PART I
SYNTHETIC APPROACHES TO 8b, 8c-DIMETHYLPYRACYCLENE

PART II
A STUDY OF BIS-DIELS-ALDER ADDUCTS OF DIMETHYL ACETYLENEDICARBOXYLATE AND CERTAIN FURANS

Thesis for the Degree of Ph. D.
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JAMES DUANE SLEE
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This is to certify that the

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PART I: SYNTHETIC APPROACHES
TO 8b, 8c-DIMETHYLPYRACYCLENE

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ABSTRACT

PART I

SYNTHETIC APPROACHES TO 8b,8c-DIMETHYLPYRACYCLENE

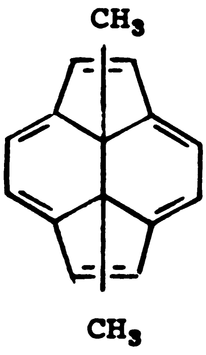
PART II

A STUDY OF BIS-DIELS-ALDER ADDUCTS OF DIMETHYL ACETYLENEDICARBOXYLATE AND CERTAIN FURANS

By

James Duane Slee

Synthetic methods for preparing 8b,8c-dimethylpyracyclene (4) were investigated. A useful precursor to 4 appeared to be dimethyl 2a,4a:6a,8a-diepoxy-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene-8b,8c-dicarboxylate (7) (1).



4

Reduction of 7 with lithium aluminum hydride in tetrahydrofuran gave 2a,4a:6a,8a-diepoxy-8b,8c-di(hydroxymethyl)-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene (12).

Treatment of diol **12** with *p*-toluenesulfonyl chloride in pyridine led to 2a,4a:6a,8a-diepoxy-8b,8c-di(hydroxymethyl *p*-toluenesulfonate)-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene (**16**). Reduction of **16** with lithium aluminum hydride gave rise to diol **12**. Displacement of the tosylate groups of **16** with sodium iodide under various conditions failed.

Conditions necessary for the preparation of the di(methanesulfonate) of diol **12** were not found. Treatment of **12** with one equivalent of methanesulfonyl chloride in pyridine gave rise to 2a,4a:6a,8a:9,10-triepoxy-8b,8c-di(methylene)-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene (**15**).

Experiments designed to convert the hydroxyl groups of diol **12** to a halide were unsuccessful. When **12** was treated with thionyl chloride cyclic sulfite **14** was obtained.

Saponification of **7** was accomplished with suspension of sodium hydroxide in dimethyl sulfoxide. The resulting diacid **10** was then converted to its anhydride **11**.

Another pyracyclene precursor, 2a,4a:6a,8a-diepoxy-8b,8c-bis(trifluoromethyl)-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene (**21**) was prepared by allowing hexafluorobutyne-2 to react with [2.5](2,5)-furophane. Catalytic hydrogenation gave the corresponding octahydro derivative **23**.

Attempts to cleave the ether bridges in compounds **7**, **21** and **23** were unsuccessful.

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PART II

Dimethyl acetylenedicarboxylate reacts with furan at room temperature to give 7-oxabicyclo[2.2.1]hept-2,5-diene-2,3-dicarboxylate (27) (2). A second mole of furan reacts with 27 at room temperature resulting in the formation of dimethyl (*exo*-*endo*)1,4:5,8-diepoxy-1,4,5,8-tetrahydronaphthalene-4a,8a-dicarboxylate (34). When the same reaction is run at 100° dimethyl (*exo*-*exo*)1,4:5,8-diepoxy-1,4,4a,5,8,8a-hexahydronaphthalene-2,3-dicarboxylate (37); dimethyl (*exo*-*endo*)1,4:5,8-diepoxy-1,4,4a,5,8,8a-hexahydronaphthalene-2,3-dicarboxylate (38) and dimethyl 1,4:5,10:6,9-triepoxy-1,4,4a,5,5a,6,9,9a,10,10a-decahydroanthacene-2,3-dicarboxylate (41).

While the Diels-Alder adduct of dimethyl acetylenedicarboxylate and 2,5-dimethylfuran does not react with a second mole of 2,5-dimethyl furan at room temperature at 100° dimethyl (*exo*-*endo*)1,4:5,8-diepoxy-1,4,5,8-tetramethyl-1,4,4a,5,8,8a-hexahydronaphthalene-2,3-dicarboxylate (46) is formed. Exhaustive catalytic hydrogenation of 46 gave the *cis*-decahydro ester 49. Saponification of 49 led to its *trans*-diacid 50. Oxidative bisdecarboxylation gave (*exo*-*endo*)1,4:5,8-diepoxy-1,4,5,8-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro naphthalene (51). Catalytic reduction let to the parent compound of this system, (*exo*-*endo*)1,4:5,8-diepoxy-1,4,5,8-tetramethyldecahydronaphthalene (52).

Controlled catalytic hydrogenation of **46** gave rise to dimethyl (*exo*-*endo*)1,4:5,8-diepoxy-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2,3-dicarboxylate (**63**). Pyrolysis of **63** led to dimethyl 2,5-dimethylfuran-3,4-dicarboxylate, 2,5-dimethylfuran and ethylene. Dimethyl 2,5-dimethylfuran-2,3-dicarboxylate and *p*-xylene were obtained when **63** was treated with trifluoroacetic acid.

Two additional bis-Diels-Alder adducts were synthesized. Dimethyl (*exo*-*endo*)1,4:5,8-diepoxy-1,4,5-trimethyl-1,4,4a,5,8,8a-hexahydronaphthalene-2,3-dicarboxylate (**58**) was prepared by allowing 2-methylfuran to react with 7-oxa-1,4-dimethylbicyclo[2.2.1]hept-2,5-diene-2,3-dicarboxylate at 100°. Dimethyl (*exo*-*endo*)1,4:5,8-diepoxy-1,5,8-trimethyl-1,4,4a,5,8,8a-hexahydronaphthalene-2,3-dicarboxylate **61** was synthesized in a similar manner from 2,5-dimethylfuran and 7-oxa-1-methylbicyclo[2.2.1]hept-2,5-diene-2,3-dicarboxylate. The saturated derivatives of these two compounds were also prepared.

References

1. D. J. Cram and G. R. Knox, *J. Am. Chem. Soc*., **83**, 2204 (1961).
2. O. Diels and K. Alder, *Ann*., **410**, 243 (1931).

PART I

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A THESIS

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To My Parents

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Part I

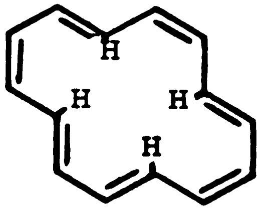
Studies Concerning the Synthesis of 8b,8c-Dimethylpyracyclene

INTRODUCTION

The concept of intramolecular ring currents which are induced by external magnetic fields was originally introduced to explain the high diamagnetism and the resulting anisotropy associated with benzenoid aromatic hydrocarbons (1,2). More recently the ring current theory has been used to account for chemical shifts in nuclear magnetic resonance (nmr) spectra (3,4). The hydrogen atoms on the periphery and in the plane of a benzenoid system resonate at low fields (i.e. they are deshielded) whereas the hydrogen atoms within and above the ring resonate at high fields (i.e. they are shielded). These chemical shifts are attributed to the anisotropy of the aromatic system.

The work of Sondheimer and his coworkers (5), with the conjugated, monocyclic polyenes known as annulenes, has extended the concept of aromaticity to include compounds other than benzenoid aromatic systems. Annulenes which obey Hückel's rule (6), (e.g., planar monocyclic conjugated polyenes possessing $4n + 2$ π-electrons ($n = 1,2,3,\ldots$etc)) have ^{1}H chemical shifts characteristic of aromatic systems.

Thus, diamagnetic ring currents associated with aromatic systems have been experimentally observed for [4n + 2] annulenes by means of low temperature nmr spectroscopy. The low temperature nmr spectrum of [14] annulene 1 serves to illustrate the effects of the diamagnetic ring current.

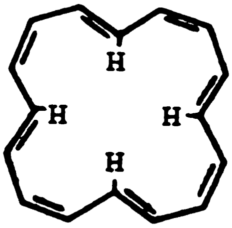


1

A single conformer of [14] annulene can be observed at -60°. The ten hydrogen atoms on the periphery of the molecule resonate at τ 2.4 and the four internal hydrogens resonate at τ 10.0. The signal at τ 2.4 is typical of benzenoid aromatic hydrogen atoms whereas the signal at τ 10.0 is the result of shielding within the ring.

The ^{1}H chemical shifts of annulenes containing 4n π-electrons are reversed relative to the [4n + 2] annulenes. Thus, the external hydrogen atoms of the [4n] annulenes are observed at high fields (shielded) and hydrogen atoms within the ring are found at low fields (deshielded) (5).

This reversal of chemical shift is illustrated by the low temperature nmr spectrum of [16] annulene 2 (5,9). At -120° molecular motion is slow enough to permit observation of a four hydrogen atom multiplet at τ -0.32 and a twelve hydrogen atom multiplet at τ 4.8. The resonances at τ -0.32 correspond to the inner hydrogen atoms and the resonances at τ 4.8 are a result of the external hydrogen atoms.



2

A comparison of the nmr spectra of [14] annulene and [16] annulene reveals that the hydrogens within the ring of [16] annulene are shifted 10.32 ppm down field from those of [14] annulene. Longuet-Higgins (10) and Pople (11) believe this change is too drastic to be explained merely by the loss of the diamagnetic ring current. Instead they ascribe the low field resonances of the inner hydrogen atoms of [4n]annulenes to an induced paramagnetic ring current.

Longuet-Higgins suggests that the π-electrons of a conjugated, planar, monocyclic polyene are induced to rotate around the ring when the compound is placed in a strong magnetic field such as the one of an nmr instrument (10). The net ring current is the resultant of two factors: first, a diamagnetic ring current caused by the Larmor precession of the π-electron cloud around the ring; and, second, a paramagnetic ring current flowing in the opposite direction. The magnitude of the diamagnetic ring current is a function of the electron density in the ground state of the molecule, whereas the paramagnetic ring current is the sum of the contributions of excited electronic states.

A molecular orbital diagram derived from the Hückel approximation for a 4n π-electron system such as [12]annulene indicates that all the molecular orbitals except for the highest and lowest should be doubly degenerate (11). Since the highest occupied orbital of [12]annulene contains only two electrons, one might expect its ground state to be a triplet; and, therefore be paramagnetic (Figure 1).

The ground state of [12]annulene is, however, diamagnetic meaning that the degeneracy of the highest occupied orbital has been removed. A molecular orbital diagram of [12]annulene in its singlet state places one of the two highest bonding orbitals at a slightly higher energy than the other (Figure 2).

If the energy difference between the highest occupied orbital and the lowest unoccupied orbital is small, a single electron may be promoted to the lowest unoccupied orbital to give a paramagnetic species. The field of a strong magnet can cause this electronic promotion, and as a result the molecule experiences the anisotropy of a paramagnetic ring current. This electron excitation does not occur in 4n + 2 π-electron systems because the energy difference between the highest occupied bonding orbital and the lowest unoccupied orbital is too large.

In a dehydroannulene such as 1,5-didehydro[12]annulene ($\underset{\sim}{3}$) the triple bonds, which are shorter than the other bonds, introduce bond length alternation and this perturbation is probably sufficient to remove the orbital degeneracy (5,12).

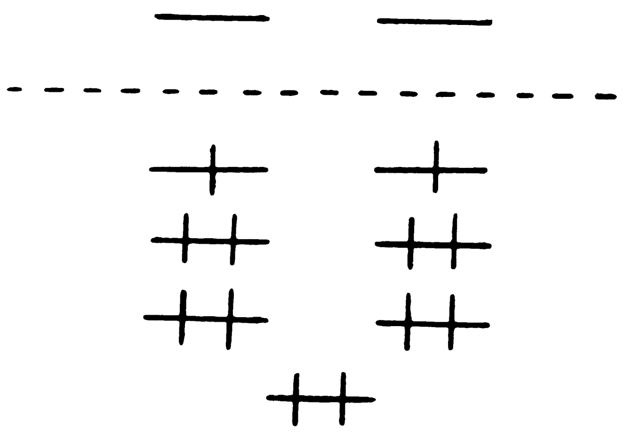


Figure 1. Molecular orbital diagram for the triplet state of [12]annulene.

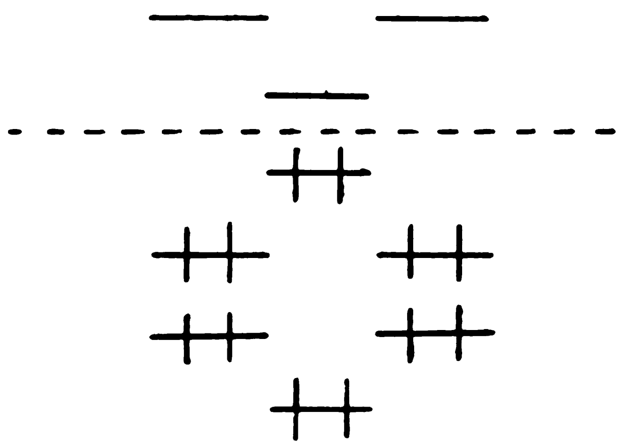
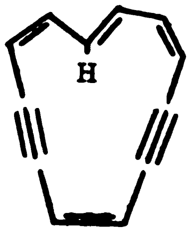


Figure 2. Molecular orbital diagram for the singlet state of [12]annulene.

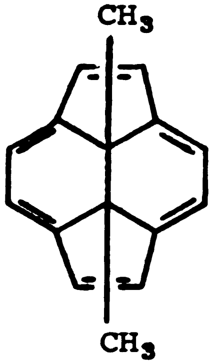


3

The flexibility of large [4n] annulene rings may also be an important factor. These molecules tend to orient themselves in their most stable conformation. As a result, single-double bond alternation occurs and causes the removal of the orbital degeneracy.

The goal of this investigation was to synthesize a compound which would reveal the structural features of a conjugated 4n π-electron polyene which are necessary for the induction of a paramagnetic ring current.

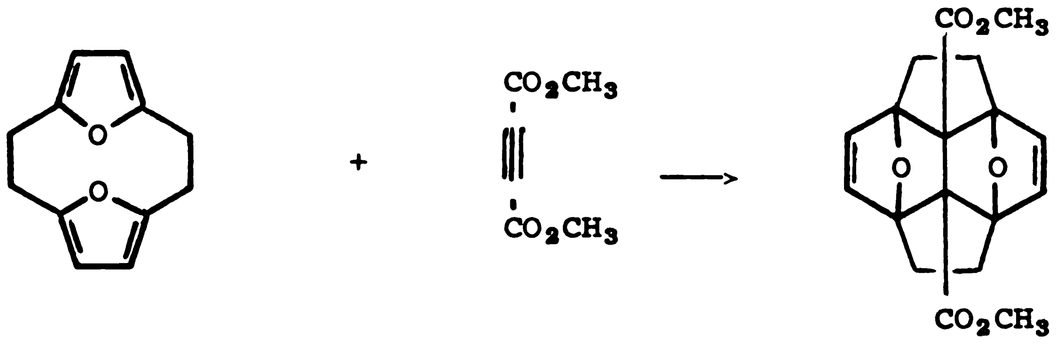
A number of criteria were used to select a compound for this study, in order to obtain more detailed information concerning induced paramagnetic ring currents. 1) The compound had to be a 4n π-electron conjugated cyclic olefin. 2) The π-electron system of the molecule must be nearly planar and rigid to allow for maximum orbital overlap. 3) The ring size of the conjugated system must be as small as possible, since it is known that ring currents decrease with increasing ring size (13). 4) There should be hydrogen atoms above the plane of the ring as well as in the plane of the ring in order to study the anisotropy of the induced paramagnetic ring current.



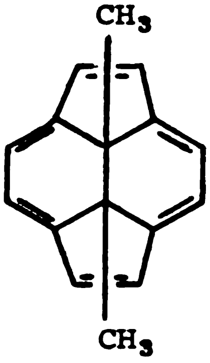
4

8b,8c-Dimethylpyracyclene (**4**) should be particularly well suited for study, since this rigid 12 π-electron system is nearly coplanar and has protons situated both in the plane of the ring and above the ring. Clearly, the nmr spectrum of this compound should reveal a great deal about the anisotropy associated with induced paramagnetic ring currents.

The carbon skeleton of 8b,8c-dimethylpyracyclene is present in a compound reported by Cram in 1961 (14,15). Reaction of [2.2] (2,5) furophane (**5**) with dimethyl acetylenedicarboxylate (**6**) gave the Diels-Alder adduct **7**.



5 **6** **7**



4

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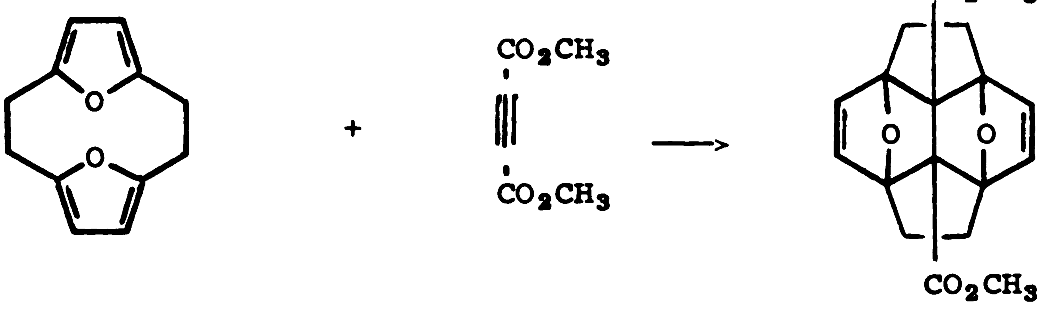
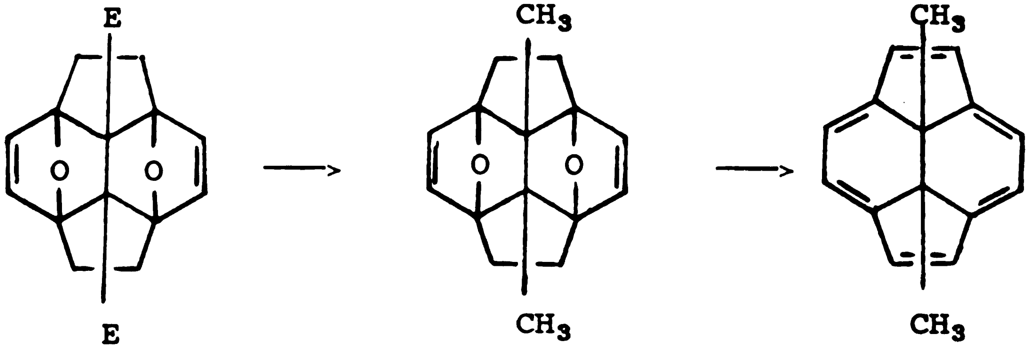


5 6 7

Basically two alterations must be made on the Diels-Alder adduct **7** in order to synthesize 8b,8c-dimethylpyracyclene (**4**). First, the carbomethoxy groups must be reduced to methyl groups to give dimethyl derivative **8**; and, second the ether linkages must be cleaved with the elimination of two equivalents of water to form the **12** π-electron ring of 8b,8c-dimethylpyracyclene (**4**).

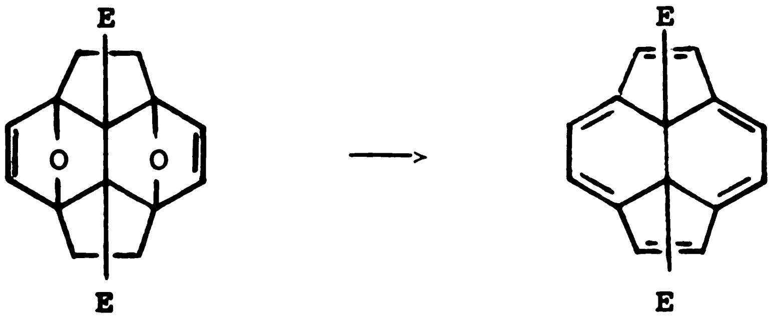


7 **8** **4**

E = CO_2CH_3

RESULTS AND DISCUSSION

The synthesis of 8b,8c-pyracyclene derivatives from the Diels-Alder adduct 7 seemed to be a relatively straight forward task. Cleavage of the ether linkages, and simultaneous or subsequent removal of two equivalents of water would lead to dimethyl pyracyclene-8b,8c-dicarboxylate 9 which would be of considerable interest in itself.



E = CO_2CH_3 7 9

A number of reagents which normally cleave ethers were tried without success. Triphenylphosphine dibromide (16) which is usually efficient in cleaving ethers gave only intractable materials when refluxed with the adduct 7 for four hours in acetonitrile. Changing the solvent to benzonitrile and heating the solution to 120° gave rise to [2.2] (2,5) furophane (5) (the result of a retrograde Diels-Alder reaction of starting adduct 7).

Since some ethers can be cleaved by strong acids (17), a small sample of 7 was dissolved in trifluoroacetic acid, and held at room temperature for three weeks. No evidence of a reaction was seen in nmr spectra which were taken during this time.

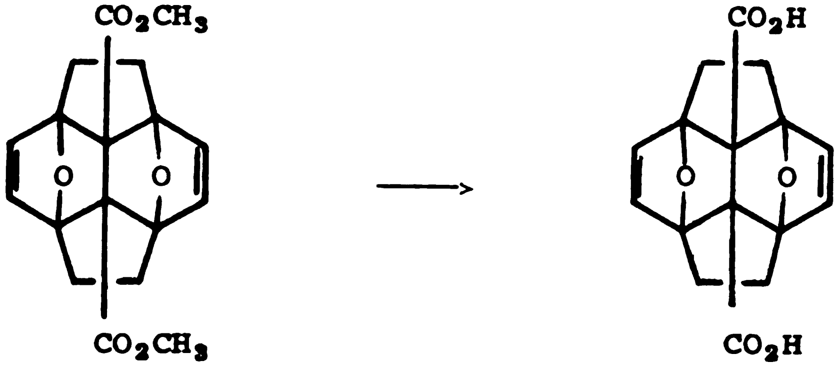
Another reagent which has been used to cleave ethers is hydrogen bromide (17,18). Several procedures which employed this reagent were tried without success. When adduct 7 was warmed to 50^0 with hydrobromic acid only intractable materials were obtained. In a more drastic experiment 7 was dissolved in acetic acid which had been saturated with hydrogen bromide (17,19). It was hoped that after the initial addition of hydrogen bromide to the double bonds had occurred the ethers would be cleaved. This, however, was not the case; only intractable tars were found. In another experiment 7 was refluxed with pyridinium hydrobromide in pyridine (a mild source of hydrogen bromide) for five hours; however, only the retrograde product, [2.2](2.5)furophane (5), was isolated.

The failure of these reagents to cleave the ether linkages of adduct 7 is most likely a result of stereochemical factors. The carbonium ion intermediate which would result from attack of an acid on the oxygen atom of the ether linkage would be relatively unstable because it would not be able to achieve planarity due to the rigidity of this molecule. As a result, if the carbon-oxygen bond is cleaved, it would readily be reformed. The tars obtained when adduct

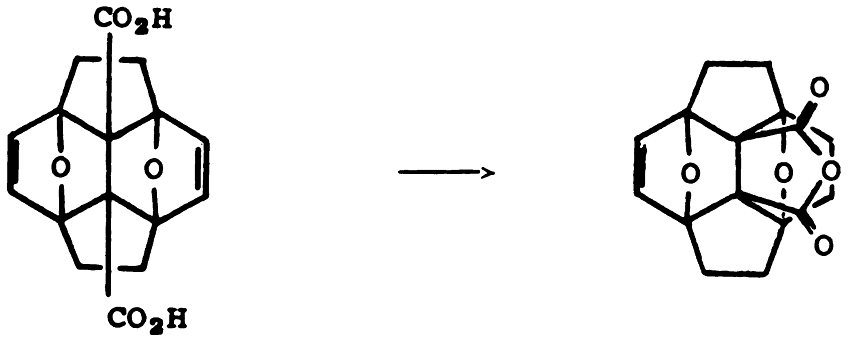
7 was treated with strong acids are probably due to carbonium ion rearrangements. In the case of triphenylphosphine dibromide a complex is probably formed with the highly electronegative carbomethoxy groups rather than with the ether linkages. The triphenylphosphine dibromide, therefore, is deactivated and is no longer effective for ether cleavage.

Attention was next focused on the carbomethoxy groups. In contrast to the behavior of normal esters, saponification of Diels-Alder adduct **7** proved to be difficult. Both aqueous sodium hydroxide and methanolic potassium hydroxide failed to hydrolize adduct **7**. When **7** was refluxed with potassium hydroxide in a dioxane-water solution, the starting material degraded *via* a retro-Diels-Alder reaction to give [2.2](2,5)furophane (**5**). Saponification was also tried with aqueous barium hydroxide in hopes of precipitating the barium salt of the diacid from solution. This method, however, also led primarily to [2.2](2,5)furophane (**5**). The difficulty encountered in saponifying Diels-Alder adduct **7** is apparently due to steric hindrance.

Saponification of adduct (**7**) was finally achieved by warming it in a suspension of sodium hydroxide in dimethyl sulfoxide (20,21). Dimethyl sulfoxide is a particularly good solvent because it does not coordinate with the hydroxide anion. The resulting "free" hydroxide anion reacted with the severely hindered ester function of adduct **7** to give diacid **10** in good yields. The diacid was easily converted to anhydride **11** by warming in acetic anhydride.



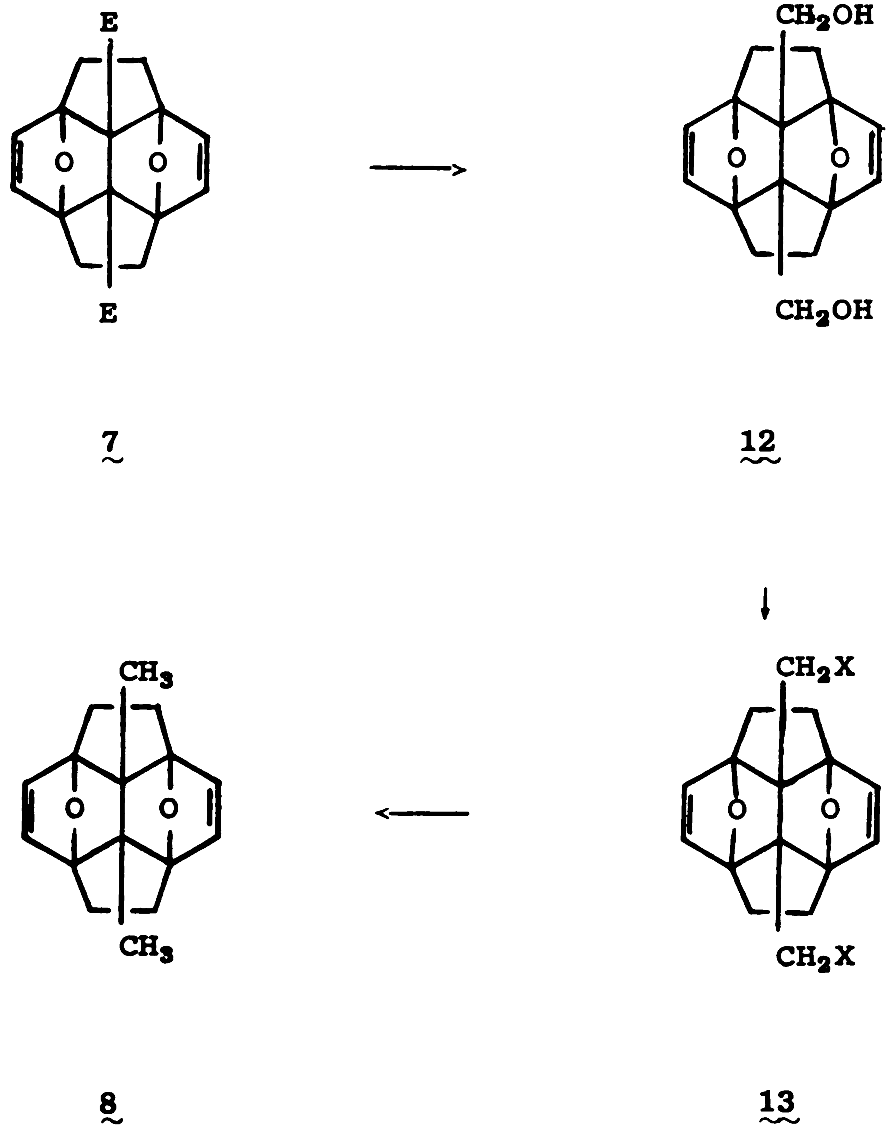
7 10



10 11

The saponification of Diels-Alder adduct 7 was not helpful in the conversion of the carbomethoxy groups into methyl groups. The reaction sequence which appeared to be the most promising for this conversion is outlined in Scheme 1. According to this plan Diels-Alder adduct 7 would be reduced to the corresponding diol 12, which, in turn, would be converted to the dihalide 13. Reduction of dihalide 13 would then lead to the desired dimethyl derivative 8.

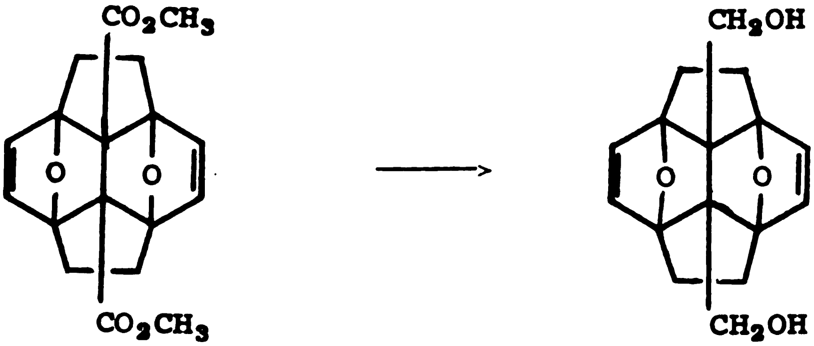
Initial experiments designed to reduce Diels-Alder adduct 7 to diol 12 were discouraging. Lithium aluminum hydride reduction in tetrahydrofuran followed either by an



E = CO_2CH_3 X = Cl, Br, or I

Scheme 1.

alkaline or by an acidic work up gave very low yields of diol 12. The low yields were finally attributed to the surprisingly high solubility of the diol in water. Good yields of 12 were finally obtained from the lithium aluminum hydride reduction by hydrolyzing the reaction with a stoichiometric amount of water.



7 12

Unfortunately suitable reaction conditions for the conversion of diol 12 to a dihalide could not be found.

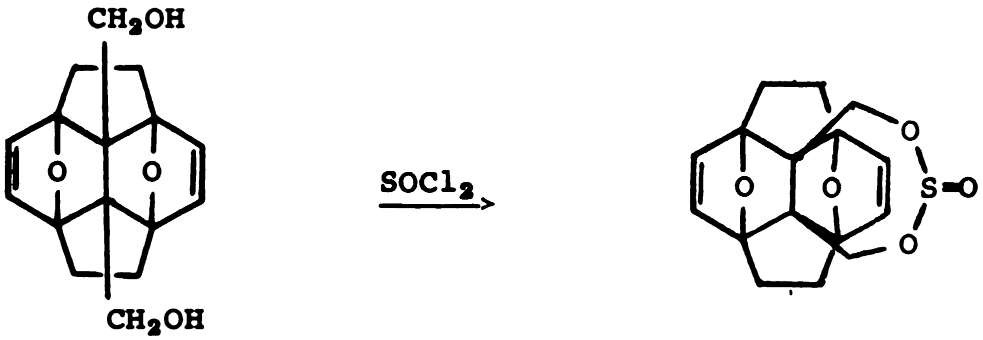
Phosphorus tribromide is one of the classical reagents used to convert an alcohol to a bromide (23). However, treatment of diol 12 with this reagent in refluxing benzene for four hours gave no trace of the dibromide.

Triphenylphosphine dibromide also has been reported to convert alcohols to bromides (24,25). When diol 12 was refluxed for six hours in an acetonitrile solution of triphenylphosphine dibromide no evidence of the desired dibromide could be found. Similar results were obtained at higher temperatures when dimethyl formamide was used as the solvent. A variation of this procedure developed for the preparation of alkyl chlorides from alcohols uses triphenylphosphine in refluxing carbon tetrachloride (26,27). As anticipated from the preceding experiments no evidence for the dichloride could be found.

Diphosphorus tetraiodide has been used to prepare iodides from diols (28). When a solution of diol 12 was refluxed with freshly prepared diphosphorus tetraiodide in tetrahydrofuran for several hours, the diiodide could not be detected.

A mild method for the conversion of alcohols to iodides has been developed by Corey (29). If an alcohol is treated with o-phenylene phosphorochloridite in an ether-pyridine solution, a phosphite ester is formed. Treatment of the phosphite ester with iodine then leads to the corresponding alkyl iodide. Unfortunately, the diiodide could not be detected when this reaction was carried out on diol 12.

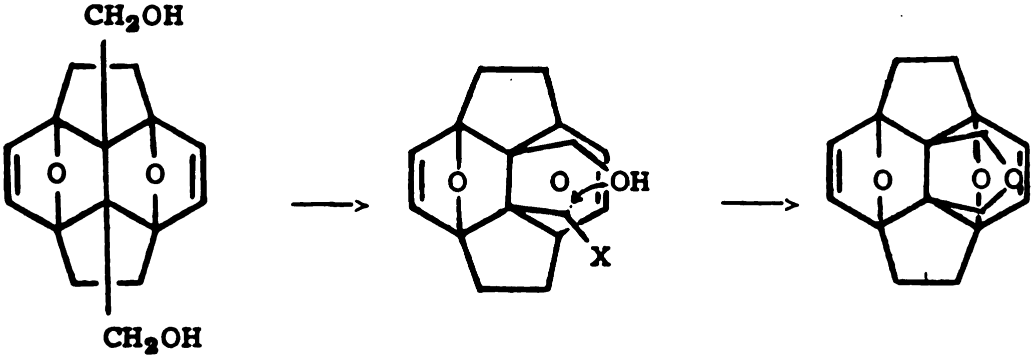
Reaction of thionyl chloride with 12 did not lead to the dichloride (30,31), but produced a small quantity of the cyclic sulfite 14 (32). Although the structure of the cyclic sulfite 14 was not rigorously proved due to purification



12

14

problems, the nmr spectrum was consistent with this structure. The formation of the cyclic sulfite reemphasizes the steric problems associated with this molecule. The hydroxymethyl groups are held in close proximity to each other and any difunctional reagent such as phosphorus tribromide, diphosphorus tetraiodide or thionyl chloride could eliminate two equivalents of hydrogen halide to form a cyclic ester. The hydroxymethyl groups are also situated so as to facilitate the formation of cyclic ether **15** by an internal displacement of a monosubstituted derivative of diol **12**



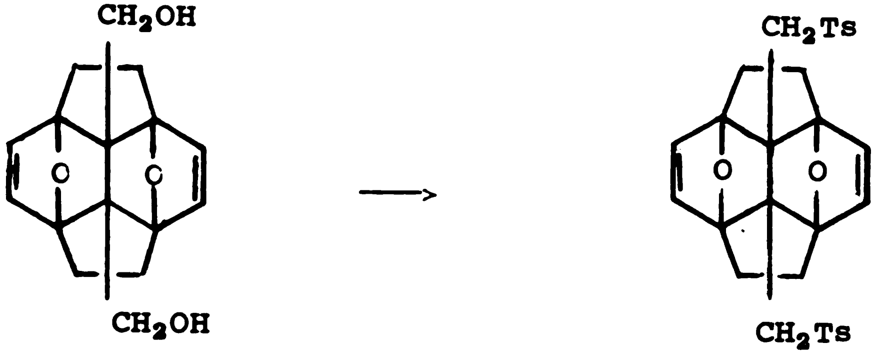
12

15

X = $-PBr_2$

The ditosylate (**16**) of diol **12** was easily prepared by treating an ice-cold pyridine solution of the diol with p-toluenesulfonyl chloride for three days (33).

Reactions designed to displace the tosyl groups of ditosylate **16** once again revealed the importance of steric factors in this molecule. In an effort to replace the tosyl



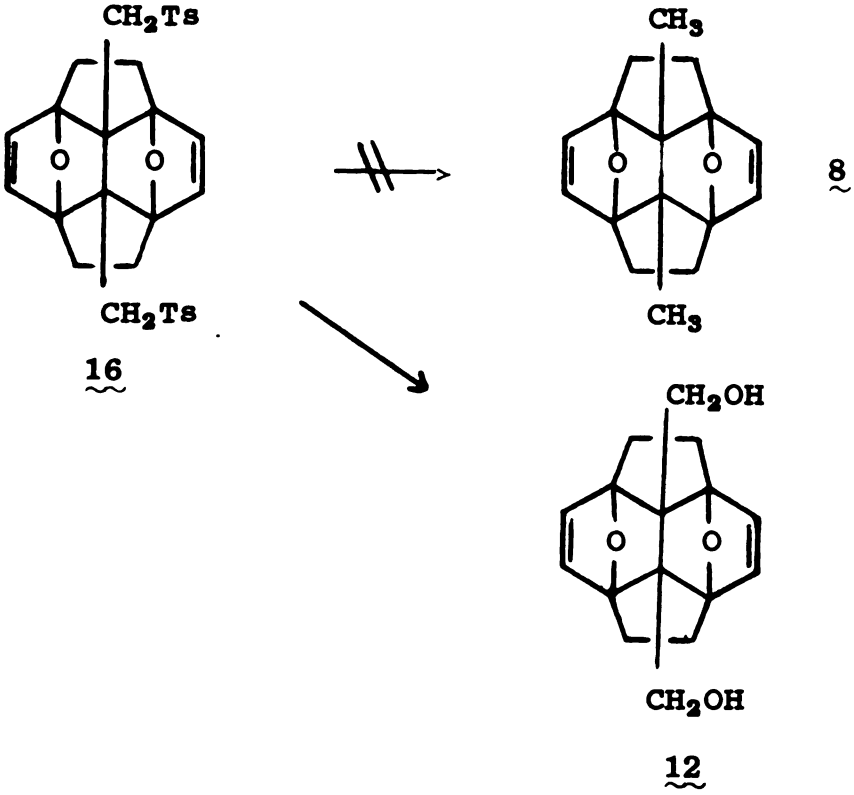
12 16

Ts = $CH_3C_6H_4SO_3$-

groups with iodine, ditosylate 16 was refluxed with sodium idoide in acetone for 24 hours (34). Nearly all of the starting ditosylate was recovered and no diodide was found. Similar results were obtained when N,N-dimethylformamide and dimethyl sulfoxide were used as solvents.

An attempt to affect displacement of the tosylate functions by warming ditosylate 16 with sodium sulfide in dimethyl sulfoxide, led only to an intractable materials.

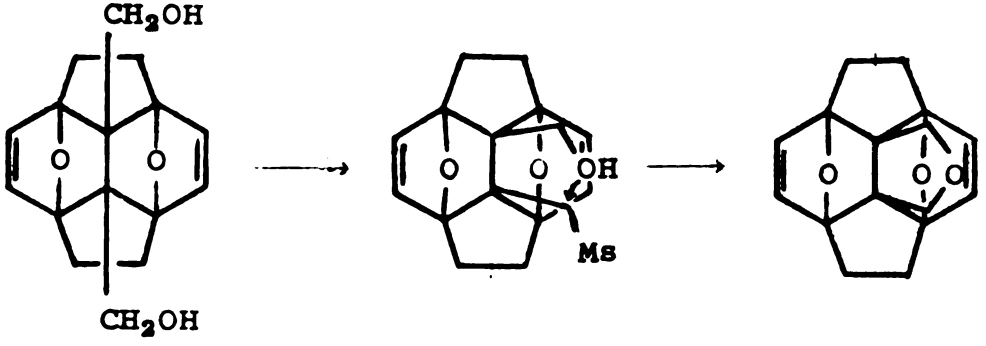
Although lithium aluminum hydride usually reacts with tosylates to give the corresponding alkanes (35), reaction of ditosylate 16 with lithium aluminum hydride in refluxing diethyl ether gave rise to diol 12 rather than to the desired alkane 8. This result is not surprising in view of the steric problems associated with this compound. Attack of the aluminum hydride anion on the sulfur atom of a tosylate rather than at carbon has been reported to predominate in certain cases (35,37). A nucleophilic displacement of



the tosyl groups in 16 is apparently prevented by the rigid, cage-like framework of this molecule. Even neopentyltosylate which is closely related to this system will undergo displacement reactions under conditions similar to those used in this investigation (37).

Because ditosylate 16 proved to be unreactive, the synthesis of the bis(methane sulfonate) of diol 12 was investigated. It was hoped that the small methane sulfonate moiety would be more susceptible to nucleophilic displacement reactions than tosylate. Unfortunately treatment of diol 12 with methane sulfonyl chloride in pyridine did not lead to the desired bis(methane sulfonate). It is believed that the monomethane sulfonate 17 is initially formed and then undergoes an internal displacement reaction to give cyclic ether 15 (39).

Ms = Methanesulfonate

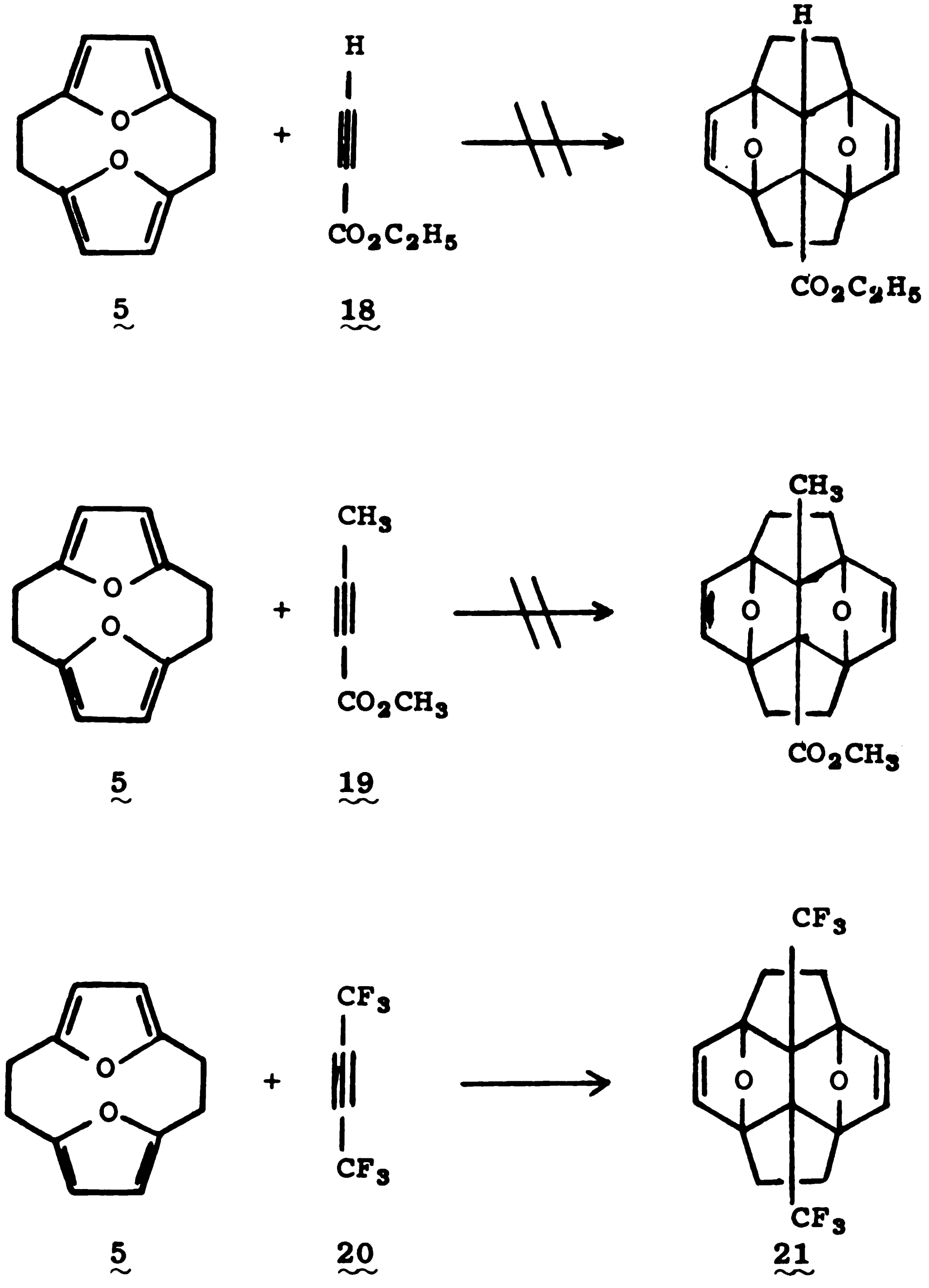


12 17 15

In support of this postulate 15 was prepared by refluxing a pyridine solution of diol 12 with one equivalent of methanesulfonyl chloride.

In an effort to circumvent some of the steric problems associated with this system, [2.2](2,5)furophane (5) was treated with three other acetylenes in hope of preparing less hindered Diels-Alder adducts. Both ethyl propiolate (18) and methyl tetrolate (19) failed to react, but hexafluoro-2-butyne (20) gave high yields of the hexafluoro-adduct 21 (40). (Scheme 2).

The hexafluoro-adduct 21 could also be a precursor to an interesting pyracyclene derivative, 8b,8c-bis(trifluoromethyl)pyracyclene 22, formed by cleavage of the ether linkages followed by the loss of two equivalents of water.


H
CO2C2H5
H
CO2C2H5
5
18
CH3
CO2CH3
CH3
CO2CH3
5
19
CF3
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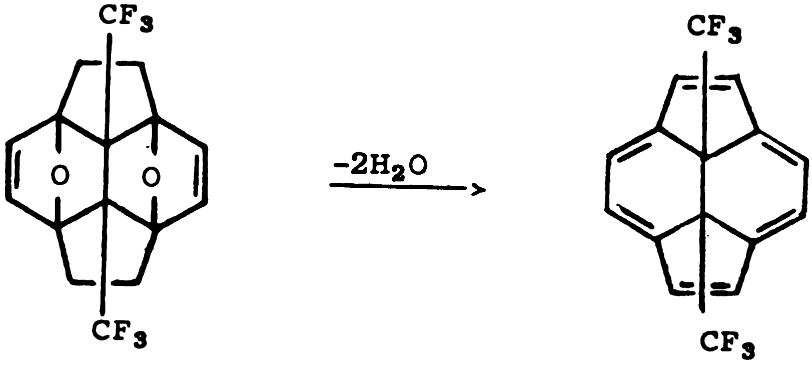
CF3
CF3
5
20
21



21 22

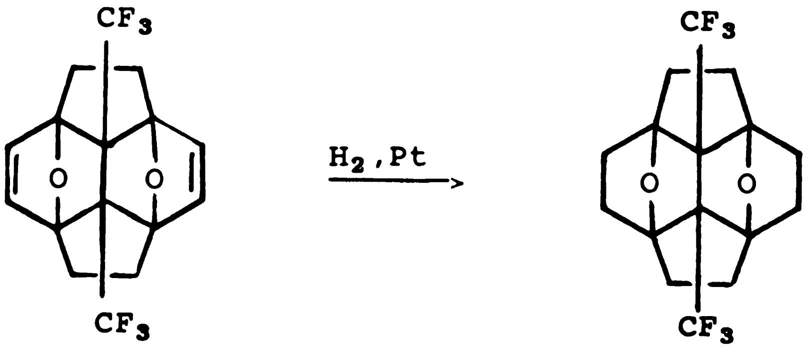
Since one of the objectives of this synthesis was to place methyl groups above the plane of the pyracyclene ring so as to investigate the influence of an induced paramagnetic ring current, it appears that the presence of the trifluoromethyl groups would defeat this purpose. Fortunately, fluorine may also be studied by ^{19}F nuclear magnetic resonance, and 21 is therefore, a useful precursor in this study.

Cleavage of the ether linkages in the hexafluoro-adduct 21 proved to be as difficult as in adduct 7. For example, heating 21 with triphenylphosphine dibromide in benzonitrile to 150° for 16 hours in a bomb, led only to recovered starting material (16).

Boron tribromide is also very efficient in ether cleavage reactions (41). When hexafluoro-adduct 21 was reacted with boron tribromide in carbon tetrachloride at room temperature or with heating, only intractable materials were obtained.

A reagent which appeared to be particularly promising was the mixed anhydride of acetic acid and *p*-toluenesulfonic acid (42). No reaction occurred on refluxing an acetonitrile solution of 21 with the mixed anhydride for 18 hours; at 120° in a bomb an intractable material was obtained.

In order to further demonstrate the extreme stability of the ether linkages in these compounds, the unsaturation in the hexafluoro-adduct 21 was removed by catalytic hydrogenation and the tetrahydro ether 23 was then treated with a number of reagents known to affect ether cleavage. Of particular interest is the experiment in which an acetic acid solution of reduced adduct 23 was treated with concentrated hydroiodic acid for 18 hours at 100°. Surprisingly most of the starting adduct 23 was recovered unreacted. Anhydrous hydrogen bromide also failed under similar conditions. Boron tribromide reacted with reduced adduct 23 in carbon tetrachloride, but failed to give identifiable products (41).



21 23

The unusual stability of the ether linkages in this system is probably due to the rigidity of the molecule. When a Lewis acid attacks the oxygen atom of the ether, carbon-oxygen bond cleavage may momentarily occur; however, since the carbonium ion which is formed cannot become planar it apparently prefers to reclose to an ether rather than to undergo further reaction.

Although the objectives of this synthesis were not realized, the chemistry of the potential precursors to the pyracyclene ring system has proven to be quite interesting. It is seldom that one finds a compound whose chemistry is dominated to such a great extent by stereochemical factors.

EXPERIMENTAL

General Procedures

The infrared spectra were recorded on a Perkin-Elmer Model 237B spectrophotometer. The nmr spectra were obtained with a Jeolco C-60 H or a Varian A-60 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane or from sodium 2,2-dimethyl-2-silapentane-5-sulfonate. Ultraviolet spectra were recorded on a Unicam Model SP-800 instrument using 1 cm quartz cells. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 mass spectrometer. Analyses by vpc were done on an Aerograph A-90-P3 instrument or a Varian Aerograph 1200 instrument.

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Molecular models were constructed from Framwork Molecular Models by Prentice-Hall, Inc., Englewood Cliffs, New Jersey.

2a,4a:6a,8a-Diepoxy-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene-8b,8c-dicarboxylic acid (Diacid **10**).

To 40 ml of dimethyl sulfoxide (dried over CaH_2) was added 4.4 g (0.1 mol) of sodium hydride which was saturated with mineral oil (conc = 54.3%). The mineral oil was removed by extracting the DMSO solution with cyclohexane. The slurry, while being continuously stirred in a nitrogen atmosphere, was heated to 60° for 3 hr. After the sodium hydride had dissolved, the solution was treated with 1.8 g (0.1 mol) of water. Adduct **7**, 4.2 g (1.27×10^{-2} mol), dissolved in 50 ml of DMSO, was then added to the sodium hydroxide-DMSO slurry. The temperature of the reaction mixture was maintained at 60° for 10 hr. During this time it was continuously stirred under a nitrogen atmosphere. After cooling the slurry to room temperature, 500 ml of diethyl ether was added. The precipitate which formed was removed by filtration and treated with 20 ml of water. Concentrated hydrochloric acid was added until the precipitate dissolved. Upon further acidification diacid **10** precipitated from solution. Filtration of the solution gave 2.3 g (60%) of diacid **10**: mp 182-183°; ir (KBr) 3400 (O-H), 3100 (C-H), 1725 (C=O) and 1675 cm^{-1}; nmr (D_2O, external TMS standard) δ6.9 (s,4,-$-CH{=}CH-$) and δ2.5 ppm (m,8,$-C\underline{H}_2C\underline{H}_2-$).

2a,4a:6a,8a-Diepoxy-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene-8b,8c-dicarboxylic anhydride (Anhydride 11).

A solution containing 1.5 g (5×10^{-3} mol) of diacid 10 in 7 ml of acetic anhydride was heated to 60° for 6 hr. The solvent was removed by vacuum distillation (aspirator). Recrystallization of the residue from ethyl acetate gave 0.4 g (27%) of anhydride 11: mp 221-223°; ir ($CHCl_3$) 2940 (C-H), 1849 (anhydride) 1785 (anhydride) and 1285 cm^{-1}, Figure 9 ; nmr ($CDCl_3$) δ6.83 (s,4,-C<u>H</u>=C<u>H</u>-), and δ2.68 ppm (m, 8,-C<u>H</u>$_2$-C<u>H</u>$_2$-) Figure 19.

<u>Anal</u>. calcd for $C_{16}H_{12}O_5$: C, 67.59; H, 4.25. Found: C, 67.69; H, 4.23.

2a,4a:6a,8a-Diepoxy-8b,8c-di(hydroxymethyl)-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene (Diol 12).

To a stirred suspension of lithium aluminum hydride, 3 g (7.9×10^{-2} mol), in 70 ml of dry tetrahydrofuran (distilled from $LiAlH_4$) was added 200 ml of a dry tetrahydrofuran solution containing 12.0 g (3.64×10^{-2} mol) of adduct 7. The reaction mixture was refluxed for 6 hr, while it was stirred under a nitrogen atmosphere. The cooled reaction mixture was treated with 6 ml of water and then stirred for 1 hr at room temperature. The solution was filtered and dried (Na_2SO_4). Filtration of the slurry followed by removal of solvent gave 8.4 g (84%) of the white crystalline diol 12: mp 196-197°; ir ($CHCl_3$) 3400 (C-OH) and 2950 cm^{-1}

(C-H) Figure 11; nmr (D_2O, standard: sodium 2,2-dimethyl-2-silapentane-5-sulfonate) δ 6.82 (s,4,RC$\underline{H}$=C$\underline{H}$R), δ 3.40 (s,4,-C$\underline{H_2}$OH) and δ 2.83 ppm (m,8,-C$\underline{H_2}$-C$\underline{H_2}$-) Figure 20.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found C, 69.85; H, 6.68.

2a,4a:6a,8a-Diepoxy-8b,8c-dimethylene-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene-9,10-sulfite (Sulfite 14).

One ml of a solution containing 0.8 g (7.4×10^{-3} mol) of thionyl chloride and 9.2 ml of pyridine was added to 1 ml of pyridine which contained 0.1 g (3.6×10^{-4} mol) of diol 12. The reaction was allowed to proceed at room temperature for 2 hr. The solution was then poured into 20 ml of 3N hydrochloric aicd. After saturating the solution with NaCl, it was extracted with three 20 ml portions of ether. The ethereal extract was dried ($MgSO_4$) and filtered. Removal of the solvent gave 0.5 g (43%) of the white crystalline sulfite 14: mp slow dec above 200°; ir ($CDCl_3$) 3005 (C-H), 2955 (C-H), 1455, 1310, 1285 and 1175 cm^{-1}; nmr ($CDCl_3$) δ 6.78 (s,2,-C$\underline{H}$=C$\underline{H}$-), δ 6.62 (s,2,-C$\underline{H}$=C$\underline{H}$-), δ 4.45 (d,2, $\underline{J}$ = 13 Hz, -C$\underline{H_2}$-OSO_2-C$\underline{H_2}$), δ 3.45 (d,2,$\underline{J}$ = 13 Hz, -C$\underline{H_2}$$OSO_2C\underline{H_2}$-) and δ 2.41 ppm (s,8,-C$\underline{H_2}$C$\underline{H_2}$-).

2a,4a:6a,8a:9,10-Triepoxy-8b,8c-dimethylene-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene (Ether 15).

To 5 ml of a dry pyridine solution containing 0.5 g (1.8×10^{-3} mol) of diol 12 was added 0.21 g (1.8×10^{-3} mol) of methanesulfonyl chloride. The solution was refluxed under nitrogen for 10 hr. Removal of the pyridine left a black oil. Column chromatography (silicic acid, $CHCl_3$) gave rise to 150 mg (32%) of cyclic ether 15: mp gradual dec above 200°; ir ($CHCl_3$) 2990 (C-H), 2930 (C-H), 2860 (C-H), 1465, 1440 and 1310 cm^{-1}; nmr ($CDCl_3$) δ 6.75 (s,4,$C\underline{H}=C\underline{H}-$), δ 3.32 (s,4,$-C\underline{H}_2OC\underline{H}_2-$) and δ 2.36 ppm (s,8,$-C\underline{H}_2-C\underline{H}_2-$), (70 eV) m/e (rel intensity) 256(3), 238(1), 162(3), 134(2) and 107(2). This compound is soluble in water.

Anal. Calcd for $C_{16}H_{16}O_3$: C, 75.06; H, 6.30. Found: C, 74.73; H, 6.44.

2a,4a:6a,8a-Diepoxy-8b,8c-di(methylene *p*-toluenesulfonate)-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene (Ditosylate 16).

A solution containing 1.32 g (4.82 x 10^{-3} mol) of diol 12, 4.6 g (2.6 x 10^{-2} mol) of *p*-toluenesulfonyl chloride and 15 ml of pyridine (distilled from CaO) was allowed to stand at room temperature for 4 days. The reaction mixture was then poured into 20 ml of ice-cold 6*N* hydrochloric acid. Ditosylate 16 precipitated as light brown crystals. The precipitate was removed from the solution by filtration and then recrystallized from 95% ethanol. The yield of the white crystalline ditosylate 16 was 2.4 g (86%): mp 162-163(dec); ir ($CHCl_3$) 2998 (C-H), 2948 (C-H), 1599, 1370 ($-SO_2-$), and 1175 cm^{-1} ($-SO_2-$) Figure 7 ; nmr ($CDCl_3$) δ 7.6 (m,8, $-SO_2C_6\underline{H}_4CH_3$,$A_2B_2$ system), δ 6.5 (s,4,$-C\underline{H}=C\underline{H}-$), δ 3.6 (s,4, $-RC\underline{H}_2OSO_2-$), δ 2.5 (s,8,$-C\underline{H}_2-C\underline{H}_2$) and δ 2.4 ppm (s,6,$-CH_3$) Figure 21.

Anal. Calcd for $C_{30}H_{30}O_8S_2$: C, 61.83; H, 5.19. Found: C, 61.97; H, 5.24.

2a,4a:6a,8a-Diepoxy-8b,8c-bis(trifluoromethyl)-1,2,5,6-tetrahydrocyclopent[f,g]acenaphthalene (Bis(trifluoromethyl) adduct 21).

Into a heavy-walled glass tube fitted with a pressure cap was placed 25 ml of an anhydrous ether solution containing 0.4 g (2.1 x 10^{-3} mol) of [2.5](2,5)Furophane 5. The tube containing the solution was then cooled in a dry ice-acetone bath. Hexafluorobutyne-2 was bubbled into the solution until 1.6 g (1 x 10^{-2} mol) had condensed in the tube. After sealing the tube the reaction was allowed to proceed at room temperature for 2 days. The solvent was then removed and the residue was recrystallized from heptane. Adduct 21, 0.38 g (52%) was isolated as a white crystalline solid: mp 192-194^{0}(bubbling); ir ($CHCl_3$) 2950 (C-H), 1340, 1290, 1165 and 1135 cm^{-1} Figure 10; ^1H nmr ($CDCl_3$) δ 6.71 (t,4,J = 1.2 Hz,$-C\underline{H}{=}C\underline{H}-$) and δ 2.53 ppm (m,8,$-C\underline{H_2}C\underline{H_2}-$, A_2B_2 system) Figure 22; ^{19}F nmr ($CDCl_3$, standard $CFCl_3$) approximately +58.4 ppm (s,CF_3); mass spectrum (70 eV) m/e (rel intensity) 350(2), 230(3), 189(3), 174(4), 150(20) and 95(20).

Anal. Calcd for $C_{16}H_{12}F_6O_2$: C, 54.90; H, 3.46. Found: C, 55.19; H, 3.52.

2a,4a:6a,8a-Diepoxy-8b,8c-bis(trifluoromethyl)-1,2,5,6,7,8-octahydrocyclopent[f,g]acenaphthalene (Reduced Bis(trifluoromethyl) adduct **23**).

To 100 ml of 95% ethanol in a Paar pressure bottle was added 1 g (2.7×10^{-3} mol) of bis(trifluoromethyl) adduct **21** and 30 mg of platinum oxide. The reduction was run in a Paar apparatus. The initial hydrogen pressure was 50 lb/in^2. When the uptake of hydrogen had ceased the reaction mixture was removed. Filtration of the solution through a glass fiber filter paper and removal of the solvent gave 0.95 g (95%) of adduct **23**: mp 274-276^0 (sublimes); ir ($CDCl_3$) 3000 (C-H), 2950 (C-H), 1330, 1295, 1290 and 1180 cm^{-1}; ^1H nmr ($CDCl_3$) 2.1 (m), Figure 23; ^{19}F nmr ($CDCl_3$, standard $CFCl_3$) approximately +58.4 ppm(s,CF_3).

Anal. Calcd for $C_{16}H_{16}F_6O_2$: C, 54.28; H, 4.56. Found: C, 54.36; H, 4.64.

Part II

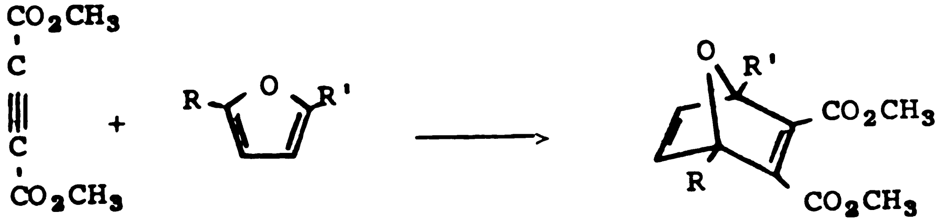
A Study of Bis-Diels-Alder Adducts of Dimethyl Acetylenedicarboxylate and Certain Furans

INTRODUCTION

A large variety of s-*cis*-1,3-dienes are known to undergo 1,4-cycloaddition reactions with strong dienophiles. One such diene, investigated by Diels and Alder, is furan (43,44,45). The 1,3-diene system of furan is particularly suited for 1,4-cycloaddition reactions because the double bonds are held in a *cis* configuration by the oxygen bridge. On the other hand, addition of a dienophile to the furan ring will be rendered more difficult by the aromaticity of the furan ring. Because of the inherent stability of the furan ring, reactions of furan and its derivatives with strong dienophiles are particularly dependent upon reaction conditions and upon stereochemical factors.

Diels and Alder found that the strong dienophile, dimethyl acetylenedicarboxylate, reacted almost quantitatively at room temperature with one equivalent of furan (**24**), 2-methylfuran (**25**) or 2,5-dimethylfuran (**26**) to give adducts **27**, **28**, **29** respectively (45,46).

These adducts contain two double bonds which have different chemical reactivities. Either one of the double bonds can function as a dienophile and selective addition of furan to either double bond can be affected by varying the reaction conditions. Diels and Olsen reported that two

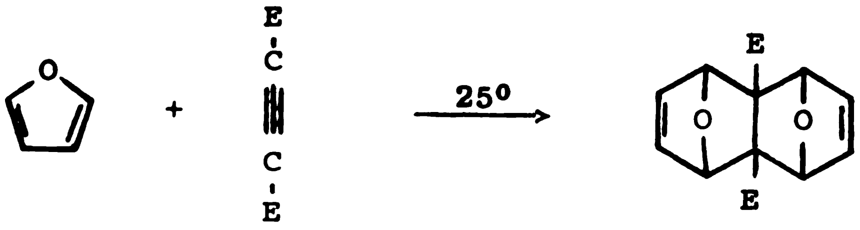


24 and 27 R = R' = H

25 and 28 R = H, R' = CH_3

26 and 29 R = R' = CH_3

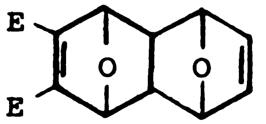
moles of furan and one mole of dimethyl acetylenedicarboxylate reacted at room temperature to yield bis-adduct 30 (47).



30

E = CO_2CH_3

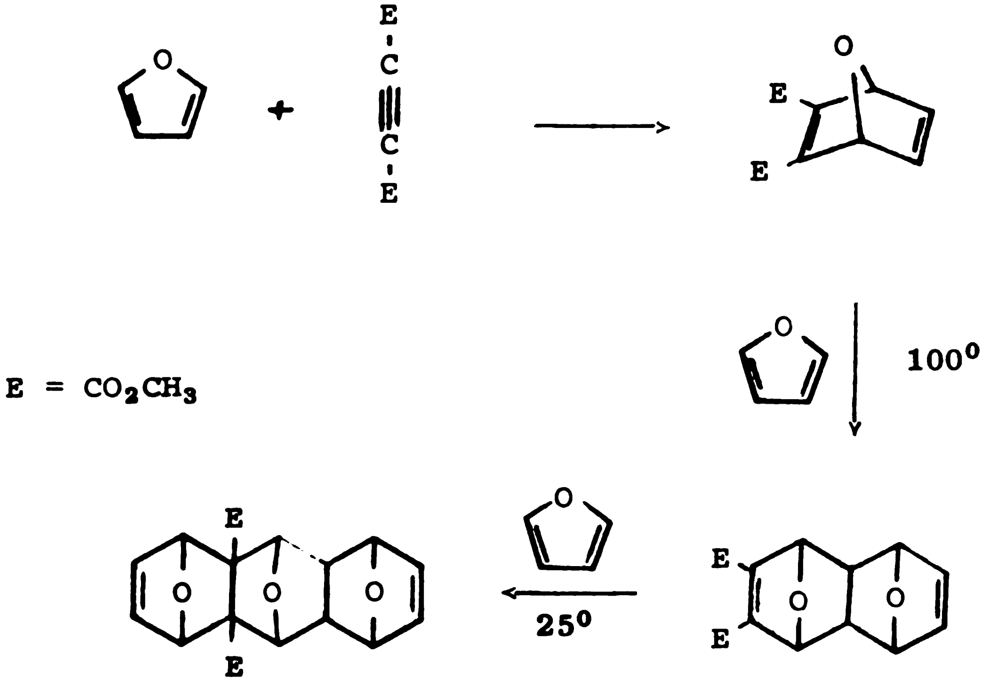
When this reaction was conducted at 100°, an adduct containing two moles of furan and one mole of dimethyl acetylenedicarboxylate was isolated (44), and the authors suggested that bis-adduct 30 was again formed. In the light of this study, however, it is more likely that the bis-adduct 31 was formed.



31

E = CO_2CH_3

In a related experiment dimethyl acetylenedicarboxylate was heated with an excess of furan to 100° for 16 hours, followed by two days at room temperature (47). The material which was isolated contained three moles of furan and one mole of dimethyl acetylenedicarboxylate. Diels and Olsen demonstrated that furan had added to both double bonds of the initially formed monoadduct 27. It appears that addition of furan to



32 31

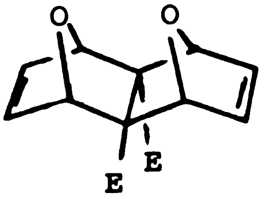
mono-adduct 27 occurred at 100^0 to give bis-adduct 31, which then reacted slowly with furan at the double bond substituted with carbomethoxy groups to form tris-adduct 32.

This study is an extension of Diels' and Alder's original work. Two systems were investigated. First, the adducts containing two moles of furan and one mole of dimethyl acetylenedicarboxylate were reinvestigated; and, second, an adduct containing two moles of 2,5-dimethylfuran and one mole of dimethyl acetylenedicarboxylate was studied.

RESULTS AND DISCUSSION

The Diels-Alder reaction of furan (2 moles) with dimethyl acetylenedicarboxylate (1 mole) at ambient temperatures proceeds very slowly. After two weeks the bis-adduct **30** represented only about 60% of the reaction mixture. In five weeks, however, the conversion to **30** was essentially quantitative.

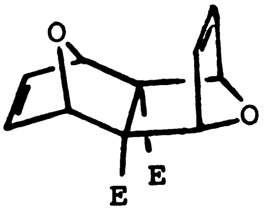
Three stereoisomeric adducts can result from the addition of two molecules of furan to dimethyl acetylenedicarboxylate. These are the (*exo*-*exo*) adduct (**33**), the (*exo*-*endo*) adduct (**34**) and the (*endo*-*endo*) adduct (**35**). Isomers **33** and **35** possess two planes of symmetry. One plane passes orthogonally through the carbon-carbon double bonds, and the other is defined by the atoms of the acetylenic ester moiety (Figure 3). Due to the symmetry elements present in adducts **33** and **35**, the vinyl protons in these compounds should



$E = CO_2CH_3$

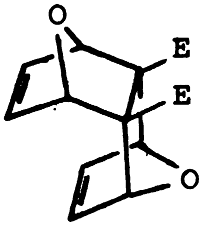
(*exo*-*exo*)

33



(*exo*-*endo*)

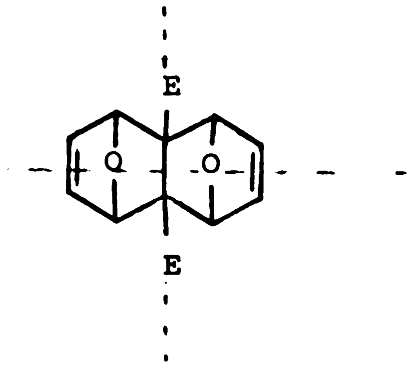
34



(*endo*-*endo*)

35

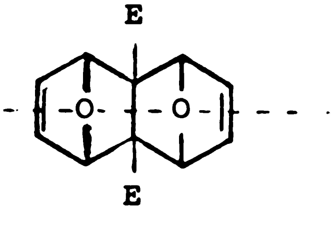
appear as a singlet in the nmr spectrum with some small coupling to the adjacent bridgehead protons. This was found to be true for adduct 34 which was independently synthesized (44,48).



E = CO_2CH_3

Figure 3.

Diels-Alder adduct 34, on the other hand, has only one plane of symmetry, bisecting the oxygen bridges and the carbon-carbon double bonds (Figure 4); consequently, the vinyl protons should appear as two singlets, each being split further by the adjacent bridgehead hydrogen atoms.



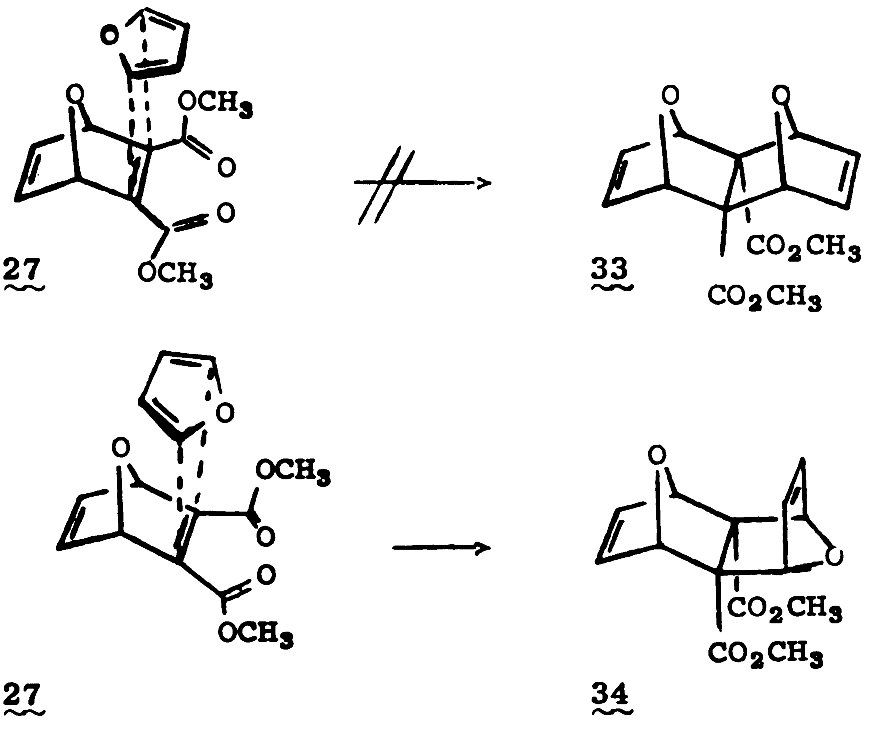
E = CO_2CH_3

Figure 4.

Since the major adduct displayed vinyl resonance signals at $\tau 3.4$ and 3.6 in the nmr, it was tentatively assigned structure 34. Each vinyl resonance was split further into an apparent triplet with a peak separation of approximately 1 Hz. It is not clear whether these triplets arise from coincidental identity of the coupling between the AB and A'B hydrogens or from virtual long-range coupling. In the latter case the observed separation of 1 Hz is the result of averaging of J_{AB} and $J_{A'B}$ in this AA' BB' system (57,58).

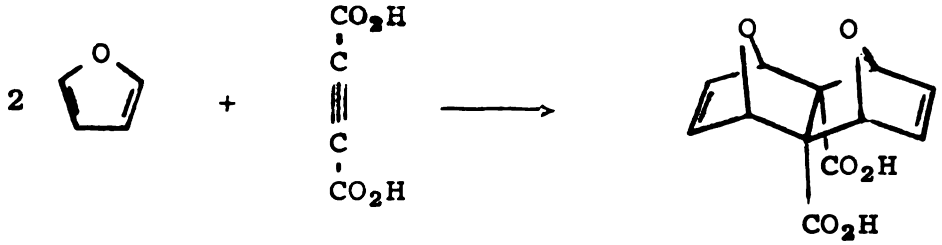
From the nmr spectrum of the crude reaction mixture, it was estimated that 6% of the (*exo*-*exo*) adduct **33** was present. No evidence for the (*endo*-*endo*) adduct **35** was found. This was not unexpected because formation would require *endo*-addition of furan to mono-adduct **27**, a mode of reaction which is unlikely because of steric hindrance.

It is interesting to note that the second mole of furan has not reacted with mono-adduct **27** in accordance with Alder's rule of maximum overlap of π-electrons in the transition state (49). Applying Alder's rule, the (*exo*-*exo*) adduct **33** should have been the major product (Scheme 3).



Scheme 3

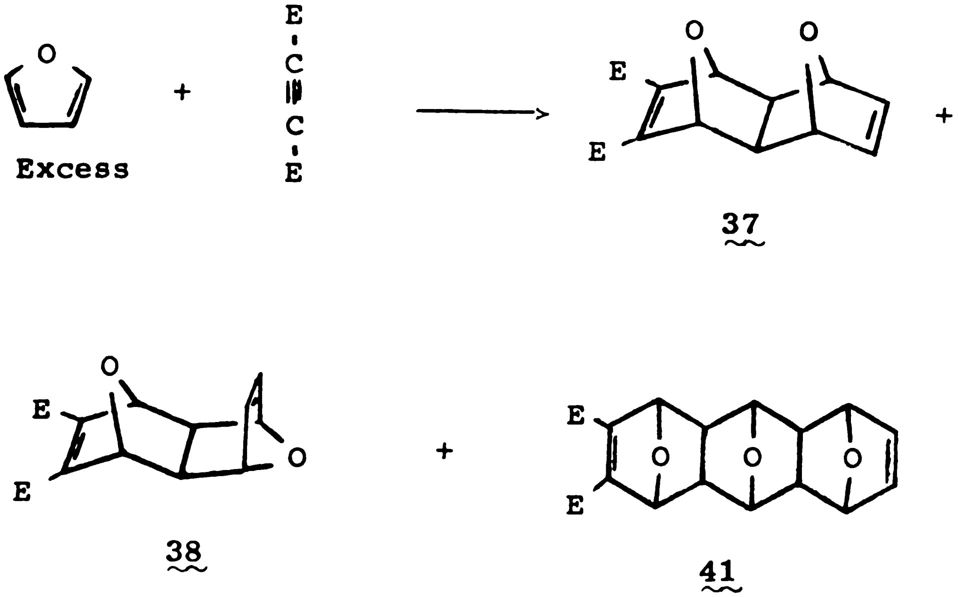
In contrast to the reaction of furan with the acetylenic ester, Alder's rule does predict the correct isomer when two moles of furan are allowed to react with acetylenedicarboxylic acid under similar conditions (44,48). The product of this reaction is (*exo*-*exo*)bis-adduct **36**. Apparently the bulk of the dimethyl ester functions in mono-adduct **27** causes the formation of (*exo*-*endo*) adduct **34** to be favored.



36

When the reaction of two moles of furan with one mole of dimethyl acetylenedicarboxylate was carried out at 100°, three different compounds were isolated. Two of the adducts were composed of two moles of furan to one mole of dimethyl acetylenedicarboxylate, and the other had a 3:1 composition ratio.

In each of these adducts the second mole of furan has added to the less substituted double bond of the initially formed mono-adduct, a fact that is immediately apparent from the nmr spectra of the adducts. Integration of the spectra revealed that each compound possessed only two vinyl hydrogen atoms. If addition had occurred at the more highly substituted double bond, four vinyl hydrogen atoms would be



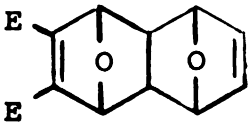
37

38

41

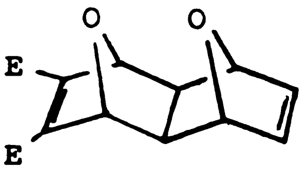
$E = CO_2CH_3$

present. The gross structure of the bis-adducts is represented by adduct **31**.



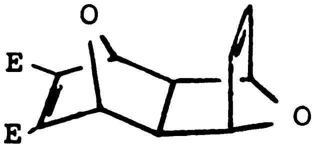
31

Four stereoisomers corresponding to **31** are possible. If furan added *exo* to adduct **27** (*exo*-*exo*) adduct **37** and (*exo*-*endo*) adduct **38** would be formed; whereas, *endo* addition to **27** would generate (*endo*-*exo*) adduct **39** and (*endo*-*endo*) adduct **40**.



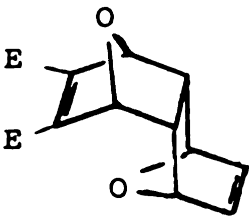
(*exo*-*exo*)

37



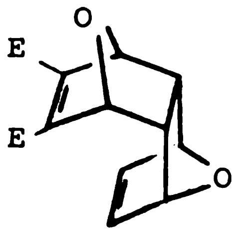
(*exo*-*endo*)

38



(*endo*-*exo*)

39



(*endo*-*endo*)

40

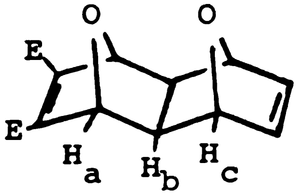
E $=CO_2CH_3$

Isomers **39** and **40** are unlikely because *endo* addition to adduct **27** is sterically unfavorable. Since the products isolated from Diels-Alder reactions carried out at elevated temperatures for long periods of time should form the thermodynamically most stable product, neither (*endo*-*exo*) adduct **39** nor (*endo*-*endo*) adduct **40** would be expected from this reaction.

The two bis-adducts which were isolated from this reaction were assigned structures corresponding to (*exo*-*exo*) adduct **37** and (*exo*-*endo*) adduct **38** on the basis of their nmr spectra.

Coupling constants between hydrogen atoms on adjacent carbon atoms in rigid systems are angularly dependent (50,51). At dihedral angles of 0° and 180°, the vicinal coupling constants are at a maximum, approximately 9 Hz, whereas at 90° the coupling constants are at a minimum, approximately 0 Hz. For a 45° angle the coupling constant should be approximately 4.5 to 5.0 Hz.

A model of (exo-exo) adduct **37** reveals that the dihedral angle between H_a and H_b as well as the angle between H_b and H_c is 90°. The expected coupling constants J_{ab} and J_{bc} would be about 0 Hz. Since the observed coupling constants J_{ab} and J_{bc} were 0 Hz in one of the two compounds isolated, the adduct was assigned structure **37**.



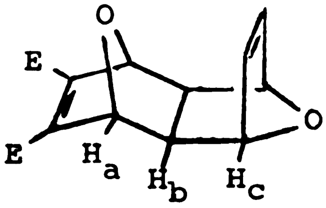
$J_{ab} = 0$

$J_{bc} = 0$

37

E = CO_2CH_3

A model of (exo-endo) adduct **38** indicates that the dihedral angle between H_a and H_b should be 90°, whereas that between H_b and H_c should be approximately 45°. The predicted coupling constants would be $J_{ab} = 0$ Hz and $J_{bc} = 4.5$ Hz. In the remaining adduct the observed coupling constants were $J_{ab} = 0$ Hz and $J_{bc} = 3$ Hz. Although J_{bc} is smaller than expected, the data is consistent with bis adduct **38**.



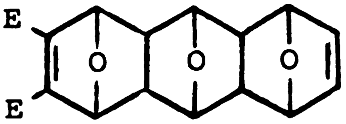
38

E = CO_2CH_3

J_{ab} = 0 Hz

J_{bc} = 3 Hz

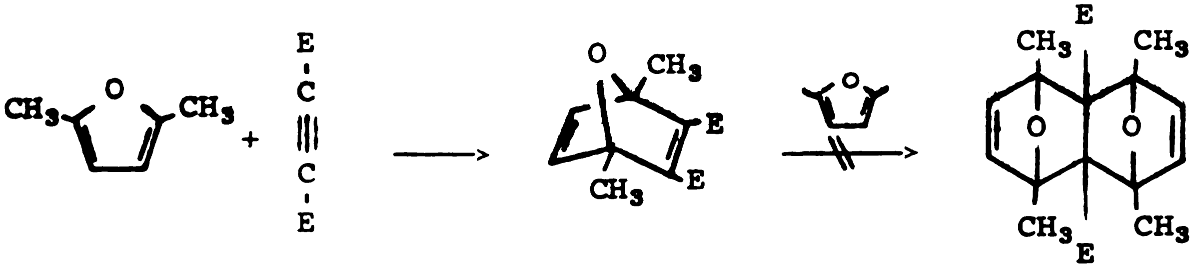
The third compound isolated from this reaction gave an elemental analysis corresponding to three moles of furan and one mole of dimethyl acetylenedicarboxylate, and displayed a single, 2-proton, resonance in the vinyl region of its nmr spectrum. Although the stereochemistry of this compound has not been determined the gross structure may be represented by the tris-adduct **41**.



E = CO_2CH_3

41

In contrast to the reaction of furan (2 moles) with dimethyl acetylenedicarboxylate (1 mole) at ambient temperatures, no evidence for a bis-adduct (i.e. **42**) could be found when 2,5-dimethylfuran (2 moles) was allowed to react with dimethyl acetylenedicarboxylate at room temperature for two weeks. Reduction of the reaction mixture, followed by vapor

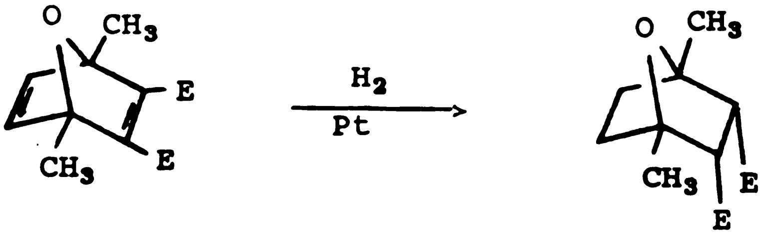


29

42

$E = CO_2CH_3$

phase chromatographic analysis showed that only one product had been formed in the reaction. The compound formed was shown to be adduct 29 by characterization of its reduction product, 43.



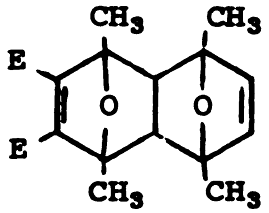
$E = CO_2CH_3$

27

43

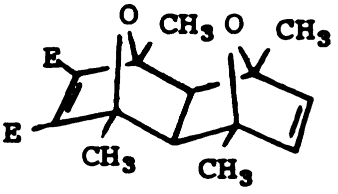
The stereochemical effect of the two methyl groups in mono-adduct 29 and those of 2,5-dimethylfuran is quite apparent. The bulk of these groups prevented a second mole of 2,5-dimethylfuran from adding to mono-adduct 29.

When the same reaction was conducted at 100° for 18 hours, a single adduct containing two moles of 2,5-dimethylfuran and one mole of dimethyl acetylenedicarboxylate was isolated. The nmr spectrum of this adduct revealed that addition of the second mole of 2,5-dimethylfuran had occurred at the less substituted double bond of the initially formed mono-adduct 29. This was evident from the single, two proton resonance found in the vinyl region of its nmr spectrum. The gross structure of this adduct may be represented as bis-adduct 44.

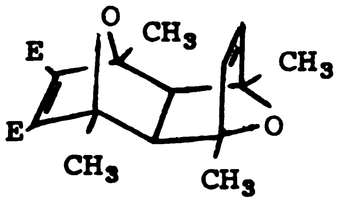


E = CO_2CH_3 44

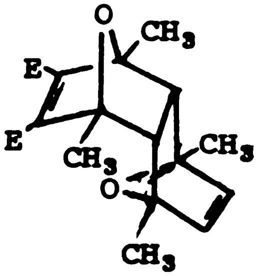
The tetramethyl adduct 44 must be one of four geometric isomers: (*exo*-*exo*) adduct 45, (*exo*-*endo*) adduct 46, (*endo*-*exo*) adduct 47 or (*endo*-*endo*) adduct 48. Models of the four isomers suggest that bis-adduct 47 would be favored in this reaction. Isomers 48 and 49 would arise from *endo* addition of 2,5-dimethylfuran to the 7-oxabicyclic system (29), and it is very unlikely that *endo* addition products would survive because the reaction conditions (100^{0}) would favor the thermodynamically more stable *exo* adducts. Since *exo* addition to 7-oxabicyclic systems under thermodynamically controlled conditions have been reported in similar reactions, (*exo*-*exo*) isomer 45 and (*exo*-*endo*) isomer 46 would be the



45

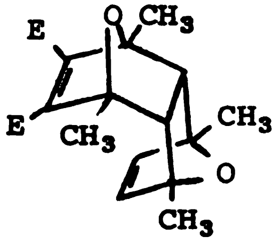


46



47

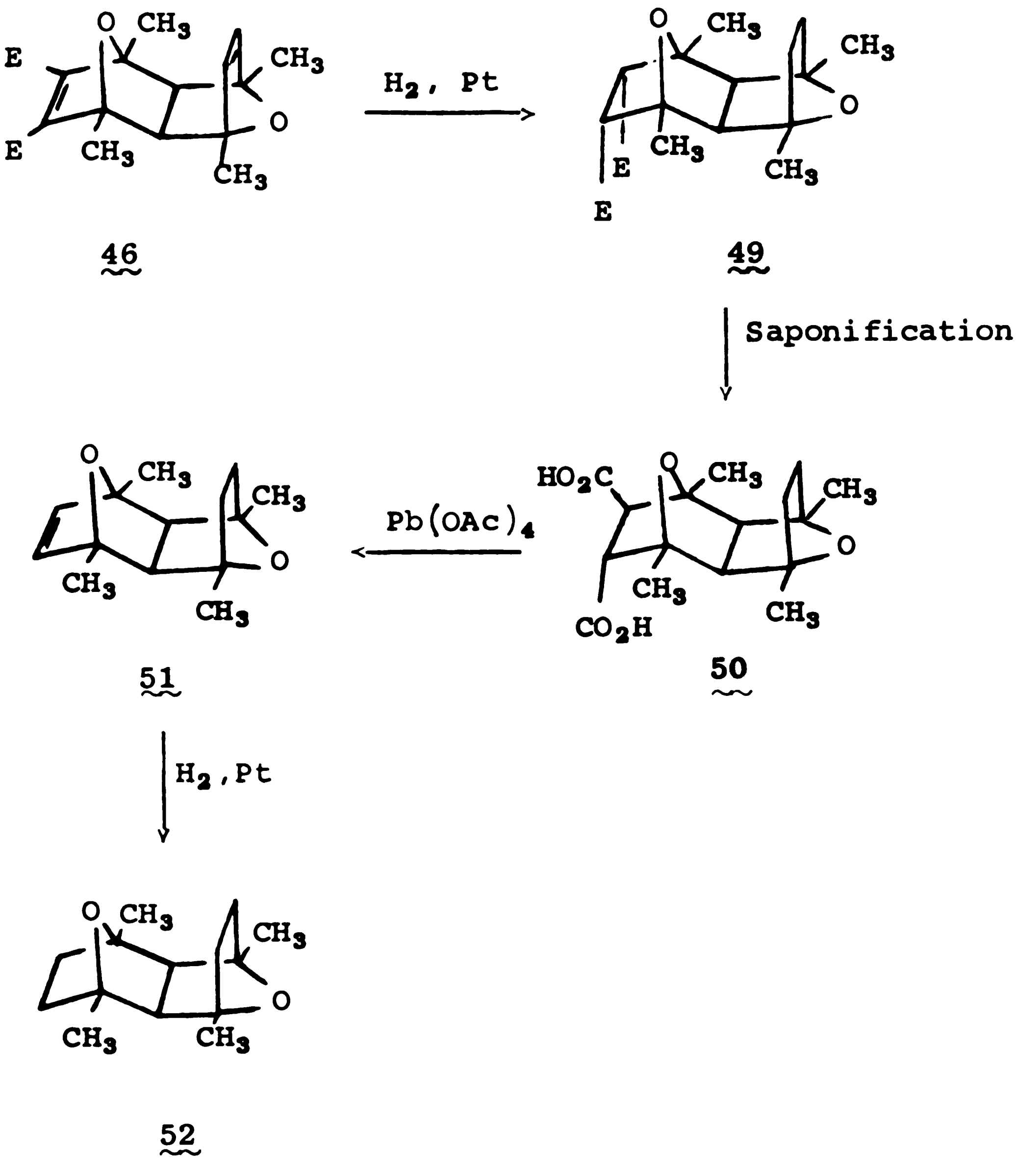
$E = CO_2CH_3$



48

expected products (51,52). Severe internal strain due to the nonbonded interactions of the methyl groups at the bridgehead positions would, however, be present in the (*exo*-*exo*) isomer 45. This strain could not be relieved to any great extent by twisting because the molecule would be quite rigid. The internal strain in (*exo*-*endo*) isomer 46 due to the 1,3-dimethyl interactions, on the other hand, is somewhat less severe because the methyl groups are slightly offset. From these considerations it appeared that isomer 46 would be the most stable bis-adduct from this reaction.

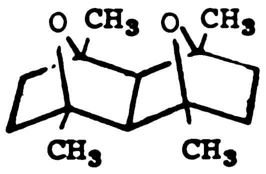
Configuration 46 was confirmed for bis-adduct 44 by transforming this compound into the saturated parent system 53 (Scheme 4).


E
E
O
CH3
CH3
O
CH3
CH3
46
H2, Pt
49
Saponification
HO2C
CO2H
50
Pb(OAc)4
51
H2, Pt
52

Scheme 4

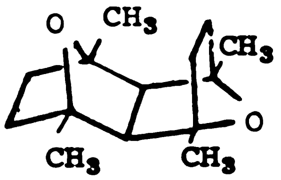
Catalytic hydrogenation of 46 gave rise to the (*endo*-*cis*) tetrahydro diester 49. Saponification of 49 occurred with epimerization to yield *trans*-diacid 50. Oxidative bisdecarboxylation with lead tetracetate in pyridine gave olefin 51 (53,54), which was reduced to 52.

The parent compound 52 could have one of three configurations: the (*exo*-*exo*) isomer 53, the (*exo*-*endo*) isomer 54 or the (*endo*-*endo*) isomer 55. The (*exo*-*exo*) isomer 53 and



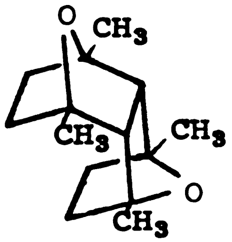
(*exo*-*exo*)

53



(*exo*-*endo*)

54



(*endo*-*endo*)

55

the (*endo*-*endo*) isomer 55 have two planes of symmetry (Figure 5). All four of the bridgehead methyl groups would have equivalent environments; and, therefore, the methyl groups of 53 and 55 should appear as a singlet in the nmr spectra.

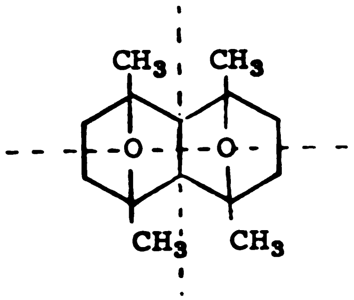


Figure 5

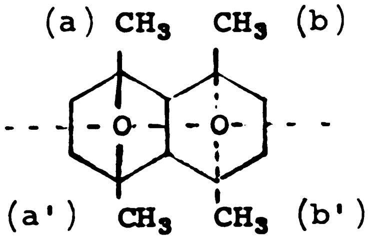
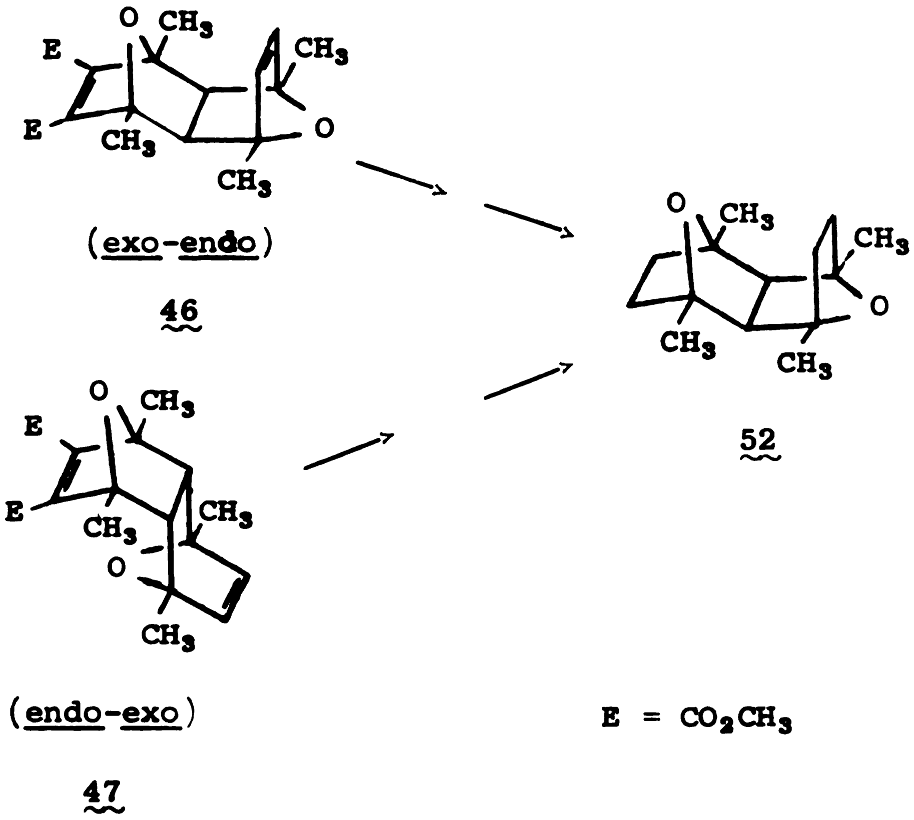


Figure 6

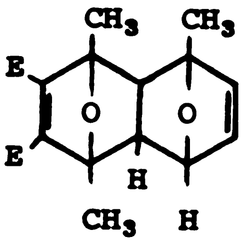
The (exo-endo) isomer **54**, on the other hand, has only one plane of symmetry (Figure 6); methyl groups (a) and (a') are in equivalent environments as are (b) and (b'); but, (a) is not equivalent to (b), nor is (a') equivalent to (b'). The methyl groups of this isomer should give two, six-proton singlets in the nmr spectrum. Experimentally it was found that the nmr spectrum of **52** displayed two, six-proton, high field singlets at τ8.57 and 8.73.

Either the (exo-endo) isomer **46** or the (endo-exo) isomer **47** could be the precursor for the parent (exo-endo) compound (**52**). Since isomer **48** would result from an unlikely endo addition to the 7-oxabicyclic system (**29**), isomer **46** most likely represents the correct configuration for bis-adduct **44**.

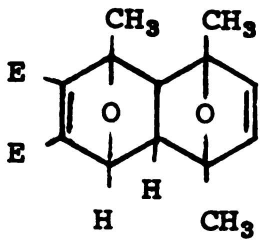


E = CO_2CH_3

In order to investigate the stereochemistry of bis-Diels-Alder reactions of this type more extensively, two bis-adducts (56 and 57) containing only three methyl groups were prepared. The purpose of replacing one methyl group with a hydrogen atom was to determine the dihedral angle between the adjacent bridgehead hydrogen atoms H_a and H_b, by noting the appropriate coupling constant.

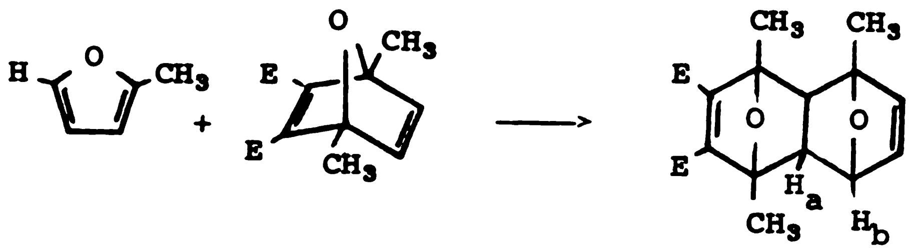


56



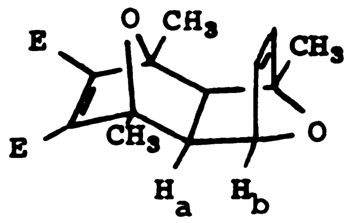
57

The first of the two trimethyl adducts investigated was bis adduct 56. This compound was synthesized by refluxing mono-adduct 29 with an excess of 2-methylfuran for 24 hours.

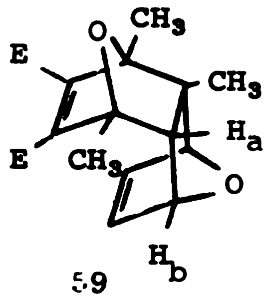


E = CO_2CH_3 29 56

The nmr spectrum of adduct 56 revealed that the vicinal coupling constant J_{ab} is 5.2 Hz. This coupling constant is consistent with a dihedral angle between H_a and H_b of about 45°. Only (*exo*-*endo*) isomer 58 and (*endo*-*endo*) isomer 59 of the four possible stereoisomers of bis-adduct 56 have a dihedral angle (45°) consistent with the observed coupling constant.



58

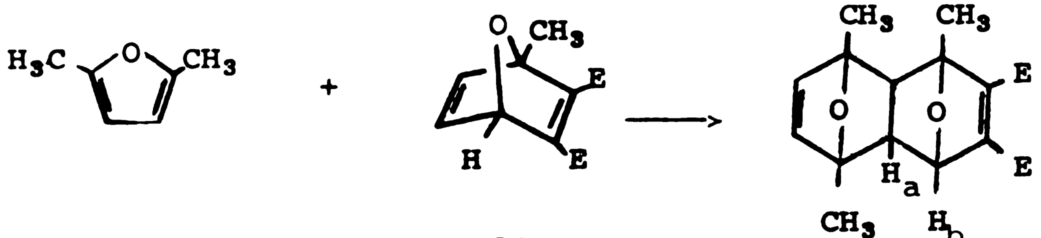


59

Since adduct 59 has severe 1,3-dimethyl nonbonding interactions, it is not expected to be the product of this reaction. Also it is probably the thermodynamically less stable of the two isomers.

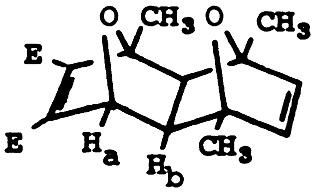
Isomer 58, on the other hand, would be expected from a stereochemical standpoint. A model of this adduct reveals that nonbonded interactions would be less severe than in adduct 59. In addition Diels-Alder reactions of 7-oxabicyclo-[2.2.1]heptadiene systems with dienes are known to give *exo*-adducts at elevated temperatures (46). For these reasons bis-adduct 56 has been assigned configuration 58. This assignment is consistent with the tetramethyl-bis-adduct 44 which also has the *exo*-*endo* configuration.

The second trimethyl adduct, bis-adduct 57, was synthesized by refluxing the mono-adduct (28) for 24 hours in 2,5-dimethylfuran. Since the coupling constant J_{ab} in 57 was found to be 0.0 Hz, the dihedral angle between H_a and H_b should be about 90°. Of the four possible isomers of bis-adduct 57 only (*exo*-*exo*) isomer 60 and (*exo*-*endo*) isomer 61 have a 90° dihedral angle between H_a and H_b.

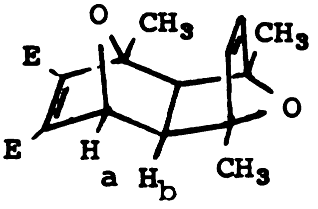


28

57



60

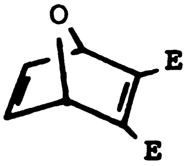


61

Models show that the severe 1,3-dimethyl interactions in the (*exo*-*exo*) isomer 60 would be reduced in the (*exo*-*endo*) isomer **61**. It is evident then that **61** is sterically favored as in the case of the trimethyl-bis-adduct **56** which also has the *exo*-*endo* configuration.

This experiment is important because it demonstrates that addition of 2,5-dimethylfuran has occurred at the *exo* side (side of the oxygen bridge) of mono-adduct **28**, presumably giving the thermodynamically most stable bis-Diels-Alder adducts.

As mentioned earlier 7-oxabicyclo[2.2.1]systems such as dimethyl acetylenedicarboxylate-furan adduct **27** are interesting because they possess two nonequivalent carbon-carbon double bond. From the reactions just described it is



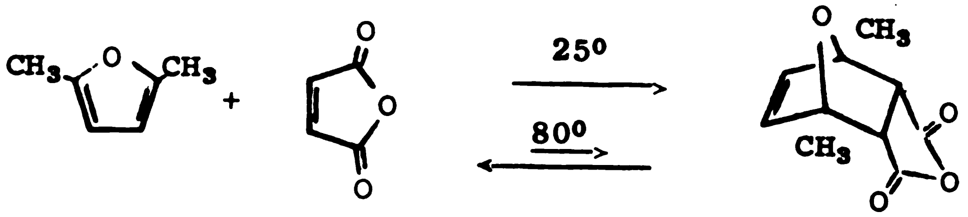
E = CO_2CH_3

27

evident that either the double bond substituted with carbomethoxy groups or the less substituted double bond may act as a dienophile depending upon the reaction conditions. This may seem unusual, since it is well known that Diels-Alder reactions are favored by dienophiles substituted with electron withdrawing substituents such as carbomethoxy groups (55). One might expect that only the double bond of adduct **27** which is flanked by carbomethoxy groups would act as a dienophile. This was found to be the case at room temperature, however, at elevated temperatures the major product is that from addition at the less substituted double bond.

At ambient temperatures electronic factors dominate the course of the reaction to give products resulting from kinetic control. At higher temperatures, on the other hand, an equilibrium is established between the reactants and products and the thermodynamically more stable product is formed.

The temperature dependence of furan Diels-Alder adducts is illustrated by the reaction of 2,5-dimethylfuran with maleic anhydride (55). At room temperature the kinetically controlled product, *endo*-adduct 62, predominates; but at 80° an equilibrium which favors the reactants is established.

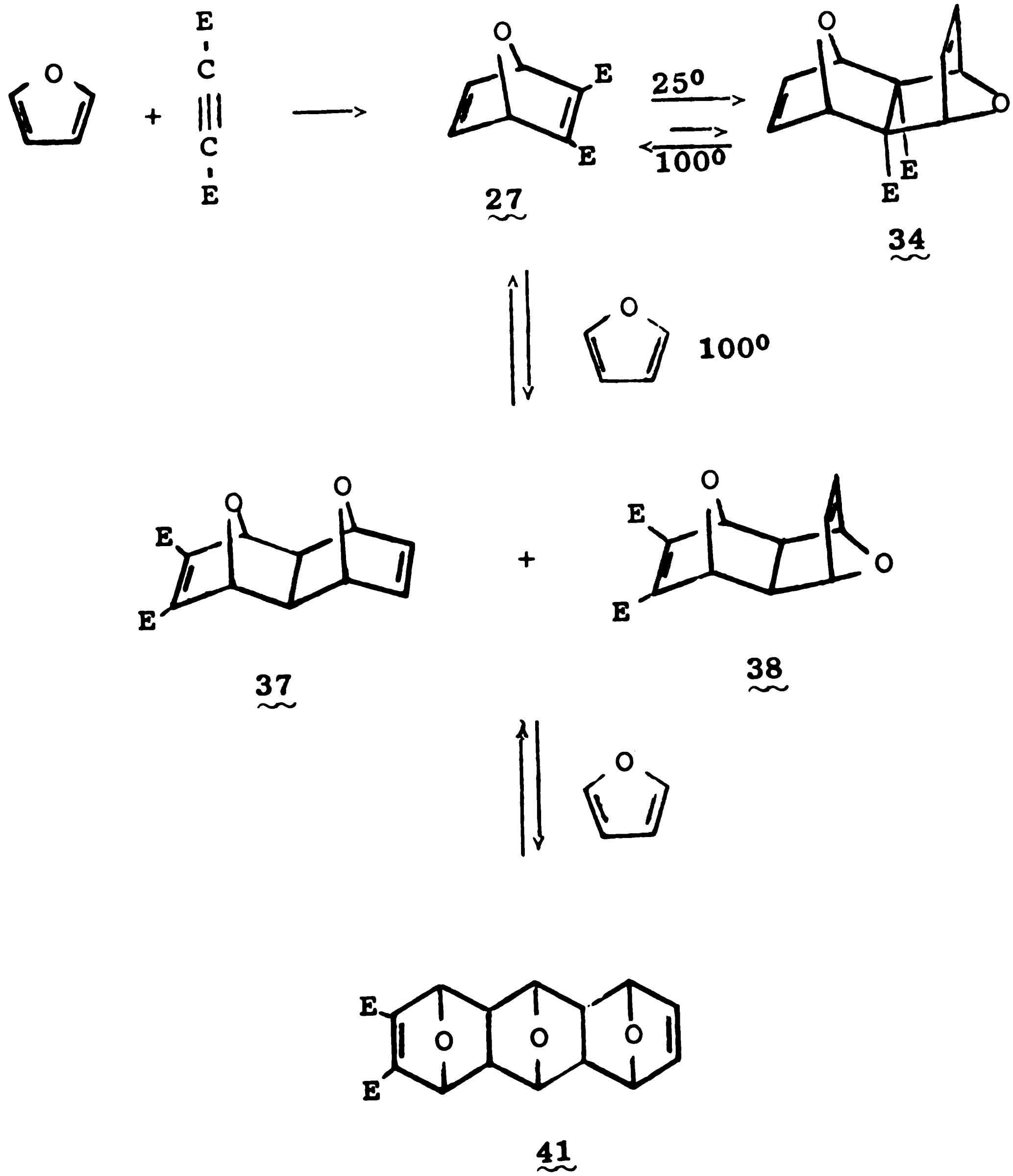


29

62

The present investigation demonstrates the importance of stereochemical factors on kinetically controlled as well as thermodynamically controlled Diels-Alder reactions of furans. The products isolated from the reaction of furan with dimethyl acetylenedicarboxylate are summarized in Scheme 5.

Initially formed mono-adduct 27 reacts slowly with furan at room temperature to give the product resulting from

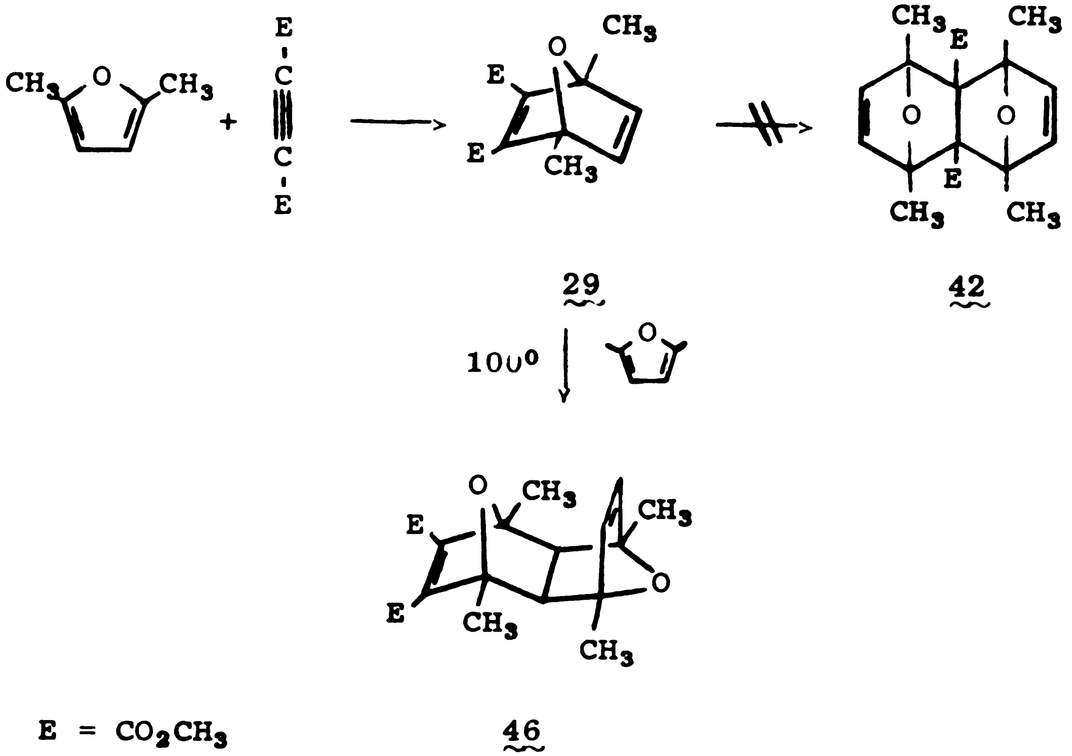


E = CO_2CH_3

Scheme 5

kinetic control, bis-adduct 34. At 100°, however, an equilibrium is established which favors mono-adduct 27 rather than bis-adduct 34, and at this temperature the less hindered double bond reacts to give the more thermally stable adducts 37 and 38. Tris-adduct 41 results from addition of furan to one of the two bis-adducts.

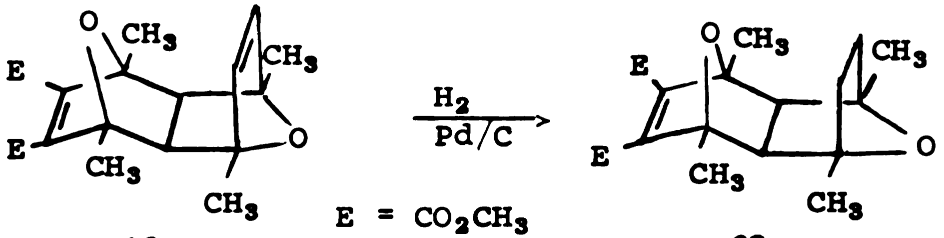
The temperature dependent equilibria involved in the reactions of 2,5-dimethylfuran with dimethyl acetylenedicarboxylate are summarized in scheme 6.



Scheme 6

At room temperature bis-adduct 43 does not form due to nonbonded steric interactions between the bridgehead methyl groups of adduct 29 and the methyl groups of 2,5-dimethylfuran. When the reaction is run at 100°, however, (*exo*-*endo*) bis-adduct 46 is formed. The stereochemistry of this adduct is undoubtedly controlled by nonbonded interactions between the bridgehead methyl groups. Since 46 is the least sterically hindered of all four stereoisomers it is probably the thermodynamically favored product.

The chemistry of tetramethyl-bis-adduct 46 is of particular interest. Catalytic hydrogenation of 46 with palladium on charcoal can be controlled to give a partially reduced adduct 63. Studies by Diels and Alder suggested



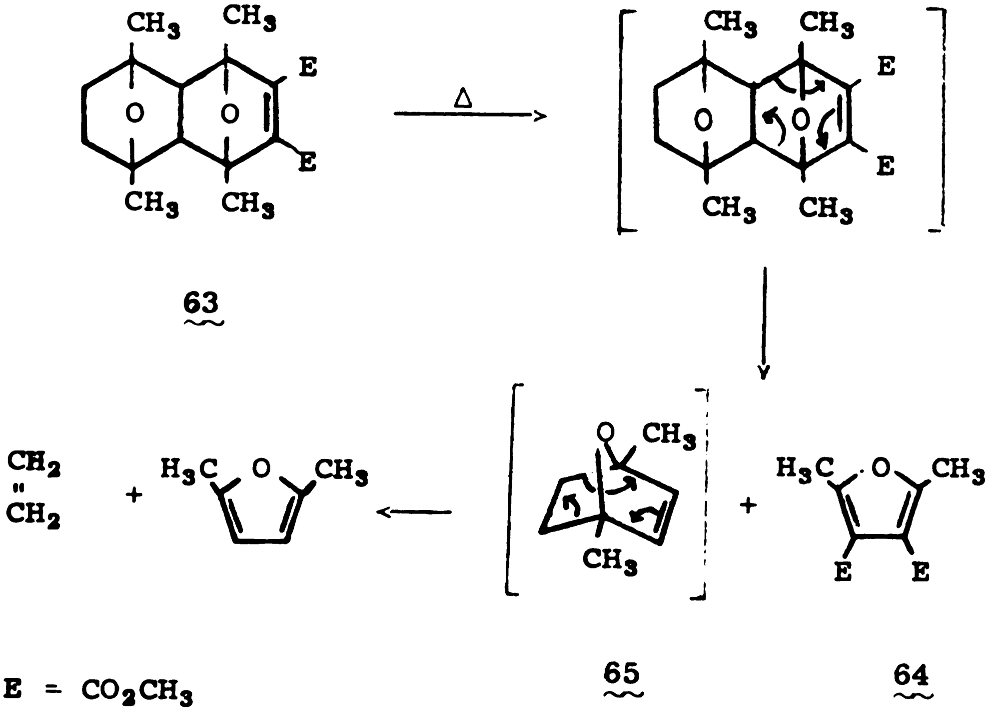
E = CO_2CH_3

46 63

that this compound should readily undergo thermal degradation (45,46), and, in fact, pyrolysis of 63 led to dimethyl 2,5-dimethylfuran-3,4-dicarboxylate 64 and 2,5-dimethylfuran (26) (Scheme 7).

This reaction proceeds *via* two retrograde Diels-Alder reactions. The first step gave dimethyl 2,5-dimethylfuran-3,4-dicarboxylate (64) and the bicyclic intermediate 65, which then cleaved to 2,5-dimethylfuran (26) and ethylene.

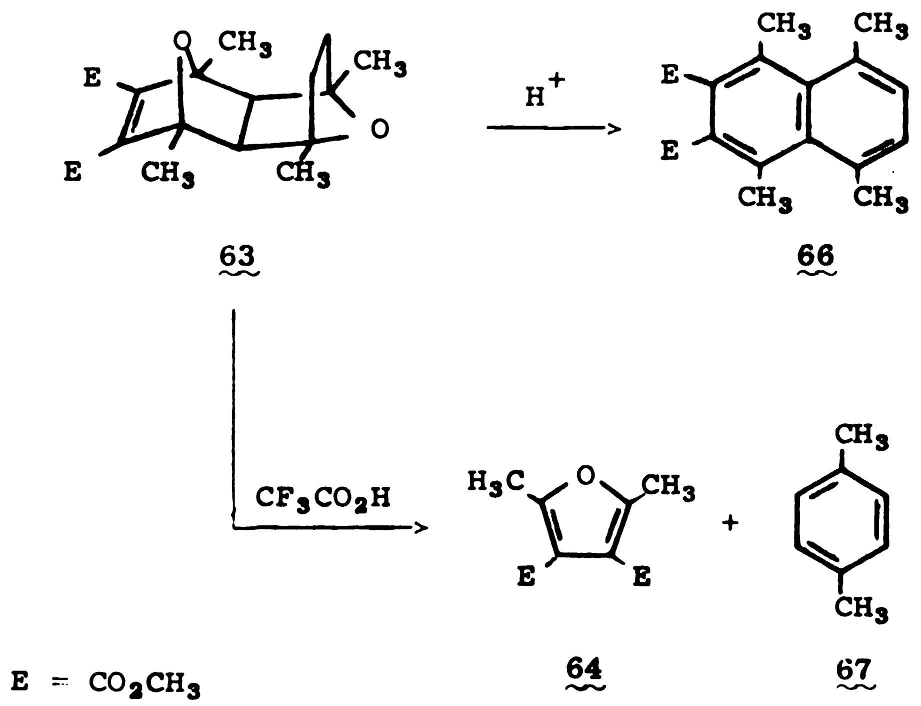
The work of Diels and Alder also suggested that treatment of 63 with strong acid might give rise to naphthalene derivative 69 (Scheme 8) by the elimination of two equivalents of water (45,46). However, when 63 was treated with trifluoroacetic acid at room temperature, it was slowly converted to



CH3
CH3
E
O
O
E
CH3
CH3
63
Δ
CH3
CH3
E
O
O
E
CH3
CH3
CH2
CH2
+
H3C
O
CH3
O
CH3
CH3
+
H3C
O
CH3
E
E
E = CO2CH3
65
64

Scheme 7

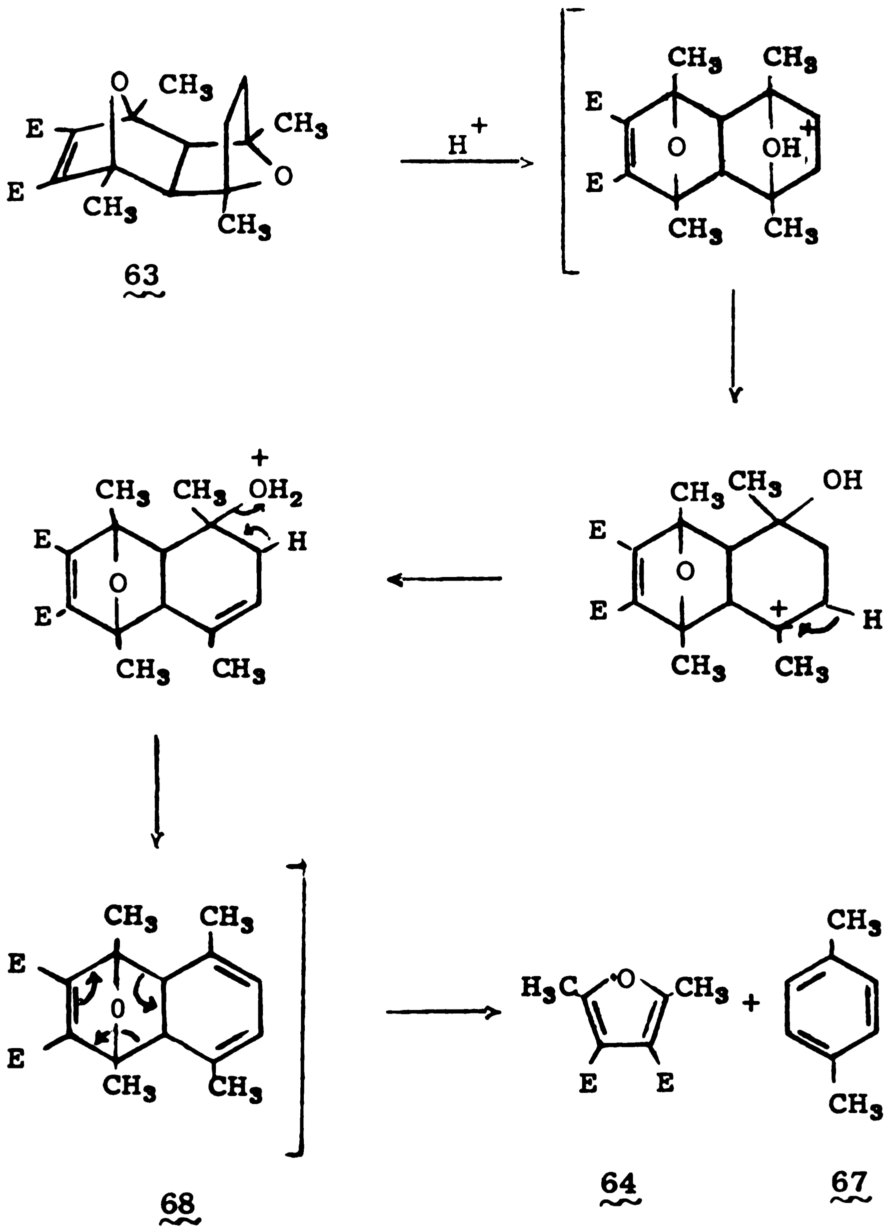
dimethyl 2,5-dimethylfuran-3,4-dicarboxylate (64) and to *p*-xylene (67). The mechanism proposed for their reaction is presented in Scheme 9.



Scheme 8

The activation energy for the retrograde Diels-Alder reaction of intermediate 68 is apparently very low, since no evidence for this intermediate was observed in the nmr spectrum of the reaction mixture at anytime during the course of this reaction. This is not surprising since the furan (64) and *p*-xylene (67) are both very stable aromatic compounds. Apparently, protonation followed by the elimination of water from intermediate 68 is much less favorable than the retrograde Diels-Alder reaction.

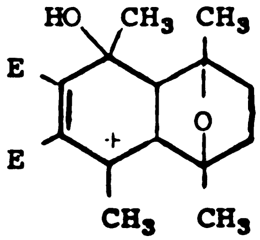
Since there are two ether bridges in the reactant (63), one might expect to find dimethyl 3,6-dimethyl-*o*-phthalate



$E = CO_2CH_3$

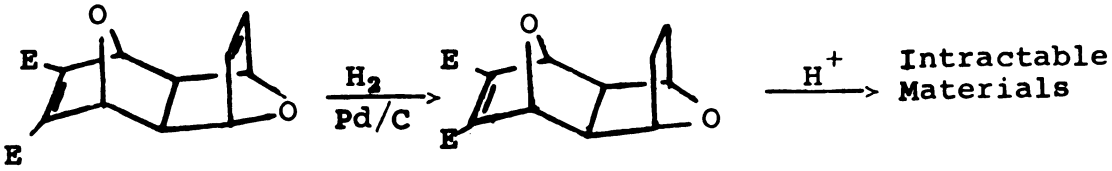
Scheme 9

and 2,5-dimethylfuran among the products. Most likely these compounds were not detected because cleavage of the ether bridge nearer the carbomethoxy groups would require the formation of a relatively unstable intermediate. This intermediate (69) which would be an allylic carbonium ion is destabilized by the electron withdrawing carbomethoxy groups.



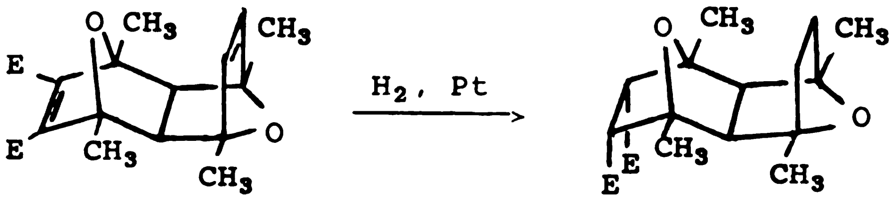
69

The acid catalyzed degradation of partially reduced bis-adduct 70 was also investigated. Catalytic reduction of 38 over palladium on charcoal gave 70; however, treatment of this compound with trifluoroacetic acid at room temperature did not lead to identifiable products.

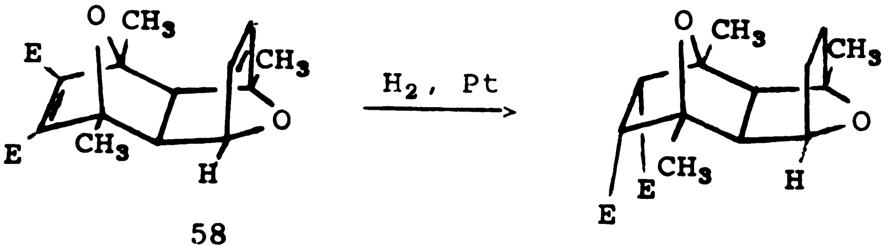


38 70

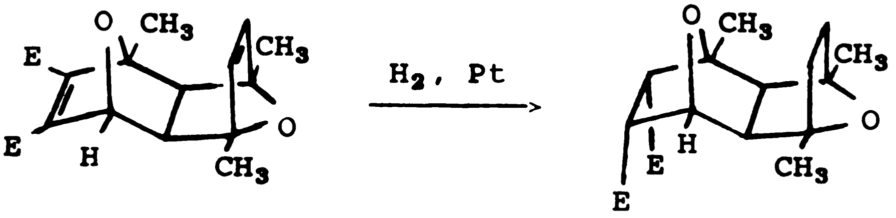
Exhaustive hydrogenation of (*exo*-*endo*) bis-adduct 46, (*exo*-*endo*) bis-adduct 58 and (*exo*-*endo*) bis-adduct 61 required two equivalents of hydrogen.



46 **49**



58 **71**

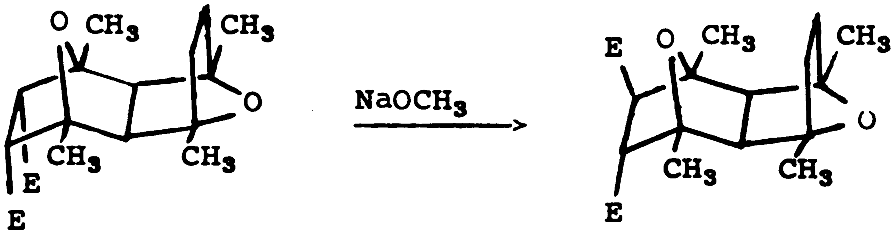


61 **72**

E = CO_2CH_3

The nmr spectrum of reduced adduct **72** indicated that reduction had occurred at the side of the oxygen bridge, (*exo*), to give *cis*-*endo* diester **72**. The vicinal coupling constant (J_{ab} = 4.5 Hz) demonstrated that the dihedral angle between H_a and H_b was 45°. Models reveal that only *endo*-diester 72 was consistent with this result.

The *cis*-diester 49 can be epimerized to the more stable *trans*-diester 73 with sodium methoxide in methanol.



49 73

E = CO_2CH_3

In summary the formation of furan-dimethyl acetylenedicarboxylate bis-adducts illustrates the importance of stereochemical factors on kinetically controlled as well as on thermodynamically controlled Diels-Alder reactions.

EXPERIMENTAL

Diels-Alder adduct of 2-Methylfuran and Dimethyl Acetylenedicarboxylate: Dimethyl 7-Oxa-1-methylbicyclo[2.2.1]hepta-2,3-dicarboxylate (**28**).

The Alder-Bachendorf (46) procedure was used, but the reaction was run at atmospheric pressure rather than in a sealed tube. Nearly quantitative yields of the oily Diels-Alder product were obtained: bp 92-94° (0.12 mm); ir ($CHCl_3$) 2995 and 2945 (C-H), 1720 (C=O) and 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.73 (s,3,$-CH_3$), δ 3.70 (s,3,$-CO_2CH_3$), δ 3.77 (s, 3,$-CO_2CH_3$), δ 5.52 (d,1,*J* = 2.1 Hz bridgehead), δ 6.90 (d, 1,*J* = 5.3 Hz - $C\underline{H}=C\underline{H}$-), δ 7.11 ppm (d,1,*J* = 5.3 Hz -CH=CH-, each signal is split into a doublet *J* = 2.1 Hz).

Diels-Alder Adduct of 2,5-Dimethylfuran and Dimethyl Acetylenedicarboxylate: Dimethyl 7-Oxa-1,4-dimethylbicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**29**).

The procedure of Alder and Bachendorf (46) was modified by carrying out the reaction at atmospheric pressure rather than in a sealed tube. Nearly quantitative yields of the colorless oil were obtained: bp 82-84° (0.3 mm); ir ($CHCl_3$) 2990 and 2950 (C-H), 1715 (C=O), and 1635 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.77 (s,6,$-C\underline{H}_3$), δ 3.76 (s,6,$CO_2C\underline{H}_3$) and δ 6.90 ppm (s,2,$-C\underline{H}=C\underline{H}$-).

Dimethyl (*exo*-*endo*)1,4:5,8 Diepoxy-1,4,4a,5,8,8a- hexahydronaphthalene-4a,8a-dicarboxylate (**34**).

Furan, 14.5 g (0.21 mol) and dimethyl acetylenedicarboxylate, 14.2 g (0.1 mole) were placed in a screw capped test tube and allowed to react at room temperature for 5 weeks. The entire reaction mixture crystallized. An nmr of the material indicated that it was primarily the (*exo*-*endo*) iosmer **34**. The (*exo*-*exo*) isomer appeared to be present in approximately 6% (determined by the ratio of $CO_2\underline{CH_3}$ resonances). Recrystallization (95% ethanol) gave adduct **34** as a white crystalline solid: mp 120-122°; ir ($CHCl_3$ 3000 (C-H), 2950 (C-H), 1735 (C=O), 1725 (C=O), 1430, and 1275 cm^{-1}; nmr ($CDCl_3$) δ 3.71 (s,6,$-CO_2\underline{CH_3}$); δ 4.50 (d,2, *J* = 1 Hz, bridgehead), δ 5.13 (d,2,*J* = 1 Hz, bridgehead), δ 6.49 (t,2,J = 1 Hz, $-C\underline{H}=C\underline{H}-$, AA' BB' system) and δ 6.62 ppm (t,2,*J*=1Hz, $-C\underline{H}=C\underline{H}-$, AA' BB' system) Figure 35.

Anal. Calcd for: $C_{14}H_{14}O_6$; C, 60.43; H, 5.08. Found: C, 60.24; H, 5.12.

Analysis of the Furan – Dimethyl Acetylenedicarboxylate reaction (2 weeks).

A 2 g sample of the preceding reaction mixture was dissolved in 100 ml of methanol and placed in a Paar pressure bottle. The reduction was carried out with a Paar hydrogenation apparatus (30 mg of 10% Pd/C catalyst). The initial hydrogen pressure was 50 lb/in². The sample was removed when the uptake of hydrogen had ceased. Vpc analysis demonstrated that the ratio of mono-adduct to bis-adduct was 2:3 *i.e.* 60% bis-adduct. The reduction products were identified by nmr.

Concentration of the reduction solution gave an oil which partially crystalized when it was treated with a small amount of pentane. Filtration of the solution gave 0.8 g (40%) of the reduction product of adduct **34**, as a white crystalline solid: mp 137-139°;ir ($CHCl_3$) 3000 (C-H), 2950 (C=H), 1725 (C=O) 1430 and 1265 cm^{-1}; nmr ($CDCl_3$) δ 4.85 (m,2, bridgehead) δ 4.35 (m,2, bridgehead) δ 3.67 (s, 6,$-CO_2C\underline{H}_3$) and δ 8.8 ppm (m,8,$-C\underline{H}_2-C\underline{H}_2-$).

The oily residue was distilled in a micro distillation apparatus. The colorless oil (reduction product of **27**) would not crystallize: (lit. mp 80-83°) (46).

Ir (NaCl plates) 2990 (C-H), 2950 (C-H), 1735, (C=O), 1430 and 1700 cm^{-1}; nmr ($CDCl_3$) δ 4.7 (m,2, bridgehead), δ 3.68 (s,6,$CO_2C\underline{H}_3$), δ 3.2 (n,1,$-C\underline{H}-CO_2$), δ 1.8 (m,4,$-C\underline{H}_2-C\underline{H}_2-$).

Diels-Alder Adducts from Dimethyl Acetylenedicarboxylate and an Excess of Furan: (exo-endo) Bis—adduct 38, (exo-exo) Bis-adduct 37 and Tris-adduct 41.

In a 75-ml glass pressure tube fitted with a teflon-lined pressure cap was placed 22.7 g (0.32 mol) of furan and 14.2 g (0.1 mol) of dimethyl acetylenedicarboxylate. The tube was heated to 100° for 18 hr. After cooling the reaction mixture was treated with 100 ml of chloroform. The insoluble materials were removed by filtration and the chloroform solution was concentrated. Column chromatography (silicic acid, chloroform) of the concentrate led to three products.

The first compound from the column was (*exo-endo*) bis-adduct **38**, 7.5 g (35%): mp 120-122°; uv max (CH_3OH) 240 mμ (ϵ 4980); ir ($CHCl_3$) 2985 (C-H), 2945 (C-H), 1760 (C=O), 1720 (C=O), 1660 (C=C) and 1460 cm^{-1} (C=C), Figure 14; nmr ($CDCl_3$) δ2.80 (d,1,*J* = 3 Hz, each signal split into a doublet, *J* = 1.6 Hz, bridgehead protons between the dihydrofuran rings), δ 3.74 (s,6,$-CO_2C\underline{H}_3$), δ 4.70 (s,2, bridgehead protons nearest the carbomethoxy groups), δ 4.78 (m,2, bridgehead protons of the least substituted dihydrofuran ring) and δ 6.24 ppm (s,2,$-C\underline{H}=C\underline{H}-$) Figure 36.

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.08. Found: C, 60.34; H, 5.06.

The second fraction contained 1.2 g (6%) of the white crystalline (*exo-exo*)-bis-adduct **37**: mp 157-159°; uv max (CH_3OH) 237 mμ (ϵ 4840); ir ($CHCl_3$) 3020 (C-H), 3000 (C-H), 2950 (C-H), 1725 (C=O), 1630 (C=C), 1430 (C=C) and 1265 cm^{-1} Figure 11; nmr ($CDCl_3$) δ 2.20 (s,2, bridgehead protons between the dihydrofuran rings), δ 3.77 (s,6,$-CO_2C\underline{H}_3$), δ 4.88 (s,2, bridgehead protons of the least substituted dihydrofuran ring), δ 5.09 (s,2, bridgehead protons nearest the carbomethoxy groups) and δ 6.40 (s,2,$-C\underline{H}=C\underline{H}-$), Figure 39.

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.08. Found: C, 60.34; H, 4.99.

The third fraction was eluted with a carbon tetrachloride-ethyl acetate (10:2) solution. Removal of the solvent gave 1.3 g (3.7%) of the white crystalline tris-adduct **41**: mp 213-215°; uv max (CH_3OH) 239 mμ (ε 4310); ir ($CHCl_3$) 2990 (C-H), 2950 (C-H), 1740 (C=O), 1715 (C=O), 1640 (C=C) and 1440 cm^{-1}; nmr ($CDCl_3$) δ 2.65 (m,4, bridgehead protons between rings), δ 3.80 (s,6,-$CO_2C\underline{H}_3$), δ 4.13 (m,2, bridgehead protons on the least substituted dihydrofuran ring), δ 4.85 (m,2, bridgehead protons on the tetrahydrofuran ring), δ 5.0 (s,2, bridgehead portons nearest the carbomethoxy groups), and δ 6.27 ppm (s,2,-$C\underline{H}$=$C\underline{H}$-); Figure 24.

Anal. Calcd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.19. Found: C, 62.22; H, 5.19.

Dimethyl 7-Oxa-1,4-dimethylbicyclo[2.2.1]heptane-2,3-dicarboxylate (**43**).

A solution containing 7.1 g (0.05 mol) of dimethyl acetylenedicarboxylate and 9.6 g (0.1 mol) of 2,5-dimethylfuran was placed in a screw-capped test tube and allowed to stand at room temperature for 16 days.

A 2 g sample of the reaction mixture was dissolved in 200 ml of methanol and placed in a Paar hydrogenation bottle. Approximately 30 mg of platinum oxide was added to the solution before reduction with a Paar apparatus at a hydrogen pressure of 50 lb/in^2 for 6 hr. Analysis of the solution by vpc indicated that a single product had been formed. Collection of this material from the vpc gave cis-endo-dimethyl 1,4-dimethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate 43: mp 41-41°; ir ($CHCl_3$) 2950 (C-H), 2865 (C-H), 1735 (C=O), 1435 and 1350 cm^{-1}; nmr ($CDCl_3$) δ 1.52 (m,8, 2-CH_3 plus 2-H of an A_2B_2 system), δ 2.2 (m,2, part of an A_2B_2 system), δ 3.03 (s,2,$-C\underline{H}-CO_2CH_3$) and δ 3.07 (s,6,$-CO_2C\underline{H}_3$).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.55, H, 7.50. Found: C, 59.73; H, 7.59.

Bis-Diels-Alder Adduct of Diester 29 and 2,5-Dimethylfuran: Dimethyl (exo-endo) 1,4:5,8-Diepoxy-1,4,5,8-tetramethyl-1,4,4a,5,8,8a-hexahydronaphthalene-2,3-dicarboxylate (46).

A solution containing 11.1 g (0.078 mol) of adduct 29 and 25 g (0.26 mol) of 2,5-dimethylfuran was heated to 95° for 18 hr in a nitrogen atmosphere. Unreacted 2,5-dimethylfuran was removed by distillation at atmospheric pressure and adduct 29 was removed by vacuum distillation. The oily residue crystallized exothermically when treated with a small amount of pentane. Recrystallization from ether gave 2.6 g (10%) of the white crystalline adduct 46: mp 107-108°; uv max (CH_3OH) 233 mμ (ϵ 4950); ir ($CHCl_3$) 2975 (C-H), 2950 (C-H), 1715 (C=O) and 1630 cm^{-1} (C=C), Figure 16; nmr ($CDCl_3$) δ 6.24 (s,2,$-C\underline{H}=C\underline{H}-$), δ 3.76 (s,6,$-CO_2C\underline{H}_3$), δ 2.72 (s,2, bridgehead), δ 1.54 (s,6,$-C\underline{H}_3$), δ 1.48 ppm (s,6,$-C\underline{H}_3$), Figure 25.

Anal Calcd for $C_{18}H_{22}O_6$: C, 64.64; H, 6.63. Found: C, 64.75; H, 6.50.

cis-Dimethyl (*exo*-*endo*) 1,4:5,8-Diepoxy-1,4,5,8-tetramethyldecahydronaphthalene-2,3-dicarboxylate (49); Reduced Adduct 49.

A suspension of platinum oxide (50 mg) in 10 ml of 95% ethanol was saturated with hydrogen. A solution of 173 mg (5.18×10^{-4} mol) of adduct 46 in 15 ml of 95% ethanol was then added. Exhaustive hydrogenation at atmospheric pressure required 23.9 ml (1.06×10^{-4} mol) of hydrogen at STP corresponding to the reduction of two double bonds (theoretical 1.04×10^{-2} mol). The platinum was removed by filtration through a fiber glass filter. Removal of solvent followed by recrystallization (pentane) gave 0.160 g (92%) of the reduced adduct 49: mp 154-156^{0}; ir ($CHCl_3$) 2950 (C-H), and 1737 cm^{-1} (C=O); nmr (CF_3CO_2H) δ 3.82 (s,6,$-CO_2CH_3$), δ 3.36 (s,2,2-$C\underline{H}CO_2$-), δ 2.86 (s,2, bridgehead), δ 2.4 (m,2, 2-H of an A_2B_2 system), δ 1.72 (s,7,2-CH_3 plus 2-H of an A_2B_2 system) and δ 1.58 ppm (s,7,2-H plus 1-H of an A_2B_2 system) Figure 27.

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.61; H, 7.69. Found: C, 63.89; H, 7.69.

trans-(exo-endo) 1,4:5,8-Diepoxy-1,4,5,8-tetramethyldecahydronaphthalene-2,3-dicarboxylic Acid (50); Saponification of Diester 49.

Diester **49**, 7.3 g (0.021 mol), dissolved in a solution containing 40 ml of water, 20 ml of methanol and 4 g of sodium hydroxide was heated to 80° for 12 hr. The cooled solution was extracted once with 40 ml of ether and then it was acidified with concentrated hydrochloric acid to a pH of 2. The aqueous layer was placed in a liquid-liquid extractor and extracted with ether for 8 hr. After drying ($MgSO_4$) and filtration, removal of the solvent gave 5.6 g (80%) of diacid **50** as a white powder: mp 255-257°(dec); ir (KBr) 3150 (O-H), 2950 (C-H), 1715 (C=O), 1390, 1210 and 810 cm^{-1}; nmr (D_2O, Na_2CO_3; internal reference; sodium 2,2-dimethyl-2-silapentane-5-sulfonate) δ 2.91 (d,1,*J* = 6.3 Hz, $NaO_2C\text{-}CH\text{-}C\underline{H}\text{-}CO_2Na$, half of an AB quartet), δ 2.70 (d,1, *J*= 6.3 Hz, $NaO_2C\text{-}C\underline{H}\text{-}CH\text{-}CO_2Na$, half of an AB quartet), δ 2.20 (m, 4, bridgehead protons plus 2 protons from the AA' BB' system of the tetrahydrofuran ring), δ 1.61 (s,3,$\text{-}C\underline{H}_3$) and 1.40 ppm (s,11,3,$\text{-}C\underline{H}_3$, plus 2-H from the AA' BB' tetrahydrofuran system) Figure 28.

Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.99; H, 7.15. Found: C, 61.67; H, 7.07.

(endo-exo) 1,4:5,8-Diepoxy-1,4,5,8-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene (51); Bisdecarboxylation of Diacid 50.

Into a 100-ml 3-necked flask fitted with a mechanical stirrer, reflux condenser and a gas inlet tube was placed 5.3 g (0.017 mol) of diacid 50 dissolved in 40 ml of dry pyridine. After saturation of the solution with oxygen, the gas inlet tube was removed and 11.4 g (0.256 mol) of lead tetraacetate (dried in a vacuum oven at 25°) was added directly to the solution. The flask containing the solution was then immersed in an oil bath preheated to 70°. After five minutes the stirred solution began to evolve carbon dioxide. As soon as the evolution of CO_2 ceased the reaction flask was cooled in an ice bath. The cooled solution was then treated with 50 ml of methylene chloride and extracted twice with 50 ml of 50% nitric acid (0°). The final traces of pyridine were removed by extraction with a 10% cadmium chloride solution followed by a final extraction with water. After drying the solution ($MgSO_4$), the methylene chloride was removed by careful distillation. The residue was treated with 15 ml of pentane and the insoluble material was removed by filtration. Removal of the pentane followed by sublimation (0.05 mm, 25°) of the oily residue gave 0.190 g (5.2%) of the white crystalline monoolefin 51: mp 60-63°; ir ($CHCl_3$) 2970 (C-H), 2935 (C-H), 1460 (C=C), 1380, 1310, 1250, 1145, and 850 cm^{-1}; nmr (CCl_4) δ 2.17 (s,1,1-H of the A_2B_2 tetrahydrofuran system), δ 2.03 (s,3,2 bridgehead protons plus one proton from the A_2B_2 tetrahydrofuran system), δ 1.45 (s,8,2-CH_3, plus 2-H of the A_2B_2 tetrahydrofuran system), δ 1.28 (s,6,2-CH_3), and δ 5.97 ppm (s,2, -CH_2=CH-) Figure 29.

<u>Anal</u>. Calcd for $C_{14}H_{26}O_2$: C, 76.43; H, 9.16. Found: C, 76.29; H, 9.26.

(exo-endo) 1,4:5,8-Diepoxy-1,4,5,8-tetramethyldecahydronaphthalene (52); Reduction of alkene 51.

A suspension of platinum oxide (20 mg) in 15 ml of methanol was saturated with hydrogen. A solution of 0.101 g (4.53×10^{-4} mol) of alkene 51 in 15 ml of methanol was then added through a rubber septum. After the uptake of hydrogen had ceased, the methanol solution was filtered through a glass fiber filter and the methanol was removed. The reduced diether 52, 0.090 g (90%) was purified by sublimation (0.05 mm, 25°): mp 54-55.5°; ir ($CHCl_3$) 2895 (C-H), 2885 (C-H), 2865 (C-H), 1460, 1380, 1140, 1080 and 850 cm^{-1}, Figure 15; nmr ($CDCl_3$) δ 2.24 (s,1, 1 proton of an A_2B_2 tetrahydrofuran system), δ 2.09 (s,3, 2 bridgehead protons plus 1-H from an A_2B_2 system), δ 1.51 (s,5,$-C\underline{H}_2-C\underline{H}_2-$ plus 1-H of an A_2B_2 system, δ 1.46 (s,7, 2-$C\underline{H}_3$ plus 1-H of an A_2B_2 system), and δ 1.42 ppm (s,6, 2-$C\underline{H}_3$), Figure 30.

<u>Anal</u>. Calcd for $C_{14}H_{22}O_2$: C, 75.74; H, 9.99. Found: C, 75.66; H, 9.81.

Dimethyl (*exo*-*endo*) 1,4,:5,8-Diepoxy-1,4,5-trimethyl-1,4,-4a,5,8,8a-hexahydronaphthalene-2,3-dicarboxylate (**58**); Diels-Alder Adduct of Diester **29** and 2-Methylfuran.

A solution of 16.8 g (0.071 mol) of adduct **29** and 24.8 g (0.3 mol) of 2-methylfuran was refluxed in a nitrogen atmosphere for 24 hr. The excess 2-methylfuran was removed by distillation at atmospheric pressure and unreacted **29** was removed by vacuum distillation: bp 82-84° (0.3 mm).

Column chromatography (silicic acid, $CHCl_3$) gave 3 g (13%) of a light yellow oil which crystallized after standing several days. Recrystallization from pentane gave adduct **58** as a white crystalline solid: mp 90-92°, ir ($CHCl_3$) 2960 and 2940 (C-H), 1715 (C=O), 1630 (C=C), 1435, 1385 and 1310 cm^{-1}, Figure 18; nmr ($CDCl_3$) δ 6.42 (d,1,J= 6.2 Hz, RCH=CHR'; each signal is split further into a doublet J = 1.8 Hz), δ 6.24 (d,1,J = 6.2 Hz, RCH=CHR), δ 4.64 (d,1,J = 5.2 Hz bridgehead on the dihydrofuran ring; each signal is split further into a doublet J = 1.8 Hz), δ 3.76 (s,6,-CO_2CH_3), δ 3.08 (d,1,J = 7.5 Hz bridgehead; each signal split further into a doublet J = 5.2 Hz), δ 2.54 (d,1,J = 7.6 Hz, bridgehead), δ 1.57 (s,3,-CH_3), δ 1.48 (s,3,-CH_3), and δ 1.46 ppm (s,3,-CH_3), Figure 32.

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.75; H, 6.29. Found: C, 63.87; H, 6.26.

Dimethyl (*exo*-*endo*) 1,4:5,8-Diepoxy-1,5,6-trimethyl-1,4,4a,5,8,8a-hexahydronaphthalene (61); Adduct of Diester 28 and 2,5-Dimethylfuran.

A solution containing 10.5 g (4.7×10^{-2} mol) of adduct 28, 9.0 g (9.4×10^{-2} mol) of 2,5-dimethylfuran and 20 ml of toluene was heated to 96° for 18 hr in a nitrogen atmosphere. The toluene and unreacted 2,5-dimethylfuran were removed by distillation at atmospheric pressure and unreacted diester 28 was removed by vacuum distillation. Column chromatography (silicic acid, $CHCl_3$) of the residue gave a yellow oil which crystallized only after standing several days. Recrystallization (ether) gave 2 g, 13%, of adduct 61 as a white crystalline solid: mp 87-89°; ir ($CHCl_3$) 2580 and 2550 (C-H), 1715 (C=O), 1630 (C=C), 1430 and 1380 cm^{-1}, Figure 15; nmr ($CDCl_3$) δ 6.27 (d,1,J = 6 Hz, $R\text{-}C\underline{H}{=}C\underline{H}\text{-}R'$), δ 6.18 (d,1,J = 6 Hz $R\text{-}C\underline{H}{=}C\underline{H}\text{-}R'$), δ 4.58 (s,1, bridgehead on furan ring), δ 3.81 (s,3,$-CO_2C\underline{H}_3$), δ 3.77 (s,3,$-CO_2C\underline{H}_3$), δ 2.65 (s,2, bridgehead), δ 1.54 (s,6,$-C\underline{H}_3$), and δ 1.47 ppm (s,3,$-C\underline{H}_3$), Figure 31.

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.75; H, 6.29. Found: C, 63.78; H, 6.24.

Dimethyl (*exo*-*endo*) 1,4:5,8-Diepoxy-1,4,5,8-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2,3-dicarboxylate (**63**); Selective Reduction of Adduct **46**.

A suspension of 10 mg of 10% palladium on powdered charcoal in 10 ml of methanol was saturated with hydrogen and adduct **46**, 0.973 g (2.41×10^{-3} mol), dissolved in 15 ml of methanol was then introduced. The reduction was stopped after 1 mole (2.93×10^{-3} mol) of hydrogen had been consumed. Filtration of the reaction mixture through a glass fiber filter followed by removal of the solvent and recrystallization (hexane) gave 0.830 g (86%) of compound **63**: mp 93-95°, ir ($CHCl_3$) 2960 and 2945 (C-H), 1710 (C=O) and 1635 cm^{-1}; nmr ($CDCl_3$) δ 3.80 (s,6,-COOC$\underline{H}_3$), δ 2.49 (s,2, bridgehead) δ 2.21 (d,2,*J* = 7.2 Hz, A_2B_2 system of furan ring), δ 1.65 (s,8,2-C$\underline{H}_3$ plus 2 protons of an A_2B_2 system), and δ 1.43 ppm (s,6,-C$\underline{H}_3$), Figure 26.

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.29; H, 7.14. Found: C, 64.44; H, 7.11.

Pyrolysis of Mono-olefin 63. Procedure A.

In a 4-ml side-arm distilling flask was placed 0.800 g (3.39×10^{-3} mol) of mono-olefin 63. The compound was heated to 280° (sand bath) for 4 hr in a nitrogen atmosphere. 2,5-Dimethylfuran (110 mg, 36%) slowly distilled from the reaction mixture (ir was identical to a known sample). No attempt was made to trap the ethylene evolved during the pyrolysis.

When the sand bath temperature was increased to 350°, 244 mg (34%) of dimethyl 2,5-dimethylfuran-2,3-dicarboxylate (64) distilled from the reaction mixture: mp 58-61° [lit (56) mp 58-61°]; ir ($CHCl_3$) 3000 (C-H), 1750 (C=O), 1693 (C=C), 1445, 1320 and 1090 cm^{-1}; nmr ($CDCl_3$) δ 3.85 (s,6, $-COOC\underline{H}_3$) and δ 2.40 ppm (s,6,$-C\underline{H}_3$).

Procedure B.

A Pyrex tube 1.5 cm in diameter packed to a height of 28 cm with granular silicon carbide (10 mesh) was preheated in a vertical tube furnance to 380°. The tube was fitted with an addition funnel and a receiver consisting of a 100-ml 3-necked flask fitted with a dry ice condenser. The collection flask was cooled in a dry ice-acetone bath. A slow stream of nitrogen was used as the carrier gas.

A solution of 0.952 g (2.85×10^{-3} mol) of monoalkene 63 in 25 ml of benzene was slowly passed through the heated column. Removal of solvent (rotoevaporator) from the material collected in the receiver gave 450 mg, (75%) of dimethyl 2,5-dimethylfuran-2,3-dicarboxylate: mp 58-61° [lit (56) 58-61°)].

Acid Catalyzed Degradation of Mono-olefin 63.

A solution containing 100 mg (3.0×10^{-4} mol) of 63 two drops of trifluoroacetic anhydride and 0.3 ml of trifluoroacetic acid was placed in an nmr tube at room temperature. An nmr taken immediately after mixing was consistent with the starting material: nmr (CF_3CO_2H) δ 3.95 (s,6, $CO_2C\underline{H}_3$), δ 2.79 (s,2, bridgehead), δ 2.32 (d,1,*J* = 5 Hz, part of an A_2B_2 system of the tetrahydrofuran ring), δ 1.83 (s,8,$-C\underline{H}_3$ plus 2 protons of an A_2B_2 system), and δ 1.62 ppm (s,6,$-C\underline{H}_3$), Figure 37.

After 12 hr the solution had turned black and the spectrum had changed completely: nmr (CF_3CO_2H) δ 7.03 (s, 4, aromatic), δ 4.26 (s,6,$-CO_2C\underline{H}_3$), δ 2.65 (s,6,$-C\underline{H}_3$), and δ 2.24 ppm (s,6,$-C\underline{H}_3$), Figure 38.

The spectrum was shown to be a mixture of dimethyl 2,5-dimethylfuran-3,4-dicarboxylate and *p*-xylene by the addition of known samples of each of the two compounds to the nmr tube. When dimethyl 2,5-dimethylfuran-2,3-dicarboxylate (64) was added the peak heights at δ and δ 2.64 ppm increased. The addition of *p*-xylene caused the peaks at δ 6.98 and δ 2.22 ppm to increase. No other peaks were observed.

cis-endo-Dimethyl (*exo-endo*) 1,4:5,8-Diepoxy-1,4,5-trimethyldecahydronaphthalene-2,3-dicarboxylate (**71**); Reduction of Adduct **58**.

A suspension of 50 mg of platinum oxide in 10 ml of 95% ethanol was saturated with hydrogen. After the reduction of the plantinum oxide was complete 156 mg (4.88×10^{-4} mol) of adduct **58** was added through a rubber septum. Exhaustive hydrogenation required 22.6 ml (10.1×10^{-3} mol) of hydrogen at STP (theoretical 9.76×10^{-3} mol). The reaction mixture was filtered through a fiber glass filter and the solvent was removed (rotoevaporator). Recrystallization (pentane) gave 130 mg (84%) of reduced adduct **71**: mp 90-92°; ir ($CHCl_3$) 2985 (C-H), 2950 (C-H), 1740 (C=O), 1435, 1380, 1150, and 1075 cm^{-1}; nmr ($CDCl_3$) δ 4.40 (m,1, bridgehead on tetrahydrofuran ring), δ 3.65 (s,6,$-CO_2C\underline{H}_3$), δ 2.76 (m,2), δ 2.05 (d,2,$-C\underline{H}_2-C\underline{H}_2-$, A_2B_2 system of tetrahydrofuran ring), δ 1.57 (s,4,$-C\underline{H}_3$ plus 1 proton of an A_2B_2 system), δ 1.55 (s,4,$-C\underline{H}_3$ plus one proton of an A_2B_2 system), and δ 1.48 ppm (s,3,$-C\underline{H}_3$).

Anal. Calcd for $C_{17}H_{24}O_6$: C, 63.02; H, 7.47. Found: C, 63.10; H, 7.57.

cis-endo-Dimethyl (exo-endo) 1,4:5,8-Diepoxy-2,5,8-trimethyl decahydronaphthalene (72); Reduction of Adduct 61.

To 100 ml of methanol in a Paar hydrogenation bottle was added 3.0 g (9.3×10^{-1} mol) of bis-adduct 61 and 30 mg of platinum oxide. The reduction was carried out in a Paar apparatus at a starting hydrogen pressure of 50 lb/in^2 until the uptake of hydrogen stopped. Filtration of the solution followed by removal of the solvent gave 2.9 g (96%) of the white crystalline *cis*-*endo*-diester 72: mp 90-92°; ir ($CHCl_3$) 2925 (C-H), 2965 (C-H), 2945 (C-H), 1735 (C=O) and 1435 cm^{-1}; nmr ($CDCl_3$) δ 4.30 (d,1,*J* = 4.5 Hz bridgehead hydrogen adjacent to the oxygen), δ 3.67 (s,3,$-CO_2C\underline{H}_3$), δ 3.65 (s,3, $-CO_2\underline{C}H_3$), δ 3.1 (m,3), δ 2.33 (s,1), δ 2.15 (m,2), δ 2.58 (s,3,$-C\underline{H}_3$), δ 1.47 (s,4,$-C\underline{H}_3$ plus 1-H of an A_2B_2 system), and δ 1.42 ppm (s,4,$-C\underline{H}_3$ plus 1-H of an A_2B_2 system), Figure 34.

Anal. Calcd for $C_{17}H_{24}O_6$: C, 63.02; H, 7.47. Found: C, 62.75; H, 6.24.

trans-Dimethyl (*exo*-*endo*) 1,4:5,8-Diepoxy-1,4,5,8-tetramethyldecahydronaphthalene (73); Epimerization of Reduced Diester 49.

To 2 ml of dry methanol was added 0.1 g of sodium in a nitrogen atmosphere. Reduced adduct 49 0.900 g (2.36×10^{-3} mol) dissolved in 5 ml of dry methanol, was then added to the sodium methoxide solution. The resulting solution was refluxed for 48 hr under nitrogen. The cooled solution was neutralized with acetic acid and then treated with an excess of diazomethane. The diazomethane was generated by treating bis(N-nitroso-N-methyl)phthalamide with a 40% KOH solution. The excess diazomethane was destroyed with acetic acid.

Removal of solvent followed by column chromatography (silicic acid, $CHCl_3$) gave 0.6 g (67%) of nearly colorless crystals of the *trans*-diester 73: mp 118-120° (pentane); ir ($CHCl_3$) 2930 (C-H), 1730 (C=O) 1440 and 1385 cm^{-1}; nmr ($CDCl_3$) δ 3.77 (s,6,-$CO_2C\underline{H}_3$), δ 3.28 (d,1,*J* = 6 Hz, $C\underline{H}CO_2CH_3$, A B system), δ 3.08 (d,1,J = 6 Hz, $C\underline{H}$-CO_2CH_3, A B system), δ 1.72 (s,3,-$C\underline{H}_3$ adjacent to exo-$CO_2C\underline{H}_3$), and δ 1.43 ppm (m,11,3-CH_3 plus 2-H of an A_2B_2 system), Figure 31.

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.61; H, 7.69. Found: C, 63.41; H, 7.63.

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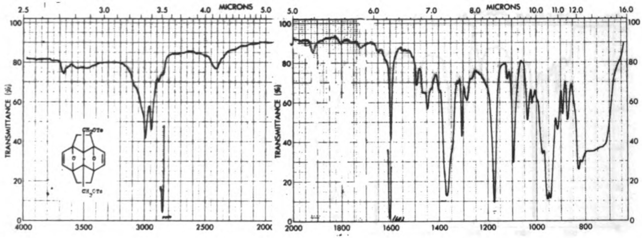

Figure 7. Infrared spectrum of ditosylate 16.

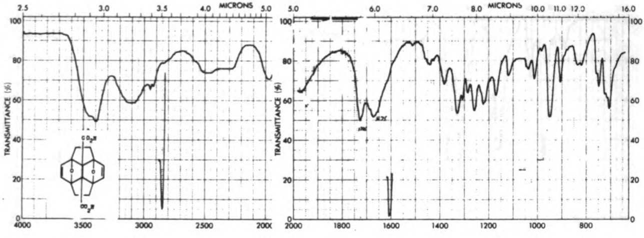

Figure 8. Infrared spectrum of diacid 10.

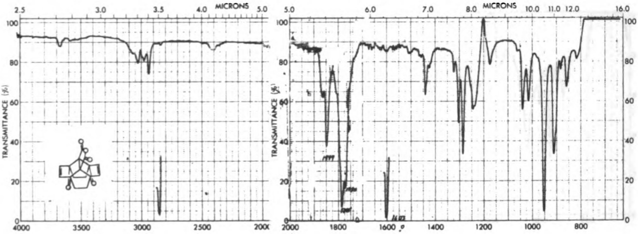

Figure 9. Infrared spectrum of anhydride 11.

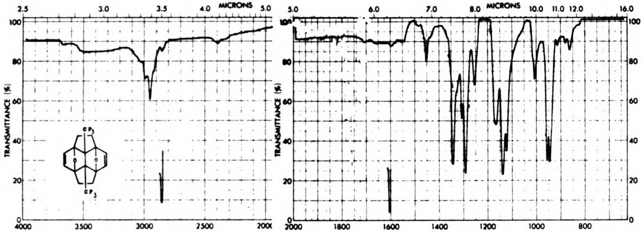

Figure 10. Infrared spectrum of hexafluoro-adduct 21.

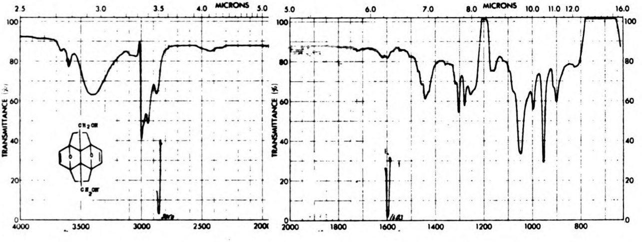

Figure 11. Infrared spectrum of diol 12.

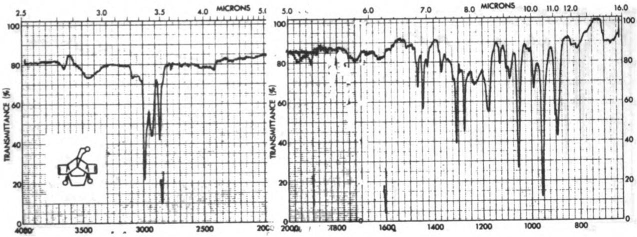

Figure 12. Infrared spectrum of ether 15.

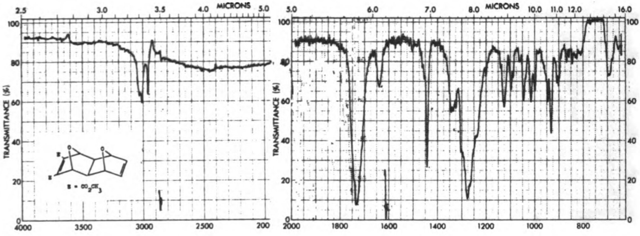

Figure 13. Infrared spectrum of adduct 37.

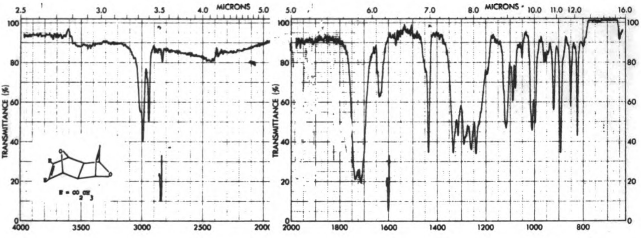

Figure 14. Infrared spectrum of adduct 38.

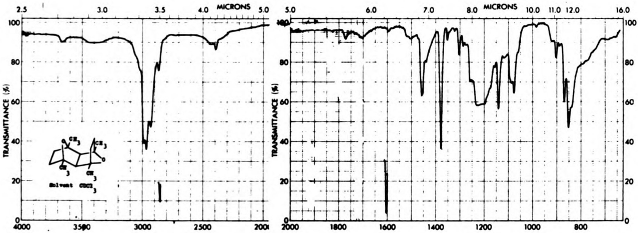

Figure 15. Infrared spectrum of compound 52.

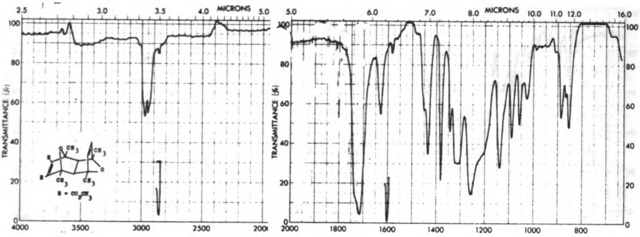

Figure 16. Infrared spectrum of adduct 46.

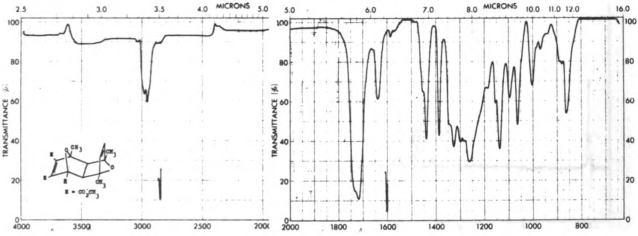

Figure 17. Infrared spectrum of adduct 61.

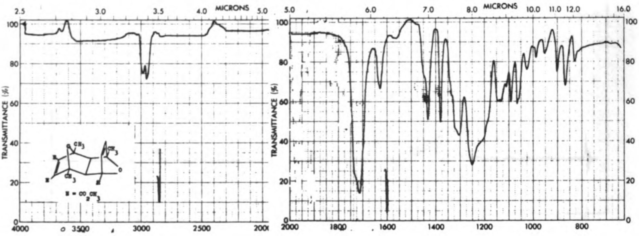

Figure 18. Infrared spectrum of adduct 58.

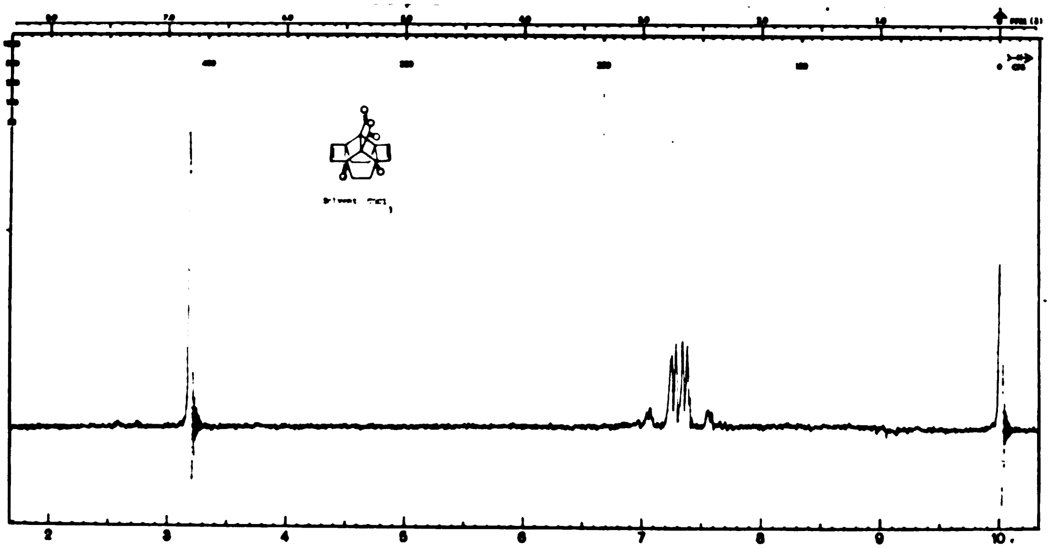

Figure 19. Nmr spectrum of anhydride 11.

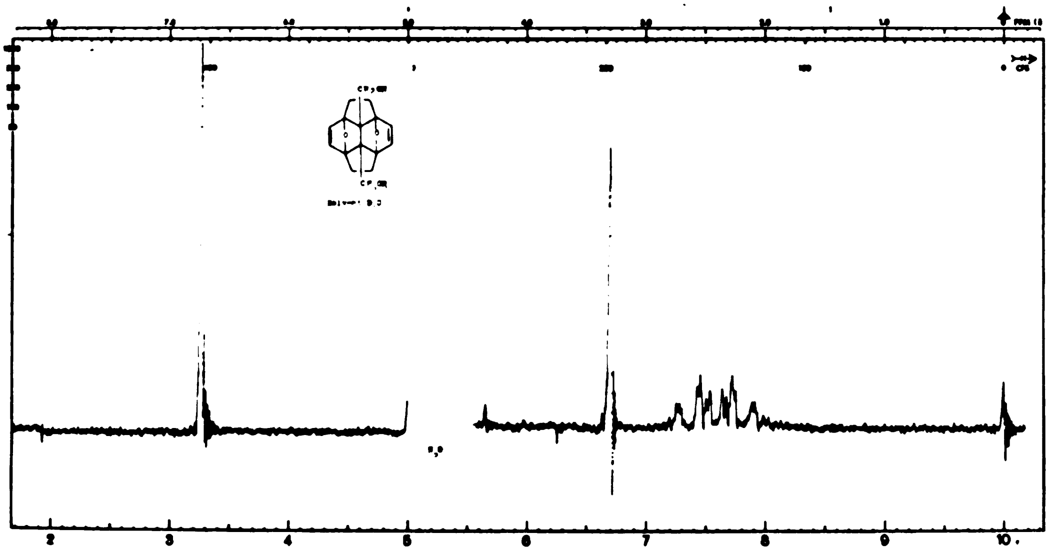

Figure 20. Nmr spectrum of diol 12.

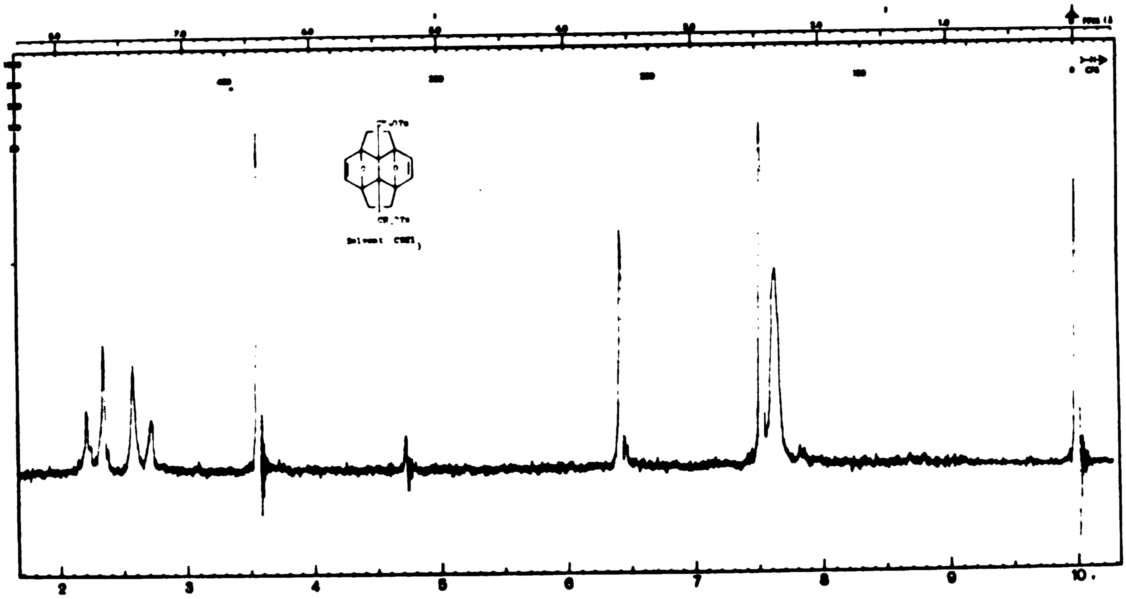

Figure 21. Nmr spectrum of ditosylate 16.

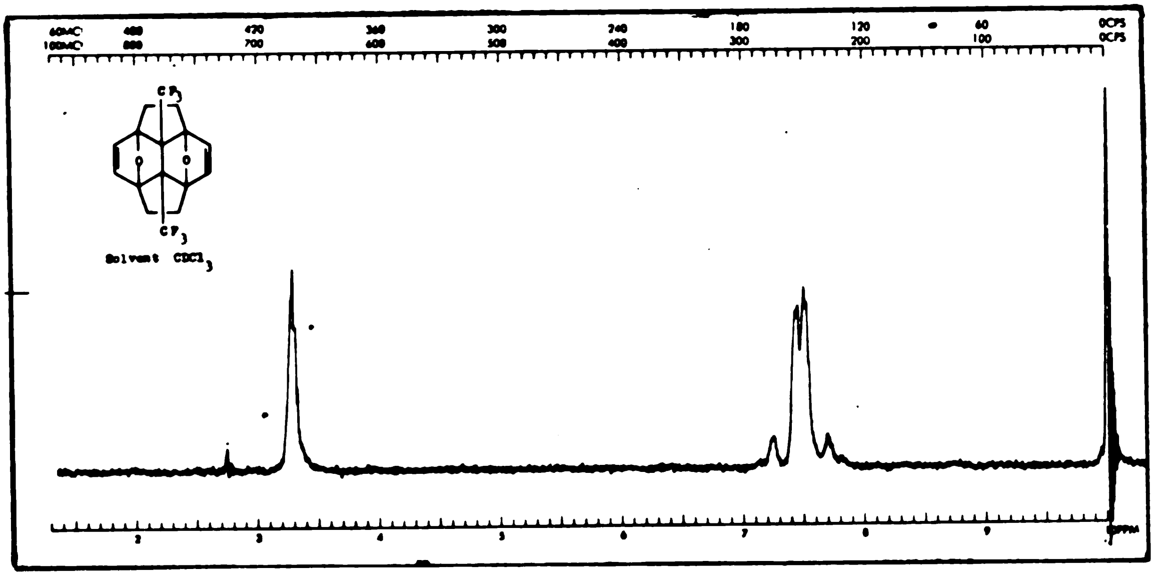

Figure 22. Nmr spectrum of hexafluoro-adduct 21.

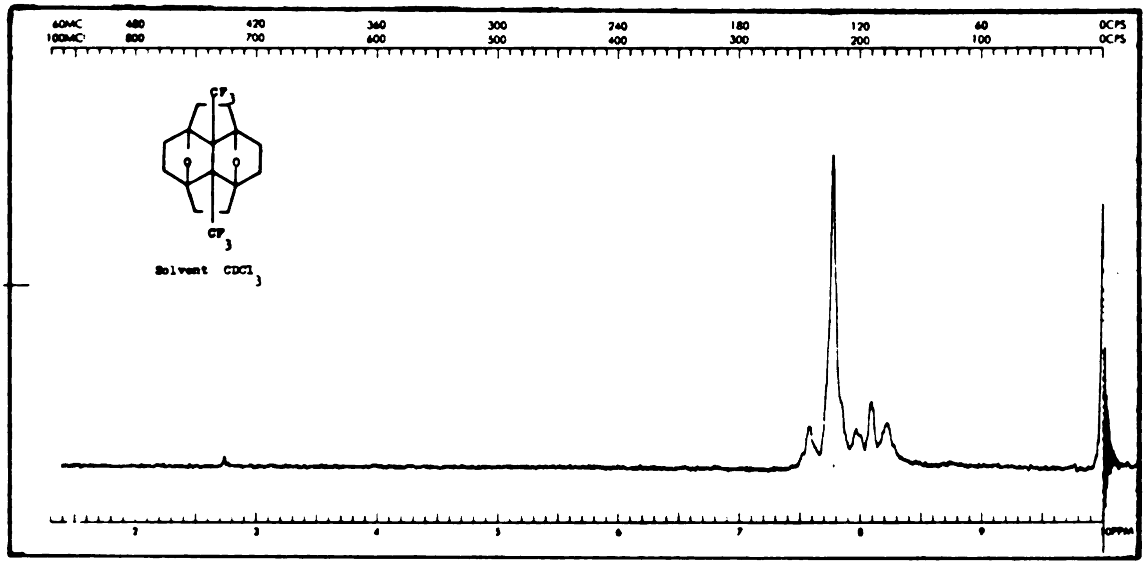

Figure 23. Nmr spectrum of hexafluoro-compound 23.

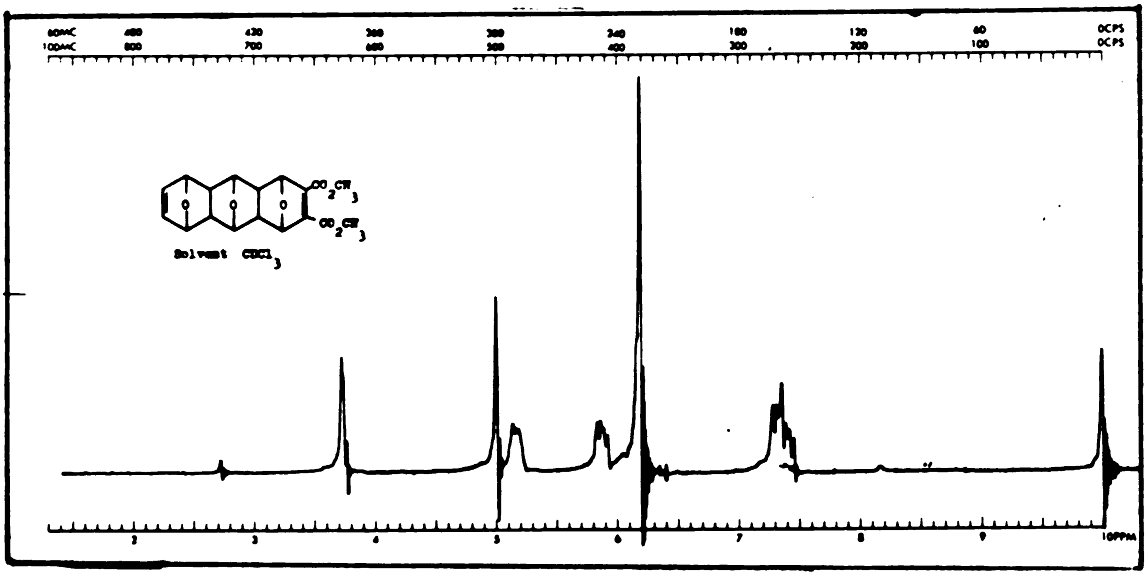

Figure 24. Nmr spectrum of tris-adduct 41.

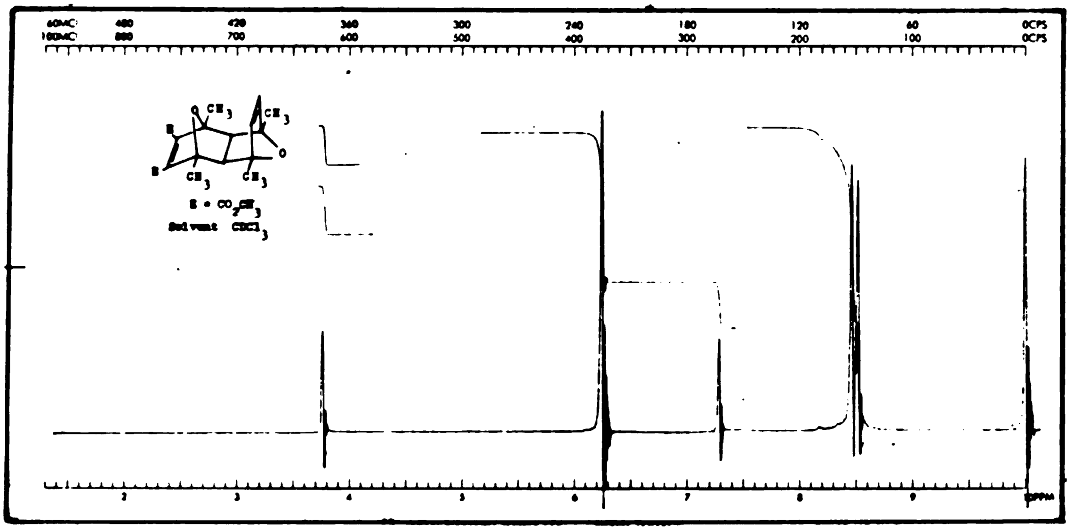

Figure 25. Nmr spectrum of tetramethyl adduct 46.

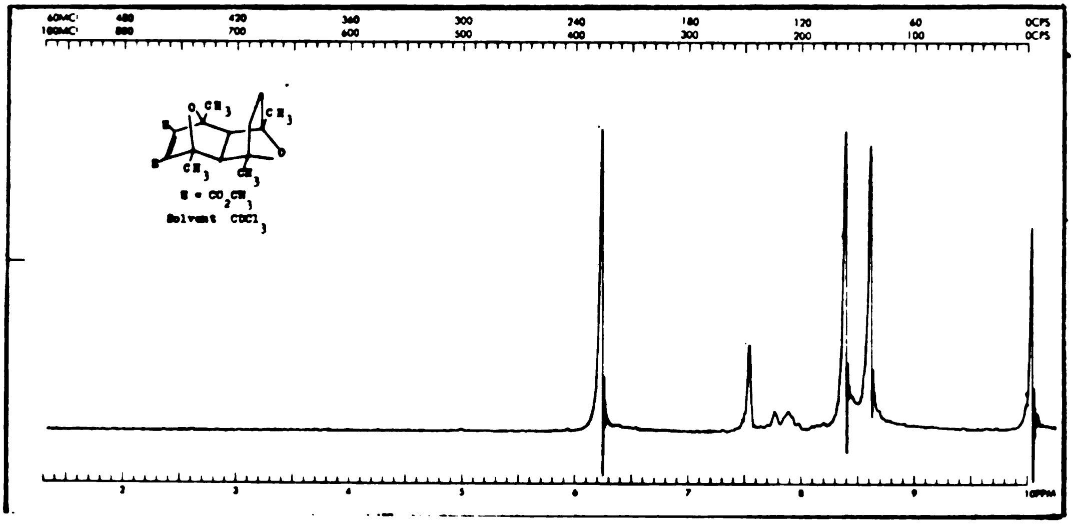

Figure 26. Nmr spectrum of adduct 63.

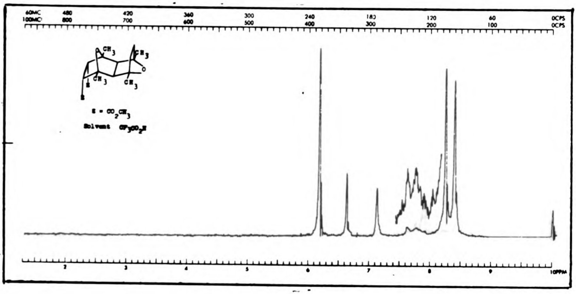

Figure 27. Nmr spectrum of compound 49.

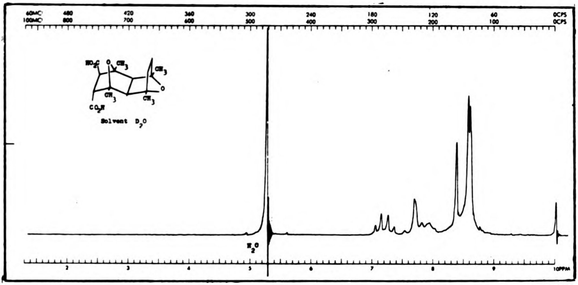

Figure 28. Nmr spectrum of diacid 50.

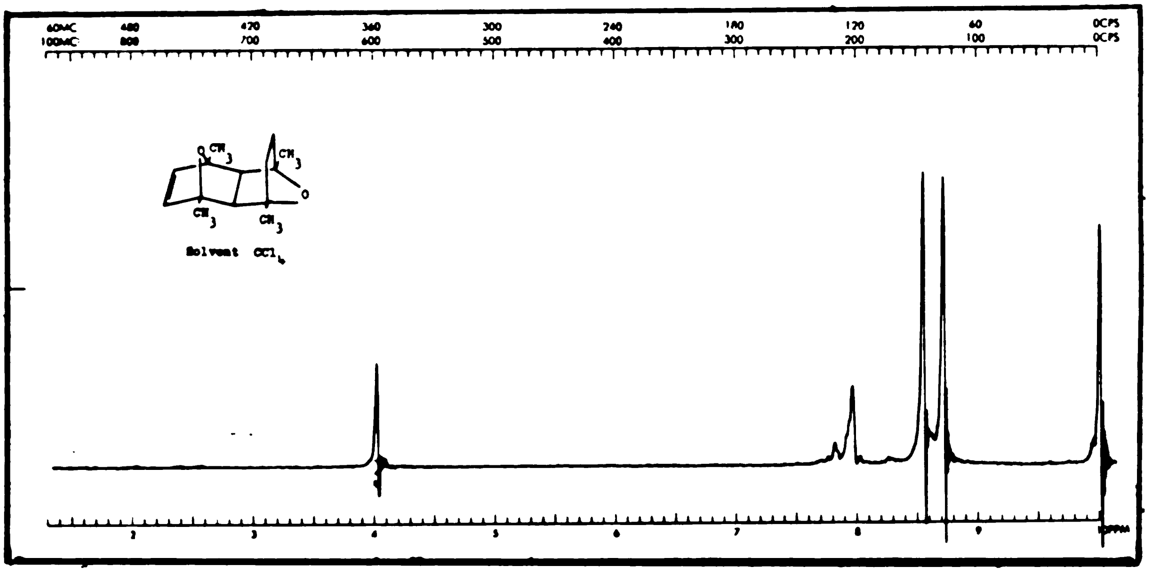

Figure 29. Nmr spectrum of compound 51.

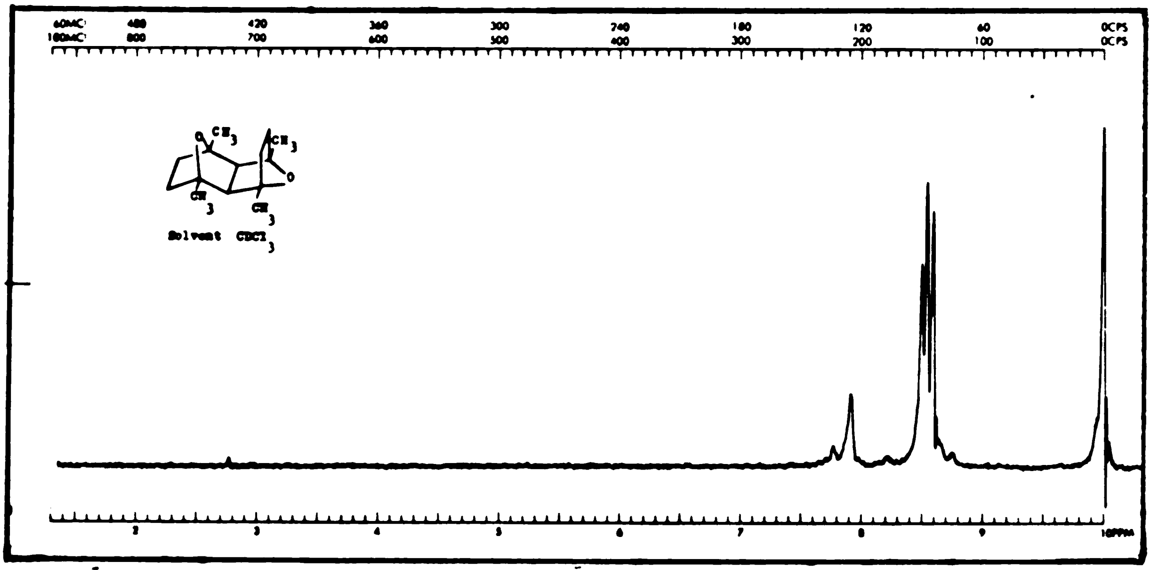

Figure 30. Nmr spectrum of compound 52.

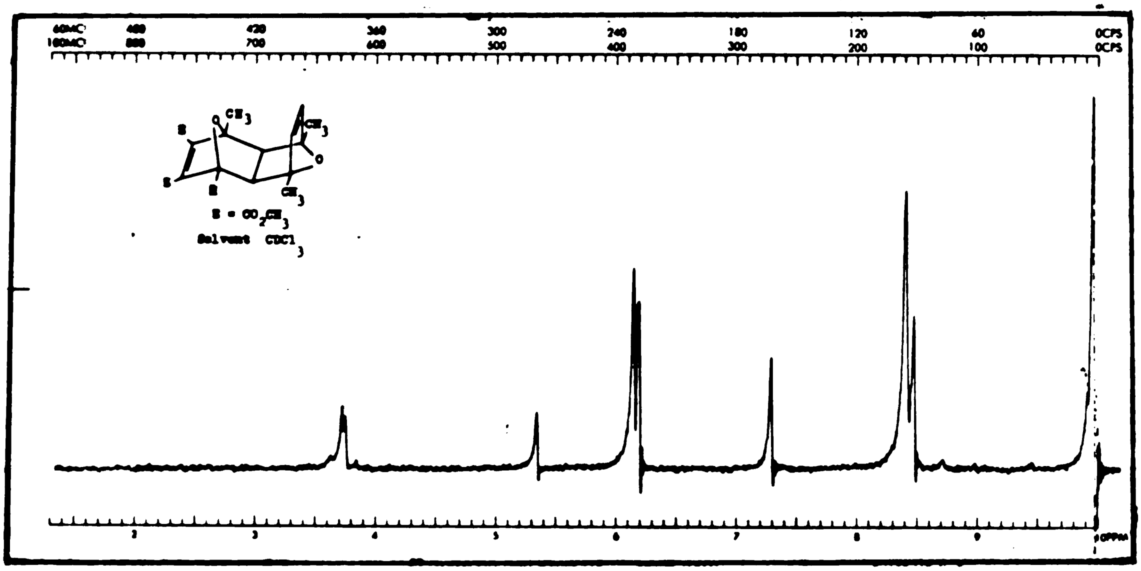

Figure 31. Nmr spectrum of trimethyl adduct 61.

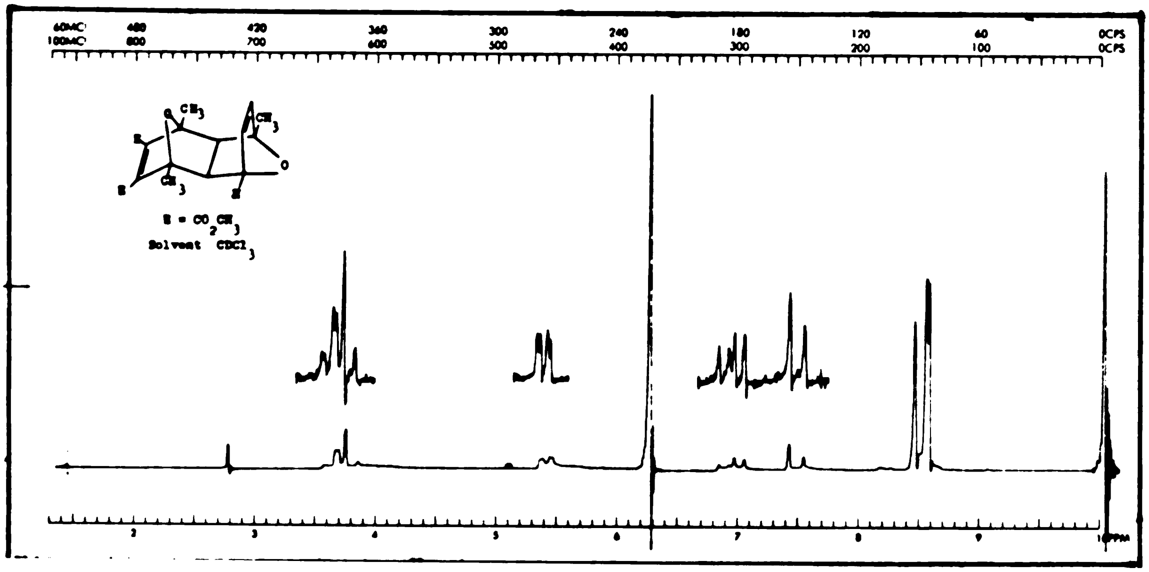

Figure 32. Nmr spectrum of trimethyl adduct 58.

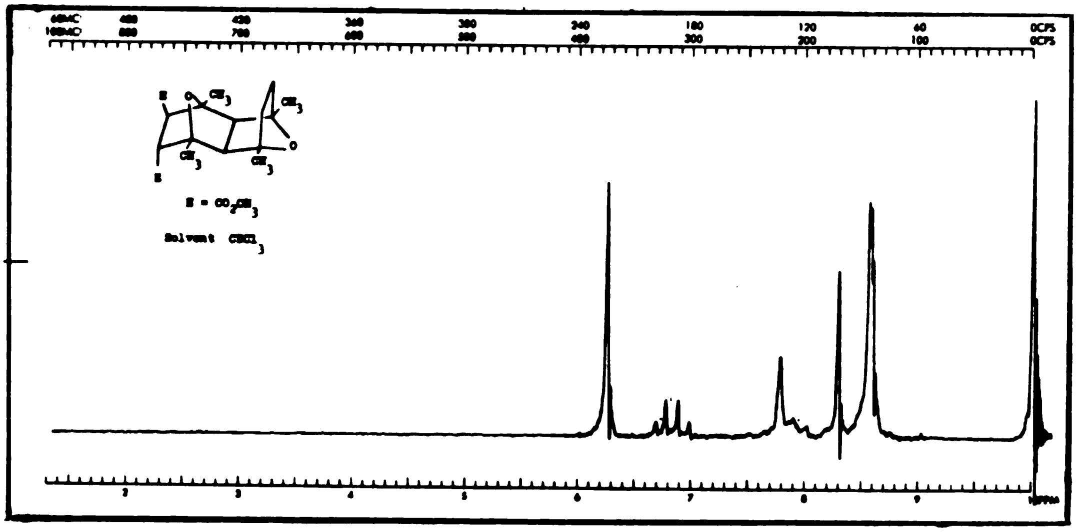

Figure 33. Nmr spectrum of trans-diester 73.

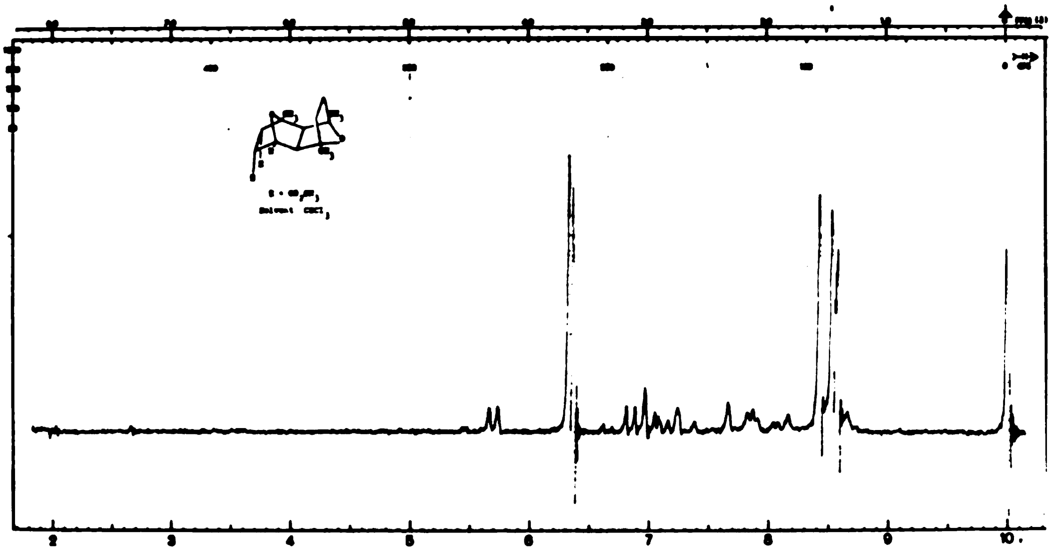

Figure 34. Nmr spectrum of compound 72.

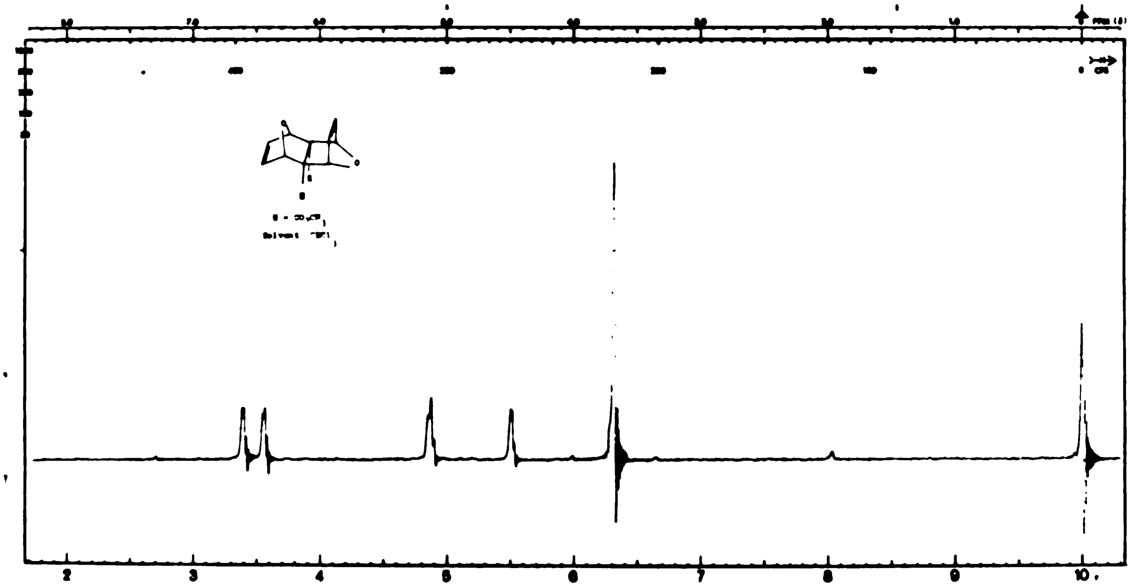

Figure 35. Nmr spectrum of adduct 34.

Figure 36. Nmr spectrum of adduct 38.

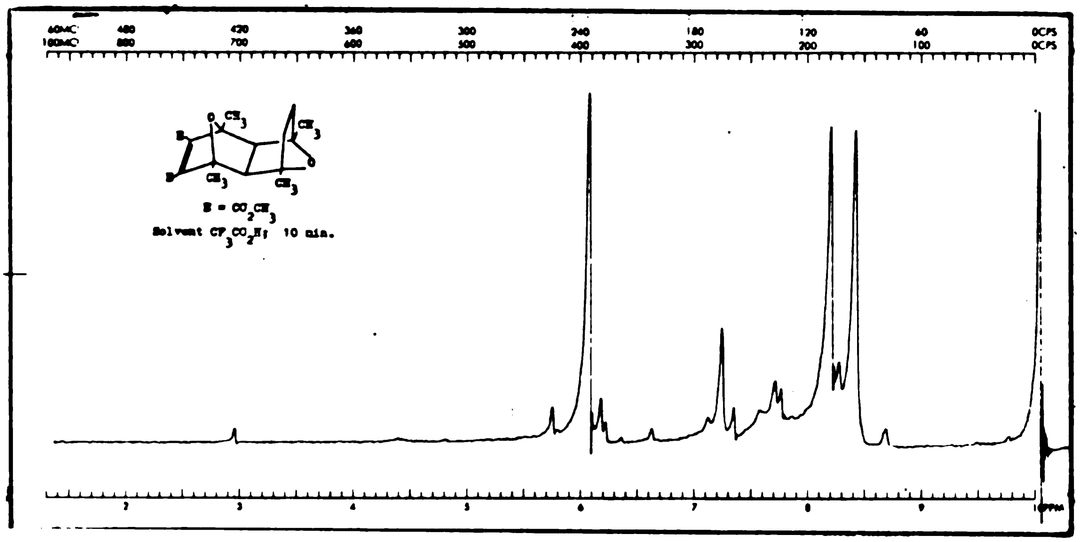

Figure 37. Nmr spectrum of adduct 63, after 10 minutes in trifluoroacetic acid.

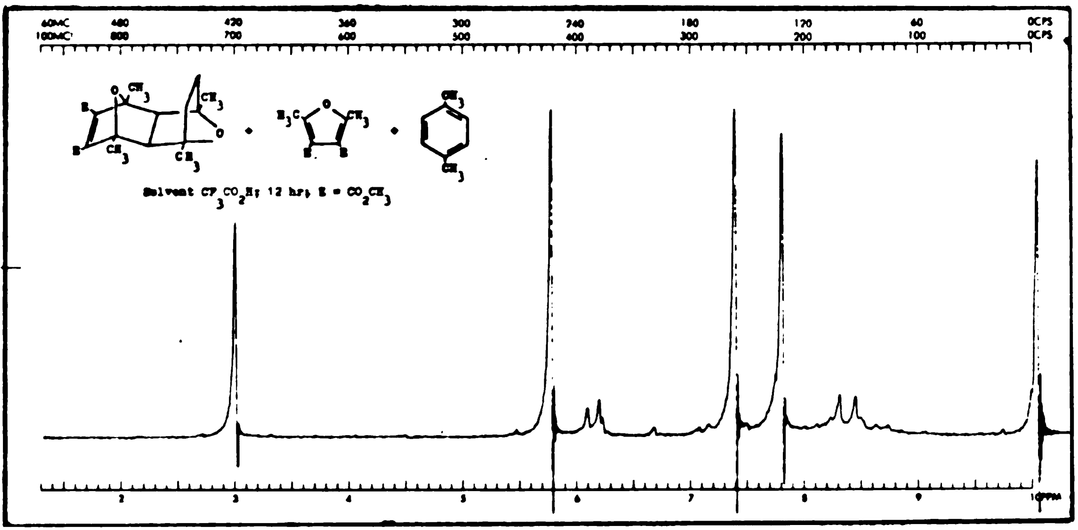

Figure 38. Nmr spectrum of adduct 63, after 10 hours in trifluoroacetic acid.

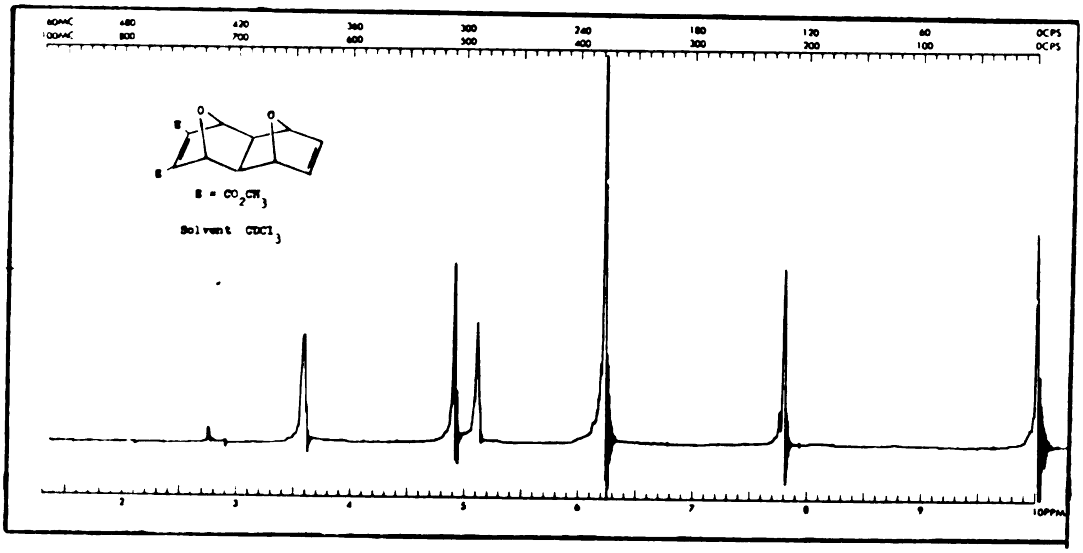

Figure 39. Nmr spectrum of adduct **37**.