OXIDATIVE AND NON-OXIDATIVE PHOTOREACTIONS OF N-NITROSAMINES AND C-NITROSOALKANES

BY

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A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT

OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in the Department

of

Chemistry

Simon Fraser University

July 1975

APPROVAL

Name: Kutten Somasekharen Pillay

Degree: Doctor of Philosophy

Title of Thesis: Oxidative and Non-Oxidative Photoreactions of N-Nitrosamines and C-Nitrosoalkanes

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ABSTRACT

OXIDATIVE AND NON-OXIDATIVE PHOTOREACTIONS

OF N-NITROSAMINES AND C-NITROSOALKANES

Novel oxidative photoadditions of N-nitrosamines to various acyclic, cyclic and bicyclic olefins are described and compared with the corresponding non-oxidative photoadditions. The results lead to a simple and efficient synthetic method of 2-amino nitrate esters and to an understanding of the reaction pattern of these esters under acidic and basic conditions. The photoaddition of a nitrosamine to an olefin under nitrogen results in the formation of a C-nitroso compound as the primary photoproduct which then can either dimerize to give the anti-dimer or, when catalyzed by light, tautomerize to give the corresponding oxime.

In the presence of oxygen, the course of the photoadditions is clearly diverted to yield 2-amino nitrate esters which are stable under acid condition. The oxidation occurs exclusively even if the irradiation has been carried out with an appropriate filter to avoid irradiation of the anti-dimer peak. Hence anti-dimers are not necessary intermediates for the oxidation process. Oxygen reacts with nitric oxide, both in the free state and in a radical pair, diverting the course of the reaction. The 2-amino nitrates gradually undergo

solvolysis and elimination reactions under basic conditions resulting in the formation of 2-aminoalcohols and 2-aminoketones. Depending upon their structure, these 2-amino nitrates can also undergo C_1-C_2 bond cleavage assisted by the lone-pair electrons of the nitrogen giving rise to the corresponding carbonyl compounds. Finally, the amino nitrates can be reduced readily to the corresponding amino-alcohols in quantitative yields.

The oxidative and non-oxidative photodecompositions of the anti-dimers of trans-1-nitroso-2-chlorocyclohexane and trans-1-nitroso-2- piperidinocyclohexane were also investigated. Irradiation of the anti-dimers of these C-nitroso compounds under nitrogen caused dissociation to the corresponding C-nitroso monomer which underwent photodisproportionation, tautomerization and dimerization. Similar irradiation under oxygen resulted principally in the formation of nitrate and nitro compounds. The nitrate formation occurs through the photodissociation of the C-nitroso monomer followed by immediate oxidation of the nitric oxide by molecular oxygen to nitrogen trioxide radical. This is in agreement with the observed oxidation during the photoaddition of N-nitrosamines to olefins. The formation of nitro compound occurs presumably via the intermediacy of an excited C-nitroso monomer. Under nitrogen the anti-dimer of trans-1-nitroso- 2-piperidinocyclohexane was photolytically tautomerized to the corresponding oxime and was oxidized predominantly to the C-nitro compound under oxygen. The

latter two processes appear to share a common intermediate, the excited C-nitroso monomer.

ACKNOWLEDGEMENTS

The author wishes to express his sincere gratitude to Professor Y.L. Chow for his genuine interest and continued guidance throughout the course of this work. He also wishes to thank Dr. T. Tezuka and Dr. K. Hanaya for their beneficial discussions and general assistance. The helpful discussions and assistance of the members of the faculty and graduate students, especially those of Professor Chow's group, are gratefully acknowledged. The author also wishes to thank the technical and support staff of Simon Fraser University for their co-operation and assistance.

The financial assistance from the National Research Council of Canada and the Department of Chemistry, Simon Fraser University, is also gratefully acknowledged.

Finally, the author is most grateful to his wife, Omana, without whose patience, assistance and encouragement this thesis would not have been possible.

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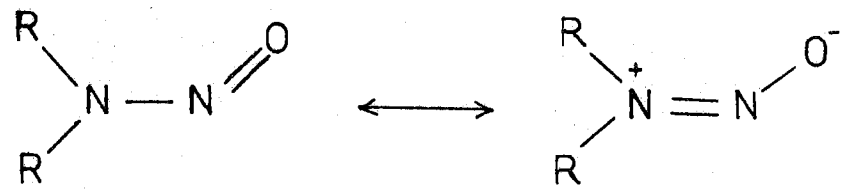
CHAPTER 1

INTRODUCTION

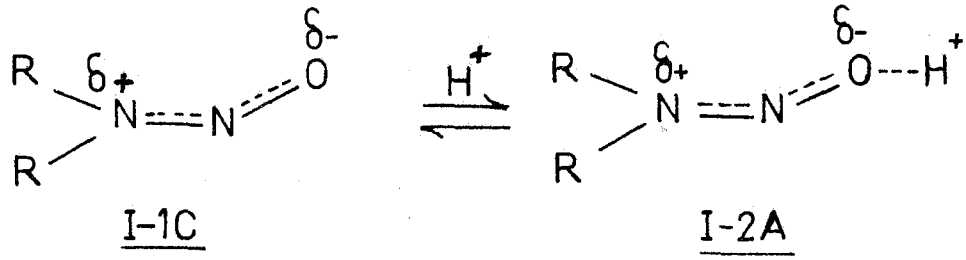
It is well known that various nitroso derivatives such as nitrite esters [1-3], N-nitrosamides [4-8] and C-nitroso compounds [9-11] are photolabile. The photochemistry of nitrite esters has been extensively investigated in the last decade by several groups, particularly by Barton and co-workers [1-3]. Irradiation of these esters in neutral solutions causes homolytic scission of the O-N bond as the primary photoprocess followed by stereospecific intramolecular hydrogen atom abstraction by the alkoxy radical. Inspired by the synthetic success of nitrite ester photolysis, Chow [4-6], Edwards [7], Kuhn [8] and their co-workers have independently investigated the photochemistry of N-nitrosamides. They concluded that the N-N bond is cleaved homolytically to generate amido and nitric oxide radicals which undergo a reaction pattern very similar to that of alkoxy radicals. In contrast, N-nitrosodialkylamines are surprisingly inert to irradiation in neutral solutions [12,13]. However, in the presence of dilute acid, N-nitrosamines readily undergo similar N-N homolysis by irradiation resulting in the formation of protonated amino radicals, so-called aminium radicals.

The dramatic dissimilarity in the photolysis pattern of nitrosamines on one hand and nitrite esters and N-nitrosamides on the other hand is believed to be related to the electronic structure of the nitrosamino group. SCF calculations [14] of ground state N-nitrosamine indicate that there is a 48% contribution of the polar resonance structure I-1B. In agreement with this prediction, considerable N-N double bond character has been indicated by infrared and n.m.r.

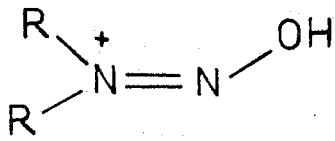


I - 1A I-1B

studies [15-18] of N-nitrosamines. The energy barrier for rotation about the N-N bond in N-nitrosodimethylamine (NND) is found to be ca. 23 kcals/mole [15]. Thus the molecule is best represented by a planar structure with the oxygen atom bearing a partial negative charge. Ultraviolet spectroscopic studies of nitrosamines in aqueous sulfuric acid have demonstrated that at low concentrations of acid (pH > 1) the proton co-ordinates with the electron-rich nitroso oxygen atom (I-2A) while at higher concentrations of acid (> 2M H_2SO_4), the nitrosamines are protonated as in I-2B [19]. The fully protonated nitrosamine is not photolabile, i.e., in the



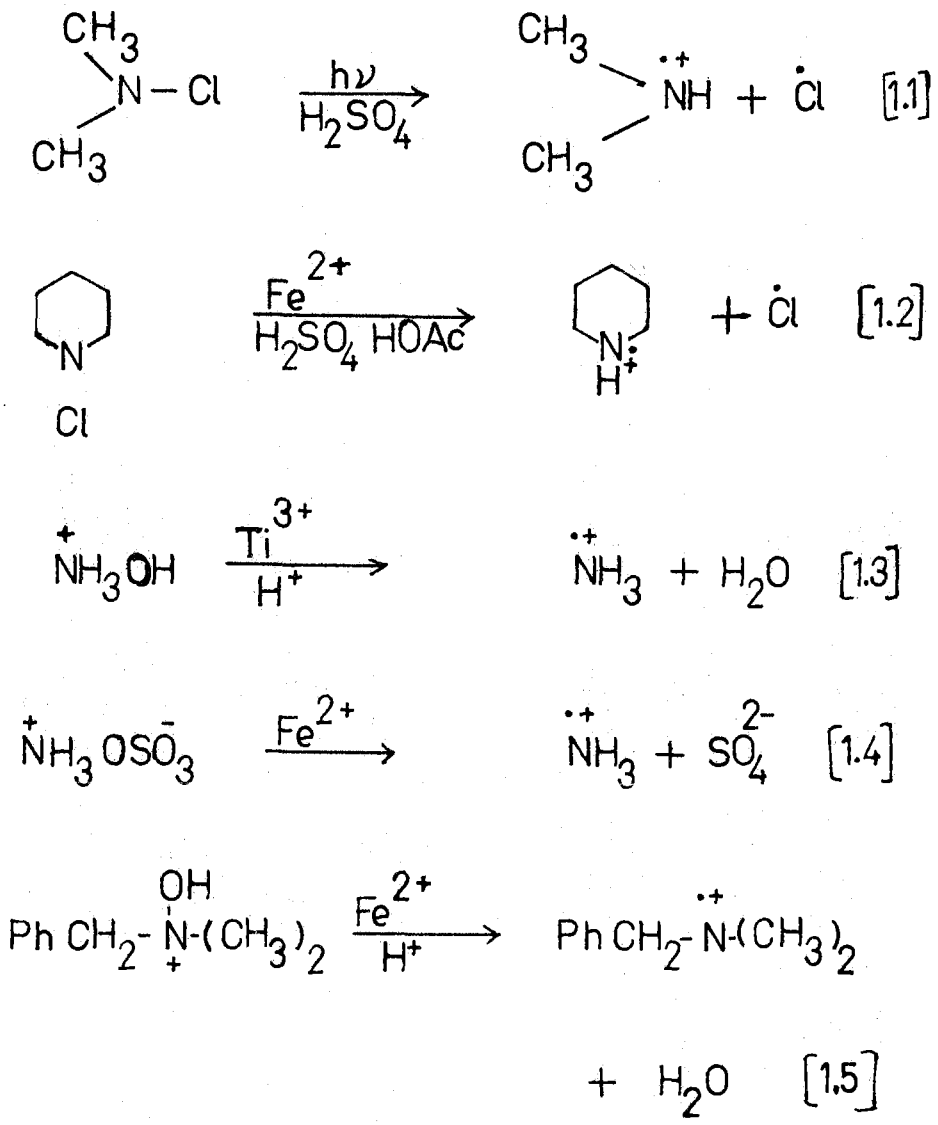
I-1C I-2A



I-2B

presence of 4M H_2SO_4 or in solutions of higher acidity, nitrosamines do not undergo photoreaction [20]. The mechanism and the synthetic utility of these photochemical reactions involving aminium radicals have been investigated by Chow and co-workers [21 and references cited therein] during the last several years.

Aminium radicals can also be generated photochemically from N-halamines in highly acidic medium [22-25] or by the reaction of metal ions such as Fe^{2+} and Ti^{3+} with N-halamines (equation 1.2) [26, 27], hydroxylamines (equation 1.3) [28], hydroxylamine-O-sulfonic acids (equation 1.4) [29] or tertiary amine oxides (equation 1.5) [30]. However, the simplicity and mild conditions used in the



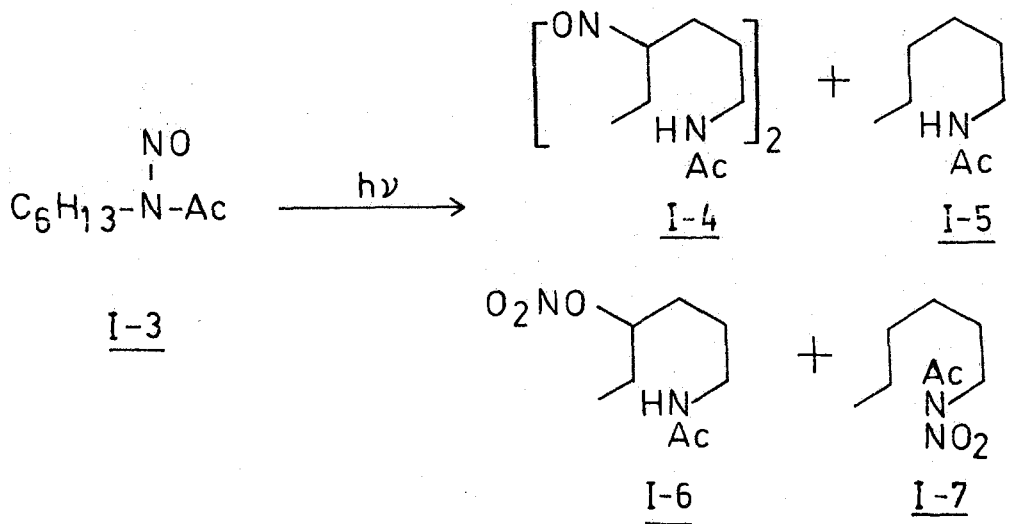
generation of aminium radicals from N-nitrosamines render these reactions more versatile in organic synthesis than the methods outlined above (equations 1.1 to 1.5). The aminium radical can undergo inter- [21] or intramolecular addition to olefins [21, 31, 32], or substitution reactions with aromatic compounds [24, 33].

Alternately, it may abstract a hydrogen atom from one of the substrate molecules [21] or undergo disproportionation [34].

The preparation and properties of N-nitrosamines have been described elsewhere [35-37]. In the presence of dilute acid, N-nitrosodialkylamines efficiently undergo photoaddition to olefins [21]. It has been established that the intermediate aminium radicals initiate electrophilic addition to the carbon-carbon double bonds. The C-radical generated scavenges a nitroso radical from nitric oxide or another nitrosamine to give a 2-aminonitrosoalkane, which is usually isolated as the tautomeric oxime under the photoaddition conditions.

The kinetic behaviour of the piperidinium radical, a typical aminium radical which is obtained by flash photolysis of N-nitrosopiperidine (NNP), has been shown to be unaffected by the presence of oxygen or by the type of excitation ($n - \pi^*$ or $\pi = \pi^*$ band excitation) [38]. It decays in aqueous acidic solution, with first-order kinetics with a rate constant of 1.85×10^4 sec^{-1}. A comparison of reaction rates measured in aqueous acidic methanol in the absence and in the presence of cyclohexene has shown that the piperidinium radical adds to the double bond 5,000 times faster than it abstracts an hydrogen atom from methanol [38]. Consequently the photoaddition can be carried out in methanol solution without appreciable competition from the abstraction reaction.

Chow and co-workers [39] have reported that, in the course of the photorearrangement of nitrites, oxygen not only fails to quench the photoreaction but diverts the major reaction pathway to form rearranged nitrates which can be regarded as the oxidation products of the corresponding C-nitroso compounds. Photorearrangement of N-nitrosamides is obviously more complex than that of nitrite esters [11, 40]. When irradiated with light > 280 nm a nitrosamide such as I-3 rearranges, and considerable amounts of oxidation products, nitrate I-6 and nitramide I-7 are formed along with anti-dimer* I-4



I-3 I-4 I-5 I-6 I-7

Scheme I.1.

* C-nitroso compounds are known to dimerize to give two stereoisomers, syn and anti [11, 118].

and parent amide I-5. However, when the photoreaction is affected with a light source > 400 nm, anti-dimer I-4 is is obtained in good yield, in addition to parent amide I-5, and no oxidation products such as nitrate I-6 or nitramide I-7 are detected. The absence of I-6 and I-7 under these conditions indicates that the oxidation products are formed from a secondary photoreaction of anti-dimer I-4. Under an oxygen atmosphere, the photoreaction results in the formation of oxidation products I-6 and I-7 but none of the anti-dimer I-4. The irradiation of anti-dimer I-4 under an inert atmosphere has been shown to result in disproportionation to give nitrate I-6 and amide I-5, and under an oxygen atmosphere I-4 is cleanly oxidized to nitrate I-6 in excellent yield [40].

These results prompted us to investigate the oxidative photoaddition of N-nitrosamines to various acyclic, cyclic and bicyclic olefins. The present work was undertaken with a view to study the potential use of these photooxidation reactions for the synthesis of complex aminonitrate esters which are otherwise inaccessible or difficult to prepare. Further, it was desired to compare these reactions with the non-oxidative photoaddition of N-nitrosamines.

In connection with this work it is pertinent to discuss here briefly the chemistry of nitrate esters and the stereochemistry of free radical addition reactions.

1-1 Nitrate Esters

Nitrate esters are colourless liquids generally boiling at slightly higher temperature than the parent alcohols. They exhibit characteristic i.r. absorptions at 1670-1625 cm^{-1} (asymmetric $-NO_2$ stretch), 1285-1270 cm^{-1} (symmetric $-NO_2$ stretch), 870-840 cm^{-1} (CO-N stretch) and 690 cm^{-1} (NO_2 bend) [41]. The more popularly known nitrate esters such as nitroglycerin and nitrocellulose are powerful explosives, being sensitive to shock, friction and heat. The most widely recognized application of these compounds is their use as ingredients of smokeless powder and rocket propellants [42].

From a physiological point of view, nitrate esters are known to be toxic [42]. These compounds may be absorbed by inhalation, through the skin or through the digestive tract. They oxidize haemoglobin to methemoglobin and by depression of the muscles in the vascular walls cause a peripheral vasodilation. This will result in lowered systolic blood pressure and increased pulse and respiratory rates. On the basis of this vasodilatory action, some of the

nitrate esters find therapeutic application in the relief of high blood pressure [42].

The preparation of nitrate esters is generally accomplished by either esterification of the appropriate alcohol or reaction of a suitable alkyl halide with silver nitrate. The most commonly used nitrating agent is a mixture of nitric and sulfuric acids which generates the nitronium ion as the reacting species [43]. In order to minimize the undesirable side reactions such as the oxidation of the alcohol by nitric acid, the reaction is run at lower temperatures and nitric acid is used in excess to minimize the dilution brought about by the water formed in the reaction [43, 44]. A small amount of urea or urea nitrate is used to destroy any nitrous acid present [44]. Often, acetic anhydride or an acetic anhydride-acetic acid mixture is used instead of concentrated sulfuric acid [42, 45]. The reaction of alkyl bromides and iodides with silver nitrate in acetonitrile is another convenient method for the preparation of nitrate esters [42, 46].

The reactions of nitrate esters with nucleophiles are complex. Results from limited studies on neutral and alkaline hydrolysis indicate that basic decomposition of nitrate esters proceeds by four distinct pathways [47-49].

(1) Nucleophilic attack on carbon (S_N1 or S_N2)

$$HO^- + RONO_2 \longrightarrow ROH + NO_3^- \qquad [1.6]$$

(2) Nucleophilic attack on nitrogen (S_N2)

$$HO^- + R\text{-}O^{18}\text{-}NO_2 \longrightarrow R\text{-}O^{18}\text{-}H + NO_3^- \qquad [1.7]$$

(3) Elimination of α-hydrogen (E2)

$$HO^- + R\text{-}CH_2\text{-}ONO_2 \longrightarrow RCH{=}O + H_2O + NO_2^- \qquad [1.8]$$

(4) Elimination of β-hydrogen (E1 or E2)

$$HO^- + R\text{-}CH_2\text{-}CH_2\text{-}ONO_2 \longrightarrow R\text{-}CH = CH_2 + H_2O + NO_3^- \qquad [1.9]$$

Thus the nitrate esters can undergo C-O as well as O-N bond scission. In general, these and other nucleophilic attacks on primary and secondary nitrate esters are slow processes. Alkaline hydrolysis of secondary nitrate esters is more complicated since the elimination reactions producing olefins and carbonyl compounds (equations 1.8 and 1.9) become important. Simple tertiary nitrate esters dissociate rapidly by a unimolecular process with exclusive C-O bond cleavage to give either alcohol or olefin [47, 49, 50]. The hydrolysis of nitrate esters is not catalyzed to any appreciable extent by mineral acid [51] because of the large positive heat of dissociation of the conjugate acids formed by preferential protonation at the alkoxy oxygen [52].

$$R\text{-}O\text{-}NO_2 \overset{H^+}{\rightleftharpoons} R\text{-}\overset{H}{\underset{+}{O}}\text{-}NO_2 \xrightarrow[\text{slow}]{\text{very}} R\text{-}OH + \overset{+}{N}O_2 \qquad [1.10]$$

The reduction of nitrate esters leads to the parent alcohol and proceeds without cleavage of the carbon-oxygen bond in the ester [42].

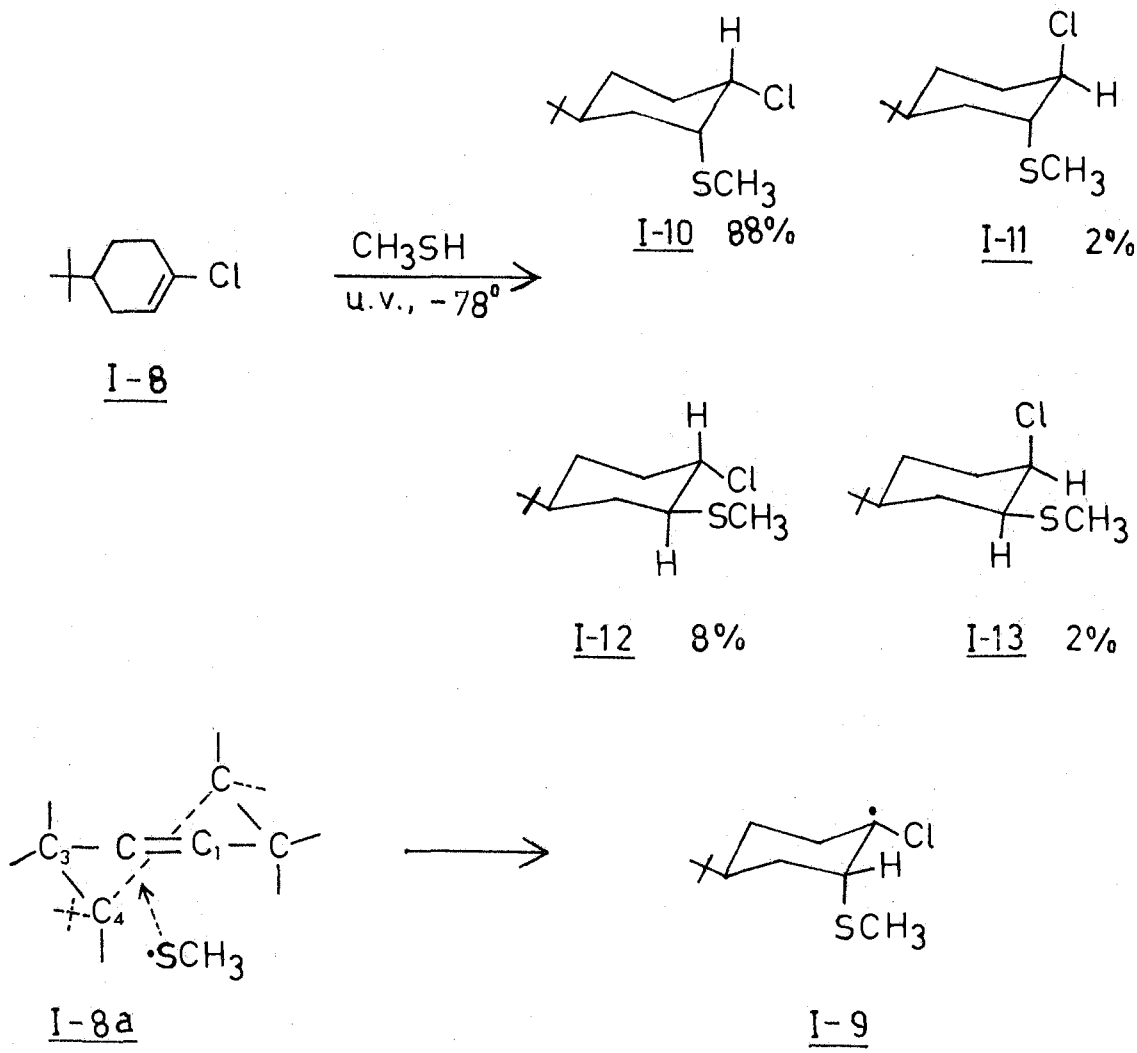
1-2 The Stereochemistry of Free-Radical Addition to Olefins

The stereochemical aspects of free-radical additions to olefins have been the subject of several monographs [53-56]. It is now generally accepted that the stereochemical course of addition depends upon the nature of the addendum, the structure of the olefin and the reaction conditions.

Addition of a halogen radical to a simple olefin is reversible which results in olefin isomerization [53]. Hence, homolytic addition of hydrogen halides to acyclic olefins is non-stereospecific due to rapid rotation about the newly-formed single bond in the intermediate radical. However, the addition becomes stereospecific if the reaction is carried out at low temperature at which rotation about the single bond is slow compared to chain transfer [57]. Thus stereospecific trans-addition is observed in the reaction of hydrogen bromide with cis- or trans-2-bromo-2-butene [58] and of deuterium bromide with cis- or trans-2-butene [57] at -80°. The trans-addition has been rationalized on the basis of a bromine bridged radical analogous to

a bridged bromonium ion [59, 60]. Some e.s.r. evidence for this type of bridged radical structure in β-bromoalkyl radicals, such as β-bromoethyl radical, has also been found at low temperatures [61, 62]. An alternative explanation for the observed stereospecificity is that chain transfer occurs so rapidly after the addition of the bromine atom that the originally formed intermediate does not have sufficient time to change conformation by rotation [53].

As expected, the best substrates for investigating the stereochemistry of free-radical additions are cyclic olefins. In general, addition to cyclic olefins proceeds preferentially in a trans fashion. Addition of hydrogen bromide to 1-bromo- and 1-methylcyclohexene yields exclusively the thermodynamically less stable cis-isomers, which are formed by a trans-addition [59]. Similar stereospecific results are observed in the addition to 1-chlorocyclohexene [60] and 1,2-dimethylcyclohexene [53]. Thiols add to cycloalkenes predominantly in a trans fashion [56, 63-65] as illustrated by the reaction of methanethiol with 4-t-butyl-1-chlorocyclohexene (I-8) (Scheme 1.2) [64]. The initial attack of the thiyl radical on C-2 takes place preferentially from the side trans to the t-butyl group (from the bottom side of structure I-8a) because such an attack encounter no steric hindrance from the pseudoaxial hydrogen at C-3, and the derived intermediate radical I-9 has the more stable chair conformation. The hydrogen transfer to the radical (I-9) occurs preferentially from the axial direction to give I-10 as the major product (Scheme 1.2).

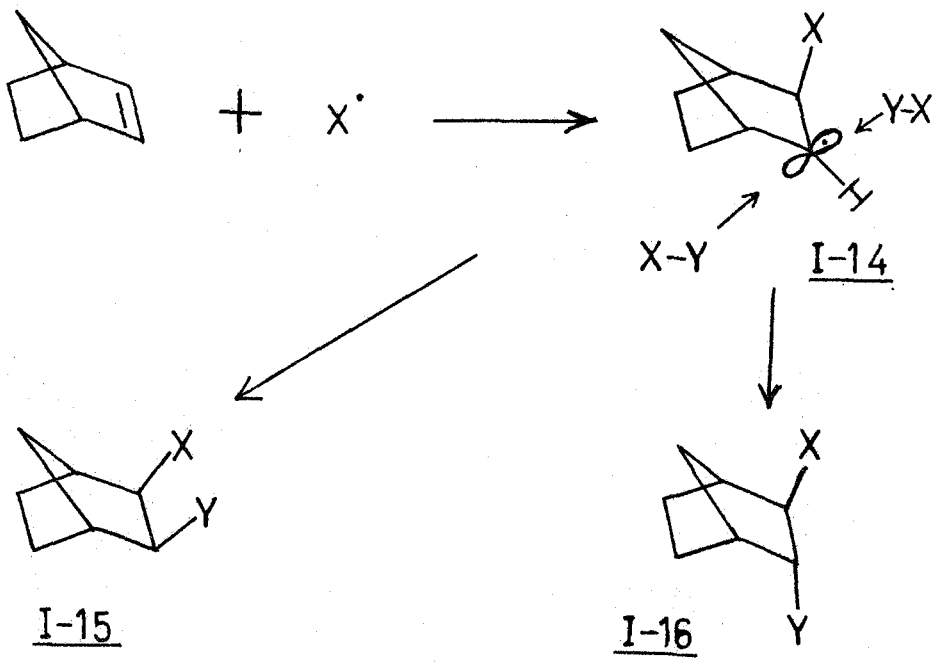


Scheme 1.2

As in the case of hydrogen bromide additon to olefins, a bridged radical intermediate has been proposed to explain the observed stereospecificity [64, 65]. However, the radical addition of thiols is far less stereospecific than that of hydrogen bromide.

The stereochemical course of nitrosyl chloride addition to olefins has been shown to be solvent-dependent [67]. Cyclohexene reacts with nitrosyl chloride to give the trans-adduct in liquid sulfur dioxide [66,67] and the cis-adduct in methylene chloride, chloroform or trichlorethylene [67]. It has been suggested that a free-radical mechanism operates in these reactions [68].

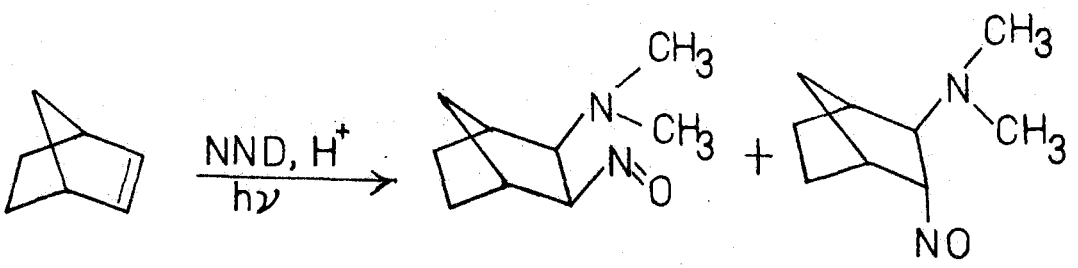
The stereochemistry of free-radical addition reactions to norbornene derivatives differs from that of the monocyclic analogues as a consequence of steric barriers to endo attack [69] and of the torsional strain effect [70]. In general, when a small addendum such as DBr is employed, a substantial amount of initial attack occurs from the less accessible endo-side indicating the absence of strong steric barriers [71]. However, when larger addenda are involved, steric factors play a dominant role in directing an attacking group; initial attack occurs invariably from the less hindered exo-side [54]. These steric factors also favour exo chain transfer of tne intermediate radical I-14 to give exo-cis-adduct I-15 (Scheme 1.3). Stereoelectronic interactions between the chain transfer agent and the 2-exo-substituent in I-14 can be sufficiently large to overcome the torsional strain, and may give predominantly endo chain transfer. Thus reagents like thiols [72], nitrosyl chloride and nitrosyl bromide [73] add to norbornene to give exclusively exo-cis-adduct while polyhalomethanes give predominantly trans-addition [74]. The reaction of nitrosyl halides with



Scheme 1.3

norbornene has been suggested initially by Meinwald [74] to occur by a concerted molecular addition mechanism. However, a free-radical mechanism cannot be entirely ruled out [68]. In the case of other reagents such as methylene chloride [72], methyl bromoacetate [72], N-chlorourethane [75], chlorine [76] and dinitrogen tetroxide [77] comparable amounts of exo-cis- and trans-adducts have been observed. The stereochemistry of the chain transfer is determined not only by the size of the group at the 2-exo-position but also by the steric

bulk of the endo-substituent at the C-5 and C-6 positions in I-14 [74]. Thus, the free-radical addition of carbon tetrachloride to norbornene has been shown to give exo-cis- and trans- adducts in the ratio 1:18.2 while addition to 5,5-dimethyl-2- norbornene gives exo-cis- and trans-adduct in the ratio 1.2:1 [74]. Again the initial attack occurs exclusively at the exo-side but the steric repulsion between the endo-5-substituent and the propagating species coupled with adverse torsional strain make the chain transfer occur exclusively from the exo-side. The photoaddition of NND to norbornene gives exo-cis- and trans-adducts (C-nitroso compounds) in which the aminium radical has approached exclusively from the exo- face of norbornene [78] (Scheme 1.4).

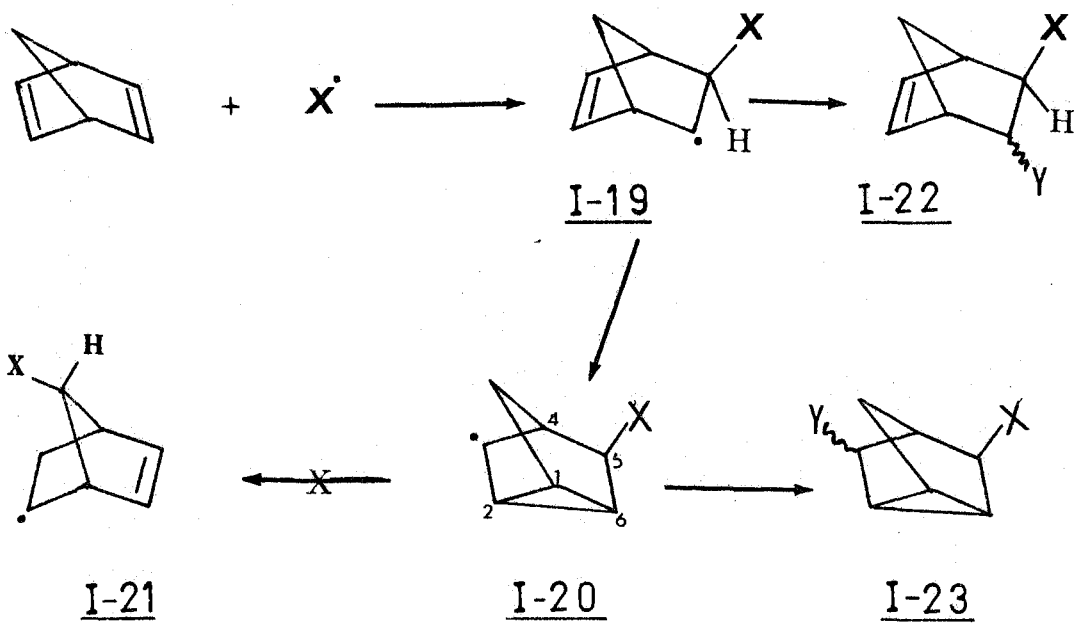


I-17 I-18

Scheme 1.4

Norbornadiene has been shown to react with free-radicals by both homoconjugative and 1,2-addition [79,80] (Scheme 1.5). The

proportion of the nortricyclene derivative I-23 in the product mixture increases at the expense of the 1,2-adducts I-22 as the reaction mixture is diluted with



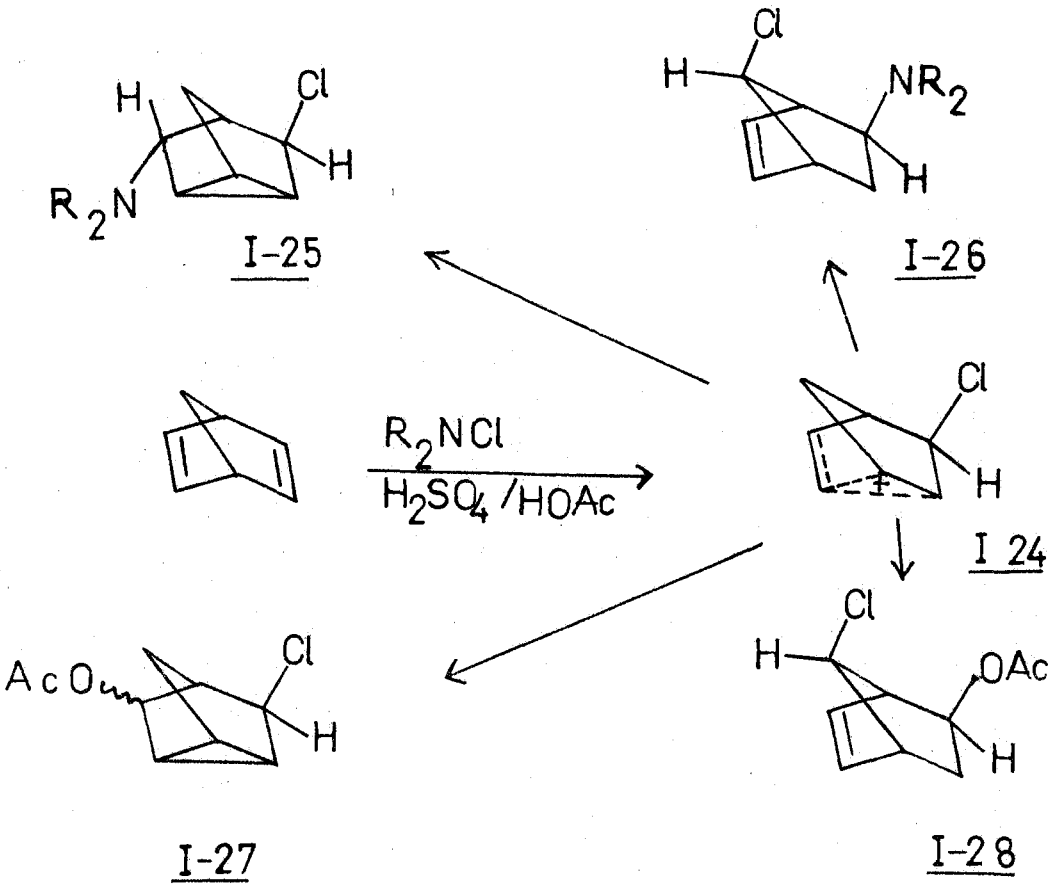
Scheme 1.5

an inert solvent or as the chain transfer reactivity of the addendum is decreased. The addition of chloroform or carbon tetrachloride to norbornadiene has been shown to afford solely nortricyclene derivatives while faster chain transfer reagents, such as thiols, are able to trap the originally formed intermediate radical I-19 before it rearranges to yield the nortricyclene radical I-20. The

addition of bromotrichloromethane which is a faster chain transfer reagent than carbon tetrachloride gives 1,2-adducts which comprise ca. 12% of the product mixture [80].

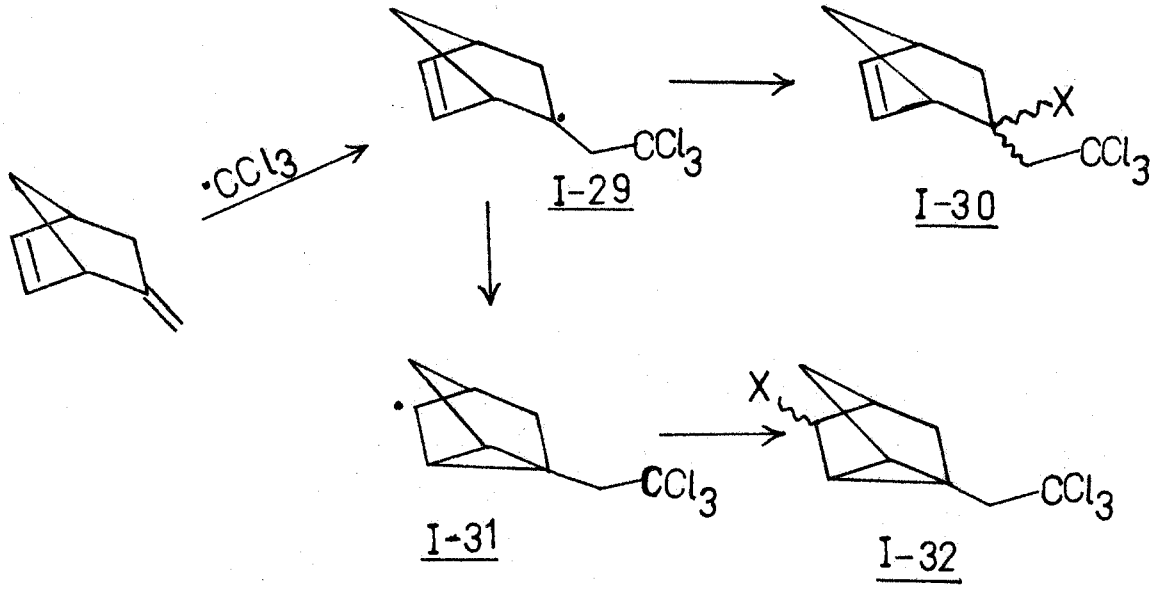
Since no skeletally rearranged products (I-21) are formed in the free radical additions to norbornadiene, it follows that radical I-20 undergoes chain transfer to give product I-23 at a very much faster rate than it can establish an equilibrium with radical I-19, or the equilibrium lies almost entirely on the side of radical I-20. The reasoning behind this deduction is that if radical I-20 is in equilibrium with radical I-19 it should also be in equilibrium with the rearranged radical I-21 since both the 1,2- and the 2,6-bonds of I-20 have an equal chance of homolytic fission [55].

The addition of N-chlorodialkylamine to norbornadiene in strongly acidic medium has been shown to give the homoconjugate adduct along with the skeletally rearranged products [81] (Scheme 1.6). All products can be accounted for by an ionic pathway in which the first step is postulated to be the exo-attack of chloronium ion on norbornadiene giving rise to a common carbonium ion intermediate, I-24.



Scheme 1.6

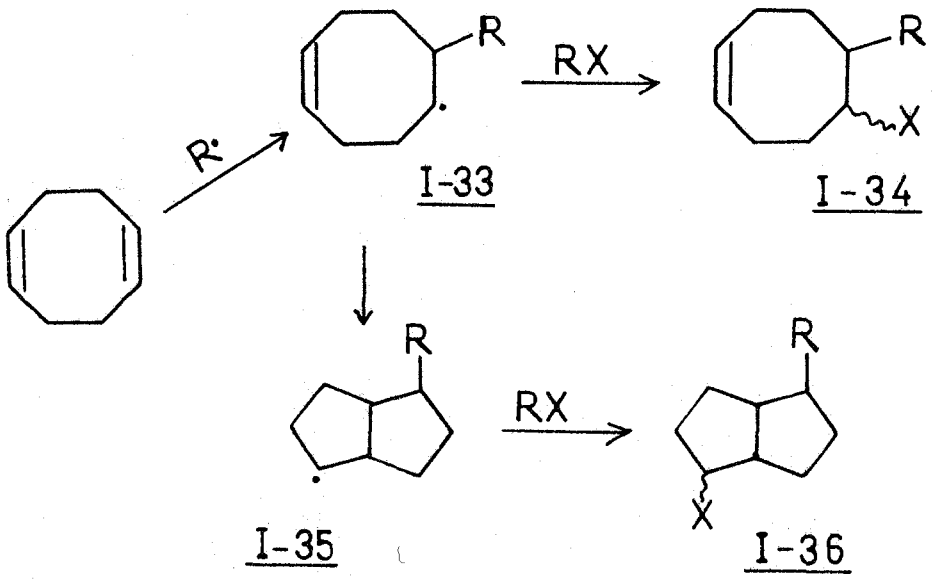
The addition of polyhalomethane to 5-methylene-2-norbornene has been shown to give tricyclene derivative I-32 as the major product [82] (Scheme 1.7). The formation of these products is readily rationalized by assuming the intermediacy of radicals I-29 and I-31; as expected, the initial attack of the trichloromethyl radical occurs at the more reactive exocyclic double bond. However, thiyl radicals have been shown to attack preferentially the endocyclic double bond of 5-methylene-2-norbornene [83].



Scheme 1.7

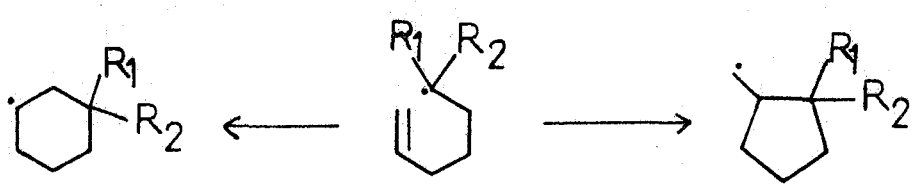
A number of studies on free-radical additions to 1,5-cyclooctadiene have been reported [53, 84-86]. The transannular ring closure has been shown to be the major pathway with slow chain-transfer addenda such as polyhalomethanes [84] while normal 1,2-addition products predominate with faster chain-transfer reagents like thiols [85] and HBr [86].

Open-chain dienes may undergo intramolecular reactions in free radical additions if the second double bond is suitably located. Studies have shown that, in general, carbon radical cyclization gives the kinetically controlled five-membered ring product I-38 in preference to a six-membered ring (I-39) [87]. The proportion of the thermodynamically more stable six-membered ring compound in the



Scheme 1.8

product mixture increases as the reaction temperature is increased or as stabilizing substituents are placed at the radical



R_1 = CN

R_2 = COOEt

Scheme 1.9

centre [87]. The preference for a five-membered ring has been attributed to the greater number of non-bonded interactions in the cyclohexane chair transition state as compared to the cyclopentane transition state [87]. An alternate explanation is that 1,5-interaction of the unpaired electron with the lowest unoccupied orbital of the unsaturated system is enormously facilitated by the geometry of the radical species leading to a five-membered ring closure [88].

CHAPTER 2

RESULTS

2-1. General

The photoreactions described in this thesis were conducted in a Pyrex photovessel (which cuts off the light below 290 nm) under an oxygen or nitrogen atmosphere. The light source was usually either a 100-watt or a 200-watt Hanovia medium-pressure mercury lamp in conjunction with a suitable filter system. A Nonex filter cutting off the light below 340 nm was found to be most useful for our studies. The photoadditions were carried out in methanol in the presence of at least one equivalent of an acid. The progress of photolysis was followed by the decrease in the u.v. absorption of the nitrosamine at ca. 345 nm or of the C-nitroso dimer at ca. 295 nm(Table5.1). In each case, a control experiment in the dark showed no significant thermal reaction at room temperature, this ascertained that the decrease of the nitrosamine concentration was due to a genuine photoprocess.

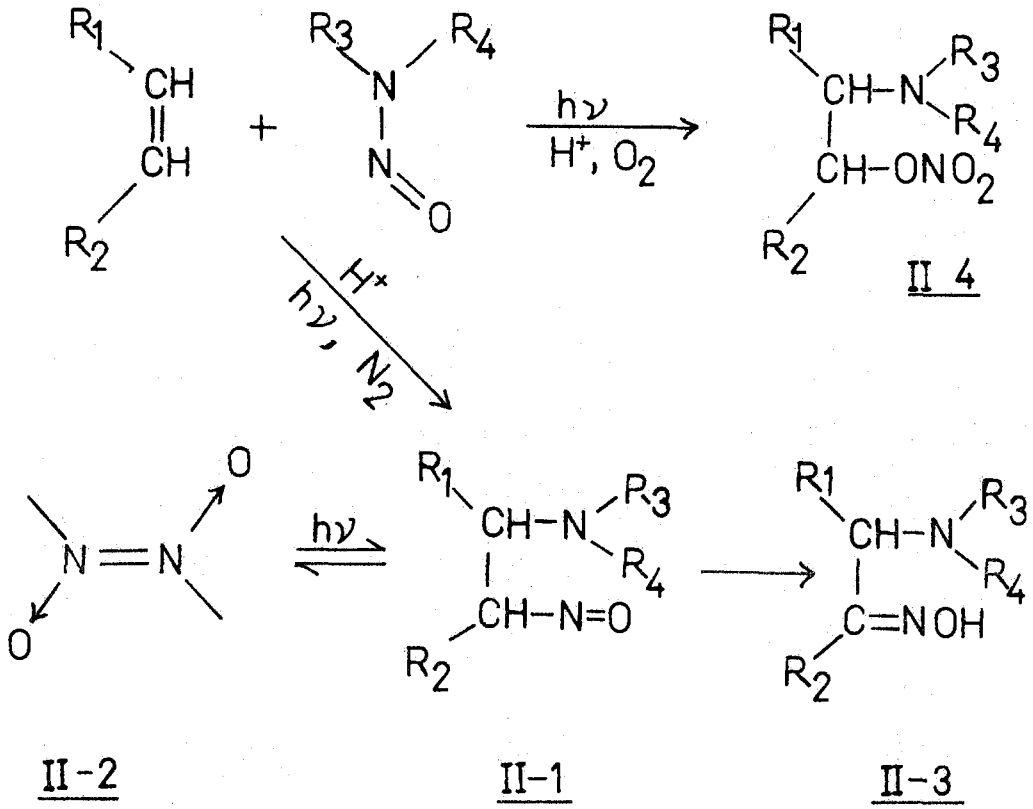
As shown later, the amino nitrates formed by oxidative photoaddition generally decomposed under basic conditions and were not suitable for direct isolation. They were either isolated as their salts or reduced immediately to amino alcohols unless other rearrangement of

nitrates occurred. Since the reduction of nitrate esters gives the corresponding alcohols without disturbing the stereochemistry [42], the alcohol yields were generally regarded as an approximate measure of the amino nitrate yields provided the decomposition of the latter was not extensive during isolation. The yields of those amino nitrates which decomposed extensively, could not be estimated.

Purification of the products was generally carried out by column chromatography wherever possible. The purity of the isolated compounds was verified by t.l.c. or v.p.c. and by n.m.r. and i.r. spectroscopy. Sometimes it was found advantageous to analyze a crude mixture and to determine the percentage yields and product structures by g.c.-m.s.

2-2. Oxidative and Non-Oxidative Photoaddition of N-Nitrosamines To Olefins

It has been established by previous workers in this laboratory that in the presence of an acid a nitrosamine photolytically adds to an olefin to give an α-dialkylaminonitrosoalkane (II-1) as the primary product. This C-nitrosoalkane can undergo various secondary reactions including dimerization to a C-nitroso dimer (II-2) and tautomerization to an α-dialkylaminoketoxime (II-3) as shown in Scheme 2.1. However, as shown in this thesis, in an oxygen



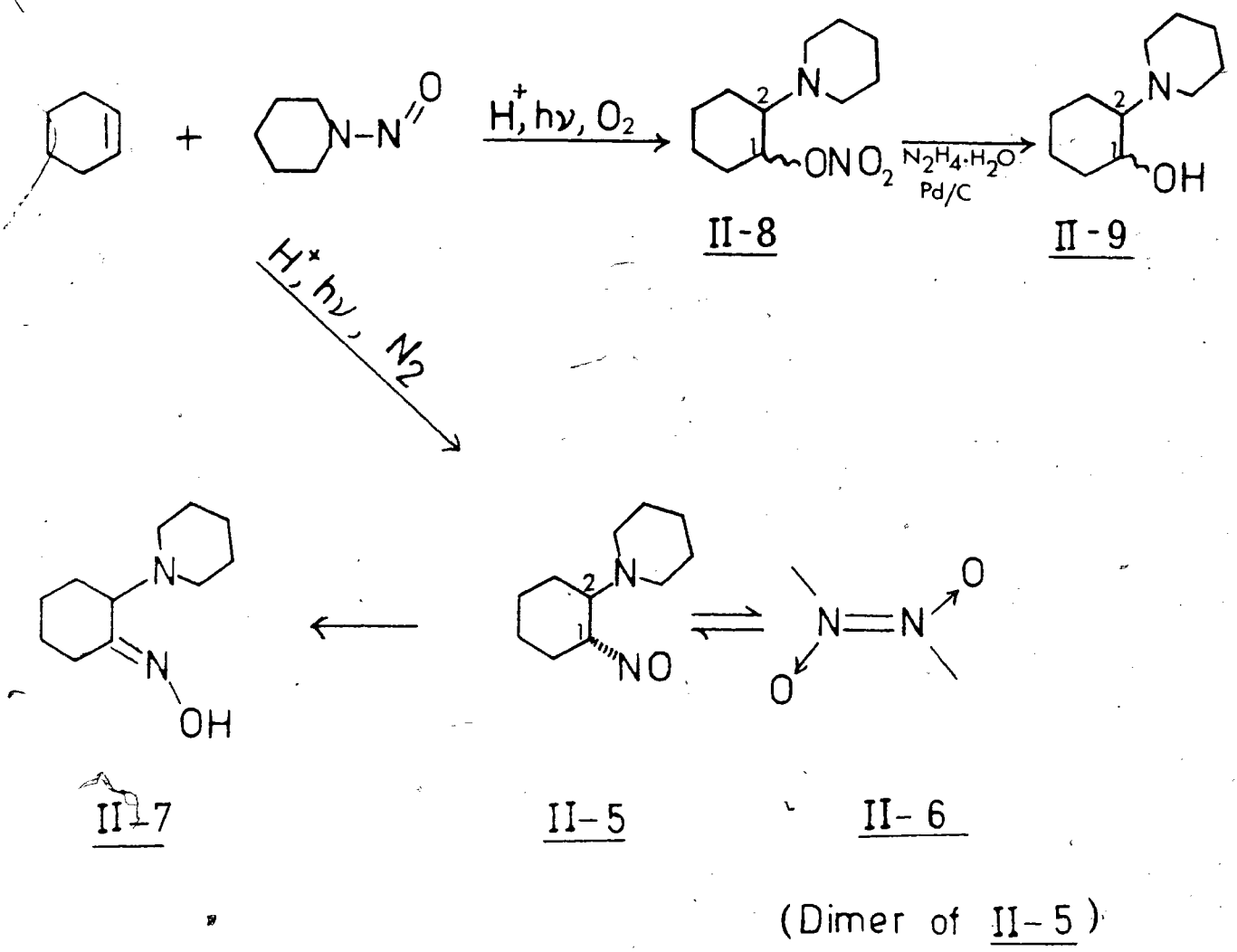
(Dimer of II-1)

Scheme 2.1

atmosphere the reaction proceeds smoothly to give an α-dialkylaminonitratoalkane (II-4) as the primary product.

2-2-1. Oxidative and Non-Oxidative Addition of N-Nitrosopiperidine (NNP) To Cyclohexene

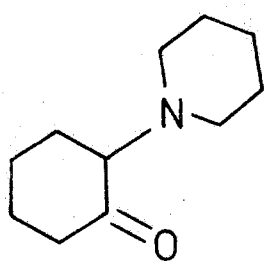
The non-oxidative photoaddition of NNP to cyclohexene has been studied extensively in this laboratory. This photoaddition was repeated with light > 350 nm and at low temperatures (-5 to -50°) in order to observe the formation and decomposition of the C-nitroso intermediate. At -50° the photodecomposition was much slower than at room temperature as indicated by the slow disappearance of the NNP absorption at 347 nm. During the irradiation a new u.v. absorption band at 290 nm appeared due to the formation of anti-dimer II-6 [89] which increased rapidly to a maximum, then decreased slowly on prolonged irradiation. After the usual work-up 2-piperidinocyclohexanone oxime (II-7) was obtained in a good yield in addition to a small quantity of trans-2-piperidino-1-nitrosocyclohexane dimer II-6. When the absorbance at 290 nm reached its maximum value, the photolysis was terminated and the reaction mixture was worked up as described in the experimental section to give II-6 in 30-35% yield. In view of the slow transformation of dimer II-6 to oxime II-7 and incomplete photoaddition, the yield of the former was probably higher than that indicated. The structure of II-6 was determined by its i.r. (strong absorption at 1210 cm^{-1}) [90] and n.m.r. (τ 4.43, c-1 proton).



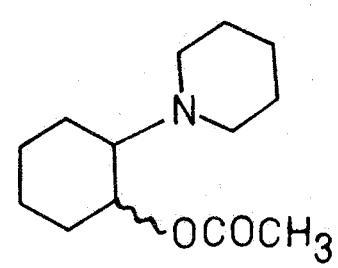
Scheme 2.2

When a methanolic solution of NNP containing an acid and cyclohexene was irradiated under an oxygen atmosphere, the u.v. profile showed a simple zero-order decrease of the 347 nm band intensity without emergence of the anti-dimer peak at 290 nm. However, under a lower concentration of oxygen, the anti-dimer absorption appeared during the photoaddition but with reduced intensity; this dimer absorption

disappeared on prolonged irradiation under oxygen. After the usual work-up, an isomeric mixture of 2-piperidino-1-nitratocyclohexanes (II-8) contaminated with a minor amount of 2-piperidinocyclohexanone (II-10) was obtained in good yield. The free bases II-8 were unstable on standing and, on attempted chromatography, decomposed to a dark red resin. The crude product was reduced with hydrazine hydrate catalyzed by Pd/C [91] to a mixture of cis- and trans-2-piperidinocyclohexanol (II-9) in good yield; this reagent specifically reduced the nitrates II-8 to the corresponding alcohols II-9 leaving cyclohexanone II-10 as the stable hydrazone. The n.m.r. spectrum of the isomeric mixture of alcohols showed methine proton signals at τ6.65 (the axial C-1 proton of trans-II-9) and 5.92 (the equatorial C-1 proton of cis-II-9) in the ratio of 2:1. This ratio



II-10

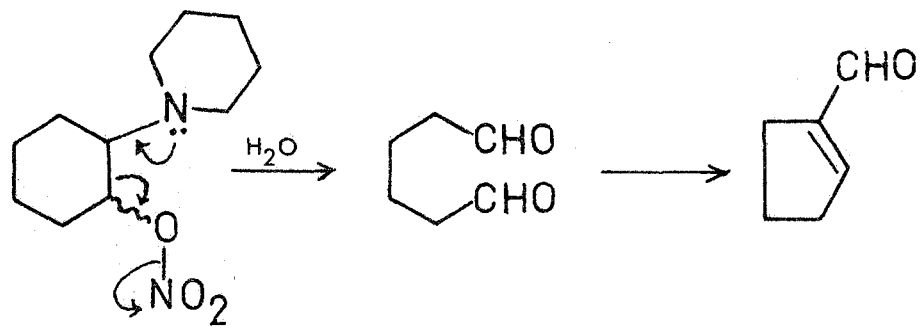


II-11

indicates that the isomeric ratio of nitrates cis-II-8 to trans-II-8 was about 1:2. The chromatography of this mixture gave trans-II-9, the n.m.r. spectrum of which showed a one-proton double triplet at τ 6.68 (axial CH-OH) with a coupling constant of 4.5 and 11.0 Hz.

Attempted p-nitrobenzoylation of the alcohol mixture II-9 was not successful; the starting materials were recovered. Treatment of cyclohexanols II-9 with acetic anhydride in pyridine gave a mixture of the expected acetates which on chromatography gave cis-2-piperidinocyclohexyl acetate (II-11). The infrared spectrum of cis-II-11 showed characteristic absorptions at 1735 and 1240 cm^{-1} due to an ester function and the n.m.r. spectrum of this compound showed a one proton multiplet at τ 4.63 (W1/2 = 6 Hz, equatorial CH-OAc) a five-proton multiplet at τ 7.46 (c-2 proton and CH_2-N protons) and a three-proton singlet at τ 7.95 (CH_3 CO-).

The amino nitrates II-8 were found to be fairly stable in aqueous acidic solution, but they gradually underwent solvolysis and elimination at pH 8-9 to give cis-II-9 (7%), trans II-9 (28%), II-10 (30%), 1,6-hexanedial II-12 (5%), 1-cyclopentenecarboxaldehyde II-13 (5%) and piperidine (10%). The aldehydes II-12 and II-13 are



II- 8 II-12 II-13

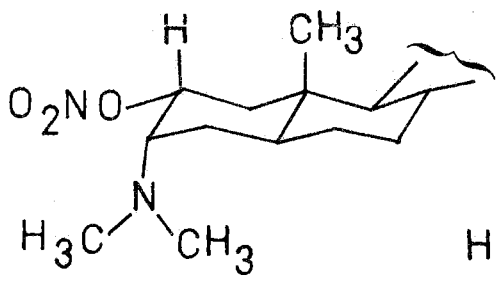
Scheme 2.3

believed to be formed by cleavage of the C_1 - C_2 bond assisted by the lone-pair electrons of the amine group as shown in Scheme 2-3.

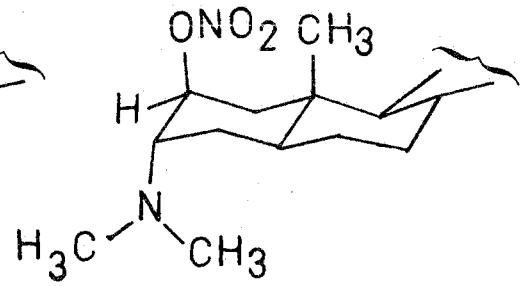
2-2-2. Attempted Oxidative Addition of N-Nitrosodimethylamine (NND) to Cholest-2-Ene (II-19)

In order to determine the stereoelectronic requirements for cleavage

of the C_1-C_2 bond of the 2-aminonitrates, (see Section 2-2-1), the oxidative photoaddition of NND to cholest-2-ene (II-19) was investigated. Although the oxidative photoaddition was expected to result in the formation of both cis- (II-20) and trans- (II-21) nitrate esters only the trans-isomer II-21 was anticipated to undergo cleavage since an antiperiplanar arrangement was believed to be essential for such heterolytic fragmentation reactions [92,93].

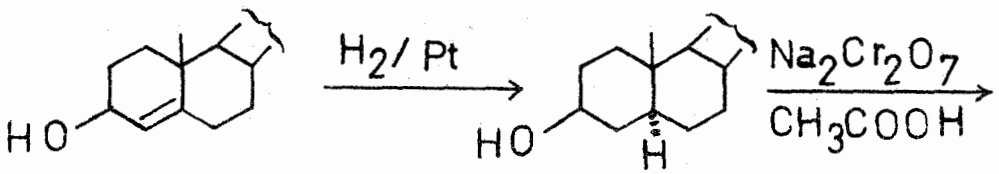


II-20

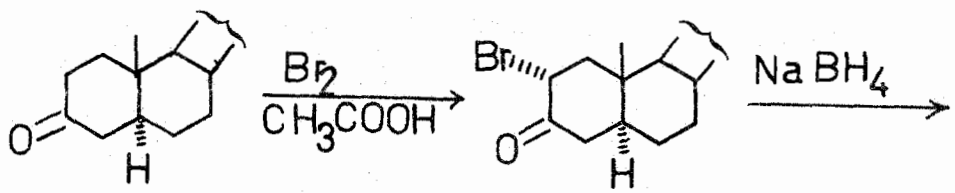


II-21

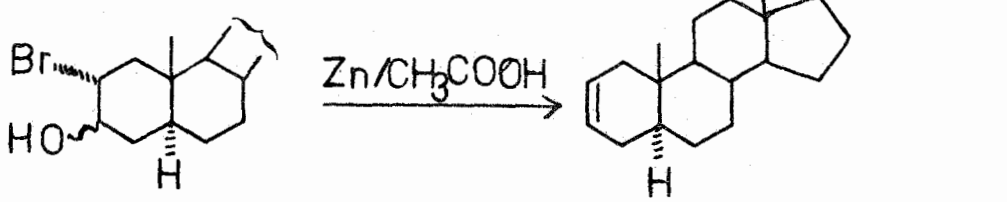
The synthesis of cholest-2-ene was accomplished [94,98] in 20.4% overall yield from cholesterol (Scheme 2.4). The oxidative



II-14 II-15



II-16 II-17



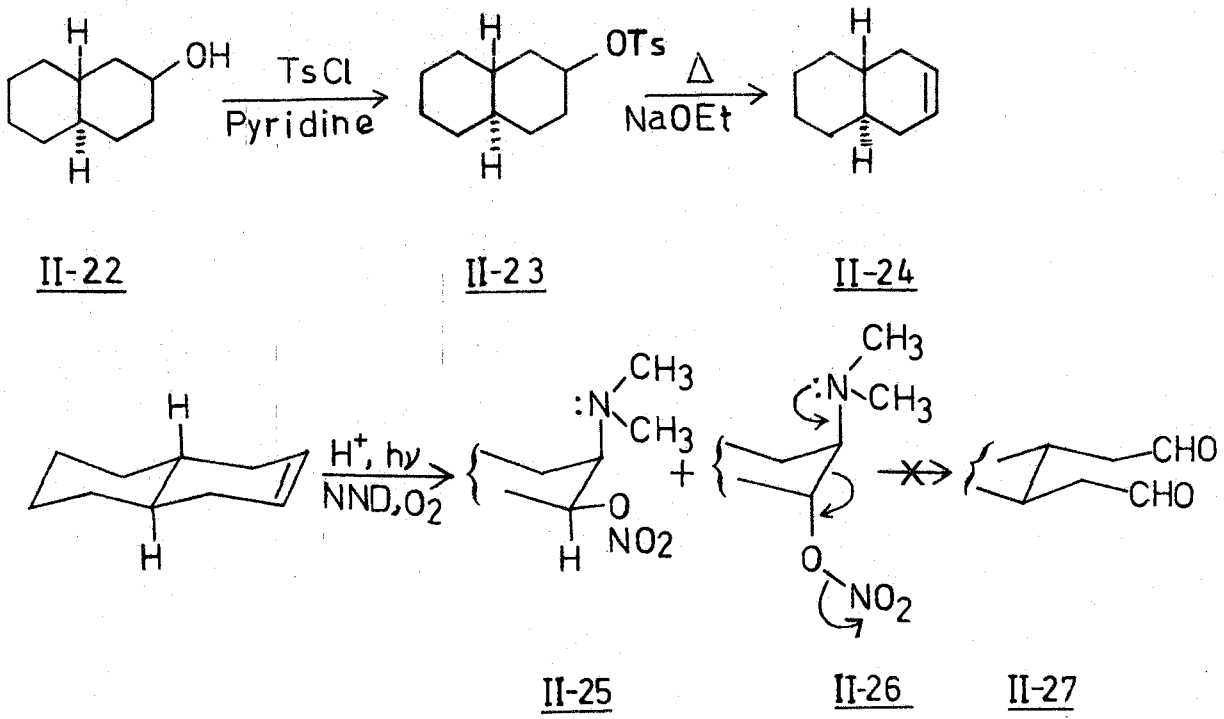
II-18 II-19

Scheme 2.4

photoaddition of NND to II-19 was attemtped in solvents such as methanol, amyl alcohol, benzene, 1,4-dioxane and acetic acid. In all cases, the N-nitrosamine decomposed on irradiation as indicated by the decrease of its u.v. absorption but failed to form any addition products; the starting olefin was recovered. The failure of this oxidative photoaddition reaction is probably due to the poor solubility of chotest-2-ene.

2-2-3. Oxidative Addition of NND To Trans-2-Octalin (II-24)

The synthesis of trans-2-octalin (II-24) was carried out as described in the literature [99,100] and is shown in Scheme 2.5. The product



Scheme 2.5

which contained 10% of an impurity was used for the oxidative photoaddition. The usual work-up of the photolysate gave a neutral fraction (22%) which was shown to be unreacted olefin (analysis by i.r. and n.m.r.). The basic fraction showed strong infrared bands characteristic of a nitrate function and weak bands at 1715 cm^{-1} for a carbonyl group and at 3440 and 1040 cm^{-1} for a hydroxyl group. After several days at room temperature, the nitrate absorption disappeared to give more intense hydroxyl absorptions. The carbonyl band remained weak. However, in the n.m.r. spectrum of the decomposed mixture, the expected aldehyde proton signal (due to II-27) was not detected.

2-2-4. Oxidative Addition To Bicyclo[2,2,1]heptene

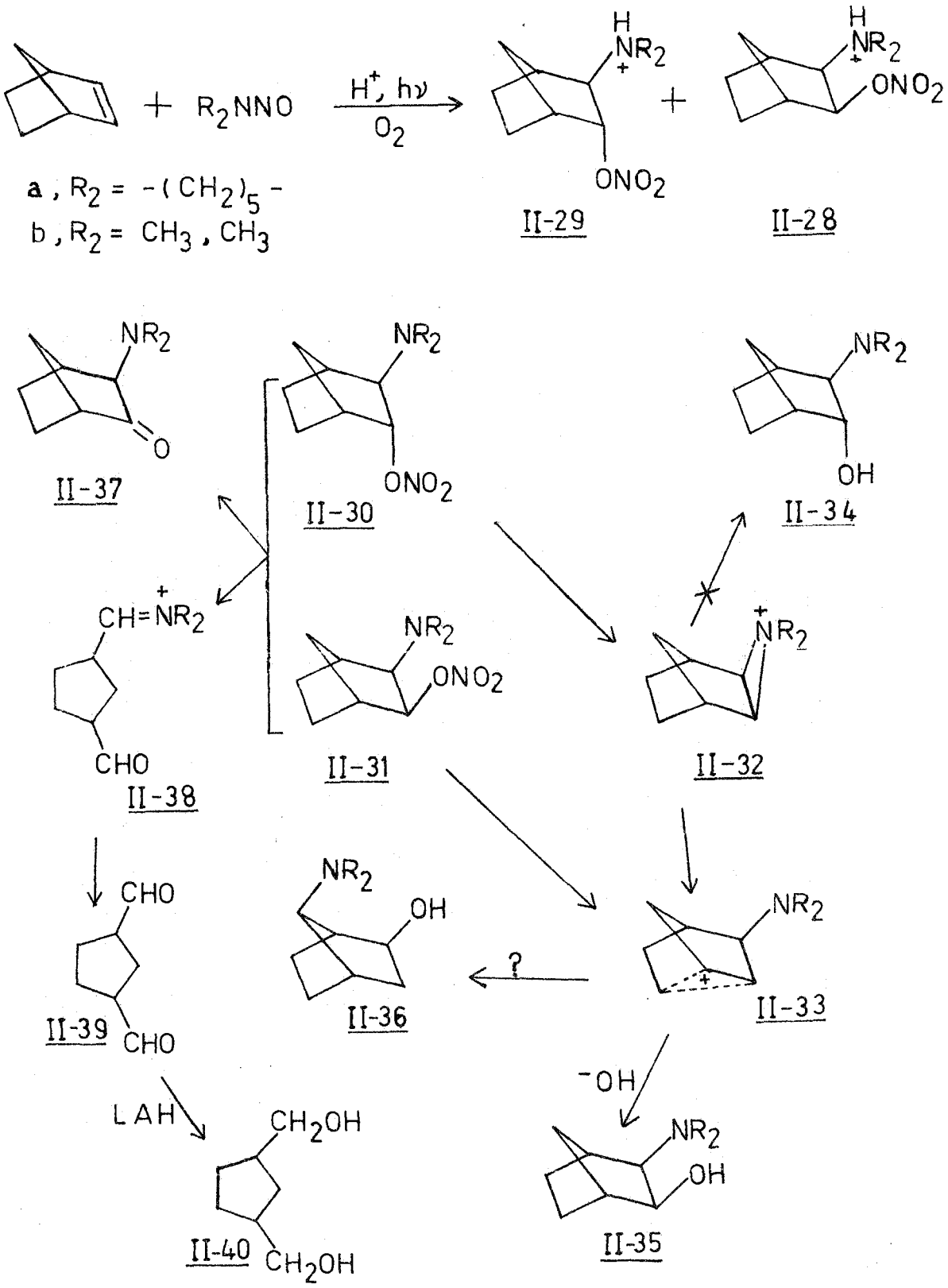
Photolysis of a methanolic solution of NNP (or NND), bicyclo[2,2,1] heptene and hydrochloric acid under an oxygen atmosphere exhibited a simple zero-order decrease of the nitrosamine n-π^* band at 345 nm without emergence of the C-nitroso anti-dimer absorption at 290 nm. On addition of base the colourless photolysate rapidly turned dark brown and gave a complex product mixture after ordinary work-up.

The initial phase of the experiments was aimed at isolating the photoadducts as their salts by running the photoaddition of NNP

to bicyclo[2,2,1]heptene under oxygen in the presence of perchloric acid. This oxidative photoaddition gave a mixture (19%) of the perchlorates of exo-2-nitrato-exo-3-piperidinobicyclo[2,2,1]heptane (II-28a) and endo-2-nitrato-exo-3-piperidinobicyclo[2,2,1]heptane (II-29a) in the ratio 1:1 (vide infra). All attempts to obtain additional amounts of perchlorate salts from the mother liquor resulted in decomposition of the solution. Basification of the above photolysate at 0^{o} and immediate extraction gave a crude mixture showing strong infrared absorptions at 1620, 1275 and 865 cm^{-1} typical of a nitrate ester group and at 1720 cm^{-1} for an aldehyde group. Immediate reduction of this crude fraction with lithium aluminium hydride gave a complex mixture of products from which a small amount of exo-3-piperidino-endo-bicyclo[2,2,1]heptan-2-ol (II-34a) was isolated as the hydrochloride salt. Its structure was determined by elemental analysis and spectroscopic methods (see Experimental Section).

In order to avoid the decomposition of the aminonitrates during basification, hydrogenolysis of the acidic photolysate in the presence of various catalysts was examined but failed to give clean reduction. It was also found that the free aminonitrate esters were resistant to reduction with excess of sodium borohydride or with sodium borohydride and platinum black. For the convenience of n.m.r. analysis as required in deciding the stereochemistry of the photoaddition, the major work was carried out using NND as the addendum.

The oxidative photoaddition of NND gave the hydrochloride of endo-2-nitrato-exo-3-dimethylaminobicyclo[2,2,1]heptane (II-29b). Efforts to isolate the corresponding exo-nitrato isomer II-28b were not successful and resulted in decomposition similar to that observed in the NNP photoaddition described above. However, when the photolysate was worked up immediately under mild conditions (pH 8.5, 0°), the basic fraction was found to contain endo-nitrate II-30b and exo-nitrate II-31b as shown by the N-CH_3 singlets in the n.m.r. spectrum at τ 7.78 and 7.52 in nearly equal intensities (see Experimental Section). The n.m.r. spectrum also demonstrated the presence of exo-3-dimethylamino-exo-bicyclo[2,2,1]heptan-2-ol (II-35b, τ 7.69 for N-CH_3), 1,3-diformylcyclopentane (II-39, τ 0.22 and 0.35; i.r. peaks at 1720 and 2720 cm^{-1}) and a small amount of exo-3-dimethylaminobicyclo[2,2,1]heptan-2-one (II-37b, 1745 cm^{-1}). Immediate reduction of this fraction with lithium aluminium hydride gave a mixture of endo-alcohol II-34b and exo-alcohol II-35b (19% overall yield) in a ratio of 3:7 as indicated by the relative intensities of the N-CH_3 singlets at τ 7.80 and 7.71. Extensive chromatography of this mixture afforded pure exo-alcohol II-35b but endo-alcohol II-34b was isolated only as a mixture with II-35b. The stereochemistry of exo-alcohol II-35b was determined by the coupling pattern of the C-2 proton (double doublet with J = 6.3 and 1.3 Hz). In contrast, the corresponding C-2 proton of endo-alcohol II-34b exhibited a triplet (J = 4 Hz) typical of an exo-oriented C-H bond (vide infra).


+ R2NNO
H+, hν
O2
a , R2 = -(CH2)5-
b , R2 = CH3 , CH3
II-29
II-28
II-37
II-30
II-34
II-31
II-32
II-38
II-39
II-36
II-33
LAH
II-40
-OH
II-35
?

Scheme 2.6

When the crude amino nitrates were allowed to decompose in an aqueous basic condition (pH 10) and the recovered oil was reduced with lithium aluminium hydride, the basic fraction accounted for only 5% of the theoretical yield and contained only exo-alcohol II-35b; endo-alcohol II-34b was neither detected by chromatography nor by n.m.r. The major decomposition product was found to be the dialdehyde II-39 which was isolated as 2,4-dinitrophenyl hydrazone from the recovered oil. The presence of this compound was further confirmed by isolation of the p-nitro benzoyl derivative of bis-1,3-(hydroxymethyl)-cyclopentane II-40 from the neutral fraction of the lithium aluminium hydride reduction.

In summary, it may be concluded that both endo-nitrates (II-29a and II-29b) and exo-nitrates (II-28a and II-28b) are formed in the oxidative photoaddition and that they are decomposed by bases to give mainly dialdehyde II-39 and exo-alcohol II-35 in addition to a small amount of ketone II-37. In order to clarify the stereochemical course of the basic decomposition, the pure hydrochloride of endo-nitrate II-29b was treated with base in aqueous solution and the extracted oil was allowed to decompose in the absence of solvent. Immediately after the basification and extraction, the basic fraction exhibited strong i.r. and n.m.r. absorptions for endo-nitrate II-30b (1625, 1285 and 870 cm^{-1}, and τ 5.03 and 7.78) and for dialdehyde II-39 (1720 cm^{-1} and τ 0.37); a small amount of exo-alcohol II-35b (τ 6.41 and 7.60) and ketone II-37b (1745 cm^{-1})

was also observed. As the nitrate absorptions gradually diminished, the absorptions due to dialdehyde II-39 and exo-alcohol II-35b built up considerably; the ketone absorption at 1745 cm^{-1}, however, remained static and finally showed as a faint shoulder of the strong 1720 cm^{-1} peak. A g.c.-m.s. analysis of the final product mixture showed that it contained dialdehyde II-39 (61%), exo-alcohol II-35b (30%) and other compounds (<8%).

The structures of the products were established on the basis of spectral data. The stereochemistry of the pure and semi-pure bicyclic derivatives was determined by the n.m.r. coupling patterns of the C-2 and C-3 protons which, in many cases, were clarified by decoupling experiments. The chemical shifts and coupling constants of compounds II-29b, II-34a and II-35b are summarized in Table 2.1 and 2.2, respectively. The 100 MHz n.m.r. spectra of compounds II-29b, II-34a and II-35b and some spin-decoupled spectra are shown in Figures 2.1, 2.2 and 2.3.

For steric reasons [54,74], an aminium radical is expected to approach from the exo-face of norbornene in the photoaddition reaction giving exo-configuration for the amine group in all bicyclic compounds. In the case of II-29b and II-35b, the C-3 endo-proton was shown to be coupled with the C-7 anti-proton through the long-range "W-plan" coupling and not (or very weakly) with the C-4 proton [101,102]. Since the C-2 protons were generally

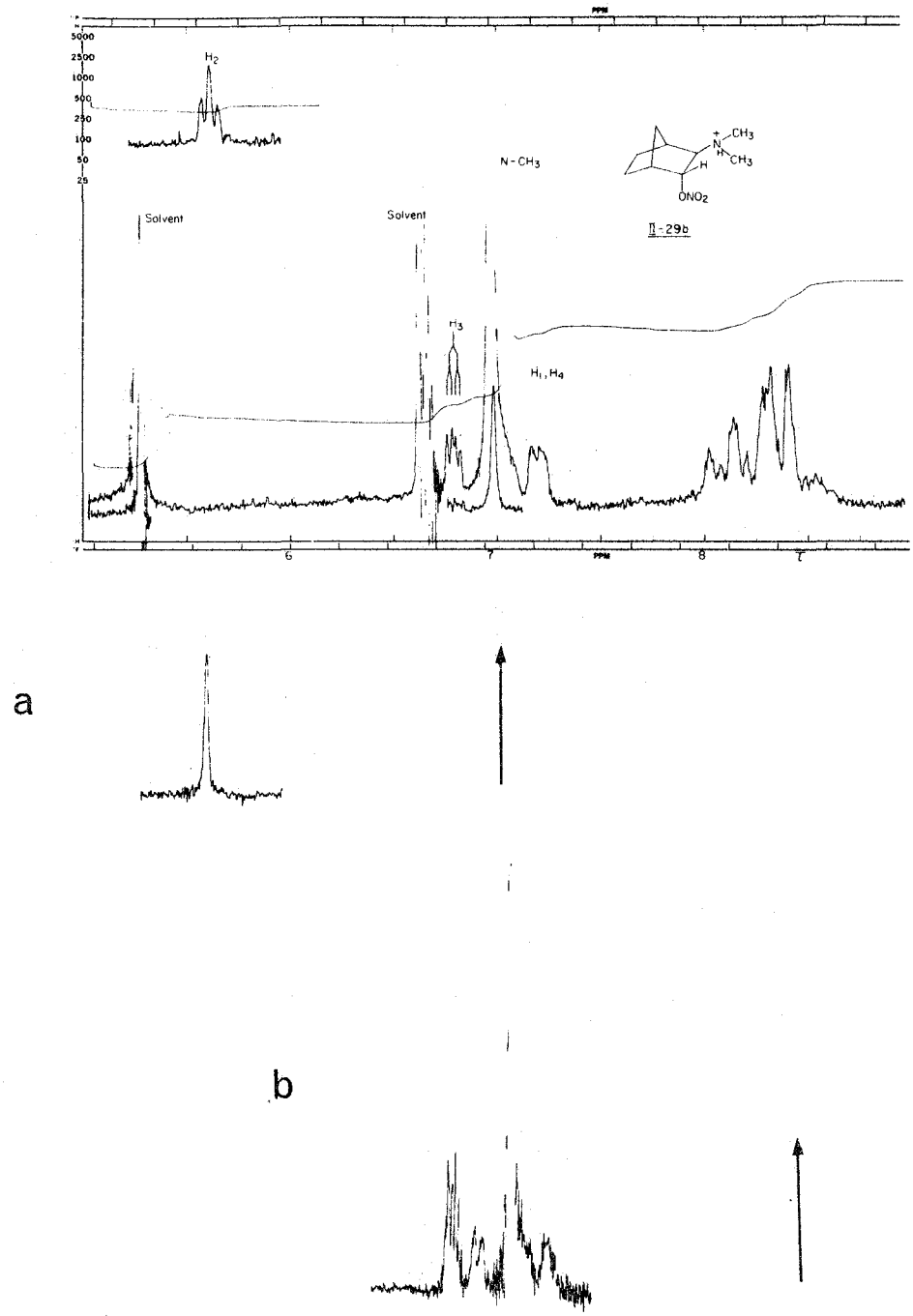
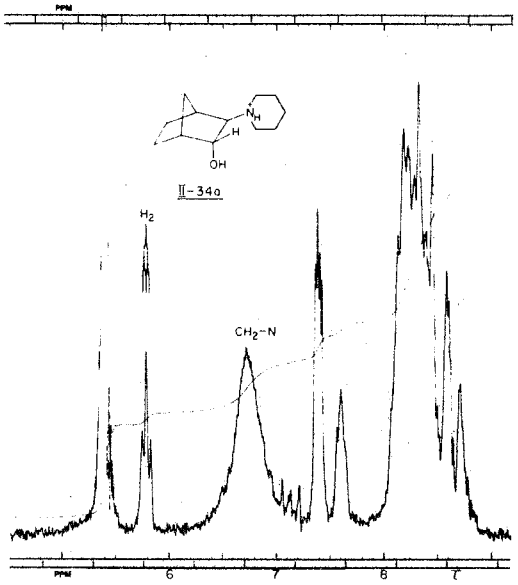


Figure 2.1 n.m.r. spectra (100 MHz) of endo-2-nitrato-exo-3-dimethylaminobicyclo[2,2,1]heptane (II-29b) : a, double irradiation of the C-1 and C-3 protons; b, double irradiation of C-7 protons. Solvent: - Methanol - d_4



a

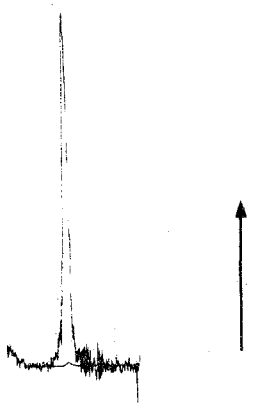


Figure 2.2 n.m.r. spectra (100 MHz) of exo-3-piperidino-endo-bicyclo[2,2,1]heptan-2-ol (II-34a): a, double irradiation of the C-1 and the C-3 protons. Solvent: - D_2O

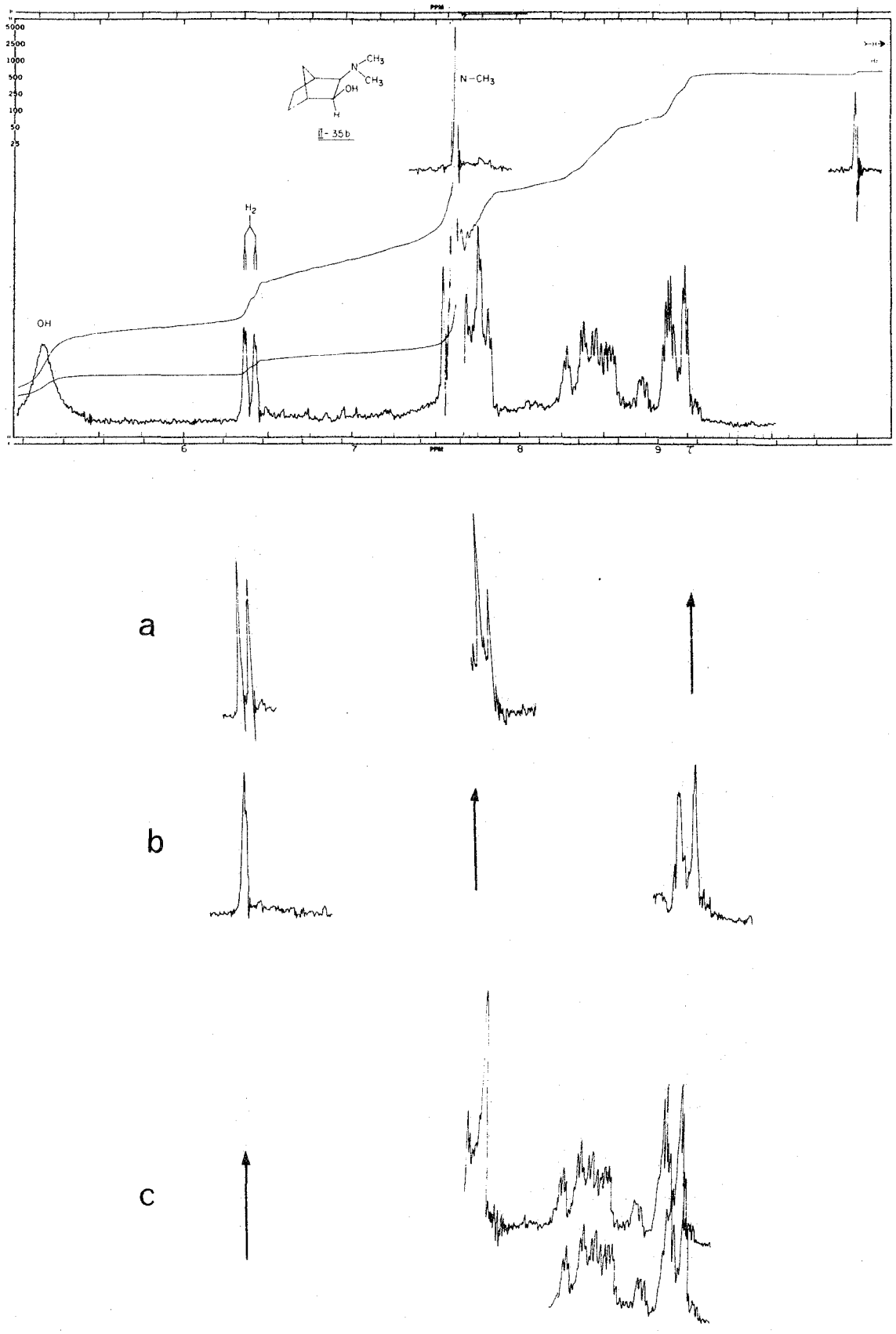
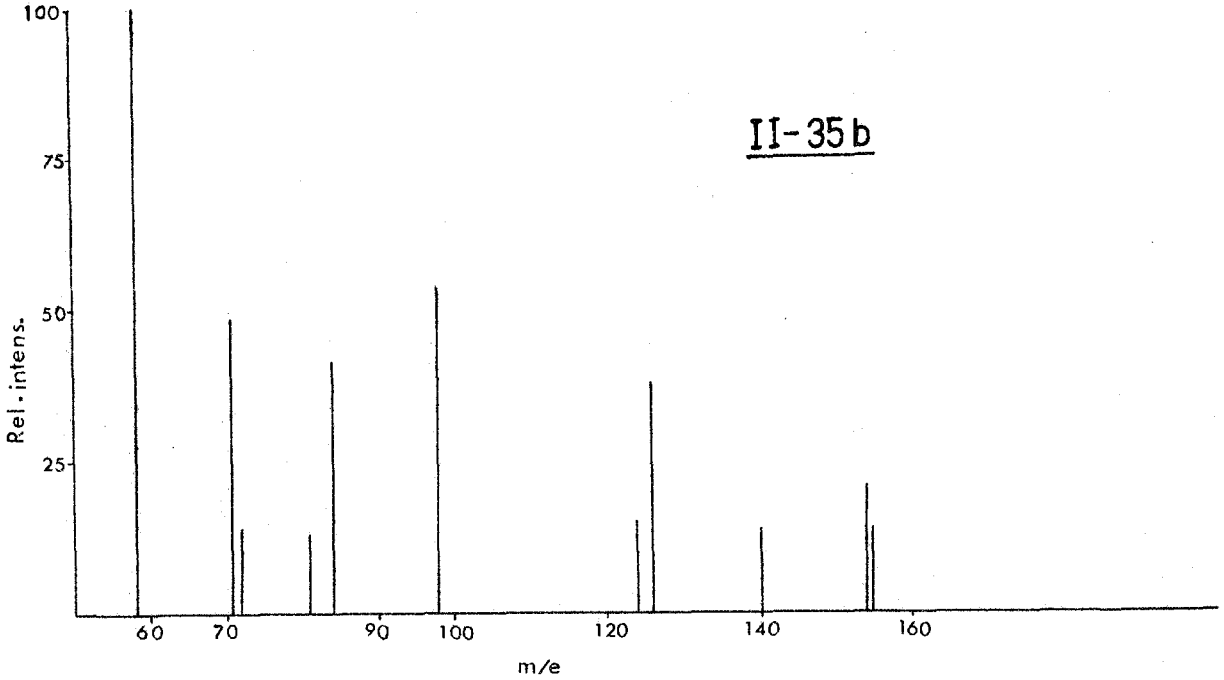


Figure 2.3 n.m.r. spectra (100 MHz) of exo-3-dimethylamino-exo-bicyclo[2,2,1]heptan-2-ol (II-35b): a, double irradiation of the C7a proton; b, double irradiation of the C-1 and the C-3 protons; C, double irradition of the C-2 proton.



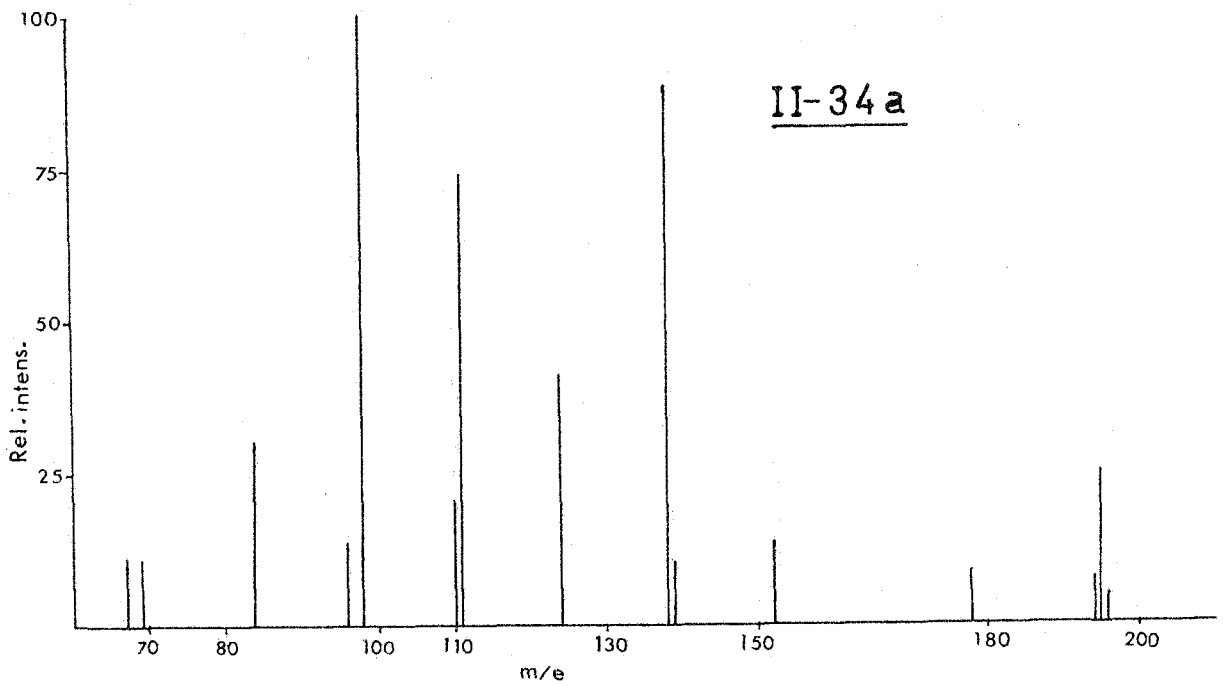


Figure 2.4 Mass spectra (80 ev) of exo-3-piperidino-endo-bicyclo [2,2,1]heptan-2-ol (II-34a) and exo-3-dimethylamino-exo-bicyclo[2,2,1]heptan-2-ol (II-35b).

Table 2.1

CHEMICAL SHIFTS (τ)

Proton	II-29b[a]	II-34a[b]	II-35b
2 exo	4.65 (t)	5.76 (t)	-
2endo	-	-	6.40 (dd)
3 endo	6.82 (dd)	7.36 (d)	7.73 (m)[c]
1	7.24 (m)	7.38 (m)	7.80 (m)
4		7.58 (m)	8.88 (m)
7 syn	7.95 - 8.74 (m)	8.30 (m)	
7 anti			8.95 (m)
5,6			8.23-8.79 (m)
$N-CH_3$	7.03 (s)	-	7.62 (s)
$N-CH_2-$	-	6.70 (m)	-
-OH	-	-	5.18 (m)

a: solvent - Methanol -d_4
b: solvent - D_2O
c: partly hidden under $N-CH_3$ peak

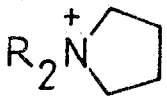
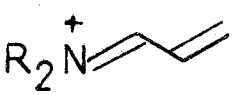
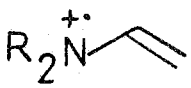
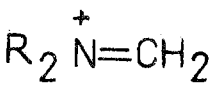
Table 2.2

COUPLING CONSTANTS (Hz)

Compound	J1,2	J 2,3	J2,7a	J3,7a
II-29b	4.0	4.0	-	2.5
II-34a	4.0	4.0	-	-
II-35b	-	6.3	1.3	-

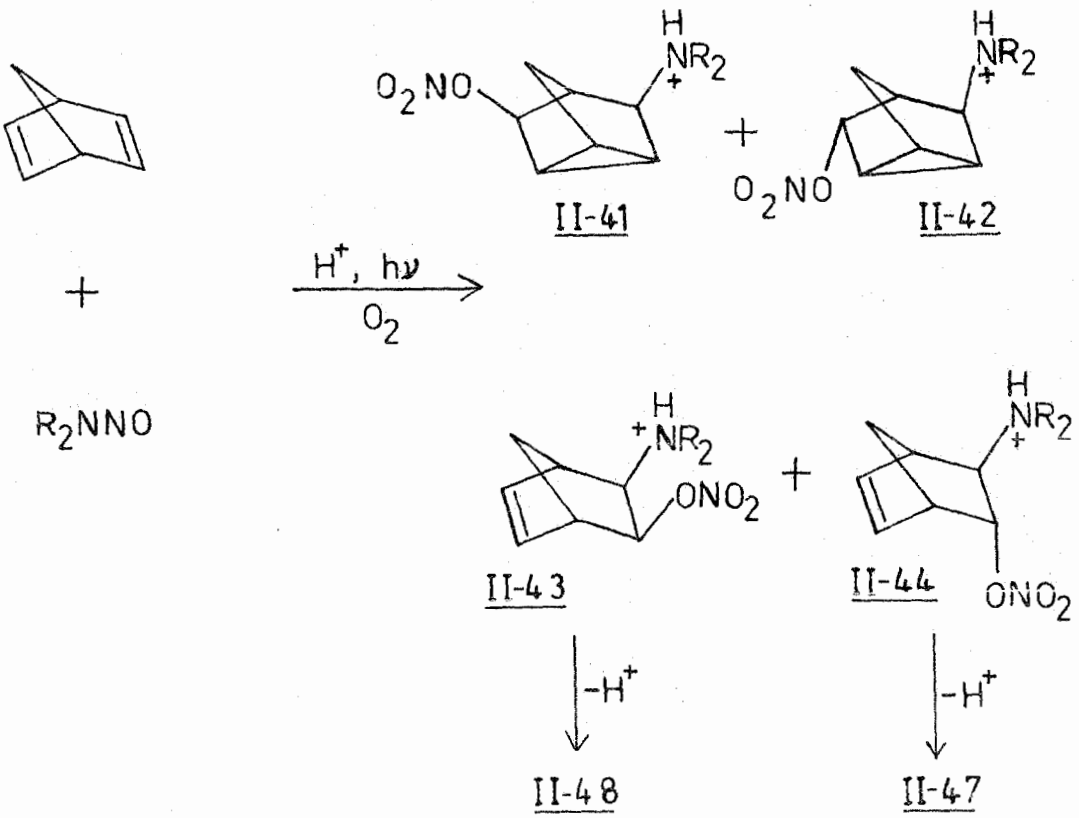
shifted further downfield, analysis of their coupling patterns was much easier than that of the C-3 proton. The trans-configuration such as in II-29a, II-29b and II-34a exhibited the C-2 exo-proton as a triplet (J = 4 Hz) indicating the expected spin interaction with the C-1 and C-3 endo-protons. The exo-cis-configuration in II-28a, II-28b and II-35b was revealed by the fact that the C-2 endo-proton was coupled with the C-3 endo-proton (J ≃ 6 Hz) and the C-7 anti-proton (J = 1-2 Hz) but not with the C-1 proton.

The mass spectral fragmentation pattern also showed some common pattern typical for bicyclic systems; for example, both alcohols II-34a and II-35b (Figure 2.4) gave strong peaks for the four fragments listed below.

	II-34a(%)	II-35b(%)
	138(100)	98(54)
	124(55)	84(44)
	111(87)	71(48)
	98(93)	58(100)

2-2-5. Oxidative Addition To Bicyclo[2,2,1]heptadiene

Photolysis of a methanolic solution of NND (or NNP) in the presence of perchloric acid and bicyclo[2,2,1]heptadiene under oxygen atmosphere exhibited the expected zero-order decrease of the nitrosamine absorption at 345 nm. The photolysis resulted in the formation of 1,5-cycloaddition products (50%), nortricyclene derivatives II-41 and II-42, as major products in addition to a small amount (2%) of normal 1,2-adducts. Specifically, the oxidative photoaddition of NND afforded the perchlorate of endo-3 nitrato-exo-5-dimethylamino-tricyclo[2,2,1,$0^{2,6}$]heptane (10%, II-42a). It analyzed correctly for $C_9H_{15}N_2O_7Cl$ and exhibited the characteristic i.r. bands of a substituted nortricyclene (103) at 3140, 828, 810 and 760 cm^{-1}. The n.m.r. spectrum (Figure 2.5) showed no vinyl hydrogens but a poorly resolved triplet (J = 1.5 Hz) at τ 4.80 for the C-3 proton and a doublet (J = 9.0 Hz) at τ 6.35 for the C-5 proton. The C-6 cyclopropyl proton appeared as a triplet (J = 5.2 Hz) at τ 7.94.



a: $R_2 = CH_3, CH_3$

b: $R_2 = -(CH_2)_5-$

Scheme 2.8

The stereochemistry of II-42a was deduced from that of the corresponding alcohol obtained by lithium aluminium hydride reduction (vide infra).

The crude basic fraction obtained after the removal of II-42a was mostly exo-3-nitrato-exo-5-dimethylaminotricyclo[2,2,1,$0^{2,6}$]heptane (II-46, 40%). A careful chromatography of this basic fraction revealed the presence of ca. 2% of the 1,2-adducts, endo-2-nitrato-exo-3-dimethylaminobicyclo [2,2,1]hept-5-ene (II-47, free base of II-44a) and exo-2-nitrato-exo-3-dimethylaminobicyclo[2,2,1]hept-5-ene (II-48, free base of II-43a). The infrared spectrum of a mixture of these two adducts showed characteristic bands at 1620, 1280 and 865 cm^{-1} for a nitrate ester. In the n.m.r. spectrum, the vinylic hydrogens of II-47 appeared as double doublets (each line further split into a doublet) at τ 3.68 (J = 6.0, 3.5 and 1.0 Hz) and at τ 4.08 (J = 6.0, 3.0 and 0.5 Hz) and the $N-CH_3$ as singlet at τ 7.87. The vinylic hydrogens of II-48 were seen as a quintet (J = 3 Hz) at τ 4.37 and the $N-CH_3$ group as a singlet at τ 7.75. Further purification of this mixture was not successful due to its decomposition.

The nitrates II-45 and II-46 were found to be isomers from their infrared spctra, both of which contained typical bands at 1625, 1280 and 865 cm^{-1} (nitrate ester) and at 3080, 825 and 815 cm^{-1} (substituted nortricyclene) and from their distinctly different

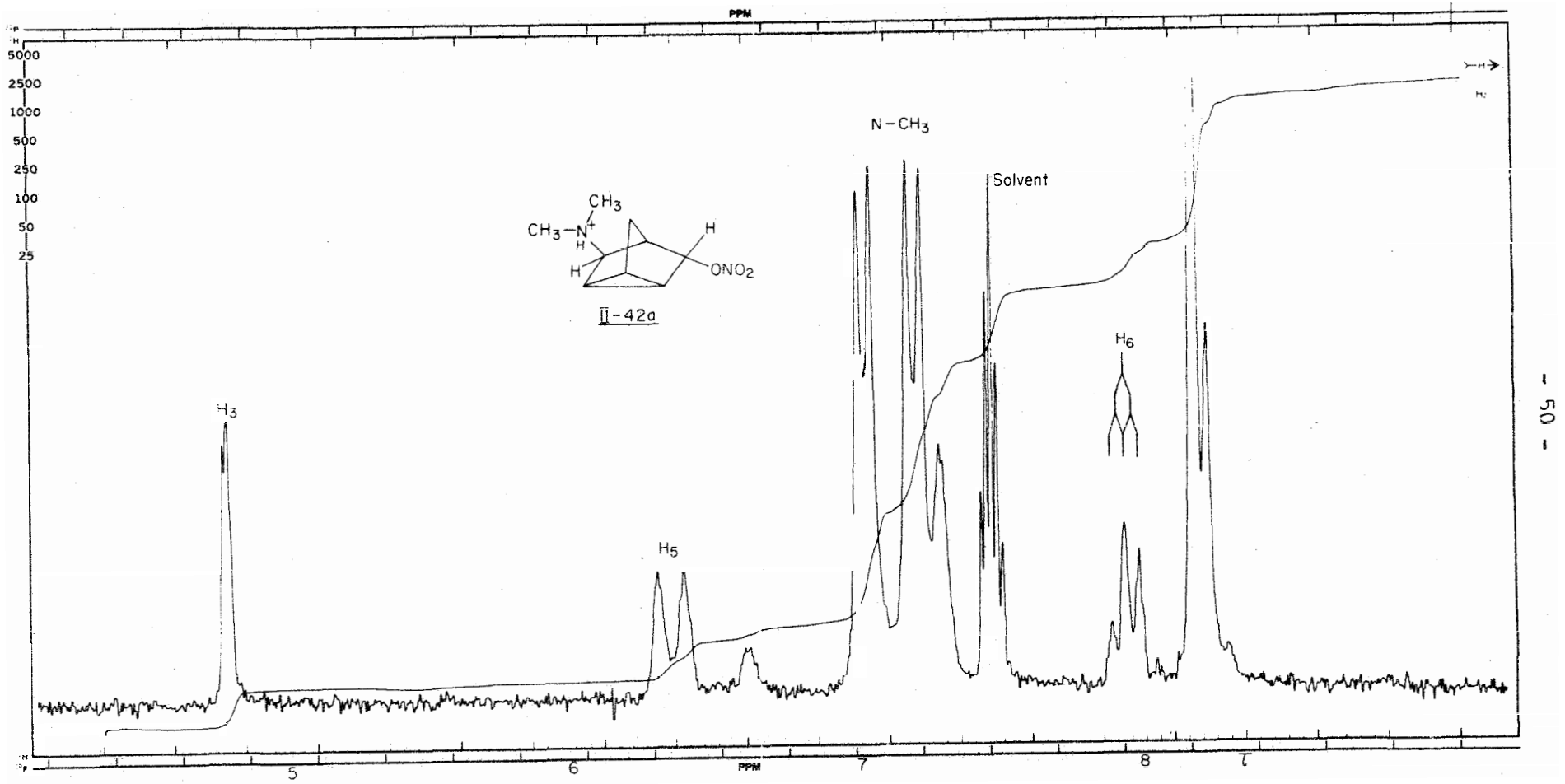
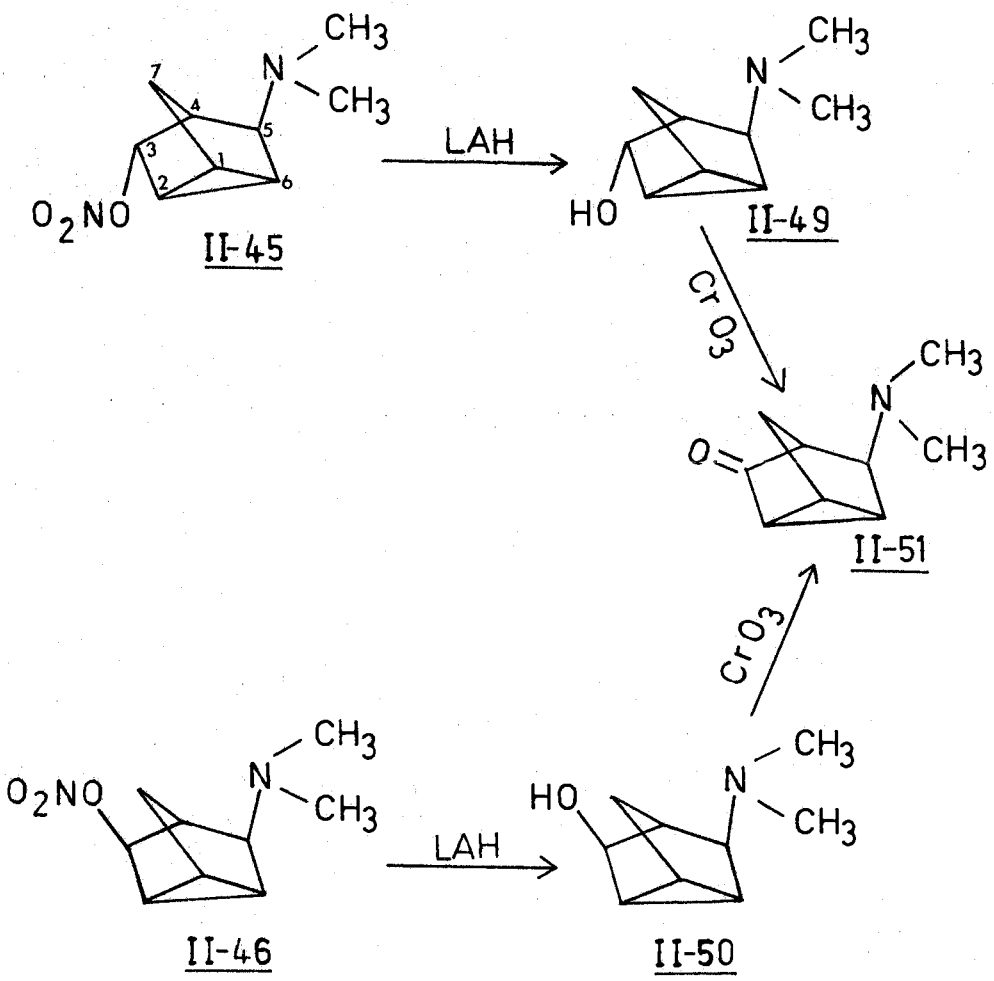


Figure 2.5 n.m.r. spectrum (100 MHz) of endo-3-nitrato-exo-5-dimethylaminotricyclo-[2,2,1,$0^{2,6}$]heptane (II-42a).
Solvent: DMSO -d_6

n.m.r. spectra (see Table 2.3 and 2.4). Further, reduction of II-45 and II-46 with lithium aluminum hydride afforded exo-5-dimethylamino-endo-tricyclo[2,2,1,$0^{2,6}$]heptan-3-ol (II-49) and exo-5-dimethylamino-



Scheme 2.9

exo-tricyclo[2,2,1,$0^{2,6}$]heptan-3-ol (II-50), respectively, in high yields.

Both of these isomeric aminoalcohols gave the expected elemental analysis for the molecular formula $C_9H_{15}NO$. The oxidation of either alcohol II-49 or II-50 with Jones reagent [104] gave a single ketone, exo-5-dimethylamino-tricyclo[2,2,1,$0^{2,6}$]heptan-3-one (II-51). The nortricyclene structure of ketone II-51 was indicated by its infrared spectrum (1760, 3073, 855, 838 and 805 cm^{-1}) [105]. In the n.m.r. spectrum (Table 2.5 and 2.6) the C-5 proton was seen as a triplet (J = 1.0 Hz) at τ 7.50 and the N-CH_3 singlet at τ 7.75. The C-7 methylene protons showed the expected [106] AB pattern (J_{AB} = 10.5 Hz), each component of which was further split into a triplet (J = 1.5 Hz). The C-6 cyclopropyl proton at τ 8.50 appeared as a triplet with a typical coupling constant (J = 5.5 Hz) for a cyclopropyl group [107]. The most intense peak in the mass spectrum (Figure 2.6) of II-51 was seen at m/e 151 ($C_9H_{13}NO$) corresponding to the molecular ion. The fragmentation pattern can be rationalized in terms of structure II-51 as depicted in Scheme 2.10.

Table 2.3

CHEMICAL SHIFTS (τ)

Proton	II-42b[a]	II-42a[a]	II-45	II-46
3 exo	4.86 (bs)	4.80 (t)[c]	5.10 (t)[c]	-
3 endo	-	-	-	5.20 (t)[c]
5 endo	6.46 (m)	6.35 (d)	7.45 (t)[c]	7.70 (m)[b]
4	6.94 (m)	7.31 (m)[b]	7.90 (m)[b]	8.20 (m)
6	7.28 (m)	7.94 (t)	8.10 (m)	8.47 (m)
1,2,7 anti	8.18 (m)	8.21 (m)	8.48 (m)	
7 syn				8.20 (m)
+NH	1.58 (m)	1.16 (m)	-	
CH_2-N	6.46 (m)	7.04 (d)	7.80 (s)	7.81 (s)
CH_3-N	-	7.22 (d)	-	-

a: solvent DMSO -d_6
b: partly hidden under N-CH_3 peak
c: not well resolved

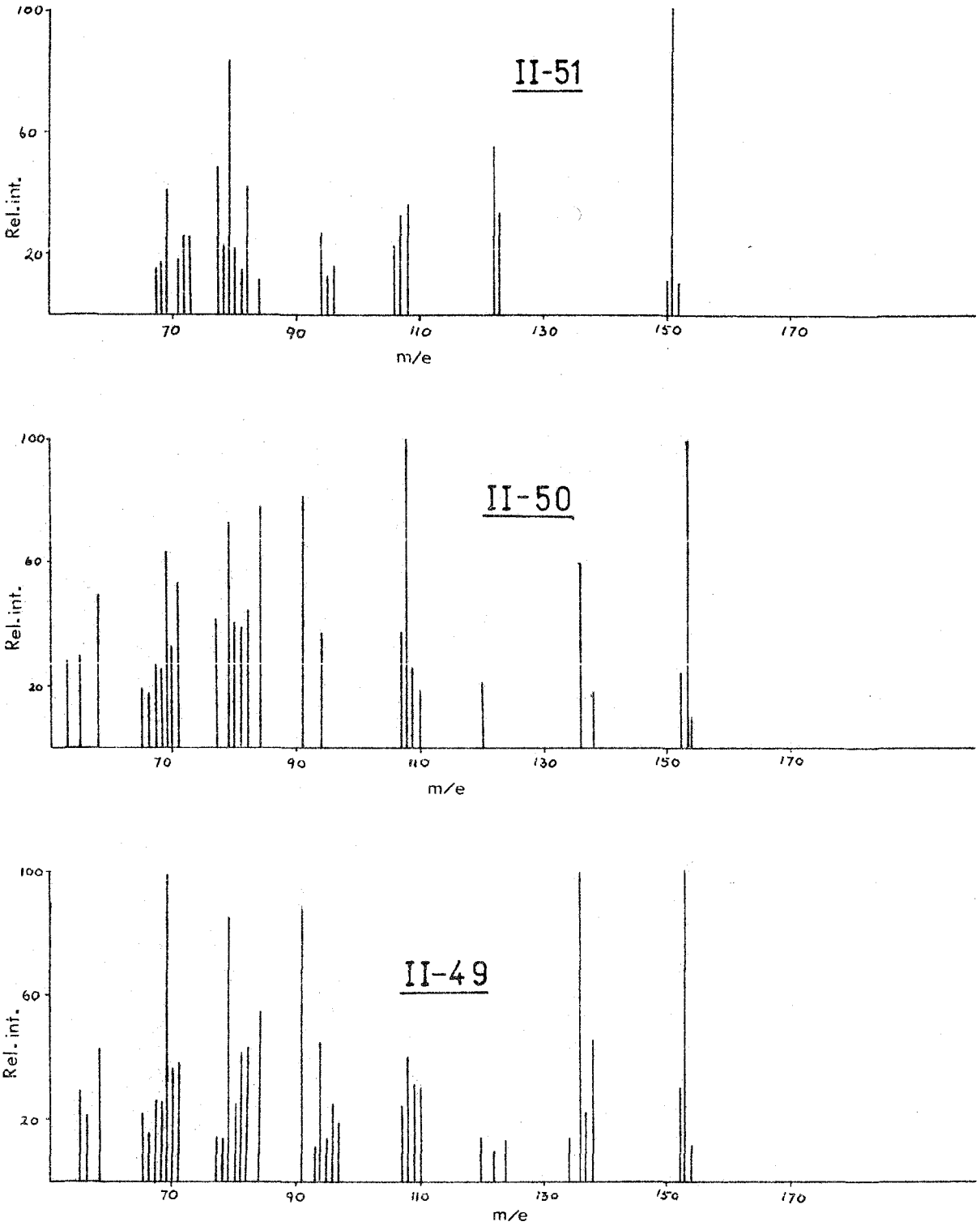
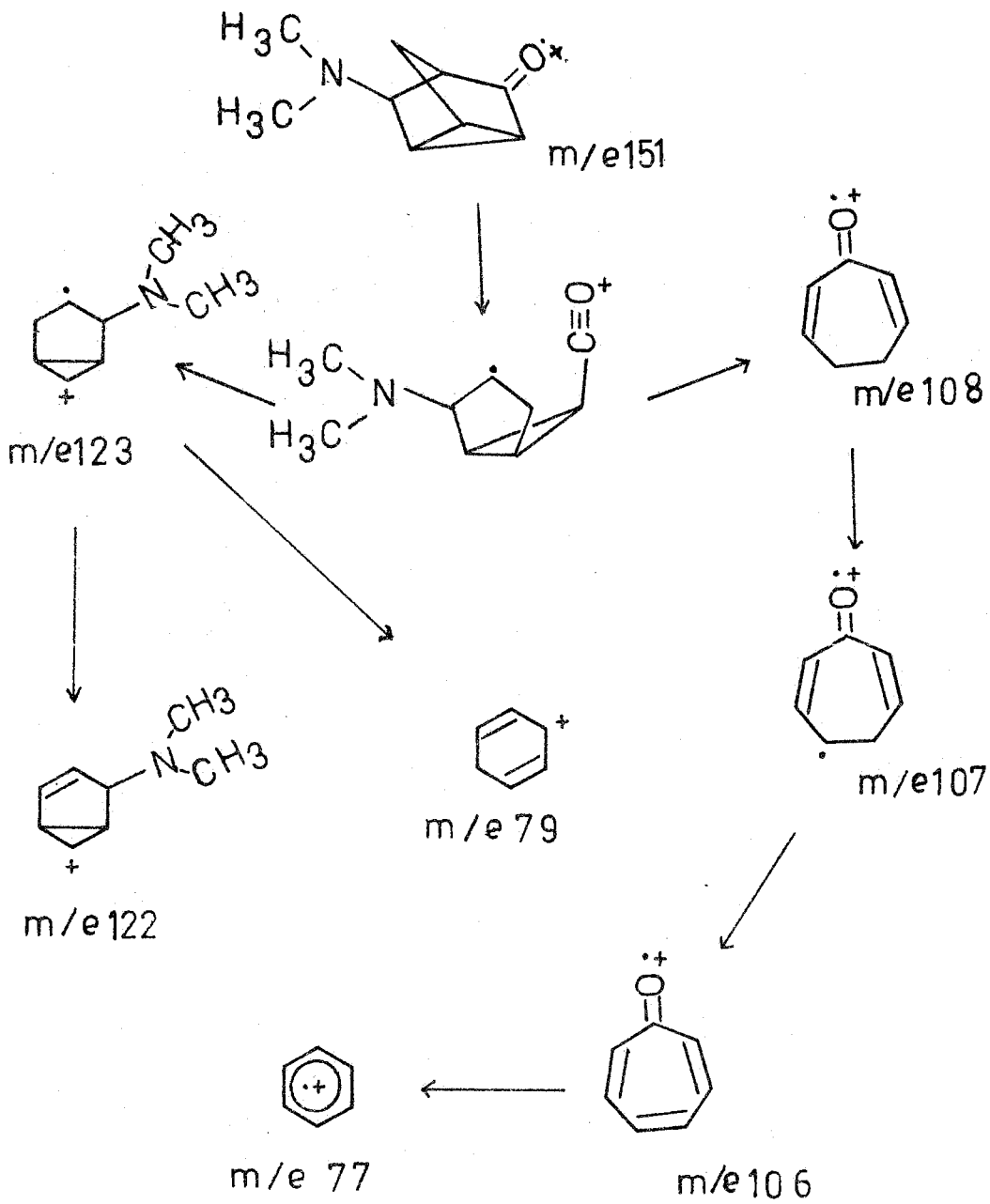


Figure 2.6 Mass spectra (80 ev) of exo-5-dimethylamino-endo-tricyclo[2,2,1,$0^{2,6}$]heptan-3-ol (II-49), exo-5-dimethylamino-exo-tricyclo[2,2,1,$0^{2,6}$]heptan-3-ol (II-50) and exo-5-dimethylaminotricyclo[2,2,1,$0^{2,6}$] heptan-3-one (II-51).

Table 2.4

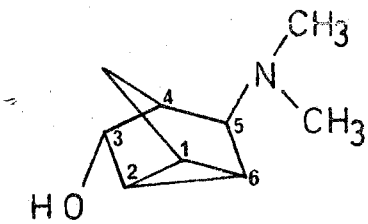
COUPLING CONSTANTS (Hz)

J	II-42a	II-45	II-46
$J_{1,6}$	5.2	-	-
$J_{2,3}$	1.5	1.5	ca. 1.5
$J_{2,6}$	5.2	-	-
$J_{3,4}$	1.5	1.5	ca. 1.5
$J_{4,5}$	ca. 1.5	ca. 1.5	-
$J_{5,6}$	ca. 1.5	ca. 1.5	-
$J_{5,\overset{+}{N}H}$	9.0	-	-
$J_{\overset{+}{N}H,CH_3}$	4.5	-	-

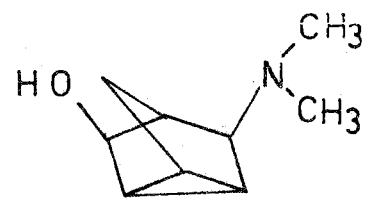


Scheme 2.10

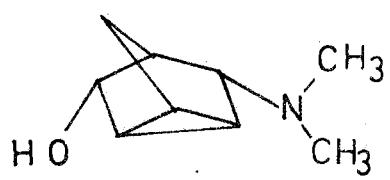
The structure and stereochemistry of the amino alcohols II-49 and II-50 were assigned on the basis of the following arguments. Both alcohols exhibited characteristic infrared absorptions for a substituted nortricyclene skeleton. In analogy to the reported n.m.r. parameters [81,106,108], the small coupling constant observed (Table 2.6) for the C-3 and C-5 protons together with the chemical shift of the cyclopropyl protons also suggested the nortricyclene skeleton. The fact that both alcohols gave a single ketone on oxidation, unequivocally established that they are isomeric at C-3. These facts limit possible structures of II-49 and II-50 to two isomeric pairs; A and B or C and D.



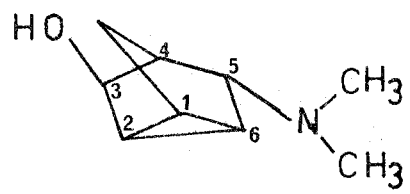
A



B



C



D

Table 2.5

CHEMICAL SHIFTS (τ)

Proton	II-49	II-50	II-51
3 exo	6.01 (t)	-	-
3 endo	-	6.21 (t)	-
5 endo	7.36 (bs)	8.08 (m)	7.5 (t)
4	8.11 (m)	8.08 (m)	7.83 (m)[c]
1	-	-	7.99 (m)
2	8.63 (m)	8.65 (m)	7.83 (m)[c]
6	-	-	8.50 (t)
7 syn	8.71 (d)[b]	8.20 (d)[a]	7.69 (m)[c]
7 anti	8.20 (d)[a]	8.29 (d)	8.12 (d)
N-CH_3	7.75 (s)	7.84 (s)	7.75 (s)
-OH	-	8.04 (m)	-

a: partly hidden under H_4 peak
b: partly hidden under ^{4}8.63 peak
c: partly hidden under N-CH_3 peak

Table 2.6

COUPLING CONSTANTS (Hz)

J	II-49	II-50	II-51
1,6	-	-	5.5
1,7	1.0	1.0	1.5
2,6	-	-	5.5
2,3	1.6	1.5	-
3,4	1.6	1.5	-
4,5	-	-	1.0
5,6	-	-	1.0
4,7	1.0	1.0	1.5
7 gem	10.5	11.0	10.5

A close examination of the n.m.r. spectra of the two alcohols (Table 2.5) revealed that the chemical shifts of the C-5 and the C-7s (syn to OH group) protons were significantly different in these isomers. While the C-5 proton of II-49 (τ 7.36) was more deshielded by 0.72 ppm than that of II-50 (τ 8.08), the C-7s proton of II-49 (τ 8.71) was more shielded by 0.51 ppm than that of II-50 (τ8.20). Since the chemical shifts of all other protons were similar for both isomers, the observed shift differences for the C-5 and C-7s protons were evidently due to electrostatic effects of the hydroxyl group inducing a positive dipole on the neighbouring C-5 hydrogen of II-49 and the C-7s hydrogen of II-50 [81,108-110]. Consequently, these protons were more deshielded. These results are consistent only with the structures A and B.

The effect of tris(dipivalomethanato)europium (III) [$Eu(DPM)_3$] on the proton chemical shifts shown in Figures 2.7, 2.8 and 2.9 provides further support for the assigned structures of II-49 and II-50. The proton assignments are based on observed splitting patterns and have been confirmed by decoupling experiments at 100 MHz.
Figure 2.9 demonstrates the linear relationship between chemical shifts and concentration of $Eu(DPM)_3$, in accordance with literature reports [111,112]. As shown in Tables 2.7, 2.8 and 2.9, alcohol II-49 showed a large induced shift (ΔEu) for the C-5 proton and a small shift for the C-7s proton while alcohol II-50 showed a large shift for the C-7s proton and a small shift for the C-5 proton. Also, the

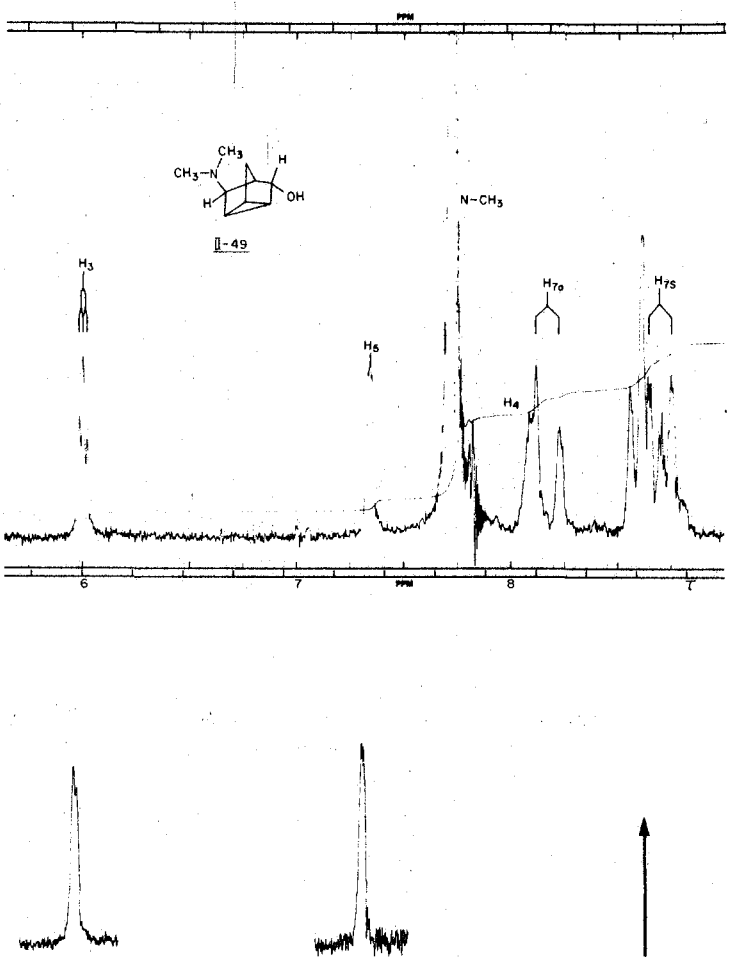
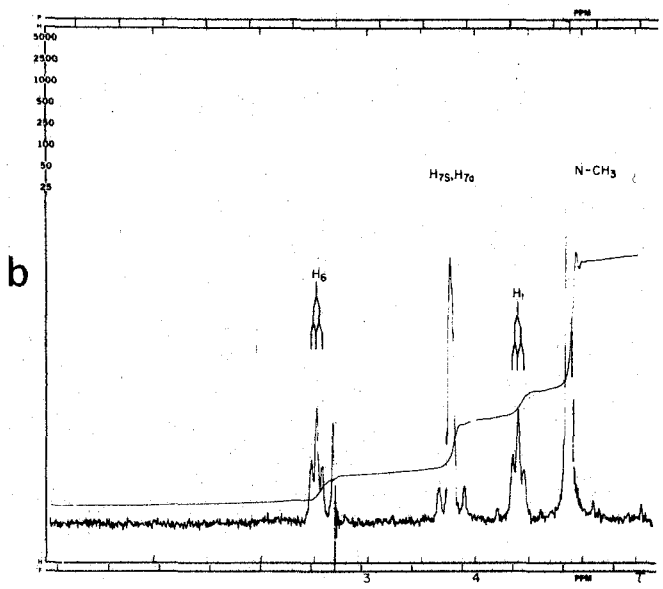


Figure 2.7 n.m.r. spectra (100 MHz) of exo-5-dimethylamino-endo-tricyclo[2,2,1,$0^{2,6}$]heptan-3-ol (II-49):
a, double irradiation of the C-2 proton;
b, in the presence of $Eu(DPM)_3$. (conc. of II-49 and $Eu(DPM)_3$: $2x10^{-4}$mol)
c, double irradiation of the C-2 proton in b;
d, double irradiation of the C-6 proton in b;

(Figure 2.7 continued on next page)



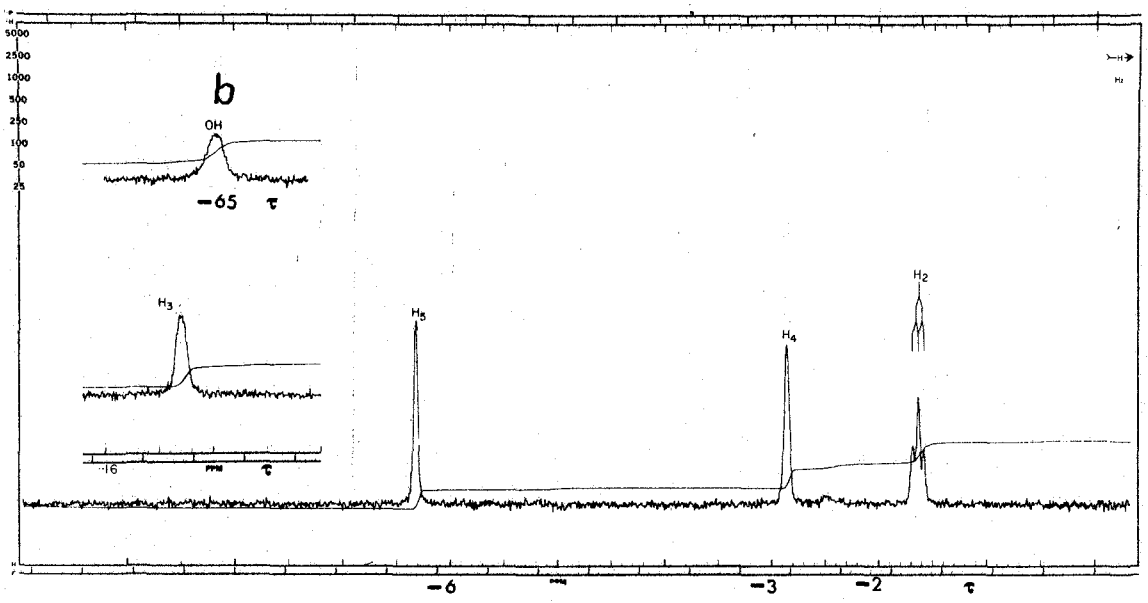


Figure 2.7 (con't) e, double irradiation of the C-1 proton in b.

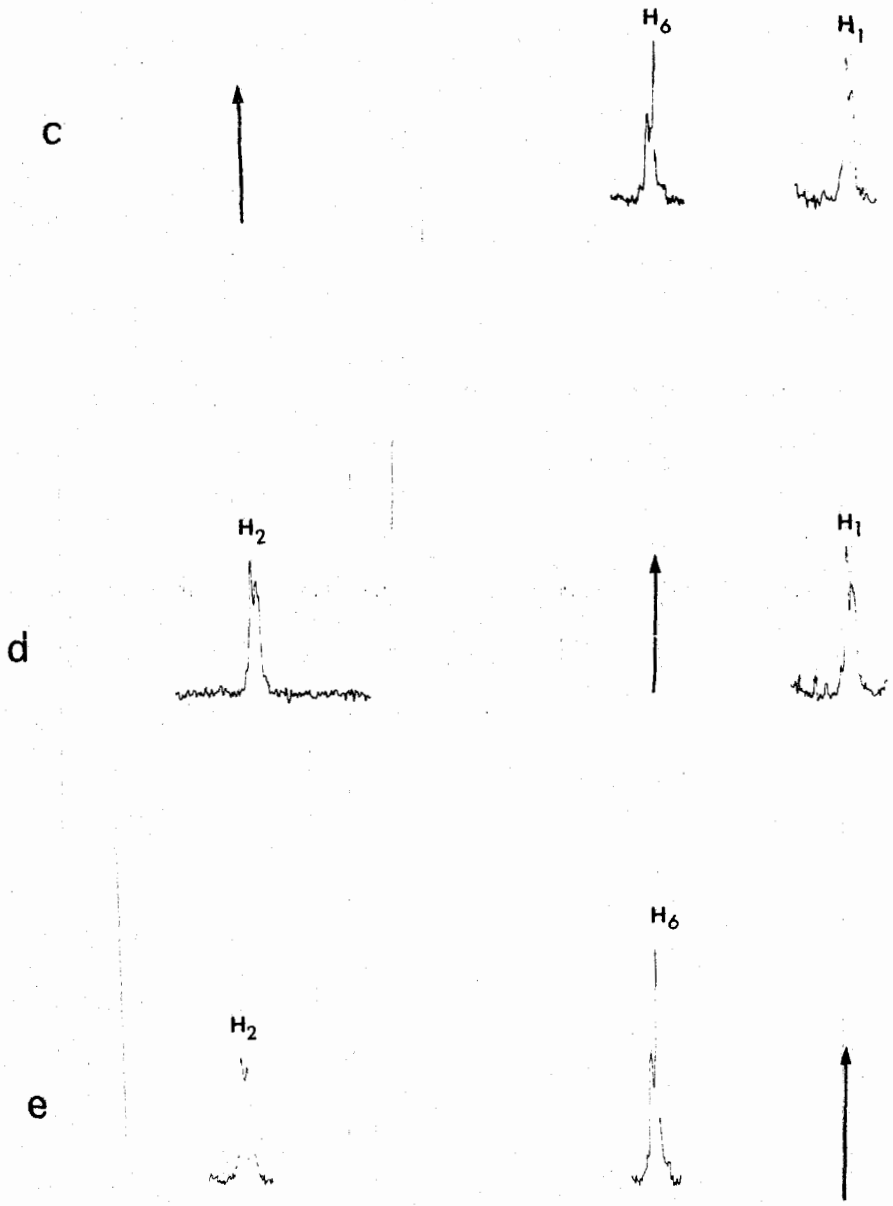


Figure 2.7 (con't)

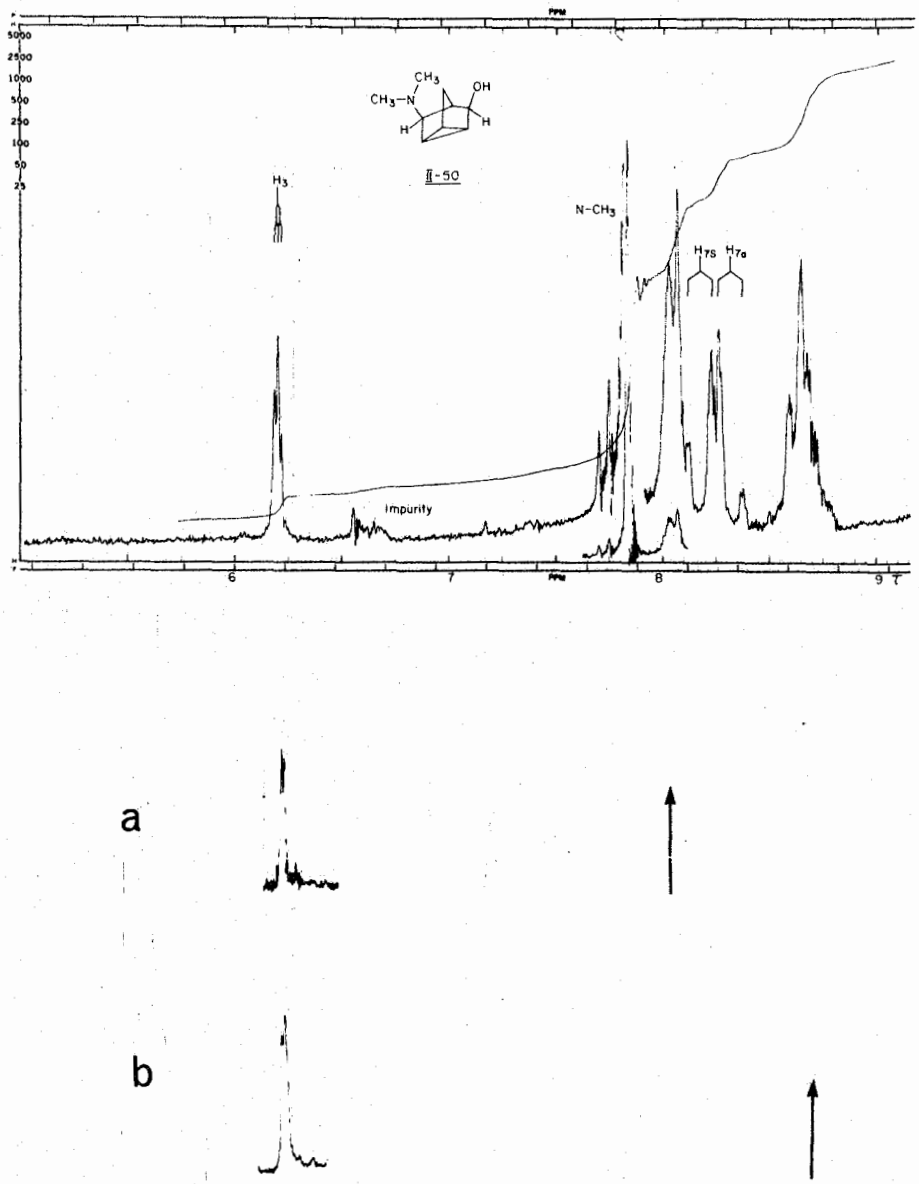
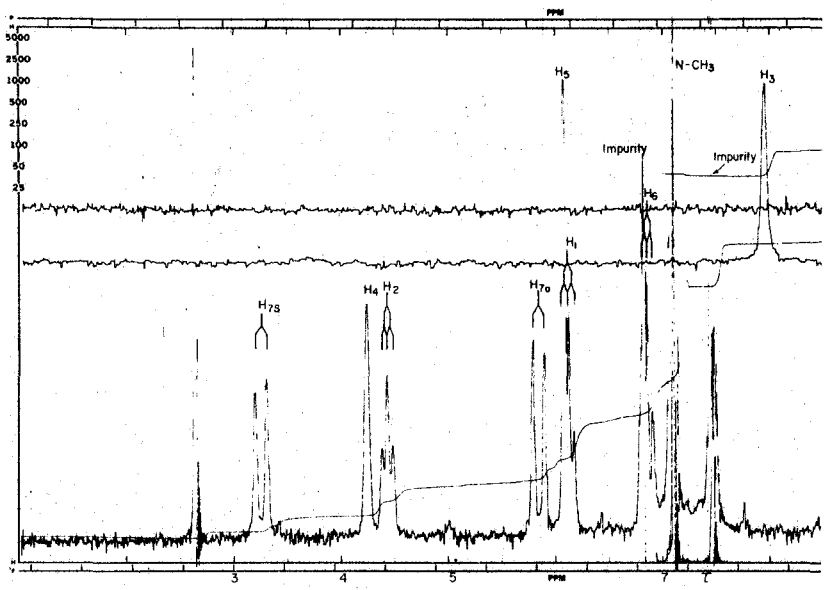


Figure 2.8 n.m.r. spectra (100 MHz) of exo-5-dimethylamino-exo-tricyclo[2,2,1,$0^{2,6}$]heptan-3-ol (II-50):
a, double irradiation of the C-4 proton;
b, double irradiation of the C-2 proton;
c, in the presence of $Eu(DPM)_3$, (conc. of II-50: $2x10^{-4}$ mol; $Eu(DPM)_3$: $0.35x^{-4}$ mol)
d, double irradiation of the C-7s proton in c;
e, double irradiation of the C-7a proton in c.

c


PPM
5000
2500
1000
500
250
100
50
25
H5
N-CH3
H3
Impurity
Impurity
H6
H1
H7s
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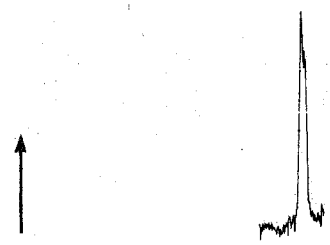
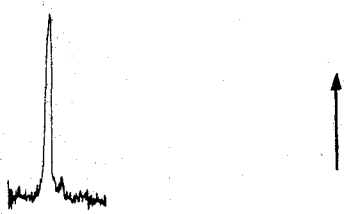
H7o
3
4
5
PPM
7
7

d



e



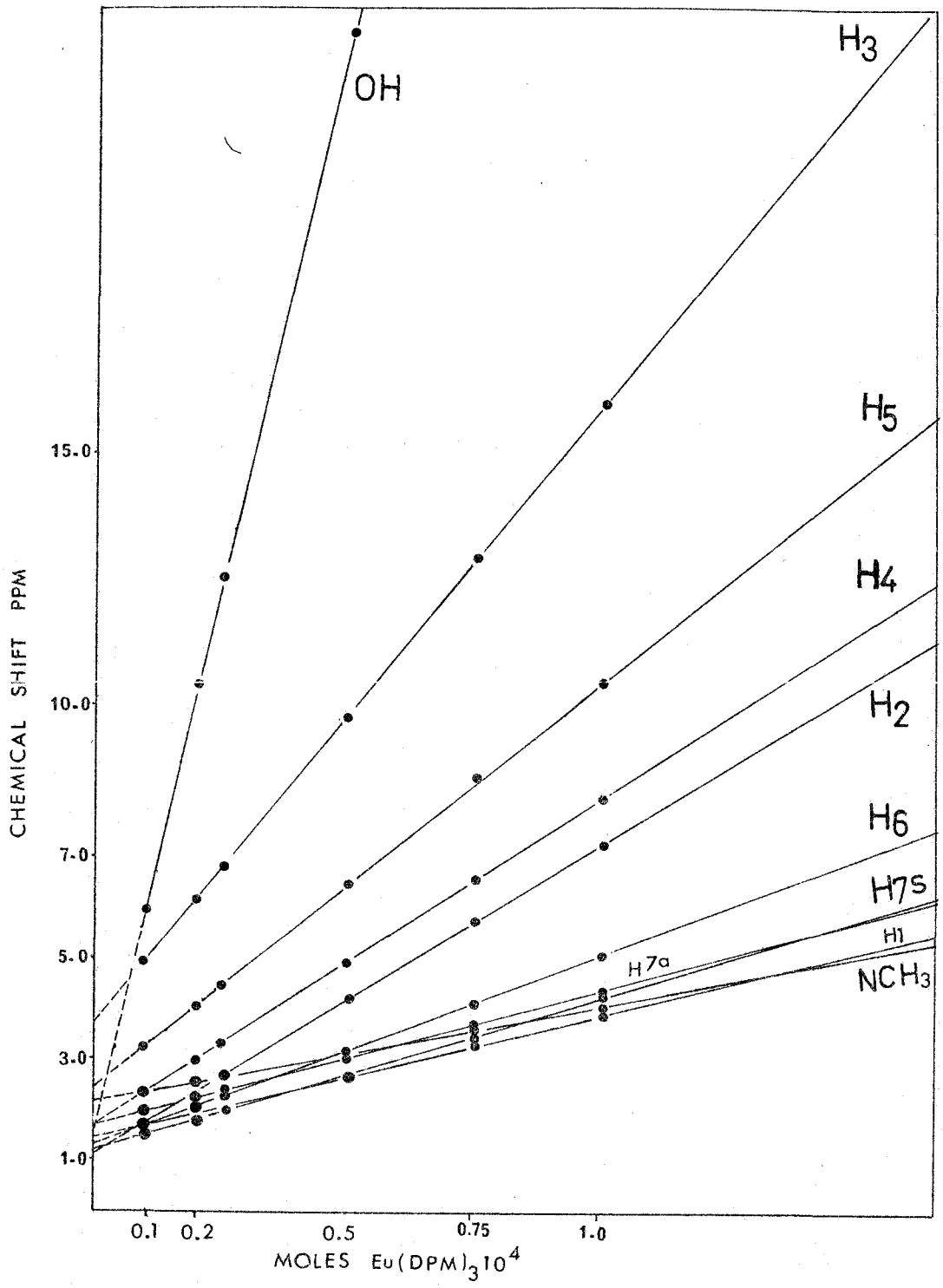


Figure 2.9 Variation in the chemical shift for the difficult protons of <u>exo</u>-5-dimethylamino-<u>endo</u>-tricyclo[2,2,1,$0^{2,6}$]heptan-3-ol (<u>II-49</u>) (2×10^{-4} mol) with increasing amounts of $Eu(DPM)_3$. Straight lines shown are least-squares derived.

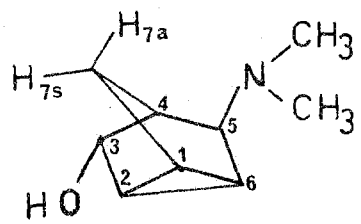
shift difference between the C-7s and the C-7a proton was small in isomer II-49 but very large in isomer II-50. Assuming that the Eu-atom co-ordinates with the dydroxyl group, the observations can be accommodated only by an endo-OH configuration in II-49 and an exo-OH configuration in II-50.

The mass spectra of alcohols II-49 and II-50 showed the same fragmentation patterns (Scheme 2.11) and differed only in the relative abundance of the various peaks (Figure 2.6). In both cases, the most intense peak was observed at m/e 153 corresponding to the molecular ion. The exact mass of this peak agreed with the molecular formula $C_9H_{15}NO$.

Table 2.7

CHEMICAL SHIFT VALUES (τ) OF II-49 IN THE PRESENCE OF $Eu(DPM)_3$

Con. of $Eu(DPM)_3$ ($x10^{-4}$)	τ - Values									
	OH	H3	H5	H4	H2	H6	H7s	H7a	H1	NCH_3
0.1	4.06	5.04	6.69	7.60	8.30	8.30	8.47	7.99	8.30	7.59
0.2	-0.40	3.78	5.84	6.92	7.63	7.91	8.16	7.71	8.13	7.38
0.25	-02.60	3.19	5.45	6.62	7.35	7.75	8.04	7.60	8.00	7.31
0.5	-13.39	0.17	3.43	5.05	5.84	6.83	7.33	6.95	7.40	6.88
0.75	-24.55	-2.98	1.29	3.34	4.22	5.82	6.48	6.20	6.67	6.36
1.0	-34.84	-5.99	-0.51	1.76	2.70	4.89	5.72	5.53	6.04	5.90
		(bs)	(bs)	(bs)	(t)	(t)	(d)	(d)	(t)	(s)



Con. of alcohol II-49: $2x10^{-4}$ mol

J1,6
J2,6 } = 5 Hz
J1,2

J7 geminal = 10.5 Hz

Table 2.8

CHEMICAL SHIFT VALUES (τ) OF II-50 IN THE PRESENCE OF $Eu(DPM)_3$

	OH	H3	H7s	H2	H4	H7a	H5	H1	H6	$N-CH_3$
τ-Value	-11.59 (m)	-2.0 (bs)	3.30 (d)	4.48 (t)	4.28 (bs)	5.90 (d)	6.12 (bs)	6.17 (t)	6.91 (t)	7.15 (s)
Shift (ΔEu)	19.63	8.21	4.94	4.17	3.80	2.37	1.96	2.48	1.74	0.69
R (Å)	0.96	2.05	2.55	2.80	2.83	3.82	3.98	3.82	4.49	-

concentration of $Eu(DPM)_3$: 0.35×10^{-4} mol;

con. of II-50 : 2.0×10^{-4} mol.

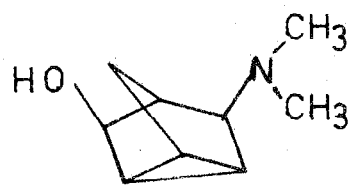
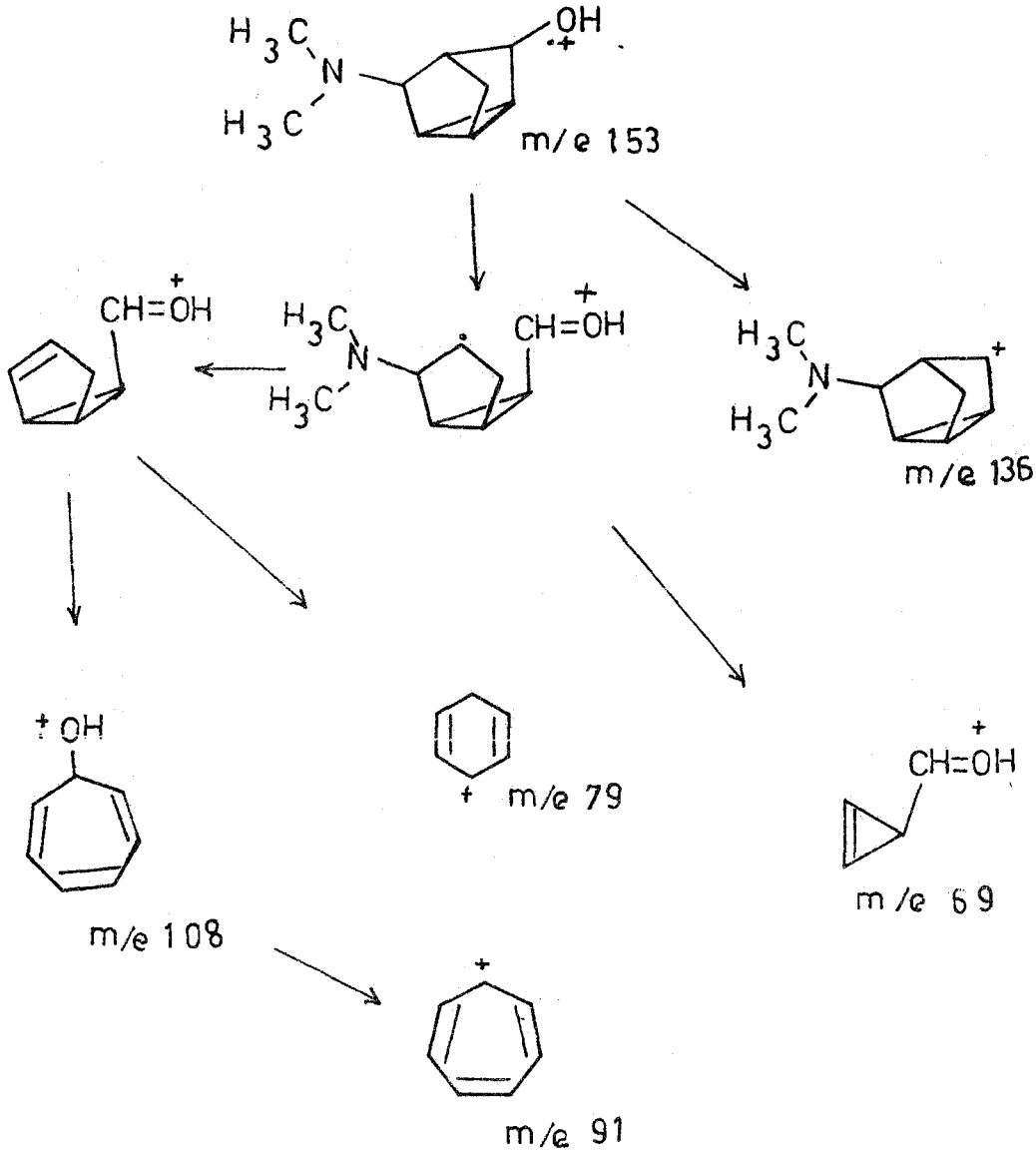


Table 2.9

SHIFT VALUES (ΔEu) FOR THE DIFFERENT PROTONS AND METHYL GROUPS IN II-49

	OH	H3	H5	H4	H2	H6	H7s	H7a	H1	$N-CH_3$
ΔEu(τ)	84.53	20.53	13.48	11.09	11.05	6.23	4.83	3.68	3.76	1.49
R (Å)	0.96	2.05	2.55	2.83	2.91	3.94	3.98	4.57	4.61	-

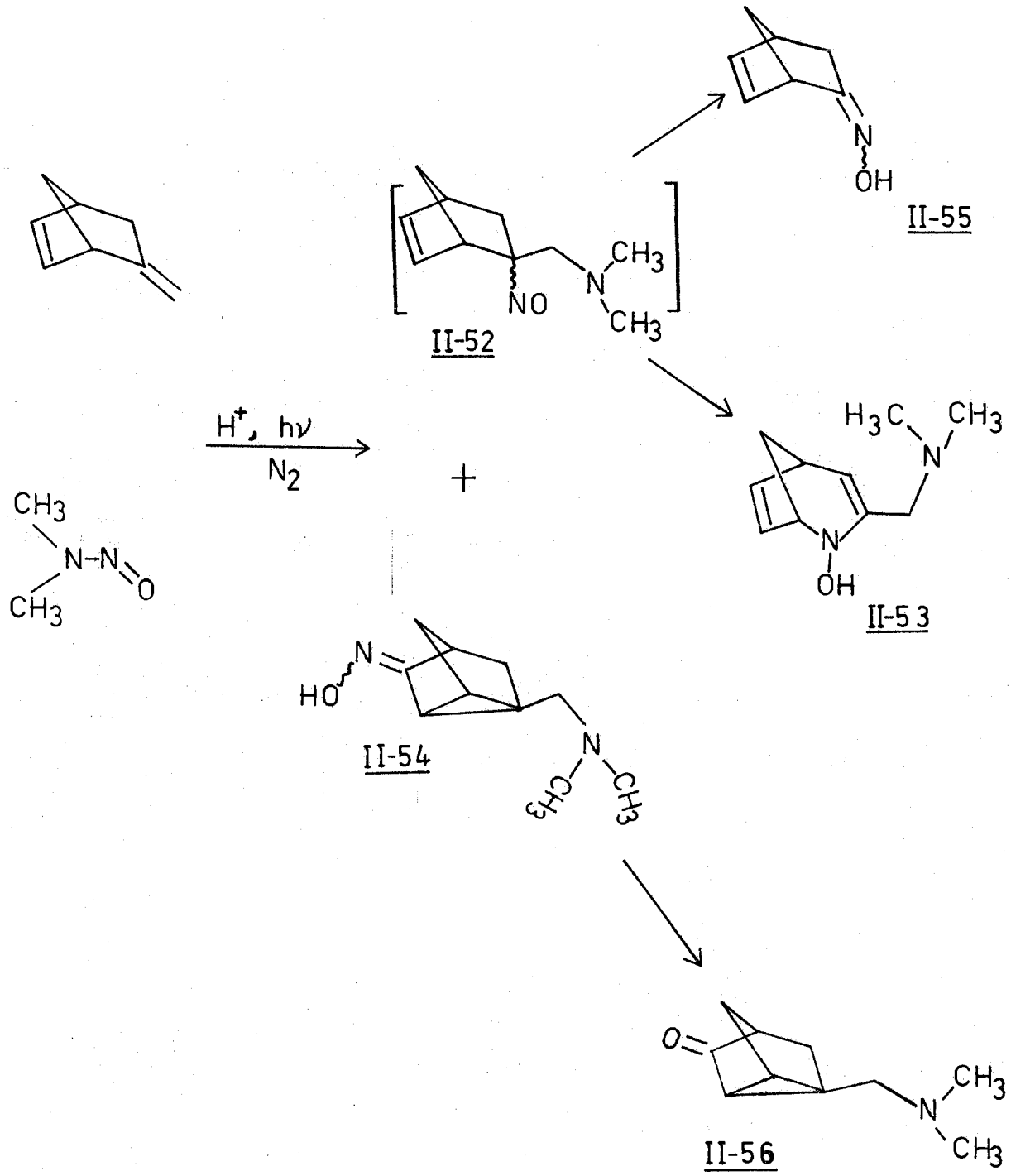
R is the distance between the hydroxyl oxygen atom and the protons in question measured on a Dreiding molecular model.



Scheme 2.11

2-2-6. Non-Oxidative Addition to 5-Methylenebicyclo[2,2,1]heptene

The non-oxidative photoaddition of NND to 5-methylenebicyclo[2,2,1] heptene with light >350 nm exhibited the emergence of a new absorption band at 295 nm which increased steadily to a maximum and then decreased slowly on further irradiation. The photolysis was discontinued when the 295 nm band reached its maximum intensity and the photolysate was worked up to give a crude mixture. The first fraction of the chromatography of this mixture afforded a blue liquid (colour is indicative of C-nitroso monomer) which showed u.v. absorptions at 207, 242 and 292 nm. It decolourized rapidly and the 292 nm absorption disappeared indicating rearrangement of the initially formed C-nitroso dimer to N-hydroxy-3-dimethylaminomethyl-2-azabicyclo[3,2,1]octa-3,6-diene (II-53, 23%), (Scheme 2.12). Compound II-53 was fairly stable at low temperature but slowly decomposed to a dark brown resin on prolonged standing at room temperature. Treatment with refluxing dilute hydrochloric acid resulted in decomposition to a complex mixture of products.



Scheme 2.12

The molecular formula of II-53 was ascertained by elemental analysis and high resolution mass spectrometry to be $C_{10}H_{16}N_2O$. The infrared spectrum exhibited prominent peaks at 3380, 1620, 1020, 930 and 845 cm^{-1}. The n.m.r. spectrum (Figure 2.10) showed three vinylic protons with one of them (C-4) appearing at considerably higher field (τ 5.5) than the other two which indicates that one of the double bonds is part of an enamine system [107]. Further, the CH_2-N protons were shifted downfield by ca. 0.6 ppm relative to the normally observed chemical shift (τ 7.5) indicating that they are attached to an allylic carbon [107].

The assignments of the ^{13}C resonance lines (Figure 2.11) are based on off-centre resonance decoupling experiments. The C-6 and C-7 carbons showed chemical shifts comparable to similar olefinic carbons in other bicyclic systems [113]. However, the olefinic carbon C-3 showed a very large shift (169.8 ppm from TMS) while C-4 appeared at considerably higher field (83.7 ppm from TMS) in accordance with the expected ^{13}C chemical shifts for the enamine type structure in II-53 [113,114].

The mass spectrum of II-53 (Figure 2.12) showed intense peaks at m/e 137 and 120 that were confirmed by high resolution mass spectroscopy to be $C_8H_{11}NO^{+\cdot}$ and $C_8H_{10}N^{+\cdot}$ fragments, respectively. The fragmentation pattern can be rationalized as shown in Scheme 2.13.

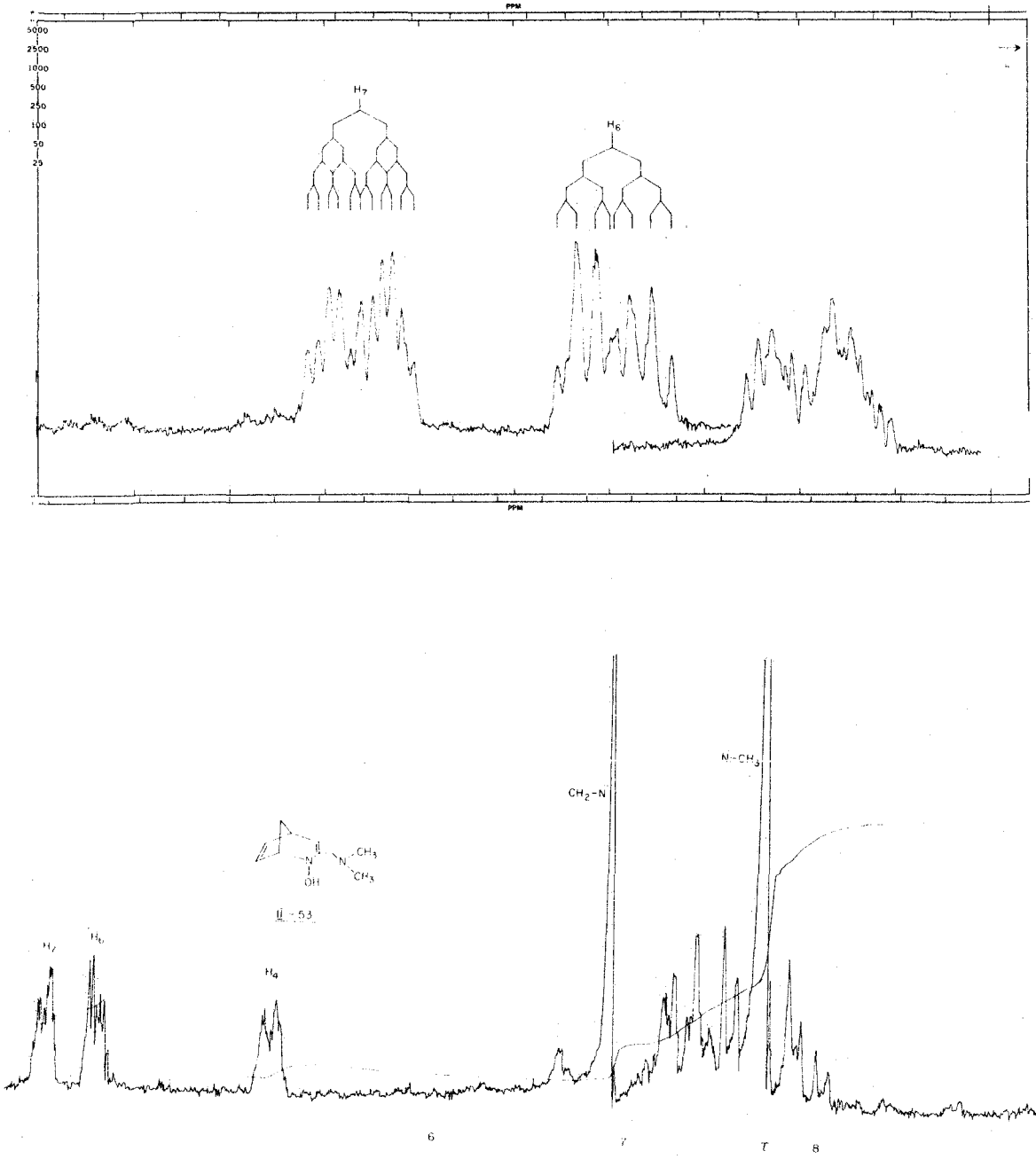


Figure 2.10 n.m.r. spectra (100 MHz) of N-hydroxy-3-dimethylamino-methyl-2-azabicyclo[3,2,1]octa-3,6-diene (II-53).

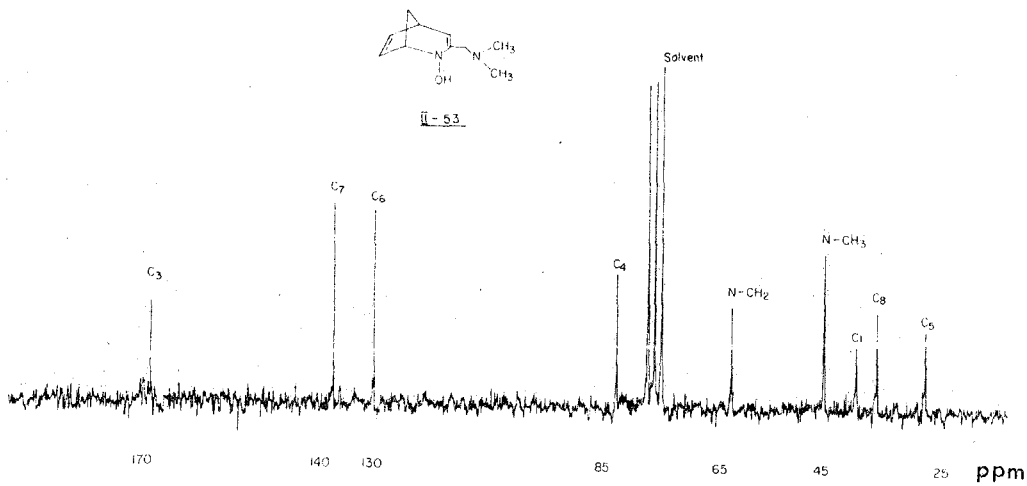
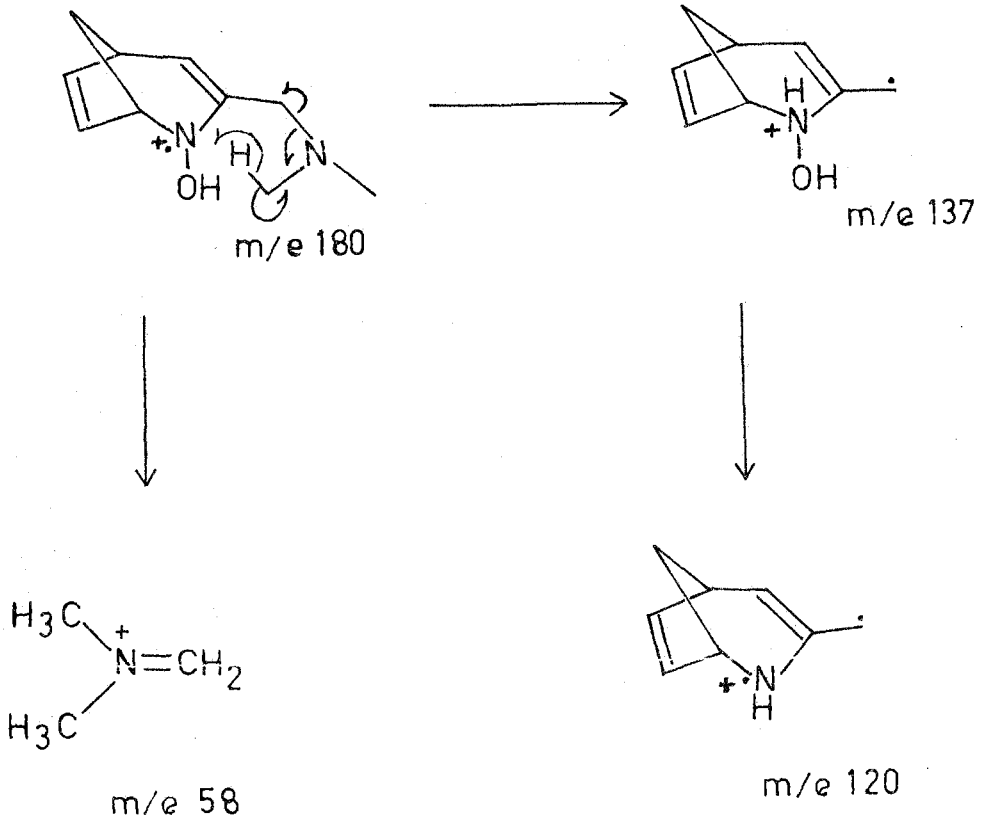
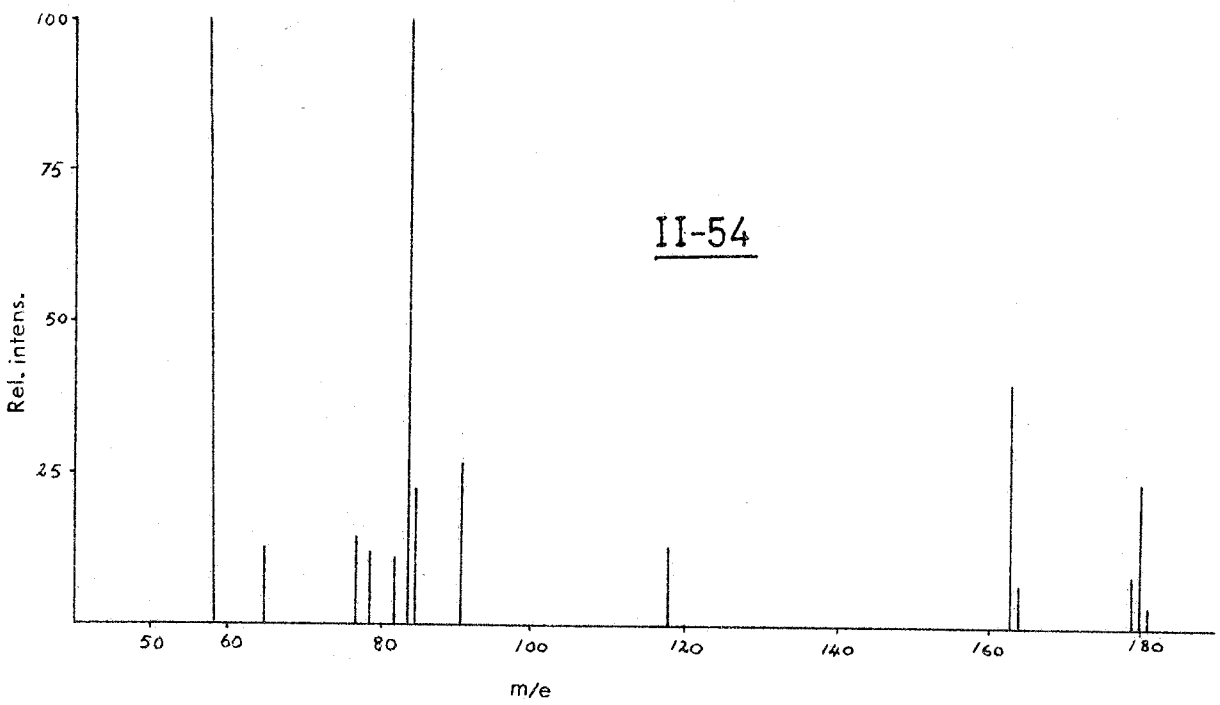


Figure 2.11 n.m.r. (^{13}C) spectra of N-hydroxy-3-dimethylamino-methyl-2-azabicyclo[3,2,1]octa-3,6-diene (II-53).



Scheme 2.13

The second major fraction isolated by chromatography was a mixture of syn- and anti-2-dimethylaminomethyltricyclo[2,2,1,$0^{2,6}$] heptan-5-one oxime (II-54, 18%) as shown by spectroscopic analysis. It exhibited i.r. absorptions at 1000-900 cm^{-1} characteristic for an oximino group and an n.m.r. singlet at τ 7.77 for the N-CH_3 protons. The mass spectrum of II-54 (Figure 2.12) showed the molecular ion peak at m/e 180 and the (M^+-OH) peak at m/e 163.



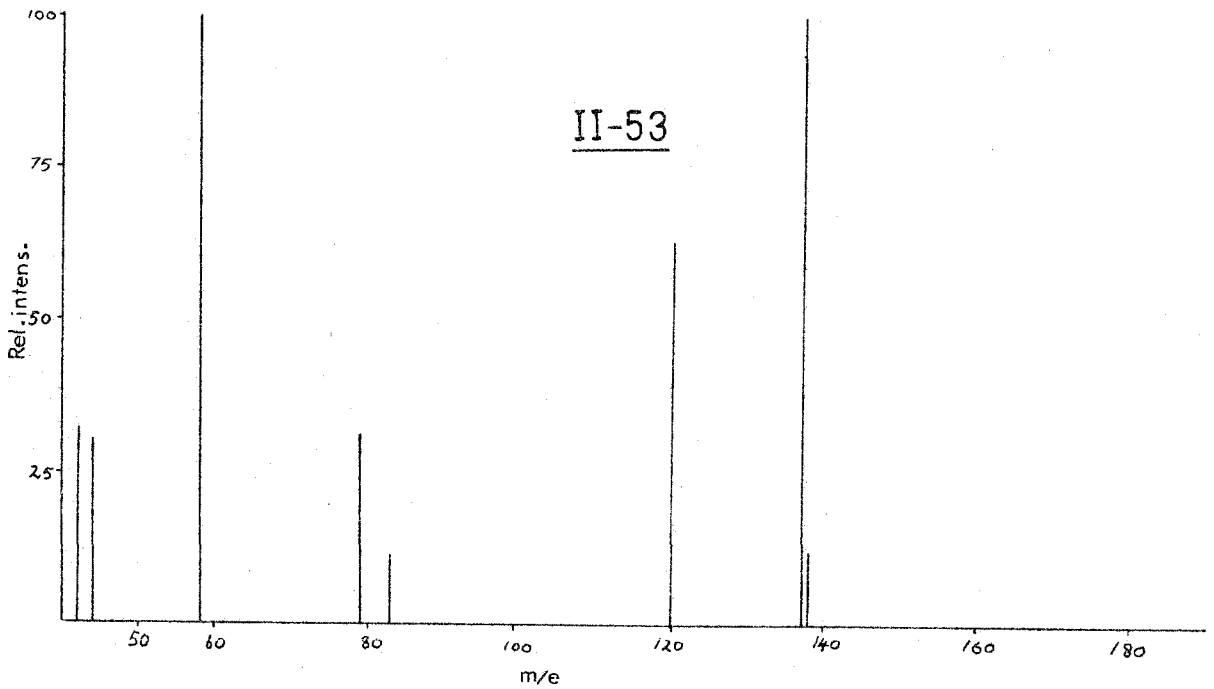


Figure 2.12 Mass spectra (80 ev) of N-hydroxy-3-dimethylaminomethyl-2-azabicyclo[3,2,1]octa-3,6-diene (II-53) and 2-dimethylaminomethyltricyclo[2,2,1,$0^{2,6}$]heptan-5-one oxime (II-54).

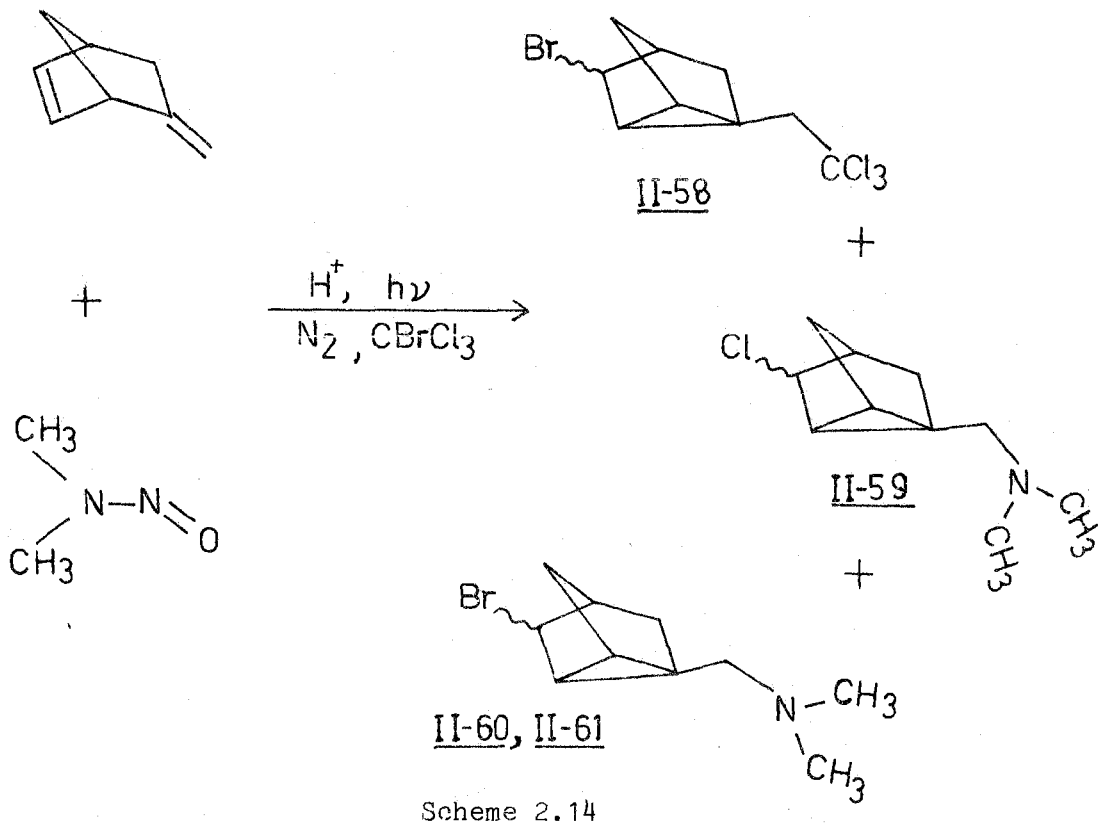
A third chromatographic fraction contained a major compound which was tentatively assigned as bicyclo[2,2,1]heptenone oxime (II-55, <4%) on the basis of a two-proton n.m.r. multiplet at τ 4.02 due to the olefinic protons and of the typical oximino absorptions in its i.r. spectrum.

When the non-oxidative photoaddition of NND was carried to completion, as evidenced by the complete disappearance of the 342 nm absorption, compounds II-53 (14%), II-54 (15%) and 2-dimethylamino-methyltricyclo[2,2,1,$0^{2,6}$]heptan-5-one (II-56, 10%) were obtained. The carbonyl stretching frequency of II-56 at 1755 cm^{-1} was identical to that reported [105] for the tricyclic ketone II-57. The i.r. spectrum also showed absorptions at 840, 830 and 820 cm^{-1} characteristic for a substituted nortricyclene skeleton. In the n.m.r. spectrum of II-56, the cyclopropyl proton at C-6 appeared as a doublet at τ 8.92 with a coupling constant of 5.5 Hz (J1,6) as expected for a nortricyclic compound [106,108; see also Section 2-2-5).

The crude oxime II-54 obtained by chromatography was contaminated by II-55 and was hydrolyzed with sodium hydrogen-sulfite to give the tricyclic ketone II-56 in 26% yield.

When the non-oxidative photoaddition was carried out in bromotrichloromethane instead of methanol, a new peak emerged at 314 nm due to trichloronitrosomethane [115] which co-distilled with

the solvent. The residue afforded a small amount of precipitate which was shown by t.l.c. to be a mixture of two compounds. The i.r. spectrum of this solid showed characteristic absorptions for a substituted nortricyclene skeleton but no absorptions for an olefinic function. Its mass spectrum showed the presence of three chlorine and one bromine atoms in the molecule as indicated by the molecular ion peaks at m/e 308, 306, 304 and 302 and $(M-Br)^+$ peaks at m/e 227, 225 and 223.



Scheme 2.14

On these grounds, the two compounds were tentatively assigned as stereoisomers of 2-(2 ,2 ,2 -trichloroethyl)-5-bromotricyclo [2,2,1,$0^{2,6}$]heptane (II-58, 3%).

The basic residue was shown by g.c.-m.s. to be a mixture of two major and one minor compounds. Both major compounds exhibited the same fragmentation pattern and showed molecular ion peaks at m/e 231 and 229 indicating the presence of one bromine atom. The minor component contained one chlorine atom as shown by molecular ion peaks at m/e 187 and 185 and at m/e 150 for M^+-Cl. This compound was tentatively assigned as 2-dimethylaminomethyl-5-chlorotricyclo[2,2,1,$0^{2,6}$]heptane (II-59).

Chromatographic separation of this mixture afforded two pure compounds which were found to be the C-5 configurational isomers of 2-dimethylaminomethyl-5-bromotricyclo[2,2,1,$0^{2,6}$]heptane (II-60 and II-61) from their spectral data. Their infrared spectra were very similar except for a few details and contained Bohlmann bands at 2820 and 2775 cm^{-1} and the characteristic absorptions at 3060, 830 and 800 cm^{-1} for a substituted nortricyclene. The n.m.r. spectra of II-60 and II-61 and the assignments are shown in Table 2.10 and Figures 2.13 and 2.14. The observed coupling constants $J_{4,5}$ and $J_{5,6}$ (1.5 Hz) were identical for both compounds regardless of the orientation of the C-5 proton in agreement with other results (see also compounds II-49 and II-50 in Section 2-2-5 and Refs. 81,108). In both cases the cyclopropyl hydrogens gave an AB quartet pattern (J_{AB} = 5.5 Hz), each line of which was further split due to coupling with other protons with a J-value of approximately 1.5 Hz [81,108]. The mass spectra of

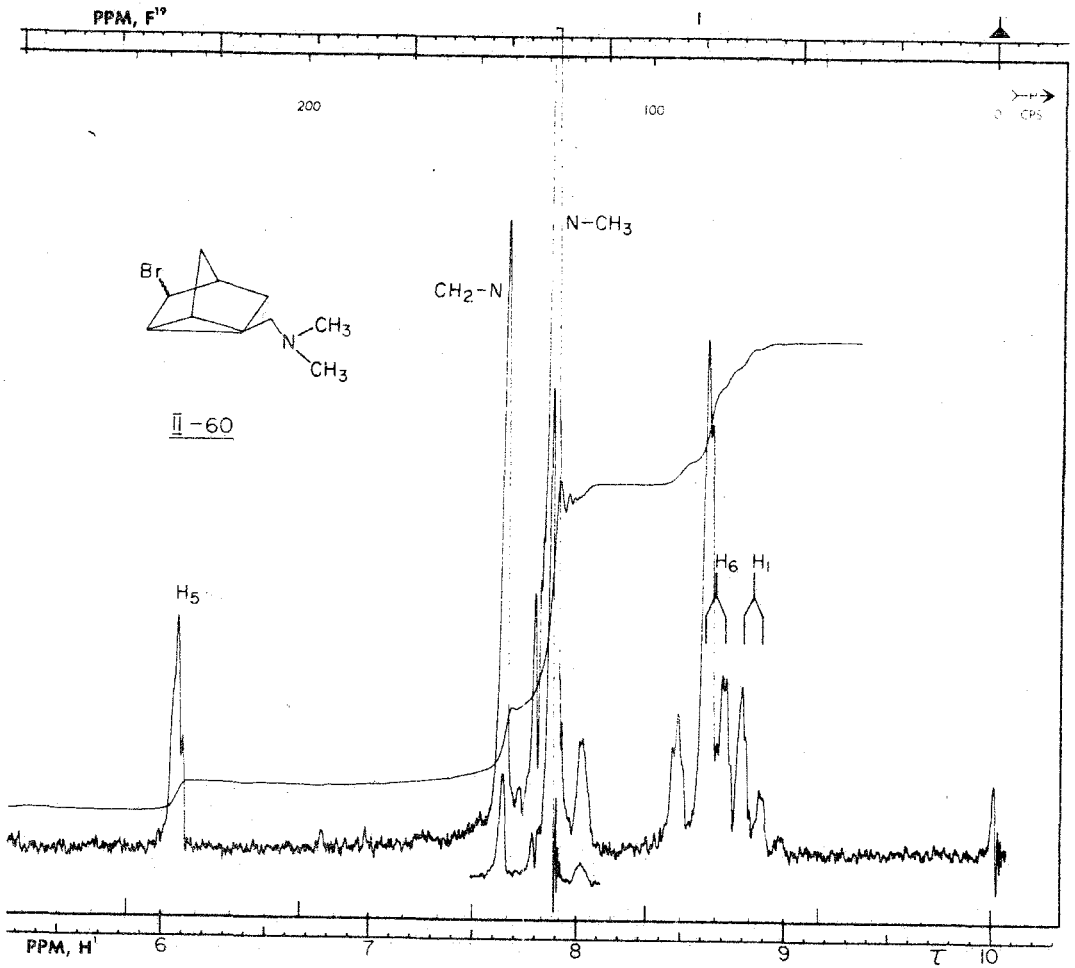


Figure 2.13 n.m.r. spectra (60 MHz) of 2-dimethylaminomethyl-5-bromotricyclo[2,2,1,$0^{2,6}$]-heptane (II-60).
Solvent: CCl_4.

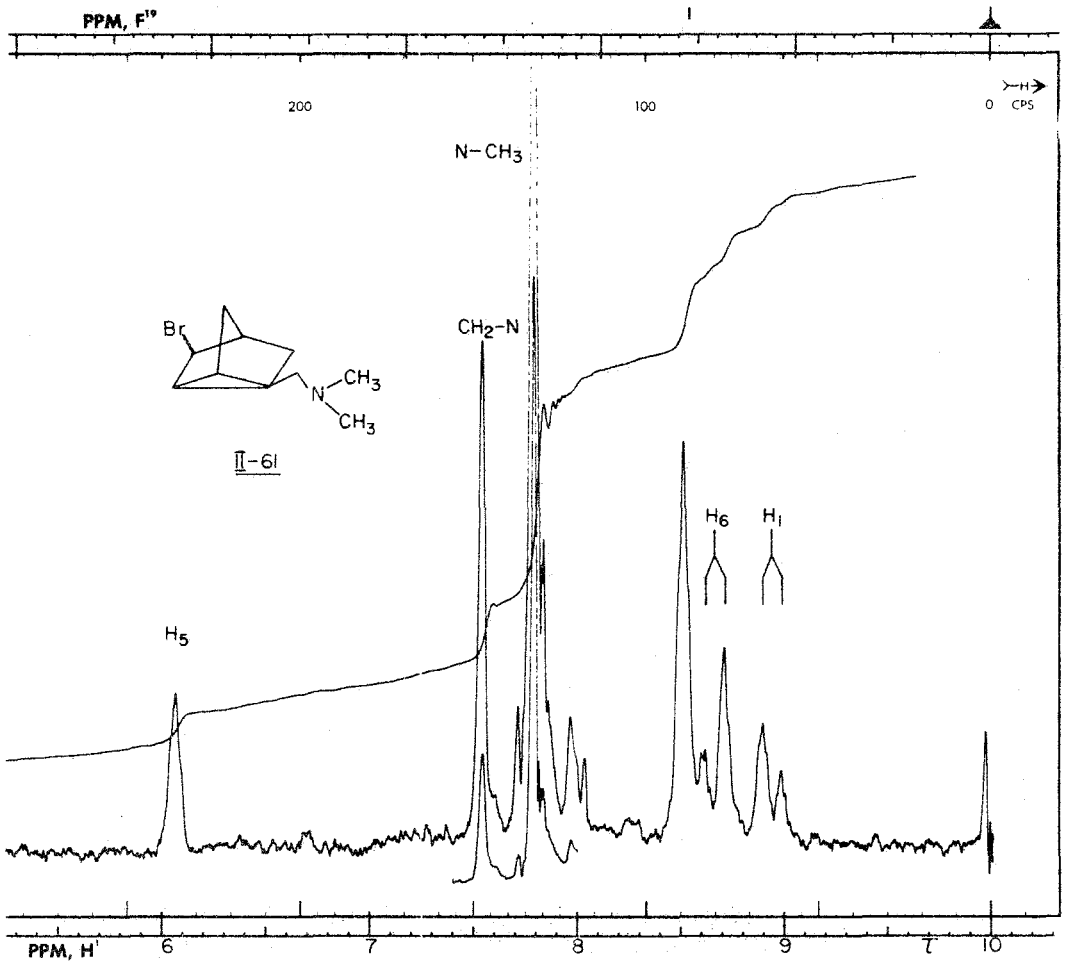
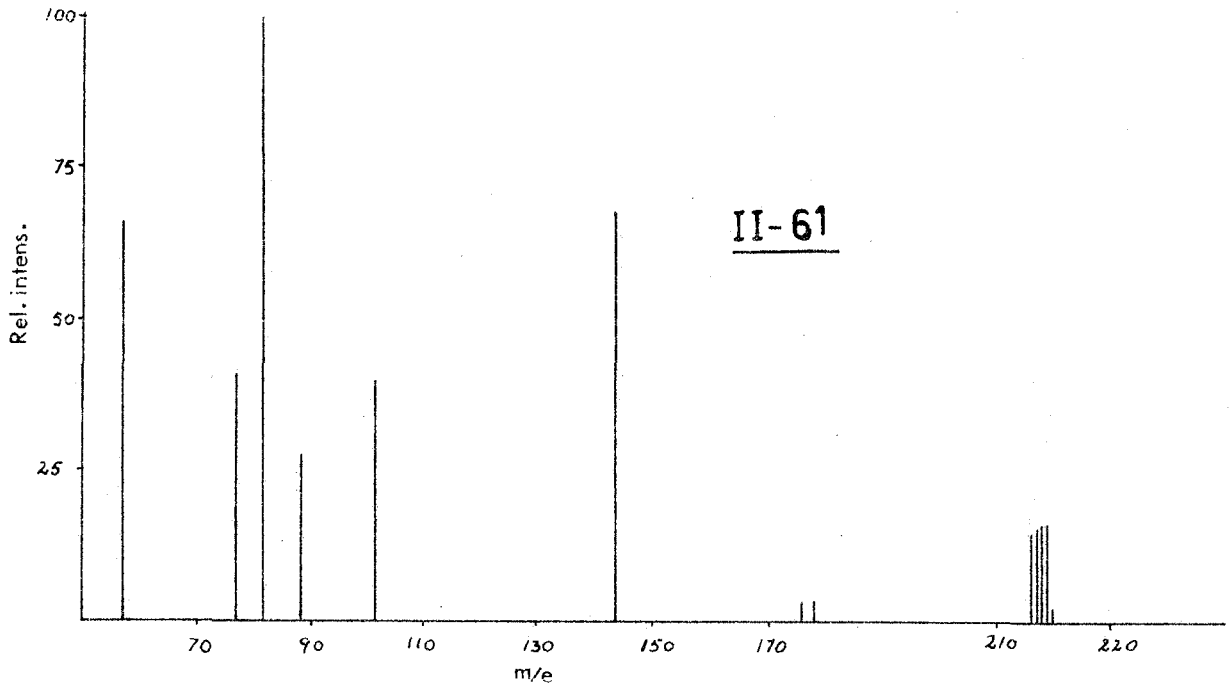


Figure 2.14 n.m.r. spectra (60 MHz) of 2-dimethylaminomethyl-5-bromotricyclo[2,2,1,$0^{2,6}$]-heptane (II-61).

Solvent: CCl_4



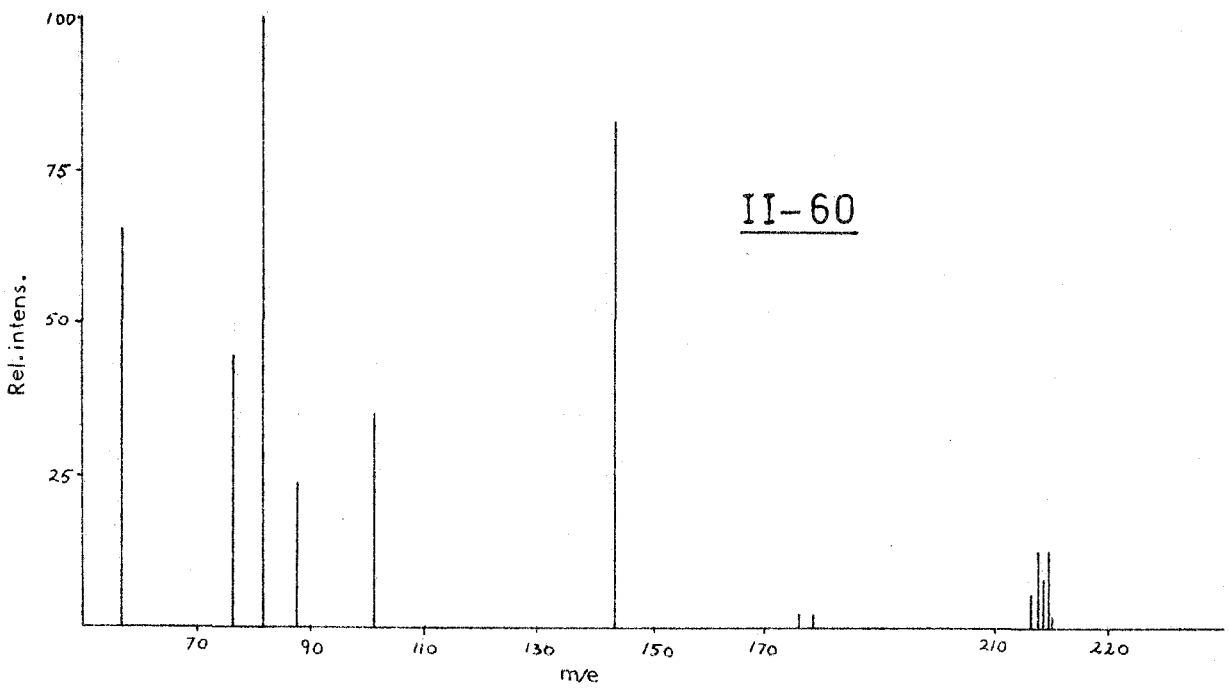


Figure 2.15 Mass spectra (80 ev) of 2-dimethylaminomethyl-5-bromotricyclo[2,2,1,$0^{2,6}$]heptane (II-60, II-61).

II-60 and II-61 were also strikingly similar except that the intensity ratios of the molecular ion peaks (M^+, m/e 231 and 229) and the M^+-1 peaks were different (Figure 2.15). Although these results showed II-60 and II-61 to be isomeric at C-5, a decision as to which compound had the endo- and which the exo-bromine configuration was difficult to make on the basis of the available data.

Table 2.10

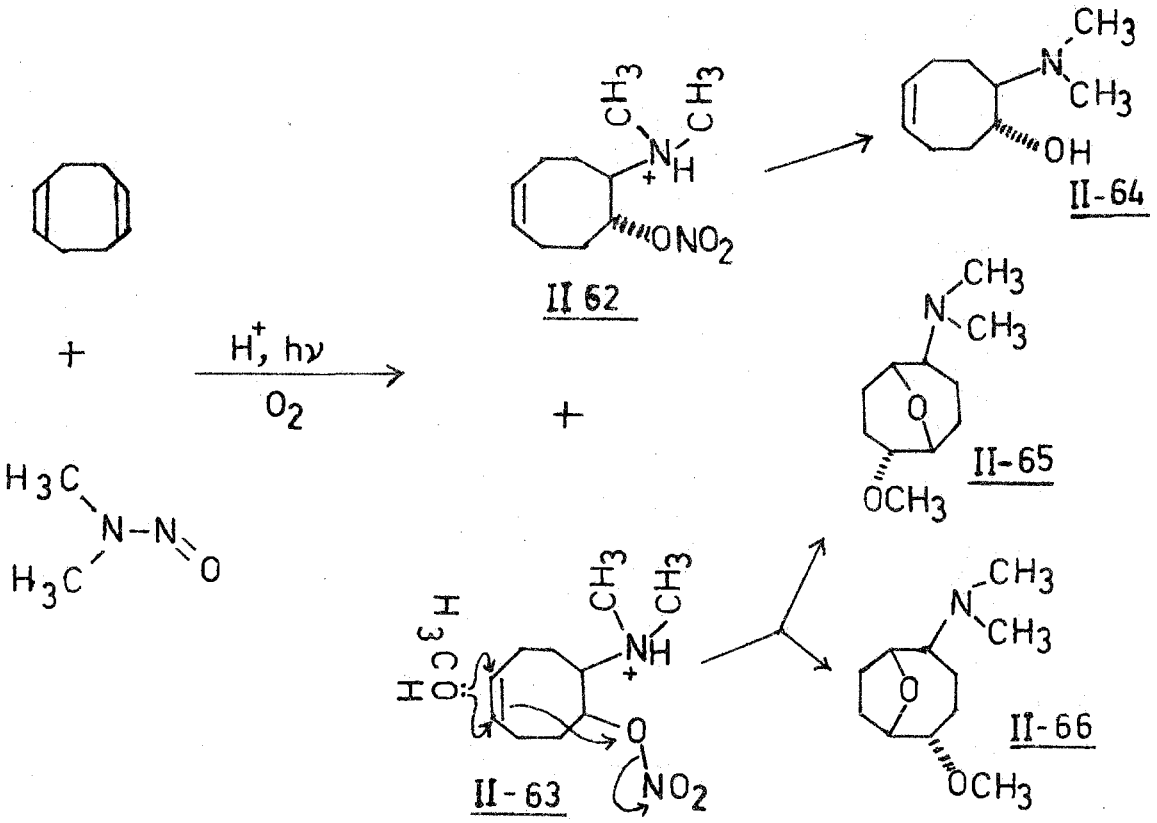
n.m.r. PARAMETERS

Proton	II-60	II-61
1	8.83 (d) J1,6 = 5.5 Hz J1,7 = 1.5 Hz	8.94 (d) J1,6 = 5.5Hz J1,7 = 1.5 Hz
5	6.06 (t) J4,5 = J5,6 = 1.5 Hz	6.08 (bs)
6	8.68 (d)	8.68 (d)
3n		7.88 (m)[a]
4	7.90 (m)	
7s		
7a	8.60 (m)	8.53 (m)
3x		
$N-CH_2$	7.63 (bs)	7.57 (bs)
$N-CH_3$	7.85 (s)	7.82 (s)

a: - partly masked by $N-CH_3$ peak; solvent CCl_4

2-2-7. Oxidative Addition to 1,5-Cyclooctadiene

The oxidative photoaddition of NND to 1,5-cyclooctadiene was carried out under the usual conditions followed by the work-up to afford a basic fraction which exhibited strong infrared bands at 1615, 1275 and 860 cm^{-1} characteristic for a nitrate ester as well as n.m.r. signals at τ 4.37 for olefinic protons and a methoxy singlet at 6.65. Reduction of the crude basic fraction with lithium aluminium hydride followed by the chromatographic separation afforded trans-2-dimethylamino-5-cycloocten-1-ol (II-64) as the major product (Scheme 2.15).



Scheme 2.15

Elemental analysis and high resolution mass spectrometry established the molecular formula of alcohol II-64 as $C_{10}H_{19}NO$. The infrared spectrum showed characteristic hydroxyl bands at 3360 and 1045 cm^{-1} and cis-RCH = CHR bands at 3010 and 715 cm^{-1}. The n.m.r. spectrum of II-64 and some spin decoupled spectra are shown in Figure 2.16 along with computer simulated spectra for the olefinic, C-1 and C-2 regions. The C-1 proton was vicinally coupled to the C-2 proton with a coupling constant of 9.0 Hz, the magnitude of which suggested that they were in a nearly anti-configuration. The configuration and conformation of the ring were further indicated by the splitting patterns and the coupling constants of the C-1 (J = 9.0, 7.0 and 3.0 Hz) and the C-2 proton (J = 10.5, 9.0 and 4.0 Hz). The configuration and conformation of II-64 will be discussed later.

The two other minor products isolated by chromatography were endo-2-methoxy-exo-6-dimethylamino-9-oxabicyclo[3,3,1]nonane (II-65) and endo-2-methoxy-exo-5-dimethylamino-9-oxabicyclo[4,2,1]nonane (II-66). The oxabicyclic compounds were shown by elemental analysis and high resolution mass spectrometry to have the molecular formula $C_{11}H_{21}NO_2$. Their i.r. and n.m.r. spectra showed the absence of unsaturation and of hydroxyl groups but the presence of an ether function (1100 cm^{-1}).

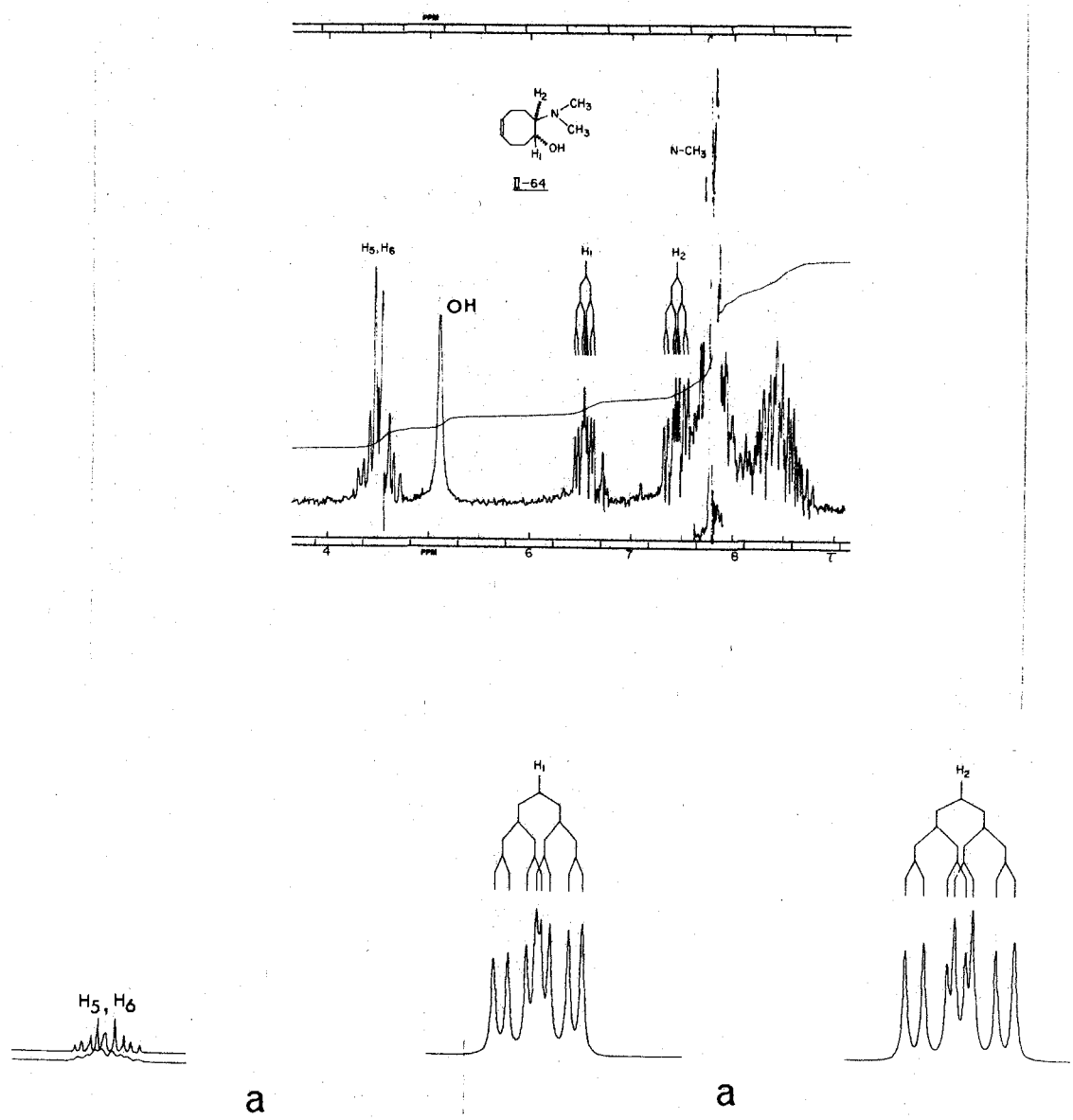
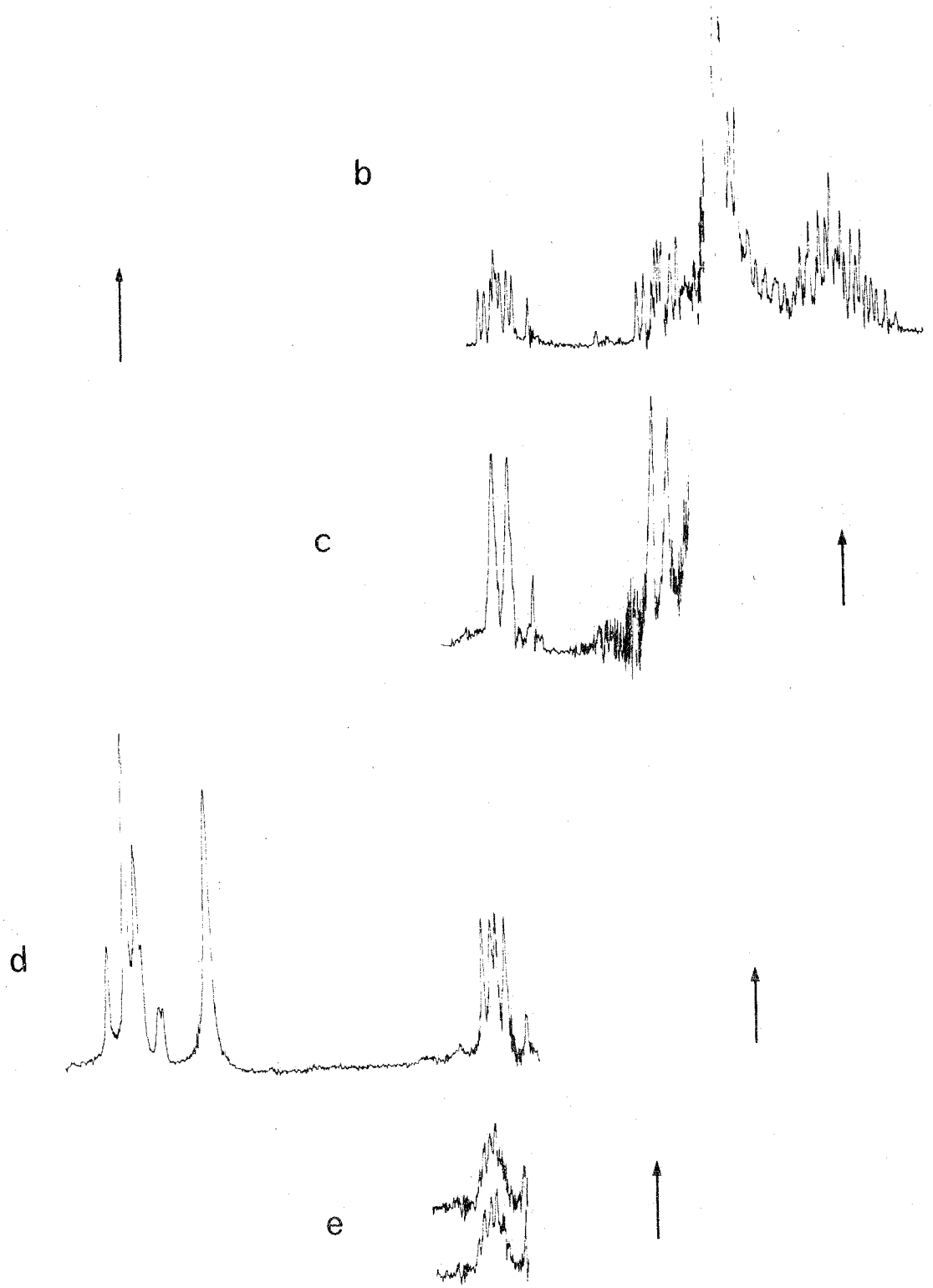


Figure 2.16 n.m.r. spectra (100 MHz) of trans-2-dimethylamino-5-cycloocten-1-ol (II-64):
a, computer simulated spectrum;
b, double irradiation of the C-5 and C-6 protons;
c, double irradiation of the C-3 and C-8 protons;
d, double irradiation of the C-4 and C-7 protons;
e, double irradiation of the C-2 proton.

(Figure 2.16 continued on next page)


b
c
d
e

The oxabicyclic compounds II-65 and II-66 exhibited distinctly different n.m.r. spectra the parameters of which are summarized in Tables 2.11 and 2.12. The observed chemical shift values (τ 6.10 and τ 5.56) for the bridge-head protons in these compounds were comparable to those reported for similar systems [116]. The C-2 and C-6 methine protons of II-65 appeared as double triplets at τ 6.49 (J=11.0 and 5.5 Hz) and at τ 7.74 (partly hidden under the $N-CH_3$ signal, J = 11.0 and 4.5 Hz) indicating axial orientations. The pseudo-axial orientations of the corresponding protons (C-2 and C-5) of II-66 were assigned on the basis of the half-height width of the multiplets due to these protons.

The mass spectra of II-65 and II-66 were obtained under identical conditions and are shown in Figure 2.17. Both of these compounds exhibited the prominent molecular ion peak at m/e 199 and II-66 showed an intense peak at m/e 168 (M^+-OCH_3). The fragmentation patterns can be readily explained on the basis of the assigned structures as shown in Scheme 2.16.

Table 2.11

CHEMICAL SHIFTS (τ)

Proton	II-64	II-65	II-66
2	7.39 (ddd)	6.49 (dt)	6.58 (m)[a]
5	4.56(ABX_2X_2')		7.5 (m)[b]
1	6.49 (ddd)	6.10 (m)	
6	4.35 (ABX_2X_2')	7.74 (dt)	5.56 (m)
4,7	7.52-7.99 (m)		
3,8	8.38 (m)	8.13 (m)	8.2 (m)
$N-CH_3$	7.72 (s)	7.77 (s)	7.71 (s)
$O-CH_3$	-	6.66 (s)	6.65 (s)
OH	5.06 (bs)	-	-

a: - Partly masked by $O-CH_3$ peak
b: - Partly masked by $N-CH_3$ peak
Solvent: - $CDCl_3$

Table 2.12

COUPLING CONSTANTS (Hz)

Compound	$J_{1,2}$	$J_{1,8}$	$J_{2,3}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$
II-64	9.0	7.0 3.0	10.5 4.0	5.0	11.5 4.5	7.0
II-65	5.5		11.0 11.0			11.0 11.0

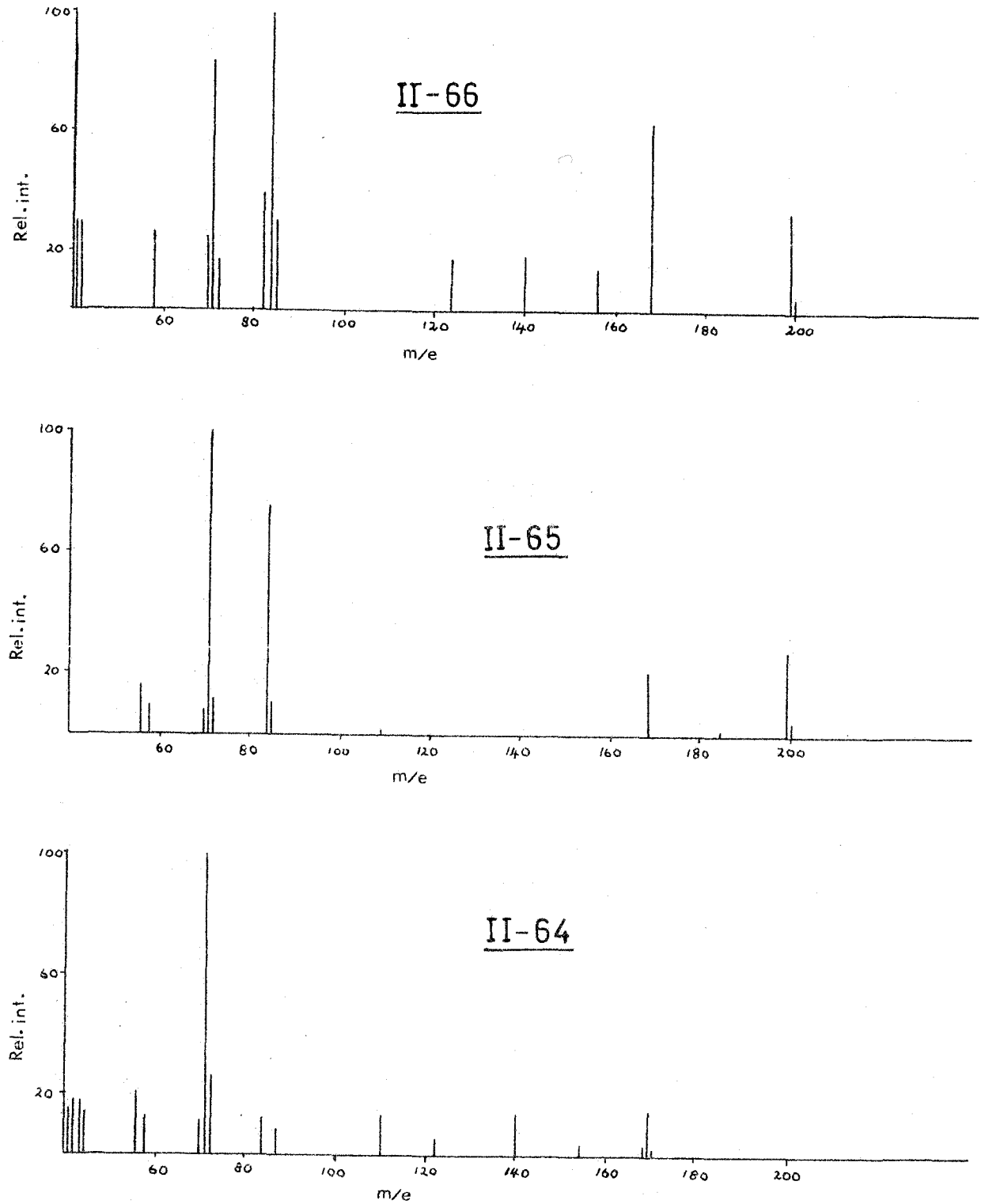
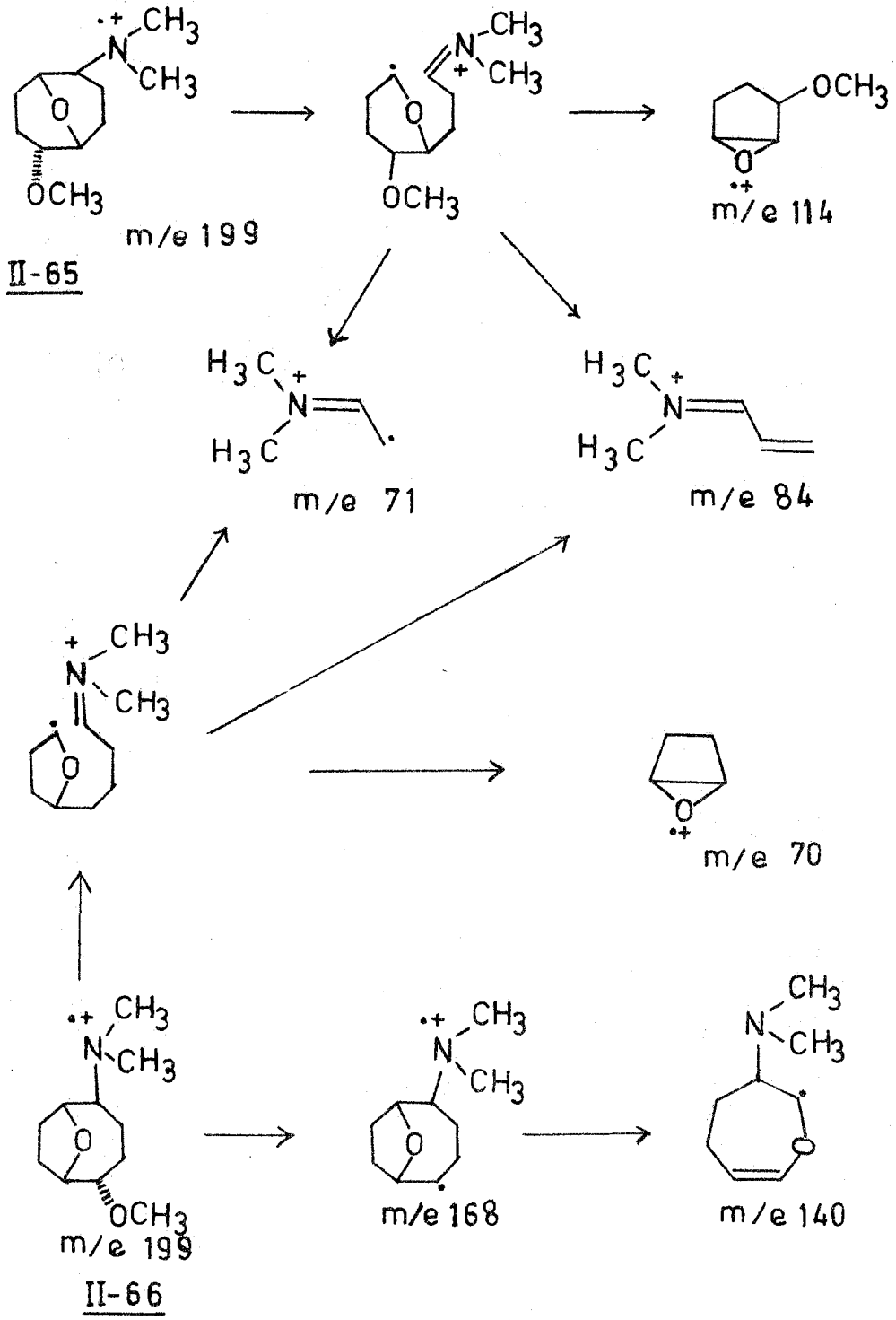


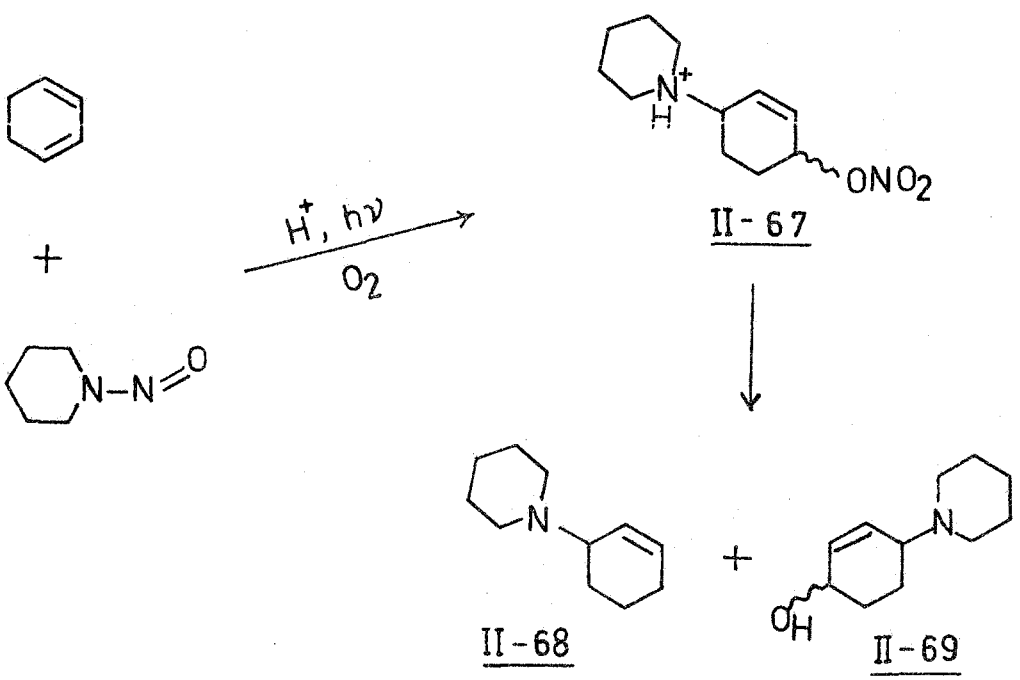
figure 2.17 Mass spectra (80 ev) of trans-2-dimethylamino-5-cycloocten-1-ol (II-64), endo-2-methoxy-exo-6-dimethylamino-9-oxabicyclo[3,3,1]nonane (II-65) and endo-2-methoxy-exo-5-dimethylamino-9-oxabicyclo[4,2,1]nonane (II-66).



Scheme 2.16

2-2-8. OXIDATIVE ADDITION TO 1,3-CYCLOHEXADIENE

The oxidative photoaddition of NNP (or NND) to 1,3-cyclohexadiene apparently resulted in the formation of cis and trans-1-nitrato-4-piperidino-2-cyclohexene (II-67) which, when extracted into ether from a basified photolysate, changed colour gradually and, on evaporation of ether, decomposed violently to a dark tar. Immediate reduction of the ether solution of the crude basic fraction



Scheme 2.17

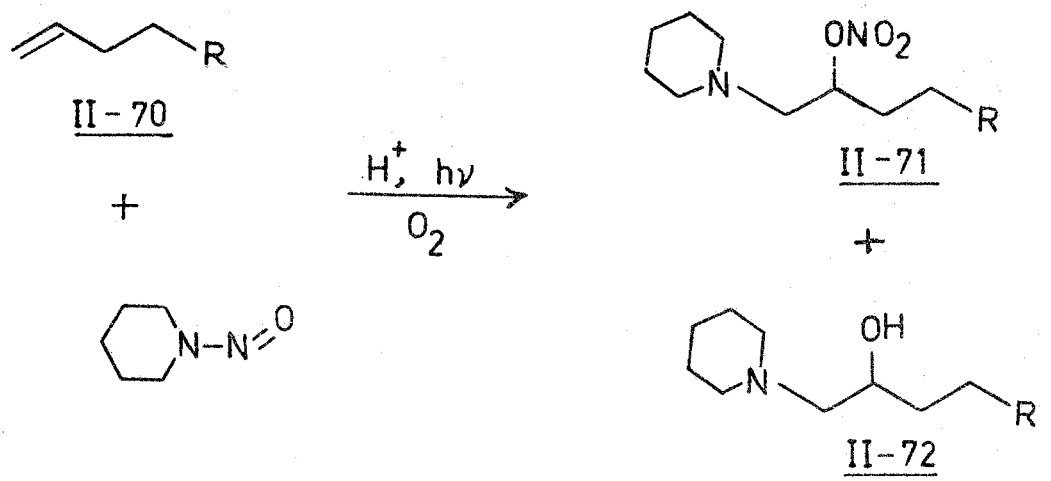
with lithium aluminium hydride followed by chromatography gave 3-piperidinocyclohexene (II-68, 20%) as the major product. Elemental analysis as well as high resolution mass spectrometry established the molecular formula of II-68 as $C_{11}H_{19}N$. The infrared spectrum showed absorptions at 2800, 2750 and 2680 cm^{-1} assigned to Bohlmann bands and at 3020 and 725 cm^{-1} to cis- RCH = CHR bands. The n.m.r. spectrum of II-68 showed a two proton multiplet at τ 4.41 for the vinyl protons. The C-3 methine proton geminal to the piperidine ring appeared as a multiplet at τ 6.9 (W1/2 = 12 H_z) and the two allylic protons as another multiplet at τ 8.0, both of which were established to be coupled to the vinyl protons.

The mass spectrum of II-68 exhibited a prominent molecular ion peak at m/e 165 and intense peaks at m/e 137 and 111 which were confirmed to be $C_9H_{15}N^{+}\cdot$ and $C_7H_{13}N^{+}\cdot$, respectively, by high resolution mass spectral measurements.

The minor product, 4-piperidino-2-cyclohexenol (II-69), could not be obtained in pure form but its presence was indicated by spectral data. The presence of the hydroxyl group was indicated by typical infrared absorptions at 3350 and 1060 cm^{-1} and the olefinic group by the n.m.r. multiplet at τ 4.3.

2-2-9. Oxidative Addition to 3-Butenyl Compounds

The oxidative photoaddition of NNP to various 3-butenyl derivatives was investigated and the results are summarized in Table 2.13. The photoaddition was carried out in the presence of perchloric acid using a nonex filter to cut off light below 350 nm. After the usual work-up, the products were identified by spectroscopic methods and by preparation of derivatives as noted below and described in the Experimental Section.



R

a,	OH	e,	$OCO.C_6H_4CN$
b,	$OCO.CH_3$	f,	Cl
c,	$OCO.C_6H_4CH_3$	g,	Br
d,	$OCO.C_6H_4OCH_3$	h,	$OSO_2.C_6H_4CH_3$

Scheme 2.18

Table 2.13

OXIDATIVE ADDITION OF NNP TO

3-BUTENYL COMPOUNDS

Olefin II-70	% Yield of Adduct (II-71 + II-72)
a	72.8
b	80.1
c	26.1
d	31.5
e	32.8
f	38[a]
g	46[a]
h	0

a: - isolated as azoniaspiro compound II-74 (vide infra)

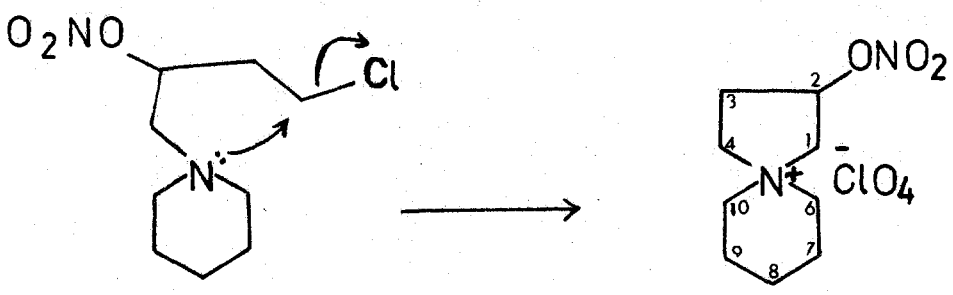
The oxidative photoaddition of NNP to 3-butenol (II-70a) afforded 3-nitrato-4-piperidinobutan-1-ol (II-71a, 51%) and 4-piperidinobutane-1,3-diol (II-72a, 21%). The infrared spectrum of nitrate II-71a contained characteristic bands at 1625, 1275 and 865 cm^{-1} for a nitrate ester and at 3370 and 1055 cm^{-1} for an hydroxyl function. Reduction of II-71a with lithium aluminium hydride gave the corresponding alcohol II-72a (i.r. absorptions at 3370 and 1150 cm^{-1}) in high yield. Attempted tosylation of II-72a in pyridine was not successful; N-tosylpiperidine was the only isolable product. Treatment of II-72a with p-nitrobenzoyl chloride in tetrahydrofuran [117] gave the hydrochloride of 3-hydroxy-4-piperidinobutyl-p-nitrobenzoate (II-73) in 60% yield. This compound showed prominent infrared bands at 1720 and 1285 cm^{-1} for an ester group and at 3260 cm^{-1} for an hydroxyl group.

The oxidative photoaddition of NNP to 3-butenyl acetate (II-70b) afforded a mixture of 3-nitrato-4-piperidinobutyl acetate (II-71b) and 3-hydroxy-4-piperidinobutyl acetate (II-72b) in the approximate ratio 1:1. This mixture showed typical infrared bands at 1740 and 1240 cm^{-1} for an acetate group, at 1630, 1280 and 865 cm^{-1} for a nitrate ester and at 3440 and 1045 cm^{-1} for an hydroxyl group. Reduction of this mixture with lithium aluminium hydride gave diol II-72a in an overall yield of 80%.

The oxidative and non-oxidative photoaddition of NNP to 3-butenyl tosylate (II-70h) failed to yield any adducts; the unreacted olefin was recovered quantitatively. However, the u.v. absorption due to the nitroso chromophore disappeared during the irradiation and NNP decomposition products such as piperidine and dipiperidinomethane were isolated in the basic fraction.

The oxidative photoaddition of NNP to p-substituted 3-butenyl benzoates (II-70c to II-70e), on the other hand, afforded adducts in 26-33% yield and the unreacted olefin was recovered in the neutral fraction. The crude adducts isolated in the usual manner contained nitrate II-71 and alcohol II-72 in approximately equal amounts. Hydrogenation of the mixture in methanol in the presence of platinum oxide gave the corresponding alcohols II-72.

The oxidative photoaddition of NNP to 3-butenyl chloride and 3-butenyl bromide gave the perchlorate salt of the expected adduct which on basification spontaneously cyclized to give the perchlorate of 2-nitrato-5-azoniaspiro[4,5]decane (II-74, 38-46%) which was isolated from the aqueous basic fraction by continuous extraction.



II-71f

II-74

The compound II-74 analyzed correctly for $C_9H_{17}N_2O_7Cl$ and its infrared spectra exhibited characteristic bands for a nitrate ester at 1643, 1293 and 870 cm^{-1}. The n.m.r. spectrum of II-74 and the assignments are shown in Figure 2.18. These assignments were confirmed by appropriate spin decoupling experiments. The lowest field signal (τ 4.04) was assigned to the C-2 proton geminal to the nitrate group, and the next lowest field resonance (τ 5.77) to the C-1 protons. The latter were geminally coupled to each other (J = 14 Hz) and vicinally coupled to the C-2 proton (J =

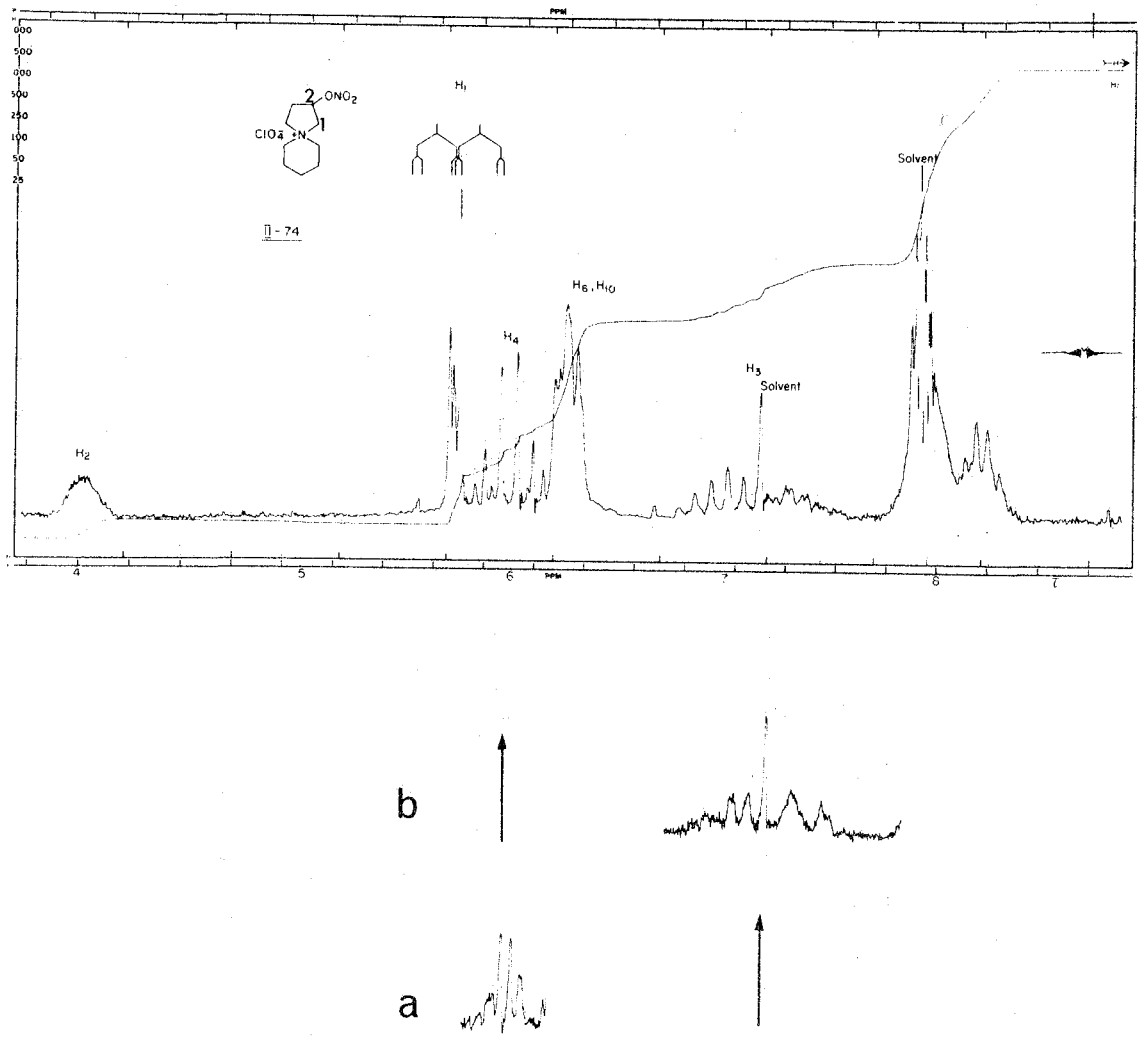
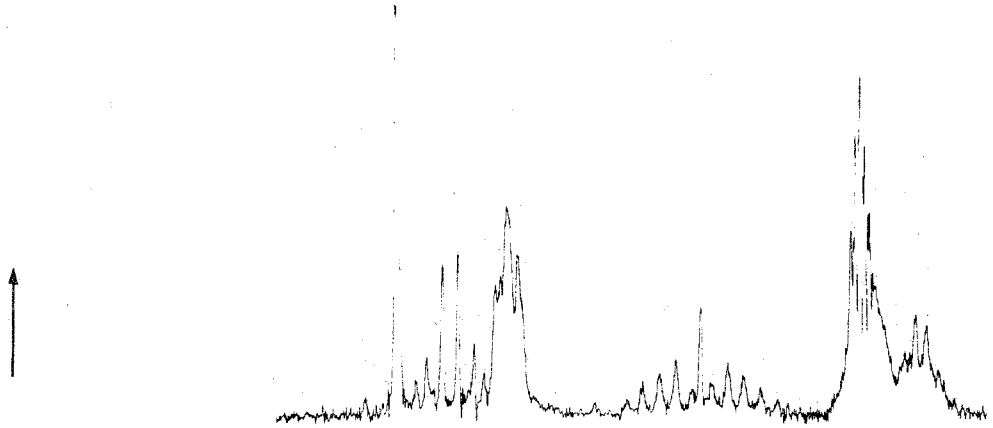


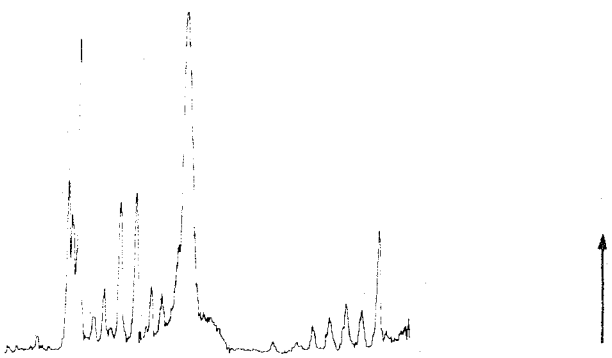
Figure 2.18 n.m.r. spectra (100 MHz) of the perchlorate of 2-nitrato-5-azoniaspiro[4,5]decane (II-74): Solvent: Acetone $-d_6$
a, double irradiation of the C-3 protons;
b, double irradiation of the C-4 protons;
c, double irradiation of the C-2 proton;
d, double irradiation of the C-7, C-8 and C-9 protons.

(Figure 2.18 continued on next page)

c



d



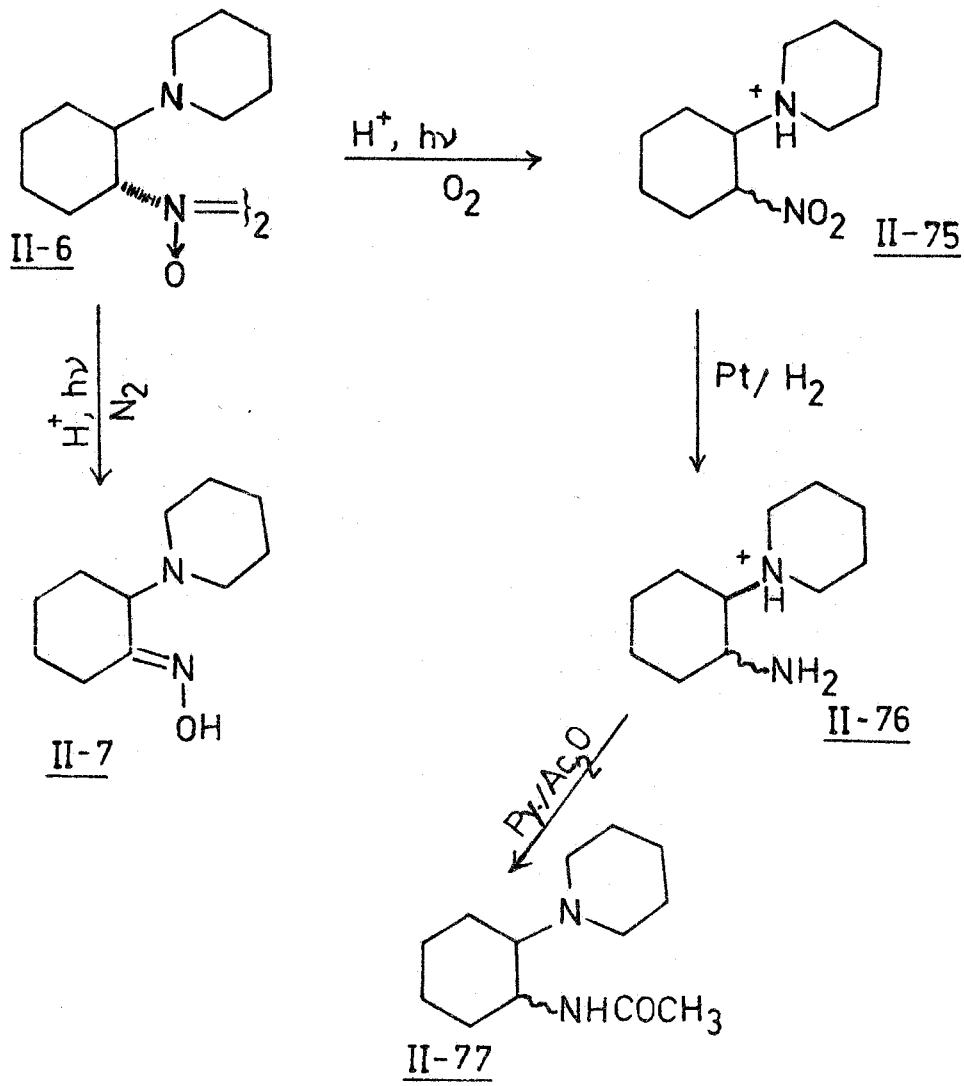
5.0 and 3.5 Hz). Irradiation of the C-4 protons at 6.02 (ABXX' pattern with J_{gem} = 5 Hz) showed that the C-3 protons (7.18) were geminally coupled to each other (J = 16 Hz) and vicinally coupled to the C-2 proton with coupling constants of 7 and 4 Hz.

2-3. Oxidative and Non-Oxidative Photodecomposition of C-Nitroso Compounds

Since all C-nitroso compounds studied are dimeric, throughout this section irradiation was carried out in a Pyrex apparatus (energy cut-off <290 nm) so that both dimer and monomer absorption bands were excited; the former excitation promotes the dissociation of dimer to the corresponding monomer [118].

2-3-1. trans-1-Nitroso-2-Piperidinocyclohexane anti-Dimer(II-6)

Irradiation of a methanol solution of the anti-dimer of trans-1-nitroso-2-piperidinocyclohexane (II-6) containing hydrochloric acid at 0-5° gave 2-piperidinocyclohexanone oxime (II-7) in 65-75% yield. The tautomerization was slow at room temperature in the dark. The crude product showed no infrared absorption characteristic of either a nitrate or a nitro group. Although there were trace amounts of other products, they could not be isolated in pure form.



Scheme 2.19

Photooxidation of anti-dimer II-6 in a methanolic solution containing hydrochloric acid gave a crude product (hydrochloride salts) which exhibited weak infrared absorptions at 1720 and 1635 cm^{-1} and strong absorptions at 1550, 1450 and 1370 cm^{-1} and which

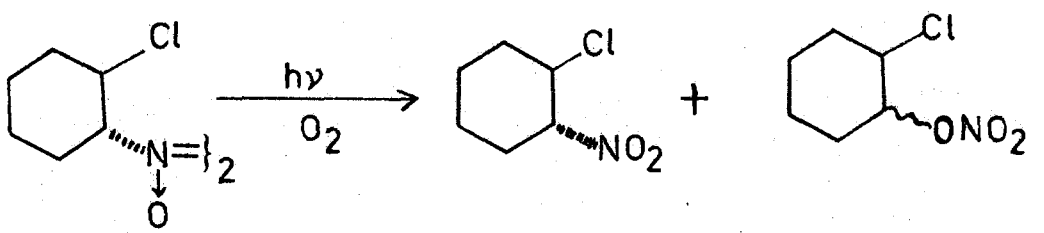
was shown to contain cis- and trans-1-nitro-2-piperidinocyclohexane (II-75) as major products together with small amounts of cis- and trans-1-nitrato-2-piperidinocyclohexane (II-8) and 2-piperidinocyclohexanone (II-10). These hydrochloride salts were hydrogenated in the presence of platinum, and then neutralized to give a crude mixture of the stereoisomeric amines II-76 which, on acetylation followed by chromatography, gave a small amount of 2-piperidinocyclohexanol (II-9) as well as cis- and trans-1-acetamido-2-piperidinocyclohexane (II-77) in the approximate ratio 2:3 (by n.m.r. analysis). The n.m.r. spectrum of a chromatographic fraction containing trans II-77 as the major product (ca. 85%) exhibited a double triplet (J = 4.0 and 10.0 Hz) at τ 6.63 for the methine proton geminal to the acetamido group. This pattern and the magnitude of the coupling constants are indicative of a trans-diaxial arrangement for the C-1 and C-2 protons. The mass spectrum exhibited a weak molecular ion peak at m/e 224.

In the n.m.r. spectra of the other fractions containing both cis- and trans-II-77, two methyl signals for the acetyl group were detected. However, the chemical shift of the C-1 methine proton of the cis-isomer was apparently superimposed on that of the trans-isomer. The signals due to the methine as well as the methyl protons of cis-and trans-II-77 were well spearated when the n.m.r. spectrum of the mixture was taken in the presence of tris (dipivalomethanato) europium. In agreement with a cis-isomer being

a better chelating ligand than a trans-isomer, the signals of the methyl and methine protons of the cis-II-77 were shifted much farther downfield than those of trans-II-77.

2-3-2. Trans-1-Nitroso-2-Chlorocyclohexane Anti-Dimer(II-78)

The anti-dimer of trans-1-nitroso-2-chlorocyclohexane (II-78) was prepared by addition of nitrosyl chloride to cyclohexene [66]. Oxidative irradiation of anti-dimer II-78 in a methanolic solution containing perchloric acid or in a benzene solution caused quick disappearance of the anti-dimer absorption at 295 nm and precipitation of syn-dimer II-78. During the photolysis in methanol a new absorption at 275 nm due to the corresponding syn-dimer was also observed. After prolonged periods of irradiation necessitated by the precipitation of the syn-isomer, trans-1-nitro-2-chlorocyclohexane (II-79) and trans-1-nitrato-2-chlorocyclohexane (II-80) were isolated by column chromatography as the major products. Analysis of the crude product by v.p.c. and n.m.r. showed it to contain these two compounds in approximately equal amounts. The infrared spectrum of II-79 exhibited characteristic bands for a nitro group at 1550 and 1370 cm^{-1}. The n.m.r. spectrum showed a double triplet (J = 4.0 and 10.0 Hz) at τ 5.495 for the methine proton geminal to the nitro group and another double triplet (J = 4.0 and 10.0 Hz) at τ 5.735 for the methine proton



II-78 II-79 II-80

Scheme 2.20

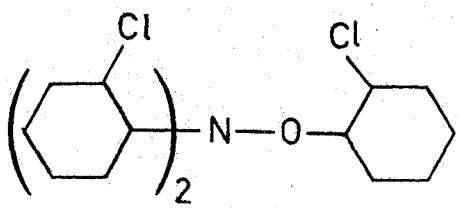
geminal to the chlorine. Hence, these protons (C-1 and C-2) must have a trans-diaxial configuration.

The infrared spectrum of nitrate II-80 showed characteristic bands at 1630, 1280 and 875 cm^{-1} for a nitrate group. In the n.m.r. spectrum of this compound, the C-1 and C-2 methine protons appeared as double triplets (J = 4.0 and 8.5 Hz) at τ 5.02 and τ 6.14 respectively, indicating a trans-diaxial configuration for these protons.

The cis-isomer of II-79 was not detected in the photolysate in spite of careful chromatography. However, the presence of a small amount of the cis-isomer corresponding to II-80 was indicated by the appearance of a small shoulder in the v.p.c. peak if II-80. Some chromatographic fractions of II-80 also showed a weak n.m.r. signal at about τ 6.0 which may be due to the CHCl proton of the cis-isomer. The weak infrared bands at 3400 and in the 900-1000 cm^{-1} region, observed in the crude product obtained from the photooxidation of dimer II-78 in methanol solution, suggested the presence of a small amount of the corresponding oxime formed by tautomerization, but was not isolated. All efforts to selectively reduce the nitrate group of II-80 and the nitro group of II-79 have failed.

Irradiation of anti-dimer II-78 in benzene solution under nitrogen affored a white crystalline compound which was shown to be the corresponding syn-dimer of II-78. The crude product isolated from the benzene solution exhibited infrared absorptions at 1640, 1280 and 880 cm^{-1} characteristic of a nitrate and at 1450 and 1210 cm^{-1} for an anti-dimer, but no absorptions for a nitro group. Chromatography afforded pure anti-dimer II-78 and a fraction which was shown to contain trans-1-nitrato-2-chlorocyclohexane (II-80) and cyclohexyl chloride (II-81) in nearly equal amounts. V.p.c. analysis showed a small shoulder on the peak of the trans-nitrate II-80 which was tentatively assigned to the corresponding cis-nitrate.

Photodecomposition of the anti-dimer II-78 in methanolic solution afforded N,N,O-tri(2-chlorocyclohexyl)-hydroxylamine (II-82) in addition to nitrate II-80 and cyclohexyl chloride.



II-82

CHAPTER 3

DISCUSSION

The oxidative and non-oxidative photoaddition reactions of N-nitrosamines to various olefins will be discussed first followed by the oxidative and non-oxidative photorearrangements of C-nitroso compounds.

3-1. Oxidative and Non-Oxidative Photoaddition of N-Nitrosamines To Olefins

The primary product of the photoaddition (under an inert atmosphere) of a nitrosamine to an olefin is a C-nitroso compound which may undergo various thermal or photochemical secondary reactions, such as tautomerization to the corresponding oxime or dimerization [21]. The tautomerization may be catalyzed by acids or protic solvents [10,89,90,118] or by light; the latter reaction will be discussed later. The secondary photoreactions of the C-nitroso compounds can be minimized or completely eliminated by avoiding irradiation of the C-nitroso dimer absorption band at about 290 nm [40,119,120]. The improved yield of anti-dimer II-6 (Scheme 2.2) obtained when the photoaddition

was carried out using an appropriate filter (such as nonex) substantiates this proposal.

In the presence of oxygen, the reaction pathway is diverted to the formation of 2-amino nitrate esters. This oxidative photoreaction is a simple and clean method for the preparation of nitrate esters that requires neither strong nitric acid nor expensive silver nitrate. Furthermore, nitrates are stable under the photolysis conditions. While the protonated amino nitrate esters are stable compounds, the free bases undergo decomposition, the mechanistic pathway of which is strongly influenced by the neighbouring amino group.

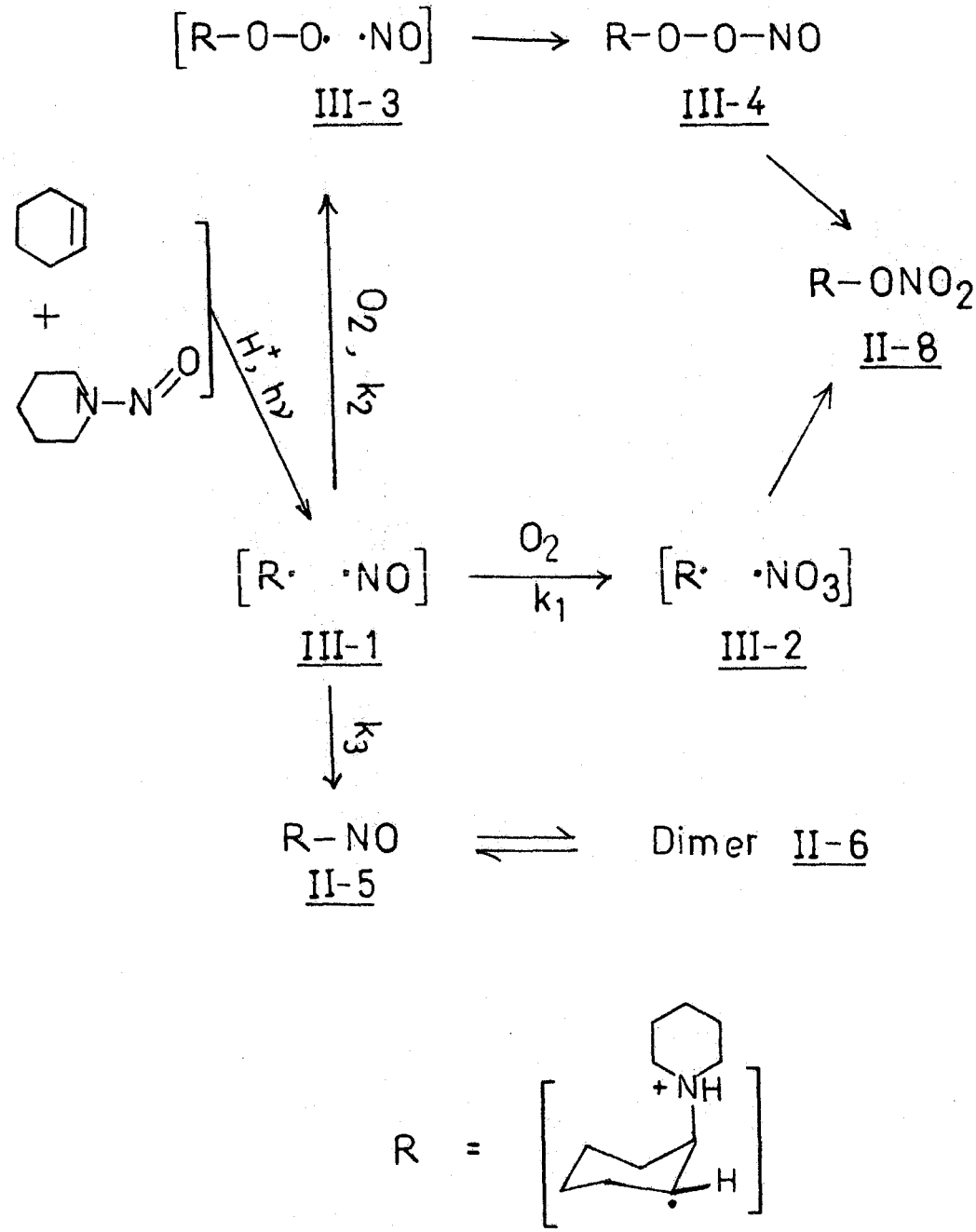
3-1-1. Addition To Cyclohexene and 2-Octalin

The oxidative photoaddition of NNP to cyclohexene gives a mixture of cis- and trans-nitrate esters II-8 in the approximate ratio 1:1.5. Since the cis-isomer undergoes hydrolytic decomposition at a faster rate than the trans-isomer (see Section 5-4-3), the ratio of the two nitrates II-8 is probably much higher than that indicated.

It is interesting to note that the acetates of cyclohexanols II-9 are hydrolyzed back to the corresponding alcohols during chromatography on alumina. This ester hydrolysis is undoubtedly facilitated by the

neighbouring amino group [117,121]. Since p-nitrobenzoate is a better leaving group than acetate, it is likely that the hydrolysis in this case did occur so rapidly (during the usual work-up) that the ester could not be isolated.

Mechanistically, photoaddition of a nitrosamine to an olefin is initiated by the electrophilic attack of an aminium radical at the π-bond resulting in the formation of an intermediate radical pair such as III-1 which, under an inert atmosphere, collapses to C-nitroso compound II-5. The lack of telomer formation during photoaddition to styrene [89] suggests that this step (III-1 $\longrightarrow$ II-5) proceeds very fast.


[R–O–O· ·NO]
III-3
R–O–O–NO
III-4
R–ONO2
II-8
+
N–N=O
H+, hν
O2, k2
[R· ·NO]
III-1
O2
k1
[R· ·NO3]
III-2
k3
R–NO
II-5
Dimer II-6
R =
+NH
H

Scheme 3.1

The stereospecific formation of trans-1-nitroso-2-dimethylamino-cyclohexane observed by previous workers [120] and of the corresponding piperidino compound II-5 obtained in the present work provides further indications that the rate of radical combination (III-1 ⟶ II-5) is much faster than the rate of the cyclohexane ring inversion in III-1.

In the presence of oxygen, the photoreaction is cleanly diverted to the formation of nitrates II-8 (Scheme 2.2). The C-nitroso dimer II-6 is not necessarily an intermediate in this oxidation process since oxidation occurs exclusively even if irradiation is carried out with an appropriate filter system to avoid the irradiation of the C-nitroso dimer absorption band. Furthermore, the products arising from the oxidative photoaddition of N-nitrosamines to alkenes and from the oxidative photorearrangement of C-nitroso compounds are quite different (vide infra). Therefore, it is envisaged that oxygen intercepts the intermediate radical pair III-1 before its collapse to C-nitroso compound II-5. This oxidation may follow either one of the two possible routes shown in Scheme 3.1 to give radical pair III-2 or III-3. Peroxy nitrite III-4 formed from III-3, would be expected to be an unstable species which rearranges rapidly to nitrate II-8, very likely by peroxy bond scission [122]. The rate of radical combination [123,124] (III-1 ⟶ II-5) is comparable to the rate of either oxidation process (III-1 ⟶ III-2 or III-3) as demonstrated by the partial formation

of C-nitroso compound II-5 under a limited supply of oxygen. When sufficient oxygen is supplied, radical pair III-1 is completely intercepted as evidenced by the absence of an u.v. absorption band at 290 nm characteristic of the C-nitroso dimer. Assuming that the oxidation has a diffusion-controlled rate constant (k_1 or k_2 = $10^{10}M^{-1}s^{-1}$) [125], the upper limit of the rate of radical combination (k_3) can be estimated to be 4.5×10^8 s^{-1} at an oxygen concentration of $4.5 \times 10^{-2}M$ at 25° [126].

Kinetic studies in the gas phase have shown that the reaction of NO with oxygen is complex, and a priori prediction of the relative importance of the two oxidation processes (III-1 ⟶ III-2 or III-3) in the liquid phase is impossible [127]. The clean nitrate formation suggests that oxygen does not attack the radical pair in a random manner. Since the rate of oxidation (III-1 ⟶ III-2 or III-3) is faster than that of the radical combination (III-1 ⟶ II-5), the pathway III-1 ⟶ III-3 ⟶ III-4 ⟶ II-8 (Scheme 3.1) should have stereospecifically afforded trans-nitrate II-8 assuming peroxy nitrite III-4 rearranges to II-8 by peroxy bond scission. This pathway is clearly untenable since experimentally we have observed scrambling of the stereochemistry in nitrate II-8. In addition, the peroxy nitrite III-4 would be expected to undergo rapid elimination of an α-hydrogen to give a carbonyl compound [122]. Although some carbonyl compounds have been obtained in certain oxidative photoaddition reactions, the results indicate that they arise from the base

catalyzed elimination of α-hydrogen from nitrate esters rather than from peroxy nitrite intermediates.

The alternative pathway III-1 ⟶ III-2 ⟶ II-8 is considered more likely and accommodates the experimentally observed stereochemistry. The cyclohexyl radical III-1 is expected to combine with nitrogen trioxide more slowly than it undergoes ring inversion. The isolation of nitrophenols during the oxidative photorearrangement of N-nitrosamides also supports the intermediacy of nitrogen trioxide which has been proposed to attack benzene followed by the nitrate rearrangement leading to the nitrophenols [6]. Among other radicals present during the oxidative photorearrangement of N-nitrosamides, neither oxygen nor NO is known to attack the benzene nucleus; a peroxy radical attack requires a circuitous route to yield nitrophenols.

Finally, it is important to mention that oxygen does not quench the excited states of N-nitrosamines from which the primary photoprocesses occur. In view of the generally accepted fact that a triplet state is susceptible to quenching by oxygen [128,129], it may be suggested that the photoreaction involves singlet states of the nitroso compounds. This has been verified by kinetic studies using flash excitation [38].

The hydrochloride of nitrate II-8 are stable compounds, but the corresponding free bases rapidly undergo solvolytic decomposition assisted by the neighbouring amino group. Among the various decomposition pathways, the nucleophilic displacement reaction giving alcohol II-9 and the elimination of α-hydrogen reaction giving ketone II-10 predominate and account for 35% and 30% of the products, respectively. No β-elimination leading to olefin has been detected. A new mode of nitrate decomposition involving the cleavage of the C_1 - C_2 bond assisted by the lone-pair electrons of the amino group has also been observed and accounts for approximately 10% of the products (see Scheme 2.3). The oxidative photoaddition of NND to trans-2-octalin gave a mixture of stereoisomeric amino nitrates which, on decomposition under basic conditions, did not give the corresponding dialdehyde; the major products were cyclohexanol and cyclohexanone derivatives. As will be seen in the forthcoming section, the structural features of the amino nitrate undoubtedly influence the facility of the cleavage reaction (vide infra).

3-1-2. Addition To Bicyclo[2,2,1]heptene

The stereochemical course of the oxidative photoaddition of a nitrosamine to bicyclo[2,2,1]heptene was expected to be strongly influenced by steric factors since even the smallest aminium radical, dimethylaminium radical, is equivalent in size to an isopropyl radical.

The observed preference of aminium radical attack from the exo-side of norbornene is in accordance with this expectation [55]. The subsequent approach of nitrogen trioxide is determined not only by the steric bulk of the amino substituent in the exo-2-position but also by the torsional strain operating in the opposite direction [69,130]. Thus, the oxidative photoaddition of NNP or NND afforded both exo-cis- and trans-nitrate esters II-31 and II-30 (Scheme 2.6). Unfortunately, all efforts to determine the ratio of the isomers have failed due to their rapid decomposition during isolation.

The probable decomposition pathways of II-30 and II-31 are summarized in Scheme 2.6. While some of these pathways have been experimentally verified (e.g., II-31 ⟶ II-35 and II-30 ⟶ II-39), others are proposed on the basis of the well-investigated solvolytic chemistry of norbornyl systems [131] and neighbouring group participations [117,121]. Since endo-nitrate II-30 solvolyzes only in its unprotonated form, the reaction is undoubtedly facilitated by participation of the neighbouring amino group, and the intermediate aziridinium ion II-32 may be postulated. The aziridinium ion intermediate II-32 is rapidly converted to non-classical carbonium ion II-33 and eventually to exo-alcohol II-35 instead of directly reacting with hydroxide ion to give endo-alcohol II-34, as the latter compound was not isolated after prolonged treatment with base. The ionization of exo-nitrate II-31 to II-33 is believed to be facilitated by the well-established σ-bond participation

in norbornyl systems [131]. The cationic charge may also be stabilized by the nitrogen lone-pair electrons but only to a small extent since subsequently hydroxide ion approaches stereospecifically from the exo-face at the 2-position to give exo-alcohol II-35. The merit of the pathway II-33 → II-35 may be questioned because of the absence of rearrangement products such as II-36. (However alcohol II-36 may have been formed in very small amounts and, therefore, escaped detection). Alternatively, it may be suggested that the 3-amino group affects the position of the entry of hydroxide ion.

Endo-alcohol II-34 is derived solely from the immediate LAH reduction of endo-nitrate II-30 before its decomposition since extended basic treatment of nitrates II-30 and II-31 affords only exo-alcohol II-35. In theory, endo-alcohol II-34 could also be obtained from LAH reduction of ketone II-37 which, however, is formed only in very low yield during basic decomposition.

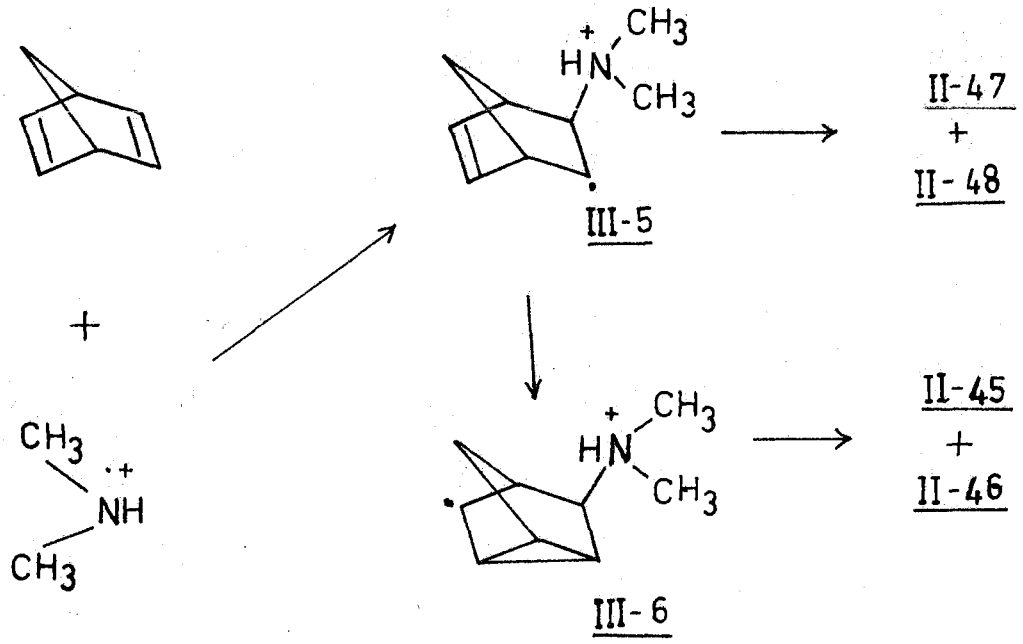
The α-elimination of HNO_2 from nitrates II-30 and II-31 is a minor side reaction and requires the assistance of hydroxide ion since it occurs only in aqueous basic solution to give a small amount of ketone II-37. Alternatively, nitrates II-30 and II-31 can eliminate nitrite ion concomitantly cleaving the C_2-C_3 bond to give immonium salt II-38, a process which obviously requires assistance from the lone-pair electrons of the amino group since it occurs only with the free base; basic hydrolysis of II-38 leads to dialdehyde II-39.

This cleavage pathway is undoubtedly facilitated by a relief in the ring strain of the bicyclic system and constitutes a novel heterolytic fragmentation reaction [132]; it probably requires an anti-periplanar arrangement of the functional groups [92,93]. This postulate is supported by the facile cleavage of trans-amino nitrate II-30 to form dialdehyde II-39. However, there is no positive proof that 2-amino nitrate II-31 with the cis,exo-arrangement does not cleave in the same manner. In view of the copious yield of II-39 it is probable that II-31 also undergoes this cleavage reaction but perhaps not as extensively as II-30.

3-1-3. Addition To Bicyclo[2,2,1]heptadiene

It is well established that the free-radical addition to norbornadiene can proceed by either homoconjugative or 1,2-addition depending upon the chain transfer constants of the addenda used [55,133]. The oxidative photoaddition of nitrosamine to bicyclo[2,2,1]heptadiene has been found to proceed preferentially by homoconjugative addition to yield tricyclic nitrates II-45 and II-46 as the major products (Scheme 2.8). A careful examination of the product mixture also revealed the formation of smalls amount of 1,2-adducts II-47 and II-48. The structures of II-45 and II-46 reveal that the aminium radical attacks the double bond exclusively from the exo-direction in agreement with the reported patterns of other radical additions to bicyclo[2,2,1]-

heptadiene [55]. The intermediate nortricyclene radical III-6, formed by rearrangement of the initially formed norbornenyl radical III-5, should be able to combine with nitrogen trioxide from both the exo-and the endo-direction to give nitrates II-46 and II-45. Both of these products have been found, with the exo-nitrate II-46 predominating. Amino group assisted solvolysis is not observed in these tricyclic systems which is probably a



Scheme 3.2

consequence of the large distance between the amino and the nitrate moiety.

The stereochemistry of the tricyclic nitrates II-45 and II-46 has been deduced from that of the corresponding alcohols obtained by LAH reduction(Scheme2.9). The assignment of the exo- and endo-configurations for alcohols II-50 and II-49, respectively, is based on n.m.r. analysis (see Results, Section 2-2-5) and is consistent with the effect of $Eu(DPM)_3$ on the resonance positions of various protons. Although the substrate molecules contain two donor functions (OH and $N(CH_3)_2$), the complexation of the europium is expected to occur preferentially at the oxygen atom since the vicinity of the nitrogen atom is sterically more crowded [134,135].

The paramagnetic shifts induced by $Eu(DPM)_3$ are predominantly of the pseudocontact type and have therefore a $1/R^3$ dependency, where R is the vector distance between the complexed europium ion and the proton in question [112,136]. However, R is difficult to define due to the uncertainty in the precise location of the co-ordinated europium ion. Hence, the distance between the hydroxyl oxygen atom and the protons in question has been taken as an approximation [112]. An examination of molecular models of exo-alcohol II-50 and endo-alcohol II-49 reveals that in the exo-isomer the H_{7s} proton is very close (2.55 Å) to the hydroxyl oxygen atom while in the endo-isomer the endo H_5 proton is close (2.55 Å) to the oxygen

atom. Furthermore, in the exo-configuration the difference between the oxygen-H_{7s} and the oxygen-H_{7a} distance is large while in the endo-configuration both of these protons are at a comparable distance from the oxygen atom. In agreement with these considerations alcohol II-50 showed a larger induced shift* (4.94 ppm) for the H_{7s} proton than for the H_5 proton (1.96 ppm) while alcohol II-49 showed a larger shift for the H_5 proton (2.66 ppm) than for the H_{7s} proton (1.01 ppm).

Also, the shift difference between the H_{7s} and the H_{7a} proton was only 0.11 ppm in the isomer II-49 but 2.57 ppm in the isomer II-50 (see Results, Table 2-7 and 2-8). This correlation of the proton chemical shift differences with the distances is consistent with the stereochemical assignments for the alcohols II-49 and II-50.

3-1-4. Addition to 5-Methylenebicyclo[2,2,1]hept-2-ene

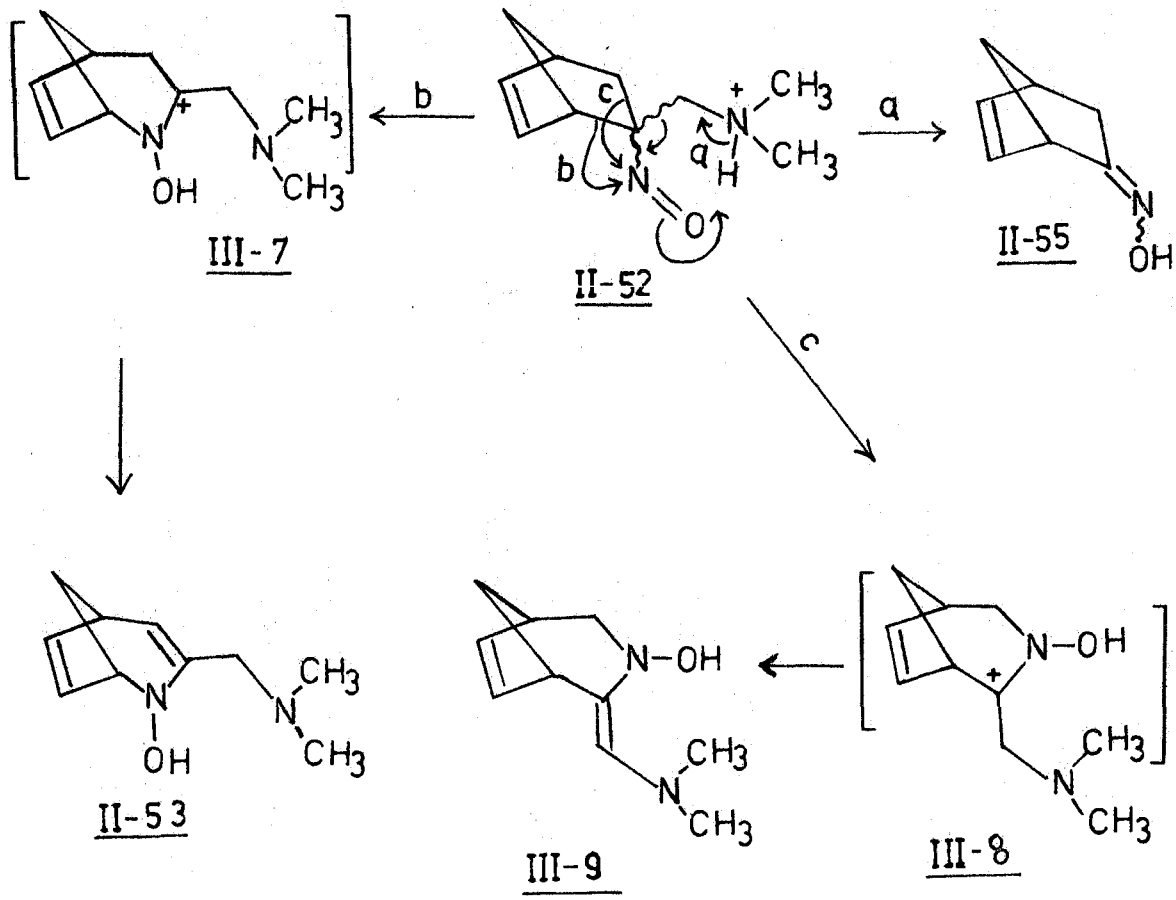
The non-oxidative photoaddition of NND to 5-methylenebicyclo-[2,2,1]hept-2-ene proceeded by both homoconjugative and 1,2-addition to give saturated tricyclene and unsaturated bicyclic derivatives. The results indicate that the attack of the aminium radical occurred exclusively at the exocyclic double bond. This is in agreement with the literature report that the exocyclic double bond of 5-methylene-

* alcohol: 2×10^{-4} mol; $Eu(DPM)_3$: 0.3×10^{-4} mol

bicyclo[2,2,1]heptene is about 4.4 times more reactive than the endocyclic double bond toward trichloromethyl radicals [82,137]. The formation of a tricyclene derivative is not unexpected since it has been demonstrated that tricyclene itself is thermodynamically more stable than norbornene [138]. Further, the close proximity of the double bond to the free-radical centre should facilitate homoconjugative addition.

As mentioned earlier, the primary photoproduct in the non-oxidative photoaddition of a nitrosamine to an olefin is a C-nitroso compound [21] which, having an α-hydrogen atom, undergoes irreversible tautomerization catalyzed by light or by acids to give the corresponding oxime [21]. This tautomerization route is blocked in C-nitroso compounds such as II-52 which contain no α-hydrogen atoms. Such tertiary nitroso compounds also undergo dimerization but slowly due to steric hindrance; the presence of an α-ammonium group leads to a hydrogen-bonded monomeric form [89] which can undergo intramolecular proton transfer with concomitant cleavage of the carbon-carbon bond to give II-55 as shown in Scheme 3.3. A cis-coplanar orientation of the functional groups has been reported to be a necessary stereochemical requirement, and a cyclic transition state has been proposed for the cleavage mechanism [139]. However, this cleavage is only a minor reaction of the C-nitroso compound II-52 since oxime II-55 is obtained in low yield. Alternatively, II-52 may undergo intramolecular

proton transfer with migration of the C_1-C_2 bond to the nitroso nitrogen atom to give the carbonium ion intermediate III-7 which is converted to the azabicyclic compound II-53 by elimination of a proton. The apparent preference of II-52 to undergo this



Scheme 3.3

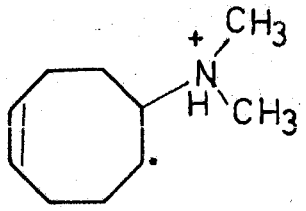
rearrangement rather than the previously described cleavage reaction is probably due to the fact that it results in the partial relief of bicyclic ring strain.
Migration of the C_2-C_3 bond is also possible and would give rise to the azabicyclic compound III-9. However, migration of the allylic C_1-C_2 bond is found to be the preferred pathway. Though the configuration of the nitroso group in II-52 has not been confirmed, it is assumed to be endo on the basis of a steric consideration of the addition process.

The non-oxidative photoaddition of NND to 5-methylenebicyclo[2,2,1]-hept-2-ene in bromotrichloromethane has been shown to proceed by homoconjugative addition to give the saturated tricyclic bromides II-60 and II-61 in the ratio 1:1. Failure to detect any 1,2-adduct may be due to its facile rearrangement to the tricyclic bromides during the work-up. Alternatively, it may be a consequence of steric crowding near the radical centre, wich inhibits the approach of the bulky bromotrichloromethane molecule.

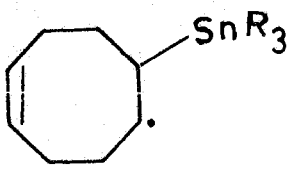
3-1-5. Addition to 1,5-Cyclooctadiene and 1,3-Cyclohexadiene

The oxidative photoaddition of NND to 1,5-cyclooctadiene apparently proceeds solely by the normal 1,2-addition route to give trans-nitrate II-62 and the oxabicyclic ethers II-65 and II-66(Scheme2.15). The absence of

transannular adducts may be attributed to the slow rate of cyclization of radicals incorporating the pent-4-enyl system, such as III-10, due to the poor overlap between the orbitals of the radical centre and of the double bond [87]. Furthermore, rapid combination of radical III-10 with nitrogen trioxide would result in preferential 1,2-addition. It appears that significant yields of cyclized products can be obtained from radicals



III-10

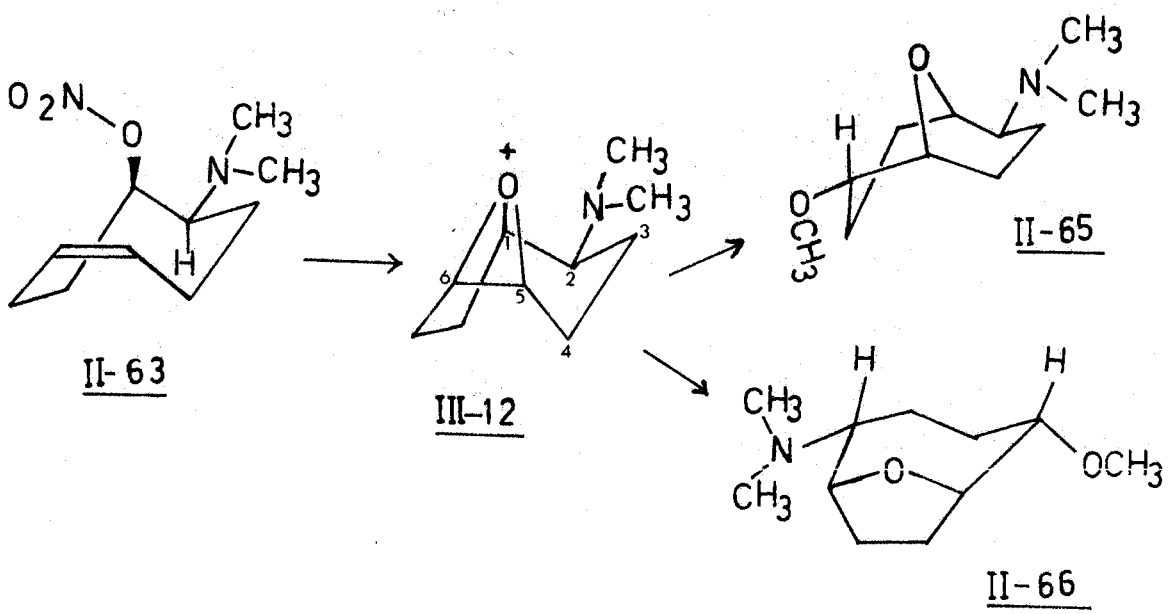


III-11

such as III-10 only with those addenda, like CCl_4, which are slow chain transfer agents [53,84,140] or when the radical contains structural features that tend to retard 1,2-addition, e.g., steric crowding near the radical centre such as is observed in radical III-11 [140].

Our results indicate that trans-nitrate II-62 is stable under the photoaddition conditions and can be isolated as the corresponding alcohol after LAH reduction. Failure to detect cis-nitrate II-63 (or the corresponding alcohol) may be due to its facile rearrangement to the oxabicyclic ethers II-65 and II-66 by elimination of nitrite ion assisted by transannular π-electron migration to the electron-deficient oxygen atom. This type of rearrangement has been hitherto unknown although transannular π-electron participation has been frequently observed in reactions of medium sized rings [116,141-143].

Examination of molecular models suggests that the cyclooctenyl nitrates II-62 and II-63 exist preferentially in a twist-boat-chair conformation to minimize non-bonded interactions. In the case of the cis-isomer (II-63) with the nitrate group occupying a pseudoaxial position, the π-lobes lie in close proximity to the nitrate oxygen atom so that direct interaction between the developing empty p-orbital of the latter and the p-orbitals of the double bond can occur. Such π-electron participation is evidently not favourable in the case of trans-nitrate II-62 where the nitrate group occupies the more stable pseudoequatorial position.



Scheme 3.4

It is likely that the afore-mentioned transannular rearrangement of cis-nitrate II-63 may involve the intermediacy of an oxonium ion (III-12) similar to the one proposed for the acetolysis of 9-oxabicyclo[4,2,1]nonan-2-yl brosylates to yield a mixture of endo-9-oxabicyclo[3,3,1]nonan-2-yl acetate and endo-9-oxabicyclo[4,2,1]

nonan-2-yl acetate [144]. Solvent attack on such an intermediate can occur at either C-5 or C-6 giving the oxabicyclic ethers II-65 and II-66. Solvent attack at the C_1-carbon of III-12 from the rear-side is not likely since nucleophilic attack to open a five-membered ring would be significantly slower than the rate of attack on a strained three-membered ring [144]; the steric crowding caused by the adjacent dimethylamino group would also be expected to inhibit attack at this position. The exclusive formation of endo-products attests to the significant steric control exerted by the proposed oxonium ion bridge over the entry of the methoxy group. The observed product ratio of 3:2 for II-65 to II-66 is indicative of their relative thermodynamic stabilities.

The oxidative photoaddition of nitrosamines to 1,3-cyclohexadiene has been found to proceed preferentially by 1,4-addition; 1,2-addition might also have occurred. Unfortunately, this reaction is of limited synthetic value since the α,β-unsaturated amino nitrate esters are highly unstable even under very mild conditions.

3-1-6. Addition to 3-Butenyl Compounds

The result of the oxidative photoaddition of NNP to 3-butenyl derivatives shows that alcohol II-70a and acetate II-70b give

excellent yields of adducts, while the corresponding benzoates react very sluggishly and tosylate II-70h is totally inert (Scheme 2.18). Since the ester group is two carbon atoms removed from the olefinic bond, the low reactivity of the latter compounds is probably not due to inductive electron withdrawal by the aromatic ring but to some ground-state interaction of the phenyl ring with the double bond although the n.m.r. spectra do not provide any evidence for this hypothesis. Alternatively, the possibility of association of a photoexcited NNP with ground state olefin to give an exciplex which subsequently decays to the ground state reactants cannot be ruled out.

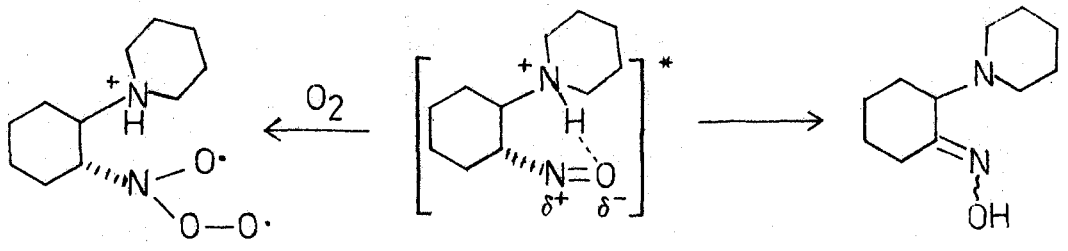
In contrast to the cyclic secondary amino nitrates (such as II-8), the acyclic analogues II-71 undergo hydrolysis to give almost exclusively the parent alcohols. As expected, the adducts II-71f and II-71g, formed from NNP and 3-butenyl halides, readily undergo cyclization to give azoniaspiro compound II-74(p 102). Such internal displacement reactions were not observed for the adducts derived from other 3-butenyl derivatives, i.e., acetate and benzoates, which contain more basic and therefore poorer leaving groups than halide.

3-2. Photooxidation and Photodecomposition of C-Nitroso Compounds

Owing to the facile interconversion of C-nitroso monomer and dimer under photolylic conditions, it is usually difficult to ascertain whether an observed reaction should be attributed to the monomer or its dimer. For this reason, the reactions of both species are treated together except for those steps where a clear distinction can be made. The results described in this thesis and those reported earlier [11] encompass a wide range of reactions that compete with each other in deciding the fate of a photoexcited C-nitroso compound. The favoured pathway is determined by the structure of the C-nitroso compound as well as by the reaction conditions. Under the experimental irradiation conditions, the dimers II-6 and II-78 (Schemes 2.19 and 2.20) rapidly dissociate to the corresponding monomers which may subsequently undergo further photoreactions, namely rapid recombination together with slow disproportionation in case of anti-dimer II-78, and mainly tautomerization in case of dimer II-6.

The photolysis of anti-dimer II-78 under nitrogen leads to the formation of the corresponding syn-isomer by a kinetically controlled dark reaction. In comparison to the syn-dimers of nitrosocyclohexane and other nitrosoalkanes, syn-II-78 is surprisingly stable. The slow photodissociation of the monomer of II-78 yields hydroxylamine II-82 (p 111), probably via the corresponding nitroxide, as well as disproportionation products.

The predominant tautomerization during photolysis of anti-dimer II-6 in acidic solution has undoubtedly its origin in the close proximity of the proton donating piperidinium group and the C-nitroso moiety. In view of the large difference in the rates observed for the photolytic and thermal (dark) tautomerization under comparable conditions, light is believed to catalyze the process by facilitating the dissociation of the dimer to the corresponding monomer.
The tautomerization of the monomer to the oxime may also be catalyzed by light. Mackor and de Boer [145,146] have reported a light-catalyzed (λ 680 nm) tautomerization of the nitrosocyclohexane monomer (generated at 80°) in cyclohexane to give cyclohexanone oxime in high yield. One may envisage a vibrationally excited C-nitroso monomer, probably formed by radiationless decay of an electronically excited species, to undergo facile tautomerization. Alternatively, photoexcitation may create a dipolar C-nitroso species, such as III-13, which triggers a facile proton transfer.



Scheme 3.5

In general, the photoxidation of anti-dimers in Pyrex apparatus as well as the red-light photooxidation of nitrosocyclohexane [145] and 2-nitroso-2-methylpropane [146] lead to the formation of nitrates and nitro compounds, although the ratios can vary considerably. It should be pointed out that nitro compounds were not formed in the photolysis under nitrogen, and that the oxidations are genuine photoreactions as shown by control reactions in the dark. Also, the oxidations are not initiated by singlet oxygen [147] and take place from a C-nitroso monomer since no reaction has been observed without irradiation at the dimer absorption near 290 nm.

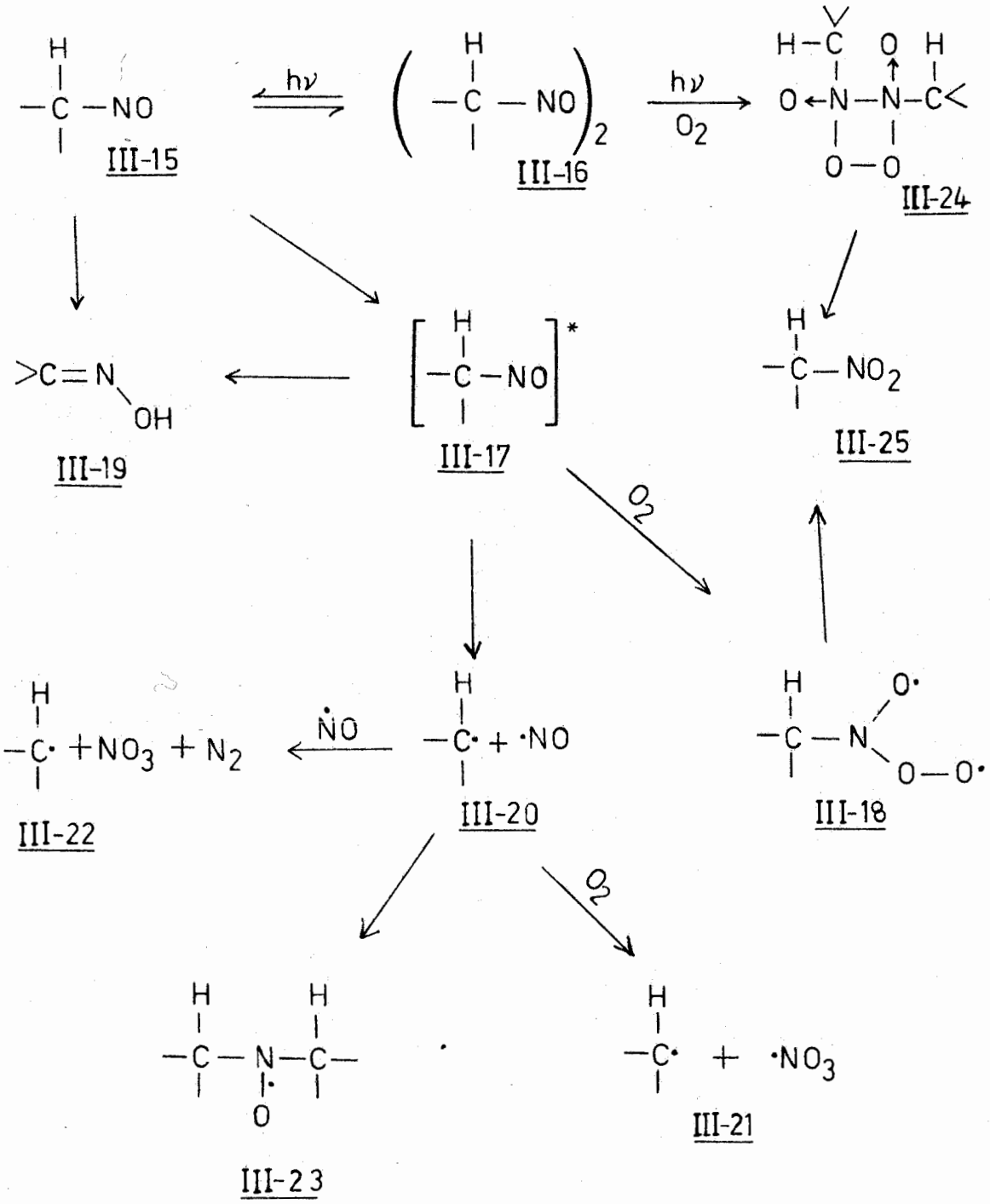
Inspection of the oxidation products shows that all the nitrates obtained by photooxidation of the anti-dimers have lost their stereochemical integrity while nitro compound II-79 maintains the original trans-configuration of anti-dimer II-78(Scheme2.20). In the photooxidation of anti-dimer II-6, acid- or base-catalyzed nitro-nitronate tautomerization may be responsible for the scrambling of the original trans-configuration in nitro compound II-75 (Scheme 2.19) [148]. The dissimilarity in the stereochemical results suggests that nitro and nitrate formation occur by separate pathways. Indeed, during red-light photooxidation of nitrosocyclohexane, Mackor and de Boer [145] have observed that while the yields of nitrocyclohexane increase as the reaction temperature is lowered, the yield of cyclohexyl nitrate remains virtually stationary.

In photooxidations, scrambling of the nitrate configurations means that at some point the C-NO bonds of the monomers are broken and C-ONO_2 bonds are formed. It follows that the nitrate formation must be due to photodissociation of C-nitroso monomers which is the pathway common to both disproportionation and oxidation. The generated nitric oxide is quickly intercepted by oxygen to become nitrogen trioxide [149] which combines with the alkyl radical thus completing the oxidation process to give the corresponding nitrate which is stable to further irradiation. This mechanistic interpretation shares a common principle with the oxidation during nitrosamine photoaddition discussed earlier, namely, oxygen captures nitric oxide quickly even if the latter exists as a radical pair with the alkyl radical.One may conclude from these results that any C-nitroso compound capable of photodissociation should be able to give the corresponding nitrate by photooxidation with an efficiency which is limited only by the life-time of the C-nitroso monomer and by the ease of scission of its C-N bond. In agreement, the C-nitroso monomer derived from dimer II-6 is oxidized to nitrate less efficiently than the one derived from dimer II-78, due to its facile conversion to nitro compound II-75 (vide infra).

Since conservation of the trans-configuration in the formation of nitro compound II-79 requires that the C-NO bond remain intact during the reaction, some primary photochemical act other than photodissociation must be responsible for the oxidation of II-78 to II-79. Since

C-nitroso compound II-6 which undergoes facile tautomerization is also oxidized efficiently to the corresponding nitro compound, we believe that this photooxidation reaction shares a common reactive intermediate with the process of tautomerization in the corresponding photolysis under nitrogen. Therefore, we have tentatively ascribed a vibrationally excited C-nitroso monomer, such as III-13 (Scheme 3.5), to this intermediate. Probably oxygen captures this excited species before it can undergo other processes, leading to a peroxy diradical (III-14) which has also been proposed by de Boer's group [10,145]. In the presence of a suitable substrate, III-14 may abstract a hydrogen atom or add to a reactive olefin [10]; otherwise it may shed the extra oxygen atom by oxidizing a second molecule of the C-nitroso monomer to give two molecules of nitro compound II-75.

The various photochemical processes available to C-nitroso compounds are summarized in Scheme 3.6. It is assumed that the


III-15
III-16
III-24
III-19
III-17
III-25
III-22
III-20
III-18
III-23
III-21
hν
O2
NO
O2

Scheme 3.6

same excited state III-17 is responsible for all the primary photochemical reactions. The mechanism of nitro compound formation discussed above assumes excited C-nitroso monomers as the reactive species, on the basis of the facile dissociation of a C-nitroso dimer to the corresponding monomer on irradiation at -190° [118] and the formation of the corresponding C-nitro compound during photooxidation of a C-nitroso monomer [10,145] with red light. However, the alternative possibility of a photoexcited dimer (III-16, for example II-6 or II-78) reacting with oxygen to form intermediate III-24 which subsequently decomposes to a nitro compound (III-25, for example II-79 or II-75) cannot be completely ruled out. A distinction between these two mechanistic pathways awaits clarification in the future.

CHAPTER 4

SUMMARY AND CONCLUSIONS

The oxidative photoaddition reactions of N-nitrosamines to various olefins have been investigated in an attempt to develop a simple and efficient synthetic route for 2-amino nitrate esters which are otherwise inaccessible or difficult to prepare. In the preceding chapters, the stereochemistry and possible mechanistic pathways of these photoreactions have been presented and compared with the corresponding non-oxidative reactions. It is concluded that the oxidative photoaddition involves the electrophilic attack of an aminium radical at the π-bond of the olefin resulting in the formation of a C-radical and nitric oxide. Oxygen captures nitric oxide quickly, even if the latter exists as a radical pair with the former, to give nitrogen trioxide which,subsequently combines with the C-radical to yield a 2-amino nitrate ester. The results of our study of the oxidative photodecomposition of C-nitroso compounds further substantiate this mechanism.

In basic solution, the 2-amino nitrate esters undergo a variety of reactions the mechanistic pathways of which are strongly influenced by the neighbouring amino group. The major reactions are solvolysis and elimination to give the corresponding amino alcohols and amino

ketones. Solvolysis of these compounds is obviously facilitated by participation of the neighbouring amino group. Depending upon their structure, they may also undergo various other types of reactions.

The non-oxidative photoaddition of N-nitrosopiperidine to cyclohexene gives the C-nitroso compound II-5 as the primary product which may undergo tautomerization to the corresponding oxime or dimerization. In the presence of oxygen, however, the photoaddition gives an isomeric mixture of 2-amino nitrates II-8 in good yield. These nitrates are stable in their protonated forms but they undergo amino group assisted hydrolytic decomposition on basification to give predominantly amino alcohol II-9 and ketone II-10. Therefore, these compounds have been isolated as the corresponding alcohols after LAH reduction.

The oxidative photoaddition of NNP or NND to bicyclo[2,2,1]heptene afforded a mixture of the perchlorates of exo-cis- and trans-amino nitrate II-30 and II-31 which were difficult to isolate as the free bases due to their facile decomposition during basification. The major decomposition pathway in this case is C_1-C_2 bond cleavage assisted by the lone electron pair of the nitrogen atom to give the corresponding carbonyl compounds. The nitrates II-30 and II-31 may also undergo solvolysis with participation of the neighbouring amino group and/or the C_1-C_6 σ-bond to give alcohol II-35.

The oxidative photoaddition of NNP or NND to bicyclo[2,2,1]-heptadiene resulted in the formation of 1,5-adducts II-41 and II-42 as major products, in addition to small amounts of 1,2-adducts II-47 and II-48. The tricyclic amino nitrates were found to be stable enough to be isolated which is probably due to the fact that the amino group is not located at an interacting distance with the ester group.

The non-oxidative photoaddition of NND to 5-methylenebicyclo-[2,2,1]hept-2-ene gave both homoconjugative (II-54) and 1,2-adducts (II-52). The C-nitroso compound II-52 was found to rearrange rapidly to the azabicyclic compound II-53. When this photoaddition was carried out in bromotrichloromethane, the major products were tricyclic bromides II-60 and II-61. No 1,2-adducts could be isolated from this reaction.

The oxidative photoaddition of NND to 1,5-cyclooctadiene gave both cis- and trans-nitrate esters II-63 and II-62. The trans-nitrate II-62 is stable under the photoaddition conditions and can be isolated as the corresponding amino alcohol after LAH reduction. However, the cis-nitrate II-63 rapidly rearranges to the oxabicyclic ethers II-65 and II-66 by elimination of nitrite ion assisted by transannular π-electron migration to the electron deficient oxygen atom. Transannular reaction to form bicyclo[3,3,0]octane derivatives was not observed in the photoaddition.

The oxidative photoaddition of nitrosamines to 1,3-cyclohexadiene gave the expected 1,4-adducts, but on basification the nitrates rapidly decomposed to a complex mixture.

The oxidative photoaddition of NNP to 3-butenol and 3-butenyl acetate gave excellent yields of the corresponding adducts. However, the corresponding benzoates reacted very sluggishly and the tosylate was completely inert towards the photoaddition. As expected, the adducts II-71f and II-71g, formed from NNP and 3-butenyl halides, readily underwent cyclization to give azonia spiro compound II-74.

The non-oxidative photodecomposition of anti-dimers II-6 and II-78 results in rapid dissociation to the corresponding monomers which subsequently undergo further photoreactions, namely, rapid dimerization together with a slow disproportionation in case of anti-dimer II-78, and mainly tautomerization in the case of dimer II-6.

The oxidative photodecomposition of dimer II-78 gives the corresponding cis- and trans-nitrates II-80 and trans nitro compound II-79 while dimer II-6 mainly gives nitro compound II-75. It is concluded that the nitrate formation must be due to the photodissociation of the C-nitroso monomer to the alkyl radical and nitric oxide which is the pathway common to both disproportionation

and oxidation. Mechanistically the nitro compound formation probably shares a common reactive intermediate, such as a vibrationally excited C-nitroso monomer, with the tautomerization process in the corresponding non-oxidative photodecomposition reaction. In the former case, it is assumed that oxygen attacks the vibrationally excited C-nitroso monomer followed by rearrangements to give the nitro compounds.

In summary, the oxidative photoaddition of a nitrosamine to an olefin in the presence of a dilute acid is a general reaction and represents a simple and efficient synthetic method for 2-amino nitrate esters. Since these compounds were found to be stable only in their protonated forms, they could be isolated only as salts or as the corresponding amino alcohols after LAH reduction. Nevertheless, this photoreaction represents a useful synthetic tool for the simultaneous introduction of nitrogen and oxygen functionalities into a molecule.

The N-nitrosamines are extremely potent carcinogens for many animal species capable of producing tumors at many body sites [153]. The nitrosamines can be formed from precursors such as secondary or tertiary amines and nitrosating agents such as nitrites, nitrous gases (NO and NO_2) or nitrates under reducing conditions. Such substances occur widely in the environment. Hence a detailed understanding of the chemistry of nitrosamines is useful in the investigation of the nitrosamine carcinogenesis at the molecular level.

CHAPTER 5

EXPERIMENTAL

5-1. General

Unless otherwise stated the following conditions were used.

Infrared (i.r.) spectra were taken either on a Unicam SP 200 or a Perkin-Elmer 457 Spectrophotometer, using liquid films or nujol nulls of the samples. The absorption bands (cm^{-1}) are designated as s, m, w and b for strong, medium, weak and broad, respectively. Ultraviolet (u.v.) spectra were recorded either on a Unicam SP 800 or a Cary 14 spectrophotometer. Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian A 56/60 or a Varian XL-100 spectrophotometer using deuterochloroform as solvent and tetramethylsilane as internal standard. Chemical shifts are reported in τ values, coupling constants (J) and half-height widths (W1/2) in hertz (Hz). The splitting patterns are designated as s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triplet), q (quartet), qi (quintet), sx (sextet), o (octet), m (multiplet), bm (broad multiplet) and bs (broad singlet) and the number of protons in the corresponding signal by H. The D_2O

exchangeable proton is indicated by D_2Oexch. The decoupling experiments were performed by Mr. John Pastucha or by the author on an XL-100 spectrometer. Mass spectra (m.s.) and high resolution mass spectra (h.m.s.) were obtained on a Hitachi-Perkin-Elmer model RMU-6E instrument with an ionization voltage of 80 ev; the intensity of the peaks is given as percentage of the base peak. The g.c.-mass spectra (g.c.-m.s.) were obtained on a Varian 1400 gas chromatograph using a 20% SE-30 column coupled to the mass spectrometer.

The vapour phase chromatographic (v.p.c.) analyses were performed on a Varian 1200 equipped with a flame ionization detector using a 20% SE-30 (10′ x 1/8") stainless steel column, and the recorder was equipped with a disc chart integrator (model 244). Thin layer chromatographic (t.l.c.) analyses were performed on alumina or silica gel plates (0.3 mm thickness) which were examined under u.v. light or developed with iodine. The separations by column chromatography were performed on neutral or basic alumina, Brockmann (Activity I, 80 - 200 mesh), silica gel (Baker analysed, 60 - 200 mesh) or silicic acid Mallinckrodt (analytical reagent, 100 mesh).

Melting points (uncorrected) were determined either on a Fisher-Johns hot stage or a Gallenkamp heating block apparatus. Elemental analyses were performed by Mr. M.K. Yang with a Perkin-Elmer 240 Microanalyser.

5-2. Materials

The solvents (reagent grade) used for the photoreaction and for the chromatographic separations were distilled and stored over molecular sieves. The anhydrous ether and tetrahydrofuran (THF) used for the metal hydride reductions were distilled from lithium aluminium hydride. Reagent grade pyridine was stored over potassium hydroxide pellets. N-nitrosodimethylamine (NND, Eastman 7370) and N-nitrosopiperidine (NNP, Eastman 2277) and the olefins were distilled before use.

The gaseous reagents were supplied by Matheson. The nitrogen gas was purified by scrubbing through Fieser's solution followed by lead acetate solution and then dried through concentrated sulfuric acid. Platinum oxide (M C and B) and platinum black (Fisher Scientific) were used as hydrogenation catalysts. Concentrated hydrochloric acid, sulfuric acid and glacial acetic acid were supplied by Allied Chemical Inc., perchloric acid by Mallinckrodt Chemical Works, lithium aluminium hydride (LAH, 97%) by Wilshire Chemical Co. and sodium borohydride ($NaBH_4$, 98%) by Fisher Scientific.

5-3. General Procedure of Photolysis

The photolyses were carried out in a previously described (151) pyrex photovessel (Figure 5.1). The condenser was fitted with a gas trap. Either cold water or an externally cooled filter solution was circulated through the cold finger. The reactants were dissolved in an appropriate solvent and were introduced into the photocell. The solution was then stirred with a magnetic stirrer while a stream of gas was bubbled through the solution for 10 - 15 minutes. The solution was externally cooled by immersing the photocell either in an ice bath or in a dry-ice acetone bath. In the latter case, a vacuum jacket was used to separate the cold finger from the cold solution. The photocell (Figure 5.1) was then filled to the mark and the solution was irradiated by placing a light source, either an Hanovia 8A36 (100 watts), Hanovia 654A36 (200 watts) medium pressure mercury lamp or a Rayonet 3500 Å lamp into the lamp well. Sometimes a cylindrical glass filter was used. The reaction was monitored by recording the u.v. spectra of properly diluted aliquots of the photolysate removed at suitable intervals. The solution was irradiated until the u.v. absorption at ca. 350 nm of the N-nitrosamine (or at ca. 290 nm of the C-nitroso compound, Table 5.1) has disappeared. A zero-hour control sample was retained in the dark; its u.v. spectrum, recorded at the completion of the photolysis revealed no noticeable change indicating the absence of thermal reactions.

TABLE 5.1

ULTRAVIOLET SPECTRAL DATA OF NITROSO COMPOUNDS

Compound	Solvent	λmax nm
NNP	water	338(ε87) 235(ε~8000)
NND	methanol	345(ε98) 230(ε~7500)
II-6	methanol	295(ε~10000)
II-78	ethanol	295(ε~8000)

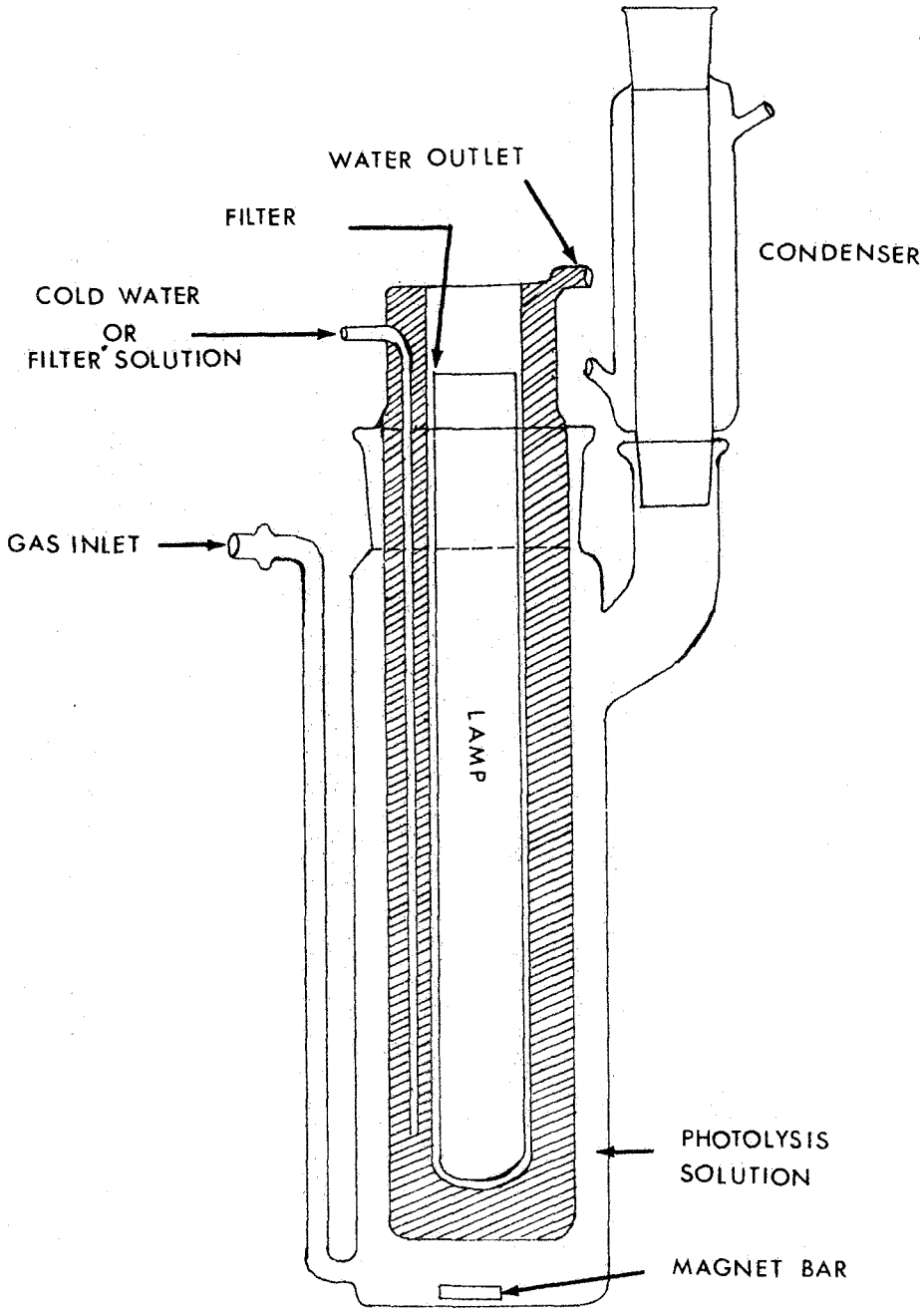


Figure 5.1 Photovessel (Pyrex)

After irradiation, the photolysate was concentrated under vacuum using a rotory evaporator at ca. 10°. The residual solution was cooled in a refrigerator to precipitate product salts. The filtrate was diluted with water and extracted with ether to remove the "neutral fraction". The aqueous solution was cooled to 0-5° and basified with saturated sodium carbonate or potassium carbonate solution. The aqueous solution was immediately extracted with ether or methylene chloride. The organic extracts were washed with water, dried over magnesium sulfate and evaporated under vacuum at or below room temperature. The residues were examined by t.l.c. and g.c. and i.r. and n.m.r. spectroscopy and then immediately stirred with LAH in THF or ether as solvent. The reduced products were purified by column chromatography followed by recrystallization or sublimation.

In cases where the photoreactions were carried out under a nitrogen atmosphere, the basic residue was directly subjected to chromatographic separation.

5-4. Oxidative and Non-Oxidative Photoaddition of N-Nitrosamines to Olefins

5-4-1A. Addition of NNP to Cyclohexene at 0°

A solution of NNP (6.84 g, 0.06 mol), cyclohexene (M C and B, 3.28 g, 0.04 mol) and concentrated hydrochloric acid (6 ml) in methanol (340 ml) was irradiated with a 200 watt Hanovia lamp under nitrogen at 0°. A cold filter solution of 2,7-dimethyl-3, 6-diazacyclohepta-1, 6-diene perchlorate was circulated through the cold finger. The filter solution and the pyrex filter cut off u.v. light shorter than 350 nm. The photolysis was stopped when the emerging peak at 295 nm was most intense (2 hours). The bluish green photolysate was neutralized immediately with sodium carbonate to give a precipitate which was filtered and washed with water to give a white solid (1.65 g). Concentration of the filtrate gave a second crop of crystals (0.73 g). The combined crops (2.35 g, 30.4%) were recrystallized from methylene chloride-methanol to give the anti-dimer of trans-1-nitroso-2-piperidinocyclohexane (II-6) as white needles : m.p. 170 - 172°; i.r. 1210 (s), 1185 (s), 1100 (s), 1055 (m), 1030 (m) and 695 (s) cm^{-1}; n.m.r. τ 4.43 (m, W1/2 = 25 Hz, H_1), 6.85-7.84 (m, 5H), 7.84-8.44 (m, 6H) and 8.6 (m, 8H).

B. Addition of NNP to Cyclohexene at -25°

A solution of NNP (4.5 g, 0.04 mol), cyclohexene (4.92 g, 0.06 mol) and concentrated hydrochloric acid (3.5 ml) in methanol (500 ml) was cooled to -25° and was irradiated as described above. After the completion of the photolysis (2.5 hours), sodium carbonate (5.5 g) was added to the bluish green photolysate with stirring to give a precipitate which was filtered and washed with water to give anti- dimer II-6 (1.73 g). The filtrate was concentrated yielding a second crop of crystals (0.55 g) and raising the total yield to 2.28 g(29.1%).

C. Addition of NNP to Cyclohexene at -50°

A solution of NNP (4.5 g, 0.04 mol), cyclohexene (3.28 g, 0.04 mol) and concentrated hydrochloric acid (3.5 ml) in methanol (500 ml) was cooled to -50° and was irradiated as described above. The photolysis was sluggish as indicated by the slow decrease of the N-nitrosamine absorption at 347 nm. After irradiation (3 hours), the bluish-green photolysate was basified with sodium carbonate to give a precipitate which was filtered and washed with water to afford anti- dimer II-6 (1.0 g, 12.8 %).

5-4-2. Oxidative Addition of NNP to Cyclohexene

A methanol solution (340 mol) of NNP (6.84 g, 0.06 mol), cyclohexene (3.28 g, 0.04 mol) and concentrated hydrochloric acid (6 ml) was irradiated with a 200 watt Hanovia lamp under oxygen at -10°. A cold filter solution of 2,7-dimethyl-3,6-diaza-cyclohepta-1,6-diene perchlorate was circulated through the cold finger to cut off the u.v. light below 350 nm. The u.v. spectra showed no C-nitroso peak at 295 nm. The photolysis was complete within 3 hours as indicated by the absence of the nitrosamine absorption at 347 nm. The bulk of methanol was removed. The residual solution was diluted with water and extracted with ether to give an oil (248 mg) containing NNP and several minor components. The aqueous acidic solution was neutralized with sodium carbonate to pH 7.5 and extracted with chloroform to give a dark brown oil (9.1 g) which showed strong i.r. absorptions at 1625, 1275 and 865 cm^{-1} for a nitrate ester group and a medium peak at 1715 cm^{-1} for a carbonyl group. This oil was unstable and decomposed to a dark red resin on standing.

The crude basic fraction (9.0 g) was reduced (24 hours) with hydrazine hydrate (4M, 40 ml) in the presence of Pd/C (1.0 g) in methanol solution (89) and the product was isolated in the usual manner to give an oil which exhibited no i.r. absorptions typical of nitrate and carbonyl groups. The oil was distilled under vacuum

(0.5 mm Hg) to give a major fraction boiling at 84° (4.33 g, 59.2 %) : i.r. 3440 (s), 1305 (s), 1105 (s), 1080 (s) and 1060 (s) cm^{-1}; n.m.r. τ 5.98 (m, W1/2 = 7 Hz), 6.28 (D_2O exch.), 6.65 (dt, J = 9 and 4 Hz), 7.1 - 7.93 (m) and 7.93 - 9.1 (m); m.s. m/e (%) 183 (M^+, 26), 140 (12), 125 (35), 124 (100), 111 (54), 98 (93) and 84 (50). This fraction solidified at room temperature, a part of which (1.5 g) was chromatographed on an alumina column (60 g). Elution with methylene chloride gave a fraction (334 mg) which showed a single spot on a t.l.c. plate. This fraction was distilled to give trans-2-piperidinocyclohexanol (II-9) : i.r. 3460 (s), 1315 (s), 1110 (s) and 1090 (s) cm^{-1}; n.m.r. τ 6.68 (dt, J = 11.0 and 4.5 Hz, H_1), 7.5 (m, 5H), 8.5 (m, 14H) and 5.07 (bs, D_2O exch., 1H).

Further elution with 5% methanol gave a mixture of cis- and trans-2-piperidinocyclohexanol II-9 as shown by the n.m.r. signals at τ 5.98 and 6.65. When this mixture was treated with p-nitrobenzoyl chloride in pyridine and was worked up in the usual manner, the starting material, a mixture of cis- and trans-alcohol II-9, was recovered.

The isomeric alcohols II-9 (2.0 g) were subsequently acetylated by stirring (24 hours) with an excess of acetic anhydride (10 ml) in anhydrous pyridine (20 ml). The reaction mixture was worked up in the usual manner to give a dark brown oil (2.16 g) which showed

strong i.r. absorptions at 1735 and 1240 cm^{-1}. A part of this oil (700 mg) was chromatographed on neutral alumina (25 g). Elution with benzene afforded an oil (125 mg) which showed a single spot on a t.l.c. plate and, on distillation at 55°/0.02 mm, gave cis-2-piperidinocyclohexyl acetate (II-11) as a colourless liquid : i.r. 2860 (m), 2800 (m), 1735 (s) and 1240 (s) cm^{-1}; n.m.r. τ 4.63 (m, W1/2 = 6.0 Hz, H_1), 7.46 (m, 5H), 7.95 (s, 3H) and 8.35 (m, 14H); m.s. m/e (%) 225 (m^+, 9), 182 (19), 166 (11), 125 (12), 124 (100), 111 (6), 110 (5), 98 (8), 84 (9) and 43 (8). It gradually decomposed on storage.

Subsequent fractions (227 mg) eluted with 0-20% chloroform in benzene consisted of mixtures of acetate II-11 and alcohols II-9 as shown by the n.m.r. signals at τ 4.63, 6.0 and 6.6. Further elution with 20 - 100% chloroform in benzene afforded a mixture (220 mg) of cis- and trans-cyclohexanols II-9.

5-4-3. Hydrolytic Decomposition of 1-Nitrato-2-piperidinocyclohexane (II-8)

A solution of NNP (5.47 g, 0.048 mol), cyclohexene (3.28 g, 0.04 mol) and concentrated hydrochloric acid (4.8 ml) in methanol (320 ml) was photolysed under oxygen as described earlier. After the completion of the photolysis (2.5 hours), the photolysate was

concentrated to a small volume under vacuum at 10°. The residual solution was diluted with water to ca. 100 ml and washed with ether. The aqueous solution was basified with saturated sodium carbonate solution to pH 8 at 0° and stirred at room temperature during which time it turned yellow and then dark brown. Aliquots (ca. 15 ml) were withdrawn at various intervals (0 hour, 20 hours and 44 hours), extracted with methylene chloride (4 x 25 ml), washed with water (3 x 20 ml) and dried over magnesium sulfate. The solvent was removed at 10° and the residual oil was analyzed by i.r., n.m.r. and g.c.-m.s. (6′ x 1/8", 20% SE - 30).

The zero-hour sample showed strong i.r. absorptions at 1625, 1275, 870 and 865 cm^{-1} for nitrate II-8, a medium intensity peak at 3430 and 1105 cm^{-1} for alcohol II-9 and at 1710 cm^{-1} for ketone II-10 : n.m.r. τ 4.5 (m, W1/2 = 7Hz, H_1 of cis-II-8), 5.0 (dt, J = 10.0 and 5.0 Hz, H_1 of trans-II-8), 6.0 (m, H_1 of cis-II-9) and 6.65 (m, H_1 of trans-II-9) in the ratio 3: 4.5 : 1 : 4.

After 20 hours, the sample showed strong i.r. absorptions at 3440, 1710, 1625, 1275, 1100, 870 and 865 cm^{-1}. The ratio of cis-II-9 : trans-II-8 : cis-II-9 : trans-II-9 was estimated to be 1 : 3 : 1.4 : 5.6 from the n.m.r. signals at τ 4.52, 4.99, 6.0 and 6.66.

After 44 hours the i.r. absorptions at 3440, 1710 and 1100 cm^{-1} increased considerably in intensity relative to the nitrate

peaks and the n.m.r. spectrum no longer showed the signal at τ 4.5 for cis II-8; the signal at τ 4.99 due to trans II-8 was very weak and could be seen only with higher amplification. The cis to trans ratio of alcohol II-9 was estimated to be 1:4 from the intensities of the signals at τ 6.0 and 6.65. Analysis by g.c.-m.s. (150° for 10 minutes, increased to 200° at a rate of 4°/minute) showed the sample to contain 7 compounds : 0.1 minutes (8 - 9 %, piperidine) m/e (%) 85 (M^+, 70), 84 (100), 70 (16), 57 (40), 56 (42), 44 (32), 43 (23) and 42 (25); 0.2 minutes (5%, 1-cyclopentene carboxaldehyde II-13) m/e (%) 96 (M^+, 69), 95 (36), 67 (100), 41 (34) and 39 (29); 0.4 minutes (3-4%, 1, 6-hexanedialdehyde II-12) m/e (%) 114 (M^+, 18), 112 (10), 70 (100), 57 (74) and 44 (26); 1.9 minutes (7-8%, unknown) m/e (%) 180 (31), 163 (100), 162 (71), 84 (79), 80 (35), 79 (34) and 77 (28); 2.2 minutes (30%, 2-piperidinocyclohexanone II-10) m/e (%) 181 (M^+, 8), 153 (15), 124 (100), 110 (30) and 84 (8); 2.3 minutes (35%, II-9) m/e (%) 183 (M^+, 14), 124 (100), 111 (12), 110 (8), 98 (31) and 84 (11); 2.8 minutes (8-9%, II-8) m/e (%) 183 (5), 180 (14), 179 (100), 178 (56), 150 (92), 124 (49) and 84 (45).

In a separate experiment, a methanol solution (320 ml) of NNP (5.47 g, 0.048 mol), cyclohexene (3.28 g, 0.04 mol) and concentrated hydrochloric acid (4.8 ml) was photolyzed as described above. The colourless photolysate was concentrated to ca. 100 ml under vacuum at 10° and subsequently stirred at room temperature with solid

sodium carbonate (pH 8-8.5). Aliquots were withdrawn at various intervals (0, 3, 24 and 96 hours) and filtered to remove insoluble inorganic salts. The solvent was evaporated at 10° and the residual pasty mass was extracted with methylene chloride. The residual oil obtained after removal of the methylene chloride was analysed by i.r., n.m.r. and g.c.-m.s. (20% SE - 30) giving results similar to those described in the previous experiment except that the II-10 : II-9 ratio was considerably lower.

5-4-4. Attempted Preparation of 1,6-Hexanedialdehyde (II-12)

A suspension of LAH (475 mg, 0.0125 mol) in THF (50 ml) was treated with t-butyl alcohol (3.0 g, 0.04 mol) and the resulting solution was added slowly with stirring to adipoyl chloride (1.098 g, 0.006 mol) in THF (50 ml) at -75°. The mixture was then slowly warmed to room temperature, hydrolyzed with water and filtered. The inorganic solid was washed several times with THF. The filtrate and the washing were combined and dried over magnesium sulfate, and the solvent was removed to give an oil which showed an i.r. absorption at 1720 cm^{-1} and a multiplet at τ 0.23 in the n.m.r. spectrum. Analysis by g.c.-m.s. (20% SE - 30, 130°, programmed to increase at 8°/minute to 200°) revealed the presence of more than 10 compounds. The first major g.c. peak was identified by m.s. as 1-cyclopentene carboxaldehyde II-13 : m/e (%) 96 (M^+, 89) 95 (44), 67 (100), 41 (35) and 39 (35).

5-4-5. Preparation of Cholest-2-ene (II-19)

Cholesterol (Fisher, 25 g) after recrystallization from ethyl acetate was hydrogenated in ethyl acetate in the preence of platinum oxide (250 mg) according to the method of Hershberg et al., [94] to give cholestanol (II-15, 21.838 g, 87%) : m.p. 138 - 142° (lit. 139 - 142°) [94]; i.r. 3360 (s) and 1045 (s) cm^{-1}; n.m.r. τ 9.35 (s), 9.18 (s), 9.08 (s) and 6.45 (m). Oxidation [96] of 20.17 g of cholestanol with sodium dichromate (21.0 g) in acetic acid (252 ml) and recrystallization of the product from ethanol-acetone (4:1) gave 3-cholestanone (II-16, 11.785 g, 59%) : m.p. 130 - 131° (lit. 127 - 128°) [96]; i.r. 1715 (s) cm^{-1}; n.m.r. τ 8.98 (s) and 9.08 (s). The ketone II-16 (10 g) was brominated [97] with 1M bromine (26 ml) in acetic acid (270 ml) to give crude 2-bromo-5-cholestan-3-one (II-17, 6.738 g, 56%) : m.p. 166 - 168° (lit. 174 - 174.5°) [97]; i.r. 1725 (s) and 580 (s) cm^{-1}; n.m.r. τ 5.24 (dd, J = 13.0 and 6.0 Hz, H_2), 8.92 (s) and 9.08 (s). The crude bromoketone II-17 (6.71 g) was reduced with sodium borohydride (0.6 g) in etnanol (250 ml) at 25° and the product was dehydrohalogenated [98] using zinc (7.538 g) in glacial acetic acid (115 ml) to give a solid (3.8 g, 71%) which was chromatographed on neutral alumina (100 g) and eluted with pentane. Evaporation of the solvent and recrystallization of the residue from a mixture of ethyl acetate and methanol gave 5α-cholest-2-ene

(II-19) : m.p. 74 - 75° (lit. 74 - 75°) [98]; i.r. 3020 (s) and 668 (s) cm^{-1}; n.m.r. τ 4.4 (m, 2H), 9.09 (s) and 9.18 (s).

5-4-6. Attempted Oxidative Addition of NND to Cholest-2-ene (II-19)

A. In Methanol

Cholest-2-ene (124 mg, 3.3×10^{-4} mol) in finely divided form was added to a solution of NND (123 mg, 16.6×10^{-4} mol) and concentrated hydrochloric acid (0.2 ml) in methanol (100 ml). After 3 hours of irradiation under oxygen, using a 100 watt Hanovia lamp and a nonex filter the nitrosamine absorption at 345 nm had disappeared completely and the mixture was filtered to give a solid (111 mg. 90%) which exhibited i.r. and n.m.r. peaks identical to those of cholest-2-ene.

B. In Amyl Alcohol.

A solution of NND (123 mg, 16.6×10^{-4} mol), cholest-2-ene (124 mg, 3.3×10^{-4} mol) and concentrated hydrochloric acid (0.2 ml) in amyl alcohol (100 ml) was irradiated as described above. After the completion of the photolysis (2.5 hours), the photolysate was concentrated under reduced pressure. The residual solution was

diluted with water and extracted with methylene chloride to give cholest-2-ene (115 mg, 93%) as shown by its i.r. and n.m.r. spectrum. The aqueous solution was basified with sodium carbonate solution and extracted with methylene chloride. On evaporation of the solvent no residue remained.

C. In Benzene

The photolysis in benzene was carried out as described above. After irradiation (2 hours), the photolysate was concentrated under vacuum. The residue was diluted with water and extracted with methylene chloride to give a semi-solid (100 mg) which exhibited i.r. absorptions due to cholest-2-ene and also at 1640, 1280 and 855 cm^{-1}. The n.m.r. spectrum showed it to be predominantly cholest-2-ene (no $N-CH_3$ absorptions). No residue remained when the aqueous solution was basified with sodium carbonate, extracted with methylene chloride and the solvent was evaporated.

D. In 1,4-Dioxane

The photolysis was repeated as described above, using dioxane (100 ml) as solvent. After irradiation (2 hours) the photolysate was worked up in the usual manner to give a neutral fraction (97 mg) which gave i.r. and n.m.r. absorption peaks characteristic of cholest-2-ene and additional bands at 1725, 1570, 1170 and 1130

cm^{-1}. No $N-CH_3$ absorptions was observed in the n.m.r. spectrum.

E. In Acetic Acid

A solution of NND (123 mg, 16.6 x 10^{-4} mol), cholest-2-ene (124 mg, 3.3 x 10^{-4} mol) and concentrated hydrochloric acid (0.2 ml) in glacial acetic acid (100 ml) was irradiated with a Rayonet 3500 Å lamp under oxygen for 5 hours. The photolysate was worked up in the usual manner to give a neutral fraction (155 mg) which showed in absorptions at 1730, 1640, 1280, 1240 and 855 cm^{-1}.

The aqueous solution was basified (pH 9-10) with sodium carbonate solution and extracted with chloroform. The chloroform extract was worked up in the usual manner and gave no residue on evaporation of the solvent.

The neutral fraction was chromatographed on neutral alumina (5 g). Elution with pentane gave II-19 (37 mg) as shown by i.r. and n.m.r. spectroscopy. The second fraction (60 mg), eluted with benzene, was tentatively assigned as 3-cholestanyl acetate on the basis of its i.r. and n.m.r. spectrum : i.r. 1745 (s), 1235 (s) cm^{-1}, n.m.r. τ 4.95 (m, W1/2 = 7 Hz), 7.98 (s), 9.08 (s), 9.18 (s) and 7.5 - 9.43 (m).

5-4-7. Preparation of trans-2-Octalin (II-24)

Tosylation of β-hydroxy-trans-decalin (Columbia, 15.4 g, 0.1 mol) was carried out as described in the literature [99] to give β-tosyloxy-trans-decalin (II-23, 25.1 g, 81.5%) : i.r. 1598 (m), 1190 (s), 1360 (s), 930 (s), 575 (s) and 560 (s) cm^{-1}; n.m.r. τ 2.33 (A - part of A_2B_2, J_{AB} = 8.0 Hz, $\Delta\nu_{AB}$ = 27 Hz, 2H), 2.68 (B - part of A_2B_2, 2H), 5.47 (m, 1H), 7.58 (s, 3H) and 8.46 (m).

Tosylate II-23 (25 g) was heated to 90° for 10 hours with sodium ethoxide prepared from 8 g of sodium and 62.5 g of ethanol [99]. The resultant mixture was steam-distilled. The ethereal extract of the distillate was washed with water and dried over magnesium sulfate. The solvent was evaporated and the residue was chromatographed on neutral alumina using pentane as eluant, to give crude trans-2-octalin (II-24, 8.16 g, 74%) : i.r. 3015 (s), 1445 (s), 720 (s) and 655 (s) cm^{-1}; n.m.r. τ 4.42 (m, 2H), 8.03 (m) and 8.55 (m). V.p.c. analysis (20% SE-30, 130°) of the crude product showed the presence of ca. 10% of an impurity (probably the Δ′-isomer).

5-4-8. Oxidative Addition of NND to trans-2-Octalin (II-24)

A methanol solution (320 ml) of NND (0.89 g, 0.012 mol), trans-2- octalin (1.36 g, 0.01 mol) and perchloric acid (70%, 2 ml) was irradiated with a 200 watt Hanovia lamp using a nonex filter under oxygen at 0°. After irradiation (1 hour), the colourless photolysate was concentrated to a small volume under vacuum. The residual solution was diluted with water and extracted with ether to give unreacted trans-2-octalin (0.3 g, 22.1%). The aqueous solution was cooled to 5°, basified (pH 10) with saturated sodium carbonate solution and extracted with methylene chloride to give a colourless oil (1.6 g) : i.r. 3440 (W), 1715 (W), 1623 (s), 1278 (s), 1040 (m) and 863 (s) cm^{-1}; n.m.r. τ 4.93 (m, W1/2 = 21 Hz), 6.17 (bs, D_2O exch.), 6.62 (m), 7.7 (s), 7.73 (s) and 8.52 (m).

This oil turned dark brown on standing at room temperature. After 72 hours the intensities of the i.r. absorptions at 3440 and 1040 cm^{-1} increased considerably while those of the nitrate peaks decreased. The carbonyl absorption at 1715 cm^{-1} remained weak. The n.m.r. spectrum did not show any aldehyde protons, not even after storage of the sample for several additional days. In the n.m.r. spectrum, the peak intensities at τ 4.93 (m) and 7.73 (s) decreased while those at τ 6.62 (m) and 7.7 (s) increased.

5-4-9. Oxidative Addition of NNP to Bicyclo[2,2,1]hept-2-ene

A methanol solution (300 ml) of NNP (6.84 g, 0.06 mol), bicyclo [2,2,1]hept-2-ene (Aldrich, b.p. 95-96°, 3.76 g, 0.04 mol) and perchloric acid (60%, 10 ml) was irradiated (200 watt Hanovia lamp) through a nonex filter under oxygen at 0° for 4.5 hours. At the end of photolysis, the absorption at 345 nm disappeared completely and a colourless solution was obtained. The solvent was distilled under reduced pressure at 10°. The residue was crystallized from ethyl alcohol-petroleum ether to afford a white solid (2.61 g, 19%) which was recrystallized from methanol to give a mixture of the perchlorates of endo-2-nitrato-exo-3-piperidinobicyclo[2,2,1]heptane (II-29a) and exo-2-nitrato-exo-3-piperidinobicyclo[2,2,1]heptane (II-28a) : m.p. 130-162° (decomposition with evolution of gas); i.r. 1645 (s), 1275 (s), 1100 (s), 1080 (s), 1065 (s) and 840 (s) cm^{-1}; n.m.r. (DMSO-d_6) τ 1.0 (m, D_2O exch., 1H), 4.58 (t, J = 4Hz) and 4.73 (d, J = 7Hz). The intensity ratio of the last two signals was 1:1.

After separating the salts, the filtrate was evaporated under vacuum, and the residue was washed with ether and neutralized with saturated potassium carbonate solution to pH 7.5. Subsequent extraction with methylene chloride gave a reddish oil (4.81 g) which was not investigated further : i.r. 1740, 1720, 1620, 1275 and 865 cm^{-1}.

A methanol solution (300 ml) of NNP (5.472 g, 0.048 mol), bicyclo[2,2,1]hept-2-ene (3.76 g, 0.04 mol) and concentrated hydrochloric acid (4.8 ml) was irradiated as described above. After the completion of the photolysis (2 hours), the photolysate was concentrated to ca. 100 ml under vacuum at 10^{o} and hydrogenated at 60 p.s.i. in the presence of platinum oxide (500 mg) for 48 hours after which time no more hydrogen was absorbed. An aliquot of the solution was withdrawn and was worked up in the usual manner to give a basic oil showing strong absorptions at 1620, 1280 and 865 cm^{-1} due to a nitrate group, at 1745 cm^{-1} for a carbonyl group and medium intensity peaks at 3300 and 1100 cm^{-1} for a hydroxyl function. Subsequent hydrogenation with platinum black and Pd/C (5%), respectively, as catalysts at 60 p.s.i. gave identical results.

A crude basic fraction (7 g) was dissolved in anhydrous THF (50 ml) added to a suspension of LAH (3.04 g, 0.08 mol) in THF (50 ml) and stirred for 24 hours. The resultant reaction mixture was hydrolyzed with water and filtered. The solid was washed thoroughly with THF. The filtrate and washings were combined and dried over magnesium sulfate and the solvent was evaporated to give a viscous, colourless oil (6.25 g) : i.r. 3360 (s), 1105 (m), 1050 (s) and 1010 (m) cm^{-1}; n.m.r. τ 5.93 (m), 6.35 (m, partial D_2O exch.), 7.63 (m) and 8.5 (m).

Treatment with ether containing a small amount of HCl afforded a crystalline solid (500 mg, 5%) which was recrystallized from methanol to give the hydrochloride of exo-3-piperidino-endo-bicyclo[2,2,1]heptan-2-ol (II-34a) : sublimation point 165°; i.r. 3345 (s), 3295 (s), 2660 (s), 2550 (m), 1090 (s), 1080 (s) and 1070 (s) cm^{-1}; n.m.r. (D_2O) (see Figure 2.2) τ 5.76 (t, J = 4.0 Hz, H_2), 6.70 (m, 4H), 7.36 (d, J = 4 Hz, H_3), 7.38 (m, H_1), 7.58 (m, H_4) and 8.30 (m, 12 H); m.s. m/e (%) 195.1633 (24; calcd. 195.1623), 194 (6), 178 (8), 138 (88), 124 (42), 111 (73), 98 (100) and 84(30). On irradiation of the signals at τ 7.35 (H_3) and 7.38 (H_1), the triplet resonance at τ 5.76 (H_2) collapsed to a singlet. When the triplet at τ 5.76 (H_2) was irradiated, the doublet at τ 7.36 Hz(H_3) collapsed to a singlet.

Anal. calcd. for $C_{12}H_{22}NOCl$: C, 62.19, H, 9.57; N, 6.05. Found : C, 61.91; H, 9.67; N, 6.16.

The hydrochloride (30 mg) was dissolved in saturated sodium carbonate solution and extracted with methylene chloride to give the free base of alcohol II-34a (20 mg) : m.p. 95-97°; i.r. 3200 (s, b), 2830 (s), 1060 (s) and 1045 (s) cm^{-1}; m.s. m/e (%) 195 (M^+, 41), 194 (10), 178 (11), 152 (22), 138 (100), 124 (55), 111 (87), 110 (27), 98 (93) and 84 (33).

5-4-10. Oxidative Addition of NND to Bicyclo[2,2,1]hept-2-ene

A solution of NND (3.552 g, 0.048 mol) bicyclo[2,2,1]-hept-2-ene (3.76 g, 0.04 mol) and concentrated hydrochloric acid (4.8 ml) in methanol (320 ml) was photolysed as described above. After irradiation (2 hours), the methanol was removed at 10°. The residual solution was diluted with water and extracted with ether to give an oil (480 mg) which showed several spots on a t.l.c. plate and gave rise to a complex n.m.r. spectrum containing no $N-CH_3$ absorptions. The aqueous solution was basified (pH 8.5) with saturated sodium carbonate solution and extracted with methylene chloride to give a yellow oil containing at least 10 compounds (g.c. analysis at 150°, 20% SE-30) : i.r. 2830 (m), 2780 (m), 2720 (m), 1745 (m), 1720 (s), 1625 (s), 1280 (s), and 870 (m) cm^{-1}; n.m.r. τ 0.22 (d, J = 2 Hz), 0.35 (d, J= 2 Hz), 7.52 (s), 7.69 (s) and 7.78 (s).

The crude basic fraction was reduced with LAH (3.42 g, 0.09 mol) in THF (100 mol) for 24 hours and the product was isolated in the usual manner to give an oil (3.5 g) which exhibited i.r. absorptions at 3400, 1050 and 1035 cm^{-1} due to a hydroxyl function. Neutral products (350 mg) formed by decomposition of the nitrate before LAH reduction were removed by extraction. The basic fraction (1.76 g, 19%) contained exo-3-dimethylamino-endo-bicyclo[2,2,1]heptan-2-ol (II-34b) and

exo-3-dimethylamino-exo-bicyclo[2,2,1]-heptan-2-ol (II-35b) in the ratio 3:7 as shown by the intensities of the N-CH_3 singlets at τ 7.80 and 7.71 and by t.l.c. (two intense spots) : i.r. 3400 (s), 2830 (s), 2780 (s), 1140 (m), 1050 (s) and 1035 (s) cm^{-1}.

Chromatography of a portion of this mixture (500 mg) on neutral alumina (45 g) and elution with 0-10% chloroform in benzene gave an oil (92 mg) which showed one spot on a t.l.c. plate and a single peak at 5.3 minutes on the gas chromatogram (20% SE-30, 150°) and which, on distillation at 25°/0.03 mm afforded pure exo-alcohol II-35b as a colourless oil : i.r. 3300 (m), 2830 (m), 2785 (m), 1050 (s) and 1035 (s) cm^{-1}; n.m.r. (see Figure 2.3) τ 6.40 (dd, J = 1.3 and 6.3 Hz, H_2), 7.62 (s, 6H), 7.73 (m, H_3), 7.80 (m, H_1), 8.23-8.79 (m, 4H), 8.88 (m, 2H), 8.95 (m, H_7 anti) and 5.18 (m, D_2O exch., 1H); m.s. (90°) m/e (%) 155 (M^+, 15), 154 (21), 126 (38), 124 (15), 98 (54), 84 (44), 71 (48) and 58 (100). On irradiation of tne multiplet at τ 8.95 (H_7 anti), the double doublet at τ 6.40 (H_2) collapsed to a doublet (J = 6.3 Hz) and the fine-splitting in the multiplets centered at τ 7.73 (H_3) and 7.80 (H_1) disappeared. On irradiation of the multiplets at τ 7.73 (H_3) and 7.80 (H_1), the double doublet at τ 6.40 (H_2) collapsed to a doublet (J = 1.3 Hz) and the fine- splitting in the multiplets at τ 8.95 (H_7 anti) and 8.88 (H_7 syn) disappeared. Irradiation at τ 6.40 (H_2) eliminated the large splitting in the multiplet centered at τ 7.73 (H_3).

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02.
Found : C, 69.30, H, 11.01; N, 9.20.

Subsequent fractions (392 mg) eluted with 20-50% chloroform in benzene consisted of various mixtures of endo-alcohol II-34b and exo-alcohol II-35b and showed to peaks (5.3 and 5.7 minutes) on the gas chromatogram (20% SE-30, 150°); i.r. 3400 (s), 1050 (s) and 1035 (s0 cm^{-1}; n.m.r. τ 7.73 (s) and 7.9 (s).

In a separate experiment, a solution of NND (3.552 g, 0.048 mol), bicyclo[2,2,1]hept-2-ene (3.76 g, 0.04 mol) and concentrated hydrochloric acid (4.8 ml) in methanol (320 ml) was irradiated as described above. The methanol was distilled under reduced pressure, and the residue was washed with ether and basified to pH10 with saturated sodium carbonate solution. The aqueous solution was left for 24 hours and then extracted with methylene chloride to give a reddish oil (2.3 g) which was reduced (24 hours) with LAH (1.52 g, 0.04 mol) in ether. The product was isolated in the usual manner to give a basic fraction (310 mg, 5%) : i.r. 3350 (s), 1050 (s) and 1030 (s) cm^{-1}; n.m.r. τ 6.55 (dd, J = 6.5 and 1.5 Hz) and 7.67 (s). This oil was purified by chromatography on neutral alumina to give exo-alcohol II-35b. No endo-alcohol II-34b was detected in the n.m.r. spectrum of the crude product.

The neutral fraction from the LAH reduction was isolated in the usual manner and an aliquot (233 mg) was heated with p-nitrobenzoyl chloride (555 mg, 0.003 mol) in pyridine (10 ml) on a steam bath for one hour. The reaction mixture was poured into ice-water which resulted in the separation of a solid which was washed thoroughly with sodium carbonate solution followed by water. It was recrystallized from methanol to give the bis-p-nitrobenzoate of 1,3-bis-hydroxymethylcyclopentane (II-40, 356 mg, 46%) : m.p. 117-118°; i.r. 1720 (s), 1605 (m), 1530 (s), 1520 (s), 1345 (s), 1285 (s), 1275 (s), 1120 (s), 1100 (s) and 720 (s) cm^{-1}; n.m.r. τ 1.74 (m, 8H), 5.65 (m, 4H), 7.48 (m, 2H) and 7.25-9.11 (m, 6H); m.s. (240°) m/e (%) 428 (M^+, < 0.1), 261 (4), 150.0228 (63; calcd. 150.0191) 104 (22), 94.0762 (100; calcd. 94.0782) and 79 (56).

Anal. Calcd. for $C_{21}H_{20}N_2O_8$: C, 58.88; H, 4.71; N, 6.54. Found : C, 58.86, H, 4.64; N, 6.70.

A portion of the crude basic photolysis product (300 mg) was treated with 2,4-dinitrophenylhydrazine solution in ethanol at room temperature and the crude yellow product (821 mg, 71%) was recrystallized from acetone to give 2,4-DNPH of 1,3-bis-formyl-cyclopentane II-39 m.p. 224-225° [lit. 225-226° (150)].

5-4-11. Decomposition of endo-2-Nitrato-exo-3-dimethylaminobicyclo[2,2,1]heptane (II-29b)

A methanol solution (320 ml) of NND (3.552 g, 0.048 mol), bicyclo [2,2,1]hept-2-ene (3.76 g, 0.04 mol) and concentrated hydrochloric acid (4.8 ml) was photolysed under an oxygen atmosphere as described before. The solution was concentrated by evaporation of most of the methanol at 10°, diluted with ether and left at -5° for several months to afford a small amount (600 mg) of a solid which was recrystallized from 2-propanol to give the hydrochloride of endo-2-nitrato-exo-3-dimethylamino-bicyclo[2,2,1]heptane (II-29b) as a white crystalline compound : m.p. (161-162° (d); i.r. 3100 (w), 1645 (s), 1310 (s), 1285 (s), 1100 (s, b) and 850 (s) cm^{-1}; n.m.r. (methanol $-d_4$) (see Figure 2-1) τ 4.65 (t, J = 4.0 Hz, H_2), 6.82 (dd, J = 4.0 and 2.5 Hz, H_3), 7.03 (s, 6H), 7.24 (m, 2H) and 7.95-8.74 (m, 6H). Irradiation of the signals at τ 6.82 (H_3) and 7.24 (H_1 and H_4) resulted in the collapse of the triplet resonance at τ 4.65 (H_2) to a singlet and changed the coupling pattern of the multiplet at τ 7.95-8.74. When the complex multiplet at τ 7.95-8.74 was irradiated, the double doublet at τ 6.82 (H_3) collapsed to a doublet (J = 4.0 Hz).

The hydrochloride II-29b (300 mg) was then dissolved in water and basified with saturated sodium carbonate solution to pH10 at

0^{o}. The solution was immediately extracted with methylene chloride, the extract was washed with cold water and dried over magnesium sulfate, and the solvent was evaporated to give an oil (238 mg) : i.r. 3350 (w), 2830 (s), 2780 (s), 1745 (w), 1720 (m), 1625 (s), 1285 (s), 870 (s) and 855 (s) cm^{-1}; n.m.r. τ 0.37 (m), 5.03 (t, J = 3.5 Hz) and 6.41 (d, J = 6.0 Hz) in the ratio 3.5:4.5:2. At various intervals (17, 24 and 44 hours), aliquots were withdrawn from this oil at room temperature (the mixture darkened on standing) and analyzed by i.r., n.m.r. and g.c.-m.s. (20% SE-30).

After 17 hours, the sample showed strong i.r. absorptions at 1720 cm^{-1} for dialdehyde II-39, at 1625, 1285, 870 and 855 cm^{-1} for endo-nitrate II-30b and a weak peak at 3350 cm^{-1} for exo-alcohol II-35b. The ratio of II-39 : II-30b : II-35b was estimated to be 3.5:4:2 from the n.m.r. signals at τ 0.37, 5.02 and 6.35. After 24 hours, this ratio had changed to 5:2:2; the intensity of absorption at 3350 cm^{-1} remained weak while that at 1720 cm^{-1} had increased considerably compared to that of the nitrate peaks.

After 44 hours, the absorption at 3350 cm^{-1} was still weak but the intensity at 1720 cm^{-1} had increased enormously at the expense of the nitrate absorptions; the weak carbonyl absorption of II-37b (1745 cm^{-1}) observed for the zero-hour sample was now a

barely visible shoulder merging with the 1720 cm^{-1} band. The sample was analyzed by g.c.-m.s. (100 to 200°, programmed to increase at 10°/minute) and found to be a mixture of four compounds with the following retention times : 1.03 minutes (30.5%, cis-II-39) m/e (%) 126 (M^+, 47), 108 (11), 98 (26), 97 (27), 80 (23) 79 (100), 70 (48), 69 (30), 67 (88) and 57 (52); 1.07 minutes (30.5%, trans-II-39) m/e (%) 126 (M^+, 6), 98 (48), 80 (22), 79 (30), 67 (43) and 57 (100); 1.27 minutes (8.4%, unknown) m/e (%) 125 (21), 85 (10) and 84(100); 1.33 minutes (30.5%, II-35b) m/e (%) 155 (M^+, 35), 140 (26), 126 (49), 98 (100), 84 (74), 71 (81), 58 (86), 45 (27), 44 (42) and 42 (37).

5-4-12. Oxidative Addition of NNP to Bicycly[2,2,1]hepta-2,5-diene

A methanol solution (300 ml) of NNP (2.736 g, 0.024 mol), bicyclo [2,2,1]heptadiene (Aldrich, b.p. 89.5-90.5°, 1.84 g, 0.02 mol) and perchloric acid (60%, 4 ml) was irradiated (200 watt Hanovia lamp) through a nonex filter under oxygen at 0° for 1.5 hours. The colourless solution obtained after complete disappearance of the 347 nm absorption was concentrated under reduced pressure at 10° to afford a crystalline solid (0.628 g) which was filtered and recrystallized from methanol to give the perchlorate of endo-3-

nitrato-exo-5-piperidinotricyclo[2,2,1,$0^{2,6}$]heptane (II-42b) : m.p. 175-217° (decomp.) ; i.r. 3100 (s), 1630 (s), 1280 (s), 1110 (s), 1070 (s, b) 1030 (s), 1000 (s), 850 (s) and 620 (s) cm^{-1}; n.m.r. (DMSO - d_6) τ 1.58 (m, D_2O exch.), 4.86 (bs, W1/2 = 5 Hz), 6.46 (m), 6.94 (m), 7.28 (bs, W1/2 = 6Hz), 7.94 (dd, J = 5, 10Hz) and 8.18 (m).

The filtrate was hydrogenated at 60 p.s.i. in the presence of platinum black (250 mg) for 48 hours after which time no more hydrogen was absorbed. The usual work-up gave an oil which showed strong i.r. absorptions at 1625, 1280 and 865 cm^{-1} due to a nitrate group. This oil was treated with sodium borohydride (0.757 g) in ethanol at room temperature for 12 hours. The resulting solution was hydrolysed with dilute hydrochloric acid followed by basification with sodium carbonate. Extraction with methylene chloride gave an oil (2.8 g) showing strong absorptions at 3400 and 1080 cm^{-1} for a hydroxyl function and a medium peak at 1745 cm^{-1} for a carbonyl group.

5-4-13. Oxidative Addition of NND to Bicyclo[2,2,1]hepta-2,5-diene

A solution of NND (3.552 g, 0.048 mol), bicyclo [2,2,1]hepta-2, 5-diene (3.68 g, 0.04 mol) and perchloric acid (60%, 8 ml) in

methanol (300 ml) was photolysed as described above. After irradiation (4 hours), the photolysate was filtered to afford a white solid (1.19 g, 10%) which was recrystallized twice from ethanol-water to give the perchlorate of endo-3-nitrato-exo-5-dimethylaminotricyclo[2,2,1,^{2,6}]heptane (II-42a): m.p. 211-215° (decomp.); i.r. 3140 (s), 1635(s), 1305 (s), 1290 (s), 1100 (s, b), 1070 (s), 1060 (s), 1040 (s), 870 (s), 838 (s), 828 (m), 810 (m) and 760 (m) cm^{-1}; n.m.r. (DMSO-d_6) (see Figure 2-5) τ 1.16 (m, D_2O exch., NH), 4.80 (t, J = 1.5 Hz, H_3), 6.35 (d, J = 9 Hz, H_5), 7.04 (d, J = 4.5 Hz, N-CH_3), 7.22 (d, J = 4.5 Hz, N-CH_3), 7.31 (d, J = 1.5 Hz, H_4), 7.94 (t, J = 5.2 Hz, H_6) and 8.21 (m, 4H).

Anal. Calcd. for $C_9H_{15}N_2O_7Cl$: C, 36.19; H, 5.06; N, 9.38.
Found : C, 36.22; H, 5.01; N, 9.33.

The filtrate was concentrated to a small volume, treated with water (50 ml) and extracted with ether (50 ml x 3) to give an oil (620 mg) which showed several spots on a t.l.c. plate and a complex n.m.r. spectrum containing no N-CH_3 absorptions. The aqueous acidic solution was basified with saturated sodium carbonate solution and extracted with methylene chloride (50 ml x 5) to give a reddish brown oil (3.3 g): i.r. 2830 (s), 2780 (s), 1625 (s), 1295 (s), 1280 (s), and 865 (s) cm^{-1}; n.m.r. τ 5.20 (t, J = 1.5 Hz, 1H) and 7.82 (s, 6H).

A portion of this oil (1 g) was chromatographed on neutral alumina (30 g) with chloroform as eluant to give two main fractions the second of which (272 mg) was shown to contain mostly the nortricyclyl nitrate II-46 on the basis of spectral and t.l.c. analysis. The first fraction (683 mg) showed more than one spot on a t.l.c. plate and its i.r. spectrum exhibited characteristic absorptions for a nitrate group. This fraction was rechromatographed on neutral alumina (40 g), using benzene as eluant, to give an initial fraction (94 mg) which showed again the characteristic nitrate absorptions at 1620, 1280 and 865 cm^{-1} and which was found by n.m.r. analysis to contain exo-3-nitrato-exo-5-dimethylaminotricyclo[2,2,1,$0^{2,6}$]heptane (II-46, vide infra) and probably endo-2-nitrato-exo-3-dimethylaminobicyclo [2,2,1] hept-5-ene (II-47) as well as exo-2-nitrato-exo-3-dimethylaminobicyclo[2,2,1]hept-5-ene (II-48) in the ratio 3.1:1.9:2.7. n.m.r. τ 3.68 (d of dd, J = 6.0, 3.5 and 1.0 Hz, 1H), 4.08 (d of dd, J = 6.0, 3.0 and 0.5 Hz, 1H) 4.37 (q, J = 3.0 Hz, 2H), 5.18 (t, J = 1.5 Hz, 1H), 7.75 (s, 6H), 7.81 (s, 6H) and 7.87 (s, 6H).

Further fractions (349 mg) eluted with 0-50% chloroform in benzene were mixtures containing mostly the exo-nitrate II-46 as shown by the presence of the n.m.r. signal at τ 7.82.

The crude basic fraction (2.3 g) was reduced with LAH (2.28 g) in THF (200 ml) for 24 hours to give a viscous oil (1.96 g) which exhibited i.r. absorptions at 3360, 1055 and 1040 cm^{-1} due to a hydroxyl function. Chromatography on neutral alumina (60 g) with benzene as eluant gave an initial fraction (165 mg) which was found to be butylated hydroxy toluene, a stabilizing agent present in the reagent grade THF used for the extraction. m.p. 62-63.5°; i.r. 3640 (s), 1315 (s), 1250 (s), 1230 (s), 1155 (s), 1120 (s) and 860 (s) cm^{-1}. Elution with 10-50% chloroform in benzene gave a semi solid (615 mg) which was sublimed at 20°/0.5 mm to give exo-5-dimethylamino-exo-tricyclo [2,2,1,$0^{2,6}$]heptan-3-ol (II-50) as fine needles : m.p. 82- 84°; i.r. 3140 (s), 3060 (s), 3005 (s), 2830 (s), 2785 (s), 1093 (s), 1040 (s), 1008 (s), 820 (s) and 805 (s) cm^{-1}; n.m.r. (see Figure 2.8) τ 8.65 (m, 3H), 8.29 (A - part of AB, J_{AB} = 11.0 Hz, $\Delta\nu_{AB}$ = 9.5 Hz, each peak further split into a triplet, J = 1.0 Hz, H_7 anti), 8.20 (B - part of AB, each peak further split into a triplet, J = 1.0 Hz, H_7 syn), 8.08 (m, 2H), 8.04 (m, D_2O exch., 1H), 7.84 (s, 6H) and 6.21 (t, J = 1.5 Hz, H_3); m.s. (125°) m/e (%) 153.1146 (M^+, 100; calcd. 153.1154), 152 (26), 136.1137 (60; calcd. 136.1126), 108.0561 (100; calcd. 108.0575), 91.0525 (81, calcd. 91.0548), 84 (79), 79 (73), 71 (55), 69 (63) and 58 (50). Irradition of either multiplet at τ 8.65 (H_2) or at τ 8.08 (H_4) resulted in the collapse of the triplet at τ 6.21 (H_3) to a doublet (J = 1.5 Hz). The n.m.r. spectrum of II-50 was taken in the prsence of $Eu(DPM)_3$ in $CDCl_3$; the chemical shift values are listed in Table 2.8 (see Results).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87, N, 9.14. Found : C, 70.70, H, 10.17, N, 9.15.

Subsequent elution with chloroform gave a mixture (348 mg) which contained alcohol II-50 and 1,4-butanediol. The latter compound was presumably formed by the action of LAH on THF. Elution with 5% methanol in chloroform gave a fraction (321 mg) containing mostly 1,4-butanediol and a small amount of II-50. Further elution with 10% methanol in chloroform gave a fraction (84 mg) consisting of an unidentified compound: i.r. 3360 (s, b), 2830 (s), 2790 (s) and 1025 (s, b) cm^{-1}; n.m.r. τ 5.88 (bs), 6.32 (dt, J = 6.5 and 2.5 Hz), 7.20-8.0 (m) and 8.0-8.97 (m).

5-4-14. Reduction of endo-3-Nitrato-exo-5-dimethylaminotricyclo[2,2,1,$0^{2,6}$]heptane (II-45)

The perchlorate salt of endo-3-nitrato-exo-5-dimethylaminotricyclo[2,2,1,$0^{2,6}$]heptane (II-42a) was dissolved in cold water, neutralized with saturated sodium carbonate solution and immediately extracted with ether to give nitrate II-45 as a colourless oil : i.r. 3080 (m), 2830 (s), 2780 (s), 1625 (s), 1305 (s), 1280 (s), 1270 (s), 985 (s), 865 (s), 830 (s) and 815 (m) cm^{-1}; n.m.r. (CCl_4) τ 5.10 (t, J = 1.5 Hz, H_3), 7.45 (t, J = 1.5 Hz, H_5), 7.80 (s, 6H), 7.90 (m, H_4), 8.10 (m, H_6) and 8.48 (m, 4H).

A solution of this oil (400 mg) in dry ether (50 ml) was added to a suspension of LAH (304 mg, 0.008 mol) in dry ether (100 ml) at 0°. The reaction mixture was stirred for 24 hours at room temperature, hydrolyzed with calculated amount of water and filtered. The inorganic solid was washed thoroughly with ether, and the filtrate and the washings were combined and dried over magnesium sulfate. After removal of the ether a low melting solid (250 mg) remained which was purified by sublimation at 20°/0.5 mm to give white crystals of

exo-5-dimethylamino-endo-tricyclo[2,2,1,$0^{2,6}$]heptan-3-ol (II-49): m.p. 95-98°; i.r. 3140 (s, b), 3070 (s), 2835 (s), 2790 (s), 1325 (s), 1310 (s), 1082 (s), 825 (m), 812 (m) and 805 (m) cm^{-1}; n.m.r. (see Figure 2-7) τ 6.01 (t, J = 1.6 Hz, H_3), 7.36 (bs, H_5), 7.75 (s, 6H), 8.11 (m, H_4), 8.20 (A part of AB, J_{AB} = 10.5 Hz, each line further split into a triplet, J = 1.0 Hz, H_7 anti), 8.63 (m, 3H) and 8.71 (B part of AB, each line further split into a triplet, J = 1.0 Hz, H_7 syn) m.s. (50°) m/e (%) 153.1128 (M^+, 100; Calcd. 153.1154), 152 (31), 138 (46), 136.1109 (100; Calcd. 136.1126), 110 (31), 109 (31), 108.0565 (52; Calcd. 108.0575), 107 (25), 94 (46), 91.0527 (88; Calcd. 91.0548), 84 (55), 79 (86), 77 (47), 71 (39), 69 (100) and 58 (43). On irradiation of the multiplet at τ 8.63 (H_2), the triplet at τ 6.01 (H_3) collapsed to a doublet (J = 1.6 H_2). The n.m.r. spectrum of II-49 was recorded in the presence of $Eu(DPM)_3$ in $CDCl_3$; the chemical shifts are listed in Tables 2.7 and 2.9 (see Results).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found : C, 70.76, H, 9.96; N, 9.05.

5-4-15. Oxidation of exo-5-Dimethylamino-endo-tricyclo [2,2,1,$0^{2,6}$]heptane-3-ol (II-49) and its exo-Isomer(II-50)

A solution of endo-alcohol II-49 (100 mg, 6.5 x 10^{-4} mole) in acetone (2 ml) was stirred with Jones reagent (7 x 10^{-4} mole) at room temperature for 3 hours (101). Water (2 ml) was added, and the acetone was evaporated. The resulting mixture was basified with sodium carbonate solution and extracted with methylene chloride to give an oil (85 mg) which was distilled at 20°/0.5 mm to give exo-5-dimethylaminotricyclo[2,2,1,$0^{2,6}$]heptan-3-one (II-51) as a colourless oil : i.r. 3073 (m), 3030 (m), 2830 (s), 2783 (s), 1760 (s), 1055 (s), 1045 (s), 863 (s), 855 (m), 838 (s) and 805 (m) cm^{-1}; n.m.r. τ 7.50 (t, J = 1.0 Hz, H_5), 7.69 (m, H_7 syn), 7.75 (s, 6H), 7.83 (m, 2H), 7.99 (m, H_1), 8.12 (d, J = 10.5 Hz, each line further split into a triplet, J = 1.5 Hz, H_7 anti) and 8.50 (t, J = 5.5 Hz, each line further split into a doublet, J = 1.0 Hz, H_6); m.s. (120°) m/e (%) 151.1010 (M^+, 100; Calcd. 151.0997), 123 (34), 122 (57), 108 (36), 107 (33), 94 (27), 82 (39), 79 (82), 77 (50) and 69 (48).

Oxidation of the exo-alcohol II-50 (80 mg) with Jones reagent (101) in acetone as described above and distillation of the crude product (40 mg) at 20°/0.5 mm afforded the same tricyclic ketone II-51.

5-4-16. Addition Of NND To 5-Methylenebicyclo[2,2,1]hept-2-ene

A solution of NND (3.552 g, 0.048 mol), 5-methylenebicyclo[2,2,1]hept-2-ene (Aldrich, b.p. 35°/35 mm, 4.24 g, 0.04 mol) and concentrated hydrochloric acid (4.8 ml) in methanol (320 ml) was cooled to 0° and was irradiated with a 200 watt Hanovia lamp through a nonex filter under nitrogen. During the irradiation the u.v. absorption at 295 nm for a C-nitroso dimer built up gradually and reached its maximum intensity after 5 hours at which time the irradiation was stopped and sodium carbonate was added with stirring. Evaporation of the solvent at 10° gave a dark brown oil (6.5 g): i.r. 3240 (s, b), 3060 (m), 1265 (s), 1030 (s) and 930 (s) cm^{-1}; n.m.r. τ 3.40 (m, D_2O exch.), 3.73-4.32 (m), 4.83-5.35 (m), 6.88 (bs), 7.67 (s) and 7.70 (s).

A portion of this residue (2.0 g) was chromatographed on a silicic acid column (60 g) and eluted with methylene chloride containing increasing amounts of methanol. Elution with 1% methanol in methylene chloride gave a bluish oil which exhibited u.v.

absorptions at 207 (shoulder), 242 (ϵ 1530) and 292 (ϵ 113) nm and decolourized rapidly. Distillation of this fraction (400 mg) at 20°/3.5 mm afforded N-hydroxy-3-dimethylaminomethyl-2-azabicyclo[3,2,1]octa-3,6-diene (II-53) : u.v. (CH_3OH) 208 (shoulder) and 423 (ϵ 1620) ; i.r. ($CHCl_3$) 3380 (m), 3060 (m), 2830 (s), 2785 (s), 1620 (m), 1268 (s), 1038 (s), 1018 (s), 988 (s), 930 (s), 905 (s), 845 (s), 825 (s) and 695 (m) cm^{-1}; n.m.r. (see Figure 2.10) τ 3.95 (d of dt, J = 5.6, 2.0 and 1.0 Hz, H_7), 4.21 (d of q, J = 5.6 and 2.0 Hz, H_6), 5.15 (m, H_4), 6.93 (m, 2H), 7.7 (s, 6H) and 7.0-8.12 (m, 5H); ^{13}C n.m.r. ppm (from TMS) 169.8 (C-3), 136.3 (C-7), 128.8 (C-6), 83.7 (C-4), 62.5 ($N-CH_2$), 45.2 ($N-CH_3$), 39.3 (C-1), 35.5 (C-8), and 26.4 (C-5); m.s. m/e (%) 180.1244 (M^+, 1; Calcd. 180.1263), 163 (1), 138 (11), 137.0822 (100; Calcd. 137.0840), 120.0798 (62; Calcd. 120.0813), 79 (31), 58 (100), 44 (30) and 42 (33).

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95; N, 15.54. Found : C, 66.77; H, 8.99; N, 15.47.

Elution with 5% methanol in methylene chloride gave several fractions (100 mg) containing mostly II-53 contaminated with a small amount of a compound with a lower R_f value. The major component present in the fraction (60 mg) eluted with 10% methanol in methylene chloride was tentatively assigned as bicyclo-[2,2,1]hept-5-en-2-one oxime (II-55): i.r. 3240 (s, b),

3060 (s), 1650 (w), 1080 (s), 1035 (s), 1000 (s) and 940 (s) cm^{-1}; n.m.r. τ 4.02 (m).

Elution with 20-50% methanol in methylene chloride gave a mixture (325 mg) of 2-dimethylaminomethyltricyclo[2,2,1,$0^{2,6}$]heptan-5-one (II-56) and the corresponding oxime II-54. The remaining material (120 mg), eluted with 50-100% methanol in methylene chloride, was mainly one compound (by t.l.c.) which, after two sublimations, gave 2-dimethylaminomethyltricyclo[2,2,1,$0^{2,6}$]heptan-5-one oxime (II-54) as a white crystalline solid: m.p. 67-68°; i.r. 3240 (s, b), 2820 (s), 2780 (s), 1265 (s), 1020 (s), 1040 (s), 920 (s), 880 (s), 860 (s) and 840 (s) cm^{-1}; n.m.r. τ 1.85 (m, D_2O exch., 1H), 6.84 (m, 1H), 7.38 (m, 2H), 7.55 (m, 1H), 7.77 (s, 6H), 7.78 (m, 1H) and 8.27 (m, 4H); m.s. m/e (%) 180 (M^+, 23), 163 (40), 91 (25), 85 (21), 84 (100) and 58 (100).

A methanol solution (320 ml) of NND (3.552 g, 0.048 mol), 5-methylenebicyclo[2,2,1]hept-2-ene (4.24 g, 0.04 mol) and concentrated hydrochloric acid (4.8 ml) was irradiated as described above. After the completion of the photolysis (5 hours), the yellow photolysate was concentrated to a small volume under vacuum at 10°. The residual solution was diluted with water to ca. 100 ml and extracted with ether (4 x 50 ml) to give an oil (95 mg) which showed several spots on a t.l.c. plate.

The aqueous acidic solution was basified (pH 9-10) with saturated sodium carbonate solution, extracted with methylene chloride (8 x 50 ml) and worked up in the usual manner to give a brown coloured oil (4.21 g): i.r. 3200 (m, b), 3060 (m), 1755 (s), 1265 (s), 1030 (s), 1095 (m), 1060 (m) and 840 (m) cm^{-1}; n.m.r. τ 3.95 (m), 4.22 (m), 5.18 (m), 6.93 (bs), 7.75 (s) and 7.0-9.2 (m). Chromatography of this oil (2.0 g) on neutral alumina (60 g) and elution with methylene chloride afforded the azabicyclic compound II-53 (218 mg). The fractions (505 mg) eluted with 1% methanol in methylene chloride consisted of a mixture of II-53 and the tricyclic ketone II-56 and were rechromatographed on silicic acid (12 g) to afford pure II-53 (148 mg) on elution with methylene chloride. Subsequent elution from the silicic acid column with 2-10% methanol in methylene chloride gave an oil (118 mg) which was distilled at 20^{o}/0.2 mm to give 2-dimethylaminomethyltricyclo[2,2,1,$0^{2,6}$]-heptan-5-one (II-56) as a colourless oil : i.r. 3020 (w), 2820 (s), 2770 (s), 1755 (s), 1030 (s), 840 (s), 830 (m), and 820 (m) cm^{-1}; n.m.r. (CCl_4) τ 7.48 (bs, 2H), 7.80 (s, 6H), 8.15 (m, 6H), and 8.92 (d, J = 5.5 Hz, H_6).

The fractions eluted from the alumina column with 2% methanol in methylene chloride were mixtures (331 mg) of the oximes II-54 and II-55 containing various amounts of ketone II-56. Elution with 5% methanol in methylene chloride and up to 100% methanol gave mixtures (390 mg) of these oximes. A portion (110 mg) of this mixture was

refluxed with sodium bisulfite (258 mg) in 5 ml ethanol-water (1:1) for four hours. The solution was diluted with water, acidified with excess of 0.1N hydrochloric acid (15 ml) and extracted with methylene chloride; no residue remained after evaporation of the solvent. Subsequent basification (pH 9) with sodium carbonate solution, extraction with methylenechloride (4 x 30 ml) and distillation of the residue (26 mg) at 20°/0.2 mm gave the tricyclic ketone II-56 (identified by i.r. and n.m.r.).

5-4-17. Acid Treatment of Azabicyclic Compound II-53

A solution of azabicyclic compound II-53 (100 mg) in 1N hydrochloric acid (5 ml) was stirred at room temperature for 24 hours. The resultant solution was extracted with ether (15 ml x 2). The ether extract did not yield any residue. The aqueous solution was basified (pH 9-10) with saturated sodium carbonate solution and then extracted with methylene chloride (3 x 20 ml) to give an oil (60 mg) which was shown to be the starting material (identified by i.r. and n.m.r.).

A solution of II-53 (147 mg) and 0.1N hydrochloric acid (9 ml) in methanol (9 ml) was refluxed for 20 hours, diluted with water and extracted with methylene chloride (30 ml x 2) to give a semi-solid (15 mg) which showed i.r. absorptions at 1725 (m, b), 1260 (s),

1075 (s, b), 1020 (s) and 800 (s) cm^{-1}. The aqueous solution was basified (pH 9) with saturated sodium carbonate solution and extracted with methylene chloride (3 x 30 ml) to give unreacted starting material (88 mg).

5-4-18. Addition of NND to 5-Methylenebicyclo[2,2,1]hept-2-ene in Bromotrichloromethane

A solution of NND (1.776 g, 0.024 mol), 5-methylenebicyclo[2,2,1]hept-2-ene (2.12 g, 0.02 mol) and concentrated hydrochloric acid (2.4 ml) in bromotrichloromethane (100 ml) was photolysed as described above. During the irradiation a new peak emerged at 315 nm.After 2 hours, the asorption at 345 nm had completely disappeared and the bluish green (colour indicative of nitrosotrichloromethane monomer) photolysate was concentrated under vacuum. The resulting precipitate was filtered and washed with ether to give a white solid (197 mg, 3%) wich showed two spots on a t.l.c. plate : i.r. 3070 (w), 1235 (s), 890 (m), 805 (w), 790 (w) and 660 (m) cm^{-1}; m.s. m/e (%) 308 (M^+, 1), 306 (M^+, 3), 304 (M^+, 5), 302 (M^+ 3), 227 (9), 225 (27), 223 (28), 189 (19), 187 (56), 185 (32), 143 (14), 141 (36), 127 (38), 109 (37), 105 (72), 91 (69), 79 (100), 77 (43) and 66 (76). Since the molecular peak indicated that the compounds might contain one bromine and three chlorine atoms they were tentatively assigned as the two stereoisomers of 2-(2 ,2 ,2 - trichloroethyl)-5-bromo-tricyclo[2,2,1,$0^{2,6}$]heptane (II-58).

The filtrate was diluted with water, washed with ether (the ether washings weighed 619 mg and contained several compounds as shown by the t.l.c. and n.m.r. analysis), basified (pH 9.5) with saturated sodium carbonate solution and extracted with methylene chloride to give an oil (2.64 g) : i.r. 2820 (s), 2770 (s), 1220 (s), 1030 (s), 800 (s), 730 (s) and 640 (m) cm^{-1}; n.m.r. (CCl_4) τ 6.07 (m), 7.82 (s) and 7.87 (s). Analysis by g.c.-m.s. (6' x 1/8" 20% SE-30, 120°, programmed to increase at 10°/minute) showed this oil to contain two major and two minor components. The first major g.c. peak appeared to be due to a monobromo compound on the basis of its g.c.-m.s. pattern : m/e (%) 231 (M^+, 26), 230 (29), 229 (26), 228 (25), 150 (81), 105 (42), 84 (100), 79 (43) and 58 (75); the second major peak in the g.c. appeared to be an isomer of the first compound : m.s. m/e (%) 231 (5), 230 (5), 229 (5), 228 (4), 150 (77), 105 (37), 84 (100) and 58 (44).

The minor peak observed in the g.c. contained one chlorine atom and was tentatively assigned as 2-dimethylaminomethyl-5-chlorotricyclo [2,2,1,$0^{2,6}$]heptane (II-59) on the basis of its m.s. pattern: m/e (%) 187(M^+,4), 186(5), 185 (M^+, 11), 150 (45), 105 (20), 84 (30), 79 (25) and 58 (100).

Chromatography of the basic fraction on basic alumina (260 g), elution with 1% methanol in methylene chloride and distillation of the colourless oil (355 mg) at 20°/0.5 mm gave 2-dimethylaminomethyl-5-bromotricyclo[2,2,1,$0^{2,6}$]heptane (II-60)

: i.r. 3060 (w), 2820 (s), 2775 (s), 1220 (s), 1150 (s), 1030 (s), 880 (s), 830 (m), 800 (s) and 730 (s) cm^{-1}; n.m.r. (CCl_4) (see Figure 2-14) τ 6.06 (t, J = 1.5 Hz, H_5), 7.63 (bs, 2H), 7.85 (s, 6H), 8.6 (m, 3H), 7.9 (m, 2H), 8.68 (A part of AB, J_{AB} = 5.5 Hz, $\Delta\nu_{AB}$ = 11.0 Hz, each line further split, J = 1.5 Hz, H_6) and 8.83 (B part of AB, each line further split, J = 1.5 Hz, H_1); m.s. (20°) m/e (%) 231 (M^+, 11), 230 (7), 229 (M^+, 11), 228 (6), 150 (83), 105 (41), 91 (24), 84 (100), 79 (46) and 58 (66).

Anal. Calcd. for $C_{10}H_{15}NBr$: C, 52.42; H, 6.60; N, 6.11.
Found : C, 52.65, H, 7.05; N, 6.40.

Continued elution with 1% methanol in methylene chloride afforded an epimeric mixture (812 mg) of bromonortricyclenes II-60 and II-61 as shown by the N-CH_3 singlets at τ 7.8 and 7.75. Further elution with the same solvent gave an oil (145 mg) which was distilled at 20°/0.5 mm to give 2-dimethylaminomethyl-5-bromotricyclo[2,2,1,$0^{2,6}$]-heptane (II-61) as a colourless oil: i.r. 3060 (w), 2820 (s), 2775 (s), 1200 (s), 1030 (s), 860 (s), 830 (m), 795 (m) and 725 (s) cm^{-1}; n.m.r. (CCl_4) (see Figure 2.13) τ 6.08 (bs, W1/2 = 4Hz, H_5), 7.57 (bs, 2H), 7.82 (s, 6H), 7.88 (m, 2H), 8.53 (m, 3H), 8.68 (A part of AB, J_{AB} = 5.5 Hz, $\Delta\nu_{AB}$ = 15.5 Hz, each line further split, J = 1.5 Hz, H_6) and 8.94 (B part of AB, each line further split, J = 1.5 Hz, H_1); m.s. (20°) m/e (%) 231 (M^+, 16), 230 (16), 229

(M^+,15), 228 (15), 150 (68), 105 (40), 91 (28), 84 (100), 79 (41) and 58 (68).

Elution with 5% methanol in methylene chloride gave a mixture (55 mg) containing a small amount of the bromonortricyclene derivative II-61.

5-4-19. Oxidative Addition of NND to 1,5-Cyclooctadiene

A solution of NND (3.552 g, 0.048 mol), 1,5-cyclooctadiene (Aldrich, b.p. 48-49°/28 mm, 4.327 g, 0.04 mol) and perchloric acid (70%, 7 ml) in methanol (320 ml) was cooled to 0° and irradiated with a 200 watt Hanovia lamp through a Nonex filter under oxygen for 3 hours at which time, the absorption at 343 nm had completely disappeared. The colourless photolysate was concentrated to ca. 50 ml under reduced pressure at 10°, diluted with water (ca. 50 ml) and extracted with ether (5 x 50 ml). The ether extract was washed with water (3 x 50 ml) and dried over magnesium sulfate, and the ether was removed to give a pale yellow oil (223 mg) which showed no $N-CH_3$ signal in its n.m.r. spectrum.

The aqueous acidic solution was cooled to 0°, basified (pH 9.5) with saturated sodium carbonate solution and immediately extracted with methylene chloride (5 x 75 ml). The extract was washed with water (3 x 50 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure at 10° to give a

yellowish viscous oil (7.21 g): i.r. 3400 (s, b), 1615 (s), 1275 (s), 1100 (m), 1030 (m), 860 (s), 735 (m) and 720 (m) cm^{-1}; n.m.r. τ 4.37 (m), 4.8 (m), 6.65 (s), 7.70 (s) and 7.77 (s). The intensities of the n.m.r. signals at τ 4.37 and 6.65 indicated the presence of an olefinic and a methoxy compound in the approximate ratio 2.5:1 and the t.l.c. showed two strong and three weak spots.

The crude basic fraction was dissolved in dry THF (50 ml), added with stirring (at 0^{o}) to a suspension of LAH (6.08 g, 0.16 mol) in THF (50 ml), allowed to warm to room temperature and stirred for another 24 hours. After hydrolysis, filtration and thorough washing of the inorganic solid residue with THF, the filtrate and washings were combined and dried over magnesium sulfate. Removal of the solvent gave an oil (6.6 g) which showed one major and two minor spots on a t.l.c. plate: i.r. 3400 (s, b), 3010 (m), 1045 (s) and 1030 (s) cm^{-1}; n.m.r. (CCl_4) τ 4.48 (m), 6.72 (s), 7.73 (s), 7.8 (s) and 7.83 (s). The ratio of the three $N-CH_3$ signals in the n.m.r. spectrum was estimated to be 6:3:1.

This mixture (6.2 g) was chromatographed on basic alumina (100 g). The first fraction (A, 4.3 g) eluted with methylene chloride showed two predominant spots on a t.l.c. plate. Continued elution with 0-1% methanol in methylene chloride gave an oil (1.75 g) which contained predominantly amino-alcohol II-64 (identified by i.r. and n.m.r.). Elution with 2-10% methanol in methylene chloride furnished 1,4-butanediol containing traces of aminoalcohol II-64.

Fraction A (2.3 g) was rechromatographed on basic alumina (230 g) and gave on elution with 2% methanol in methylene chloride a fraction (336 mg, colourless oil) which showed one spot on a t.l.c. plate and, on distillation at 20°/0.5 mm, afforded endo-2-methoxy-exo-6-dimethylamino-9-oxabicyclo[3,3,1]nonance (II-65): i.r. 2820 (s), 2770 (s), 1130 (s), 1120 (s), 1100 (s), 1085 (s), 1055 (s), 890 (s) and 880 (s) cm^{-1}; n.m.r. τ 6.10 (m, H_1 and H_5), 6.49 (dt, J = 11.0 and 5.5 Hz, H_2), 6.66 (s, 3H), 7.74 (dt, J = 11.0 and 4.5 Hz, H_6), 7.77 (s, 6H) and 8.13 (m, 8H); m.s. (20°) m/e (%) 199.1569 (M^+, 27; Calcd. 199.1572), 168.1372 (11; Calcd. 168.1388), 114 (1), 84 (77), 71 (100) and 56 (16). On irradiation of the multiplet at τ 8.13, the signal at τ 6.49 (H_2) collapsed to a doublet (J = 5.5 Hz) and the multiplet at τ 6.10 (H_1 and H_5) collapsed to two doublets (J = 5.5 and 4.5 Hz).

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03.
Found : C, 66.08; H, 10.79; N, 7.25.

Continued elution with 2% methanol in methylene chloride gave an oil (405 mg) which exhibited no hydroxyl absorptions in the i.r. spectrum. This oil contained II-65 and a second compound (II-66) in the ratio 1:2.7 as estimated from the relative intensities of the $N-CH_3$ singlets at τ 7.75 and 7.72 and of the OCH_3 singlets at τ 6.7 and 6.65. A portion of this oil (300 mg) was rechromatographed

on basic alumina (50 g). The first fraction, eluted with 1% methanol in methylene chloride, was an oil (242 mg) containing II-65 and II-66 in an approximate ratio 1:2. The next fraction (46 mg, colourless oil) was distilled at 20°/0.5 mm to give endo-2-methoxy-exo-5-dimethylamino-9-oxabicyclo[4,2,1]nonane (II-66): i.r. 2820 (s), 2770 (s) and 1100 (s) cm^{-1}; n.m.r. τ 5.56 (m, W1/2 = 32 Hz, H_1 and H_6), 6.58 (m, H_2), 6.65 (s, 3H), 7.5 (m, H_5), 7.71 (s, 6H) and 8.2 (m, 8H); m.s. (20°) m/e (%) 199 (M^+, 34), 168 (63), 154 (19), 140 (8), 124 (18), 85 (31), 84 (100), 82 (19), 71 (83), 70 (27), 58 (26) and 56 (20).

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.93.
Found : C, 66.56; H, 10.78; N, 7.16.

Subsequent elution with 2% methanol in methylene chloride gave a mixture (150 mg) containing II-66 and aminoalcohol II-64 in the approximate ratio 1:1 as shown by i.r. and n.m.r. analysis, and several consecutive fractions consisting of a single compound (one t.l.c. spot). These fractions were combined (647 mg) and sublimed at 20°/0.05 mm to give trans-2-dimethylamino-5-cycloocten-1-ol (II-64): i.r. 3360 (s), 3010 (s), 2830 (s), 2790 (s), 1045 (s), 1030 (s), 730 (s) and 715 (s) cm^{-1}; n.m.r. (see Figure 2.16) τ 4.35 (A-part of ABX_2X_2' pattern, J_{AB} = 11.5 Hz, J_{AX} = 5.0 Hz, $\Delta\nu_{AB}$ = 21.0 Hz, H_6), 4.56 (B-part of ABX_2X_2' pattern, J_{BX} = 7.0 Hz, H_5), 5.06 (bs, D_2O exch., 1H), 6.49 (d of dd, J

= 9.0, 7.0 and 3.0 Hz, H_1), 7.39 (d of dd, J = 10.5, 9.0 and 4.0 Hz, H_2), 7.72 (s, 6H), 7.52-7.99 (m, 4H) and 8.38 (m, 4H); m.s. (20°) m/e (%) 169.1461 (M^+, 17; Calcd. 169.1467), 140 (13), 110 (14), 84 (13), 72 (27), 71 (100), 56 (21) and 42 (17). On irradiation of the multiplet at τ 7.52-7.99 (allylic protons), the signal at τ 4.45 (vinyl protons) collapsed to an AB quartet with a J_{AB} value of 11.5 Hz. When the multiplet at τ 8.38 was irradiated, the signals at τ 6.49 (H_1) and 7.39 (H_2) collapsed to doublets (J = 9.0 Hz). On irradiation of the signal at τ 7.39 (H_2), the signal at τ 6.49 (H_1) collapsed to a doublet doublet (J = 7.0, and 3.0 Hz) and the multiplet at τ 8.38 showed some changes in its coupling pattern. Irradiation at τ 4.45 (vinyl protons) and at τ 6.49 (H_1) changed the coupling pattern of the multiplets at τ 7.52-7.99 (allylic protons) and at τ 8.38, respectively.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 70.86; H, 11.55; N, 8.48.

The material remaining on the column (760 mg) was eluted with 5-10% methanol in methylene chloride and consisted mainly of the amino- alcohol II-64 (analysis by t.l.c., i.r. and n.m.r.).

5-4-20. Oxidative Addition of NND to 1,3-Cyclohexadiene

A methanol solution (320 ml) of NND (3.552 g, 0.048 mol), 1,3-cyclohexadiene (Aldrich, b.p. 79°, 3.20 g, 0.04 mol) and perchloric acid (60%, 8 ml) was irradiated (200 watt Hanovia lamp) through a nonex filter under oxygen at 0°. After 3 hours the absorption at 345 nm had completely disappeared and a yellow solution was obtained. The solvent was distilled under reduced pressure at 10°, and the residual solution was diluted with water and washed with ether. The aqueous solution was cooled to 0°, basified (pH 9) with sodium carbonate (colour turned to dark brown) and extracted with ether. The ether extract (colour gradually darkened) was washed with water and dried over magnesium sulfate, and the ether was removed at 10° to give an oil which decomposed explosively to a dark tar.

5-4-21. Oxidative Addition of NNP to 1,3-Cyclohexadiene

A solution of NNP (5.472 g, 0.048 mol), 1,3-cyclohexadiene (3.20 g, 0.04 mol) and concentrated hydrochloric acid (4.8 ml) in methanol (320 ml) was photolysed as described above. After the completion of the photolysis (4 hours), the yellow photolysate was concentrated to ca. 50 ml under reduced pressure at 10° (the solution turns black at room temperature), diluted with water to ca.

100 ml and extracted with ether to give a yellow semi-solid (1.55 g) which exhibited i.r. absorptions at 3440 (m), 1720 (s), 1690 (s), 1630 (s), 1550 (s), 1275 (s), 1050 (s) and 860 (s) cm^{-1}. The aqueous acidic solution was cooled below 0^{o}, basified (pH 8) with saturated sodium carbonate solution and extracted immediately with cold ether. The ethereal extract was washed with cold water, dried over magnesium sulfate, added to a suspension of LAH (6.08 g, 0.16 mol) in anhydrous ether (250 ml) at 0^{o} and stirred at room temperature for 24 hours. The resultant mixture was worked up in the usual manner to give a basic fraction (2.3 g) which exhibited i.r. absorptions at 3380 (s), 3020 (m), 1160 (s), 1105 (s), 1060 (s) and 1035 (s) cm^{-1}. The t.l.c. of this mixture showed the presence of one major and three minor components.

A portion of this mixture (1.75 g) was chromatographed on basic alumina (60 g). Elution with methylene chloride afforded a colourless oil (411 mg) which showed a single spot on a t.l.c. plate and gave, on distillation at $20^{o}/0.5$ mm, 3-piperidinocyclohexene (II-68) : i.r. 3020 (s), 2800 (s), 2750 (s), 2680 (m), 1325 (s), 1305 (s), 1160 (s), 1120 (s) and 725 (s) cm^{-1}; n.m.r. (CCl_4) τ 4.41 (m, 2H), 6.9 (m, W1/2 = 12 Hz, H_3), 7.52 (m, W1/2 = 12 Hz, 4H), 8.0 (m, 2H) and 8.54 (m, 10H); m.s. (20^{o}) m/e (%) 165.1500 (M^{+}, 32; Calcd. 165.1517), 137.1217 (72; Calcd. 137.1204), 122 (51), 111.1081 (100; Calcd. 111.1048), 110 (31), 96 (41), 84 (23), 81 (25), 55 (25), 42 (20) and

41 (38). Irradiation of the multiplets at τ 6.9 and 8.0 changed the coupling pattern of the multiplet at τ 4.41 (vinyl protons).

Anal. Calcd. for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.47. Found : C, 79.85, H, 11.76; N, 8.54.

Further elution with methylene chloride gave II-68 (128 mg) contaminated with a small amount of another compound of a lower Rf value.

The fraction (454 mg) eluted with 1% methanol in methylene chloride was a mixture of aminoalcohols contaminated with II-68 as shown by the t.l.c., i.r. and n.m.r. analysis.

Subsequent elution with 1-5% methanol in methylene chloride gave a viscous oil (551 mg) which consisted of several components (by t.l.c.) and, on distillation at 20°/0.5 mm gave an oil containing predominantly 4-piperidino-2-cyclohexenols (II-69): i.r. 3350 (s), 3025 (w), 2810 (s), 1155 (m), 1100 (s), 1060 (s), 1035 (s), 955 (m) and 740 (m) cm^{-1}; n.m.r. τ 4.3 (m, 2H), 5.82 (m, W1/2 = 25 Hz, 1H), 6.86 (m, W1/2 = 23 Hi_Z, 1H), 7.52 (m) and 8.5 (m); m.s. (50°) m/e (%) 181 (M^+, 27), 153 (94), 137 (87), 124 (100), 111 (51), 98 (70), 84 (76) and 55 (39).

5-4-22. Preparation of 3-Butenyl Esters

Acetylation of 3-butenol (II-70a) with acetic anhydride in pyridine gave 3-butenyl acetate (II-70b, 90.4%): i.r. 3080 (m), 1740 (s), 1645 (m), 1240 (s), 1040 (s) and 920 (s) cm^{-1}; n.m.r. τ 4.18 (t of dd, J = 18.0, 9.0 and 6.5 Hz, 1H), 4.93 (m, 1H), 4.94 (m, 1H), 5.82 (t, J = 6.5 Hz, 2H), 7.62 (q, J = 6.5 Hz, each line further split by an allylic proton, J = 1.5 Hz, 2H) and 7.98 (s, 3H).

Treatment of 3-butenol (II-70a) with p-toluene sulfonyl chloride in pyridine gave 3-butenyl tosylate (II-70h, 60%): i.r. 3080 (w), 1643 (w), 1598 (m), 1360 (s), 1190 (s), 1180 (s), 1175 (s), 960 (s), 905 (s), 815 (s), 572 (s) and 558 (s) cm^{-1}; n.m.r. τ 2.22 (A-part of A_2B_2 J_{AB} = 8.5 Hz, $\Delta\nu_{AB}$ = 26.0 Hz, 2H), 2.65 (B-part of A_2B_2, 2H), 4.27 (t of dd, J = 17.5, 9.0 and 6.0 Hz, 1H), 4.93 (m, 1H), 4.95 (m, 1H), 5.92 (t, J = 6.5 Hz, 2H), 7.61 (q, J = 6.5 Hz, further fine splitting J = 1.5 Hz, 2H) and 7.55 (s, 3H).

The 3-butenyl-p-methylbenzoate (II-70c) was prepared in 68.8% yield from 3-butenol: i.r. 3080 (w), 3040 (w), 1720 (s), 1645 (w), 1615 (s), 1275 (s), 1180 (s), 1110 (s), 1025 (s), 845 (m) and 758 (s) cmm^{-1}; n.m.r. τ 2.09 (A part of A_2B_2, J_{AB} = 8.0 Hz, $\Delta\nu_{AB}$ = 44 Hz, 2H), 2.83 (B part of A_2B_2, 2H), 4.12 (t of dd, J

= 17.0, 9.5 and 6.5 Hz, 1H), 4.82 (m, 1H), 4.92 (m, 1H), 5.66 (t, J = 6.5 Hz, 2H), 7.52 (q, J = 6.5 Hz, 2H) and 7.64 (s, 3H).

Alcohol II-70a was converted in 92% yield to 3-butenyl-p-methoxy-benzoate (II-70d): i.r. 3080 (w), 1710 (s), 1640 (w), 1605 (s), 1510 (m), 1278 (s), 1260 (s), 1170 (s), 1100 (s), 850 (m) and 772 (s) cm^{-1}; n.m.r. τ 2.02 (A-part of A_2B_2, J_{AB} = 9.0 Hz, 2H), 3.12 (B-part of A_2B_2, 2H), 4.11 (t of dd, J = 17.0, 9.0 and 6.5 Hz, 1H), 4.86 (m, 1H), 4.90 (m, 1H), 5.66 (t, J = 6.5 Hz, 2H), 6.19 (s, 3H) and 7.5 (q, J = 6.5 Hz, 2H).

Esterification of 3-butenol with p-cyanobenzoyl chloride gave 3-butenyl-p-cyanobenzoate (II-70e) in 100% yield: i.r. 3080 (w), 2230 (m), 1720 (s), 1640 (w), 1610 (w), 1275 (s), 1118 (s), 1105 (s), 863 (m), 768 (m) and 690 (m) cm^{-1}; n.m.r. τ 1.86 (A-part of A_2B_2, J_{AB} = 8.0 Hz, $\Delta\nu_{AB}$ = 22.6 Hz, 2H), 2.25 (B-part of A_2B_2, 2H)4.08 (t of dd, J = 17.5, 9.5 and 6.5 Hz, 1H), 4.84 (m, 1H), 4.87 (m, 1H), 5.56 (t, J = 6.5 Hz, 2H) and 7.45 (q, J = 6.5 Hz, fine splitting J = 1.0 Hz, 2H).

5-4-23. Oxidative Addition of NNP to 3-Butenyl (II-70a)

A solution of NNP (2.736 g, 0.024 mol), 3-butenol (1.44 g, 0.02 mol) and perchloric acid (70%, 4 ml) in methanol (320 ml) was

irradiated (200 watt Hanovia lamp) through a nonex filter under oxygen at 0°. After 1.5 hours, the absorption at 350 nm disappeared completely and a colourless solution was obtained. The photolysate was concentrated under reduced pressure at 10°, then diluted with water to ca. 100 ml and extracted with ether (4 x 50 ml) to give an oil (66 mg) which contained unreacted 3-butenol as shown by i.r. and n.m.r. analysis. The aqueous acidic solution was cooled to 5°, basified with saturated sodium carbonate solution (pH 9.5) and extracted with methylene chloride (5 x 50 ml). The methylene chloride extract was worked up in the usual manner to afford 3-nitrato-4-piperidinobutanol (II-71a) as an oil (2.209 g, 51%): i.r. 3370 (m), 2800 (m), 1625 (s), 1275 (s), 1055 (m), 865 (m) and 855 (m) cm^{-1}; n.m.r. τ 4.78 (qi, J = 6.0 Hz, 1H), 4.85 (bs, D_2O exch., 1H), 6.29 (t, J = 5.5, 2H), 7.42 (d, J = 6.0 Hz, 2H), 7.55 (m, 4H), 8.03 (q, J = 6.0 Hz, 2H) and 8.5 (m, 6H).

Continuous extraction of the colourless aqueous basic solution with methylene chloride gave 4-piperidino-1,3-butanediol (II-72a) as an oil (710 mg, 21%): i.r. 3370 (s), 2800 (m), 1075 (s), 1050 (s) and 1040 (s) cm^{-1}; n.m.r. τ 5.38 (s, D_2O exch., 2H), 6.13 (qi, J = 6.5 Hz, 1H), 6.28 (t, J = 6.0 Hz, 2H), 7.53 (m, 4H), 7.6 (d, J = 6.5 Hz, 2H), 8.32 (q, J = 6.0 Hz, 2H) and 8.47 (m, 6H); m.s. m/e (%) 174 (M^+, 7), 128 (30), 99 (37), 98 (100), 84 (17), 55 (28), 42 (25) and 41 (31).

Reduction of the aminonitrate II-71a (2.2 g) with LAH (1.9 g, 0.05 mol) in ether (150 ml) for 24 hours followed by the usual work-up afforded diol II-72a (1.824 g).

Treatment of diol II-72a (173 mg) with p-nitrobenzoyl chloride (186 mg) in dry THF (2 ml) (114) gave a solid which was recrystallized from 2-propanol to give the hydrochloride of 3-hydroxy-4-piperidinobutyl-p-nitrobenzoate (II-73, 216 mg, 60%): m.p. 192- 193° (d); i.r. 3260 (s), 1720 (s), 1525 (s), 1350 (s), 1340 (s), 1285 (s) and 720 (s) cm^{-1}; n.m.r. τ 8.05 (m, 8H), 6.07-7.25 (m, 6H), 5.7 (m, 1H), 5.43 (t, J = 6.5 Hz, 2H) and 1.7 (m, 4H).

Anal. Calcd. for $C_{16}H_{23}N_2O_5Cl$: C, 53.56; H, 6.46; N, 7.82. Found: C, 53.86; H, 6.28; N, 7.92.

Diol II-72a (400 mg, 2.3 mmol) was treated with p-toluene sulfonyl chloride (458 mg, 2.4 mmol) in anhydrous pyridine (7 ml) at 5° for 24 hours. The reaction mixture was hydrolyzed with ice-water, basified with sodium carbonate solution and extracted with methylene chloride to give N-tosyl piperidine (110 mg). Continuous extraction of the aqueous solution with methylene chloride and evaporation of the solvent gave no residue.

5-4-24. Oxidative Addition of NNP to 3-Butenyl Acetate (II-70b)

A methanol solution (320 ml) of NNP (4.56 g, 0.04 mol), 3-butenyl acetate (3.306 g, 0.029 mol) and perchloric acid (70%, 6 ml) was irradiated under oxygen for 2.5 hours. The colourless photolysate was concentrated under pressure at 10°, then diluted with water and extracted with ether to give an oil (100 mg) which contained mostly unreacted 3-butenyl acetate as shown by i.r. and n.m.r. analysis. The aqueous acidic solution was cooled to 5°, basified with saturated sodium carbonate solution (pH 9.5) and extracted with methylene chloride to afford an oil (5.724 g) consisting of 3-nitrato-4-piperidinobutyl acetate (II-71b) and 3-hydroxy-4-piperidinobutyl acetate (II-72b) in the approximate ratio 1:1 as shown by the intensities of the n.m.r. signals at τ 5.77 and 5.82: i.r. 3440 (m), 1740 (s), 1630 (s), 1280 (s), 1240 (s), 1045 (s), 895 (s), 865 (s) and 855 (s) cm^{-1}; n.m.r. τ 4.73 (qi, J = 6.0 Hz), 5.23 (bs, D_2O exch.), 5.77 (t, J = 6.5 Hz), 5.82 (t, J = 6.5 Hz), 6.28 (qi, J = 5.5 Hz), 7.53 (m), 7.96 (s) and 8.48 (m).

Reduction of the crude basic fraction (5.6 g) with LAH (4.173 g, 0.11 mol) in ether (250 ml) for 24 hours gave diol II-72a (3.938 g) in an overall yield of 80%.

5-4-25. Oxidative Addition of NNP to 3-Butenyl-p-methylbenzoate (II-70c)

A methanol solution (320 ml) of NNP (1.37 g, 0.012 mol), 3-butenyl-p-methylbenzoate (1.902 g, 0.01 mol) and perchloric acid (70%, 2 ml) was photolysed under oxygen as described above. After irradiation (1 hour), the photolysate was worked up in the usual manner to give a neutral fraction (1.406 g, 74%) containing only unreacted starting olefin II-70c (identified by i.r. and n.m.r.). The basic fraction (1.256 g) contained 3-nitrato-4-piperidinobutyl-p-methylbenzoate (II-71c) and 3-hydroxy-4-piperidinobutyl-p-methylbenzoate (II-72c) in a 1:1 ratio as shown by the intensities of the n.m.r. signals at τ 5.51 and 5.57: i.r. 3420 (m), 1720 (s), 1630 (s), 1278 (s), 1180 (s), 1108 (s), 860 (s) and 758 (s) cm^{-1}; n.m.r. τ 8.49 (m), 7.58 (s), 7.5 (m), 4.63 (qi, J = 6.5 Hz), 5.51 (t, J = 6.5 Hz), 5.57 (t, J = 6.0 Hz), 6.33 (s, D_2O exch.), 6.2 (m), 2.76 (A-part of A_2B_2, J_{AB} = 8.0 Hz, $\Delta\nu_{AB}$ = 41 Hz) and 2.08 (B-part of A_2B_2).

This mixture was hydrogenated in methanol (50 ml) in the presence of platinum oxide (125 mg) to afford 3-hydroxyl-4-piperidinobutyl-p-methylbenzoate (II-72c) as an oil (943 mg): i.r. 3400 (s), 1715 (s), 1280 (s), 1180 (m), 1105 (s) and 755 (s) cm^{-1}; n.m.r. τ 8.47 (m), 8.15 (q, J = 6.5 Hz, 2H), 7.58 (s, 3H), 7.60 (m, 6H), 6.1 (qi, J = 6.5 Hz, 1H), 5.5 (t, J =

6.5 Hz, 2H), 5.05 (m, D_2O exch., 1H), 2.77 (A-part of A_2B_2, J_{AB} = 8.5 Hz, $\Delta\nu_{AB}$ = 42 Hz, 2H) and 2.07 (B-part of A_2B_2, 2H).

Aminoalcohol II-72c was dissolved in ether and treated with HCl to afford a solid which was recrystallized from 2-propanol to give the hydrochloride of II-72c as a white crystalline compound: m.p. 184-185 °; m.s. m/e (%) 291 (M^+, 2), 142 (11), 128 (15), 119 (17), 99 (30), 98 (100), 91 (17) and 55 (15).

5-4-26. Oxidative Addition of NNP to 3-Butenyl-p-methoxybenzoate (II-70d)

A solution of NNP (1.37 g, 0.012 mol), 3-butenyl-p-methoxybenzoate (2.06 g, 0.01 mol) and perchloric acid (70%, 2 ml) in methanol (320 ml) was photolysed as described before. After irradiation (one hour) and the usual work-up of the pale yellow photolysate, unreacted 3-butenyl-p-methoxybenzoate (1.412 g, 69%) was obtained in the neutral fraction. The basic fraction (1.433 g) contained 3-nitrato-4-piperidinobutyl-p-methoxybenzoate (II-71d) and 3-hydroxy-4-piperidinobutyl-p-methoxybenzoate (II-72d) in the approximate ratio 1:1 as indicated by the intensities of the n.m.r. signals at τ 5.53 and 5.58: i.r. 3420 (m), 1703 (s), 1630 (s), 1608 (s), 1280 (s), 1260 (s), 1173 (s), 1100 (s), 1033 (s), 853 (s)

and 773 (s) cm^{-1}; n.m.r. τ 8.5 (m), 7.54 (m), 6.14 (s), 5.58 (t, J = 6.0 Hz), 5.53 (t, J = 6.5 Hz), 4.63 (qi, J = 6.5 Hz), 5.88 (s, D_2O exch.), 6.24 (m), 3.08 (A-part of A_2B_2, J_{AB} = 9.0 Hz), and 2.01 (B-part of A_2B_2).

This mixture was hydrogenated in methanol (50 ml) in the presence of platinum oxide (125 mg) to give II-72d as an oil (1.123 g): i.r. 3400 (s), 1710 (s), 1605 (s), 1280 (s), 1260 (s), 1170 (s), 1100 (s), 1030 (m) and 770 (m) cm^{-1}; n.m.r. τ 8.46 (m), 8.16 (q, J = 6.5 Hz, 2H), 7.6 (m), 6.13 (s, 3H), 6.21 (m, 1H), 5.52 (t, J = 6.5 Hz, 2H), 5.34 (m, 1H), 3.08 (A-part of A_2B_2, J_{AB} = 9.0 Hz, 2H) and 2.0 (B-part of A_2B_2, 2H).

Aminoalcohol II-72d was dissolved in ether and treated with HCl to afford a solid which was recrystallized from 2-propanol to give the hydrochloride of II-72d as a white crystalline compound: m.p. 159 - 160° : m.s. m/e (%) 307 (M^+,3), 152 (6), 135 (27), 128 (13), 99 (38), 98 (100), 77 (11) and 55 (18).

Anal. Cald. for $C_{17}H_{26}NO_4Cl$: C, 59.38; H, 7.62; N, 4.07.
Found : C, 59.36; H, 7.63; N, 4.19.

5-4-27. Oxidative Addition of NNP to 3-Butenyl-p-cyanobenzoate (II-70e)

A methanol solution (320 ml) of NNP (1.37 g, 0.012 mol), 3-butenyl- p-cyanobenzoate (2.012 g, 0.01 mol) and perchloric acid (70%, 2 ml) was photolysed as described before. After irradiation (1 hour), the photolysate was worked up in the usual manner to give unreacted 3-butenyl-p-cyanobenzoate (1.351 g, 67%) in the neutral fraction. The basic fraction (1.268 g) was composed of 3-nitrato-4-piperidinobutyl-p-cyanobenzoate (II-71e) and 3-hydroxy-4-piperidino-butyl-p-cyanobenzoate (II-72e) in a 1:1 ratio as judged from the intensities of the n.m.r. signals at τ 5.45 and 5.49: i.r. 3400 (m), 2230 (m), 1725 (s), 1628 (s), 1275 (s), 1105 (s), 1120 (s), 860 (s), 768 (s) and 690 (s) cm^{-1}; n.m.r. τ 1.87 (A-part of A_2B_2, J_{AB} = 8.0 Hz, $\Delta\nu_{AB}$ = 22.6 Hz), 2.25 (B-part of A_2B_2), 4.65 (qi, J = 6.0 Hz), 5.45 (t, J = 6.5 Hz), 5.49 (t, J = 6.0 Hz), 6.03 (m), 6.02 (bs, D_2O exch.), 7.55 (m) and 8.5 (m).

5-4-28. Oxidative Addition of NNP to 3-Butenyl Chloride (II-70f)

A methanol solution (320 ml) of NNP (2.74 g, 0.024 mol), 3-butenyl chloride (1.811 g, 0.02 mol) and perchloric acid (70%, 3.5 ml) was photolysed under oxygen as described before. After irradiation (1.5 hours), the colourless photolysate was concentrated

under reduced pressure at 10°, diluted with water and washed with ether. The ethereal washings gave 62 mg of neutral material which was not further investigated. The aqueous acidic solution was cooled to 5°, basified with saturated sodium carbonate solution (pH 9.5) and extracted with methylene chloride to give an oil (520 mg) which contained predominantly piperidine and dipiperidinomethane as indicated by the i.r. and n.m.r. spectra. The aqueous basic solution was re-extracted continuously with methylene chloride for several days to give a solid (2.263 g, 38%) which was recrystallized from methanol to give the perchlorate of 2-nitrato-5-azoniaspiro [4,5]decane (II-74): m.p. 134.5-135.5°; i.r. 3040 (w), 1643 (s), 1303 (s), 1293 (s), 1275 (s), 1095 (s), 870 (s), 860 (s) and 625 (s) cm^{-1}; n.m.r. (acetone - d_6) (see Figure 2.18) τ 4.04 (M, H_2), 5.77 (AB-part of ABX pattern, J_{AB} = 14.0 Hz, J_{AX} = 5.0 Hz and J_{BX} = 3.5 Hz, 2H), 6.02 (AB-part of ABXX' pattern, J_{AB} = 5 Hz, 2H), 6.29 (m, 4H), 7.18 (m, 2H) and 7.76-8.42 (m, 6H). On irradiation of the multiplet at τ 4.04 (H_2), the signal at τ 5.77 (H_1 protons) collapsed to an AB quartet (J_{AB} = 14.0 Hz) and the multiplet at τ 7.18 (H_3 protons) showed some changes in its coupling pattern. Irradiation at τ 5.77 (H_1 protons) and at τ 7.18 (H_3 protons) changed the coupling pattern of the multiplet at τ 4.04 (H_2). When the signal at τ 6.02 (H_4 protons) was irradiated, the complex multiplet at τ 7.18 (H_3 protons) collapsed to an ABX pattern (J_{AB} = 16 Hz, J_{AX} = 7 Hz and J_{BX} = 4 Hz). On irradiation of the multiplet at τ 7.18 (H_3 protons), the signal

at τ 6.02 (H_4 protons) collapsed to an AB quartet (J_{AB} = 5 Hz). Irradiation of the multiplet at τ 7.76-8.42 decoupled the multiplet at τ 6.29 to give a broad singlet.

Anal Calcd. for $C_9H_{17}N_2O_7Cl$: C, 35.95; H, 5.70; N, 9.31.
Found: C, 36.01, H, 5.84; N, 9.31.

5-4-29. Oxidative Addition of NNP to 3-Butenyl Bromide (II-70g)

A solution of NNP (1.37 g, 0.012 mol), 3-butenyl bromide (1.35 g, 0.01 mol) and perchloric acid (70%, 2 ml) in methanol (320 ml) was photolysed under oxygen for one hour as described before. The colourless photolysate was concentrated at 10° and the residual solution was basified with saturated sodium carbonate solution (pH 9.5) and extracted continuously with methylene chloride for several days to give a solid (1.367 g, 46% which, after recrystallization from methanol, afforded the perchlorate of spirocompound II-74 (identified by i.r. and n.m.r.).

5-4-30. Attempted Non-Oxidative Addition of NNP to 3-Butenyl Tosylate (II-70h)

A solution of NNP (1.14 g, 0.01 mol) II-79h (2.037 g, 0.009 mol) and perchloric acid (70%, 1.5 ml) in methanol (320 ml) was irradiated (200 watt Hanovia lamp) through a nonex filter under nitrogen at 0°. After 70 minutes, the absorption at 350 nm had disappeared completely and the photolysate was concentrated to ca. 40 ml under vacuum at 8°. The residual solution was diluted with water and extracted with ether (4x50 ml) to give unreacted starting olefin II-70h (1.93 g, 95%).

The aqueous solution was basified (pH 10) with saturated sodium carbonate solution and extracted with methylene chloride (5x50 ml) to give a yellowish viscous oil (355 mg) which contained predominantly piperidine and dipiperidinomethane as shown by i.r., n.m.r. and g.c.-m.s. analysis.

5-4-31. Attempted Oxidative Addition of NNP to 3-Butenyl Tosylate (II-70h)

A methanol solution (320 ml) of NNP (1.14 g, 0.01 mol), II-70h (1.8 g, 0.008 mol) and perchloric acid (70%, 1.5 ml) was irradiated under oxygen for one hour as described in the previous experiment.

The photolysate was worked up in the usual manner to give a neutral fraction (1.28 g, 71%) which was shown to be unreacted olefin II-70h by comparison of the i.r. and n.m.r. spectra with those of an authentic sample. The basic extract gave a crude product (350 mg) whose i.r., n.m.r. and t.l.c. behaviour were identical to those of the crude basic extract obtained in the previous experiment.

5-5. Oxidative and Non-Oxidative Photodecomposition Of C-Nitrosocompounds

5-5-1. Photodecomposition of the anti-Dimer of trans-1-Nitroso-2-piperidinocyclohexane (II-6)

A solution of anti-dimer II-6 (250 mg) and concentrated hydrochloric acid (0.3 ml) in methanol (300 ml) was irradited with a 200 watt Hanovia lamp under nitrogen at 0°. After 0.5 hours, the methanol solution was basified with sodium carbonate and evaporated under reduced pressure to ca. 10 ml. The residual solution was diluted with water and extracted with methylene chloride. The methylene chloride extract was washed with water and dried over magnesium sulfate, and the solvent was removed to give a semi-solid (210 mg) which was chromatographed on silicic acid (10 g). Elution with 4-5% methanol in chloroform gave 2-piperidinocyclohexanone oxime (II-7, 145 mg): m.p. 111-114° (lit. 118-120°) (152);

i.r. 3250, 2940, 2300, 1220, 1120, 990, 975, 940, 920, 890 and 780 cm^{-1}.

5-5-2. Oxidative Photodecomposition of the anti-Dimer of trans-1-Nitroso-2-piperidinocyclohexane (II-6)

A methanol solution (320 ml) of anti-dimer II-6 (300 mg) and concentrated hydrochloric acid (0.3 ml) was cooled to 0° and irradiated with a 200 watt Hanovia lamp under oxygen. After 0.5 hours the dimer absorption at 295 nm had disappeared completely and the photolysate was concentrated to ca. 20 ml under reduced pressure. The residual solution was diluted with water, basified (pH 8) with sodium carbonate and extracted with methylene chloride to give a semi-solid (248 mg). The i.r. spectrum of this crude residue showed strong absorptions at 1550, 1450 and 1370 cm^{-1} for a nitro group and weak absorptions at 1710 and 1630 cm^{-1}. Chromatography of this residue on an alumina column gave several fractions consisting of mixtures of cis- and trans-1-nitro-2-piperidinocyclohexane (II-75) as shown by n.m.r. signals at τ 5.33 (dt, J = 11.0 and 5.0 Hz) and 5.15 (m, W1/2 = 6 Hz).

In a separate experiment a solution of anti-dimer II-6 (1.0 g) and concentrated hydrochloric acid (2.5 ml) in methanol (500 ml) was cooled to -15° in a dry ice-acetone bath and irradiated as

described above. After 4 hours, the solvent was evaporated under vacuum at room temperature to give a semi-solid the i.r. spectrum of which exhibited weak absorptions at 1720 and 1635 cm^{-1} but strong absorptions at 1550, 1450 and 1370 cm^{-1} for a nitro group. This crude product was hydrogenated in methanol (50 ml) in the presence of platinum black (250 mg) for 24 hours. The product was basified with potassium carbonate and extracted with methylene chloride to give an oil (840 mg) a portion of which (420 mg) was stirred overnight (16 hours) with acetic anhydride (2 ml) and freshly fused sodium acetate (160 mg). The reaction mixture was worked up in the usual manner to afford an oil (360 mg): i.r. 3300 (s), 2800 (s), 2740 (m), 1640 (s), 1545 (m), 1265 (s) and 1255 (s) cm^{-1}; n.m.r. τ 8.05 (s) and 7.93 (s) in the intensity ratio 3:2.

Chromatography of this product on basic alumina (40 g) and elution with 20% chloroform in benzene gave various mixtures of cis- and trans-1-acetamido-2-piperidinocyclohexane (II-77) (200 mg, 35%). One of the above fractions contained ca. 85% of the trans-isomer and was sublimed to give an oil: i.r. 3300 (s), 3080 (m), 2800 (s), 2740 (s), 1640 (s), 1545 (s), 1305 (m), 1255 (m) and 1105 (s) cm^{-1}; n.m.r. τ 8.57 (m, 14H), 8.05 (s, 3H), 7.5 (m, 5H), 6.63 (dt, J = 10.0 and 4.0 Hz , H_1) and 3.27 (m, D_2O exch., 1H); m.s. (50°) m/e (%) 224 (M^+, 1%), 179 (15), 165 (15), 124 (68), 111 (20), 110 (18), 98 (24), 96 (24), 84 (50), 73 (49), 56 (40), 55 (44), 43 (80), 42 (58) and 41 (100).

A mixture of cis- and trans-acetamide II-77 in $CDCl_3$ solution in the presence of tris(dipivalomethanato) europium exhibited n.m.r. signals at τ 4.63 (m, W1/2 = 23 Hz) and 6.47 (s) for the trans-isomer and 3.83 (m, W1/2 = 10 Hz) and 5.24 (s) for cis-isomer.

Further elution with 0-5% methanol in chloroform gave a mixture of cis- and trans-2-piperidinocyclohexanol (II-9) (62 mg, 13%).

The trans-1-acetamido-2-piperidinocyclohexane (II-77) was also prepared by reduction of the anti-dimer II-6 with LAH in ether followed by acetylation with acetic anhydride and sodium acetate.

5-5-3. Oxidative Photodecomposition of the anti-Dimer of trans-1-Nitroso-2-chlorocyclohexane (II-78)

The anti-dimer II-78 was prepared according to the method of Ponder et al., [66] and recrystallized from absolute ethanol: m.p. 150-152° (lit. 152-153°) (66); i.r. 1325 (s), 1250 (s), 1225 (s), 1215 (s), 1195 (s), 800 (s) and 745 (s) cm^{-1}; n.m.r. τ 4.28 (m) and 5.5 (m) in the intensity ratio of 1:1.

A solution of anti-dimer II-78 (1.0 g) in benzene (320 ml) was photolysed under oxygen with a 200 watt Hanovia lamp. During the irradiation a white solid precipitated gradually at the sides of the

cold finger. This solid disappeared slowly and the irradiation was continued for 7 hours when the dimer absorption at 300 nm had disappeared completely. The yellow photolysate was evaporated under vacuum at room temperature to give an oil (1.5 g) which contained trans-1-nitrato-2-chlorocyclohexane (II-80) and trans-1-nitro-2-chlorocyclohexane (II-79) in the approximate ratio 1:1; i.r. 1725 (w), 1630 (s), 1555 (s), 1375 (s), 1325 (s), 1280 (s), 875 (s), 860 (s) and 750 (s) cm^{-1}; n.m.r. (CCl_4) τ 5.07 (m), 5.67 (m), 6.15 (dt, J = 8.0 and 4.0 Hz) and 8.37 (m). Attempted reduction of this mixture with a 3:1 mixture of LAH and aluminium chloride in ether or THF at room temperature was unsuccessful. Further attempts to reduce the mixture with this reagent in refluxing THF resulted in the partial reduction of the nitro group. Hydrogenation of this mixture in the presence of platinum catalyst in various solvents such as acetic anhydride, acetic acid, ethyl acetate and methanol was not successful. Partial reduction of the nitrate group was observed with methanol as solvent but hydrogenolysis of C-Cl bond had occured simultaneously.

Chromatography of the crude material (1.0 g) on silica gel (50 g) and elution with petroleum ether gave a colourless oil (241 mg) which was distilled at $35^{o}/0.03$ mm to give trans-1-nitrato-2-chlorocyclohexane (II-80): i.r. 1630 (s), 1280 (s), 875 (s), 860 (s) and 750 (m) cm^{-1}; n.m.r. τ 5.02 (dt, J = 8.5 and 4.0 Hz, H_1), 6.14 (dt, J = 8.5 and 4.0 Hz, H_2), 7.82 (m, 2H) and 8.40

(m, 6H); m.s. (150°) m/e (% at 15 ev) 136 (10), 134 (30), 121 (40), 119 (100), 85 (80), 84 (90), 70 (55) and 69 (65).

Continued elution with petroleum ether gave mixtures (172 mg) of nitrate II-80 and nitro compound II-79 and, finally, with 20% benzene in petroleum ether a fraction of oil (201 mg) which showed a single spot on a t.l.c. plate. This oil was distilled at 35°/0.03 mm to give a colourless oil of trans-1-nitro-2-chlorocyclohexane (II-79): i.r. 1550 (s), 1370 (s), 850 (m) and 745 (m) cm^{-1}; n.m.r. τ 5.495 (dt, J = 10.0 and 4.0 Hz, H_1), 5.735 (dt, J = 10.0 and 4.0 Hz, H_2), 7.70 (m, 2H) and 8.30 (m, 6H); m.s. (130°) m/e (%) 127 (4), 118 (2), 116 (5), 97 (4), 81 (100), 79 (31) and 77 (12).

Further elution with 0-10% methanol in chloroform gave a mixture (175 mg) containing nitro compound II-79 and 2-chlorocyclohexanone II-83 as shown by its i.r. and n.m.r. spectra.

A solution of anti-dimer II-78 (1.0 g) and perchloric acid (60%, 1.2 g) in methanol (300 ml) was cooled to 0° and irradiated with a 200 watt Hanovia lamp under oxygen. The original u.v. absorption of the anti-dimer at 295 nm shifted to 275 nm in 0.5 hours of irradiation and syn-dimer precipitated out gradually. The precipitate disappeared slowly and finally the peak at 275 nm disappeared after 5 hours of irradition. The photolysate was

concentrated under vacuum at room temperature. The residual solution was neutralized with saturated potassium carbonate solution and extracted with methylene chloride to give a pale yellow oil (1.024 g) which contained nitrate II-80, nitro compound II-79 and a small amount of 2-chlorocyclohexanone II-83 as shown by its i.r. and n.m.r. spectra.

V.p.c. analysis (3% SE-30 column at 90°) of the crude product from either photooxidation in methanol or in benzene showed the presence of nitrate II-80 (Rf. 2.7 minute, with a shoulder due to the cis-isomer) and nitro compound II-79 (Rf 3.2 minute) in the approximate ratio 1:1.

The anti-dimer II-78 (500 mg) and rose bengal (100 mg) were dissolved in methanol (250 ml) and irradiated under oxygen with a 300 watt tungsten lamp while the photovessel was cooled externally with cold water. The photolysis was followed by t.l.c. After 38 hours of irradiation, the methanol was removed under vacuum and the residue was taken up in ether and filtered to give the syn-dimer of II-78 (90 mg): i.r. 1330 (s), 1300 (s), 1215 (m), 1100 (s), 1040 (s) and 743 (s) cm^{-1}; n.m.r. (DMSO-d_6) τ 4.62 (m, W1/2 = 24 Hz) and 5.68 (m).

Decolourization of the filtrate with activated charcoal and evaporation of tne solvent gave a solid (343 mg) which contained

predominantly anti-dimer II-78 and very small amounts of nitrate II-80 and nitro compound II-79 (identified by i.r.and n.m.r.). Chromatography of this mixture on neutral alumina (20 g) and elution with benzene gave an initial fraction (33 mg, semi-solid) which was a mixture of anti-dimer II-78 and nitrate II-80 (identified by i.r. and n.m.r.). The subsequent fractions contained only II-78.

5-5-4. Photodecomposition of the anti-Dimer of trans-1-Nitroso-2-chlorocyclohexane (II-78)

A solution of anti-dimer II-78 (1.0 g) in benzene (100 ml) was photolysed under nitrogen with a 200 watt Hanovia lamp. In 0.5 hours, a precipitate covered the photocell. The white crystals were scraped off occasionally and irradiation was continued for 7 hours. The precipitate was washed with ether and dried overnight (260 mg): m.p. 135-140°. Its u.v. spectrum (in ethanol) exhibited an absorption band at 275 nm which shifted gradually to 295 nm after 10 hours. Recrystallization from benzene gave white crystals that exhibited identical i.r., n.m.r. and m.s. as those of anti-dimer II-78. The residue left after evaporation of the benzene showed i.r. absorptions at 1640, 1285, 1210 and 850 cm^{-1}. Alumina chromatography of this crude product gave II-78 (540 mg) and an oily fraction: i.r. 1635, 1280, 860 and 750 cm^{-1}; n.m.r. τ 5.05 (m), 6.10 (m), and 6.40 (m). V.p.c. analysis (3% SE-30 column at 90°)

of this fraction showed the presence of nitrate II-80 (with a shoulder due to the cis-isomer) and cyclohexyl chloride (II-81) in the approximate ratio 1:1.

A solution of anti-dimer II-78 (1.0 g) in methanol (100 ml) was photolysed under nitrogen with a 200 watt Hanovia lamp until the absorption at 295 nm had disappeared (37 hours). The photolysate was worked up in the usual manner and the resulting oil (950 mg) was taken up in methanol to give a solid product (145 mg) which was recrystallized from methanol to afford white crystals of N,N,O-tri(2-chlorocyclohexyl)hydroxylamine (II-82): m.p. 110-112°; i.r. 1045 and 730 cm^{-1}; m.s. m/e 381 (M^+), 383, 385, 264, 266, 231 and 229. The residue that remained after the removal of II-82 exhibited strong absorptions at 1640, 1285, 850 and 750 cm^{-1} and was shown by v.p.c. analysis to contain nitrate II-80 and cyclohexyl chloride (II-81) in the approximate ratio 1:1.

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