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TITLE OF THESIS/*TITRE DE LA THÈSE* The Synthesis of Azapolycyclic Compounds and the Photochemistry of N-Nitramines

UNIVERSITY/*UNIVERSITÉ* Simon Fraser University

DEGREE FOR WHICH THESIS WAS PRESENTED/*GRADE POUR LEQUEL CETTE THÈSE FUT PRÉSENTÉE* Doctor of Philosophy

YEAR THIS DEGREE CONFERRED/*ANNÉE D'OBTENTION DE CE DEGRÉ*

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THE SYNTHESIS OF AZAPOLYCYCLIC COMPOUNDS AND THE PHOTOCHEMISTRY OF N-NITRAMINES

By

Robert William Lockhart

B.Sc.(Hons.) Simon Fraser University, 1968

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
in the Department of
Chemistry

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Degree: Doctor of Philosophy

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The Synthesis of Azapolycyclic Compounds and the Photochemistry of N-Nitramines

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ABSTRACT

THE SYNTHESIS OF AZAPOLYCYCLIC COMPOUNDS AND THE PHOTOCHEMISTRY OF N-NITRAMINES

The photolysis of N-nitrosamines in dilute acidic solution generates aminium radicals which undergo an intermolecular addition reaction with suitably located internal double bonds to yield products possessing 5-membered aza rings. This reaction was utilized to synthesize bridged azatricyclic and azatetracyclic compounds possessing the 2-azatricyclo[4,2,1,$0^{4,8}$]nonane, 2-azatricyclo[4,3,1,$0^{4,9}$]decane, and 1-azatetracyclo[5,2,1,$0^{1,5}$,$0^{3,8}$]decane ring systems. When the photolysis was done in the presence of various radical trapping agents diversely functionalized azacyclic compounds were isolated. The crystal and molecular structures of two of the reaction products, N-methyl-2-azatricyclo[4,3,1,$0^{4,9}$]decan-10-one-syn-oxime hydrochloride and exo-10-methoxy-N-methyl-2-azatricyclo[4,3,1,$0^{4,9}$]decane, were unambiguously determined by X-ray diffraction techniques.

In certain cases the azatricyclic derivatives formed underwent a facile and stereospecific bond cleavage reaction to form azabicyclic compounds which retained the stereochemistry of the reacting intermediate.

As an alternate means of synthesizing bridged azacylic compounds the thermolysis of some N-chloramines was investigated. In some cases this proved to be an efficient alternate means of constructing 5-membered azapolycyclics and also resulted in additional variations in the functionality of the products formed.

The solution photochemistry of N-nitropiperidine was investigated and it was established that the piperidine radical and the piperidinium radical are the reactive intermediates under neutral and acidic conditions, respectively. A reaction mechanism is postulated.

ACKNOWLEDGEMENTS

The author wishes to thank Professor Y.L. Chow for his direction and interest throughout this work. Thanks are also extended to Professor F.W.B. Einstein for his invaluable aid in the determination of crystal and molecular structures. The assistance of the technical and support staff of the Chemistry Department is gratefully acknowledged.

Acknowledgement is also extended to the National Research Council of Canada for financial support in the form of a bursary and scholarships. The financial assistance of the Sidney Hogg Graduate Memorial Scholarship Fund is also acknowledged.

The author thanks his wife, Cheryl, and daughter, Randeen, for their love and encouragement during the course of this work.

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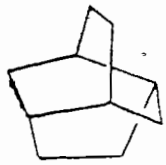
TABLES

CHAPTER 1

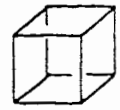
INTRODUCTION

1.1 Synthesis of Azapolycyclic Compounds

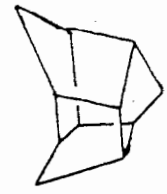
The synthesis and chemical investigation of bridged polycyclic compounds are problems currently attracting the attention of organic chemists. The synthesis of carbocyclic molecules possessing the twistane, cubane, and trishomocubane skeletons (1,2,3) are some prominent examples in which these challenges are being met. Because of their structural features compounds of these and other (4,5) bridged ring systems possess some unusual chemical properties (2-5). Interest in bridged polycyclic compounds, however, has extended beyond carbocyclic ring systems to those containing various heteroatoms. These heteroatomic bridged polycyclic compounds are not only of chemical interest but also of biological interest since, for example, there are several classes of alkaloids which possess bridged ring structures (6).



twistane

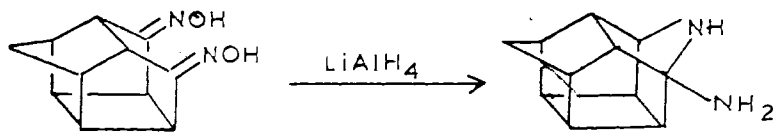


cubane



trishomocubane

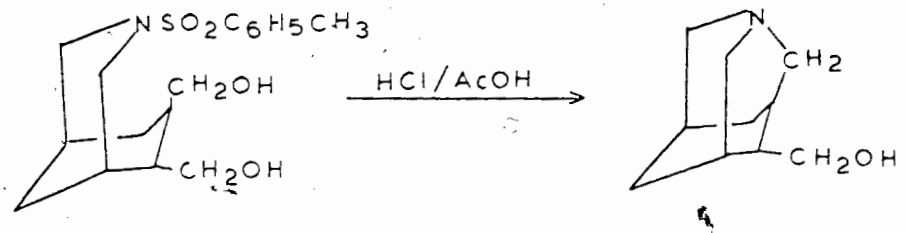
The synthesis of bridged heterocyclic compounds has been achieved by a wide variety of means. Most of these synthetic schemes are characterized by a key cyclization step leading to the compound of interest. This cyclization reaction may be one of a variety of intramolecular condensation (Scheme 1.1)(7), displacement (Scheme 1.2)(8,9), or addition reactions (Scheme 1.3)(10).



Scheme 1.1

Investigations in this laboratory on the generation of azabicyclic ring systems by the intramolecular cyclization of N-nitrosamines (11,12) have inspired us to extend this study towards the synthesis of more complex azatricyclic and azatetracyclic bridged ring compounds.

N-Nitrosamines exhibit a strong π-π^* absorption at 250 nm (ε~8000) and a weak n-π^* at about 340 nm (ε~100). The irradiation of either the π-π^* or n-π^* band of N-nitrosamines in dilute acidic solution generates aminium radicals ($R_2\dot{N}H$) and nitric oxide ($\dot{N}O$) which undergo



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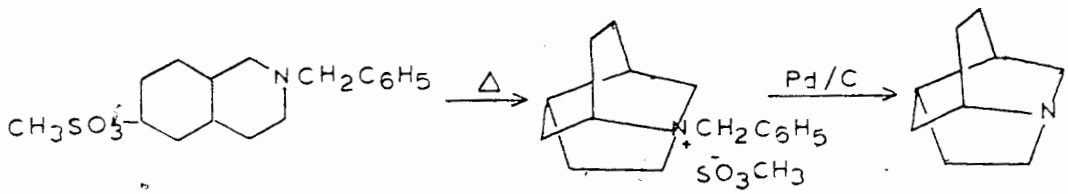
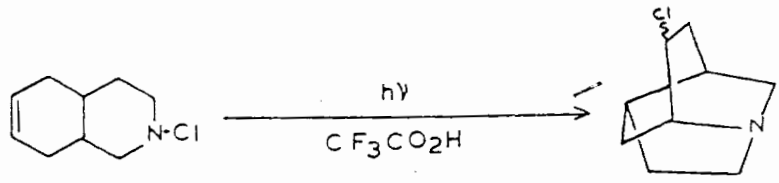


(9)

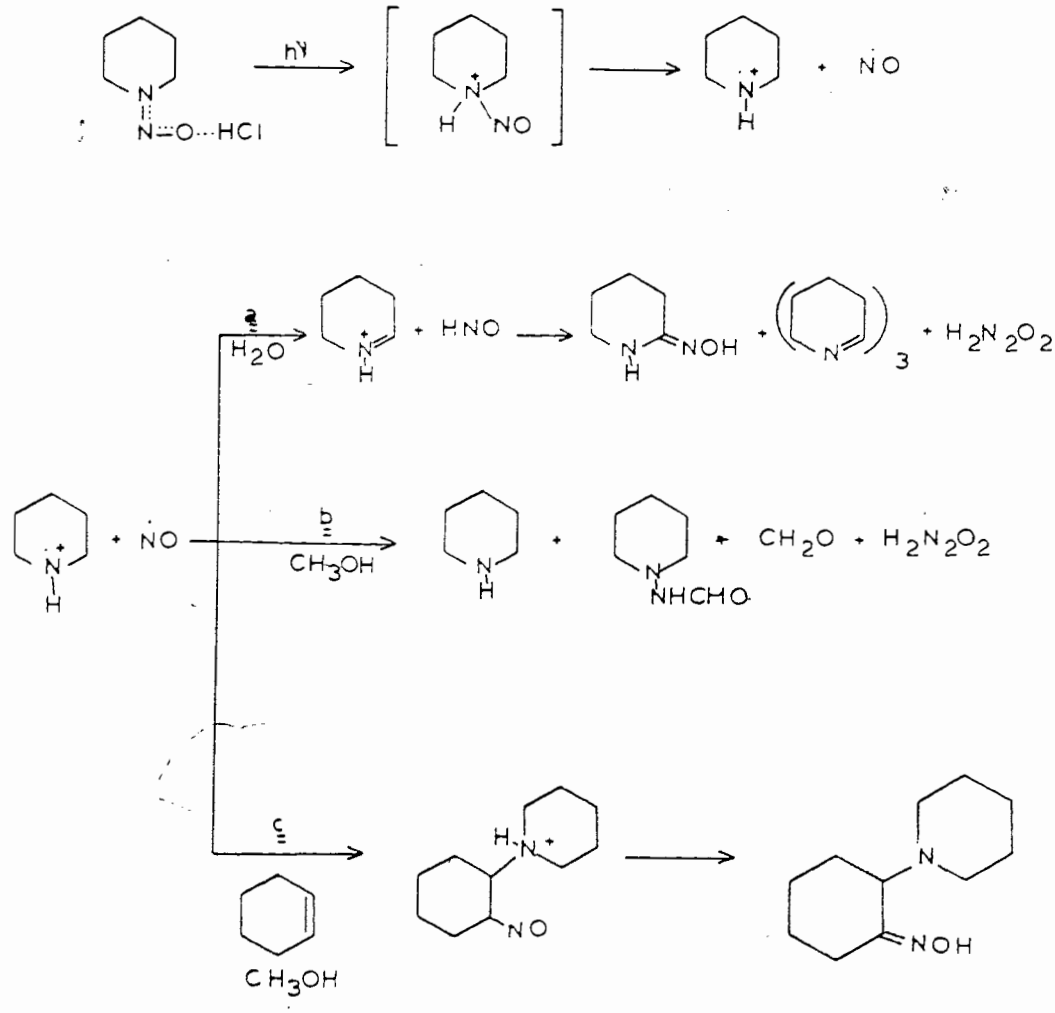
Scheme 1.2



Scheme 1.3

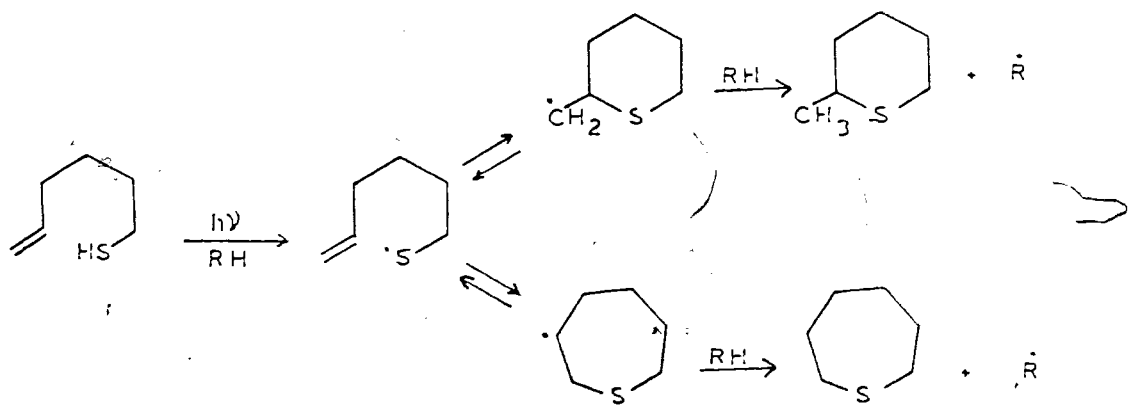
various reactions (11). The fate of these intermediates is dependent upon the conditions of the experiments; observed reactions such as photoelimination (path a), photoreduction (path b) and photoaddition

(path c) are summarized in Scheme 1.4 (11) for N-nitrosopiperidine. The addition of the intermediate piperidinium radical to an olefinic center (path c) is by far the most efficient of these reaction pathways (11). As a result the application of intramolecular addition reactions of N-nitrosamines has been established to be an extraordinarily efficient means of synthesizing various azacyclic compounds (12,13).



Scheme 1.4

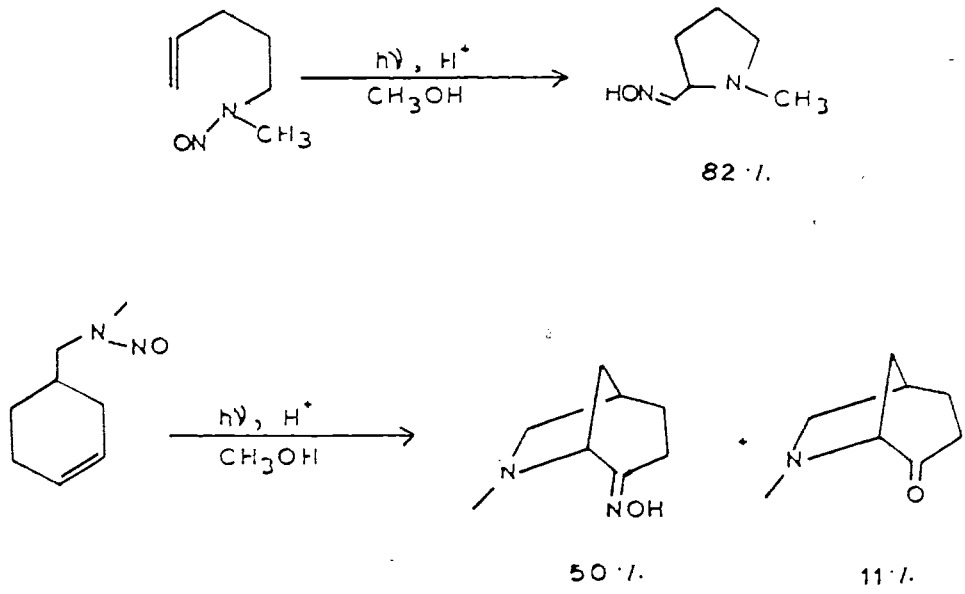
Intramolecular radical additions to olefins have become an important synthetic route to cyclic compounds. While most radical cyclization studies have centered on reactions of carbon radicals (14-18) heteroatomic radical cyclizations have also been examined (19-25). It is remarkable that both cyclizations occur regiospecifically to form the kinetically favored product; five-membered rings are formed when there is a choice between the formation of five- or six-membered rings. Surzur (23) has demonstrated for sulfur radicals (Scheme 1.5) the reversibility of radical cyclization and the possibility of thermodynamic control of the reaction. At low temperature (-65°) cyclization occurs preferentially to the seven-membered ring while at an elevated temperature (80°) the six-membered ring product is formed in greatest yield.



Scheme 1.5

On the basis of a series of carbon radical cyclizations, Julia (14) has concluded that radical stability and steric interactions between the reacting centers are dominant factors in determining the ring size of the cyclic product. Alterately, Beckwith (18) has emphasized the importance of the stereoelectronic requirement that maximum overlap of the radical orbital with the lowest unoccupied orbital of the π-bond system is achieved. An alternate model might be the overlap of the radical p-orbital with the bonding π orbital. Since both the π and π^* molecular orbitals of an olefinic bond lie in the same plane (116) it is difficult to distinguish between these processes.

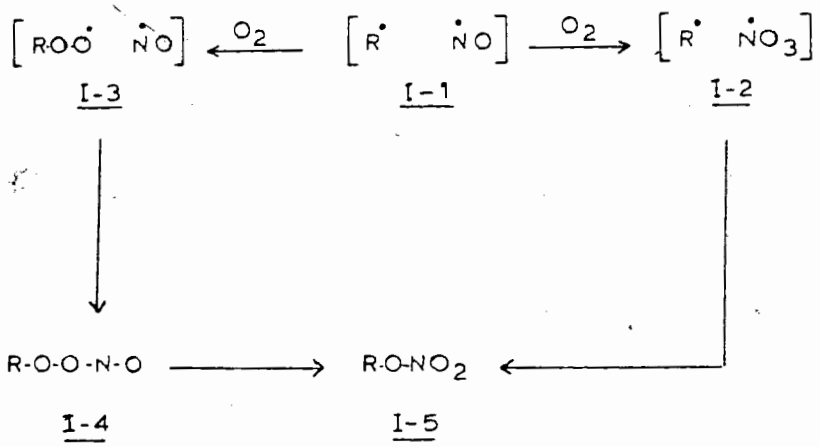
Representative examples of N-nitrosamine cyclizations are shown in Scheme 1.6 (11).



Scheme 1.6

There are several advantages to the use of N-nitrosamines in the synthesis of azacyclic compounds. These include the following: N-nitrosamines are stable, radical addition is preferred over the alternate side reactions, the final azacyclic product also contains a potentially useful functional group and finally, the photolysis conditions can be manipulated to alter this functional group. Under an inert nitrogen atmosphere oximes are formed; such products may be reduced to primary amines or hydrolysed to ketones. However, in the presence of radical trapping agents such as oxygen or $CBrCl_3$, the corresponding nitrate esters or bromo compounds are obtained.

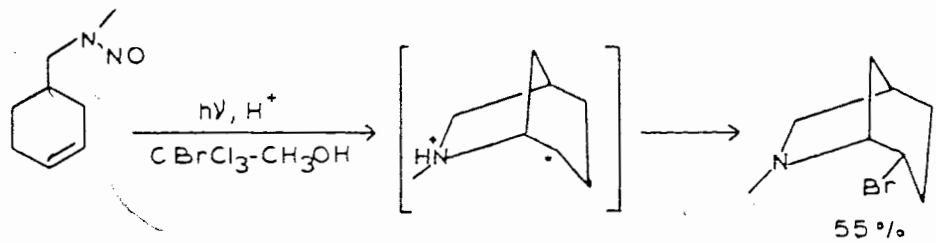
Nitrosamine photoaddition to olefins under an oxygen atmosphere gives nitrate esters exclusively (11,26,27). Since the photoaddition generates a radical pair, I-1, it has been proposed that these intermediates can be oxidized in two possible ways (Scheme 1.7) to give radical pair I-2 or I-3 (27). Peroxy nitrite I-4 is expected to be an unstable species which in analogy with the corresponding peroxy nitrate (28) rearranges rapidly to I-5 by a peroxy bond scission. The relative importance of these two pathways has not been verified but experiments in our laboratory (29) suggest oxidation via I-2 to be the more likely process.



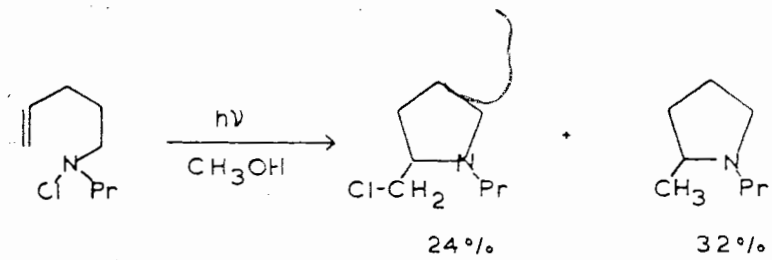
Scheme 1.7

This oxidative photoreaction is a simple and clean preparative method for nitrate esters. Although the nitrates are stable under acidic conditions (29) they undergo extensive base catalysed decomposition (30). Reduction of the nitrate product gives the corresponding amino alcohol.

Photolysis of N-nitrosamines in the presence of $CBrCl_3$ results in the isolation of amino bromides (11,12). The efficient radical scavenging (31) of $CBrCl_3$ completely traps the cyclized radical intermediate (Scheme 1.8) (12).



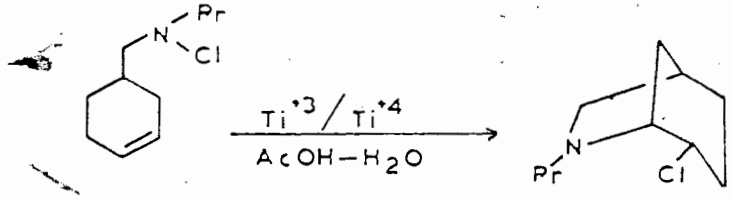
Scheme 1.8



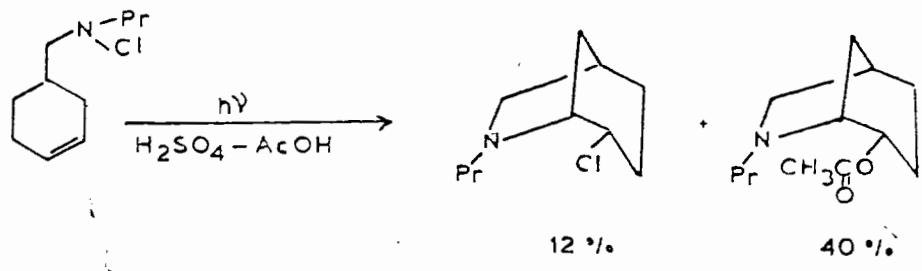
Scheme 1.9

Other synthetically useful examples of nitrogen radical cyclizations are seen in the reactions of N-chloramines (32). Photolysis of N-chloramines (Scheme 1.9) (20) or initiation by a redox system as shown in Scheme 1.10 (22) leads to cyclization of the intermediate amine radical. In the latter example there is a possibility however (24) that the reactive intermediate is an amine

radical-metal complex ($R_2\dot{N}:\rightarrow M^+$). Photolysis of N-chloramines in acidic solution generates aminium radicals which cyclize to 5-membered aza rings as shown in Scheme 1.11 (25). The major product in the example shown is derived, however, from a competitive reaction involving ionic addition of chlorine to the double bond followed by a Hofmann-Loffler type cyclization (25). The synthesis of chloro azatwistanes by the photolysis of the bicyclic chloramine shown in Scheme 1.3 is the only known example in which an aminium radical has cyclized to a 6-membered ring rather than a 5-membered ring. This is probably the result of steric restraints forcing cyclization to occur to the 6-membered ring.

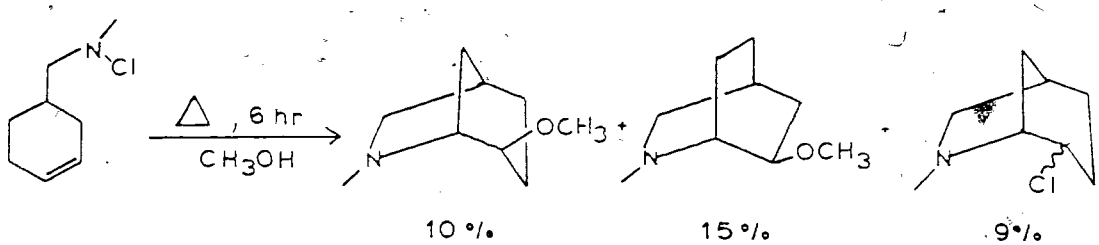


Scheme 1.10

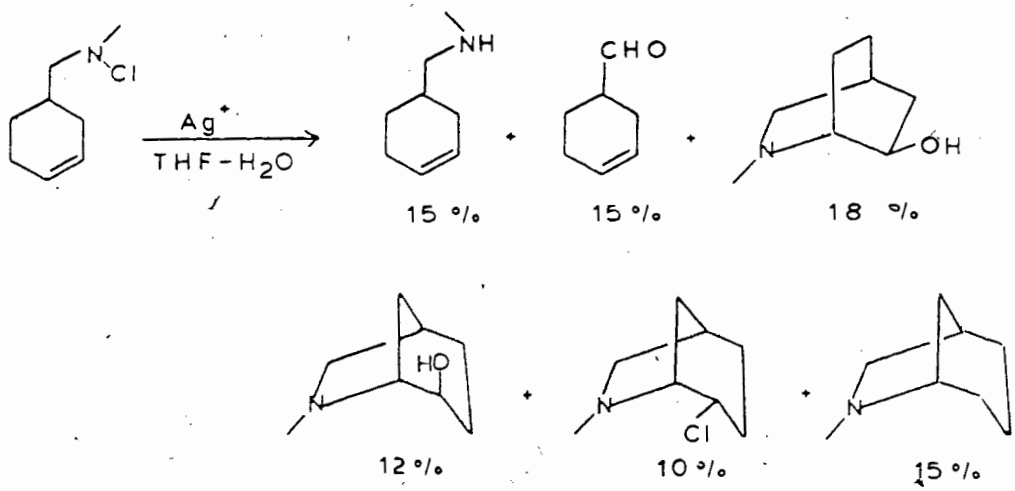


Scheme 1.11

While amine and aminium radicals generated from N-chloramines undergo intramolecular addition reactions to form the kinetically more favored product (23,24), thermolysis of N-chloramines in neutral protic solvent, with or without silver catalysis (Schemes 1.12 and 1.13) (33) leads to a less specific intramolecular cyclization reaction. Gassman (33) has suggested that these reactions follow an ionic pathway involving discrete nitrenium ion intermediates. From simple molecular orbital theory two electronic configurations of this ion can be considered. In its singlet state the nitrenium ion undergoes carbonium ion type reactions such as rearrangement (34) while in the triplet state the nitrenium ion resembles cation radicals and undergoes H-abstraction or addition reactions (32).



Scheme 1.12



Scheme 1.13

Singlet Triplet

Nitrenium ion

The above interpretation of these chloramine cyclization reactions has received much criticism however (35,36). Edwards and coworkers (35) have examined the reaction described in Scheme 1.12 in detail and found that it had a 1-3 hour induction period, that benzoyl peroxide

eliminated this induction period, and that under an oxygen atmosphere the reaction was slower and the main product became the parent amine. This suggests that a radical intermediate is involved in the reaction. While studying a similar reaction Hobson (36) concluded that neutral amine radicals, resulting from homolytic cleavage, rather than triplet nitrenium ion species may be the most probable intermediates in neutral chloramine cyclization reactions. Neutral amine radicals have been observed to undergo H-abstraction in preference to addition to olefinic bonds (37,38); in cases where the olefinic bond was suitably located within the chloramine molecule, amine radical addition has apparently occurred (20,22). However, intermediation of an aminium radical can not be completely eliminated since an amine radical may be protonated by hydrochloric acid which is generated during chloramine thermolysis.

Although the direction of cyclization during N-chloramine thermolysis is not always as specific as that involving aminium radical intermediates this alternate cyclization route might provide some flexibility in the synthetic design in some particular cases.

1.2 The Photochemistry of N-Nitramines

The nitramines ($R_2N\text{-}NO_2$) are generally low melting solids or liquids which show no basic properties. The primary nitramines are acidic while secondary nitramines are neutral (39). The structure of several N-nitramines have been determined crystallographically and the nitramine portion of the molecule is found to be planar with a short N-N bond length of 1.3Å indicating a major contribution from the

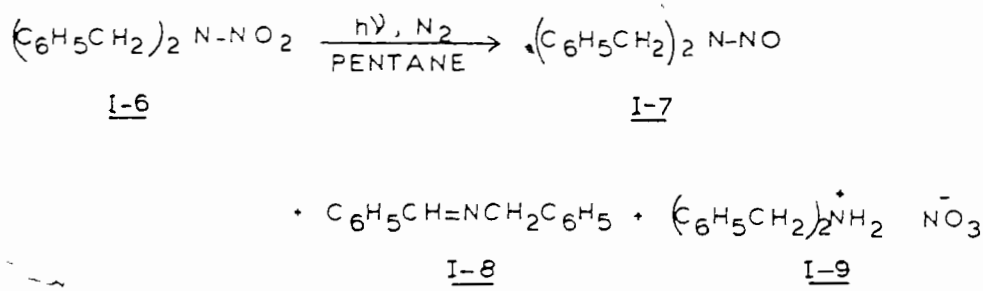
$R_2\dot{N}=\dot{N}O_2^{2-}$ structure (39). Presumably the partial double bond character of the N-N bond results in a restricted rotation about this bond.

The ultraviolet spectra of nitramines exhibit a strong (ε~5,500 for secondary nitramines, ε~7000 for primary) π-π^* transition in the 240 nm region (40). They do not exhibit an n-π^* transition in the 350 nm region as observed for N-nitrosamines, however, a weak band (ε~40) at about 300 nm is observed in n-hexane, probably due to an n-π^* transition (40). The infrared spectra of dialkyl nitramines exhibit strong asymmetic and symmetric stretching bands of the nitro group at 1540-1505 cm^{-1} and at 1315-1260 cm^{-1}, respectively (42). Other prominent bands occur in the regions 1130-1100 cm^{-1} and 760-755 cm^{-1}.

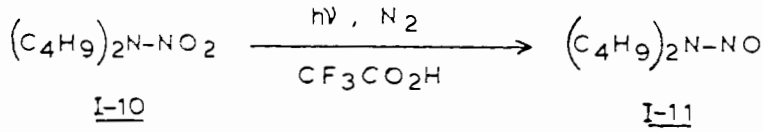
The photochemistry of dialkyl nitrosamines has been studied extensively by this research group (11). These investigations have shown N-nitrosamines to be photochemically stable under neutral conditions, while in dilute acidic media aminium radicals are generated. The photochemistry of dialkyl N-nitramines, although reported periodically (41,43-46), is not nearly so well understood.

Lavanish (43) reported that the irradiation of dibenzyl nitramine, I-6, in pentane (Scheme 1.14) gave N-nitrosodibenzylamine, I-7, N-benzylidine benzylamine, I-8, and dibenzylamine nitrate, I-9, as the main products.

Irradiation of I-6 in ethanol increased the yield of nitrate I-9 while irradiation in trifluoroacetic acid gave only a trace of I-9. Irradiation of dibutyl nitramine, I-10, in trifluoroacetic acid (Scheme 1.15) (43) gave dibutyl nitrosamine, I-11, as the only product detected.



Scheme 1.14



Scheme 1.15

Photolysis of dimethyl nitramine in either n-hexane, 95% ethanol, or acetonitrile gave only N-nitrosodimethylamine (41). On irradiation of an equimolar mixture of dimethyl nitramine doubly labelled with N^{15} and unlabelled dimethyl nitramine or dimethyl nitrosamine in the solid state (44) no isotope crossover was observed. It was concluded therefore that in the solid state nitrosamine was formed by an N-O bond cleavage.

Different results were obtained by Bodnar (45) and Moon (46). They irradiated nine cyclic nitramines in 1,2-propanediol cyclic carbonate and in the solid state and observed the formation of nitroxide, $R_2N\text{-}\dot{O}$, by E.S.R. The oxidation of an amine radical by air to the stable nitroxide (47) would account for these results.

In this work we shall demonstrate that the solution photolysis of N-nitramines under neutral conditions generates amine radicals whereas under acidic conditions the aminium radical is generated. A reaction mechanism is postulated.

The intentions of this research can be outlined as follows:

1. To synthesize substituted azatricyclic and azatetracyclic compounds using aminium radical intramolecular cyclizations.

2. To investigate the diversion of these reactions using radical trapping agents.

3. To investigate the utility of N-chloramine thermolysis reactions as an alternate means of synthesizing azacyclic compounds.

4. To determine if the addition of N-nitrosamines to unconjugated dienes would result in radical cyclization.

5. To investigate the solution photochemistry of N-nitramines.

CHAPTER 2

RESULTS

Photochemical and synthetic studies were undertaken to increase our understanding of amine radical reactions and to further establish the ultility of some of these reactions to the synthesis of heterocyclic compounds. The experimental conditions and procedures are presented in Chapter 4 and the structures of the products resulting from this work are given in Appendix I. The results of the photolysis of N-nitropiperidine under neutral and acidic conditions are presented first.

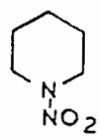
2.1 The Generation of Amine and Aminium Radicals from N-nitramines

Unless otherwise specified N-nitropiperidine photolyses were conducted in methanol under a nitrogen atmosphere in an ice bath. A medium pressure mercury lamp placed in a Corex filter served as the light source to irradiate the π-π^* transition band of the nitramine.

2.1.1 The Photodecomposition of N-Nitropiperidine in Methanol

The photolysis of a methanol solution of N-nitropiperidine, II-1, under a nitrogen atmosphere was monitored by the disappearance of the π-π^* absorption at 249 nm. The peak intensity decreased rapidly on photolysis while it showed no change in the dark. Inspection of the

undiluted u.v. spectrum of the photolysate showed no new absorption maxima at 350 nm, as expected if N-nitrosopiperidine were formed as reported previously (43). Analysis of the crude photolysate by gas chromatography (g.c.) and by gas chromatography-mass spectrometry (g.c.-m.s.) showed the presence of piperidine, II-2, and N-formylpiperidine, II-3, (48) in a ratio of 1.2:1, respectively, as the major photodecomposition products. Examination of the crude photolysate by the diphenylamine test (49) gave a distinct positive response indicating the presence of nitrate ion.



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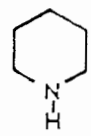
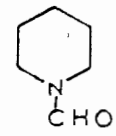


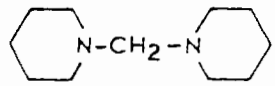
II-2



II-3

A similar photolysis of II-1 in the presence of dilute hydrochloric acid proceeded slightly faster than under neutral conditions. Formaldehyde was isolated as its 2,4-dinitrophenyl hydrazone (2,4-DNPH) derivative from the trapped distillate whereas this compound was not isolated from the corresponding distillate of the previous neutral photolysis. The residual material deposited piperidine hydrochloride (16%) on treatment with 2-propanol (48). Basification and extraction with ether gave piperidine (52%) as the only other product. However, when the basic fraction was extracted with CH_2Cl_2, piperidine was

also isolated, in part, as its dipiperidinomethane derivative, II-4, as a result of alkylation of piperidine (12).



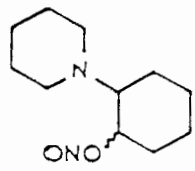
II-4

2.1.2 The Photolysis of N-Nitropiperidine in the Presence of Cyclohexene

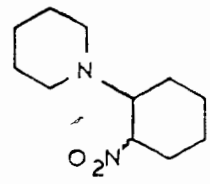
When II-1 was photolysed in methanol in the presence of cyclohexene no products resulting from addition to cyclohexene could be detected in the crude residue. Only the previously described photodecomposition products formed under neutral conditions, e.g., piperidine, N-formylpiperidine and dipiperidinomethane, could be detected.

Under acidic conditions, however, the photolysis of II-1 in the presence of cyclohexene proceeded significantly slower than when II-1 was irradiated under neutral conditions. It was obvious that a photolabile intermediate was formed since a u.v. absorption appeared as a shoulder at about 210 nm and subsequently disappeared during the irradiation. This intermediate was believed to be nitrite II-5 (50) since it was well known that such nitrites were photolabile (51). Under these conditions the photolysis afforded a complex mixture of addition

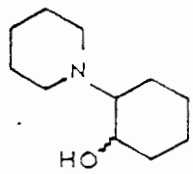
and decomposition products. The addition products* were characterized by g.c.-m.s. analysis as 1-nitro-2-piperidinocyclohexane, II-6 (9%), 2-piperidinocyclohexanol, II-7 (20%), 2-piperidinocyclohexanone oxime, II-8 (22%), 1-methoxy-2-piperidinocyclohexane, II-9 (10%), and a piperidinocyclohexene, (12%).



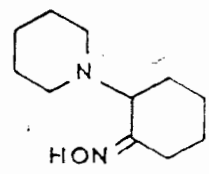
II-5



II-6



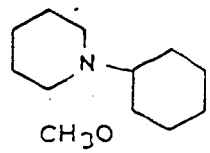
II-7



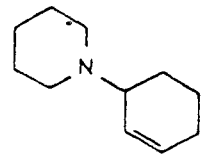
II-8

The mass spectrum of II-6 was idential to a 2:3 mixture of cis- and trans-1-nitro-2-piperidinocyclohexanes (29). The i.r. spectrum of the crude mixture also exhibited a distinctive band at 1550 cm^{-1} indicating the presence of a nitro product (42). The mass spectrum of II-7 was identical to an authentic sample of the trans-isomer.

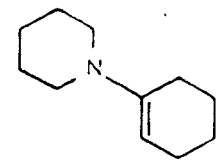
*The present yields were estimated from g.c. peak areas relative to the total area of the g.c. volatile products.



II-9



II-10



II-11

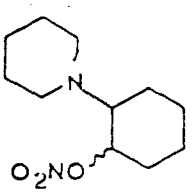
The m.s. of II-8 was identical to that of an authentic sample. Methoxy amine II-9 had a molecular ion peak at m/e 197 and a base peak at m/e 124 which was common to all the piperidinocyclohexane derivatives in addition to a strong m/e 182 peak presumably due to the loss of a CH_3 fragment.

The m.s. of the last addition product exhibited an M^+ peak at m/e 165 and the fragmentation pattern was similar to that of an authentic sample of 3-piperidinocyclohexene, II-10. The base peak of this compound appeared at m/e 137 however while that of II-10 appeared at m/e 111. This suggested that this compound is more likely to be II-11 than its isomer, 3-piperidinocyclohexene, II-10.

2.1.3 The Photolysis of N-Nitropiperidine in the Presence of Cyclohexene Under Oxygen

The disappearance of nitropiperidine when irradiated under an oxygen atmosphere in acidic methanol containing cyclohexene proceeded at

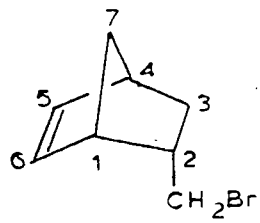
approximately twice the rate of the corresponding reaction under a nitrogen atmosphere. The major products of this oxidative photolysis were 1-nitrato-2-piperidinocyclohexanes, II-12, as indicated by typical i.r. absorptions at 1625, 1275 and 865 cm^{-1} (42, p.301). In view of the instability of these nitrates (29) the crude product was reduced with lithium aluminum hydride (LAH) to give cis-2-piperidinocyclohexanol and the corresponding trans-isomer in a 1:2 ratio, respectively (29). This ratio was taken to represent the steroisomeric ratio of the amino nitrates II-12.



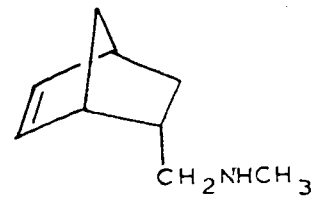
II-12

2.2 Synthesis of Amines

A 7:3 mixture of 2-endo-bromomethylbicyclo[2,2,1]hept-5-ene, II-13, and the corresponding exo-isomer was prepared by the Diels-Alder reaction (52) of cyclopentadiene with allyl bromide. This mixture was treated with methylamine to give the same isomeric mixture of 2-endo-methyl-aminomethylbicyclo[2,2,1]hept-5-ene, II-14, and the corresponding exo-isomer. Amine II-14 was utilized without further purification.



II-13

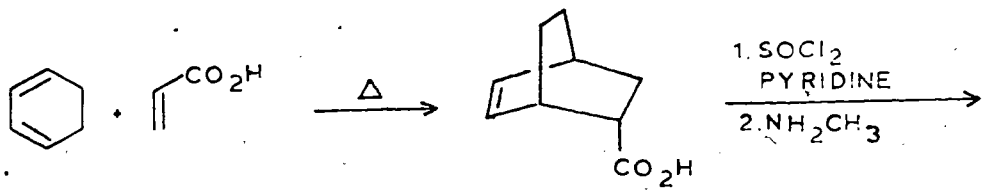


II-14

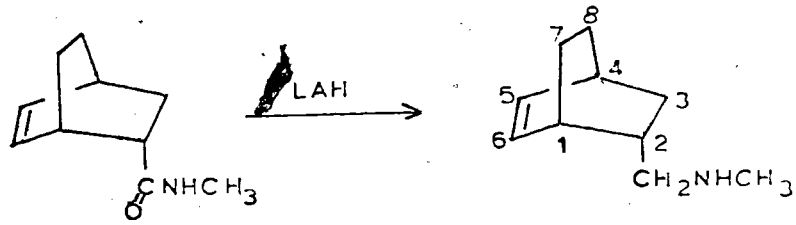
The n.m.r. spectrum of II-13 showed a doublet of double doublet pattern at τ9.41 (J=11.5, 4, and 2.5 Hz) which was assigned to the C_3-endo-proton. The corresponding proton in II-14 appeared as a broadened doublet at τ9.50 (J=10Hz). The shift to a high field has been attributed (53,54) to the anisotropic effect of the C_2-endo-methylene substituent.

The reaction of 1,3-cyclohexadiene with acrylic acid (55) gave, after distillation, endo-2-carbomethoxylbicyclo[2,2,2]oct-5-ene, II-15, in 46% yield. The carboxylic acid was modified by the sequence shown in Scheme 2.1 to give the desired amine II-17 in an overall yield of 59%.

While in the literature carboxamide II-16 was reported to have m.p. 103-105° (55), our preparation gave a crystalline solid of m.p. 135-136°. Elemental analysis of our sample gave the correct analysis for $C_{10}H_{15}NO$ and the i.r. exhibited the appropriate amide bands at 1640 and 1555 cm^{-1}. Our compound was further supported by conversion of II-16 to amine II-17 whose n.m.r. spectrum exhibited a one proton multiplet at τ9.13 for the C_3-endo-proton (53).



II-15

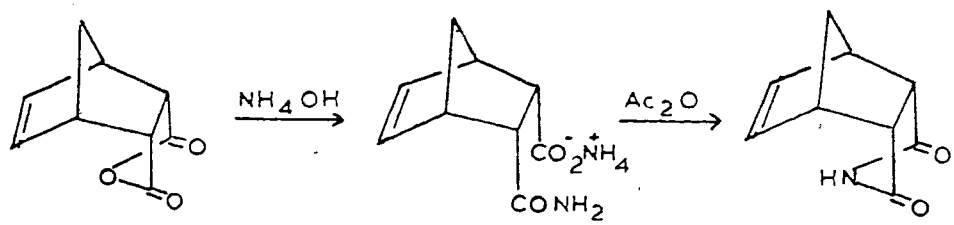


II-16 II-17

Scheme 2.1

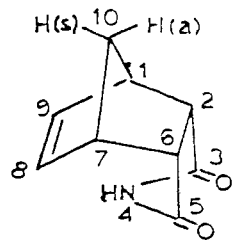
A crude sample of endo-norbornene-cis-5,6-dicarboxylic anhydride, II-18, was recrystallized from water as white needles melting at 164-165° (Lit.165°) (56). The reaction of II-18 with NH_4OH (56) as shown in Scheme 2.2 gave an intermediate salt believed to be amide II-19 which exhibited i.r. bands due to the carboxylic acid salt at 1710 and 1628 cm^{-1} as well as amide bands at 1660 and 1530 cm^{-1}. Treatment of II-19 with acetic anhydride gave imide II-20 (56) which exhibited the appropriate i.r. bands at 1760 and 1700 cm^{-1}. The n.m.r. spectrum

of II-20 exhibited an AB quartet displaying weak secondary coupling for the C_{10}-syn and -anti protons* at τ 8.44 ($\Delta\nu$ = 15 Hz, J=9 Hz).

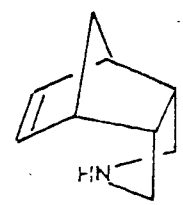


II-18 II-19 II-20

Scheme 2.2



II-20



II-21

* In the description of n.m.r. spectra the terms syn and anti will be used in the following ways. When referring to bridge protons of a cyclic olefin, syn is applied to the proton nearest the olefin. Anti will refer to the proton furthest from the olefin. When referring to aldoximes, syn is in reference to the isomer with the oxime hydroxy function cis to the aldoxime proton. In reference to heterocyclic oximes, the syn isomer is the one in which the oxime hydroxy function is on the same side as the ring heteroatom. Finally, in the description of N-nitrosamine geometrical isomers, syn will refer to the isomer with the nitroso group cis to the smaller substituent. Anti will refer to the alternate geometrical isomer.

Reduction of imide II-20 with LAH by the known procedure (57,58) did not give directly the amine II-21 but instead what appeared to be an inorganic complex of this amine exhibiting a strong NH_2 deformation band at 1625 cm^{-1} (42). The m.s. of this volatile amine salt exhibited a peak at m/e 135 and a base peak at m/e 68 for $C_4H_6N^+$ as determined by high resolution mass spectroscopy indicating the presence of a pyrrolidine ring (59). High resolution mass spectroscopy on the peak at m/e 135 gave the exact mass for $C_9H_{13}N$, the required molecular ion for amine II-21. The n.m.r. spectrum of this compound exhibited a narrow two proton multiplet for the olefinic protons at τ3.78 and the expected AB quartet at τ8.52 ($\Delta\nu$=11.5 Hz, J=8.5 Hz) for the C_{10}-syn and anti-protons. Since this complex could be transformed directly into the N-nitroso derivative of II-21, which gave the correct elemental analysis for $C_9H_{12}N_2O$, further characterization was not pursued.

2.3 Nitrosation and Chlorination of Amines

Nitrosation of the bicyclic and tricyclic amines was achieved using either sodium nitrite ($NaNO_2$), dinitrogen tetroxide (N_2O_4), or nitrosotetrafluoroborate ($NOBF_4$) as nitrosating agents. The conditions used for the nitrosation with $NaNO_2$ (60) proved to be too vigorous for the nitrosation of an amine carrying a strained double bond. Under these conditions nitrous acid added extensively across the double bond giving a complex mixture of nitroso, nitrite, and nitro products (61,62).

Dinitrogen tetroxide (63) proved to be a milder nitrosating agent as did $NOBF_4$ (64). The reagent of choice was, however, $NOBF_4$ in the presence of pyridine (65) which left the olefinic bond almost completely intact.

The N-nitrosamines synthesized exhibited very complex n.m.r. spectra as a result of the presence of syn- and anti- isomers arising from the restricted rotation of the nitrosamino group. The yields of the nitroso compounds and their spectral characteristics are listed in Table 2.1.

The N-chloro compounds were prepared using well established procedures employing sodium hypochlorite solutions (12,66) and were used without further purification. Iodometric titrations of these samples indicated an active chlorine content of ca.95%. The yields and spectral data for the N-chloramines are summarized in Table 2.2.

2.4 The Photolysis of N-nitroso Alkenylamines Under Nitrogen

Unless otherwise specified all photolyses were conducted in methanol, containing at least one equivalent of hydrochloric acid, under a nitrogen atmosphere in an ice bath. A medium pressure mercury lamp placed in a Nonex filter served as the light source to irradiate the $n-\pi^*$ transition band of the nitrosamines.

Table 2.1

Preparation and Spectral Properties of N-Nitrosamines

Compound	Nitrosating Agent	Yield(%)	i.r.[1] cm^{-1}	λmax nm(ϵ)[2]	n.m.r. τ values[3] olefinic protons	syn-isomer N-CH_3	anti-isomer N-CH_3
II-22	$NaNO_2$ / N_2O_4	31 / 70	1430 / 1035	344(97)	3.75 / 3.98	6.92	6.20
II-23	$NOBF_4$	61	1430 / 1035	345(100)	3.70	6.97	6.25
II-24	$NOBF_4$	73	1412 / 1312	348(87)	3.82	CH_2 6.60	CH_2 5.90

1. I.r spectra run as a neat film/or nujol mull.
2. U.v. spectra taken in methanol.
3. N.m.r. spectra taken in $CDCl_3$.

Table 2.2

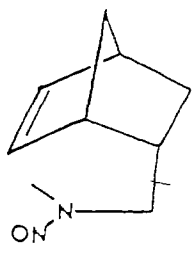
Yield and Spectral Properties of the N-Chloramines[1]

			N.M.R.τ-Values		
Compound	Crude Recovery(%)	λmax nm(ε)	olefinic protons	$-CH_2-NCl-CH_3$	
II-25	90	277(315)	3.75	7.03	7.10
II-26	68	267(440)	3.80	7.10	

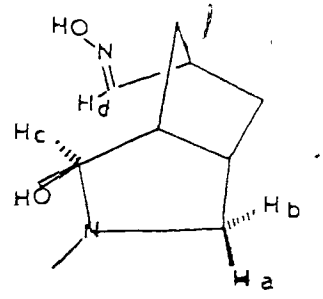
1. See footnotes on Table 2.1.

2.4.1 N-Nitroso-2-endo-methylaminomethylbicyclo[2,2,1]hept-5-ene, II-22

The photolysis of nitrosamine II-22, containing about 30% of the corresponding exo-isomer, in methanol under a nitrogen atmosphere proceeded rapidly as shown by the disappearance of the n-π^* transition band of the nitrosamine in the u.v. spectrum of the photolysate. This was accompanied by the appearance of a strong band attributed to the formation of an intermediate C-nitroso dimer (11,12) at 290 nm. No starting N-nitrosamine was recovered from the photolysate. The major products isolated were the azabicyclic-syn-aldoxime II-27 (22%) and hydroxy lactam II-28 (29%). Also isolated was a small amount of unidentified olefinic material exhibiting a triplet in the n.m.r. spectrum at τ3.90 (J=1.5Hz) attributed (67) to products originating from the approximately 30% of the exo-bicyclo[2,2,1]-isomer which was present in the starting nitrosamine II-22.



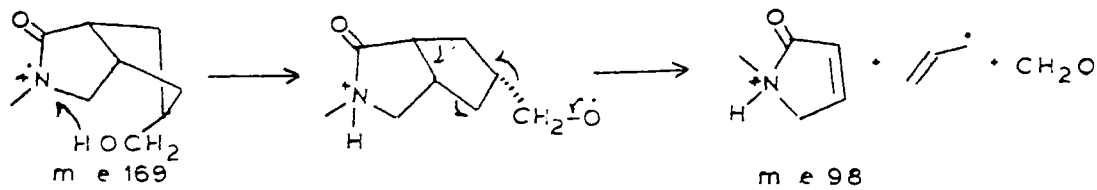
II-22



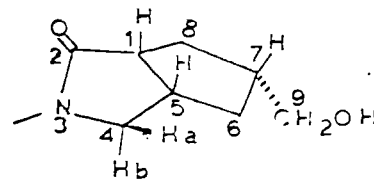
II-27

Aldoxime II-27 was isolated as an unstable solid. The i.r. spectrum confirmed the presence of an oxime function with bands at 3300, 3040, 920, 890 and 860 cm^{-1} and the M^+-2 ion at m/e 182 analysed correctly for $C_9H_{14}O_2$. The n.m.r spectrum exhibited a doublet at τ2.72 (J=7Hz, Hd) indicating II-27 to be the syn-aldoxime (68), a broad doublet at τ5.30 (J=5.5Hz) was assigned to Hc, and a broadened doublet at τ6.55 (J=8Hz) to H_b which should couple geminally to H_a and only weakly to the bridgehead proton at C_5 since the dihedral angle with this proton is approximately 90° (69). The ease by which II-27 was converted to hydroxy lactam II-28 by an intramolecular redox reaction (70) on treatment with sodium bisulphite (71) indicated that the hydroxy function was exo to the cis fused ring system.

Elemental analysis established the molecular formula of hydroxy lactam II-28 as $C_9H_{15}NO_2$. The i.r. spectrum of II-28 showed absorption at 3300 cm^{-1} for the hydroxyl group and at 1660 cm^{-1} for the γ-lactam function (12). The mass spectrum of II-28 gave a strong M^+ ion at m/e 169 and a prominent peak at m/e 98. the latter peak is common to the mass spectra of substituted N-methyl γ-lactams (72) and is postulated to be generated from II-28 as shown in Scheme 2.3. The n.m.r. spectrum of the lactam exhibited a three proton multiplet at about τ6.4 assigned to the two protons at C_9 and H_a at C_4. The double doublet at τ6.92 (J=10 and 1 Hz) was assigned to H_b which should weakly couple to the bridge proton at C_5.



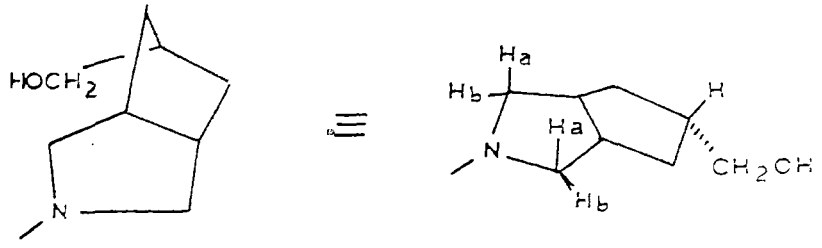
Scheme 2.3



II-28

Reduction of II-28 with sodium bis-(2-methoxyethoxy)aluminum hydride gave the bicyclic amine II-29 which was analysed as its picrate. The m.s. of amine II-29 gave the molecular ion at m/e 155 and the i.r. spectrum exhibited alcohol absorptions at 3300 and 1020 cm^{-1}. Taking advantage of the fact that II-29 possessed a plane of symmetry the structure was confirmed by the presence of a sharp doublet at τ6.38 (J=5Hz) in the n.m.r. spectrum due to the two magnetically equivalent protons at C_9. The spectrum also exhibited a two proton doublet at

τ7.39 (J=8.5Hz) assigned to the two H_b protons which would not be expected to couple to the bridgehead protons since their dihedral angles with these protons approximated 90°. The two protons geminal to the H_b protons appear as a two proton multiplet at τ7.45.

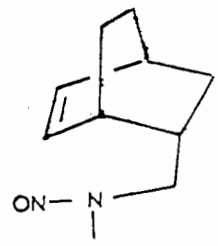


II-29

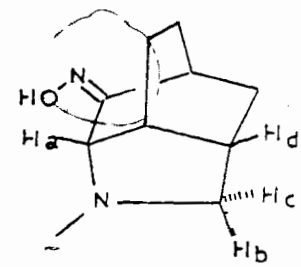
2.4.2 N-Nitroso-2-endo-methylaminomethylbicyclo[2,2,1]oct-5-ene, II-23

Photolysis of nitrosamine II-23 under nitrogen gave tricyclic syn-oxime II-30 (53%), in part as its hydrochloride, and the corresponding anti-oxime II-31 (13.5%). Oxime II-30 exhibited i.r. bands at 3180, 3040, 940 and 920 cm^{-1} for the oxime function. The n.m.r. spectrum showed a doublet at τ6.02 (J=4Hz) for H_a, and a double doublet at τ6.98 (J=9.5 and 4Hz) was assigned to H_b which was coupled geminally to H_c and also to H_d since the dihedral angle between H_b and H_d was approximately 30° (69). The n.m.r. spectrum of oxime II-30 was recorded in the presence of increasing amounts of tris(dipivalomethanato)europium(III) shift reagent. The

presence of a doublet originally at about τ7.5 (J=9-10Hz) was revealed in this manner. This doublet was assigned to H_c which was not expected to couple to H_d since the H_c and H_d dihedral angle was approximately 90° (69).



II-23



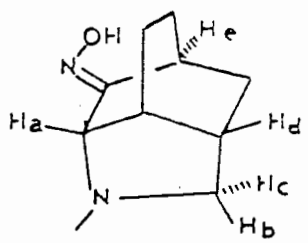
II-30

The hydrochloride of II-30 has i.r. bands due to the oxime function at 3125, 3060, 958, 945 and 905 cm^{-1} as well as bands due to the protonated amine at 2660, 2580 and 2550 cm^{-1}. A crystallographic analysis of the hydrochloride (Chapter 5) verified the structure. Treatment of the hydrochloride with base followed by extraction gave syn-oxime II-30.

In addition to oxime II-30 a crystalline compound was isolated as a minor product which was assigned as anti-oxime II-31 by comparison of the spectral data of this product to those of oxime II-30. The i.r.

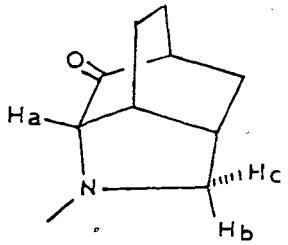
spectrum of II-31 exhibited the required oxime bands at 3180, 3060, 965 and 920 cm^{-1} and the mass spectra of II-30 and II-31 were the same except that II-31 exhibited a more intense molecular ion peak at m/e 180.

The doublet for H_a which resonated at τ6.02 in the syn-oxime was shifted upfield to τ6.86 (J=4.5Hz) in the n.m.r. spectrum of anti-oxime II-31. In addition, the n.m.r. spectrum of II-31 exhibited a triplet at τ6.25 (J=6.5Hz) and was assigned to H_e which was obviously shifted downfield due to the anisotropic effect of the anti-oxime group (73). The double doublet at τ6.72 (J=11 and 4.5Hz) was attributed to H_b. Irradiation of H_d at τ7.7 decoupled the double doublet of H_b into a doublet with J=11-12Hz. Similarly, irradiation at the τ8.3 region caused the H_e triplet at τ6.25 to collapse to a singlet.



anti-oxime II-31

Treatment of syn-oxime II-30 or a mixture of syn-oxime II-30 and anti-oxime II-31 with sodium bisulfite (71) gave tricyclic ketone II-32. The i.r. spectrum of II-32 exhibited a strong carbonyl band at 1720 cm^{-1} and the n.m.r. spectrum again displayed the double doublet for H_b at τ6.78 (J=9 and 4Hz) and the doublet for H_a at τ6.98 (J=5Hz).



II-32

2.5 Photolysis of N-Nitrosamines in the Presence of Radical Trapping Agents

2.5.1 Photolysis of Nitrosamine II-22 Under Oxygen

When nitrosamine II-22, containing about 30% of the corresponding exo-isomer, was photolysed under oxygen, the reaction was clearly redirected. The absorption band at 290 nm associated with the formation of an intermediate C-nitroso dimer (11) was absent from the u.v. spectrum of the photolysate. After the usual work-up, the crude basic residue of the photolysate exhibited strong i.r. bands at 1620 and 1275 cm^{-1} which were consistent with the formation of alkyl nitrates during the oxidative photo-addition of nitrosamines to olefins (28). A strong

carbonyl band at 1720 cm^{-1} in the i.r. spectrum and a weak signal in the n.m.r. spectrum at τ0.25 were attributed to the formation of aldehydes (28). To prevent extensive decomposition of the primary photoproducts the crude residue was immediately reduced with LAH. The mother liquor of the crude residue was continuously extracted to yield lactam II-28 (vide supra).

The LAH reduction of the crude residue gave tricyclic amino alcohol II-33 (12%), bicyclic amino alcohol II-29 (40%), and a small amount of olefinic material (10%). Amino alcohol II-33 was purified as its picrate which gave the correct elemental analysis for $C_{12}H_{18}N_4O_8$. The mass spectrum of II-33 had M^+ ion peak at m/e 153 and the i.r. spectrum exhibited strong alcohol bands at 3350 and 1015 cm^{-1}. The n.m.r. spectrum of the hydrochloride of II-33 was consistent with the proposed structure (Figure 2.1). The proton at $C_9(H_d)$ appeared as a multiplet at τ5.90 ($W_{\frac{1}{2}}$=3Hz). This proton must therefore be endo since in this orientation the dihedral angle to adjacent protons approximated 90° leading to weak couplings. For the same reason H_a appeared as a doublet at τ6.69 (J=5Hz) coupled only to the C_8 proton (74,75). The protons at C_3 were again coupled geminally to one another with H_c as a doublet at τ6.72 (J=10.5Hz) and H_b, having a dihedral angle of approximately 30° with the proton at C_4, appeared as a double doublet at τ7.09 (J=10.5 and 5Hz), a part of which was overlapped with the N-CH_3 signal..

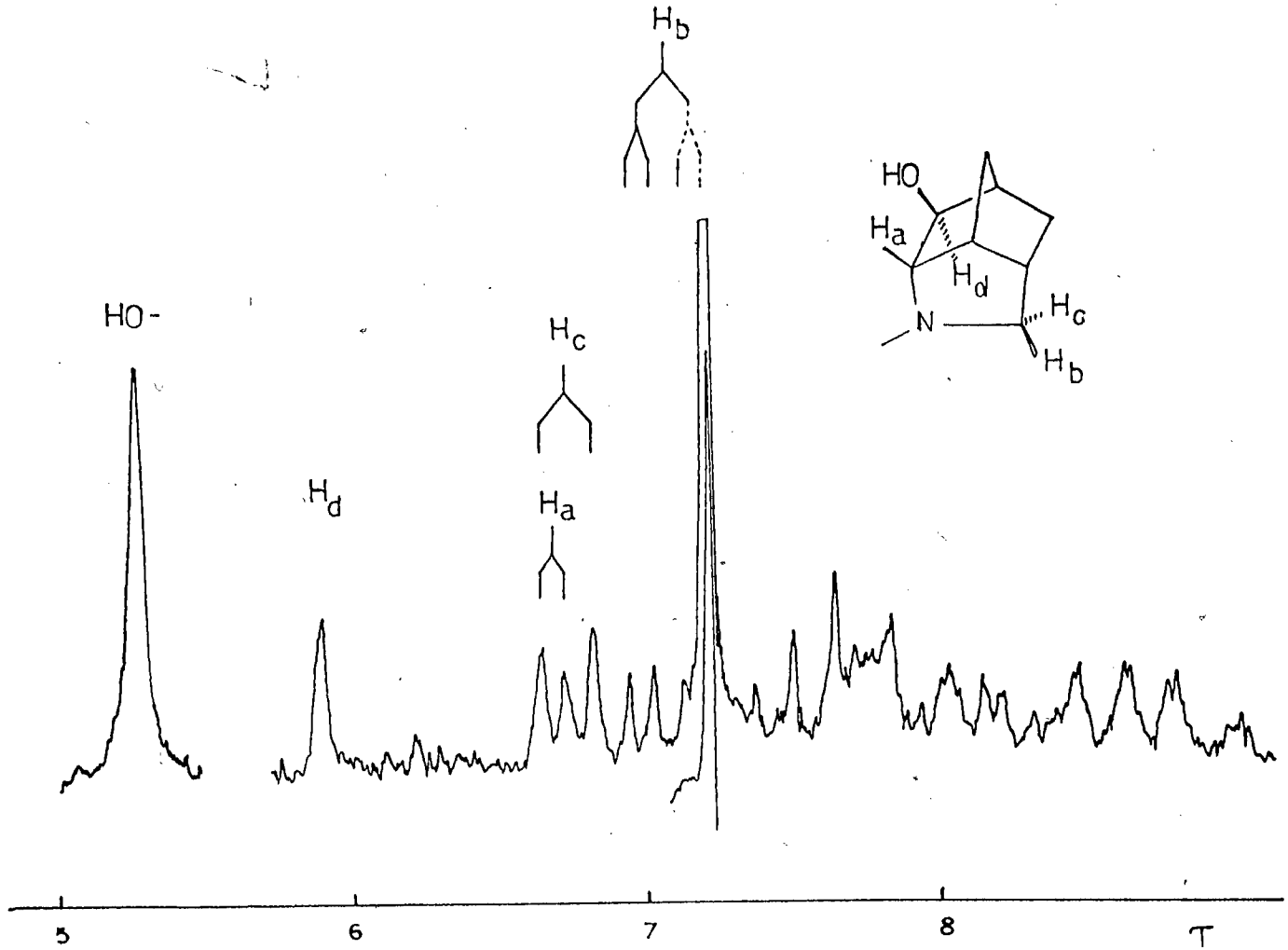
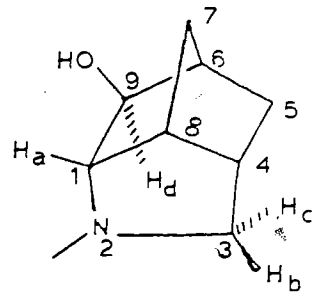
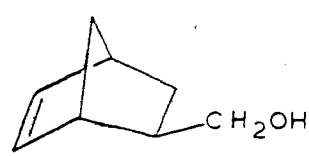


Figure 2.1: The N.M.R. Spectrum of the Hydrochloride of Amino Alcohol II-33 in $CDCl_3$.



II-33

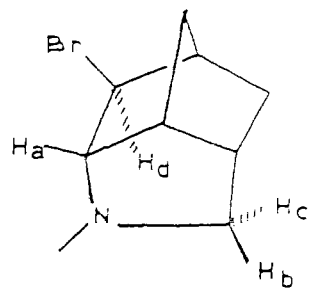
The major product isolated from the reduced fraction was a bicyclic amino alcohol which by spectral comparison and mixed melting point determination of picrate derivatives was identical to amino alcohol II-29. The olefinic material isolated from the reduced fraction was predominantly alcohol II-34 as determined by comparison of the n.m.r. spectrum of this sample with that of authentic II-34 (53). This compound was assumed to be derived from the approximately 30% of the exo-bicyclo[2,2,1] isomer which was present in the starting nitrosamine II-22.



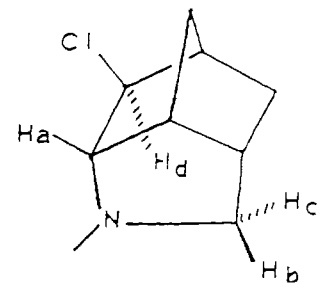
II-34

2.5.2 Photolysis of Nitrosamine II-22 in $CBrCl_3$

Photolysis of II-22 in a heterogeneous mixture of $CBrCl_3$ and hydrochloric acid under nitrogen gave a mixture exhibiting blue fluorescence. The source of this coloration has been previously identified as CCl_3NO (12,76). Two products with very similar spectral data were isolated. Mass spectral analysis of the major product demonstrated it to be a mono-bromo compound with the molecular formula $C_9H_{14}NBr$ as determined by high resolution mass spectrometry on the M^+ ion at m/e 215. The m.s. of the minor product exhibited most of the corresponding peaks to those of the major product with the exception that the M^+ ions were recorded at m/e 171 and 173 indicating that it was a mono-chloro compound. High resolution mass spectroscopy on the m/e 171 peak gave the molecular formula as $C_9H_{14}NCl$.

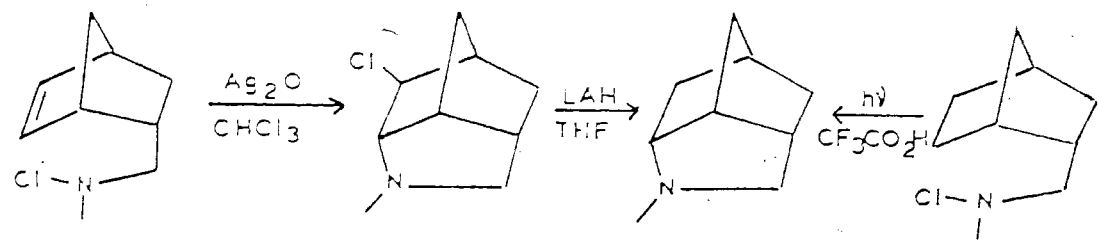


II-35



II-36

Comparison of the n.m.r. spectra of the bromo and chloro compounds indicated that the ring structures and stereochemistry of the two compounds were identical. The structures were shown to be II-35 and II-36, respectively, by direct comparison of the spectral data of the chloro derivative with those of the chloramine synthesized by B. Waegell (77,78) according to the method shown in Scheme 2.4. The n.m.r. spectra of II-35 and II-36 are shown in Figure 2.2. The halogen substituent was exo to the ring since H_d exhibited only weak coupling with the adjacent protons and appeared as a broadened singlet at τ6.15 in the spectrum of II-35 and at τ6.25 in the corresponding spectrum of II-36. The H_b protons appeared as double doublet signals at τ7.10 (J=9.5 and 5Hz) in both spectra. Doublets centered at τ7.50 (J=9.5Hz) and encompassing the N-CH_2 signals of both II-35 and II-36 were attributed to the H_a protons.



Scheme 2.4

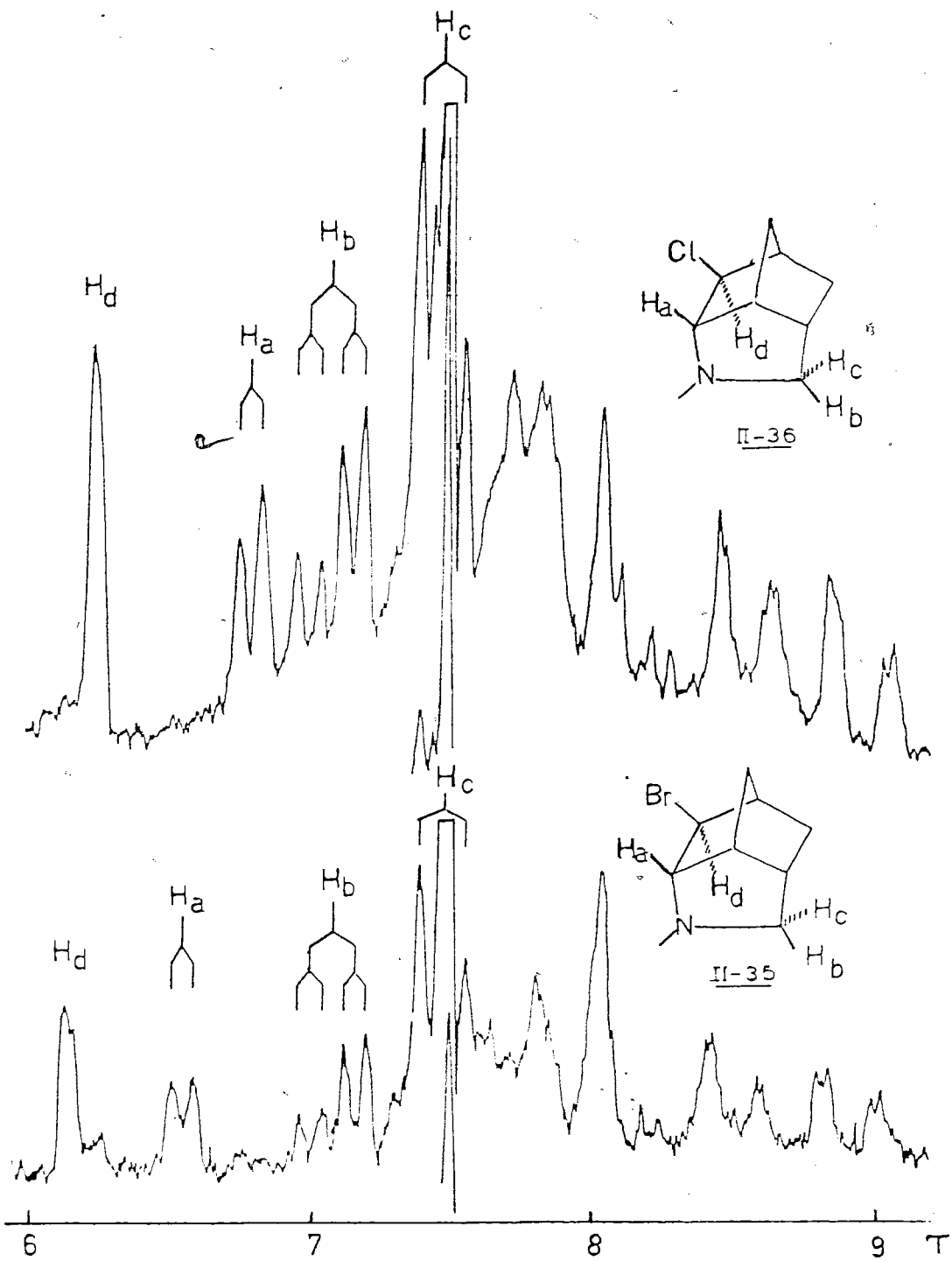


Figure 2.2: The N.M.R. Spectra of II-35 and II-36 in $CDCl_3$.

2.5.3 Photolysis of Nitrosamine II-22 in CCl_4

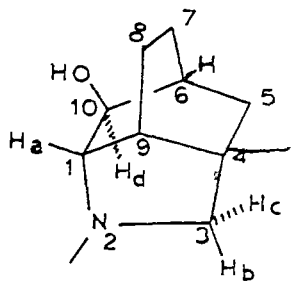
Photolysis of a heterogeneous mixture of nitrosamine II-22, hydrochloric acid and CCl_4 gave a basic fraction composed of II-36 and starting amine II-14 in a ratio of 6:1, respectively, as determined by g.c. Identifications of II-36 and II-14 were based on their characteristic n.m.r. signals and comparison by g.c. with authentic samples.

2.5.4 Photolysis of Nitrosamine II-23 Under Oxygen

Photolysis of II-23 under an oxygen atmosphere was immediately followed by LAH reduction of the basic ether extract. Chromatographic separation of the reduced material gave tricyclic amino alcohol II-37 (13%), bicyclic amino alcohol II-38 (13%) and an olefinic fraction (~17%). Further extraction of the photolysate mother liquor with CH_2Cl_2 gave additional basic material composed mainly of a nitrate (i.r. 1625 and 1270 cm^{-1}) and a ketone (i.r. 1710 cm^{-1}) in an aproximately 1:1 ratio.

Amino alcohol II-37 had an M^+ ion peak at m/e 167 for $C_{10}H_{17}NO$ as determined by high resolution mass spectroscopy and a pair of base peaks at m/e 94 and 82. The i.r. spectrum exhibited strong bands characteristic of an alcohol at 3350, 1052 and 1025 cm^{-1}. The molecular structure of this amino alcohol was firmly established by oxidation (79) to ketone II-32 obtained previously by the

hydrolysis of oximes II-30 and II-31. The structure of II-30 was unequivocally proven by X-ray diffraction studies. The n.m.r. spectrum of amino alcohol II-37 (Figure 2.3) was interpreted as follows: H_a was assigned to the doublet at τ 7.19 (J=4.5Hz) resulting from coupling to the C_9 proton since molecular models revealed a dihedral angle of approximately 30° between this proton and H_a. Coupling between H_a and H_d was not expected since the dihedral angle between these protons was approximately 90°. The doublet at τ7.26 (J=10Hz) was attributed to H_c, resulting from coupling to H_b, and the doublet of H_b was further split into a double doublet at τ7.47 (J=10 and 4.5Hz, partly overlapped with the N-CH_3 signal) by coupling to the C_4 exo proton (69). The doublet at τ6.20 (J=4Hz) was attributed to H_d resulting from coupling to the C_6 proton since the angle between these protons was approximately 30°.



II-37

The second compound isolated exhibited strong alcohol absorptions in the i.r. at 3350 and 1050 cm^{-1} and the mass spectrum gave a molecular ion peak at m/e 169 for $C_{10}H_{19}NO$ as determined by high

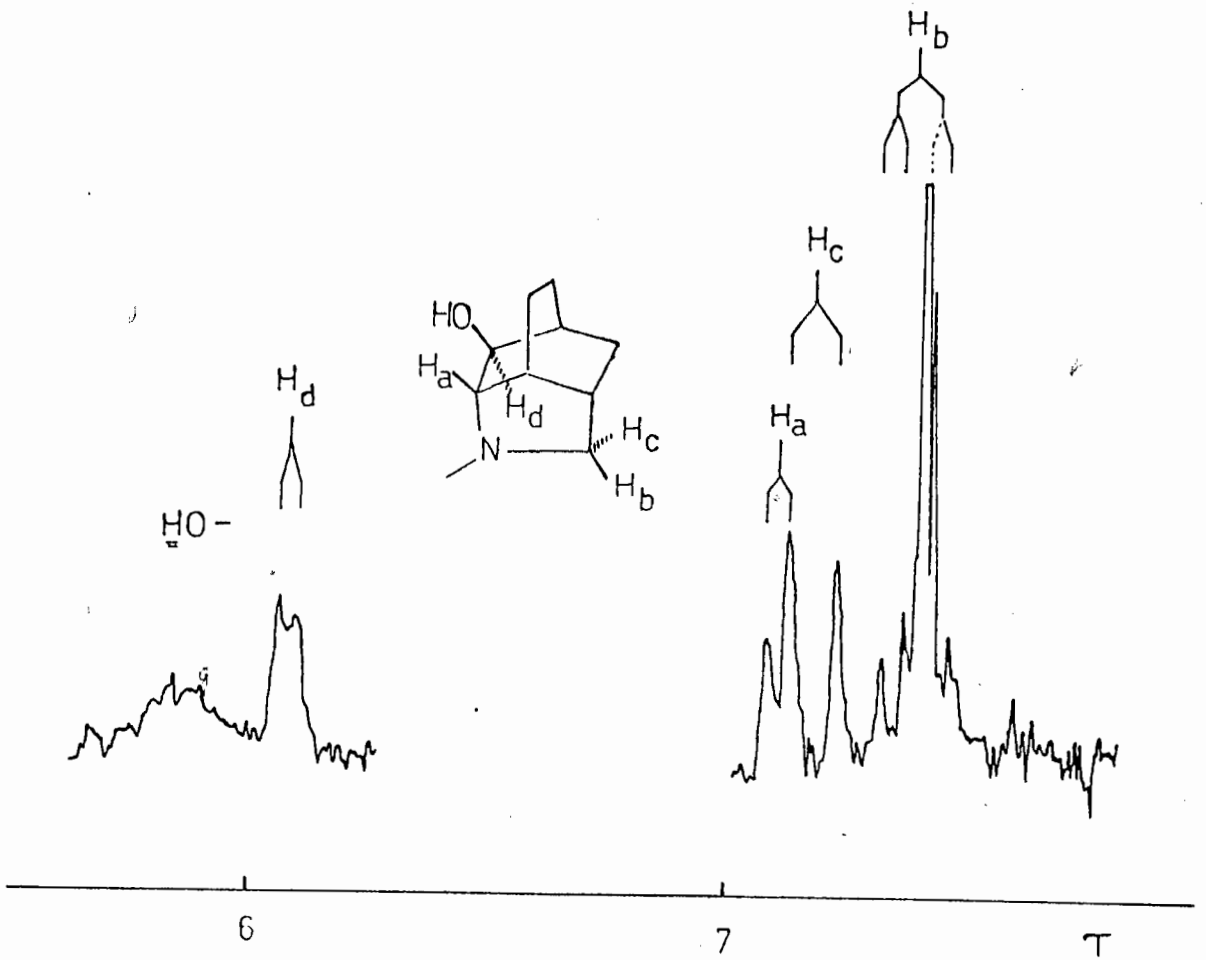
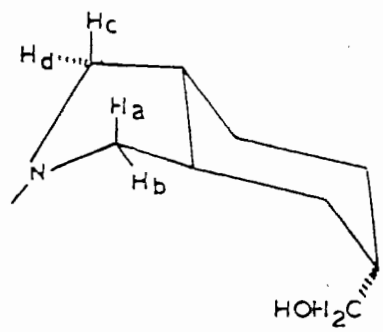


Figure 2.3: The N.M.R. Spectrum of Amino Alcohol II-37 in $CDCl_3$.

resolution mass spectroscopy. These data required that the compound was a bicyclic amino alcohol.

In analogy to the formation of aldoxime II-27 and amino alcohol II-29 this product was probably formed by the cleavage of a carbon-carbon bond (29,30) of a primary cyclization product. Since the photolysis of nitrosamine II-23 under both nitrogen and oxygen gave tricyclic products possessing 5-membered aza rings the cleavage pathway would lead to the formation of II-38. The N-methyl signal in the n.m.r. spectrum of II 38 (Figure 2.4) appeared at τ 7.62. Around this N-methyl singlet four protons believed to be H_a-H_d appeared at τ 7.0-7.75. The presence of the N-methyl signal hampered attempts to interpret these complex patterns. The multiplet at τ 6.50 was attributed to $-CH_2OH$ and was collapsed to two unresolved singlets on irradiation at τ 8.4.



II-38

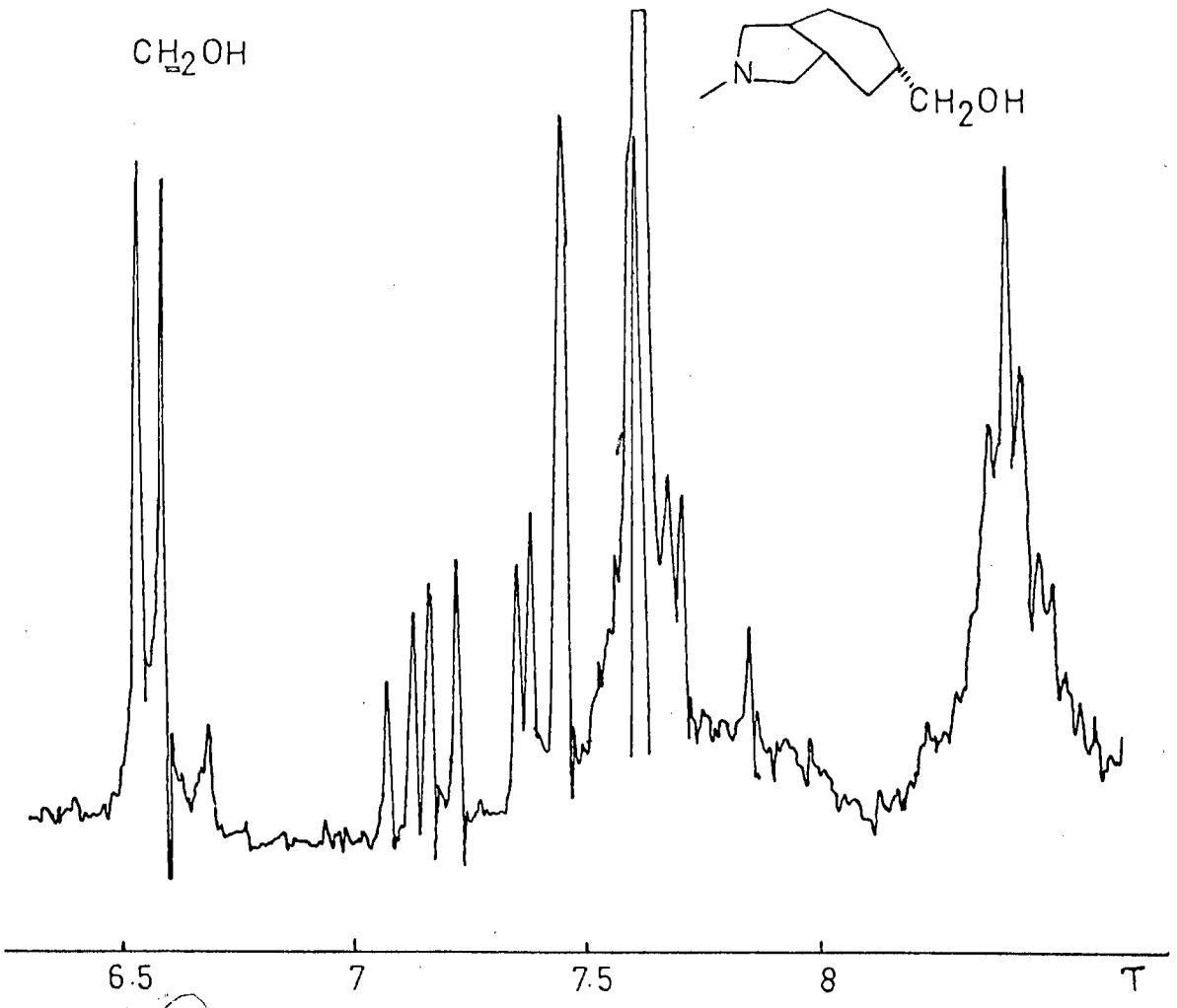
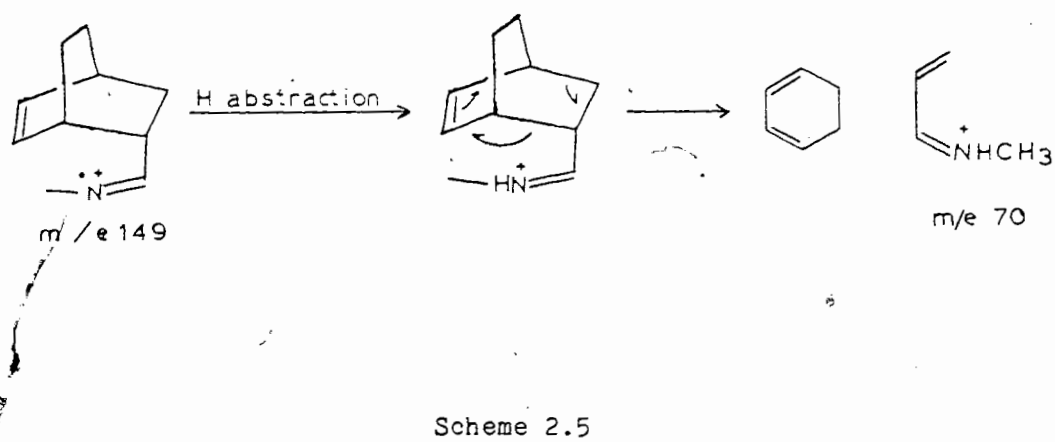


Figure 2.4: The N.M.R. Spectrum of Amino Alcohol II-38 in $CDCl_3$.

The chromatographic fraction containing olefins showed four peaks when examined by g.c.-m.s. The first peak eluted had a molecular ion peak at m/e 149 and a base peak at m/e 70 and was assigned the structure II-39. The m/e 70 fragment probably resulted from the retro Diels-Alder fragmentation of the bicyclo[2,2,2]hexene ring system as depicted in Scheme 2.5. The last three peaks, in order of elution, were characterized as amine II-17, amide II-16, and tricyclic amino alcohol II-37 by comparison of their fragmentation patterns with those of authentic samples.

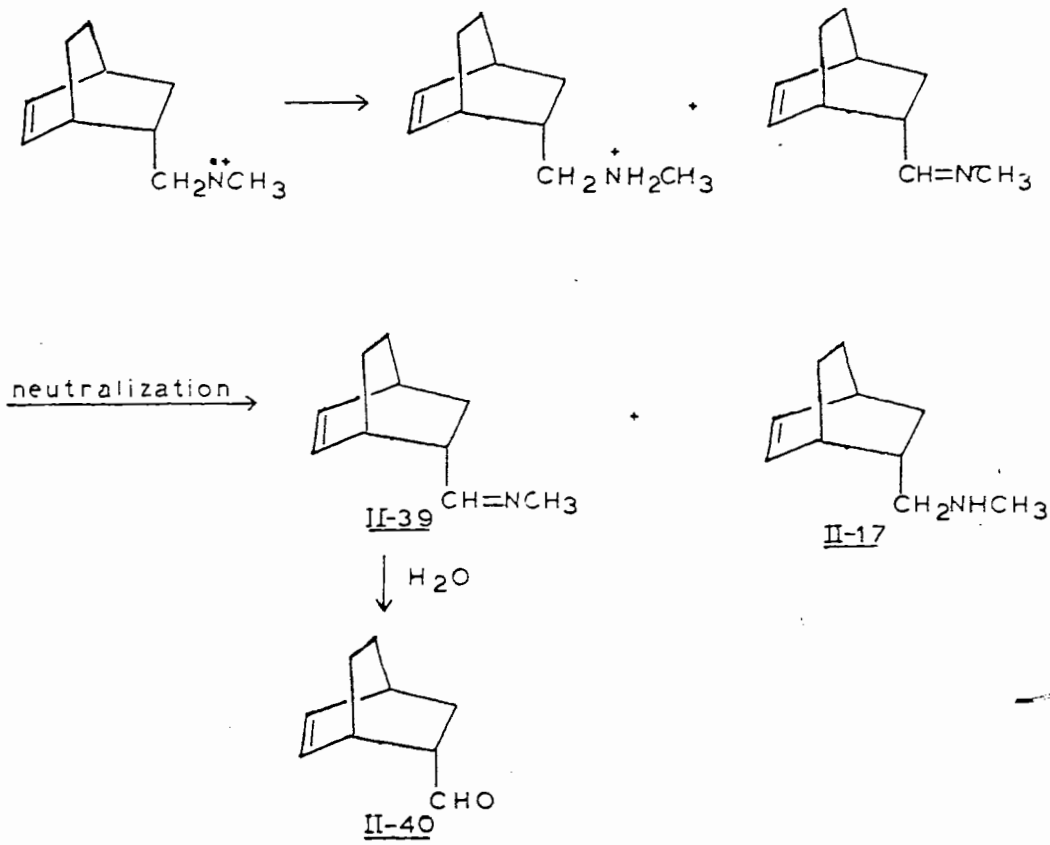


Scheme 2.5

2.5.5 Photolysis fo Nitrosamine II-23 in $CBrCl_3$

Photolysis of II-23 in a heterogenous mixture of hydrochloric acid and $CBrCl_3$ gave a blue solution which yielded a mixture of amine II-17, II-39, and a tricyclic bromo amine in the ratio of 4.1:1.2:1.0, respectively, as determined by g.c. The product mixture was examined by

g.c.-m.s. analysis. The identification of amine II-17 as the major product was based on its m.s. pattern and its g.c. retention time in comparison with an authentic sample. The structure of II-39 was also based on its m.s. fragmentation pattern. The formation of these products was rationalized as in Scheme 2.6. It is expected that the hydrolysis of II-39 should be a facile reaction resulting in the formation of aldehyde II-40. The crude acidic extract did in fact exhibit a weak multiplet in the n.m.r. spectrum at τ0.6 as well as a medium intensity i.r. band at 1720 cm^{-1} attributed to an aldehyde.

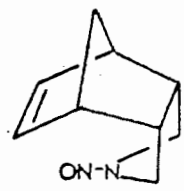


Scheme 2.6

The third product was a bromo amine having molecular ions at m/e 231 and 229 indicating that it was a tricyclic compound. Chromatographic isolation of this minor product was unsuccessful.

2.5.6 Photolysis of N-Nitrosamine II-24 Under Oxygen

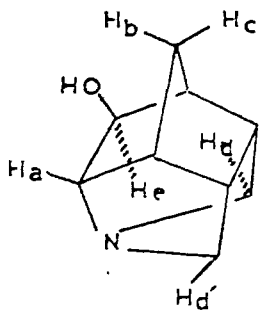
Photolysis of nitrosamine II-24 under oxygen was immediately followed by LAH reduction of the basic ether extract. Thin layer chromatography of the reduced material indicated the presence of only



II-24

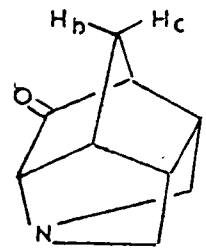
one major compound which was isolated by preparative scale t.l.c. and characterized as tetracyclic amino alcohol II-41. Elemental analysis of the picrate of II-41 established the molecular formula as $C_{15}H_{16}N_4O_8$. The i.r. spectrum of II-41 exhibited strong alcohol absorptions at 3200, 1040, and 1005 cm^{-1} and the mass spectrum gave the correct molecular ion at m/e 151. The n.m.r. spectrum of a slightly impure sample of II-41 featured proton coupling patterns similar to those exhibited by the tetracyclic halides II-43 and II-47

(vide infra). The narrow multiplet at τ 5.70 ($W_{\frac{1}{2}}$=5 Hz) was attributed to H_e. The absence of any substantial coupling between H_e and the adjacent protons indicated that it was endo since in this orientation the dihedral angles with adjacent protons were about 90°. The multiplet at τ6.41 was attributed to H_a while H_b and H_c appeared as a slightly broadened AB quartet at τ8.35 ($\Delta\nu$=38, J=10.5Hz). The double doublet at τ6.75 (J=12 and 2Hz) was attributed to either H_d or $H_{d'}$ since both protons possess the correct geometry to couple weakly to the adjacent bridgehead proton (vide infra).



II-41

Oxidation of II-41 with chromium trioxide (79) gave a ketone which exhibited a strong carbonyl band in the i.r. at 1750 cm^{-1} and a sharp AB quartet attributed to H_b and H_c at τ8.45 ($\Delta\nu$=24, J=11.5Hz) in the n.m.r. spectrum. The mass spectrum of this compound exhibited the correct molecular ion at m/e 149 for the tetracyclic ketone II-42.



II-42

2.5.7 Photolysis of Nitrosamine II-24 in $CBrCl_3$

Photolysis of an acidic solution of II-24 in a solution of methanol and $CBrCl_3$ (1:4) gave a cloudy blue solution which on work-up gave a tetracyclic amino bromide in 46% yield as the only isolatable product. This compound was purified as its picrate which gave the correct analysis for $C_{15}H_{15}N_4O_7Br$. The m.s. of this amino bromide had molecular ion peaks at m/e 213 and 215 and a base peak resulting from loss of the bromine atom at m/e 134. This compound was assigned the structure of tetracyclic amino bromide II-43. The n.m.r. spectrum of II-43 (Figure 2.5) was similar to that of the corresponding sulfonium salt II-44 (80). The unresolved signal at τ6.60 ($W_{\frac{1}{2}}$=9 Hz) was assigned to H_a; the corresponding proton in II-44 appeared as a doublet with J=5Hz (80). The narrow multiplet at τ5.30 was attributed to H_e which, in the endo orientation, did not couple to the adjacent protons but did couple, as shown by decoupling studies, to H_c which appeared as a broad doublet

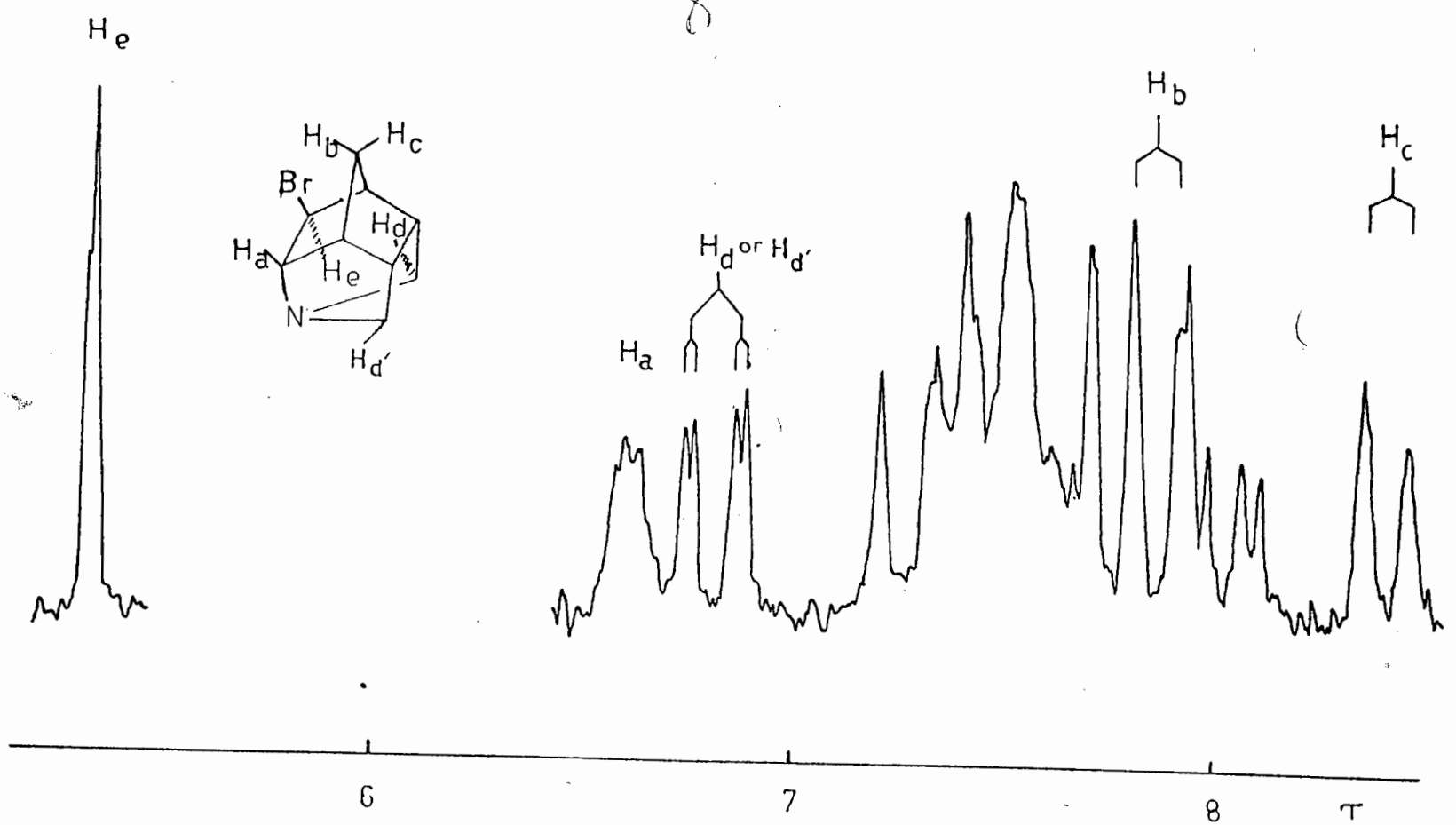
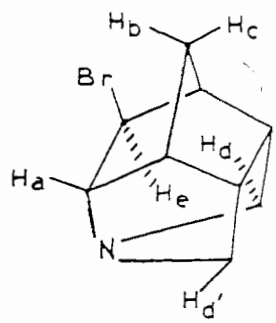
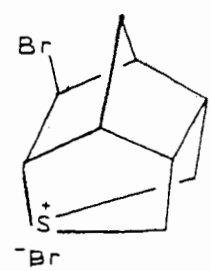


Figure 2.5: The N.M.R. Spectrum of Amino Bromide II-43 in $CDCl_3$.

at τ8.41 (J=10.5Hz). Recording the n.m.r. spectrum of II-43 in the presence of $Eu(DPM)_3$ revealed that the doublet of H_c was part of a slightly broadened AB quartet centered at τ8.13 ($\Delta\nu$=35, J=10.5Hz) attributed to H_b and H_c (80). Irradiation in the τ4.6 region (H_e) of this europium treated sample sharpened the higher field pair of the AB quartet indicating that this signal must be due to H_c which should couple by long range interaction with H_e (82). The double doublet at τ6.79 (J=12.5 and 2.5Hz) was attributed to either H_d or $H_{d'}$.



II-43



II-44

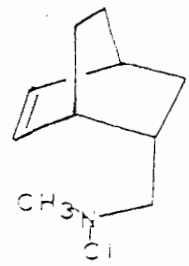
2.6 Cyclization of N-Chloramines

While the photolytic intramolecular cyclization of N-nitrosamines specifically forms 5 membered aza rings, the thermolysis of N-chloramines forms a mixture of products possessing either 5- or 6-membered aza rings (33,35,36). It was considered that the flexibility

of the synthetic sequence might be enhanced by an investigation of some analogous chloramine cyclizations.

2.6.1 Thermolysis of II-25 in Water

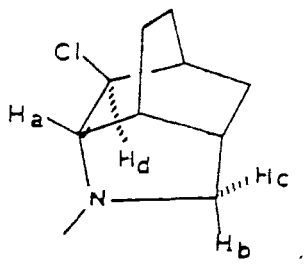
An aqueous dioxane solution of N-chloramine II-25 was refluxed for 1.25 hours at which time iodometric titration indicated that less than 5% of the starting chloramine remained. Work-up and chromatography of the basic extract gave amino alcohol II-37 (12%, [illegible] (9%) and an amino chloride (6%).



II-25

The identifications of amino alcohol II-37 and amine II-17 were based on the comparison of g.c. retention times, infra red, and n.m.r. spectra with previously isolated samples. The structure of II-37 was confirmed by oxidation (79) to ketone II-32.

Analysis of an impure sample of the amino chloride by g.c.-m.s. showed that it contained about 5% of amine II-17. The chloride exhibited molecular ion peaks at m/e 187 and 185 and a prominent peak due to the loss of chlorine at m/e 150. Attempts to purify this compound as its picrate were unsuccessful. Although the n.m.r. spectrum of the mixture was difficult to interpret, the tricyclic structure II-45 was tentatively assigned to the amino chloride. On this basis a doublet at τ7.22 (J=8Hz, H_c) and a double doublet at τ7.60 (J=8 and 4Hz, H_b) were attributed to the C_3 protons in analogy to the C_3 protons of II-37 in which H_c appeared as a doublet at τ7.26 (J=10Hz) and H_b appeared as a double doublet at τ7.47 (J=10 and 4.5Hz). A doublet in the n.m.r. spectrum of the mixture at τ5.97 (J=6.5Hz) was tentatively assigned to the C_{10} endo-proton (H_d) of II-45 which was expected to couple only with the adjacent bridgehead proton at C_6 by ca. 6Hz (69). The dihedral angle between H_d and H_a in a model of II-45 was approximately 90°, as a result the coupling between these protons should be very small. No clear signal attributed to H_a could be located in the spectrum of the crude sample, a broad multiplet at τ6.35 was at too low a field for H_a and is probably due to impurities in the sample.



II-45

2.6.2 Solvolysis of Chloramine II-25 in Methanol

Solvolysis of chloramine II-25 in refluxing methanol gave a mixture of basic material containing a tricyclic methoxy amine (59%), imine II-39 (6.5%), amine II-17 (2.5%) and an unidentified compound (5.5%) as determined by g.c.-m.s. analysis. The methoxy compound was isolated by preparative gas chromatography and was purified as a picrate which gave the correct elemental analysis for $C_{17}H_{22}N_4O_8$. The mass spectrum of this methoxy amine exhibited a molecular ion peak at m/e 181 and a base peak attributed to the loss of a methyl fragment at m/e 166. The i.r. spectrum showed a strong ether absorption at 1095 cm^{-1}.

The structure of the methoxy amine was firmly established as II-46 (Figure 2.6) by X-ray diffraction techniques (Chap.5). The double doublet in the n.m.r. spectrum of II-46 (Figure 2.7, Table 2.3) at τ7.32 (J=9 and 4.5Hz) was attributed to H_b which had a dihedral angle of about 30° with the adjacent C_4 proton. The doublet at τ7.58 (J=9Hz) was attributed to H_c which was coupled geminally to H_b but did not couple with the C_4 proton since the dihedral angle between these protons was approximately 90° (69). The doublet appearing at τ6.71 (J=4.5Hz) was assigned to H_d (vide supra) implying that the methoxy group was exo to the ring system. A signal at approximately τ7.50 attributed to H_a was revealed at τ5.38 when the n.m.r. spectrum was recorded in the presence of europium shift reagent.

2.6.3 Cyclization of Chloramine II-26 in Methanol

A methanol solution of chloramine II-26 was refluxed for 65 hours at which time iodometric titration indicated 13% positive chlorine

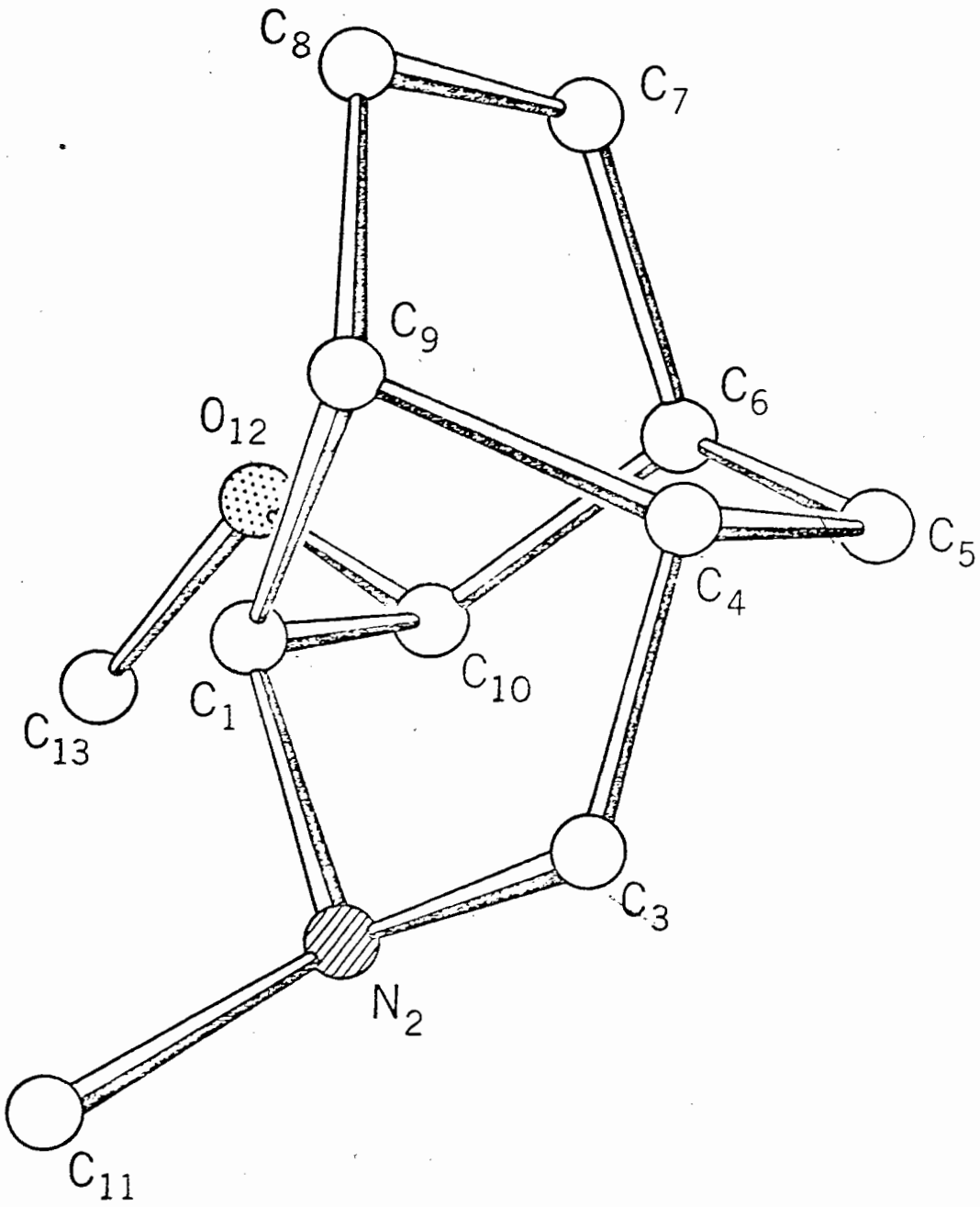


Figure 2.6: The Molecular Structure of Methoxy Amine II-46.

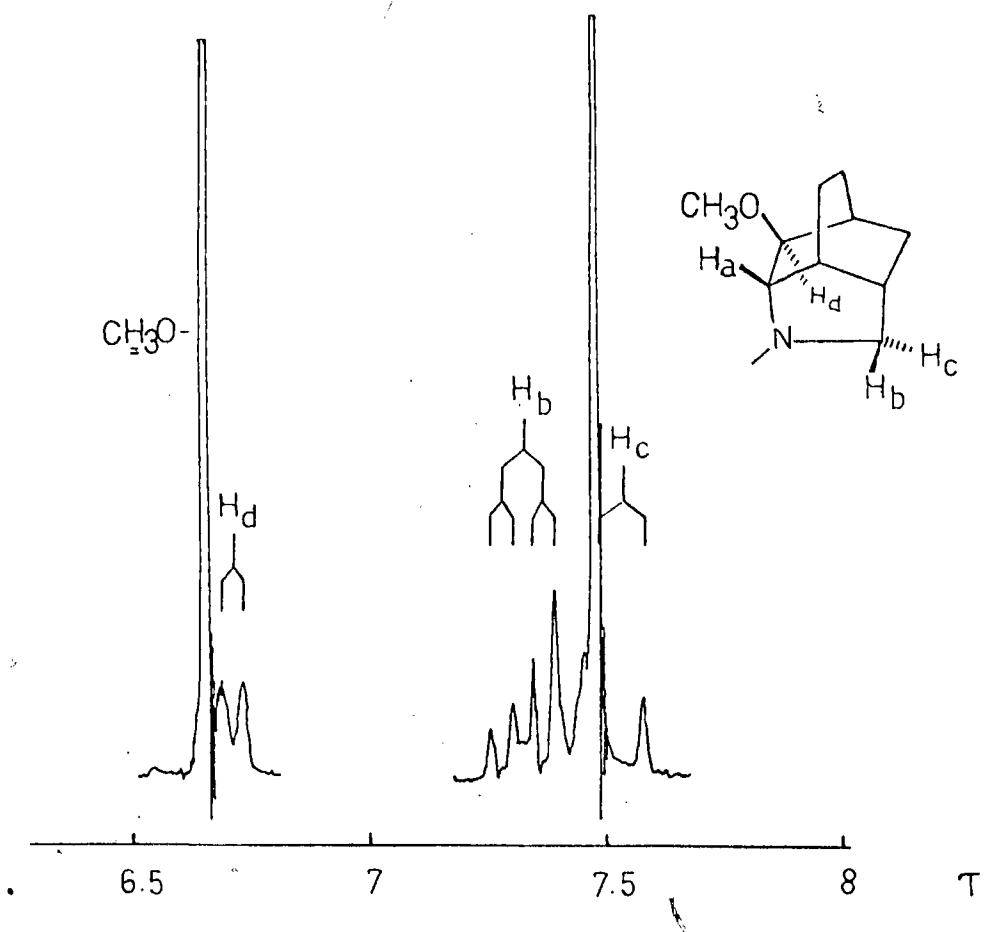
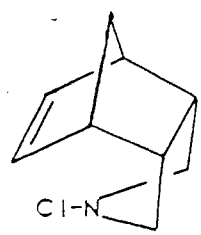
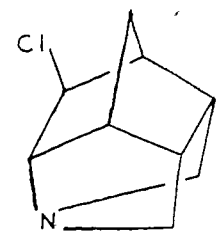


Figure 2.7: The N.M.R. Spectrum of Methoxy Amine II-46 in $CDCl_3$.

remained. Work-up gave the tetracyclic amino chloride II-47 (32%) amine II-21 (27%), and an unidentified olefinic compound (23%).



II-26



II-47

Amino chloride II-47 was isolated by preparative scale t.l.c. and was purified as a picrate which gave the correct elemental composition for $C_{15}H_{15}N_4O_7Cl$. The m.s.of II-47 had molecular ion peaks at m/e 171 and 169 and a base peak due to the loss of chlorine at m/e 134. A strong chlorine-carbon stretching band was exhibited in the i.r. at 785 cm^{-1}. The n.m.r. spectrum of II-47 was analogous to that of tetracyclic amino bromide II-43 (Table 2.6).

The unidentified olefin was isolated by preparative t.l.c. as a white solid. The mass spectrum of this compound exhibited no obvious molecular ion peak however the base peak was at m/e 66, a fragment which is characteristic of the cyclopentadienyl cation observed in the mass

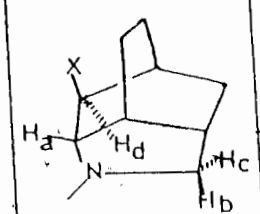
spectra of bicyclo[2,2,1]heptene systems (84). The n.m.r. exhibited a two proton multiplet at τ3.98 ($W_{\frac{1}{2}}$=4.5Hz) attributed to the olefinic protons and an AB quartet at τ8.55 ($\Delta\nu$=13, J=8Hz; 2H) which, taken together, suggest the presence of a bicyclo[2,2,1]olefin skeleton (69).

2.7 The N.M.R. Spectra of the Polycyclic Amines

The characteristic resonances in the n.m.r. spectra of the bridged polycyclic amines are tabulated in Tables 2.3-2.6. The observed differences in the chemical shifts of the C_3 protons of the tricyclic amines (Table 2.3 and 2.4) were initially attributed to be the result of structural differences as observed for the ethers listed in Table 2.7. The distinctive difference is the coupling observed, which is dependent upon the size of the heterocyclic ring, between the H_b and H_c protons with the adjacent bridgehead protons. In the two examples possessing 5-membered heterocyclic rings the double doublet patterns appearing at τ6.25 and τ6.19 are attributed to the H_b protons which have dihedral angles of approximately 30° with the adjacent bridgehead protons. The H_c protons appear at τ6.35 and τ6.34 as doublets resulting from geminal coupling between the H_b and H_c protons. They do not couple to the adjacent bridgehead protons since the dihedral angle with the bridgehead protons is approximately 90°. In the unsubstituted ether possessing a 6-membered heterocyclic ring (Table 2.7) the twisting of the molecular structure changes the dihedral angles of the H_b and H_c protons with the adjacent bridgehead protons. The angle between the H_b proton and the bridgehead proton approaches 90° and the H_b proton appears as a doublet

Table 2.3

The N.M.R. Spectra of Azatricyclic Decanes[1]

	H_a			H_b			H_c			H_d		
	τ	M	J	τ	M	J	τ	M	J	τ	M	J
X = OH II-37	7.19	d	4.5	7.47	dd^2	10 4.5	7.26	d	10	6.20	d	4
X = Cl II-45[3]	not observed			7.60	dd	8 3	7.22	d	8	5.97	d	6.5
X = OCH_3 II-46	~7.5[2]			7.32	dd	9 4.5	7.58	d^2	9	6.71	d	4.5

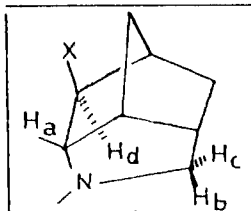
1. τ, Chemical Shift; M, Multiplicity; J, Coupling Constant.

2. Partially obscurred by the N-methyl signal.

3. Tentative assignment.

Table 2.4

The N.M.R. Spectra of Azatricyclic Nonanes [1]

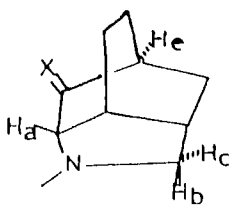
	H_a			H_b			H_c			H_d		
	τ	M	J	τ	M	J	τ	M	J	τ	M	J
X = OH II-33(HCl)	6.69	d	5	7.05	dd[2]	10.5 5	6.72	d	10.5	5.90	m	
X = Br II-35	6.56	d	4.5	7.10	dd	9.5 5	7.50	d	9.5	6.15	m	
X = Cl II-36	6.80	d	5	7.10	dd	9.5 5	7.50	d	9,5	6.25	m	

1. τ, Chemical Shift; M, Multiplicity; J, Coupling Constant.

2. Partially obscurred by the N-methyl signal.

Table 2.5

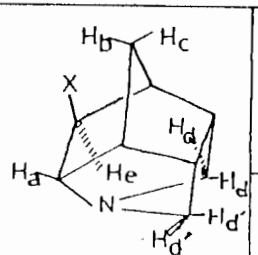
The N.M.R. Spectra of Azatricyclic Decanone Derivatives[1]

	H_a			H_b			H_c			H_e		
	τ	M	J	τ	M	J	τ	M	J	τ	M	J
ketone II-32, X=O	6.98	d	5	6.78	dd	9,4	hidden			hidden		
syn-oxime II-30, X=NOH	6.02	d	4	6.98	dd	9.5,4	hidden[2]			hidden		
anti-oxime II-31, X=NOH	6.86	d	4.5	6.72	dd	11,4.5	hidden			6.25	t	6.5

1. τ, Chemical Shift; M, Multiplicity; J, Coupling Constant (Hz).
2. Located by europium shift experiments as a doublet originally at τ~7.5 (J=9-10Hz).

Table 2.6

The N.M.R. Spectra of Azatetracyclic Amines[1]

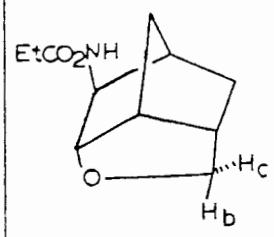
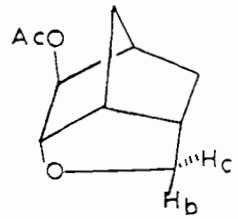
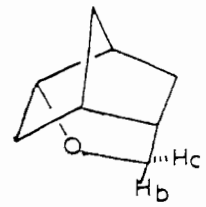
	H_a			H_b[2]			H_c[2]			1 of $H_{d/d'}$			H_e		
	τ	M	J	τ	M	J	τ	M	J	τ	M	J	τ	M	J
X = OH II-41	6.41	m		8.04	d	10.5	8.67	d	10.5	6.75	dd	12,2	5.70	m	
X = Br II-43	6.60	m		7.87	d	10.5	8.43	d	10.5	6.72	dd	12.5 2.5	5.30	m	
X = Cl II-47	6.80	d	2	7.95	d	10.5	8.52	d	10.5	6.81	dd	12 2.5	5.47	m	
X, H_e = O II-42	hidden			8.25	d	11.5	8.61	d	11.5	hidden			-		

1. τ, Chemical Shift; M, Multiplicity; J, Coupling Constant (Hz)

2. H_b and H_c appear as broadened doublet signals ($W_{1/2}$=4 Hz)

Table 2.7

The N.M.R. Data of Some Tricyclic Ethers[1]

Compound	H_b			H_c			
	τ	M	J	τ	M	J	Reference
	6.25	dd	8,4	6.35	d	8	(74)
	6.19	dd	8,3.6	6.34	d	8	(81)
	6.12	d	9	6.47	dd	9,3	(82)

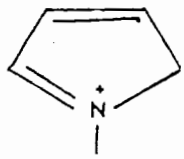
1. τ, Chemical Shift; M, Multiplicity; J, Coupling Constants (Hz)

at τ6.12. Coupling between the H_c proton and the bridgehead proton is observed, however, and the H_c proton appears as a double doublet at τ6.47.

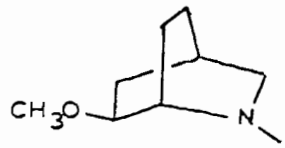
Examination of the n.m.r. signals of the H_b and H_c protons of the tricyclic amines synthesized was not reliable for determining the chemical structures. Differences, similar to those observed (Table 2.7) for structurally different tricyclic ethers, were observed in the relative chemical shifts of the H_b and H_c protons for several of the tricyclic amines possessing 5-membered aza rings. Assuming that all H_b signals should be split as double doublets and all H_c signals as doublets, all of the tricyclic coumpounds except amino alcohols II-33 and II-37 exhibited H_b at a lower field than H_c. The hydroxyl groups of II-33 and II-37 appear to effect a reversal in the relative chemical shifts of H_b and H_c. However, we have found no precedence for these observations and an explanation for them must entail further research.

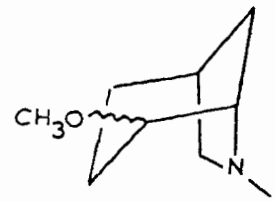
2.8 The Mass Spectra of the Tricyclic Amines

A major fragment at m/e 82, attributed to the cation II-48, is generally found in the mass spectra of azabicyclic compounds containing an N-methylpyrrolidine ring (85,86). The presence or absence of this fragment has frequently been used as the basis of structural assignments (36,59,87). Recently Edwards (35) has demonstrated, however, that the isomeric amines II-49 and II-50 exhibited a common base peak at m/e 82. The presence of a peak at m/e 82 did not appear therefore to be of diagnostic value in distinguishing between tricyclic compounds possessing either 5- or 6-membered aza rings.



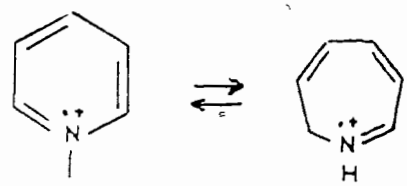
m/e 82





II-48 II-49 II-50

The peak at m/e 82 has also appeared in all of the tricyclic amines isolated, accompanied by another common fragment at m/e 94 (Table 2.8), the latter generally being the more intense peak. Many azabicyclic compounds containing a pyrrolidine ring undergo a ring expansion in the mass spectrometer to form a fragment at m/e 96 (85). It was believed that the peak observed at m/e 94, attributed to the cations II-51, was formed by a similar ring expansion reaction of the tricyclic amines.

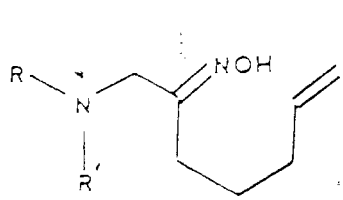


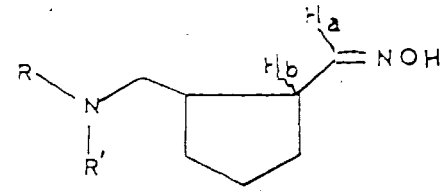
II-51

2.9 The Photolysis of N-Nitrosamines in the Presence of Unconjugated Dienes.

A preliminary study of the addition of N-nitrosamines to unconjugated dienes was carried out to determine if radical cyclization

would occur (14,88,89). The addition of N-nitrosodimethylamine to 1,5-heptadiene gave a complex mixture of 1:1 addition products which was not thoroughly investigated. The addition of N-nitrosopiperidine to 1,6-heptadiene gave the uncyclized amine II-52 (20%) and a cyclized amino aldoxime II-53 (24%). The corresponding dimethylnitrosamine addition products, II-54 and II-55, were obtained by similar photolysis in the presence of 1,6-heptadiene. The above products were all obtained as isomeric mixtures of syn- and anti-oximes.



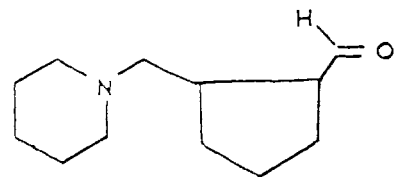


II-52 R R′ = $-(CH_2)_5-$ II-53 RR′ = $-(CH_2)_5-$

II-54 R R′ = CH_3, CH_3 II-55 RR′ = CH_3, CH_3

The 1,2-adduct II-52 had mass spectral peaks at m/e 210 (M^+), 193, and a base peak at m/e 98, typical of the piperidino group (90). The i.r. spectrum exhibited oxime bands at 3200, 3080, 937, 910 and 860 cm^{-1} and the n.m.r. spectrum had the multiplet pattern of a mono substituted olefin at τ3.8-5.2. The two singlets at τ6.75 and 7.02 for the methylene groups attached to the piperidine nitrogen indicated that the syn to anti ratio was 1:4 (73).

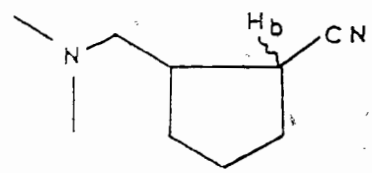
Aldoxime II-53 was isolated as a mixture of isomers due to the cis-trans isomerization of the substituent groups around the ring and the syn-anti isomerism of the oximino group. While the two compounds isolated were shown to be a syn- and an anti-oxime, their cis-trans isomerism was not determined. The m.s. had peaks at m/e 210 (M^+) and 193 and a base peak at m/e 98 (90). The i.r. spectrum exhibited bands at 3200, 3080, 1115, 945 and [illegible] cm^{-1} attributed to the oxime function. The presence of two doublets of equal intensity in the n.m.r. spectrum at τ2.58 (J=7.5Hz) and τ3.22 (J=7.5Hz) indicated a syn- to anti-aldoxime ratio of 1:1. Aldoxime II-53 also exhibited weak multiplets at τ6.60 (H_b, anti) and τ7.20 (H_b, syn). The former was coupled to the aldoxime proton at τ3.22 and the latter to the corresponding proton at τ2.58 as shown by decoupling experiments. Deoximation (71) of a mixture of syn- and anti-aldoximes II-53 gave, after distillation, aldehyde II-56 containing a trace of nitrile. The i.r. spectrum exhibited a strong carbonyl band at 1720 cm^{-1} and the n.m.r. spectrum exhibited one low field doublet at τ0.35 (J=2Hz) showing that only one aldehyde isomer was present.



II-56

Aldoxime II-55 was a mixture of all four possible isomers. The two major isomers showed the aldoxime proton at τ2.65 (d, J=6.5, H_a, syn) and τ3.25 (d, J=6.5Hz, H_a, anti) similar to those observed in the n.m.r. spectrum of II-53. The minor compounds, which could not be removed by recrystallization, showed the aldoxime proton at τ3.04 and 3.86. A one proton multiplet appearing at τ6.65 was attributed to the H_b proton of an anti-isomer and a triplet at τ7.05 (J=7Hz) was assigned the H_b proton of a syn-isomer.

Dehydration of an isomeric mixture of aldoximes II-55 gave a mixture of nitriles which could not be purified. A broad absorption at about 1710 cm^{-1} in the i.r. was attributed to a carbonyl impurity. The presence of multiplets in the n.m.r. spectrum at τ7.19 and 7.55 attributed to the H_b protons and two singlets at τ7.70 and 7.72 attributed to N-methyl protons suggested that II-57 was a 1:1 mixture of cis- and trans-isomers.



II-57

CHAPTER 3

DISCUSSION

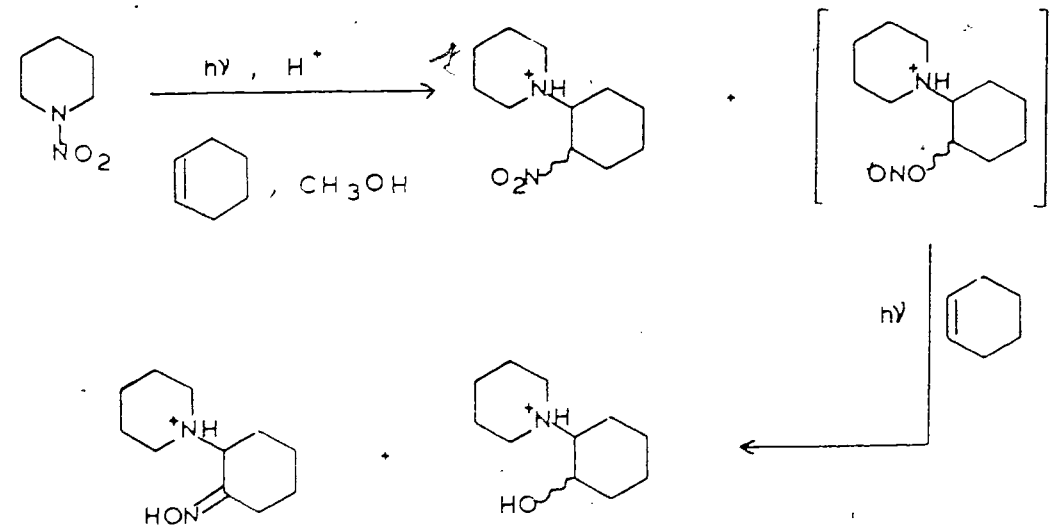
3.1 The Solution Photochemistry of N-Nitramines

In continuation with our interest in amine radical chemistry we became interested in the photochemistry of N-nitramines. The observed photochemical reactions described in Chapter 1 are decidedly different from those of N-nitrosamines (11). To obtain a better understanding of the solution photochemistry of nitramines, N-nitropiperidine was used as a model compound and its photoreactions were studied.

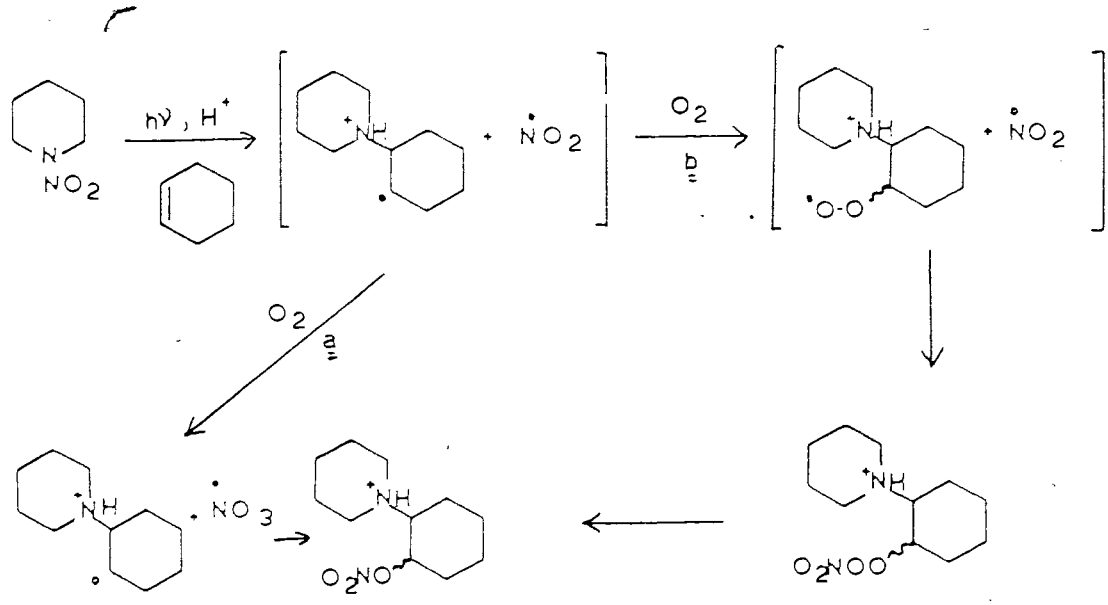
The formation of addition products, as observed when an acidic solution (0.04N HCl) of nitropiperidine is photolysed in the presence of cyclohexene, is typical of aminium radicals (11). This is in contrast to the complete absence of cyclohexene addition products when the photolysis is carried out in the absence of acid. In the latter case only the photoreduction product, piperidine, and associated oxidation products are formed. These products undoubtedly arise from a hydrogen abstraction, a reaction associated with neutral amine radicals (37,38). It is concluded therefore that the photolysis of nitramines gives amine radicals under neutral conditions and aminium radicals under acidic conditions.

Under a nitrogen atmosphere in an acidic solution the photoaddition of nitropiperidine to cyclohexene gives a complex mixture due to two major factors. First, nitrogen dioxide, one of the primary photoproducts, is an amphoteric species (92) which can add to the C-radical intermediate either as a nitrogen centered radical to give nitro compounds or as an oxygen centered radical to give a nitrite (Scheme 3.1). Secondly, nitrites are photolabile (51) under the irradiation conditions. The product distribution of this photoaddition reaction was greatly simplified when run under an oxygen atmosphere. It is significant tha oxygen does not quench the excited states of the nitramine but instead oxidizes the radical intermediates to yield 1-nitrato-2-piperinocyclohexanes, II-12. Two possible mechanisms by which oxidation can occur are shown in Scheme 3.2 but the present results do not differentiate between these two possibilities. The intermediate peroxy nitrate formed in path b has been shown (28) to give the corresponding nitrate as a major decomposition product.

In the absence of an olefin one can not readily distinguish between the reactions of amine and aminium radicals since both intermediates can abstract hydrogen from a suitable donor. Certain dissimilarities were observed however in the photodecomposition of nitropiperidine under neutral and acidic conditions. Although piperidine, resulting from hydrogen abstraction, was observed in both cases N-formyl piperidine which was found under neutral conditions was not detected in the acidic



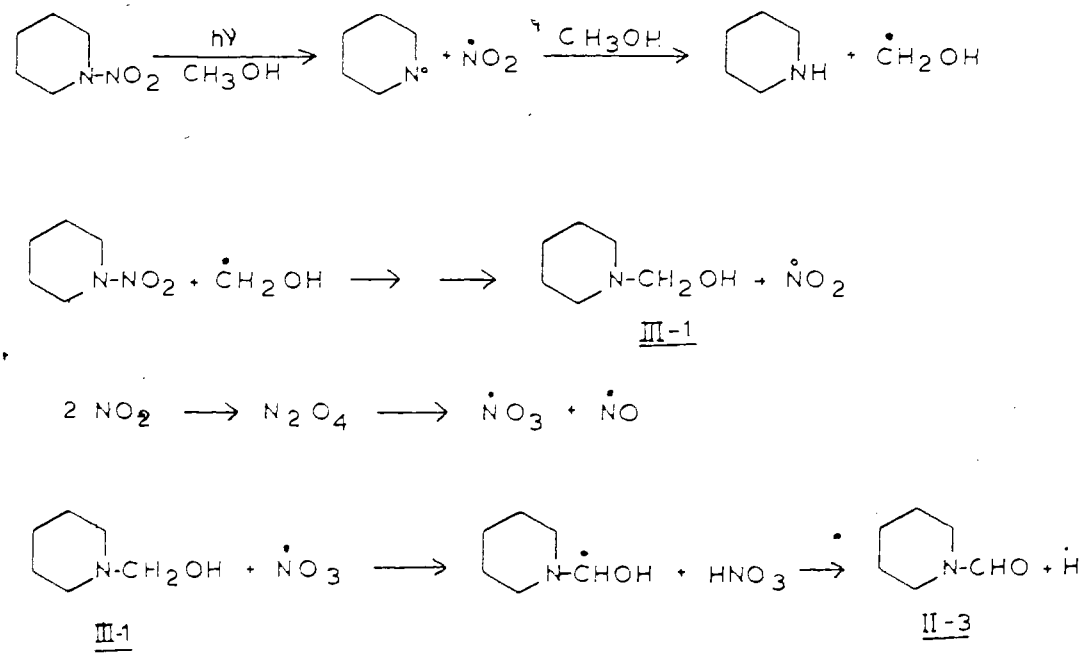
Scheme 3.1



II-12

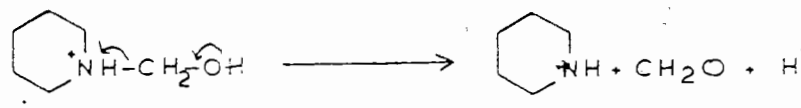
Scheme 3.2

photolysis. In the latter case formaldehyde was isolated instead. The first step in the photoreaction under both conditions is believed to be the abstraction of hydrogen from methanol (11) to generate piperidine (or the piperidinium cation under acidic conditions) and the hydroxymethyl radical. This radical then reacts with nitropiperidine in some as yet undetermined way to give an intermediate α-amino alcohol, III-1. Under neutral conditions III-1 is readily oxidized by $\dot{N}O_3$, formed by the disproportionation of $\dot{N}O_2$ (91), to yield N-formyl piperidine, II-3, and nitrate ion (Scheme 3.3).



Scheme 3.3

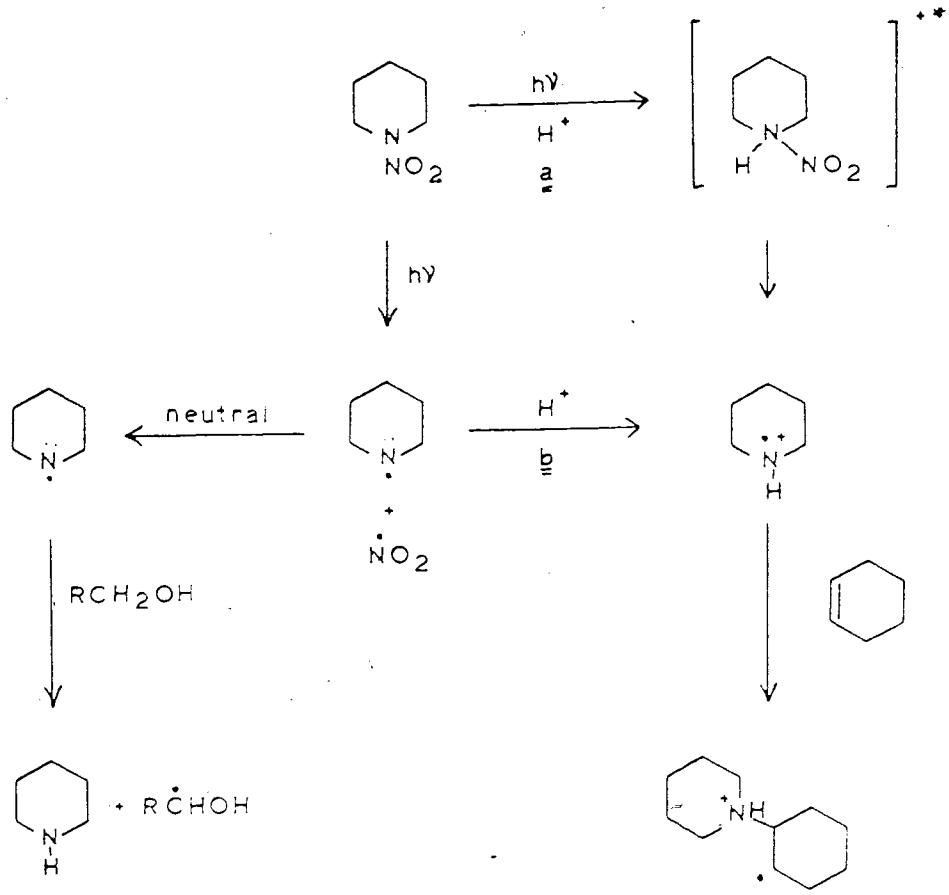
Under acidic conditions the reaction obviously follows some alternate pathway, possibly as suggested in Scheme 3.4, since N-formyl piperidine was not detected. Oxidation of the intermediate α-amino alcohol under acidic conditions by $\dot{N}O_3$ may not be as favorable since it would necessitate H-abstraction from a carbon adjacent to a protonated amine function.



Scheme 3.4

We have established that under neutral conditions the primary photoprocess in the photochemical reactions of nitramines is the cleavage of the N-N bond to give an amine radical and $\dot{N}O_2$. Surjanaryanan (41) has suggested that two processes may be involved in the photoreaction of dimethylnitramine; one involving cleavage of the N-N bond and the other without such a step. The evidence presented by these workers strongly supports a mechanism involving cleavage of the N-N bond of the nitramines as the primary photoreaction. These results are in contrast to the study by the same workers on the photolysis of dimethylnitramine in the solid state (44) in which the evidence from labelling experiments demonstrated that under these conditions nitramine photolysis involved N-O bond cleavage.

Under acidic conditions the role of acid in the photoreaction of nitramines has not been firmly established. Protonation of the nitramine is not expected in dilute acid (0.1-2N) since secondary nitramines are reported to be neutral species (39). Kinetic studies have shown (93) that the quantum yield and rate of nitropiperidine photolysis are unchanged in dilute acid but decrease in 5N H_2SO_4 or above. It is believed that at this acidity and above nitropiperidine is converted to a photostable protonated nitropiperidine the structure of which is however unknown. It is believed that under these highly acidic conditions nitropiperidine is protonated giving an as yet undefined photochemically stable species. It is concluded therefore that photochemical decomposition of nitropiperidine occurs from the unprotonated species under both neutral and acidic conditions (Scheme 3.5). From the above information protonation may occur on the photoexcited nitramine (path a, Scheme 3.5) or on the amine radical (path b). Conjugated acids of dialkyl amine radicals have a pK_a in the range 6.5-7.5 (94) hence protonation of an amine radical would be extensive in a 0.1-2N H_2SO_4 solution. While protonation of the amine radical would be an efficient reaction, protonation of the excited nitramine (path a) appears unlikely since kinetic studies (93) have also shown that the quantum yield (7.2±0.2) for the disappearance of nitramine is independent of acid concentration in the range 0.1-2.0N. Assuming that the rates of decay of the postulated protonated and non-protonated excited nitramine species are not the same, this implies that the acid does not take an active role during the decay of the excited nitramine. The results can however be interpreted as the generation of an amine radical followed by protonation of this radical (path b) to form an aminium radical.



Scheme 3.5

The quantum yield (4.8) for the photolysis of nitropiperidine in neutral methanol is significantly lower than the values obtained in dilute acid. In neutral solution it is suggested that the amine radicals may recombine with $\dot{N}O_2$ to generate the starting nitramine and subsequently lower the quantum yield.

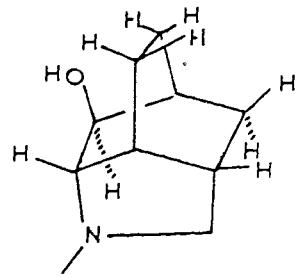
At no time during our photochemical studies of nitropiperidine in neutral methanol solutions did we detect the formation of the corresponding N-nitrosamine as observed by others (43-46). These workers photolysed the nitramines in neutral solvents with no readily abstractable hydrogen, except for one experiment when ethanol was used (43), to give the corresponding nitrosamine. The absence of a readily abstractable hydrogen may result in the accumulation of N-nitroso-dialkylamines formed by the combination of amine radicals with $\dot{N}O$, generated by the disproportionation of $\dot{N}O_2$ (91). Since nitrosamines are stable under neutral conditions (11) they would not undergo photochemical decomposition. In a hydrogen donating solvent such as methanol H-abstraction is possible and photoreduction products are isolated.

3.2 Aminium Radical Cyclizations

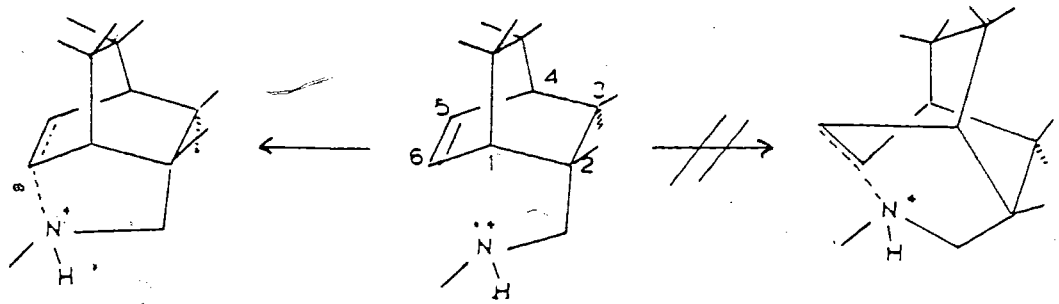
The study of cyclization reactions of aminium radicals generated by the photolysis of nitrosamines carrying a suitably located double bond has lead to the synthesis of several new azatricyclic and azatetracyclic compounds. The study undertaken was directed towards defining the utility of certain nitrosamine cyclizations as key steps in synthetic designs of azapolycyclic compounds. The yields in the majority of the cyclization reactions can be improved particularly in the oxidative photolysis of nitrosamines where rapid isolation and reduction of the nitrates produced is of utmost importance.

The aminium radicals undergo a stereospecific cyclization to form 5-membered aza rings. The specific formation of 5-membered aza rings in the competing cyclization to either 5- or 6-membered rings agrees with the previous work (12) on azabicyclic syntheses and with the published observations on other radical cyclizations.

An examination of the aminium radical cyclization of II-23 indicates that the reaction is under kinetic rather than thermodynamic control (95). The 5-membered ring products formed (II-30, II-31, and II-37) exhibit at least three hydrogen-hydrogen and one carbon-hydrogen eclipsing interactions with a total energy value of about 5 kcal/mole (95). Amino alcohol II-37 also exhibits eclipsing interactions between the hydroxy group and the adjacent exo-hydrogen and between the ring nitrogen and the endo-hydrogen at C_{10}. These significant steric interactions would have been removed had twisting occurred, during product formation, to give the corresponding thermodynamically more favorable azatwistane skeleton (Scheme 3.6). The formation of 5-membered aza rings is undoubtedly a result of irreversible cyclization involving a minimum amount of molecular motion to the most accessible terminus of the double bond; since the aminium radical is much nearer to the C_6-end of the double bond orbital overlap between the aminium radical and the double bond is much more extensive at the C_6-position than at the C_5-position.



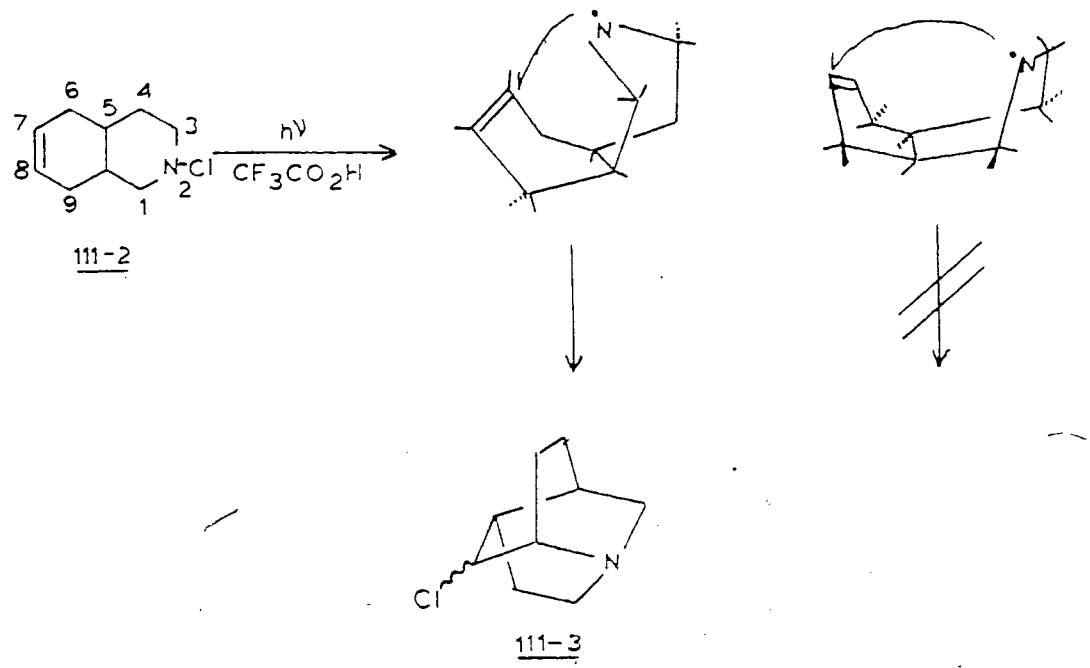
II-37



Scheme 3.6

Heusler's (10) aminium radical cyclization of III-2 to the chloroazatwistanes III-3 is controlled by steric interactions. In this case the ring system of III-2 is much more flexible than that of II-23

and the intermediate aminium radical can approach either terminus of the double bond (Scheme 3.7). The eclipsing and bowsprit-flagpole interactions encountered as the aminium radical approaches the C_8-position are substantially greater than those encountered as the radical approaches the C_7-position forcing cyclization to form a 6-membered aza ring.



III-2

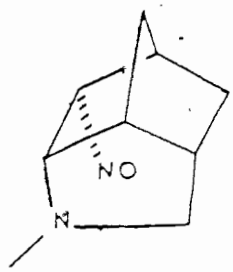
III-3

Scheme 3.7

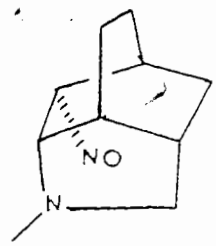
3.2.1 Radical Cyclization Under Nitrogen

Intramolecular cyclization of aminium radicals derived from II-22 and II-23 gives products possessing 5-membered aza rings. These cyclizations proceed via the C-nitroso intermediates III-4 and III-5,

respectively. Intermediate III-5 tautomerizes readily to give the corresponding amino oximes II-30 and II-31, however, III-4 apparently underwent a rapid cleavage reaction to give II-27. This difference can only be attributed to significantly greater ring strain in III-4.

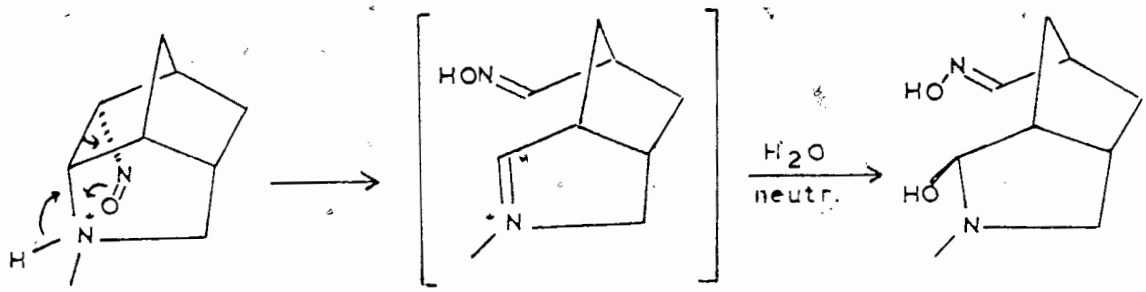


III-4



III-5

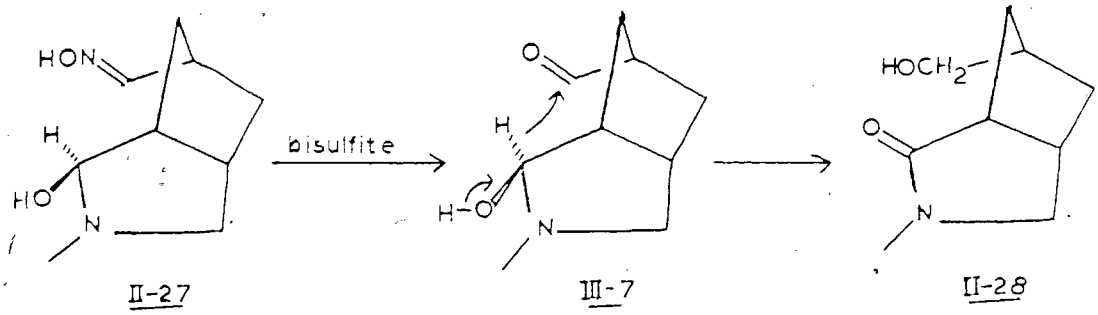
The cleavage reaction observed has been proven (96) to require a cis-coplanar orientation of the functional groups and a cyclic transition state as shown in Scheme 3.8 has been implied. This mechanism also requires that the nitrosamine group adds cis across the double bond to give III-4. Davies (97) has shown that reagents like thiols and nitrosyl chloride add to norbornene to give exclusively exo-cis-adducts hence entirely cis addition to the olefinic bond is not unreasonable. It should be noted however that only exo hydroxyl, bromo and chloro tricyclic products, II-33, II-35 and II-36, resulting from trans addition (vide infra), are isolated from radical trapping experiments with II-22. Although II-22 was irradiated several times in an effort to isolate tricyclic products, possibly resulting from trans addition, only decomposition products could be isolated.



III-4 III-6 II-27

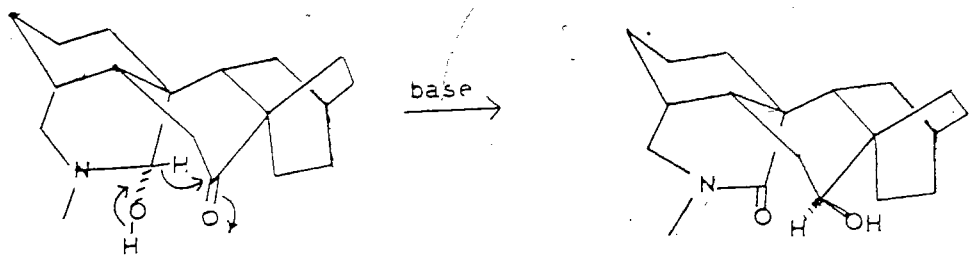
Scheme 3.8

Treatment of aldoxime II-27 with bisulfite gives an aldehyde, III-7, which undergoes a facile intramolecular hydride transfer as shown in Scheme 3.9 to give hydroxy lactam II-28. The latter process is similar to that observed by Edwards (70) in ajaconine derivatives (Scheme 3.10). The formation of II-28 can occur by this mechanism only if the hydroxy function of III-7 and subsequently II-27 is exo so that the intramolecular hydride transfer is possible. The all cis stereochemistry of the bicyclic immonium ion III-6 no doubt forces hydration to occur from the sterically least hindered exo side of the molecule to give II-27 with the hydroxy function exo to the ring system.



II-27 III-7 II-28

Scheme 3.9



Scheme 3.10

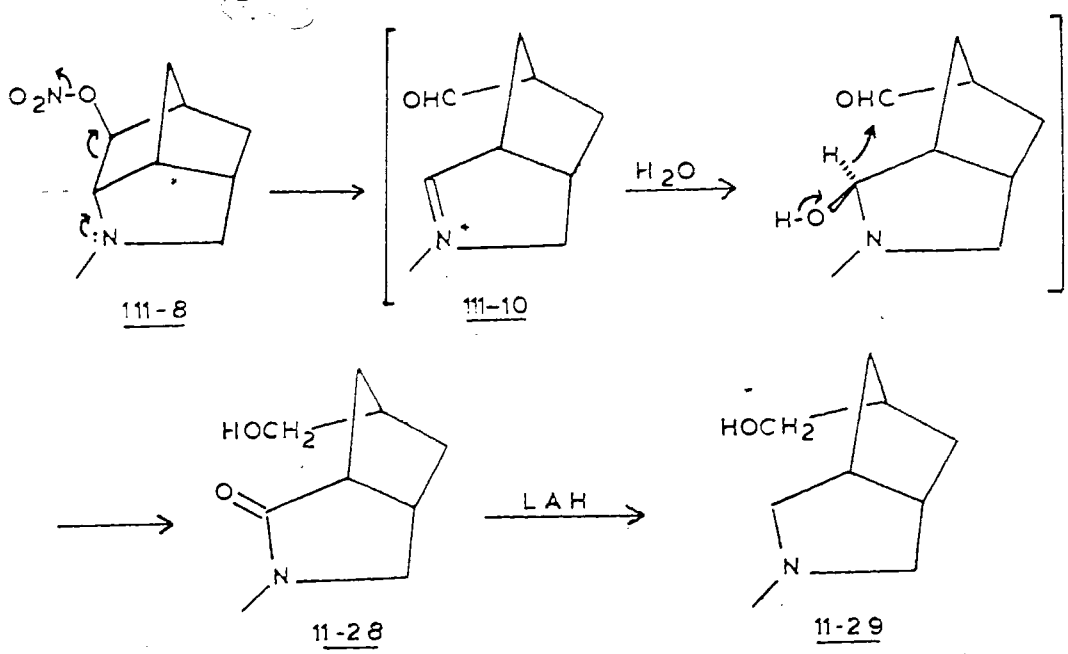
3.2.2 Radical Trapping Reactions

Intramolecular addition of alkenyl nitrosamines appears to proceed via a stepwise radical mechanism since in the presence of radical trapping agents, or radical scavengers, products other than those derived from C-nitroso adducts are obtained. In the presence of oxygen the intermediate radicals are oxidized to yield nitrates while in the presence of $CBrCl_3$ or CCl_4 amino halides are isolated. Since no oxime products are obtained in the trapping reactions the reaction of the intermediate radicals with the radical scavengers must be faster than their recombination. It is apparent, therefore, that aminium radicals intramolecular addition reactions do not occur within a solvent cage.

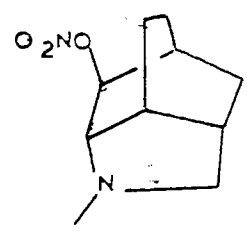
Stereochemically, radical cyclization can occur with either cis or trans addition across the double bond. This is readily demonstrated in the cyclization of III-2 (10) in which a 4:3 ratio of cis-and trans-chloroazatwistanes are obtained. In contrast to these results the tricyclic (II-33, II-35, II-36 and II-37) and tetracyclic (II-41 and II-43) products resulting from radical trapping experiments all have exo ring substituents indicating that addition has occurred trans across the double bond. It is believed that this specificity is the result of substantial steric interaction from the endo side of the ring system, in the radical transfer, preventing attack from this side.

Many of the amino nitrates formed when alkenyl N-nitrosamines are photolysed under an oxygen atmosphere undergo an efficient intra-

molecular base catalysed decomposition which probably requires a trans diaxial orientation of the amino and nitrato functions (29). For this reason no attempt was made to isolate the amino nitrates formed during the oxidative photolysis. Tricyclic amino nitrates III-8 and III-9 were readily decomposed by this route as shown in Scheme 3.11 for amino nitrate III-8. The intermediate immonium ion III-10 (98) is expected to react in a manner similar to that observed for III-6 (Scheme 3.8 and 3.9).

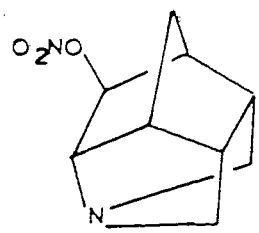


Scheme 3.11



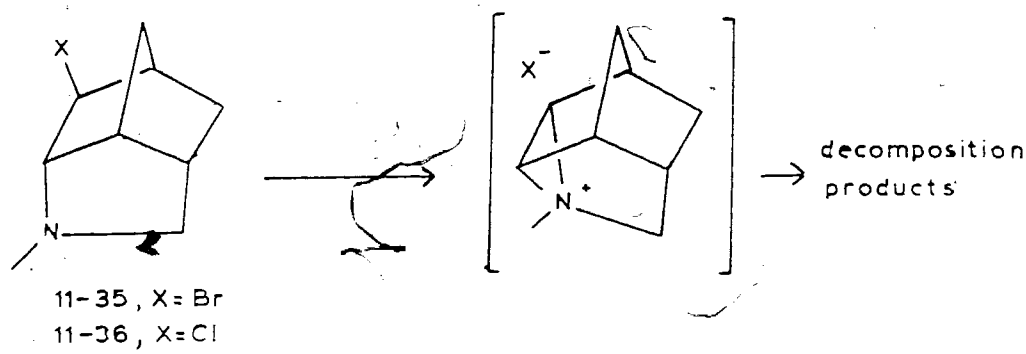
III-9

While the described decomposition reaction is prominent for amino nitrates III-8 and III-9 no decomposition products are isolated following the oxidative photolysis of nitrosamine II-24. This is undoubtedly due to the inability of the amine nitrogen electrons of amino nitrate III-11 to participate in the elimination of nitrite ion since the decomposition would place a carbon-nitrogen double bond at a strained bridgehead position.



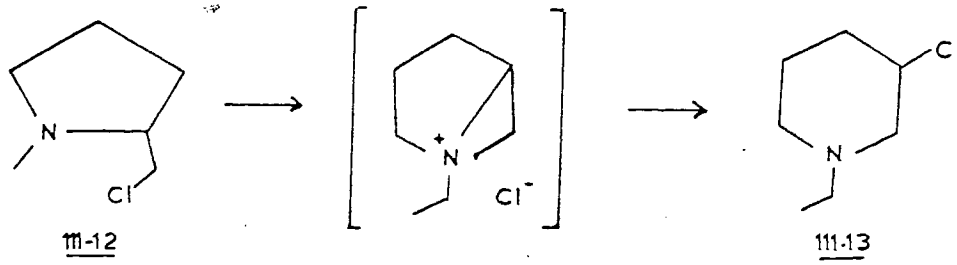
III-11

The photolysis of nitrosamine II-22 in the presence of $CBrCl_3$ or CCl_4 gives good yields of the tricyclic amino halides II-35 and II-36. These compounds were quite unstable and underwent complex decomposition reactions believed to result from intramolecular displacement of the halogen to form an aziridinium intermediate as shown in Scheme 3.12. The rapid decomposition of C-nitroso intermediate III-4 and amino nitrate III-8 indicate that the ring structures of II-35 and II-36 are strained and susceptible to molecular rearrangement. Intramolecular nucleophylic displacements of halogens by nitrogen are not uncommon (29,77) and Hamer (100) has obtained strong evidence from synthetic, kinetic and optical activity studies for the existence of an aziridinium intermediate in the spontaneous rearrangement of III-12 to III-13 at room temperature (Scheme 3.13).



11-35, X = Br
11-36, X = Cl

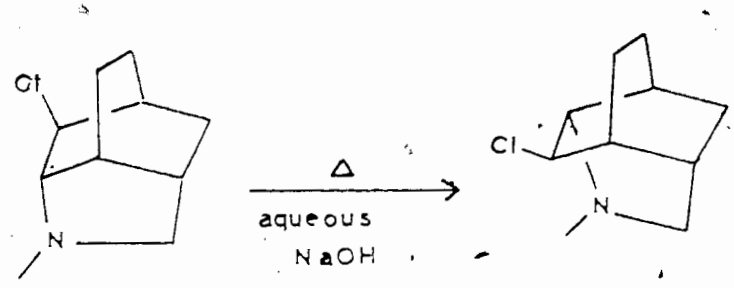
Scheme 3.12



III-12 III-13

Scheme 3.13

Cyclization products were not isolated following the photolysis of II-23 in $CBrCl_3$. The formation of a small quantity of an unidentified bromoamine was indicated, however, by g.c.-m.s. analysis of the reaction mixture. The inability to isolate any cyclic bromoamine might be due to the ease of rearrangement to a mixture of products possessing an azatwistane skeleton. This reaction may provide an efficient synthesis of azatwistane derivatives; for example, compounds possessing an isotwistane structure such as II-45 under the appropriate conditions (100) may give azatwistane products (Scheme 3.14).

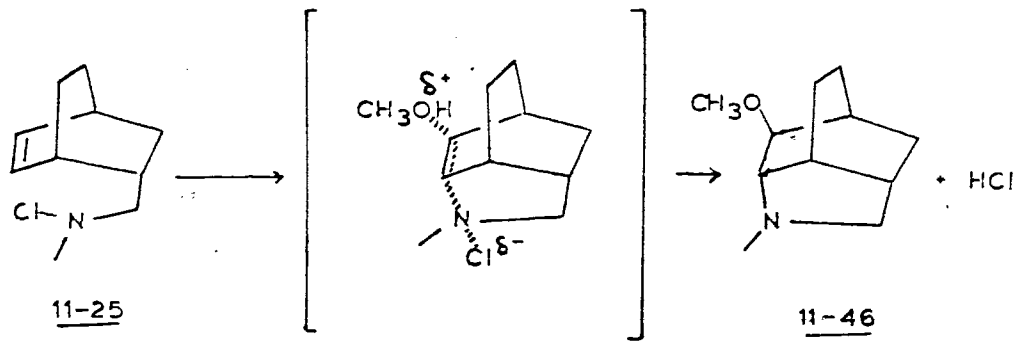


Scheme 3.14

3.3 Thermolysis of N-Chloramines

The thermolysis of chloramines carrying suitably located olefinic bonds gives cyclization products possessing both 5- and 6-membered aza rings (33,34,35,36). The mechanisms of these reactions have been interpreted to involve either nitrenium ions (33,87) or amine radicals (35,36). Since there are arguments in favour of both mechanisms and our studies made no attempt to distinguish between these mechanisms the nitrenium ion intermediate will be used to interpret our results.

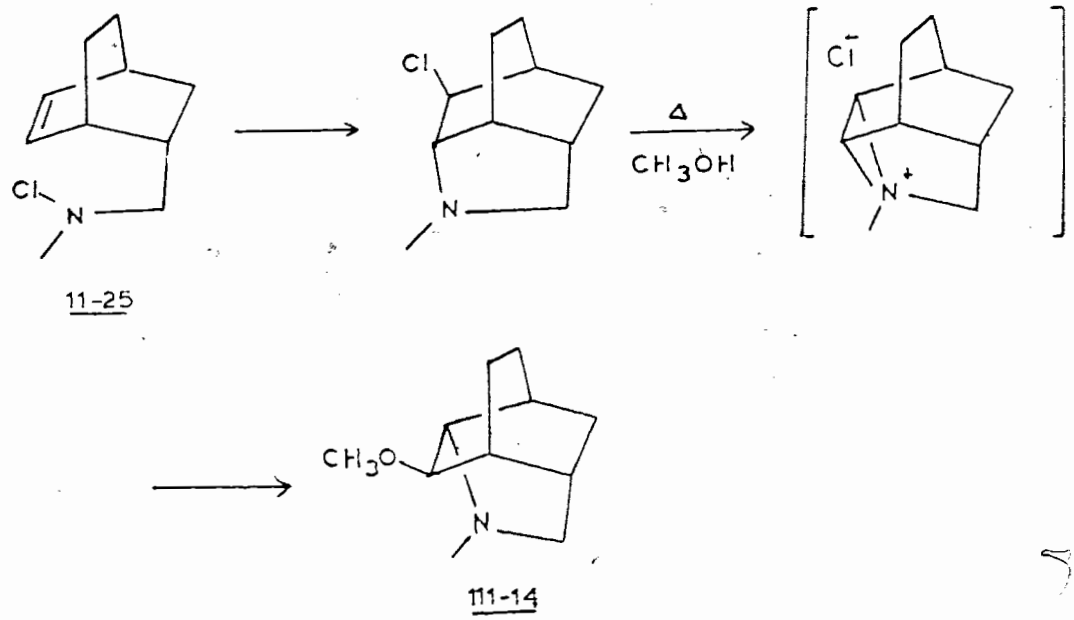
The thermolysis of II-25 in methanol gives the solvolysis product II-46. The formation of such a product possessing a 5-membered ring is best explained by the formation of an ionic intermediate, possibly involving anchimeric assistance by the olefinic bond or solvent participation as shown in Scheme 3.15.



II-25 II-46

Scheme 3.15

Radical cyclization, on the other hand, might result in the solvolysis of an initally formed C-chloro compound in which an aziridinium ion intermediate (35,100) might be involved as shown in Scheme 3.16. From thermodynamic considerations discussed previously an intermediate of this type would collapse preferentially to the twisted compound III-14.



II-25

III-14

Scheme 3.16

The thermolysis of II-25 in aqueous dioxane is approximately five times faster than the corresponding reaction in methanol. An increase in reaction rate of this degree with increasing solvent polarity is also indicative of a heterolytic reaction (101).

The formation of a significant amount of amine II-21 and the extended reaction period required for the thermolysis of tricyclic chloramine II-26 leads us to believe that the cyclization of II-26 is more difficult than for II-25. Molecular models reveal that ring closure in II-26 involves considerable strain. The ease of cyclization of the intermediate nitrenium ion is therefore decreased and it must react by some alternate pathway such as hydrogen abstraction (33). If one assumes that anchimeric assistance by the double bond plays an important role in the heterolytic cleavage of the N-Cl bond then the extended reaction time required becomes understandable.

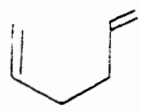
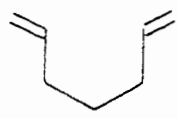
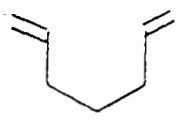
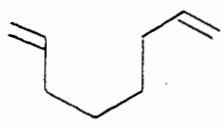
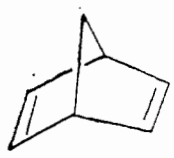
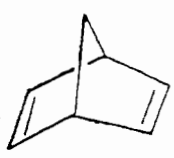
3.4 The Addition of N-Nitrosamines to 1,6-Heptadiene

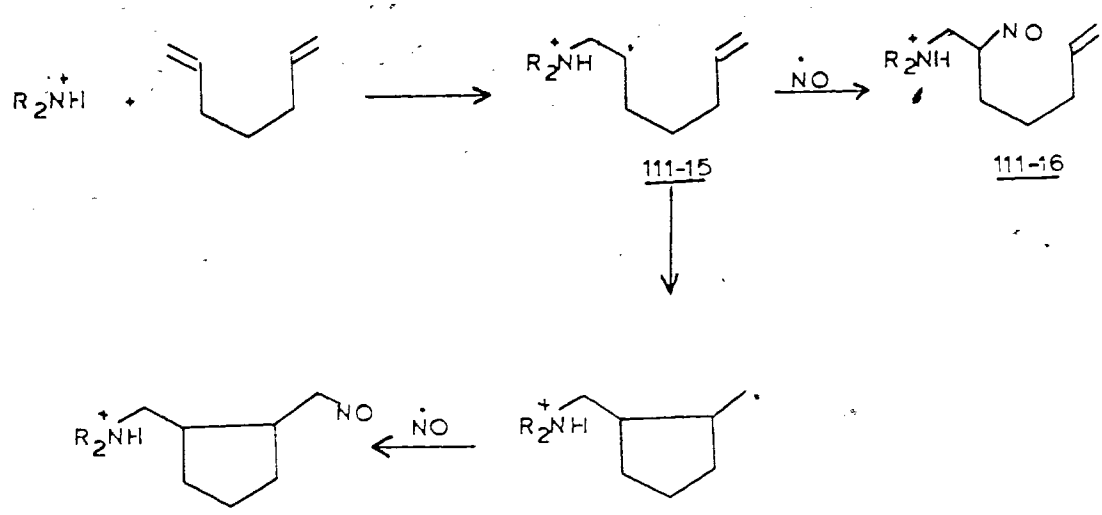
Intramolecular cyclization of carbon radicals has been thoroughly investigated (14,15,16,18). The direction of these cyclizations appear to be controlled by both steric (14) and electronic (18) factors and the kinetically more favored cyclization product is preferentially formed although equilibrization to the thermodynamically more stable product has been demonstrated in some cases (14). The photochemical addition of nitrosamines to unconjugated dienes was investigated to determine the extent of intramolecular carbon radical cyclization (Table 3.1).

Aminium radicals generated by the photolysis of nitrosamines in dilute acidic media add preferentially to the unsubstituted terminus of a mono-substituted olefin to give the more stable secondary carbon radical intermediate (III-15, Scheme 3.17) (11).

Table 3.1

Radical Addition to Unconjugated Dienes

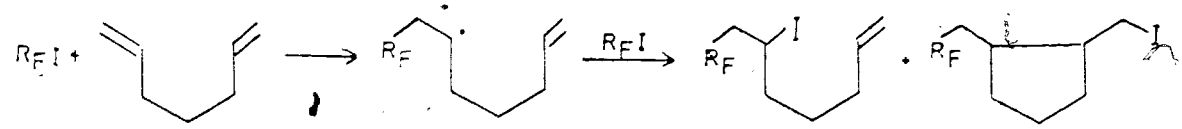
Addenda	Diene	% Cyclization	Ring Size	Reference
$CF_3(CF_2)_3I$		0		88
$CF_3(CF_2)_3I$		23.5	5	88
$BrCl_3$		97	5	103
$CF_3(CF_2)_3I$		0		88
$CF_3(CF_2)_3I$		100	3	88
$(CH_3)_2NNO$		50	3	29



Scheme 3.17

The cyclization of the intermediate carbon radical (III-15, Scheme 3.17) generated by the addition of either nitrosopiperidine or nitrosodimethylamine to 1,6-heptadiene is not extensive since the cyclization products II-53 and II-55 are formed in only 25% and 5% yields, respectively. The main reaction products are derived from III-16 formed by 1:2 addition of the nitrosamine to a double bond. The reason for inefficient radical cyclization is undoubtedly the rapid combination of the C-radical intermediate, III-15, with NO (11). Brace (88) has demonstrated in a similar system that the ratio of linear to cyclic adducts was dependent upon the availability of the radical donor in the propagation step (Scheme 3.18). A high concentration of perfluoroalkyl iodides (R_FI) led to 1:2 addition products while a lower concentration of perfluoroalkyl iodides gave an increased yield of

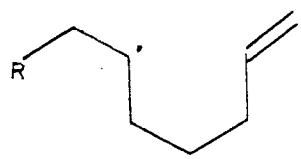
cyclization products. The photoaddition of nitrosamines to unconjugated dienes in the presence of oxygen might be worthy of investigation. Interception of NO by oxygen to generate NO_3 (29) might sufficiently delay product formation to allow for a substantial increase in the yield of cyclization products.



Scheme 3.18

The cis-trans stereochemistry of the cyclization products, II-53 and II-55, formed during the photoaddition of nitrosamines to 1,6-heptadiene has not been established. While the piperidine intermediate III-15 (R_2 = $-(CH_2)_5-$) cyclizes to the syn- and anti-aldoximes possessing a unique stereochemistry on the ring, the dimethyl intermediate III-15 ($R=CH_3$) gives all possible cis-and trans-aldoxime isomers. Studies by Brace (88,103) have shown that III-17a cyclizes preferentially to trans-cyclopentane derivatives; the exact cis/trans ratio being dependent upon the reaction conditions. On simple thermodynamic grounds trans cyclization would be expected to be more favorable than cis since the transition state, III-18, for trans cyclization is subject to fewer non-bonded interactions than is that for cis cyclization, III-19 (103). On the same grounds, aldoximes II-53 are assumed to have

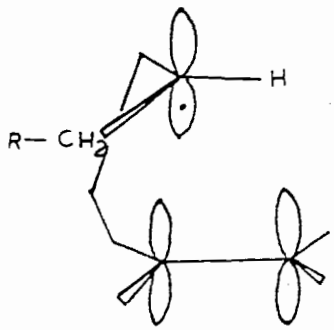
trans-configuration: the driving force for the stereochemical integrity is presumed to be due to the bulky piperidino group causing more steric crowding in the cis-orientation. Recently, Beckwith has reported (102) the preferential cyclization of the intermediate carbon radical III-17b to cis substituted cyclopentane derivatives (cis/trans, 2.3). Beckwith (102) has attributed the predominant formation of cis-isomers to secondary attractive interaction between the alkyl substituent of III-17b and the olefinic bond as depicted in III-19. Secondary attractive interactions between alkyl substituents carrying either piperidino or dimethylamino groups and the olefinic bond of III-15 are expected to be equivalent and would probably not account for differences in the direction of radical cyclization.



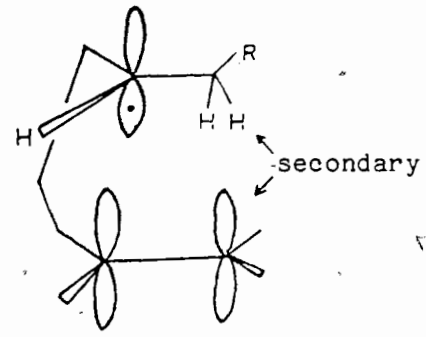
a, R = $CF_3(CF_2)_3$

b, R = CH_3

III-17



III-18



III-19

3.5 Conclusions

The photolysis of suitable olefinic nitrosamines has been established as a valuable method of synthesizing bridged polycyclic compounds possessing 5-membered aza rings. The mild conditions necessary for reaction further increase the value of this pathway. The synthetic flexibility was increased by the thermolysis of some corresponding chloramines. The products synthesized also possessed a second potentially useful functional group which could be altered.

Although most of the nitrosamine cyclization reactions were almost quantitative, several of the tricyclic compounds synthesized were unstable. The fate of these compounds was to undergo efficient ring cleavage reactions involving the amine group to give azabicyclic compounds. The amino nitrates III-8 and III-9, for example, readily

underwent nitrogen assisted elimination of NO_2^- to give, after reduction, the bicyclic amino alcohols II-29 and II-38, respectively. The stereochemical purity of the bicyclic products isolated indicate that the nitrogen assisted cleavage reactions encountered are efficient ways of synthesizing certain azabicyclic compounds.

Studies of the solution photochemistry of N-nitropiperidine have clarified some of the photoreactions involved. We have confirmed that the primary photoprocess is the cleavage of the N-N bond of the nitramines. This is in contrast to the solid state photochemistry of nitramines where N-O bond cleavage appears to be the primary reaction. The acid catalysed oxidative photoaddition of nitramines to olefins may prove to be an efficient means of synthesizing amino nitrates.

CHAPTER 4

EXPERIMENTAL

4.1 General Techniques

Unless otherwise indicated the following general conditions prevail. Infrared (i.r.) spectra were measured on a Perkin-Elmer model 457 Spectrometer as liquid films or as nujol mulls for solid samples. Ultraviolet (u.v.) spectra were recorded on a Unicam SP 800 Spectrometer; spectral bands are reported as λ_{max} nm (ε). Nuclear Magnetic Resonance (n.m.r.) spectra were recorded on a Varian A56/60 or a Varian XL100 Spectrometer using deuterochloroform as solvent and TMS as internal standard. The decoupling experiments were performed on the latter instrument. Chemical shifts are reported in τ units, coupling constants (J) in Hertz (Hz), the coupling patterns as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet), and br (broad), the width at the half height of a signal is given as $W_{\frac{1}{2}}$. Gas chromatography (g.c.) was performed on a Varian 1200 flame ionization chromatograph using a 20% SE-30, 10 ft by 1/8 inches stainless steel column. Preparative g.c. runs were done on the Varian 1720-10 using a 20% SE-230, 20 ft x 3/8 in, aluminum column. Mass spectra (m.s.) and high resolution mass spectra (H.r.m.s.) were recorded with a Hitachi-Perkin-Elmer RMU-6E spectrometer with an ionizing voltage of 80 Ev. and were reported as m/e (approximate relative abundance).

The gas chromatographic-mass spectral (g.c.-m.s.) analyses were done using a Varian 1400 gas chromatograph coupled to the mass spectrometer.

Melting points were determined on a Fisher Johns hot stage apparatus and were not corrected. Elemental analysis were performed by Mr. M.K. Yang, Department of Biological Sciences.

Separations by column chromatography were performed using Brockman alumina (neutral or basic, activity I, 80-200 mesh), Baker silica gel (60-200 mesh), or Mallinckroft silicic acid (100 mesh). Thin layer chromatogrphy (t.l.c.) was performed on silica gel plates (0.25-0.30 nn thickness) impregnated with u.v. indicator. The reported yields were estimated from column chromatography or by area determination of g.c. peaks.

4.2 Chemicals

Reagent grade solvents were distilled before use and benzene and methanol were stored over sodium ribbon and molecular sieve (Type 3A), respectively. Reagent grade pyridine was stored over potassium hydroxide pellets.

Cyclohexene (MC and B), 1,3-cyclohexadiene (Aldrich), allyl bromide (Fisher), N-nitrosopiperidine (Eastman), and N-nitrosodimethylamine (Eastman) were distilled before use. Cyclopentadiene was prepared by the destructive distillation (104) of 3a,4,7,7a-tetrahydro-

4,7-methanoindene (MC and B), 1,5-heptadiene (Aldrich), 1,6-heptadiene (K and K), acrylic acid (Mc and B), hydrogen peroxide (Fisher), bromotrichloromethane (Aldrich), methylamine, and nitrogen dioxide (Matheson Gas Company), lithium aluminum hydride (LAH, Wilshire, 97%), sodium bis-(2-methoxyethoxy)aluminum hydride ("Red Al", 70% solution in benzene, Aldrich), and nitrosofluoroborate (D.F. Goldsmith) were used as supplied.

Endo-norbornene-cis-5,6-dicarboxylic anhydride was obtained from the undergraduate organic laboratory and was recrystallized before use (m.p. 164°, Lit. 165°) (105). Perfex Bleach (Bristol Meyers Co., NaOCl>6%) was used in the preparation of N-chloramines.

4.3 General Photolysis and Thermolysis Conditions

4.3.1 Light Sources and Photolysis Apparatus

The solutions were irradiated with a medium pressure lamp (200 Watt, Hanovia 654A36; 100 Watt, Hanovia 8A36) placed within the lamp well of Apparatus I (Figure 4.1) or Apparatus II (Figure 4.2), both of which could be fitted with a cylindrical glass filter if required. Tap water passed through the cooling jacket and an external ice bath were used for cooling the photolysis solution. Nitrogen (scrubbed with Fiesers' solution, then lead acetate solution, followed by concentrated H_2SO_4) or oxygen was bubbled through the gas inlet. A magnetic bar stirred the photolysate (ca. 200 ml) in Apparatus I while a stream of

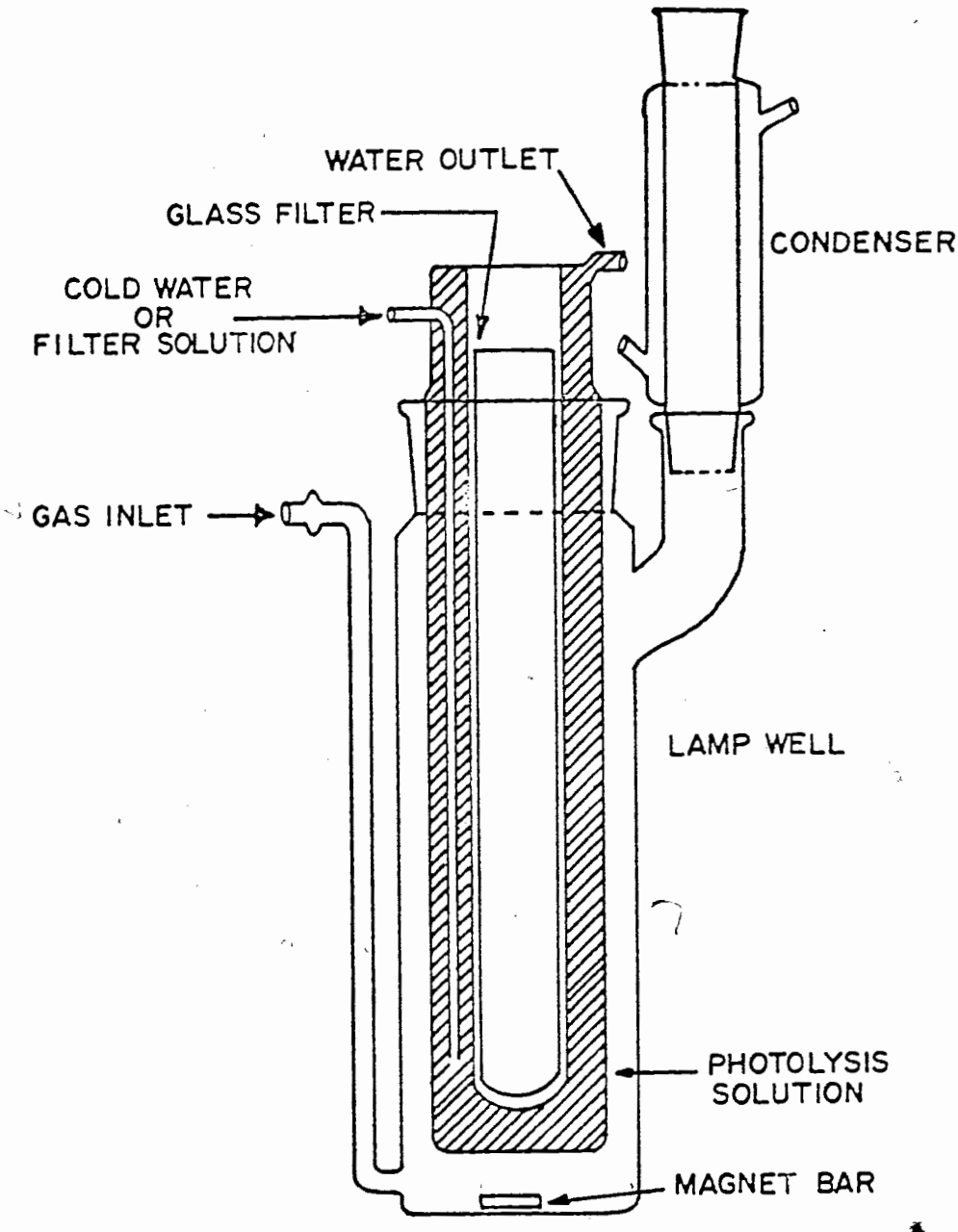


Figure 4.1: Photolysis Apparatus I

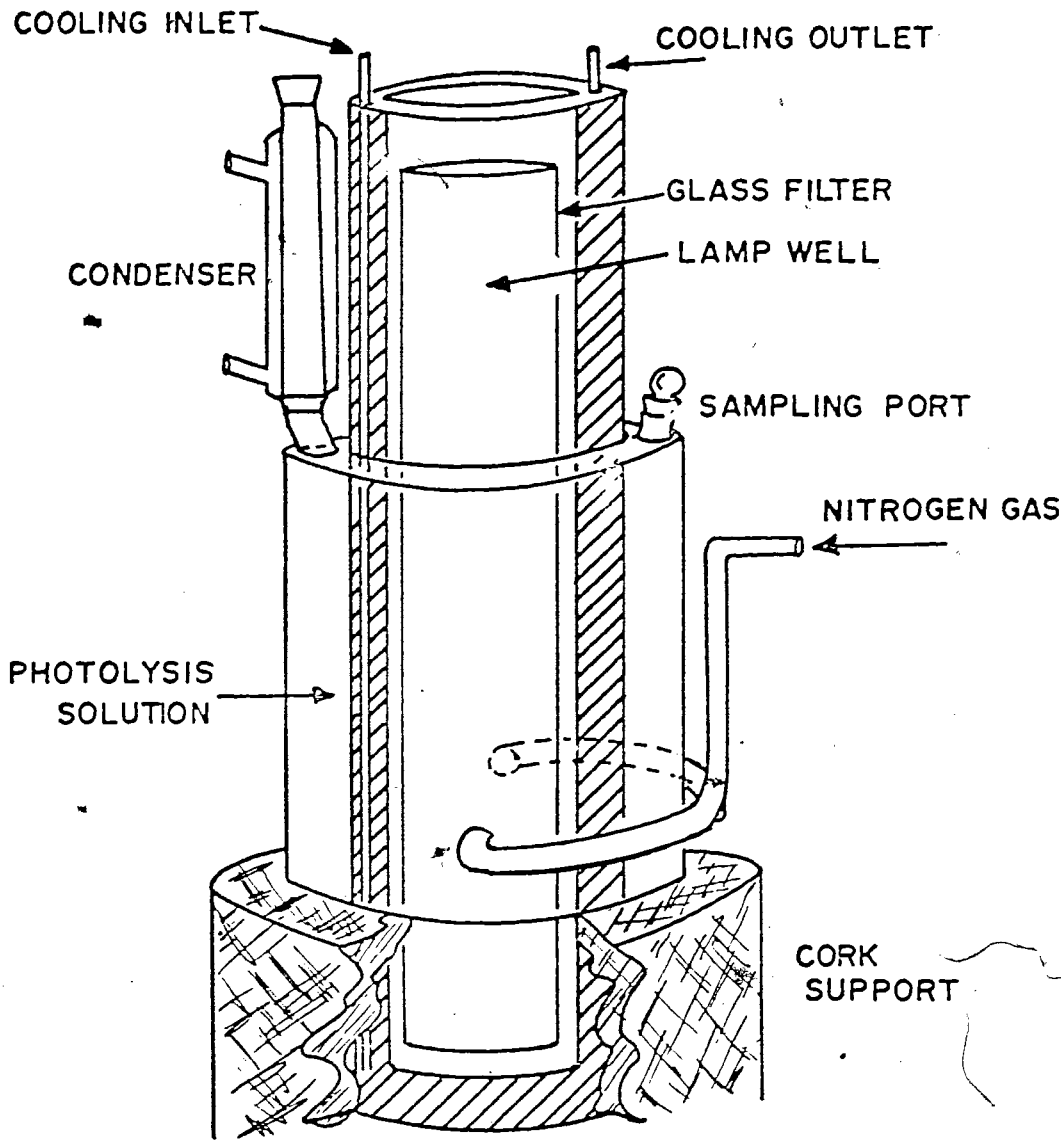


Figure 4.2: Photolysis Apparatus II

nitrogen or oxygen served to agitate the solution in Apparatus II (ca. 130 ml).

4.3.2 Photolysis of N-Nitropiperidine

The reaction conditions for photolysis of N-nitropiperidine were variable. Generally, a methanol solution of N-nitropiperidine (ca. 0.04M) was placed in a quartz apparatus fitted with a Corex glass filter (50% transmission at 275 nm). To this was added the required quantity of concentrated hydrochloric acid and cyclohexene. The solution was flushed with N_2 or O_2 gas for 10-15 minutes before and also throughout the irradiation. The mixture was photolysed until the π-π^* absorption (249 nm) of N-nitropiperidine had disappeared as determined by u.v. monitoring of alequots taken from the photolysate. A zero hour sample was retained in the dark and the u.v. spectrum examined at the completion of the photolysis. No noticeable decrease in the u.v. absorption of this sample was observed.

The methanol solvent was removed under vacuum at 10-20°. In some cases, the solvent was removed by distillation through a Vigreaux column and trapped in a receiver cooled by a dry ice-acetone bath. The collected solvent was treated with a 2,4-dinitrophenylhydrazine (2,4-DNPH) solution to detect any volatile carbonyl compound that might be present.

If the reaction had been done under neutral conditions the photolysate residue was directly analysed by g.c.-m.s. Alternately, the residue was diluted with an HCl solution (1.0N, 50 ml) and extracted with ether to remove the neutral (non-basic fraction) material. The solution was basified to pH-9 with a saturated Na_2CO_3 solution and the basic fraction was extracted. The solvent extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated.

4.3.3 Photolysis of N-Nitrosamines

A methanol solution of the nitrosamine (ca. 0.04M) and concentrated hydrochloric acid (ca. 0.04M) was placed in the apparatus equipped with a Nonex filter (50% transmission at 320 nm). Gas was bubbled through this solution for 10-15 minutes prior to and also throughout the photolysis. The mixture was irradiated until the $n-\pi^*$ absorption (ca. 350 nm) of the nitrosamine had disappeared as determined by u.v. monitoring of aliquots taken from the photolysate. A zero hour sample maintained in the dark indicated that no thermal reaction was occurring over the photolysis period.

After the photolysis the methanol was removed under vacuum at 10-20° and the residue was diluted with water (50 ml). After extraction of the neutral fraction with ether, the solution was basified to pH 9-11 with a Na_2CO_3 or NaOH solution. The basic fraction was extracted with ether or methylene chloride. In some cases, continuous liquid-liquid extraction with CH_2Cl_2 was employed to recover

additional material. The extracts were dried over $MgSO_4$, filtered, and evaporated. The residues were examined by various spectral techniques and separated by chromatography.

If the photolysis had been performed under an oxygen atmosphere the ether extract of the basic fraction was immediately dried over $MgSO_4$ and the solution was treated with LAH. After stirring overnight with LAH this solution was worked-up by treatment with a 10% aqueous NaOH solution, filtered, dried over $MgSO_4$, filtered again and evaporated. The reduced product was then analysed.

4.3.4 Thermolysis of N-Chloramines

A solution of N-chloramine (ca. 0.01 mole) in an appropriate solvent (150 ml) was refluxed in the dark. Thermolysis was continued until iodometric titration of aliquots of the solution with sodium thiosulfate indicated virtual absence of positive chlorine (0-5%). The solvent was removed under vacuum at room temperature and the residue was diluted with 1.0N aqueous HCl (50 ml). After extraction of the neutral material with ether, the solution was basified to pH 11-12 with an NaOH solution. Extraction with CH_2Cl_2 which was dried over $MgSO_4$, filtered, and evaporated gave the basic fraction. The basic residue was analysed by various spectroscopic and chromatographic techniques.

4.4 Preparation of N-Nitropiperidine

The procedure of Emmons (106) was used to oxidize N-nitrosopiperidine to N-nitropiperidine except that 50% H_2O_2 was used in place of 90% H_2O_2. This necessitated that the oxidation be repeated once to ensure a more complete oxidation to the nitramine. The remaining traces of nitroso compound (i.r. 1180 and 1090 cm^{-1}) were precipitated as the hydrochloride when dry HCl was bubbled through an anhydrous ether solution of the crude product for 2 hours. The ether solution was filtered, washed with water, dried over $MgSO_4$, and evaporated. Distillation at 100-105°/23 mm gave N-nitropiperidine (107) as a clear oil (48%): i.r. 1530(m), 1330(m), 1280 and 1241 cm^{-1}; n.m.r. τ 6.20 (m,4H) and 8.33 (m,6H); u.v. (MeOH) 249 nm (ε,5,500).

4.5 Synthesis of Alkenyl Amines

4.5.1 Diels Alder Reaction of Cyclopentadiene with Allyl Bromide

Allyl bromide (56g) was treated with cyclopentadiene (25g) by the described method (52). Distillation of the crude product gave a clear oil (50g, 70.5%) consisting principally of 2-endo-bromomethylbicyclo[2,2,1]hept-5-ene, II-13, containing about 30% of the corresponding exo-isomer: i.r. 3060(m), 720(s) and 630(s) cm^{-1}; n.m.r. τ 3.77 (dd, J=6 and 3Hz, 1H), 4.00 (dd, J=6 and 3Hz, 1H), 6.57 (d, J=8Hz, H_8-exo, 0.3H), 6.88 (dd, J=8 and 4Hz, H_8-endo, 0.7H), 7.05(m), 7.45 (m,1H),

8.05 (ddd, J=11.5, 8.5 and 3.5Hz, H_3-exo), 8.55(m) and 9.41 (ddd, J=11.5, 4, and 2.5Hz, H_3-endo, 0.7H). This sample was utilized without further purification.

4.5.2 Preparation of 2-endo-Methylaminomethylbicyclo[2,2,1]hept-5-ene, II-14

A solution of methylamine (27g) and II-13 (25g) in ether (125 ml) was placed in an autoclave which was heated in an oil bath at 100° for 67 hours. The product was extracted with 1.0N HCl (3x50ml) which was washed with ether. The acidic aqueous phase was basified to pH 10-11 with aqueous NaOH and extracted with CH_2Cl_2 which was dried over $MgSO_4$, filtered, and evaporated to a light yellow oil, II-14 (12.8g): i.r. 3300(w), 3060(m), 1250 and 720(s) cm^{-1}; n.m.r. τ 3.90 (dd, J=6 and 3Hz, 1H), 4.12 (dd, J=6 and 3Hz, 1H), 7.20 (m,2H), 7.40 (d, J=7, 0.7H), 7.55 (s, N-CH_3, 0.9H), 7.61 (s, N-CH_3, 2.1H), 7.80 (M,2H), 8.68 (M,2H), 9.04 (s,D_2O exch.,1H) and 9.50 (br.d, J=10Hz, H_3-endo, 0.7H); m.s. m/e 137(M^+,10), 71(66), 70(61) and 44(100). This oil contains 30% of exo-isomer as shown by the ratio of the N-CH_3 signals.

4.5.3 Diels Alder Reaction of Cyclohexadiene with Acrylic Acid

Acrylic acid (30g) was reacted with cyclohexadiene (25g) as described by Boehme (55). Distillation at 148-150°/13mm gave an oily solid which was recrystallized from pentane several times to give II-15 (24.3g, 46%): m.p. 56-57° (Lit.56-57°) (55), i.r. (nujol) 3200-2500 (s,br), 1700(s), 1240(s), 940 and 700(s) cm^{-1}; n.m.r. τ -2.02 (s,D_2O exch.),

3.80 (m,2H), 7.05 (M,1H), 7.40 (m,2H) and 8.1-9.0 (unresolved, 6H); m.s. m/e 152 (M^+,11), 80 (100) and 79(83).

4.5.4 Preparation of N-Methyl-2-endo-carboxamide-bicyclo[2,2,2]oct-5-ene, II-16

Acid II-15 (10g, 0.066M) was mixed with pyridine (6.0g) and thionyl chloride (9.45g) in dry benzene (200 ml) at 0° for 20 minutes. Methylamine was bubbled into this solution until it was basic to moist pH paper. The benzene solution was washed with 10% aqueous Na_2CO_3 solution, and water, dried over $MgSO_4$, filtered, and evaporated to give a solid. Recrystallization from hexane gave white needles of N-methyl-2-endo-carboxamide-bicyclo[2,2,2]oct-5-ene, II-16 (8.8 g, 81%): m.p. 135-136°; i.r. 3285(s), 3040(w), 1640(s), 1555(s) and 690(m) cm^{-1}; n.m.r. τ 3.70 (m,2H), 4.2 (br.m, D_2O exch.), 7.25 (d, J=4.5Hz, 3H), 7.40 (m,2H) and 8.0-9.0 (unresolved, 6H).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.86, H, 9.14; N, 8.41.

4.5.5 Preparation of 2-endo-Methylaminomethylbicyclo[2,2,2]oct-5-ene, II-17

Amide II-16 (8.8g, 0.053 mole) was added slowly in portions to a stirring suspension of LAH (4.05g, 0.1 mole) in ether. This mixture was stirred at room temperature for 20 hours. After the usual work-up the ether solution was distilled through a Vigreaux column leaving amine

II-16 which was a light yellow oil (5.8g, 73%); i.r. 3280(w), 3040(m), 1610(w), 1150, 1130 and 700 cm^{-1}; n.m.r. τ 3.80 (m,2H), 7.4-7.8 (unresolved, 3H), 7.61 (s, $N-CH_3$), 8.0-9.0 (unresolved, 6H) and 9.10 (m,1H); m.s. m/e (15 Ev) 151 (M^+,16), 85(75), 83(100) and 44(66).

4.5.6 Preparation of endo-Norbornene-cis-5,6-dicarboximide, II-20

Endo-norbornene-cis-5,6-dicarboxylic anhydride, II-18, (50g) and concentrated NH_4OH (150 ml) were stirred at room temperature (56) for 20 hours. A white precipitate was recovered by filtration and was dessicated under vacuum in the presence of concentrated H_2SO_4 to yield II-19 (23.3g): m.p.>250°; i.r. 3460(s), 3200(s), 1710(m), 1660(s), 1628(s), 1530, 1412(s), 1290, 1270, 1232(s) and 730(s) cm^{-1}. This solid was heated in acetic anhydride (12 ml) to give a homogeneous solution which was refluxed for 2 hours. After cooling the mixture was basified with aqueous NaOH (15%) to yield a precipitate which was recrystallized from water to give II-20 (19.75g): m.p. 186-187° (Lit. 185-186.5°) (56): i.r. 3155, 3060(s), 1750, 1700(s), 1295(s), 1230(m), 1190, 1120, 992(s), 840, 738 and 640(s) cm^{-1}; n.m.r. τ 1.50 (m,D_2O exch.), 3.80 (m,2H), 6.67 (m,4H), 8.22 (A portion of AB pattern, J=9Hz, syn-H_{10}) and 8.48 (B portion of AB pattern, J=9Hz, anti-H_{10}).

4.5.7 Reduction of endo-Norbornene-cis-5,6-dicarboximide, II-20

Imide II-20 (16g, 0.1 mole) in dry THF (200 ml) was added slowly to a suspension of LAH (16g, 0.41 mole) in THF (550 ml) and the mixture was

refluxed for 42 hours (57,58). The condenser outlet was protected with a $CaCl_2$ drying tube. The mixture was treated with aqueous NaOH (10%) and the resulting white suspension was filtered. The residual solid was thoroughly washed with THF and the combined filtrate was dried over $MgSO_4$, filtered, and evaporated to yield a semisolid (15.5g). Recrystallization from ethyl acetate-petroleum ether (30-60°) or vacuum sublimation (25°/0.05 mm) gave a derivative of 4-azatricyclo[5,2,1,$0^{2,6}$]dec-8-ene, II-21: m.p. 59-60°; i.r. 3350(s,br), 3050(w), 2720(w), 2460(w), 1625(m), 1512(s), 1255, 1230(m), 820, 752 and 720(m) cm^{-1}; n.m.r. τ 3.78 (m,$W_{\frac{1}{2}}$=4Hz,2H), 5.00 (s,D_2O exch., 2H), 7.11 (m,8H), 8.45 (A portion of AB pattern, J=8.5Hz, syn-H_{10}) and 8.60 (B portion of AB pattern, J=8.5Hz, anti-H_{10}); m.s. m/e 135(41), 134(10), 94(53), 69(41) and 68(100).

Anal. Found: C, 48.8; H, 6.39; N, 6.02. H.r.m.s. on m/e = 135: Calcd for $C_9H_{13}N$, 135.1048. Found: 135.1038. H.r.m.s. on m/e = 68: Calcd for C_4H_6N, 68.0500. Found: 68.0507.

4.6. Preparation of N-Nitroso Compounds

Purification of the N-nitrosamines was done by chromatography through neutral alumina or silicic acid (benzene or CH_2Cl_2 as elutants).

(a) Sodium nitrite ($NaNO_2$) nitrosation: The compounds were prepared by the known method (108). An amine (0.02 mole) was dissolved in water (100 ml) containing concentrated HCl (2 ml, 0.06 mole) to which ether (100 ml) was added. To the stirred mixture at 0° was added $NaNO_2$ (1.5g, 0.022 mole) in portions and the mixture was stirred for 6 hours. The ether layer was separated and the aqueous phase was washed with additional ether. After drying the combined ether extracts were evaporated to give the nitrosamine.

(b) Dinitrogen tetroxide (N_2O_4) nitrosation: The method of White (60) was modified as below. An amine (0.015 mole) and anhydrous sodium acetate (4g, 0.5 mole) in CH_2Cl_2 (125 ml) were stirred and cooled in an acetone-ice bath. To this mixture was added dropwise over a 1 hour period a cold solution (ca. 0°) of N_2O_4 (1.5g, 0.016 mole) in CH_2Cl_2 (50 ml). The mixture was stirred at -10° for another 10 minutes. The solvent was filtered and washed with dilute Na_2CO_3 (10%) and was dried and evaporated to give the corresponding nitrosamine.

(c) Nitrosotetrafluoroborate ($NOBF_4$) nitrosation: The method of Nagasawa (65) was used except that CH_2Cl_2 was used as solvent. To a suspension of $NOBF_4$ (6.4g, 0.055 mole) in CH_2Cl_2 (100 ml) at 0° was added an amine (0.036 mole). To this stirred mixture was added dropwise over 15 minutes a solution of pyridine (4.32g, 0.055 mole) in CH_2Cl_2 (50 ml). The conditions were maintained for another 1 hour

at which time the solvent was filtered, washed with aqueous Na_2CO_3 (10%), dilute HCl (0.1N), then water. The CH_2Cl_2 was dried and evaporated to give the nitrosamine.

4.6.1 N-Nitroso-2-endo-methylaminomethylbicyclo[2,2,1]hept-5-ene, II-22

Amine II-14 was nitrosated with $NaNO_2$ using method 4.6a or with N_2O_4 using method 4.6b to give, after chromatography, an oil characterized as N-nitrosamine II-22 in 31% and 70% yields, respectively: i.r. 3060(m), 1430(s), 1270, 1155, 1035(s) and 720(s) cm^{-1}; m.s. m/e 167(1), 166(M^+,1), 165(1), 149(22), 136(24), 101(35), 91(40), 82(88) and 66(100); u.v. (methanol) 344 nm (ε, 97). The olefinic protons appeared in the n.m.r spectrum as a pair of double doublets at τ 3.75 (J=6 and 3Hz) and 3.98 (J=6 and 3Hz). The N-methyl protons attributed to the syn-isomer resonated at τ6.92(s) and the C_8 protons of this isomer appeared as a complex pattern centered at τ6.0. The N-methyl signal of the corresponding anti-isomer appeared at τ6.20(s). The ratio of the N-methyl signals for the syn- and anti-isomers was 81:19 (109). Other resonances appeared at τ7.20 (m,3H), 8.10 (m,H_3-exo), 8.65 (m,2H) and 9.30 (ddd, J=11.5, 4 and 2.5Hz, H_3-endo).

4.6.2 N-Nitroso-2-endo-methylaminomethylbicyclo[2,2,2]oct-5-ene, II-23

Amine II-17 (5g, 0.033 mole) was nitrosated with $NOBF_4$ (method 4.6c) to give N-nitrosamine II-23 (3.64g, 61%): i.r. 3040(w), 1430(s),

1330, 1310, 1268, 1155(m), 1030(s) and 700(s) cm^{-1}; m.s. m/e 180 (M^+, 32), 163(18), 150(35) and 79(100); u.v. (methanol) 345 nm (ε, 100). The olefinic protons appeared as a two proton multiplet at τ3.70. The N-methyl protons attributed to the syn-isomer appeared at τ6.97(s) and the C_9 protons of this isomer appeared as a complex pattern at τ6.1. The N-methyl signal of the corresponding anti-isomer resonated at τ6.25(s) while the C_9 protons appeared as a complex pattern centered at τ6.7. The ratio of the N-methyl signals for the syn- and anti-isomers was 82:18. The remaining protons appeared in unresolved patterns at τ7.3-9.2 (9H). An analytical sample of II-23 was prepared by repeated distillation at 25°/0.05 mm.

Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95; N, 15.54. Found: C, 66.90; H, 9.12; N, 15.71.

4.6.3 N-Nitroso-4-azatricyclo[5,2,1,$0^{2,6}$]dec-8-ene, II-24

The LAH reduction product of imide II-20 was treated with $NOBF_4$ (method 4.6c) to yield N-nitrosamine II-24 (3.45g). An analytical sample was prepared by repeated sublimation (25°/0.5 mm): m.p. 73-73.5°; i.r. 3060(w), 1452(s), 1412(s), 1312(s), 1220, 842, 802, 770, 742(m) and 720(m) cm^{-1}; n.m.r. τ3.82 (m,2H), 5.90 (m, H_5, 2H), 6.60 (m, H_3, 2H), 6.97 (m, 5H), 8.35 (A portion of AB pattern, J=9Hz, syn-H_{10}) and 8.53 (B portion of AB pattern, J=9Hz, anti-H_{10}); m.s. m/e 164 (M^+, 62), 134(29), 105(54), 79(71), 68(91), 67(54) and

66(100); u.v. (methanol) 348 nm (ε, 87).

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.80; H, 7.22; N, 17.11.

4.7 Preparation of N-Chloro Compounds

A standard procedure was used to prepare the N-chloramines (66, 110). A secondary amine (0.01 moles) dissolved in CH_2Cl_2 (50 ml) was stirred at 0° while a sodium hypochlorite solution (50 ml, Perfex bleach) was added. After 1 hour the layers were separated and the aqueous phase extracted with CH_2Cl_2. The combined CH_2Cl_2 was dried and evaporated to yield the N-chloramine. Due to their instability (39) the N-chloramines were utilized, without purification, immediately after preparation.

4.7.1 N-Chloro-2-endo-methylaminomethylbicyclo[2,2,2]oct-5-ene, II-25

Chloramine II-25 (1.67g) was prepared from amine II-17 (1.5g) by the method outlined: i.r. 3040(m), 1615(w), 1180, 1170(m), 1045(m) and 710(s) cm^{-1}; n.m.r. τ 3.75 (m,2H), 7.05 (m, 2H), 7.10 (s,3H), 7.45 (m,3H) and 8.0-9.2 (unresolved, 7H); u.v. (methanol) 277 nm (ε, 315).

4.7.2 N-Chloro-4-azatricyclo[5,2,1,$0^{2,6}$]dec-8-ene, II-26

Chloramine II-26 (1.1g) was prepared from II-21 (1.3g, as salt) as

above: i.r. 3050(m), 1700(vw), 1650(vw), 1250, 1235(m), 890, 880, 805, 780(s), 735(s) and 682(m) cm^{-1}; n.m.r. τ 3.80 (m, $W_{\frac{1}{2}}$=4Hz, 2H), 6.55 (m,2H), 7.10 (m,4H), 7.50 (m,2H), 8.23 (A portion of AB pattern, J=8Hz; syn-H_{10}) and 8.46 (B portion of AB pattern, J=8Hz, anti-H_{10}); u.v. (methanol) 267 nm (ε, 440). The n.m.r. spectrum of II-26 exhibited a weak signal due to an impurity at τ 5.46(m).

4.8 Photolysis of N-Nitropiperidine

4.8.1 N-Nitropiperidine In Neutral Methanol

Nitropiperidine (1g, 0.008 mole) in methanol (200 ml) was photolysed in Apparatus I under N_2 for 2.15 hours. The solvent was distilled through a Vigreau column and the distillate was trapped (170 ml) in a vessel cooled in dry ice. Treatment of 50 ml of this with a 2,4-dinitrophenylhydrazine reagent solution (20 ml) gave no hydrazone. The residue from the photolysate (1.03g) which exhibited a strong i.r. band at 1655 cm^{-1} and n.m.r signals at τ 2.00(s) and 2.90 (m, D_2O exch.) was examined by g.c. (20% SE30, 130°) and found to contain two components. Peak matching g.c. and g.c.-m.s. characterized the first component, which exhibited peaks at m/e 85 (M^+, 61), 84(100), 57(50) and 56(54), as piperidine (54%; g.c. retention time, 1.2 min.) and the second component (45%; g.c. retention time, 5 min.), which exhibited peaks at m/e 114(10), 113(M^+, 100), 84(45) and 56(61), as N-formyl piperidine (48).

The residue from the photolysate exhibited a blue color in the diphenylamine test (49) indicating the presence of nitrate ion.

4.8.2 N-Nitropiperidine In Acidic Methanol

Nitropiperidine (1g, 0.008 mole) and concentrated HCl (1 ml, 0.06N) in methanol (200 ml) were photolysed in Apparatus I under N_2 for 2 hours at which time the reaction mixture was worked-up as above. A mixture of the distillate (50 ml) and 2,4-dinitrophenylhydrazine reagent solution (20 ml) was evaporated to approximately 20 ml and was cooled. A yellow precipitate formed and was recrystallized from methanol (m.p. 159-162°); a mixed melting point with an authentic sample of formaldehyde 2,4-dinitrophenylhydrazone (m.p. 166°) was 161-163°.

The residue from the photolysate (1g) was dissolved in hot 2-propanol (48) which on cooling gave white crystals (150 mg, m.p.> 200°) which exhibited identical i.r. and m.s. spectra to those of an authentic sample of piperidine hydrochloride: i.r. 2520(m), 2420(m), 1590(m), 1160, 1028, 940 and 860(m) cm^{-1}. The mother liquor was evaporated and the residue was diluted with water (50 ml) and worked-up in the usual manner. Extraction of the basic fraction with ether gave crude piperidine (250 mg): i.r. 3300(w), 1650(w), 1100(m), 860 and 795 cm^{-1}. Analysis by g.c. (20% SE30, 130°) gave a single peak superimposable with that of piperidine.

In a separate experiment the crude photolysate was worked-up directly using CH_2Cl_2 to extract the basic components (530 mg):

i.r. 3350(w,br), 2665(w), 2520(w), 2420(w), 1590(w), 1295, 1265, 1160(s), 1130(s), 1035, 862 and 780(m) cm^{-1}; n.m.r. τ 6.55(m), 7.15(s), 7.57(m) and 8.50(m). Three peaks with retention times of 1.2, 2.4 and 12.7 min. were observed when this mixture was examined by g.c. (20% SE30, 130°). By peak matching g.c. and g.c.-m.s. the first and third peaks were determined to be piperidine (37%) and piperidine hydrochloride (21%). The second peak exhibited m.s. fragments at m/e 96(19), 95(100), 94(78) and 67(72) and was characterized as dipiperidinomethane, II-4, (41%) by comparison with the mass spectrum of an authentic sample (12). The percentages quoted are based on the relative area of each peak eluted on g.c.

4.8.3 Photolysis of N-Nitropiperidine in the Presence of Cyclohexene

(a) Neutral conditions: A solution of N-nitropiperidine (1g, 0.008 mole) and cyclohexene (0.65, 0.008 mole) in methanol (200 ml) was photolysed in Apparatus I under N_2 for 2.15 hours. The work-up gave a neutral fraction (150 mg) and a basic fraction (280 mg). Continuous liquid-liquid extraction of the basic mother liquor with CH_2Cl_2 gave a semisolid (250 mg). The neutral extract exhibited an i.r. absorption at 1650 cm^{-1} and n.m.r. signal at τ 2.0(s) and was shown by g.c.-m.s. (20% SE30, 130°) to contain predominantly N-formylpiperidine (g.c. retention time 7.8 min.).

The basic extract exhibited i.r. bands at 3400(m,br), 1660(s), 1260, 1130, 1040, 1000, 865 and 785 cm^{-1} and n.m.r. signals at τ2.00(s), 6.55(m), 7.0(m), 7.15(s), 7.25(m), 7.60(m) and 8.50(m). By g.c.-m.s. this fraction was found to contain piperidine and N-formyl piperidine (1:1) and a trace of dipiperidinomethane. The semisolid

obtained from the basic mother liquor was shown by i.r. and n.m.r. to contain piperidine hydrochloride and N-formylpiperidine: i.r. 3400(m,br), 2630(m), 2530(m), 2430(m), 1660(s), 1590, 1030, 1000, 945(m) and 860 cm^{-1}; n.m.r. τ2.00(s), 2.35(m, D_2O exch.), 6.60(m), 7.00(m) and 8.30(m). The ratio of the hydrochloride signal at τ2.35 to the signal at τ2.00, due to the N-formyl proton, was approximately 4:1.

(b) Acidic conditions: A solution of N-nitropiperidine (1g, 0.008 mole), cyclohexene (0.65g, 0.008 mole), and concentrated HCl (0.67 ml, 0.04N) in methanol (200 ml) was photolysed in apparatus I under N_2 for 4.5 hours. As the 249 nm band of N-nitropiperidine in the u.v. spectra of the photolysate slowly disappeared it was replaced by a new absorption at about 210 nm which subsequently disappeared with further irradiation. The work-up gave a neutral fraction (40 mg; i.r. 1620 cm^{-1}) and a basic fraction (770 mg): i.r. 3300(w), 1550(m), 1155 and 1115(m) cm^{-1}; n.m.r. τ4.30(m), 6.70 (d, J=6Hz), 7.6(m) and 8.5(m). The complex basic fraction was analysed by g.c.-m.s. (20% SE30, temperature programmed to increase from 110 to 200° at 8°/min) and found to be a mixture of eight compounds with the following retention times: 3.0 min. (16%, piperidine) m.s. m/e 85(M^+, 60), 84(100), 57(49) and 56(55); 6.0 min. (5.5%, dipiperidinomethane) m.s. m/e 95(100), 94(80) and 67(69); 14.1 min. (2%, N-formylpiperidine) m.s. m/e 114(10), 113(M^+, 100), 84(40) and 56(56); 18.3 min. (12%) m.s. m/e 165(M^+, 42), 164(18), 150(15), 137(100), 124(64), 122(88), 84(50) and 81(48); 20.7 min. (10%) m.s. m/e 197(M^+, 32), 182(80), 124(100), 98(41), 85(25) and 84(27); 21.2 min. (20%, 2-piperidinocyclohexanol) m.s. m/e 183(M^+, 45), 182(12), 166(7), 124(100), 98(52) and 84(31); 24.6 min. (22%, 2-piperidinocyclohexanone

oxime) m.s. m/e 196(M^+, 2), 179(22), 178(31), 124(100), 110(23), 98(10) and 84(25); and 26.1 min. (9%, 1-nitro-2-piperidinocyclohexane) m.s. m/e 212(M^+, 16), 166(23), 124(100), 111(25), 98(14) and 84(37). The above identifications were made by comparison of mass spectra with those of authentic samples. The compounds eluting after 18.3 min. and 20.7 min. were tentatively identified as a piperidinocyclohexene and 1-methoxy-2-piperidinocyclohexane, respectively, from the mass spectra. The percentage values quoted are based on the relative area of each peak as eluted on g.c.

4.8.4 N-Nitropiperidine in the Presence of Cyclohexene Under Oxygen

A solution of nitropiperidine (1g, 0.008 mole), cyclohexene (0.65, 0.008 mole), and concentrated HCl (0.67 ml, 0.04N) in methanol (200 ml) was photolysed in Apparatus I under oxygen for 1 hour. The photolysate was worked up in the described manner to yield the basic extract (1.48g): i.r. 3400(w,br), 1710(w), 1620(s), 1272(s), 1100 and 865(s) cm^{-1}. The basic extract was dissolved in THF (100 ml) and reduced with LAH (1.2g, 0.03 mole). The usual work-up gave an oil (1.01g) which slowly solidified: i.r. 3440(m), 1305, 1268, 1155, 1125, 1100, 1075, 1035, 1000(m) and 865 cm^{-1}; n.m.r. τ 5.98(m), 6.50(m), 7.1-8.0(unresolved) and 8.48(m).

The reduced basic extract was chromatographed on alumina (40g). The first fraction (300 mg, 25%) eluted with 0.5% methanol-CH_2Cl_2 as a solid which was sublimed (25°/0.5mm) to give trans-2-piperidinocyclohexanol, II-7: m.p. 30.5-32° (Lit. 35-36°) (103); i.r. (nujol) 3450(s), 1305, 1195, 1160, 1100(s), 1078(s), 1005,

940 and 870 cm^{-1}; n.m.r. τ6.75(m,1H), 6.75(s, D_2O exch.), 7.80(m,1H), 7.2-8.2 (unresolved,5H), 8.50(m,10H) and 8.80(m,3H). The second fraction (150 mg, 12%) was eluted with 1% methanol-CH_2Cl_2 as a crystalline solid which was sublimed twice (25°/0.5mm) to give cis-2-piperidinocyclohexanol, II-7: m.p. 83-85°; i.r.(nujol) 3170(w), 1190, 1105, 985 and 870 cm^{-1}; n.m.r.(CCl_4) τ6.10(m,1H), 7.45(m,6H) and 7.9-9.0 (unresolved, 14H). Resublimation (25°/0.5mm) gave an analytical sample of the cis-alcohol melting at 87-89° (Lit. 93-94°) (103).

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.77, H, 11.43; N, 7.67.

4.9 Photolysis of N-Nitroso-2-endo-methylaminomethylbicyclo[2,2,1]hept-5-ene, II-22

4.9.1 Under Nitrogen

A solution of nitrosamine II-22 (1.5g, 0.009 mole) and concentrated HCl (0.8 ml, 0.048N) in methanol (200 ml) was photolysed in Apparatus I under N_2 for 1.5 hours. The usual workup gave a neutral fraction (80 mg) and a basic fraction (A, 850 mg). The mother liquor was further basified from pH9 to pH-13 with NaOH solution then continuously extracted for 5 days with CH_2Cl_2 to yield 200 mg of additional extract, B.

A portion of the basic extract A (750 mg) was chromatographed on silica gel (30). Elution with 2% methanol-CH_2Cl_2 gave crystals (237

mg, 22%) which were rechromatographed on a preparative scale t.l.c. plate (silica gel, 10% methanol-CH_2Cl_2) to give syn-aldoxime II-27: m.p. 109-112°; i.r. 3200(w,br), 3040(w,br), 1260, 920(s) and 890(s) cm^{-1}; n.m.r. τ 2.72(d, J=7Hz, 1H), 5.30(d, J=5.5Hz, H_d), 6.55(br.d, J=8Hz, H_b), 7.28 (s, N-CH_3), 7.5-8.0 (unresolved, 4H) and 8.5(m,3H); m.s. m/e 184(M^+,1), 183(5), 182(11), 168(22), 152(17), 82(78), 57(100) and 49(89).

Anal. Calcd for $C_9H_{16}N_2O_2$: N, 15.19. Found: N, 15.20
H.r.m.s. at m/e 182(M^+-2): Calcd for $C_9H_{14}N_2O_2$, 182.1055.
Found: 182.1037.

Elution with 5% methanol-CH_2Cl_2 gave an intractable mixture of aldoxime and olefinic material: i.r. 3300(s,br), 3060(w), 920(m) and 870 cm^{-1}; n.m.r. τ 2.60(m), 3.10(m, D_2O exch.) and 3.90(t, J=1.5Hz).

The material isolated by continuous extraction (B) was vacuum distilled (40°/0.025 mm) to give hydroxy lactam II-28 (29%): i.r. 3400(s,br), 1662(s), 1500(m), 1400, 1300, 1270(m), 1115, 1070, 1045 and 1015(m) cm^{-1}; n.m.r. τ 6.00(m, D_2O exch.), 6.42(m, H_a and C_9 protons, 3H). 6.92 (dd, J=10 and 1Hz, H_b), 7.18(s, N-CH_3) and 7.83(m,6H); m.s. m/e 169(M^+,90), 152(10), 98(100), 86(50) and 84(77).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28.
Found: C, 63.51; H, 8.83; N, 8.39.

An aqueous ethanol (50%) solution of crude aldoxime II-27 (600 mg) was refluxed with $NaHSO_3$ (1.3g) for 4 hours (71). The solvent was removed by distillation (78-80°) and the residue was acidified with dilute HCl (0.1N). Extraction with $CHCl_3$ (3x20 ml) gave no neutral extract. The aqueous mother liquor was basified (pH~13) with aqueous NaOH and continuously extracted with CH_2Cl_2 for 5 days to give hydroxy lactam II-28 (403 mg; i.r. 1662 cm^{-1}) containing a small amount of nitrile impurity: i.r. 2220(w) cm^{-1}.

A mixture of hydroxy lactam II-28 (100 mg, 0.006 mole) and "Red Al" (0.43g of 70% benzene solution, 0.015 mole) in benzene (10 ml) was stirred at 50° for 0.5 hours then at room temperature for another 2 hours. The mixture was decomposed with water and filtered. The residual solid was washed with additional benzene and the combined benzene filtrate was dried and evaporated to an oil (15 mg) exhibiting i.r. bands similar to those of amino alcohol II-29. The picrate of this oil (m.p. 134-136°) gave a mixed melting point of 135-137° with an analytical sample of the picrate of II-29 (m.p. 138-139°; vide infra).

4.9.2 Under Oxygen

A solution of N-nitrosamine II-22 (2g, 0.011 mole) and concentrated HCl (1.0 ml, 0.06N) in methanol (200 ml) was photolysed in Apparatus I under oxygen for 3 hours. The usual work-up gave a neutral fraction (130 mg): i.r. 3350(m,br), 3055(w), 1715(w), 1640(m), 1550(m) cm^{-1};

n.m.r. τ0.20 (d,J=2.5Hz), 3.90(m). The mother liquor was basified and extracted with CH_2Cl_2 (3x50ml) which was dried and evaporated to the crude basic residue (1.8 g): i.r, 3300(w,br), 3060(w), 1720(m), 1670(m), 1620(s), 1275(m) and 865(m) cm^{-1}. After 24 hours the i.r. band at 1720 cm^{-1} of this fraction became relatively stronger.

In a similar experiment the basified mother liquor was extracted with ether (4x50ml) which was dried and treated immediately with LAH (2g). The work-up of this reduced basic extract gave a yellow oil (C, 1.2g): i.r. 3380(s,br), 1650(w), 1130, 1045(m) 862(w) and 700(w) cm^{-1}. After extraction with ether the aqueous mother liquor was further extracted with CH_2Cl_2 (3x50ml) to give oil D (130 mg). Finally, the basic mother liquor was continuously extracted with CH_2Cl_2 for 3 days to afford crude hydroxy lactam II-28 (180 mg): i.r. 3380(s,br), 1655(s), 1065, 1040 and 1020(m) cm^{-1}; n.m.r. τ6.45(m,3H) and 6.92(dd, J=10 and 1Hz, 1H).

The reduced extract C (1.0g) was chromatographed on neutral alumina (50g). Elution with 0.4% methanol-CH_2Cl_2 gave a crude olefinic alcohol (110 mg): i.r. 3380(m), 3055(m), 1660(w), 1030(m), 778 and 705(s) cm^{-1}; m.s. m/e 124(8), 106(9) and 66(100). The n.m.r spectrum of this oil exhibited the characteristic resonances of authentic alcohol II-34 at τ3.93(m,2H), 6.40(dd, J=6 and 2Hz, 1H), 7.05(m, D_2O exch.), 7.22(m,3H), 7.75(m,3H) and 8.70(m,5H) along with minor impurity peaks at

4.00(m) and 9.43(m).

H.r.m.s. on m/e 124 (M^+): Calcd for $C_8H_{12}O$, 124.0888. Found, 124.0863.

Elution with 1% methanol-CH_2Cl_2 gave an unidentified mixture (200 mg): i.r. 3400(s,br), 3055(w), 2690(w), 2550(w), 1650(m), 1135, 1050(m) and 705(m) cm^{-1}; n.m.r. τ3.48(m,D_2O exch.), 3.90(m), 5.77(d, J=6.5Hz), 7.10(m), 7.38(s) and 7.6-8.2 (unresolved). Elution with 2% methanol-CH_2Cl_2 gave an oil (267 mg, 30%) which was distilled at 25°/0.5 mm to give bicyclic amino alcohol II-29: i.r. 3300(s,br), 1150, 1135(w), 1020(m), 985(w) and 865(m) cm^{-1}; n.m.r. τ6.38 (d, J=5Hz, CH_2OH), 6.84(s, D_2O exch.), 7.39(d, J=8.5Hz, H_b), 7.45(m,2H), 7.70(s, N-CH_3), 7.90(m,4H) and 8.80(m,2H); m.s. m/e 155(M^+,10), 154(17), 124(19) and 57(100). The picrate of II-29 was recrystallized twice from ethanol to give yellow needles: m.p. 138-139°.

Anal. Calcd for $C_{15}H_{20}N_4O_8$: C, 46.88; H, 5.52; N, 14.58. Found: C, 46.64; H, 5.52; N, 14.53.

Continued elution with 3-5% methanol-CH_2Cl_2 gave slightly impure tricyclic amino alcohol II-33 (216 mg, 12.5%): i.r. 3350(s,br), 1650(w), 1130, 1040(m), 1015(s) cm^{-1}; n.m.r. τ6.31(m, $W_{\frac{1}{2}}$=3.5Hz, H_d), 7.05(m, D_2O exch.), 7.27(m,3H), 7.50(s,N-CH_3), 7.68(m,1H),

7.90(m,3H), 8.2-9.1 (unresolved, 4H); m.s. m/e 154(4), 153(M^+,37), 152(7), 136(12), 124(22), 96(91), 95(36), 94(100), 82(62), 57(45); n.m.r. (HCl salt) τ5.28 (m, D_2O exch.), 5.90 (m, $W_{\frac{1}{2}}$=3Hz, H_d), 6.69(d, J=5Hz,H_a), 6.72(d, J=10.5Hz, H_c), 7.02(dd, J=10.5 and 5Hz, H_b), 7.20(s, N-CH_3). Amino alchohol II-33 was purified as its picrate which was recrystallized three times from ethanol: m.p. 185-187°.

Anal. Calcd for $C_{15}H_{18}N_4O_8$: C, 47.12; H, 4.76; N, 14.65. Found: C, 46.84; H, 4.66; N, 14.55.

The basic extract D was reduced with LAH (2g) in THF (200 ml) and was worked-up and purified in the usual manner to give crude amino alcohol II-29 (46 mg, 5%): i.r. 3350 (s,br), 1020(m) and 865(m) cm^{-1}; n.m.r. τ6.40(d, J=5Hz), 6.68(s, D_2O exch.), 7.39(d, J=8.5Hz) and 7.70(s, N-CH_3).

4.9.3 In Bromotrichloromethane

A mixture of nitrosamine II-22 (1g, 0.006 mole), concentrated HCl (0.55 ml), and $CBrCl_3$ (100 ml) was photolysed in Apparatus II under N_2 for 2 hours. The fluorescent blue mixture was evaporated under vacuum and the residue was separated into neutral (350 mg) and basic (666 mg) fractions. The neutral fraction exhibited no N-methyl signal in the n.m.r. spectrum. The basic fraction exhibited one major spot at R_f0.37 and a faint spot at R_f0.19 on a silica gel t.l.c. plate (10%

methanol-CH_2Cl_2); the n.m.r. spectrum was essentially that of II-35 (ca. 90%) with weaker signals due to II-36. Silicic acid chromatography (1% methanol-CH_2Cl_2) of this fraction (500mg) afforded an oily bromo amine, II-35 (148mg): i.r. 1185, 1165(s), 935(s) and 6.90(s) cm^{-1}; n.m.r. τ6.15(m, $W_{\frac{1}{2}}$=4Hz, H_d), 6.56(d, J=4.5Hz, H_a), 7.10(dd, J=9.5 and 5 Hz, H_b), 7.50(d, J=9.5Hz, H_c), 7.50(s, superimposed on doublet, N-CH_3), 7.80(m,2H) and 8.4-9.0(m,3H); m.s. m/e 217 (16), 215(M^+Br^{79}, 16), 136(100), 96(38), 95(27), 94(100) and 82(30).

H.r.m.s. on m/e 215 (M^+ Br^{79}): calcd for $C_9H_{14}NBr^{79}$, 215.0295; Found: 215.0310.

The bromo amine II-35 gave a dark tar on attempted vacuum distillation and the picrate derivative (m.p. 180-190°, decomp.) decomposed on repeated attempts at recrystallization.

The minor component of the basic fraction was isolated by preparative scale g.c. (6 ftx1/4 inch, 20% SE30, 150°, g.c. retention 10.8 min.) as an oily chloro amine, II-36: i.r. 3300(v.w), 1630(v.w), 940(m) and 740(m) cm^{-1}; n.m.r. τ6.25(m, $W_{\frac{1}{2}}$=3.5Hz, H_d), 6.80(d, J=5Hz, H_a), 7.10(dd, J=9.5 and 5Hz, H_b), 7.50(d, J=9.5Hz, H_c), 7.50(s, superimposed on the doublet, N-CH_3), 7.80(m,3H) and 8.0-9.0(m,3H); m.s. m/e 173(10), 171(M^+Cl^{35},30), 136(85), 96(46), 95(29), 94(100) and 82(19).

H.r.m.s. on m/e 171 (M^+Cl^{35}): Calcd for $C_9H_{14}NCl$, 171.0814, Found, 171.0825.

4.9.4 In Carbon Tetrachloride

A mixture of nitrosamine II-22 (0.5g, 0.003 mole), concentrated HCl (0.3 ml) and CCl_4 (100 ml) was photolysed in Apparatus II under nitrogen for 3.5 hours to give a fluorescent blue solution. The fluorescent material was distilled with the CCl_4 and the acidic residue was diluted with water (50 ml). The usual work-up gave a neutral fraction (183 mg) containing some unreacted nitrosamine II-22: i.r. 1425(s) and 1035(m) cm^{-1}; n.m.r. τ3.90(m), 6.20(s) and 6.92(s). The basic fraction (210 mg) had the following physical constants: i.r. 3300(w,br), 3050(w), 1218, 940, 740 and 720 cm^{-1}; n.m.r. τ 3.90(m), 5.38(m), 6.30(m, $W_{\frac{1}{2}}$=4Hz), 6.50(m), 6.80(d, J=5Hz), 7.51(s,N-CH_3) and 9.47(br.d, J=11Hz). This fraction was analysed by g.c. (20% SE30, 180°) and was shown to contain chloroamine II-36 (Rt=2.6 min) and amine II-14 (Rt=1.5 min) in a 6:1 ratio, respectively, by peak matching with previously isolated samples.

4.10 Photolysis of N-Nitroso-2-endo-methylaminomethylbicyclo[2,2,2]oct-5-ene, II-23

4.10.1 Under Nitrogen

A solution of nitrosamine II-23 (1g, 0.0055 mole) and concentrated HCl (0.5 ml, 0.03N) in methanol (200 ml) was photolysed in Apparatus I under nitrogen for 1.5 hours. The usual work-up gave a neutral fraction (20 mg) and a basic fraction (620 mg). In addition, continuous liquid-liquid extraction of the basic mother liquor with CH_2Cl_2 gave a semisolid (150 mg).

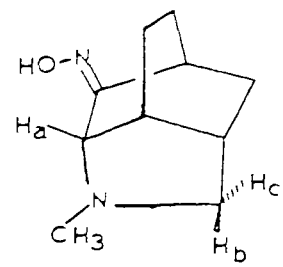
The neutral fraction exhibited typical i.r. and n.m.r. absorptions for aldehyde and olefinic groups: i.r. 3040(m), 1720(s) and 700(s) cm^{-1}; n.m.r. τ 0.60(d, J=1.5Hz) and 3.70(m). The basic extract (600 mg) was chromatographed on a silica gel column (40g). Elution with 5% methanol-CH_2Cl_2 gave crude syn-oxime II-30 (233 mg, 23%) which was purified by preparative scale t.l.c. (silica gel; 10% methanol-CH_2Cl_2, R_f 0.29) to give a clear oil: i.r. 3220(s,br), 3060(m,br), 1660(w), 1285(w), 1130(m), 940(s) and 918(s) cm^{-1}; n.m.r. τ 3.49(m, D_2O exch.), 6.02(br.d, J=5Hz, H_a), 6.98(dd, J=9.5 and 4Hz, H_b), 7.40(s,N-CH_3), 7.4-7.9 (unresolved,5H) and 8.30(m, $W_{\frac{1}{2}}$=5.5Hz, 7H); m.s. m/e 180(M^+,15), 164(24), 163(100), 162(28), 108(24), 94(49), and 82(16). The n.m.r. spectrum of oxime II-30 was examined in the presence of increasing amounts of Eu(DPM)$_3$ shift reagent (Table 4.1).

Elution with 5-8% methanol-CH_2Cl_2 gave a 1:1 mixture of syn-oxime II-30 and anti-oxime II-31 (80 mg, 8%). Crystallization from CH_2Cl_2 gave anti-oxime II-31 (20 mg): m.p. 153-154°; i.r. 3180(w), 3060(w), 1600(w), 1210, 1138, 965(s), 920(s), 868, 770 and 720 cm^{-1}; n.m.r. τ 6.25(t, J=6.5Hz, H_e), 6.72(dd, J=11 and 4.5Hz, H_b), 6.87(d, J=4.5Hz, H_a), 7.40(part of H_c doublet), 7.50(s,N-CH_3), 7.70(m,3H) and 8.33(m,5H); m.s. m/e 181(7), 180(M^+,42), 179(4), 164(54), 163(100), 162(39), 108(40), 94(55) and 82(22). Irradiation at τ 7.75 resulted in collapse of the double doublet pattern at τ 6.72 (H_b) to a doublet (J=11Hz) and the coalescence of the doublet at τ 6.87 (H_a). Irradiation at τ 8.3 resulted in collapse of the triplet at τ 6.25 (H_e) to a singlet.

Table 4.1

The Effect of $Eu(DPM)_3$ on the N.M.R. Spectrum of Oxime II-30

	Shift* (Hz)			
$Eu(DPM)_3$ wt (mg)	H_a	H_b	H_c	$N-CH_3$
19	132	100	100	170
29	240	140	142	236



II-30

* All shift values given in Hertz from the chemical shift value assigned to each proton in the absence of $Eu(DPM)_3$.

H.r.m.s. on m/e 180 (M^+): calcd for $C_{10}H_{16}N_2O$, 180.1263, Found, 180.1249.

Finally, elution of the silica gel column with 20% methanol-CH_2Cl_2 gave an unidentified olefinic fraction (50 mg): i.r. 3040(m) and 750(s) cm^{-1}; n.m.r. τ3.66(m).

The semisolid, isolated by continuous extraction, was recrystallized several times from ethanol-ethylacetate to give the hydrochloride of syn-oxime II-30: m.p. 215-219°; i.r. (nujol) 3125(s), 3060(s), 2660(m), 2580(m), 2550(m), 1040(m), 990, 958(s), 945(s), 905(s) and 745 cm^{-1}; m.s. m/e 180(s), 163(22), 108(88), 94(18) and 83(100).

Anal. Calcd for $C_{10}H_{17}N_2OCl$: C, 55.42; H, 7.91; N, 12.92. Found: C, 55.28, H, 8.04; N, 12.94.

H.r.m.s. on m/e 180: Calcd for $C_{10}H_{16}N_2O$, 180.1263. Found, 180.1242.

This compound caused a green flame when subjected to the Beilstein test for halogens. The hydrochloride (600 mg) was dissolved in water, basified to pH13-14 with aqueous NaOH, and extracted with CH_2Cl_2 (3x50 ml) to yield syn-oxime II-30 (80 mg): n.m.r. τ6.02(d, J=5Hz, H_a), 7.00(dd, J=9.5 and 4Hz, H_b), 7.43(s, N-CH_3). Continuous

extraction of the aqueous solution with CH_2Cl_2 recovered crystalline hydrochloride of II-30 (300 mg): i.r. 3120, 3060(m), 2660(m), 2580, 2550(m), 958, 945, 905(m) and 745(m) cm^{-1}.

Treatment of syn-oxime II-30 (120 mg) with bisulfite (71) as previously described (Section 4.9.1) gave a ketone (48 mg) containing some nitrile impurity: i.r. 2220(w) and 1720(s) cm^{-1}. The bisulfite hydrolysis of a mixture of syn-oxime II-30 and anti-oxime II-31 gave the identical mixture which was chromatographed on neutral alumina with CH_2Cl_2 to give amino ketone II-32: i.r. 1720(s), 1220, 1130 and 1100 cm^{-1}; n.m.r. τ6.78(dd, J=9 and 4Hz, H_b), 6.98(d, J=5Hz, H_a), 7.40(s, N-CH_3), 7.50(m,2H), 7.72(m,2H) and 8.12(m, $W_{\frac{1}{2}}$=4.5Hz, 5H); m.s. m/e 165(M^+,18), 137(100), 96(31), 95(47), 94(78) and 82(82).

H.r.m.s. on m/e 165(M^+): Calcd for $C_{10}H_{15}NO$, 165.1154. Found, 165.1151.

4.10.2 Under Oxygen

A solution of nitrosamine II-23 (2g, 0.011 mole) and concentrated HCl (1.0 ml, 0.06N) in methanol (200 ml) was photolysed in Apparatus I under oxygen for 1.5 hours. The work-up gave an oily neutral fraction (80 mg): i.r. 2700(w), 1718(m), 1640(s), 1545(m) and 700(s) cm^{-1}; n.m.r. τ0.22(m), 0.59(d, J=1.5Hz) and 3.70(m). The mother liquor was basified and extracted with ether (3x50ml) which was dried and stirred overnight with LAH (2g). Work-up in the usual way gave the reduced

photolysate (980 mg). After ether extraction the mother liquor was further extracted with CH_2Cl_2 (3x50ml) to give an additonal basic extract (420 mg): i.r. 3380(m,br), 3040(m), 1700(s), 1625(s), 1270(m) and 1050(m) cm^{-1}; n.m.r. τ6.2(m), 6.67(s), 7.15(m), 7.48(s), 7.6(m) and 8.2(m).

The reduced extract (980 mg) was chromatographed on neutral alumina (50 g). Elution with 0.5% methanol-CH_2Cl_2 gave an olefinic fraction (340 mg): i.r. 3040(m) and 692(s) cm^{-1}; n.m.r. τ 3.70(m). Examination of this fraction by g.c.-m.s.(20% SE30, 170°) showed it to be a complex mixture of II-39 (vide infra, 1.8min), amine II-17 (2.2min), amide II-15 (2.4min.) and a trace of tricyclic amino alcohol II-37 (vide infra, 5.4min.).

Elution with 1% methanol-CH_2Cl_2 gave bicyclic amino alcohol II-38 (254 mg, 13%) which was distilled at 30°/0.05mm; i.r. 3350(s,br) and 1040(s) cm^{-1}; n.m.r. (Figure 2.4) τ6.58(m, CH_2OH), 7.0-7.75(complex 4 proton pattern), 7.62 (s, N-CH_3, superimposed on part of complex pattern), 7.8-8.2 (unresolved, 2H) and 8.4(m,6H); m.s. m/e 169 (M^+,33), 168(38), 152(10), 138(45) and 57(100). Irradiation at τ8.4 resulted in collapse of the pattern at τ6.58 to a broadened singlet ($W_{1/2}$=4Hz).

H.r.m.s. on m/e 169 (M^+): Calcd for $C_{10}H_{19}NO$, 169.1467. Found, 169.1446.

Attempts to prepare the p-nitrobenzoate and picrate derivatives of II-38 were unsuccessful.

Elution with 2% methanol-CH_2Cl_2 gave exo-amino alcohol II-37 (269 mg, 13%) as an oil which on sublimation at 30°/0.05mm gave white crystals: m.p. 73-74°, i.r. 3350(s,br), 1052(s), 1025(s) and 980 cm^{-1}; n.m.r. τ6.01(m, D_2O exch.), 6.20(d, J=4Hz, H_d), 7.19(d, J=4.5Hz, H_a), 7.26(d, J=10Hz, H_c), 7.47(dd, J=10 and 4.5Hz, H_b), 7.48(s, superimposed on dd. N-CH_3), 8.0(m,2H), 8.20(m, $W_{\frac{1}{2}}$=4.5Hz, 3H), 8.67(m,1H) and 8.85(m,1H); m.s. m/e 168(11), 167(M^+,77), 166(29), 150(16), 110(71), 97(17), 96(21), 95(60), 94(100) and 82(100). Irradiation at τ8.0 resulted in collapse of the doublet at τ6.20 (H_d) to a singlet and coalescence of the doublet at τ7.19 (H_a).

H.r.m.s. on m/e 167 (M^+): Calcd for $C_{10}H_{17}NO$, 167.1310. Found, 167.1302.

Treatment of II-37 with a saturated benzene solution of picric acid gave a picrate (yellow needles, slow decomp. 160-200°) which decomposed on repeated attempts at recrystallization.

An acetone solution (3 ml) of amino alcohol II-37 (65 mg) was treated with CrO_3-H_2SO_4 in acetone (7g) at 0°. The green solution was stirred for 1.5 hours. The acetone was evaporated and the residue was basified with aqueous Na_2CO_3 and extracted with

CH_2Cl_2 (4x15ml) to give a clear oil (25 mg). The n.m.r. and i.r. spectra of this oil were identical with those of ketone II-32, isolated previously.

4.10.3 In Bromotrichloromethane

A mixture of nitrosamine II-23 (0.5g, 0.0028 mole), concentrated HCl (0.3 ml) and $CBrCl_3$ (100 ml) was photolysed in Apparatus II under N_2 for 2.75 hours. The mixture was distilled under vacuum at 20° and the blue distillate was trapped in a cooled receiver (12). The neutral extract (204 mg) was a mixture of at least six components as determined by g.c. and exhibited no N-methyl signal in the n.m.r. The basic fraction (205 mg) had the following physical constants: i.r. 3300(w,br), 3040(m), 1720(w), 1660(w), 1162, 950 and 700(m) cm^{-1}; n.m.r. τ3.75(m), 5.60(m), 5.80(m, D_2O exch.) and 7.0-9.0 (unresolved). Analysis of this fraction by g.c.-m.s. (20% SE30, 150°) showed three peaks in the ratio of 1.2:4.1:1.0, which gave the following data: peak 1 had a retention time of 3.2 minutes and exhibited m.s. fragments at m/e 149(24) and 70(100); peak 2 had a retention time of 3.5 minutes and exhibited m.s. fragments at m/e 151(48) and 44(100); and peak 3 had a retention time of 9.3 minutes and exhibited m.s. fragments at m/e 231(7), 229(7), 150(46), 94(100) and 82(40). The major component (peak 2) was identified as amine II-17 by comparison of the mass spectrum with that of an authentic sample; peak 1 was assumed to be imine II-39. An attempt to isolate the third component by silicic acid chromatography was unsuccessful.

4.11 Photolysis of N-Nitroso-4-azatricyclo[5,2,1,$0^{2,6}$]dec-8-ene, II-24

4.11.1 Under Oxygen

A solution of nitrosamine II-24 (2g, 0.012 mole) and concentrated HCl (1.1 ml, 0.066N) in methanol (200 ml) was photolysed in Apparatus I under oxygen for 2.75 hours. The work-up gave the neutral extract (15 mg) while the basic fraction was extracted into ether (4x50 ml) which was immediately dried and stirred overnight with LAH (2g). The usual work-up gave the reduced extract as a clear oil (1.0g) which showed one major spot at R_f0.12 on t.l.c. (silica gel, 10% methanol-CH_2Cl_2); the n.m.r. spectrum was essentially that of II-41 with weak signals of unidentified product. Preparative scale t.l.c. of this oil (100 mg) gave a semisolid (36 mg, 20%) which was recrystallized several times from ether to give tetracyclic amino alcohol II-41: m.p. 150-153°; i.r. 3200(s,br), 1270(m), 1140, 1092(m), 1040(s), 1005(s), 960, 940, 902, 815 and 778(m); n.m.r. τ4.92(s, D_2O exch.), 5.70(m, $W_{\frac{1}{2}}$=4Hz, H_e), 6.41(m, H_a), 6.75(dd, J=12 and 2 Hz, H_d), 6.98(m,1H), 7.2-7.85 (unresolved,7H), 8.35(AB quartet, $\Delta\nu$ =38, J=10.5Hz, H_b and H_c) and 8.40(m,1H); m.s. m/e 151(M^+,45), 134(33), 122(55), 85(55), 80(50), 79(50), 68(44) and 57(100).

The picrate of II-41 was prepared in the normal manner and recrystallized three times from ethanol-petroleum ether (30-60°): m.p. 245-255° (decomp).

Anal. Calcd for $C_{15}H_{16}N_4O_8$: C, 47.37; H, 4.24; N, 14.73. Found: C, 47.70; H, 4.47; N, 14.53.

Amino alcohol II-41 (30 mg) in acetone (3 ml) was treated with CrO_3-H_2SO_4 (79) at 0°. The green solution was stirred for 10 minutes at which time the acetone was evaporated and the residue was basified with aqueous Na_2CO_3. Extraction with CH_2Cl_2 gave crystalline ketone II-42 (18 mg, 62%): m.p. 115-117°; i.r. 1750(s), 1490(w), 1282, 1162, 990, 958(m), 820, 770 and 732(m) cm^{-1}; n.m.r. τ 6.8-7.5 (unresolved,8H) and 8.45 (AB quartet, $\Delta\nu$=24, J=11.5Hz, 2H); m.s. m/e 149(M^+,11), 121(100), 120(60), 100(54), 93(60), 80(48), 79(54) and 77(55).

4.11.2 In Bromotrichloromethane

A solution of nitrosamine II-24 (1g, 0.006 mole) and concentrated HCl (0.52 ml) in methanol-$CBrCl_3$ (1:4, 120 ml) was photolysed in Apparatus II under nitrogen for 1.5 hours. The blue solvent mixture was distilled under vacuum and the usual work-up gave a neutral extract (260 mg) and a basic extract (750 mg). The neutral extract exhibited signals in the n.m.r. spectrum at τ -.14 (m, D_2O exch.), 6.20(q, J=7Hz) and 8.73 (t, J=7Hz). The basic extract was shown by g.c. (20% SE30, 150°) to contain a mixture of minor products and one major component (ca. 80%) having a retention time of 6.3 minutes. The basic fraction (500 mg) was chromatographed on silica gel where elution with ethyl acetate gave bromoamine II-43 (335mg): i.r. 1505(w), 1300, 1280, 1260, 1228(m), 1180, 1130, 1055, 1008, 928(m), 880(s), 802, 770, 745(s), 730 and 678(m) cm^{-1}; n.m.r. τ 5.30(m, $W_{\frac{1}{2}}$=3.5Hz, H_e), 6.60(m, $W_{1/2}$=9Hz, H_a), 6.79(dd,

J=12.5 and 2.5Hz, H_d), 7.3-7.8 (unresolved, 5H), 7.90(m,1H) and 8.40(d, J=10.5Hz, H_c); m.s. m/e 215(1.5), 213(M^+ with Br^{79}, 1.5) and 134(100). The n.m.r. spectrum of II-43 (35 mg) was examined in the presence of $Eu(DPM)_3$ shift reagent (5 mg). A diffuse spectrum was observed except in the high field region where an AB quartet ($\Delta\nu$=35, J=10.5Hz) at τ 7.84 was clearly evident. Irradiation of a multiplet at τ 4.6 (H_e, originally at τ 5.30) in this europium shifted sample resulted in sharpening of the high field portion of the AB quartet (H_c, originally at τ 8.12).

The picrate of II-43 was prepared in the normal manner and was recrystallized four times from ethanol to give yellow needles: m.p. 225-235°, slow decomposition.

Anal. Calcd for $C_{15}H_{15}N_4O_7Br$: C, 40.65; H, 3.41; N, 12.64. Found: C, 40.85; H, 3.31; N, 12.84.

4.12 Thermolysis of N-Chloramines

4.12.1 N-Chloro-2-endo-methylaminomethylbicylco[2,2,2]oct-5-ene, II-25, in Water

A solution of chloramine II-25 (2g, 0.011 mole) in aqueous dioxane (60%, 250 ml) was refluxed in the dark for 1.25 hours. The solvent was evaporated and the acidic residue was worked-up in the usual manner (Section

4.3.4) to give 1.14 g of basic extract. The basic fraction (1.0g) was chromatographed on silica gel (40g) to give, with ethyl acetate, a fraction (146 mg, 6%) containing one major product (g.c. retention time, 2.7 min.) and a trace of II-17 (1.1 min.) as determined by g.c. peak matching (3% SE30, 155°). This fraction (95 mg) was rechromatographed on silica gel (5g) to give a clear oil assumed to be chloroamine II-45 (45 mg) which was still contaminated by a trace of amine II-17: i.r. 3040(v.w), 1670(w), 1110(m), 852, 730 and 695 cm^{-1}; n.m.r. τ3.75(m), 5.97(d, J=6.5Hz, H_d), 6.35(m), 7.22(d, J=8Hz, H_b), 7.45(s, N-CH_3), 7.60(dd, J=8 and 3Hz, H_c), 8.0(m,2H) and 8.39(m,9H); g.c.-m.s. (3% silar 10-C column, 150°); m.s. m/e 187(10), 186(5), 185(M^+Cl^{35}, 31), 184(5), 150(66), 95(26), 94(100) and 82(49). The picrate of II-45 (m.p. 230-233°) decomposed on all attempts at recrystallization.

Elution with 1-10% methanol in ethyl acetate gave the parent amine II-17 (164 mg, 9%); elution with 50% methanol in ethyl acetate gave tricyclic amino alcohol II-37 (260 mg, 12%). Oxidation (79) of this alcohol (50 mg) gave ketone II-32 (35 mg, 70%) which showed identical i.r., n.m.r., and mass spectra with those of previous samples.

4.12.2 N-Chloro-2-endo-methylaminomethylbicyclo[2,2,2]oct-5-ene, II-25, in Methanol

A solution of chloramine II-25 (1.68g, 0.009 mole) in methanol (150 ml) was refluxed for 10.75 hours. The methanol was evaporated and the residue was portioned into neutral (76 mg) and basic fractions (1.07g).

The basic fraction was shown by g.c.-m.s. (20% SE30, 155°) to contain several minor and one major component: peak 1 (2.5%, 5.8min.) had m.s. fragments at m/e 149(25) and 70(100) as observed for previously characterized samples of II-39; peak 2 (6.5%, 6.9min.) had the same m.s. fragmentation pattern as that of authentic amine II-17; peak 3 (5.5%, 10.0min.) had m.s. fragments at m/e 146(57), 145(43) and 44(100); and peak 4 (59%, 11.1min.) had m.s. fragments at m/e 181(28), 167(19), 166(100), 96(20), 95(20), 94(29) and 82(35). The major component of this basic fraction (peak 4) was isolated by preparatve scale g.c. (20% SE30, 135°) to afford methoxy amine II-46: i.r. 2765(m), 1225, 1095(s), 1020, 965 and 830 cm^{-1}; n.m.r. (Figure 2.7) τ6.65 (s, OCH_3), 6.71(d, J=4.5Hz, H_d), 7.32(dd, J=9 and 4.5Hz, H_b), 7.49(s, $N-CH_3$), 7.65(high field portion of H_c doublet) and 7.8-9.0 (unresolved, 11H). When the n.m.r. spectrum was recorded in the presence of $Eu(FOD)_3$ shift reagent a signal at τ5.38, attributed to H_a originally at approximately τ7.5, began to emerge from beneath the N-methyl signal. A doublet originally at τ7.58 (J=9Hz, H_c) was clearly resolved in the presence of shift reagent.

Methoxy amine II-46 was purified as its picrate which was recrystallized three times from ethanol as yellow needles: m.p. 171-171.5°.

Anal. Calcd for $C_{17}H_{22}N_4O_8$: C, 49.76; H, 5.40; N, 13.65. Found: C, 49.77; H, 5.38; N, 13.80.

4.12.3 N-Chloro-4-azatricyclo[5,2,1,$0^{2,6}$]dec-8-ene, II-26, in Methanol

A solution of tricyclic chloramine II-26 (1.0g) in methanol

150ml) was refluxed for 65 hours. The solvent was evaporated and work-up of the residue gave the neutral (26 mg) and basic (820 mg) fractions. The basic fraction (100 mg) was chromatographed on preparative scale t.l.c. (silica gel, ethyl acetate) and three components were individually isolated. The slowest fraction (15 mg, R_f0.03) had the identical m.s. fragmentation pattern and g.c. retention time as the amine II-21 (as salt, section 4.5.6). The second fraction (R_f0.08) afforded an oil (21.5mg) whose n.m.r. spectrum was reminiscent of that of bromo amine II-43. Further spectral analysis indicated that this oil was predominantly the chloro amine II-48: i.r. 1312(m), 1300, 1230(m), 1010, 928(m), 885(s), 872, 840, 810(m), 785(s) and 768 cm^{-1}; n.m.r. τ5.47 (m, $W_{\frac{1}{2}}$=3.5Hz, H_e), 6.80(d, J=2Hz, H_a), 6.81(dd, J=12 and 2.5Hz, H_d), 7.3-7.8 (unresolved,5H), 8.0(m,2H), and 8.52(d, J=10.5Hz, H_c); m.s. m/e 171(1) 169(M^+Cl^{35},3) and 134(100). Chloro amine II-48 was purified as its picrate which was recrystallized twice from ethanol to give yellow needles: m.p. 180°, slow decomposition.

Anal. Calcd for $C_{15}H_{15}N_4O_7Cl$: C, 45.18; H, 3.79; N, 14.05. Found: C, 44.90; H, 3.63; N, 14.14.

The last fraction (R_f0.21) was isolated as an unidentified solid (16 mg): m.p. 77-78°; i.r. 3060(w), 1300, 1220, 1182, 980, 800, 780 and 742(s) cm^{-1}; n.m.r. τ 3.98(m, $W_{\frac{1}{2}}$=4.5Hz, 2H), 6.0-6.85 (unresolved,4H), 7.06(m,4H) and 8.55(AB quartet, $\Delta\nu$=13, J=8Hz, 2H); m.s. m/e 149(4), 133(9), 132(11), 68(86), 67(44) and 66(100).

4.13 Photolysis of N-Nitrosamines in the Presence of 1,6-Heptadiene

4.13.1 N-Nitrosopiperidine

A solution of N-nitrosopiperidine (2.3g, 0.02 mole), 1,6-heptadiene (1.92g, 0.02 mole) and concentrated HCl (1.8 ml, 0.11N) in methanol (200 ml) was photolysed in Apparatus I under nitrogen for 3.5 hours. The solvent was evaporated and the distillate was trapped in a cooled receiver. When treated with Br_2 in CCl_4 the distillate gave a clear solution indicating the presence of olefinic material. The residue of the photolysate was portioned into neutral (30 mg) and basic (1.62g) fractions and the basic fraction (750 mg) was chromatographed on silica gel (50g). Elution with 3-5% methanol-CH_2Cl_2 gave an olefinic fraction (246 mg) which was distilled at 60°/0.1mm to give a 1:4 mixture (76) of syn- and anti-oxime isomers II-52: i.r. 3200(m,br), 3080(m), 1640(m), 1115, 910(m), 860 and 785 cm^{-1}; n.m.r. τ 2.10(m, D_2O exch.), 4.3(m,1H), 5.0(m,2H), 6.75(s, 0.2H, syn-isomer), 7.05(s, 0.8H, anti-isomer), 7.6(m,5H), 7.95(t, J=6.5Hz, 2H) and 9.50(m,7H); m.s. m/e 210(M^+,3), 193(35), 98(100) and 84(37).

Elution with 40-80% methanol-CH_2Cl_2 gave a 1:1.2 mixture (73) of syn-and anti-aldoximes II-53 (160 mg, 24%): m.p. 55-60°; i.r. 3300(m), 3070(m,br), 1650(w), 1600(m), 1100(m), 950 and 780 cm^{-1}; n.m.r. τ 0.38(m, D_2O exch.), 2.58(d, J=7.5Hz, H_a, syn, 0.4H), 3.22(d, J=7.5Hz, H_a, anti, 0.5H), 6.60(m, H_b, anti), 7.20(m, H_b, syn), 7.60(m,5H) and 8.40(m,10H); m.s. m/e 210(M^+,3), 193(12), 98(100) and 84(21). The n.m.r. spectra of the chromatography fractions containing

cyclization products revealed no other aldoxime protons than those described. Irradiation of the signal τ6.60 (H_b,anti) resulted in coalescence of the doublet at τ 3.22 (H_a,anti). Similarly, irradiation at τ7.20(H_b,syn) resulted in coalescence of the doublet at τ2.58(H_a,syn). Irradiation at τ3.22 slightly altered the multiplet at τ6.60, however, irradiation at τ2.58 caused no apparent change in the n.m.r. spectrum.

Treatment of a 1:1 mixture of syn- and anti-aldoximes II-53 (90 mg) with sodium bisulfite in the described manner (section 4.9.1) gave an oil (80 mg, 86%) which showed one major spot (R_f0.47) on t.l.c. (silica gel, 10% methanol-CH_2Cl_2). Distillation at 22°/0.2mm gave aldehyde II-56 as clear oil: i.r. 1720(s), 1155, 1125(m), 1040, 860, 782 and 755 cm^{-1}; n.m.r. τ 0.35(d, J=2Hz, 1H), 7.60(m,8H) and 8.40(m,12H). A weak absorption in the i.r. at 2200cm^{-1} showed that the distilled oil contained a trace of nitrile impurity.

4.13.2 N-Nitrosodimethylamine

A solution of N-nitrosodimethylamine (3.1g, 0.04 mole), 1,6-heptadiene (3.8g, 0.04 mole), and concentrated HCl (3.6 ml, 0.22N) in methanol was photolysed in Apparatus I under nitrogen for 5.85 hours. The solvent was evaporated and the residue was diluted with water (50 ml). Extraction with ether (3x50ml) gave a neutral fraction (100 mg) containing unreacted N-nitrosodimethylamine: i.r. 1040(s) cm^{-1}. The aqueous mother liquor was neutralized to pH7 and extracted with CH_2Cl_2 (3x50ml) to yield N-nitrosodimethylamine as shown by an i.r. band at 1040(s) cm^{-1} and n.m.r. signals at τ6.20(s) and 6.95(s) as a 1:1 mixture (0.84 g) with II-54 (vide infra).

The aqueous mother liquor was basified to pH10 with aqueous Na_2CO_3 and reextracted with CH_2Cl_2 (3x50ml) to give a basic extract (1.24g). This fraction (850 mg) was chromatographed on silicic acid (50g). Elution with 5% methanol-CH_2Cl_2 gave a 1:1 mixture of syn- and anti-oximes II-54 (138 mg): i.r. 3200(s,br), 3080(m), 1640(m), 1000(s), 910 and 850(s) cm^{-1}; n.m.r. τ1.80(m, D_2O exch.), 4.4(m,1H), 4.8-5.2(m,2H), 6.70(s,1H, syn-isomer), 7.70(m,1H, anti-isomer, singlet obscurred by impurity), 7.70(s,NCH_3) and 7.5-8.5 (unresolved, 7H).

Elution with 50% methanol-CH_2Cl_2 gave several fractions of solid which showed a major pair of aldoxime protons at τ 2.65 and 3.25 (ratio 1:2) and a minor pair at τ 3.04 (d, J=6Hz) and 3.86 (d, J=7Hz); reprecipitation of the combined solid (200mg) did not eliminate the minor pair of aldoxime signals. Precipitation from ether at -30° gave a mixture of syn- and anti-aldoximes II-55: i.r. 3160(m), 3050(m), 1640(w), 1250, 1170, 1020, 930(s) and 835(s) cm^{-1}; n.m.r. τ0.10(m, D_2O exch.), 2.65(d, J=6.5Hz, 0.6H, H_a, syn), 3.25(d, J=6.5Hz, 0.3H, H_a, anti), 6.65(m,H_b,anti), 7.05(t, J=7Hz, H_b, syn), 7.75(s, N-CH_3, slightly broadened by superposition of two signals) and 8.30(m, 10H); m.s. m/e 170(M^+,12), 153(11) and 58(100).

Aldoxime II-55 (81 mg, syn to anti ratio 1:2) was dissolved in acetic anhydride (2 ml) and the solution was refluxed for 20 min. then cooled over ice. Water (10 ml) was added and the mixture was basified (pH9) with solid Na_2CO_3. The heterogeneous mixture was extracted with CH_2Cl_2(3x25ml) which was dried ($MgSO_4$) and evaporated to an oil (42.5 mg): i.r. 2220(m) cm^{-1}. This oil was distilled to give

impure nitrile II-57: 25°/2mm; i.r. 2220(m) and 1710 cm^{-1}; n.m.r. τ6.90(m), 7.19(s), 7.55(m), 7.70(s, N-CH_3), 7.72(s, N-CH_3) and 7.8-8.8 (unresolved). The ratio of the two N-CH_3 signals was ca. 1:1.

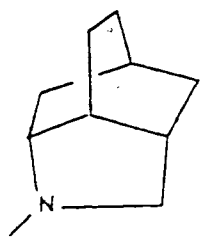
CHAPTER 5

THE CRYSTAL AND MOLECULAR STRUCTURES OF THE HYDROCHLORIDE OF OXIME II-30 AND II-46

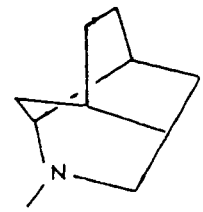
5.1 Introduction

It was determined by spectral analysis of reaction products that the aminium radical cyclization of nitrosamine II-23 forms products possessing the 2-azaisotwistane skeleton V-1 and not the alternate 2-azatwistane skeleton V-2. To confirm this assignment the crystal and molecular structures of the hydrochloride of oxime II-30 were determined. This amino oxime carried two functional groups capable of hydrogen bonding (39), hence, it also became of interest to examine the role of each of these two functions in the formation of the hydrochloride.

Differences in the n.m.r. spectra (Table 2.3) of methoxy amine II-46, formed during the thermolysis of chloramine II-25 in methanol, and amino alcohol II-37 led us initially to assign the 2-azatwistane structure, III-14, to this methoxy compound (111). It became necessary to reevaluate this assignment following a report by Waegell (77) that the thermolysis of II-25 in methanol in the presence of Ag_2O gave methoxy amine II-46. Comparison of spectral data demonstrated that the methoxy compounds were identical. To resolve this discrepancy the crystal and molecular structures of the picrate of the methoxy compound were determined.



V-1



V-2

5.2 Results and Discussion

The final atomic coordinate and temperature factors for the hydrochloride of oxime II-30 are listed in Table 5.1 and the observed and calculated structure factors are given in Table 5.2. Selected interatomic distances and angles and their estimated standard deviations are listed in Table 5.3. The molecular configuration and the labelling of the cation are shown in Figure 5.1. These results confirm that N-nitrosamine II-23, when photolysed in dilute acidic media, cyclizes to give tricyclic products possessing the isotwistane ring structure V-1.

The hydrogen bonding contacts are listed in Table 5.4. The N-H---Cl and Cl---H-O interatomic distances presented are both less than the sum of the van der Waals radii and are nearly linear (112). These non-binding contacts exhibited by the molecular structure indicate that the chloride ion is hydrogen bonded to the amine nitrogen of one cation and the oxime oxygen of an adjacent cation.

Table 5.1

Final Atomic Coordinates and Thermal ($Å^2$) Parameters[1] for Oxime II-30·HCl

(a) Atomic coordinates ($x10^4$) for non-hydrogen atoms

Atom	x	y	z
Cl	1066(2)	3961(2)	2346(1)
C_1	2583(7)	1217(7)	1337(5)
N_2	1549(6)	1582(5)	1876(4)
C_3	493(8)	1439(8)	1286(6)
C_4	1017(8)	1230(7)	368(9)
C_5	1463(9)	2242(7)	-108(6)
C_6	2768(9)	2292(8)	-98(6)
C_7	3273(10)	1357(7)	590(6)
C_8	2847(11)	323(8)	-168(5)
C_9	2037(8)	520(7)	613(5)
C_{10}	3073(8)	2144(8)	868(7)
C_{11}	1445(9)	987(8)	2764(5)
N_{12}	3849(8)	2928(7)	1180(4)
O_{13}	3952(4)	2626(4)	2013(5)

(b) Anisotropic thermal parameters ($x10^3$) for non-hydrogen atoms[2]

Atom	U11	U22	U33	U12	U13	U23
Cl	78(2)	50(1)	76(1)	-9(2)	20(1)	7(1)
C_1	65(6)	39(6)	61(5)	14(6)	-13(5)	2(5)
N_2	75(5)	49(4)	52(4)	6(4)	2(4)	5(4)
C_3	68(6)	76(8)	64(6)	-21(5)	-19(6)	16(6)
C_4	71(6)	65(6)	44(5)	-15(6)	-9(5)	-4(4)
C_5	82(8)	70(8)	51(6)	-20(6)	-9(6)	6(5)
C_6	95(9)	66(8)	54(7)	-3(7)	-7(6)	19(5)
C_7	135(9)	50(7)	72(6)	-8(7)	17(7)	1(6)
C_8	127(12)	62(9)	107(9)	-8(7)	16(8)	-21(7)
C_9	92(7)	36(6)	53(5)	-15(6)	19(6)	-5(5)
C_{10}	69(7)	41(6)	115(9)	-7(5)	5(6)	-34(6)
C_{11}	109(8)	73(6)	59(6)	1(9)	-3(6)	2(5)
N_{12}	148(8)	148(8)	30(4)	103(8)	17(5)	28(5)
O_{13}	66(4)	79(4)	138(5)	-7(4)	-6(4)	16(4)

(c) Atomic coordinates and isotropic thermal parameters for hydrogen atoms ($x10^3$)

Atom	x	y	z	U
H_1	313(6)	86(6)	117(4)	70
H_2	21(6)	231(6)	127(4)	70
H_3	5(6)	90(6)	151(5)	70
H_4	44(5)	70(5)	2(4)	70
H_5	109(6)	275(6)	29(4)	70
H_6	128(6)	208(6)	75(5)	70
H_7	301(6)	289(6)	33(4)	70
H_8	310(6)	151(6)	-120(5)	70
H_9	432(6)	153(6)	52(4)	70
H_{10}	242(6)	-14(7)	-57(4)	70
H_{11}	345(6)	-5(6)	5(5)	70
H_{12}	168(5)	-12(6)	88(4)	70
H_{13}	61(6)	135(6)	311(4)	70
H_{14}	144(6)	14(5)	263(4)	70
H_{15}	216(6)	108(7)	298(5)	70
H_{16}	461	303	221	70
H_{17}	156(5)	245(5)	197(4)	70

1. The estimated standard deviations in the last significant are given in parenthesis in this and in subsequent tables.
2. Expression of the form: $\exp[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)]$.

Table 5.2

Observed and Calculated Structure Factors for Oxime II-30 HCl

L	FO	FC
H=	0, K=	0
2	2*	8
4	141	142
6	21	-24
8	55	56
10	1*	2
12	15	-16
14	8*	2
H=	0, K=	2
0	127	-125
1	15	-20
2	24	-23
3	51	-89
4	46	43
5	109	104
6	53	-50
7	65	-61
8	11	-11
9	26	25
10	47	-40
11	21	-17
12	8	6
13	15	15
14	7*	1
H=	0, K=	4
0	63	-57
1	17	17
2	140	137
3	57	-56
4	1*	[illegible]
5	1*	-5
6	57	56
7	13	-13
8	9	-7
9	1*	-3
10	55	55
11	6	[illegible]
12	10	22
13	9	14
H=	0, K=	6
0	75	-90
1	5*	4
2	43	46
3	26	27
4	79	-77
5	62	-61
6	34	33
7	30	32
8	27	-30
9	25	26
10	6*	5
11	49	49
12	12	-13
H=	0, K=	8
0	81	76
1	58	-58
2	23	-19
3	49	43
4	28	27
5	19	-19
6	1*	3
7	12	10
8	16	15
9	12	-14
10	5*	-2
H=	0, K=	10
0	16	13
1	13	11
2	[illegible]	-40
3	13	-20
4	27	25
5	15	16
6	34	-32
7	12	[illegible]
8	22	[illegible]
H=	0, K=	12
0	25	-22
1	25	23
H=	1, K=	0
2	177	-162
4	62	62
6	26	24
8	41	40
10	5*	-7
12	11	10
14	14	17
H=	1, K=	1
1	34	37
2	[illegible]	-5
3	1*	5
4	[illegible]	[illegible]
5	[illegible]	[illegible]
6	37	-23
7	14	47
8	[illegible]	-21
9	29	-27
10	6*	-6
11	12	13
12	8	15
13	20	-24
14	6*	-3
H=	1, K=	2
1	147	-155
2	51	54
3	36	-37
4	48	-48
5	27	28
6	10	-10
7	35	-34
8	27	-25
9	47	47
10	8	2
11	17	-16
12	12	11
13	17	19
14	3*	-6
H=	1, K=	3
1	48	-45
2	67	-66
3	28	27
4	1*	2
5	7*	-4
6	38	-39
7	40	-39
8	19	18
9	9	-6
10	27	-26
11	5*	-4
12	6	7
13	10	19
H=	1, K=	4
1	5*	6
2	4*	1
3	20	-21
4	24	-23
5	28	26
6	5*	0
7	14	-13
8	33	31
9	14	15
10	30	33
11	11	9
12	8	4
13	6*	11
H=	1, K=	5
1	10	11
2	54	54
3	51	-50
4	16	-16
5	30	32
6	25	21
7	35	-33
8	5*	-3
9	38	37
10	9	8
11	20	-19
12	3*	5
13	15	13
H=	1, K=	6
1	19	-19
2	14	14
3	44	-44
4	16	18
5	34	-35
6	12	11
7	14	20
8	10	-9
9	18	-19
10	3*	2
11	9	-10
12	14	-14
H=	1, K=	7
1	1*	-6
2	1*	2
3	12	-12
4	9*	9
5	1*	-3
6	3*	3
7	5*	2
8	1*	-9
9	5*	-2
10	16	20
11	1*	-3
H=	1, K=	8
1	5*	-7
2	5*	-6
3	29	29
4	20	22
5	22	-22
6	0	4
7	24	25
8	1*	-2
9	10	-4
10	19	-19
H=	1, K=	9

L	FO	FC
1	7*	-2
2	15	-15
3	19	18
4	15	-14
5	12	-11
6	4*	6
7	19	19
8	4*	-7
9	7*	-9
H=	1, K=	10
1	31	-33
2	6*	1
3	25	-24
4	1*	-6
5	1*	4
6	10	8
7	20	-19
H=	1, K=	11
1	7*	-6
2	5*	4
3	8*	6
4	8*	7
5	12	-10
H=	2, K=	0
0	144	-153
2	132	-133
4	27	-27
6	15	-14
8	14	14
10	12	-11
12	12	-14
14	10	-10
H=	2, K=	1
0	61	-63
1	12	-14
2	95	97
3	103	-98
4	122	-112
5	13	12
6	6*	-6
7	57	-56
8	16	-15
9	16	14
10	16	14
11	17	-15
12	9	-13
13	12	14
14	8*	1

L	FO	FC
H=	2, K=	2
0	11	-11
1	59	60
2	7	12
3	35	-34
4	15	13
5	3*	1
6	7	9
7	17	-16
8	15	17
9	9	-10
10	13	15
11	6*	-4
12	12	11
13	1*	-6
H=	2, K=	3
0	201	-206
1	40	41
2	135	140
3	74	74
4	62	-67
5	77	-79
6	75	79
7	34	34
8	27	-23
9	12	-9
10	11	14
11	10	10
12	11	9
13	12	-10
H=	2, K=	4
0	51	-51
1	8*	10
2	59	-59
3	7*	1
4	43	-45
5	17	16
6	5*	-7
7	6*	-1
8	10	-10
9	11	10
10	8	-9
11	8	-9
12	2	-9
13	6*	-7
H=	2, K=	6
0	55	59
1	67	-73
2	53	-56
3	75	80

L	FO	FC
4	7*	-1
5	6*	-9
6	17	19
7	46	48
8	3*	-7
9	13	-16
10	19	19
11	7*	6
12	10	-8
H=	2, K=	6
0	5*	1
1	6*	0
2	24	23
3	32	33
4	15	-12
5	20	17
6	7*	4
7	1*	-3
8	10	10
9	21	-20
10	6*	0
11	14	-13
12	1*	-2
H=	2, K=	7
0	50	53
1	15	-17
2	30	-33
3	17	-17
4	53	54
5	11	-14
6	35	-33
7	14	-15
8	41	43
9	4*	-1
10	13	-16
11	7*	3
H=	2, K=	8
0	7*	-3
1	20	-20
2	4*	-4
3	1*	0
4	10*	6
5	6*	-7
6	9*	-10
7	12	14
8	13	-14
9	7*	-6
10	4*	-2
H=	2, K=	9

L	FO	FC
0	15	17
1	34	34
2	17	-16
3	21	-20
4	27	27
5	23	23
6	13	-16
7	14	-11
8	8*	3
9	8*	6
H=	2, K=	10
0	11	11
1	4*	4
2	3*	2
3	4*	1
4	18	15
5	8*	-10
6	7*	-5
7	8*	-9
H=	2, K=	11
0	16	-14
1	23	22
2	23	21
3	9*	-7
4	29	-26
5	15	17
H=	3, K=	0
2	74	-69
4	61	-60
6	17	16
8	54	-54
10	12	-5
H=	3, K=	1
1	23	23
2	32	-32
3	7	-6
4	6	-5
5	13	14
6	52	52
7	6*	3
8	17	17
9	29	29
10	18	-17
11	15	-14
12	2*	-4
13	13	14
H=	3, K=	2

L	FO	FC
H=	3, K=	2
1	23	22
2	43	46
3	58	-55
4	27	-29
5	16	16
6	3*	0
7	29	-29
8	7*	-4
9	41	41
10	5*	4
11	20	-23
12	7	5
13	23	24
H=	3, K=	3
1	13	-12
2	52	51
3	1*	3
4	46	46
5	56	55
6	21	20
7	19	21
8	1*	-2
9	5*	2
10	4*	0
11	19	23
12	1*	1
13	13	-12
H=	3, K=	4
1	2	4
2	1*	-2
3	6*	4
4	19	19
5	19	20
6	23	23
7	17	-18
8	11	-14
9	1*	-2
10	9	11
11	13	-13
12	12	-15
13	5	12
H=	3, K=	5
1	44	-11
2	39	-39
3	31	31
4	14	14
5	24	-23
6	22	-22
7	15	14
8	11	11
9	17	-16
10	8*	6
11	14	12
12	7*	-9
H=	3, K=	6
1	44	45
2	6*	-7
3	32	32
4	24	-25
5	9	-9
6	25	28
7	6*	9
8	19	-17
9	8*	-11
10	11	8
11	7*	12
H=	3, K=	7
1	14	19
2	15	16
3	13	15
4	11	-9
5	6*	-8
6	9	10
7	11	8
8	1*	-1
9	1*	3
10	3*	-5
11	13	-13
H=	3, K=	8
1	9*	-11
2	12	-8
3	23	29
4	1*	2
5	13	-13
6	31	-31
7	14	13
8	11	10
9	25	-24
10	6*	-9
H=	3, K=	9
1	10	10
2	7*	10
3	11	-11
4	10	7
5	8*	6
6	7*	6
7	14	10
8	10	-9
H=	3, K=	10
1	13	12
2	8*	1
3	12	-9
4	1*	-2
5	5*	7
6	7*	-13
7	1*	-1
H=	3, K=	11
1	1*	-3
2	12	-9
3	1*	-3
4	5*	0
H=	4, K=	0
0	156	-160
2	115	121
4	98	-101
6	50	48
8	12	-8
10	1*	-1
12	5*	4
H=	4, K=	1
0	51	-53
1	40	41
2	52	-51
3	28	-28
4	10	12
5	55	53
6	28	26
7	6*	6
8	21	-23
9	3*	-8
10	11	11
11	10	-12
12	1*	0
13	1*	-2
H=	4, K=	2
0	63	60
1	69	-75
2	17	17
3	16	10
4	10	-12
5	10	-12
6	21	21
7	60	60
8	15	-15
9	34	-32
10	16	17
11	16	18
12	9	-10
13	1*	6
H=	4, K=	3
0	39	-43
1	5*	10
2	36	38
3	54	52
4	27	-25
5	4*	-4
6	8	-7
7	14	-14
8	16	-14
9	18	18
10	1*	3
11	7*	7
12	13	7
H=	4, K=	4
0	43	43
1	15	-14
2	20	-20
3	34	34
4	31	30
5	14	-16
6	34	-35
7	1*	1
8	1*	-1
9	6*	5
10	16	-19
11	15	17
12	11	9
H=	4, K=	5
0	20	22
1	37	-42
2	7*	3
3	14	15
4	6*	-11
5	29	-27
6	18	-15
7	22	22
8	4*	-8
9	1*	1
10	16	-17
11	6*	4
12	14	-11
H=	4, K=	6
0	47	45

L	FO	FC
1	16	14
2	41	-41
3	32	-32
4	36	37
5	9*	2
6	26	-27
7	21	-20
8	23	23
9	17	20
10	13	-10
11	14	-13
H=	4, K=	7
0	31	34
1	1*	3
2	2*	-6
3	1*	4
4	6*	5
5	8*	7
6	14	-14
7	4*	5
8	1*	-3
9	19	-20
10	9	-9
H=	4, K=	8
0	30	-29
1	43	43
2	13	14
3	22	-24
4	33	-34
5	13	14
6	15	14
7	14	-13
8	6*	9
9	11	8
H=	4, K=	9
0	6*	-9
1	1*	1
2	23	-23
3	24	-24
4	9*	6
5	1*	-3
6	7*	-5
7	13	-13
8	4*	-4
H=	4, K=	10
0	24	-27
1	20	-22
2	15	13
3	8*	6
4	23	-22
5	3*	2
6	26	23
H=	4, K=	11
0	22	-22
1	14	12
2	1*	3
H=	5, K=	0
2	16	-17
4	16	-15
6	25	25
8	2*	-3
10	18	-21
12	22	22
H=	5, K=	1
1	21	-23
2	17	-20
3	27	-27
4	18	17
5	12	12
6	6*	8
7	37	-35
8	11	-11
9	6*	8
10	6*	8
11	17	-15
12	4*	-11
H=	5, K=	2
1	5*	-9
2	12	-12
3	14	15
4	19	20
5	25	23
6	7*	9
7	27	-27
8	14	14
9	23	-22
10	1*	3
11	20	20
12	5*	-1
H=	5, K=	3
1	21	49
2	22	21
3	1	3
4	51	-52
5	24	-24
6	27	27
7	5*	-2
8	19	-18
9	9	-8
10	36	35
11	4*	0
12	6*	-2
H=	5, K=	4
1	16	-16
2	42	39
3	5*	1
4	11	12
5	21	-19
6	24	-22
7	12	10
8	1*	-3
9	1*	-1
10	19	18
11	5*	-7
H=	5, K=	5
1	21	-20
2	17	-19
3	21	22
4	4*	2
5	15	-14
6	28	-26
7	20	18
8	3*	-3
9	32	-35
10	13	-12
11	9	9
H=	5, K=	6
1	4*	3
2	1*	0
3	9*	-13
4	15	-16
5	6*	-6
6	14	17
7	11	10
8	4*	-4
9	11	12
10	5*	-4
H=	5, K=	7
1	4*	-1
2	10	-10
3	9*	-13
4	10	-8
5	1*	-2
6	21	-16
	4*	1
8	1*	7
9	16	11
H=	5, K=	8
1	1*	-3
2	12	-13
3	19	-17
4	1*	-2
5	10	7
6	8*	6
7	6*	-8
8	5*	-6
H=	5, K=	9
1	20	-23
2	1*	-4
3	1*	-11
4	8*	4
5	15	12
6	9*	-12
7	3*	-4
H=	5, K=	10
1	8*	-7
2	1*	0
3	11*	15
4	10*	12
H=	6, K=	0
0	36	-34
2	30	29
4	15	-14
6	3*	10
8	27	-29
10	9	11
12	15	11
H=	6, K=	1
0	51	49
1	29	-28
2	17	16
3	8	9
4	58	58
5	27	-28
6	8	-8
7	15	16
8	10	11
9	14	-14
10	3*	-2
11	12	14
12	16	17

L	FO	FC
H=	6, K=	2
0	7*	-7
1	45	-44
2	5*	-7
3	62	58
4	2*	-1
5	17	-15
6	8	7
7	11	13
8	5*	-1
9	12	10
10	1*	1
11	2*	0
H=	6, K=	3
0	41	38
1	5*	4
2	75	-73
3	21	-22
4	22	25
5	7*	2
6	26	-25
7	14	-15
8	15	17
9	10	12
10	10	-12
11	9	-7
H=	6, K=	4
0	25	25
1	5*	-2
2	3*	0
3	14	13
4	5*	-1
5	24	-23
6	13	-14
7	5*	5
8	26	29
9	16	-14
10	2*	-9
11	6*	4
H=	6, K=	5
0	16	-13
1	41	[illegible]
2	26	[illegible]
3	1[illegible]	-21
4	[illegible]	[illegible]
5	11	1[illegible]
6	14	15
7	31	-32
8	16	20
9	1*	3

L	FO	FC
10	7*	5
H=	6, K=	6
0	31	29
1	4*	-3
2	27	-28
3	36	-38
4	19	20
5	1*	6
6	1*	-1
7	6*	-5
8	1*	-4
9	4*	-7
H=	6, K=	7
0	32	-34
1	10*	-10
2	10	11
3	3*	-7
4	26	-25
5	12	10
6	20	21
7	17	16
8	14	-15
H=	6, K=	8
0	22	-22
1	19	19
2	4*	8
3	13	-12
4	2*	-4
5	32	31
6	1*	-4
7	15	-15
H=	6, K=	9
0	7*	-4
1	2*	-5
2	15	17
3	32	31
5	10*	-7
H=	6, K=	-10
0	[illegible]	-14
1	4*	4
2	13	14
H=	7, K=	0
[illegible]	13	13
4	15	-13
6	[illegible]	27

L	FO	FC
8	10	-11
10	29	30
H=	7, K=	1
1	5*	3
2	1*	-2
3	1*	-5
4	16	17
5	15	15
6	1*	5
7	7	8
8	1*	2
9	6*	6
H=	7, K=	2
1	15	-15
2	3*	-6
3	23	24
4	6*	4
5	12	-10
6	5*	-7
7	24	24
8	1*	-5
9	13	-18
10	4*	-1
11	4*	8
H=	7, K=	3
1	12	-12
2	6*	8
3	10	8
4	7*	0
5	8	-8
6	13	13
7	8	6
8	14	-14
9	5*	3
10	1*	-1
H=	7, K=	4
1	13	15
2	12	-12
3	11	-13
4	14	-18
5	10	-17
6	17	-14
7	6*	4
8	3*	5
9	4*	1
10	14	-14
H=	7, K=	5

L	FO	FC
1	19	19
2	12	13
3	8*	10
4	1*	0
5	3*	4
6	8*	9
7	1*	4
8	1*	3
9	8*	5
H=	7, K=	6
0	1*	0
1	16	-17
2	13	-13
3	1*	-2
4	22	22
5	11	12
6	2*	-11
7	9*	-12
8	10	10
H=	7, K=	7
1	12	-13
2	1*	-3
3	7*	-10
4	11	13
5	1*	1
6	1*	-1
7	10	-7
H=	7, K=	8
1	1*	2
2	15	15
3	4*	-5
4	5*	-3
5	1*	5
6	15	17
H=	7, K=	9
1	14	14
2	9*	1
3	10*	8
H=	8, K=	0
0	[illegible]	29
2	[illegible]	-34
4	26	29
6	1*	-1
8	26	24
10	9	-5

L	FO	FC
H=	9, K=	1
0	27	-26
1	35	-32
2	5*	-4
3	32	33
4	5*	9
5	1*	-4
6	24	-27
7	16	17
8	1*	-3
9	4*	-2
10	14	-17
H=	9, K=	2
0	10	-8
1	20	18
2	2*	-5
3	13	-15
4	4*	-3
5	13	15
6	13	-12
7	15	-19
8	1*	3
9	1*	5
H=	9, K=	3
0	52	49
1	19	21
2	8	-9
3	7*	-7
4	30	31
5	4*	-2
6	1*	-3
7	1*	0
8	1*	2
9	5*	-5
H=	9, K=	4
0	8*	-10
1	1*	-3
2	16	16
3	11	-11
4	15	-13
5	7*	10
6	13	13
7	1*	3
8	3*	-3
H=	9, K=	5
0	12	-7
1	29	27
2	10	-12
3	19	-20
4	23	-25
5	16	15
6	9	-6
7	13	-14
8	6*	-2
H=	8, K=	6
0	24	-24
1	8*	7
2	11	10
3	27	26
4	9*	-9
5	5*	-6
6	5*	4
7	9	9
H=	8, K=	7
0	13	-13
1	6*	-7
2	14	12
3	9*	-7
4	10	-9
5	10	8
H=	8, K=	8
0	17	20
1	17	-13
2	6*	-6
3	7*	7
H=	9, K=	0
2	1*	3
4	8	8
6	23	23
8	11	-12
H=	9, K=	1
1	1*	-2
3	13	15
5	14	11
6	10	-11
8	10	-9
9	10	-11
7	1*	0
8	1*	-3
H=	9, K=	2
1	1*	-1
2	1*	1
3	13	16
4	4*	-3
5	10	-8
6	1*	2
7	6*	-7
8	1*	-1
H=	9, K=	3
1	1*	2
2	9	-8
3	13	-12
4	13	11
5	1*	5
6	14	-16
7	7*	0
H=	9, K=	4
1	5*	4
2	7*	9
3	5*	2
4	5*	1
5	3*	5
6	8*	-7
7	3*	4
H=	9, K=	5
1	6*	-3
2	7*	-9
3	14	-17
4	4*	-7
5	1*	-4
6	9	7
H=	9, K=	6
1	9*	7
2	10	-7
3	10	-10
4	1*	7
H=	9, K=	7
1	7*	-1
2	1*	1
H=	10, K=	0
0	20	19
2	9	-10
4	21	20
6	21	-20
H=	10, K=	1
0	3*	-1
1	7*	6
2	1*	3
3	1*	-4
4	6*	-4
5	5*	4
6	12	9
H=	10, K=	2
0	1*	1
1	31	31
2	3*	4
3	19	-21
4	7*	7
5	4*	-3
6	5*	2
H=	10, K=	3
0	17	-12
1	6*	-6
2	6*	8
3	5*	2
4	8*	-11
5	1*	-5
H=	10, K=	4
0	8*	2
1	1*	3
2	7*	0
3	7*	-9
4	23	-20
H=	10, K=	5
0	8*	5
1	13	-11
2	6*	0
H=	11, K=	0
2	5*	-5
H=	11, K=	1
1	4*	0
2	1*	2
H=	11, K=	2
1	1*	2

Table 5.3

Interatomic Distances (Å) and Angles (Deg.)

(a) Interatomic Distances (Å)

$C_1 - N_2$	1.520(9)	$C_5 - C_6$	1.522(11)
$- C_9$	1.529(10)	$C_6 - C_7$	1.508(12)
$- C_{10}$	1.470(11)	$- C_{10}$	1.486(11)
$N_2 - C_3$	1.524(9)	$C_7 - C_8$	1.522(13)
$- C_{11}$	1.526(9)	$C_8 - C_9$	1.522(12)
$C_3 - C_4$	1.525(11)	$C_9 - C_1$	1.529(10)
$C_4 - C_5$	1.544(10)	$C_{10} - N_{12}$	1.414(10)
$- C_9$	1.528(10)	$N_{12} - O_{13}$	1.306(7)

(b) Bond Angles (Deg.)

$C_{10} - C_1 - C_9$	105.9(7)	$C_4 - C_5 - C_6$	111.2(8)
$C_{10} - C_1 - N_2$	108.9(7)	$C_5 - C_6 - C_7$	110.4(9)
$C_9 - C_1 - N_2$	102.4(7)	$C_5 - C_6 - C_{10}$	104.5(8)
$C_1 - N_2 - C_3$	107.4(5)	$C_7 - C_6 - C_{10}$	106.7(8)
$C_1 - N_2 - C_{11}$	112.1(7)	$C_6 - C_7 - C_8$	109.1(8)
$C_3 - N_2 - C_{11}$	112.4(6)	$C_7 - C_8 - C_9$	112.5(8)
$N_2 - C_3 - C_4$	102.6(7)	$C_{10} - N_{12} - O_{13}$	100.0(9)

Table 5.4

Hydrogen Bonding Geometry

(a) Distances (Å)

$N_2 - H_{17}$	1.09(7)	$O_{13}^* - H_{16}$	0.963(5)
$N_2 \cdots Cl$	3.110(7)	$O_{13}^* \cdots Cl$	3.12
$H_{17} \cdots Cl$	2.05(7)	$H_{16}^* \cdots Cl$	2.16

(b) Angles (Deg.)

$N_2 - H_{17} \cdots Cl$	160.7
$O_{13}^* - H_{16}^* \cdots Cl$	179.3
$H_{16} \cdots Cl \cdots H_{17}^*$	79.0

* Refers to atoms on a molecule adjacent to that containing the N-H---Cl bond.

This association of molecular units through hydrogen bonding undoubtedly adds significantly to the stability of the crystal lattice.

The major discrepancies in the final electron density difference map occur in the general region of the oxime function. This, together with the unusually high degree of anisotropic motion of the nitrogen and oxygen atoms of the oxime does not allow confidence in the oxime dimensions of 1.41 (1)Å for the C=N bond and 1.30 (1)Å for the N-O bond. The former is significantly longer than the 1.26(4)Å expected while the N-O bond length is shorter than the 1.42(3)Å characteristic of oximes (114). Assuming that the oxime bond length values are correct, however, this situation can be rationalized if the oxime double bond character is distributed over both the C-N and N-O bonds. This condition might be expected since the oxime hydrogen is partially associated via hydrogen bonding with a chloride ion.

The thermolysis of chloramine II-25 gave a tricyclic methoxy amine. The crystal and molecular structures of the picrate of this compound were determined using similar techniques to those described for the hydrochloride of oxime II-30. The methoxy amine had the 2-azaisotwistane structure II-46 (Figure 2.6). Crystal data for the picrate: $C_{17}H_{22}N_4O_8$, yellow needles, monoclinic, space group $P2/c$, a=7.651(4), b=12.441(6), c=19.793(8) Å and β=94.08(4)°, U=1884.0 Å^3, Dm=1.44g cm^{-3}, Z=4, Dc=1.44. The structure was refined to R=0.080 for 1502 observed reflections.

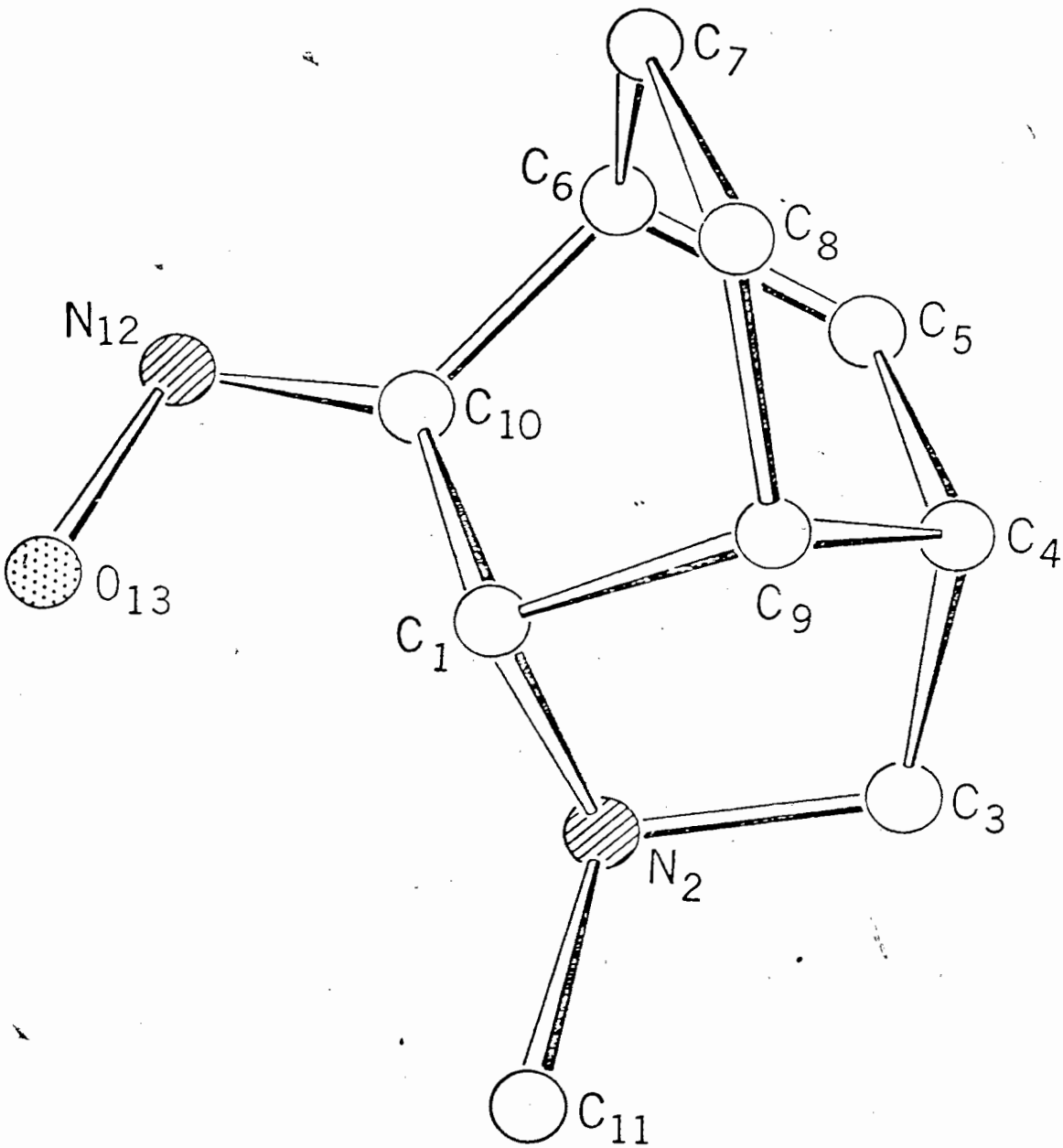


Figure 5.1: The Molecular Structure of Oxime II-30.

Methoxy amine II-46 and amino alcohol II-37 have the same isotwistane structures. Discrepancies between the n.m.r. spectra of these compounds are not the result of structural differences and an explanation for them must await further research. Waegell has recently synthesized N-methyl-2-azatwistane (113); although the n.m.r. spectrum is argued to reflect structural differences between 2-azatwistane and 2-azaisotwistane derivatives, the exact spectral differences have not yet been reported.

5.3 Experimental

5.3.1 Crystal Data for II-30 Hydrochloride

The hydrochloride of II-30 was recrystallized from ethanol-ethyl acetate as clear plates elongated along the b axis. Weissenberg and precission photographs were obtained on a crystal of dimensions 0.62x5.12x0.09 mm. Diffraction data was obtained on a separate crystal measuring 0.62x0.22x0.09 mm. Both crystals were mounted on Lindeman glass capillaries with the longest dimension approximately parallel to the rotation axis.

A zero level Weissenberg photograph using CuK_α (λ=1.5418Å) radiation, together with MoK_α (λ=0.7107Å) precession photographs of the 0 k l, k 0 l, k k 0, k k k, 2k k h, h k 1, and 1 k l layers, showed systematic absences for 0 k l, k=2n+1, h 0 l, l=2n+1, and h k 0, h=2n+1. This combined with the Laue symmetry m m m, allowed the space group to be unambiguously assigned as the orthorhombic Pbca.

The measurements were made with a computer controlled four-circle diffractometer equipped with scintillation counter and pulse height analysis. Two reflections were identified and carefully centered to determine the setting of the crystal. This was achieved by setting the 2θ value for one reflection with $X=0^{\circ}$ and ϕ was driven until the reflection was located. A second reflection, with $\phi \approx 90^{\circ}$ away from the first, was then aligned by setting the 2θ angle and driving X. The orientation matrix was then obtained from the two reflections and the unit cell dimensions.

Accurate cell dimensions and their standard erorrs were determined for a least squares fit to the 2θ, λ, ϕ, and W values of eleven strong reflections ($2\theta > 26^{\circ}$) which were accurately centered on the Mo-$K_{\alpha 1}$ peak, $\lambda=0.70926\text{Å}$, at 21°.

Crystal data - $C_{10}H_{17}N_2OCl$, M=216.7, orthorhombic. $\underline{a}=11.655(5)$, $\underline{b}=12.514(5)$, $\underline{c}=14.947(6)$, $V=2180.0\text{Å}^3$, $Dm=1.31\text{g cm}^{-3}$ (by floatation in CCl_4-toluene mixed solvent systems), $Dc=1.32\text{g cm}^{-3}$, Z=8. Space group $P\underline{bca}$.

Reflection intensities for the unique set of data (one-eighth of the limiting sphere of reflection) were collected in two sets by the θ-2θ scan method using niobium filtered MoK_{α} radiation, $\lambda=0.7107\text{Å}$. For the inner set ($2\theta < 30^{\circ}$) each reflection was scanned over a base width of 1.2° in 2θ (increased to allow for dispersion effects) at a

rate of 1° min^{-1}. For the outer set of data ($30^{\circ}<2\theta<40^{\circ}$) each reflection was scanned over a base width of 0.75° in 2θ (increased to allow for dispersion effects) at a rate of 1° min^{-1}. Background counts were measured at both scan limits for 20 sec.

5.3.2 Solution of the Structure of II-30 Hydrochloride

The computer programs used in the solution of the structure have been described elsewhere (115). The raw intensity data was converted to unscaled structure factors (F). The net intensities were corrected for Lorentz and polarization effects; absorption corrections were neglected. A reflection was considered unobserved if the net count was less than 2.3σ where

$$\sigma = [\text{scan count} + (\frac{\text{scan time}}{\text{background scan time}})^2 \text{ total background} + (0.03 \text{ net count})^2]^{1/2}$$

A total of 1022 reflections were measured of which 653 were regarded as observed.

A three dimensional Fourier difference map was computed and after several cycles of least squares refinement all non-hydrogen atoms were located with an R value of 0.144, $R = \sum (|Fo| - |Fc|) / \sum |Fo|$). Hydrogen atoms on C_1, C_5, and C_9 were then located as peaks on difference Fourier maps while the theoretical positions of the oxime hydrogen and

those on C_3, C_4, C_6, C_7, C_8 and C_{11} were calculated. Further difference maps and least squares refinement indicated that all non-hydrogen atoms were moving anisotropically. Refinement of the additional variables needed lead to a final discrepancy value of R=0.064 (all coordinates and anisotropic temperature factors for non-hydrogen atoms were varied, isotropic temperature factors of the hydrogen atoms were fixed).

An electron density difference map computed after refinement showed the maximum positive and negative peaks with intensity values of 0.33(10)e/Å^3 and -0.26(10)e/Å^3, respectively, in the region of the oxime function.

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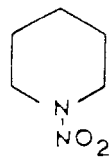
APPENDIX

APPENDIX
STRUCTURES



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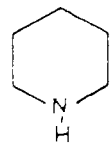

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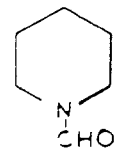

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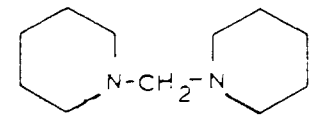

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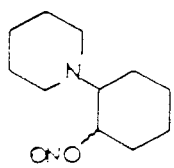

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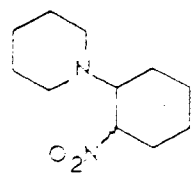

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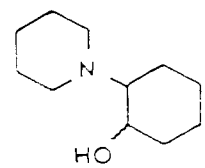

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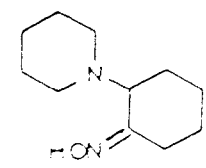

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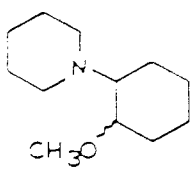

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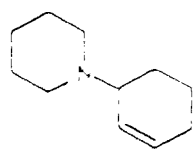

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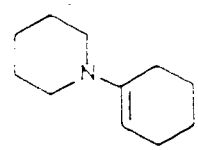

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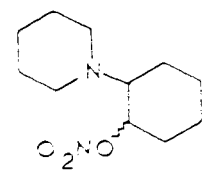

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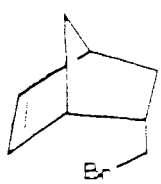

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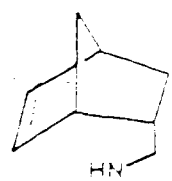

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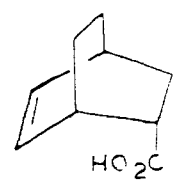

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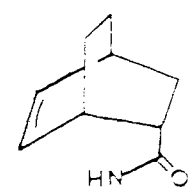

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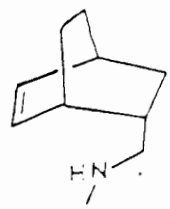

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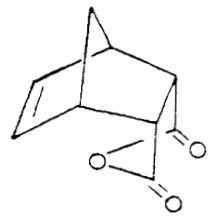

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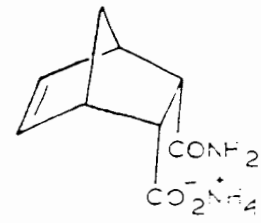

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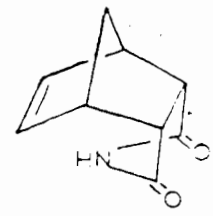

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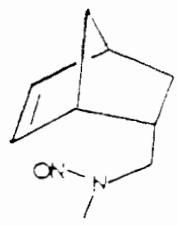

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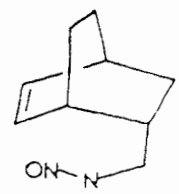

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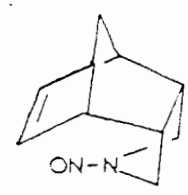

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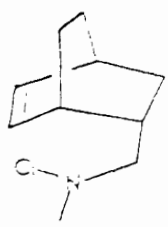

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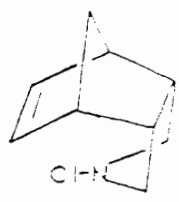

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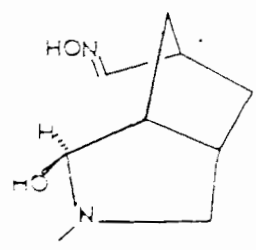

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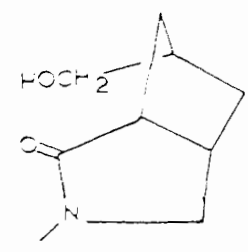

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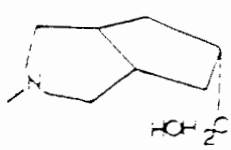

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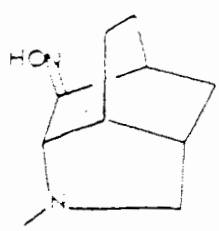

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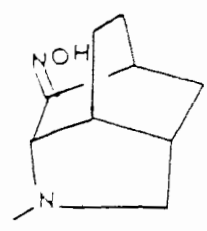

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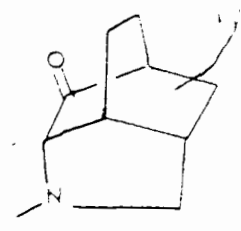

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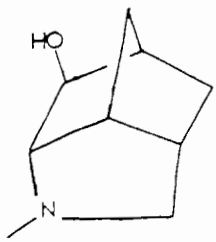

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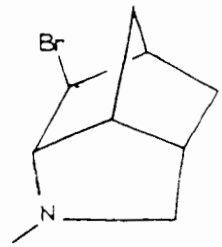

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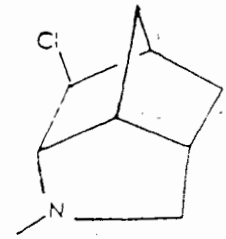

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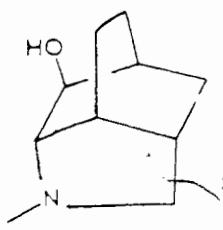

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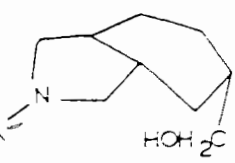

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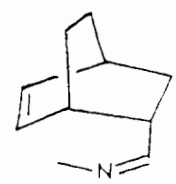

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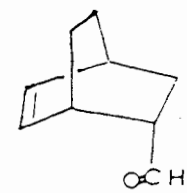

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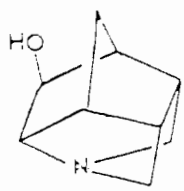

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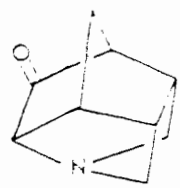

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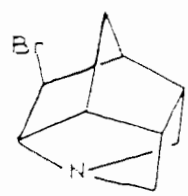

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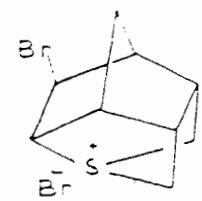

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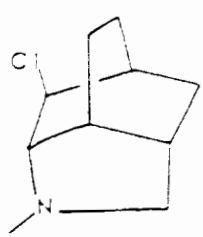

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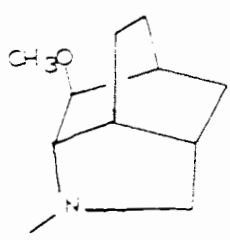
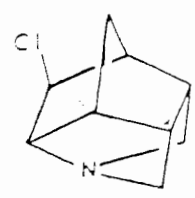
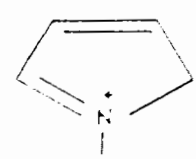


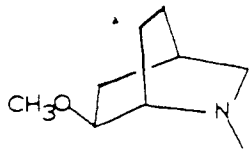
II-46



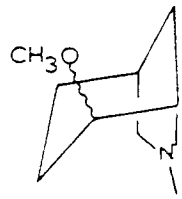
II-47



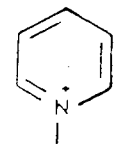
II-48



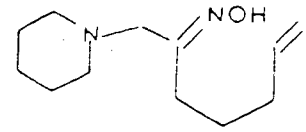
II-49



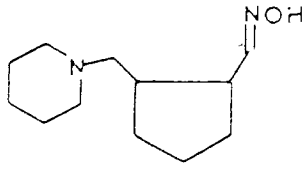
II-50



II-51



II-52



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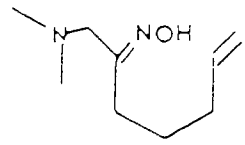

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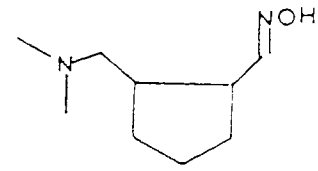
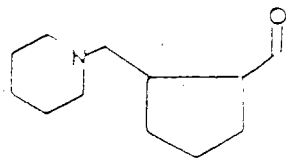
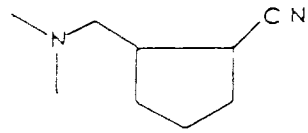


II-55



II-56



II-57