A STUDY OF THE DIELS-ALDER ADDITION OF NITROSOBENZENE TO CYCLIC DIENONES

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SAMBHARAMADOM K. RAMASWAMI
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This is to certify that the

thesis entitled

A STUDY OF THE DIELS-ALDER ADDITION OF
NITROSOBENZENE TO CYCLIC DIENONES

presented by

Sambharamadom K. Ramaswami

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Harold Hart
Major professor

Date June 5, 1970

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ABSTRACT

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By

[illegible] [illegible] N. Ramaswami

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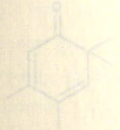

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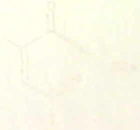

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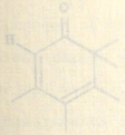

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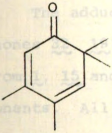

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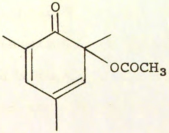

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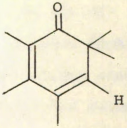

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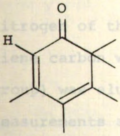

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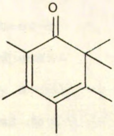

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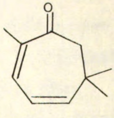

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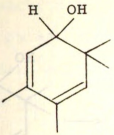

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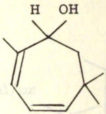
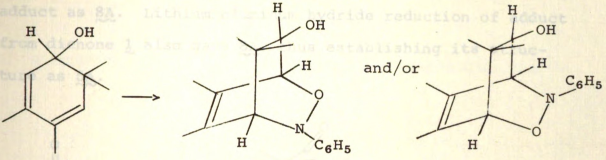


39

The number and position of the methyl groups in the dienones influenced their reactivity, stability of the product and orientation of addition. Among the dienones, 1 was the most reactive and 25 the least. Dienol 7 was exceptionally reactive and gave a single adduct, possibly due to hydrogen bonding between the hydrogen of the dienol O-H bond and the nitroso oxygen. This may lower the transition state energy for adduct formation.

The adducts from dienols 7 and 39 as well as the dienones 32, 19 and 21 were stable in solution, whereas those from 1, 15 and 25 showed a tendency to dissociate into components. All the adducts were thermally unstable and decomposed into the components almost quantitatively on heating, as during a vpc analysis.

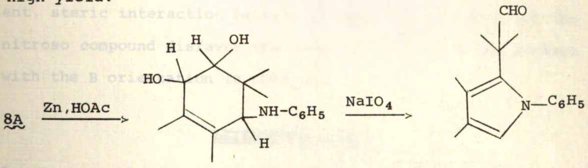
The orientation of addition (either the oxygen or the nitrogen of the nitrosobenzene may become attached to the diene carbon which is adjacent to the carbonyl or hydroxyl group) was elucidated by a combination of nmr spectral measurements and chemical degradation. For example, dienol 7 may give adduct 8A or 8B (neglecting the two epimeric possibilities for the alcohol function).



7 8A 8B

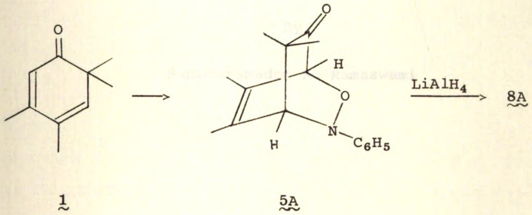
The bridgehead proton adjacent to the -CHOH group was a doublet and appeared at lower field than the other bridgehead proton, which was a singlet. Since Kresze[1] has shown that in 3,6-dihydro-1,2-oxazines the proton adjacent to oxygen appears at lower field than the proton adjacent to nitrogen, structure 8A was assigned.

Chemical degradation of the adduct from 7 supported the assignment based on the nmr spectrum. Cleavage of the N-O bond with zinc and acetic acid gave a monocyclic amino diol. Further oxidation with sodium metaperiodate gave an open-chain dialdehyde, which further underwent facile intramolecular cyclization and dehydration to give pyrrole 14 in high yield.



9 14

This reaction sequence established the structure of the adduct as 8A. Lithium aluminum hydride reduction of adduct from dienone 1 also gave 8A, thus establishing its structure as 5A.



Similar nmr correlations and chemical degradation established that the adducts from 15, 19, 32, and 39 all had the A orientation. Structures with the B orientation are favored for the nitrosobenzene adducts of 21 and 25.

In most cases the oxygen of the nitrosobenzene becomes attached to the diene carbon which has an adjacent electron-withdrawing oxygen function. In the absence of other factors, this electronic effect seems to control the orientation. However when C-5 of the dienone has a methyl substituent, steric interaction between it and the aryl group of the nitroso compound disfavor the usual orientation, and product with the B orientation is obtained.

LITERATURE CITED

1. G. Kresze and J. Firl, Tetrahedron, 24, 1043 (1968).

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A THESIS

Submitted to
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Dedicated to my wife Annam and to my
sons Kishan and Shankar

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The author wishes to thank Professor Harold Hart for his guidance and encouragement throughout the course of this investigation.

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INTRODUCTION

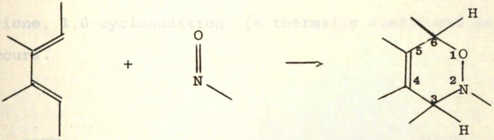
History

The use of dienophiles which contain hetero atoms in the Diels-Alder reaction has been the subject of many investigations in recent years and the results are discussed in review articles.[1-3] Nitroso compounds constitute one such class of dienophiles and two excellent reviews summarize the present knowledge with regard to the preparation of the adducts, kinetics of their formation, orientation of addition as well as the properties of the adducts and their usefulness as intermediates in synthesis.[4] Since the first reported addition of nitroso compounds to a 1,3-diene system by Dilthy and co-workers, numerous investigations have dealt with the use of nitroso compounds in the diene synthesis.[4] As a result of these investigations, many facts have been accumulated regarding the utility and the mechanism of the reaction.

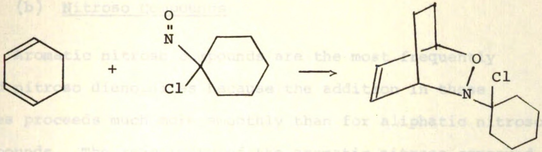
Scope of the Reaction

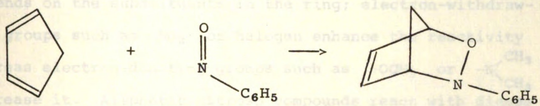
(a) Dienes

Much of the earlier work was carried out using 1- and 2-substituted butadienes. The reaction was found to proceed rapidly at room temperature in good yield and in a variety of solvents. 1,4-Disubstituted butadienes, however, were found to add rather slowly, probably due to steric reasons. In analogy with the diene synthesis using C=C dienophiles, the diene reactivity is influenced by the nature of the substituents on the diene.[5,6] Electron-withdrawing groups appreciably decrease the rate of addition. 2,3-Disubstituted dienes are also very reactive with nitroso compounds. The product of the reaction, in the case of a simple symmetrical aliphatic diene has a cyclic six-membered ring structure (a 3,6-dihydro-1,2-oxazine).

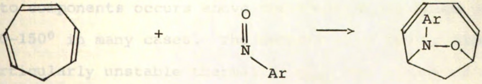


Cyclic dienes are converted to bridged bicyclic adducts. Thus cyclopentadiene, cyclohexadiene and its derivatives, and cyclooctadienes have been used;[7-9] the following examples are typical.





Cycloheptadiene gave no adducts,[8] whereas with cycloheptatriene, 1,6-cycloaddition (a thermally disallowed process) occurs.



(Ar = C_6H_4-p-Cl)

This has been explained[10] as a step-wise process, in which the first step was considered to be a nucleophilic attack by the cycloheptatriene on the positively polarized nitrogen atom.

(b) Nitroso Compounds

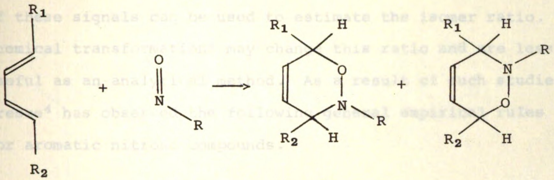
Aromatic nitroso compounds are the most frequently used nitroso dienophiles because the addition in these cases proceeds much more smoothly than for aliphatic nitroso compounds. The reactivity of the aromatic nitroso compound depends on the substituents in the ring; electron-withdrawing groups such as NO_2 or halogen enhance the reactivity whereas electron-donating groups such as $-OCH_3$ or $-N\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$ decrease it. Aliphatic nitroso compounds react with dienes only when the α-carbon atom carries an electron-withdrawing substituent, such as Cl, CN, CCl_3 or CF_3.

(c) Reversibility of the Reaction

As in the case of the C=C dienophiles, the diene addition with nitroso compounds is reversible. Cleavage into components occurs above the temperature range of 100-150° in many cases. The adducts with cyclic dienes are particularly unstable thermally; e.g. the adduct of cyclopentadiene with nitrosobenzene decomposes appreciably above 0°.

Orientation of Addition

When a nitroso compound adds to an unsymmetrically substituted butadiene, two positional isomers, having structures **A** and **B** may be obtained.



A

B

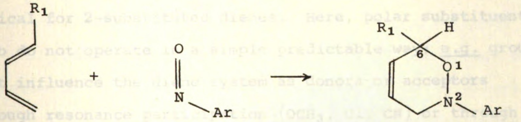
With vinyl compounds as dienophiles, the orientation of addition has been well-studied and the results are discussed in reviews.[6,12,13] The conclusion in this case is that the polarity of the addends is not the deciding factor in the orientation of addition.

The addition of nitroso compounds to 1,3-dienes offers an excellent opportunity to study orientation preferences in the Diels-Alder reaction. Since the addition proceeds smoothly with a large number of dienes under relatively mild conditions, the influence of various substituents on the diene or dienophile on the reaction rate and on the yield and orientation of the products can be investigated. In cases where both structural isomers A and B are formed, the more subtle influences caused by the variation of the substituents can be detected by using either chemical or spectroscopic methods to analyze the product mixtures. The nmr spectra of the isomeric adducts are very well differentiated, especially with regard to the signals of the protons at the 3- and 6-positions of the resulting

3,6-dihydro-1,2-oxazines. Integration of the intensities of these signals can be used to estimate the isomer ratio. Chemical transformations may change this ratio and are less useful as an analytical method. As a result of such studies, Kresze[4] has observed the following general empirical rules for aromatic nitroso compounds.

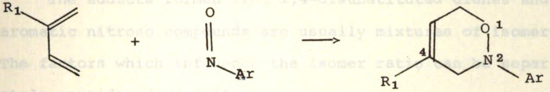
1-Substituted Dienes

The main product with all 1-substituted butadienes (except pentadiene, $R_1 = CH_3$) is the 6-substituted-3,6-dihydro-1,2-oxazine. Examples include R_1 = *t*-Bu, $CH_3\overset{O}{\overset{\|}{C}}O$, $CH_3\text{-}O\text{-}\overset{O}{\overset{\|}{C}}$, C_6H_5, *p*-$NO_2C_6H_4$, *p*-Cl-C_6H_4, *p*-CH_3-C_6H_4, *p*-$OCH_3C_6H_4$ and Ar = C_6H_5, *p*-Cl-C_6H_4 and *p*-CH_3-C_6H_4. Thus the orientation is governed mainly by steric factors; the transition state in which R_1 and Ar are remote from one another is favored.



2-Substituted Dienes

With all the 2-substituted butadienes, the 4-substituted adduct is obtained.



R_1 = CH_3, CF_3, Cl, CN, CH_3O, C_6H_5, p-$CH_3C_6H_4$, p-$CH_3OC_6H_4$;
Ar = C_6H_5, p-Cl-C_6H_4, p-$CH_3OC_6H_4$.

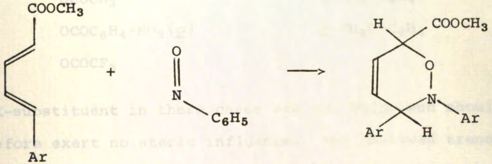
Whereas in the case of 1-substituted dienes, the isomer ratio can be attributed to steric factors, this cannot be logical for 2-substituted dienes. Here, polar substituents also do not operate in a simple predictable way; e.g. groups that influence the diene system as donors or acceptors through resonance participation (OCH_3, Cl, CN) or through their inductive effect (CH_3, CF_3) all lead to the same orientation. These results are similar to those obtained in the Diels-Alder reaction of dienes with vinylic dienophiles of structure CH_2=CHX (X is an electron-withdrawing group such as COOH, CN, Cl etc.); the carbon carrying the X-substituent is equivalent to the oxygen in the aromatic nitroso compound. At the moment there does not seem to be an adequate explanation for the marked orientation preference in additions to 2-substituted butadienes.

1,4-Disubstituted Dienes

The adducts formed from 1,4-disubstituted dienes and aromatic nitroso compounds are usually mixtures of isomers. The factors which influence the isomer ratio can be separately considered as follows:

(a) Steric Factors

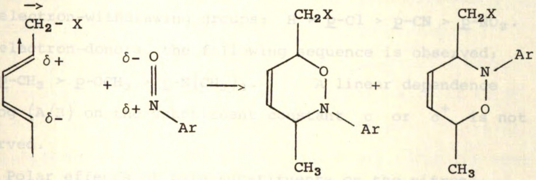
The isomer ratio is influenced by steric factors, when both substituents differ in their size. Since both the diene and the dienophile are arranged in parallel planes in the transition state, the difference in energy content for the transition states for the two isomers could be large for bulky substituents, with the result that one isomer may predominate substantially over the other. This is exemplified in the case of 4-arylbutadiene carboxylic acid methyl ester. In the series Ar = phenyl, α-naphthyl and 9-anthryl, the fraction of isomer A (in which the aryl residue and the N-aryl group are close to each other) decreases in this order from 80 to 74 to 5%.



A

(b) Polar Factors

A clear-cut separation of the polar influences is more difficult than the steric influences. However, some indications have been obtained in the case of the following sorbinol derivatives as the dienes:



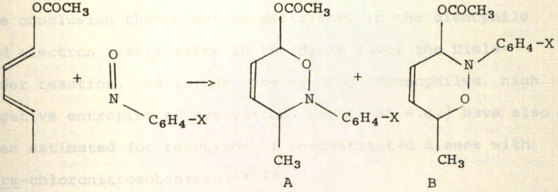
A B

X = OH
$OSi(CH_3)_3$
$OCOCH_3$
$OCOC_6H_4-NO_2$(p)
$OCOCF_3$

Ar = C_6H_5
p-$Cl-C_6H_4$
p-$CH_3-C_6H_4$
p-$CH_3O-C_6H_4$

The X-substituent in these cases are not bulky and should therefore exert no steric influence. The observed trend in orientation can be stated thus: the stronger the electron withdrawing nature of X, the greater the proportion of isomer A in which the O-atom of the N=O group is bound to the C-atom carrying the X-group in the product. This result is understandable if one considers that the inductive effect of the X-group polarizes the diene as indicated and bond formation occurs preferentially between the terminals with opposite polarities. However, the influence of polar effects is often complex as for example in the case of *para*-substituted 4-phenylbutadienecarboxylic acid esters in which steric influences do not vary. Here, the isomer ratio A/B in the product decreases according to the following sequence for electron-withdrawing groups: H > *p*-Cl > *p*-CN > *p*-NO_2. For electron-donors, the following sequence is observed: H > *p*-CH_3 > *p*-OCH_3 > *p*-$N(CH_3)_2$. A linear dependence of log (A/B) on the substituent constant σ or σ^+ is not observed.

Polar effects of *para*-substituents on the nitrosobenzene do not have any effect on the isomer ratio in the case of reaction of sorbinyl acetate with nitrosobenzenes.



X = *p*-Cl (A = 79%), H (A = 80.5%), *p*-CH_3 (A = 80.5%), *p*-OCH_3 (A = 82%)

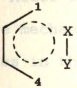
Kinetic Studies

The influence of structural changes on the kinetics of the Diels-Alder reaction have been investigated using nitroso compounds as the dienophile. The kinetics is second order up to 60-70% reaction;[14-17] beyond that, complications from side reactions occur. A Hammett study[16] of the reaction of 1,3-cyclohexadiene with substituted nitrosobenzenes showed that electron-withdrawing substituents increase the rate and electron-donating groups decrease it. Similar studies on aryl-substituted dienes have shown that the effect of substitution on the diene is considerably smaller than that in the case of the nitroso component. The ρ value for the reaction of cyclohexadiene with substituted nitrosobenzenes has been found to be +2.57 at 2^0 and for 2,3-dimethylbutadiene +2.51 at 25^0 when the reactions are carried out in methylene chloride. For the reaction of 1- and 2-phenylbutadienes with p-chloronitrosobenzene, the ρ values vary between -0.25 to -0.43 (at $15\text{-}44^0$). From these ρ values, there is support for the conclusion that electron deficiency in the dienophile and electron availability in the diene favor the Diels-Alder reaction. As in the case of C=C dienophiles, high negative entropies of activation (about -35 e.u.) have also been estimated for reactions of unsubstituted dienes with para-chloronitrosobenzene.[14,18]

Mechanism

The nature of the transition state in the reaction of dienes with nitrosobenzene has been discussed in detail by Kresze.[4] It is presumed that the diene and the dienophile are in two parallel planes and bond formation results from interaction of the bonding π-orbitals of the reacting components.[19] The extent of bond formation on the individual reacting center is, however, dependent on the particular structure of the components. Changes in the nature of the substituents on the diene or nitroso compound can influence the bonding in the transition state.

In principle, if the polarity of the dienophile X-Y is indicated as $\overset{\delta-}{X} - \overset{\delta+}{Y}$, then three limiting cases are possible.



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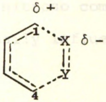

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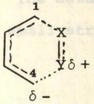


C

In A, simultaneous bond formation takes place at C_1 and C_4. Preferred bond formation at C_4 and partial charges at C_1 and X is indicated in B. The reverse situation, viz. preferred bond formation at C_1 and partial charges at C_4 and Y are shown in C. For aromatic nitroso compounds as dienophiles (X = O; Y = NAr), the observed orientation rules can be generally explained by the assumption that polar forms such as B do contribute to the structure of the transition state, although not to a large extent. The transition state, therefore, in the first approximation in all cases, can be described by means of the non-polar form A. The mechanism may vary within these limits according to the nature of the substituents. Contribution of the polar form C may be present only in the exceptional case of 1-arylbutadiene in which the <u>para</u>-position of the benzene ring has a -CN group and where the reaction rate is actually enhanced by this group, in comparison to, say, a CH_3 group.

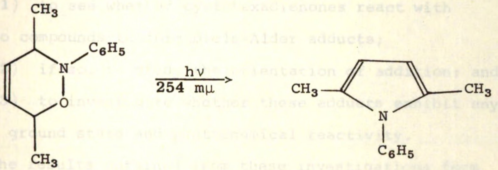
From these results, it is clear that one single mechanism cannot fully explain all the observations in the Diels-Alder reaction with nitroso compounds. The details of the mechanism can be easily influenced by small structural changes in the components.

Synthetic Utility

From a synthetic point of view, the Diels-Alder reaction with nitroso compounds provides an easy route to a variety of heterocyclic structures. The adducts undergo facile transformations with various simple reagents and thus lead to many heterocyclic ring systems[4] which are otherwise accessible only with difficulty.

Photochemistry

There has been great interest in recent years in the photochemistry of N-containing heterocyclic compounds. A recent article[20] which appeared while the present work was in progress deals with the photochemistry of simple 3,6-dihydro-1,2-oxazines resulting from the Diels-Alder reaction of substituted 1,3-butadienes with nitrosobenzene. The following reaction is typical:



The reaction has been claimed to be useful in the synthesis of substituted pyrroles. The photochemistry of bridged bicyclic 1,2-oxazines has not been reported so far.

Present Work

Conjugated cyclohexadienones have been the subject of intensive studies in the past several years in our laboratory. New methods have been discovered for preparation of various alkyl-substituted cyclohexadienones, and from these, many such compounds have now become easily available.[21-23] Also under exhaustive study is the photochemistry of these dienones and their Diels-Alder adducts. The dienones form adducts with a variety of dienophiles, e.g. maleic anhydride,[21] dimethyl acetylenedicarboxylate,[24] diethyl azodicarboxylate,[21] benzynes,[24] 2-butyne,[25] diphenylacetylene,[24] vinyl acetate,[26] etc. The dienones, the adducts, and their derivatives undergo interesting rearrangements when subjected to ultraviolet irradiation.[21-23,26-32]

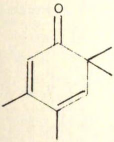
In the light of these interesting observations, the present work was undertaken with the following aims:

(1) to see whether cyclohexadienones react with nitroso compounds to form Diels-Alder adducts;

(2) if so, to study the orientation of addition; and

(3) to investigate whether these adducts exhibit any useful ground state and photochemical reactivity.

The results obtained from these investigations form the subject matter of this thesis. By using nitrosobenzene as the dienophile, Diels-Alder adducts have been prepared from the following dienes: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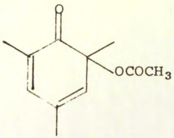

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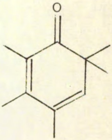
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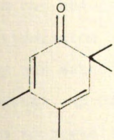
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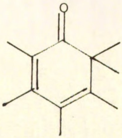
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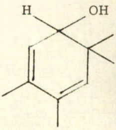

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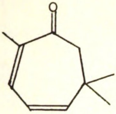

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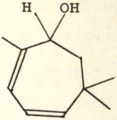

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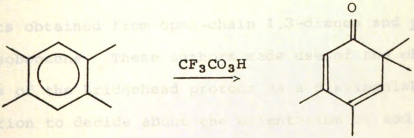
The structure elucidation of these adducts is discussed in detail in the Results and Discussion section of this thesis. Preliminary studies on the photochemistry of these adducts indicate that they are photochemically reactive.

RESULTS

The Diels-Alder Adduct from 3,4,6,6-Tetramethyl-2,4-cyclohexadienone (1) and Nitrosobenzene: N-Phenyl-7-oxa-8-aza-3,3',5,6-tetramethylbicyclo[2.2.2]oct-5-ene-2-one

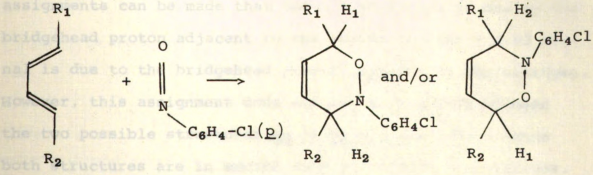
A simple cyclohexadienone available for the Diels-Alder studies appeared to be the tetramethyl derivative, viz., 3,4,6,6-tetramethyl-2,4-cyclohexadienone 1, which is easily prepared from durene.[22] The 2- and 5-positions in this dienone have hydrogens as substituents, and these, after



1

the Diels-Alder reaction, will form the bridgehead positions in the adduct. This should make the assignment of the orientation of the N and O in the adduct relatively easy by nmr methods. The tetramethyldienone 1 formed a single adduct, mp 62-63°, in 51% yield. When attempts were made to recrystallize this product, however, partial dissociation into the components was observed, as indicated by the appearance in solution of the green color of nitrosobenzene. This was a serious problem while working with this adduct in solution. A recrystallized sample from pentane had nmr signals (Figure 1) at τ 5.92 (singlet, 1H) and 5.63 (singlet, 1H) due to the bridgehead protons and two quartets ($\underline{J}$ = 1.2 Hz) at τ 8.53 and 8.15 respectively due to the allylic methyl groups, in addition to the aromatic protons (5H) at 2.7-3.2. The question about the correct assignment of the chemical shifts of the bridgehead protons was solved by a combination of methods such as analogy to literature, labeling experiments and reduction of the carbonyl group to the alcohol.

The nmr results were compared with those obtained by Kresze and co-workers[33] in their extensive studies with adducts obtained from open-chain 1,3-dienes and p-chloronitrosobenzene. These authors made use of the chemical shifts of the bridgehead protons as a distinguishing criterion to decide about the orientation of addition of the dienophile to the diene. As a general case, if a 1,3-diene such as 2 reacts with p-chloronitrosobenzene 3, the two possible structures can be represented by 4A and 4B.



2 3 4A 4B

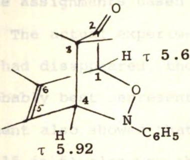
Starting with various dienes having different substituents R_1 and R_2, the authors prepared the corresponding adducts and elucidated the structures by chemical degradation. Thus, from a knowledge of the orientation of addition from chemical evidence, a correlation between the nmr chemical shifts of the bridgehead protons and the structures corresponding to them was obtained. Some typical results are tabulated in Table I.

From the table, it is evident that the proton adjacent to the oxygen, i.e., $H^{(1)}$ is deshielded more than that adjacent to the nitrogen, i.e., $H^{(2)}$, and that attachment of electron withdrawing groups to the carbon atoms carrying these protons enhances this deshielding effect. It would be expected from these findings that in the [2.2.2] bridged heterocyclic systems formed from cyclohexadienones, the same effect would be present with the result that the bridgehead proton adjacent to oxygen would be deshielded relative to that adjacent to nitrogen.

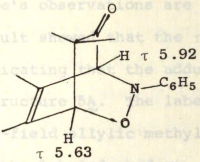
The bridgehead protons in the adduct from tetramethyldienone 1 show signals at τ 5.63 and 5.92. If the Kresze correlations are applicable in this bridged system, the assignments can be made that the τ 5.63 signal is due to the bridgehead proton adjacent to the oxygen and the τ 5.92 signal is due to the bridgehead proton adjacent to the nitrogen. However, this assignment does not serve to decide between the two possible structures 5A or 5B for the adduct since both structures are in accord with the Kresze correlations.

Table I. Chemical shifts of the ring protons signals in the nmr spectra of 3,6-dihydro-1,2-oxazines

R_1	R_2	H^1 [C$\underline{\text{H}}$(O)]	H^2 [C$\underline{\text{H}}$(N)]
(a) Adducts with structure 4A from 1-substituted dienes			
H	H	5.59	6.29
Me	H	5.43	6.32
CMe_3	H	5.75	6.30
COOMe	H	5.02	6.24
Ph	H	4.55	6.29
OCOMe	H	3.68	6.34
(b) Adducts with structure 4A from 1,4-substituted dienes			
Ph	Me	4.54	5.92
Ph	$CHMe_2$	4.77	6.27
Ph	Ph	4.40	4.99
COOMe	Me	5.02	6.05
CH=CH-COOMe	Me	4.87	5.97
CN	Me	4.95	6.08
$CONH_2$	Me	4.98	5.95
CH_2COOMe	Me	5.37	6.05
COOMe	COOMe	4.95	5.25
COOMe	Ph	4.98	5.12
CN	Ph	4.90	5.14
(c) Adducts with structure 4B			
Me	H	5.70	6.08
COOMe	Ph	4.54	5.20
COOMe	α-Furyl	4.45	5.22

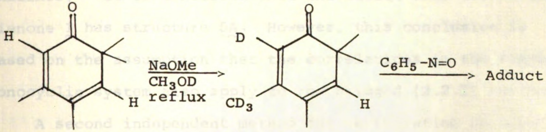


5A



5B

This question was unambiguously resolved by labeling the starting tetramethyldienone 1 with deuterium at C_2 by heating under reflux with sodium methoxide in methanol-d (CH_3OD).



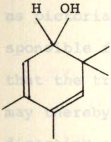
1 6

The resulting labeled dienone 6 had deuterium at the positions indicated, as revealed by nmr. The τ 4.32 broad signal and the τ 7.98 quartet[22] were absent in the spectrum of the labeled dienone 6. This was then reacted with nitrosobenzene and the nmr spectrum of the resulting adduct was examined. If the adduct had structure 5A, the τ 5.63 signal should disappear; if it had structure 5B, the τ 5.92 signal should disappear. Thus this experiment enables an easy distinction between the two possible structures, provided that the assignments based on Kresze's observations are valid. The actual experimental result showed that the τ 5.63 signal had disappeared, thereby indicating that the adduct was probably best represented by structure 5A. The labeling experiment also showed that the low-field allylic methyl at τ 8.15 in 5A also was absent in the labeled product, thus enabling a clear-cut assignment to this methyl as the one attached to C-7 in the adduct. This result is significant and will be considered in greater detail later.

Thus by analogy to Kresze's correlations of chemical shifts of the ring proton signals in simple 3,6-dihydro-1,2-oxazines,[33] it is concluded that the adduct from tetramethyldienone 1 has structure 5A. However, this conclusion is based on the assumption that the correlations in the simple monocyclic system also apply to the bridged [2.2.2] system.

A second independent method for verification of these chemical shift assignments was accomplished by reducing the dienone 1 to the dienol 7 with lithium aluminum hydride and conversion to an adduct with nitrosobenzene. The formation of the adduct from the dienol was complete in 2 hr at 0°. This is in contrast to the lesser reactivity of the dienone 1, which required at least 4 hr at room temperature. The enhanced reactivity may be explained as arising out of the improved dienic character of the dienol. The adduct, obtained in 78% yield, could be recrystallized conveniently from pentane (mp 82-83°). It was thermally quite stable, could be purified in good yield by sublimation, and did not show any evidence of dissociation in solution.

The nmr spectrum (Figure 2) was particularly helpful in assigning a structure to the adduct. The low-field bridgehead proton appeared at τ 5.77 as a doublet ($\underline{J}$ = 1.6 Hz) as a result of coupling with the adjacent C$\underline{H}$-OH proton. This coupling requires that the low-field bridgehead proton be adjacent to the hydroxyl-bearing carbon. The high-field bridgehead proton appeared as a singlet at τ 6.47. A noteworthy feature in the spectrum is the greater separation between the two bridgehead protons (0.7 ppm) whereas in the spectrum of the dienone-adduct, this separation was only about 0.3 ppm. These differences in the chemical shifts of the bridgehead protons in the two adducts are somewhat surprising and may be attributed to subtle changes in the conformation of the molecule and the resultant ring strain while going from the dienone-adduct having an sp^2 hybridized carbon in the bridge to the dienol-adduct in which this is absent. The Kresze correlations may be more valid in the case of the dienol-adduct, and if this is true, structure **8A** should be more favored than **8B** for the dienol-adduct.



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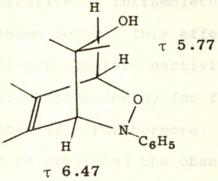
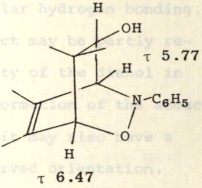
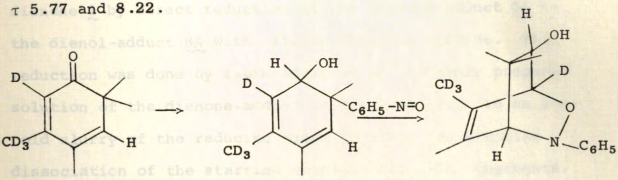


8A



8B

The allylic methyls in the adduct showed signals at τ 8.62 and 8.22 as quartets ($\underline{J}$ = 1.2 Hz). Reduction of the labeled dienone 6 with lithium aluminum hydride and conversion of the resulting labeled dienol to an adduct was then carried out to confirm the nmr assignments. The nmr spectrum of the labeled dienol-adduct lacked the signals at τ 5.77 and 8.22.



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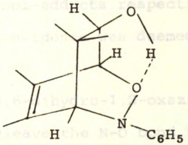
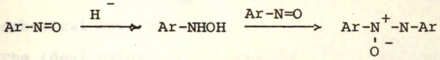
8A

The ir spectrum of the dienol-adduct (in very dilute solution in carbon tetrachloride) showed the O-H absorption as a fairly sharp band at 3576 cm^{-1} which did not change position on dilution, indicative of intramolecular hydrogen bonding, as pictorially shown below. This effect may be partly responsible for the spectacular reactivity of the dienol in that the transition state energy for formation of the adduct may thereby be lowered. Furthermore, it may also have a directing effect in obtaining the observed orientation.



8A

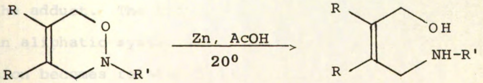
The orientation of addition of nitrosobenzene to the dienol 7 has been shown to be the same as that to the dienone 1 by direct reduction of the dienone-adduct 5A to the dienol-adduct 8A with lithium aluminum hydride. This reduction was done by rapid addition of a freshly prepared solution of the dienone-adduct in ice-cold ether to an ice-cold slurry of the reducing agent in ether, to minimize dissociation of the starting material into the components. Dissociation of the dienone-adduct to the components, reduction of the dienone to the dienol and formation of the adduct within this short time is unlikely; moreover, the nitrosobenzene would also be reduced under these conditions to hydroxylamine (which further condenses with nitrosobenzene to azoxybenzene very rapidly)[34] and thus would not be available for reaction with the dienol.



$$\mathrm{Ar{-}N{=}O} \xrightarrow{\mathrm{H}^{-}} \mathrm{Ar{-}NHOH} \xrightarrow{\mathrm{Ar{-}N{=}O}} \mathrm{Ar{-}}\underset{\mathrm{O}^{-}}{\mathrm{N}^{+}}\mathrm{{-}N{-}Ar}$$

Thus, assuming that the Kresze correlations are also applicable to the [2.2.2] bridged systems, the nmr evidence strongly supports structures 5A and 8A for the dienone- and the dienol-adducts respectively. However, independent chemical evidence was deemed desirable to support this assumption.

In the simple 3,6-dihydro-1,2-oxazine systems, the earliest method to cleave the N-O bond is the one used by Arbuzov and his co-workers[35], viz. reduction with zinc and acetic acid, to form an amino alcohol.



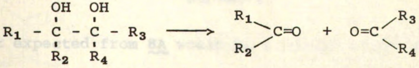
The dienol-adduct was found to be well suited for this type of degradation since it did not dissociate into its components under the conditions of the reduction. Moreover, the resulting amino diol turned out to be a key intermediate suitable for further degradation. The bicyclic adduct, now designated as 8A from nmr evidence, was reduced with zinc and acetic acid and gave an oily product having all the spectral characteristics of the expected amino diol 9 (Note: the formulas 8-12 in Scheme I do not have any stereochemical implications).

The ideal oxidant to cleave the resulting α-glycol (or α-amino alcohol from structure 8B) appeared to be sodium metaperiodate (the Malaprade reaction)[36], since the oxidation is fast and specific, requires only very mild conditions, produces no side-products, and above all, work-up is simple.

The crude amino diol obtained from zinc-acetic acid reduction of the dienol-adduct 8A reacted rapidly with the reagent, as shown by the formation of a precipitate of sodium iodate. Thus, reduction with zinc and acetic acid followed by cleavage with sodium metaperiodate appeared to be a useful sequence of reactions to determine the structure of the adduct. The bicyclic system can thus be opened up to an aliphatic system with great ease and further characterization becomes relatively a simple matter.

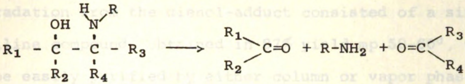
The reaction of periodates with α-glycols and α-amino alcohols in general is outlined in the following equations:[36]

α-glycols:



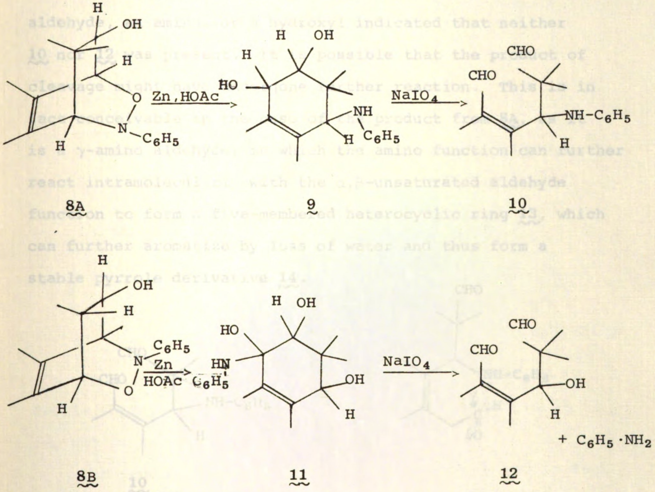
$$R_1-\overset{\displaystyle OH}{\underset{\displaystyle R_2}{C}}-\overset{\displaystyle OH}{\underset{\displaystyle R_4}{C}}-R_3 \longrightarrow \begin{matrix}R_1\\R_2\end{matrix}\!\!>C=O \;+\; O=C\!<\!\!\begin{matrix}R_3\\R_4\end{matrix}$$

α-amino-alcohol (N-secondary amine)



$$R_1-\overset{OH}{\underset{R_2}{C}}-\overset{HNR}{\underset{R_4}{C}}-R_3 \longrightarrow \begin{matrix}R_1\\R_2\end{matrix}\!>C=O + R-NH_2 + O=C\!<\!\begin{matrix}R_3\\R_4\end{matrix}$$

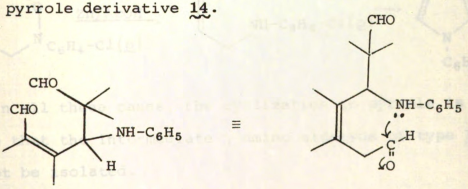
The expected cleavage products from each of the structures 8A and 8B are given in Scheme I.



Scheme I

Product expected from 8A would be a single amino aldehyde, whereas that from 8B would consist of two fragments, a hydroxy dialdehyde and aniline.

The actual product isolated from this two-step sequence of degradation from the dienol-adduct consisted of a single crystalline compound, obtained in 87% yield mp 59-60^0, which could be easily purified by either column or vapor phase chromatography. The ir spectrum (Figure 17) showed characteristic bands of an aliphatic aldehyde at 1715 and 2720 cm^{-1}. The absence of absorption typical of an α,β-unsaturated aldehyde, an amine, or a hydroxyl indicated that neither 10 nor 12 was present. It is possible that the product of cleavage might have undergone further reaction. This is in fact conceivable in the case of the product from 8A, as it is a γ-amino aldehyde, in which the amino function can further react intramolecularly with the α,β-unsaturated aldehyde function to form a five-membered heterocyclic ring 13, which can further aromatize by loss of water and thus form a stable pyrrole derivative 14.



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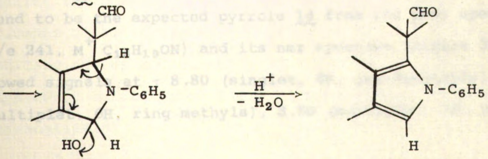
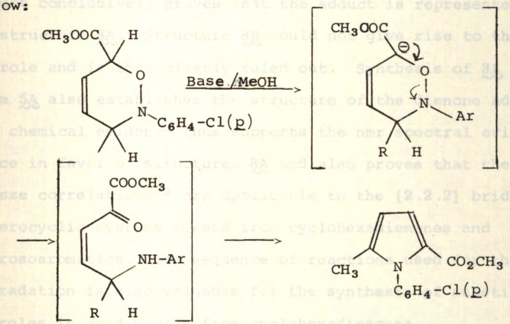
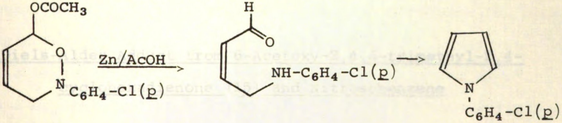


13

14

Many examples of such intramolecular reaction to form pyrroles from 3,6-dihydro-1,2-oxazines have been reported by Kresze and co-workers.[37] Two typical examples are given below:





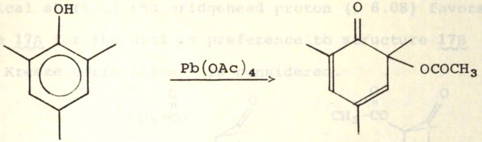
In all these cases, the cyclization to pyrrole is so facile that the intermediate γ-amino aldehyde of type 10 can not be isolated.

The product obtained from the dienol-adduct was in fact found to be the expected pyrrole 14 from its mass spectrum (m/e 241, M^+ $C_{16}H_{19}ON$) and its nmr spectrum (Figure 3), which showed signals at τ 8.80 (singlet, 6H, gem-dimethyls), 8.00 (multiplet, 6H, ring methyls), 3.60 (multiplet, 1H, ring proton), 2.68 (multiplet, 5H, benzene protons) and 0.62 (singlet, 1H, aldehyde proton).

The degradative formation of a pyrrole from the dienol-adduct conclusively proves that the adduct is represented by structure 8A. Structure 8B could not give rise to the pyrrole and is thus clearly ruled out. Synthesis of 8A from 5A also establishes the structure of the dienone adduct. The chemical evidence thus supports the nmr spectral evidence in favor of structures 8A and also proves that the Kresze correlations[33] are applicable to the [2.2.2] bridged heterocyclic systems formed from cyclohexadienones and nitrosoaromatics. The sequence of reactions used for this degradation is also valuable for the synthesis of substituted pyrroles in good yields from cyclohexadienones.

The Diels-Alder Adduct from 6-Acetoxy-2,4,6-trimethyl-2,4-cyclohexadienone (15) and Nitrosobenzene

The next cyclohexadienone chosen for Diels-Alder reaction with nitrosobenzene was the 6-acetoxy-2,4,6-trimethyldienone 15. The substitution pattern of this dienone is quite different from that of the tetramethyldienone 1, thus offering the possibility for further understanding of the influence of substituents on the reactivity of the dienone, stability of the adduct, etc. The dienone was readily prepared by oxidation of 2,4,6-trimethylphenol with lead tetraacetate:[38]



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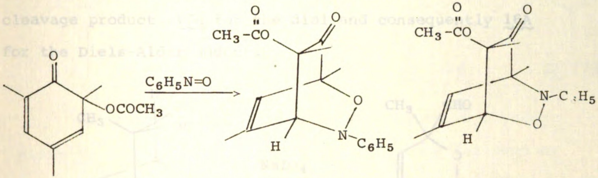
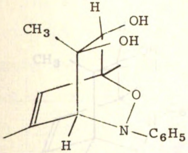
The Diels-Alder adduct is formed when the components are mixed and stirred together in a solvent for 9 hr at room temperature. The stability of the adduct was found to be the lowest of all the adducts prepared in this series. Simple dissolution of the adduct in most solvents resulted in partial dissociation into components as judged by the formation of the green color of the dienophile. Hence nmr spectral determination was hampered by the appearance of signals due to the starting dienone (Figure 4). Reduction of the adduct with lithium aluminum hydride in ether at 0° gave a crystalline diol having considerably better stability. It could be purified by sublimation to a stable solid mp 94-95°. The nmr spectrum of this diol (Figure 5) could be analyzed since there was no evidence of any dissociation in solution. The only bridgehead proton in the diol showed a signal as a doublet at τ 6.08 ($\underline{J}$ = 1.8 Hz) due to coupling with the vinylic proton); the other signals were at τ 8.80 (singlet, 3H), 8.50 (doublet, $\underline{J}$ = 1.4 Hz, 3H, allylic methyl), 8.45 (singlet, 3H), 7.08 (broad, 1H), 6.33 (broad, 1H), 5.73 (broad, 1H), 4.27 (broad, 1H, olefinic proton) and multiplet at τ 3.05 (5H, aromatic protons).

The chemical shift of the bridgehead proton (τ 6.08) favors structure 17A for the diol in preference to structure 17B when the Kresze correlation[33] is considered.

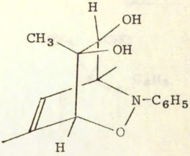


15　　　16A　　　16B



τ 6.08

17A



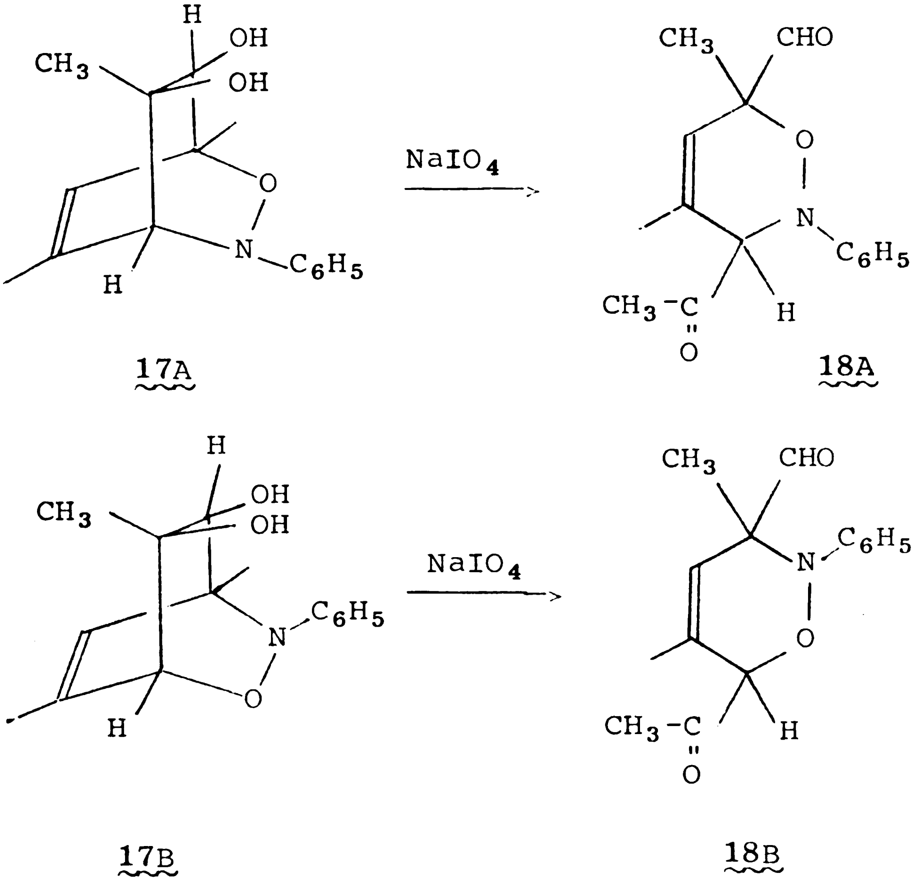
τ 6.08

17B

(Note: No stereochemistry is implied in these structures.)

The diol 17A was further degraded by using sodium metaperiodate. The cleavage products expected from 17A and 17B are indicated in Scheme II given below:

The nmr spectrum of the cleavage product (Figure 6) showed a broad singlet at τ 5.63 for the tertiary hydrogen which previously was at the bridgehead position in the diol. In structure 18B, the proton signal would be expected to be shifted farther downfield, from comparisons with the chemical shifts of similar compounds recorded in Table I. Thus, from nmr evidence, **18A** is the favored structure for the cleavage product, **17A** for the diol and consequently **16A** for the Diels-Alder adduct.



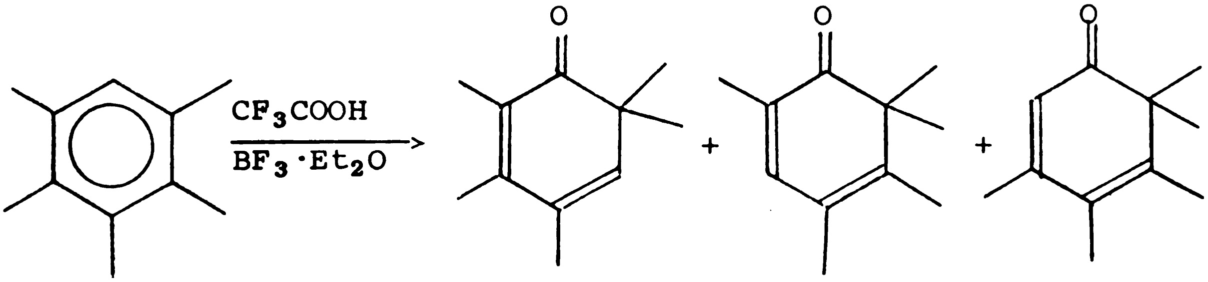
17A **18A**

17B **18B**

Scheme II

The Diels-Alder adduct from 2,3,4,6,6-Pentamethyl-2,4-cyclohexadienone (**19**) and Nitrosobenzene

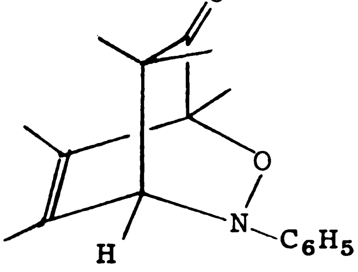
Oxidation of pentamethylbenzene with trifluoroperacetic acid yields a mixture of pentamethyldienones (**19** to **21**) in the yields indicated:[23]



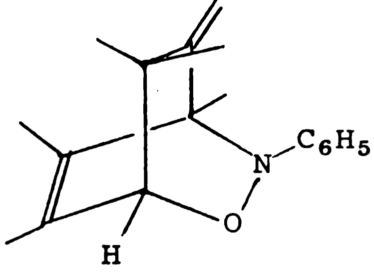
19 (37%) 20 (33%) 21 (7%)

The individual dienones can be isolated in a pure state by a preliminary column chromatography followed by preparative scale vapor phase chromatography. Sufficient amounts of dienones 19 and 21 were prepared by this method for the Diels-Alder reaction with nitrosobenzene.

The 2,3,4,6,6-pentamethyldienone (19) formed an adduct, mp 99-100^{0}, in 38% yield on refluxing a solution of the dienone and nitrosobenzene in methylene chloride. The nmr spectrum (Figure 7) had signals at τ 8.87, 8.55 and 8.50 (all singlets, 3H each), 8.52 and 8.33 (quartets, J = 1.2 Hz, allylic methyls), 5.98 (broad singlet, 1H, bridgehead proton), and τ 2.95-3.1 (multiplet, 5H, aromatic protons). Considering the chemical shift of the bridgehead proton signal at τ 5.98, application of the Kresze's correlations indicates that structure 22A is favored over structure 22B.

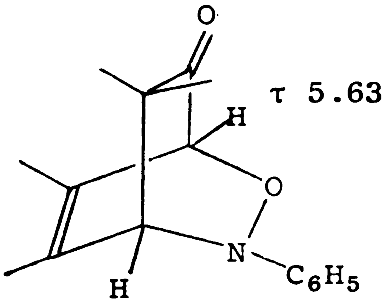


22A



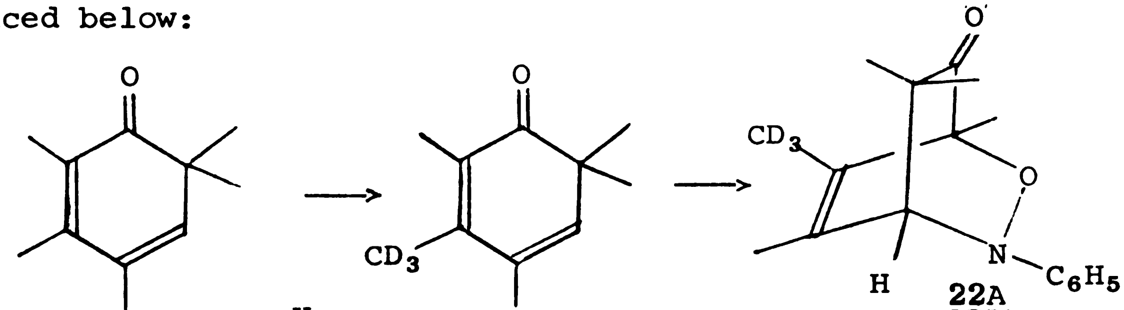
22B

This conclusion is mainly based on the similarity to the chemical shift of the bridgehead proton in adduct **5A** obtained from tetramethyldienone **1**, reproduced below.

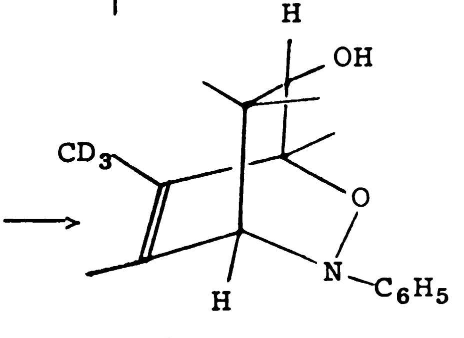


5A

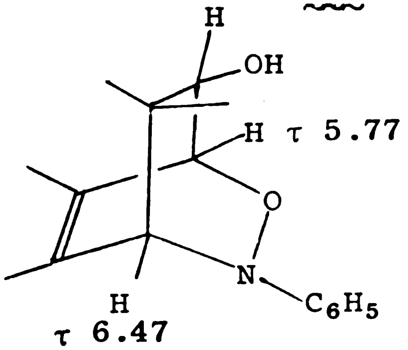
Labeling **19** at C-3 with CD_3 by deuterium exchange, and formation of adduct indicated exclusive formation of one crystalline isomer, the nmr spectrum of which did not have the low-field allylic methyl at τ 8.33. This result is similar to that for adduct **5A** from the tetramethyldienone **1**. The adduct **22A** was reduced with lithium aluminum hydride in ether solution at 0^0 to the corresponding alcohol (**23A**) in almost quantitative yield. There was no evidence of dissociation when 22A was dissolved in ether, in sharp contrast with 5A. Recrystallization of the reduced product from pentane gave a solid, mp 113-114° whose nmr spectrum (Figure 8) indicated it to be pure 23A. It had signals at τ 9.03 (singlet, 3H), 8.73 (singlet, 3H), 8.60 (quartet, J = 1.2 Hz, 3H), 8.55 (singlet, 3H), 8.32 (quartet, J = 1.2 Hz, 3H), 7.88 (broad, 1H), 7.05 (broad, 1H), 6.43 (singlet, 1H) and 2.73-3.23 (multiplet, 5H). The chemical shift of the bridgehead proton signal at τ 6.43 is very similar to that in 8A reproduced below:



22A



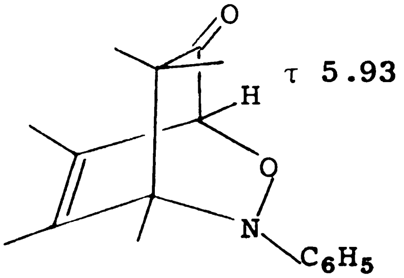
23A



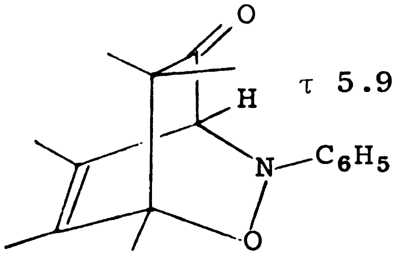
8A

The Diels-Alder Adduct from 3,4,5,6,6-Pentamethyl-2,4-cyclohexadienone (21) and Nitrosobenzene

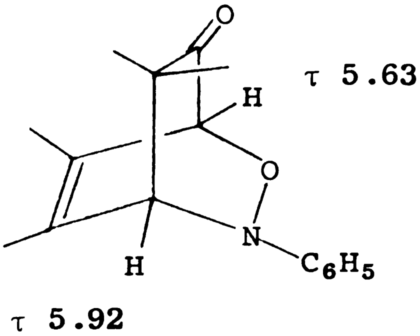
The pentamethyldienone (21) is the most polar of all the pentamethyldienones, possibly because of the lack of methyl substitution at the 2-position; it is eluted last from chromatographic columns. Dienone (21) formed an adduct, mp 70^{0}, in low yields. The nmr spectrum of the adduct (Figure 9) had signals at τ 9.07 (singlet, 3H), 8.83 (singlet, 3H), 8.60 (singlet, 3H), 8.52 (quartet, *J* = 1.1 Hz, 3H), 8.23 (quartet, *J* = 1.1 Hz, 3H), 5.93 (singlet, 1H, bridgehead proton), and 2.7-2.9 (multiplet, 5H). The appearance of the bridgehead proton signal at τ 5.93 indicates that structure 24B is preferred to 24A when chemical shifts of the bridgehead protons in 5A, and 22A are also taken into consideration.



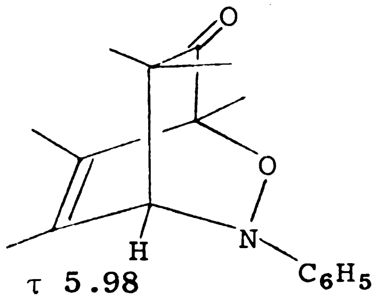
24A



24B



5A

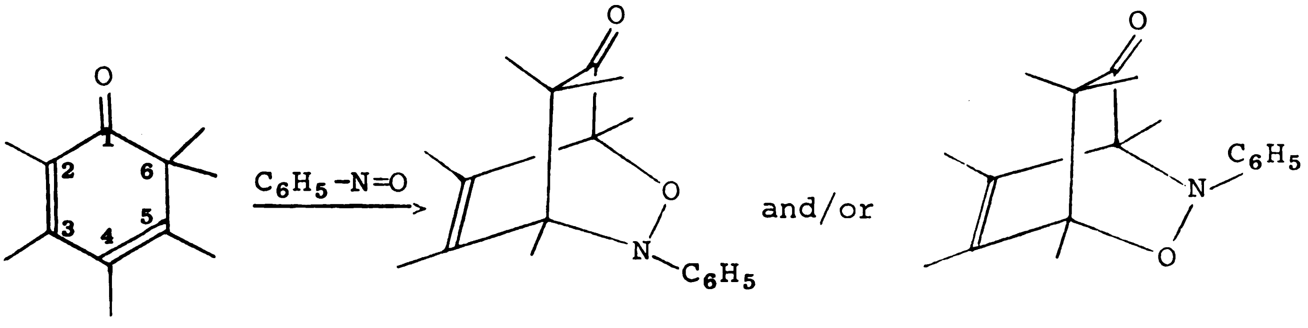


22A

Thus it appears from the nmr evidence alone, that these two dienones, *viz*., 19 and 21 (the 5H- and 2H-pentamethyldienones respectively) differ in their mode of addition to nitrosobenzene. A property which may in some way explain this is the observed difference in polarities between these dienones, as indicated during both column and vapor phase chromatography.

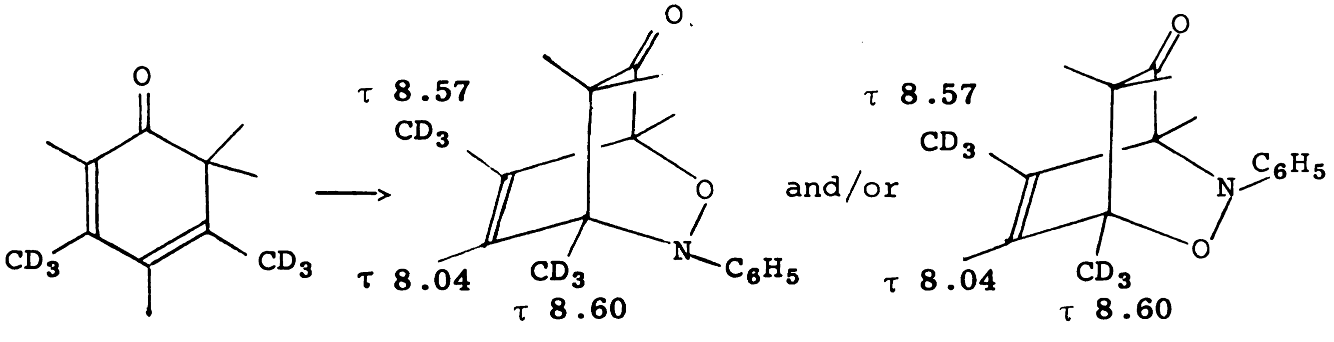
The Diels-Alder Adduct from 2,3,4,5,6,6-Hexamethyl-2,4-cyclohexadienone (**25**) and Nitrosobenzene

2,3,4,5,6,6-Hexamethyl-2,4-cyclohexadienone **25** [21,39] reacts with nitrosobenzene when the components are dissolved in a solvent such as 1,2-dichloroethane and refluxed for 2 hr. The crystalline adduct, mp 78-79°, is obtained in about 50% yield. The nmr spectrum (Figure 10) had signals at τ 9.03, 8.89, 8.76, 8.60 (all singlets, 3H each, methyls), 8.57 and 8.04 (quartets, *J* = 1.2 Hz, 3H each, allylic methyls), and 2.94-3.00 (multiplet, 5H, aromatic protons).



25 **26A** **26B**

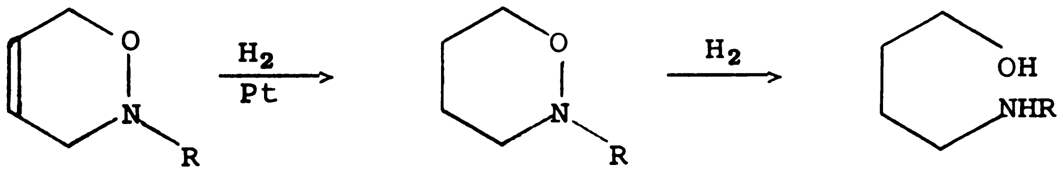
Labeling the starting dienone **25** with deuterium at the C-3 methyl group[21] and conversion of the labeled dienone to the adduct showed that the τ 8.57 quartet was absent in the nmr spectrum of the product. Labeling at both the 3- and 5-positions of the starting dienone[21] showed that both the τ 8.57 and the 8.60 signals disappeared. This enables assignment of these two signals as follows in both 26A and 26B.



25 26A 26B

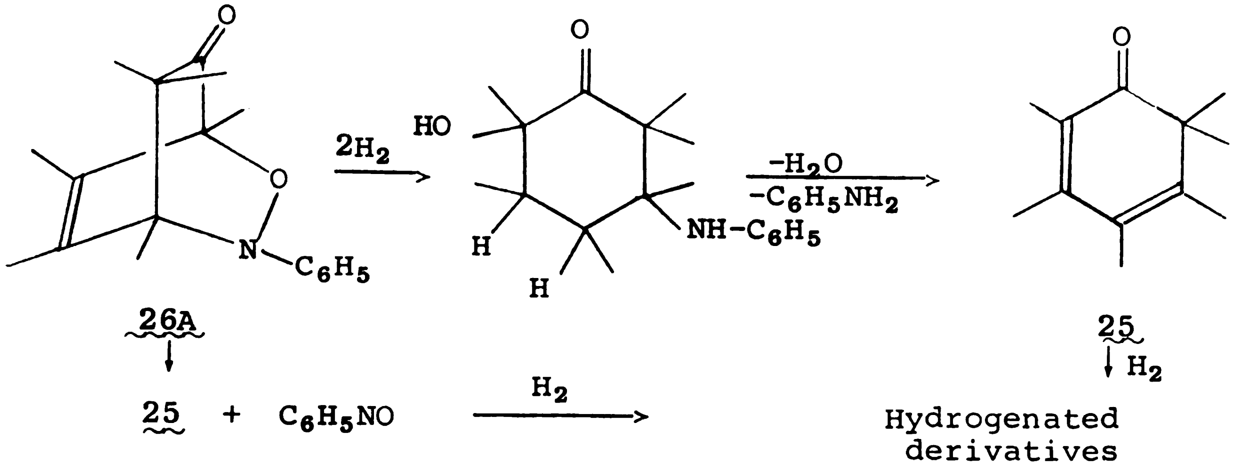
It is significant here that labeling at C-3 of the dienone removes the high-field allylic methyl signal at τ 8.57 from the nmr spectrum of the adduct. (Similar labeling of tetramethyldienone 1 at C-3 and conversion to the nitrosobenzene adduct resulted in removal of the low-field allylic methyl signal, at τ 7.98.)

One of the methods used to degrade simple six-membered ring 3,6-dihydro-1,2-oxazines is catalytic hydrogenation.[4] The reaction path is shown below:



It is thus possible to cleave the N-O bond and obtain an open-chain amino alcohol.

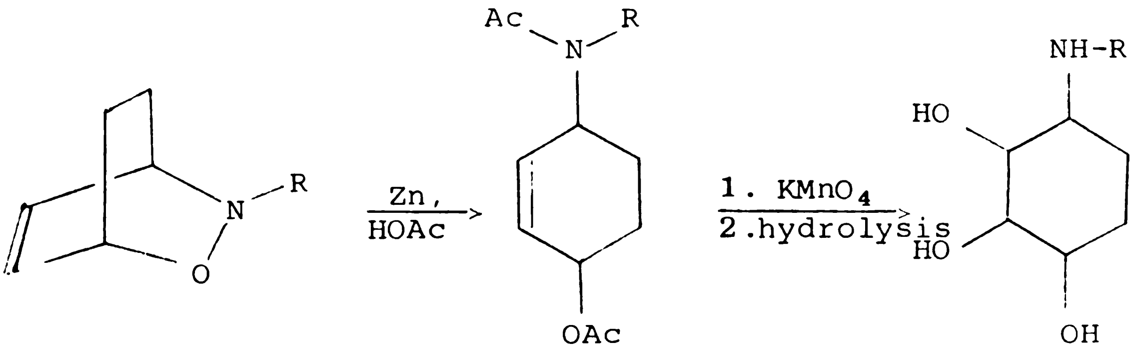
The adduct from the hexamethyldienone 25 was catalytically hydrogenated in glacial acetic acid solution using a platinum oxide catalyst at room temperature and atmospheric pressure. The result was rather unexpected in that 4-5 moles of hydrogen were absorbed under these conditions. The hydrogenated product was isolated and examined for its nmr spectrum, when surprisingly, no signals corresponding to aromatic protons were detected. There was some loss of material during work up which corresponded to the loss of aniline during removal of last traces of solvent under reduced pressure. The ir spectrum of the product had a strong band at 1700 cm^{-1} and weak bands at 3500 and 1660 cm^{-1}. These results can be explained as arising partly from the initial dissociation of the adduct into the components (dienone 25 and nitrosobenzene) followed by rapid uptake of hydrogen by these to form saturated materials, and partly by the cleavage of the N-O bond followed by the loss of water and aniline from the product. Considering 26A as a possible structure of the adduct, this scheme is given below:

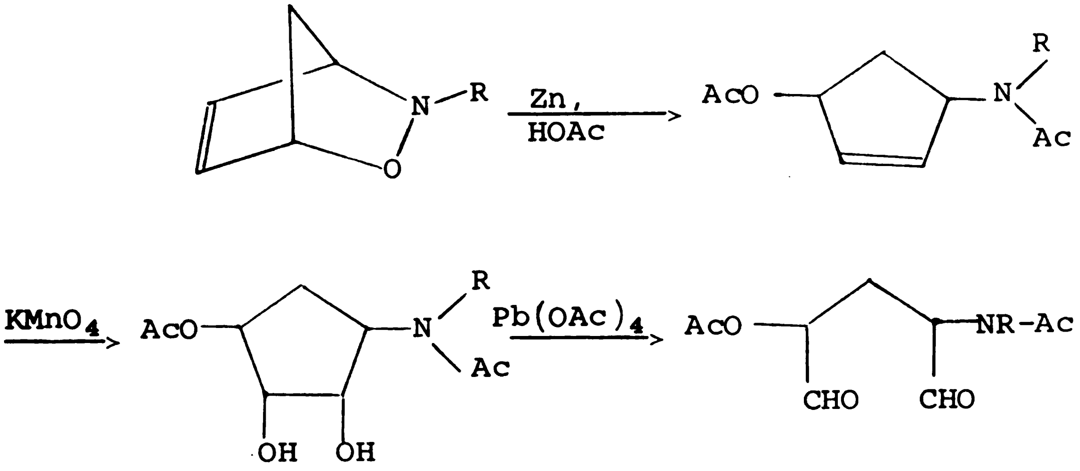


A similar reaction is also possible with structure 26B, giving rise to the same products.

Further hydrogenation experiments by using different catalyst (Pd/C) and solvent (ethyl alcohol) did not appreciably change the results. A homogeneous product useful for characterization was not obtained. In one case, by careful column chromatography of the hydrogenated product, one fraction characterized as aniline was actually isolated, along with fractions which did not contain nitrogen. The ease with which the elements of water and aniline are eliminated from the resulting amino alcohol after cleavage of the N-O bond is not surprising, as the O-H and the -NH-C_6H_5 are both attached to tertiary carbon centers. Thus, catalytic hydrogenation was found to be rather unsuitable for degradation of this adduct.

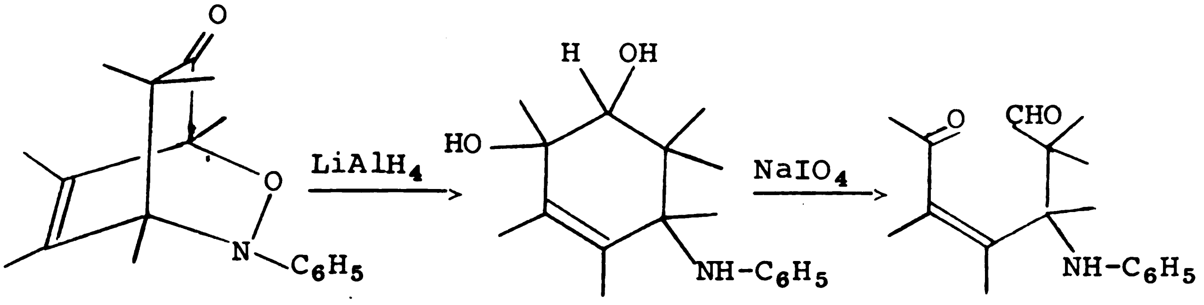
The next degradative experiment attempted for the dienone-adduct was reduction with zinc and acetic acid. This reaction has been used in simple cases with good results as shown in the following examples:[40,41]



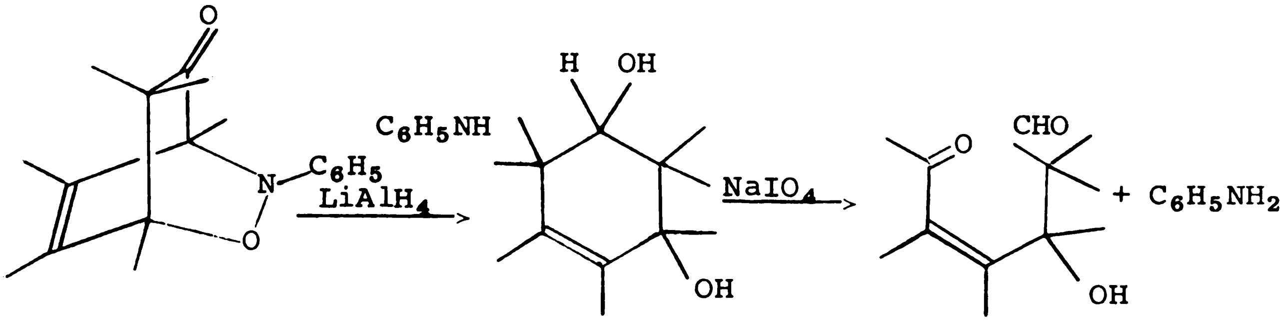


When the hexamethyldienone adduct was subjected to zinc acetic acid reduction, the product consisted of a complex mixture. The ir spectrum had strong bands at 1700, 1620, and medium bands at 3400 and 3500 cm^{-1}. These data indicate that reduction to amino alcohol might have proceeded to some extent. However, the nmr spectrum was quite complex. A preliminary thin layer chromatography indicated the presence of at least four components. Chromatographic separation on a packed column gave fractions containing no aromatic protons, as in the case of catalytic hydrogenation. Here again, elimination of aniline seems to occur. Also, partial dissociation into components might readily proceed under the conditions of the experiment, which required maintaining a temperature of 40-50° for 4 hr.

Attempts were then made to effect the reduction by metal hydrides at low temperatures. A report claims that lithium aluminum hydride is useful in cleaving the N-O bond.[42] However, when the dienone-adduct was reduced with this reagent at 0° in ether solution, a simple reduction of the carbonyl group to the hydroxyl function was the only change observed. The product had a strong band at 3500 cm^{-1} and no carbonyl band in the ir spectrum (Figure 25). The nmr spectrum had signals at τ 9.17 (multiplet), 8.92, 8.77, 8.67, 8.58, 8.10 (multiplet) all integrating for 3H each, due to the six methyl groups, and in addition signals at τ 8.30 (1H), 7.05 (broad, 1H) and 2.85-3.10 (5H). The nmr spectrum indicated that the product was mainly a single component, viz, the [2.2.2] alcohol resulting from reduction of the carbonyl group in the dienone-adduct, although the presence of epimers is not ruled out. No loss of the aromatic fragment was observed. Reduction with lithium aluminum hydride in tetrahydrofuran followed by refluxing for 4 hr did not produce any appreciable change in the nature of the products, as judged from the ir and nmr spectra. To test whether any product resulting from cleavage of the N-O bond was formed even in small amounts, the reaction product was treated with sodium metaperiodate, which would instantly react with any α-glycol such as 27 (derived from 26A)to give keto aldehyde 29 or perhaps more sluggishly[34] with the α-amino alcohol 28 (derived from 26B)to give keto aldehyde 30 and aniline according to the following scheme:



26A 27 29



26B 28 30

The ir spectrum of the product showed no carbonyl bands, and was identical to that of the starting material, indicating lack of any reaction. This would support one of two conclusions: (1) that the N-O bond did not cleave under these conditions and thus products that could react with periodate were not formed, or (2) that if any product was indeed formed, it could not be 27 but might be 28 which being an α-amino alcohol, is much less reactive toward periodate than an α-glycol.

The adduct was found to be inert to both ozonolysis and epoxidation reactions at the double bond, possibly due to steric hindrance to the approach of the reagents.

Since the alcohol obtained by reduction of the adduct was found to be more stable thermally than the dienone-adduct itself, attempts were made to reduce this material further with zinc and acetic acid. The ir spectrum of the product from this reaction showed only a medium intensity band in the hydroxyl region at 3400 cm^{-1}, but had in addition a medium intensity band at 1720 cm^{-1} indicating the presence of a carbonyl group. Thus one of the hydroxyl groups in the expected diol (**27** or **28**) or the amino group might have been acetylated under these conditions. The nmr spectrum had a strong signal at τ 7.80 confirming the presence of an acetoxy function, but was again complex indicating that the product contained more than one component. However, no loss of the aromatic protons was noticed. Oxidation of the product with sodium metaperiodate resulted in recovered starting material, thus showing absence of any oxidizable material. Attempts to separate this mixture by means of column chromatography did not give any pure material; moreover, loss of the aromatic fragment was indicated by nmr. Reduction of the entire mixture containing the acetates with lithium aluminum hydride was then tried with the aim of getting the expected diol **27** or **28**. These attempts were also unsuccessful as no identifiable homogeneous product which would react with sodium metaperiodate to give a carbonyl compound was obtained.

From the degradative experiments so far described, it has not been possible to isolate any single identifiable product that may serve in deciding unambiguously between the two possible structures **26A** and **26B**. However, the following features have to be emphasized:

(1) The failure to react with periodate as readily as in the case of the α-glycol **9** from the tetramethyldienol-adduct **8A** points to the possibility that a similar glycol was not formed and that the adduct from **25** may have the opposite orientation as in **26B**.

(2) Examination of models reveals more steric crowding in the transition state for orientation **26A** than for **26B**.

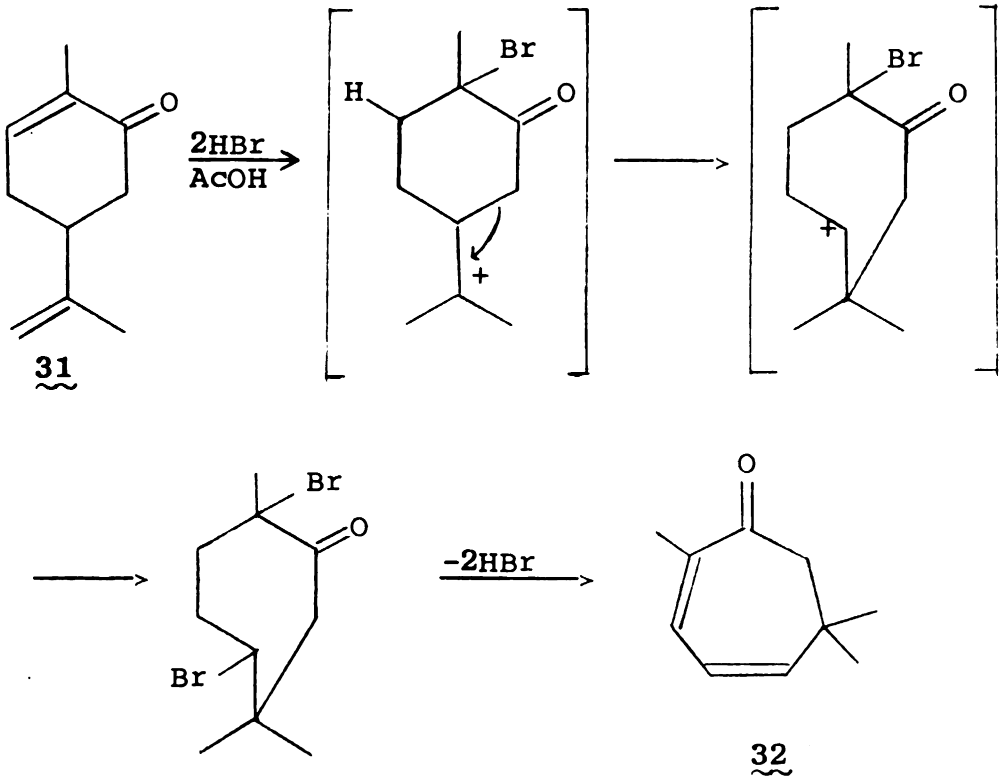
(3) The result of labeling the dienone **25** at C-3 is the same as for dienone **21**, *viz*., the high-field allylic methyl signal in the nmr spectrum of the adduct is removed. This is in contrast to the results from adducts **5A** and **22A**, which have been assigned the opposite orientation. A possible correlation of the chemical shift of the allylic methyl group with the orientation of the adduct is proposed on page 66 in the Discussion Section.

From a consideration of these factors structure **26B** is favored over **26A** for the adduct.

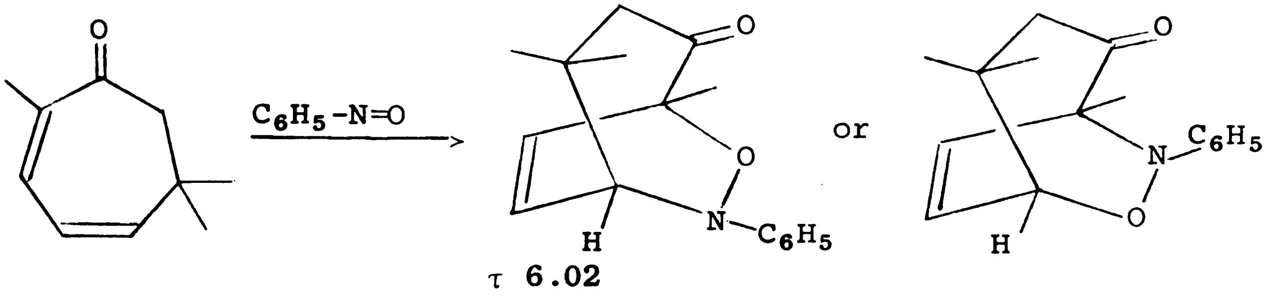
The Diels-Alder Adduct of Eucarvone (**32**) and Nitrosobenzene

Eucarvone (**32**), being a seven-membered ring dienone, would be expected to give an adduct having a [3.2.2] bridged bicyclic structure which might be less strained and hence more stable than the [2.2.2] systems obtained from cyclohexadienones. Thus, a study of the Diels-Alder reaction of this dienone permitted a comparison of the stabilities of this adduct with those obtained from the cyclohexadienones.

Eucarvone 32 was readily prepared by hydrobromination followed by dehydrobromination of carvone (31), a commercially available natural product, according to the following sequence.[43]



Eucarvone 32 reacted readily with nitrosobenzene at room temperature to give an adduct, mp 56-57°, in 77% yield. Depending upon the orientation of addition, the adduct can be represented by one of the two possible structures 33A or 33B.

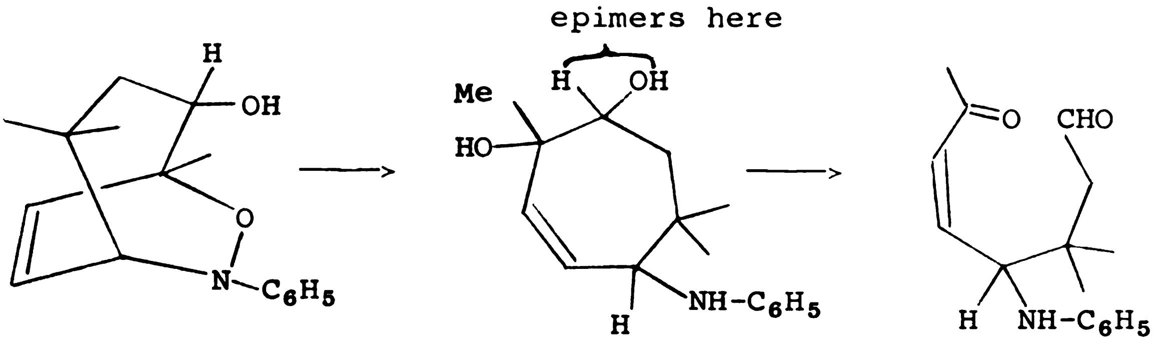


32 33A 33B

The nmr spectrum (Figure 11) of the adduct showed signals at τ 8.93, 8.55 and 8.38 (singlets, 3H each) for the three methyl groups, 7.74 and 6.59 (doublets, 1 H each, *J* = 22 Hz, methylene protons), 6.02 (doublet, 1H, *J* = 10 Hz, bridgehead proton), 3.72-3.95 (mulitplet, 2H, olefinic protons), and 2.60-3.08 (multiplet, 5H, aromatic protons). When the Kresze correlation is applied to this [3.2.2] system, the bridgehead proton appears to be adjacent to a nitrogen, thus favoring structure 33A rather than 33B. This conclusion is substantiated by the isolation and characterization of an open-chain cleavage product from the bicyclic adduct as described below.

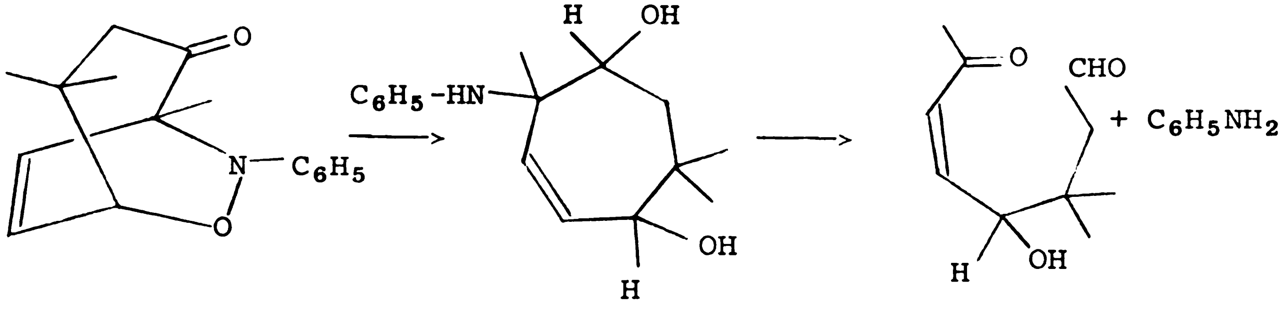
Lithium aluminum hydride reduction of the adduct in ether at 0° yielded a 1:1 mixture of alcohols (epimeric), one of which crystallized as a light, white, fibrous solid, mp 159-160°, leaving the other isomer as a viscous liquid. The nmr spectrum (Figure 12) had signals at τ 8.95 (singlet, 3H), 8.72 (singlet, 3H), 8.40 (singlet, 3H), 6.33 (broad, 1H, hydroxyl proton), 6.11 (broad, multiplet, 1H, bridgehead proton), 3.85-4.17 (multiplet, 2H, olefinic protons), and 2.80-3.18 (multiplet, aromatic protons). The two -CH$_2$- protons and the CH-OH proton were not well-resolved and had signals in the region τ 8.27-8.75. The appearance of the bridgehead proton signal at τ 6.11 supports structure 34 for this alcohol.

Alcohol 34 was further cleaved to a monocyclic seven-membered ring system by reduction with zinc and acetic acid to give quantitative yield of a crystalline amino diol 35 mp 118-119^0. Similar reduction of the liquid isomer gave a different amino diol, mp 95-96^0. These two compounds were distinctly different as shown by their mp, ir, and nmr spectra, and probably constitute the *cis*- and *trans*- diols. Oxidation of either of these two compounds with sodium metaperiodate in the usual manner gave the same cleavage product, characterized as 36, still containing the arylamine function.



34 35 36

Structure 33B, on the other hand, would also give rise to a keto aldehyde, but having an additional hydroxyl function, as in 38 *via* diol 37. Furthermore, aniline would be released as a separate fragment which would be lost during the work-up.



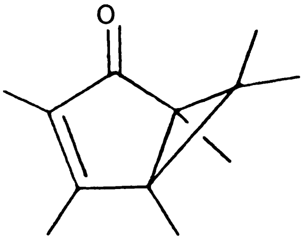
33B 37 38

Absence of O-H absorption in the ir spectrum of the product as well as the presence of aromatic protons in the nmr spectrum point to structure 36 and not structure 38 for the product. The ir spectrum (Figure 31), in addition, showed two strong carbonyl bands at 1687 (α,β-unsaturated ketone) and 1715 cm^{-1} (aldehyde). The nmr spectrum (Figure 13) of the product was complex and could not be analyzed with accuracy. Repeated column chromatography failed to give a pure product. The cleavage product thus appears to be unstable and may have undergone secondary reactions. The amino function in 36 could react with either of the carbonyl functions to give a complex mixture of products.

Eucarvone was reduced to eucarveol 39 with lithium aluminum hydride, and the dienol thus obtained was allowed to react with nitrosobenzene. The addition proceeded quite well, although not as spectacularly fast as in the case of the tetramethyldienol 7, and the product consisted of a mixture of epimeric alcohols from which 17% yield of a solid alcohol-adduct mp 159-160° could be obtained. This was found to be identical (mp, ir and nmr spectra) with the solid alcohol 34 obtained by lithium aluminum hydride reduction of the eucarvone-adduct 33A. Assuming that 34 is the major product of reaction, the orientation of addition of nitrosobenzene to eucarvone and eucarveol is the same, as was found in the case of the six-membered ring dienone 1 and the corresponding dienol 7. However, the difference between the two ring systems is manifested in the enhanced thermal stability of the [3.2.2] system derived from eucarvone as compared to the facile thermal reversibility of the [2.2.2] system from the cyclohexadienone. The dienol-adducts in both cases, on the other hand, were found to be stable.

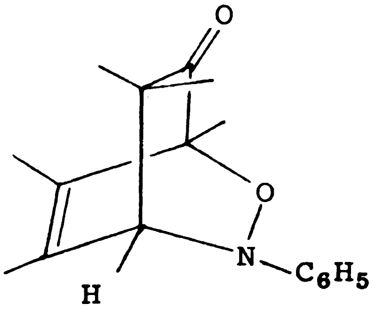
Preliminary Irradiation Studies

One of the objectives of the present study was to investigate the photoisomerization of the various Diels-Alder adducts prepared in this work. The dissociation of some of the dienone-adducts in solution was a serious problem in the analysis of the products. As a typical example, irradiation of the adduct 26B from hexamethyldienone 25 in ether solution in Pyrex with a 450 watt Hanovia lamp gave the bicyclic ketone 40, a product derived from photochemical transformation of the dienone 25.[21]

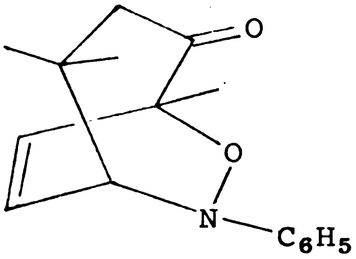


40

The two dienone-adducts which were fairly stable in solution at room temperature were 22A from pentamethyldienone 19, and 33A from eucarvone 32.



22A



33A

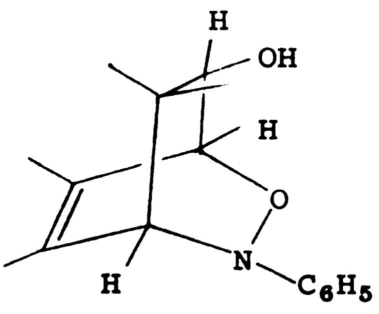
The adduct 22A showed λ_{max}^{EtOH} 308 nm (ϵ = 6489), 282 nm (ϵ = 6561), 249 nm (ϵ = 7987) and 208 nm (ϵ = 10,700). The first attempts were directed towards selective excitation of the n → π^* band in the molecule. When irradiated in 1% ether solution through Pyrex with a Hanovia type L mercury lamp for two hours, the solution turned dark and a gummy residue was deposited on the walls of the vessel. The progress of the reaction was followed by uv and the results shown in Figure 33. The nmr spectrum of the product showed only slight change. When separation was attempted by vpc, only pure 19 (resulting from thermal dissociation of the adduct) was collected. Hence it is evident that the photoreaction is extremely slow and accompanied by much tar formation.

The above irradiation was repeated using acetone as the solvent. The progress was followed by uv and the results shown in Figure 34. The photolysis appeared to be complete in 12 hr. The nmr spectrum of the product indicated that it was a mixture. Attempts to separate the product by chromatography were unsuccessful.

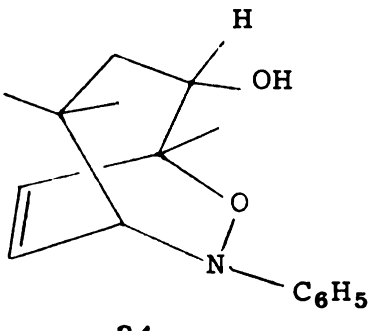
The adduct 33A from eucarvone 32 had λ_{max}^{MeOH} 285 nm (ϵ = 162), 244 nm (ϵ = 7558), and 208 nm (ϵ = 10,400). Irradiation of a 1% solution in ether with a 450 watt Hanovia type L mercury lamp through vycor was attempted to see whether any reaction due to the excitation of the carbonyl function selectively could be detected. Slow reaction was observed in 8 hr and the progress was followed by uv (Figure 35). The nmr spectrum of the product appeared to be much less complex than in the previous cases; however, the product was still a mixture, and contained much starting material. In one experiment, the photolysis was continued for 22 hr. The ir and nmr spectra of the product were quite similar to those of the starting material, and showed that there was no appreciable reaction after this long period. The lack of reaction in the [3.2.2]-nonenones comparable to that in the [2.2.2]-octenones may be explained as due to the decreased electronic interaction between the orbitals of the carbonyl group and the β,γ-double bond in this system.

Attempts were then made to excite the N-O bond selectively in these adducts by irradiation in the Rayonet chamber with light of wavelength 2537 Å.[20] The adduct 33A from eucarvone 32 was irradiated in ether solution at this wavelength in a quartz test tube. The progress of the reaction was followed by uv and is shown in Figure 36. After 5 hr, separation of product was attempted by vpc, when only pure eucarvone was collected. Column chromatography failed to give any pure product.

Attention was then turned to the dienol-adducts 8A from tetramethyldienol 7 and 34 from eucarveol 39. 8A showed λ_{max}^{MeOH} 206 nm (ϵ = 9063), 250 nm (ϵ = 6889) and 284 nm (ϵ = 91). Irradiation of 8A in methanol solution



8A



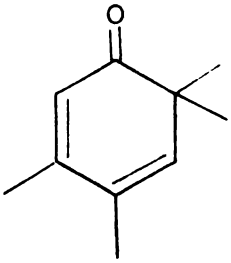
34

at 2537 Å was followed by uv (Figure 37). The maximum at 245 nm shifted progressively to 238 nm and a new shoulder developed at 282 nm. The ir spectrum of the product showed strong absorption at 3500 cm^{-1} (O-H) and medium absorption between 1710 and 1660 cm^{-1}. Column chromatography of the product gave one fraction, eluted with ether, and from ir and nmr spectra, appeared to be a single photo-product. The ir spectrum (Figure 32) had strong absorption at 3450 cm^{-1} (O-H) and medium absorption at 1660 cm^{-1}. The nmr spectrum (Figure 14) had signals at τ 9.07, 8.92, 8.65 and 8.48, all singlets for the four methyl groups, 8.05 (singlet, 1H), 6.98 (triplet, $\underline{J}$ = 10 Hz), 6.30-6.50 (broad, 2H) and 2.8-3.4 (5H). The absence of two quartets for the allylic methyls would indicate absence of double bond in the product. The mass spectrum had parent peak at m/e 269 M^+ $C_{16}H_{21}O_2N$, isomeric with starting material. Further characterization was not possible due to paucity of material.

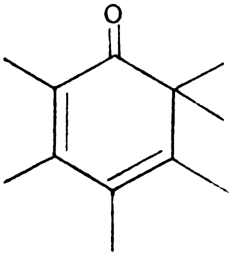
Irradiation of adduct **34** from eucarveol **39** under similar conditions was followed by uv as shown in Figure 38. Repeated attempts to isolate any pure photo-product by column chromatography were unsuccessful.

DISCUSSION

The present study has shown that cyclohexadienones readily react with nitrosobenzene to give Diels-Alder adducts. The conditions required for the reaction vary depending on the nature and position of the substituents on the diene component. As expected, the carbonyl group retards the reaction; simple dienes carrying no electron-withdrawing substituents give good yields of adducts within a few hours at room temperature.[4] The dienones examined in the present study were less reactive than such dienes, since most of them required heating the components in a solvent. The tetramethyldienone **1** appeared to be most reactive, and formed an adduct at room temperature after 4 hr. The least reactive of the dienones was the hexamethyldienone



1



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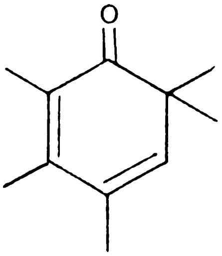

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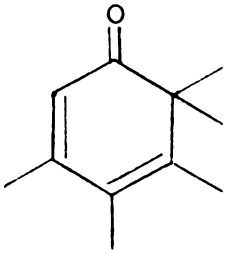

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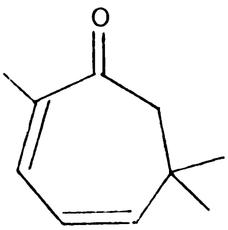
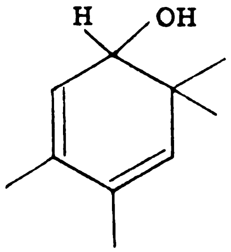


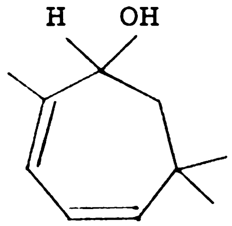
32

25; it required refluxing the components in 1,2-dichloroethane (bp 92°). The pentamethyldienones 19 and 21 only required a lower-boiling solvent such as methylene chloride (bp 40°). The seven-membered ring dienone, eucarvone 32 showed comparable reactivity to the six-membered ring dienones.

Reduction of the carbonyl group to the CH-OH group produced a dramatic activating effect for dienol 7. This effect was less pronounced for eucarveol 39, however.

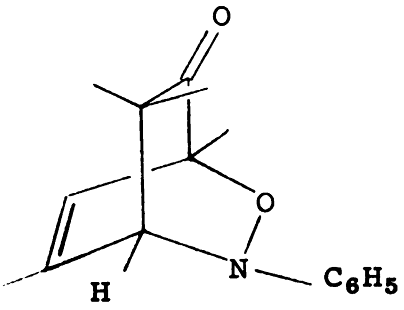


7

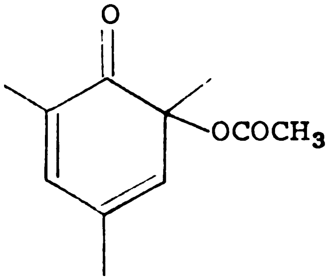


39

The stability of the adducts varies widely. In the solid state, the adducts can be sublimed under reduced pressure without decomposition, though adduct 16A from the acetoxydienone 15 was unstable at room temperature. The



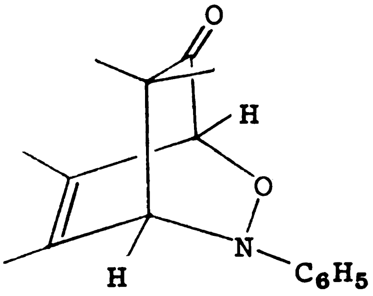
16A



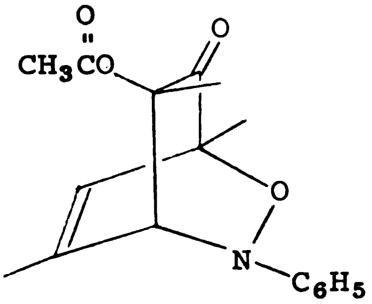
15

most stable of all the adducts were those derived from eucarvone and eucarveol, possibly because these adducts with a three-carbon bridge are relatively less strained than the [2.2.2] systems from the cyclohexadienones.

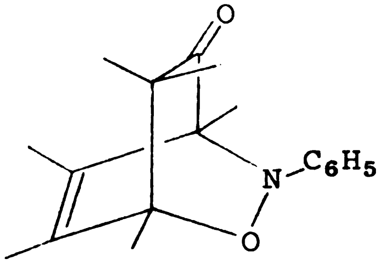
The behavior of the adducts in solution also varied. Adducts 5A (from tetramethyldienone 1) and 16A (from acetoxydienone 15) partially dissociated when dissolved in most solvents. The adduct 26B from the hexamethyldienone 25 showed similar behavior, though to a lesser extent. In contrast, adducts 22A from the pentamethyldienone 19, and 24B from 21 did not show any sign (green color of nitrosobenzene) of dissociation in solution. This behavior is rather surprising and difficult to explain. The adduct 33A



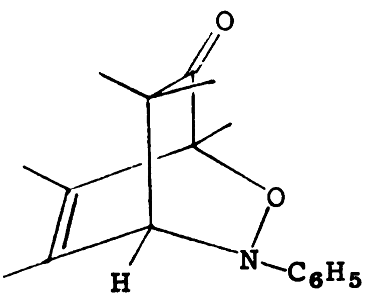
5A



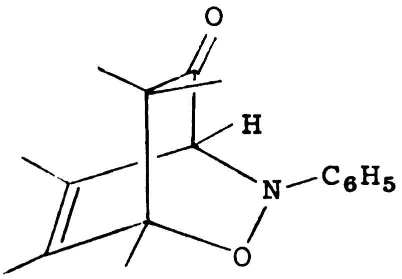
16A



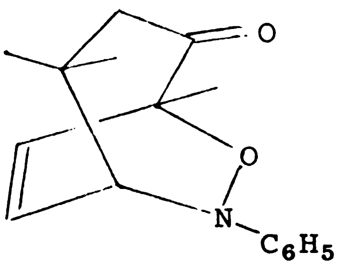
26B



22A



24B

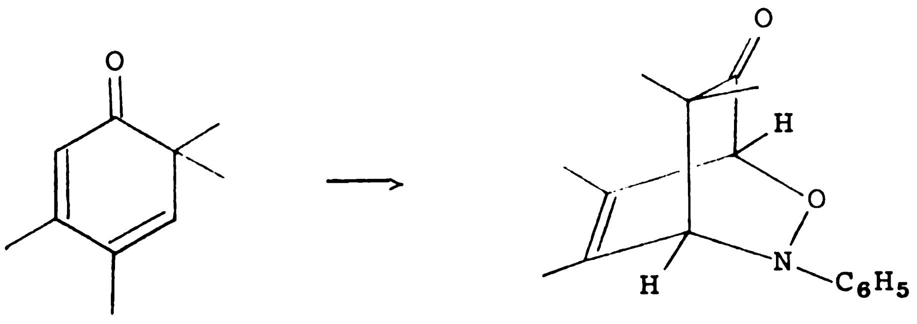


33A

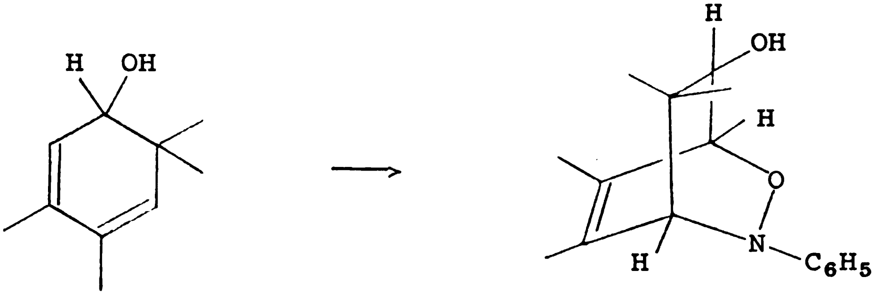
from eucarvone also shows no sign of dissociation in solution. The dienol-adducts **8A**, **17A**, **23A** and **34** as well as the alcohol derived from the adduct (**26B**) all behaved similarly and were stable in solution. A possible explanation for this difference is that a [2.2.2] system carrying an sp^2 hybridized carbon of the carbonyl group may be more strained than a similar system with an sp^3 carbon (CH-OH group).

Two noteworthy features in the Diels-Alder reaction of nitrosobenzene with dienones are the high specificity in orientation of the nitroso component with respect to the carbonyl group and the marked dependence of this orientation on the nature and position of substituents on the dienone. The results so far described have led to the following conclusions with respect to orientation in the various Diels-Alder adducts:

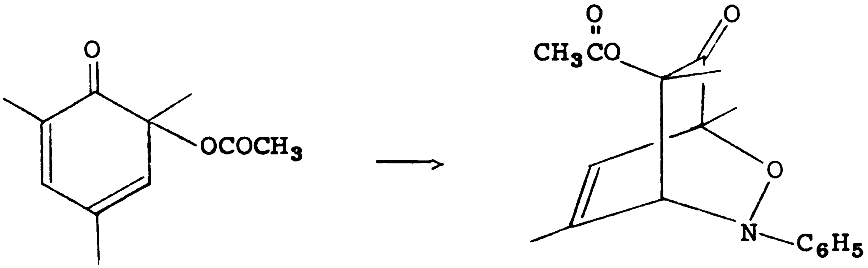
Orientation A (with the O-atom of the nitroso group bonded to C-2, the carbon carrying the electron-withdrawing substituent and the N-atom bonded to C-5 of the diene) has been observed with the dienes **1**, **7**, **15**, **19**, **32** and **39**.



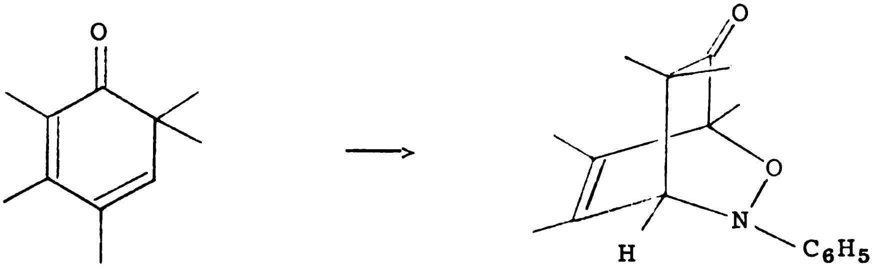
1 **5A**



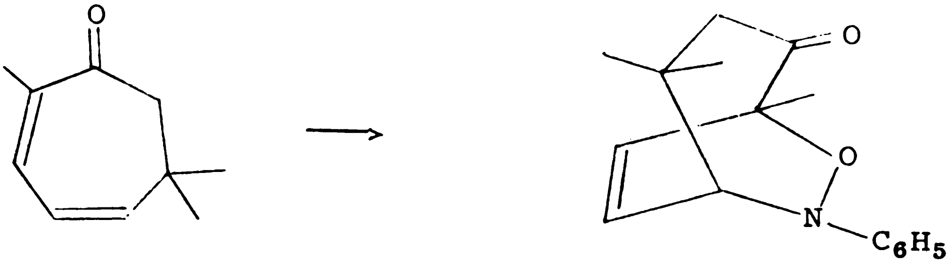
7 8A



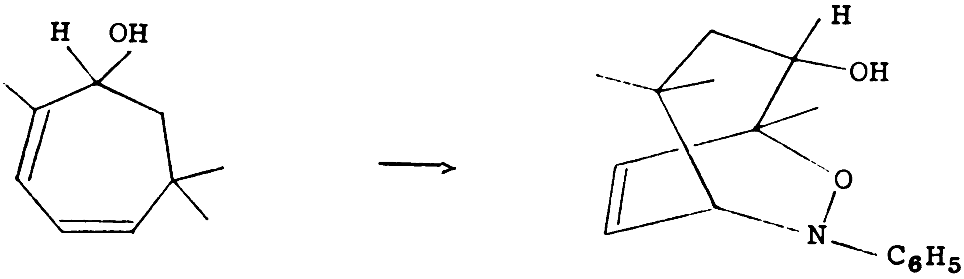
15 16A



19 22A

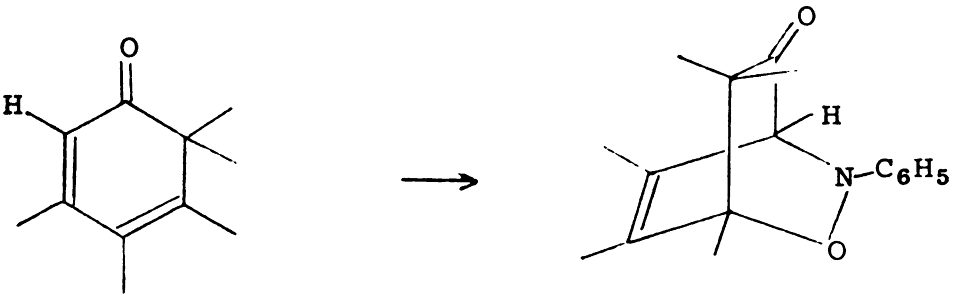


32 33A

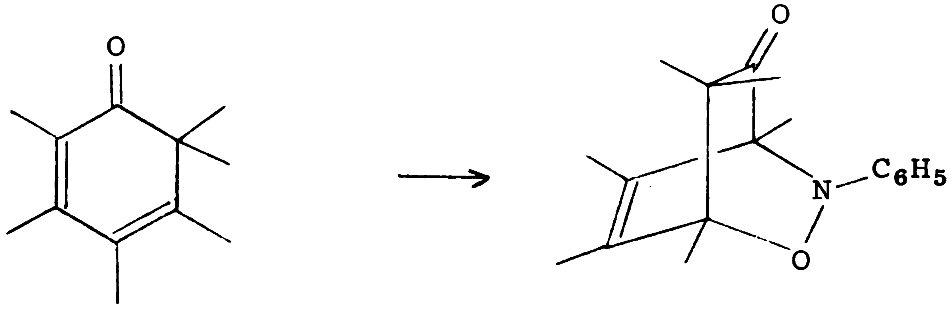


39 34

Orientation B (with the N-atom of the nitroso group bonded to C-2 and the O-atom bonded to C-5 of the diene) has been observed with the dienes 21 and 25.

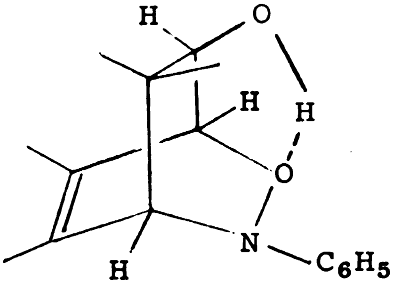


21 24B



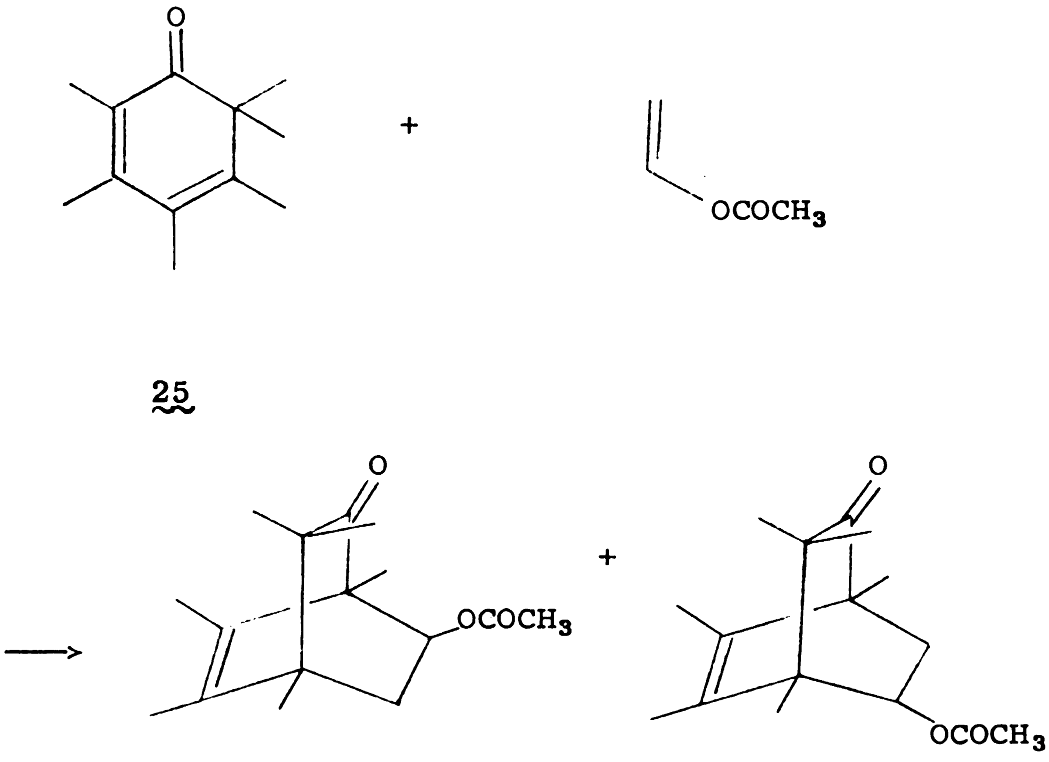
25 **26B**

For the tetramethyldienone **1**, the orientation is according to expectation. The results with dienes such as the simple sorbinol derivatives studied by Kresze[4] show that the O-atom of the N=O group attaches itself to the carbon carrying the electron-withdrawing group, in this case the carbonyl group. The formation of an adduct having the same orientation from the tetramethyldienol **7** cannot be attributed solely to the inductive effect of the -CH-OH substituent, as it is much less electron-withdrawing than the C=O group. The same argument may be applicable for acetoxy-dienone **15** and eucarvone **32**. The detection of intramolecular hydrogen bonding (as shown in **8A**) in the ir spectrum of this adduct indicates that the energy for transition state for the particular orientation may thereby be lowered and as a result this orientation is favored.



8A

The orientation in the case of the pentamethyldienones 19 and 21 and the hexamethyldienone 25 is probably controlled exclusively by the steric requirements of the gem-dimethyl groups at C-6 and the methyl groups at C-2 and C-5 of the dienones, and the aromatic ring of the nitrosobenzene. In 19 and 21 opposite orientations are obtained because in the transition state the aromatic ring of the nitrosobenzene takes up the space where the methyl group is absent. In the hexamethyldienone 25, more drastic conditions are required to bring the components together, and the aromatic ring can only orient in the gap of the only small group in the molecule of the diene viz., the carbonyl group. In this connection, it may be worthwhile to compare the results of the Diels-Alder reaction of the hexamethyldienone 25 with the unsymmetrical dienophile, vinyl acetate. It was found[26] that the product with vinyl acetate consisted of a mixture of both isomers, with A predominating in the ratio 4:1.



25

A
Major

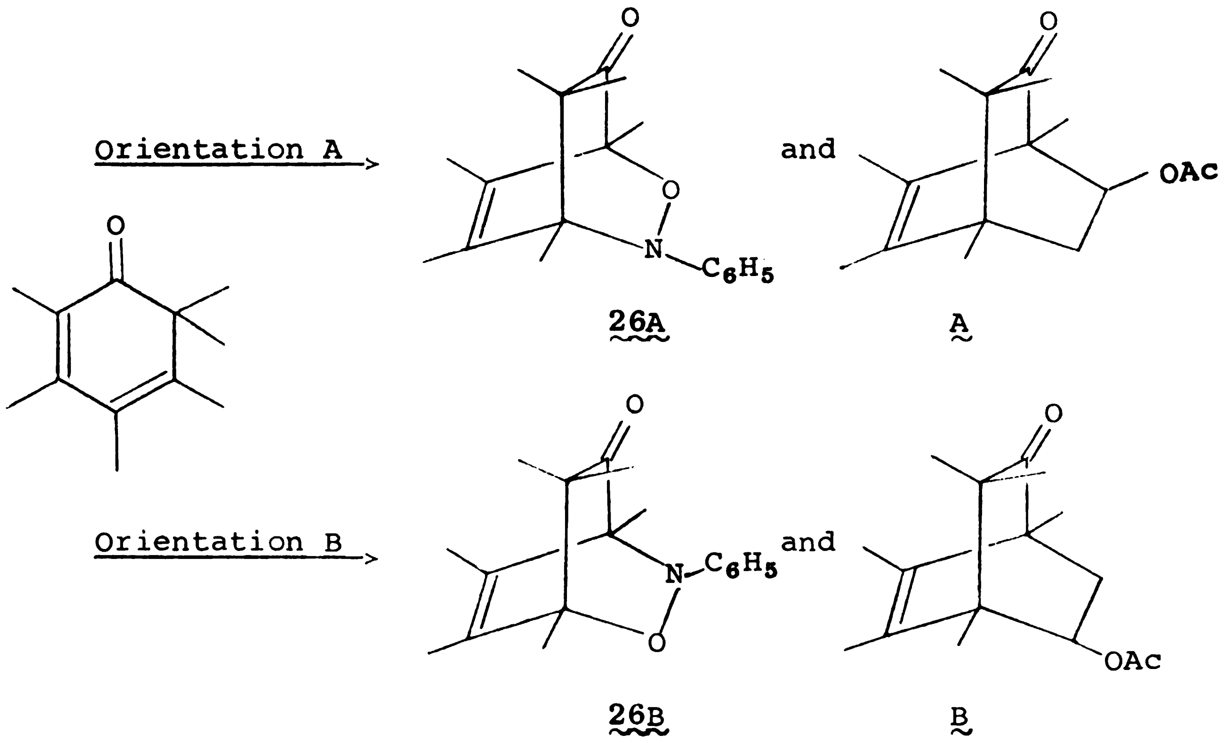
B
Minor

It was mentioned in the Introduction (p. 7) that if the two dienophiles are arranged according to their polarity, the following parallel is obtained:

$$\mathrm{Ar}-\overset{\delta+}{\mathrm{N}} = \overset{\delta-}{\mathrm{O}}$$

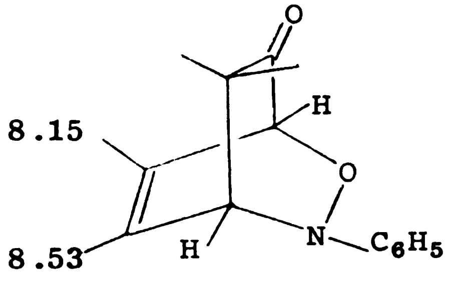
$$\overset{\delta+}{\mathrm{CH_2}}=\overset{\delta-}{\mathrm{CH}}-\mathrm{OAc}$$

According to this scheme, if polar factors influenced the orientation of addition of the dienophiles in both cases, the following isomers would be expected from 25 for each orientation.

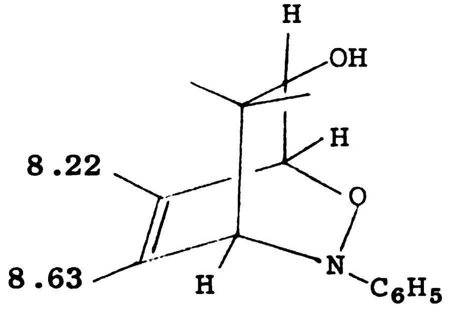


The result from the vinyl acetate addition is in agreement with the expectation, if it is assumed that polar factors influence the orientation. The acetate group is a much smaller group than the aromatic ring and hence the steric influence on the orientation would be much less than that for nitrosobenzene. If polar factors also influenced the orientation in the case of nitrosobenzene, the major expected product would be 26A. The fact that 26B is the favored structure for the adduct actually isolated, supports the conclusion that polar factors are superceded by steric factors in this case.

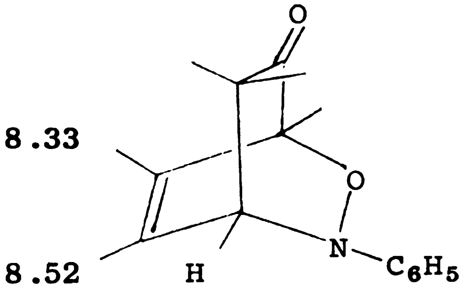
The results of the labeling experiments with the dienone-adducts reveal an interesting feature. Labeling the starting dienone, e.g. 1 at C-3 with CD_3 removes one of the two allylic methyl signals, in this case, the low-field one of the adduct. In adducts having orientation A, this means that the nmr signal of the allylic methyl group opposite to the N-atom appears at higher field compared to the other, which is opposite the O-atom. Typical chemical shift τ values are given below:



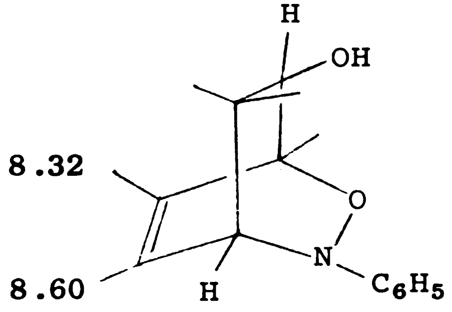
5A



8A

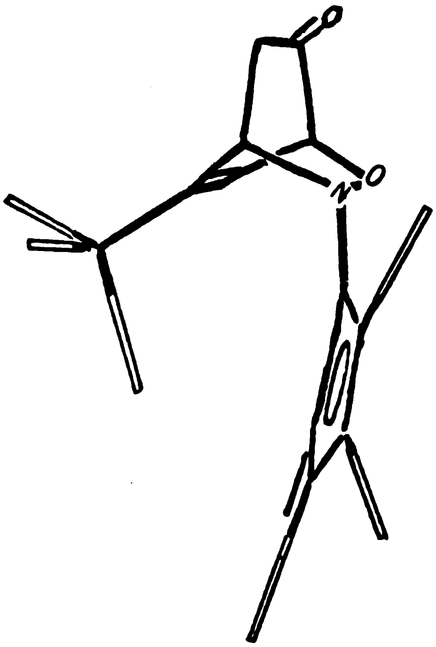


22A



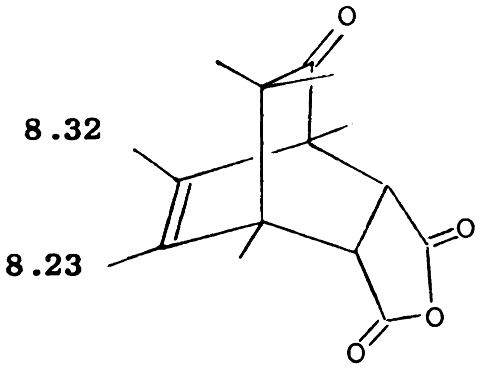
23A

This difference can be attributed to a shielding effect, which is clearly discernable when a model of the adduct is examined. Here, the assumption is made that the aromatic ring is endo to the boat-shaped 3,6-dihydro-1,2-oxazine ring of the bicyclic system, since in this arrangement, there is least steric interactions with the gem-dimethyl group on the adjacent carbon bridge. This favored conformation is shown below in the diagram.

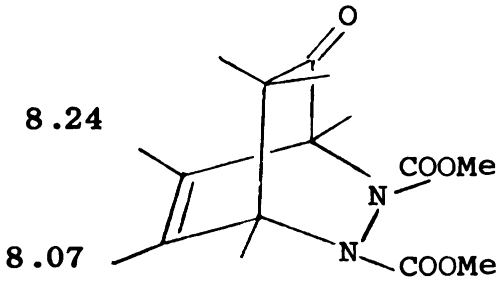


The allylic methyl giving the high-field signal is found to be in the region where the diamagnetic anisotropy of the benzene ring produces a shielding effect. If this explanation is valid, it is possible to determine the orientation of addition in such systems by this simple labeling experiment. In the hexamethyldienone-adduct (tentatively assigned structure 26B), labeling removes the high-field allylic methyl signal, in contrast to adducts having orientation A. If the above explanation is the real cause for the difference in chemical shifts, then the orientation in this adduct is opposite to that in 5A, 8A, 22A and 23A.

The chemical shift values of the allylic methyl groups in the Diels-Alder adducts prepared in this work have been discussed so far. It may now be relevant to compare these results with similar values of various other Diels-Alder adducts prepared in this laboratory during the past few years. Representative examples of such adducts, their structures, the assigned chemical shift values of the allylic methyl groups, and the relevant references in parentheses are given below:



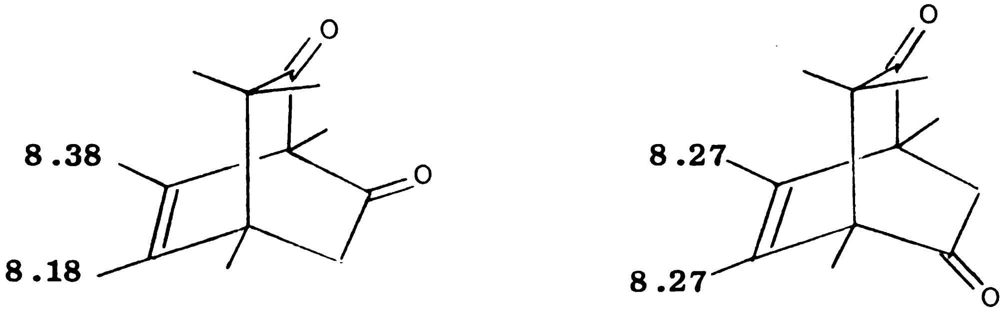
(ref. 21)



(ref. 44)

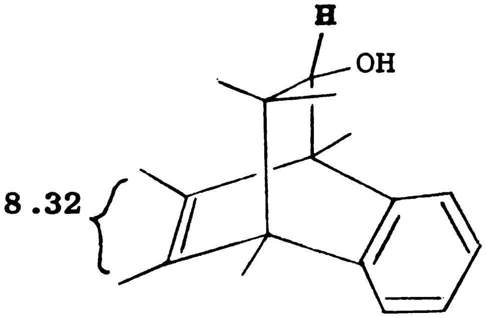
The methyl group adjacent to the carbonyl group is at higher field as revealed by labeling. This indicates that the carbonyl group has a small shielding effect on the methyl group through its diamagnetic anisotropy. (Alternatively, the allylic methyl remote from the carbonyl function may be deshielded due to a homoconjugative interaction between the carbon-carbon double bond and the carbonyl group.) The incorporation of a second carbonyl group on the remaining bridge of the [2.2.2]-octenones has an effect depending upon its position as indicated in the following two structures: the effect is additive when the two carbonyls are adjacent to each other and to the methyl group as in the first example.

In the second case, both allylic methyls are shielded by a carbonyl group and hence the chemical shift values are

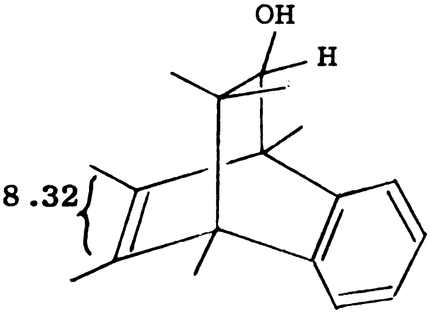


(ref 26)

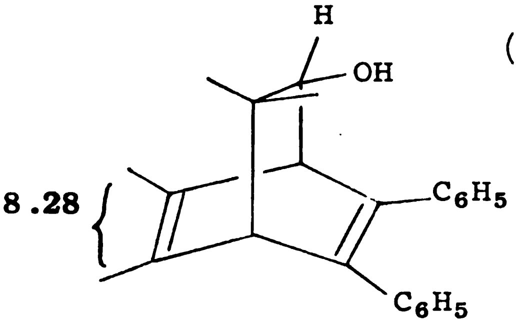
shifted upfield to the same extent. When the carbonyl group in the [2.2.2]-adducts is reduced to the CH-OH group, this shielding effect is no longer present as shown in the following examples.



(syn)
(ref 24)

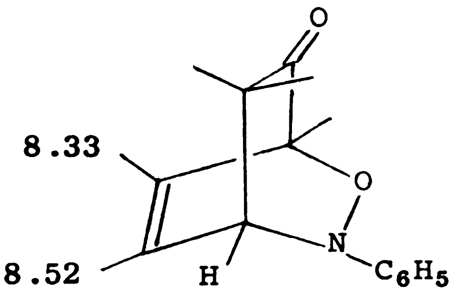


(anti)
(ref 24)

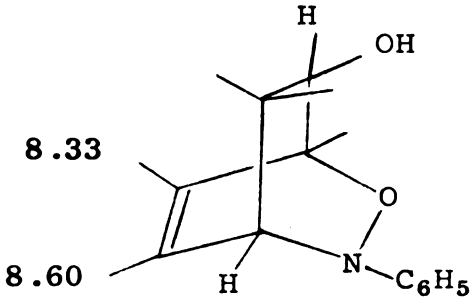


(ref 24)

Thus it is evident that the carbonyl group in the Diels-Alder adducts from nitrosobenzene must also have a shielding effect on the allylic methyl group near to it and this effect should be absent for the corresponding alcohols. In the adducts prepared in this work, the chemical shift value difference is much more (about 0.2 to 0.4 ppm) than in the case of the examples cited above and the explanation for this must lie in the anisotropy due to the aromatic ring on the nitrogen atom. As expected, this difference is more pronounced for the alcohols than for the ketones as illustrated in the following two structures:



22A



23

From the synthetic point, the Diels-Alder reaction of nitrosobenzene with dienones and their derivatives provides access to novel heterocyclic bridged systems. Formation of pyrrole **14** in almost quantitative yield from **8A** also offers synthetic utility. Further synthetic potential has not been explored in the present study.

EXPERIMENTAL

1. General Procedures

The nmr spectra were recorded with a Varian Model A-60 using $CDCl_3$ solutions (unless otherwise stated) with tetramethylsilane as an internal standard. The ir spectra were obtained with a Unicam Model SP-200 Infrared Spectrophotometer, and the spectra were calibrated (polystyrene). The uv spectra were measured with a Unicam Model SP-800 Ultraviolet Spectrophotometer. The mass spectra were obtained by Mrs. Lorraine Guile with a Hitachi-Perkin Elmer RMU-6 Mass Spectrometer. Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Michigan or Clark Microanalytical Laboratory, Urbana, Illinois. Melting points were determined with a Gallenkamp Melting Point Apparatus and are uncorrected.

2. The Diels-Alder Adduct (**5A**) from 3,4,6,6-Tetramethyl-2,4-cyclohexadienone (**1**) and Nitrosobenzene

The dienone **1**[22] (1.5 g, 0.01 mol), nitrosobenzene (1.07 g, 0.01 mol, Aldrich Chemical Co.) and methylene chloride (20 ml) were stirred together at room temperature until the green color of the solution had disappeared (about 4 hr). The solvent was evaporated at room temperature using a rotary evaporator and the last traces of solvent were removed *in vacuo*. There was obtained a dark, viscous oil which was redissolved in the minimum amount of pentane; warming the mixture to effect dissolution was avoided to minimize the facile thermal dissociation of this adduct into its components. The solution was cooled in the refrigerator overnight, which resulted in deposition of crystals of the adduct. These were removed by decantation: yield 1.35 g (51%). Recrystallization from pentane yielded light yellow crystals of the adduct, mp 62-63°. The ir spectrum (Figure 15, Nujol) indicated absorption at 1720 ($>$C=O), 1600 (w), 1595 (m), 1220 (m), 1020 (w), 903 (m), 770 (s) and 700 cm^{-1} (s). The nmr spectrum (Figure 1, CCl_4 solution) had signals at τ 8.92 (singlet, 3H), 8.60 (singlet, 3H), 8.53 (quartet, 3H), 8.15 (quartet, *J* = 1.2 Hz, 3H), 5.92 (singlet, 1H), 5.63 (singlet, 1H), and 2.7-3.2 (multiplet, 5H).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44
Found: C, 74.59; H, 7.56; N, 5.44.

3. The Diels-Alder Adduct from 4,6,6-Trimethyl-3-methyl-d_3-2,4-cyclohexadienone-2d (6)

Dienone 1 (1 g, 0.007 mol) in methanol-d (50 ml) containing sodium methoxide (1.25 g) was heated under reflux in an atmosphere of nitrogen for 24 hr. The methanol was evaporated under reduced pressure and the residue was extracted with hot benzene. The benzene extract was washed with water and dried. Removal of solvent yielded a yellow oil (0.85 g, 85% yield). Inspection of the nmr spectrum of the product indicated that the signals at τ 4.32 (vinylic proton at C-2) and τ 7.98 (C-3 methyl) were absent in the labeled product.

The nmr spectrum of the Diels-Alder adduct from this labeled dienone 6 and nitrosobenzene lacked the signals at τ 5.63 (bridgehead proton adjacent to oxygen) and τ 8.15 (low-field allylic methyl at C-7 in 5A).

4. The Diels-Alder Adduct (8A) from 2,3,6,6-Tetramethyl-2,4-cyclohexadienol (7) and Nitrosobenzene

Tetramethyldienone 1 (1.5 g, 0.01 mol) dissolved in 80 ml of anhydrous ether was added gradually to a mechanically stirred slurry of lithium aluminum hydride (0.2 g, 0.005 mol, excess) in 40 ml of anhydrous ether at 0^0. The reaction mixture was stirred at 0^0 for an additional 2 hr. Excess hydride was destroyed by addition of moist ether. Filtration of the white precipitate followed by evaporation of the clear filtrate at reduced pressure and room temperature gave a quantitative yield of a light yellow syrupy liquid. The ir spectrum of the product (neat) indicated complete absence of absorption in the carbonyl region and presence of a strong band in the O-H region at 3400 cm^{-1}. The dienol was found to be unstable at room temperature,[22] but could be handled without decomposition for a few hours if kept in the refrigerator. In the present case, the dienol was reacted with nitrosobenzene immediately after isolation. Thus, the above product (1.50 g, 0.01 mol) was dissolved in ice-cold methylene chloride (20 ml), and nitrosobenzene (1.05 g, 0.01 mol) was added. The mixture was stirred magnetically until all the nitrosobenzene dissolved to give a green solution. This solution was then kept in the refrigerator. The green color disappeared in 2 hr. The solvent was then evaporated at reduced pressure and the residue was dissolved in pentane. Cooling the pentane solution gave light yellow crystals of the adduct (yield 2.1 g, 78%), mp 98-99°. Further purification was achieved by sublimation at 0.1 mm and 90-100°. The ir spectrum (Figure 16, Nujol) had principal bands at 3330 (O-H), 1597 (m), 1130 (m), 1065 (s), 964 (w), 833 (s), 765 (s), 730 (doublet, s) and 700 cm^{-1} (s). The nmr spectrum (Figure 2, $CDCl_3$ solution) showed signals at τ 9.03 (singlet, 3H), 8.72 (singlet, 3H), 8.62 (quartet, $\underline{J}$ = 1.2 Hz, 3H), 8.22 (quartet, $\underline{J}$ = 1.2 Hz, 3H), 7.50 (broad, 1H, disappears when sample is shaken with D_2O), 6.85 (broad, 1H), 6.47 (singlet, 1H), 5.77 (doublet, $\underline{J}$ = 1.6 Hz) and 2.67-3.28 (multiplet, 5H).

Reduction of 4,6,6-trimethyl-3-methyl-d_3-2,4-cyclohexadienone-2d ($\underset{\sim}{6}$) with lithium aluminum hydride and conversion of the resulting labeled dienol to the Diels-Alder adduct and inspection of its nmr spectrum showed that the τ 5.77 doublet and the τ 8.22 quartet disappeared and the τ 8.62 signal became a singlet.

<u>Anal</u>. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40

Found: C, 74.04; H, 8.13; N, 5.34.

5. Reduction of the Adduct (8A) with Zinc and Acetic Acid: Diol (9)

The adduct (1.3 g, 0.005 mol) was dissolved in glacial acetic acid (15 ml) in a 100 ml three-necked flask equipped with a mechanical stirrer. To this stirred solution, zinc powder (5 g) was added and stirring was continued for 6 hr with the reaction flask immersed in an oil bath at 50^{0}. The reaction mixture was then cooled, diluted with ether and the residual zinc was removed by filtration. The solvent and most of the acetic acid was removed under reduced pressure. Water (25 ml) was added to the residue and the remaining acetic acid was neutralized with concentrated ammonium hydroxide. The neutralized mixture was then extracted with ether, the ether extract was washed with water, and dried ($MgSO_4$). Evaporation of solvent yielded a brown oil (1.26 g). The ir spectrum (neat) of this product showed an intense band between 3450 and 3550 cm^{-1} (O-H). The nmr spectrum of the crude product ($CDCl_3$ solution) had signals at τ 9.10, 8.93, 8.68, 8.28 (each 3H), 5.70-6.78 (broad, 5H), and 2.83-3.47 (5H, aromatic protons). The product was not further purified, but was used directly in the next experiment.

6. Cleavage of the Diol (9) with Sodium Metaperiodate: Pyrrole (14)

The crude diol (9) obtained from the above reaction was oxidized with sodium metaperiodate without further purification. The diol (1.25 g, 0.005 mol) was dissolved in absolute ethanol (20 ml) and to this stirred solution at room temperature was added a solution of sodium metaperiodate ($NaIO_4$, 1.1 g, 0.005 mol) in water (8 ml). Within 10 min, a white precipitate was deposited from the previously clear solution. Stirring was continued at room temperature for a further 30 min. The reaction mixture was then filtered and the clear filtrate was evaporated under reduced pressure, when a semi-solid residue contaminated by some inorganic material was obtained. This was diluted with water (5 ml) and extracted with ether. The ether extract was washed with water and dried. Removal of solvent yielded a dark, viscous oil (1.09 g, 87%).

The ir spectrum (Figure 17, neat) of the crude product showed bands at 1715 (s, $\rangle C=O$), 2720 (w, aldehyde), 1600 (m), 1500 (s), 1464 (m), 1402 (s), 1375 (s), 1220 (m), 1110 (m), 920 (w), 788 (s), 755 (m), and 760 (s) cm^{-1}. The nmr spectrum (Figure 3, $CDCl_3$ solution) showed signals at τ 8.80 (singlet, 6H), 8.00 (multiplet, 6H), 3.60 (multiplet, 1H), 2.68 (multiplet, 5H) and 0.62 (singlet, 1H). The mass spectrum had parent peak at m/e = 241 corresponding to M^+, $C_{16}H_{19}NO$.

The above product could be purified by vapor phase chromatography (10' x 1/4" SE-30 column at 220°, He flow rate of 85 ml/min) and had a retention time of 12 min. The pure material thus obtained was a solid, mp 59-60°.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80

Found: C, 79.44; H, 7.97; N, 5.75.

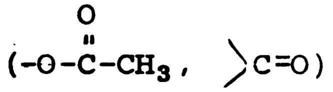
7. Reduction of the Adduct (5A) with Lithium Aluminum Hydride

The adduct (5A) (0.257 g, 0.001 mol) was dissolved in ice-cold anhydrous ether (25 ml) and this solution was added rapidly to an ice-cold, mechanically stirred, slurry of 0.5 g (excess) of lithium aluminum hydride in dry ether (20 ml). Stirring was continued for 1/2 hr at 0°. Excess hydride was destroyed by the addition of moist ether and the white precipitate was removed by filtration through a sintered funnel. The filtrate was evaporated to give a yellowish brown oil (quantitative yield).

The ir spectrum of this oil (neat) showed a strong band at 3500 cm^{-1} (O-H) and was identical to the spectrum of the adduct 8A. This product was dissolved in a minimum volume of pentane and cooled; the crystals thus obtained were filtered (yield 0.211 g, 84%) mp 90-92°. The nmr spectrum ($CDCl_3$ solution) had signals at τ 9.04 (singlet, 3H), 8.73 (singlet, 3H), 8.62 (quartet, *J* = 1.2 Hz, 3H), 8.21 (quartet, *J* = 1.2 Hz, 3H), 7.60 (broad, 1H), 6.83 (broad, 1H), 6.43 (singlet, 1H), 5.75 (broad, 1H), 2.70-3.19 (multiplet, 5H).

8. The Diels-Alder Adduct (16A) from Dienone (15) and Nitrosobenzene

The dienone 15[38] (4.16 g, 0.02 mol) and nitrosobenzene (2.14 g, 0.02 mol) were dissolved in methylene chloride

(20 ml) and the resulting green solution was stirred at room temperature until the green color completely disappeared (9 hr). The solvent was removed under reduced pressure and the oily residue was redissolved in pentane (50 ml). On cooling the solution in the refrigerator overnight, yellow crystals of the adduct were deposited. These were removed by decantation (yield 3.60 g, 57%), mp 73-75°. The ir spectrum (Figure 18, Nujol) had a broad band at 1720-1740 cm^{-1}  $(-O-\overset{\overset{O}{\|}}{C}-CH_3,\ >C=O)$ and bands at 1640 (w), 1590 (m), 1245 (s), 1115 (s), 1030 (s), 1003 (s), 980 (s), 850 (s), 780 (s), 765 (w), 706 cm^{-1} (s). The nmr spectrum (Figure 4, $CDCl_3$ solution) showed evidence for partial dissociation of the adduct into components; the adduct had signals at τ 8.40 (singlet, 6H, methyls), 8.10 (quartet, J = 1.2 Hz, 3H, allylic methyl), 7.87 (singlet, 3H, $-O\ CO-CH_3$), 4.5 (doublet, J = 2 Hz, 1H, bridgehead proton), 4.20 (multiplet, 1H, vinylic proton) and 2.7-3.2 (multiplet, 5H, aromatic protons).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65

Found: C, 67.75; H, 6.39; N, 4.65.

9. Reduction of Adduct (16A) with Lithium Aluminum Hydride: Diol (17A)

The adduct (16A) (0.5 g, 0.0017 mol) was dissolved in ice-cold dry ether (50 ml) and the resulting solution was added rapidly (2 min) to an ice-cold, stirred slurry of lithium aluminum hydride (0.35 g, excess) in 50 ml of dry ether. The reaction mixture was stirred at 0^0 for 2 hr. The excess hydride was decomposed by cautious addition of water (5 ml) and the resulting white precipitate was removed by filtration. The filtrate was dried and evaporated to yield a viscous oil (yield 0.325 g). The product was crystallized from pentane-ether mixture, mp $94-96^0$. The ir spectrum (Figure 19, Nujol) indicated complete absence of carbonyl absorption and had an intense band at 3450 cm^{-1}. The nmr spectrum (Figure 5, $CDCl_3$ solution) had signals at τ 8.80 (singlet, 3H), 8.50 (doublet, *J* = 1.4 Hz, 3H, allylic methyl), 8.45 (singlet, 3H), 7.08 (broad, 1H), 6.33 (broad, 1H), 6.08 (doublet, *J* = 1.8 Hz, 1H), 5.73 (broad, 1H), 4.27 (broad, olefinic proton) and multiplet centered at 3.05 (5H).

10. Cleavage of Diol (17A) with Sodium Metaperiodate

To a stirred solution of diol (17A) (0.322 g, 0.0012 mol) in absolute ethanol (30 ml) was added a solution of sodium metaperiodate (0.3 g, 0.0014 mol) in water (4 ml). Within a few minutes, a crystalline precipitate was deposited from the solution. Stirring was continued for 1 hr and then the mixture was filtered. Evaporation of the filtrate under reduced pressure gave a semi-solid residue. Water (5 ml) was added to this and then the mixture was extracted with methylene chloride. The extract was dried and evaporated to yield a brown viscous oil (yield 0.285 g, 90%). The ir spectrum (Figure 20, neat) showed a strong absorption between 1700 and 1735 cm^{-1}. The nmr spectrum (Figure 6, CCl_4 solution) had signals at τ 8.60 (singlet, 3H), 8.23 (quartet, *J* = 1.4 Hz, allylic methyl), 8.05 (singlet, 3H), 5.63 (broad, 1H), 4.17 (multiplet, 1H), 2.78 (multiplet, 5H, aromatic protons), and -0.67 (singlet, 1H, aldehyde proton).

11. The Diels-Alder Adduct (**22A**) from 2,3,4,6,6-Pentamethyl-2,4-cyclohexadienone (**19**) and Nitrosobenzene

The dienone **19**[23] (1.081 g, 0.006 mol), nitrosobenzene (0.705 g, 0.006 mol) and methylene chloride (15 ml) were refluxed for 4 hr when the green color of the solution disappeared. The solvent was removed by using a rotary evaporator and the oily residue was diluted with petroleum ether (30-60°). The clear solution at the top was decanted from some sludge which separated. Cooling the solution overnight in the refrigerator gave some solid crystals of the adduct. This was removed and once again recrystallized from the same solvent. The recrystallized product had a light brown color, yield 0.628 g (38%), mp 99-102°. The ir spectrum (Figure 21, Nujol) indicated bands at 1720 (s), 1590 (m), 1210 (w), 1030 (m), 800 (w), 765 (s), 720 (w), and 700 cm^{-1} (w). The nmr spectrum (Figure 7, $CDCl_3$ solution) had signals at τ 8.87, 8.55 and 8.52 (all singlets, each 3H), 8.52 and 8.33 (quartets, *J* = 1.2 Hz, each 3H), 5.98 (singlet, 1H) and 2.95-3.10 (multiplet, 5H).

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.35; H, 7.82; N, 5.18
Found: C, 75.24; H, 7.80; N, 5.16.

Dienone 19 was labeled at C-3 with CD_3 by deuterium exchange under mild conditions.[21] Thus 0.811 g (0.005 mol) of 19 was dissolved in 10 ml of methanol-d containing 0.2 g of sodium and the clear solution was kept for 4 hr at room temperature. It was then diluted with 200 ml of methylene chloride and washed thrice with ice-cold water and dried ($MgSO_4$). Removal of solvent yielded 0.727 g of the labeled dienone, the nmr spectrum ($CDCl_3$ solution) of which lacked the τ 7.97 quartet due to the allylic methyl group at C-3.[23]

Preparation of the adduct with nitrosobenzene from the labeled dienone and inspection of its nmr spectrum showed that the low-field allylic methyl signal at τ 8.33 was absent.

12. Reduction of Adduct 22A with Lithium Aluminum Hydride: Alcohol 23A

The adduct (1.36 g, 0.005 mol) dissolved in 25 ml of ice-cold ether was added to a slurry of 1 g (excess) of lithium aluminum hydride in 50 ml of ether at 0° within 5 min. No evidence of dissociation of the adduct was noticed when it was dissolved in ether. Stirring was continued at 0° for 2 hr. Excess hydride was decomposed cautiously with water, and the mixture was filtered. Evaporation of filtrate gave quantitative yield of a solid product. Recrystallization from pentane gave a crystalline material, mp 113-114°, yield 1.16 g (85%). The ir spectrum

(Figure 22, Nujol) had principal bands at 3300 (s, O-H), 1598 (s), 1205 (m), 1170 (m), 1140 (m), 1060 (s), 1035 (m), 1000 (w), 920 (m), 820 (m), 780 (s), 760 (s) and 700 (s) cm^{-1}. The nmr spectrum (Figure 8, CDCl$_3$ solution) had signals at τ 9.03 (singlet, 3H), 8.73 (singlet, 3H), 8.60 (quartet, *J* = 1.2 Hz, 3H), 8.55 (singlet, 3H), 8.32 (quartet, *J* = 1.2 Hz, 3H), 7.88 (broad, 1H), 7.05 (broad, 1H), 6.43 (singlet, 1H), and 2.73-3.23 (multiplet, 5H).

13. The Diels-Alder Adduct **24B** from 3,4,5,6,6-Pentamethyl-2,4-cyclohexadienone (**21**) and Nitrosobenzene

The dienone **21**[23] (0.250 g, 0.015 mol), nitrosobenzene (0.164 g, 0.015 mol) and methylene chloride (2.5 ml) were stirred together at room temperature. The green color of the solution disappeared after 18 hr. The solvent was evaporated at reduced pressure and the viscous oil that was obtained was dissolved in petroleum ether (30-60°) and cooled in the refrigerator. After several days, crystals were deposited and these were removed. The recrystallized adduct had a mp of 70°. The ir spectrum (Figure 23, Nujol) had principal bands at 1730 (s, >C=O), 1630 (>C=C<), 1600 (m), 1395 (m, doublet, *gem*-dimethyl), 1300 (w), 1170 (m), 1120 (m), 870 (w), 800 (s), 725 (s) and 710 (m) cm^{-1}. The nmr spectrum (Figure 9, CCl$_4$) showed signals at τ 9.07 (singlet, 3H), 8.83 (singlet, 3H), 8.60 (singlet, 3H), 8.52 (quartet, *J* = 1.1 Hz, 3H), 8.23 (quartet, *J* = 1.1 Hz, 3H), 5.93 (singlet, 1H), and 2.7-2.9 (multiplet, 5H).

14. The Diels-Alder Adduct (26B) from 2,3,4,5,6,6-Hexamethyl-2,4-cyclohexadienone (25) and Nitrosobenzene

The dienone 25[21,39] (1.78 g, 0.01 mol), and nitrosobenzene (1.07 g, 0.01 mol) were dissolved in 1,2-dichloroethane (25 ml) and the green solution thus formed was refluxed in an oil bath at 100-110° until the color disappeared (2 hr). The solvent was removed using a rotary evaporator, leaving a residue as a brown viscous oil. This was dissolved in petroleum ether (30-60°) and cooled overnight in the refrigerator. The first crop of crystals that were deposited were removed (yield 1.4 g, 50%) and had mp 77-78°. The ir spectrum of the mother liquor was identical to that of the crystalline adduct. This was further redissolved in petroleum ether and cooled when a second crop of crystals of the adduct was obtained (0.42 g, 15%). The ir spectrum (Figure 24, Nujol) indicated absorption at 1720 (C=O), 1640 (w), 1590 (m), 1392 (s), 1300 (w), 1220 (m), 1120 (w), 1090 (m), 1080 (m), 1035 (m), 950 (w), 815 (w), 788 (s), and 707 (s) cm^{-1}. The nmr spectrum (Figure 10, CCl_4) had signals at τ 9.03 (singlet, 3H), 8.89 (singlet, 3H), 8.76 (singlet, 3H), 8.60 (singlet, 3H), 8.57 (quartet, *J* = 1.2 Hz, 3H), 8.04 (quartet, *J* = 1.2 Hz, 3H) and 2.94-3.00 (multiplet, 5H).

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91

Found: C, 75.85; H, 8.25; N, 4.92.

15. The Diels-Alder Adduct from 2,4,6,6-Tetramethyl-3,5-dimethyl-d_6-2,4-cyclohexadienone

The labeled dienone was prepared from **25** according to the procedure reported in lit.[21] The labeled adduct was prepared from 1.74 g (0.01 mol) and nitrosobenzene (1.07 g, 0.01 mol) as described before. The adduct was obtained in crystalline form only after cooling the solution in petroleum ether for several days in the refrigerator. Inspection of the nmr spectrum of the product ($CDCl_3$) showed that the signals at τ 8.60 and 8.57 were absent, and that the quartet at τ 8.04 became a singlet.

16. Catalytic Hydrogenation Studies on the Adduct (**26B**)

The adduct (0.57 g, 0.002 mol) was dissolved in 25 ml of glacial acetic acid and hydrogenated at atmospheric pressure using pre-reduced Adams' catalyst (~ 40 mg). The volume of hydrogen absorbed corresponded to 5 mols. Work up of the product yielded 0.33 g of an oil having a typical amine-like odor. The ir spectrum showed strong absorption at 1700 cm^{-1} (ketone) and weak absorption at 3500 cm^{-1}.

The hydrogenation was repeated in ethanol solution using the same catalyst. Uptake of hydrogen corresponded to 2 mols under these conditions. Work-up of product gave a low yield (0.22 g) of an oil. The ir spectrum had strong absorption at 1660 cm^{-1} and medium absorption at 3400-3500 cm^{-1}.

Column chromatography of the hydrogenated product gave fractions rich in aniline (characterized by ir and nmr) and products arising out of hydrogenation of the starting dienone. The later fractions exhibited bands in the ir (neat) in the 1700 cm^{-1} region and gave no signals for aromatic protons in the nmr.

17. Reduction of Adduct (26B) from Hexamethyldienone 25 with Zinc and Acetic Acid

The adduct (2.85 g, 0.01 mol) was dissolved in glacial acetic acid (120 ml) in a 500-ml three-necked flask. Zinc dust (25 g) was then added portionwise in the course of 1/2 hr while the mixture was stirred with a mechanical stirrer. Stirring was continued for 3 hr and the product worked up by dilution with ether, followed by filtration. The clear filtrate was evaporated using a rotary evaporator until all the ether and most of the acetic acid was removed under reduced pressure. The residue was diluted with water, neutralized with sodium bicarbonate and extracted twice with benzene and the benzene extract was dried. Removal of solvent gave a reddish oil (yield 2.247 g). The ir spectrum (liquid film) had strong bands at 3500, 3400 (N-H and O-H), 1700 (carbonyl), 1620 and 1600 cm^{-1}. The nmr spectrum of the product indicated that the product was impure. The product was then subjected to column chromatography using 50 g of Florisil. The first fractions eluted with methylene chloride had strong bands in the ir spectrum at 1700 cm^{-1}

and no aromatic protons in the nmr spectrum. The subsequent fractions from the column were rich in aniline as judged from ir and nmr spectra and comparison with an authentic sample.

18. Reduction of Adduct **26B** with Lithium Aluminum Hydride

The adduct (0.285 mg, 0.001 mol) was dissolved in 15 ml of dry ether and added dropwise in 1/2 hr to a slurry of 0.5 g of lithium aluminum hydride in 20 ml of dry ether. The mixture was stirred for a further period of 1 hr at 0°. Excess hydride was decomposed by cautious addition of water, and the resulting suspension was filtered through a sintered funnel. The filtrate was dried ($MgSO_4$) and solvent removed under reduced pressure. The product was a yellow viscous oil, yield 241 mg (85%). The ir spectrum of the crude product (Figure 25, neat) showed complete absence of carbonyl absorption; a strong band at 3500 cm^{-1} indicated presence of O-H. The nmr spectrum ($CDCl_3$) had signals at τ 9.17 (multiplet), 8.92, 8.77, 8.67, 8.58 (quartet, *J* = 1.2 Hz), 8.10 (quartet, *J* = 1.2 Hz) all integrating to approximately 3H each, due to the six methyl groups. None of the methyl signals were sharp singlets, as would be expected from a pure product; additional signals were noted at τ 8.30 (1H), 7.05 (broad, 1H) and 2.85-3.10 (5H).

In another experiment, the adduct (285 mg, 0.001 mol) was dissolved in 20 ml of dry tetrahydrofuran and this solution added dropwise to 0.3 g of lithium aluminum hydride in

50 ml of tetrahydrofuran with stirring and cooling. Addition was completed in 15 min. After being stirred at 0^{o} for 2 hr, the mixture was refluxed for 4 hr. It was then cooled, and excess hydride was decomposed by careful addition of water. The suspension was then filtered and the filtrate was evaporated to yield an oil (260 mg). The ir and nmr spectra of the product were very similar to those of the product from reduction in ether solution.

19. Attempted Oxidation of the Alcohol with Sodium Metaperiodate

The product obtained from the lithium aluminum hydride reduction (in tetrahydrofuran, as described above) was submitted to periodate cleavage. Thus 480 mg (0.0017 mol) of the reduction product was dissolved in 25 ml of absolute ethanol and to this stirred solution, an aqueous solution of 0.5 g (excess) of sodium metaperiodate in 5 ml of water was added and the mixture was stirred for 1/2 hr. Some suspended matter separated from the solution. This was removed by filtration and the filtrate was evaporated under reduced pressure. The residue consisted of a white solid and a yellow oil. This was further diluted with water and extracted with methylene chloride. The extract was washed with water and then dried ($MgSO_4$). Removal of solvent yielded 430 mg of a viscous liquid. The ir spectrum did not show any carbonyl absorption and was identical with that of the starting material.

20. Reduction of the Alcohol (from Lithium Aluminum Hydride Reduction of Adduct 26B) with Zinc and Acetic Acid, and Attempted Oxidation

The alcohol (409 mg, 0.0014 mol) from lithium aluminum hydride reduction of 26B , was dissolved in 10 ml of glacial acetic acid in a 100-ml three-necked flask and to this mechanically stirred solution was added 1.8 g of zinc dust. The flask was warmed in an oil bath at 50° and stirring continued for 9 hr. The product was worked up as described in the reduction of the adduct 26B; the yield of a brown mobile liquid was 352 mg. The ir spectrum indicated a strong carbonyl band at 1720 cm^{-1} (acetate) and a strong hydroxyl band at 3400-3500 cm^{-1}. The nmr spectrum had a strong signal at τ 7.80, but was otherwise complex and pointed to the presence of more than one component. Column chromatography on silica gel (10 g) resulted in obtaining fractions having no aromatic protons in the nmr spectra, but having vinylic protons between τ 4.75 and 5.05.

Periodate oxidation as described for the dienone-adduct 26B above did not give any carbonyl-containing fragment. The oxidation was repeated after further reduction of the acetates with lithium aluminum hydride. In this case also no identifiable single product was obtained. The ir spectrum of the product showed no carbonyl absorption.

21. The Diels-Alder Adduct (**33A**) from Eucarvone (**32**) and Nitrosobenzene

Eucarvone (**32**) was prepared according to the method of Corey and Burke.[43] The nmr spectrum (CCl_4 solution) had signals at τ 8.93 (singlet, 6H), 8.13 (doublet, *J* = 1.7 Hz), 7.43 (singlet, 2H), 4.0-4.5 (2H, multiplet) and 3.6 (1H, doublet, further split to quartets).[45] Eucarvone (7.5 g, 0.05 mol), nitrosobenzene (5.35 g, 0.05 mol) and methylene chloride (150 ml) were stirred together at room temperature for 10 hr, by which time the green color of the solution disappeared. The solvent was removed at reduced pressure and the residual oil was redissolved in pentane and cooled overnight in the refrigerator. The crystals which were deposited were removed and amounted to 9.8 g (77% yield). Recrystallization from the same solvent yielded light yellow crystals of the adduct, mp 56-57°. The uv spectrum had λ_{max}^{MeOH} 285 nm (shoulder), ϵ = 162; 244 nm, ϵ = 7558; 208 nm, ϵ = 10,400. The ir spectrum (Figure 26, Nujol) had strong absorption at 1705 ($>$C=O), 1655 ($>$C=C$<$), 1595, 1375, 1240, 1180, 1090, 1020, 862, 770 and 700 cm^{-1}. The nmr spectrum (Figure 11, $CDCl_3$) had signals at τ 8.93 (singlet, 3H), 8.55 (singlet, 3H), 8.38 (singlet, 3H), due to the three methyl groups, two doublets at 7.74 and 6.59 (1H each, *J* = 22 Hz, geminal coupling of the methylene protons; the former doublet was split into further doublets with *J* = 1 Hz due to long-range coupling with the bridgehead proton), 6.02 (doublet, 1H, *J* = 10 Hz, further split into multiplets, bridgehead proton), 3.72-3.95 (multiplet, 2H, olefinic protons) and 2.60-3.08 (multiplet, 5H, aromatic protons).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44

Found: C, 74.86; H, 7.60; N, 5.55.

22. Reduction of Adduct (33A) with Lithium Aluminum Hydride: Alcohol (34)

A solution of the adduct (1.3 g, 0.005 mol) in dry ether (100 ml) was added dropwise to a mechanically stirred slurry of lithium aluminum hydride (0.5 g, excess) in 200 ml of ether at 0°. Stirring was continued for a further period of 2 hr at 0°. Excess hydride was decomposed by cautious addition of water and the product was filtered through a sintered funnel. The solvent was removed at reduced pressure when a semi-solid residue was obtained in quantitative yield. This was recrystallized from a 1:1 mixture of ether-petroleum ether (40-60°). The yield of a light, white, fibrous solid amounted to 0.65 g (50%), mp 159-160°. The ir spectrum (Figure 27, Nujol) had principal bands at 3250 (O-H), 1600, 1230, 1055, 1035, 1020, 850, 760, and 700 cm^{-1}. The nmr spectrum (Figure 12, $CDCl_3$ solution) showed signals at τ 8.95 (singlet, 3H), 8.72 (singlet, 3H), 8.40 (singlet, 3H) for the three methyl groups. The two $-CH_2-$ protons and the -C<u>H</u>OH proton were not well resolved and had signals in the region 8.27-8.75; other signals were at τ 6.33 (broad, 1H, hydroxyl proton), 6.11 (broad, multiplet, 1H, bridgehead proton), 3.85-4.17 (multiplet, 2H, olefinic protons) and 2.80-3.18 (multiplet, 5H, aromatic protons).

Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40

Found: C, 74.14; H, 8.10; N, 5.37.

The liquid portion which failed to crystallize had principal bands in its ir spectrum (Figure 28, neat) at 3450 (O-H), 1600, 1220, 1145, 1040, 950, 860, 820, 760 and 700 cm^{-1}. The nmr spectrum ($CDCl_3$) showed signals at τ 9.02 (singlet, 3H), 8.62 (singlet, 3H), 8.45 (singlet, 3H) due to the three methyl groups, 8.30 (doublet, *J* = 6 Hz, 2H, $-CH_2-$), 7.35 (broad, 1H) and 6.38 (broad, 1H), 6.17 (multiplet, 1H, bridgehead proton), 3.93-3.95 (multiplet, 2H, olefinic protons) and 2.83-3.15 (multiplet, 5H, aromatic protons).

23. Reduction of Alcohol 34 with Zinc and Acetic Acid: Amino Diol 35

The crystalline alcohol 34 (1.30 g, 0.005 mol) was dissolved in 55 ml of glacial acetic acid in a three-necked flask fitted with a mechanical stirrer and a reflux condenser. Zinc dust (5 g, excess) was added and the mixture was stirred at 50-55° (oil bath) for 14 hr. It was then cooled, extracted with ether and the ether extract was filtered. Ether was removed at reduced pressure, the residue was diluted with water and neutralized with concentrated ammonium hydroxide. The neutral mixture was then extracted with ether and the ether extract was washed with water and dried.

Removal of solvent gave a light pink solid material in quantitative yield. This was recrystallized from ether and had mp 118-119^0. The ir spectrum (Figure 29, Nujol) had principal bands at 3400 (O-H), 3260 (N-H), 1600, 1520, 1325, 1100, 1055, 1020, 950, 760 and 700 cm^{-1}. The nmr spectrum ($CDCl_3$ solution) had signals at τ 8.93 (singlet, 3H), 8.90 (singlet, 3H), 8.63 (singlet, 3H), 8.18 (doublet, *J* = 6 Hz, 2H, $-CH_2-$), 7.15 (broad, 2H), 6.00-6.35 (unresolved, 3H), 4.15-4.85 (multiplet, 2H, olefinic protons) and 2.77-3.58 (multiplet, 5H, aromatic protons).

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36

Found: C, 73.37; H, 8.77; N, 5.30.

Similar reduction of the liquid alcohol 34 with zinc and acetic acid gave a quantitative yield of a different amino diol, mp 95-96^0. The ir spectrum (Figure 30, Nujol) had principal bands at 3380 (O-H), 3260 (N-H), 1600, 1310, 1260, 1140, 1030, 900, 760 and 730 cm^{-1}. The nmr spectrum ($CDCl_3$) had signals at τ 8.98 (singlet, 3H), 8.88 (singlet, 3H), 8.62 (singlet, 3H), 7.63-8.40 (multiplet, 3H), 6.25-6.53 (broad, 4H), 4.34-4.37 (multiplet, 2H, olefinic protons) and 2.77-3.50 (multiplet, 5H, aromatic protons).

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36

Found: C, 73.31; H, 8.87; N, 5.23.

24. Oxidation of Amino Diol (35) with Sodium Metaperiodate

The isomer mp 118-119^0 of the crystalline amino diol 35 (261 mg, 0.001 mol) was dissolved in 30 ml of methanol and to this was added a solution of 0.45 g (0.002 mol) of sodium metaperiodate dissolved in 5 ml of water. The mixtures was stirred magnetically at room temperature for 3 hr. Precipitation of sodium iodate was observed within a short time. This was filtered, and the filtrate was evaporated at reduced pressure. The residue was diluted with water and extracted with methylene chloride. The extract was washed twice with 10-ml portions of water and dried. The solvent was removed at reduced pressure and the residue was evacuated at 0.1 mm for 30 min to remove any volatile fragments resulting from the oxidation. Final yield of product did not change as a result of the evacuation, indicating that fragments such as aniline were not formed. The product was obtained as a brown oil. This was chromatographed through a column of silica gel (5 g) and the first fraction eluted with benzene (yield 105 mg) was collected as a yellow oil. The ir spectrum (Figure 31, neat) had principal bands at 3050 (aldehyde), 1718 (aldehyde), 1690 (α,β-unsaturated ketone), 1600, 1185, 1050, 770 and 690 cm^{-1}. The nmr spectrum (CCl_4) indicated that the product was still contaminated with probably secondary products. However, the signal due to the aldehyde proton was clearly noticeable at τ 0.60 as a triplet ($\underline{J}$ = 3 Hz) due to coupling with the adjacent methylene protons.

Oxidation of the isomeric amino diol **35**, mp 102-103°, also gave the same unstable aldehyde in comparable yield, after column chromatography, in a purer state. The nmr spectrum (Figure 13, CCl_4) had prominent sharp bands at τ 8.82 (singlet, *gem*-dimethyls), 8.23 (singlet, $CH_3-\overset{O}{\overset{\parallel}{C}}-$), 7.82 (doublet, -C*H*$_2$-), 4.23 (multiplet, olefinic protons), 2.75 (aromatic protons) and 0.60 (triplet, *J* = 3 Hz). The integration was approximately in agreement with this assignment. However, there were a few other signals also in the nmr spectrum with much lower intensities.

25. Reduction of Eucarvone by Lithium Aluminum Hydride: Eucarveol (**39**)

Eucarvone (1.5 g, 0.01 mol) dissolved in 30 ml of dry ether was added during 15 min to a well stirred slurry of 0.5 g (excess) of lithium aluminum hydride in 100 ml of ether at 0°. The mixture was stirred for a further period of 2 hr. Excess hydride was destroyed by cautious addition of water and the mixture was filtered. Evaporation of solvent under reduced pressure, followed by removal of last traces of solvent and moisture at 0.1 mm gave an oil (yield 1.36 g). The ir spectrum (neat) had principal bands at 3400 (O-H), 1640, 1620 ($>C=C<$), 1135, 1080, 1030, 930 and 760 cm^{-1}. The nmr spectrum ($CDCl_3$ solution) had signals at τ 8.97 (singlet, 3H) and 8.92 (singlet, 3H) due to the *gem*-dimethyls, 8.15 (quartet, *J* = 1.5 Hz, 3H, allylic methyl), 8.03-8.25 (multiplet, 2H, -CH$_2$-), 6.78 (broad, 1H, disappears on shaking with D_2O, hydroxyl proton), 5.77 (broad doublet, *J* = 15 Hz, C*H*-OH) and 4.62 (singlet, 3H, vinylic protons).

26. The Diels-Alder Reaction of Eucarveol (**39**) with Nitrosobenzene: Adduct (**34**)

Eucarveol (1.36 g, 0.009 mol), nitrosobenzene (0.91 g, 0.009 mol) and methylene chloride (50 ml) were stirred together at room temperature for 24 hr. The solvent was evaporated under reduced pressure and the residual oil redissolved in 1:1 mixture of ether-petroleum ether (40-60°) and cooled in the refrigerator overnight. Crystals deposited and were filtered (yield 0.4 g, 17%, mp 159-160°). The ir and nmr spectra were superimposable with those of alcohol **34**. A mixed mp did not show any depression. The liquid portion which did not crystallize even on prolonged cooling was found to contain some unreacted starting materials and was not further investigated.

27. Irradiation of Adduct **26B** from Hexamethyldienone **25**

The uv spectrum of the adduct **26B** had λ_{max}^{EtOH} 308 nm (ϵ = 5698), 281 nm (ϵ = 6045) and 208 nm (ϵ = 12610). The adduct (100 mg) was dissolved in 10 ml of ether and degassed with purified N_2 for 15 min. It was then irradiated in a Pyrex test tube with a 450 watt Hanovia L Type lamp for 2 hr. The uv spectra indicated a new maximum at 245 nm. The product was separated by vpc. The ir and nmr spectra of the product indicated it to be pure 1,3,4,5,6,6-hexamethylbicyclo[3.1.0]hex-3-ene-2-one (**40**).[21]

28. Irradiation of Adduct 22A from Pentamethyldienone 19

The adduct 22A (67 mg) was dissolved in anhydrous ether to make up a 1% solution, and after degassing with N_2 for 1/2 hr, the solution was irradiated in a Pyrex test tube with a 450 watt Hanovia Type L lamp. The progress of the reaction was followed by uv measurements (Figure 33). The maxima at 308 nm and 282 nm gradually decreased while that at 249 nm increased during 45 min. The nmr spectrum of the product indicated that much of the starting material was still unchanged. Vpc separation gave only one fraction which was identified as the dienone 19 resulting from thermal dissociation of the adduct.

When the irradiation was repeated under the above conditions, but using acetone as solvent, photolysis appeared to be complet in 12 hr, as shown by uv analysis (Figure 34). The nmr spectrum of the product was complex. Attempts to separate the product by chromatography were unsuccessful.

29. Irradiation of Adduct 33A from Eucarvone 32

The adduct (70 mg) was dissolved in 7 ml of ether, and after degassing by flushing with N_2 for 15 min, irradiated using a 450 watt Hanovia lamp through vycor. Progress of reaction was followed by uv (Figure 35). At the end of 22 hr, product was worked up. The ir and nmr spectra indicated mainly starting material.

Irradiation of 33A was then repeated in ether solution using light of wavelength 2537 Å in a Rayonet chamber. Thus 60 mg of adduct dissolved in 10 ml of dry ether in quartz test tube was irradiated for 5 hr. The progress was followed by uv (Figure 36). Separation of product by vpc gave pure eucarvone, resulting from thermal dissociation.

30. Irradiation of Adduct 8A from Tetramethyldienol 7

The adduct (518 mg) was dissolved in 50 ml of methanol. The solution was flushed with purified N_2 for 45 min. The solution was taken in the inner chamber of a quartz well and closed with a two-holed rubber stopper carrying an inlet tube for purified N_2. The gas was bubbled into the solution throughout the photolysis to keep the solution stirred. The progress of reaction was followed by taking uv spectra at frequent intervals (Figure 37). At the end of 5 1/2 hr the photolysis was stopped and the product subjected to column chromatography using Florisil. Nine fractions were collected, using progressively polar solvents. Only the ether fraction (107 mg) showed spectra that could be attributed to a reasonably pure material. The ir spectrum (Figure 32) had strong absorption at 3450 (O-H), and medium absorption from 1700-1640 cm^{-1}. The nmr spectrum (Figure 14, $CDCl_3$) had signals at τ 9.12 (singlet, 3H), 8.93 (singlet, 3H), 8.70 (singlet, 3H), 8.53 (singlet, 3H), 8.17 (singlet, 1H), 6.77-7.20 (broad, 3H) and 2.75-3.33 (5H).

31. Irradiation of Adduct 34 from Eucarveol 39

In a typical experiment, 518 mg of the adduct was dissolved in 100 ml methanol. The solution was flushed with N_2 for 1/2 hr and then irradiated in the Rayonet chamber at 2537 Å for 10 hr. The uv spectra are given in Figure 38. The product was chromatographed over silica gel. No fraction, sufficiently pure for characterization was obtained.

SPECTRA

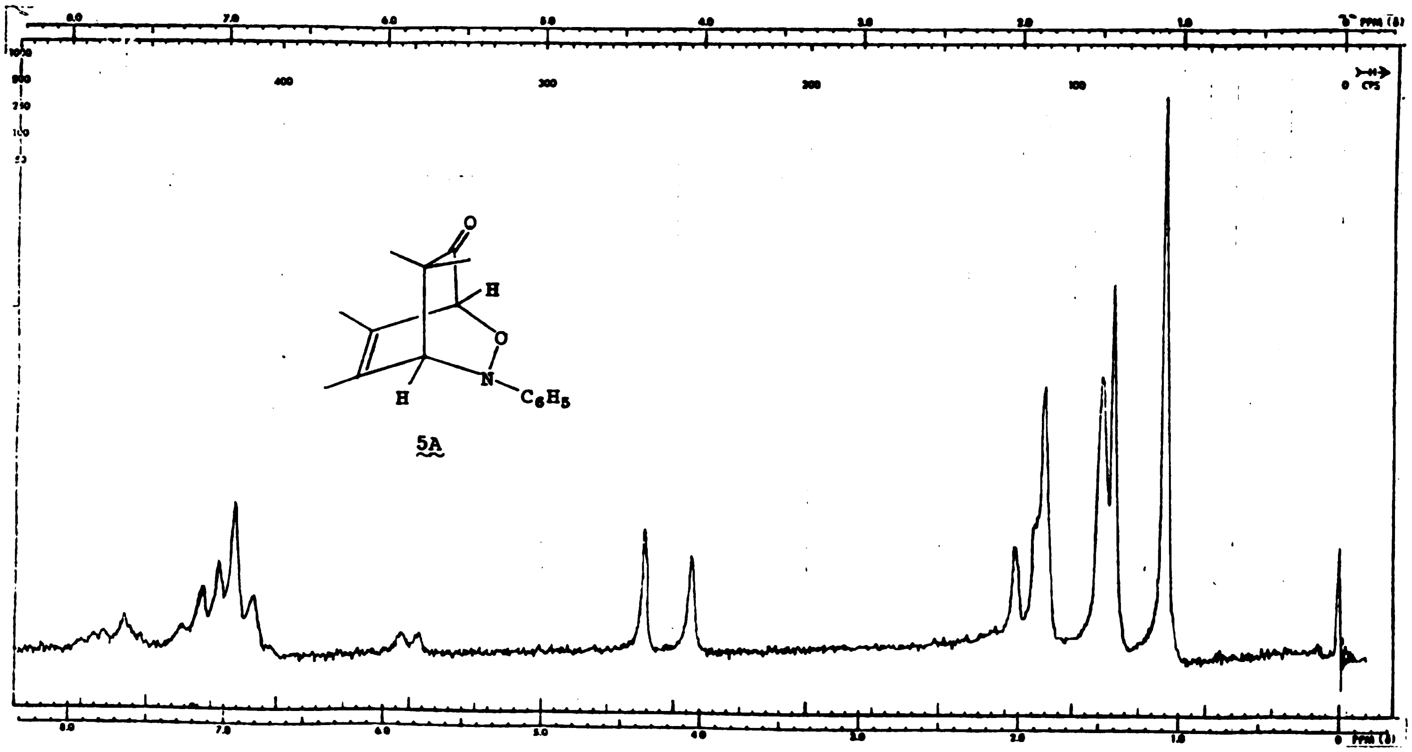


Figure 1. Nmr spectrum (CCl_4) of adduct 5A from 3,4,6,6-tetramethyl-2,4-cyclohexadienone (1).

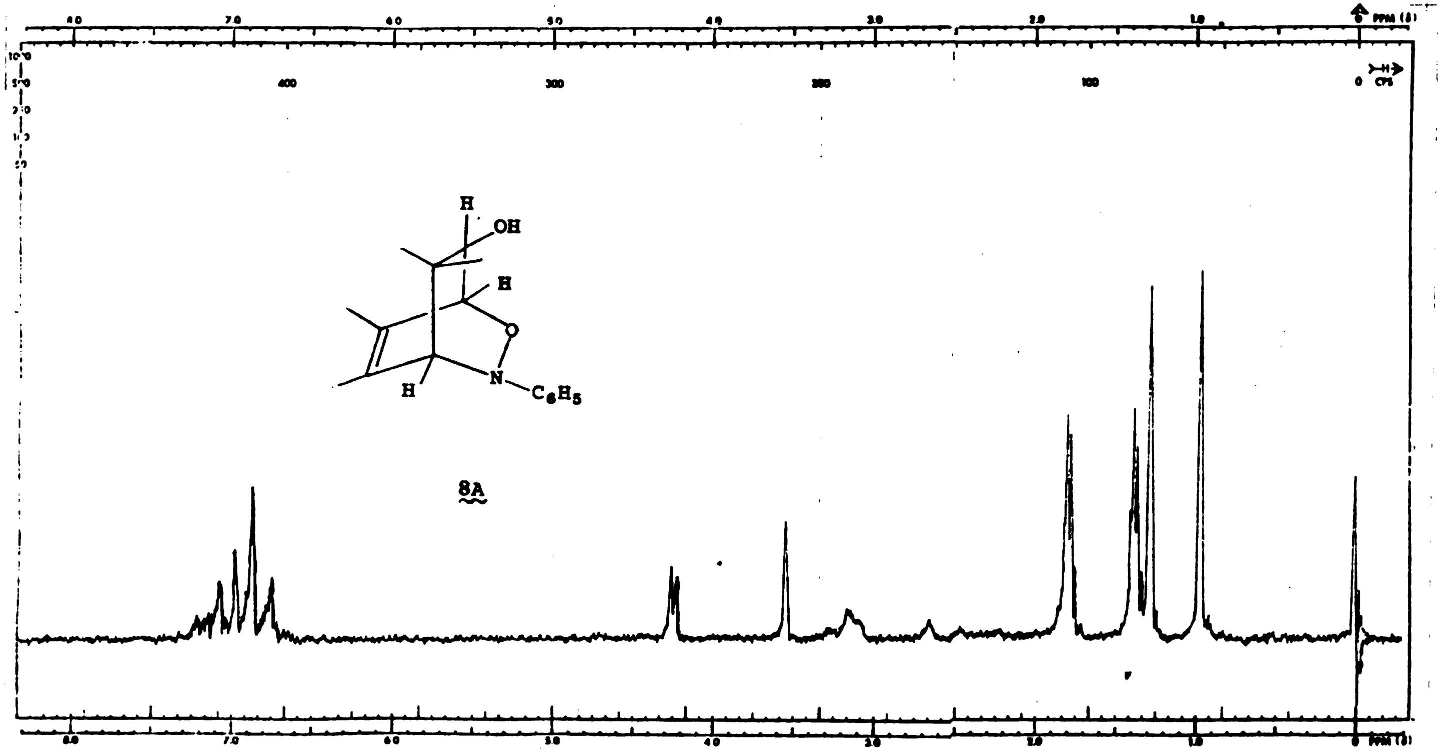


Figure 2. Nmr spectrum (CDCl$_3$) of adduct 8A from 3,4,6,6-tetramethyl-2,4-cyclohexadienol (7).

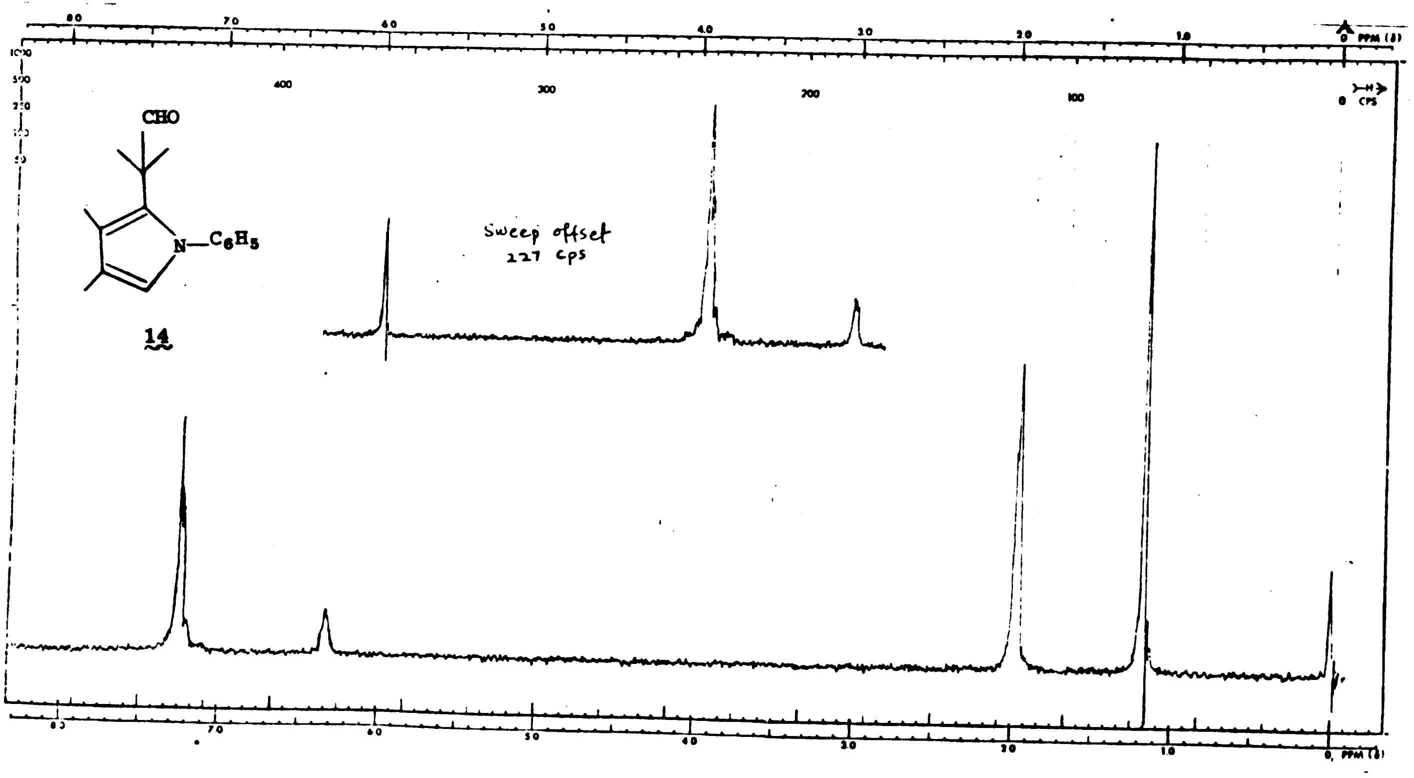


Figure 3. Nmr spectrum ($CDCl_3$) of pyrrole 14.

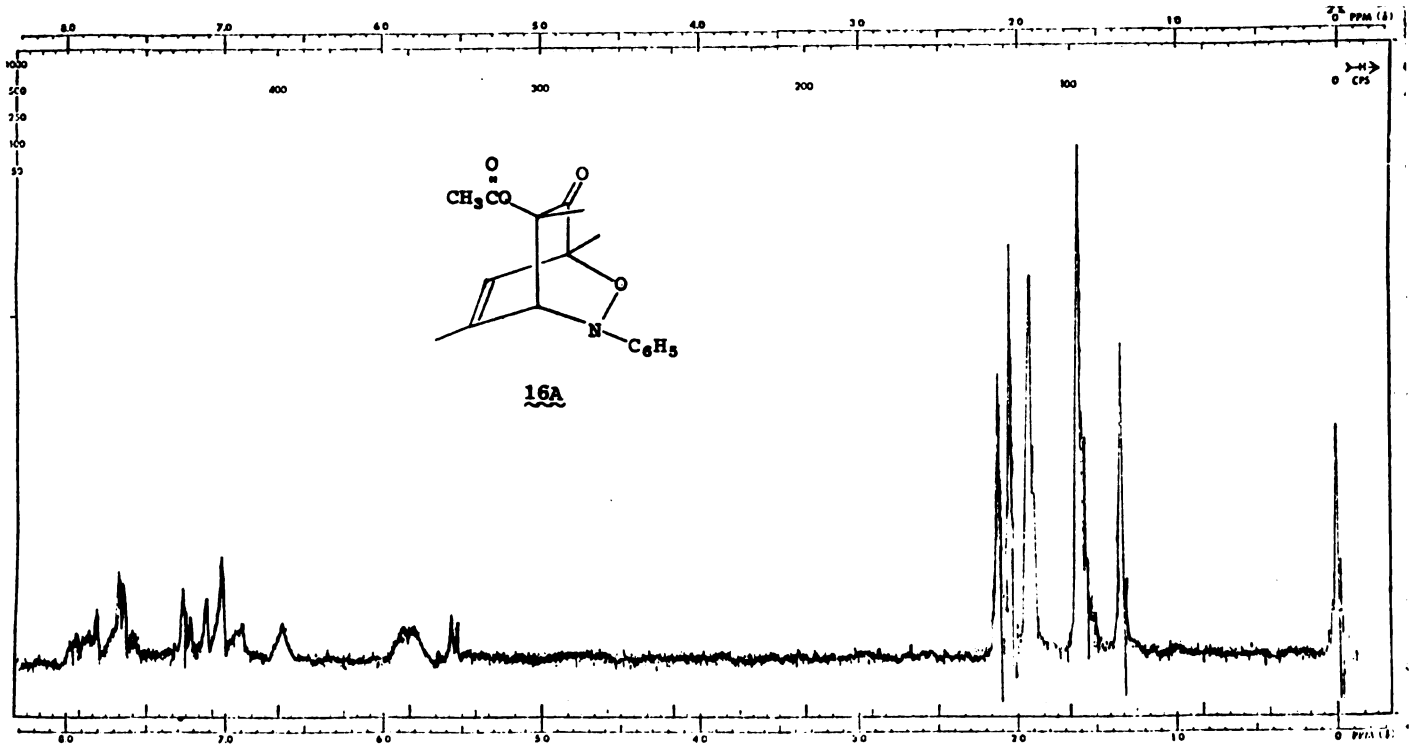


Figure 4. Nmr spectrum ($CDCl_3$) of adduct 16A from 6-acetoxy-2,4,6-trimethyl-2,4-cyclohexadienone (15).

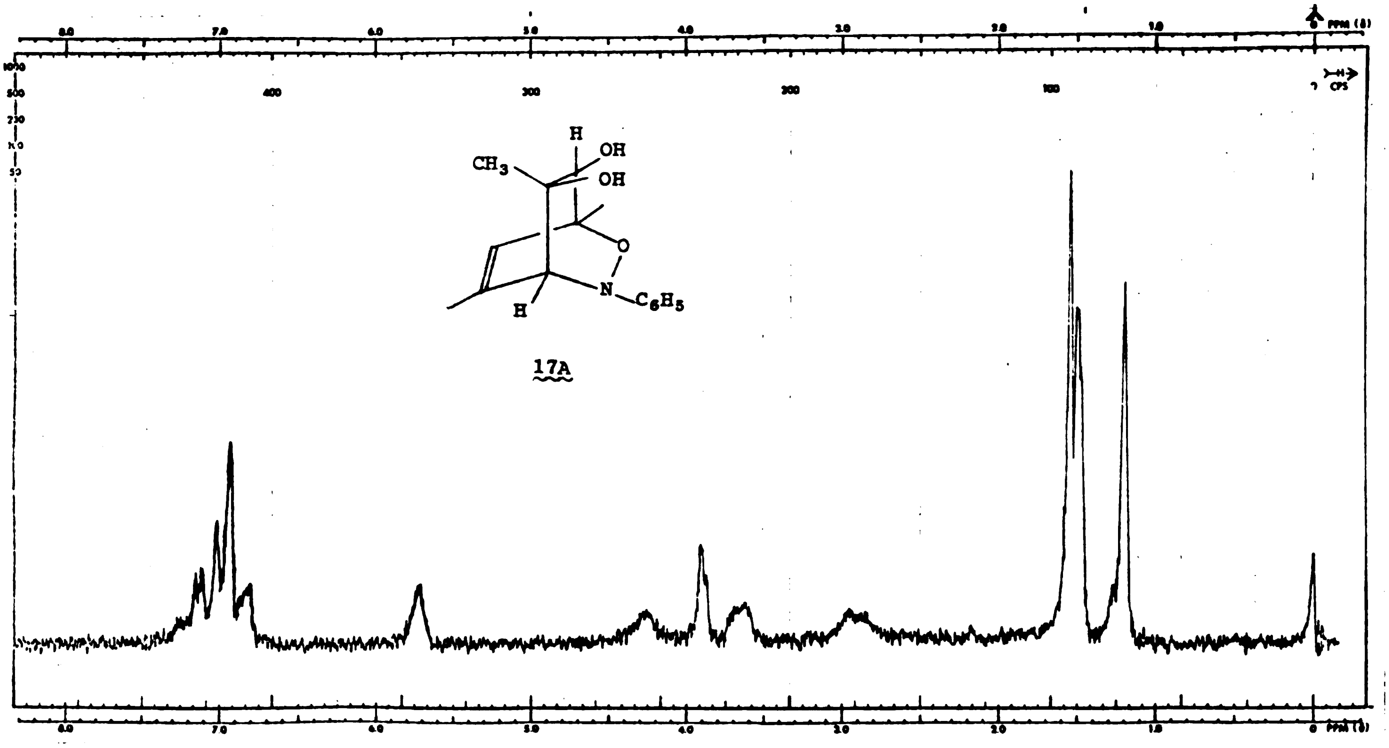


Figure 5. Nmr spectrum ($CDCl_3$) of diol 17A.

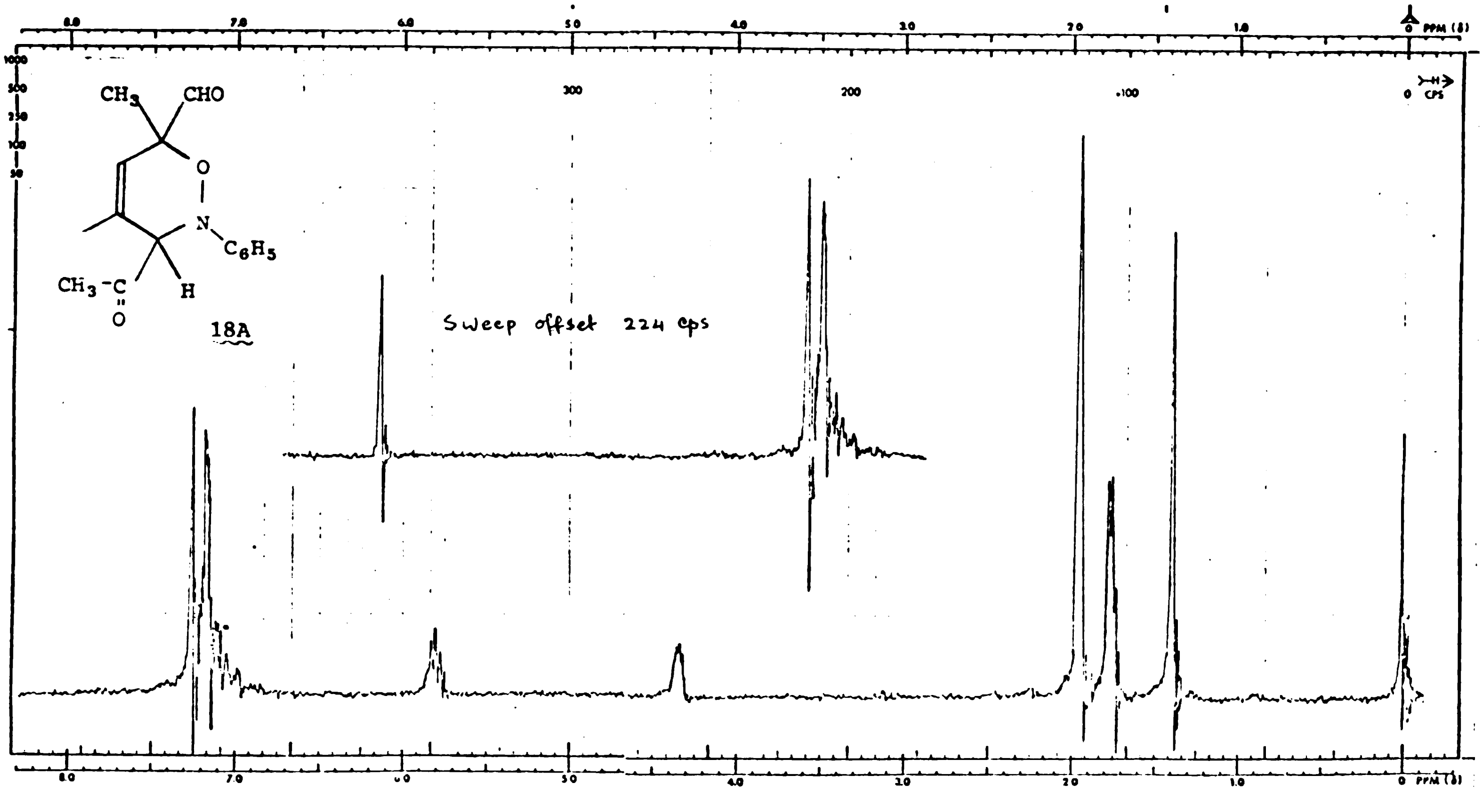


Figure 6. Nmr spectrum (CCl_4) of periodate-cleavage product 18A from diol 17A.

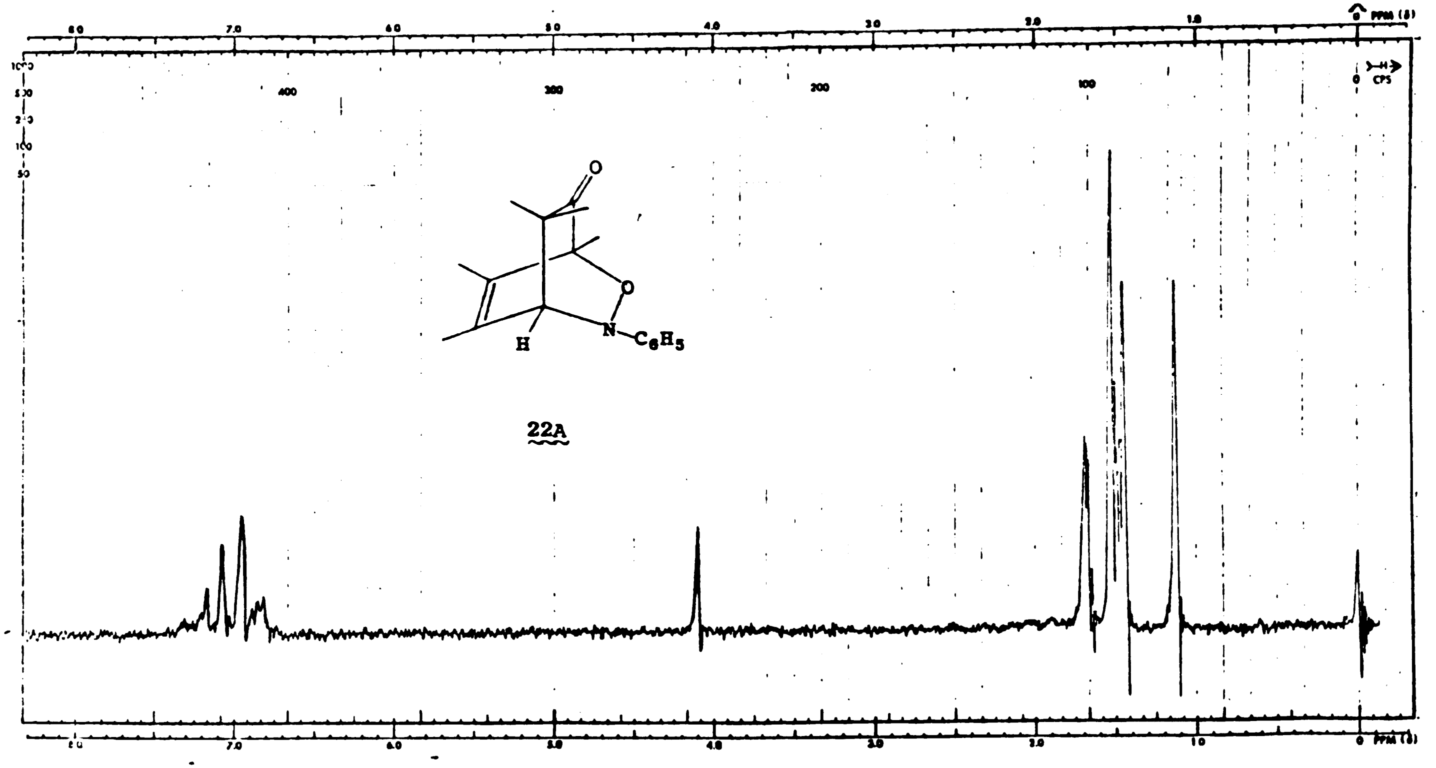


Figure 7. Nmr spectrum ($CDCl_3$) of adduct 22A from 2,3,4,6,6-pentamethyl-2,4-cyclohexadienone (19).

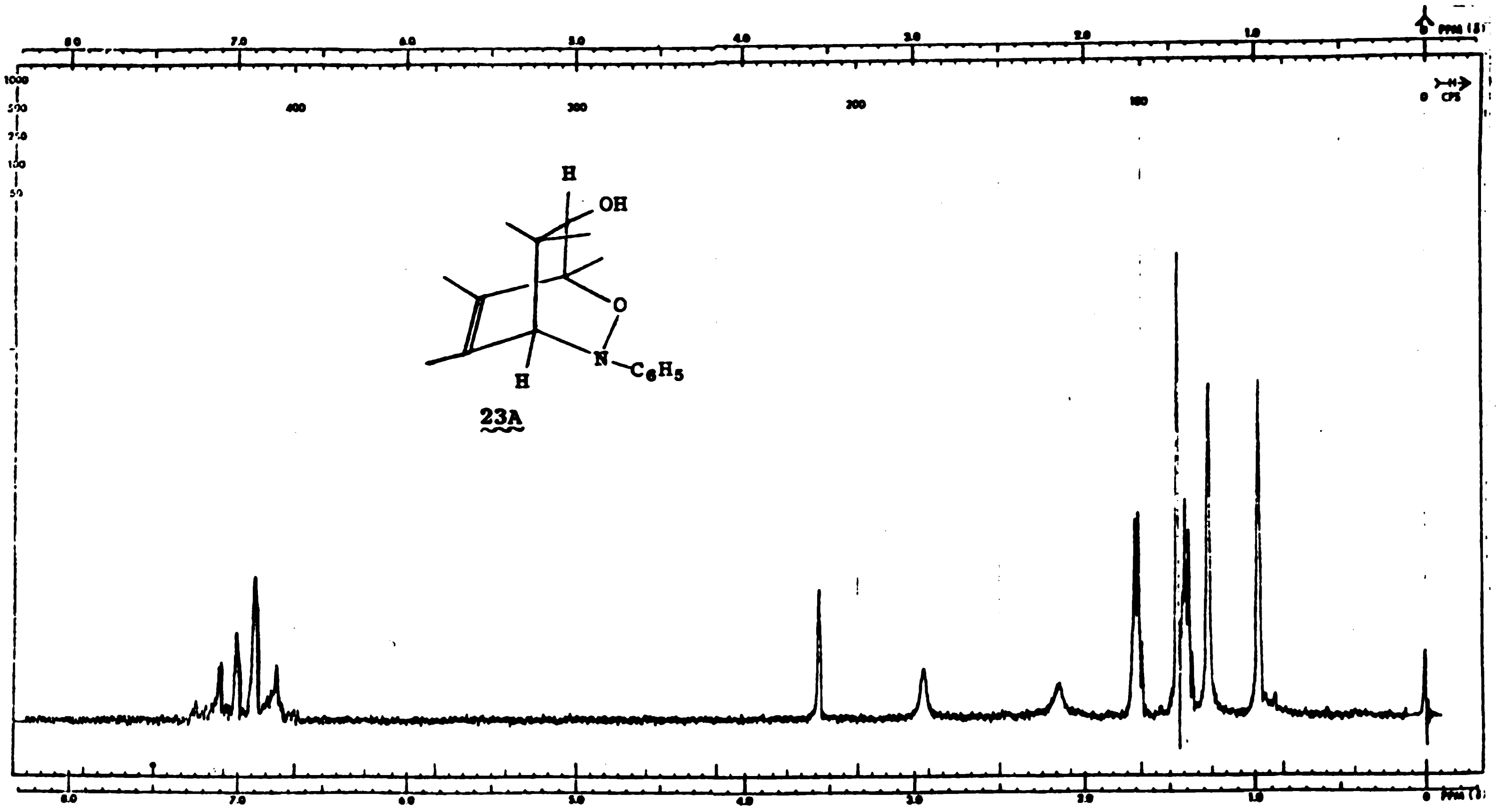


Figure 8. Nmr spectrum ($CDCl_3$) of alochol 23A from reduction of adduct 22A.

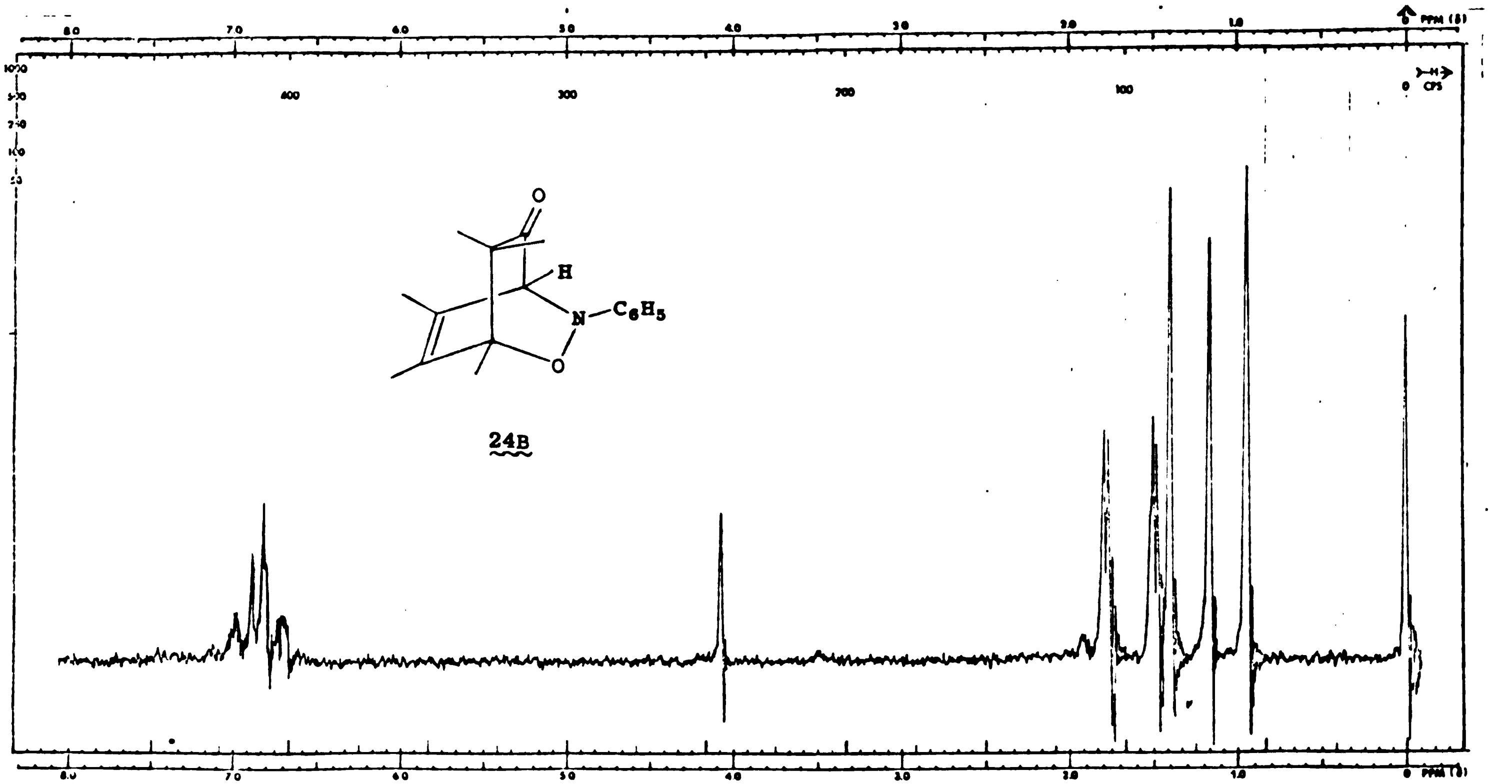


Figure 9. Nmr spectrum (CCl$_4$) of adduct 24B from 3,4,5,6,6-pentamethyl-2,4-cyclohexadienone (21).

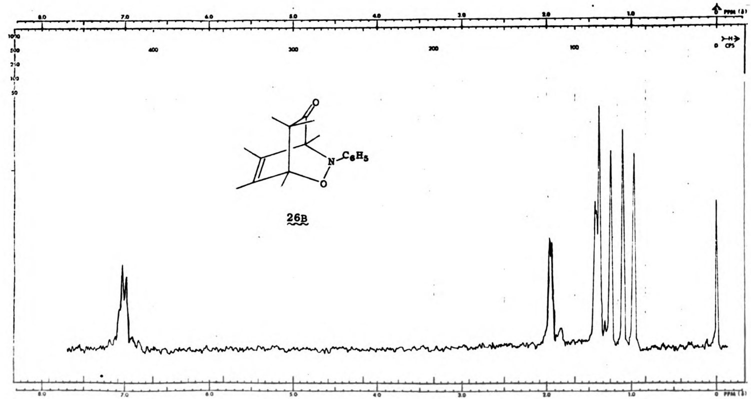
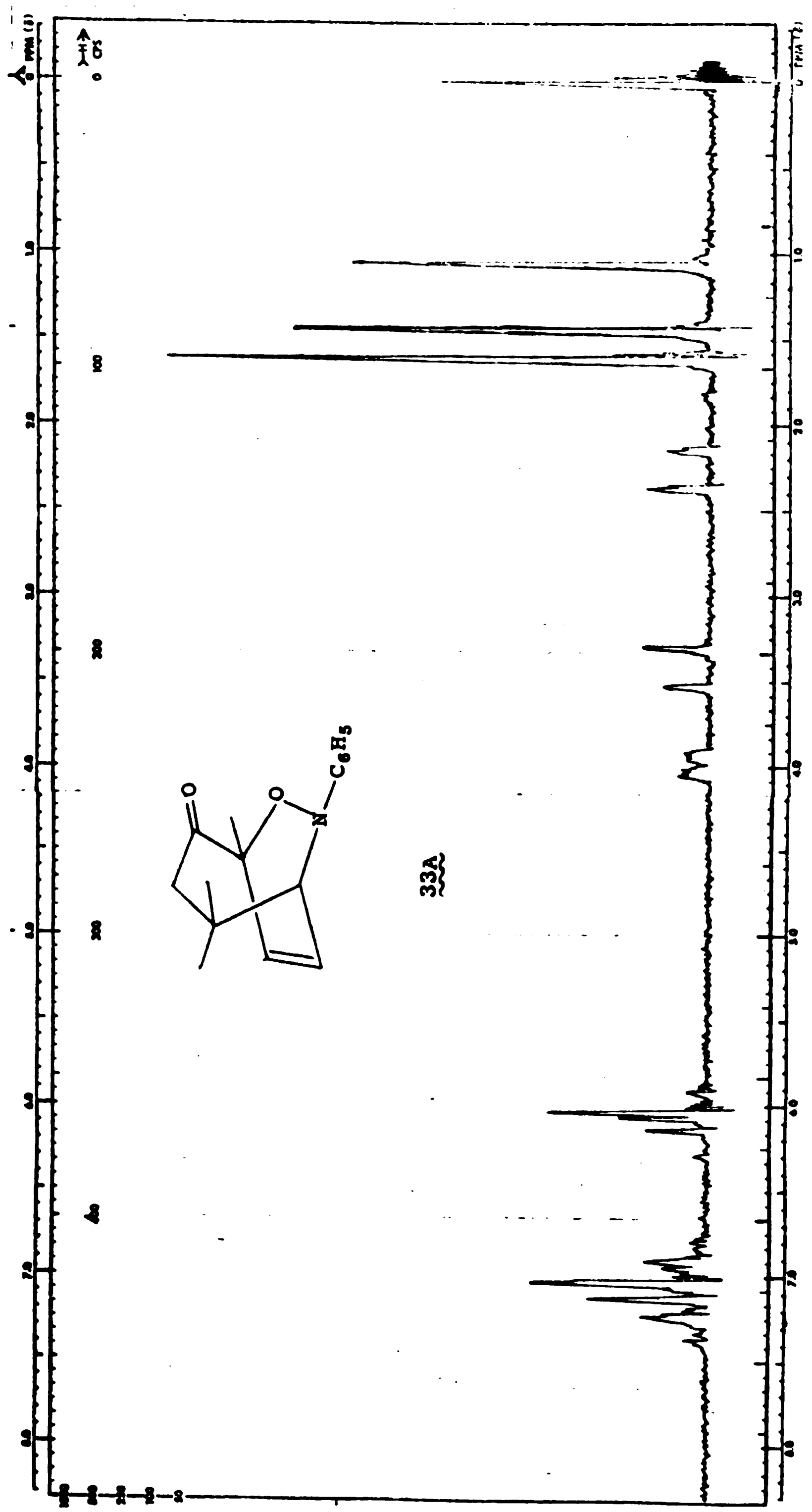
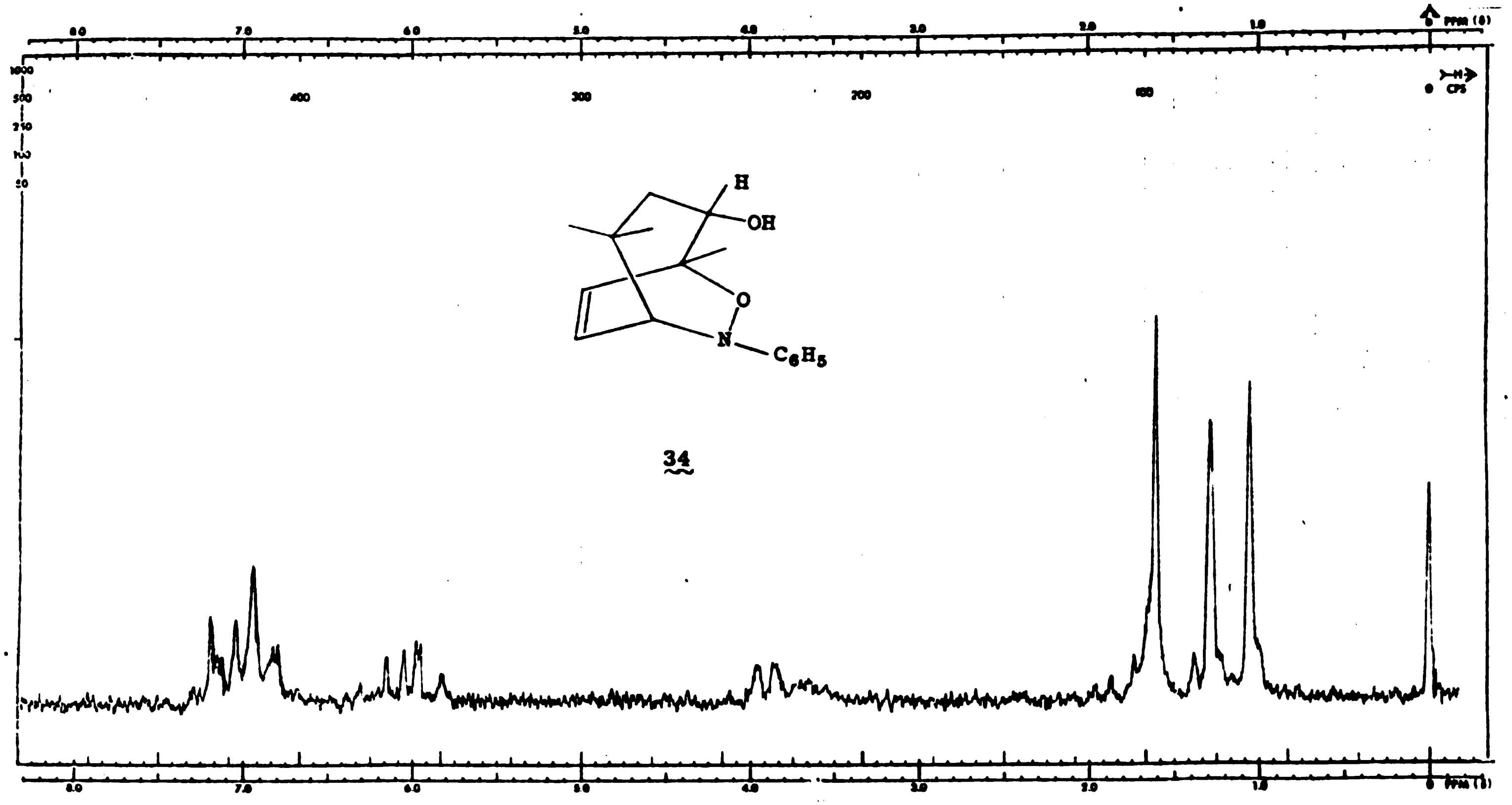


Figure 10. Nmr spectrum (CCl_4) of adduct 26B from 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (25).



33A

Figure 11. Nmr spectrum ($CDCl_3$) of adduct 33A from eucarvone 32.



34

Figure 12. Nmr spectrum ($CDCl_3$) of solid alcohol 34 from reduction of adduct 33A.

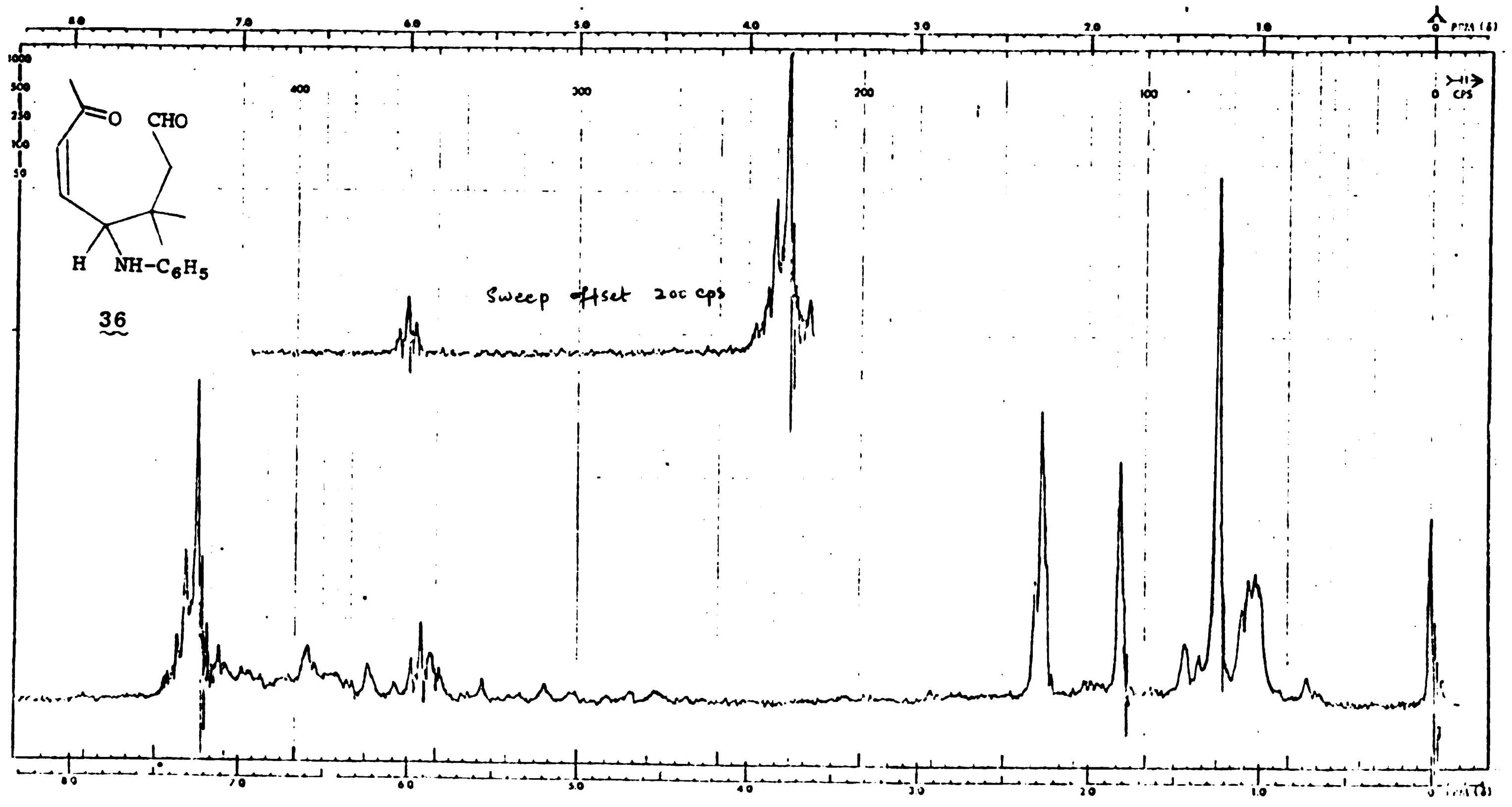


Figure 13. Nmr spectrum (CCl_4) of periodate cleavage product from amino diol 35

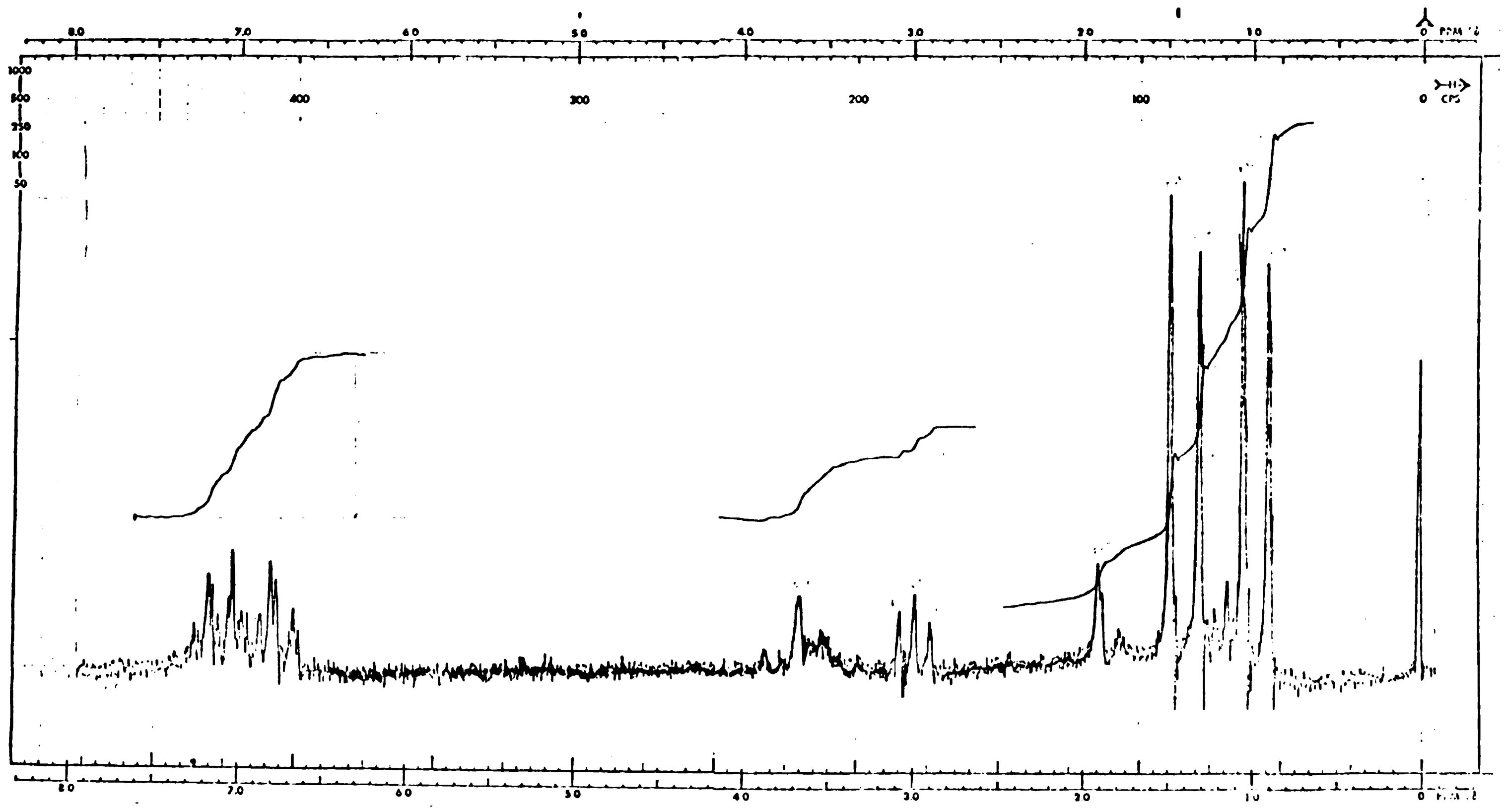


Figure 14. Nmr spectrum ($CDCl_3$) of photo-product from adduct 8A.

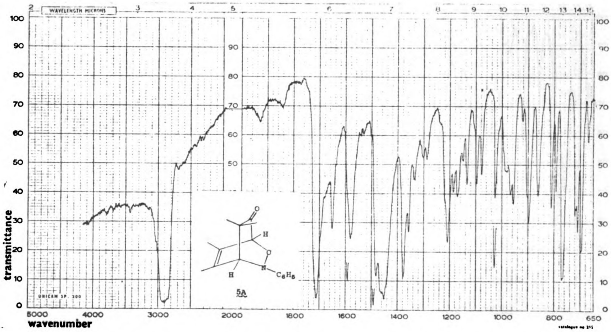


Figure 15. Ir spectrum (Nujol) of adduct 5A from 3,4,6,6-tetramethyl-2,4-cyclohexadienone (1).

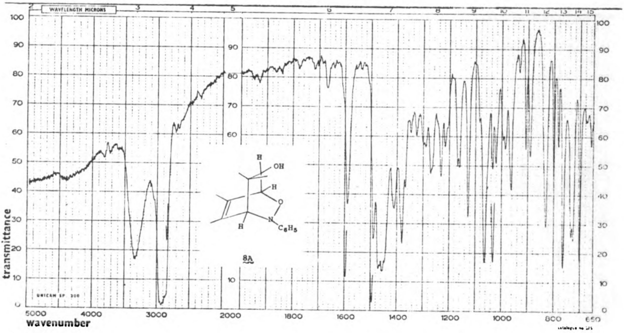


Figure 16. Ir spectrum (Nujol) of adduct 8A from 3,4,6,6-tetramethyl-2,4-cyclohexadienol (8A)

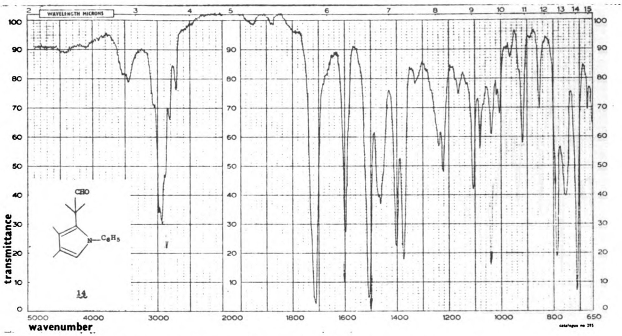


Figure 17. Ir spectrum (neat) of pyrrole 14.

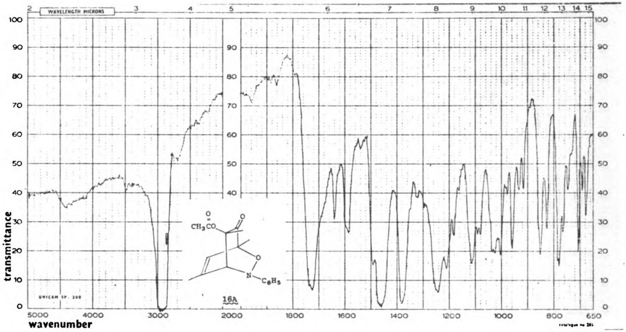


Figure 18. Ir spectrum (Nujol) of adduct 16A from 6-acetoxy-2,4,6-trimethyl-2,4-cyclohexadienone.

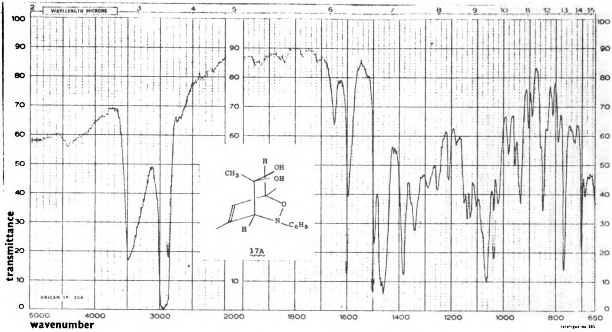


Figure 19. Ir spectrum (Nujol) of diol 17A.

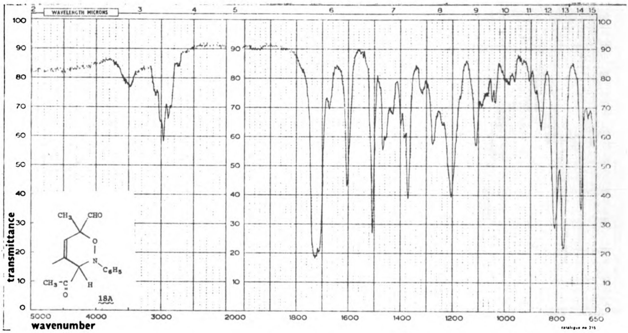


Figure 20. Ir spectrum (neat) of periodate-cleavage product 18A from diol 17A.

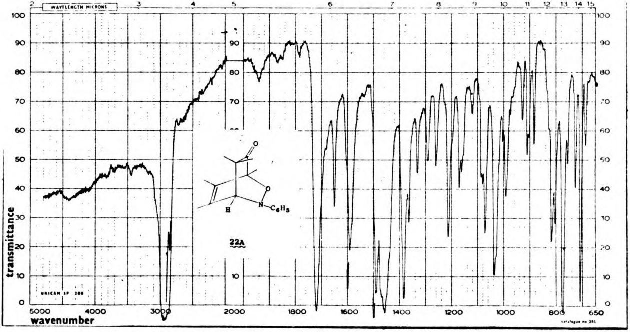


Figure 21. Ir spectrum (Nujol) of adduct 22A from 2,3,4,6,6-pentamethyl-2,4-cyclohexadienone (19).

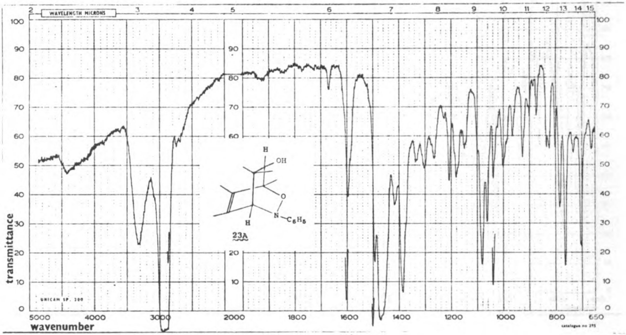


Figure 22. Ir spectrum (Nujol) of alcohol 23A from adduct 22A.

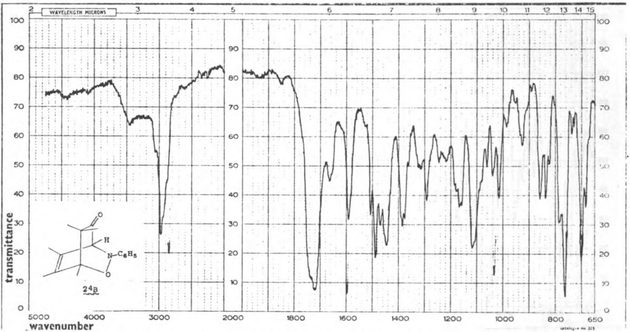


Figure 23. Ir spectrum (neat) of adduct 24B from 3,4,5,6,6-pentamethyl-2,4-cyclohexadienone (21).

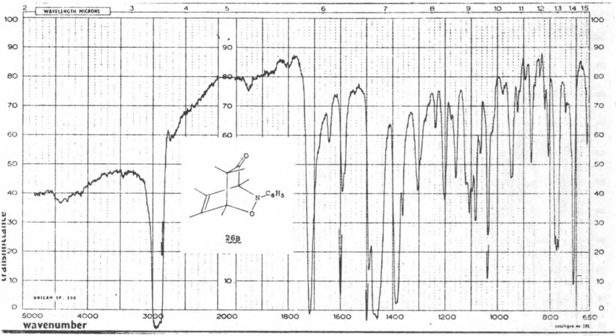


Figure 24. Ir spectrum (Nujol) of 26B from 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (25).

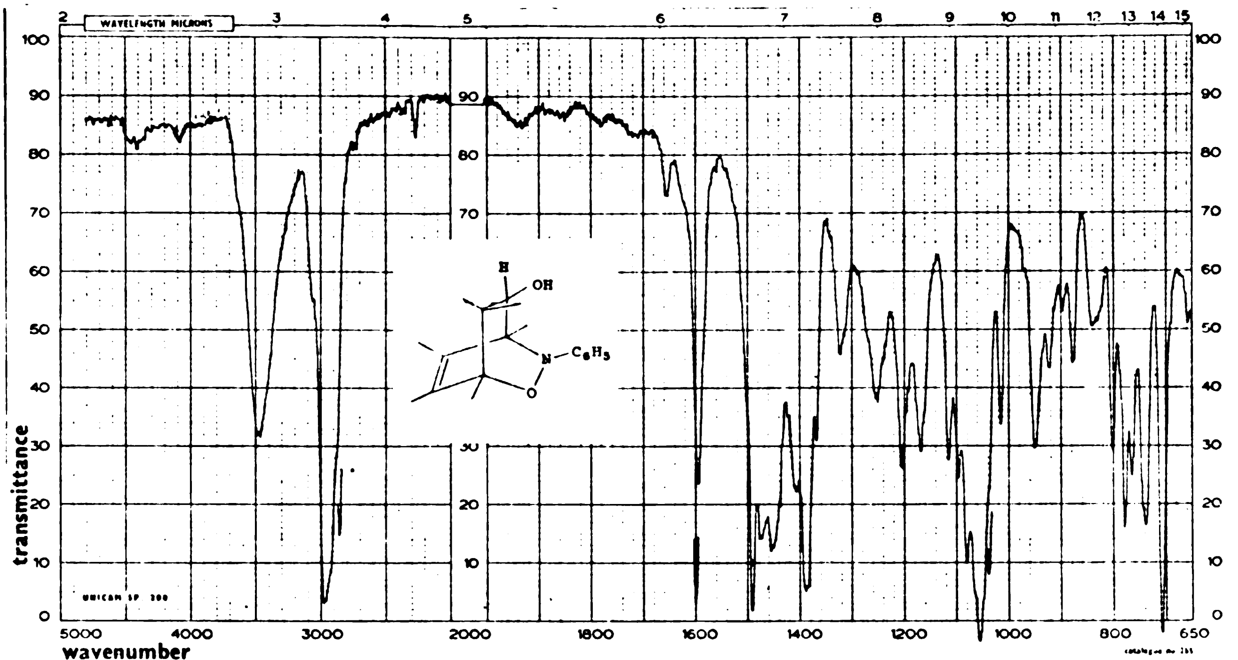


Figure 25. Ir spectrum (neat) of alcohol from reduction of adduct $\underset{\sim\sim}{26B}$.

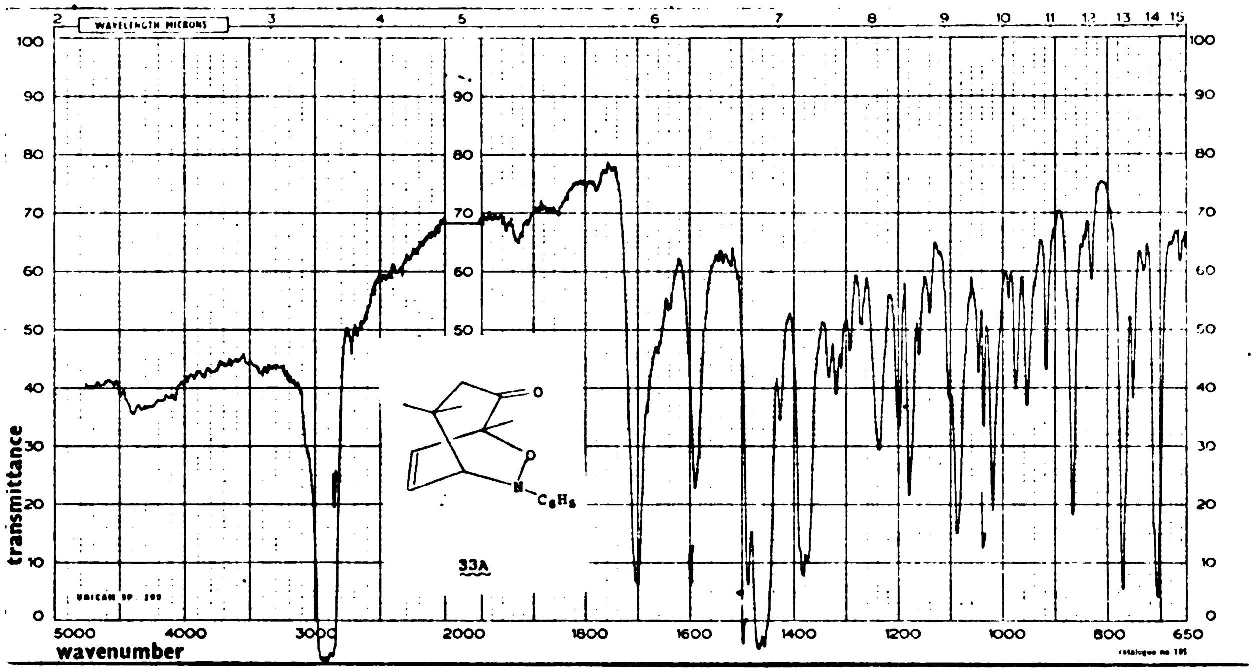


Figure 26. Ir spectrum (Nujol) of adduct $\underset{\sim\sim}{33A}$ from eucarvone $\underset{\sim\sim}{32}$.

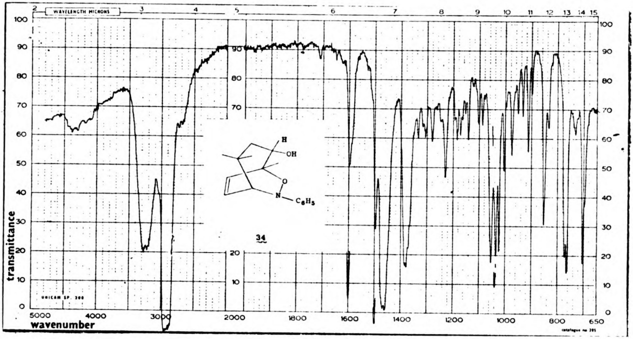


Figure 27. Ir spectrum (Nujol) of solid alcohol from reduction of adduct 33A.

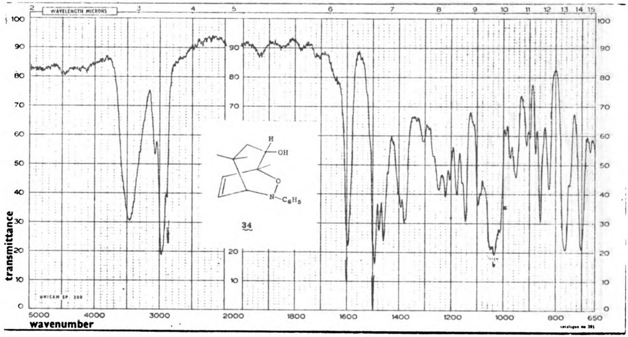


Figure 28. Ir spectrum (neat) of liquid alcohol from reduction of adduct 33A.

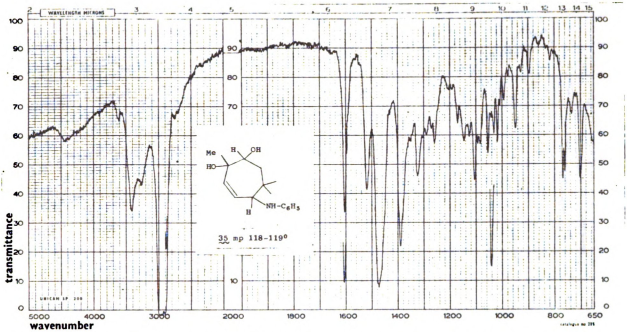


Figure 29. Ir spectrum (Nujol) of amino diol mp 118-119°.

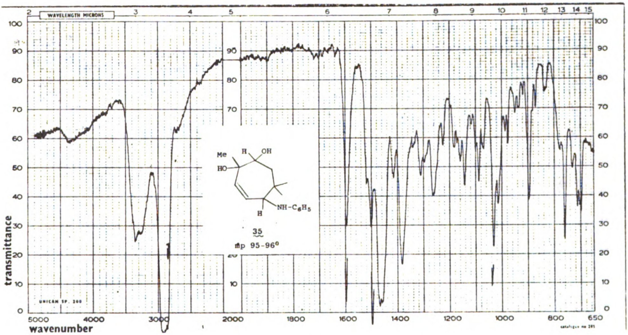


Figure 30. Ir spectrum (Nujol) of amino diol mp 95-96°.

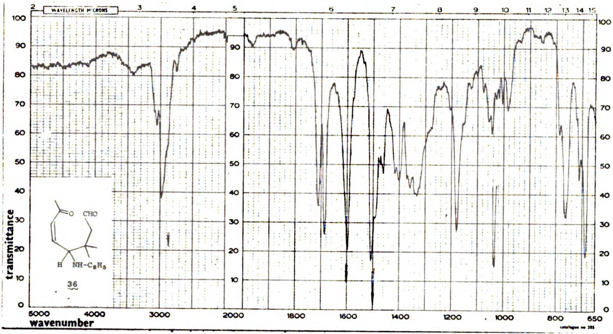


Figure 31. Ir spectrum (neat) of periodate-cleavage product 36 from amino-diol 35.

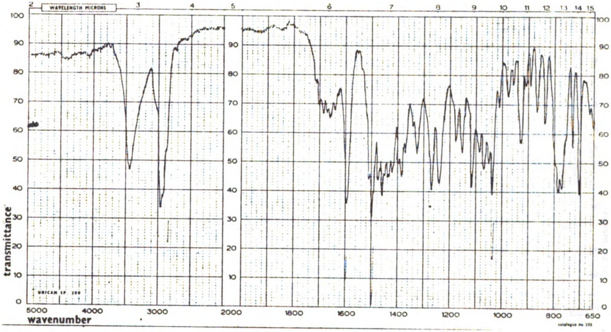


Figure 32. Ir spectrum (neat) of photo-product from adduct 8A.

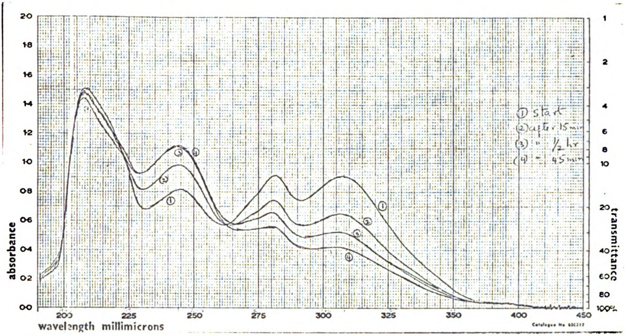


Figure 33. Photolysis of adduct 22A: in etner: uv spectra as a function of irradiation time.

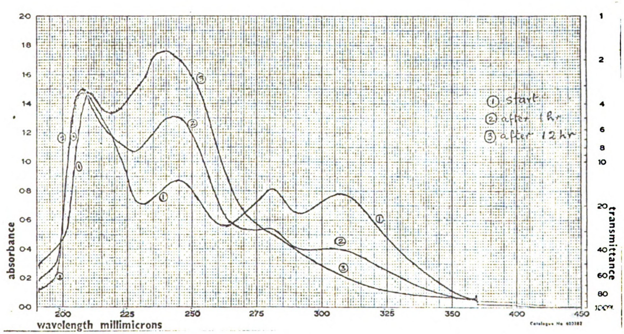


Figure 34. Photolysis of adduct 22A in acetone: uv spectra as a function of irradiation time.

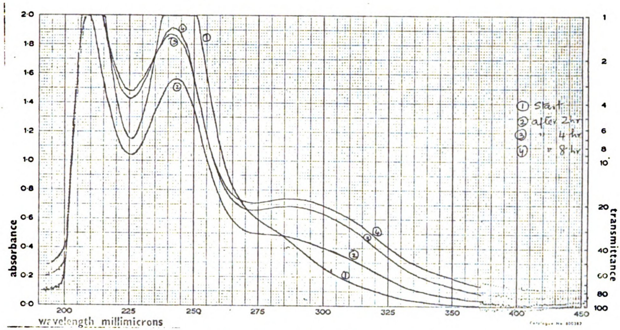


Figure 35. Photolysis of adduct 33A in ether: uv spectra as a function of irradiation time.

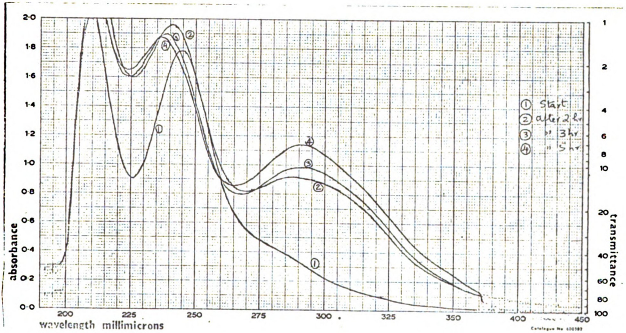


Figure 36. Photolysis of adduct 33A in ether at 2537 Å; uv spectra as a function of irradiation time.

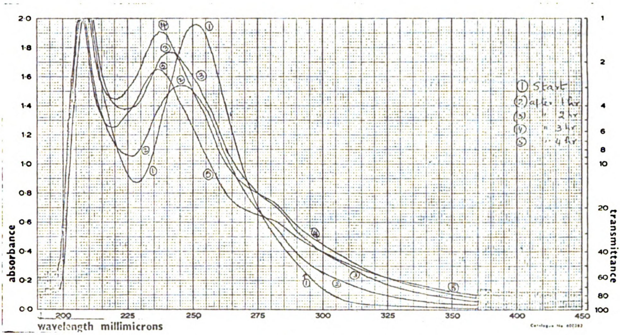


Figure 37. Photolysis of adduct 8A in methanol at 2537 Å; uv spectra as a function of irradiation time.

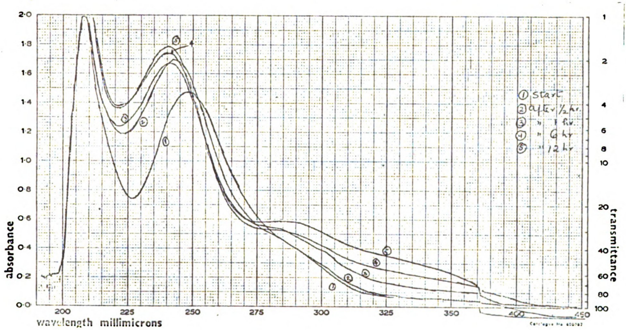


Figure 38. Photolysis of adduct 34 in methanol at 2537 Å; uv spectra as a function of irradiation time.

Table II. Nomenclature of compounds described in this thesis.

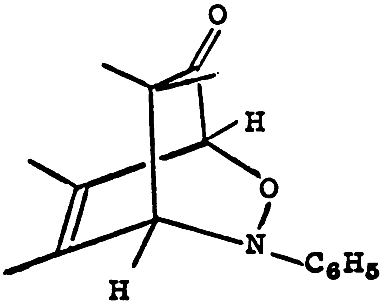
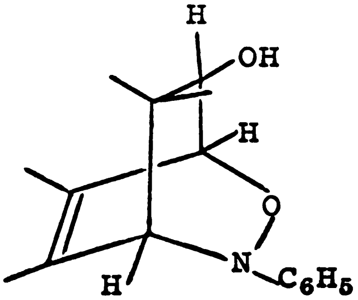
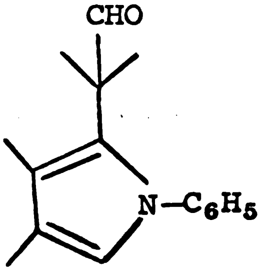
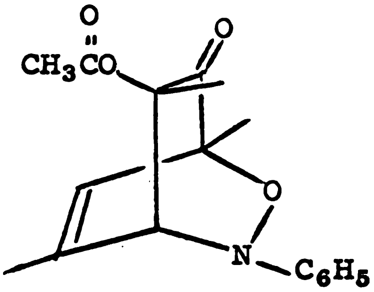
Compound Number	Structure	Name
5A		N-Phenyl-7-oxa-8-aza-3,3',5,6-tetramethylbicyclo[2.2.2]oct-5-ene-2-one
8A		N-Phenyl-7-oxa-8-aza-3,3',5,6-tetramethylbicyclo[2.2.2]oct-5--2-ol
14		2-Methyl-2[N-phenyl-3',4'-dimethyl-2'-pyrryl]propanal
16A		N-Phenyl-7-oxa-8-aza-3-acetoxy-1,3,5-trimethylbicyclo[2.2.2]oct-5-ene-2-one

Table II. (Cont.)

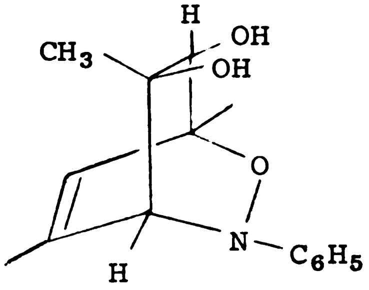
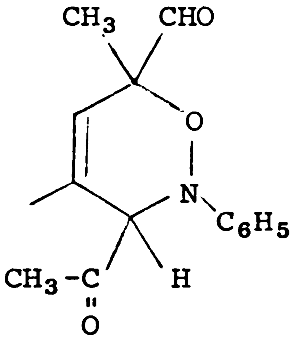
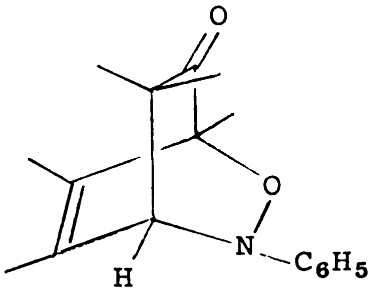
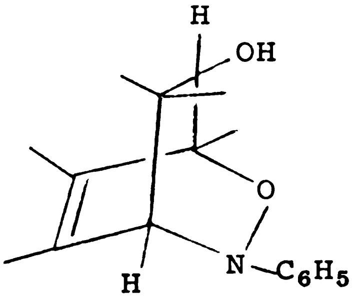
Compound Number	Structure	Name
17A		N-Phenyl-7-oxa-8-aza-1,3,5-trimethylbicyclo[2.2.2]octa-5-ene-2,3-diol
18A		N-Phenyl-4,6-dimethyl-6-formyl-3-acetyl-3,6-dihydro-1,2-oxazine
22A		N-Phenyl-7-oxa-8-aza-1,3,3',5,6-pentamethylbicyclo[2.2.2]oct-5-ene-2-one
23A		N-Phenyl-7-oxa-8-aza-1,3,3',5,6-pentamethylbicyclo[2.2.2]oct-5-ene-2-ol

Table II. (Cont.)

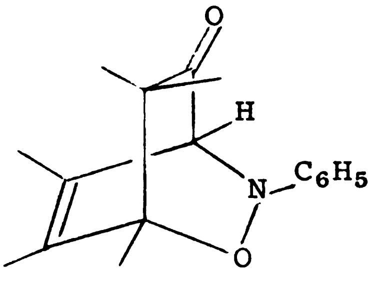
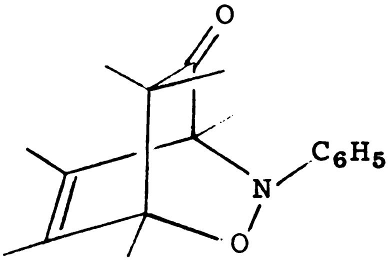
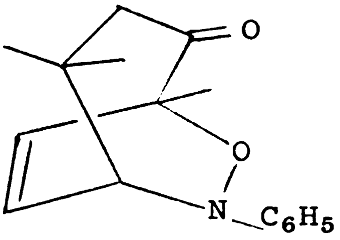
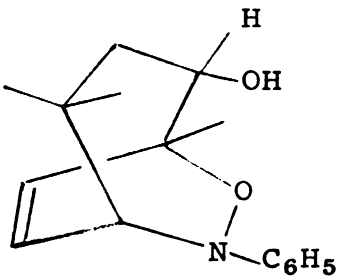
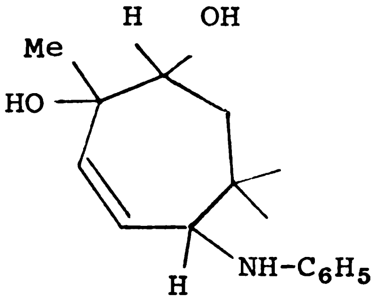
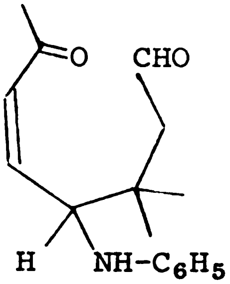
Compound Number	Structure	Name
24B		N-Phenyl-7-aza-8-oxa-3,3,4,5,6-pentamethylbicyclo[2.2.2]oct-5-ene-2-one
26B		N-Phenyl-7-aza-8-oxa-1,3,3,4,5,6-hexamethylbicyclo[2.2.2]oct-5-ene-2-one
33A		N-Phenyl-8-oxa-9-aza-1,4,4-trimethylbicyclo[3.2.2]non-6-ene-2-one
34		N-Phenyl-8-oxa-9-aza-1,4,4-trimethylbicyclo[3.2.2]non-6-ene-2-ol

Table II. (Cont.)

Compound Number	Structure	Name
35		2,6,6-Trimethyl-5-anilino-cyclohept-3-ene-1,2-diol
36		3,3-Dimethyl-4-anilino-oct-5-ene-7-one-1-al

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