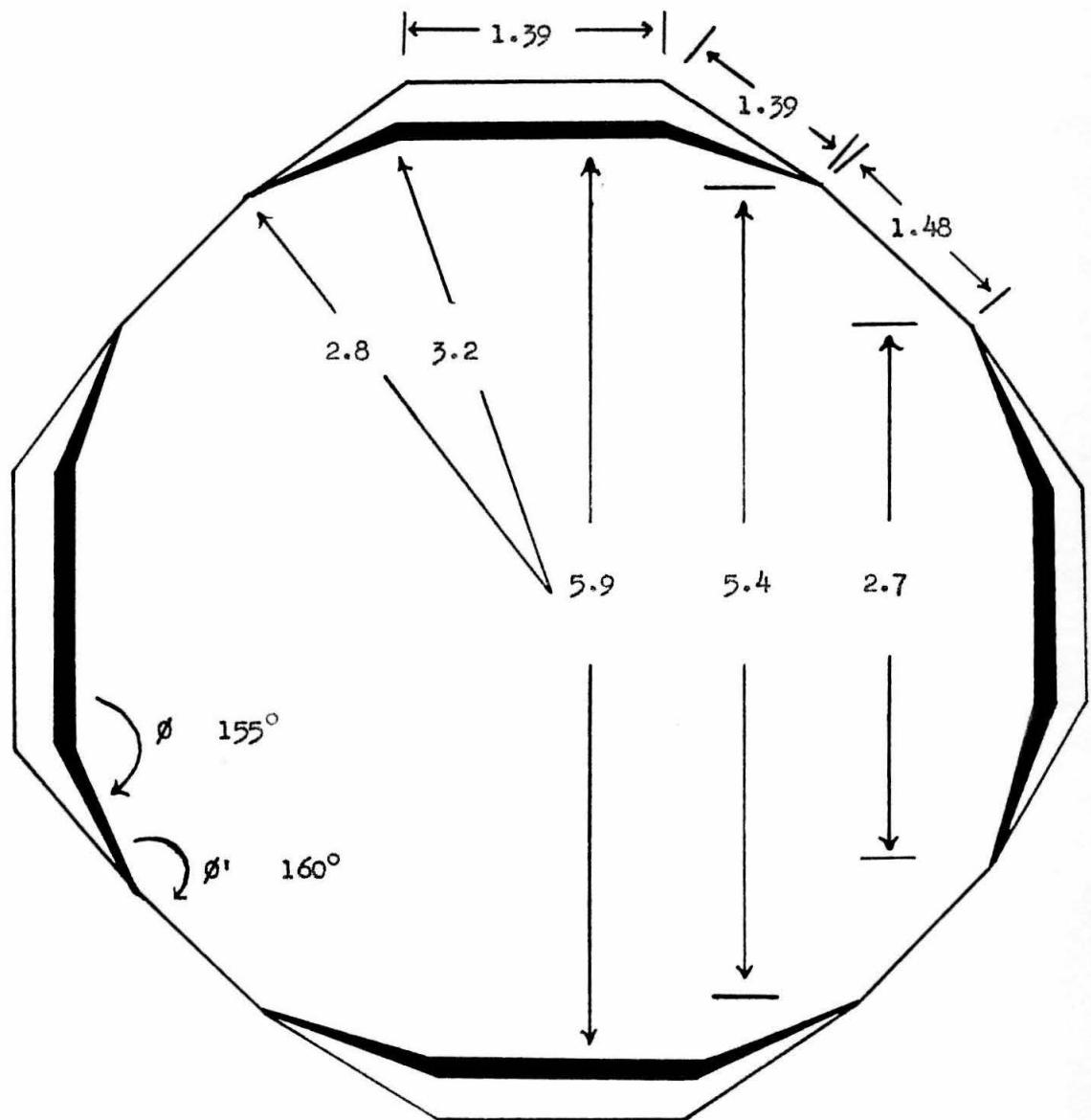
PARACYCLOQUATERPHENYL

All bond lengths and interatomic distances are given in Å. units.

Fig. 2

positions, a deformation of 360° must be distributed symmetrically around the carbon skeleton. This requires that the angles φ and φ' (Fig. 2) be of the order of 155° and 160°, respectively. The corresponding angles in the smallest known paracyclophane, (2.2)-paracyclophane diene, are about 163° and 167°, respectively (6).

A rough idea of the magnitude of the strain in such a molecule might be obtained from a consideration of the low-frequency, out-of-plane bending potential function,

$$V = -\tfrac{1}{2} K z^2$$

for benzene, where z is the perpendicular displacement of the C_1 and C_4 atoms from the plane of the ring, and K is the appropriate force constant. Such a function which takes into consideration the particular symmetry requirements of a system such as I is not readily available; however, Coulson and Senent (5) have derived an expression, for which the constant K may be approximated, which is valid for the case of benzene where one nuclear carbon atom is perpendicularly displaced from the plane of the otherwise rigid system. The K thus obtained is about 0.34×10^5 dynes/cm., and the strain energies for the angular displacement one carbon atom through 20° to 25° are 5.5 to 8.5 kcal./mole based on this value. The energy involved in displacing two carbon atoms situated para to one another will be higher, in part due to the steric repulsion arising from the closer approach of the

displaced carbon atoms. In view of this, it seems likely that the strain in I due to these non-planar distortions in the carbon framework would amount to about 10 to 16 kcal. per benzene ring (7). Also, contrary to the case of the smaller paracyclophanes, one would expect very little strain, if any, due to "compression" of the eclipsed benzene rings, since the anticipated transannular distance is of the order of 5 Å, which is considerably larger than the usual Van der Waals separations. In fact, it seems likely that this "openness" of the molecule might very well make it difficult to recrystallize I (if solid) free of intrained solvent molecules.

Molecular Orbital Treatment of Paracycloquaterphenyl

The fundamental problem involved in even the simple Molecular Orbital (MO) treatment given here for paracycloquaterphenyl is the estimation of the resonance integrals, β_{ij}, between the various carbon centers, whose p-orbitals are not strictly parallel to one another. This has been accomplished by means of the Mulliken relationship (8),

$$\beta_{ij} = \beta \, \frac{S_{ij}/(1 + S_{ij})}{S/(1 + S)}$$

where β and S are the standard resonance and overlap integrals, and the value of S is taken to be 0.280 (9). The S_{ij} were computed using Kopineck's tabulations (10) in the manner outlined by Roberts (9).

The S_{ij} and the corresponding β_{ij} computed for paracycloquaterphenyl using the geometry shown in Figure 2 are compiled in Table I; the numbering corresponds to that of I.

Molecular orbital calculations were carried out, utilizing the D_{4h} symmetry of I, at two low levels of approximation, both of which neglect overlap integrals. The first of these was the simple Hückel approximation (zeroth order), where the resonance integrals between neighboring centers were given the values shown in Table I, and given the values zero for non-neighbors. The eigenvalues obtained are given in Table II and are shown schematically in Figure 3.

The assumption that the resonance integrals for non-neighboring centers be zero is particularly bad in the case of certain non-planar systems, where "non-neighboring" p-orbitals may be twisted into rather close proximity. Hence, a first order approximation was carried out in which all resonance integrals greater than 0.1 β were included in the secular determinant. The eigenvalues (Table II), eigenvector coefficients, bond orders, free valence indices, and charge distributions (Fig. 4) were computed using the IBM 7090 Computor at the Jet Propulsion Laboratory.

These calculations support the belief that paracycloquaterphenyl should be stable in spite of the large deformations imposed on the π-network. The bond lengths (Fig. 4) determined by the first order

Table I

i, j	S_{ij}	β_{ij}
1, 2	0.248	0.917
1, 3	0.047	0.206
1, 4	0.038	0.174
1, 19	0.242	0.885
1, 20	0.034	0.154
2, 3	0.280	1.000
2, 5	< 0.010	ca. 0
2, 6	0.046	0.201
6, 20	0.030	0.137

Overlap and resonance integrals for paracycloquaterphenyl based on geometry shown in Figure 2.

Table II

MO	Zeroth Order (Hückel) Approximation	First Order Approximation
1	2.24	3.010
2	2.24	2.620
3	1.67	2.620
4	1.67	1.809
5	1.54	1.427
6	1.54	0.936
7	1.00	0.808
8	1.00	0.808
9	1.00	0.662
10	1.00	0.492
11	0.36	0.492
12	0.36	-0.207
13	-0.36	-0.613
14	-0.36	-1.021
15	-1.00	-1.021
16	-1.00	-1.064
17	-1.00	-1.210
18	-1.00	-1.210
19	-1.54	-1.338
20	-1.54	-1.378
21	-1.67	-1.456
22	-1.67	-1.689
23	-2.24	-1.689
24	-2.24	-1.788

Energy levels (in units of β) of the 24 molecular orbitals of paracycloquaterphenyl calculated by a simple zeroth order and by a first order approximation.

Molecular Orbital Energy Levels of

PARACYCLOQUATERPHENYL
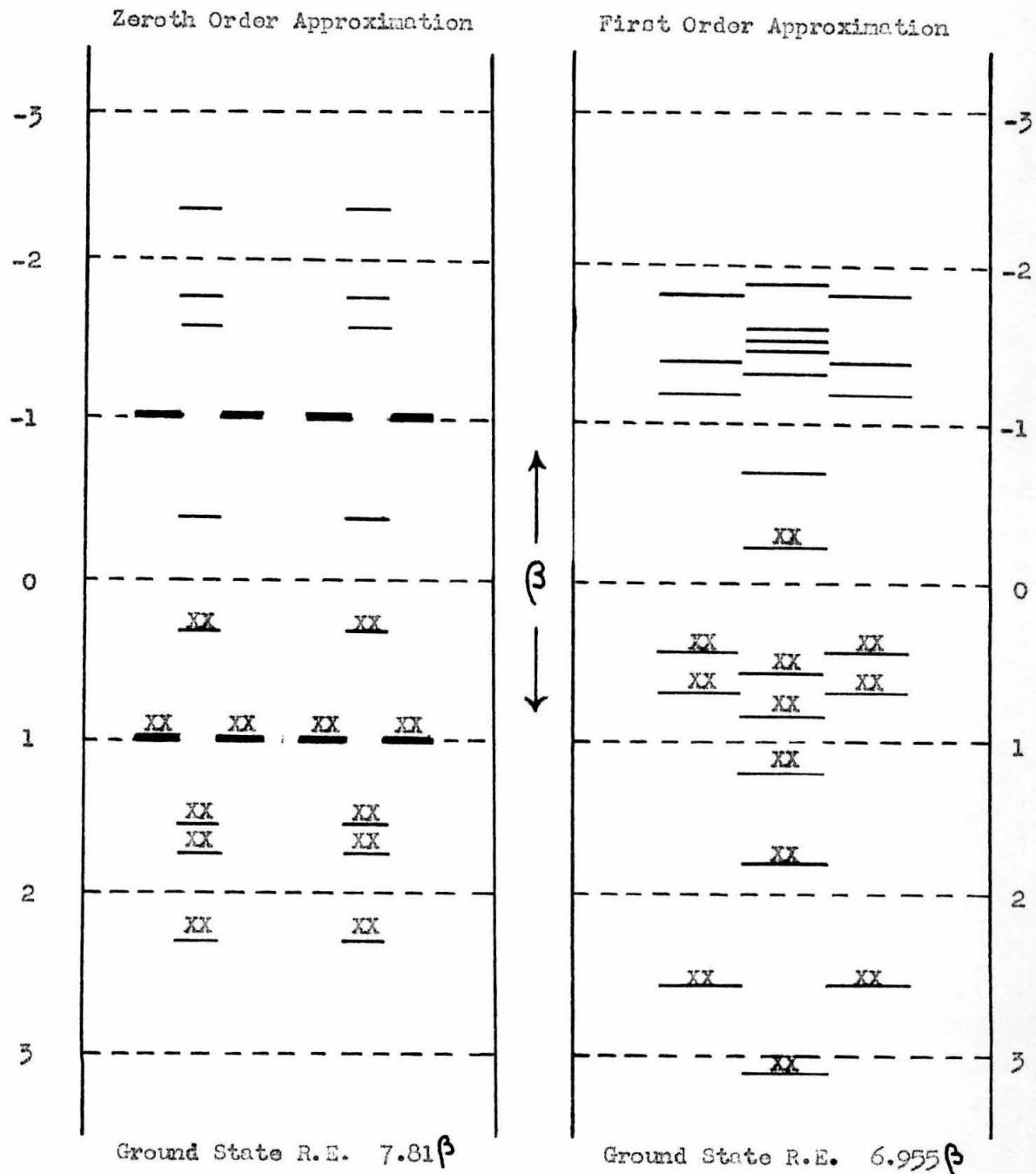
Fig. 3
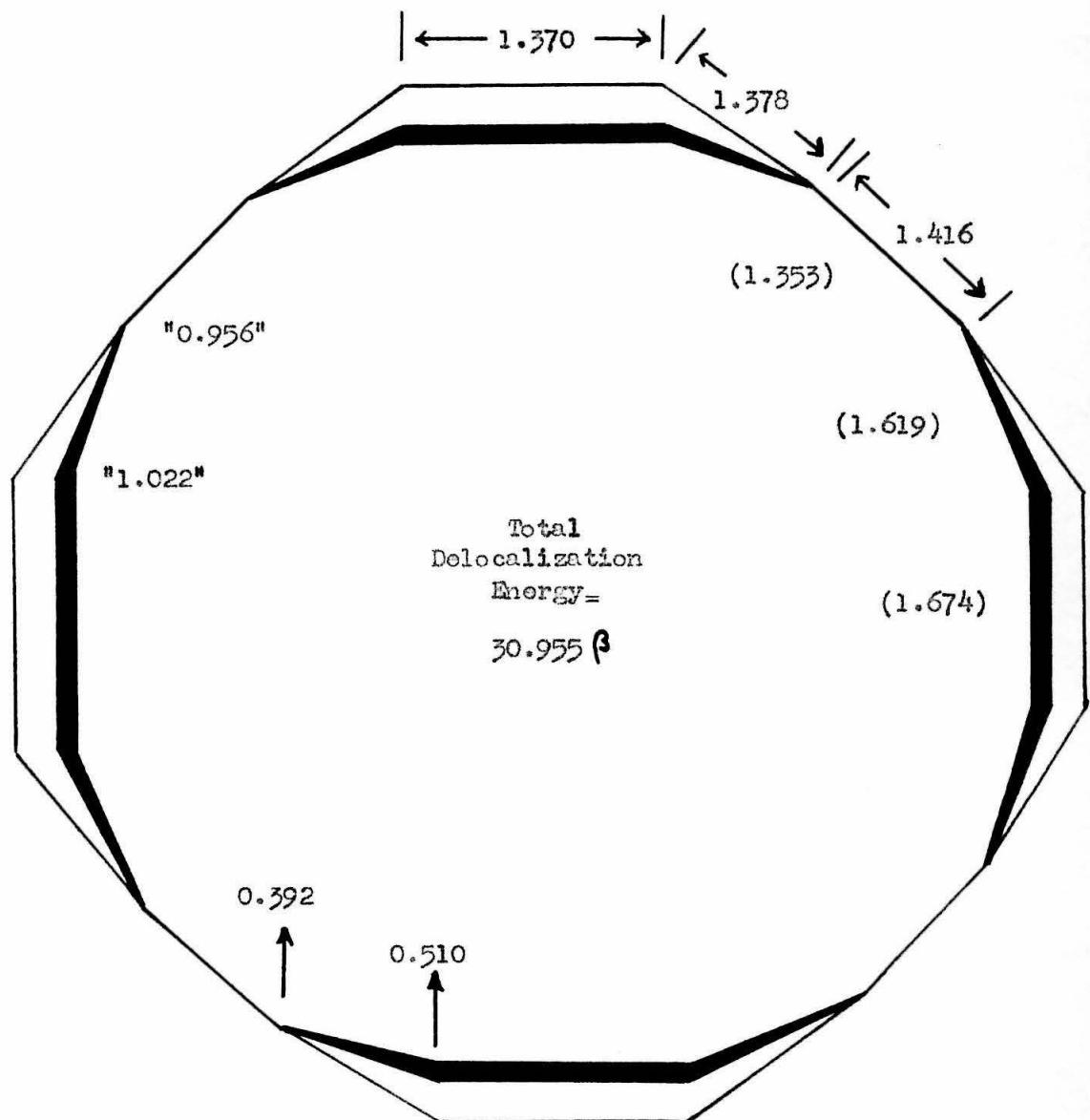
PARACYCLOQUATERPHENYL

Legend: |←— —→| Bond lengths in $\overset{o}{A}$.; (−) Bond orders, P_{ij};
—→ Free valence indices, F_i; "−" Charge distributions, c_i.

Fig. 4
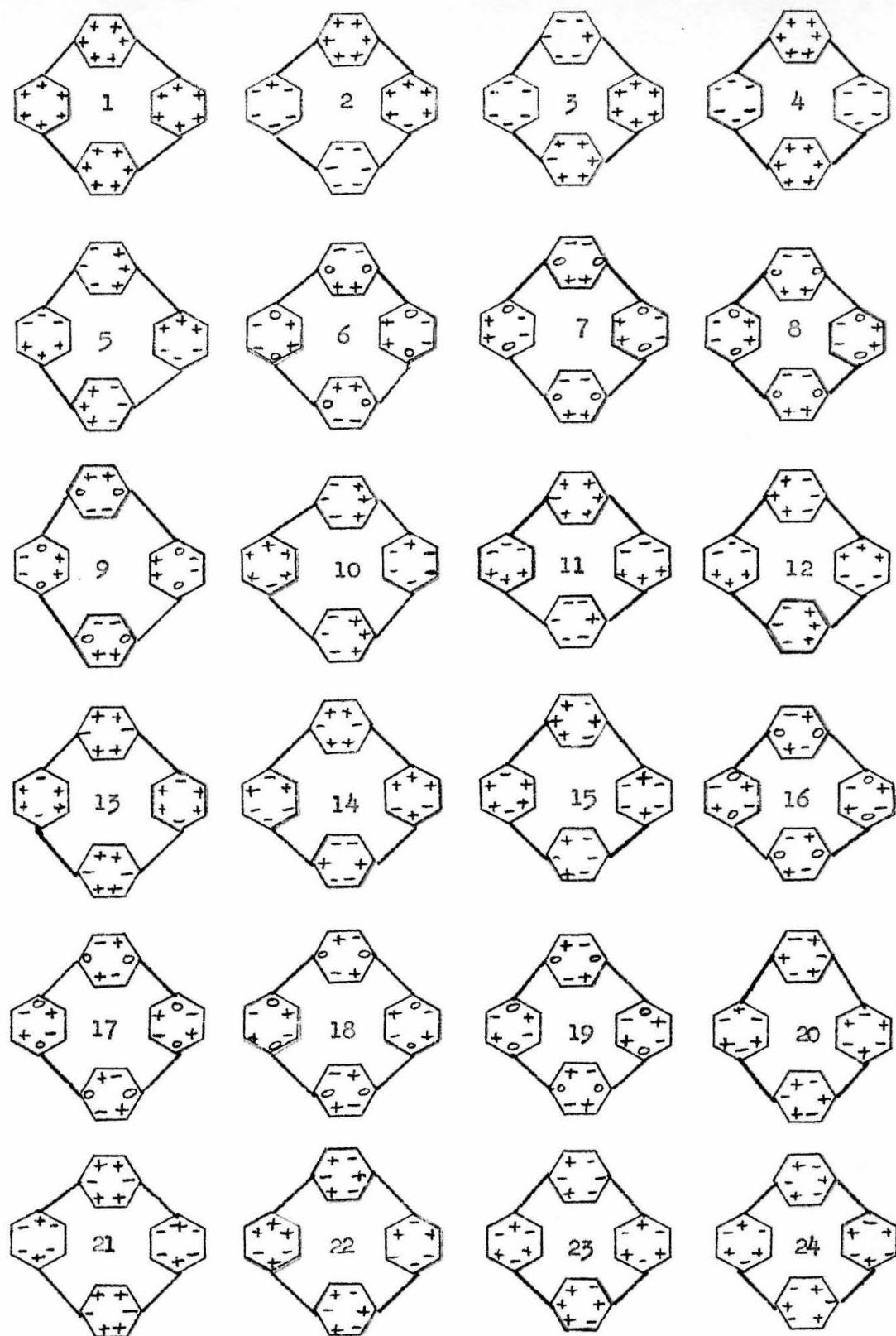
Fig. 5: Molecular Orbitals of Paracycloquaterphenyl

approximation indicate that the macrocyclic structure would probably be significantly constricted relative to the dimensions assumed in Figure 2. Even higher values for the resonance energy of this system would undoubtedly obtain if these calculations were repeated using the bond lengths and charge distributions shown in Figure 4.

This simple approximation predicts that both electrophilic and free radical reagents should attack preferentially at a carbon atom bonded to hydrogen. Further, this molecule should be readily oxidized to the dication (R.E. = 7.369 β), where the electrons removed are those of the lowest antibonding molecular orbital. Similarly, paracyclo-quaterphenyl should function well as the donor component of a donor-acceptor complex.

References

1. D. J. Cram and K. C. Dewhirst, J. Am. Chem. Soc., 81, 5963 (1959).

2. Wagner-Jauregg, Ber., 63, 2662 (1930).

3. O. Diels, K. Alder, and P. Pries, Ber., 62, 2081 (1929).

4. C. A. Coulson, J. Chem. Soc., 1813 (1955).

5. C. A. Coulson and S. Senent, J. Chem. Soc., 1819 (1955).

6. K. C. Dewhirst and D. J. Cram, J. Am. Chem. Soc., 80, 3115 (1958).

7. Private discussions with Dr. G. Wilse Robinson.

8. R. S. Mulliken, J. Phys. Chem., 56, 295 (1952).

9. J. D. Roberts, "Notes on Molecular Orbital Calculations," W. A. Benjamin, Inc., New York, 1961.

10. H. J. Kopineck, Z. Naturforsch., 5-A, 420 (1950).

PROPOSITION II

It has been shown that cyanogen (1) and, more recently, carbonyl cyanide (2), are suitable dienophiles in the Diels-Alder reaction with butadiene, and give rise to heterocyclic products. Inasmuch as there are relatively few ways in which a heteroatom is introduced into a ring system via a Diels-Alder condensation (3), it would be of value to examine the potential usefulness of these reactions as a synthetic tool. In view of this, the following proposals are made:

A. Dienes containing sulfur frequently undergo elimination of hydrogen sulfide under the conditions of the Diels-Alder reaction (4). It may be possible to carry out condensations of this type by introducing the sulfur via the dienophile.* Such a dienophile might be thiocarbonyl cyanide. Possible synthetic routes to this compound are discussed.

B. It is proposed that a general survey be made of the dieno-phile reactivities of cyanogen, carbonyl cyanide, and thiocarbonyl cyanide. In particular, it is proposed that a study be made of the Diels-Alder condensation of these compounds with cyclopentadienes to give the heteronorbornene adducts. The latter should be convenient intermediates for the preparation of a number of heteronorbornyl sys-tems, which should be useful in the study of anchimeric assistance

---

* Since this proposition was originally prepared, Middleton (5) has reported the condensation of thiocarbonyl difluoride with cyclo-pentadiene to give the expected 3,3-difluoro-2-thianorborn-4-ene (2,2-difluoro-[2.2.1]-bicyclo-1-thia-4-heptene).

to solvolysis by non-bonding electrons of heteroatoms. The possible synthesis and theoretical importance of these compounds are discussed.

DISCUSSION

A. The sulfur analogue of carbonyl cyanide, thiocarbonyl cyanide, has not been reported in the literature. The following are presented as possible routes to thiocarbonyl cyanide:

1) This method is directly analogous to that used in the preparation of carbonyl cyanide from 3-ketoglutaric acid (6). The formation of the 3-thioketoglutaric acid is based on a procedure which has

$$\text{HOOCCH}_2\overset{\overset{\text{O}}{\|}}{\text{C}}\text{CH}_2\text{COOH} \xrightarrow[\text{0°}]{\text{dry HCl, H}_2\text{S}} \text{HOOCCH}_2\overset{\overset{\text{S}}{\|}}{\text{C}}\text{CH}_2\text{COOH} \xrightarrow{\text{Na}_2\text{NO}_2}$$

$$\text{HO-N=CHC}\overset{\overset{\text{S}}{\|}}{\text{C}}\text{CH=N-OH} \xrightarrow{\text{Acetic Anhydride}} \text{NC-}\overset{\overset{\text{S}}{\|}}{\text{C}}\text{-CN}$$
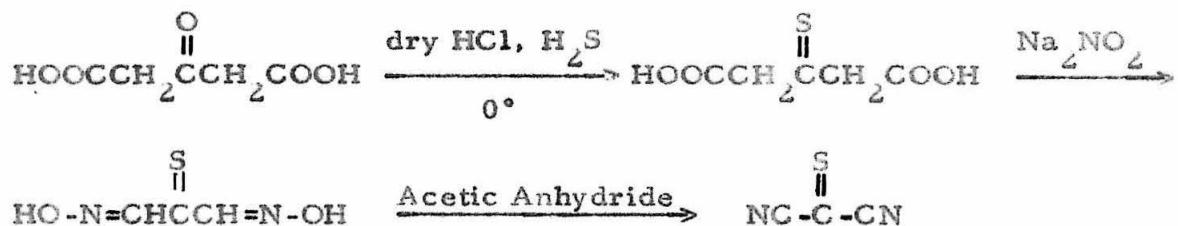
been quite successfully employed in the preparation of several dialkyl, diaryl, and mixed alkyl-aryl thiones (7).

2) This method consists of the low temperature dehydration of 2-thiomesoxalamide by $SOCl_2$ (8), $POCl_3$ (9), or by P_2O_5 (10). These conditions have been shown to be mild enough so as to preserve other

$$\text{C}_2\text{H}_5\text{O}_2\text{C}\overset{\overset{\text{S}}{\|}}{\text{C}}\text{CO}_2\text{C}_2\text{H}_5 \xrightarrow{\text{NH}_4\text{OH}} \text{H}_2\text{NC}\overset{\overset{\text{S}}{\|}}{\text{O}}\text{COONH}_2 \xrightarrow{-2\text{H}_2\text{O}} \text{NC-}\overset{\overset{\text{S}}{\|}}{\text{C}}\text{-CN}$$
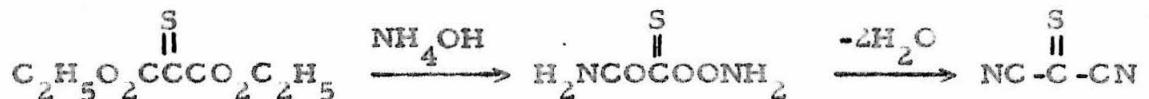
carbonyl functions in the molecule. No work, however, seems to have been done on the dehydration of amides carrying a thiocarbonyl group to give the corresponding nitrile.

3) The possibility that thiocarbonyl cyanide might result from the pyrolysis of thiophosgene with an inorganic cyanide should not be disregarded. Extensive polymerization might well be expected, which may account for the fact that no attempt to produce carbonyl cyanide by pyrolysis has been reported. Homogeneous reaction conditions

$$\underset{\text{Cl-C-Cl}}{\overset{\overset{\text{S}}{\|}}{}} + 2\,M^+CN^- \xrightarrow{\Delta} \underset{\text{NC-C-CN}}{\overset{\overset{\text{S}}{\|}}{}} + 2\,M^+Cl^-$$

might be obtained by using dimethylsulfoxide as the solvent medium.

* * *

B. In view of the recent work done on the solvolyses of various norbornyl systems (11), it would be of considerable interest to study the stereochemistry and kinetics of the solvolyses of several hetero-norbornyl systems, such as those indicated by I → IV. This discussion will be concerned only with compounds of types I and II.
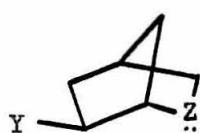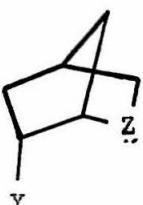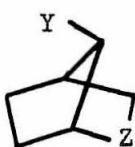

I   II   III   IV

The proposed synthesis of azanorbornylene is shown in Figure 1.
The initial step is the condensation of cyanogen with cyclopentadiene
under conditions similar to those used by Janz and coworkers (1).
This is followed by hydrolysis and decarboxylation at a temperature
low enough not to encourage retrodiene scission (12). The imine is
then selectively reduced with a reagent such as lithium aluminum hydride.

The hydration of azanorbornylene to give the exo-4-substituted
product is based on the expectation that such a system might behave
somewhat like a vinylamine , due to the proximity of the nitrogen atom's
non-bonded electrons to the π-electron system of the double bond.
This type of interaction would then give rise to a resonance form such
as V. It might even be possible to observe such an interaction spectro-
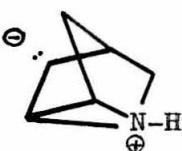
V

scopically. The separate works of Winstein (13) and Roberts (14)
and their coworkers suggest that the exo-product should be strongly
favored if such "homovinylic" character is observed. Although the
stereochemistry given in the last three steps of Figure 1 is based on
that of analogous norbornyl systems (15), the steric requirements of
the heterocyclic compound are undoubtedly quite different; the results
obtained from sterically controlled processes, consequently, may not
parallel those obtained in carbocyclic systems.
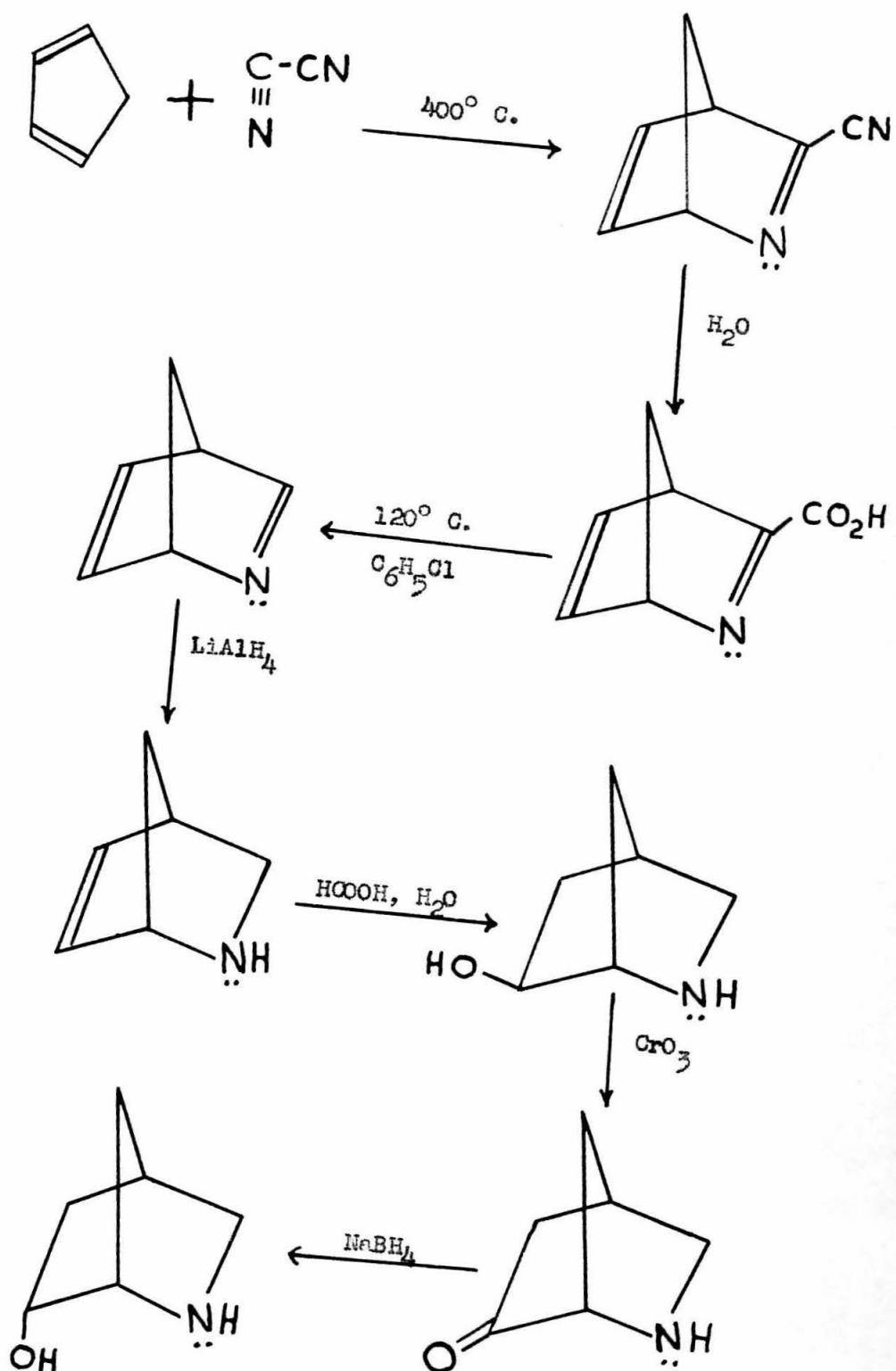
Fig. 1

The proposed syntheses of the oxa- and thianorbornyl derivatives parallel that given for the aza-compounds. The initial condensation with cyclopentadiene could probably be carried out at a much lower temperature in consequence of the greater dienophilic nature expected for the dicyanides. This would be especially important in the reaction with thiocarbonyl cyanide where polymerization and desulfurization processes may be significant. The oxa- and thianorbornylenes may also exhibit some "homovinyl" properties deriving from canonical forms similar to V; this may be particularly significant in the case of the sulfur compound due to the large size of the heteroatom and the possibility of interaction with the vacant d-orbitals. The nature of the addend used in step 5 (Fig. 1) may be chosen from any of several known γ-addition reactions of vinyl amines, ethers, and sulfides (16).

It is expected that a kinetic study of the solvolysis of the exo-4-heteronorbornyl tosylates would reveal a substantial anchimeric rate enhancement similar to that observed in the norbornenyl systems (13, 14; cf. 17). For example, in the oxanorbornyl system (Fig. 4), ionization might be facilitated by the participation of the non-bonded oxygen electrons leading (in the case of total involvement) to the symmetrical oxonium ion. This ion in turn could then suffer attack by a nucleophile at either C-4 or C-5 on the side opposite the oxygen atom to give a racemic product.

"active"   "symmetric"   "racemic"

Fig. 2

Fig. 3

"active"   "symmetric"   "racemic"

"active"   "asymmetric"   "active"
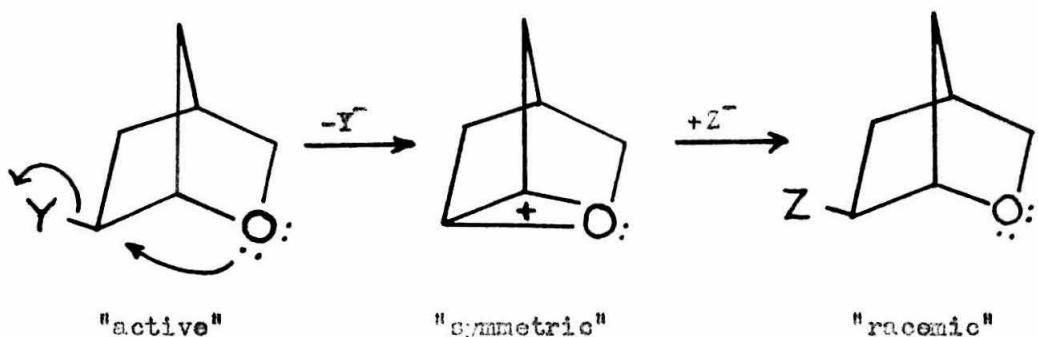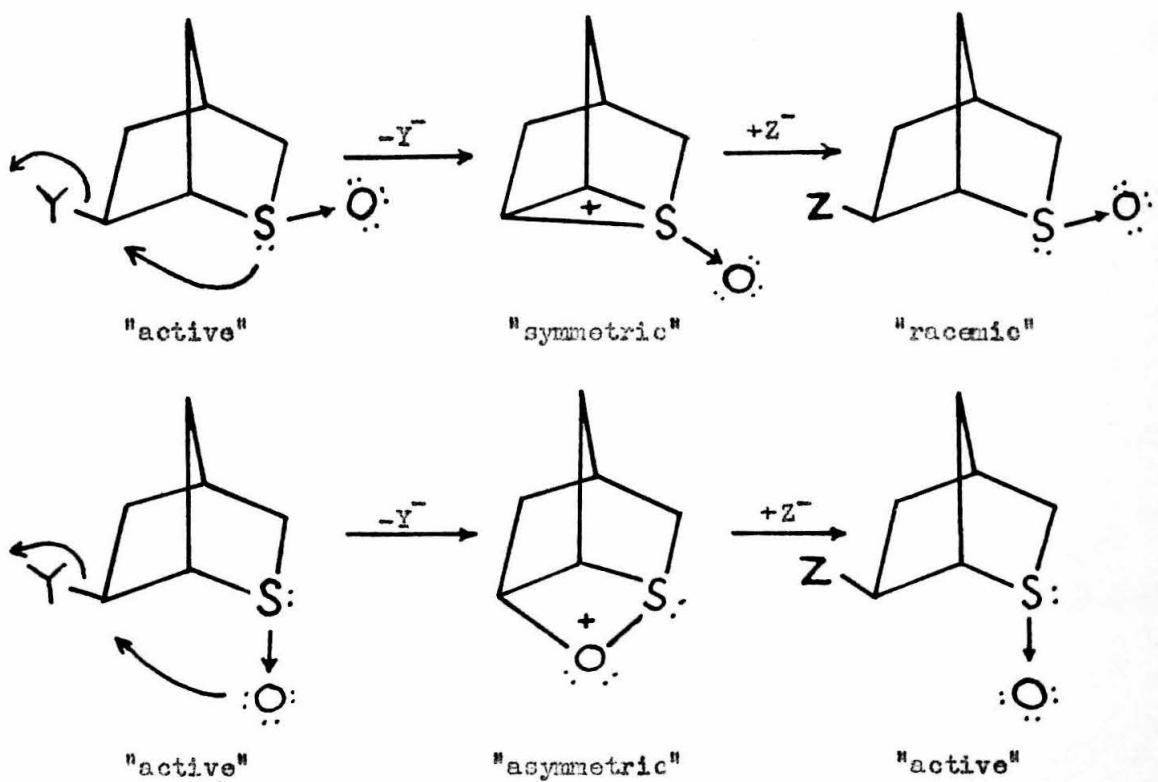
While solvolysis of the corresponding tosylate of thianorbornane is expected to display similar behavior, the endo- and exo-sulfoxides of this compound are anticipated to show rather unique solvolytic features (Fig. 3). The exo-sulfoxide-exo-tosylate, if optically active, should lead to a racemic product if sulfur participation is observed. The corresponding endo-sulfoxide, on the other hand, would very likely participate through the electrons on oxygen to give an asymmetrical intermediate; the products derived would be expected to have retained the original configuration.

References

1. G. J. Janz, et al., Can. J. Res., 25-B, 331 (1947).

2. O. Ackmatowicz and A. Zamojski, Bull. acad. polon. sci., Class III, 5, 927 (1957); Chem. Abstr., 58, 6333d (1958).

3. S. B. Needleman and M. C. Chang Kuo, Chem. Revs., 62, 405 (1962).

4. a) M. C. Kloetzel, Org. Reactions, 4, 1 (1948).

   b) H. L. Holmes, Org. Reactions, 4, 60 (1948).

   c) L. W. Butz and A. W. Rytina, Org. Reactions, 5, 136 (1949).

   d) See also reference 3.

5. W. J. Middleton, J. Am. Chem. Soc., 83, 2590 (1961).

6. a) H. v. Pechmann and K. Wehsarg, Ber., 19, 2465 (1886).

   b) R. Malakowski, et al., Ber., 70-B, 1012 (1937).

7. E. Campaigne and W. B. Reid, Jr., J. Am. Chem. Soc., 68, 769 (1946).

8. H. Goldstein and R. Vogeli, Helv. Chim. Acta, 26, 1125 (1943).

9. D. Price and F. D. Pickel, J. Am. Chem. Soc., 63, 1067 (1941).

10. S. M. McElvain and R. L. Clark, J. Am. Chem. Soc., 69, 2657 (1947).

11. a) S. Winstein and E. Stafford, J. Am. Chem. Soc., 79, 505 (1957).

    b) S. Winstein, et al., J. Am. Chem. Soc., 74, 1127 (1952).

12. S. Hoogewerff and W. A. van Dorp, Rec. trav. chim., $\underline{1}$, 121 (1882).

13. S. Winstein and D. S. Trifan, J. Am. Chem. Soc., $\underline{71}$, 2953 (1949); idem., $\underline{74}$, 1154 (1952).

14. J. D. Roberts and C. C. Lee, J. Am. Chem. Soc., $\underline{73}$, 5009 (1951).

15. D. C. Kleinfelter and P. von R. Schleyer, Org. Syns., $\underline{42}$, 79 (1962); see references cited therein.

16. a) J. R. Alexander and H. McCombie, J. Chem. Soc., 1913 (1931).

    b) M. F. Shostakovski and N. A. Gerstein, Zhur. Obshch. Khim., $\underline{16}$, 937 (1946).

    c) M. G. Voronkov, Zhur. Obshch. Khim., $\underline{19}$, 293 (1949).

17. a) J. C. Martin and P. D. Bartlett, J. Am. Chem. Soc., $\underline{79}$, 2533 (1957).

    b) E. E. van Tamelen and C. I. Judd, J. Am. Chem. Soc., $\underline{80}$, 6305 (1958).

    c) See also: C. H. DePuy, et al., J. Am. Chem. Soc., $\underline{83}$, 1668 (1961).

PROPOSITION III

Xylindein is a brilliant green pigment isolated originally in 1813 by Döbereiner (1) from the wood infecting fungus Chlorociboria aeruginosa. Todd and coworkers (2) have recently proposed for this pigment a dimeric isocoumarin-quinone structure (XIII). A total synthesis of this compound is proposed.

DISCUSSION

Xylindein (XIII) is a nearly planar polycyclic molecule with a perpendicular plane of symmetry. Consequently, its synthesis poses no problem of stereochemistry. Although reasonably stable toward mild oxidation in acid media, it deteriorates readily in basic solution under the influence of oxidants (3).

A reasonable approach to the synthesis of xylindein would appear to be one which takes advantage of the molecule's symmetry features. Two pathways can be envisioned: 1) construction of the A-B-C fragment, followed by oxidative dimerization, or 2) building symmetrically from a residue which will contain the center of symmetry. The chief problem of using the first method would probably be the dimerization step. The polyfunctionality of the A-B-C moiety and the similarity between the groups along the upper and lower peripheries of this fragment suggest that it would be quite difficult to control the orientation during the coupling process. The second method, which was chosen for the scheme

outlined in this proposal, suffers from the fact that yields will be less than ideal, simply because a given reaction must occur twice within the same molecule for the product to be of value.

Diphenoquinone (II) is used to provide the backbone for xylindein. This is condensed (4) with any of a variety of 1,4-dialkoxy- or 1,4-dicarboalkoxy-1,3-butadienes (I) to give a mixture of tetracyclic Diels-Alder adducts including III, which would be readily distinguished by its ultraviolet spectrum. Possibly III may aromatize under the reaction conditions (4,5) to give IV. Either III or IV should be readily oxidizable to V with a variety of mild reagents (6). Since rotation around the interannular biphenyl bond is not entirely free, V should have the same configuration as III. Acid cleavage of the ether bonds of rings B and B' accompanied by gentle oxidation (7) should close the D and D' rings to give 3,9-dihydroxy-4,10-xanthenoxanthenone, VI. This type of reaction has considerable precedence in the chemistry of the chromones (8), and is related to the customary method of preparing xanthenoxanthenes by oxidative coupling of β-dinaphthols (9).

At this point the basic chromophore of xylindein has been completed, and the success of the synthesis may be conveniently checked by comparing the ultraviolet and visible spectra of VI with those of the natural pigment.

The reaction of VI, preferably under neutral conditions, with 2-bromomethyl-1-pentene* would give the allylic ether, VII. The

---

* Prepared by allylic bromination of 2-methyl-1-pentene (10).
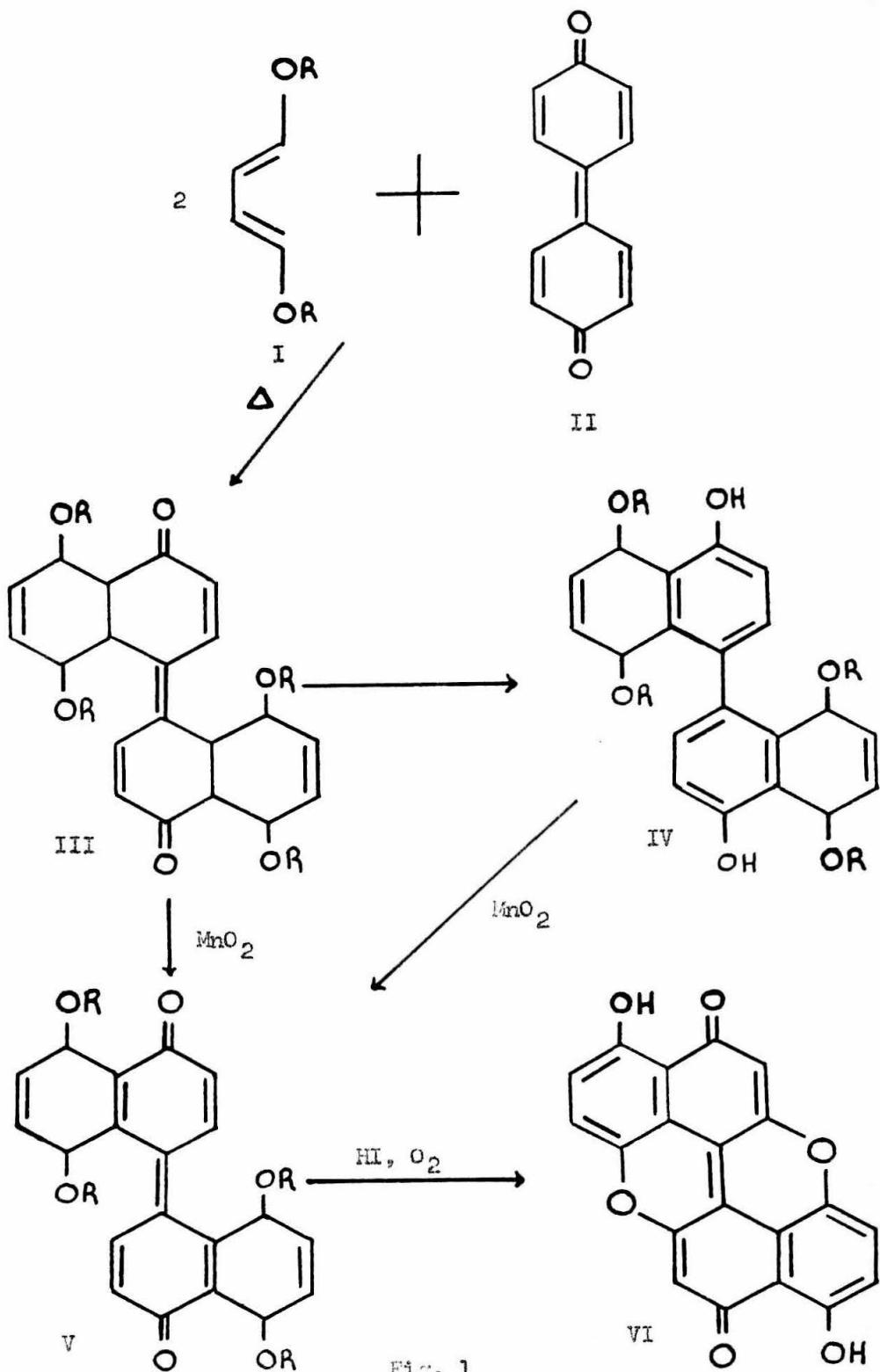
FIG. 1

3,9-dihydroxy-
4,10-xanthenoxanthenone

Xylindein
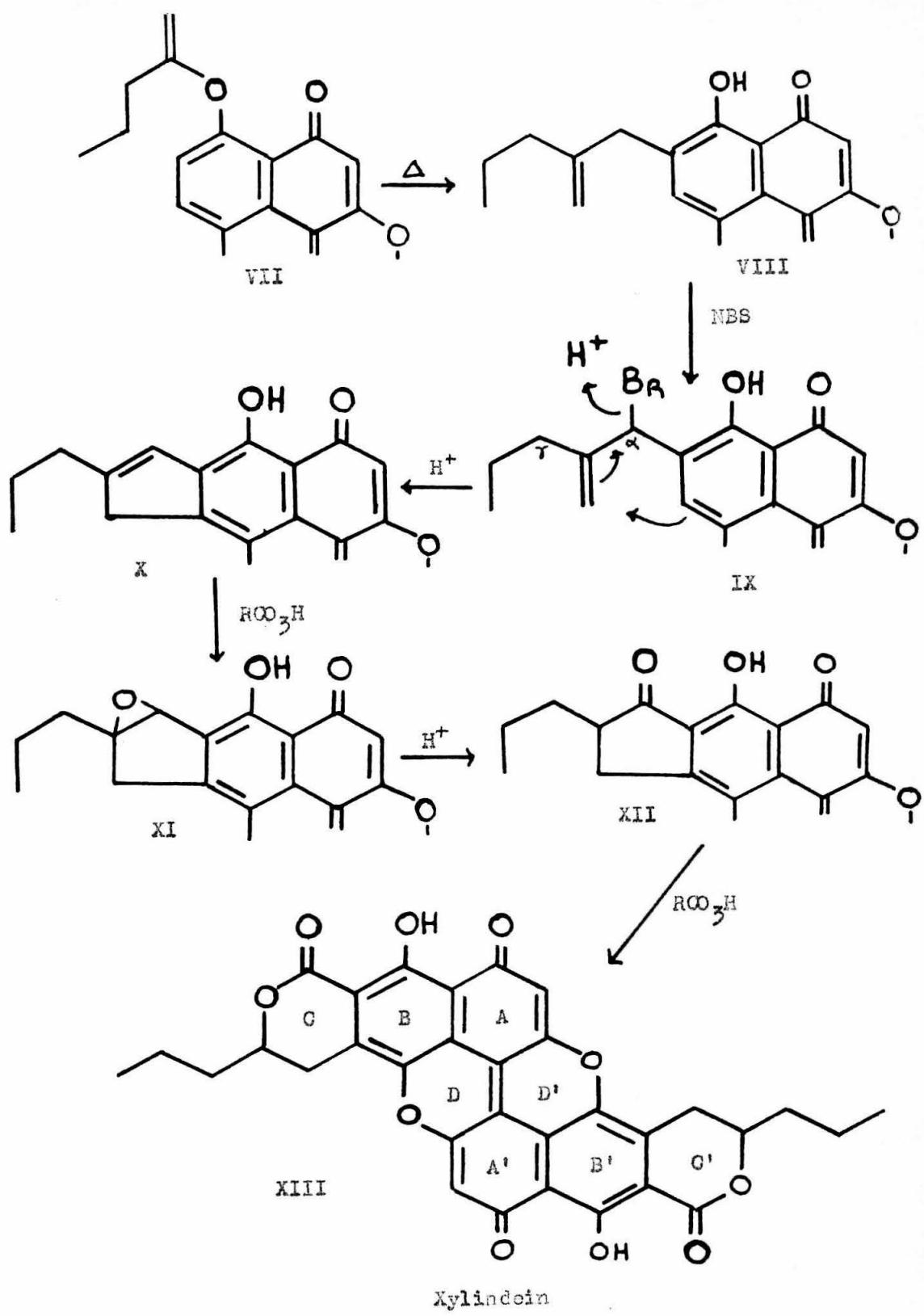
Fig. 2

Claison rearrangement (11) of VII in the absence of oxygen is expected to give VIII. The benzylic carbon of VIII being doubly activated should undergo the Wohl-Ziegler bromination reaction (10) quite smoothly to give the α-bromide, IX, in preference to the γ-isomer. This bromide (IX) should be extremely reactive, and in the presence of acid would most certainly undergo displacement to give X. In fact, the presence of the neighboring phenol might be sufficient to prevent the isolation of IX. In order to discourage side reactions during the Wohl-Ziegler step and latter stages of the sequence, the dimethyl ether or the diacetate of VIII could be employed to advantage.

Epoxidation of X (or the diacetate) under neutral conditions with a peracid (12) or with N-bromoacetamide (13) would give XI (or the di- acetate), leaving the rest of the system untouched. Rearrangement of the epoxide (XI) with dilute acid (14) is expected to give the cyclopen- tanone, XII, since alkyl migration is less facile than hydrogen migration (14a).

The final step of this synthesis is the enlargement of the fused cyclopentanone ring (XII) to the isocoumarone structure (rings C and C') of xylindein (XIII) by a Baeyer-Villiger oxidation. Studies of the oxidation of mixed aryl-alkyl ketones indicate that alkyl cleavage is preferred (15). This reaction may also be carried out using a peracid (16) or an N- haloimide (13). Again, during this reaction it may be necessary to protect the phenol groups.

References

1. E. Döbereiner, Schweiggers Journal, 9, 160 (1813); see reference 2 below.

2. G. M. Blackburn, A. H. Nielson, and Lord Todd, Proc. Chem. Soc., 327 (1962).

3. a) C. Liebermann, Ber., 7, 1102 (1874).

   b) F. Kögl and G. von Taeuffenbach, Ann., 445, 170 (1925).

   c) F. Kögl and H. Erxleben, Ann., 484, 65 (1930).

4. L. W. Butz and A. W. Rytina, Org. Reacs., 5, 136 (1949).

5. E. Clar, "Aromatische Kohlenwasserstoffe, Polycyclische Systeme," Springer-Verlag, Berlin, pp. 79ff., 1941.

6. a) T. Posternak, et al., Helv. Chim. Acta, 31, 525 (1948).

   b) H. J. Teuber and W. Rau, Ber., 86, 1036 (1953).

   c) A. G. Brook, J. Chem. Soc., 5040 (1952).

   d) R. Kuhn and I. Hammer, Ber., 83, 413 (1950).

7. a) K. T. Zilch, Microfilms Abstr., 9, No. 3, 45 (1950).

   b) H. E. Ungenade and K. T. Zilch, J. Org. Chem., 15, 1108 (1950).

   c) H. E. Ungenade and K. T. Zilch, J. Org. Chem., 16, 64 (1951).

8. S. M. Sethna and N. M. Shah, Chem. Revs., 36, 1 (1945).

9.   a) R. Pummerer, et al., Ann., **553**, 103 (1942).

      b) W. Brackman and E. Havinga, Rec. trav. chim., **74**, 1021 (1955).

      c) I. S. Travkin, Org. Chem. Ind. (USSR), **2**, 221 (1936);

      Chem. Abstr., **31**, 1021[2] (1937).

      d) A. Rieche and W. Rudolph, Ber., **73-B**, 335 (1940).

10.   C. Dejarassi, Chem. Revs., **43**, 271 (1948).

11.   a) D. S. Tarbell, Chem. Revs., **27**, 495 (1940).

      b) D. S. Tarbell, Org. Reacs., **2**, 1 (1944).

12.   D. Swern, Org. Reacs., **7**, 378 (1953).

13.   R. Filler, Chem. Revs., **63**, 21 (1963).

14.   a) S. Winstein and R. B. Henderson, "Heterocyclic Compounds,"

      R. C. Elderfield (ed.), Vol. I, p. 1, John Wiley & Sons, Inc.,

      New York, 1950.

      b) A. D. Cross, Quart. Revs., **14**, 317 (1960).

15.   S. L. Friess and N. Farnham, J. Am. Chem. Soc., **72**,

      5518 (1950).

16.   C. H. Hassall, Org. Reacs., **9**, 73 (1957).

PROPOSITION IV

Ruzicka and coworkers (1) in 1955 suggested two mechanisms for the conversion of squalene to lanosterol. Only one of these mechanisms is consistent with data obtained from subsequent carbon-14 labeling experiments (2). Another mechanism, consistent with the Ruzicka theory of terpenoid cyclization, is proposed together with a chemical method of differentiating between the two possibilities.

DISCUSSION

Heilbron and coworkers (3) as early as 1926 indicated that there might be a relationship between the sterols and the acyclic triterpene, squalene, but it was not until 1932 that any attempt was made to detail this relationship. At this time Sir Robert Robinson (4) showed how cholesterol might be derived from a particular folding of squalene, followed by the loss of three methyl groups. By examining the radiocarbon distribution in cholesterol derived from labeled acetate, R. B. Woodward and K. Bloch at Harvard (5) and W. G. Dauben and coworkers at Berkeley (6) were able to infer that lanosterol, whose structure had been recently determined (7), might be an intermediate product in the conversion of squalene to cholesterol. The first experimental proof that this was indeed the case came four years later (8).

In the meantime, a detailed theory of the cyclization process was put forth by L. Ruzicka's E. T. H. group at Zürich. This theory, which was a modernization of the biogenetic isoprene rule proposed earlier by Ruzicka, has been considered in some detail in Part I of this thesis. It was pointed out that up to the present, the greatest test of the Ruzicka theory has been its ability to adequately explain the conversion of squalene to lanosterol.

At the inception of this theory, its proponents recognized that lanosterol, the first isolable tetracyclic precursor of cholesterol, could arise in either of two ways from squalene: one way involved two 1,2-methyl shifts, while the other required a single 1,3-methyl shift. In order to differentiate between the two possibilities, an American group under the direction of Bloch (2a) and an English group directed by J. W. Cornforth (2c), working independently, devised carbon-14 labeling experiments which indicated conclusively that two 1,2-methyl shifts were involved, and hence, that ring B evolves from a boat folding of that section of the squalene chain.* This substantiated the earlier belief of Ruzicka. His mechanism, shown in Figure 1, also involves a pair of 1,2-hydride transfers. This scheme requires that the all-trans form of squalene be the substrate in the reaction, and indeed, it has been shown (2a) that all-trans squalene, the major isomeric constituent of natural squalene, can be converted to cholesterol.

* See reference 2a for proof that ring A derives from a chair-folded segment of the chain.
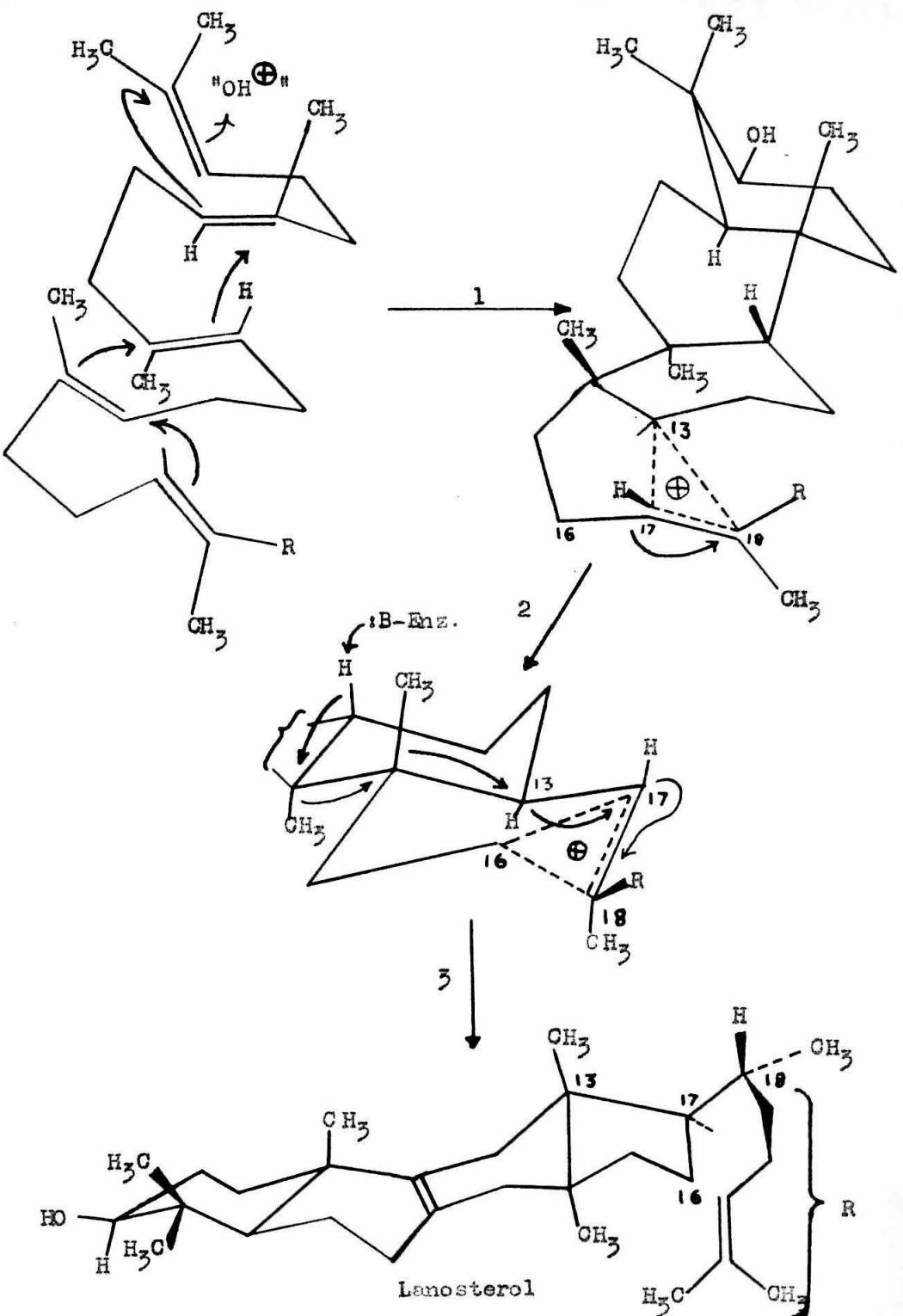
Fig. 1

However, another concerted mechanism can be written involving a 1,3-hydride transfer, which is in some ways simpler than the mechanism of Figure 1. This mechanism, which is shown in Figure 2, differs from the former one in the manner in which the hydrocarbon chain is originally folded (a function specifically reserved for the enzyme). As seen in Figure 2, this process demands that the original conformation of the squalene chain be chair-boat-chair-chair-linear, while that of Figure 1 requires the conformation to be chair-boat-chair-boat-linear.

The principal difference between these two mechanisms is the means by which the stereochemistry at the asymmetric center C-17 (of squalene) is achieved. In Figure 1, a 1,2-alkyl shift is proposed in which C-16 is transferred from C-17 to C-18 (step 2); this process develops the proper relative configurations at C-13, C-17, and C-18 for the pair of concerted 1,2-hydride shifts which follow (step 3) and which result in inversion at C-17. The mechanism proposed in Figure 2 achieves this result more directly. The proper stereochemistry at C-17 is potentially produced by allowing that initially the part of the squalene chain which is to become ring D be folded in the chair conformation. The desired configuration at C-17 results when the bond between C-13 and C-17 matures. The final stage of the concerted process (step 2) achieves the necessary steric results by the same pair of 1,2-methyl shifts together with a single 1,3-hydride migration. In
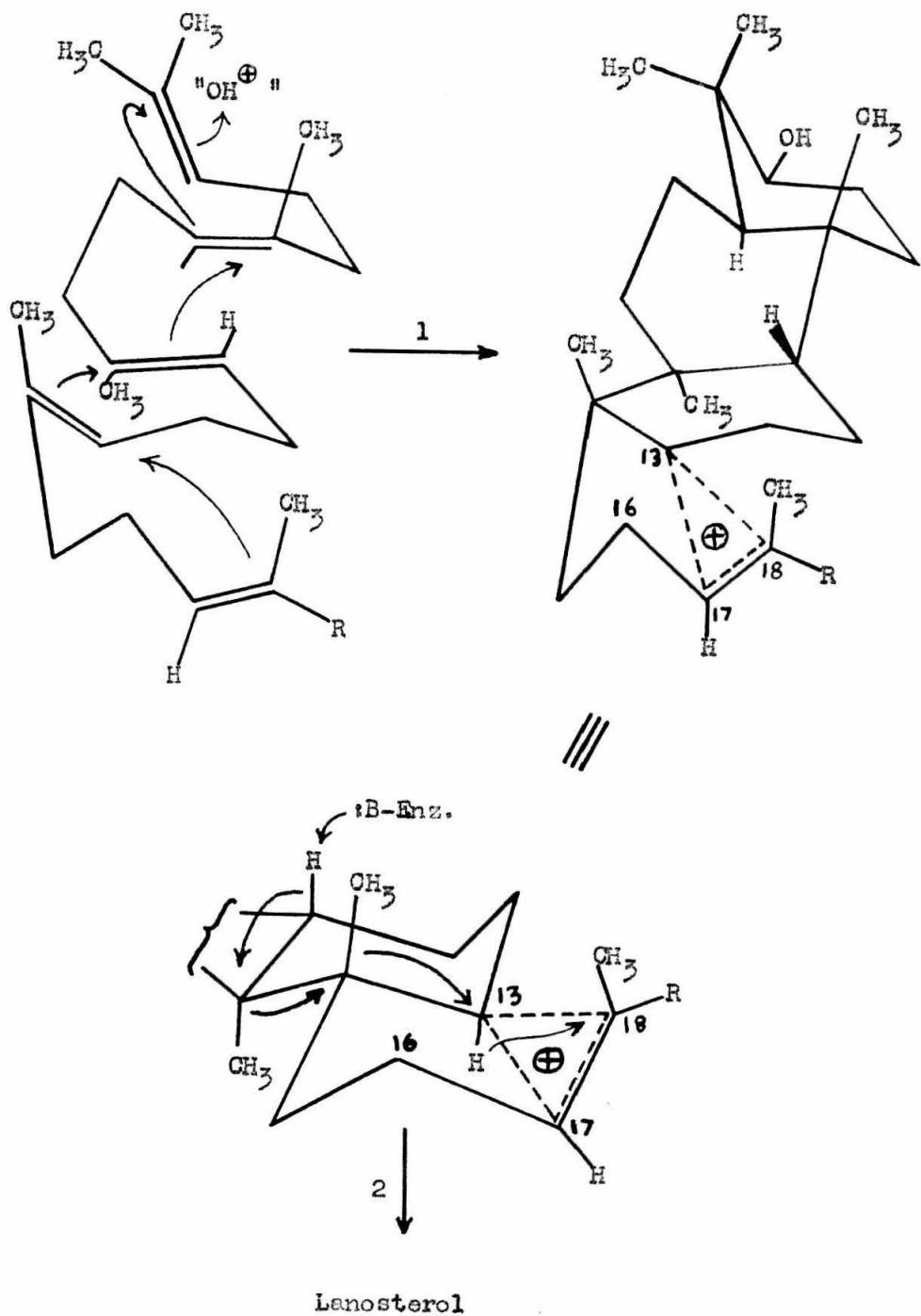
Fig. 2

Figure 1 the energy necessary to bring about the 1,2-alkyl migration of step 2 could result, at least in part, from the relief in strain associated with the conformational reorganization which occurs in ring D (i.e. in going from boat to chair (9)). The scheme presented in Figure 2, however, obviates the need for both the conformational reorganization and the 1,2-alkyl migration. It is a propos to note here that although 1,3-methyl shifts are virtually unknown processes in organic chemistry, several examples of 1,3-hydride transfers are known (10), while multiple 1,2-hydride shifts of the type required by the mechanism of Figure 1 have not been established.

It is proposed, therefore, that an appropriately deuterated (or tritiated) form of squalene could be employed to distinguish between the two types of hydride migration (Fig. 3). The position of tritium in the product could be determined by established degradative procedures (11) using the technique of isotopic dilution. A more attractive means of locating the isotope could be based on a procedure reported by Jones and coworkers (12). This is a method of characterizing the side chains of steroids which involves the pyrolytic fission of the bond between C-17 and C-20 (steroid numbering). Here the volatile fragment could be purified by gas chromatography and subjected to isotope analysis. Other methods of locating the isotopic atom which might supplant the tedious degradative approach are low voltage (10-15 v.) mass spectroscopy (13), nuclear magnetic resonance spectroscopy (14), and differential infrared spectroscopy (15).

Fig. 3
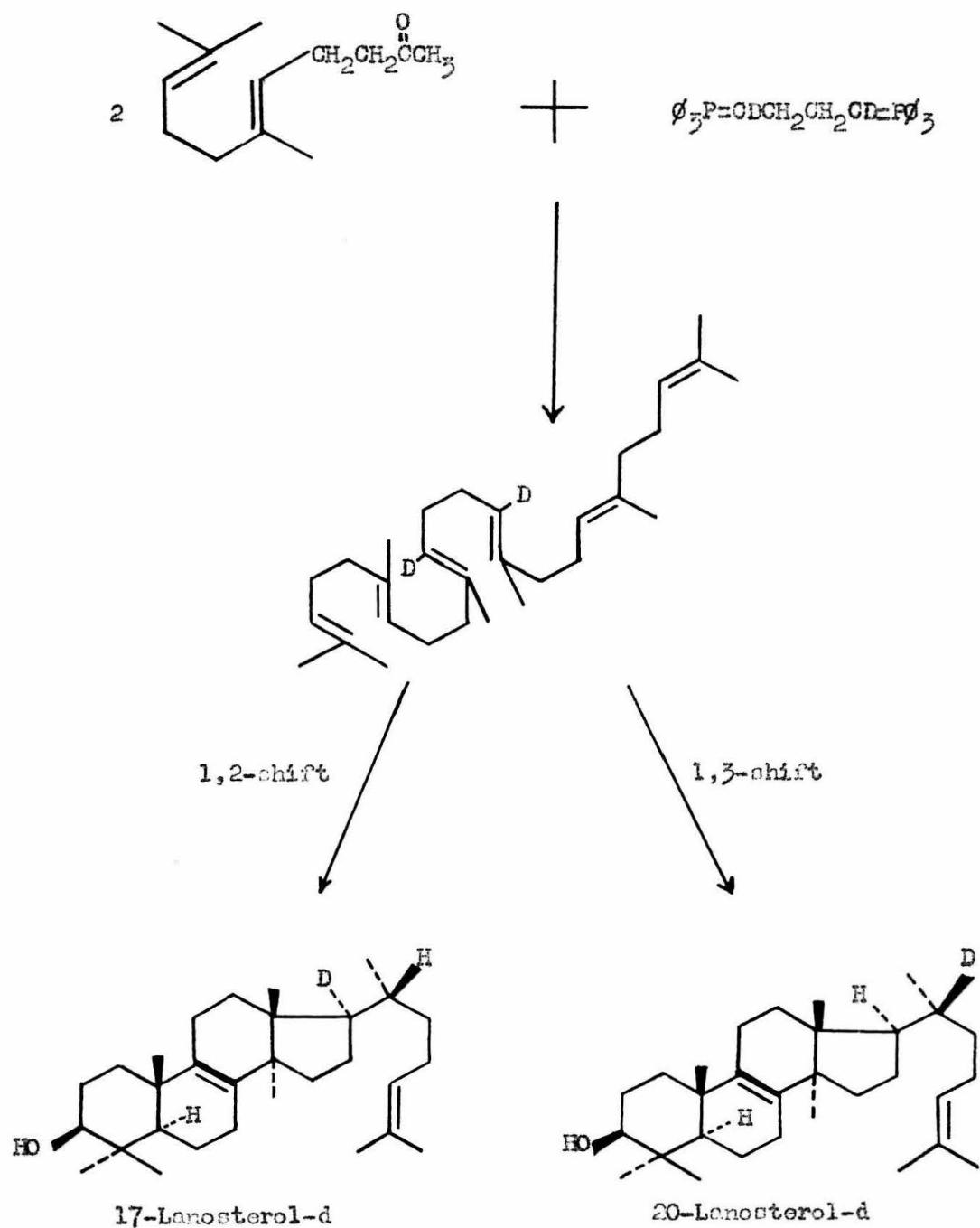
The particular deuterium substituted squalene proposed for this experiment is the all-trans 11, 14-dideuterosqualene. The choice of this compound rests on the following considerations: 1) Squalene is symmetrical with respect to the bond joining C-12 and C-13, hence cyclization will proceed with equal probability from either end of the chain. 2) Cyclization of this dideuterosqualene is expected to lead to a homogeneous monodeuterated lanosterol, if one of the mechanisms presented above predominates (providing no randomization of deuterium occurs; such a product would be far more tractable to the methods of analysis prescribed above than would an isomeric mixture. 3) Synthetic routes to the symmetrically substituted squalene are more direct, and hence would probably give higher yields. 4) Routes to an alternatively labeled 6, 17-dideuterosqualene seem to be more complicated and result in isomeric mixtures and/or more highly deuterated hydrocarbons. In addition, 6, 17-dideuterosqualene would be expected to retain both deuterium atoms, making it inevitably more difficult to analyse the cyclic product by spectroscopic methods.

The method proposed here for the preparation of 11, 14-dideuterosqualene is based on a known procedure for obtaining synthetic all-trans squalene (16) and is outlined in Figure 3. The Wittig reagent used in this reaction is to be prepared from 1, 4-dibromo-1, 1, 4, 4-tetradeuterobutane. Some of the possible preparative schemes for this labeled material are suggested below.

A. Kolbe electrolysis (17) of 3-bromo-3,3-dideuteropropanoic acid:

$$\text{BrCD}_2\text{CH}_2\text{COO}^- \text{Na}^+ \xrightarrow{\text{Kolbe Electrolysis}} \text{BrCD}_2\text{CH}_2\text{CH}_2\text{CD}_2\text{Br}$$
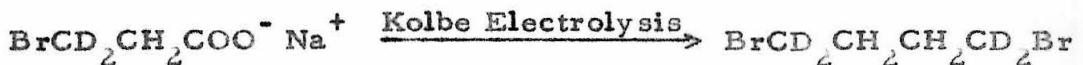
The appropriate propanoic acid could be prepared from bromodideutero-acetic acid (commercially available) by means of the Arndt-Eistert synthesis (18), or from 3,3,3-trideuteropropanoic acid (19) by bromination (20), dehydrobromination, followed by reverse hydrobromination (21).

B. Reduction of dimethyl succinate with commercially available lithium aluminum deuteride, followed by bromination, should also give the desired product:

$$\text{CH}_3\text{O}_2\text{CCH}_2\text{CO}_2\text{CH}_3 \xrightarrow{\text{LiAlD}_4} \text{HOCD}_2\text{CH}_2\text{CH}_2\text{CD}_2\text{OH} \xrightarrow{\text{HBr}} \text{BrCD}_2\text{CH}_2\text{CH}_2\text{CD}_2\text{Br}$$
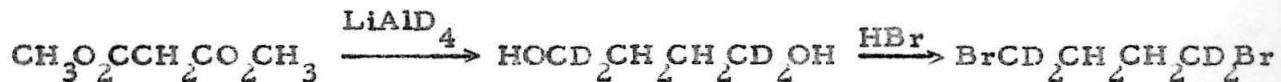
References

1. A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni,
   Helv. Chim. Acta, 38, 1890 (1955).

2. a) R. K. Maudgdal, T. T. Tchen, and K. Bloch, J. Am. Chem.
   Soc., 80, 2589 (1958).

   b) J. W. Cornforth, et al., Tetrahedron, 5, 311 (1959).

   c) J. W. Cornforth, et al., Proc. Chem. Soc., 112 (1958).

3. I. M. Heilbron, E. D. Kamm, and W. M. Owens, J. Chem. Soc.,
   1630 (1926).

4. R. Robinson, J. Soc. Chem. Ind., 51, 464 (1932).

5. R. B. Woodward and K. Bloch, J. Am. Chem. Soc., 75,
   2023 (1953).

6. W. G. Dauben, et al., J. Am. Chem. Soc., 75, 3038 (1953).

7. L. F. Fieser and M. Fieser, "Steroids," Rheinhold Publishing
   Corp., New York, pp. 403-420, 1959; see references cited
   therein.

8. T. T. Tchen and K. Bloch, J. Biol. Chem., 226, 921 (1957).

9. a) J. S. E. Holker, et al., J. Chem. Soc., 2987 (1958).

   b) R. M. Carmen, G. Hassen, and R. B. Johns, J. Chem.
   Soc., 130 (1959).

   c) A. D. Cross, Quart. Revs., 14, 317 (1960).

10. J. D. Roberts, et al., J. Am. Chem. Soc., 76, 4501 (1954).

11. L. F. Fieser and M. Fieser, "Steroids," loc. cit., pp. 364-378; see references cited therein.

12. J. S. G. Cox, L. B. High, and E. R. H. Jones, Proc. Chem. Soc., 234 (1958).

13. a) P. de Mayo and R. I. Reed, Chem. Ind., 1481 (1956).

    b) S. S. Friedland, et al., Anal. Chem., 31, 169 (1959).

14. J. N. Shoolery and M. T. Rogers, J. Am. Chem. Soc., 80, 5121 (1958).

15. E. A. Braude and F. C. Nachod (eds.), "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, p. 195 (1955).

16. D. W. Dicker and M. C. Whiting, Chem. and Ind., 351 (1956).

17. a) Papers by H. Kolbe, "The Electrolysis of Organic Compounds," re-issue edition, E. and S. Livingstone, Ltd., London, 1949.

    b) C. L. Wilson and W. J. Lippincott, J. Am. Chem. Soc., 78, 4290 (1956).

    c) G. Swain, et al., Org. Syn., 21, 48 (1941).

    d) P. Karrer, et al., Helv. Chim. Acta, 15, 1218 (1932).

18. a) F. Arndt, B. Eistert, and J. Amende, Ber., 61, 1949 (1928).

    b) R. Adams (ed.), "Organic Reactions," Vol. I, John Wiley & Sons, Inc., p. 38 (1942).

19. a) P. Hölemann and K. Clusius, Ber., <u>70</u>, 819 (1937).

     b) B. Nolin, Can. J. Chem., <u>31</u>, 1257 (1953).

20. E. C. Horning (ed.), "Organic Syntheses," Coll. Vol. III,

     John Wiley & Sons, Inc., p. 343 (1955).

21. E. Kowski, Ann., <u>342</u>, 127 (1905).

22. J. W. Cornforth, <u>et al.</u>, Biochem. J., <u>66</u>, 10p (1957).

PROPOSITION V

It is proposed that the solvolysis and acid-catalyzed reactions of certain <u>cis</u>- and <u>trans</u>-Δ^4-hexenylmethylcarbinyl derivatives would be of value in interpreting the mechanism of cyclization of 1,5-dienes.

DISCUSSION

The cyclization of <u>cis, cis</u>- and <u>trans, trans</u>-2,6-octadiene in acid medium gave rise to only those two isomers of 2,3-dimethyl-cyclohexanol in which the methyl groups were <u>trans</u> to one another (1). This was interpreted as implying that the initial protonation of the diene gave rise to a non-classical species such as a π-complex (2) as opposed to the classical secondary ion.

The <u>trans</u> or diequatorial dispostion of the methyl groups in the products of these reactions is the thermodynamically favored geometry for this system. For this reason the observed products may also be consistent with some equilibrium process in which stereochemical integrity was lost. It would be of considerable interest, then, to know the course of the subsequent cyclization reaction if indeed a classical carbonium ion were produced instead of the presumed π-complex. The desired ionic intermediates might be prepared in a number of ways. Examples are the deamination (3) of Δ^4-hexenylmethylcarbinylamine

with nitrous acid and the treatment of Δ^4-hexenylmethylcarbinol with strong acid.

Another question of interest concerns the degree to which the double bond may participate in the cationic processes occurring at C-2. Indeed, anchimeric assistance to solvolysis of several cyclic 1, Δ^5-alkenyl sulfonate esters (4) has been reported in which ring formation was observed. In acyclic molecules, however, this process may well be less facile due to the greater entropy requirements imposed by the highly flexible chain. A study of the solvolyses of Δ^4-hexenylmethyl-carbinyl bromide, sulfonate esters, or the mercurichloride versus the saturated analogue would shed light on this important question.

Possible synthetic routes to the required cis- and trans-Δ^4-hexenylmethylcarbinyl derivatives are shown in Figures 1-3. In Figure 1 the starting material could be either the cis, cis- or the trans, trans-diene. The disadvantage of this scheme is that the isomerization or reductive cleavage of the epoxide should lead to approximately equal quantities of the readily distinguishable C-2 and C-3 isomers. Figure 2 presents a method which should lead primarily to the trans-alcohol via a selective dehydrobromination (5) of 1,5-dibromohexane. A method of obtaining the corresponding cis-alcohol is outlined in Figure 3. The last two synthetic schemes utilize commercially available starting materials.
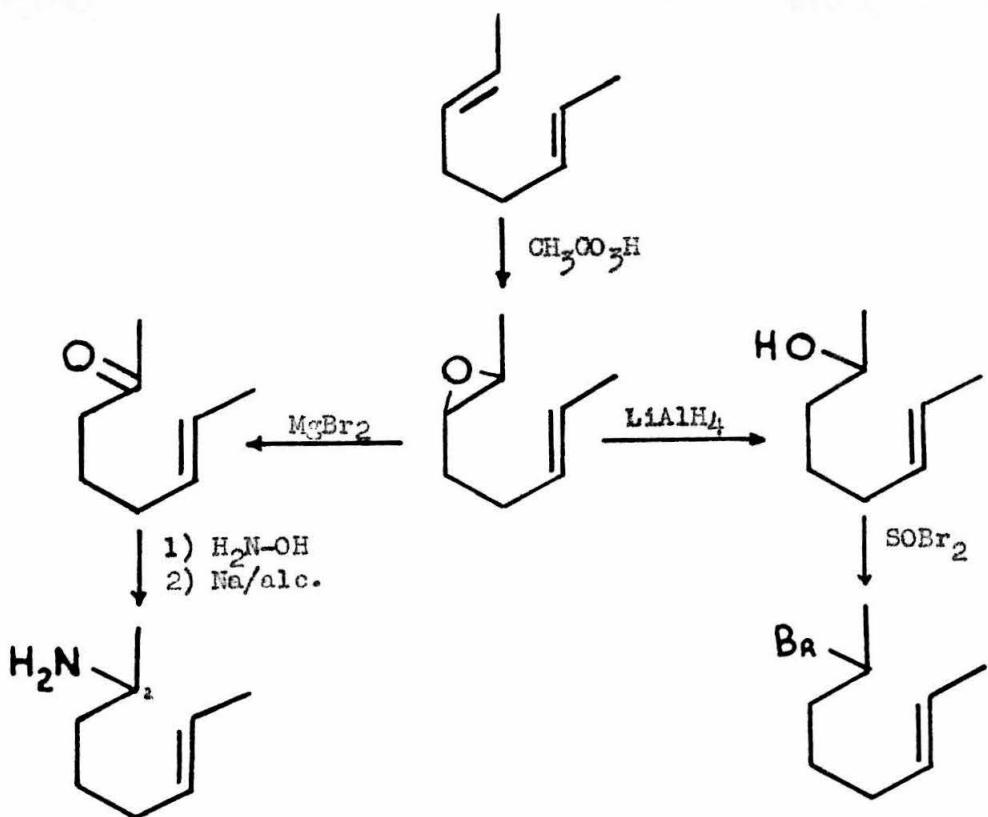
Fig. 1

Fig. 2
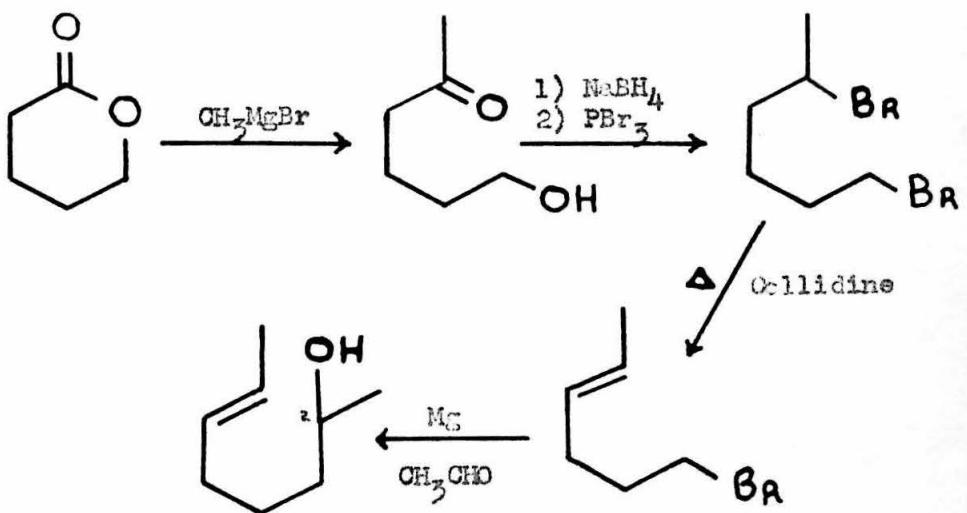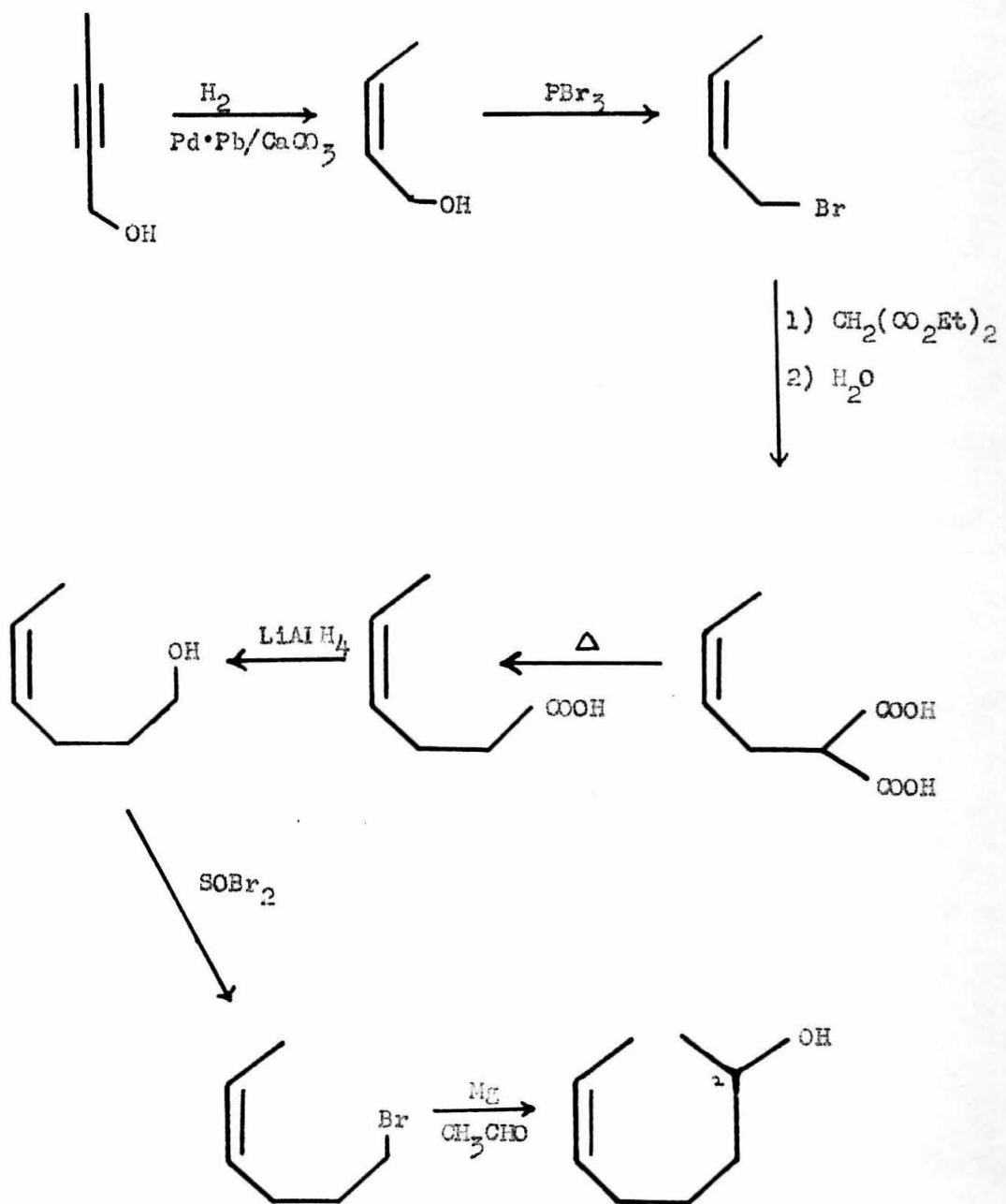
Fig. 3

References

1. See Part III of this thesis.

2. E. L. Purlee and R. W. Taft, J. Am. Chem. Soc., 78, 5807 (1956).

3. a) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, J. Am. Chem. Soc., 76, 4420 (1954).

   b) A. Streitwieser, Jr., J. Org. Chem., 22, 861 (1957).

4. a) R. G. Lawton, J. Am. Chem. Soc., 83, 2399 (1961).

   b) P. D. Bartlett and S. Bank, J. Am. Chem. Soc., 83, 2591 (1961).

   c) S. Winstein and P. Carter, J. Am. Chem. Soc., 83, 4485 (1961).

5. L. Williman and H. Schinz, Helv. Chim. Acta, 35, 2401 (1952).