PART I

MECHANISM OF THE THERMAL ISOMERIZATION OF

2-NORBORNENE-5,6-endo-DICARBOXYLIC ANHYDRIDE

PART II

THE ALDOKETENE DIMER REARRANGEMENT

Thesis by

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To My Wife Anne

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ABSTRACT

PART I

The Diels-Alder adduct of cyclopentadiene and maleic anhydride,
2-norbornene-5,6-endo-dicarboxylic anhydride, may be rearranged
thermally to its exo-isomer. This isomerization is known to occur in
part through an internal mechanistic pathway. In order to study the
mechanism of this rearrangement, an attempt was made to synthesize
2-norbornene-5,6-endo-dicarboxylic anhydride stereospecifically
labeled with carbon-14 in one carboxyl group, rearrange this material
under conditions favoring the internal pathway, and degrade the exo-
anhydride in a stereospecific fashion, measuring the carbon-14
activities of each carbonyl group separately.

Three synthetic approaches to the stereospecifically labeled
endo-anhydride, through the intermediates ethyl cis-β-cyanoacrylate,
(-)-menthyl hydrogen maleate, and (-)-menthoxymalealdehydic acid,
have not been successful. Rearrangement of the endo-anhydride in
the presence of tetracyanoethylene gave exo-anhydride from the internal
mechanism and 2,2,3,3-tetracyanonorborn-5-ene from the external
process. Degradation of 2-norbornene-5,6-exo-dicarboxylic anhydride
by hydrogenation and reaction with (-)-menthol gave two diasteromeric
(-)-menthyl hydrogen 2,3-exo-norbornanedicarboxylates, whose absolute
configurations were established by degradation of one to an optically
active 2-exo-norbornanecarboxylic acid.

2,3-<u>Endo</u>-norbornanedicarboxylic anhydride was rearranged

to its <u>exo</u>-isomer when heated to 250° for 18 hours.

PART II

The neutral phenylketene dimer has been synthesized, identified

as 3-hydroxy-2,4-diphenyl-3-butenoic lactone, reduced to α, γ-

diphenylbutyric acid, and rearranged with base to an acidic isomer,

tentatively postulated to be 2,4-diphenylcyclobutanedione or 2,4-

diphenylcyclobutenolone.

Structural assignments for neutral methylketene dimer, acidic

methylketene dimer, 3,5-dimethyl-6-ethylpyronone, 3,5-diphenyl-

4-hydroxy-6-benzylpyrone, and 3,5-dimethyl-4-hydroxy-6-ethylpyrone

have been confirmed or corrected.

TABLE OF CONTENTS

PART I

MECHANISM OF THE THERMAL ISOMERIZATION OF

2-NORBORNENE-5, 6-endo-DICARBOXYLIC ANHYDRIDE

PART I

Introduction. Mechanism of the Diels Alder Reaction

The Diels-Alder reaction consists of a stereospecific cis

1,4-addition combining a cisoid conjugated diene and another unsat-

urated molecule, a dienophile. When several adducts are possible,

the one derived from a presumed activated complex having a maximum

accumulation of unsaturated centers usually predominates. The reac-

tion of trans-piperylene (I) with maleic acid (II) to form the adduct III

may serve as a specific example of the Diels-Alder reaction which

illustrates its general stereochemical characteristics (1).
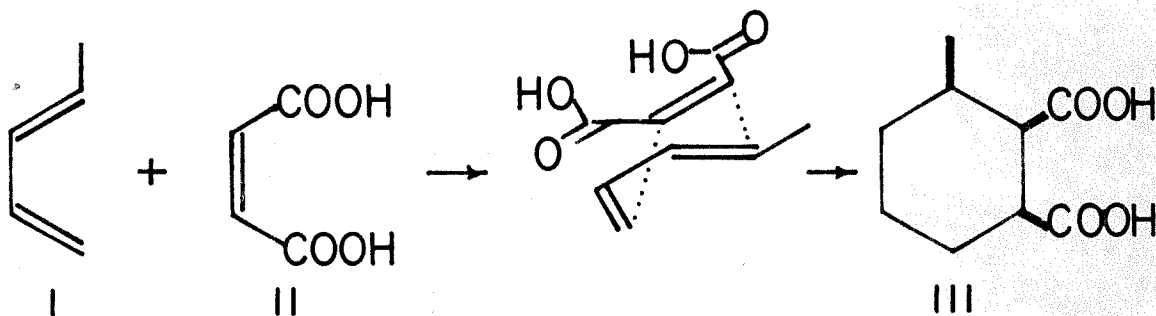
The facility with which the Diels-Alder reaction produces new

carbon-carbon bonds in a predictably stereospecific fashion gives it

great utility in organic syntheses (2).

The mechanism of the Diels-Alder reaction has been the subject

of many investigations (3). These investigations have produced quanti-

ties of data, but no totally satisfactory theory to account for the idio-

syncrasies of the Diels-Alder reaction has been developed.

A fresh surge of investigation and controversy on the mechanism of the Diels-Alder reaction was stimulated by Woodward and Katz in 1959 (4). In this paper, previous mechanistic views of the Diels-Alder reaction are divided into two categories. In the first are put those formulations in which the reaction is regarded as taking place in one step, with the two new bonds being formed simultaneously. The second category contains those formulations in which the reaction takes place in two or more steps, with the new bonds being formed during different stages of the reaction.

Woodward and Katz consider the evidence adduced in support of the various interpretations of the reaction according to steric considerations, thermodynamic considerations, and the effects of substituents.

The stereochemical features of the reaction, which were mentioned above, seem to support the one-step mechanism. This is because after one bond is formed in a two-step mechanism, stereochemical specificity could well be lost before the second bond is formed.

The thermodynamic data for the Diels-Alder reaction requires that the activated complex for the addition have a highly ordered geometrical arrangement similar to that of the product. This requirement also seems to favor a one-step mechanism.

Substituents at any of the three unsaturated centers taking part in the Diels-Alder reaction effect the speed and steric outcome of the addition. While the one-step mechanism seems unable to explain the observed effects, the two-step mechanism plausibly rationalizes them by considering probable stabilities of the postulated initially formed intermediates, as has been done for cycloaddition reactions (5).

Analysis of the nature of the Diels-Alder reaction as described by one-step and two-step mechanisms and by experimental data for the addition indicated that, in spite of many investigations, an understanding of the Diels-Alder reaction in complete harmony with all available evidence had not been achieved.

Woodward and Katz then present their new data. At 200°, dicyclopentadiene (IV) dissociates to two molecules of cyclopentadiene (V). At 140°, α-1-hydroxydicyclopentadiene (VI) isomerizes to syn-8-hydroxydicyclopentadiene (VII); and β-1-hydroxydicyclopentadiene (VIII) forms anti-8-hydroxydicyclopentadiene (IX). Both rearrangements are equilibrium processes and both are stereospecific, for stereochemical integrity is preserved throughout the isomerizations. For instance, no syn-8-hydroxydicyclopentadiene (VII) is formed from β-1-hydroxydicyclopentadiene (VIII), and the optically active 1-hydroxy-dicyclopentadienes (VI and VIII) rearrange without racemization.
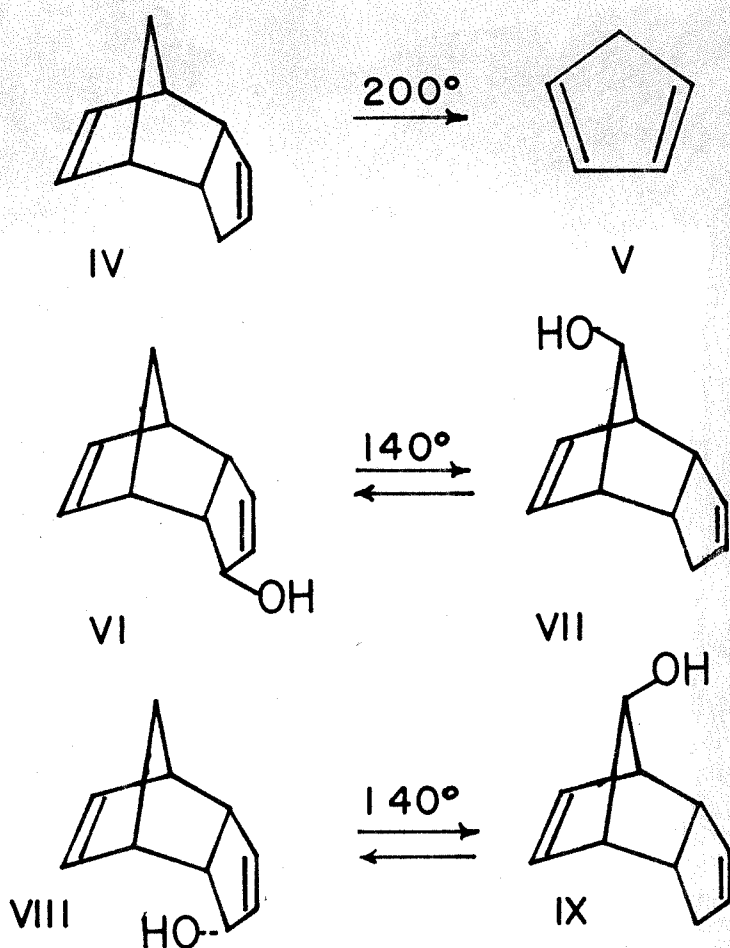
Woodward and Katz recognize the isomerizations as special cases of the Cope rearrangement and accordingly interpret them in terms of intermediates derived from the cleavage of bond ab in expression X. Their diagrammatic representation is a more sophisticated version of the sequence from structure X to XII. All electron spins remain appropriately paired at all times.
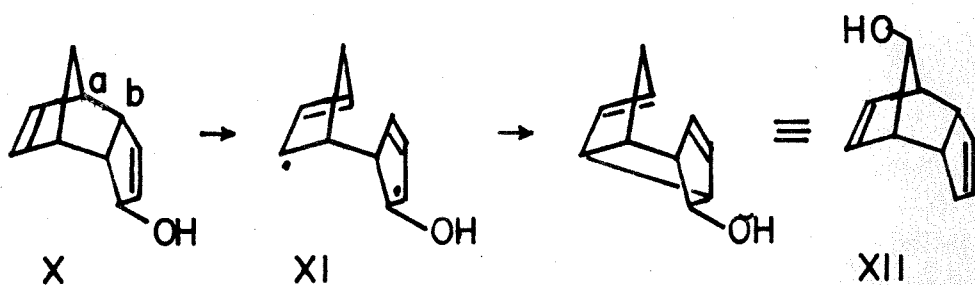
Since at 140°, one bond in a dicyclopentadiene system cleaves to permit the isomerization, and at 200° two bonds break to effect the Diels-Alder retrogression, the authors suggest that in the Diels-Alder addition of two molecules of cyclopentadiene, "the rate-controlling process is the formation of a single bond" and the reaction then proceeds "with relatively facile formation of a second bond, to the product."

The rest of the paper harmonizes these conclusions with the steric, thermodynamic and substituent effect characteristics of the Diels-Alder reaction to produce a new "two-stage" theory for its mechanism. A cisoid conjugated diene and a dienophile approach in parallel planes and a single bond is formed between them in the rate-controlling step. Conformational specificity is determined "by secondary attractive forces involving the electrons not directly associated with the primary bond process" (cf. XIII). "Formation of the single bond at ab is first completed" (cf. XIV) and the reaction concludes as the second full bond is constructed at ed (cf. XV).
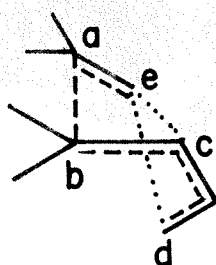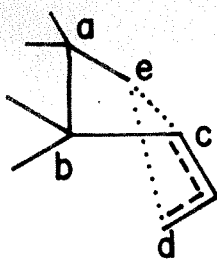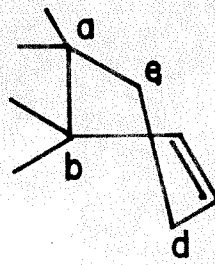
XIII   XIV   XV

The first among several subsequent papers concerned with the Woodward-Katz theory for the Diels-Alder reaction was by Dewar (6). After adducing some evidence and arguments in support of a one-step mechanism for the Diels-Alder reaction, he asserted that "since the transition state for the rearrangement observed by Woodward and Katz is necessarily different to the transition state for the Diels-Alder reaction, the two reactions are unrelated and no conclusions concerning the mechanism of one can be drawn from that of the other."

Woodward and Katz reaffirmed their previous interpretation (7), but perhaps without squarely meeting Dewar's objections.

The next papers extended the range and generality of the type of rearrangement observed by Woodward and Katz. Yates and Eaton (8) found that 4,5,6,7-tetrachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-8-one (XVI) rearranged to the isomer XVII, and Cookson, Hudec, and Williams (9) observed a similar rearrangement with 8-ketodicyclopentadiene (XVIII). Both of these isomerizations were catalyzed by proton acids or Lewis acids, and both were interpreted according to the theory of Woodward and Katz.
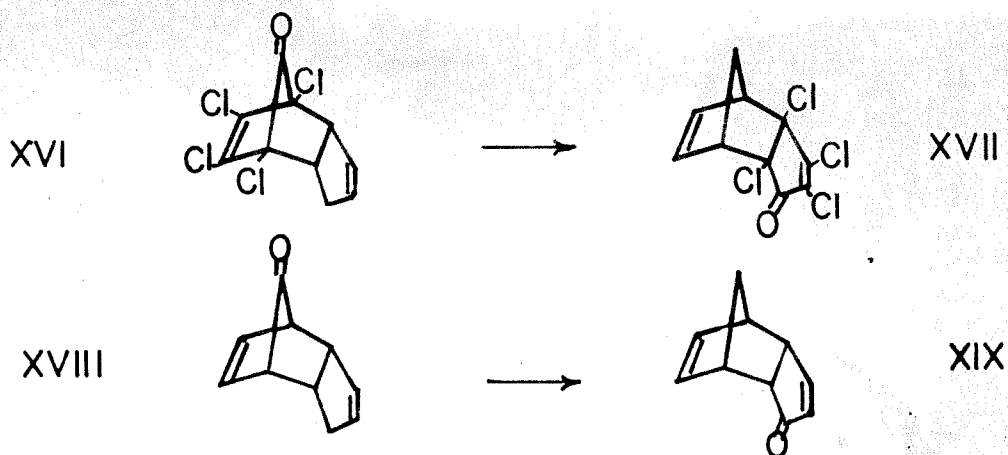
Lutz and Roberts (10) investigated the thermal isomerization

of a deuterium-labeled methacrolein Diels-Alder dimer (XX) and

found that a similar rearrangement occurred; the results showed that

in this case, involving species identical but for the

position of the deuterium label, the reverse Diels-Alder reaction

is very much in competition with the isomerization process, and com-

plete optical integrity is preserved throughout the rearrangement.

Lutz and Roberts suggested that the results of their experiment provide

support for the "presumption that the rearrangements and the reverse

Diels-Alder reaction proceed along the same energy path," but they

allowed that the possibility of different transition states was not

excluded.
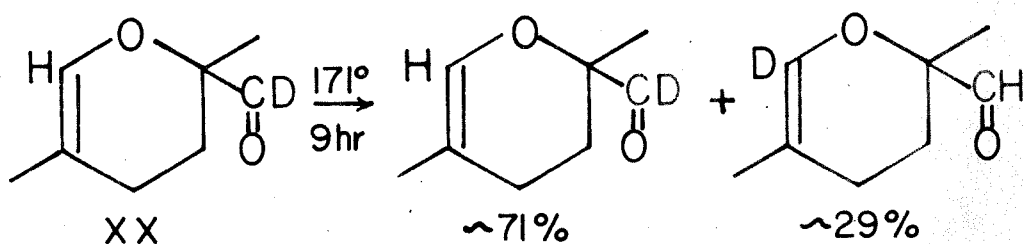
Berson and Remanick (11) have criticized the Woodward-Katz theory of the Diels-Alder reaction on two main points. First, its concept of simultaneity in the bond-making processes according to which "the formation of the two bonds takes place in separable, even if overlapping, processes, discretely delineated in structural terms and displaced in time," is not deduced but is added _ad hoc_. Second, its originators inconsistently claim that "resolution of the extremely subtle problems associated with defining the precise topography of the energy surface for the reaction after passage of the first barrier is irrelevant" while they base their theory on evidence assumed to be indicative of this portion of the energy surface (cf. Ref. 4).

Recent studies by Berson and co-workers have produced new results pertinent to the nature of the reaction. For example, an optically active sample of the _exo_-adduct of methyl methacrylate and cyclopentadiene (XXI) was found to isomerize at 170° to the racemic _endo_-adduct XXII with concurrent self-racemization (12). In this rearrangement, the rupture of no one bond is of primary importance; complete dissociation and recombination occurs. The result was

interpreted as evidence for a four-center mechanism for the Diels-Alder reaction, in which the two new carbon-carbon bonds are made in one process.
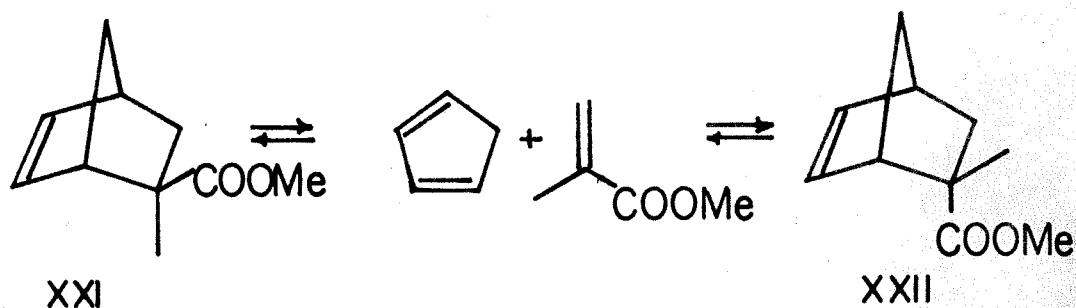
Berson and co-workers have also shown that the relative proportions of exo- and endo-addition products from cyclopentadiene and methyl methacrylate (and similar addends) are linearly related to a consistently defined solvent parameter (13). In some solvents, the Alder Rule (14) is abrogated and other factors determine the stereochemical outcome of the addition. This result demonstrates that stereospecificity in the Diels-Alder reaction is a function of solvent as well as of the adducts, and weakens arguments for the one-step mechanism based solely upon the general validity of the Alder Rule.

A crucial issue still to be settled is the relationship between the Diels-Alder reaction and the type of Cope rearrangements of Diels-Alder adducts observed by Woodward and Katz.

Mechanism of the Thermal Isomerization of 2-

Norbornene-5,6-endo-dicarboxylic Anhydride

The molecular rearrangement that will receive particular attention in the sequel is the thermal isomerization of the Diels-Alder adduct of cyclopentadiene and maleic anhydride, 2-norbornene-5,6-endo-dicarboxylic anhydride (XXIII). In 1952, Craig noted that at 190° the endo-adduct XXIII rearranged to its exo-isomer XXIV, and demonstrated that the rearrangement was an equilibrium process (15).

XXIII   **XXIV**
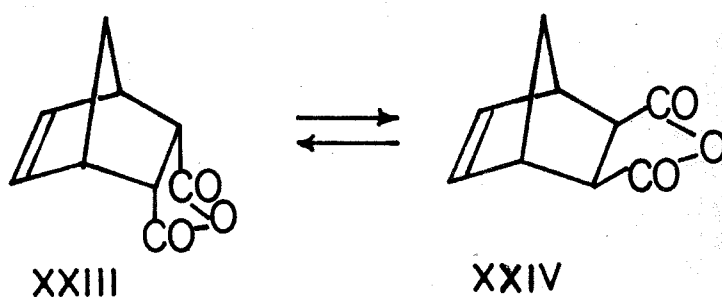
In 1955 and 1956, Berson and co-workers (16) reexamined this isomerization by radiochemical labeling, and found that the degree of exchange in radioactivity between the substrates and added maleic anhydride implied that the rearrangement proceeded by two pathways. The first, internal route, occurred without exchange of radioactivity between the maleic anhydride moiety of the Diels-Alder adduct and added maleic anhydride, while in the second, external route, both sources of maleic anhydride equilibrated their activities during the rearrangement.
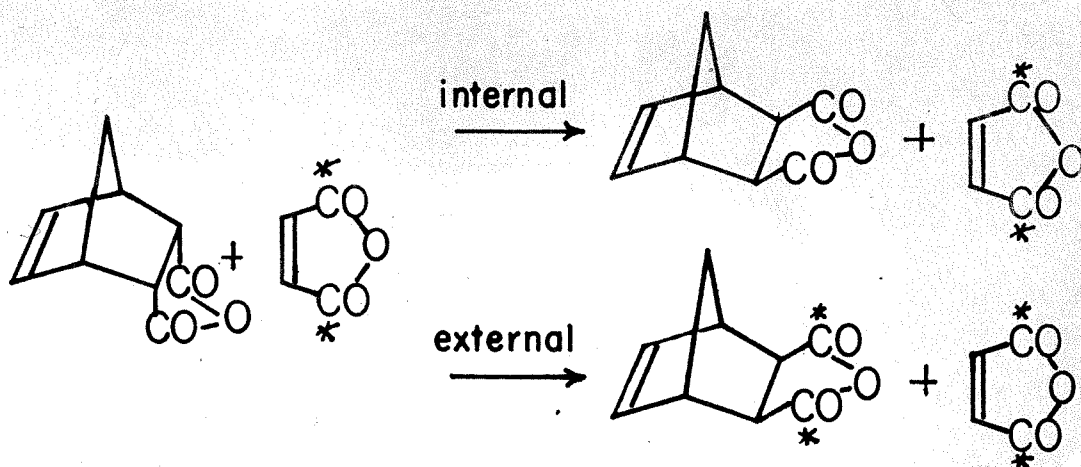
A number of proposed mechanisms for the internal isomeriza-
tion pathway are outlined in Chart 1, page 13.

A precise knowledge of the mechanism of this reaction is of

interest not only for its own sake, but also because it would help to

evaluate the nature of the Diels-Alder reaction. Some mechanistic

pathways in Chart 1 are related to the Diels-Alder reaction, and some

are not. For instance, mechanisms 5 and 6 posit restricted

geometry and considerable affinity between the Diels-Alder addends,

and therefore, if operative, would be of general significance. But in

mechanism 2, the bond which breaks to permit isomerization is not

one of the bonds cleaved in a Diels-Alder retrogression; if this pathway

be correct, one would wish to separate, rather than to unite, consider-

ation of the details of such a mechanistic novelty and the common

Diels-Alder reaction.

Each of the mechanisms in Chart 1 predicts the fate of a hypo-

thetical label on just one of the carbonyl carbon atoms.

Mechanisms 1, 2, 3, and 5 predict that the labeled structure

would produce the labeled structure XXVI, wherein the labeled atom is

still joined to the same carbon atom of the norbornene skeleton.

13
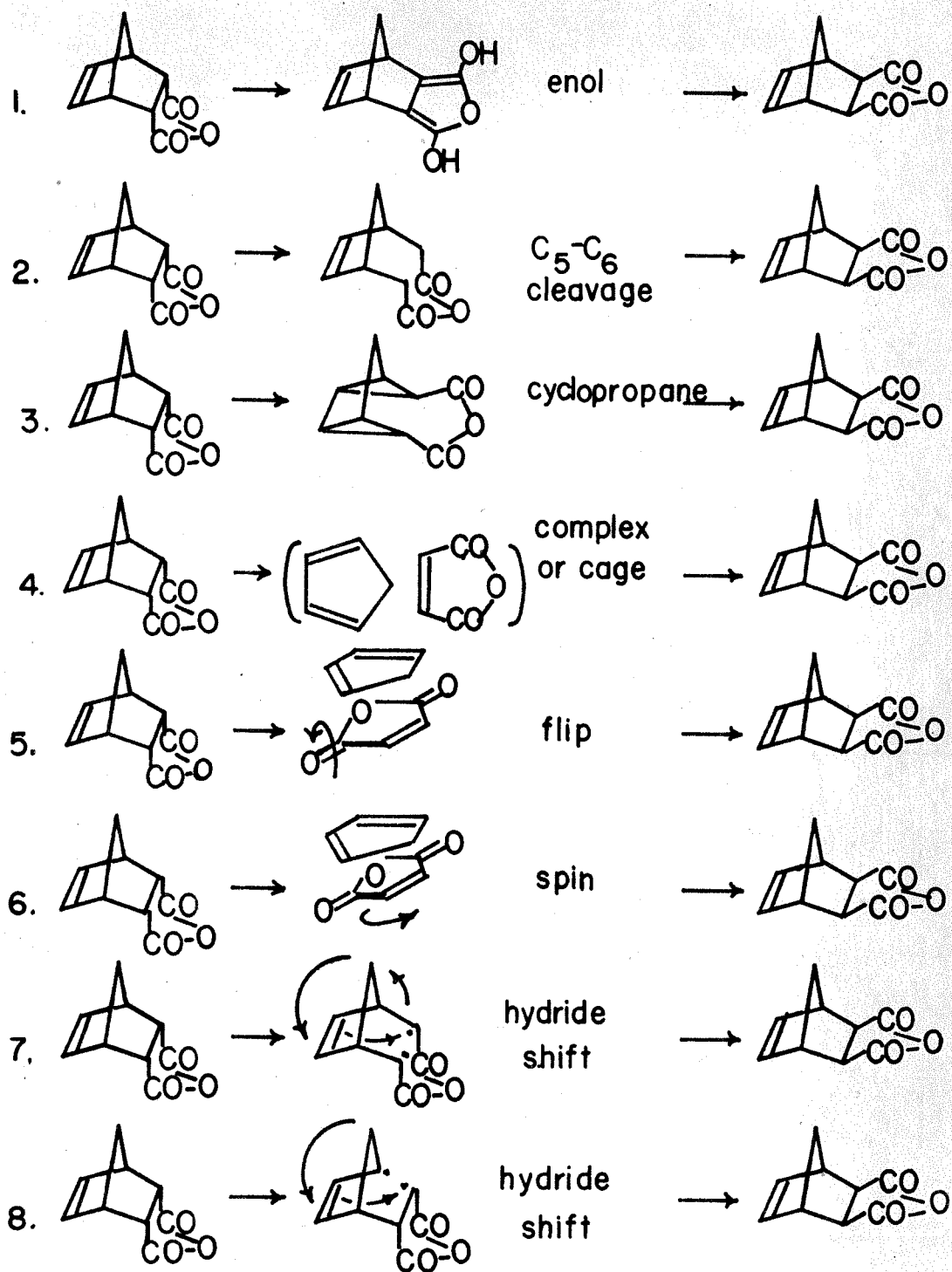
Chart 1. Proposed mechanisms for the internal thermal isomerization of 2-norbornene-5,6-endo-dicarboxylic anhydride (17).

XXV   XXVI
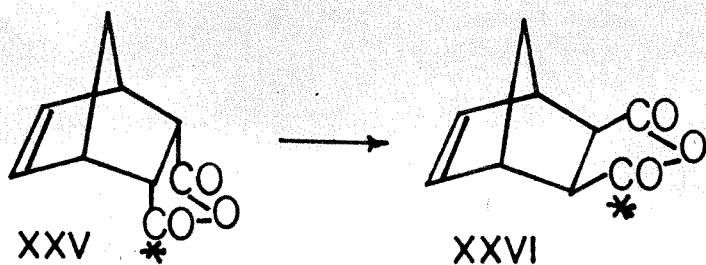
Mechanisms 6, 7, and 8 predict that the labeled carbon from

XXV would migrate to the other position in the norbornene system

during rearrangement to give the exo-isomer XXVII.

XXV   XXVII
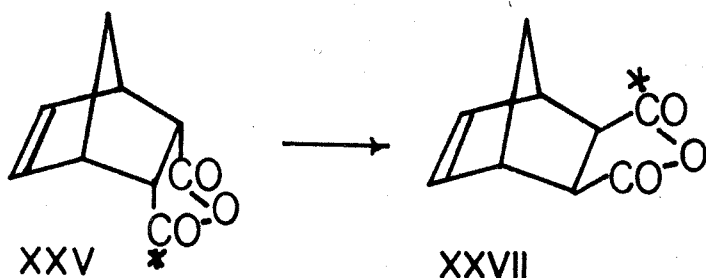
Mechanism 4 predicts complete mixing of the label in the

product between the two possible positions.

XXV
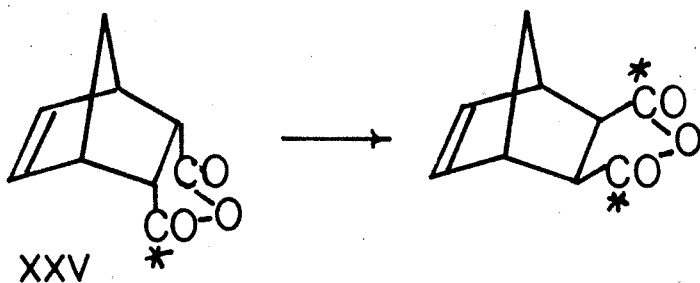
Finally, certain combinations of mechanisms, e.g., 5 and 6,

could obtain and the stereochemical result of the rearrangement would

be intermediate between complete stereospecificity and complete

racemization of the label.

Since the mechanism of the internal thermal isomerization of

2-norbornene-5,6-endo-dicarboxylic anhydride may have direct bearing

on the mechanism of the Diels-Alder reaction, and since the various possible mechanisms greatly distinguish themselves through their predictions concerning the fate of a label on only one carbonyl carbon atom, an experimental test of these predictions was undertaken.

An attempt was made to develop a synthesis of 2-norbornene-5,6-endo-dicarboxylic anhydride, stereospecifically labeled with carbon-14 in only one carbonyl group; to find conditions for the rearrangement that would effectively separate and distinguish between the exo-anhydride product originating through the external and internal rearrangement routes; and to discover procedures for a stereospecific degradation of 2-norbornene-5,6-exo-dicarboxylic anhydride that would enable one to measure the radioactivity of each carbonyl carbon atom separately.

Synthesis of Stereospecifically Labeled 2-Norbornene-5,6-endo-dicarboxylic Anhydride

The first scheme for the synthesis of stereospecifically labeled 2-norbornene-5,6-endo-dicarboxylic anhydride which was attempted is outlined in Chart 2. It depends upon the construction of ethyl cis-β-cyano-C^{14}-acrylate, Diels-Alder addition of this intermediate to cyclopentadiene, selective hydrolysis of the ester group, resolution, and conversion of one of the optically active cyanoacid antipodes to the stereospecifically labeled anhydride by way of the diacid.

Chart 2. First attempted synthesis of stereospecifically labeled 2-norbornene-5,6-endo-dicarboxylic anhydride; the symbol * indicates the C^{14} label.

Both the reaction of hydrogen cyanide with ethyl propiolate and the reaction of sodium cyanide with ethyl-α-chloroacrylate in an aqueous medium gave ethyl trans-β-cyanoacrylate. With the second method, yields as high as 50% were achieved. Ethyl trans-β-cyano-acrylate was converted in high yield to the cis-isomer through cyclical photoisomerization and separation of the cis- and trans-compound by distillation.

Inactive ethyl cis-β-cyanoacrylate was obtained more conveniently by the reaction of maleamic acid with ethyl chloroformate.

The Diels-Alder reaction of ethyl cis-β-cyanoacrylate and cyclopentadiene gave ethyl 2-norbornene-5-endo-cyano-6-endo-carboxylate in nearly quantitative yield. Hydrolysis of this cyanoester proved less efficient. Extensive epimerization during hydrolysis led to a mixture of isomers (XXVIII, XXIX, and XXX) which were difficult to separate by fractional crystallization.
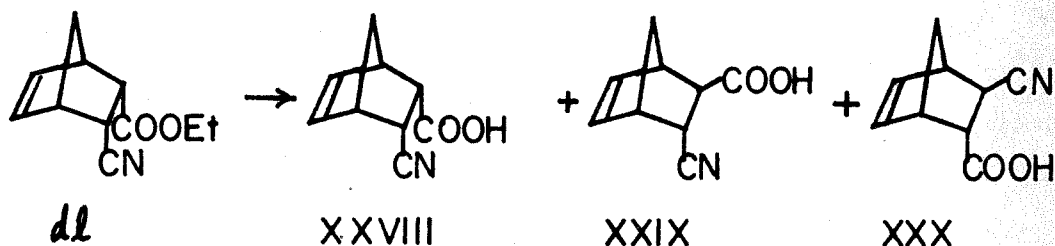
A more serious difficulty was encountered during the resolution phase of the synthetic work. The brucine salt of 2-norbornene-5-endo-cyano-6-endo-carboxylic acid was obtained but resolution through this salt was achieved only slowly, incompletely, and inefficiently.

One attempt to utilize the method of Chart 2 using carbon-14 labeled material was unsuccessful; less than optimum yields on some reactions and large dilutions with inactive materials (which were considered necessary in light of the material requirements of the resolution step) led to a brucine salt of 2-norbornene-5-endo-cyano-C^{14}-6-endo-carboxylic acid whose activity was too low to be useful.

During the course of this synthetic work, a degradation of 2-norbornene-5-endo-cyano-6-endo-carboxylic acid was developed. The principal features of the procedure will be apparent from Chart 3 on the following page. The absolute configuration of the optical antipodes of the final product in the degradation, 2-endo-norbornane-carboxyamide, is known (18). This degradation would have revealed the position of the label in the 2-norbornene-5,6-endo-dicarboxylic anhydride derived from the optically active cyanoacid.

The scheme of Chart 2 could be satisfactorily employed if some efficient agent for effecting the resolution could be found. The other difficulties experienced were those usually associated with a large number of steps: some obtained in only moderate yields. The yields on the few weak links in the chain of reactions could have been improved through an expenditure of more time and effort, but lacking a ready solution to the resolution difficulties, such action seemed a poor invest-ment and this synthetic approach was abandoned.
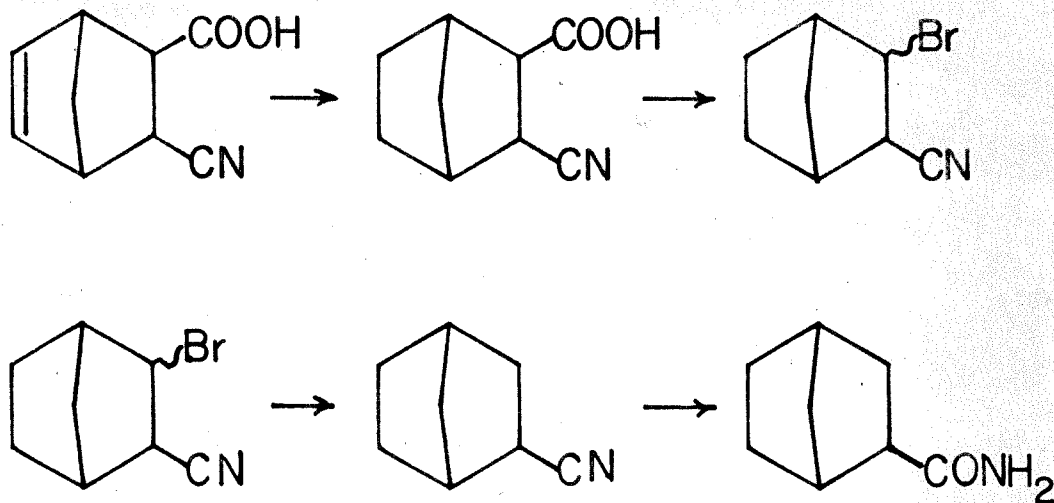
Chart 3. Degradation of 2-norbornene-5-endo-cyano-6-endo-carboxylic acid to 2-endo-norbornanecarboxyamide

The second scheme adopted for synthesizing stereospecifically labeled 2-norbornene-5,6-endo-dicarboxylic anhydride is outlined in Chart 4.

The synthesis of (-)-menthyl hydrogen maleate, labeled in only one carbonyl carbon atom, proved to be elusive. The Grignard reagent from (-)-menthyl propiolate could be made easily, but it did not react with carbon dioxide or ethyl carbonate. Ethyl carbonate-C^{14} could be prepared from the commercially available phosgene-C^{14}.

The Grignard reagent from (-)-menthyl propiolate did react with acetaldehyde to give (-)-menthyl 4-hydroxypent-2-ynoate in nearly

a. $\overset{*}{C}O_2 + BrMgC \equiv C-COOC_{10}H_{19} \longrightarrow HOO\overset{*}{C}C \equiv CCOOC_{10}H_{19}$

b. $(EtO)_2\overset{*}{C}O + \quad " \quad \longrightarrow EtOO\overset{*}{C}C \equiv CCOOC_{10}H_{19}$

$EtOO\overset{*}{C}C \equiv CCOOC_{10}H_{19} \longrightarrow HOO\overset{*}{C}C \equiv CCOOC_{10}H_{19}$

c. $CH_3\overset{*}{C}HO + BrMgC \equiv CCOOC_{10}H_{19} \longrightarrow CH_3\overset{*}{C}HOHC \equiv CCOOC_{10}H_{19}$

$CH_3\overset{*}{C}HOHC \equiv CCOOC_{10}H_{19} \longrightarrow HOO\overset{*}{C}C \equiv CCOOC_{10}H_{19}$
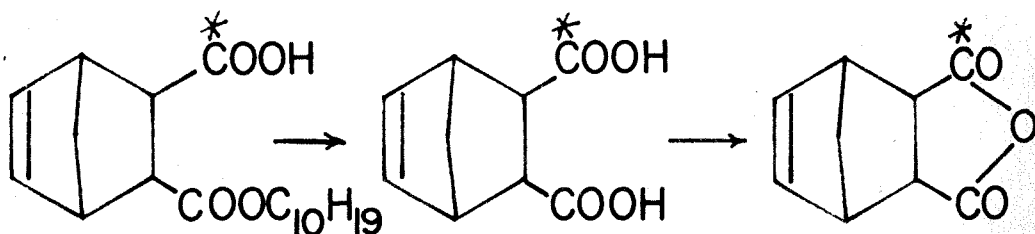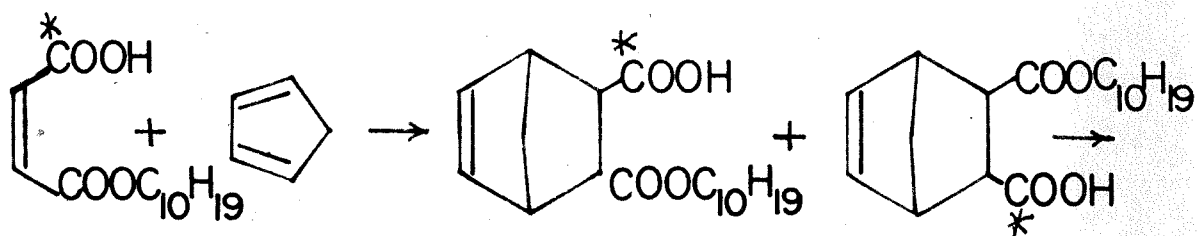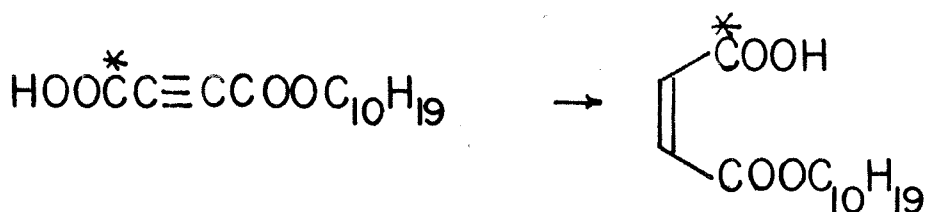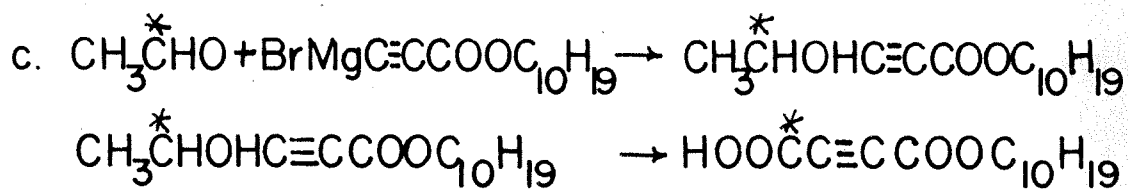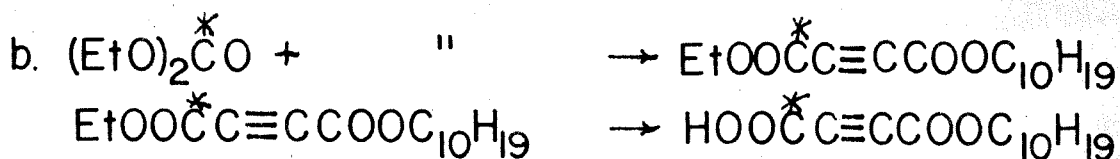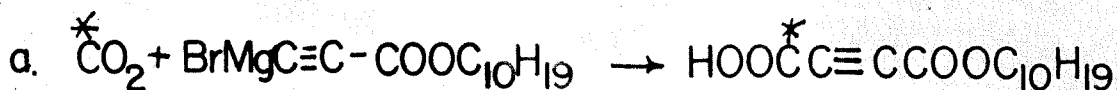
Chart 4. Second attempted synthesis of stereospecifically labeled 2-norbornene-5,6-endo-dicarboxylic anhydride; the symbol * indicates the C[14] label.

quantitative yield. Acetaldehyde-1-C^{14} may be prepared from the commercially available ethanol-1-C^{14}. (-)-Menthyl 4-hydroxypent-2-ynoate would be expected to give the desired half-ester through haloform oxidation and hydrogenation over a Lindlar catalyst (19), or vice versa. But the sterically hindered triple bond resisted hydrogenation and the reaction of sodium hypochlorite with (-)-menthyl-4-hydroxypent-2-ynoate did not give a satisfactory yield of acidic product. This behavior may be due to attack on the triple bond, or to cleavage of the intermediate XXXI to an ethynyl anion rather than to the trichloromethyl anion.

$$H_{19}C_{10}O_2CC\equiv CC(O)(OH)CCl_3 \longrightarrow H_{19}C_{10}O_2CC\equiv CCOOH + \bar{C}Cl_3$$

XXXI

$$\longrightarrow H_{19}C_{10}O_2CC\equiv \bar{C} + CCl_3CO_2H$$
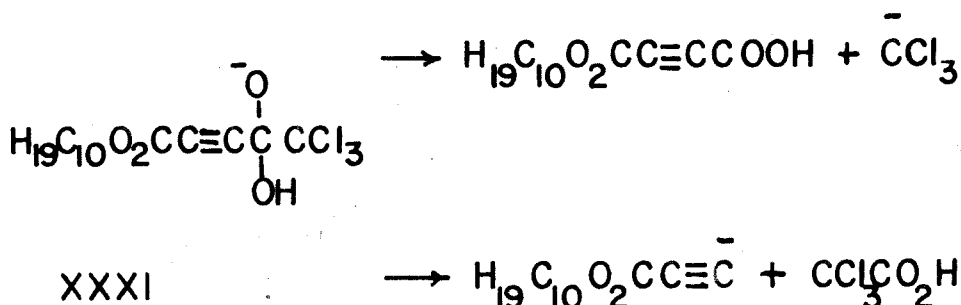
Another difficulty was noted at the hydrolysis step converting the (-)-menthyl half-ester to 2-norbornene-5,6-endo-dicarboxylic acid. Under acidic conditions, the lactone XXXII formed, while under basic conditions, epimerization preceded hydrolysis.

XXXII
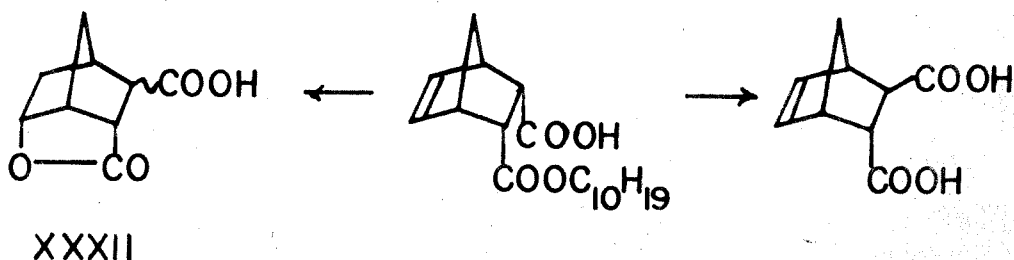
The relative unreactivity of the (-)-menthyl ester, which was an advantage earlier in the synthesis when a Grignard reagent was being made elsewhere in the molecule, now became an apparently insurmountable roadblock.

The third synthetic approach to stereospecifically labeled 2-norbornene-5,6-endo-dicarboxylic anhydride which was followed is presented in Chart 5, page 23.

Ethyl orthoformate may be synthesized by the reaction of hydrogen cyanide with hydrogen chloride and ethanol in better than 90% yield (20). The inexpensive sodium cyanide-C^{14} would serve as a primary source of radioactivity for a synthesis of ethyl ortho-formate-1-C^{14}.

The reaction of ethyl or orthoformate with ethyl propiolate was patterned after similar reactions reported by Howk and Sauer (21). Ethyl propiolate combined with ethanol under the reaction conditions to give ethyl trans-β-ethoxyacrylate. Accordingly, at least a two-fold excess of ethyl propiolate should be used in this preparation. No loss in radioactivity would occur from a side reaction of ethanol from ethyl orthoformate-1-C^{14}.

Attempts to synthesize malealdehydic acid from furfural for experiments with unlabeled material led to maleic anhydride.
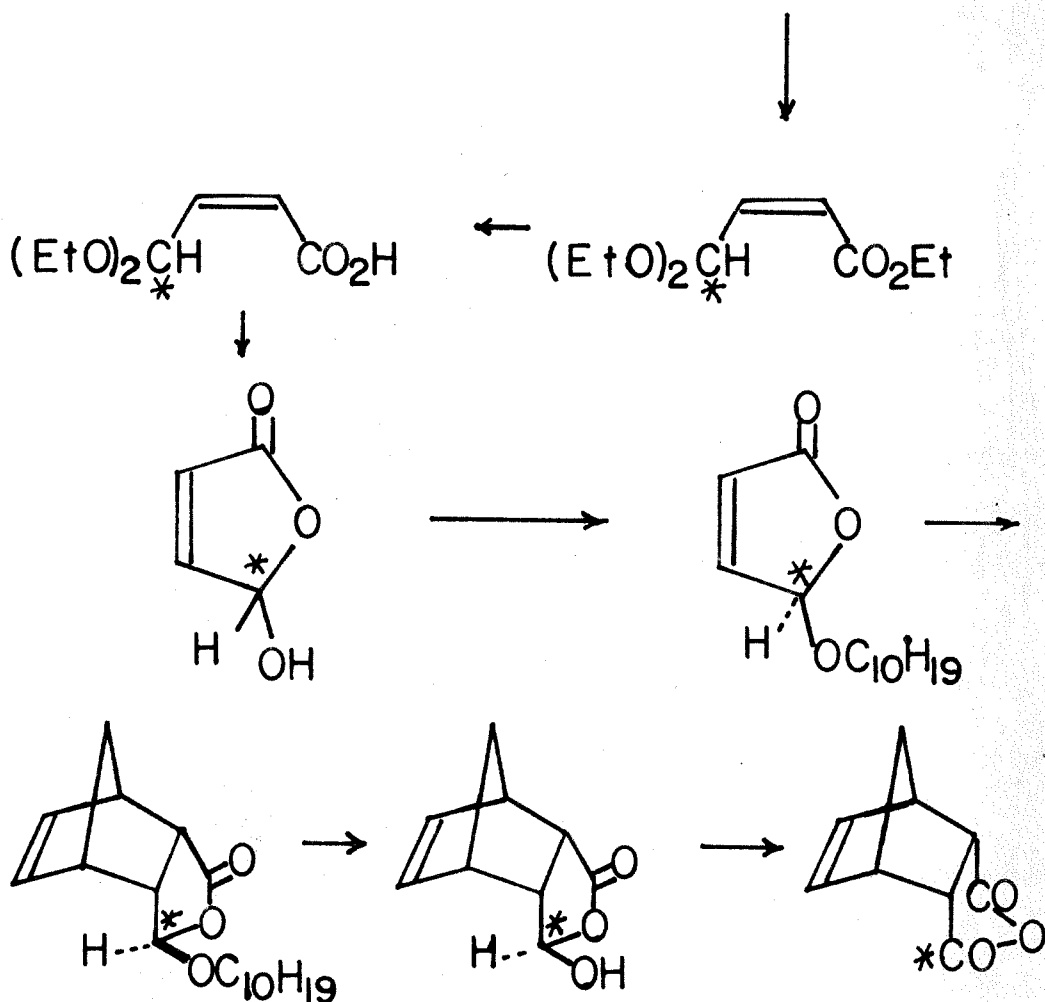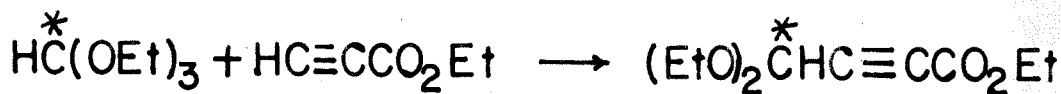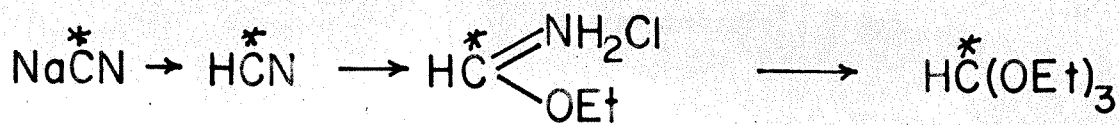
Chart 5. Third attempted synthesis of stereospecifically labeled 2-norbornene-5,6-endo-dicarboxylic anhydride; the symbol * indicates the C^{14} label.

XXXIV   **X XX V**
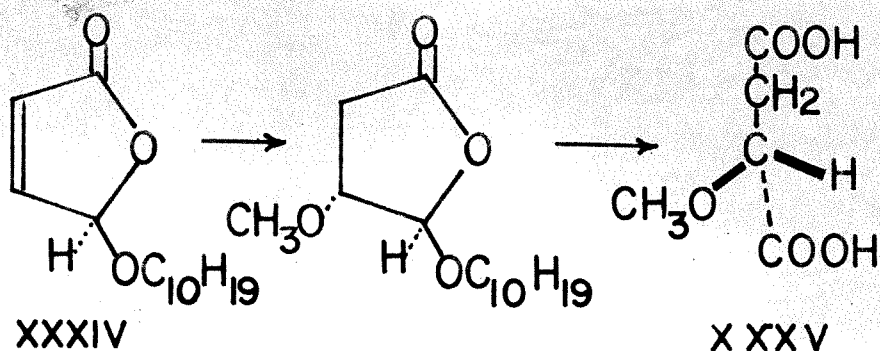
The absolute stereochemistry of an optical isomer (-)-menthoxy-malealdehydic acid, e. g., XXXIV, and hence the position of radioactive label in the 2-norbornene-5,6-endo-dicarboxylic anhydride derived therefrom, could be established by converting it to a methyl ether of malic acid whose absolute stereochemistry is known (22), e. g., XXXV.

The Diels-Alder reaction of XXXIV with cyclopentadiene would be expected to give the adduct XXXVI.

XXXV
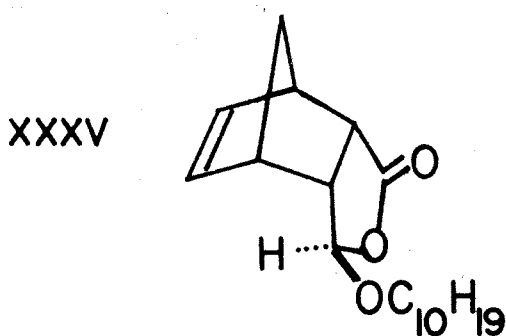
The remaining steps in this sequence are to be investigated by Dr. Ulrich Scheidigger.

Internal Mechanism in the Thermal Isomerization of

2-Norbornene-5,6-endo-dicarboxylic Anhydride

The second major goal of this study was to discover appropriate conditions for the rearrangement step.

The technique used for the labeling experiments of Berson and co-workers (16) was adequate for the purpose of demonstrating an internal pathway for the rearrangement, but it was unsuited for the current work. Berson's experiments made it clear that the relative rapidity with which labeled 2-norbornene-5,6-endo-dicarboxylic anhydride and its exo-isomer equilibrated radioactivity with maleic anhydride during rearrangement demanded that the reaction be stopped after a low conversion to the exo-anhydride, the exo-anhydride isolated through a carrier-dilution procedure, and the data analyzed through a graphical extrapolation approximation.

In this study, using stereospecifically labeled 2-norbornene-5,6-endo-dicarboxylic anhydride, ideal experimental conditions would permit high conversion to the exo-anhydride, no loss in activity through dilution with inactive carriers, and analytical analysis of data.

More efficient methods for separating the exo- and endo-anhydrides following the rearrangement were introduced, but they did not materially improve the situation. For even if it were possible to

isolate from the rearrangement mixture completely pure samples of

2-norbornene-5,6-endo-dicarboxylic anhydride, the exo-isomer, and

maleic anhydride, no calculation could indicate what percentage of the

activity found in the exo-anhydride came by the internal rearrangement

pathway (and accordingly might be expected to show some stereospeci-

ficity) and what percentage of activity came by the external pathway

(and should then be equally distributed on both carbonyl carbon atoms).

Such a calculation would be possible only if preliminary rate studies

with non-stereospecifically labeled endo-anhydride established accurate

relationships between the relative activity of each of the three anhy-

drides as a function of time at a certain temperature. If these data

were available, one could assume with Berson (16) that the activity

of the exo-anhydride produced during some particular interval of time

by the internal mechanism would be equal to that of the endo-anhydride

at that time, and similarly the exo-anhydride produced during some

particular interval of time through the external mechanism would have

an activity equal to that of the maleic anhydride pool at that time.

The considerable experimental labor and difficult calculations demanded

by such a program precluded its use in the current investigation.

Kinetic analysis makes clear that information on the compara-

tive importance of the external and internal rearrangement paths can-

not be obtained by varying the relative maleic anhydride concentrations

in a series of rearrangements of the endo-anhydride.
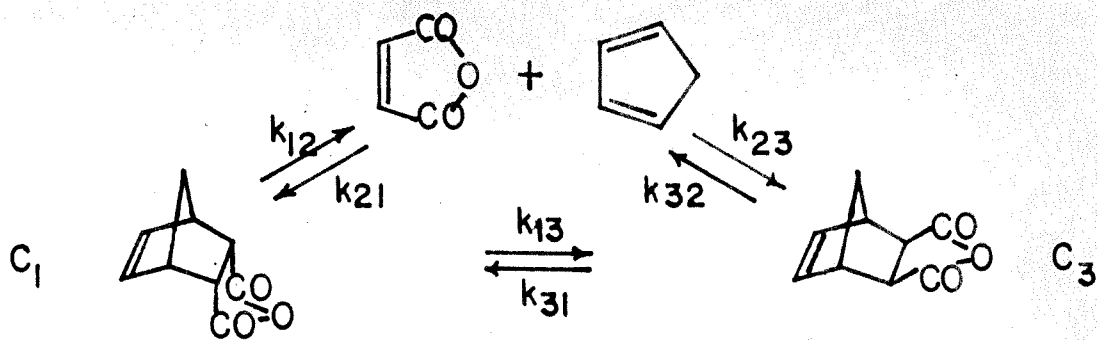
The differential equations describing the rearrangement may be solved by making the steady state approximation and assuming that C_1 plus C_3 is constant.

$$C_3 = \frac{A}{B}(1 - e^{-Bt}) \qquad A = \frac{K(k_{13}k_{23} + k_{13}k_{21} + k_{12}k_{23})}{(k_{21} + k_{23})}$$

$$K = C_1 + C_3 \qquad B = \frac{A}{K} + \frac{(k_{32}k_{21} + k_{31}k_{21} + k_{31}k_{23})}{(k_{21} + k_{23})}$$

A kinetic study of the thermal rearrangement of 2-norbornene-5,6-endo-dicarboxylic anhydride in its exo-isomer gave an apparent activation energy of 36.7 kcal. per mole. This value may be compared with an apparent activation energy of 36 kcal. per mole obtained from the data of Berson and Mueller (23) for the dissociation of the 9-phenyl-anthracene-maleic anhydride Diels-Alder adduct. No deviation from linearity in the Arrhenius plot was observed, as shown in Figure 1 on the following page.

An attempt to gain information on the effect of temperature on
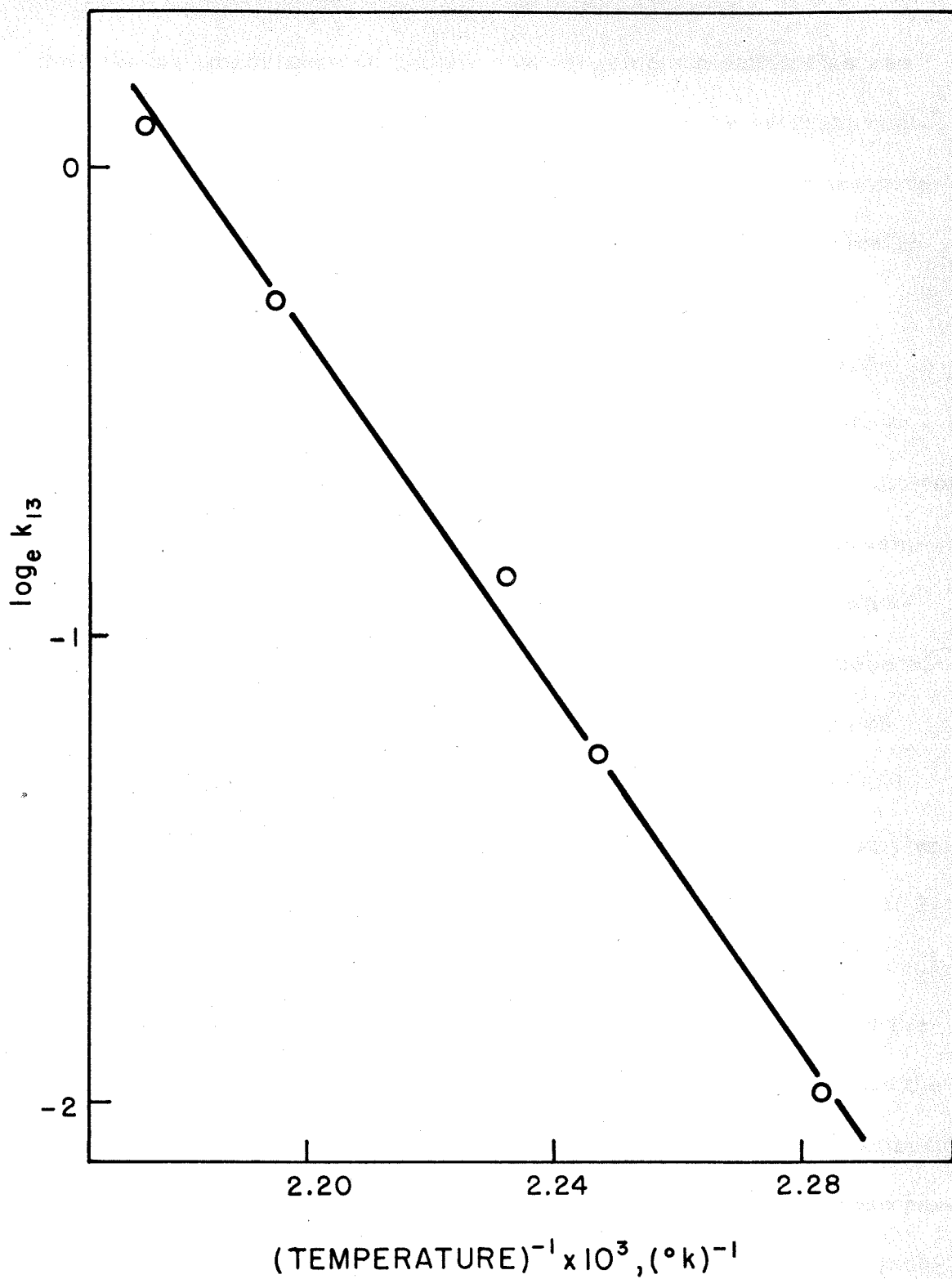
Figure 1. Arrhenius plot for the thermal isomerization of 2-norbornene-5,6-endo-dicarboxylic anhydride

the relative importance of the two rearrangement mechanisms was
made by trapping the cyclopentadiene produced on the external route
with tetracyanoethylene. The results indicate that at lower tempera-
tures the internal pathway is greatly favored, as shown graphically
in Figure 2, page 30.

The association of the ratio of concentrations of 2,2,3,3-
tetracyanonorborn-5-ene to 2-norbornene-5,6-exo-dicarboxylic an-
hydride with the relative importance of the external versus the internal
mechanistic pathway is based on the assumption that, over the tem-
perature range studied, the reaction of cyclopentadiene with tetra-
cyanoethylene is much faster than the reaction of cyclopentadiene with
maleic anhydride. This assumption seems reasonable in light of
recently published rate data on the addition of cyclopentadiene and
maleic anhydride (24) and of the great reactivity of tetracyanoethylene
in Diels-Alder reactions (25). This assumption will be tested. If 2-
norbornene-5,6-exo-dicarboxylic anhydride from the rearrangement
of radioactive 2-norbornene-5,6-endo-dicarboxylic anhydride in the
presence of tetracyanoethylene and inactive maleic anhydride has the
same radioactivity as the starting endo-anhydride, then the assumption
is valid. If the exo-anhydride were less active, then some would have
been produced by the external mechanism, in spite of the tetracyano-
ethylene present.
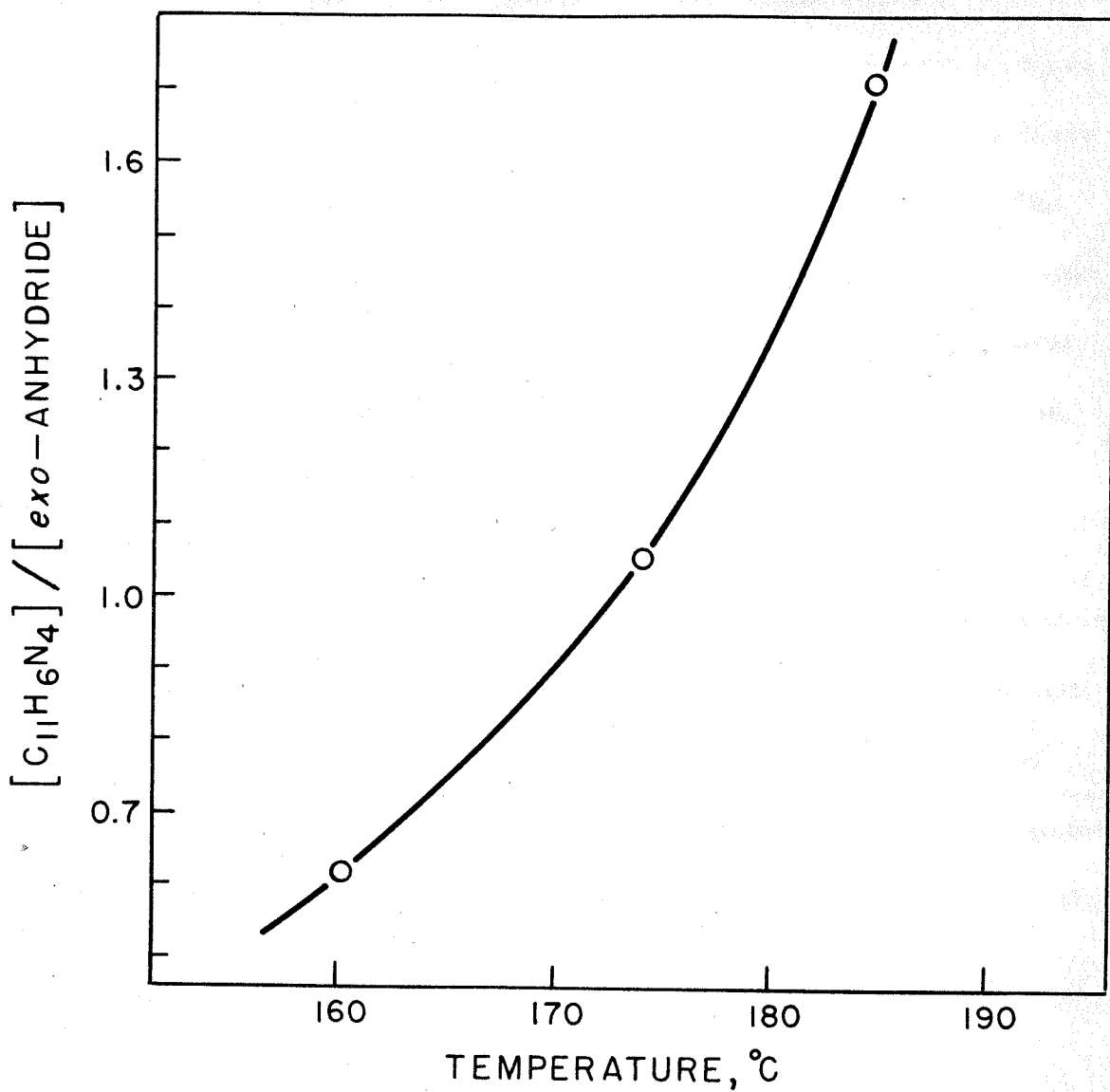
Figure 2. Temperature-dependent participation of an internal isomerization route in the thermal rearrangement of 2-norbornene-5,6-endo-dicarboxylic anhydride

A preliminary preparative scale rearrangement of 2-norbornene-5,6-endo-dicarboxylic anhydride in the presence of maleic anhydride and tetracyanoethylene was conducted by refluxing a solution of these components in s-tetrachloroethane of b.p. 144° for 25 hours. The rearrangement went satisfactorily. The exo-anhydride may be separated from the other components in the mixture by adding anthracene to destroy the remaining tetracyanoethylene, removing the solvent, and subjecting the residue to fractional sublimation.

These results indicate how to effect rearrangement of 2-norbornene-5,6-endo-dicarboxylic anhydride under conditions favoring the internal mechanistic pathway, separate the two pathways so that all exo-anhydride produced stems from the internal process, and remove the exo-anhydride efficiently from the rearrangement mixture. All three goals of the second phase of the labeling experiment are thus achieved.

Stereospecific Degradation of 2-Norbornene-5,6-exo-dicarboxylic Anhydride

The third and final major experimental challenge posed by the labeling experiment for investigating the mechanism of the thermal isomerization of 2-norbornene-5,6-endo-dicarboxylic anhydride demanded a stereospecific degradation of the product from the rearrangement, 2-norbornene-5,6-exo-dicarboxylic ahydride, that would

distinguish between the two carboxyl carbon atoms and measure their

radioactivities separately. Such a degradation would delineate the

fate of the carbon-14 from stereospecifically labeled 2-norbornene-

5,6-endo-dicarboxylic anhydride.

The general scheme selected for the degradation is given

in Chart 6, page 33.

Initial experiments with the degradation employed methanol

to cleave the anhydride. After the double bond of 2-norbornene-5,6-

exo-dicarboxylic anhydride had been reduced, the anhydride function

was opened with methanol to produce methyl hydrogen 2,3-exo-

norbornanedicarboxylate. This acid ester was decarboxylated to

methyl 2-bromo-3-exo-norbornanecarboxylate, which was converted

in several steps to 2-exo-norbornanecarboxylic acid.

Decarboxylation of methyl hydrogen 2,3-exo-norbornanedi-

carboxylate (XXXVII) was accomplished with red mercuric oxide and

bromine (26). A substantial amount of 2,3-exo-norbornanedicarboxylic

anhydride (XXXIX) was obtained as a side product.
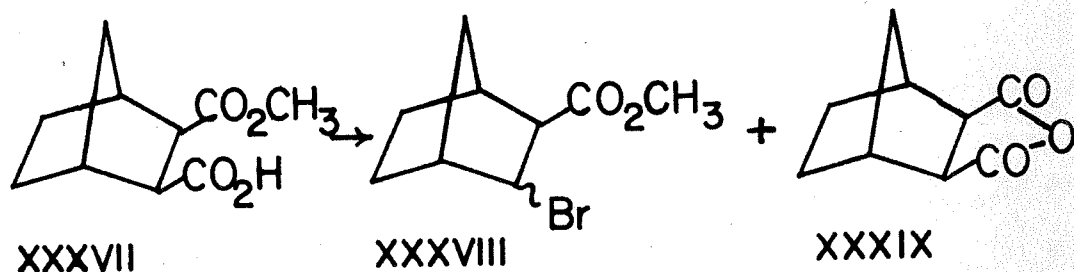
This anhydride-making reaction has not been previously reported.
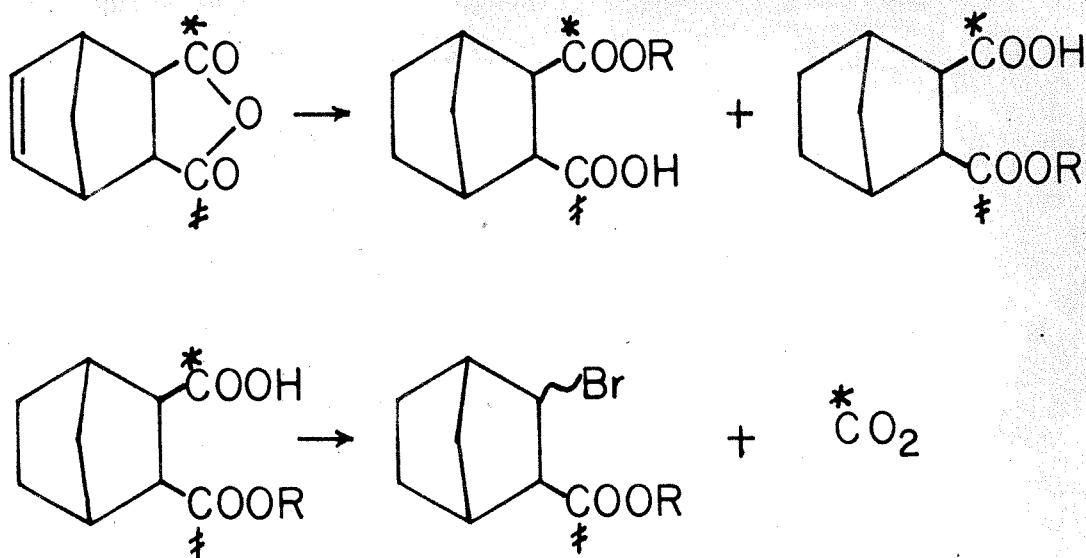
Chart 6. Stereospecific degradation of 2-norbornene-5,6-exo-dicarboxylic anhydride; the symbols * and ‡ represent different C^{14} activities.

It presumably takes the course depicted below.
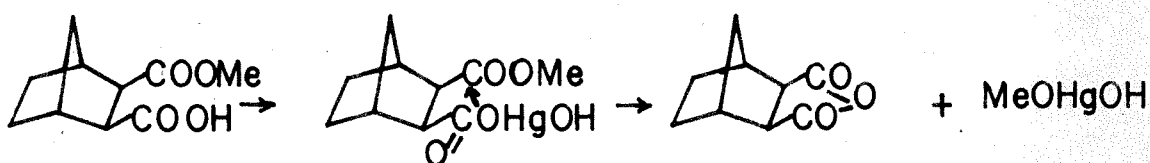
The remainder of the degradation was identical to one described for (-)-menthyl 2-bromo-3-exo-norbornanecarboxylate included in Chart 7 on page 36.

Conversion of 2-norbornene-5,6-exo-dicarboxylic anhydride to methyl hydrogen 2,3-exo-norbornanedicarboxylate (XXXVII) and

degradation of this acid ester to 2-exo-norbornanecarboxylic acid

demonstrated methods for the stereospecific chemistry required by

the radiochemical objectives. The absolute configuration of an optically

active antipode of methyl hydrogen 2,3-exo-norbornanedicarboxylate

could be established and the radioactivities of its two carbonyl carbon

atoms could be independently determined. The final requirement of

the third phase of the project, complete resolution of methyl hydrogen

2,3-exo-norbornanedicarboxylate, was not achieved.

Methyl hydrogen 2,3-exo-norbornanedicarboxylate and brucine

gave a crystalline salt. A sample of the acid ester regenerated from

a brucine salt recrystallized several times from absolute ethanol gave

a satisfactory elemental analysis and had a rotation of $[\alpha]_D^{27}$ + 0.02°.

The enantiomorphic methyl hydrogen 2,3-exo-norbornanedi-

carboxylates may foster an ester interchange or internal transesteri-

fication which could vitiate all resolution endeavors.
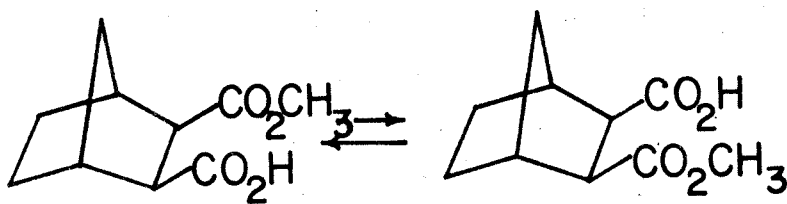
The resolution problem was overcome through a slightly modified

approach. The saturated exo-anhydride XL was opened with (-)-menthol

and the two diasteromeric (-)-menthyl hydrogen 2,3-exo-norbornane-

dicarboxylates XLI and XLII were fairly readily separated. These

two compounds, of m.p. 120-123° and $[\alpha]_D^{28}$ -45.5°, and of m.p.

140-142° and $[\alpha]_D^{25}$ -59.2°, were designated isomer A and isomer B

respectively.
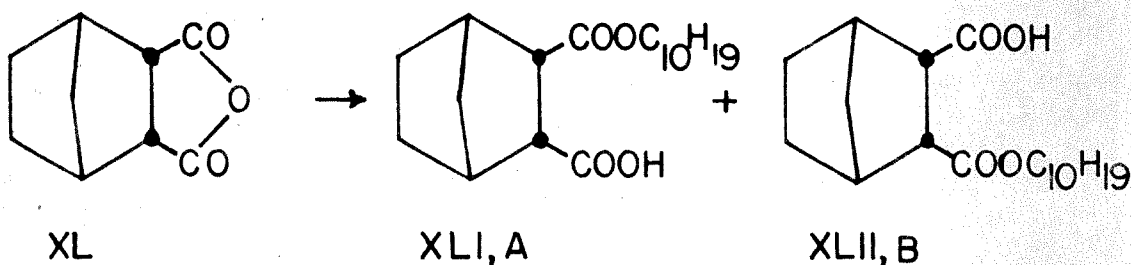
The absolute stereochemistry of the two acid esters was

established. Reaction of XLI with red mercuric oxide and bromine

gave 2,3-exo-norbornanedicarboxylic anhydride rather than a bromo-

ester (cf. page 32), but decarboxylation of XLII was achieved through

the Hunsdiecker reaction. The rest of the degradation is outlined in

Chart 7.

The absolute configuration of (-)-2-exo-norbornanecarboxylic

acid is as shown in XLIII; the reported optical rotation is $[\alpha]_D^{25}$ -27.8°

(27). The sample of (-)-2-exo-norbornanecarboxylic acid derived from

XLII had $[\alpha]_D^{23}$ -21.0°. The infrared spectrum of this sample con-

firmed its identity and showed that it was contaminated with an impurity.

This degradation of XLII also led to a sample of trans 2,3-

norbornanedicarboxylic acid having $[\alpha]_D^{25}$ -28.3°. After the Huns-

diecker reaction, acidic impurities were extracted and discarded; the
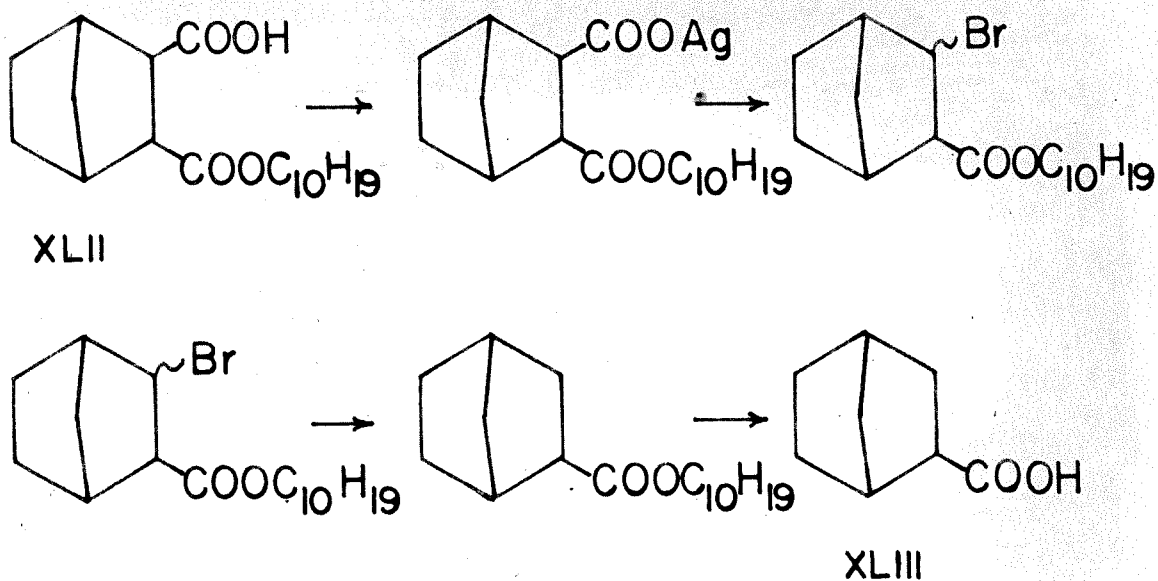
Chart 7. Degradation of (-)-menthyl hydrogen 2,3-<u>exo</u>-norbornane-
dicarboxylate, $[\alpha]_D^{25}$ - 59.2°, to (-)-2-<u>exo</u>-norbornanecarboxylic acid

infrared spectrum of the neutral products contained only one carbonyl

absorption. Accordingly, the material from the Hunsdiecker reaction

which subsequently gave <u>trans</u> 2,3-norbornanedicarboxylic acid may

have been XLIV.
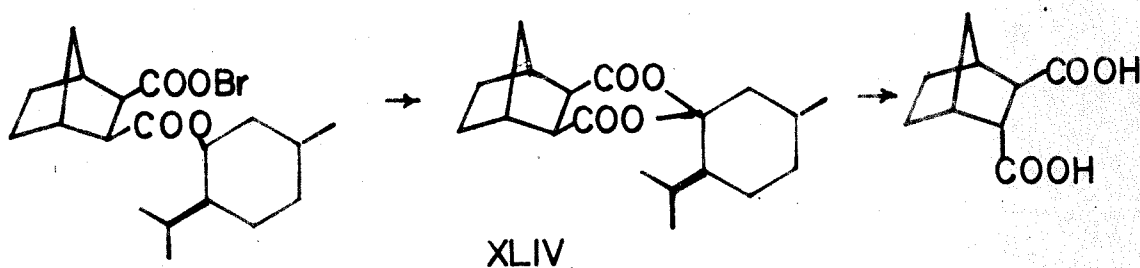
A benefit accruing to the project from this degradation variation,

besides complete resolution of the necessary chemical steps for the

selective radioactivity counting and for establishment of the absolute

stereochemistry of the intermediate acid esters, is the large increase

in molecular weight as 2,3-exo-norbornanedicarboxylic anhydride is

opened with (-)-menthol.

This circumstance, the total separation of products from the

internal and external mechanistic rearrangement pathways, and the

efficient recovery of the exo-anhydride from the rearrangement mixture

developed in the second phase of this work may well make dilution of

the exo-anhydride with inactive carrier unnecessary.

The chemical means for the stereospecific degradation of

2-norbornene-5,6-exo-dicarboxylic anhydride, and the demonstrated

absolute configurations of the intermediate (-)-menthyl hydrogen

2,3-exo-norbornanedicarboxylates, stand ready for application.

Thermal Isomerization of 2,3-endo-

Norbornanedicarboxylic Anhydride

Mechanisms 1 and 2 postulated for the internal isomerization

of 2-norbornene-5,6-endo-dicarboxylic anhydride (XLV) in Chart 1,

page 13, assign no crucial role to the carbon-carbon double bond. If

one of these hypothetical mechanisms be correct, then the analogous

saturated system 2,3-endo-norbornanedicarboxylic anhydride (XLVII)

might be similarly isomerized to its exo-isomer (XLVIII).
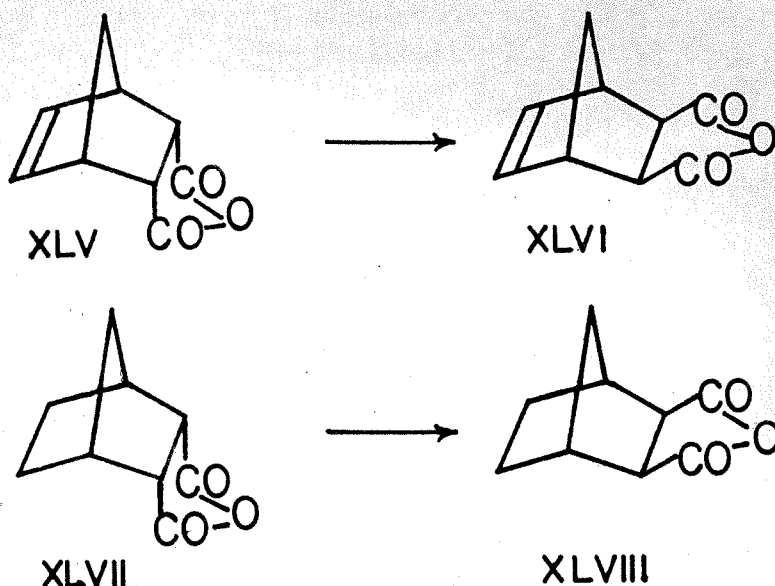
Craig (15) reported unsuccessful attempts to rearrange

2,3-endo-norbornanedicarboxylic anhydride (XLVII) to the exo-anhydride

(XLVIII) at 255° and 275-280° for two minutes. These experiments

at least show that the isomerization is not as fast as that of 2-

norbornene-5,6-endo-dicarboxylic anhydride (XLV). This difference

is not unreasonable since XLV surely has a more strained ring

system than XLVII. Thus even without invoking a special mechanism,

the norbornene endo-anhydride (XLV) is expected to be able to rear-

range at a lower temperature than the norbornane endo-anhydride

(XLVII).

2,3-exo-Norbornanedicarboxylic anhydride was heated in a

sealed tube at 250° for 18 hours to give a mixture containing 22% of

2,3-exo-norbornanedicarboxylic anhydride and 78% of 2,3-endo-

dicarboxylic anhydride. Analysis of this mixture was achieved with

n.m.r. spectroscopy, as shown on the following page in Figure 3.

FREQUENCY IN PPM (δ)

4.0   3.0   2.0   1.0   0 ppm

A

152 132   68 51   0 cps

B

137 122   40 20   0 cps

C

152 132 122   68 50   0 cps

FREQUENCY IN CPS
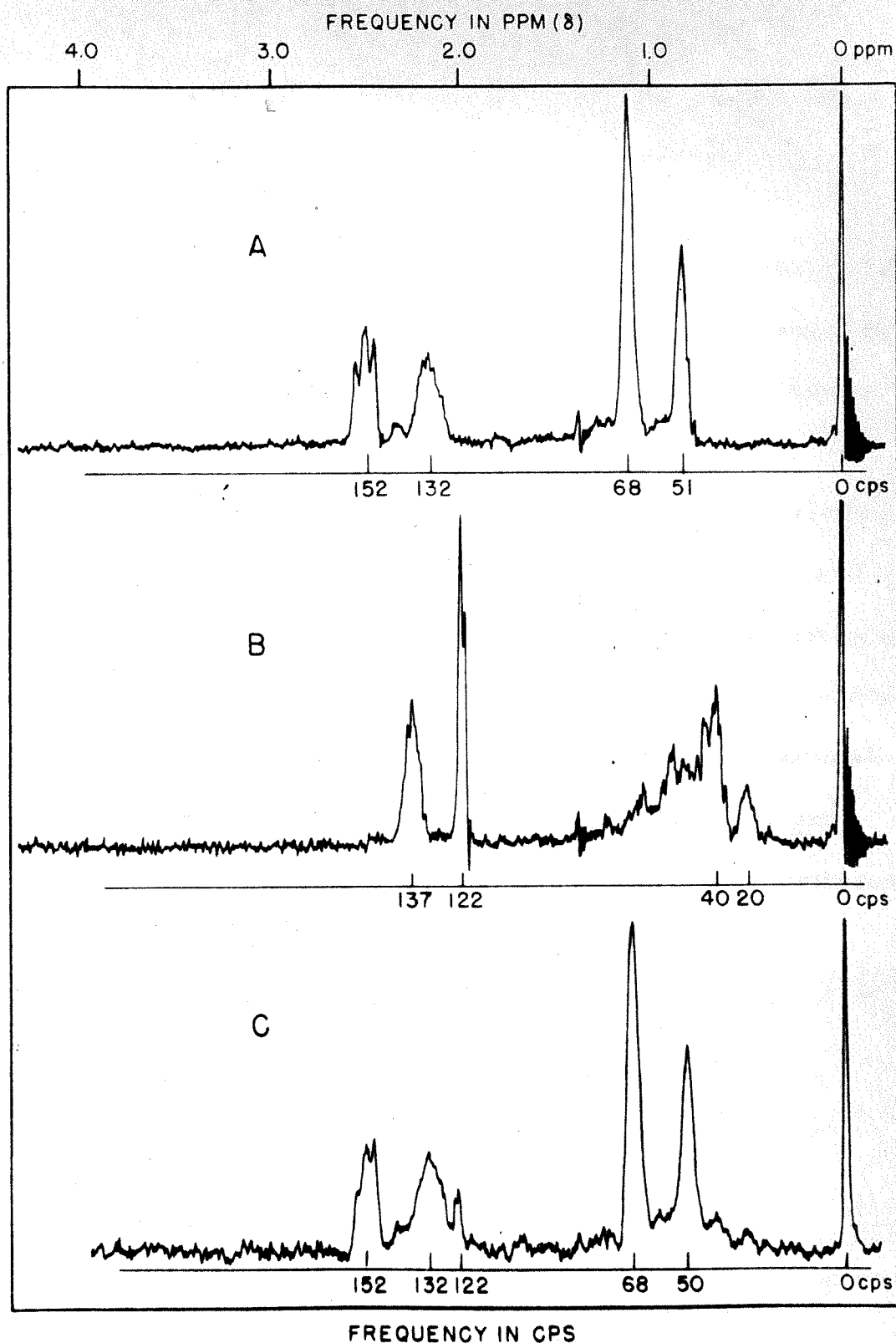
Figure 3. N. m. r. spectra of 2, 3-endo-norbornanedicarboxylic
anhydride (A); 2, 3-exo-norbornanedicarboxylic anhydride (B);
mixture of exo- and endo-isomers from the rearrangement of
the endo-anhydride (C).
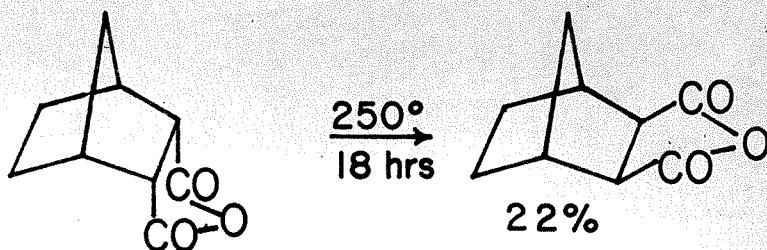
The thermal rearrangement of 2,3-endo-norbornanedicarboxylic

anhydride to its exo-isomer indicates that the internal rearrangement

of 2-norbornene-5,6-endo-dicarboxylic anhydride to its exo-isomer

may occur via rupture of the C_5-C_6 bond.

Mechanisms 7 and 8 postulated for the internal isomerization

of 2-norbornene-5,6-endo-dicarboxylic anhydride in Chart 1, page 13,

predict a migration of a hydride ion from the C_7 methylene group to

C_2. An ideal experiment to test this possibility would be the thermal

rearrangement of 7,7-dideutero-2-norbornene-5,6-endo-dicarboxylic

anhydride (XLIX). The position of the deuterium label in the exo-

anhydride (L or LI) could be easily determined by n.m.r. spectroscopic

analysis.
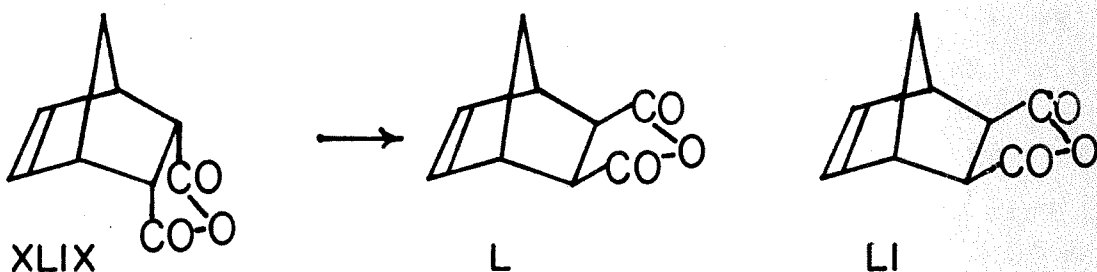
Attempts were made to thermally isomerize two more readily

accessible compounds, 1,2,3,4-tetrachloro-7,7-dimethoxy-2-

norbornene-5,6-endo-dicarboxylic anhydride (LII) and 1,2,3,4-

tetrachloro-2-norbornene-5,6-<u>endo</u>-dicarboxylic anhydride (LIII).

Methoxyl or hydride migration from C_7 to C_2 in these compounds would

be evident through infrared and n.m.r. spectroscopy.
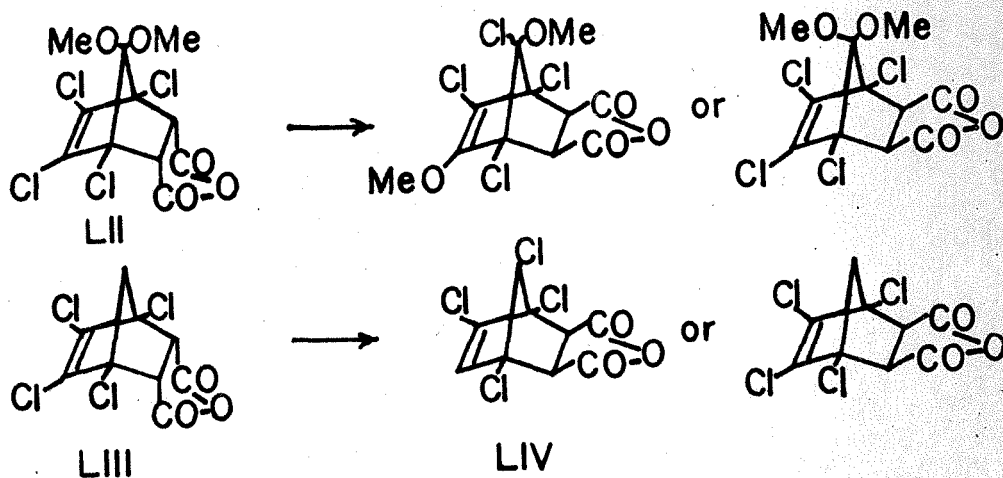
Compound LII was heated to 220° for 1.5 hours without evidence

of rearrangement. Compound LIII was thermally isomerized at 190°

to a mixture of products including LIV. The evidence for this inference

was an n.m.r. absorption shown by one rearrangement product at

328 cps below tetramethylsilane, corresponding to an olefinic hydrogen

(28).

No significant mechanistic conclusions can be drawn from these

results. Compound LIII did not rearrange when heated at 170° for

1.4 hours, but at 170-180° <u>in vacuo</u> it decomposed to give tetrachloro-

cyclopentadiene. Hence the formation of LIV may have occurred

entirely through an external mechanistic pathway, and interconversion

of the isomers of tetrachlorocyclopentadiene is not startling (29).

Summary

Attempts to synthesize stereospecifically labeled 2-norbornene-5,6-endo-dicarboxylic anhydride through ethyl cis-β-cyanoacrylate and (-)-menthyl hydrogen maleate were unsuccessful, primarily because dl-2-norbornene-5-endo-cyano-6-endo-carboxylic acid could not be efficiently resolved and (-)-menthyl hydrogen maleate labeled in only one carboxyl group could not be prepared.

A synthetic approach utilizing the Diels-Alder addition of a diasteromer of (-)-menthoxymalealdehydic acid with cyclopentadiene, shows more promise.

The thermal rearrangement of 2-norbornene-5,6-endo-dicarboxylic anhydride to its exo-isomer has an apparent activation energy of 36.7 kcal. per mole. The internal and external rearrangement routes may be separated by conducting the rearrangement in the presence of tetra-cyanoethylene. This procedure also permits running the rearrangement at low temperatures for long times, thus achieving a high internal conversion of endo-anhydride to exo-isomer.

2-Norbornene-5,6-exo-dicarboxylic anhydride has been stereo-specifically degraded through reduction, reaction with (-)-menthol, separation of the (-)-menthyl hydrogen 2,3-exo-norbornanedicarboxyl-ates, and decarboxylation. The absolute configurations of the (-)-menthyl hydrogen 2,3-exo-norbornanedicarboxylates have been estab-lished.

The thermal rearrangement of 2,3-endo-norbornanedicarboxylic anhydride to its exo-isomer occurred at 250°. This result suggests that the double bond in 2-norbornene-5,6-endo-dicarboxylic anhydride may not play a mechanistically vital role in its thermal rearrangement.

PART II

THE ALDOKETENE DIMER REARRANGEMENT

PART II

Introduction

Chick and Wilsmore's first report on diketene in 1908 (30) initiated a half-century of investigation culminating just a decade ago in consensus favoring expression I as its structural formulation.

$$CH_3COCH=C=O$$

II
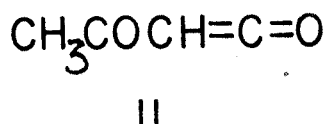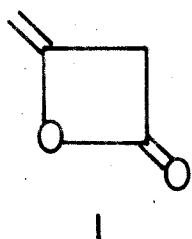
During the quest for an adequate structural designation for diketene, several alternate representations received support. Chick and Wilsmore (30) originally identified diketene as acetylketene (II). The following year, Staudinger and Bereza (31) postulated a cyclo-butenol-3-one structure (III) for the molecule. Chick and Wilsmore (32) countered this suggestion with a new proposal, 1,3-cyclobutane-dione (IV). In 1935, Hurd and co-workers (33) argued for structure V, β-crotonolactone, and in 1940, Williams (34) advanced the correct formula (I).
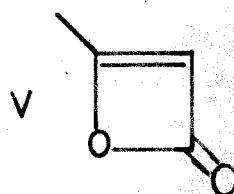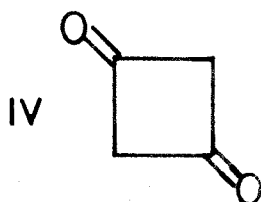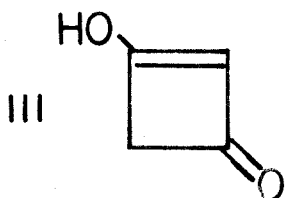
After 1940, physical methods dominated new investigations of this structural problem, and several interpretations were advanced which posited two molecular forms for diketene. For example, when ultraviolet spectroscopic studies indicated diketene to be IV (35) and therefore were suspect in light of its dipole moment of 3.31 D (36), diketene was suggested to be a mixture of III and IV (35). Further, the infrared spectrum of diketene was reported markedly temperature dependent, and this was rationalized in terms of an equilibrium between structures I and V (37). Another interpretation of the infrared spectrum of diketene represented diketene as an equilibrium mixture of forms I and IV (38).

Finally, x-ray and electron diffraction studies (39) and the hydrogenation of diketene to β-butyrolactone (40) firmly established the structure as I or V, and this last ambiguity was resolved in favor of structure I with the aid of n.m.r. spectroscopy (41).

A review article on the chemistry of diketene appeared in Uspekhi Khimia in 1956 (42).

Aldoketenes (VI) are capable of forming both neutral and acidic dimers. Structure VII is generally accepted for the neutral dimers (43)

and structure VIII has been assigned to the acidic methylketene dimer

(44).
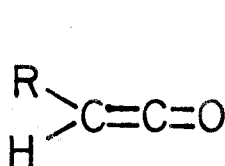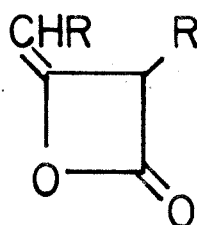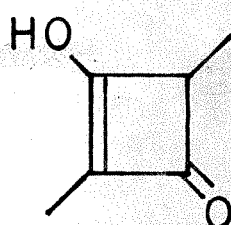
| VI | VII | VIII |

Ketoketenes (IX) dimerize to produce tetrasubstituted cyclo-

butane-1,3-diones (X) (45). Recently the isomerization of tetramethyl-

cyclobutane-1,3-dione (XI) to the β-lactone XII has been reported (46).
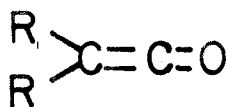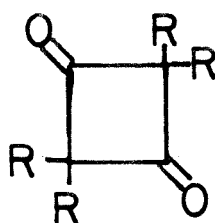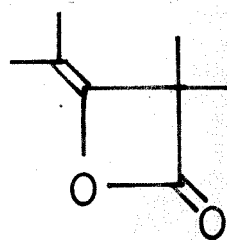
| IX | X XI, R=CH₃ | XII |

With these basic structural assignments for diketene, aldoketene

dimers, and ketoketene dimers secured, research has been initiated on

other aspects of ketenes and ketene dimers. Newman and co-workers

have synthesized di-t-butylketene, the first stable ketene (47). Two

unstable diketenes, XIII and XIV, were isolated in 1957 (48). Yates

and Chandross have established structures XV and XVI for the ketene

dimers derived from d-camphor-3-carboxyl chloride (49). In 1958,

Grenter observed a ketene dimerization reaction from the thermal

splitting of 21-diazo-20-keto-5α-pregnane (50) (however, compare Ref.

51). And, most recently, several groups have studied the reactions

of tetramethylcyclobutane-1,3-dione, which is now commercially

available (52).
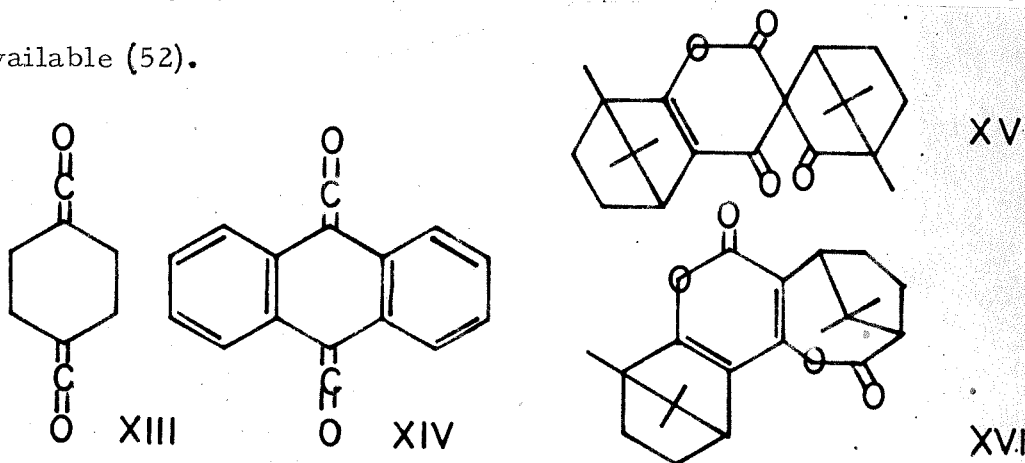
This fresh interest in ketene dimers has partially obscured an

unresolved question concerning the structural work. Staudinger reported

a base-catalyzed rearrangement of the neutral phenylketene dimer to

its acidic isomer (53) and of the neutral methylketene dimer to its

acidic form (54). In terms of his structural formulations these

isomerizations were interpreted as simple tautomerizations.
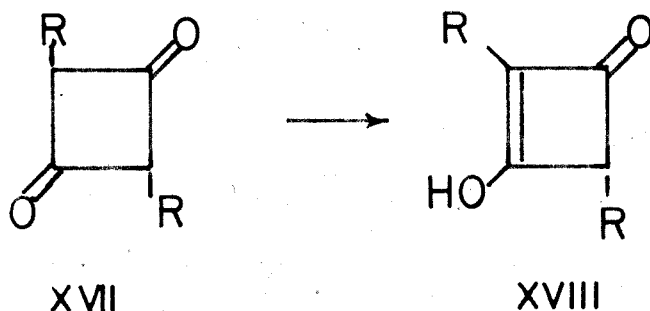
In terms of the presently accepted structures, these aldoketene

dimer rearrangements would involve an extensive structural reorgan-

ization.
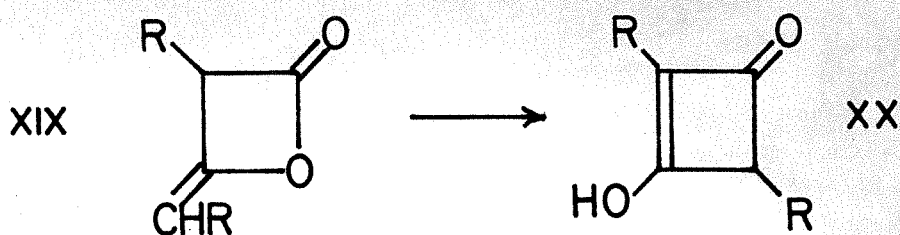
This dilemma could be resolved in several ways. One or both of the currently accepted structural formulas for the neutral and acidic aldoketene dimers may be in error. There may be two neutral aldoketene dimers (55), and only one of these may enter the rearrangement. The rearrangement may not occur. Or the rearrangement does occur and may be rediscovered.

The present work addressed these alternatives concerning the aldoketene dimer rearrangement. Its results are now presented.

Results and Discussion

First, the currently accepted structures for the neutral and acidic methylketene dimers were confirmed. Published evidence on these compounds (56) and their n.m.r. spectra combine to demonstrate rigorously the validity of their representation by formulas XXI and XXII. These n.m.r. spectra are reproduced in Figure 4, page 50. Of particular note is the extraordinary deshielding of the enolic hydrogen in the acidic dimer XXII, whose signal appears 627 cps below tetramethylsilane. The spectrum of the neutral methylketene dimer is not consistent
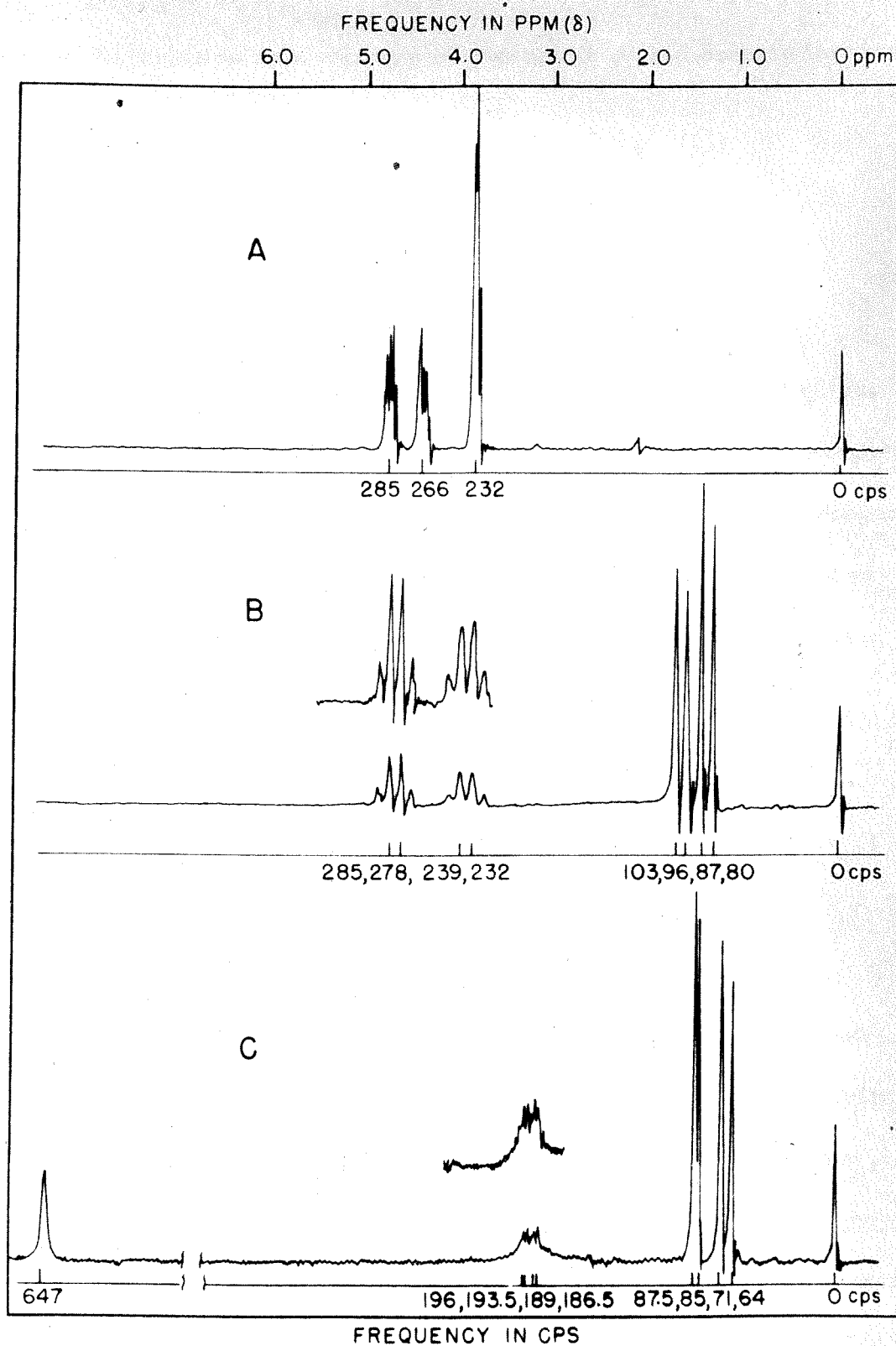
Figure 4. N.m.r. spectra of diketene (A); neutral methylketene dimer (B); acidic methylketene dimer (C)

with its formulation as a mixture of geometric or tautomeric isomers.
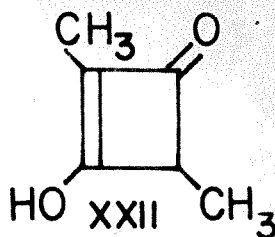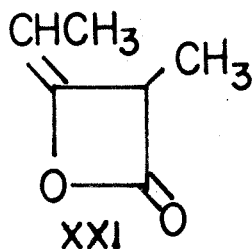
Second, the neutral phenylketene dimer was reinvestigated.

Structure XXIII for this dimer was established by its known reactions

(53), spectral properties, and consumption of two moles of hydrogen

to give α,γ-diphenylbutyric acid (XXIV). A portion of the infrared

spectrum of neutral phenylketene dimer is shown in Figure 5, page

52.
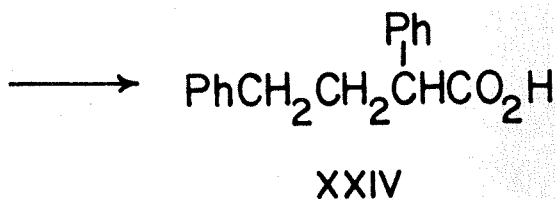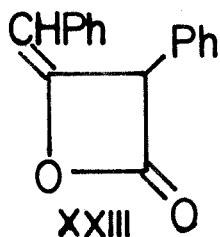
The geometry about the exo-cyclic double bond in the neutral

methylketene and phenylketene dimers remains unsettled. The ultra-

violet absorption spectra of diketene, neutral methylketene dimer,

and dimethylketene β-lactone dimer are strikingly similar, as shown

in Figure 6, on page 53; thus no conclusions concerning the geometry

of the neutral methylketene dimer can be deduced from them. The

n.m.r. spin-spin coupling constants between the olefinic and methine
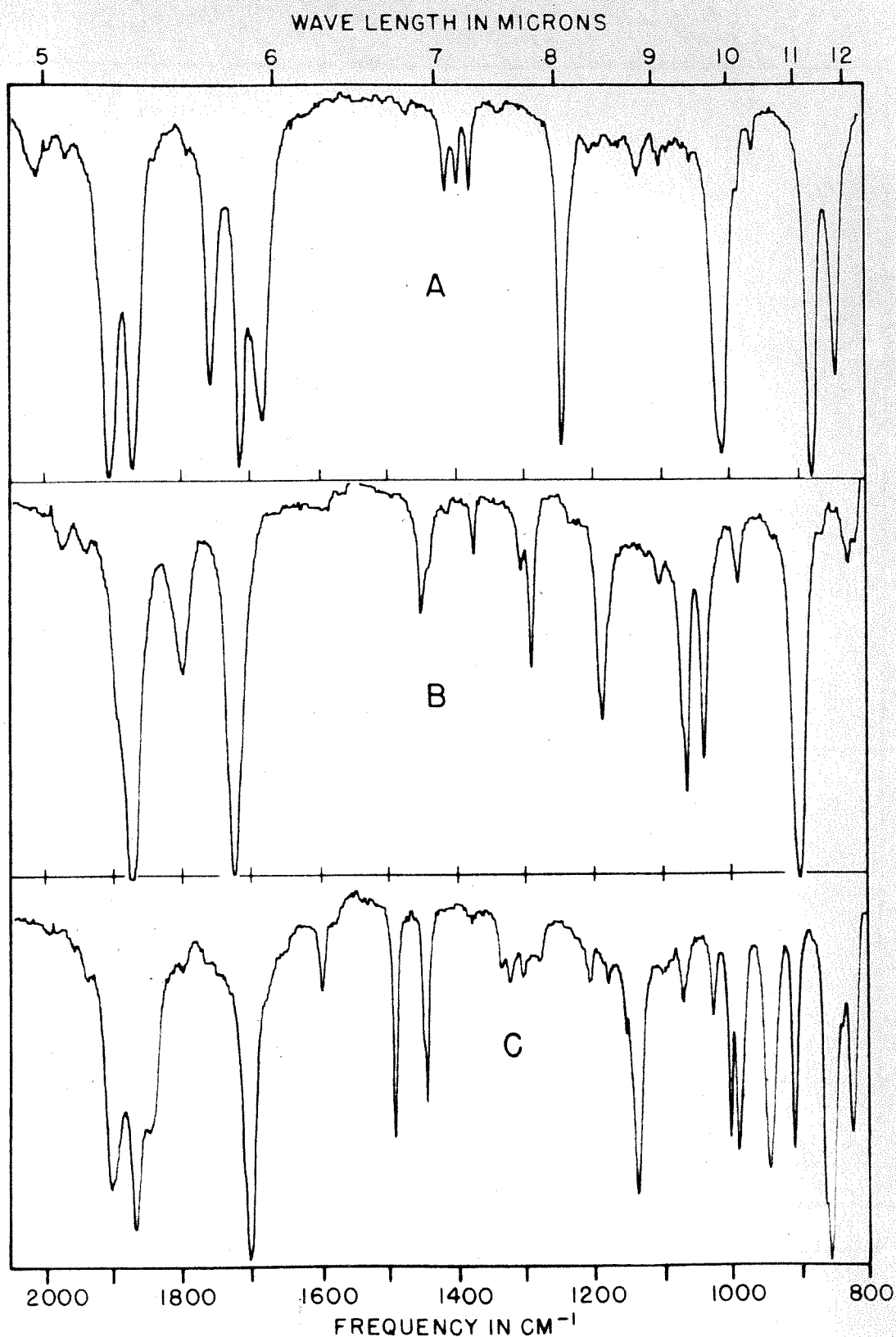
Figure 5. Infrared absorption spectra of diketene (A); neutral methylketene dimer (B); neutral phenylketene dimer (C)
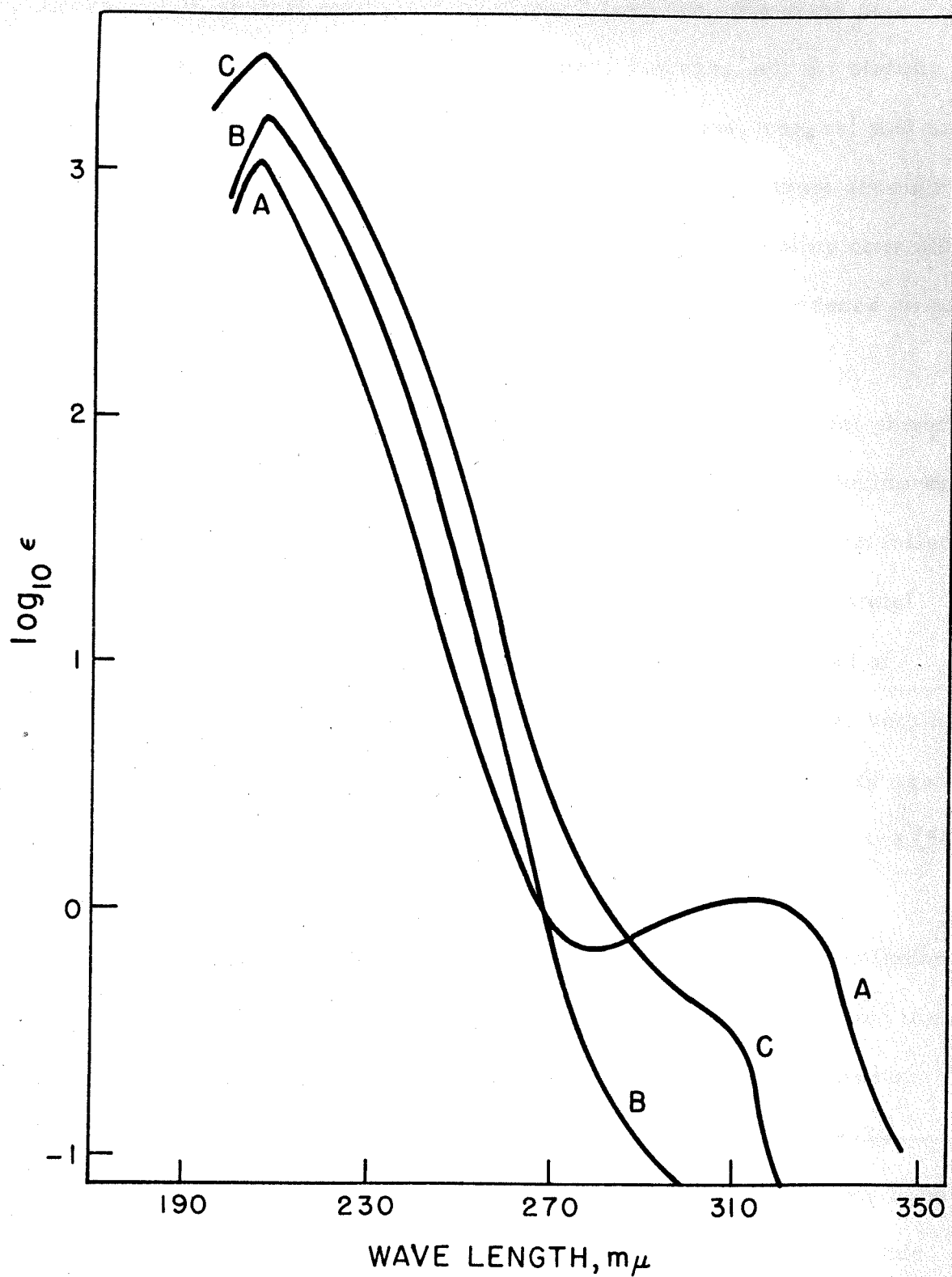
Figure 6. Ultraviolet absorption spectra of diketene (A); neutral
methylketene dimer (B); dimethylketene β-lactone dimer (C)

hydrogens in neutral methylketene dimer, 1.41 cps, the same pair

of hydrogens in neutral phenylketene dimer, 1.4 cps, and the olefinic

and methylene protons in diketene, 1.48 and 1.89 cps, suggest that the

neutral methylketene and phenylketene dimers have the same geometry.

While lacking a rigorous assignment for the two 1,4-coupling constants

in diketene (cf. Ref. 57), no decision based on n.m.r. evidence as to

the geometry of the neutral aldoketene dimers can be made.

Some difficulties were encountered in preparing neutral phenyl-

ketene dimer through dechlorination of phenylchloroacetyl chloride with

zinc. Two alternate synthetic approaches were tested, but both failed

to produce the desired dimer. Dehydrochlorination of phenylacetyl

chloride under mild conditions gave a mixture of products void of

neutral phenylketene dimer. Photolysis of diazoacetophenone, both in

the presence and absence of ferric dipivaloylmethide, a valuable agent

for catalyzing multiplicity changes during photochemical reactions (58),

gave mainly a colorless intractable solid (cf. Ref. 59).

Third, a by-product from the synthesis of neutral methylketene

dimer was investigated, on the possibility that it might have been the

geometrical isomer of the dimer. This substance was identified as

3,5-dimethyl-6-ethylpyronone (XXV) on the basis of its elemental

analysis, molecular weight, and spectral properties. Its strong bands

in the infrared spectrum at 1785 and 1765 cm^{-1} are carbonyl bands

for the vinylogous anhydride system, the absorption at 1660 reveals a

carbon-carbon double bond, while the carbon-oxygen stretching

vibrations in the lactone are found at 1145 and 1105 cm^{-1}. The ultra-

violet absorption maximum at 234 mμ is close to the predicted maxi-

mum of 238 mμ obtained by neglecting any solvent correction between

cyclohexane and hexane (60). The n.m.r. spectrum of this substance

contained absorptions centered at 219 cps from a single proton split

twice into quartets (J = 7.0, 2.3 cps), a quartet centered at 157 cps

from two protons (J = 7.5 cps), and a complicated methyl-proton region

dominated by sharp signals of approximately equal intensity at 97, 94.7,

74, and 67 cps.
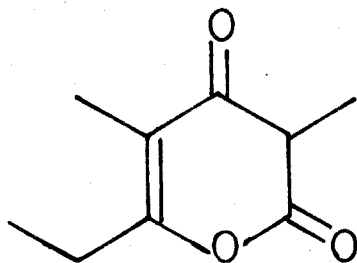
XXV

Wedekind has reported a methylketene trimer of m.p. 151°

as 3,5-dimethyl-6-ethylpyronone, and a phenylketene trimer of m.p.

171-172° as 3,5-diphenyl-6-benzylpyronone (61). The latter was syn-

thesized and found to contain strong infrared absorptions at 3490,

1700, and 1560 cm^{-1}. This new evidence and Wedekind's results

suggest that the phenylketene trimer of m.p. 171-172° is probably

best reformulated as XXVI. Similarly, Wedekind's methylketene trimer

of m.p. 151°, which can be titrated sharply with standard alkali (61),

should be assigned the structure XXVII.
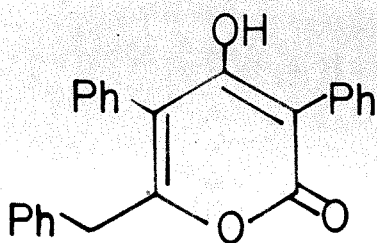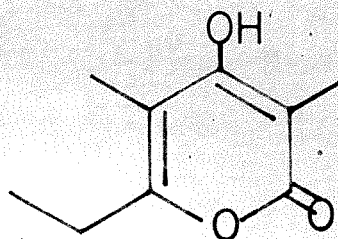
XXVI   XXVII

Fourth, attempts to effect the aldoketene dimer rearrangement
with the neutral methylketene dimer gave two polymerization products.
In the presence of mild basic catalysts, the neutral methylketene dimer
dimerized, while under stronger basic conditions, it trimerized. No
rigorous structural assignments could be made for these compounds;
possible formulations consistent with the available information (cf.
Experimental) are XXVIII and XXIX.
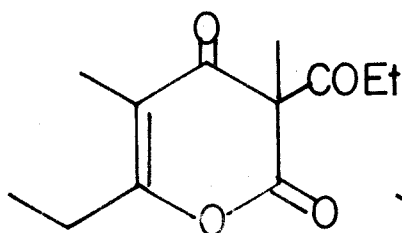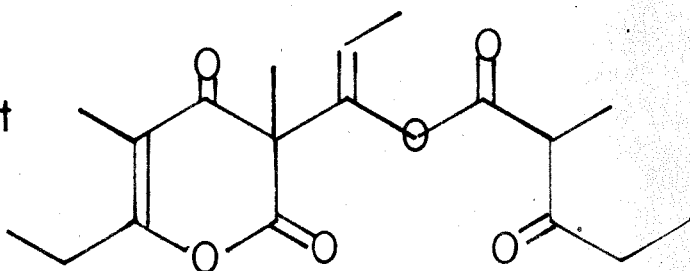
XXVIII   XXIX

Fifth, the base-catalyzed rearrangement of neutral phenyl-
ketene dimer to an acidic isomer reported by Staudinger and Bereza
in 1911 (53) was successfully repeated.
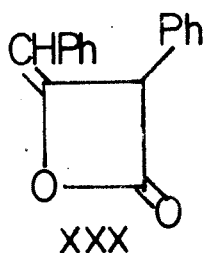
XXX $C_{16}H_{12}O_2$
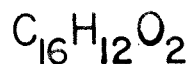
XXXI

Elemental analysis and a neutralization equivalent of 237.7

($C_{16}H_{12}O_2$ requires 236) established the molecular formula of the

acidic product as $C_{16}H_{12}O_2$ (53). It discolors permanganate and bro-

mine solutions and gives a positive ferric chloride color test. Its

infrared spectrum contains no bands characteristic of an alcohol or

carboxylic acid, but has a strong carbonyl absorption at 1708 cm^{-1}.

The acidic methylketene dimer has no infrared absorptions

corresponding to an alcohol, and its carbonyl band occurs at 5.8 μ

(1724 cm^{-1}) (62). The infrared and concentration-dependent ultra-

violet absorption spectra for acidic methylketene dimer indicate that

the solid dimer exists in the diketo form, but in solution it is in equi-

librium with and almost entirely converted to the enolic form.

The chemical and infrared spectroscopic evidence then may be

interpreted to support structure XXXII or XXXIII for the acidic phenyl-

ketene dimer. N.m.r. spectroscopy did not provide conclusive

evidence. A dimethylsulfoxide solution of the dimer showed three

groups of signals: at 470-450 (2.0 protons), 450-420 (10 protons) and

274 cps (1.6 protons). This spectrum implies that the acidic phenyl-

ketene dimer, whatever its structure, had reacted with the solvent.

There are several possible mechanistic paths for the rearrangement of neutral phenylketene dimer to its acidic isomer. For instance, the hydroxide ion could abstract the α-hydrogen to produce a ketene intermediate, or attack the carbonyl carbon, or add to the <u>exo</u>-cyclic double bond.
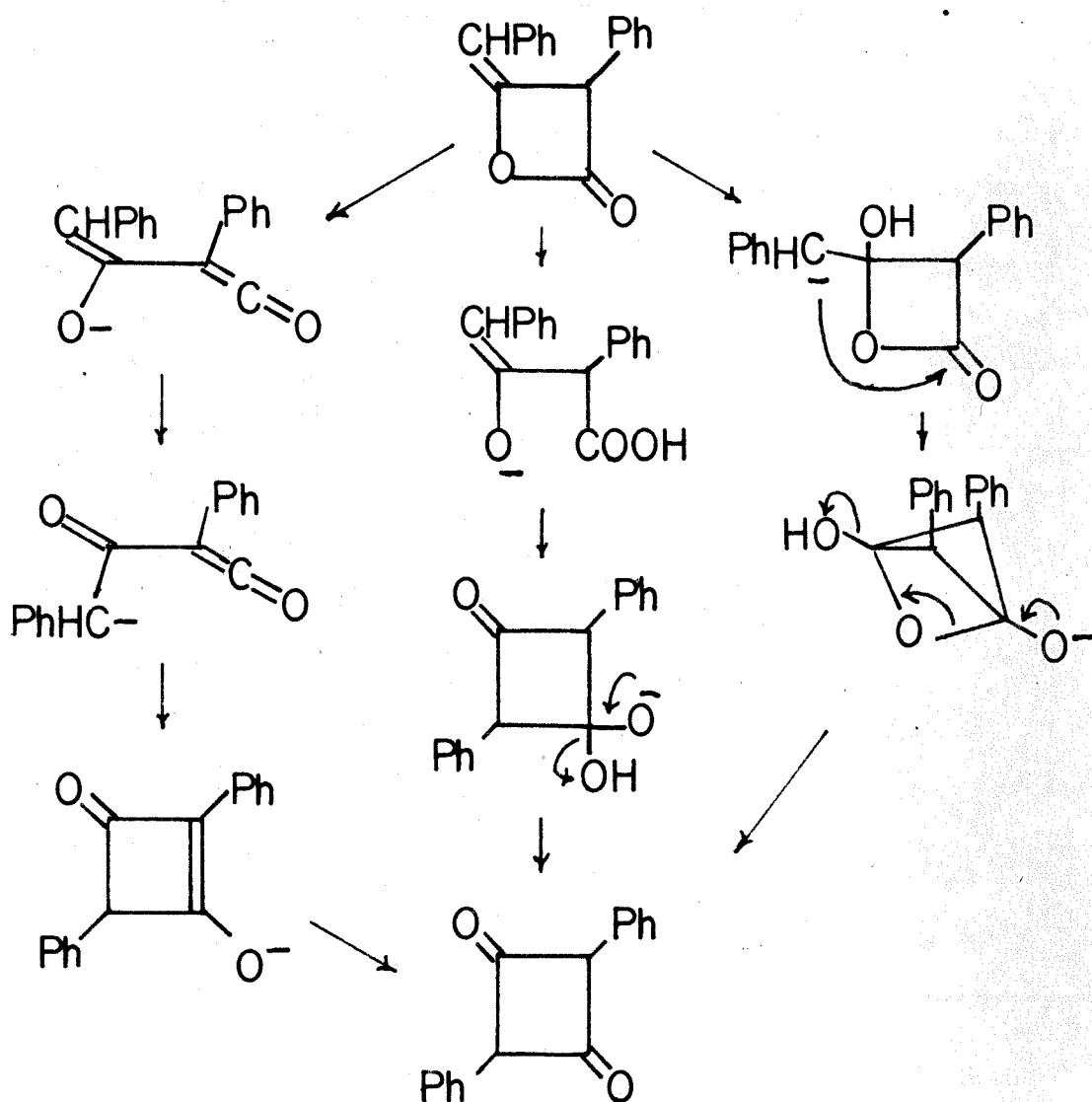
Summary

This study, then, has produced the following results. The established structures of the neutral and acidic methylketene dimers have been confirmed by n.m.r. data. Neutral methylketene dimer has been shown to be a single species, and not a mixture of tautomeric or geometric isomers. The neutral phenylketene dimer has been synthesized, identified, and converted to α, γ-diphenylbutyric acid. 3,5-Dimethyl-6-ethylpyronone and 3,5-diphenyl-4-hydroxy-6-benzyl-pyrone have been synthesized and identified. Attempts to effect the aldoketene dimer rearrangement were unsuccessful with neutral methylketene dimer, but neutral phenylketene dimer did undergo this rearrangement. Finally, tentative suggestions for the structure of Wedekind's methylketene trimer of m.p. 151° and the structure of the acidic phenylketene dimer have been made.

EXPERIMENTAL

EXPERIMENTAL

Elemental analyses were performed by Dr. Adalbert Elek,

Elek Microanalytical Laboratories, Los Angeles, California, and by

the Spang Microanalytical Laboratories, Ann Arbor, Michigan.

All melting points and boiling points are uncorrected. Melting

points were determined on a Reichert Kofler Block apparatus or with

a modified Hershberg melting-point apparatus.

Infrared absorption spectra were recorded using a Perkin-

Elmer double-beam infrared spectrometer, Model 21, or a Perkin-

Elmer NIR 137-G Infracord spectrometer, or a Beckman infrared

spectrometer, Model IR-7.

Ultraviolet absorption spectra were obtained using a Cary

recording spectrometer, Model 11M, with cyclohexane as solvent.

Nuclear magnetic resonance spectra were taken at 60 Mc. on

either a Varian Model V4300 D spectrometer having a 12-inch magnet

equipped with Super Stabilizer, constant-temperature magnet cooling,

and field homogeneity control coils, or a Varian A-60 High Resolution

Spectrometer. Chemical shift values are quoted in cps relative to

tetramethylsilane as an internal standard.

Vapor phase chromatographs were obtained with a Perkin-

Elmer Vapor Fractometer, Model 154-B. Column designations refer

to the following stationary phases: Column C, dimethylsiloxane polymer

(silicone oil DC-200); Column K, polyethylene glycol (carbowax 1500).

Optical rotations were measured with a Winkel-Zeiss polarimeter (Göttingen, Nr. 100542) and a 1-dm. polarimetry tube, or with a Model 200S Rudolph High-precision Photoelectric Spectropolarimeter with oscillating polarizer and a 2.085-dm. or 2.120-dm. polarimetry tube. The use of the latter instrument was made possible through the courtesy of Professor R. L. Sinsheimer and Dr. C. Sander of the Biology Division. Rotations lacking a solvent citation were measured in 95% ethanol.

PART I

Maleamic Acid. - (63) Forty grams of maleic anhydride and 450 ml. of xylene were placed in a 1-liter three-necked flask equipped with a gas inlet, mechanical stirrer, reflux condenser and a thermometer. The mixture was stirred and brought to 65°; then ammonia was conducted into the flask above the surface of the reaction mixture until it was no longer consumed (about 20 minutes) while the temperature reached 88°. The flask was cooled and the maleamic acid was collected, washed with xylene and vacuum-dried to give 47 g. (100% yield) of product, m.p. 154-157°. In other reactions, products having melting points as high as 164-167° in yields as low as 85% were obtained. The literature melting point is 165-168° (64).

Ethyl cis-β-Cyanoacrylate. - (65) A mechanically stirred mixture of dichloromethane (1350 ml.) and maleamic acid (132 g., 1.14 mole) was cooled to 0°; dry triethylamine (240 g., 2.37 mole) was added, and the reaction mixture was again cooled to 0°. Ethyl chloroformate (255 g., 2.35 mole) was added over a 3.2-hour period while the temperature of the reaction mixture was kept between 0 and +5°. The reaction flask was stoppered and left to stand overnight.

In the morning, the triethylamine hydrochloride was removed by filtration and the dichloromethane distilled from the filtrate under reduced pressure. The residue was taken up in dry ether, filtered

and again concentrated by distillation under reduced pressure. The product was distilled and redistilled through a 30-cm. Holzman column, b.p. 60-63° (1 mm.), n_D^{25} 1.4509, 115 g. (81% of theory) (lit. b.p. 53-54° (0.15 mm.), n_D^{25} 1.4510 (65)).

Propiolic Acid. - (66) The mono-potassium salt of acetylene-dicarboxylic acid (98.4 g.) in 300 ml. of water was heated for 3 hours on a steam bath. The aqueous solution was cooled, acidified with sulfuric acid, saturated with ammonium sulfate, and continuously extracted with ether overnight. In the morning, the ethereal extract was dried by repeated treatment with calcium chloride and finally with Drierite, filtered, and concentrated by distilling the ether off through a 90-cm. glass helix-packed column. The propiolic acid was distilled through an 18-cm. Vigreux column and had b.p. 62-64° (18 mm.); the yield was 23.6 g. (52% of theory). In other preparations, yields of 29-34% were obtained.

Ethyl Propiolate. - (67) A solution of propiolic acid (32.7 g.), concentrated sulfuric acid (10 ml.) and absolute ethanol (100 ml.) was heated almost to reflux for one hour, allowed to stand at room temperature for 21 hours, and poured into an excess of cold sodium bicarbonate solution. The ester was extracted with ether and the ethereal solution was dried over calcium chloride, filtered and concentrated by distillation of the ether through a 90-cm. glass helix-packed column. The crude product was distilled through a 30-cm.

Holzman column to give two fractions of b.p. 110-117° (745 mm.),
n_D^{25} 1.4088, 4.43 g., and b.p. 117° (745 mm.), n_D^{25} 1.4094,
24.7 g., whose combined weights represent a yield of 64%.

Ethyl trans-β-Cyanoacrylate from Ethyl Propiolate. - (68) Dry
hydrogen cyanide was prepared according to the recommendations of
Vogel (69). Five grams of ethyl propiolate, 2.2 g. of hydrogen
cyanide and 0.4 g. of sodium cyanide were stirred at 35-40° for 7
hours. Distillation of the reaction mixture gave 0.5 g. (8% of theory)
of ethyl trans-β-cyanoacrylate with b.p. 56-60° (4 mm.) which was
identified by infrared spectroscopic and v.p.c. analyses.

Ethyl trans-β-Cyanoacrylate from Sodium Cyanide and Ethyl
α-Chloroacrylate. - This preparation was patterned after the procedure
of Crawford, McLeish, and Wood (70) (see also Ref. 65). To a 200-ml.
three-necked flask equipped with an all-glass mechanical stirrer which
contained 30 g. (0.22 mole) of ethyl α-chloroacrylate, 0.1 g. of hydro-
quinone and 20 g. of acetone was added a solution of sodium cyanide
(8 g., 0.16 mole) and sodium bicarbonate (1 g.) in 25 ml. of water.
The addition was completed in 15 minutes while the temperature of
the reaction mixture was kept below 40°. After the reaction mixture
had been stirred another 6 hours, it was extracted with dichloromethane.
Distillation of the organic material gave 14.3 g. of material with b.p.
36-49° (1 mm.) which v.p.c. analysis indicated to be 35% ethyl
trans-β-cyanoacrylate. The principal impurity was unreacted ethyl

α-chloroacrylate. Distillation of material caught in a Dry Ice trap

during the first distillation gave 5.2 g. of product, b.p. 90-93° (34

mm.). The combined yield of these two lots of ethyl trans-β-cyano-

acrylate amounted to 50% of theory.

Ethyl trans-β-cyanoacrylate had a retention time of 2.7 minutes

on a Perkin-Elmer v.p.c. Column C at 189° and 25 psi of helium.

Ethyl cis-β-cyanoacrylate had a retention time of 7.1-7.2 minutes on

a Perkin-Elmer v.p.c. Column K at 140° and 25 psi of helium; the

trans-isomer under these conditions came off the column in 16.6-16.9

minutes.

The synthesis of ethyl trans-β-cyanoacrylate described above

gives a reaction mixture that is black, opaque and prone to form

emulsions. When the reaction mixture is kept at lower temperatures

during the addition, e.g., below 25°, it remains clear and only slightly

discolored, but the yields from the preparation are greatly reduced.

Photoisomerization of cis and trans Ethyl β-Cyanoacrylate. -

Solutions of cis and trans ethyl β-cyanoacrylate and a photosensitizer

(acetophenone, 2-acetonaphthone, or benzil) in benzene were prepared

and placed before light from a Hanovia quartz immersion reactor.

Analysis of the isomerization products was done through examination

of the appropriate vinyl proton n.m.r. signals. The equilibrium mix-

ture of the two isomers, approached from either side, was attained

within 20 hours and contained approximately 45% of the cis-form.

Ethyl 2-Norbornene-5-endo-cyano-6-endo-carboxylate. - Ethyl

cis-β-cyanoacrylate (140 g., 1.12 mole) was added in 80 minutes to

freshly distilled cyclopentadiene (87 g., 1.32 mole). The reaction

mixture was stirred mechanically and cooled with an ice bath during

the addition; it was allowed to stand overnight, and, in the morning,

the product was distilled directly from the reaction flask. There was

obtained 212 g. (99% yield) of distillate having b.p. 102-107° (1 mm.).

This distillate crystallized and the crystals had m.p. 36-37.6°.

2-Norbornene-5-endo-cyano-6-endo-carboxylic Acid. - A mix-

of ethyl 2-norbornene-5-endo-cyano-6-endo-carboxylate (4.41 g., 23.1

mmole) and a solution of sodium hydroxide (0.95 g., 23.1 mmole) in

25 ml. of distilled water was refluxed for 1.5 hours. The resulting

pale yellow solution was cooled and acidified with hydrochloric acid.

The oil which separated was transformed into a pasty solid through

scratching and cooling. The following day, the solid was collected by

suction filtration and thoroughly dried to give 2.4 g. (64% of theory)

of material of m.p. 87-111°. Recrystallization of this solid from

water-acetic acid raised the melting point to 124-126°. An analytical

sample of m.p. 125.5-126.5° was prepared by sublimation followed

by recrystallization from water.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56. Found:

C, 66.11; H, 5.63.

Several other hydrolytic approaches for this preparation were

found to be less effective. These included trials with more dilute aqueous sodium hydroxide, dilute sodium bicarbonate, glacial acetic acid and hydrochloric acid, ethanolic potassium hydroxide, and aqueous-alcoholic sodium hydroxide.

Resolution of 2-Norbornene-5-endo-cyano-6-endo-carboxylic Acid. - The brucine salt of 2-norbornene-5-endo-cyano-6-endo-carboxylic acid was prepared from 13.6 g. of the acid and 36 g. of brucine by dissolving the components in hot acetone, filtering the solution and allowing the solution to cool. The salt was subjected to systematic fractional recrystallization from absolute ethanol (71). Samples of the brucine salt from the various crops were decomposed with dilute hydrochloric acid and the active cyanoacids were collected. The optical rotations of the brucine salts and the corresponding acids are linearly related. A sample of cyanoacid which gave no increase in rotation on further resolution through its brucine salt was not obtained. The data are recorded in Table 1.

Norbornane-2-endo-cyano-3-endo-carboxylic Acid. - A mixture of 2-norbornene-5-endo-cyano-6-endo-carboxylic acid (3.06 g.), ethyl acetate (30 ml.) and platinum oxide (25 mg.) was placed in a Parr bomb and hydrogenated. The catalyst was removed by filtration and the solvent was removed under reduced pressure to give norbornane-2-endo-cyano-3-endo-carboxylic acid (m.p. 82-83°, 2.98 g., 96% of theory).

Table 1

Crop	Weight, g.	$[\alpha]_D$, Brucine Salt	$[\alpha]_D$, Cyanoacid
1	21.3	-28°	-10°
2	6.0	-25	- 9
3	8.6	-21	+ 6
4	14.7	-17	+ 9
1A	15.6	-34	-15
2A	7.5	-27	- 8
3A	7.3		
4A	13.3	-20	+ 7
1B	10.7	-40	-15
2B	7.1		
3B	6.8		
4B	10.9		
1C	7.5	-54	-17
2C	8.0	-34	
3C	5.5	-31	
4C	10.6	-20	
1D		-43	-23
1E	2.2	-60	-29
1F		-51	-23
1G	0.5	-57	-33
1' (from ML-4A-C)		- 6	+22
2'		+ 3	+26

(All rotations were determined at 26-30° with chloroform as solvent.)

2-Bromonorbornane-3-endo-nitrile. - A solution of bromine

(1.01 g., 6.3 mmole) and norbornane-2-endo-cyano-3-endo-carboxylic

acid (1.04 g., 6.3 mmole) in 15 ml. of chloroform was added dropwise

to a magnetically stirred mixture of red mercuric oxide (0.76 g., 3.5

mmole) and chloroform (2 ml.). The reaction mixture was heated

over a hot water bath during the addition and was stirred for one hour

thereafter. Excess bromine was destroyed with solid sodium bisulfite.

The cooled reaction mixture was filtered through sintered glass and

the filtrate was washed first with aqueous sodium bicarbonate and then

with saturated sodium chloride. The chloroform solution was dried

over calcium chloride, decanted and concentrated by distillation under

reduced pressure to leave 0.47 g. of liquid residue; this crude material

was used directly in the following preparation, since attempts to purify

the decarboxylation product through vacuum distillation were not suc-

cessful in earlier experiments.

2-endo-Norbornanecarboxyamide. - A solution of crude 2-

bromonorbornane-3-endo-nitrile (0.47 g.) in 25 ml. of methanol, 2.5 g.

of Busch and Stöve catalyst (72) and 25 ml. of 10% methanolic potassium

hydroxide were placed in a Parr bomb and hydrogenated. The catalyst

was removed by filtration and washed with methanol; after 7 ml. of

water was added to the filtrate, 65 ml. of methanol and water were

distilled. The residue was made acidic with concentrated hydrochloric

acid and extracted twice with 10-ml. portions of ether. The combined

ether extracts were washed with 2 ml. of brine and dried over calcium chloride. The dry ethereal solution was filtered and concentrated by distillation to leave 0.29 g. of residue. The crude product was dissolved in acetonitrile, treated with charcoal, and filtered. The filtrate was concentrated and cooled overnight in the refrigerator; the crystals which deposited were collected by centrifugation, washed with acetonitrile and dried to give 15 mg. of 2-endo-norbornanecarboxyamide, m.p. 200-203°. This material was recrystallized from methanol to give crystals of m.p. 201-202° (lit. m.p. 205-206° (73)); the compound had a carbonyl absorption in the infrared at 1703 cm^{-1}.

2-Norbornene-5,6-endo-dicarboxylic Acid. - Ethyl 2-norbornene-5-endo-cyano-6-endo-carboxylate (0.65 g.) was hydrolyzed by heating for 3.5 hours in 13 ml. of 1.3 N aqueous sodium hydroxide solution under reflux. The reaction mixture was cooled, washed once with 10 ml. of ether, acidified with hydrochloric acid, and placed in the refrigerator. The crystals which were deposited from the solution and isolated through centrifugation had m.p. 175-179° and amounted to 0.51 g. (92% of theory). One recrystallization from water raised the melting point to 179-181°. The literature gives m.p. 177-179° (74) and 192-194° (75) for 2-norbornene-5,6-endo-dicarboxylic acid.

A solution of 2-norbornene-5-endo-cyano-6-endo-carboxylic acid (0.85 g.) in 6 ml. of 2 N sodium hydroxide was refluxed for 5 hours. The solution was treated with Supercal, centrifuged, transferred to a

fresh test tube and acidified with concentrated hydrochloric acid. The

solid was collected and recrystallized from water to give 0.72 g.

(76% of theory) of the diacid having m.p. 180-188°.

Direct hydrolysis of 2-norbornene-5,6-endo-dicarboxylic

anhydride with dilute hydrochloric acid gave colorless crystals of the

diacid of m.p. 192-194°.

2-Norbornene-5,6-endo-dicarboxylic Anhydride from 2-

Norbornene-5,6-endo-dicarboxylic Acid. - A mixture of 3.99 g. (22

mmole) of 2-norbornene-5,6-endo-dicarboxylic acid, m.p. 192-194°,

and freshly distilled acetic anhydride (2.25 g., 22 mmole) in a 15-ml.

centrifuge tube, which was fitted with an air condenser, was heated on

a steam bath for 1 hour and with a microburner for 1 minute. The

reaction solution was allowed to stand overnight. In the morning, the

product was collected by centrifugation and was vacuum-dried, m.p.

162-163°, 3.49 g. (97% of theory).

Synthesis of the Brucine Salt of 2-Norbornene-5-endo-cyano-

C^{14}-6-endo-carboxylic Acid. - A total of 2.0 mc. of sodium cyanide-

C^{14} and 0.52 mole of inactive sodium cyanide was used in two prepara-

tions of ethyl trans-β-cyano-C^{14}-acrylate (see page 65). The crude

product, 16.6 g., was combined with 100 ml. of benzene and 1 g. of

acetophenone in an immersion reactor and irradiated for 18 hours.

The ethyl trans-β-cyanoacrylate, b.p. 90-93° (34 mm.) and ethyl

cis-β-cyanoacrylate, b.p. 62-63° (1.2 mm.) were separated by

distillation of the former through a 30-cm. Holzman column. The

trans-isomer was re-isomerized a second and a third time. The com-

bined distillation residues of ethyl cis-β-cyanoacrylate from the three

photoisomerization cycles and 15.8 g. of inactive ethyl cis-β-cyano-

acrylate were distilled to give 26.2 g. of material, b.p. 57° (1.7 mm.)-

70° (2.4 mm.), which v.p.c. analysis showed contained 88% of ethyl

cis-β-cyanoacrylate.

The Diels-Alder reaction of 26.2 g. of ethyl cis-β-cyano-C^{14}-

acrylate and cyclopentadiene (see page   67) gave 29.4 g. (84%) of

ethyl 2-norbornene-5-endo-cyano-C^{14}-6-endo-carboxylate, which

was hydrolyzed (see page   67) to give 21.7 g. (87%) of crude 2-

norbornene-5-endo-cyano-C^{14}-6-endo-carboxylic acid. The brucine

salt of this cyanoacid was obtained in 63% yield (see page   68). Its

radioactivity was determined in duplicate and found to be

0.0041 ± 0.0018 μcurie/mmole.

Reaction of Phenyllithium with Ethyl Propiolate. Attempted

Synthesis of Ethyl Hydrogen Acetylenedicarboxylate. - To a 500-ml.

three-necked flask equipped with magnetic stirrer, addition funnel,

and thermometer, containing 5.5 g. (0.056 mole) of ethyl propiolate

and 250 ml. of dry ether and flushed with dry nitrogen was added

50 ml. of 1.12 N ethereal phenyllithium (0.056 mole) (76). During

the 30-minute addition the reaction mixture was stirred and kept at

-40 to -10°. The reaction mixture was stirred another 10 minutes while its temperature climbed to 20° and was then carbonated by decantation through a glass tube leading below the surface of a vigorously stirred mixture of 200 g. of Dry Ice and 100 ml. of ether. No acidic product was obtainable from the carbonation mixture.

The reaction of phenyllithium with ethyl propiolate was also conducted at room temperature, but again no acidic products could be isolated from the carbonation mixture.

(-)-Menthyl Propiolate. - A mixture of (-)-menthol (43 g., 0.28 mole), propiolic acid (13.8 g., 0.20 mole) and 5 ml. of concentrated sulfuric acid was placed in a 200-ml. round-bottomed flask protected by a drying tube. The mixture was heated on a steam bath for 9 hours. The resulting mass was cooled and poured into an excess of aqueous sodium bicarbonate. The ester layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, dried over calcium chloride and filtered. The ether was distilled off and hexane was added; as the hexane solution cooled, crystals appeared. They were collected and washed twice with pentane to give 31.9 g. (72%) of product, m.p. 87-91°. One recrystallization from hexane gave long colorless needles, m.p. 89.5-90.5° $[\alpha]_D$ - 78.2°.

Attempted Synthesis of (-)-Menthyl Hydrogen Acetylenedicarboxylate from (-)-Menthyl Propiolate. -   (-)-Menthyl propiolate (4.3 g., 0.02 mole) was added under a nitrogen atmosphere to 100 ml.

of a magnetically stirred ethereal solution containing 0.017 mole of

isopropylmagnesium bromide. An exothermic reaction occurred,

gas was liberated and the solution became dark red. After the solution

was stirred a further 15 minutes, it was frozen with liquid nitrogen

and subjected to a vacuum of 0.5 mm. The carbonation reaction was

conducted with the apparatus and procedure of Dauben, Reid, and

Yankwich (77). Carbon dioxide was generated from 1.97 g. (0.01 mole)

of barium carbonate and 16 ml. of concentrated sulfuric acid. The

carbon dioxide appeared to be consumed as it was condensed in portions

into the reaction flask with liquid nitrogen, sealed in by closing the

appropriate stopcock on the manifold, allowed to warm, and stirred

magnetically. At the end of the reaction, the reaction mixture was

poured into 50 ml. of 5% sulfuric acid and 50 g. of crushed ice. The

ethereal layer was separated and extracted with aqueous sodium bi-

carbonate, acidified, and extracted twice with 100-ml. portions of

ether. The combined ether extracts were dried over Drierite,

decanted, and distilled. No residue was obtained.

A second preparation was conducted with 0.01 mole of (-)-

menthyl propiolate and 0.01 mole of isopropylmagnesium bromide in

8 ml. of ether and 70 ml. of tetrahydrofuran. The ethynyl Grignard

was prepared under a nitrogen atmosphere in a 200-ml. three-

necked flask which was connected to vacuum, to a manometer and

bubbler, and to a source of dry nitrogen or carbon dioxide. No heating

effect, gas evolution, or color change was noted. An atmosphere of 200-400 mm. of carbon dioxide was established; the gas was avidly and regularly consumed to the extent of 1.2% of theory; no further carbon dioxide consumption was observed.

(-)-Menthyl 4-Hydroxypent-2-ynoate. - This preparation was modeled on the work of Marshall and Whiting (78). Five ml. of 1.3 N ethereal isopropylmagnesium bromide (6.5 mmole) was added slowly to a magnetically stirred solution of 1.47 g. (6.5 mmole) of (-)-menthyl propiolate in 15 ml. of ether. About 3 ml. of acetaldehyde in 10 ml. of ether was added in 4 minutes to the stirred, cooled Grignard solu-tion. After the reaction mixture had been stirred one hour at room temperature, it was poured onto 25 g. of crushed ice and 2 ml. of sulfuric acid. The ether layer was washed once with 20 ml. of 10% sulfuric acid and once with 20 ml. of water. The ethereal layer was dried over Drierite, decanted, and concentrated by rotary evaporation to give 1.85 g. (105% of theory) of a dark red oil. The infrared spec-trum of this material contained no absorption corresponding to the ethynyl hydrogen in (-)-menthyl propiolate; strong bands indicative of an hydroxyl group or carbon-carbon triple-bonds were also absent. The ultraviolet spectrum showed no maximum above 210 mμ, $\epsilon(210 \text{ m}\mu) = 5500$, $\epsilon(230 \text{ m}\mu) = 2850$. The n.m.r. spectrum of the red oil was consistent with the assigned structure, (-)-menthyl 4-hydroxypent-2-ynoate (cf. Ref. 79).

Attempted Oxidation of (-)-Menthyl 4-Hydroxypent-2-ynoate to
(-)-Menthyl Hydrogen Acetylenedicarboxylate. - The conditions for this
reaction were modeled after the hypochlorite oxidation of mesityl
oxide described in Organic Syntheses (80). A solution of sodium hypo-
chlorite was prepared by passing chlorine into a solution of 10 g.
(0.25 mole) of sodium hydroxide in 13 ml. of water and 40 ml. of
crushed ice until 8.5 g. (0.12 mole) was adsorbed. (-)-Menthyl 4-
hydroxypent-2-ynoate (4.6 g.) and 40 ml. of dioxane were placed in a
300-ml. three-necked flask equipped with a mechanical stirrer, reflux
condenser, and addition funnel. The hypochlorite solution was added
to the stirred reaction mixture over 10 minutes. The reaction flask
became warm but its contents did not reflux. The reaction mixture was
stirred another hour, and then its pH was brought to 10 by the addition
of dilute sodium hydroxide. The alkaline solution was thoroughly
extracted with ether, acidified with sulfuric acid and extracted three
times with 30-ml. portions of ether. The combined ether extracts
were dried over Drierite, decanted, and concentrated by rotary
evaporation and finally in vacuo to give 0.5 g. (12% yield) of yellow
liquid products which were not separated and characterized.

Attempted Hydrogenation of (-)-Menthyl 4-Hydroxypent-2-
ynoate to (-)-Menthyl cis-4-Hydroxypent-2-enoate. - A solution of
crude (-)-menthyl 4-hydroxypent-2-ynoate (1.7 g.) and 25 ml. of
petroleum ether, b.p. 85-100°, was placed over 0.2 g. of Lindlar

catalyst (19) and hydrogenated at 1 atmosphere at room temperature.
When only 10 ml. of hydrogen was consumed in 2 hours, 1.2 g. of
catalyst was added and the hydrogenation was continued. The hydrogen
consumption remained slow and became slower: another 33 ml. was
taken up in the next two hours. Platinum on charcoal and the Busch
and Stöve catalyst (72) were similarly without great utility, but about
one-half of the theoretical amount of hydrogen was consumed within
25 hours. The crude product from the hydrogenation showed two
carbonyl bands in the infrared, at 1714 and 1725 cm^{-1}. (The carbonyl
band in (-)-menthyl 4-hydroxypent-2-ynoate comes at 1714 cm^{-1}.)

(-)-Menthyl Hydrogen Maleate. - A mixture of 22.7 g. of maleic
anhydride, 40 g. of (-)-menthol and 25 ml. of toluene was placed in a
200-ml. round-bottomed flask protected from the atmosphere with a
calcium chloride tube and refluxed for 3.5 hours. The reaction mix-
ture was cooled and the solvent was removed by rotary evaporation.
The residue was mixed with 20 ml. of petroleum ether, b.p. 30-60°,
and started to crystallize by a brief cooling with Dry Ice. The balance
of the product crystallized at room temperature. The yield was 40 g.
of material, m.p. 60-75°. Two recrystallizations from petroleum
ether, b.p. 60-70°, were necessary to obtain the pure acid-ester of
m.p. 85-87°, $[\alpha]_D^{25}$ -75.5° (lit. m.p. 85° (81)), in 35% overall
yield.

Diels-Alder Addition of Cyclopentadiene and (-)-Menthyl
Hydrogen Maleate. - A solution of 6. 0 g. (23. 6 mmole) of (-)-menthyl
hydrogen maleate in 20 ml. of benzene was added in 7 minutes to 1.57
g. (23.7 mmole) of freshly distilled cyclopentadiene; the reaction mix-
ture was stirred magnetically, cooled with an ice bath and protected
with a drying tube. It was stirred for 2 hours after the end of the
addition; benzene was then removed by rotary evaporation under reduced
pressure to give 7. 6 g. (100% yield) of crude product, m.p. 115-123°.
This solid was dissolved in 25 ml. of hot petroleum ether, b.p. 85-100°,
and the solution was filtered and allowed to cool. The crystals which
deposited were collected and dried to give 6.6 g. of material, m.p.
121-124°, $[\alpha]_D^{25}$ - 59.6°. One additional recrystallization from
petroleum ether gave 5.55 g. of solid, m.p. 128-130°, $[\alpha]_D^{25}$ - 60.2°
(73.4% overall yield). Recrystallization of this material from petroleum
ether gave material with m.p. 128.5-130.5°, $[\alpha]_D^{25}$ -60.2°.

Degradation of (-)-Menthyl Hydrogen 2-Norbornene-5,6-endo-
dicarboxylate, $[\alpha]_D^{25}$ - 60.2°. - Four grams of (-)-menthyl hydrogen
2-norbornene-5,6-endo-dicarboxylate, m.p. 128-130°, $[\alpha]_D^{25}$ - 60.2°,
was dissolved in 70 ml. of ethyl acetate and hydrogenated over 30 mg.
of platinum oxide. The catalyst was removed by filtration and the
filtrate was concentrated by rotary evaporation to give 4.03 g. (100%
yield) of (-)-menthyl hydrogen 2,3-endo-norbornenedicarboxylate ,
m.p. 147-149°.

Silver (-)-menthyl 2,3-<u>endo</u>-norbornanedicarboxylate was

prepared by neutralizing (-)-menthyl hydrogen 2,3-<u>endo</u>-norbornane-

dicarboxylate with dilute aqueous potassium hydroxide (82) and adding

an aqueous solution of 2.12 g. of silver nitrate. The silver salt was

collected and dried to give 5.6 g. of material (104% of theory).

The Hunsdiecker reaction of silver (-)-menthyl 2,3-<u>endo</u>-

norbornanedicarboxylate and bromine was conducted in the usual man-

ner (see page   92). The crude product was 5.0 g. of a yellow oil,

whose infrared spectrum contained strong bands at 1725 and 1590

cm^{-1}.

The crude product from the Hunsdiecker reaction was combined

with 300 ml. of 5% methanolic potassium hydroxide and 15 g. of

catalyst (72) and hydrogenated in a Parr bomb. After the catalyst had

been removed by filtration, 200 ml. of methanol was distilled from the

filtrate, 50 ml. of water was added, and the distillation was continued

until the boiling point reached 99°. The acidic material was separated

from the hydrolysate through acidification and ether extraction. There

was obtained 0.39 g. of <u>trans</u> 2,3-norbornanedicarboxylic acid having

m.p. 183-190°, $[\alpha]_D^{25}$+ 0.9° (cf. page 35).

A sample of 2-<u>endo</u>-norbornanecarboxylic acid was obtained by

treating 0.9 g. of unreacted (-)-menthyl 2-<u>endo</u>-norbornanecarboxylate

with 10 ml. of sulfuric acid, pouring this solution into 60 ml. of cold

water, isolating the acidic material through an appropriate series of

extractions, and distilling the crude material from a bath at 100°

under 3-5 mm. pressure. The acid amounted to 0.55 g. (32% yield

from (-)-menthyl hydrogen 2-norbornene-5,6-endo-dicarboxylate),

$[\alpha]_D^{25}$ -1.0°.

Reaction of Ethyl Propiolate and Ethyl Orthoformate. Ethyl

trans-β-Ethoxyacrylate and Ethyl 4,4-Diethoxytetrolate. - A mixture

of redistilled ethyl orthoformate (13.5 g., 73% pure by v.p.c. analysis,

0.0663 mole), ethyl propiolate (6.7 g., 0.0683 mole) and zinc nitrate

(0.3 g.) was heated from 100 to 150° in three hours. The reaction

flask was fitted with a 30-cm. Holzman column and during the reac-

tion, 2.1 g. of ethanol and ethyl propiolate distilled. The cooled reac-

tion mixture was filtered and distilled to give a low-boiling forerun,

3.2 g. of ethyl trans-β-ethoxyacrylate having b.p. 72-76° (5 mm.),

n_D^{25} 1.4436, and 3.8 g. of ethyl 4,4-diethoxytetrolate with b.p. 103-

115° (1-2 mm.), n_D^{25} 1.4368.

The n.m.r. spectrum of ethyl trans-β-ethoxyacrylate contained

signals from two ethyl groups and an AM quartet with J = 12.5 cps.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found:

C, 58.63, 58.43; H, 8.96, 8.94.

V.p.c. analysis on Column K at 132° and 25 psi indicated the

forerun contained 49% of the original ethyl orthoformate (ret. time

1.6 min.). The yield of distilled ethyl 4,4-diethoxytetrolate based

on recovered ethyl orthoformate was 58% of theory.

Attempted Preparation of Malealdehydic Acid from Furfural. -

(83) Thirty-two grams of furfural was added to 220 g. of 40% peracetic acid in 30 minutes while the mechanically stirred reaction mixture was maintained at 28-38° with external cooling. After the addition was complete, the reaction mixture was stirred another 7 hours and distilled. The product came over at about 70° (5 mm.) and crystallized in the condenser and collection flask. The crystals melted at 50-53° (lit. m.p. 55° (83)) and weighed 13.5 g.

In another preparation, an explosion occurred during the distillation just as the last of the acetic acid distilled.

The crude product was sublimed at 1 mm. from a bath at 50° to give an 80% recovery of crystals having m.p. 53-54°. This material was identified by infrared and n.m.r. spectroscopy as maleic anhydride.

2-Norbornene-5,6-endo-dicarboxylic Anhydride. - To a stirred, ice-cooled solution of maleic anhydride (41 g.) in benzene (85 ml.) was added 27.6 g. of freshly distilled cyclopentadiene during 17 minutes. The reaction mixture was allowed to stand overnight. The crystalline product was collected and a second crop of crystals was obtained by diluting the mother liquor with hexane. The product had m.p. 160-165° and amounted to 63.8 g. (93% of theory). One recrystallization from benzene gave long needles of m.p. 167.5-168.5° (lit. m.p. 164-165° (84)).

2-Norbornene-5,6-exo-dicarboxylic Anhydride. - Twenty grams of 2-norbornene-5,6-endo-dicarboxylic anhydride was heated in an open 50-ml. round-bottomed flask at 190° --measured with a thermometer immersed in the molten anhydride--by an oil bath for 1.5 hours. The solid which formed as the flask cooled was recrystallized from benzene; this material was collected, benzene was distilled from the mother liquor, and the residue was heated at 190° for 0.5 hour. The recycling process was continued to produce five crops of material.

Crop	M.p., °C.	Wt., g.
1	116-138	7.85
2	133-141	2.48
3	137-142	2.73
4	130-139	1.49
5		1.45

The five crops were combined, sublimed to give 15.9 g. of colorless material, and recrystallized from benzene to give 12.7 g. (64% of theory) of the _exo_-anhydride, m.p. 141-143° (lit. m.p. 142-143° (15)).

Kinetics of the Thermal Rearrangement of 2-Norbornene-5,6-_endo_-dicarboxylic Anhydride. - About 0.3 g. of recrystallized 2-norbornene-5,6-_endo_-dicarboxylic anhydride, m.p. 167.6-168.6°, and 1 ml. of decalin were placed in each of a series of 10 x 75-mm. test tubes. The tubes were corked or sealed and placed in an oil bath. They were withdrawn at intervals, quenched in ice water, and opened. The decalin was decanted off and the residue was freed of solvent at 1 ml. and 80°. The dried residue was analyzed by taking its melting point and by using the published melting point-composition diagram for this system (15). The results of these studies are tabulated in Table 2. The slopes of the _exo_-anhydride concentration versus time plots at each temperature were obtained graphically and are recorded in Table 3.

From the Arrhenius plot, shown in Figure 1, page 28, one obtains an apparent activation energy for the conversion of 2-norbornene-5,6-_endo_-dicarboxylic anhydride to its _exo_-isomer of 36.7 kcal. mole^{-1}.

Table 2. Rate Data on the Thermal Isomerization of 2-Norbornene-5,6-endo-dicarboxylic Anhydride to 2-Norbornene-5,6-exo-dicarboxylic Anhydride

Temp., °C.	Tube	Time, min.	M.p., °C.	Percent exo-Anhydride
187	1	10	154	13
	2	22	144	23
	3	34	131	36
	4	44	124	43
182.5	1	5	163	4
	2	10	158	9
	4	20	152	15
	5	25	152	15
	6	35	142	25
	7	44	138	29
	8	54	123	43
	9	69	120	47
175	1	86	130	37
	2	162	116	51
	3	13	162	5
	4	27	157	10
	5	40	151	16
	6	74	131	36
172	1	10	162	5
	2	21	160	7
	3	36	155	12
	4	54	153	14
	5	75	147	20
	6	111	135	32
	7	204	116	51
165	1	180	142	25
	2	240	135	32
	4	360	121	46
	5	60	160	7
	6	120	153	14

Table 3. Data for Arrhenius Plot

Temp., °K.	$(T)^{-1} \times 10^3$ $(°K)^{-1}$	$k_{13}(min.^{-1})$	$\ln k_{13}$
460	2.174	1.09	0.086
455.5	2.195	0.704	-0.35
448	2.232	0.42	-0.87
445	2.247	0.277	-1.25
438	2.283	0.128	-1.98

(The rate constant k_{13} is defined on page 27.)

Tetracyanoethylene was synthesized from 97 g. of malono-
nitrile according to the procedure of Carboni (85). All 334 g. of the
intermediate dibromomalononitrile-potassium bromide complex was
used. The yield of recrystallized tetracyanoethylene was 46.2 g.
(47% of theory) and had m.p. 199-200.5°.

Rearrangement of 2-Norbornene-5,6-endo-dicarboxylic
Anhydride in the Presence of Tetracyanoethylene. - Sealed 10 x 75 mm.
test tubes, each containing approximately 0.3 g. of a mixture of
tetracyanoethylene (47 mole percent) and 2-norbornene-5,6-endo-
dicarboxylic anhydride (53 mole percent) in about 1 ml. of decalin
were heated by an oil bath for definite times and at definite tempera-
tures. The tubes were cooled and opened; decalin was decanted from
the black solid, and the solid was washed once with hexane. The
residue was freed of solvent and maleic anhydride at 1 mm. and 80-
100° until the norbornenyl anhydrides just started to sublime; it was
then treated with Norite, Supercel, and 1 ml. of chloroform. Centri-
fugation gave a clear solution of the two norbornenyl anhydrides and
2,2,3,3-tetracyanonorborn-5-ene. Analysis of mixtures was accom-
plished by integration of their n.m.r. spectra. The results are listed
in Table 4; a plot of this data may be found on page 30.

The n.m.r. analyses were done through the use of scaling
factors derived empirically from known mixtures of the endo-anhydride

Table 4

Run	Temp., °C.	Time, min.	% endo-Anhd.	% exo-Anhd.	Tetracyano-norbornene	exo-Anhd. / Tetracyano-norbornene
1	185	46	32	25	43	1.72
2	174	80	38	30	32	1.07
3	160	282	51	30	19	0.63

and of the exo-anhydride with 2,2,3,3-tetracyanonorborn-5-ene. A test mixture of all three components was analyzed:

Anal. Calcd.: endo-Anhydride, 52.3; exo-anhydride, 30.5; tetracyanonorbornene, 17.2. Found: endo-anhydride, 52.5; exo-anhydride, 30.2; tetracyanonorbornene, 17.3.

Maleic anhydride and/or tetracyanoethylene do not interfere with this analytical technique.

2,3-exo-Norbornanedicarboxylic Anhydride. - A solution of 31.2 g. of 2-norbornene-5,6-exo-dicarboxylic anhydride in 500 ml. of ethyl acetate was hydrogenated, in installments, in a Parr bomb over platinum dioxide. The hydrogenation product was filtered and the filtrate was freed of solvent by rotary evaporation. The residue was thoroughly mixed with petroleum ether, collected by suction filtration, and dried to give 30.4 g. (96%) of product with m.p. 80-83° (lit. m.p. 78-79° (86)).

Methyl Hydrogen 2,3-exo-Norbornanedicarboxylate. - Crude 2,3-exo-norbornanedicarboxylic anhydride, derived from the hydrogen-

ation of 93.7 g. of 2-norbornene-5,6-endo-dicarboxylic anhydride,

was refluxed for 1 hour with 150 ml. of absolute methanol. The hot

solution was treated with charcoal and Supercel and was filtered.

Solvent was removed from the filtrate by rotary evaporation to give

107 g. (97% of theory) of product with m.p. 70-93°. A sample re-

crystallized from aqueous ethanol gave an 80% return of material

with m.p. 93-96° (lit. m.p. 96-97° (86)).

Attempted Resolution of Methyl Hydrogen 2,3-exo-Norbornane-

dicarboxylate. - Crystalline salts of methyl hydrogen 2,3-exo-

norbornanedicarboxylate were not obtained with cinchonine and

cinchonidine, but a crystalline brucine salt was formed from an acetone

solution of the acid ester and brucine. Regeneration of the acid ester

from the brucine salt through acidic hydrolysis produced 2,3-exo-

norbornanedicarboxylic acid, while acidic hydrolysis followed by

prompt ether extraction gave the crude acid ester of m.p. 70-90°.

A sample of the acid ester, regenerated from its brucine salt

after three recrystallizations of the salt from fresh absolute ethanol,

was recrystallized from hexane-ethyl acetate and submitted for

analysis, m.p. 94-97°.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found:

C, 60.47; H, 7.19.

A sample of the acid ester obtained from its brucine salt after

four recrystallizations of the salt from acetone showed a rotation of

$[\alpha]_D$ - 1°. No samples with higher rotations were obtained from other

crops or through the use of acetone-methanol as the solvent for the

brucine salt recrystallizations.

Degradation of Methyl Hydrogen 2,3-exo-Norbornanedicarboxyl-

ate to 2-exo-Norbornanecarboxylic Acid. - A solution of methyl hydro-

gen 2,3-exo-norbornanedicarboxylate (6.4 g.) and bromine (5.2 g.) in

chloroform (50 ml.) was added to a stirred mixture of 3.7 g. of red

mercuric oxide, following the method and procedure of Meek and Osuga

(26). The reaction flask was heated to 50-60° during the addition.

After excess bromine was destroyed with sodium bisulfite, the reaction

mixture was filtered. The filtrate was washed twice with 25-ml.

portions of aqueous sodium bicarbonate and once with 25 ml. of brine.

The solution was dried over calcium chloride, filtered and evaporated

to constant weight under reduced pressure to give 2.3 g. of products.

The infrared spectrum of this material contained bands characteristic

of methyl 2-bromonorbornane-3-exo-carboxylate and 2,3-exo-

norbornanedicarboxylic anhydride.

A solution of this impure methyl 2-bromonorbornane-3-exo-

carboxylate in 110 ml. of absolute methanol was combined with 10 g.

of Busch and Stöve catalyst (72) and 100 ml. of 10% methanolic potas-

sium hydroxide in a Parr bomb and hydrogenated. The alkaline solu-

tion was filtered from the catalyst and concentrated by distillation.

The residue was made acidic with concentrated hydrochloric acid and extracted twice with 17-ml. portions of ether. The combined ether extracts were concentrated by rotary evaporation. The residue was treated with water, methanol, and acetonitrile, whereupon crystals were obtained of m.p. 55-60° (lit. m.p. 58-58.5° (27)). Flash distillation gave 0.76 g. of the acid.

The Two Diasteromers of (-)-Menthyl Hydrogen 2,3-exo-Norbornanedicarboxylates. - 2,3-exo-Norbornanedicarboxylic anhydride (11.95 g.), (-)-menthol (20 g.) and 10 ml. of dry xylene were heated to 110-130° for 30 hours. (Analysis of the crude reaction products by infrared spectroscopy indicated that some anhydride was still present.) The toluene solution was diluted with 50 ml. of ether, the acid esters were extracted with 160 ml. of 3% sodium hydroxide solution, and the extract was washed with 80 ml. of ether, cooled in ice water and acidified with sulfuric acid. The excess aqueous material was removed from the viscous, colorless mass of crude products by decantation and filtration. The amorphous solid was dissolved in hot absolute ethanol; the crystals which were deposited from this alcoholic solution were collected and dried. The solid amounted to 12.4 g. (53%) and had m.p. 105-125°. Two recrystallizations from cyclohexane gave 3.4 g. of isomer B, m.p. 140-142°, $[\alpha]_D^{25}$ -59.2°.

Recrystallization from wet ethanol of the crude mixture of acid esters from another preparation gave isomer A, which had m.p. 120-123°, $[\alpha]_D^{25}$ -45.5°.

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.53; H, 9.22.

Silver (-)-Menthyl 2,3-exo-Norbornanedicarboxylate. - Isomer B of (-)-menthyl hydrogen 2,3-exo-norbornanedicarboxylate (m.p. 140-142°, $[\alpha]_D^{25}$ - 59.2°, 3.0 g., 9.3 mmole) was placed in a 150-ml. beaker and was neutralized to the phenolphthalein end-point with 15% ammonium hydroxide. A solution of silver nitrate (1.58 g., 9.3 mmole) in 30 ml. of water was added and the mixture was heated to give a clear solution. The silver salt precipitated several hours later. Three crops were collected by suction filtration and dried at 80° and 1-2 mm. for three days, with daily crushing of the solid with a glass rod. The yield of thoroughly dry product was 3.6 g., 90% of theory.

Hunsdiecker Reaction of Bromine and Silver (-)-Menthyl-2,3-exo-Norbornanedicarboxylate. - About 80 ml. of dry carbon tetra-chloride was filtered from phosphorous pentoxide into a dry 100-ml. two-necked flask which contained 3.6 g. of silver (-)-menthyl 2,3-exo-norbornanedicarboxylate (derived from the acid ester isomer B, m.p. 140-142°, $[\alpha]_D^{25}$ - 59.2°). About 25 ml. of the carbon tetra-chloride was distilled under a dry, oxygen-free nitrogen atmosphere. The distilling head was replaced by a reflux condenser. An addition funnel, charged with a dry solution of bromine (1.34 g., 84 mmole) in 10 ml. of carbon tetrachloride, was fitted to the flask. The reaction mixture was cooled in an ice bath and the bromine solution was added

in 15 minutes. The mixture was stirred another 45 minutes at room

temperature, brought to boiling for 1 minute, stirred for 1.2 hours,

boiled for a further 15 minutes, and finally stirred for 2 hours. The

reaction mixture was decomposed with 5 ml. of 10% sodium carbonate

and a few drops of aqueous sodium hydroxide, stirred 5 minutes, and

filtered through a Supercel mat. The organic phase was washed with

10 ml. of water and separated. The carbon tetrachloride and water

were removed by distillation and the last traces of solvent were

removed under reduced pressure to give 2.7 g., 90% of theory, of

a viscous yellow liquid, whose infrared spectrum was interpreted to

indicate a (-)-menthyl ester with no contamination from an anhydride.

The bromo ester was used directly, without purification, in the follow-

ing reaction.

(-)-2-exo-Norbornanecarboxylic Acid. - The crude product

(2.7 g.) from the Hunsdiecker reaction described immediately above,

10 g. of Busch and Stöve catalyst (72), 100 ml. of absolute methanol

and 100 ml. of 10% methanolic potassium hydroxide were placed in a

Parr bomb and hydrogenated. The hydrogenation mixture was filtered,

methanol was distilled from the filtrate, 30 ml. of water was added,

and the combination was refluxed for 4 hours. The hydrolysate was

washed twice with 10-ml. portions of ether, acidified with dilute

sulfuric acid and extracted with ether. The ether extract was evap-

orated to dryness; the residue was taken up in hot acetonitrile,

filtered and allowed to cool. Crystals of m.p. 188-195°, $[\alpha]_D^{25}$ -28.3, were obtained. This solid was identified as <u>trans</u> 2,3-norbornane-dicarboxylic acid.

Neut. Equiv. Calcd. for $C_9H_{12}O_4$: 92. Found: 96, 99.

Material for analysis was recrystallized from water, m.p. 192-194°. The literature melting point for racemic <u>trans</u> 2,3-norbornanecarboxylic acid is 194-195° (84).

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 59.05, 58.86; H, 7.28, 7.21.

Distillation of the mother liquor over a bath at 120° at a pressure of 0.8 mm. gave 141 mg. of clear liquid. This distillate was redistilled to give 117 mg. of material having $[\alpha]_D^{23}$ -21.0°; the infrared spectrum was identical with that of racemic 2-<u>exo</u>-norbornane-carboxylic acid (page 90) but for additional peaks at 1780, 945, and 910 cm^{-1}.

2,3-<u>endo</u>-Norbornanedicarboxylic Anhydride. - Catalytic hydrogenation of a solution of 2-norbornene-5,6-<u>endo</u>-dicarboxylic anhydride (10.0 g.) in 100 ml. of ethyl acetate over 30 mg. of platinum oxide gave 2,3-<u>endo</u>-norbornanedicarboxylic anhydride, m.p. 164-165°, 10.1 g. (99.6% of theory). One recrystallization from benzene-cyclohexane gave long needles having m.p. 169.5-170° (lit. m.p. 167-168° (87)).

Thermal Rearrangement of 2,3-endo-Norbornanedicarboxylic

Anhydride to Its exo-Isomer. - Isomerization of 2,3-endo-norbornane-

dicarboxylic anhydride in a sealed tube at 250° for 18 hours gave a

mixture of anhydrides which was analyzed by n.m.r. spectroscopy

and found to contain 22% of 2,3-exo-norbornanedicarboxylic anhydride

and 78% of the endo-isomer. The n.m.r. spectra on the two anhydrides

and the rearrangement mixture may be found on page 39.

Diethylfulvene. - (88) To a mechanically stirred mixture of

cyclopentadiene (19.4 g., 0.29 mole) and 3-pentanone (24.1 g., 0.28

mole) in a 300-ml. three-necked flask was added a solution of 7 g. of

sodium in 120 ml. of ethanol over a 50-minute period. During the

addition, the reaction mixture was cooled with an ice bath. Following

the addition, the reaction mixture was stirred for 1.6 hours, diluted

with 50 ml. of cold water, and extracted with 125 ml. of ether. The

ether extract was washed with 50 ml. of water; the combined aqueous-

alcoholic material was washed once with ether and distilled until the

boiling point reached 82°. The residue was diluted with an equal

volume of ether and dried with two portions of calcium chloride; the

ether layer was filtered and distilled through a Claisen head with an

8-cm. Vigreux sidearm. The two fractions had b.p. 53-54° (5.4 mm.),

$n^{25}D$ 1.5287, 8.77 g., and b.p. 50-53° (5.4 mm.), $n^{25}D$ 1.5253, 6.38 g.,

and amounted to a combined yield of 15.15 g. (40%).

The n.m.r. spectrum of diethylfulvene has only one line for the

olefinic hydrogens. The ultraviolet spectrum shows λ_{max} 361 mμ

(ϵ = 274), λ_{max} 270 mμ (ϵ = 15,700).

Diels-Alder Reaction of Diethylfulvene and Maleic Anhydride. -
Diethylfulvene (14.6 g., 0.108 mole) was added to a magnetically

stirred mixture of maleic anhydride (10.7 g., 0.108 mole) and benzene

(22 ml.). During the 40-minute addition, the reaction mixture was

cooled in an ice bath. Benzene was evaporated from the adducts under

reduced pressure. The crude product was examined by n.m.r.

spectroscopy and seen to be an approximately 2:1 mixture of exo:endo

Diels-Alder adducts (see Ref. 89).

1,2,3,4-Tetrachloro-5,5-dimethoxycyclopentadiene. - (90) A
solution of potassium hydroxide (250 g., 3.8 mole) in 1 ℓ. of methanol

was added during 2.2 hours to a stirred solution of hexachlorocyclo-

pentadiene (485 g., 1.78 mole) in 1 ℓ. of methanol. The temperature

of the reaction solution reached 63° during the addition; thereafter,

the solution was stirred for 1 hour and then combined with 1.5 ℓ.

of water in a 4-ℓ. separatory funnel. The two layers were separated,

and aqueous layer was extracted with 400 ml. of chloroform, and

the combined organic layers were dried over Drierite, filtered and

distilled to give 334 g. (72% of theory) of 1,2,3,4-tetrachloro-5,5-

dimethoxycyclopentadiene, b.p. 115-120° (13 mm.) n_D^{20} 1.5264

(lit. b.p. 108-110° (11 mm.), n_D^{20} 1.5288 (90)).

1,2,3,4-Tetrachloro-7,7-dimethoxy-2-norbornene-5,6-endo-
dicarboxylic Anhydride. - A mixture of 1,2,3,4-tetrachloro-5,5-

dimethoxycyclopentadiene (89.8 g., 0.34 mole), maleic anhydride

(31.6 g., 0.32 mole) and xylene (500 ml.) was refluxed for 1.3 hours.
The clear solution was allowed to cool to room temperature and was
placed in a refrigerator for an hour. The colorless crystalline product
which appeared was collected and thoroughly vacuum-dried to give
85.5 g. (71% of theory) of material of m.p. 199-200.5° (lit. m.p.
192° (91)). No attempt was made to isolate a second crop from the
mother liquor.

Attempted Thermal Rearrangement of 1,2,3,4-Tetrachloro-
7,7-dimethoxy-2-norbornene-5,6-endo-dicarboxylic Anhydride. - A
sealed tube containing 10.9 g. of 1,2,3,4-tetrachloro-7,7-dimethoxy-
2-norbornene-5,6-endo-dicarboxylic   anhydride was heated in an
oil bath at 220° for 1.5 hours. The tube was cooled and the solid from
the tube (10.7 g.) was dissolved in boiling benzene, treated with char-
coal and Supercel, and filtered. Three crops of crystalline material
were isolated which had the following m.p.'s: 199-201°, 200-201°,
and 197-198°. The third crop was shown to be identical with the first
two and with the starting anhydride through comparison of their infra-
red and n.m.r. spectra. These three crops of solid amounted to
9.94 g., or a 93% recovery of the starting anhydride.

1,2,3,4-Tetrachlorocyclopentadiene. - Fifty-two grams of
zinc dust was washed with a solution of 5 g. of copper sulfate in 100 ml.
of water and with several portions of distilled water. A slurry of the

zinc dust and water, hexachlorocyclopentadiene (83.4 g., 0.305 mole) and petroleum ether, b.p. 30-60° (50 ml.) was placed in a 500-ml. three-necked flask equipped with a Hershberg stirrer, reflux condenser and addition funnel. A solution made from 63 ml. each of concentrated hydrochloric acid and water was added to the vigorously stirred reaction mixture in 20 minutes. The reaction mixture was filtered and the petroleum ether layer was separated from the aqueous portion of the filtrate. On cooling, crystals deposited from the organic solution; these were collected, washed with petroleum ether and dried in vacuo. The product (35.7 g., 57% yield) was faintly orange and had m.p. 59-64° (lit. m.p. 62-63° (92)). No attempt was made to isolate a second crop from the mother liquor.

1,2,3,4-Tetrachloro-2-norbornene-5,6-endo-dicarboxylic Anhydride. - A mixture of 1,2,3,4-tetrachlorocyclopentadiene (35.7 g., 0.175 mole), maleic anhydride (17.2 g., 0.175 mole) and benzene (50 ml.) was heated nearly to reflux for 6 hours and allowed to cool overnight. In the morning, the product was collected, washed with benzene, and dried to give 35.5 g. (67% of theory) of material of m.p. 173-175°. One recrystallization from benzene gave material with m.p. 175-176° (lit. m.p. 172.2-173° (93)). No attempt was made to isolate a second crop from the mother liquor.

Thermal Rearrangement of 1,2,3,4-Tetrachloro-2-norbornene-5,6-endo-dicarboxylic Anhydride. - Four grams of 1,2,3,4-tetra-chloro-2-norbornene-5,6-endo-dicarboxylic anhydride was heated to 170-175° for 1.4 hours. Infrared spectoscopic analysis of the cooled product indicated that little rearrangement had occurred. The an-hydride was heated to 190° for 1 hour, and the infrared spectrum of the cooled product contained strong absorptions not shown by the starting material at 1060 and 930 cm^{-1}. The crude product was distilled over a bath at 140-150° under a pressure at 1 mm. to give 2.4 g. of colorless viscous liquid. This liquid was dissolved in hot chloroform; the crystals which were deposited from the cooled solution melted at 120-136°. Recrystallization from carbon tetrachloride gave material having m.p. 138-140° and an n.m.r. spectrum with an unsplit absorption at 328 cps.

Attempted distillation of the crude rearrangement product at 170-180° and 1 mm. gave colorless crystals of tetrachlorocyclo-pentadiene, m.p. 58-61°, which was identified by infrared spec-troscopy.

PART II

Attempted Preparation of 6-Methoxy-3,5-dimethylpyronone. -
Dimethyl acetonedicarboxylate was made with the collaboration of
Mr. Thomas Creighton according to a procedure in Organic Syntheses
(94). The compound was obtained from citric acid in 43% yield,
b.p. 93-104° (1-2 mm.). Dimethyl α,α'-dimethylacetonedicarboxylate,
b.p. 85-91° (1 mm.), was prepared from dimethyl acetonedicar-
boxylate and methyl bromide (44). Two attempts to convert this
diester into 6-methoxy-3,5-dimethyl-2,4-pyronone following the
method of Woodward and Small (44) were completely unsuccessful.

α-Bromopropionic acid was prepared through the Hell-
Volhard-Zelinsky reaction. Bromine (115 g., 2.2 mole) was added
in 50 minutes to 164 g. (2.2 mole) of propionic acid and 2 g. of red
phosphorous. The reaction mixture was heated on the steam bath for
6 hours. Distillation gave 276 g. (81%) of α-bromopropionic acid,
b.p. 194-204° (lit. b.p. 203.5° (95)).

α-Bromopropionyl Bromide. - α-Bromopropionic acid (241 g.,
1.58 mole) and phosphorous tribromide (127 g., 1.56 equivalents)
were placed in a 500-ml. flask, stirred magnetically overnight, and
then heated to reflux for 2 hours. The reaction mixture was distilled
at reduced pressure to give 199 g. of distillate, b.p. 58-85° (48 mm.);
this distillate was redistilled to give 182 g. (54%) of α-bromopropionyl
bromide with b.p. 65-68° (49 mm.), b.p. 77° (59 mm.) .

The Reaction of α-Bromopropionyl Bromide with Zinc.

Preparation of the Methylketene Dimers. - A modified version of the

apparatus and procedure described by Reid and Groszos was used (62).

α-Bromopropionyl bromide (86.6 g., 0.40 mole) in 225 ml. of absolute

ether was placed in the additional funnel. The reaction flask was

charged with fused zinc chloride (0.4 g.), activated zinc dust (52.4 g.,

0.80 mole) (96) and absolute ether (725 ml.). The system was swept

with anhydrous oxygen-free nitrogen for 40 minutes; the reaction

mixture was then heated to reflux and the addition of ethereal α-

bromopropionyl bromide initiated. The rates of addition and external

heating were regulated so that the ether boiled vigorously. The addi-

tion was completed in 30 minutes. Ether and methylketene were dis-

tilled from the mixture until the distillation temperature reached 45°

(40 minutes). The distillate was stored in the refrigerator while the

residue in the reaction flask was filtered free of solid material. The

filtrate and washings were combined, diluted with 50 ml. of ether and

50 ml. of pentane, washed four times with 25-ml. portions of water

and dried over Drierite. The solution was pressure-filtered through

sintered glass, concentrated by flash distillation and distilled. Two

main fractions were collected which had b.p. 45° (10 mm.),

$\underline{n}^{25}\underline{D}$ 1.4323, 0.94 g., and b.p. 42-44° (9 mm.), $\underline{n}^{25}\underline{D}$ 1.4325, 0.90

g. These two fractions represent a yield of 8.2%. The n.m.r. spec-

trum of this material was identical with that of the neutral methylketene

dimer, pages 50 and 104.

The distillate from the reaction of α-bromopropionyl bromide with zinc was allowed to stand at 4° for 11 days. The ether was then distilled through a 90-cm. glass helix-packed column until about 50 ml. of liquid remained. The solid which was deposited during the distillation was collected and washed with dry ether. Four crops of the acidic methylketene dimer were collected; the colorless material, m.p. 123-127°, weighed 1.19 g. (5.3% of theory). Its n.m.r. spectrum is given on page 50.

Propionyl chloride was prepared from benzoyl chloride (454 g., 3.2 mole) and propionic acid (149 g., 2 mole) by Brown's method (97). Redistillation of the crude product gave 121 g. (67% yield) of the acid chloride, b.p. 77-78° (740 mm.).

Neutral Methylketene Dimer. - A solution of 61.2 g. (0.66 mole) of propionyl chloride in 500 ml. of absolute ether was placed in a dry 2-ℓ. three-necked flask; this flask was equipped with a reflux condenser, mercury-sealed mechanical stirrer, additional funnel, nitrogen line, and drying tube. Triethylamine (68 g., 0.67 mole, distilled from α-naphthylisocyanate (98)) was added to the stirred mixture in an atmosphere of nitrogen during 2.2 hours; the stirring was discontinued and the reaction mixture was allowed to stand for 5 days. The ethereal methylketene dimer solution was separated from the triethylamine hydrochloride through inverted filtration, and the ether was

evaporated from the filtrate on a steam bath under reduced pressure. The crude dimer was distilled through a 1.5 x 22-cm. glass helix-packed column and collected in receivers cooled with Dry Ice.

Fraction	B.p., °C.	Press., mm.	Wt., g.	n_D^{24}
I	53	18.3	2.52	1.4347
II	53-54	18.4	4.87	1.4341
III	53-54	18.5	2.19	1.4337
IV	38	3	2.22	1.4270

The first three fractions amount to 9.6 g. (26% of theory). The pot residue, 14.2 g., was distilled through a Claisen head to give a colorless liquid, b.p. 83-87° (2 mm.) and a yellow liquid, b.p. 147-155° (2 mm.).

An ethereal solution of the dimer and aniline deposited the anilide derivative of the neutral methylketene dimer; this derivative was recrystallized three times from cyclohexane-ethyl acetate and had m.p. 119.5-121°.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37. Found: C, 70.29; H, 7.18.

The p-nitrophenylhydrazone derivative of the neutral methyl-ketene dimer was prepared by the procedure of McElvain (101); it was recrystallized from methanol and had m.p. 225-226.5°.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29, H, 5.30; N, 17.00. Found: C, 58.07; H, 4.85; N, 16.89.

Spectra for the neutral methylketene dimer may be found on pages 50, 52, and 53. The n.m.r. spin-spin coupling constant between the olefinic and methine hydrogens is 1.41 ± 0.03 cps.

3,5-Dimethyl-6-ethylpyronone. - Four grams of a liquid, b.p. 40-70° (1-2 mm.), b.p. 83-87° (2 mm.), obtained during preparations of the neutral methylketene dimer was redistilled through a glass wool-packed microcolumn to give four fractions.

Fraction	B.p., °C.	Pres., mm.	n^{25}_D
I	50.56	0.65	1.4471
II	56-59	0.65	1.4542
III	59-61	0.65	1.4556
IV	61-64	0.9	1.4561

Material from the fourth fraction was submitted for analysis.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.21; H, 7.43.

The molecular weight was determined cryoscopically in cyclohexanol (99). Calcd. for $C_9H_{12}O_3$: 168. Found: 160, 164.

The ultraviolet spectrum had λ_{max} 234 mµ (ε = 10,500). The infrared spectrum had strong bands at 1785, 1765, 1660, 1145, and 1105 cm^{-1}. The n.m.r. spectrum contained absorptions centered at

219 cps from a single proton split twice into quartets $(J = 7.0, 2.3$ cps), a quartet centered at 157 cps from two protons $(J = 7.5$ cps), and a complicated methyl-proton region dominated by sharp signals of approximately equal intensity at 97, 94.7, 74, and 67 cps.

Phenylchloroacetyl Chloride. - Mandelic acid (124 g., 0.81 mole) and phosphorous pentachloride (340 g., 1.63 mole) were placed in a 1-ℓ. flask which was fitted with a reflux condenser and a calcium chloride drying tube. The mixture was heated gently until it became homogeneous; the solution was then refluxed for 4.5 hours and was allowed to stand overnight. After distillation of the phosphorous oxy-chloride from the solution under reduced pressure, the product was distilled and gave 116 g. of a colorless liquid of b.p. 65-78° (1 mm.). Redistillation through a 15-cm. Vigreux column gave 96.4 g. (63% yield) or phenylchloroacetyl chloride, b.p. 68-69° (1 mm.).

Neutral Phenylketene Dimer. - To a dry 1-ℓ. three-necked flask containing 30 g. (0.46 mole) of zinc dust and 270 ml. of absolute ether was added under a nitrogen atmosphere a solution of 42.9 g. (0.23 mole) of phenylchloroacetyl chloride in 60 ml. of absolute ether. The reaction commenced vigorously several minutes after the begin-ning of the addition and the ether then refluxed throughout the 20-minute addition. The reaction mixture was stirred another hour, diluted with 200 ml. of petroleum ether, b.p. 30-60°, stirred one more hour and

washed repeatedly with water, 5% hydrochloric acid, 10% sodium

bicarbonate, and water. The ethereal solution was dried over mag-

nesium sulfate, decanted and concentrated by distillation. The orange-

red oily residue was distilled under 1 mm. of pressure. When the

distillate was diluted with petroleum ether, crystals deposited and

were collected, m.p. 63-66°. Two recrystallizations from pentane-

cyclohexane gave 1.07 g. of material having m.p. 69-70° (lit. m.p.

73°. (53)).

<u>Anal</u>. Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found:

C, 80.98; H, 5.17.

The phenylketene dimer gave no color test with methanolic

ferric chloride. Its ultraviolet absorption spectrum had λ_{max} 289 mμ

(ϵ = 784), λ_{max} 253 mμ (ϵ = 32,200). The infrared absorption spec-

trum had unusual intense bands at 1910, 1875, and 1850 cm^{-1} (Figure

5, page 52). The n.m.r. spectrum of the dimer shows two non-

equivalent non-aromatic protons which absorb at 317 and 339 cps

below tetramethylsilane and have a mutual coupling of 1.4 cps.

Some five attempts to repeat this synthesis of the neutral phenyl-

ketene dimer were not successful. The reaction itself always gave a

good yield (75-77%) of crude oily material whose infrared spectrum

bespoke of a high content of the dimer, but vacuum distillation attempts

led to apparent thermal decomposition of the product.

Attempts to isolate the dimer through absorption chromatography on alumina were unsuccessful. Steam distillation of reaction mixtures led to ethyl phenylacetate, b.p. 60-70° (1 mm.), n^{25}_D 1.5077. During some attempts to obtain the dimer in crystalline form through a suitable combination of solvent and temperature conditions, dibenzylketone was isolated, m.p. 33-34° (lit. m.p. 34° (100)); its oxime had m.p. 121-122° (lit. m.p. 123° (100)) and its phenylhydrazone had m.p. 117-118° (lit. m.p. 121° (100)).

Crystals of the neutral phenylketene dimer were obtained on one other occasion when the reaction mixture was diluted with hexane instead of petroleum ether and when the washed and dried organic solution was concentrated, diluted with dichloromethane and stored in a refrigerator for several weeks.

Quantitative hydrogenation of neutral phenylketene dimer was accomplished by the procedure described by Clauson-Kaas and Limborg (103). Commercial hydrogen was used without purification and the catalyst was platinum oxide. The data are summarized in Table 5.

Hydrogenation of Neutral Phenylketene Dimer to α,γ-Diphenylbutyric Acid. - A 0.2 g. sample of crude neutral phenylketene dimer, m.p. 55-59°, was dissolved in 20 ml. of ethyl acetate and hydrogenated over 10 mg. of 5% palladium on carbon. The catalyst was removed by

TABLE 5

Determination	I	II	III	IV	V
Weight of sample (mg.)	6.19	3.52	3.60	4.45	2.91
Temperature (°C)	19.9	18.6	20.0	19.1	20.9
Vapor pressure of ethanol (mm. Hg)	42.8	39.7	43.5	41.0	45.9
Barometric pressure (mm. Hg)	748.5	749.6	750.4	744.0	741.5
Hydrogen consumption (ml.)	2.921	0.731	1.027	2.176	0.713
Hydrogen consumption (moles)	2.04	1.92	2.6	4.5	2.19

(The vapor pressure data for ethanol are based on Ref. 104. Determination I was a trial run with sorbic acid. Palladium on carbon was the catalyst in V. In runs II and III, two moles of hydrogen were consumed within a few minutes and additional hydrogen was slowly consumed as the hydrogenations were continued for 3 hours and 7 hours, respectively.)

filtration and the filtrate was concentrated by rotary evaporation.

The residue was dissolved in warm hexane and as this solution cooled

it deposited crystals of m.p. 61-72°. Recrystallization from hexane

gave material of m.p. 69-73°, whose infrared spectrum was identical

to that of an authentic sample of α,γ-diphenylbutyric acid of m.p.

73-74.5°. An intimate mixture of α,γ-diphenylbutyric acid and the

hydrogenation product from the neutral phenylketene dimer melted at

68-73°.

α-Phenyl-β-benzoylpropionitrile was synthesized by the method

described in Organic Syntheses (105). A solution of potassium cyanide

(4.46 g., 68.4 mmole) in 14 ml. of water was added, beneath the

surface, to a magnetically stirred solution of benzalacetophenone

(7.13 g., 34.2 mmole) and glacial acetic acid (2.06 g., 34.2 mmole)

in 110 ml. of 95% ethanol at 35-36°. The addition required 7 minutes

and the solution at 35-37° was stirred another 2.8 hours. The loosely

stoppered 200-ml. Erlenmeyer reaction flask was allowed to stand at

room temperature for 24 hours and was then chilled at 4° for 18 hours.

The precipitate was collected, washed once with 50% aqueous ethanol

and 3 times with cold water, and dried. The colorless crystals of

α-phenyl-β-benzoylpropionitrile, m.p. 123.5-125.5° (lit. m.p. 125°

(105)) weighed 7.38 g. (92% of theory).

Two attempts to obtain this compound following the procedure

of Newman (106) gave a yellow solid, m.p. 186-189°. This compound

had strong bands in the infrared at 1685 and 1646 cm^{-1} and is pre-

sumed to be 5-phenyl-5-styrylhydantoin (lit. m.p. 189-190° (107)).

α-Phenyl-β-benzoylpropionic acid was synthesized following

the approach of Lapworth and Wechsler (108). α-Phenyl-β-benzoyl-

propionitrile (7.34 g.), sulfuric acid (37 g.), and water (19 ml.) were

mixed together, heated on a steam bath for 3 hours and allowed to

stand at room temperature overnight. In the morning, the product

was collected, dissolved in hot 5% sodium hydroxide solution, and

filtered. Acetic acid followed by hydrochloric acid were added to

the alkaline solution; the resulting precipitate was cooled, collected,

washed twice with cold water, and dried. The product (7.41 g.,

93.5% of theory) melted at 145-149° (lit. m.p. 153° (108)).

α,γ-Diphenylbutyric Acid. - Zinc dust (75 g.), mercuric

chloride (5.6 g.), water (94 ml.), and concentrated hydrochloric

acid (4 ml.) were placed in a 200-ml. round-bottomed flask and shaken

vigorously for 10 minutes. The aqueous solution was decanted from

the amalgamated zinc, the zinc was covered with 45 ml. of hydrochloric

acid, and 7.4 g. of α-phenyl-β-benzoylpropionic acid was added. The

mixture was heated to reflux for 22 hours; during this period 45 ml.

of additional hydrochloric acid was added in portions to the reaction

mixture. When the reaction mixture had cooled it was extracted three

times with 50-ml. portions of petroleum ether, b.p. 60-70°. Evaporation of the extract gave 2.8 g. of colorless product, m.p. 63-70°.
Three recrystallizations from hexane raised the melting point to
73-74.5° (lit. m.p. 75° (109)).

The Reaction of Phenylacetyl Chloride with Triethylamine.
3,5-Diphenyl-6-benzylpyronone and 3,5-Diphenyl-4-hydroxy-6-
benzylpyrone . - To a dry 1-ℓ. three-necked flask equipped with a
reflux condenser, addition funnel, and nitrogen inlet, which contained
92 g. (0.59 mole) of phenylacetyl chloride and 300 ml. of dry ether
was added 64 g. (0.63 mole) of triethylamine at a rate which caused
the ether to reflux gently. After the 45-minute addition to the stirred
reaction mixture, the mixture was allowed to cool to room tempera-
ture, diluted with 200 ml. of pentane, and was stirred for 40 minutes.
Triethylamine hydrochloride was removed by filtration and washed
repeatedly with pentane and ether. Distillation of the volatile material
from the combined filtrates gave a honey-like residue.

This residue was treated with 700 ml. of boiling 9% sodium
carbonate solution. The aqueous solution was decanted from the oil
which did not dissolve and acidified; the solid which was deposited
was collected, washed with cold water, and dried to give 10.1 g. of
material, m.p. 185-195°. Recrystallization of 0.33 g. of this solid
from aqueous ethanol gave 0.07 g. of 3,5-diphenyl-4-hydroxy-6-
benzylpyrone, m.p. 171-172° (see page 55). It had sharp bands in

the infrared at 3490, 1700 and 1560 cm^{-1}.

The oil which would not dissolve in concentrated boiling sodium carbonate was dissolved in carbon tetrachloride. Distillation gave water-carbon tetrachloride, carbon tetrachloride, ethyl phenylacetate (1 g., b.p. 53° (1 mm.)), and 6 g. of a liquid with b.p. 118-125° (1 mm.). A sample of this liquid was redistilled, b.p. 115-120° (0.7 mm.), and had strong absorptions in the infrared at 1715 and 1625 cm^{-1}.

Diazoacetophenone. - Ethereal diazomethane, prepared from nitrosomethylurea in the manner and scale described by Arndt (110), was dried over potassium hydroxide pellets and used directly in a synthesis of diazoacetophenone (111). The product, m.p. 39-43°, was obtained in 91% yield.

Photolysis of Diazoacetophenone. - A solution of 6.07 g. of diazoacetophenone in 135 ml. of dry benzene was photolyzed for 22 hours. A low-pressure mercury arc immersion lamp (Hanovia, 300 watt) and a Pyrex filter, cutting out light below 3500 Å , were used. The nitrogen evolved during the photolysis was collected over water; it corresponded to 92% of theory. At the end of the reaction, the reaction mixture was filtered; a colorless solid of m.p. 268-269° and weighing 0.43 g. (9% of theory) was obtained. This compound gave a cherry-red color in sulfuric acid.

Solvent was distilled from the filtrate. The residue was examined by infrared spectroscopy; it did not contain the neutral phenylketene dimer.

A solution of 5.94 g. of diazoacetophenone and 81 mg. of ferric dipivaloylmethide in 135 ml. of dry benzene was photolyzed for 40 hours. A colorless solid, 1.35 g., m.p. 264-265°, was the only product isolated (112).

Attempted Rearrangement of Neutral Methylketene Dimer. - Attempts to rearrange neutral methylketene dimer with potassium t-butoxide in ether and sodium methoxide in carbon tetrachloride-dimethylsulfoxide are described on pages 114 and 115.

A stoppered solution of 4.5 g. of neutral methylketene dimer in 700 ml. of dry ether was allowed to stand at room temperature for 15 days. The ether was distilled through a glass helix-packed column and the residue was examined by infrared spectroscopy and found to be the starting material, neutral methylketene dimer.

A stoppered solution of 4.5 g. of the neutral methylketene dimer and 5 ml. of pyridine in 750 ml. of ether was allowed to stand at room temperature for 2 days. The reaction solution was extracted twice with 170-ml. portions of 1% hydrochloric acid, dried thoroughly over calcium chloride, filtered and concentrated by distillation. The residue was examined by infrared spectroscopy and found to contain absorptions corresponding to the neutral methylketene dimer and tetramer

(cf. pages 52 and 56) and additional bands at 1685 and 1650 cm^{-1}.

The residue was extracted with aqueous sodium bicarbonate and this

extract had an n.m.r. spectrum giving no evidence of the presence

of the acidic methylketene dimer in the mixture of products.

Base-Catalyzed Dimerization of the Neutral Methylketene

Dimer. - A mixture of 2.83 g. of the neutral methylketene dimer,

0.5 g. of potassium t-butoxide, and 880 ml. of absolute ether in a

stoppered flask was allowed to stand at room temperature for 9 days.

The ethereal solution was decanted, washed with 100 ml. of 2%

hydrochloric acid and dried thoroughly over Drierite. The dried

solution was filtered and the ether was distilled from the filtrate through

a 90-cm. glass helix-packed column. The infrared spectrum of the

liquid residue, which amounted to 3.0 g. of material, showed it to be

neither the neutral methylketene dimer nor the neutral methylketene

dimer-trimer; the spectrum showed strong absorptions at 1755, 1717,

and 1120 cm^{-1}. An attempt to distill the liquid at 7 mm. gave 1 g. of

3-pentanone, n_{D}^{25} 1.3982 (lit. n_{D}^{25} 1.3905 (113)), which had a

carbonyl band in the infrared at 1710 cm^{-1}, and 0.4 g. of distillate

whose infrared spectrum bore no resemblance to that of the starting

material. A suggested structure for the product obtained in this

base-catalyzed reaction of the neutral methylketene dimer is given

on page 56.

A Trimer of Neutral Methylketene Dimer. - Neutral methyl-

ketene dimer (4.75 g.), sodium methoxide (21 mg.), dimethyl sul-

foxide (1.1 ml.), and carbon tetrachloride (9.5 ml.) were combined

in a 25-ml. Erlenmeyer flask. After six hours the reaction mixture

was extracted with 65 ml. of ether; the extract was washed with 10 ml.

of dilute hydrochloric acid, dried over Drierite, and filtered. The

ether was distilled and the carbon tetrachloride was removed at reduced

pressure to give 5.22 g. of crude product, which gave a strong yellow-

green color with ferric chloride, a positive ferric hydroxymate test

for esters, and no 2,4-dinitrophenylhydrazine derivative under the

usual test conditions.

Molecular distillation of the crude product at 10^{-4} mm. and

140-150° gave a mobile yellow liquid which was redistilled and col-

lected as three fractions having n_D^{25} 1.4730, 1.4913, and 1.4914.

The n.m.r. spectra of these fractions indicated that they were not

the original trimer.

Attempts to purify the trimer by absorption and partition

chromatography on silicic acid were not successful. A descending

chromatogram of the trimer on Whatman No. 1 paper was eluted with

n-butanol:ethanol:water (114) and developed with basic hydroxylamine

and ferric chloride solutions (115); it showed a single ester spot,

Rf. 0.81. A 24 x 240-mm. column of Whatman Cellulose Powder,

Standard Grade, was packed as a slurry with n-butanol:ethanol:water;

chromatography of 0.73 g. of the crude trimer with the same solvent

system gave a series of 25-ml. fractions which were analyzed by paper

spot-tests. The ester was found only in the third fraction, 0.66 g.,

85% of theory.

The molecular weight of the trimer was determined cryoscopic-

ally in cyclohexanol (99) with the chromatographed material.

Calcd. for $C_{18}H_{24}O_6$: 336. Found: 349, 326.

The ultraviolet spectrum of the chromatographed trimer had

λ_{max} 207 mμ (ε = 28,000) and inflection points at 220, 252, and 290

mμ. The infrared spectrum had carbonyl absorptions at 1740, 1707,

and 1680 cm^{-1}.

Dehydroacetic Acid (3-Aceto-6-methylpyronone). - The black,

solid residue from the distillation of commercial diketene was re-

crystallized twice from aqueous ethanol and sublimed to give dehydro-

acetic acid, m.p. 111.4-111.8° (lit. m.p. 109° (116)). Its carbonyl

bands in the infrared are at 1740 and 1720 cm^{-1}.

Diketene was purchased from Aldrich Chemical Company and

distilled three times, b.p. 68-69° (95 mm.). Its n.m.r. spectrum

is reproduced on page 52. The spin-spin coupling constants between

the olefinic and methylene hydrogens are 1.48 ± 0.03 and 1.89 ± 0.04

cps.

Dimethylketene β-lactone dimer (3-hydroxy-2,2,4-trimethyl-3-pentanoic lactone) was prepared by the isomerization of tetramethyl-1,3-cyclobutanedione (46). The crude product, obtained in 85% yield, was redistilled through a 30-cm. Holzman column to provide a sample with b.p. 156-162° (745 mm.), $n^{25}\underline{D}$ 1.4387 (lit. $n^{25}\underline{D}$ 1.4380 (46)), and λ_{max} 206 mμ (ε = 2870). This spectrum is shown on page 53.

Acidic Phenylketene Dimer. - A solution of 431 mg. of neutral phenylketene dimer in 3 ml. of ether was treated with 3 ml. of ice-cold aqueous sodium hydroxide. The two-phased mixture was centrifuged 15 minutes later, the aqueous layer was separated and acidified with acetic acid and hydrochloric acid, and the crystals which separated from the acidified solution were collected and dried to give 38 mg. of acidic phenylketene dimer, m.p. 147-150° (lit. m.p. 150° (53)). This material gave a reddish green color with methanolic ferric chloride. The infrared spectrum determined with a potassium bromide disc showed no hydroxyl absorptions, a strong carbonyl band at 1708, and other bands at 1540, 1455, 1360, 1325, 765, 708, and 695 cm^{-1}. A dimethylsulfoxide solution of the acidic dimer had n.m.r. absorptions at 470-450 (relative weight, 2.0 protons), 450-420 (10 protons), and 274 cps (1.6 protons).

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PROPOSITIONS
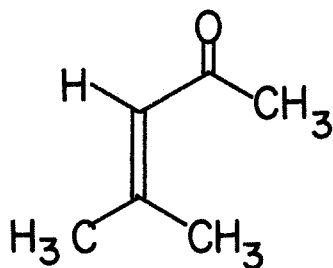
PROPOSITION 1

The N. m. r. Spectrum of Mesityl Oxide

The proton n. m. r. spectrum of mesityl oxide contains a doublet at 8. 14 τ (relative weight, 3 protons), a singlet at 7.95 τ (6 protons) and a broad signal at 4. 03 τ (1 proton) (1). Jackman assigned the doublet at 8. 14 τ to one of the two isopropylidene methyl groups by arguing that "the doublet at higher frequency cannot be due to the CH_3CO- protons since these could not couple with the olefinic proton to give splittings of the observed order" (1). More recently and apparently independently, Hatton and Richards made the same assignment (2).

Another interpretation of the spectrum of mesityl oxide is now proposed: the doublet at 8. 14 τ should be assigned to the CH_3CO- protons which are coupled with the olefinic hydrogen.

The observed coupling at 1. 4 cps (2) over four "saturated" bonds is not surprising when one views mesityl oxide as a resonance hybrid of structures I and II.
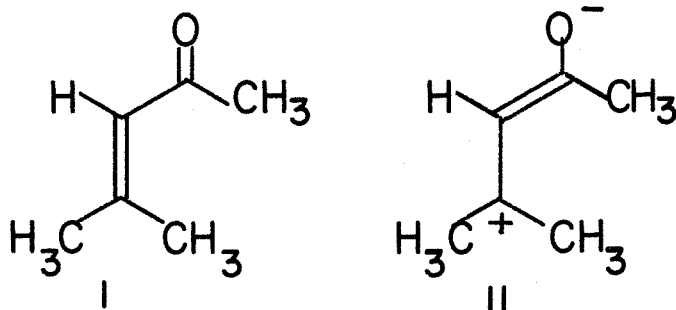
A decisive choice between these two interpretations, and an indicative choice between the conceptions of bonding they presuppose, could be made by comparing the n.m.r. spectra of mesityl oxide (III) and the deuterium labeled analogue IV. The latter compound could be easily synthesized from methyl **3,3**-dimethylacrylate (3) and perdeutero-methylmagnesium bromide.
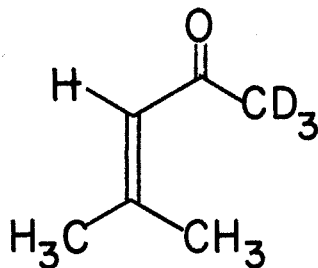

III   IV

PROPOSITION 2

Cope Rearrangement of syn-7-Vinylnorbornene

It is proposed that syn-7-vinylnorbornene (I) will rearrange

thermally to cis-$\Delta^{1,4}$-bicyclo[4.3.0]nonadiene (II) at 140° within

6 hours. The mild conditions suggested for this isomerization

may be compared with 300° for 24 hours, required for even in-

complete thermal rearrangement of III to IV (4). Examination of

molecular models shows that the double bonds in syn-7-vinylnorbornene

may overlap in a boat-like fashion to accommodate the Cope rear-

rangement (5).
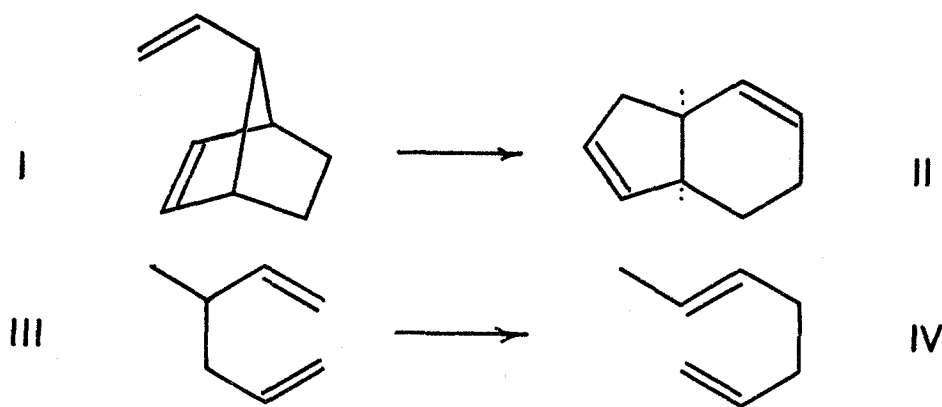
If this molecular rearrangement of syn-7-vinylnorbornene

does occur at 140°, it would show that the carbon-carbon double bond

in the norbornenyl system is a better participant in Cope rearrange-

ments than are acyclic double bonds. It would also raise the pos-

sibility that the rearrangements observed by Woodward and Katz (6),

for instance the isomerization of V to VI, are simply further examples

of low-temperature Cope rearrangements from norbornenyl systems

in which the broken bond happens to be the one cleaved in Diels-Alder
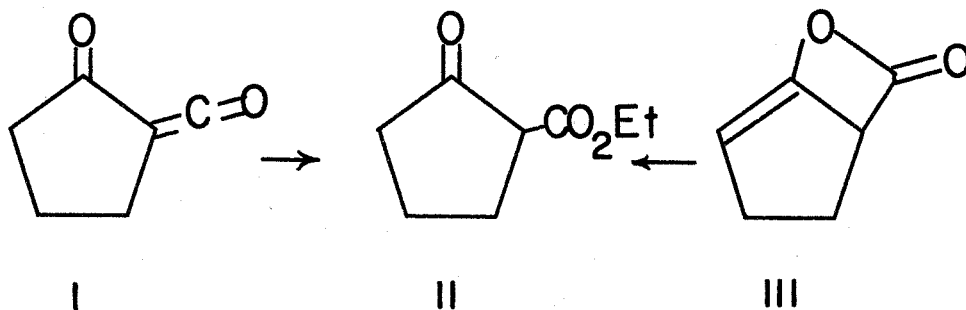
retrogressions (cf. Ref. 7).
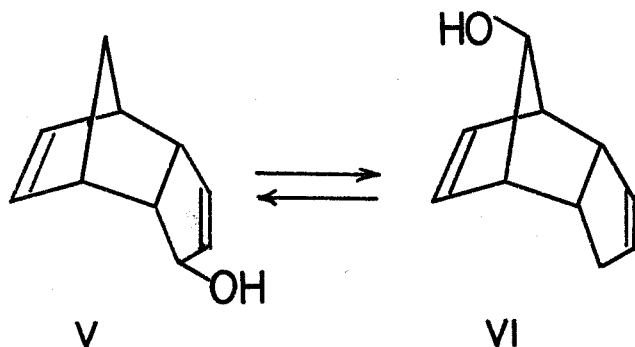
One sequence of reactions which might lead to syn-7-vinyl-

norbornene is given below.
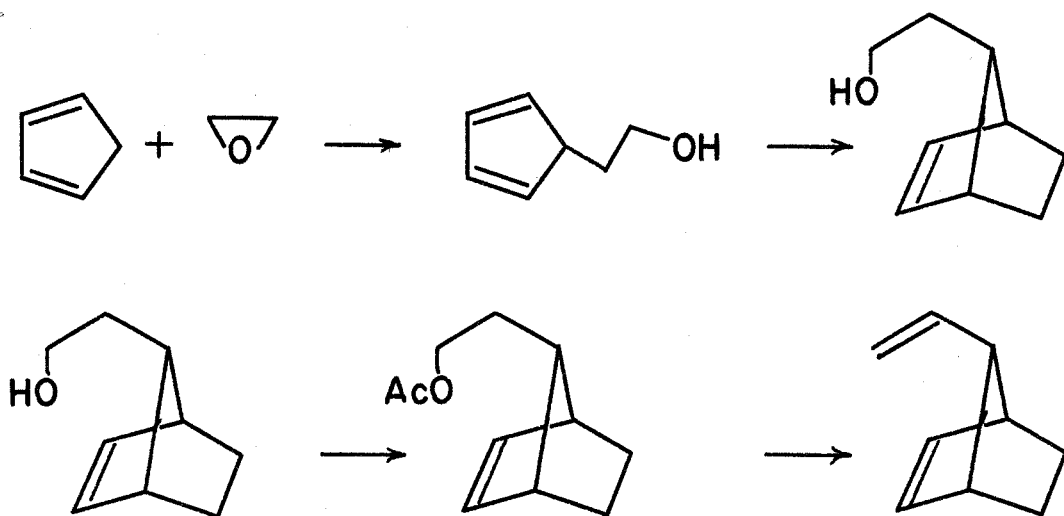
PROPOSITION 3

Cyclic Ketene Dimers

The product from the dehydrohalogenation of adipyl dichloride reacts with ethanol to give 2-carbethoxycyclopentanone (II) (8). Sauer has suggested that I is an intermediate in this reaction (8).


By analogy with the known chemistry of aldoketenes (9) and applications of intramolecular reactions of difunctional ketenes in syntheses of medium ring compounds (10), it seems possible that the intermediate which leads to 2-carbethoxycyclopentanone should be reformulated as III. Structure I would be expected to be unstable and to dimerize.

It is proposed that the dehydrohalogenation of adipyl dichloride be reinvestigated in an attempt to isolate the cyclic ketene dimer III.

If this cyclic ketene dimer is obtained, comparison of its physical properties with those of the neutral methylketene dimer (IVa or IVb) may give new information pertinent to the presently unknown geometry of the latter dimer (cf. Ref. 11).
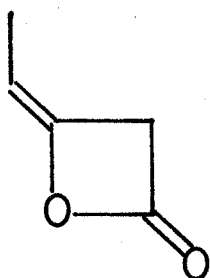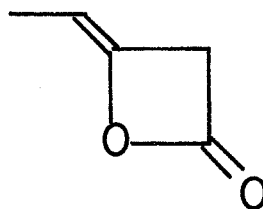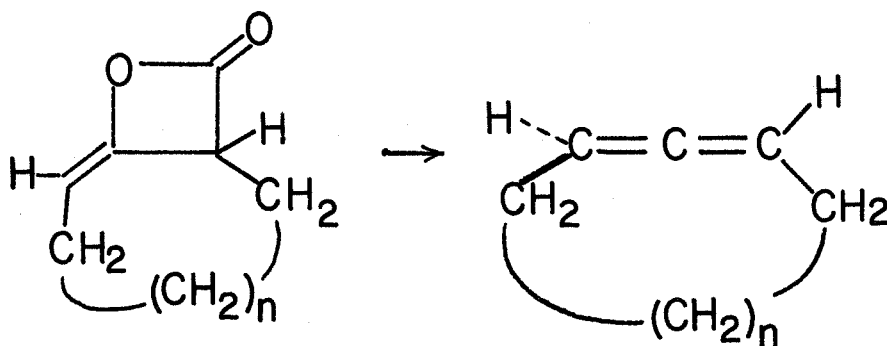
IV a   IV b

Since diketene may be cleaved thermally to give carbon dioxide and allene, one may reasonably expect suitable cyclic ketene dimers to be useful intermediates in syntheses of cyclic allenes.

PROPOSITION 4

Mechanism of the Pinacol Rearrangement

The penultimate paragraph in Collins' 1960 review article

on the pinacol rearrangement admits some exceptions to his general

"solution to the primary mysteries of the pinacol rearrangement" (12):

> Although some slight progress has been made with
> respect to the influence of steric properties of reactants
> upon the course of the rearrangement, this problem,
> particularly in the case of tetra-substituted glycols, is
> still not well understood. The role of oxides in the
> pinacol and related aldehyde-ketone rearrangements also
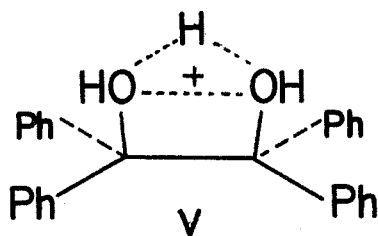> remains unsolved.

This proposition outlines an experiment designed to reduce

these two uncertainties.

In 1954, Gebhardt and Adams studied the rearrangement of

benzpinacol (I) to benzpinacolone (II) and found that the epoxide (III)

was an intermediate (13). They rationalized the formation of III in

terms of the transition state represented by expression IV.
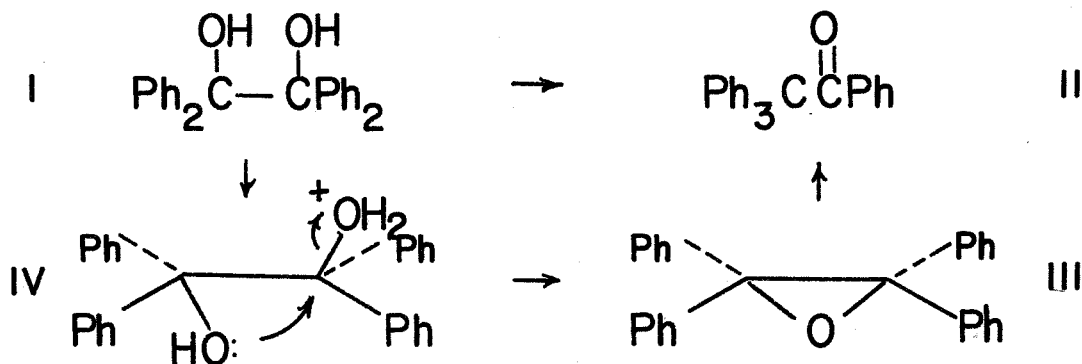
The possibility that transition states of type V may be involved in pinacol-pinacolone rearrangements has never been adequately tested. The formulation V posits a geometry in which both oxygen atoms are on the same side of the molecule.

$$
\begin{array}{c}
\text{H} \\
\text{HO----} \overset{+}{\cdots} \text{----OH} \\
\text{Ph}\diagdown \quad | \qquad | \diagup \text{Ph} \\
\text{Ph}\diagup \qquad \diagdown\text{Ph} \\
\text{V}
\end{array}
$$

An experimental examination of this suggestion is now proposed. The pinacol-pinacolone rearrangement of <u>erythro</u> and <u>threo</u> 1,2-diphenyl-1,2-di-<u>p</u>-tolylethyleneglycol (VI and VII), under the conditions used by Gebhardt and Adams (13) when they isolated the intermediate III, should lead to a similar epoxide (VIII or IX). The geometry of this epoxide should clearly indicate whether it came through a back side displacement or a front side collapse.
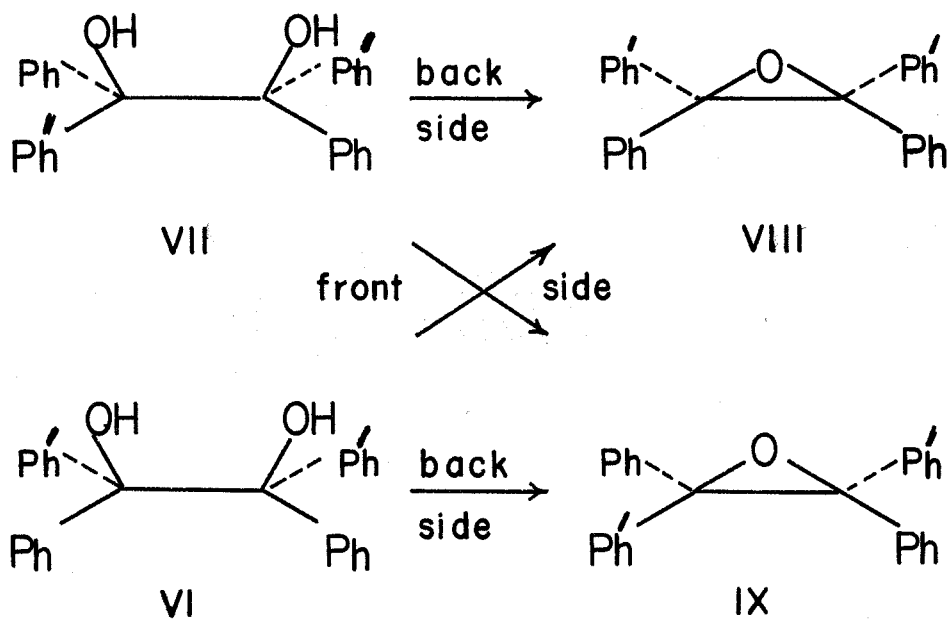
Results from this experiment should clarify the geometry of the transition state leading to epoxide formation in pinacol-pinacolone rearrangements. Synthesis of the necessary α-glycols VI and VII could be accomplished through standard methods (14).

PROPOSITION 5

Mechanism of 1,3-Cycloaddition Reactions

During the past four years Rolf Huisgen and co-workers have recognized some unifying characteristics in 1,3-cycloaddition reactions and discovered many new examples of this reaction type (15). They term these reactions, such as the addition of diphenyl nitrone (I) and styrene (II) to give triphenylisoazolidine (III), 1,3-dipolar cycloadditions, and label the addends 1,3-dipolar reagents and dipolarophiles.
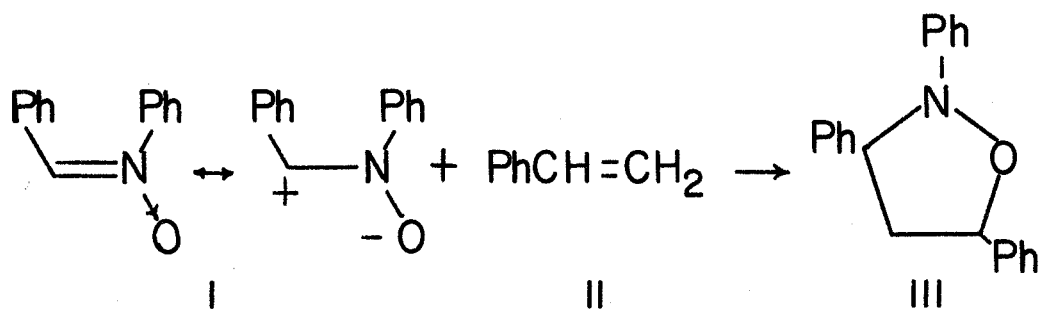

While the significance of this work cannot be impugned, the mechanism of 1,3-cycloadditions does not seem to be established beyond question.

This proposition sets forth a specific experiment designed to test the Huisgen mechanism in a specific case.

Alder and Stein (16) found that phenylcyclopentanotriazoline (IV) eliminated nitrogen at 100° to produce cyclopentanone anil (V).

IV → V
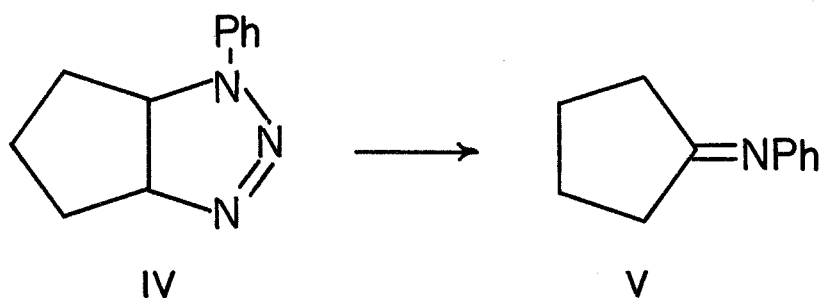
Huisgen noted (17) that the elimination of nitrogen from IV

could give a zwitterion (VI), which should have the properties of a

1,3-dipolar reagent. He was able to trap the intermediate VI with

phenyl isocyanate or phenyl isothiocyanate to give a five-membered

cyclic product (VII). He interpreted the reaction in the absence of a

dipolarophile as a hydride-shift process.

IV → VI

PhNCX
X= O,S

VII
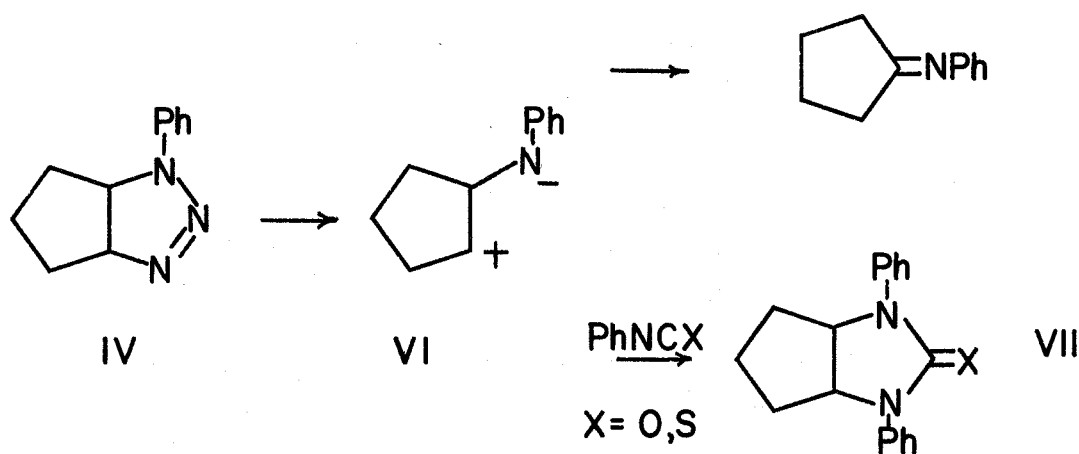
Another description of these two reactions is now proposed.

The triazole IV eliminates nitrogen to form an ethylenimine (VIII),

which is unstable at 100° and dissociates to form the observed

products. The ethylenimine may give an intermediate 1,3-diradical

(IX), which isomerizes to the anil (V) or combines with phenyl

isocyanate to give the 1,3-cycloaddition product (VII).
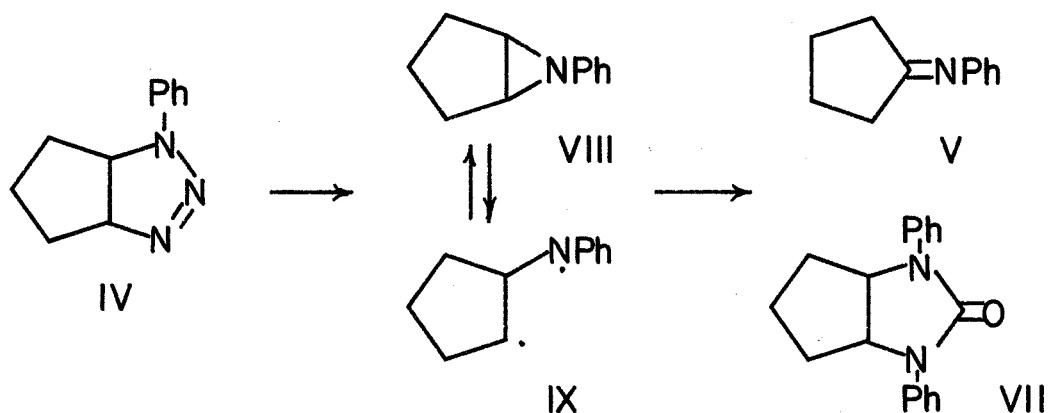
This proposal stems from the following analogies. Many tri-azoles eliminate nitrogen to give ethylenimines (18). Ethylenimines do, in some cases, give 1,3-cycloaddition products directly (19). The intermediate in this reaction may be a 1,3-diradical, correspond-ing to the probable intermediate in the thermal rearrangement of cyclopropane to propene (20).

To test this proposal, the following experiment should be run. The ethylenimine VIII should be heated to 100° in the presence of phenyl isocyanate. If the 1,3-cycloaddition product VII is obtained, this result would suggest the intermediacy of the ethylenimine VIII in the thermal elimination of IV, and perhaps justify a labeling experi-ment. The two mechanisms in question differ markedly in their predictions concerning the fate of the label in structure X during reaction.
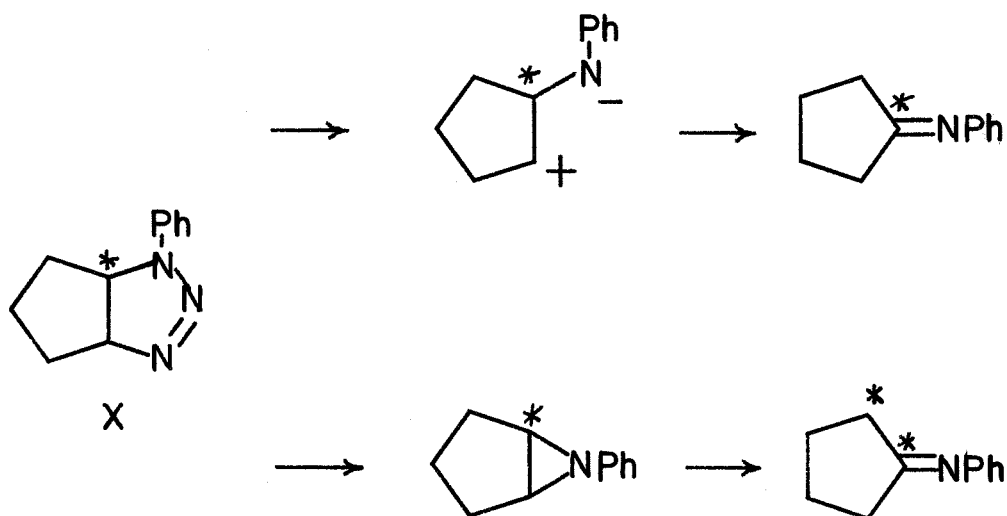
While the results from this study could not be extrapolated directly to all 1,3-cycloaddition reactions, if they were as proposed, they would indicate that 1,3-cycloaddition reactions need not invariably go through the Huisgen dipolar mechanism.

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