SYNTHESIS AND PRELIMINARY SOLVOLYTIC STUDIES OF DERIVATIVES OF BICYCLO[3.2.1]OCT-6-EN-3-OL

Thesis for the Degree of M. S.

MICHIGAN STATE UNIVERSITY
ROBERT E. BOTTO

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by

Robert E. Botto

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ABSTRACT

SYNTHESIS AND PRELIMINARY SOLVOLYTIC STUDIES
OF DERIVATIVES OF BICYCLO[3.2.1]OCT-6-EN-3-OL

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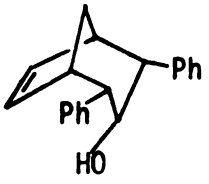
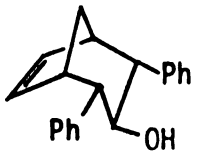
The synthesis and characterization of cis-endo-2,4-diphenyl-bicyclo[3.2.1]oct-6-en-endo-3-ol (XVIII) and cis-endo-2,4-diphenyl-bicyclo[3.2.1]oct-6-en-exo-3-ol (XXII), and derivatives thereof are reported.



(XVIII)



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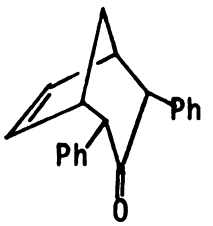
These alcohols are obtained via bicyclic ketone (XVI). Lithium aluminum hydride reduction of the ketone produces the endo-alcohol (XVIII) as the only reduction product, whereas Bouveault-Blanc reduction results in the isolation of the exo-alcohol (XXII) along with its epimer, trans-2,4-diphenylbicyclo[3.2.1]oct-6-en-exo-3-ol (XXIII).



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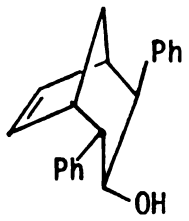
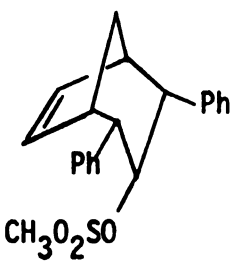


(XXIII)

Solvolyses of the <u>endo</u> and <u>exo</u> methanesulfonates (compounds (X) and (XI) respectively) show that the reaction mixtures contain predominately elimination product, diene (XXVII).



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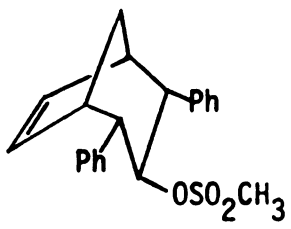

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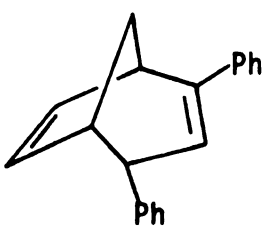

(XXVII)

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The author would like to express both his thanks and appreciation to:

... Dr. Donald G. Farnum for his guidance and understanding throughout the course of this project - whose friendship is cherished - whose excellence as a chemist is surpassed only by his idealism - and whose ping-pong playing is atrocious.

... my fellow graduate students: Glennie, Raghu, Rog, Big Al, Bill, and last, but least, Gabone (and Myrn).

... a nobleman second class, Lord Eric.

... Local Board #4 without whose undying effort this thesis would never have been written.

to my parents,

this is more

theirs

than it is

mine

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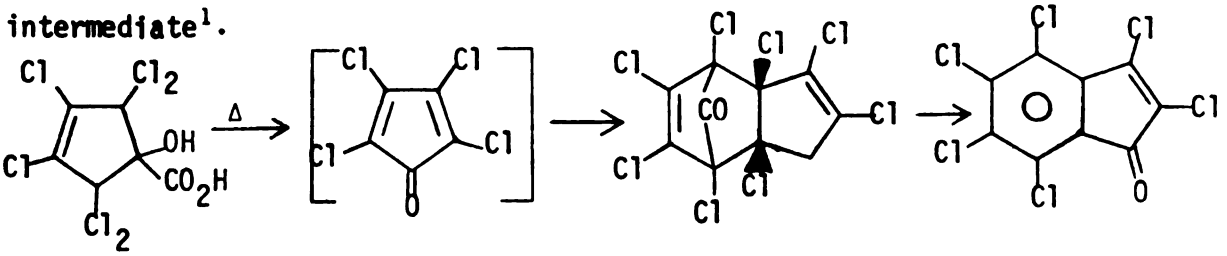
INTRODUCTION

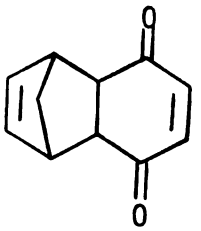
Cycloadditions of conjugated dienes have claimed the interest of synthetic and mechanistic chemists for nearly forty years. However, isolated examples of diene additions have been found as early as the turn of the century.

In 1893 Zincke correctly explained the formation of perchloroindenone (II) in the pyrolysis of 1-hydroxyperchlorocyclopent-3-ene carboxylic acid (I) suggesting perchlorocyclopentadienone as an intermediate[1].



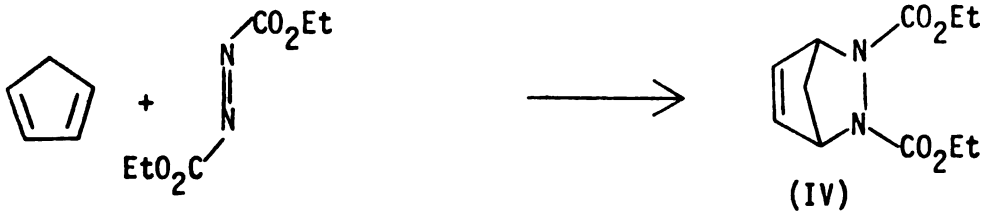
(I) (II)

In the years following, controversy arose as to the actual structures of the adducts formed. Staudinger and Albrecht proposed structures involving cyclobutane rings, but these later proved to require revision. It was not until some thirty years later, when Diels and Alder elucidated the structure of the 1:1 adduct (III) of p-benzoquinone and cyclopentadiene[2], that the nature of the reaction became evident.



(III)

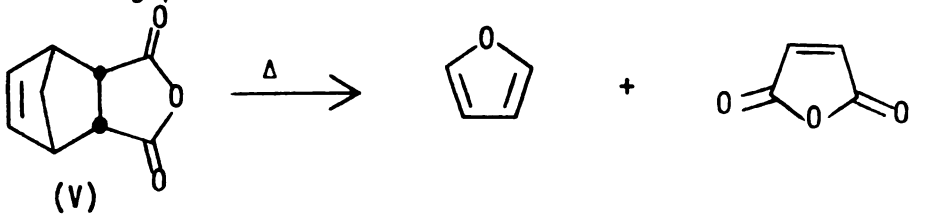
This introduced the fruitful preparative and mechanistic investigations of these authors. The structure of the 1:1 addition compound (IV) from cyclopentadiene and diethyl azodicarboxylate[3] illustrated the diversity of this reaction type.



(IV)

Indeed, the literature contains a wealth of examples concerning this one step reaction, and the wide variation in reactants allows access to many important classes of compounds[4].

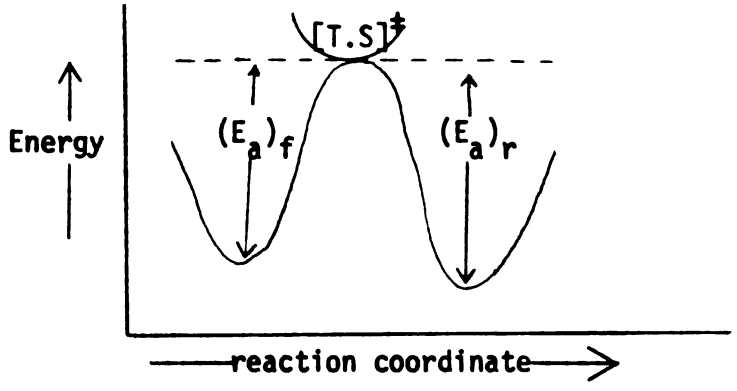
The history of the retro-diene reaction is as old and diversified as the cycloaddition itself. In 1929 Diels and Alder demonstrated that an adduct of furan and maleic anhydride (V) decomposed into its addends at its melting point of 125°[5].



(V)

Many examples have been reported in the literature since this discovery[6].

It is also important to note that the reverse process most often occurs at similar or higher temperatures than the forward process. This is a direct consequence of enhanced thermodynamic stability of the adduct over that of the starting materials since forward and reverse processes have identical transition states (Figure I).



$(E_a)_r \gtrless (E_a)_f$

FIGURE I. Energy Profile For a Diels-Alder Reaction

where $(E_a)_f$ = activation energy for forward process

$(E_a)_n$ = activation energy for reverse process

$[T.S.]^{\ddagger}$ = transition state

The theory of concerted transformations has been refined and extended by the contributions of Woodward and Hoffmann[7]. Their molecular orbital approach has helped immensely in understanding the structuro-selectivity of the Diels-Alder and related addition reactions. It is from them that we learn that conservation of orbital symmetry dictates a reaction pathway.

If we consider the [4 + 2] cycloaddition of butadiene to ethylene, then a reasonable approach is characterized by a single plane of symmetry bisecting the two components. This can be justified for the following reasons. First it is the most sterically accessible approach for the

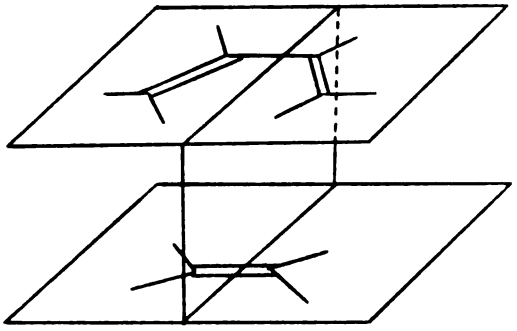
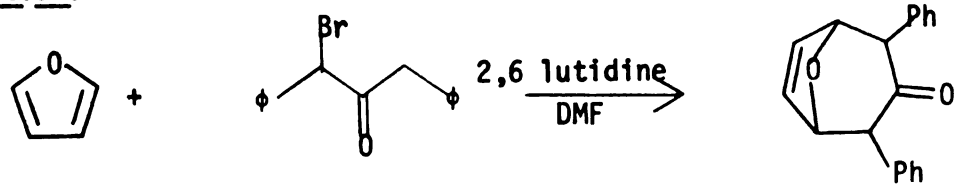


FIGURE 2. Symmetric Approach of Butadiene and Ethylene in the Diels-Alder Reaction.

two molecules. And second, it allows maximum π-overlap of the approaching orbitals leading to the transition state. There are six essential levels involved in the reaction which can be illustrated in the the following correlation diagram (Figure 3). Delocalized σ-bond combinations and π-bond combinations must be constructed for both product and reactants, respectively. Every bonding level of reactants correlates with a bonding product level; there is no correlation between bonding and antibonding orbitals. The transformation is a symmetry allowed ground state process and, therefore, thermally allowed.

As already noted, there have been many examples of [4 + 2] cycloadditions, but none so intriguing as those involving ionic components. The first example of this novel transformation has been observed by Fort, et.al.[8].



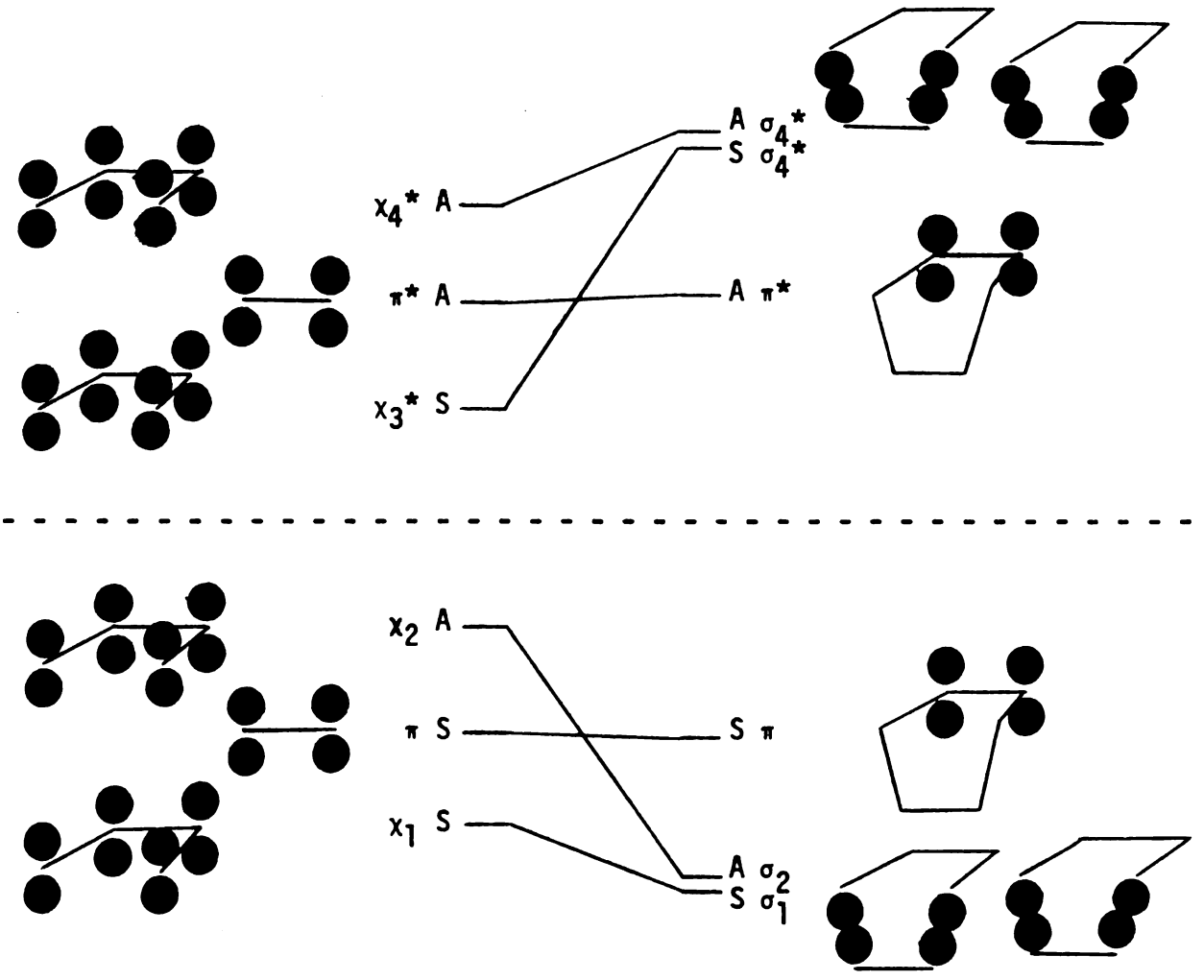
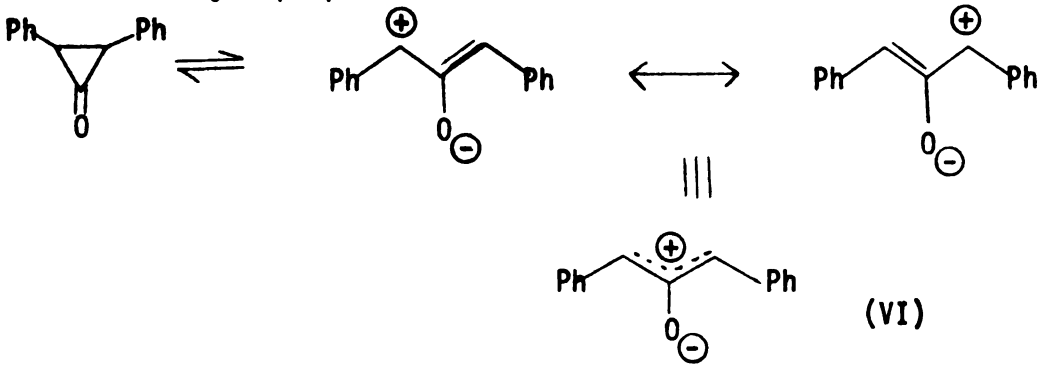


FIGURE 3. Correlation Diagram for the Diels-Alder Reaction of Butadiene with Ethylene.

It has been suggested that the reaction actually involves the isomeric dipolar form of cyclopropanone (VI), although there is some question as to whether cyclopropanone itself reacts[9].



(VI)

Since orbital symmetry dictates the number of electrons, not the total number of orbitals, the ionic component in the above reaction is treated as though it were a simple 2π-electron moiety. Here again, a reasonable approach is a plane bisecting the two components (Figure 4).

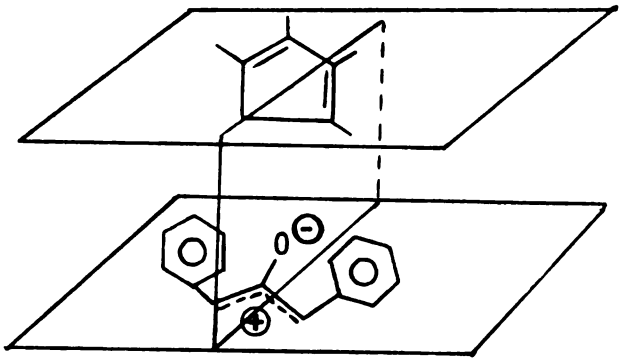
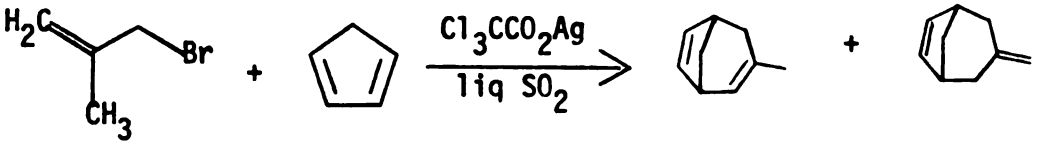
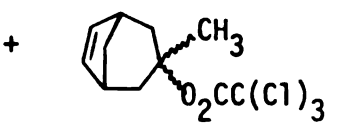


FIGURE 4: Symmetric Approach of Cyclopropanone and Cyclopentadiene.

However, substituent π-interaction with the conjugated diene may help to lower the transition state energy and must therefore be considered. This would account for the stereospecificity of the product.

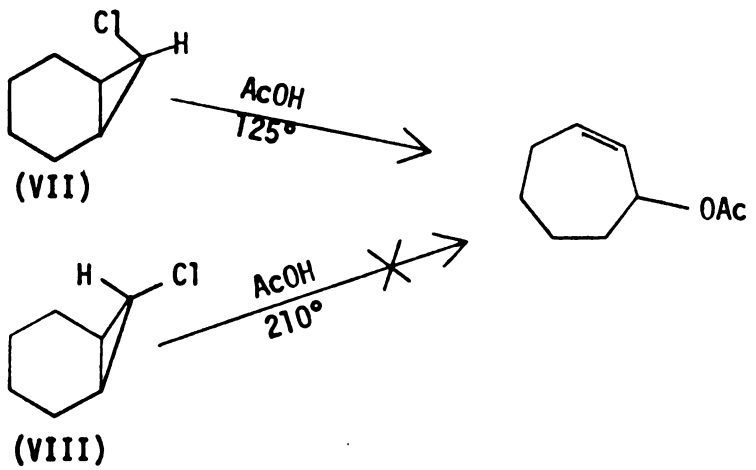
More recently, Hoffman reported the first direct combination of a simple allyl cation with cyclopentadiene[10].





(mixture of exo and endo)

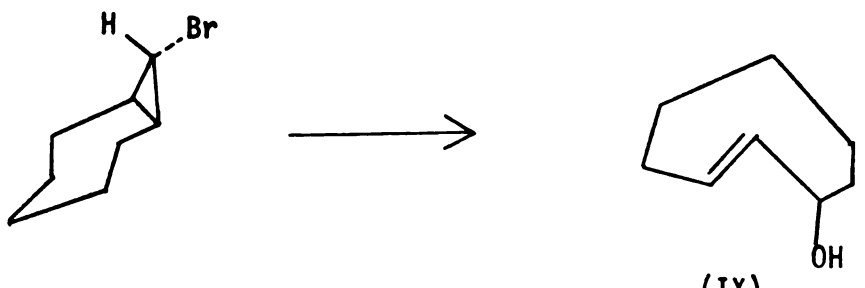
Retrodiene cleavage concerted with ionization is possible during solvolysis provided orbital symmetry is conserved and bond reorganization is not accompanied by excessive strain energy. Electrocyclic transformations during solvolysis are well established. Cristol, et.al.[11], have demonstrated that syn-7-chlorocarane (VII) undergoes solvolysis readily at 125°, whereas its epimer (VIII) remains unchanged after prolonged treatment with acetic acid at 210°.



(VII)

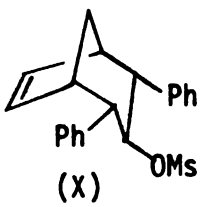
(VIII)

These results can be interpreted in terms of a concerted disrotatory opening of the 1,6 bond which becomes available for backside displacement of the leaving group. When the leaving group is anti to the ring system, rotation would lead to a trans, trans-allyl cation which is severly strained. Whitham has shown that the solvolysis of exo-8-bromobicyclo-[5.1.0]octane[12] gives the expected trans-cyclooctenol (IX) clearly establishing the concertedness of the reaction.



(IX)

It seems likely, therefore, that a concerted ionic [4 + 2] fragmentation is plausible. We have chosen to study the solvolysis of exo and endo bicyclo[3.2.1]octenyl mesylates (compounds (X) and (XI), respectively) to investigate this possibility.



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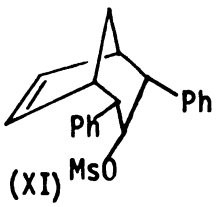
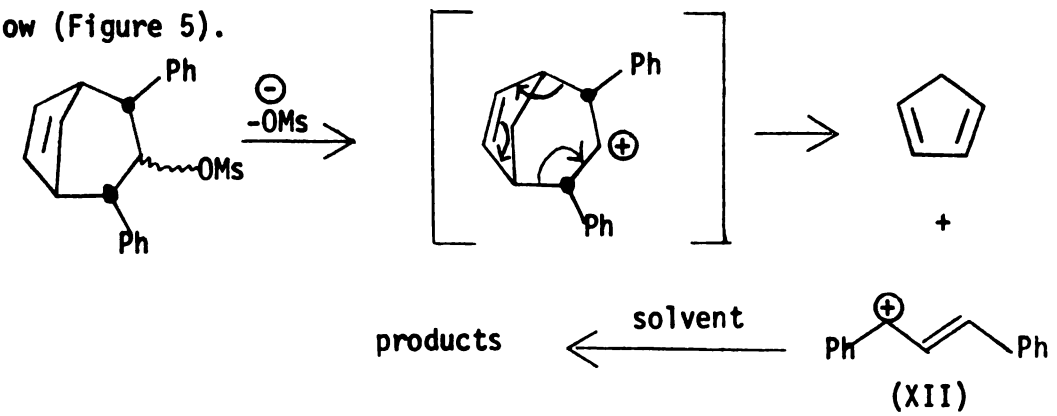


(XI)

These particular systems have two distinct advantages: the steric influence of the phenyl substituents hinders nucleophilic attack at the cationic center, and fragmentation would lead to an energetically favorable species, namely the 1,3-diphenylpropenyl cation (XII) shown below (Figure 5).



(XII)

FIGURE 5. Classical Fragmentation Pathway (Thermally Allowed)

Fragmentation could be concerted with ionization if there is a trans-anti-parallel relationship of the two neighboring carbon-carbon bonds and the carbon-oxygen bond. In the transition state of (X) the leaving group (designated by Y) does attain this anti relationship (Figure 6). As X leaves, the developing positive charge could become

stabilized by the developing p-orbitals in the alpha-positions, i.e., the p-orbitals produced from the concerted fragmentation of the 1,2 and 4,5 σ-bonds become available for backside displacement of the leaving group. There might also be a bonding contribution from the π-orbitals at carbons 6 and 7.

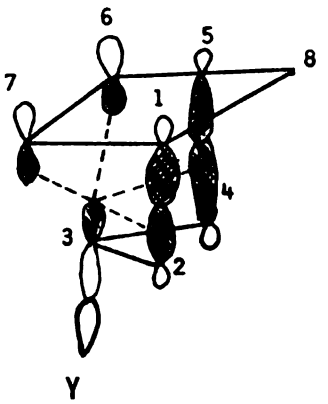


FIGURE 6. Transition State for Concerted Fragmentation of Exo Mesylate (X) (Y = OSO_2CH_3)

note: substituents omitted for simplicity

However, this mode of ionization is impossible for the endo isomer (XI) which must ionize without such participation. Thus, one might predict a lower transition state energy for the exo compound (X). The implications for the energetics of the reaction are depicted below (Figure 7).

Fragmentation need not occur in order to observe rate acceleration. Thus ionization of the exo-isomer (X) might proceed to delocalized non-classical cation (XIII), which could react with solvent without fragmentation to give bicyclic products. This would lead to a

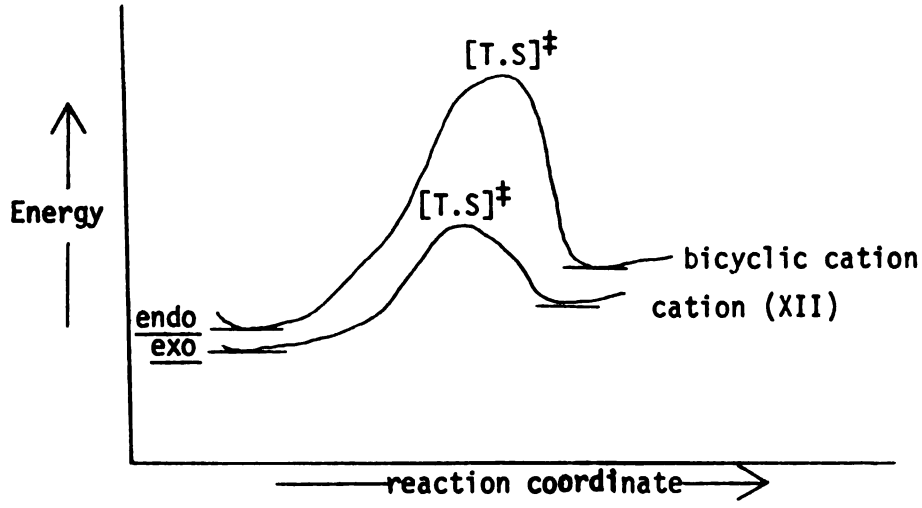


FIGURE 7. Energy Diagram for Solvolysis of Compounds (X) and (XI). With Concerted Fragmentation.

transition state in which the developing positive charge is delocalized over a much larger precentage of the molecule and should be stabilized by such a charge distribution (Figure 8).

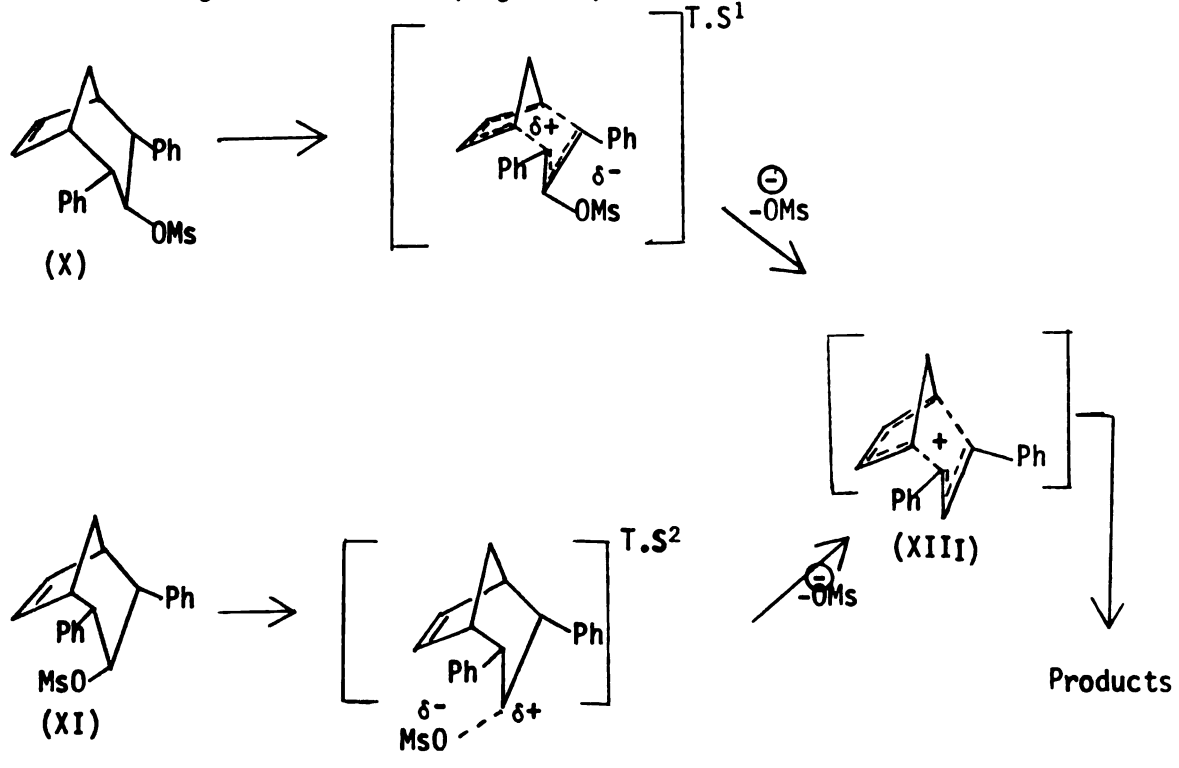
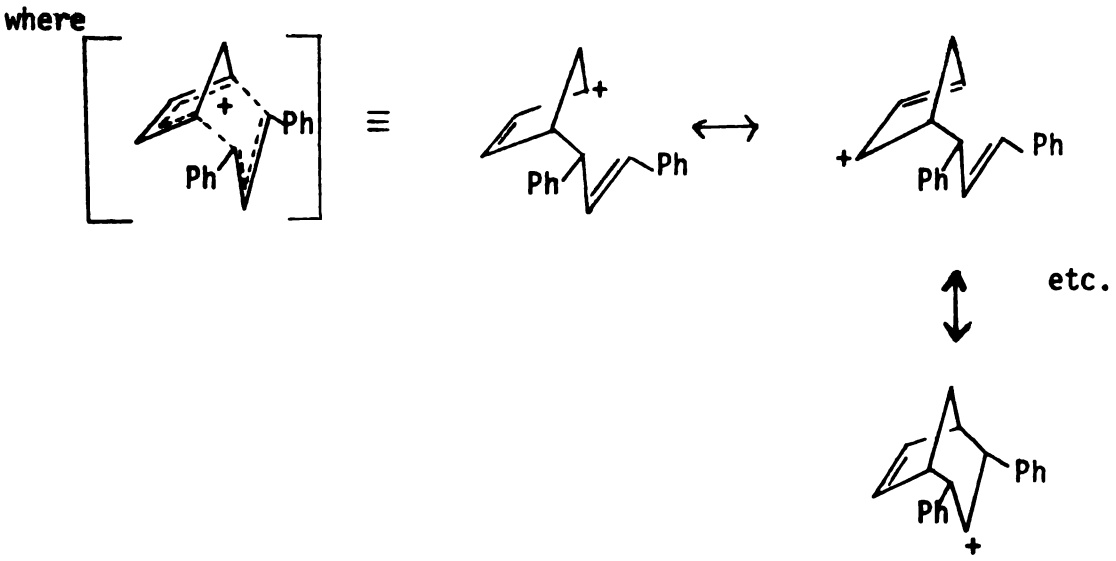


Figure 8. Reaction Path Without Fragmentation



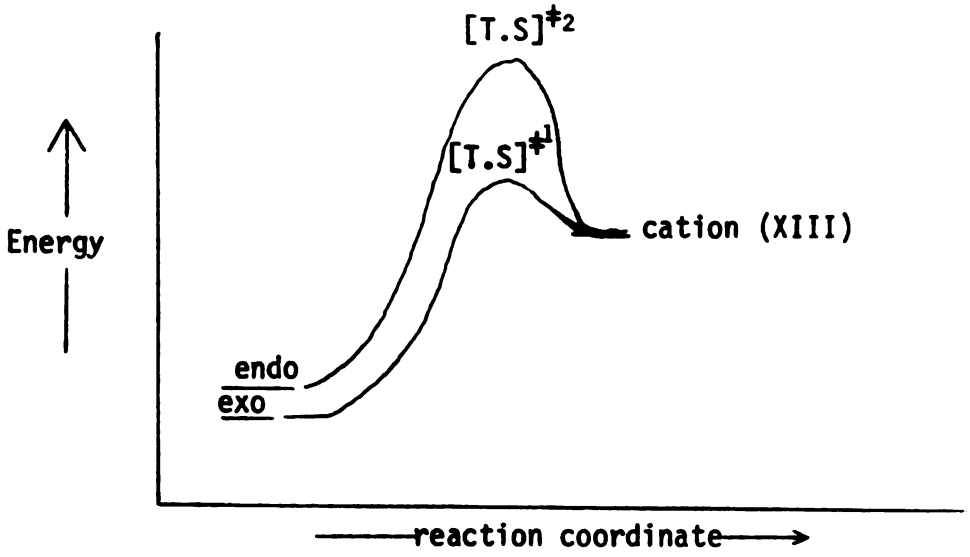
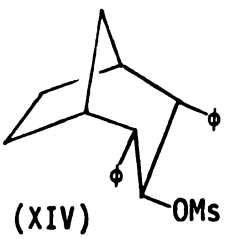


Figure 9. Energy Profile Without Fragmentation

The cations resulting from ionization of (X) and (XI) are subject to the same nonclassical resonance, hence, these intermediates are identical in energy. The difference occurs in the transition state - the delocalization inherent in the intermediate is reflected in the transition state of the exo species only. Assuming that the ground state energy difference between compounds (X) and (XI) is negligible, delocalization should lower the energy of the exo transition state and, consequently, must lower the energy of activation (Figure 9) necessary to achieve it.

Steric acceleration to ionization in compound (XI) is an important factor which should not be overlooked. The endo leaving group is not only situated under the ring system but cis to both phenyl moieties. This should appreciably enhance the rate of (XI) relative to (X). Since two opposing factors are in operation a kinetic study would prove meaningless. Only by comparing the rates of the saturated analogues, (XIV) and (XV), can we estimate steric rate acceleration in the absence of delocalization. Furthermore, comparing the rates of (X) and (XIV)



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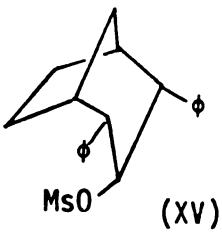


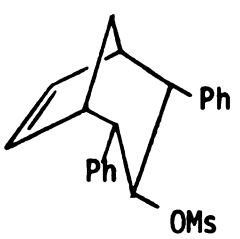
(XV)

should establish the rate enhancement due to participation since it seems very unlikely that the transition state resulting from ionization of (XIV) is subject to the same delocalization as its unsaturated analogue - ionization of (XIV) should lead to a classical secondary cation. Thus, compound (X) should solvolyze faster than (XIV).

This thesis describes the synthesis and preliminary solvolytic study of (X), (XI), (XIV), and (XV).

RESULTS AND DISCUSSION

A reasonable synthetic approach to compounds (X) and (XI) seemed to be via bicyclic ketone (XVI) which had previously been prepared by two different methods. Fort and coworkers treated benzyl-α-chlorobenzyl ketone with 2,6-lutidine in the presence of cyclopentadiene[8]. Although the specific reaction conditions were not given Cookson's preparation



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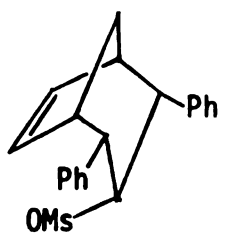

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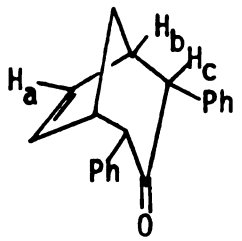

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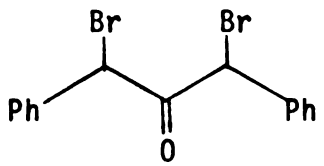
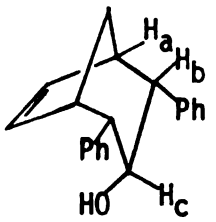


(XVII)

of the same adduct involved reduction of dibromide (XVII) with sodium iodide in acetone[9]. The later method seemed the more attractive in view of the milder conditions required.

Using the procedure outlined in the experimental section (vide infra) we were able to obtain optimum yields of 73% on large quantities of material following Cookson's suggestions. The spectral properties of our compound were in complete agreement with those reported in the literature. The simplicity of the nmr spectrum suggested that a plane of symmetry existed through the carbonyl moiety. The very weak $n \rightarrow \pi^*$ absorption for the carbon-oxygen double bond demonstrated that the two phenyl substituents assume an equatorial positon[13]. Since the orientation of the benzylic hydrogens had been established, we could determine the conformation of the six-membered ring system on the basis of coupling (observed: $J = 4$ cps) between the benzylic hydrogen atoms (H_c) and the bridgehead hydrogens (H_b). If the six-membered ring assumes a boat configuration the dihedral angle between H_b and H_c would be ca. 90°; consequently, the coupling constant between them should be zero. On the other hand, if configuration (XVI) is assumed the dihedral angle becomes approximately 45°, and the estimated coupling is in accord with that observed experimentally. The spectroscopic evidence agreed with the conviction that the adduct (XVI) arises from endo addition of the cyclopropanone - like intermediate to cyclopentadiene.

Treatment of ketone (XVI) with lithium aluminum hydride in refluxing ethyl ether afforded cis-endo-diphenylbicyclo[3.2.1]oct-6-en-endo-3-ol (XVIII) as the only reduction product in 65% yield. The unreacted starting material was mechanically separated from the alcohol since recrystallization from hexane afforded two distinct crystal forms which were quite easily recognized.



(XVIII)

Compound (XVIII) exhibited only free hydroxyl absorption in the infrared at 2.81 μ (sharp) which is characteristic of a sterically hindered alcohol. That a plane of symmetry still existed was verified by the simplicity of both the phenyl and olefinic regions of the nmr spectrum. The retention of the chair conformation during reduction was born out by the coupling between H_a and H_b in the product (J = 1.8 cps). If the six-membered ring assumed a boat conformation the dihedral angle between the two protons should be nearly 0°, hence the coupling between them would be large. The rather small coupling constant showed that, in fact, the dihedral angle increased over that of ketone (XVI) due to changes in hybridization at C-3. The coupling (J = 4.5 cps) between the methine proton (H_c) and the benzylic hydrogens (H_b) was consistent with cis-coupling in similar systems[14]. Consequently, the hydroxyl moiety must be syn to the two-carbon bridge. Shaking the sample with deuterium oxide resulted in the disappearance of the signal located at τ 8.55.

The mass spectrum of alcohol (XVIII) exhibited a parent peak at m/e 276 (calcd: 276). Analysis confirmed the molecular formula $C_{20}H_{20}O$.

The formation of only the endo-isomer is quite easily rationalized. The attack of the metal hydride must occur approximately perpendicular to the plane of the carbonyl double bond (Figure 9) designated by axis C^{15}.

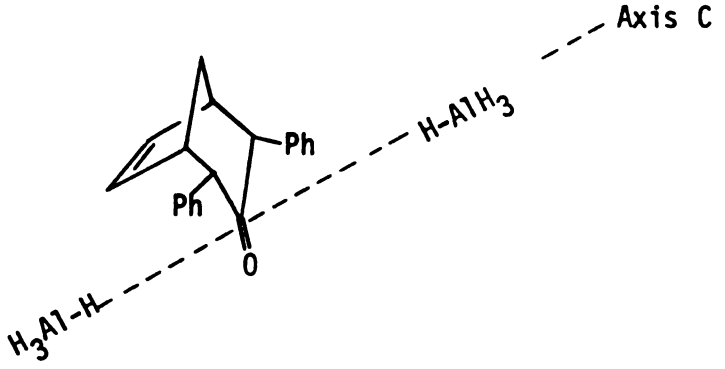


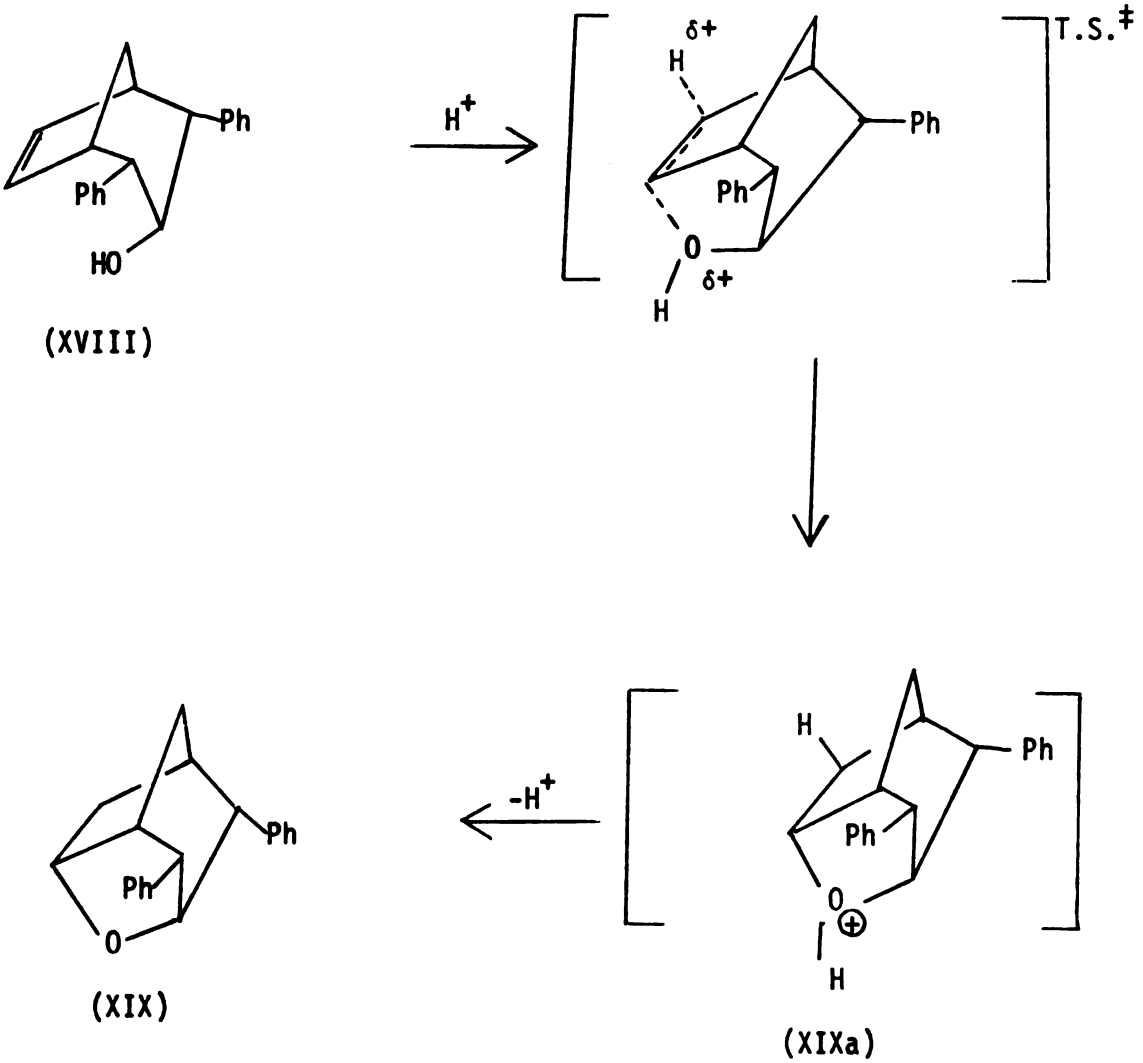
Figure 10. Approach of Metal Hydride in the Reduction of Ketone (XVI).

By far the less sterically favorable approach of the large metal hydride is from the underside of the molecule. Here the reducing agent encounters steric repulsion from both the two-carbon bridge and the large equatorial phenyl substituents. Attack from the top involves only two alpha-hydrogen repulsions.

Internal cyclization can occur only if the hydroxyl moiety is syn to the double bond and the six-membered ring assumes a chair conformation. It is reasonable that protonation of the double bond would lead directly to oxonium ion (XIXa), that is, concerted oxygen participation would occur during protonation (Scheme I). Subsequent loss of a proton would result in the formation of (XIX). Such neighboring group participation

is well established in the literature especially if it occurs via a favorable 5-membered transition state[16].

Scheme I



Refluxing endo-alcohol (XVIII) in 30% sulfuric acid led to the isolation of tricyclic ether (XIX), syn-syn-4,9-diphenyl-2-oxatricyclo-[3.2.1.1^{3,7}]nonane, which exhibited infrared absorption at 9.89 μ. The structural assignment was based mostly on the nmr data. There was no

olefinic resonance present. Two signals located at τ 5.32 and 5.62 were characteristic of two methine protons adjacent to an ether linkage. The absence of any coupling to the lower field benzylic hydrogen (τ 6.79) reflected the severe distortion present in the cyclohexane ring system. Both the adjacent bridgehead proton and the methine hydrogen at carbon-3 do become perpendicular to this low-field-axial-benzylic proton by such distortion in molecular models.

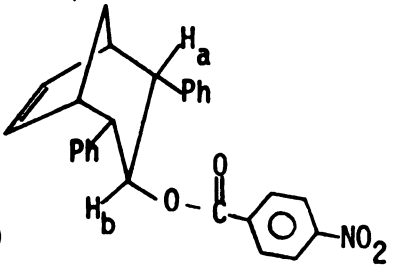
The mass spectrum of the tricyclic ether exhibited a parent peak at m/e 276 (calcd. 276), but its fragmentation pattern was quite different from that of the starting alcohol. The compound analyzed correctly for $C_{20}H_{20}O$. The data presented confirmed our suspicion that acid catalysis mediates structural isomerization of alcohol (XVIII).

Lithium aluminum hydride reduction of ketone (XVI) made us aware of the large steric factors inherent in such a ring system. Thus the relatively convenient Bouveault-Blanc reduction of the ketone should produce the more thermodynamically stable reduction product, namely the exo-alcohol (XXII) (vide infra). Reduction of ketone (XVI) with sodium and ethanol in refluxing toluene did yield a red oil whose spectral properties suggested the presence of a mixture of products. Since crystallization of the crude material was extremely difficult, it was thought that separation of the p-nitrobenzoate derivities of these isomers could be more easily accomplished.

The crude mixture was treated with p-nitrobenzoyl chloride and an equivalent amount of pyridine in ethyl ether. Fractional recrystallization from 95% ethanol afforded long-yellowish needles, m.p. 181.5-184.5°, which were purified further. Eventually a colorless solid, cis-endo-

2,4-diphenylbicyclo[3.2.1]oct-6-ene-exo-3-p-nitrobenzoate (XX), was obtained whose infrared spectrum possessed characteristic ester absorption at 5.75 μ. The A_2B_2 quartet centered at τ 2.19 in the nmr further established the presence of the p-nitrobenzoyl moiety. The unusually low-field methine resonance (H_b) (τ 4.08, t, J = 9.8) could only be explained by the anisotropic effect of the three phenyl rings and the ester function which encompass it.

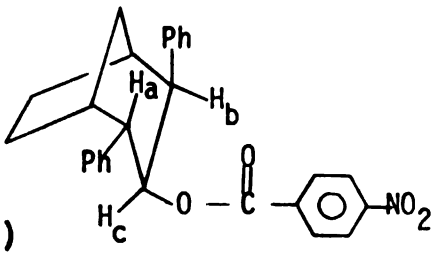
(XX)



The assignment of the exo ester function was based on the large coupling (9.8 cps) observed between H_b and the axial-benzylic protons (H_a), and is typical of trans-diaxial coupling found in similar rigid cyclohexane ring systems[14]. Analysis for the compound was consistent with a molecular formula of $C_{27}H_{23}NO_4$ while the highest peak in the mass spectrum was m/e 258 (calcd. 425) due to quantitative elimination of p-nitrobenzoic acid (P-167).

Concentration of the remaining ethanol solution afforded another solid, trans-2,4-diphenylbicyclo[3.2.1]oct-6-ene-exo-3-p-nitrobenzoate (XXI), m.p. 139°, whose infrared absorption at 5.78 μ was also characteristic of an ester carbonyl group. The rather complex nmr spectrum reflected the annihilation of the symmetry. This was confirmed by the two distinct chemical shifts of the benzylic protons, H_a and H_b, and their different coupling to the methine hydrogen (H_c). Perhaps the

most convincing evidence as to the exo-nature of the p-nitrobenzoyl moiety was the large coupling (J = 11.5 cps), typical of trans-diaxial coupling in such systems, between the methine proton and the axial-benzylic proton (H_a). The surprisingly large coupling (J = 7.6 cps)



(XXI)

between H_b and H_c can be rationalized in terms of ring distortion created by repulsions of the axial phenyl moiety (Figure 10).

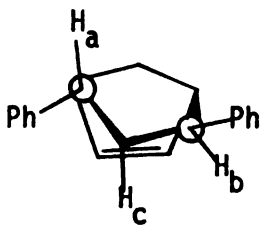
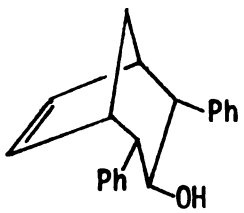


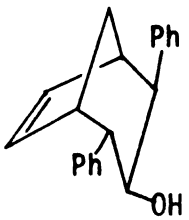
Figure 11. Distorted Conformation of Epimerized p-Nitrobenzoate (XXI).

As the phenyl substituent assumes a pseudo-equatorial position the hydrogen (H_b) must attain some axial character; consequently, the dihedral angle between H_b and H_c approaches 0° and the coupling between them increases. Confirmation of the molecular formula, $C_{27}H_{23}NO_4$, was obtained from analysis.

Hydrolysis of the two p-nitrobenzoates with 8% alcoholic potassium hydroxide led to the isolation of their respective alcohols, exo alcohol (XXII) and exo-epimerized alcohol (XXIII).



(XXII)



(XXIII)

The infrared spectrum of exo-alcohol (XXII) exhibited both free and intermolecularly bonded hydroxyl absorption (2.83 and 2.88 μ) while that of (XXIII) only showed absorption at 2.82 μ. The nmr spectra (Appendix) for these compounds parallel those of their respective precursors and will not be discussed. Both compounds analyzed correctly for $C_{20}H_{20}O$ and their mass spectral analyses were consistent with a molecular weight of 276.

Refluxing compounds (XXII) and (XXIII) in 30% H_2SO_4 yielded only starting material. There was no evidence for tricyclic-ether formation.

A more comprehensive structure analysis was undertaken by reoxidation of the two alcohols. Acidic and basic conditions were avoided to prevent epimerization of the ketone formed during the reaction. Oxidation of the exo-alcohol (XXII) with Collins reagent (see Experimental) led to the isolation of ketone (XVI) which was identified by comparison with a sample prepared in the reaction of the cyclopropanone with cyclopentadiene (vide supra). When alcohol (XXIII) was subjected to the same conditions a different ketone was isolated, trans-2,4-diphenylbicyclo[3.2.1]oct-6-en-3-one (XXIV). The absorption at 5.84 in the infrared spectrum was characteristic of a cyclic (six-membered ring) ketone. The prominent feature of the nmr spectrum seemed to be the different chemical shifts of the two bridgehead protons

and reflected the dissymetry of the molecule. The ultraviolet spectrum of this ketone was quite informative. An axial-phenyl interaction with the carbonyl chromophore is known to shift the $n \rightarrow \pi^*$ transition to longer wavelengths and increase the extinction coefficient[13]. This, in fact, does occur (Table 1). The compound analyzed correctly for $C_{20}H_{18}O$.

TABLE I: Ultraviolet Absorptions (Carbonyl Chromophore) of Ketones (XVI) and (XXIV).

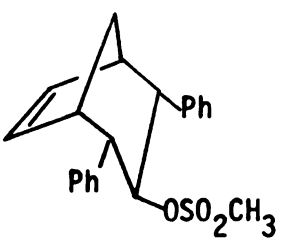
Compound	$n \rightarrow \pi^*$ transition (nm)	extinction coefficient
(XVI)	290	29
(XXIV)	300	115

Treatment of ketone (XVI) with sodium methoxide and methanol in toluene for 6 days gave epimerized ketone (XXIV) in 68.8 ± 1.1% yield. This established that the two ketones were indeed epimers. Interestingly, the ketone which contained an axial phenyl substituent was the thermodynamically predominant product. The only explanation that can be given requires that the energy involved in axial-repulsions (consider the six-membered ring) is less than those encountered through interaction with the bridgehead hydrogens and the two-carbon bridge when the phenyl moiety is equatorial. On the other hand, diepimerization would lead to a higher energy state because of the 1,3 diaxial diphenyl interaction produced.

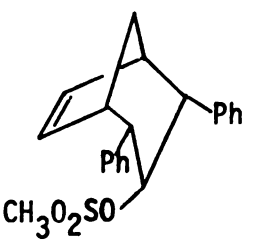
Epimerization during the sodium-alcohol reduction can be understood in terms of the above equilibration experiment. Integration of the two methine resonances centered at τ 5.80 revealed that the exo-trans

diphenyl alcohol (XXIII) comprised 48.1 ± .4% of the total reduction product. This means epimerization (which is favored over reduction by the presence of protic solvent) occurs at a rate more slowly than reduction under these reaction conditions. However, it is still quite competitive. Longer reaction times would favor epimerization until thermodynamic equilibrium is ultimately reached. Accordingly, optimum yields of the desired alcohol (XXII) were obtained employing short reaction lifetimes and low concentration of ethanol.

Every attempt to prepare the p-toluenesulfonate of the endo-alcohol (XVIII) failed, probably due to the enormous steric repulsions implicated for attack by such a large molecule. However, treatment of the endo-alcohol with methanesulfonyl chloride in pyridine at 0° led to the isolation of cis-endo-2,4-diphenylbicyclo[3.2.1]oct-6-en-endo-3-methanesulfonate (XI) in 65% yield. The infrared spectrum of this compound exhibited characteristic covalent sulfonate absorptions at 7.39 and 8.54 μ. The nmr displayed a sharp three proton singlet at τ 8.26 (sulfonate methyl); the rest of this spectrum was similar to that of its parent alcohol (Appendix). Cis-endo-2,4-diphenylbicyclo-[3.2.1]oct-6-en-exo-3-methanesulfonate (X) was prepared in the same fashion (72% yield).



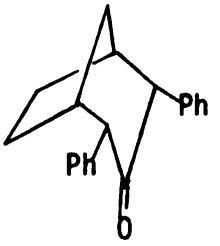
(X)



(XI)

Infrared absorptions of this sulfonate appeared at 7.39 and 8.52 μ. The methyl singlet in the nmr now appeared at τ 8.57. Both compounds analyzed correctly for $C_{21}H_{22}SO_3$. Their mass spectra exhibited parent peaks at m/e 354 (calcd. 354). The fragmentation patterns for the two compounds were remarkably similar except for slight differences in relative intensities of the fragments.

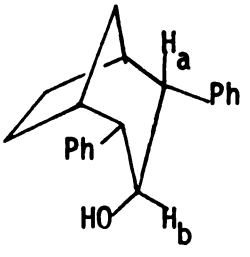
The preparation of the saturated analogues of compounds (X) and (XI) was first attempted following the reaction sequence described above on saturated ketone (XXV). The saturated ketone was prepared by diimide reduction of ketone (XVI).



(XXV)

The infrared spectrum of (XXV) exhibited absorption at 5.83 μ; nmr: τ 2.86 (10H, phenyl), 6.22 (2H, benzylic), 7.35 (2H, bridgehead), 7.60-8.55 (6H, methylene). The n → π* transition in the ultraviolet was found at 290 nm (ε = 30). The compound analyzed for $C_{20}H_{20}O$.

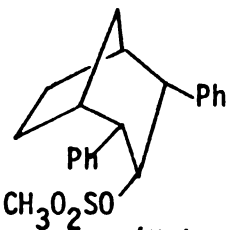
Lithium aluminum hydride reduction of ketone (XXV) gave cis-endo-2,4-diphenylbicyclo[3.2.1]octan-endo-3-ol (XXVI) in 90% yield. Hydroxyl absorptions at 2.81 and 2.89 μ in the infrared were characteristic of free and intermolecularly bonded interactions. The small coupling



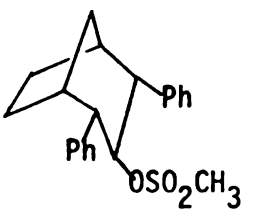
(XXVI)

(J = 3.8 cps) between the methine proton (H_b) and the benzylic hydrogens (H_a) in the nmr established the axial nature of the hydroxyl moiety. Confirmation of the molecular weight was obtained from mass spectrometry with a parent peak of m/e 278 (calcd. 278). The molecular formula $C_{20}H_{20}O$ was verified by analysis. All attempts to prepare the methanesulfonate derivative of this alcohol met with defeat, probably as a direct consequence of the greater (to its unsaturated analogue) steric hindrance created by the endo hydrogens on the now saturated two-carbon bridge. The alternative which remained was reduction of the unsaturated mesylates (X) and (XI) themselves.

Diimide reduction of endo-mesylate (XI) produced cis-endo-2,4-diphenylbicyclo[3.2.1]octane-endo-3 methanesulfonate (XV) in 88% yield. The infrared spectrum showed absorption at 7.43 and 8.57 μ; nmr: τ 4.33 (1H, t, J = 3.9 cps) methine proton, 8.41 (3H, s) sulfonate methyl. The parent peak in the mass spectrum was in complete accord for the addition of one mole of hydrogen, m/e 356. Analysis was consistent for a molecular formula of $C_{21}H_{24}SO_3$. Reduction of the exo-mesylate



(XV)



(XIV)

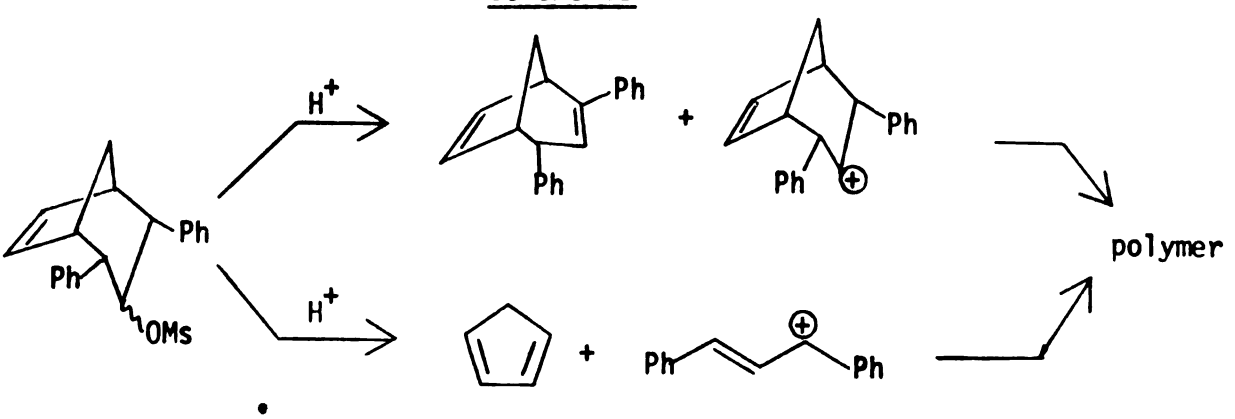
(X) led to the isolation of its saturated analogue, cis-endo-2,4-diphenylbicyclo[3.2.1]octane-exo-3-methanesulfonate (XIV); infrared: 7.41 and 8.52 μ; nmr: τ 4.31 (1H, t, 10.4 cps) methine proton, 8.14 (3H, s) sulfonate methyl; mass spect: m/e 356. This compound also analyzed correctly for $C_{21}H_{24}SO_3$.

Since the four methanesulfonates (vide supra) had been isolated and their structures elucidated it was possible to commence with our solvolytic investigation. It should be realized that the results discussed here evolve from a very primitive study of only compounds (X) and (XI). The primary purpose for such an investigation was the discovery of the proper solvolytic conditions necessary to initiate ionization, and characterization of the major products; the kinetic rates of reaction were not determined and will not be discussed.

Acetolysis of either the endo or exo mesylate (X or XI) at 35° resulted in the recovery of starting material. Formolysis at 50° or 80° also proved insufficient to promote ionization of the endo-isomer. When the endo-compound was subjected to more vigorous conditions, i.e. heated to 140° in the presence of acetic acid buffered with 5% sodium acetate, only an intractable polymeric tar could be isolated.

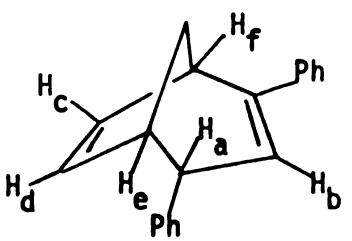
Treatment of the endo-mesylate with trifluoroacetic acid (also a run containing 5% sodium trifluoroacetate) resulted in the isolation of a yellow polymer. It was not determined whether this polymeric material had its origin from the parent system or the 1,3 diphenyl allyl cation which would be formed via our proposed fragmentation pathway (Scheme II).

Scheme II



Subsequent runs were conducted with the exclusion of acid which seemed to catalyze polymerization.

When either mesylate was heated to 140° in a 1:1 ethanol-water solvent system, with or without added triethylamine, the major solvolysis product isolated was diene (XXVII), 2-phenyl-endo-4-phenylbicyclo[3.2.1]-octa-2,6-diene. Similar results were obtained in dioxane-water. It should be noted that other products (5-15%) were formed, but they were neither isolated nor characterized. Solvolysis at 140° in a slurry of sodium carbonate and dimethylformamide containing lithium chloride produced diene (XXVII) in quantitative yield. Attempted reduction of the endo-mesylate with lithium aluminum hydride again resulted in isolation of the diene. Its ir spectrum showed characteristic olefinic and aromatic absorptions at 3.32 (doublet). The absorption at 255 nm (ϵ = 13,000) in the ultraviolet was typical of a styrenyl chromophore. The nmr spectrum was as follows: τ 2.53-3.10 (10H, phenyl), 3.61 (sym. quartet, H_d), 4.34 (quintet, H_b), 4.74 (sym. quartet, H_c), 6.23 (doublet of doublet's, H_a), 6.83 (multiplet, H_f), 7.02 (multiplet, H_e), 7.78 (complex, methylene-bridge protons). The coupling between the protons was verified by irradiation experiments (Table II).



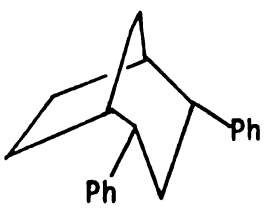
(XXVII)

TABLE II: Results of NMR Decoupling on Diene (XXVII).

Signal Irradiated	Signals Altered	Multiplicity	Coupling (cps)
H_d	H_c H_f	doublet pattern change	2.8 ——
H_b	H_a H_e H_f	doublet pattern change pattern change	4.8 —— ——
H_c	H_d H_f	doublet pattern change	2.8 ——
H_a	H_b H_f	unsym. quartet pattern change	~1.5 ——
H_f	H_b H_d	sym. quartet doublet	1.5 5.8
H_e	H_b H_b H_b^c	unsym. quartet doublet broad doublet	$\lesssim$1.5 5.8 ~3.0
H_e & H_f	H_d H_d H_b^c	doublet doublet doublet	5.8 5.8 3.0
H_f & H_b	H_c H_a^c	doublet broad singlet	5.8 —

Confirmation of the molecular weight was obtained from mass spectrometry with a parent peak of m/e 258 (calcd 258). Diene (XXVII) was isolated as a colorless oil which was fairly sensitive to air and heat on standing and was stored under nitrogen at 0°.

In lieu of purification and analysis because of its tendencies toward decomposition the diene was catalytically hydrogenated (5% palladium on charcoal) to give a bicyclic octane skeleton. Hydrogenation should and did occur from the less hindered side of the styrene moiety to produce the symmetrical octane, cis-endo-2,4-diphenylbicyclo[3.2.1]-octane (XXVIII). The ir spectrum of this compound was rather

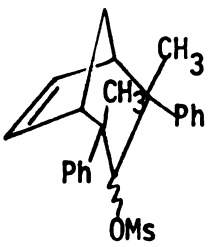


(XXVIII)

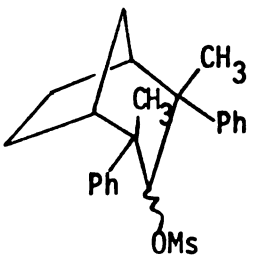
uninformative; however, the simplicity of the nmr spectrum did reflect its symmetry: τ 2.83 (10H, s) phenyl, 7.08 (2H, broad triplet) benzylic, 7.61 (2H, m) bridgehead, 7.82-8.60 (8H, complex) methylene. The mass spectrum was consistent for the addition of two moles of hydrogen: parent peak m/e 262. The analysis confirmed the molecular formula $C_{20}H_{22}$.

In conclusion elimination and not fragmentation seems to be the major solvolytic pathway. Perhaps the driving force for elimination is the formation of the stable diene system (XVII) and may be a direct consequence of the phenyl interaction which is relieved by the formation of the double bond, thus swinging the phenyl moiety away from the ring

system. The possible existence of fragmentation products can not be eliminated since the minor constituents have not yet been identified. Finally, the author would like to suggest the preparation of the α,α' dimethyl methanesulfonate analogues ((XXIX) to (XXXII)) of the mesylates discussed in this thesis on the grounds that elimination cannot occur.



(XXIX) and (XXX)



(XXXI) and (XXXII)

EXPERIMENTAL

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded by a Perkin-Elmer Grating Infrared Spectrophotometer, Model 237 B. They were calibrated with the 6.23 μ band of a polystyrene film reference. A Unicam SP 800 was used for recording ultraviolet spectra. Mass spectra analysis were performed by Mrs. R. L. Guile at Michigan State University on a Hitachi, Model RMU-6, Mass Spectrometer.

Nuclear Magnetic Resonance (nmr) spectra were obtained using a Varian A-60 Spectrometer. The decoupling experiments were performed by Eric Roach on a Varian HA-100 Spectrometer. The nmr data are presented in the following manner: τ 6.00 (2H, d of d's, J = 4). All spectra are recorded in tau (τ) units relative to tetramethylsilane (TMS). The first symbols in the parenthesis refer to the integrated band intensity (number of hydrogens), the second letter(s) indicate band multiplicity and the last symbol (J) is the observed coupling constant in cycles per second. The multiplicities are: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Others will be stated explicitly.

Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Part I: Synthesis

Cis-endo-2,4-diphenylbicyclo[3.2.1]oct-6-en-3-one (XVI). α,α'-Dibromodibenzyl ketone (240 g, 0.652 mole) in 900 ml of reagent grade acetone was added dropwise to a mechanically stirred solution of sodium iodide (240 g, 0.652 mole) in 3250 ml of acetone. An excess of cyclopentadiene (ca. 75 ml) was distilled into the reaction mixture concurrent with the addition of the dibromoketone. The mixture was maintained between -7 and -12°C throughout the course of the reaction. The solution first turned a bright yellow, then climaxed in the appearance of golden needles aimlessly drifting in a dark brown nectar. The mixture was allowed to warm to room temperature and then poured into 4 liters of water. Sodium bisulfite was added until the solution became colorless. The yellowish needles were filtered, dissolved in boiling 95% ethanol and treated with Norit A. Hot filtration and subsequent cooling afforded long colorless needles, m.p. 150.2-150.8° (total yield: 129 g, 73%), which exhibited identical spectral properties.

Cis-endo-2,4-diphenylbicyclo[3.2.1]oct-6-en-endo-3-ol (XVIII). Lithium Aluminum Hydride Reduction[20]. The bicyclic ketone (XVI) (20 g, 73 mmoles) dissolved in tetrahydrofuran (150 ml) was added dropwise to a slurry of lithium aluminum hydride (LAH) (4.5 g, 122 mmoles) in anhydrous ethyl ether. After addition was completed the mixture was refluxed overnight. The remaining LAH was destroyed by adding 2 ml of 5% sodium hydroxide solution followed by 2 ml of water for each initial gram of LAH. The fluffy white precipitate was filtered and

washed with ethyl ether. The combined organic solvents were removed in vacuo. Recrystallization twice from hexane afforded colorless prisms, m.p. 80-81.5° (12.9 g, 47 mmoles, 65% yield); infrared: λ_{max} (KBr) 2.81, 6.23, 10.00, 10.86, 10.99; nmr: τ ($CDCl_3$) 2.86 (10H, s), 3.62 (2H, broad s), 5.73 (1H, d of t's, J_1 = 8.4, J_2 = 4.5), 6.78 (2H, d of d's, J_1 = 1.7, J_2 = 4.5), 7.14 (2H, broad d, J = 5.2), 7.60 (1H, quintet, J_1 = 5.2, J_2 = 10.2), 8.25 (1H, d, J = 10.2), 8.55 (1H, d, J = 8.4); trace of acid: signal at 8.55 collapsed to a sharp singlet and signal at 5.73 collapsed to a triplet; in D_2O: signal at 8.55 disappeared; mass spect: m/e 276

Anal. Calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 87.09; H, 7.40.

Cyclization of endo-Alcohol (XVIII). Syn-syn-4,9-diphenyl-2-oxatricyclo[3.2.1.$1^{3,7}$]nonane (XIX). Method A - Acetic Acid. The endo-alcohol (0.5 g, 1.8 mmoles) was dissolved in 20 ml acetic acid. The mixture was heated on a steam bath for 24 hrs. Neutralization with Na_2CO_3 solution, extraction with ethyl ether, drying over $MgSO_4$ and finally concentration of the organic phase by flash evaporation afforded an off white solid (430 mg) which was spectroscopically identical to starting material.

Method B - Toluenesulfonic Acid. The endo - alcohol (0.7 g, 2.5 mmoles) was placed in 25 ml 1:1 ethanol - water containing toluenesulfonic acid (2 g, 11.6 mmoles). The mixture was refluxed overnight. Neutralization with Na_2CO_3 and subsequent workup afforded only starting material.

Method C - 30% Sulfuric Acid. The endo alcohol (1 g, 3.6 mmoles) was placed in a 100 ml one-neck flask containing 60 ml of 30% H_2SO_4. The mixture was refluxed for three hours. It was then allowed to cool, diluted to 200 ml, and extracted with ethyl ether. The organic layer was washed with water, 5% Na_2CO_3 solution and then more water. The organic phase was concentrated in vacuo and the solid recrystallized twice from hexane and then sublimed, m.p. 101-101.5° (0.7 g, 2.5 mmoles, 70% yield); infrared: λ_{max} (Nujol) 6.23, 9.8, 9.89, 9.96, 11.23; nmr: τ ($CDCl_3$) 2.47-3.04 (10H, complex), 5.32 (1H, broad t, J = 4), 5.62 (1H, broad s), 6.79 (1H, s), 6.91-8.46 (6H, complex), 8.39 (1H, d of t's, J_1 = 4.2, J_2 = 11.8); mass spect: m/e 276.

Anal. Calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.29.
Found: C, 87.05; H, 7.29.

Sodium-Alcohol Reduction of Ketone (XVI). The bicyclic ketone (17.5 g, 63 mmoles) in 210 ml absolute ethanol and 50 ml of dry toluene (warmed until ketone dissolved) was syringed into a refluxing solution of 400 ml toluene and molten sodium (14 g, 0.61 mole). The reaction mixture was refluxed until all the sodium dissolved. The remaining cooled solution was then poured into one liter of water and extracted with ethyl ether. The organic portion was washed twice with 2% HCl, once with 10% sodium carbonate solution and finally washed twice with water. Drying over $MgSO_4$ and concentration of the organic layer in vacuo gave a reddish oil. Recrystallization from hexane afforded 6.6 g of an off-white solid. Further concentration of the hexane afforded no additional crystalline material. Continuous shaking of the remaining oil with cold petroleum ether yielded an additional 4.9 g of impure solid

material. The infrared spectrum of the crude material possessed characteristic hydroxyl absorption; no starting ketone was present. The nmr spectrum did suggest that more than one compound was present. At this point further purification of this alcoholic mixture seemed fruitless. Preparation of the p-nitrobenzoates was undertaken in hope that separation could be achieved. (Spectral properties of the pure alcohols will be given in a later section.)

A portion of the crude product mixture was purified further for nmr studies. The red oil obtained originally was dissolved in 15 ml of acetonitrile. Continuous solvent-solvent extraction with pentane for five days afforded an off-white solid upon evaporation. The remaining acetonitrile solution was concentrated *in vacuo* to give a red residue, the infrared of which indicated that no alcohol was present and extraction was complete. The composition of each alcohol was determined by integrating the two characteristic methine resonances centered at τ 5.8. Comparison of the integrated intensity bands showed that *trans*-2,4-diphenylbicyclo[3.2.1]oct-6-en-*exo*-3-ol (XXIII) composed 48.1 ± .4% of the total reduction product. The remaining portion was *cis*-*endo*-2,4-diphenylbicyclo[3.2.1]oct-6-en-*exo*-3-ol (XXII).

Preparation of the p-Nitrobenzoates (XX) and (XXI). The crude alcoholic mixture from the previous experiment (11.5 g, ca. 42 mmoles) was placed in a round bottom flask containing pyridine (6 ml, 75 mmole) and 340 ml of anhydrous ethyl ether. p-Nitrobenzoyl chloride (11.5 g, 62 mmoles) dissolved in a minimum amount of anhydrous ether was added dropwise to the stirred solution maintained at 0°C during the period of addition. A white precipitate resulted immediately. The reaction

was continued for three hours at room temperature , and the mixture poured into a separatory funnel containing 200 ml H_2O, shaken, and the water layer discarded. The organic portion was washed twice with 1 1/2% HCl (100 ml), once with 10% sodium bicarbonate solution, and twice more with water. It was then dried with $MgSO_4$; concentration by flash evaporation gave a yellowish solid. Recrystallization from 95% ethanol afforded long-yellowish needles, m.p. 181.5-184.5°. Recrystallization a second time from a hexane-benzene mixture gave slightly yellowish needles, m.p. 185-186°. It seemed that the fractional crystallization process was complete. Further purification from acetone-water afforded colorless needles, m.p. 186-186.5° (4.9 g); infrared: λ_{max} (CCl_4) 5.75, 6.20, 9.07, 11.58; nmr: τ ($CDCl_3$) 2.19 (4H, A_2B_2 quartet, J = 9.2), 2.60-3.10 (10H, m), 3.75 (2H, broad s), 4.08 (1H, t, J = 9.8), 6.93 (2H, d of d's, J_1 = 9.8, J_2 = 2.4), 7.14 (2H, m), 7.79 (1H, d of t's, J_1 = 10.3, J_2 = 4.9), 8.06 (1H, d, J = 10.3); mass spect: m/e 258.

Anal. Calcd. for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29.
Found: C, 76.13; H, 5.50; N, 3.13.

Concentration of the ethanol solution and subsequent cooling gave another yellowish solid material, m.p. 139°. Recrystallization from acetone-water afforded long colorless needles, m.p. 139° (2.45 g); infrared: λ_{max} (CCl_4) 5.78, 6.20, 9.07, 11.59; nmr, τ ($CDCl_3$) 2.35 (4H, A_2B_2 quartet, J = 8.8), 2.58-3.05 (10H, complex), AB system: 3.75 (1H) and 3.97 (1H) (d of d's, J_1 = 4.2, $J_{2,3}$ = 2.6), 4.08 (1H, d of d's, J_1 = 7.6, J_2 = 9.5), 6.24 (1H, d of d's, J_1 = 2.6, J_2 = 7.6), 6.39 (1H, d of d's, J_1 = 2.2, J_2 = 11.5), 7.19 (2H, m), 7.83 (1H, d, J = 11.0), 8.30 (1H, d of t's, J_1 = 4.7, J_2 = 11.0); mass spect: m/e 258.

Anal. Calcd. for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29.

Found: C, 76.28; H, 5.49; N, 3.21.

The remainder of the ethanol solution was concentrated in vacuo yielding 0.80 g of solid which was an impure mixture of the two p-nitrobenzoates. The total quantity of product isolated was 8.10 g (ca. 70% yield).

Cis-endo-2,4-diphenyloct-6-en-exo-3-ol (XXII). The exo-p-nitrobenzoate (XX) (650 mg, 1.5 mmoles) was added to a solution of potassium hydroxide (8 g, 140 mmoles) in 42 ml of methanol (ca. 8% alcoholic KOH). The mixture was refluxed overnight, poured into 300 ml of ice-water, and extracted twice with ethyl ether (200 ml). The combined ether extracts were washed with 2% hydrochloric acid and then water. Recrystallization from hexane afforded colorless superfine needles, m.p. 148-149° (295 mg, 1.1 mmoles, 71% yield); infrared: λ_{max} (Nujol) 3.83 (shoulder), 3.88, 6.21, 9.07, 9.47, 10.21; nmr: τ ($CDCl_3$) 2.79 (10H, s), 3.87 (2H, broad s), 5.85 (1H, t, J = 9.2), 7.28 (4H, complex, d, J = 9.2), 7.90 (1H, quintet, J_1 = 4.9, J_2 = 10.3), 8.21 (1H, d, J = 10.3), 8.56 (1H, s); in D_2O: resonance at 8.56 disappeared; mass spect: m/e 276.

Anal. Calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.29.

Found: C, 87.05; H, 7.31.

Chromium Trioxide-Dipyridinium Complex Oxidation of exo-Alcohol (XXII). (The procedure for the preparation and use of the complex is outlined by J. C. Collins)[17]. The alcohol (0.41 g, 1.5 mmoles) was dissolved in 20 ml of methylene chloride. To this stirred solution a six-fold excess

of the complex (2.4 g, 9.3 mmoles) was added. The reaction proceeded to completion within 10 minutes (at room temperature) with decomposition of the complex to brownish-black polymeric chromium reduction products. The organic layer was then poured into 100 ml of water and extracted with ethyl ether. The remaining polymeric residue was washed three times with ether (25 ml), combined with the other organic portion and dried over magnesium sulfate. The solvent was stripped *in vacuo* and recrystallization from methanol afforded colorless needles, m.p. 150-150.5° (290 mg, 1.1 mmoles, 71% yield); the spectral properties of this compound were identical to those of the bicyclic ketone (XVI) (*vide supra*).

Trans-2,4-diphenylbicyclo[3.2.1]oct-6-en-*exo*-3-ol (XXIII). The *trans*-diphenyl-*exo*-*p*-nitrobenzoate (XXI) (2.09 g, 4.9 mmoles) was added to a solution of potassium hydroxide (24 g, 0.42 mole) in 120 ml of methanol (*ca*. 8% alcoholic KOH). The mixture was refluxed overnight. The work-up of the reaction mixture was identical to that in the hydrolysis of *exo*-*p*-nitrobenzoate (XX) (*vide supra*). Recrystallization from hexane afforded colorless superfine needles, m.p. 108.5-110.5° (1.10 g, 4.0 mmoles, 82% yield); infrared: λ_{max} (Nujol) 2.82, 6.21, 9.31, 10.21; nmr: τ ($CDCl_3$) 2.54-2.94 (10H, complex), AB system: 3.85 (1H) and 4.01 (1H) (d, of d's, J_1 = 6, $J_{2,3}$ = 2.5), 5.62 (1H, d of d's, J_1 = 10.9, J_2 = 7.2), 6.70 (1H, d of d's, J_1 = 2.6, J_2 = 7.2), 6.87 (1H, d of d's, J_1 = 2.4, J_2 = 10.9), 8.01 (1H, d, J = 10.3), 8.37 (1H, d of t's, J_1 = 10.3, J_2 = 4.9), 8.6 (1H, s); mass spect: m/e 276.

Anal. Calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.29.

Found: C, 86.73; H, 7.30.

Chromium Trioxide - Dipyridinium Complex Oxidation of trans-Diphenyl-exo-Alcohol. Trans-2,4-Diphenylbicyclo[3.2.1]oct-6-en-3-one (XXIV). The trans-diphenyl-exo-alcohol (270 mg, 0.98 mmole) was dissolved in 12.5 ml of methylene chloride. The complex (1.5 g, 6.7 mmoles) was added to the stirred solution at room temperature. The reaction proceeded to completion within 10 minutes as evidenced by the formation of a brownish-black polymeric residue. The work-up of the reaction mixture was identical to that in the oxidation of the exo-alcohol (XXII) (vide supra). Recrystallization from methanol afforded colorless shimmering needles, m.p. 131-132.5° (170 mg, 0.62 mmole, 63%); infrared: λ_{max} ($CHCl_3$) 5.84, 6.23, 7.42, 9.08; uv: λ_{max} (cyclohexane) 300 nm (ε = 115); nmr: τ ($CDCl_3$) 2.50-2.97 (10H, complex), 3.63 (2H, m), 6.07 (2H, m), 6.57 (1H, m), 6.93 (1H, m), 7.68 (2H, m).

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.56; H, 6.61.

Found: C, 87.37; H, 6.66.

Sulfuric Acid Treatment of Alcohols (XXII) and (XXIII). In separate experiments the two exo-alcohols (100 mg, 0.36 mmole) were placed in 6 ml of 30% H_2SO_4. Their mixtures were refluxed for three hours, cooled, diluted to 50 ml and extracted with ethyl ether. The ether portions were washed with 10% $NaHCO_3$ solution and twice with water; the solvent was removed in vacuo. Spectral data taken of the crude products were consistent with those of the starting materials. There was no evidence that cyclic-ether formation had occured.

Cis-endo-2,4-diphenylbicyclo[3.2.1]oct-6-en-exo-3-yl methanesulfonate (X). The exo-alcohol (XXII) (1.05 g, 3.86 mmoles) was dissolved in 40

ml pyridine. An equimolar amount of methanesulfonyl chloride (0.45 g, 3.90 mmoles) was added. The mixture was allowed to react at approximately 0°C overnight and then warmed to room temperature for 24 hrs. The mixture was diluted with 500 ml of water and the precipitate filtered. Recrystallization from ethyl ether-hexane gave yellowish needles. Further purification by cold recrystallization from acetone-water afforded colorless needles, m.p. 166.5° (dec.) (0.92 g, 2.77 mmoles, 72% yield); infrared: λ_{max} (Nujol) 6.20, 7.39, 8.52, 10.57, 10.98; nmr: τ ($CDCl_3$) 2.73 (10H, s), 3.73 (2H, broad s), 4.70 (1H, t, J = 9.8), 6.98 (2H, d of d's, J_1 = 9.8, J_2 = 2.4), 7.21 (2H, broad d, J = 4.9), 7.86 (1H, d of t's, J_1 = 10.3, J_2 = 4.9), 8.17 (1H, d, J = 10.3), 8.26 (3H, s); mass spect: m/e 354.

Anal. Calcd. for $C_{21}H_{22}SO_3$: C, 71.16; H, 6.26; S, 9.05.

Found: C, 71.17; H, 6.35; S, 9.11.

Cis-endo-2,4-diphenylbicyclo[3.2.1]oct-6-en-endo-3-yl methanesulfonate (XI). The endo-mesylate was obtained in 65% yield following the procedure for the preparation of the exo-mesylate (X) (vide supra). The compound had the following properties: m.p. 144.5° (dec.); infrared: λ_{max} (Nujol) 6.19, 7.39, 8.54, 10.87; nmr: τ ($CDCl_3$) 2.78 (10H, s), 3.57 (2H, broad s), 4.61 (1H, t, J = 4.4); 6.53 (2H, d of d of d's, J_1 = 4.4, J_2 = 1.4), 7.11 (2H, broad d, J = 5.2), 7.55 (1H, d of t's, J_1 = 5.2, J_2 = 10.4), 8.20 (1H, d, J = 10.4), 8.57 (3H, s); mass spect: m/e 354.

Anal. Calcd. for $C_{21}H_{22}SO_3$: C, 71.16; H, 6.26; S, 9.05.

Found: C, 71.30; H, 6.17; S, 9.13.

Epimerization of Bicyclic Ketone (XVI) with Sodium Methoxide. The cis-diphenyl ketone (XVI) (2.55 g, 9.25 mmoles) was treated with sodium methoxide (770 mg, 14.3 mmoles) in 52 ml of dry methanol and 122 ml toluene. The mixture was refluxed for 6 days, poured into 200 ml water, and extracted with ethyl ether. The ether portion was washed with water, twice with 1 1/2% hydrochloric acid (100 ml), again with water, and finally dried over $MgSO_4$. The solvent was removed *in vacuo* leaving a slightly yellowish solid. The amount of epimerization was determined from nmr by integrating the resonances assigned to the bridgehead protons and applying the following formula,

$$\frac{2\,A_1}{A_2 + A_1} \times 100$$

where A_1 = integrated band intensity located at τ 6.57 for one proton of (XXIV); A_2 = " " " " " τ 6.93 for two Protons of (XVI) and one proton of (XXIV).

Using the above method, it was found that 68.8 ± 1.1% of the starting ketone epimerized at one center *alpha* to the carbonyl moiety yielding *trans*-2,4-diphenylbicyclo[3.2.1]oct-6-en-3-one (XXIV).

Diimide Reduction. Cis-*endo*-2,4-diphenylbicyclo[3.2.1]octan-3-one (XXVII). (Potassium Azodicarboxylate (PADA) was used as the diimide precursor and was prepared according to Thiele[18]. Generation of diimide *in situ* was outlined in a procedure by Warren, *et.al.*[19]). The unsaturated ketone (XVI) (8.0 g, 29 mmoles) was dissolved in a slurry of 150 ml pyridine and PADA (15 g, 80 mmoles). Acetic acid (4.0 g, 67 mmoles) dissolved in 5 ml pyridine was added dropwise to the vigorously stirred

slurry. After 9 hrs. an equal amount of acid was slowly added. The absence of yellow solid indicated that the reaction was complete. Upon completion the mixture was poured into 500 ml of water and the precipitate filtered. Recrystallization from 95% ethanol afforded colorless needles, m.p. 114.5-115° (6.6 g, 24 mmoles, 83% yield); infrared: λ_{max} (Nujol) 5.83, 6.19, 9.33; u v : λ_{max} (cyclohexane) 290 nm (ϵ = 30); nmr: τ ($CDCl_3$) 2.86 (10H, s), 6.22 (2H, d, J = 2.5), 7.35 (2H, m), 7.60-8.55 (6H, complex).

Anal. Calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.29.
Found: C, 87.00; H, 7.43.

Cis-endo-2,4-diphenylbicyclo[3.2.1]octan-endo-3-ol (XVIII). The saturated ketone (3.6 g, 13 mmoles) was added dropwise to a refluxing slurry of lithium aluminum hydride (1.5 g, 39 mmoles) in anhydrous ethyl ether. The mixture was allowed to reflux overnight and followed by work-up in the usual manner (vide supra). Recrystallization from hexane afforded colorless prisms, m.p. 102.5-103.5° (3.23 g, 11.6 mmoles, 90% yield); infrared λ_{max} (Nujol) 2.81, 2.89, 6.21, 9.33, 10.22; nmr: τ ($CDCl_3$) 2.54-3.10 (10H, complex), 5.46 (1H, t, J = 3.8), 6.92 (2H, m), 7.21-8.55 (8H, complex), 8.98 (1H, s); mass spect: m/e 278.

Anal. Calcd. for $C_{20}H_{22}O$: C, 86.28; H, 7.97.
Found: C, 86.19; H, 8.05.

Attempted Mesylation of Saturated-endo Alcohol (XXVIII). The alcohol (XXVIII) (2.0 g, 7.2 mmoles) was dissolved in 80 ml pyridine. An equimolar amount of methanesulfonyl chloride (0.90 g, 7.3 mmoles) was added. It was allowed to react for 48 hrs, the first day at 0°C and the second at room temperature. Workup in the usual manner (vide supra) gave a solid whose spectral properties were identical with those of the starting alcohol.

Cis-endo-2,4-diphenylbicyclo[3.2.1]octane-endo-3-yl methanesulfonate (XV). The endo-mesylate (XI) (407 mg, .96 mmoles) was dissolved in 10 ml of pyridine containing potassium azodicarboxylate (800 mg, 5.3 mmoles). Acetic acid was added dropwise to the stirred solution in two equivalent portions, at the beginning and 9 hrs later (total of .5 g acetic acid in 5 ml pyridine). After a total of 48 hrs the mixture was poured into 300 ml water and the precipitate filtered. Recrystallization from acetone-water afforded white needles, m.p. 103° (dec.) (360 mg, 0.84 mmoles, 88% yield); infrared; λ_{max} (Nujol) 7.43, 8.57, 10.53, 10.90, 11.02, 11.50; nmr: τ ($CDCl_3$) 2.52-2.92 (10H, complex), 4.33 (1H, t, J = 3.9), 6.63 (2H, m), 7.25 (2H, m), 7.91-8.27 (6H, complex), 8.41 (3H, s); mass spec.: m/e 356.

Anal. Calcd. for $C_{21}H_{24}SO_3$: C, 70.75; H, 6.79; S, 9.00.

Found: C, 70.78; H, 6.77; S, 9.14.

Cis-endo-2,4-diphenylbicyclo[3.2.1]oct-exo-3-yl methanesulfonate (XIV). The saturated exo-mesylate (XIV) (140 mg, 0.33 mmoles) was prepared following the same procedure for the reduction of endo-compound (XI) (vide supra). Recrystallization from acetone-water afforded colorless platelets, m.p. 154.5° (dec.) (80 mg, 0.19 mmoles, 57% yield); infrared; λ_{max} (Nujol) 7.41, 8.52, 10.77, 11.79; nmr: τ ($CDCl_3$) 2.45-2.88 (10H, complex), 4.31 (1H, t, J = 10.4), 6.33 (2H, d of d's, J_1 = 10.4, J_2 = 1.8), 7.64 (2H, m), 7.84-8.83 (6H, complex), 8.14 (3H, s); mass spect: m/e 356.

Anal. Calcd. for $C_{21}H_{24}SO_3$: C, 70.75; H, 6.79; S, 9.00.

Found: C, 70.72; H, 6.77; S, 9.07.

Lithium Aluminum Hydride Reduction of Endo-mesylate (XI). 2-Phenyl-endo-4-phenylbicyclo[3.2.1]octa-2,6-diene (XXVII). The endo-mesylate (1 g., 2.4 mmoles) was treated with excess lithium aluminum hydride (1 g.) in refluxing ether. The mixture was refluxed overnight and worked up in the usual manner. A colorless oil was obtained in quantitative yield; infrared: λ_{max} (Nujol) 3.32 doublet, 7.45, 9.73, 10.73, 11.21, 11.52; uv: λ_{max} (cyclohexane) 255 nm (ε = 13,000); nmr: τ ($CDCl_3$) 2.53-3.10 (10H, complex), 3.61 (1H, d of d's, J_1 = 2.8, J_2 = 5.8), 4.34 (1H, quintet, J_1 = 1.5, J_2 = 3.0), 4.74 (1H, d of d's, J_1 = 2.8, J_2 = 5.8), 6.23 (1H, d of d's, J_1 = 3.0, J_2 = 4.8), 6.83 (1H, m), 7.02 (1H, m), 7.78 (2H, complex); mass spect: m/e 258. This compound decomposed on standing at room temperature and was stored under a nitrogen atmosphere in the refrigerator.

Catalytic Hydrogenation of Diene (XXVII). Cis-endo-2,4-diphenylbicyclo[3.2.1]octane (XXVIII). The crude diene was dissolved in 50 ml of methanol containing Norit A (250 mg.) and stored in the refrigerator with occasional mixing. The solution was filtered, diluted to 250 ml, and 5% palladium on charcoal (0.5 g.) was added. Concentration in vacuo gave a colorless oil which on cold recrystallization from acetonitrile and subsequent sublimation afforded 130 mg. of colorless needles, m.p. 92°; infrared: λ_{max} (KBr) 3.42, 3.50, 8.54, 9.90, 11.01, 11.40; nmr: τ ($CDCl_3$) 2.83 (10H, s), 7.08 (2H, broad distorted t, J ≅ 7-8), 7.61 (2H, m), 7.82-8.50 (8H, complex); mass spect: m/e 262.

Anal. Calcd. for $C_{20}H_{22}$: C, 91.55; H, 8.45.

Found: C, 91.63; H, 8.39.

Part II: Solvolysis

Acetic Acid. A) The endo-mesylate (20 mg.) was placed in an nmr tube containing 1 ml of acetic acid. A spectrum of the sample was taken every 15 min. The probe temperature (ca. 34.5°) was calculated using a methanol standard. There appeared to be no reaction after one and a half hours.

B) The exo-mesylate (20 mg.) was subjected to the same conditions as in Part A. There was no change after 1 1/2 hrs.

C) A 5% sodium acetate-acetic acid solution was prepared. The endo-mesylate (50 mg.) and 5 ml of the buffered solution were placed into a sealed tube. The solution was degassed with nitrogen for 5 minutes. Subsequent heating to 140° for 1 hr. followed by quenching in 100 ml 10% $NaHCO_3$ afforded an intractable polymeric residue.

Formic Acid. A) The endo-mesylate (50 mg.) was placed into 5 ml 90% formic acid. Heating to 50° for 1 hr. and subsequent quenching in $NaHCO_3$ yielded only starting material.

B) The exo isomer (50 mg) was subjected to the same conditions as in part A. Quenching resulted in the precipitation of a brownish material which had identical spectral properties to that of starting material.

C) The material recovered in part B was dissolved in 5 ml 50% formic acid and heated to 80° for 2 hrs. Again only starting material could be isolated.

Trifluoroacetic Acid. A) The endo mesylate (50 mg.) was dissolved in 5 ml trifluoroacetic acid and warmed to 45° for three-quarters of an hour. The solution turned a dark red which culminated with the appearance of a yellow precipitate. A similar experiment was conducted on 300 mg. of the endo compound dissolved in 7 ml trifluoroacetic acid in order to characterize the precipitate. The reaction mixture was filtered and the precipitate dissolved in d-chloroform. The resultant n m r spectrum was characteristic of polymeric material: 2.32-3.21 τ (broad multiplet), 8.2-9.4 τ (broad multiplet).

B) The endo-mesylate (50 mg.) was placed in 5 ml trifluoroacetic acid containing 5% sodium trifluoroacetate. Only polymeric material could be obtained.

Ethanol: Water. A) The endo-mesylate (100 mg.) was placed in a sealed tube containing 9 ml of 1:1 ethanol-water solution. Six drops of triethylamine was added. The solution was degassed with nitrogen for 5 minutes and heated to 145° for 1 hr. The mixture was cooled, diluted with 100 ml water, and the product extracted with pentane. The pentane was removed in vacuo leaving an oily residue which could not be purified further; infrared: λ_{max} (film) 3.32 doublet, 6.25, 6.70, 6.91, 7. 5, 9.73, 10.73, 11.21, 1..52, 13.14, 14.34; n m r : τ ($CDCl_3$) 2.53-3.10 (10H, complex), 3.61 (1H, d of d's, J_1 = 2.8, J_2 = 5.8, 4.34 (1H, quintet, J_1 = 1.5, J_2 = 3.0), 4.74 (1H, d of d's, J_1 = 2.8, J_2 = 4.8), 6.93 (2H, m), 7.78 (2H, complex).

B) The exo-mesylate (110 mg.) was placed in 10 ml 1:1 ethanol-water solution in a sealed tube. Six drops of triethylamine was added, the

solution degassed for 5 minutes with nitrogen, and heated to 145° for 1 hr. When the solution was cooled to room temperature a white solid precipitated (53 mg.) which was recovered starting material. The remaining solution was diluted with 100 ml of water and extracted with pentane. The organic layer was dried over $MgSO_4$ and concentrated in vacuo leaving a thick oil whose n m r spectrum ($CDCl_3$) could only be characterized in the lower field region: τ 2.53-3.10 (m), 3.64 (sextet, peak intensity: 1:1:2:2:1:1), 3.97 (broad, s), 4.34 (quintet), 4.74 (d of d's), 6.23 (d of d's).

C) Heating the endo-mesylate to 145° in ethanol:water without adding triethylamine gave results identical to those obtained in part A.

Dioxane:Water. The endo-mesylate (50 mg.) was dissolved in 3 ml of dioxane and syringed into a sealed tube containing 3 ml H_2O. The solution was degassed with nitrogen and heated to 140° for 1 hr. The mixture was cooled, diluted to 100 ml with water and extracted with pentane. The organic portion was dried with $MgSO_4$ and concentrated in vacuo giving an oily substance which exibited identical spectral properties to that obtained from the solvolysis of the endo-mesylate in ethanol-water (vide supra).

Dimethylformamide (DMF). A) The endo-mesylate (792 mg.) was placed in 80 ml of DMF containing 320 mg of lithium chloride and 170 mg Na_2CO_3. The mixture was heated to 140° for 1 hr. It was then cooled, diluted with water and extracted with pentane. Concentration in vacuo afforded a single compound (510 mg.) which was a slightly colored oil; infrared: λ_{max} (film) 3.32 doublet, 6.25, 9.73, 10.73, 11.21, 11.52;

nmr: τ ($CDCl_3$) 2.53-3.10 (10H, complex), 3.61 (1H, d of d's, J_1 = 2.8, J_2 = 5.8), 4.34 (1H, quintet, J_1 = 1.5, J_2 = 3.0), 4.74 (1H, d of d's, J_1 = 2.8, J_2 = 5.8), 6.23 (1H, d of d's, J_1 = 3.0, J_2 = 4.8), 6.93 (2H, m), 7.78 (2H, complex); mass spect: m/e 258.

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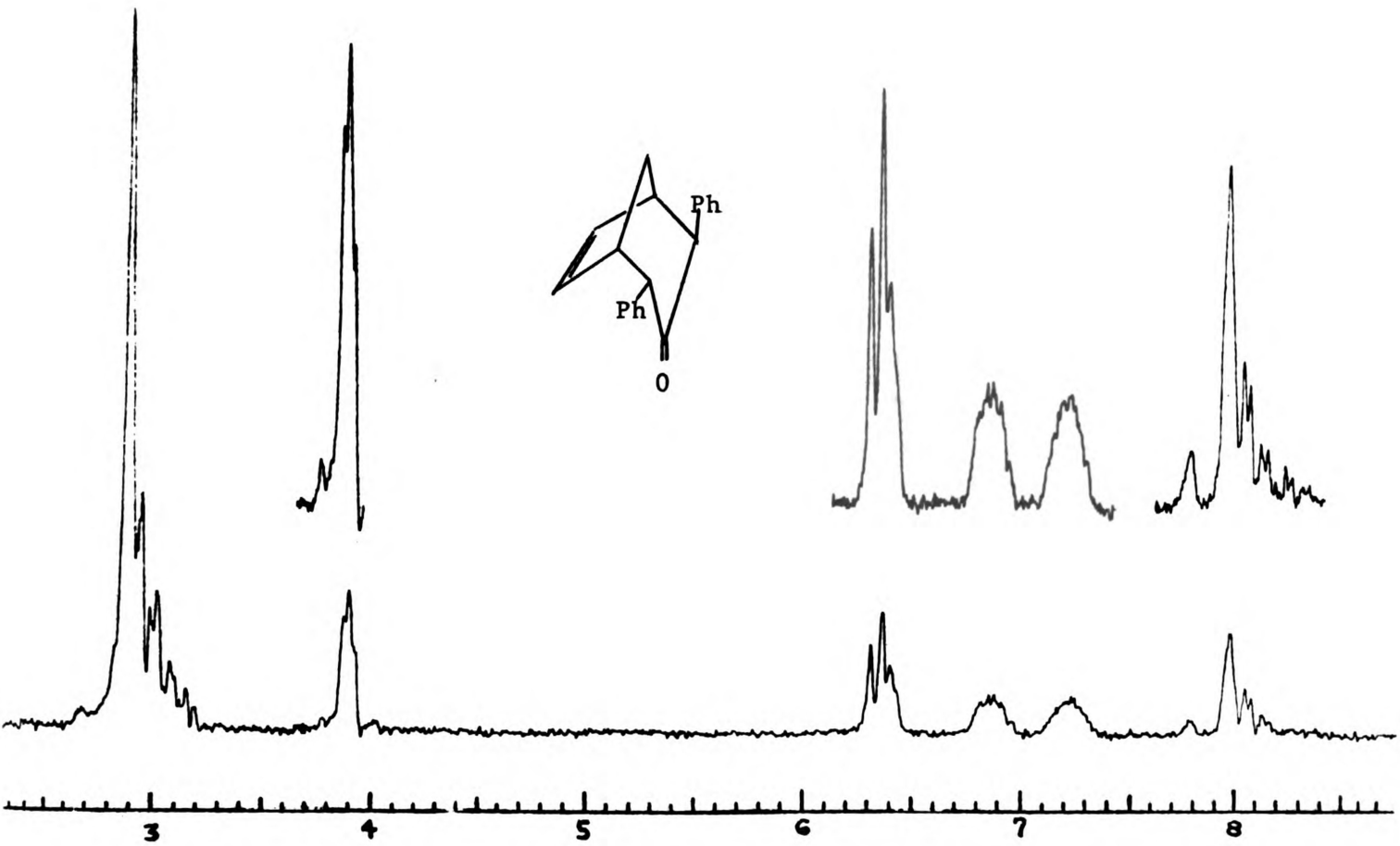
APPENDIX

NMR SPECTRA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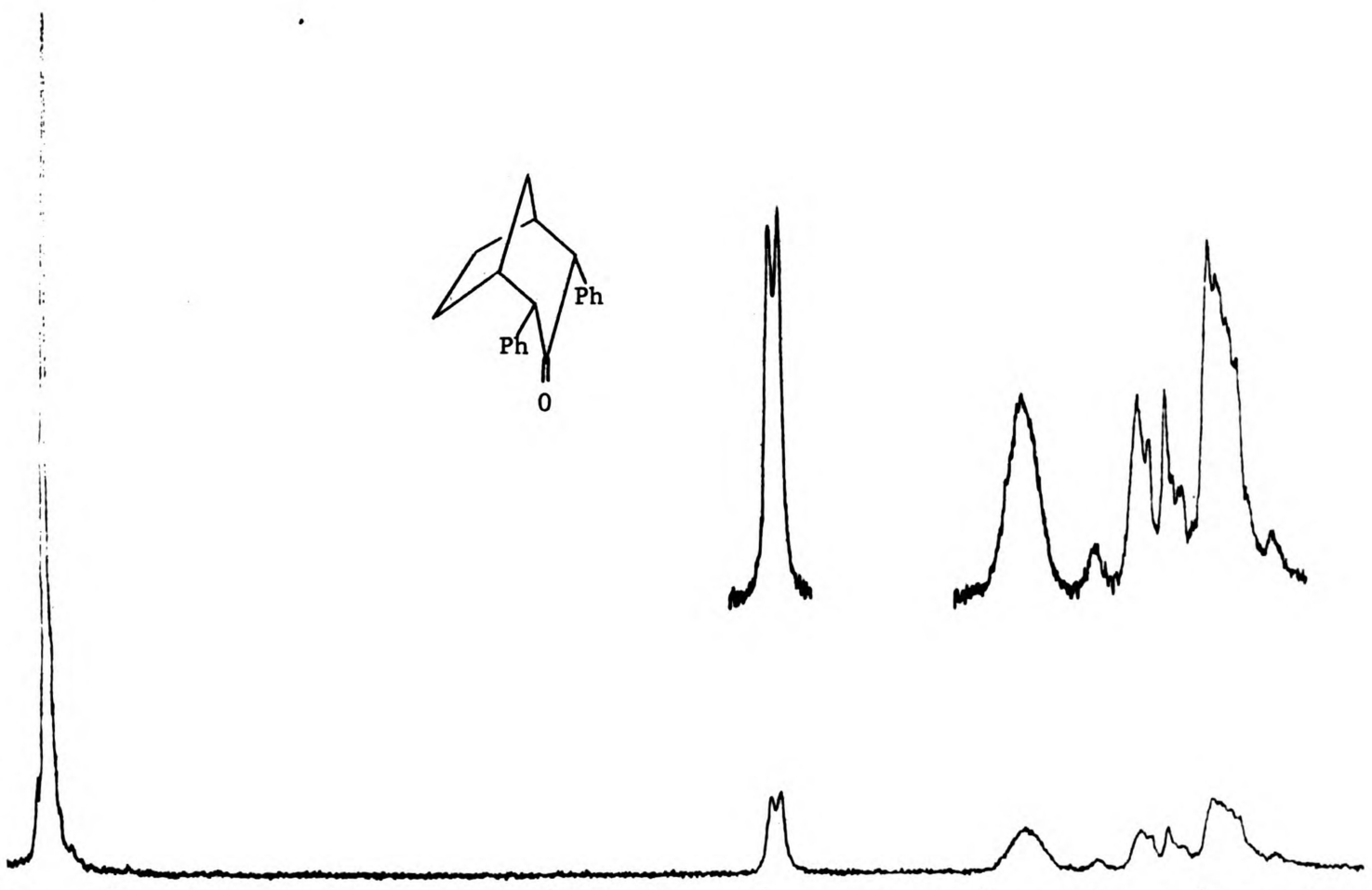
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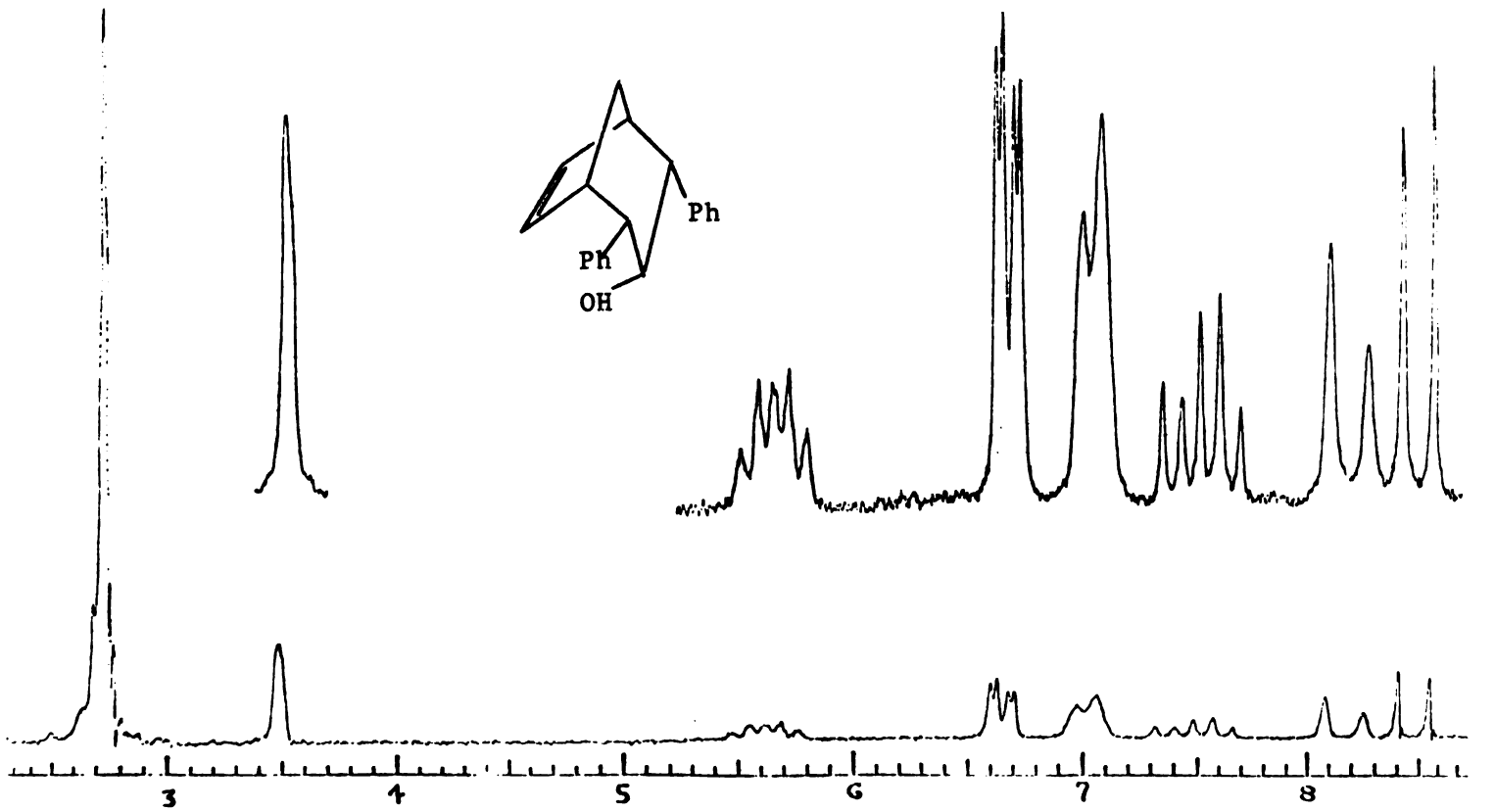
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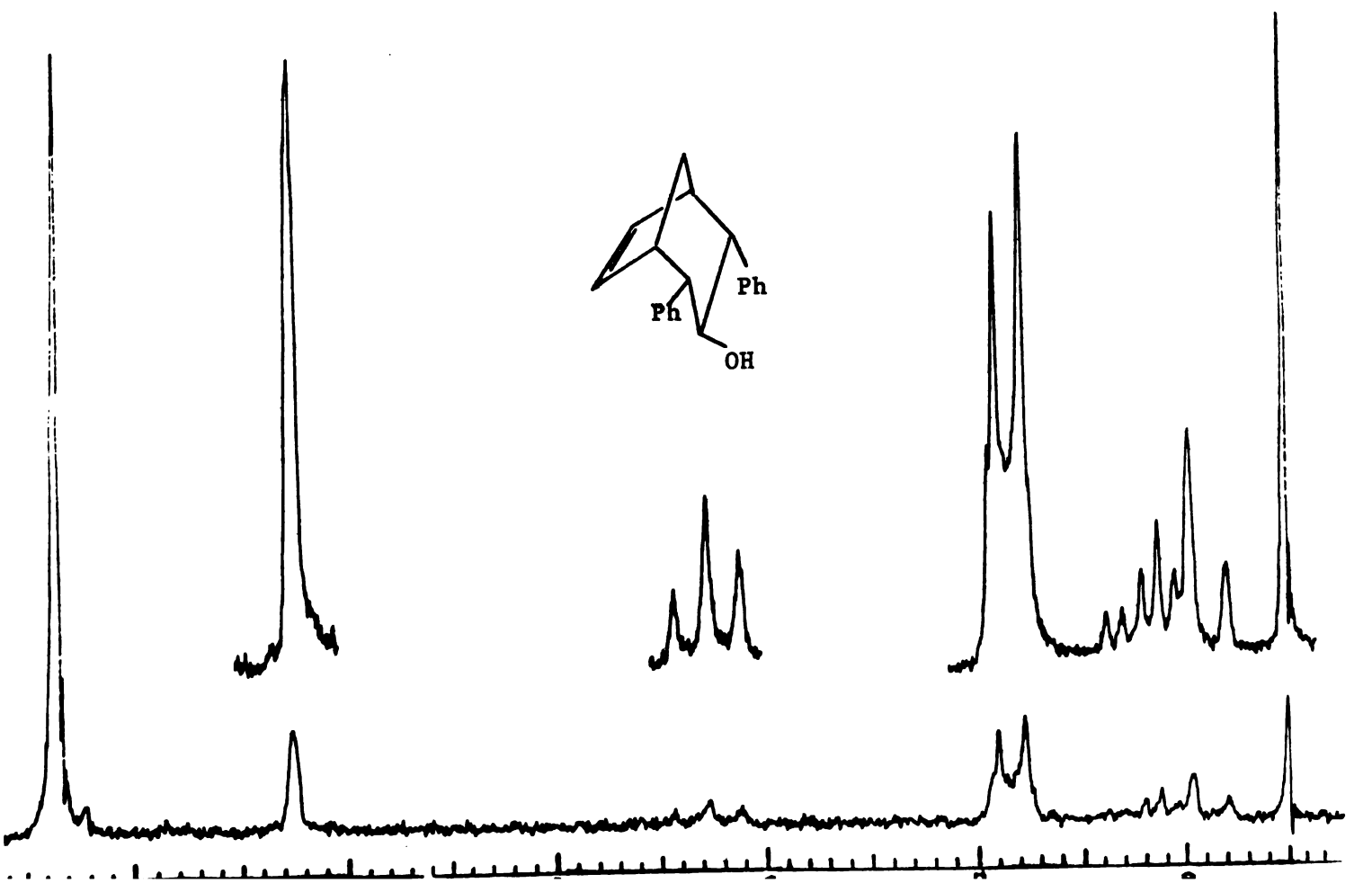
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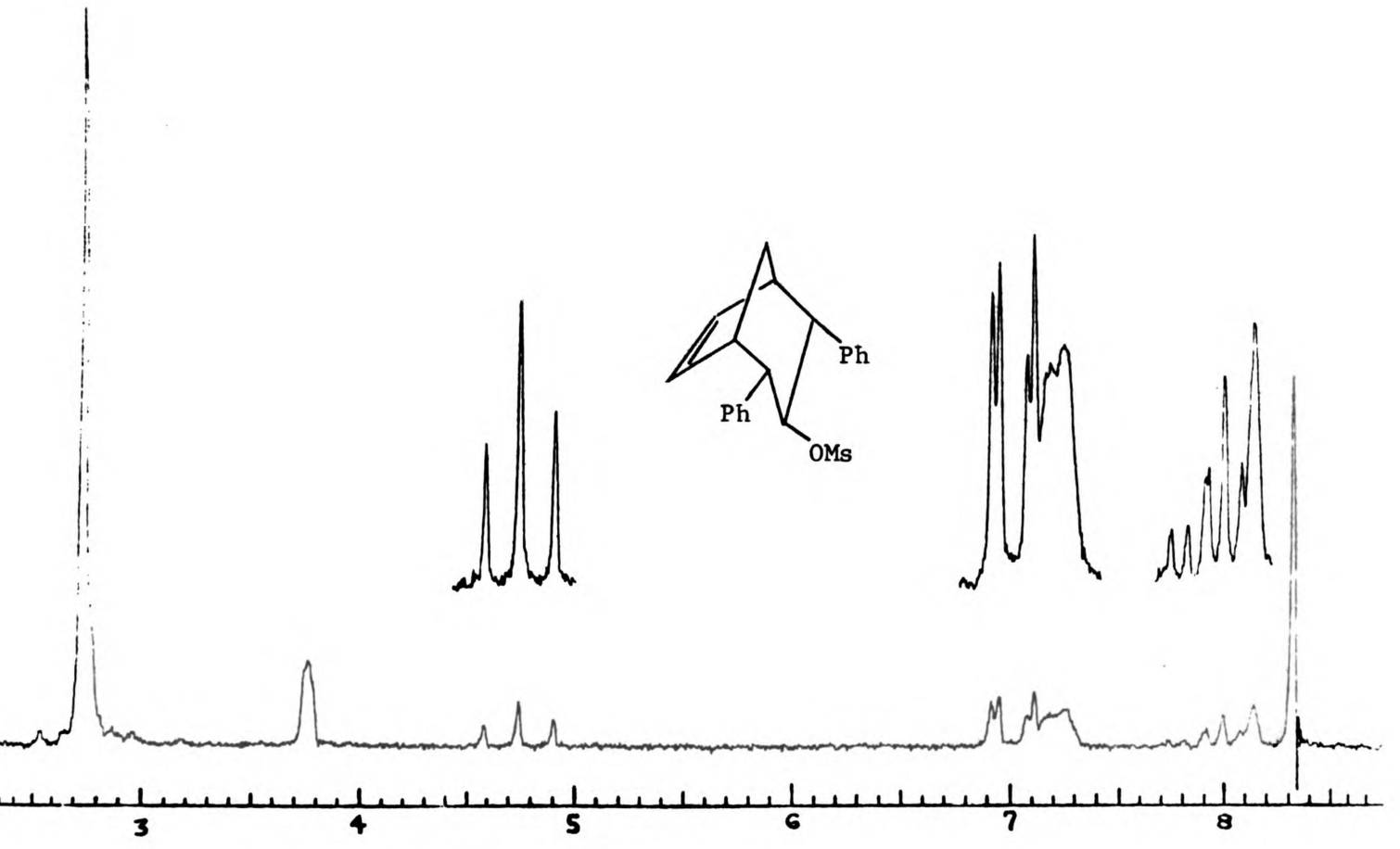
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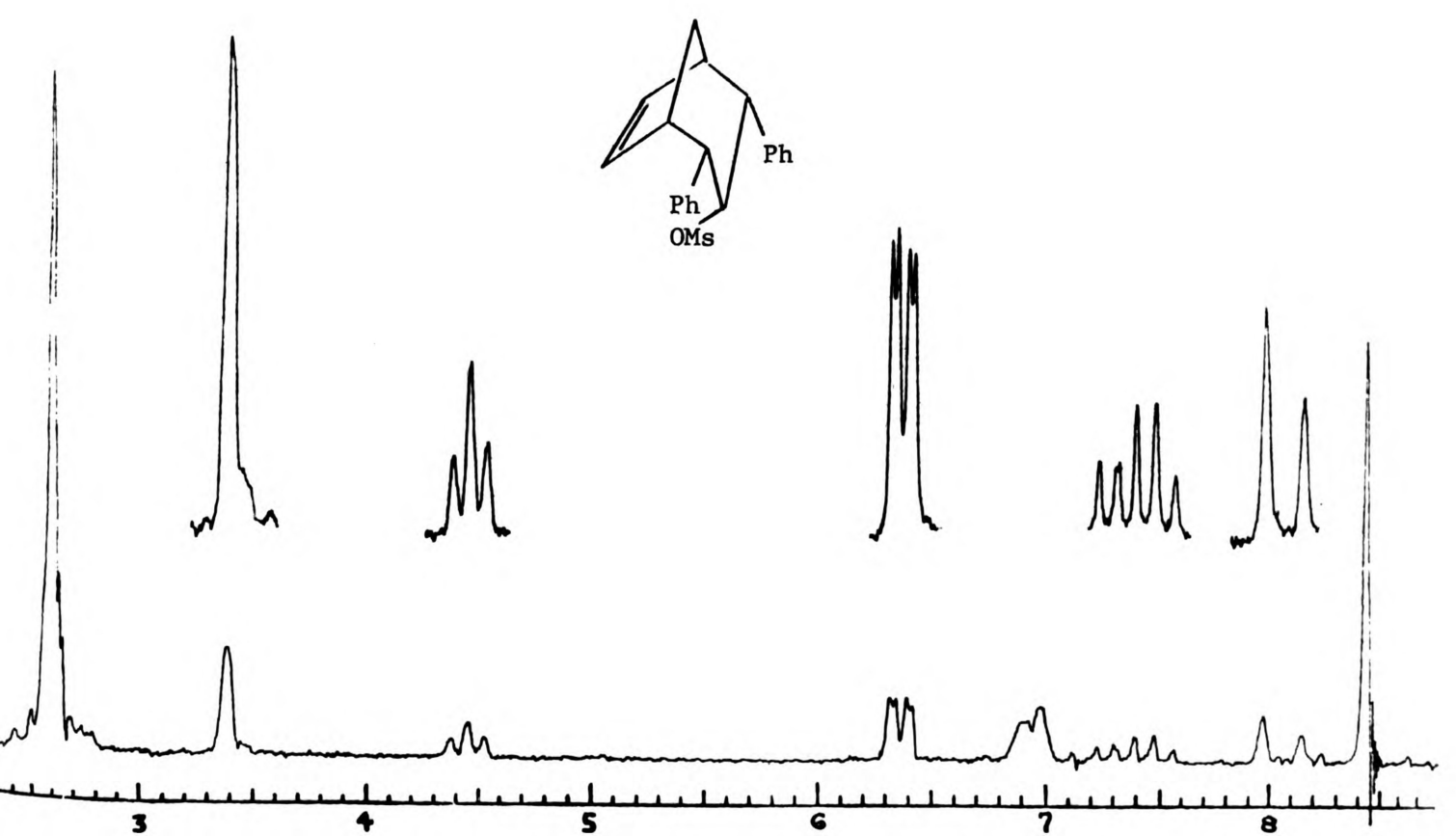
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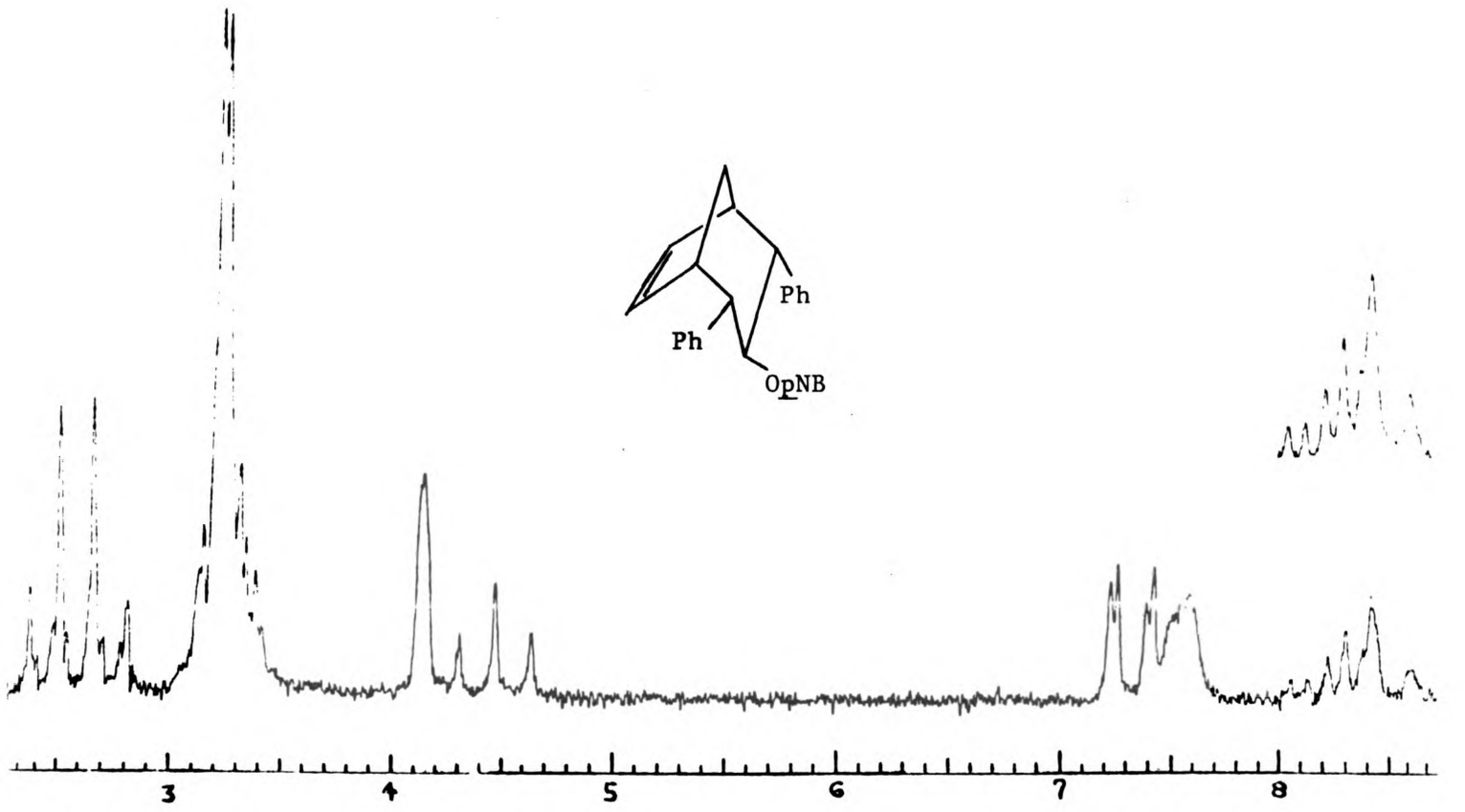
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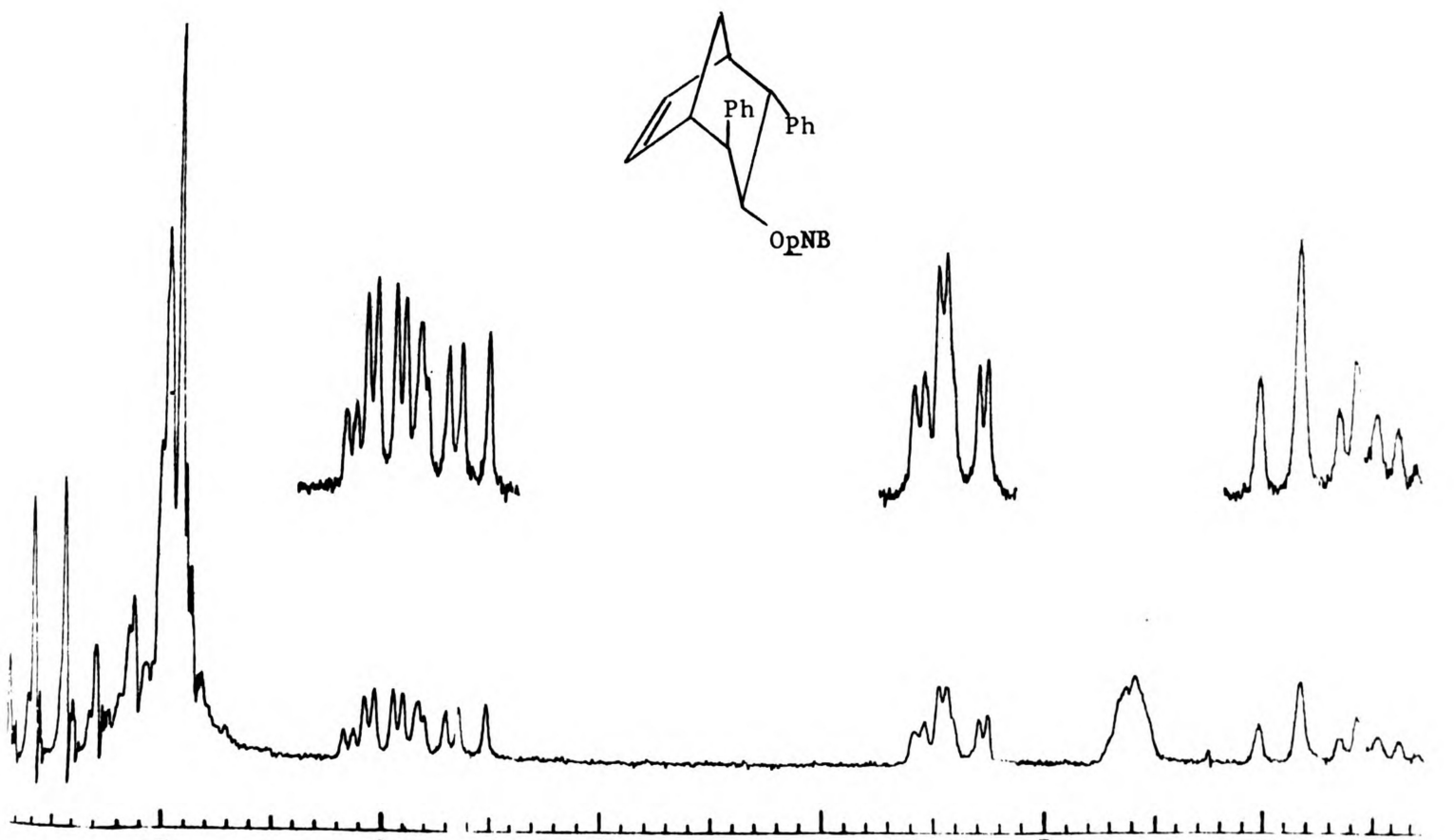
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