AMINIUM AND AMIDO RADICAL REACTIONS

by

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ABSTRACT

AMINIUM AND AMIDO RADICAL REACTIONS

The formation of azabicyclic compounds by the internal addition of an aminium or amido radical to a cyclohexene or cyclopentene moiety was examined. The radicals were generated in solution by the photochemical cleavage of the N-N bond of N-nitrosamines or N-nitrosamides, photochemical cleavage of the N-Cl bond of N-chloramides, or the reaction of iron salts with an N-chloramine. The position of the olefin relative to the radical affected the yields of the bicyclic products. N-nitroso compounds in methanol or benzene under nitrogen gas gave a range of 50-90% yields of 5-member azacyclic compounds when reacted with a $\Delta^{5,6}$-olefin (relative to the radical), and a 25-30% yield of cyclic products when reacted with a $\Delta^{6,7}$-olefin. N-chloro-N-methyl-3-cyclohexene-1-carboxamide photochemically gives a 72% yield of γ-lactams. N-nitroso-N-methyl-2-cyclohexene-1-carboxamide gave a 44% yield of β-lactam, but the reactions of other N-nitroso and N-chloro compounds containing a $\Delta^{4,5}$ olefin gave predominantly β-scission and hydrogen-abstraction products without a cyclic compound being isolated. The carbon radical intermediates resulting from the cyclization of aminium or amido radicals with a $\Delta^{5,6}$ olefin can be trapped under oxygen to form nitrates

and nitrate decomposition products in a 50-50% yield, or reacted with bromotrichloromethane solvent to form a 55-85% yield of the bromo-substituted compounds.

The aromatic substitution reaction of the aminium radical derived from photochemically excited N-nitroso-N-methylphenethylamine or the reaction of N-chloro-N-methylphenethylamine gave preferentially β-scission and hydrogen abstraction products.

An electronegatively substituted olefin was found to be required for the initiator catalysed N-chloramine intermolecular radical addition to predominate over the electrophilic chlorination reaction. Intermolecular radical addition of N-nitrosopiperidine in acid could not be initiated with other radicals or iron salts.

The exclusive preference for the benzylic hydrogen to photoeliminate in N-nitrosotetrahydroisoquinoline was demonstrated and the effect of oxygen on N-nitrosopiperidine photoelimination reactions was examined. The quantum yield of the photochemical disappearance of N-nitrosodimethylamine was determined to be less than 0.4 in aqueous acid. Investigation of the gas chromatography of low molecular weight amines and the spectra of amidoxime-metal complexes proved these methods were inadequate for small-scale quantum yield product analysis.

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Dr. Y.L. Chow for his stimulating discussions and invaluable advice throughout the course of this work. He also wishes to thank Dr. T. Tezuka for supervision during one year of the research. Many of the results were made possible by the technical support staff, and the author particularly wishes to thank G. Owens for the mass spectra and the machine shop for supporting a losing cause. The helpful discussions and aid of the members of the faculty and graduate students, especially those of Dr. Chow's group, is gratefully acknowledged.

This thesis was only possible with the aid of the author's wife, Cathy, who put up with the worst and successfully raised two children whith only part-time assistance.

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CHAPTER 1

INTRODUCTION

The chemistry pertinent to this thesis can be discussed under the general classifications of aminium, amino and amido radicals; and intramolecular addition to olefins, particularly with regard to the formation of heterocyclic compounds.

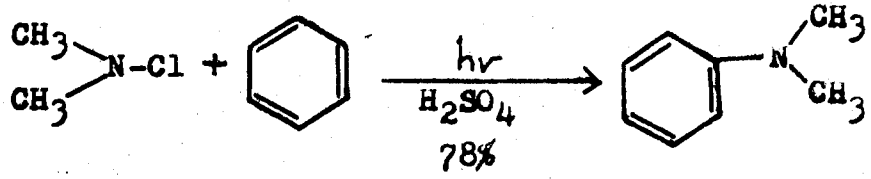
1-1 Nitrogen Radicals

Aminium radicals (cation amine radicals) are usually generated by the photolysis of a N-nitrosamine-acid complex (1-3) or by the homolytic cleavage of N- halamines in the presence of a strong acid (4-9). The reaction of N-halamines with metal ions, e.g., Fe^{2+} or Ti^{3+}, in a neutral medium (10,11) probably involves an aminium radical-metal ion coordination species and shows aminium radical characteristics (1,4,5). Other methods of generating aminium radicals involve the reaction of metal ions with hydroxylamine (12,13), hydroxylamine-O-sulfonic acids (14) or tertiary amine oxides (15), or the γ-irradiation of protonated amines (16). The preparation (17-21), properties and non-radical reactions of N-nitrosamines (19-31), as well as the preparation (4,7,32) and non-radical reactions of N- halamines (7,33-35; see however 36-38) are well documented.

The reaction of aminium radicals follow the lowest

activation energy path, which is determined by the aminium radical structure, the experimental conditions and the availability of the other reactant molecules. The electrophilic nature of the aminium radical has been demonstrated by a decrease in the amount of intermolecular addition when either the aminium radical (39) or the olefin is substituted with electron-withdrawing groups (1,39). Examples of the aminium radical reactions are given below (Eq 1.1-1.12) in an approximate order of increasing preference for the illustrated pathway. For example, intermolecular addition to an olefin (Eq 1.9) will usually occur faster than hydrogen abstraction (Eq 1.6).

Eq 1.1



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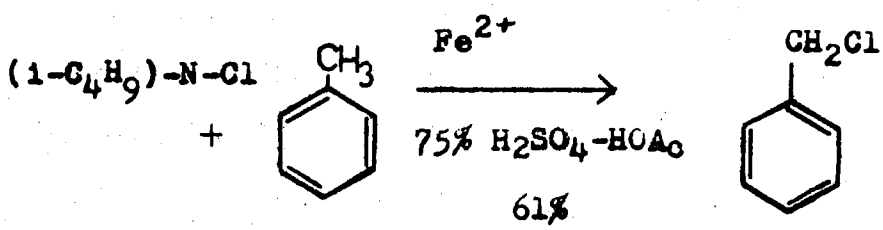
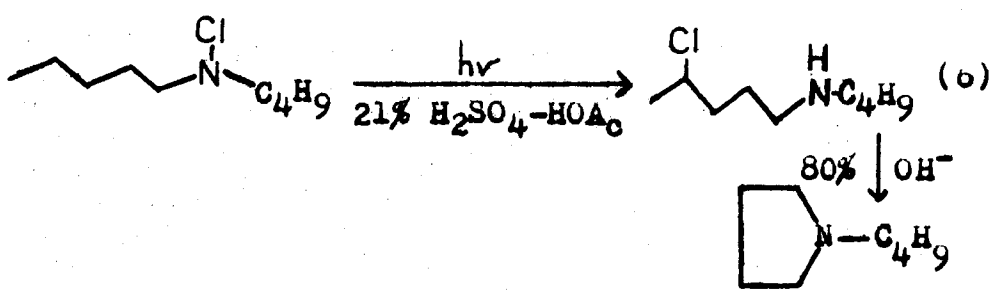
Eq 1.2

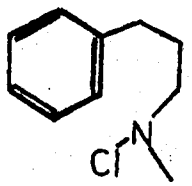
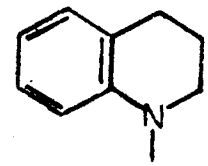


(40)

Eq 1.3



(6)

Eq 1.4  $\xrightarrow[H_2SO_4]{Fe^{2+}}$  (5)

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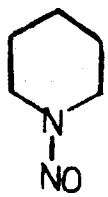
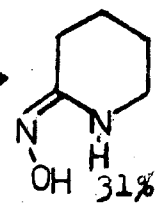
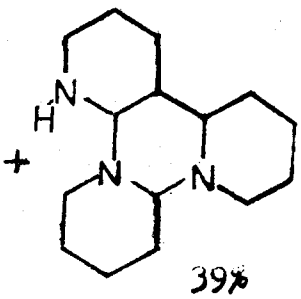
Eq 1.5  $\xrightarrow[0.3\ M\ HCl,\ H_2O]{h\nu}$  +  (41)

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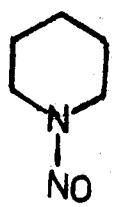
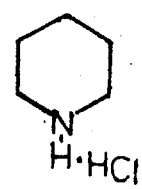
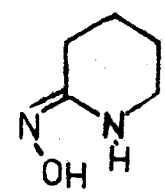
Eq 1.6  $\xrightarrow[0.3\ M\ HCl,\ H_2O]{h\nu}$  +  (41)

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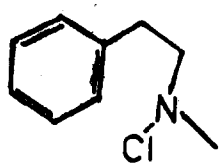
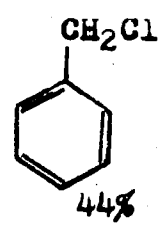
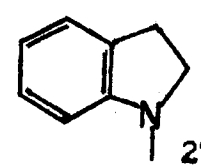
Eq 1.7  $\xrightarrow[H_2SO_4]{Fe^{2}}$  +  (5)

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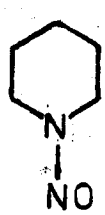
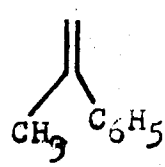
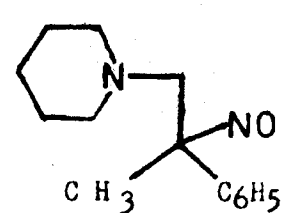
Ea 1.8  +  $\xrightarrow[0.2M\ HCl,\ MeOH]{h\nu}$  (42)

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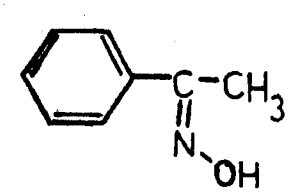
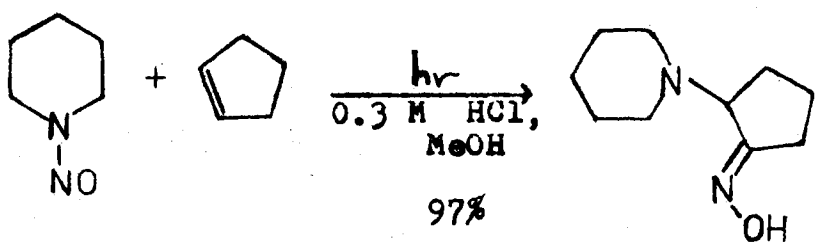
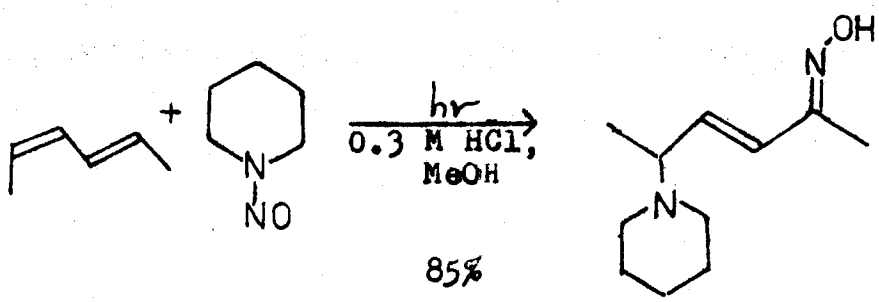


Eq 1.9

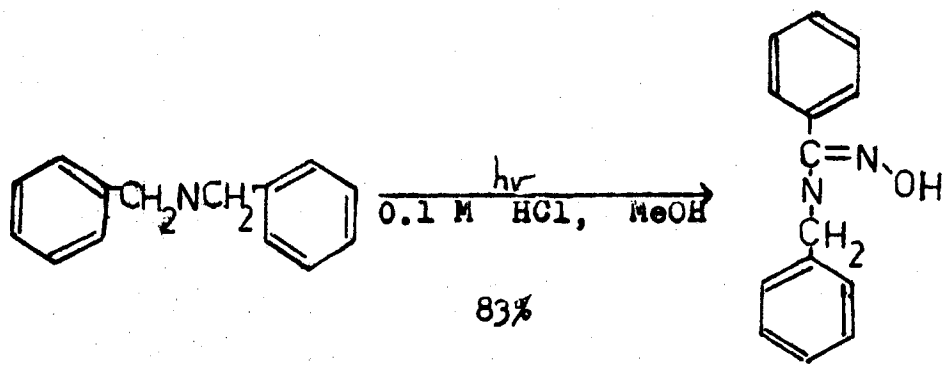


(42)

Eq 1.10

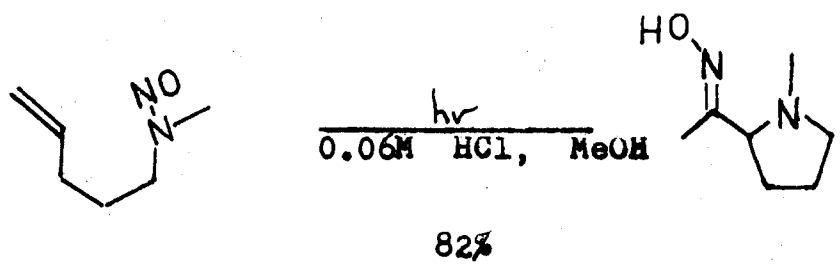


Eq 1.11



(3)

Eq 1.12



(43)

Many of the above aminium radical reactions using N-chloramines require high acid concentrations. For example, the amination of benzene (Eq 1.1) or the intra-

molecular hydrogen abstraction reaction (Eq 1.3) does not occur when N-dibutylnitrosamine is photolyzed in a 0.05 Molar trifluoracetic acid-benzene solution; instead the amidoxime product is formed (Eq 1.5) (44). Similarly, this work also shows that other pathways of aminium radicals prevail over intramolecular amination in the photolysis of N-nitroso-N-methylphenethylamine at lower acid concentrations.

That the conditions in which the aminium radical is generated can play an important role is illustrated by the work of Neale (4) with N-chloramines. At high acid concentrations a competitive electrophilic addition of Cl^+ to simple olefins occurs. When a fast ionic addition removes the olefinic centre, the aminium radical has available only the less favored abstraction pathways, e.g., Hofmann-Loffler reaction, Eq 1.3. Electronegative substituents on the olefin effectively retard the ionic mechanism and allow radical addition products to be obtained. In this work we shall show that ionic addition products predominate with alkyl olefins when the generation of an aminium radical, by AIBN* initiation, is inefficient.

In the photochemical reactions of N-chloramines the N,N-dichloramine, and possibly some impurities such as Cl_2, have been postulated as the initiators (45). Initiation by acetylhypochlorite is shown to be absent in this work.

*α ,α -azo-bis-isobuyronitrile

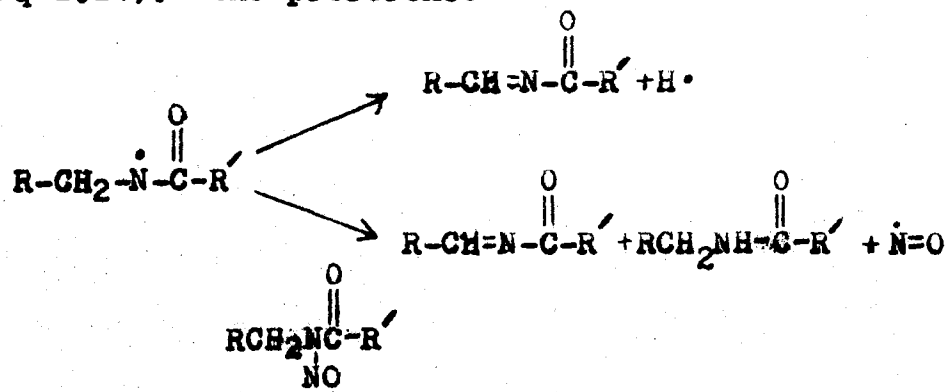
The electron spin resonance (esr) spectra of aminium and amino radicals have been recently reported (16, 46-50) and the spectra of both agree with a planar configuration, i.e., π-radical (46,48). In contrast to the facile addition reactions of aminium radicals, there are only a few suspected cases of amino radical additions to olefins (51-55). At least in one case (52) an allylic abstraction would account for the products (56). SCF and CI calculations have shown that an amino radical addition to an olefin requires an activation energy as nigh as 35-40 kcal./mole (57). The success of amino radical intramolecular additions of N-chloramines (38,53,54) may be due to a favorable geometry for the transition state of an intermolecular reaction, as will be discussed later. Alternately, an incidental generation of HCl by side reactions may supply the necessary acid to create aminium radicals.

The amino radical does not form Hofmann-Loffler reaction products, even when such a reaction is possible (58), but undergoes intermolecular hydrogen abstraction (59-61), coupling, or combination and disproportionation reactions (62-65). An example of the last reaction is the photolysis of N-nitrosamines in the gas phase (Eq 1.13) (66).

Eq 1.13 $$CH_3\overset{\overset{NO}{|}}{\underset{\cdot}{N}}-CH_3 \xrightarrow[-NO]{h\nu} CH_3-\dot{N}-CH_3 \xrightarrow{CH_3\overset{\overset{NO}{|}}{N}CH_3} CH_3\overset{\overset{H}{|}}{N}CH_3 + CH_2{=}N-CH_3$$

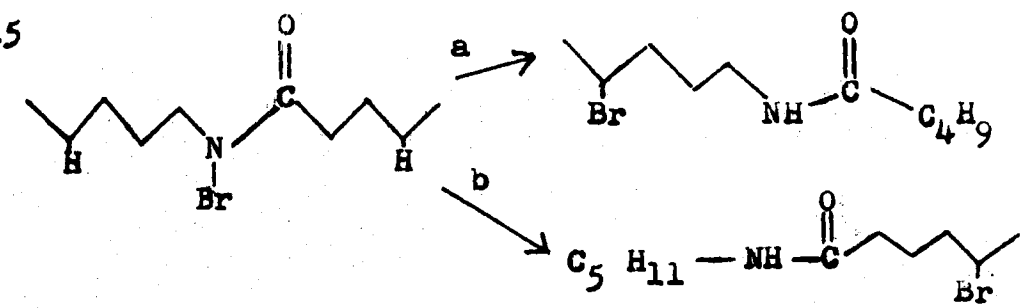
The esr spectra initially reported to be of amido radicals (67-69) were later suggested to be of nitroxides (70,71), but the postulated π-radical structure was confirmed (70). Amido radicals, generated from either N-nitrosamides (72-75) or N-haloamides (4,76-78) undergo inter- and intramolecular hydrogen abstraction and elimination (Eq 1.14). The preference

Eq 1.14



for δ-hydrogen abstraction of the N-alkyl side-chain Eq 1.15a) over the δ-hydrogen of the acyl side-chain Eq 1.15b) and the lack of O-radical reactivity in hydrogen abstraction has been demonstrated for amido radicals (79).

Eq 1.15



However, the presence of < 1% O-radical reactivity is indicated by the amido radical coupling reaction in the photolysis of N,O-diacylhydroxylamines (80).

In the presence of olefins, a secondary (N-alkyl) amido radical preferentially abstracts allylic hydrogens (4, 74) but, where there are no abstractable hydrogens available, the addition may be possible (81,82). The addition of N-bromoacetamide to cyclohexene has been shown to involve the ionic addition of N,N-dibromoacetamide (83). On the other hand, the addition of primary acetamido radicals has been reported and the yields increased when electron-withdrawing acyl groups were used (81).

1-2 Intramolecular Addition

The intramolecular addition of a reactive centre to an olefin may occur by either an ionic or a radical mechanism. The synchronous cyclization of a nucleophile and addition of an electron - deficient group to an olefin has a negative activation entropy. With a choice of five- or six-membered cyclic rings possible, usually the five-membered ring is formed, although steric effects can modify the product ratios (84). An excellent example of this preference may be found in the cyclic aminomercuration reactions (85,86).

The corresponding electrophilic cyclization involving nitrenium centres leads to the formation of five - and six-membered rings (33,87), although the intervention of amine radicals (or possibly an Ag+ co-ordinated amine radical) in the silver ion catalyzed N-chloramine reactions has been documented (36-38). The mechanism of Lewis acid-catalyzed cyclizations of N-chloramines is still undetermined (35).

Nitrene or nitrenoid mediated intramolecular addition reactions lead to unstable aziridine compounds (88,89). Upon solvolysis or hydride treatment, the ring opens to give usually the more stable six-membered rings as the major products.

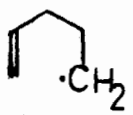
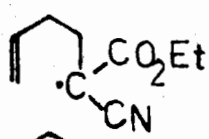
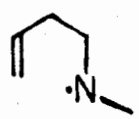
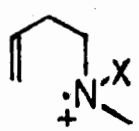
Radical intramolecular addition reactions have become an important synthetic route to cyclic compounds. Most of the work is concerned with the addition of carbon radicals to either olefins (90-92) or acetylenes (93,94); the radical species include carbonyl(95), and ketyl radicals (96), among others. The cyclization of oxygen radicals, generated from hypochlorites (97) and nitrites (97-100) by photolysis,usually produces five-membered rings. The predominance of six-membered rings in the cyclization of oxy-radicals,generated by the oxidation of alcohols with lead tetraacetate,indicates possible ionic intermediates in the reaction sequence. The formation of nitrogen heterocyclic compounds by the cyclization of amino radicals (38,53,54), aminium radicals [from either N-nitrosamines (43) or N-chloramines (11,38,54,102)], and amido radicals (103,104) all have been reported. Other heteroradical cyclizations which occur include thiyl radical additions to alkenes (105) and alkynes (106), and phosphorus radical cyclizations (107). Representative results of radical cyclizations are listed in Tables 1.1-1.3.

The majority of radical cyclizations give the kinetically - controlled five-membered ring product when there is a choice between a five- or a six-membered ring; and six-membered rings are preferred over seven-membered ones. The yields of the six-membered ring products, the products which have the lower ΔH values, increases at higher reaction temperatures or by substitution of a carbon radical centre with stabilizing groups (See Tables 1.2 and 1.3) (90).

The preference for a five-membered ring in carbon radical cyclizations has been attributed to a favorable entropy factor caused by more conformations available for a flexible cyclopentane transition state than are possible for a cyclohexane transition state (108). Alternately, the predominance of five-membered rings is suggested to be due to the stereochemical control caused by more non-bonded interactions in the cyclohexane chair transition state than the cyclopentane transition state (90). The hydrogen van der Waals interactions have been estimated at 12.7 kcal./mole for the cyclohexane form (109). The third explanation is given by Beckwith et.al. (110). They postulate that the most favorable cyclization intermediate is one in which the three electrons being redistributed are in the same plane, or as close to this requirement as possible. In other words, there should be initially maximum overlap between the half-filled p-orbital and the vacant π^*-orbital, and the emerging σ^*- and p-orbitals should be parallel.

Table 1.1

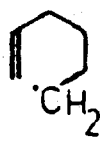
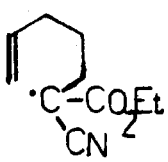
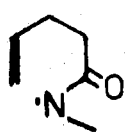
Cyclization of $\Delta^{4,5}$ Radicals

	% Cyclized*	C_1-Radical Centre Distance (A^0) (109)	Reference
	0	1.54	111
	30	-	90
	0	1.43	97
	0	1.40	112(P172)
	X = H , 0 X = Ti, 13	-	112(P150)
	39	1.81	113

* Where cyclization occurred only the 5-membered ring product was found.

Table 1.2

Cyclization of $\Delta^{5,6}$ Radicals

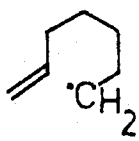
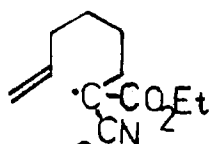
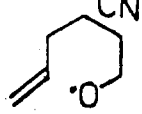
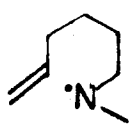
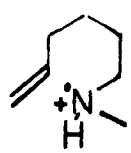
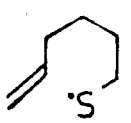
	Ring Size	Conformational(109)* Energy (Kcal/mole)	%Cyclized	Reference
	5	0	90	92
	6	12.4	tr.	
	5	–	(80°) (-70°) 9 (80%)	90
	6		49 (20%)	
	5	0	68 (50)	99
	6	15.4	0 (0)	(98)
	5	0	56	53
	6	12.2	0	
	5		45	104
	6	--	0	
	5		82 (66)**	
	6	--	0 (0)	43(11)
	5	0	16	113
	6	1	42	

* See Footnote in Table 1.3.

** When Ti^{3+} amino complex was cyclized 66% of 5-membered ring was found (112,p146).

Table 1.3

Cyclization of $\Delta^{6,7}$ Radicals

Structure	Ring Size	Conformational* Energy(kcal)(109)	% Cyclization	Reference
	6 7	3 4.5	0	111
	6 7	--	34 0	90
	6 7	4.6 4.5	0 (35) (0)	98,99 (97)
	6 7	1.8 4.5	10 (7.5) 3.5 (7.5) (-5°) (45°)	112 (P172)
	6 7	--	0 ** 0	112 (P117)
	6 7	4 5.9	31 54 14 6 (5°) (80°)	114

** When Ti^3- amino complex was cyclized 72% of 6-membered ring was found (112,P152).

* INDO calculations of the energy required to reach a chair conformation with olefin and radical overlap.

The intentions of this research can be outlined as follows:

1. To synthesize substituted azabicyclic compounds using aminium and amido radical intramolecular cyclization.

2. To determine the efficiency of cyclization with respect to the relative position of the nitrogen radical and the olefin.

3. To divert the normal products using radical trapping agents (115).

4. To investigate the intramolecular amination reaction of the N-methylphenethylaminium radical.

5. To examine the radical initiation of aminium radical intermolecular additions to olefins and the competitive electrophilic addition of N-chloramines.

6. To outline the mechanism and quantum yield of α-hydrogen elimination in several nitrosamines and evaluate methods of product analysis.

CHAPTER 2

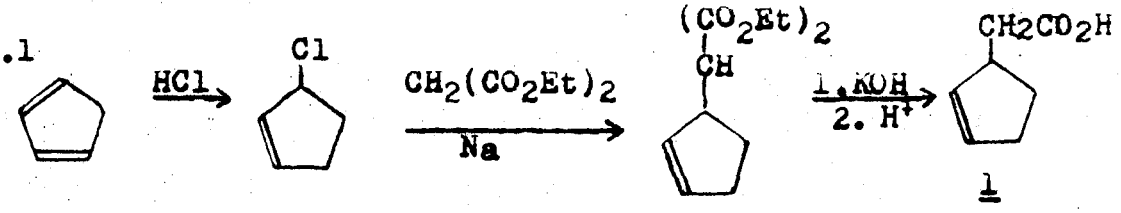
RESULTS

2-1 General

2-1-1 Synthesis of Amides and Amines

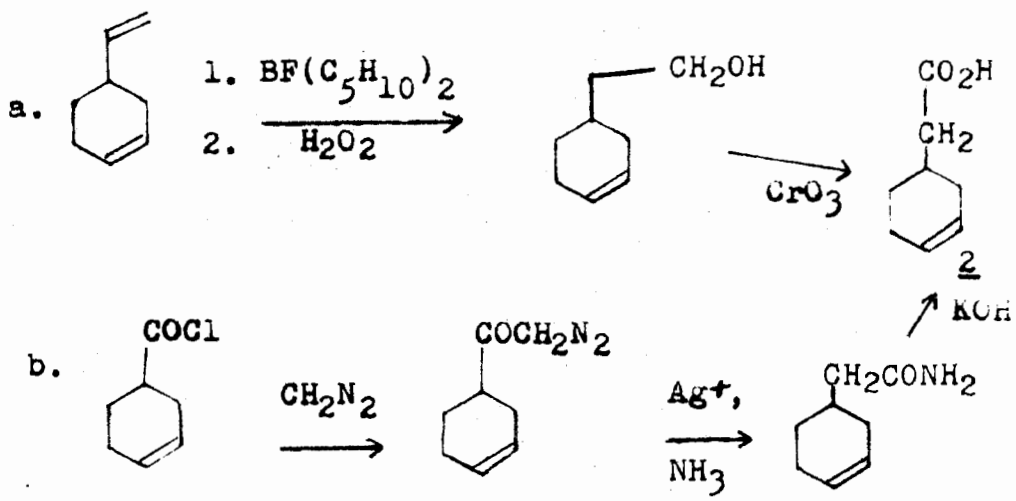
The required nitrogen compounds were generally synthesized from the suitable olefinic carboxylic acid, which were prepared in the following manner. The reaction of malonic ester with 3-chlorocyclopentene, followed by decarboxylation, (Eq 2.1) (116) gave 3-cyclopentenylacetic acid (1) in ca. 15% yield. Preparation of 4-cyclonexenylacetic acid (2) was accomplished in 30% total yield by hydroboration of 4-vinylcyclohexane (117,118) and oxidation (Eq 2.2a), or in 15% yield using an Arndt-Eistert reaction sequence (119,120), shown in Eq 2.2b. Either by reacting CO_2 with 2-cyclohexenyl-magnesium bromide (Eq 2.3a) or with the sodium salt of the allyl cyclohexenyl anion (Eq 2.3b) (121) gave 2-cyclohexenyl-carboxylic acid (3), in 4% and 18% yields respectively. Acid (4), 3-cyclohexenylcarboxylic acid, was available commercially while cyclohexanecarboxylic acid (5) was prepared by oxidation of cyclohexane carboxaldenyde.

Eq 2.1

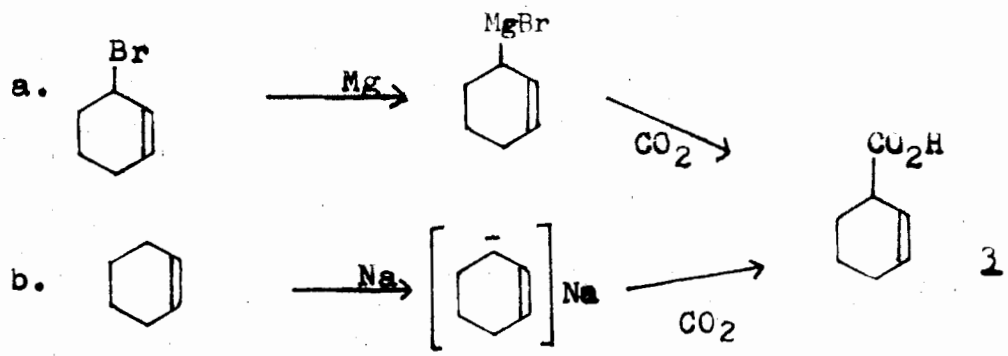


1

Eq 2.2



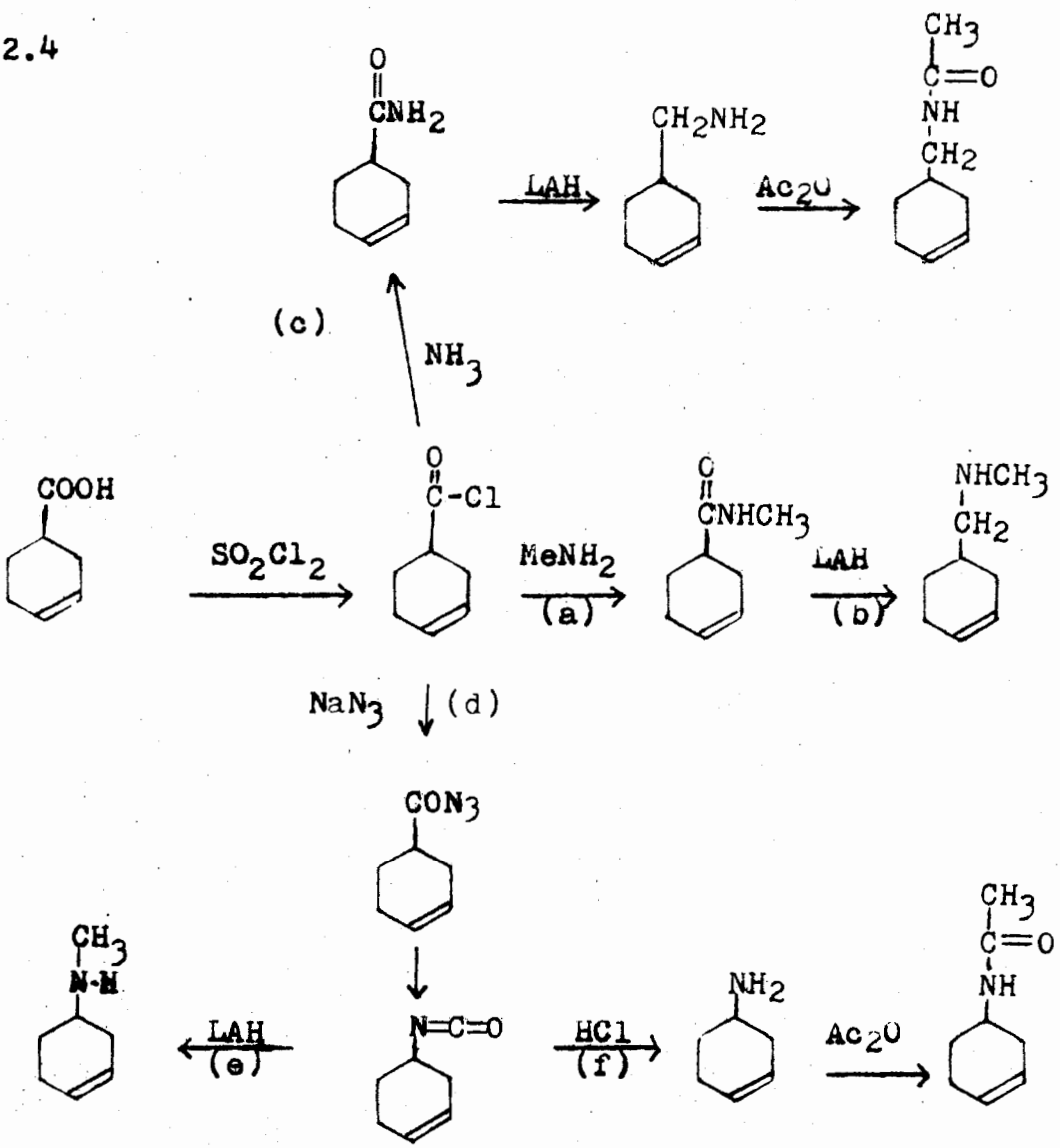
Eq 2.3



The general sequences for the synthesis of amides and amines are illustrated using carboxylic acid 4 in Eq 2.4. The presence of pyridine is recommended in the preparation of acyl chlorides from acids containing reactive olefins, such as 2. Both the acetylation of primary amines (122) and the LAH reduction of amides (123) generally gave good yields; after reduction, the loss of volatile amine was minimized by evaporation of ether through a Vigreaux column. Instead of isolating the isocyanate after rearrangement of the acyl

azide, the benzene solution was treated directly with "Red-Al"* to give the best yield of the corresponding methyl amine, analogous to the LAH reduction of isocyanates (125). Rearrangement of the cyclohexenylacyl azide required higher temperatures than that of a

Eq 2.4



*Sodium bis-(2-methoxyethoxyl) aluminium hydride (124)

cyclopentenylacyl azide (126), and an efficient condenser system must be used. The use of benzene as a solvent, rather than acetone (126), for the preparation of the acyl azide from the corresponding acyl chloride, had the advantage of suppressing side reactions such as the formation of urethane or urea, since water could be more efficiently removed. Further, there is no need to change solvents for the thermal rearrangement reaction. Diamide 11-1 was prepared by the photochemical dimerization of 2-pyridinone (6) (127).

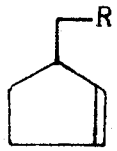
The structures of various amides and amines, and the method of preparation, are listed in Table 2.1 and Figure 2.1.

Table 2.1 Preparation of Amides and Amines

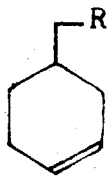
Compound	Starting Material	Reaction in Eq 2.4	Yield(%)
7-1	5	a	60
8-1	4	a	81
9-1	4	c	34
10-1	3	a	12
11-1	4	d,f	42
12-1	2	a	47
13-1	6	*	31
14-1	1	a a	54 10**
15-1	14-1	b	not isolated
16-1	12-1	b	83
17-1	4	d,e	55
18-1	1	d,e	65
19-1	8-1	b	50

* dimerization of 6

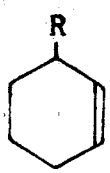
** overall yield, including Eq 2.1 steps.



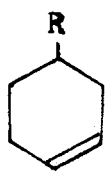
1	R	= CO_2H
14-1	R	= $CONHCH_3$
15-1	R	= CH_2NHCH_3
18-1	R	= $NHCH_3$



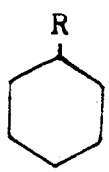
2	R	= CO_2H
12-1	R	= $CONHCH_3$
16-1	R	= CH_2NHCH_3
19-1	R	= $NHCH_3$
9-1	R	= $NHCOCH_3$
19-4	R	= NH_2



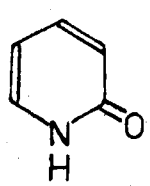
3	R	= CO_2H
10-1	R	= $CONHCH_3$



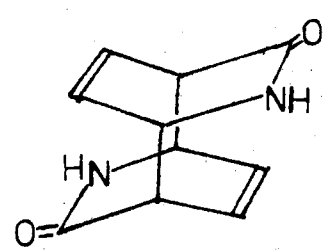
4	R	= CO_2H
8-1	R	= $CONHCH_3$
11-1	R	= $NHCOCH_3$
17-1	R	= $NHCH_3$
17-5	R	= NH_2



5	R	= CO_2H
7-1	R	= $CONHCH_3$



6

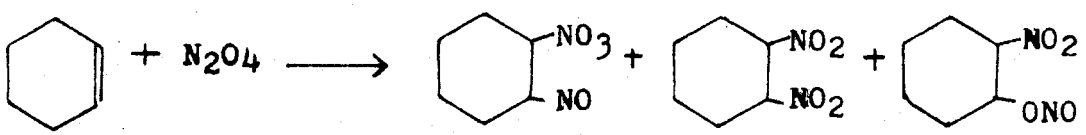


13-1

Figure 2.1

2-1-2 N-Nitroso and N-Chloro Compounds

The N-nitroso compounds were prepared either by a sodium nitrite (Experimental 5-5-1) (128,129) or a modified dinitrogen tetroxide (Experimental 5-5-2) (129) nitrosation procedure. The nitrosamides were not purified, since they were thermally unstable (130), while all the nitrosamines were purified, except 16-2 and 17-2 which were used in an unpurified form. The yields of the crude nitrosamides in several cases were greater than theoretical: this was caused by the addition of nitrosating agent to the double bond, e.g., N_2O_4 (131) shown in Eq 2.5.



Eq 2.5

The yields of the crude nitroso compounds and their spectral characteristics, including the percentage of olefin remaining intact, are listed in Tables 2.2 to 2.5. The yield of nitrosamide 9-2 was improved using N_2O_4 nitrosation in the presence of an excess of pyridine, similar to the increased yields of nitrosamines obtained when nitrosyl tetrafluoroborate and amines were reacted in the presence of pyridine (18).

Utilizing sodium hypochlorite, the N-chloro compounds were prepared using well-established procedures (Experimental 5-5-3)(32,36) and were used without further purification; the nmr spectra or iodometric titration indicated an N-chlorine content > 90%. In the case of N-chlorodimethylamine, the sulfuric acid salt was isolated using the method of Spanswick and Ingold (132). The yields and spectral data of the N-chloro compounds are summarized in Table 2.6.

Table 2.2 Preparation of Nitrosamides

Compound	Nitrosating Agent	Yield	% Olefin Unsubstituted
7-2	$NaNO_2$	87	-
8-2	$NaNO_2$	100	95
9-2	N_2O_4	100	85
10-2	N_2O_4	100	95
11-2	N_2O_4	75	75
12-2	N_2O_4	100	90
13-2	$NaNO_2$	94	100
14-2	N_2O_4	53	100

Table 2.3

Spectral Data of N-Nitrosamides

Compound	Nmr (τ -value) Olefinic Protons	CH - CO-NNO-CH_3		Ir (cm^{-1})	λ max nm (ε)
7-2	-	6.30	6.92	1725, 1500	429(115), 410(110)
8-2	4.30	6.20	6.90	1725, 1500	428(90), 408(85)
9-2	4.43	7.21[4]	6.28[5]	1725, 1500	426(90), 407(85)
10-2	4.18(m)	5.60	6.90	1725, 1500	422(50), 403(55)
11-2	4.48(t)	7.34[4]	5.70[6]	1730, 1515	423(60), 405(55)
12-2	4.33	6.85[5]	6.88	1720, 1500	421(80), 402(80)
13-2	3.5(m)[1], 4.0(m)	6.5	5.9[6]	1720,[2] 1510	442,420[3] 400
14-2	4.25[1]	6.77[5]	6.92	1725, 1500	423(95)[3], 405(90)

1. Nmr spectra taken in $CDCl_3$ except for 13-2 (CF_3COOH) and 14-2 (CCl_4).

2. Ir spectra run as neat film except for 13-2 (KBr disc).

3. Uv spectra taken in benzene except for 13-2 (CH_3COOH) and 14-2 (CCl_4)

4. CH_3 group 5. CH_2 group 6. CH group

Table 2.4 Preparation of Nitrosamines

Compound	Nitrosating Agent	Yield	% Olefin Unsubstituted
15-2	$NaNO_2$	38	100
16-2	$NaNO_2$	43	75
17-2	$NaNO_2$	43	75
18-2	N_2O_4	28	100
19-2	$NaNO_2$	88	100
20-2	$NaNO_2$	34	-
21-2	$NaNO_2$	72	-

Table 2.5

Spectral Data of N-Nitrosamines

Compound	%[1] E-isomer	Nmr τ-value: Olefinic Protons	E-isomer CH_2	E-isomer $-NNO-CH_3$	Z-isomer CH_2	Z-isomer $-ONN-CH_3$	Ir[2] cm^{-1}	λ Max nm (ε)[3]
15-2	78	4.40	5.90	7.08	6.45	6.34	1330, 1030	345 (95)
16-2	78	4.31	5.80	6.95	6.35	6.25	1335, 1040	343 (97)
17-2	91	4.25	5.5[5]	6.91	-	6.29	1330	340 (95)
18-2	80	4.30(m)	5.96	6.99	6.48	6.25	1330	345 (89)
19-2	78	4.25	5.89	6.91	6.40	6.16	1325, 1030	345 (105)
20-2	86	-	5.82	7.21	6.40	6.62	1340, 1040	345 (110)
21-2	69	-	5.50[4]	5.32[6]	6.21	4.66[6]	1350, 1050	347 (100)

1. Defined as the isomer with the nitroso group syn- to the smaller substituent, usually N-methyl.
2. Ir spectra run as neat film.
3. Uv spectra taken in a methanol-hydrochloric acid solution.
4. Nmr spectra taken in $CDCl_3$ except for 21-2 (CCl_4).
5. CH group 6. CH_2 group

Table 2.6

Physical Properties of N-Chloro Compounds

A. N-Chloramides

Compound	Yield(%)	Nmr τ-value[1] Olefinic Protons	CH - CONCl-	CH_3	Ir[2], cm^{-1}
8-3	85	4.23	6.9	6.60	1660
11-3	100	4.39	7.76	5.45(CH)[3]	1670

B. N-Chloramines

Compound	Yield(%)	Nmr τ-value[1] Olefin Protons	$-CH_2-NCl-CH_3$		Ir[2], cm^{-1}
17-3	67	4.34	7.1[4]	7.07	1440,1365
20-3	14	-	7.1	7.24	1450,1435

1. Nmr spectra taken in $CDCl_3$.
2. Ir spectra run as a neat film.
3. CH_3 group
4. CH group

2-1-3 Decomposition Conditions

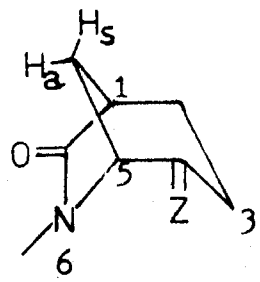
Unless otherwise specified, all the decomposition reactions were conducted under a nitrogen atmosphere. Generally, the photolysis of the N-nitroso compound in ca. 225 ml of solvent was done with a 200 watt medium-pressure lamp in a pyrex immersion-well using the appropriate filter (see Figure 5.4) chosen to irradiate only the $n \rightarrow \pi^*$ transition band. The N-nitrosamines were photolyzed in the presence of at least one equivalent of acid. The N-chloro compounds were photolyzed in a quartz apparatus using a Vycor filter. For the photolyses of N-nitroso compounds, a control reaction in the dark usually showed no significant thermal reaction ($< 5\%$ by uv analysis).

2-2 Photolysis of Alkenyl N-Nitrosamides

2-2-1 N-Nitroso-N-methyl-3-cyclohexene-1-carboxamide (8-2)

Photolysis of nitrosamide 8-2 gave a 50% yield of anti-* and syn-[3,2,1] azabicyclic oximes 22-1 and 22-2 in a 2:1 ratio and an 18% yield of azabicyclic ketone 22-3. The remaining material was tentatively assigned as a C-nitroso dimer, 23-1 or 24-1 (6%), nitrate lactam 23-2 (4%), and unsaturated oxime 25-1 (6%) obtained by intramolecular hydrogen abstraction.

* For the geometric isomers, the anti-oxime is the one in which the oxime hydroxyl is on the side opposite to the α-nitrogen substitution and the syn-isomer has the hydroxyl on the same side. When referring to groups, cis- denotes a group or atom on the same side as the hydroxyl and trans- means on the opposite side.



22-1 Z : =N-OH

22-2 Z : =N-OH

22-3 Z : =O

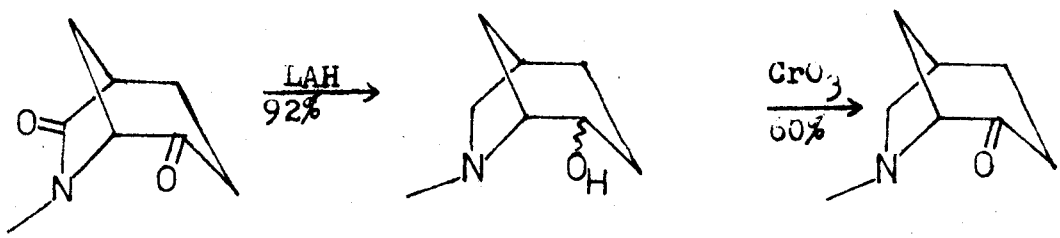
Oxime 22-1 could be crystallized from the crude photolysate, giving the correct elemental analysis and exact mass of the M^+ ion peak for $C_8H_{12}N_2O_2$. The ir peak for the lactam absorption was at 1670 cm^{-1}, higher than usually found in [2,2,2]bicyclic lactams (133-136). The nmr spectrum showed a double doublet (J= 5.5 and 1 Hz) for the bridgehead proton (H-5) at τ 5.92 in pyridine-d_5 and at τ 6.10 in $CDCl_3$. Inspection of a Dreiding model showed that the 5.5Hz coupling arises from the interaction of H-5 with H_{anti} at C-8, but H_{syn} at C-8 has a smaller coupling with H-5 since the dihedral angle approaches 90°. These coupling constants are typical of [3,2,1]bicyclic systems (137). The N-methyl singlet of 22-1 was found at τ 7.26 and τ 7.18 in pyridine-d_5 and $CDCl_3$ respectively.

The best sample of syn - oxime 22-2 contained ca.20% of anti-oxime 22-1. The $CDCl_3$ nmr spectrum of 22-2 showed the H-5 proton as a double doublet (J = 6 and 1 Hz) at τ 5.35 and the N-methyl singlet at τ 7.11, in agreement with

the general pattern of cis-protons resonating at lower field than trans-protons (2, 128). When a sample containing a major proportion of syn-oxime was stored for a time, isomerization to 22-1 was indicated by the increased τ 7.18 signal (for the trans-N-CH_3 group) at the cost of the τ 7.11 signal (cis-N-CH_3 group).

Keto-lactam 22-3 could be obtained in 56% overall yield from amide 7-1 by a bisulfite hydrolysis (138) of the crude photolysate residue. An exact mass determination of the M^+ ion peak agreed with $C_8H_{11}NO_2$. The nmr spectrum showed the double doublet pattern (J = 6 and 2Hz) for H-5 proton at τ 6.30 and the N-methyl singlet at τ 7.14. The ir spectrum contained a typical six-membered ring carbonyl absorption at 1715 cm^{-1}, but the lactam carbonyl absorption was found at 1645 cm^{-1}, lower than expected for a [3,2,1] bicyclic system (133, 135). The [3,2,1] bicyclic structure was confirmed by hydride reduction of the carbonyl groups followed by a Jones' oxidation of the volatile epimeric alcohols 26-1 and 27-1 to ketone 28-3 (Eq 2.6). The volatility of the alcohols was observed when the ether solvent was removed on a rotary evaporator.. Azabicyclic ketone 28-3 had identical spectra as that of a sample synthesized by B. Waegell et. al. (139)*.

* The author wishes to thank Dr. B. Waegell for kindly providing the spectra of their product 28-3.



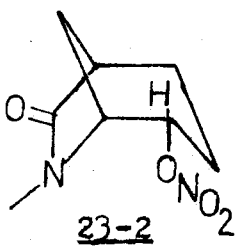
22-3 26-1, 27-1 28-3

Eq 2.6

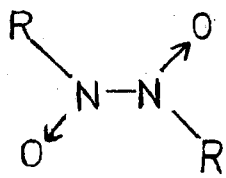
The [3,2,1]azabicyclic structure of both oximes, 22-1 and 22-2, was further confirmed by a bisulfite hydrolysis of a mixture of anti- and syn-oxime (3:2 ratio) to give only the keto-lactam 22-3 in 76% yield. Attempts to prepare amino ketones from the oximes using other methods were less successful (See Experimental 5-9-1). Particularly the metal salt-catalyzed reactions gave low product recovery. This was suspected to be caused by the ideal arrangement of the heteroatoms for complexation with the metal. Such a complex is known to occur with other α-amino oximes (140). All the efforts to selectively reduce the lactam carbonyl group of oximes 22-1 and 22-2 or ketolactam 22-3 proved unsuccessful.

The minor products could not be obtained in a pure state. An equal mixture of keto-lactam 22-3 and another compound were found in the first few chromatographic fractions.

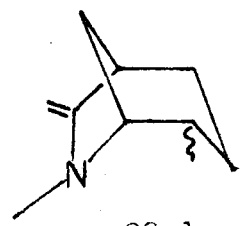
This compound was assigned as endo*-nitrato lactam 23-2, based on the ir absorptions at 1630, 1280 and 860 cm^{-1} and the τ 7.05 singlet of the N-methyl group; all of which are found in the spectra of 23-2, a major product when 8-2 was photolyzed under oxygen (See 2-4-1).



23-2

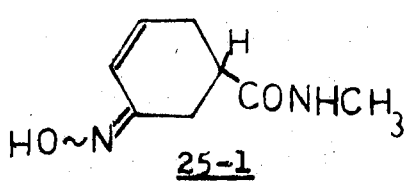


R:

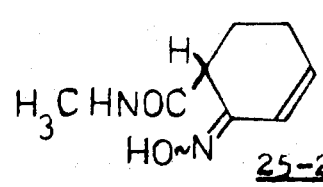


23-1

That a C-nitroso dimer, eg., 23-1, was formed, was indicated by the uv absorption at 295 nm of the photolysate during photolysis. The crude residue showed a major singlet at τ 7.09, ascribable to a dimer N-methyl group, and had a strong ir absorption at 1220 cm^{-1} (141) when the spectra were obtained immediately. However, the τ 7.11 and τ 7.18 N-methyl singlets of the oximes 22-1 and 22-2 became dominant when the nmr spectrum was checked a day later. One fraction showing the τ 7.09 singlet was obtained from chromatography; the N-methyl signal disappeared in a similar fashion, indicating that tautomerization to oximes 22-1 and 22-2 occurs rapidly.



25-1



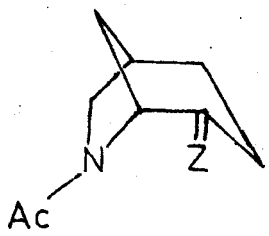
25-2

* The endo- structure in this work is defined relative to the carbon bridge not containing the nitrogen atom, i.e. endo- is on the side nearest the nitrogen bridge.

The third minor product was tentatively identified as unsaturated amide-oxime 25-1 because the ir spectrum contained an amide II peak at 1550 cm^{-1}, in addition to the 1670 cm^{-1} peak, and the characteristic oxime peaks at 3400, 1070 and 1050 cm^{-1}. The nmr spectrum showed typical α,β-unsaturated enone oxime olefinic protons (2) at τ 3.7 and τ 4.25, and the N-methyl signal at higher field (τ 7.21) than the bicyclic products. The mass spectrum pattern was different from that of oxime 22-1, although 25-1 gave the same M^+ peak at m/e = 168. The alternate structure 25-2 is considered less likely since the nmr spectrum also contained two protons in the τ 6.2 to 6.7 region, which could be assigned to the $\diagdown$CHCO proton and the α-oximino equatorial proton of 25-1(120), while only the methine ($\diagdown$CH-CO) would be expected to resonate at lower-field in 25-2. An attempt to confirm the structure by hydrolysis to the corresponding keto-amide failed, giving no isolatable product.

2-2-2 N-Nitroso-N-(3-cyclohexen-1-ylmethyl) acetamide (9-2)

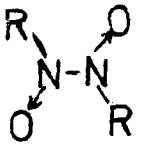
The photolysis of nitrosamide 9-2 gave anti-and syn-azabicyclic lactam oximes 29-1 and 29-2 in 35% and 9% yields respectively, in addition to keto-lactam 29-3 (14%), starting amide 9-1 (8%) and a product tentatively assigned as C-nitroso dimer 29-4 (5%).



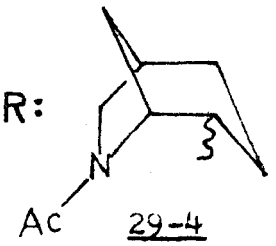
29-1 Z: =N-OH

29-2 Z: =N-OH

29-3 Z: =O



R:



29-4

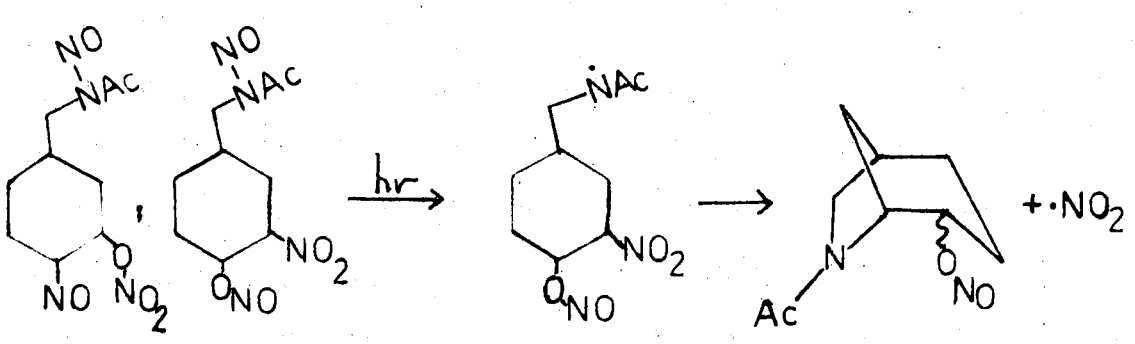
Recrystallized anti-oxime 29-1 gave correct elemental analysis and exact mass determination of the M^+ ion for $C_9H_{14}N_2O_2$. Oxime 29-1 showed ir absorptions at 3300, 955 and 940 cm^{-1} as well as the amide peak at 1615 cm^{-1}. The [3,2,1] azabicyclic structure was assigned from the double doublet (J = 5.5 and 1 Hz) at τ 5.61, as opposed to the broader peak expected for the more symmetrical[2,2,2]azabicyclic compound*. Samples of syn-oxime 29-2 were contaminated with the anti-isomer, but showed a broad doublet (J= 5.5 Hz) for H-5 at τ 4.60, lower than H-5 of 29-1.

Keto-amide 29-3 showed two carbonyl ir absorptions at 1725 and 1630 cm^{-1} and its nmr spectrum contained a broad doublet (J = 6 Hz) for H-5 at τ 5.86. The mass spectrum had the M^+ ion peak at m/e = 167 required for $C_9H_{13}NO_2$. That the amide group was less susceptible to dilute acid hydrolysis than the oxime group of 29-1 or 29-2, was shown by obtaining only ketone 29-3 and starting oximes after a five hour hydrolysis at 100°.

*Huffman et.al.(135) find a diffuse peak for the bridgehead proton in a [2,2,2] azabicyclic compound.

Parent amide 9-2 was identified by identical tlc retention and the olefinic proton signal at τ 4.34 in the nmr spectra of several chromatography fractions. The compound assigned as C-nitroso dimer 29-4 was found in the initial fractions from chromatography. The assignment was based on the uv absorption at 300 nm, the ir absorption at 1220 cm^{-1}, and a broad multiplet ($W_{\frac{1}{2}}$ = 12Hz) at τ 4.93 in the nmr spectrum (141,142); the width of the H-4 proton indicated the equatorial orientation of the nitroso group (38). In a CH_2Cl_2 solution, the dimer tautomerized to give crystals of oxime 29-1 (vide supra) after a period of time.

In order to prove that the cyclic products obtained in the photolysis were not the result of intramolecular radical displacement reactions, such as outlined in Scheme 2.1, a mixture of nitrosamide - N_2O_4 addition products (postulated as compounds such as 30-1 and 30-2) were photolyzed under the same conditions as 9-2.



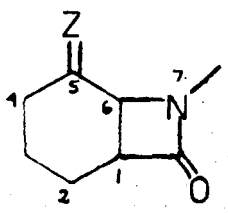
30-1 30-2 Scheme 2.1

The products recovered after chromatography were unstable and could not be purified. Although several fractions showed

similar spectral characteristics as keto-amide 29-3, the tlc retention times of the compounds did not correspond. The low recovery from chromatography (< 30%) and the extensive decomposition of the products, which is typical of nitrate esters (143), indicated that the cyclization products are not formed in a secondary photoreaction as shown in Scheme 2.1.

2-2-3 N-Nitroso-N-methyl-2-cyclohexene-1-carboxamide(10-2)

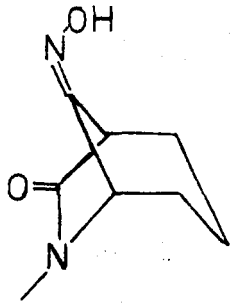
Photolysis of nitrosamide 10-2 gave 44% yield of a single β-lactam oxime, either 31-1 or 31-2, 15% of parent amide 10-1 and 7% of a compound suggested to be keto-lactam 31-3.



31-1 Z: =N-OH

31-2 Z: =N-OH

31-3 Z: =O



12

The oxime, suggested to be 31-2, had approximately equal M+1 (m/e = 169) and M^+ (m/e = 168) ion peaks in the mass spectrum. The exact mass determination of the m/e = 168 peak gave expected value for $C_8H_{12}N_2O_2$. The ir spectrum contained a lactam absorption at 1725 cm^{-1} and oxime absorptions at 3200 and 935 cm^{-1}. The nmr spectrum showed a sharp

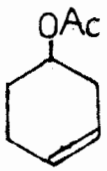
doublet at τ 5.95 (H-6, J = 5Hz) and a triplet at τ 6.45 (H-1, J = 5Hz), plus the N-methyl singlet at τ 7.18. Irradiation of any region above τ 7.1 (all the protons except H-5 and H-6) did not affect the doublet but irradiation in the τ 7.5 region caused the triplet to collapse to a doublet with 5 Hz coupling. These results are explained by a cis-configuration of the β -lactam, in analogy to the J = 5Hz couplings found by others (144,145), and rule out the 5-membered ring cyclization product 32 since both H-1 and H-5 of oxime 32 must be coupled with protons at higher field. The syn-configuration of the oxime was tentatively assigned based on the relatively low-field position of H-6, and the high-field chemical shift for equatorial H-4 (ca. τ 7.4) as compared to the expected value of τ 6.7 (2,42) of a cis-equatorial H-4 in 31-1. Upon attempted sublimation, the β -lactam decomposed and, due to the shortage of product, further reactions could not be carried out.

Keto-lactam 31-3 could not be isolated by preparative tlc techniques and the structure is inferred from the broad 1745 cm^{-1} ir absorption and the complex pattern at τ 6.4 and N-methyl singlet at τ 7.10 in the nmr spectrum.

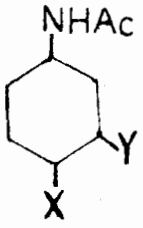
2-2-4 N-Nitroso-N-(3-cyclohexen - 1 - yl)acetamide (11-2)

During the photolysis of the sample of nitrosamide 11-2, containing ca. 25% parent amide 11-1, the uv spectrum of the photolysate showed no C-nitroso dimer peak appearing

at 295 nm and the control reaction showed ca. 25% decrease in the nitrosamide absorption. The products obtained were starting amide 11-1 (37%), 3-cyclohexenyl acetate 33 (9%) and what appeared to be 34-1, 34-2 and 34-3, the adducts of HCl and Cl_2 (8% and 1% respectively) to 11-1.



33



34-1 X = H, Y = Cl

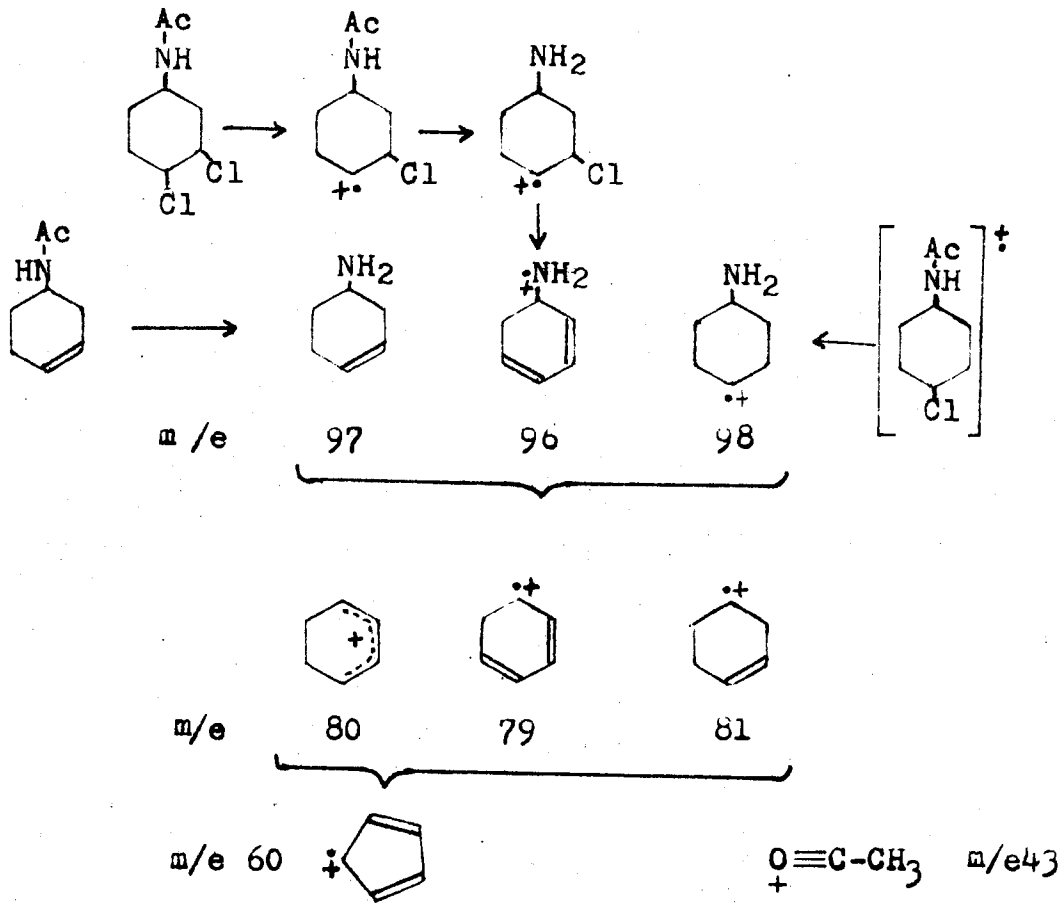
34-2 X = Cl, Y = H

34-3 X = Cl, Y = Cl

The thermal decomposition product, ester 33, had ir absorptions at 1730 (C=O), 3030 and 655 (HC=CH). The nmr spectrum contained the expected peaks at τ 4.37 for the olefinic protons, τ 5.8 for the methine proton, and the methyl singlet at τ 7.97. There was likely some loss of this volatile ester when the photolysate solvent was removed.

The chromatographic fractions containing parent acetamide 11-1 were contaminated with two minor products with longer gc retention times. Gc-mass spectral analysis of these compounds indicated the first peak corresponded to either, or both, the acetamides 34-1 and 34-2, showing an M^+ ion peak of 175 containing one chlorine. The second gc peak showed an M^+ ion peak with a two chlorine pattern at m/e = 211 and 209; the first fragmentation was loss of chlorine to give m/e = 174 containing one chlorine, as expected from 34-3. The fragmentation patterns of all the acetamides,

11-1, 34-1 or 34-2, 34-3, were similar below m/e = 80 when only the cyclohexyl ring structure remained (See Scheme 2.2).

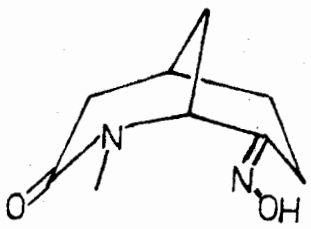


Scheme 2.2

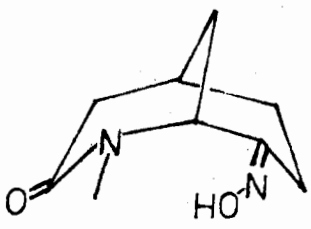
The remaining mixture of polar compounds could not be identified but showed an amide II peak in the ir spectrum at 1550 cm^{-1}, similar to acetamide 11-1.

2-2-5 N-Nitroso -N-methyl-3-cyclonexene-1-acetamide (12-2)

Column chromatography, following the photolysis of nitro amide 12-2, gave a bicyclic lactam oxime, assigned as compound 35-1, in 25% yield. This product showed ir absorptions at 1605 (lactam) and 3200, 930 cm^{-1} (oxime). The oxime contained the correct M^+ ion peak at 182 and elemental analysis agreed with $C_9H_{14}N_2O_2$. Structure 3-1, anti-oxime, was proposed based on the τ 6.15 triplet (J = 3Hz) for H-1, and the multiplet at τ 6.75 for the equatorial proton at C-7 (2,128), with the N-methyl signal found at τ 7.12. By analogy to syn-oxime 22-2, syn-oxime 35-2 might be expected to show a signal for H-1 in the region of τ 5.5. The alternative structure for this compound is the [3,2,2]azabicyclononane 35-3; the possible oximes are shown in Figure 2.2, together with the spectral data of some model compounds.

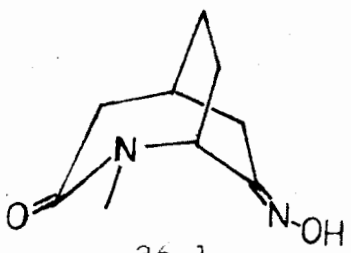


35-1

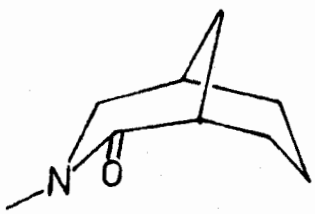


35-2

1605 cm^{-1}; H_1 τ 6.15 (t, J = 3)

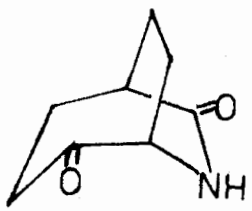


36-1



37-1

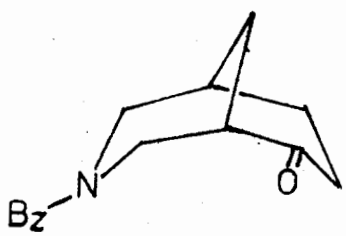
38-1



(88)

1621 cm^{-1}(145)

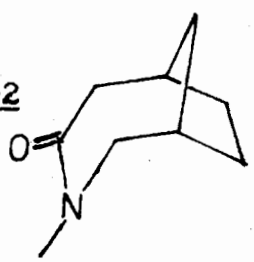
1713,1672 cm^{-1} ; H_1 τ 6.18(m, W½ = 13)



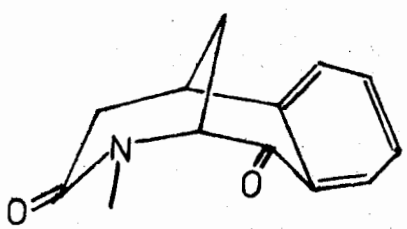
37-2

H_1 τ 7.47 (t,J = 6) (147)

38-2

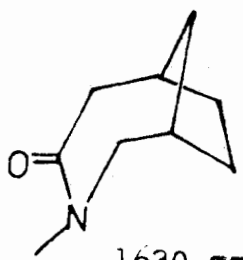


1615 cm^{-1} (148)



37-3

38-3



1690, 1650 cm^{-1}; H_1 τ 6.03 (dd, J = 4,3)(149)

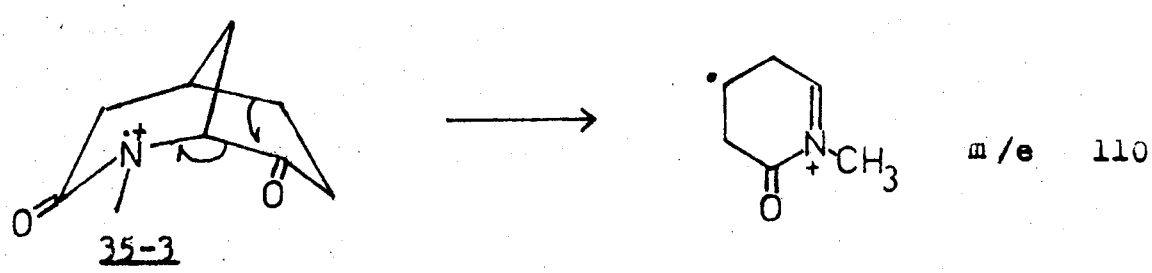
1630 cm^{-1} (133)

Figure 2.2

An examination of molecular models of the two possible azabicyclic anti-oximes indicates that the more symmetrical oxime 35-1 would be expected to give a triplet structure for H-1 with small couplings to the protons on C-9, similar to 37-3, while the less symmetrical oxime 36-1 might be expected to show couplings of ca. 7 and 2 Hz. The latter oxime should then show a broader peak for H-1, though with a lesser half-width than 38-1.

The lactam ir absorption appears to be more consistent with a less-strained 7-membered ring but when the keto-lactam was prepared using bisulfite hydrolysis of the oxime, the ir absorptions were found at 1720 and 1625 cm^{-1}; the latter carbonyl absorption is within the value expected for 35-3.

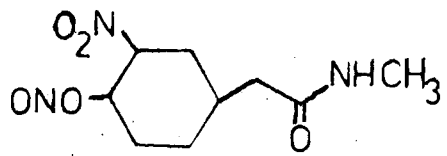
The mass spectrum of keto-lactam 35-3 contained the M^+ ion peak at 167 and 100% intensity peak at m/e = 110. The same peak (35% intensity), was found in the mass spectrum of lactam-oxime 35-1. Although the fragmentation pattern does not unambiguously distinguish between the bicyclo [3,3,1] or [3,2,2] structures, the m/e = 110 peak is suggestive of a δ-lactam (Scheme 2.3).



35-3

Scheme 2.3

From the characteristic N-methyl doublet (J = 4.5 Hz) around τ 7.2, which collapsed to a singlet upon adding D_2O, and from the ir absorptions at 1640 or 1635 and 1550 cm^{-1}, the other compounds formed in the photolysis appeared to be a mixture of secondary amides. No olefinic protons were noticed in the nmr spectrum, indicating the possible addition of N_2O_4 to the double bond to yield products such as 39. The separation and identification of these compounds was not further pursued.



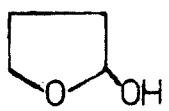
39

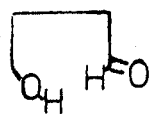
2-2-6 N,N′ - Dinitroso-anti,trans - 3, 6-pyrid-2-one Dimer (13-2)

Dinitrosamide 13-2 was not photoreactive in benzene, and photolysis in acetic acid gave only 2-pyridone (6, vide infra). The photolysis of a suspension of 13-2 in tetrahydrofuran gave parent dimer 13-1 (vide infra) in 15% yield.

Apart from polymeric material, the remaining products from the tetrahydrofuran photolysis were assigned as the compounds resulting from hydrogen abstraction from THF. The compound assigned as 2-hydroxytetranydrofuran (40-1) had ir absorptions at 3300, 1065 and 940 cm^{-1} for alcohol and ether

functionalities. The nmr spectrum contained multiplets at τ 4.4, 6.1 and 7.1 in the correct ratio, and the M^+ ion peak at 88 was consistent with 40-1. Another compound obtained showed a 1720 cm^{-1} ir absorption and a low-field broad singlet at τ 1.95, suggesting structure 40-2, γ-hydroxybutyraldehyde, resulting from tautomerization of 40-1.

40-1 

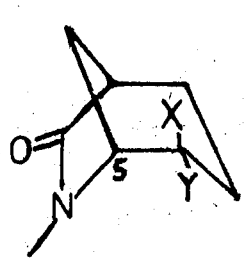
 40-2

The unusual stability of dinitrosamide 13-2 was also demonstrated by its resistance to decomposition when heated to 150°, in contrast to the facile thermal rearrangement of other nitrosamides (130,150).

2-3 Photolysis of Alkenyl N-Chloramides

2-3-1 N-Chloro-N-methyl-3-cyclohexene-1-carboxamide(8-3)

Photolysis of a benzene solution of chloramide 8-3 using a Vycor filter gave endo-chlorolactam 23-3 (33%), exo-chlorolactam 24-3 (39%) and parent amide 8-1 (7%). The percentages of the products in the crude residue were 44, 49, and 7% respectively, as measured by gc.



23-3 X = H, Y = Cl

24-3 X = Cl, Y = H

The nmr spectra of 23-3 and 24-3 are shown in Figure 2.3 in which the signals for CHCl, H-5 and N-CH_3 are readily assignable. The ir absorptions of exo-chlorolactam 24-3 were seen at 1690 and 815 cm^{-1} and exact mass determination agreed with $C_8H_{12}NOCl^{35}$.

Both chlorolactams 24-3 and 23-3 showed the same mass spectral fragmentation patterns; the latter was obtained by gc-ms since other methods only partially separated 23-3 from 24-3. A fraction containing 80% endo-chlorolactam 23-3 showed ir absorptions at 1690, 705 and 750 cm^{-1}. It is believed that the lower chemical shift values of the H-5 and N-CH_3 protons of 23-3, with respect to those of 24-3, are caused by the different orientation of the C-Cl bond in the two compounds. The coupling patterns of the CH-Cl protons (H-4) are in agreement with these orientations, and are predicted from inspection of molecular models.

The structures were confirmed by reduction of 1.2g of a crude mixture of 24-3 (48%), 23-3 (42%) and amide 8-1 (10%) to give endo-chloramine 26-2 (0.36g), bicyclic amine 41-1 (0.35g) and unsaturated amine 19-1 (0.1g). The yield of endo-chloramine 26-2, accounts for 51% of endo-chlorolactam 23-3 in the starting mixture. If all the remainder of 23-3 (ca.0.26g) had been cleanly converted to amine 41-1, it would only account for 0.20g of 41-1; the remainder of 41-1 (0.15g) must result from reduction of 24-3. The actual yield of 41-1 is likely larger since some of it would have been lost during workup due to its volatility.

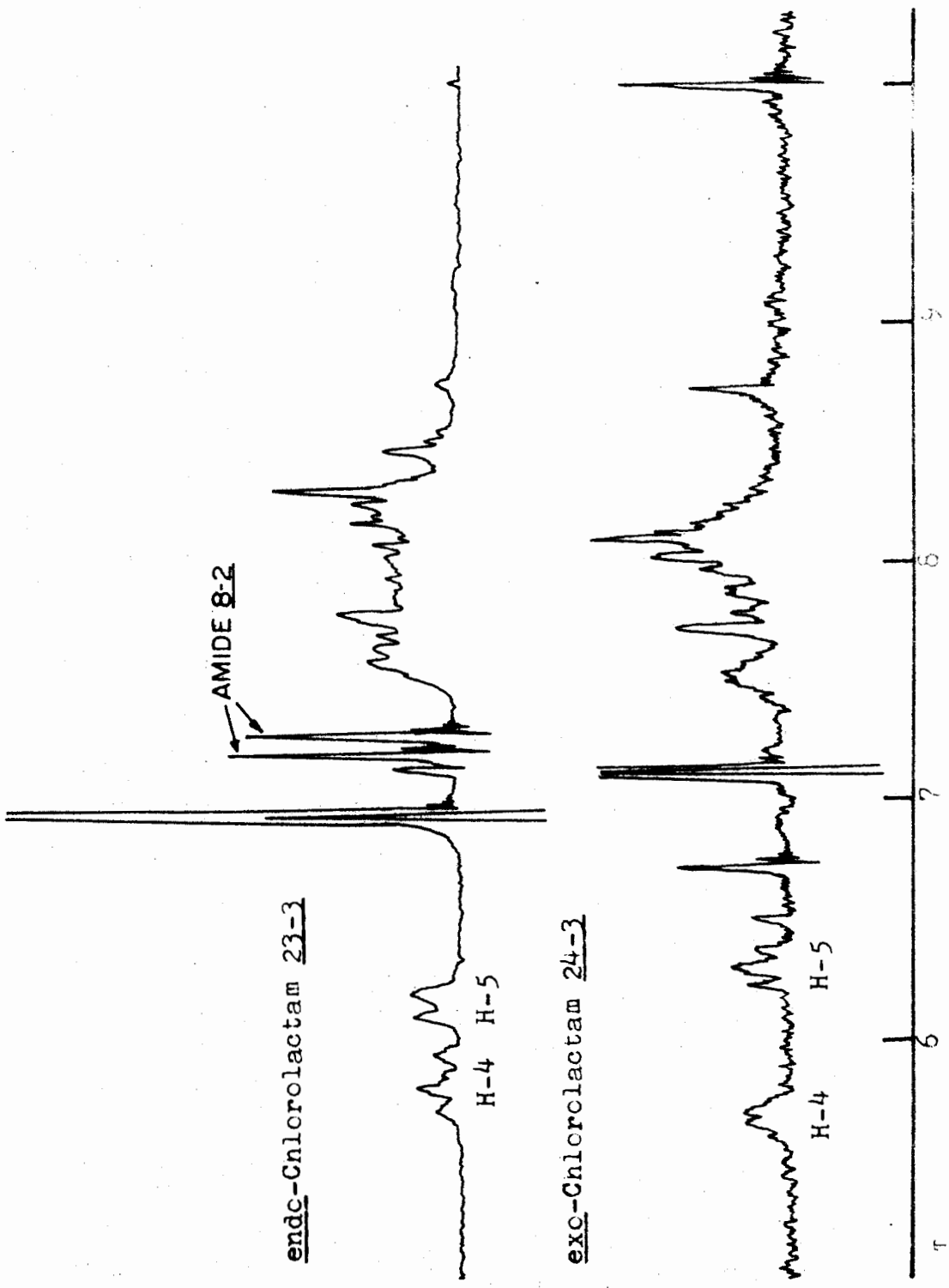


FIGURE 2.3 The NMR Spectra of Chlorolactams 23-3 and 24-3

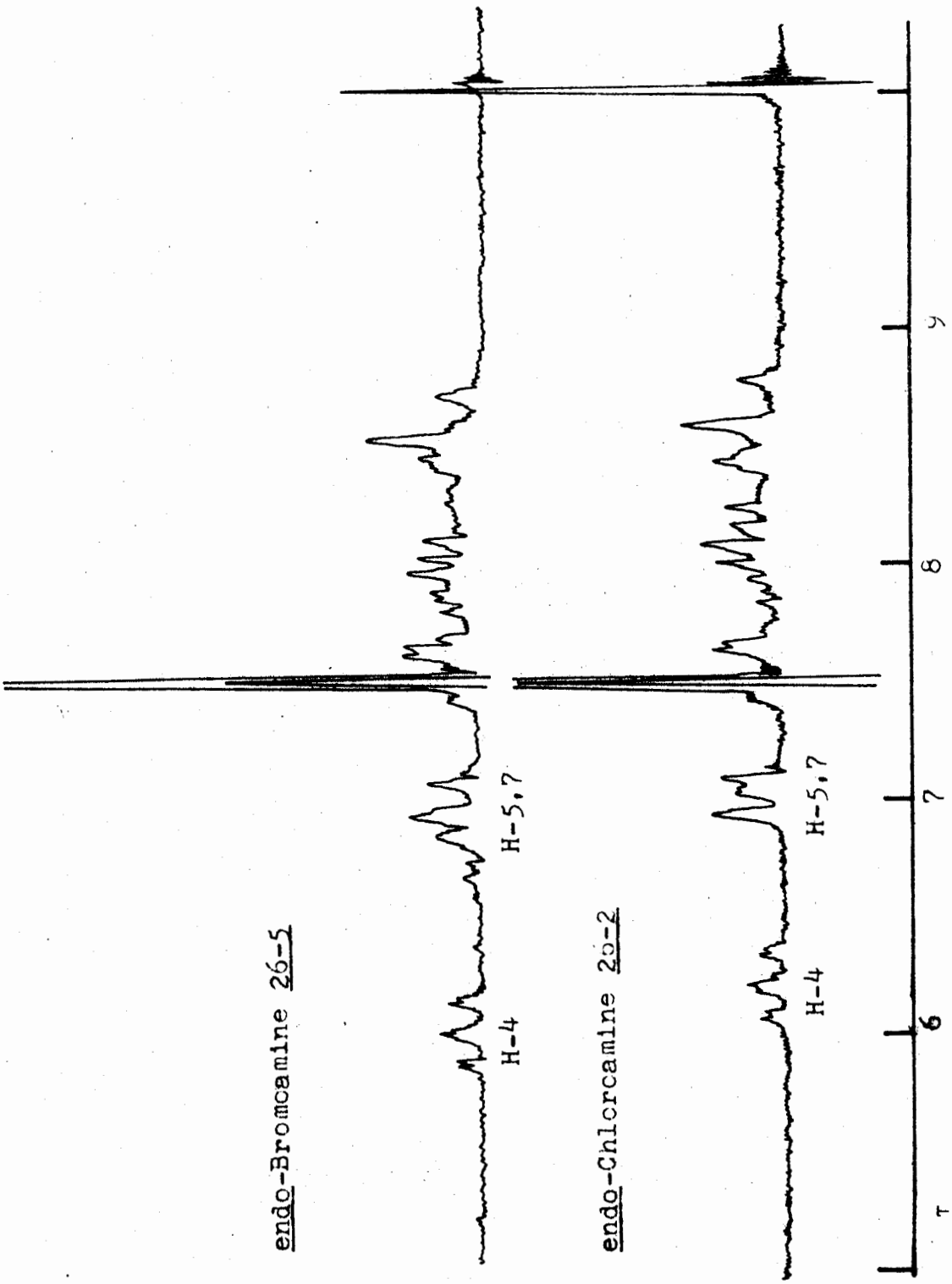
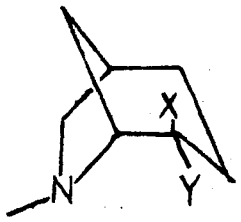


FIGURE 2.4 The NMR Spectra of endo-Chloro and bromoamines 26-2 and 26-5.



26-2	X = H, Y = Cl
27-2	X = Cl, Y = H
41-1	X,Y = H

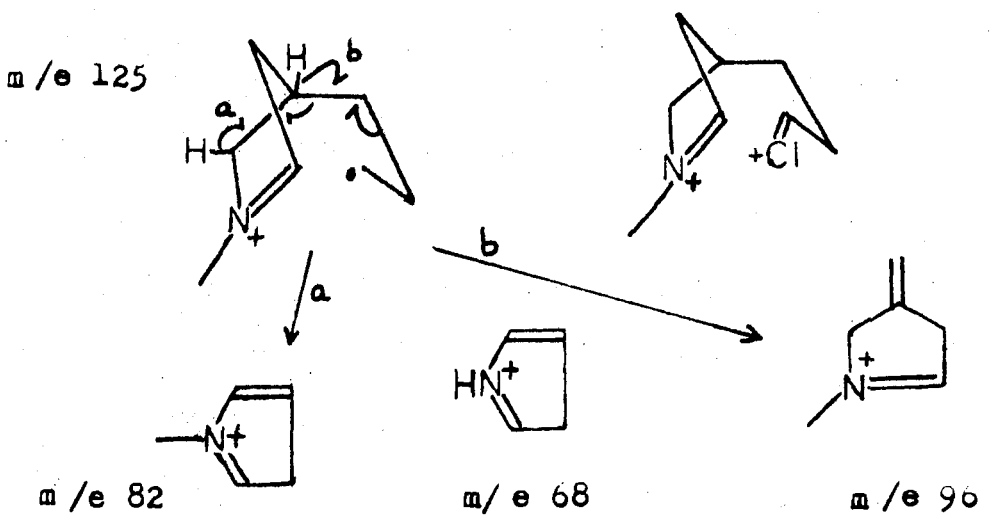
The ir absorptions of endo-chloramine 26-2 were found at 2840 cm^{-1} (amine Bohlmann bands)(151) and 780 cm^{-1} (C-Cl). The nmr signal for CH-Cl was seen at τ 6.20 (J = 9,7, and 1.5H_z), similar to the axial H-4 of 23-3 (Figure 2.4), decoupling experiments showed that this proton coupled with H-5, in the τ 7.04 region, by 1.5H_z. The mass spectrum of 26-2 had the parent ion peaks at m/e = 161 and 159 (1:3 intensity ratio) indicating the presence of one chlorine. The ir and nmr spectra were identical to those of 26-2 prepared by other groups (54, 87*, 112*).

Further reduction of 26-2 was shown by gc to produce amine 41-1. Bicyclic amine 41-1 readily formed a hydrochloride salt 41-2 in CH_2Cl_2 or $CHCl_3$. The nmr spectrum of 41-2 in D_2O showed multiplets for three protons between τ 6.2 and τ 7.0 for the ring α-amine protons and a singlet at τ 7.10 for the N-methyl group. The mass spectrum of 41-2 contained an M^+ ion peak for amine 41-1 at m/e = 125 and peaks at m/e = 36 and 38 for HCl. The picrate of 41-1 had the decomposition point at 255° (reported 250°) (152), and correct elemental analysis for $C_{14}H_{18}N_4O_7$.

The mass spectral fragmentation pattern of endo-

* The author wishes to thank both Dr. Gassman and Dr. Stella for making this date available.

chloramine 26-2 and both the HCl and picrate salts of 41-1 were similar below m/e = 100 (Scheme 2.4). Salts of amines have been shown to give similar mass spectral patterns as those of the parent amines (153). The m/e = 82 peak is usually characteristic of azabicyclic compounds containing an N-methylpyrollidine ring (38,154), although the fragmentation pathways may depend upon the substitution on the rings (155).



Scheme 2.4

LAH reduction of exo-chlorolactam 24-3 for a short reaction time gave 25% amine 41-1 and 75% of an unstable compound having ir absorptions at 2790 and 760 cm^{-1}. The nmr spectrum showed low-field multiplets at τ 0.6 and τ 7.2, integrated for 3 protons, and an N-methyl singlet at τ 7.57. This compound is believed to be exo-chloramine 27-2 which

may rapidly decompose via an aziridinium ion intermediate (See Discussion).

An attempt to remove chlorine, using sodium and t-butanol, from lactams 23-3 and 24-3 was unsuccessful, and caused hydrolysis of the amide bond. A similar relative inertness of halogens in [3,2,1] thiabicyclic system has been observed (156).

2-3-2 N-Chloro-N-(3-cyclohexen-1-yl)acetamide (11-3)

Photolysis of chloramide 11-3 in CCl_4 gave a complex mixture of products, and showed at least fourteen peaks by gc analysis. The major products were assigned as chloroacetamides 34-1 and 34-2 (30%), dichloroacetamide 34-3 (12%), and parent amide 11-1 (5%).

Acetamide 11-1 was identified on the basis of identical gc retention time and the presence of a weak olefinic signal at τ 4.37 in the nmr spectrum of the crude product. The mono- and dichloroacetamides, 34-1 or 34-2 and 34-3, were assigned on the basis of the gc-ms analysis (vide supra, 2-2-4).

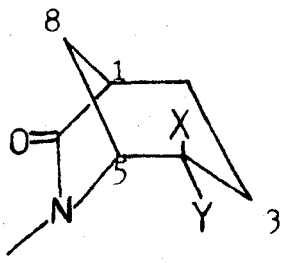
Gc-ms analysis of another compound in the crude mixture indicated the presence of perchloroethane (C_2Cl_6). The mass spectrum showed the highest peaks at m/e = 199 and above in a five chlorine pattern, suggesting a $^{+}CCl_2$-CCl_3 ion. The perchloro compound could arise from the combination of two $.CCl_3$ radicals, as found in other

photolyses in CCl_4 (157). All the remaining products were less than 5% yield and characterization of these was not attempted.

2-4 Nitrosamide Photolyses in the Presence of Trapping Agents

2-4-1 Photolysis of 8-2 Under Oxygen

When nitrosamide 8-2 was photolyzed under an oxygen atmosphere, no C-nitroso dimer absorption was observed in the uv spectrum of the photolysate. The products isolated were endo-nitratolactam 23-2 (35%), exo-nitratolactam 24-2 (17%), and starting amide 8-1 (8%).



23-2	X = H, Y = ONO_2
24-2	X = ONO_2, Y = H
23-4	X = H, Y = OH
24-4	X = OH, Y = H
23-5	X = H, Y = NO_2
24-5	X = NO_2, Y = H

The ir absorptions of endo-nitrate 23-2 were seen at 1690, 1630, 1280 and 860 cm^{-1}. The nmr spectrum exhibited a doublet of doublets at τ 4.90 (J = 9 and 7 H_z) for $CH\text{-}ONO_2$, a broad doublet at τ 6.15 (J = 6H_z) for H-5, and the N-methyl singlet at τ 7.05 (Figure 2.5). The mass spectrum at 80 ev showed the highest peak at m/e = 154 ($M\text{-}NO_2$) but, at 15 ev, the M^+ ion peak at 200 became visible

(2.5%). Distillation attempts only caused decomposition of nitrate 23-2.

The ir spectrum of exo-nitrate 24-2 had the same major absorptions as the endo-isomer. The nmr spectrum showed a multiplet at τ 4.74 ($W_{\frac{1}{2}}$ = 9 Hz) for CH-ONO_2, another multiplet at τ 6.18 for H-5, and the N-methyl signal at τ 7.08. The mass spectrum of 24-2 had a similar fragmentation pattern as 23-2 except for a small peak at m/e = 168, which may be due to loss of O_2 as is found in nitro compounds (158). The [3,2,1]bicyclic structure of the nitrates was confirmed by subjecting the nitrate lactam mixture to a reduction-oxidation sequence, similar to that shown in Eq 2.6, to give well-established ketoamine 28-3 as the sole product.

The identity of remainder of the compounds could not be established. Several fractions appeared to contain a mixture of endo- and exo-alcohols, 23-4 and 24-4, exhibiting absorptions at 3400, 1670 and 1070 cm^{-1} and nmr multiplets at τ 5.7 and τ 6.1, in addition to two singlets at τ 7.14 (major) and τ 7.17 (minor). Reaction of one of these fractions with p-nitrobenzoyl chloride gave a mixture whose ir spectrum showed a carbonyl absorption at 1715 cm^{-1} and a decreased 1070 cm^{-1} absorption, but the derivative could not be crystallized.

The material eluted last by chromatography did not contain oxime, as demonstrated by the absence of ketolactam 22-3 in the product after bisulfite hydrolysis (vide infa).

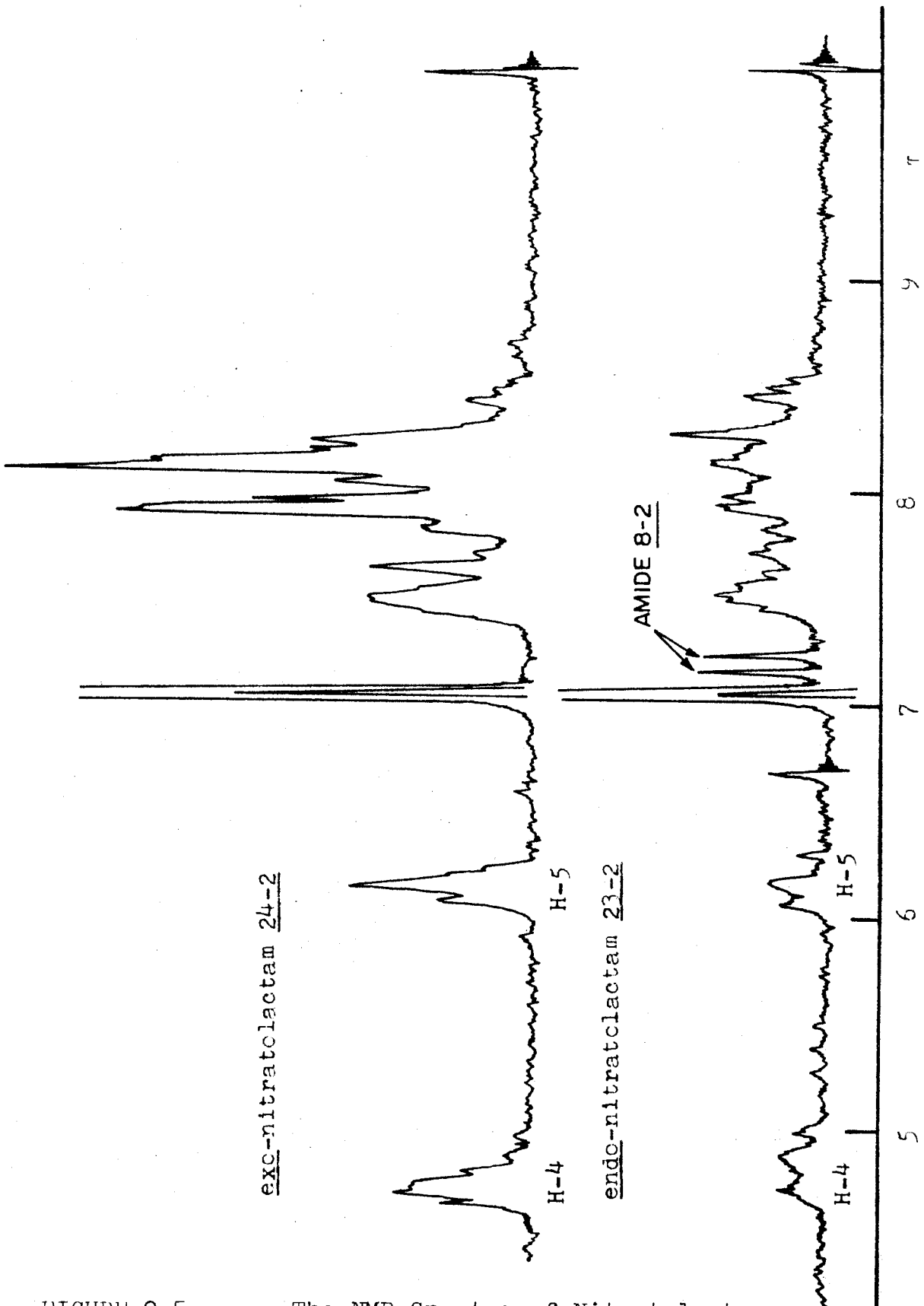
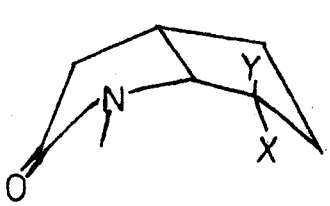


FIGURE 2.5 The NMR Spectra of Nitratolactams 23-2 and 24-2.

The presence of nitrolactams 23-5 and 24-5 was indicated by the absorptions at 1550 cm^{-1} (73), as well as by the mass spectrum of this mixture, which showed a peak at m/e = 184 corresponding to M^+ ion of 23-5 or 24-5. Nitro-compounds have been found in the oxidative photolyses of nitrosamides previously investigated in this group (142).

2-4-2 N-Nitroso-N-methyl-2-cyclopentene-1-acetamide (14-2) in $BrCCl_3$

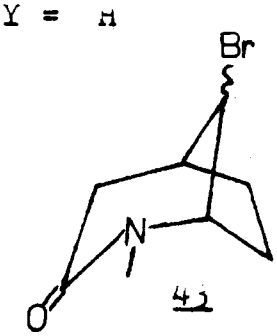
Photolysis of nitrosamide 14-2 in bromotrichloromethane under nitrogen gave an 89% yield of exo-bromolactam 42-1, based on 14-2 (47% yield from amide 14-1). The distilled solvent was blue-colored and the uv spectrum showed a weak peak at 580 nm for CCl_3NO (159).



42-1 X = H, Y = Br

42-2 X = Br, Y = H

44 X,Y = H



43

The chromatographic fractions containing bromolactam 42-1 were examined with a variety of gc columns and conditions to show only one peak, indicating a single isomer. The ir spectrum contained a lactam absorption at 1685 cm^{-1}, the same position as lactam 44 (100) but higher than that expected for the alternate cyclization product 43. The mass spectrum showed the presence of one bromine and gave the acceptable exact mass for $C_8H_{12}NOBr^{(9)}$.

The nmr spectrum in $CDCl_3$ did not clarify the structure but the addition of $Eu(fod)_3^*$ made possible a more definite assignment, shown in Figure 2.6. The shifts obtained are comparable to those of a 3-aza-4-keto-[4,2,1] bicyclic lactam (101), and indicate that the europium is coordinated to the oxygen. Decoupling experiments were carried out on the solution containing $Eu(fod)_3$. Irradiation at H-4 caused the H-8 doublet to collapse and

* $Eu(fod)_3$ = tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)europium(III)

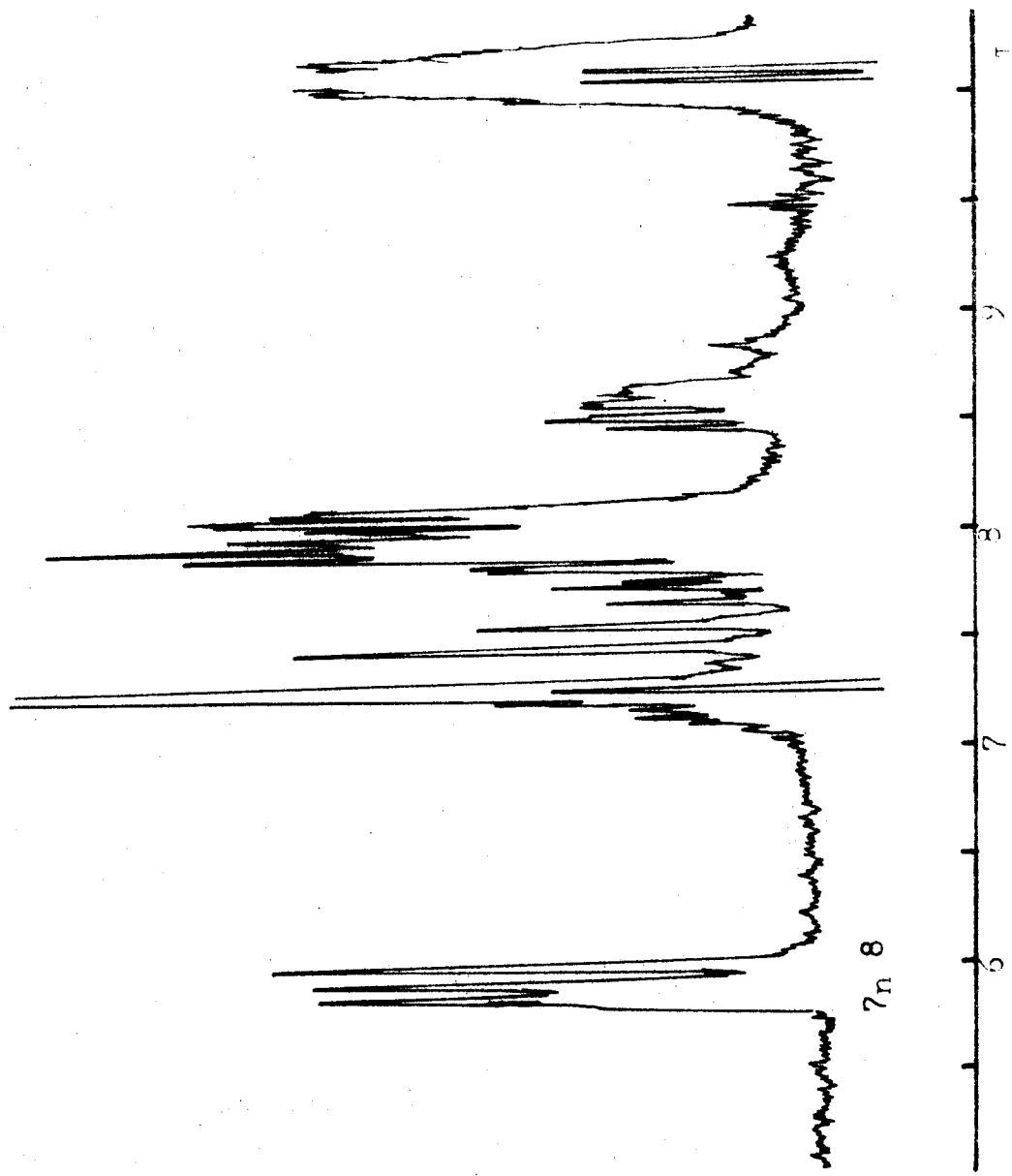


FIGURE 2.6a The NMR Spectra of endo-Bromolactam 42-1.

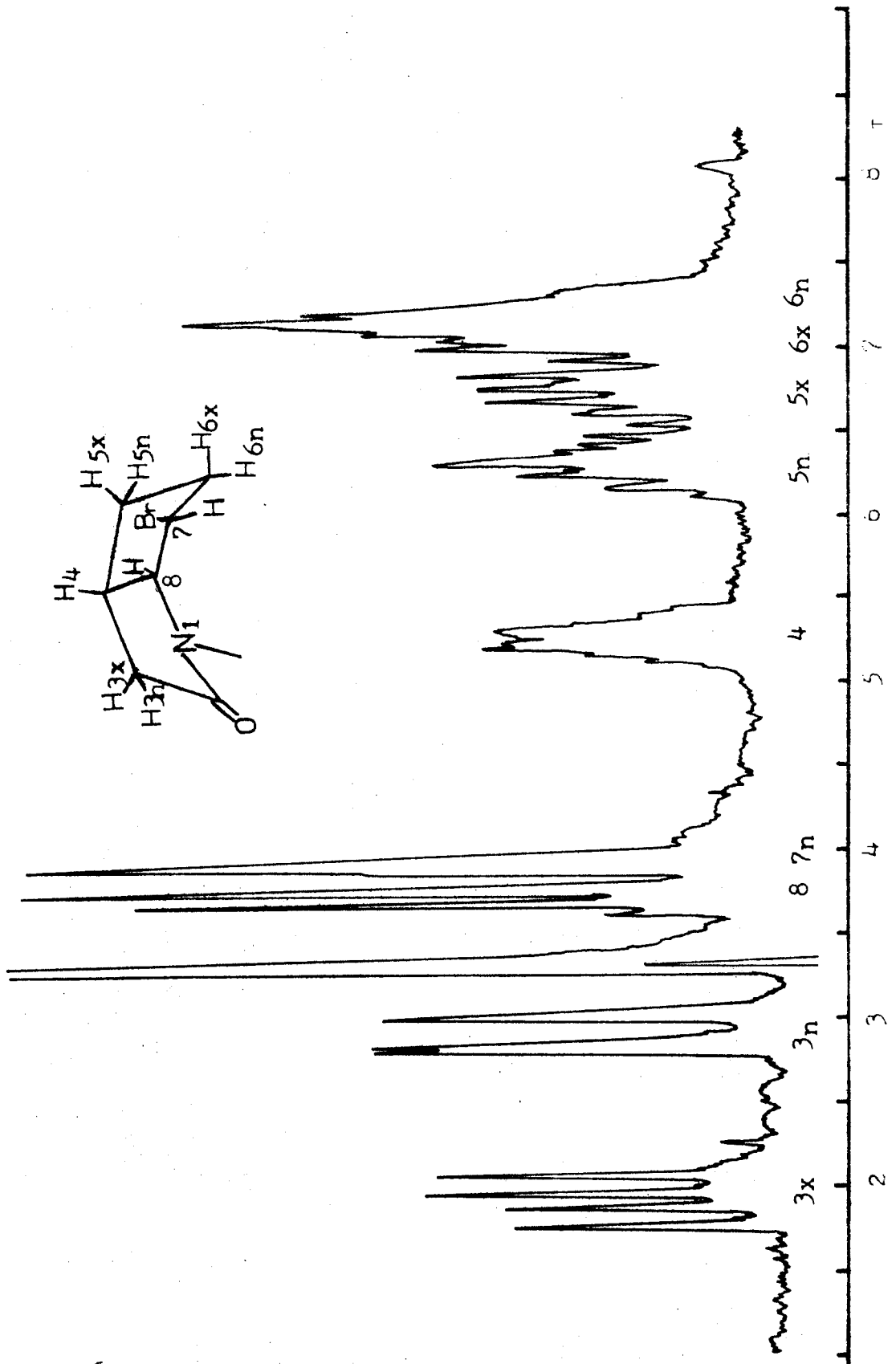


FIGURE 2.6b The NMR Spectra of Bromolactam 42-1 in the presence of $Eu(fod)_3$

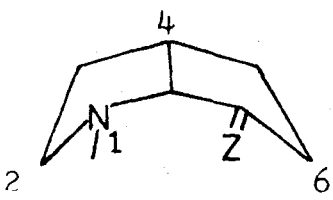
H-3_n and H-3_x to become an AB quartet (J= 18.5 Hz), as well as changing the H-5_x splitting pattern. Irradiation of H-3_n caused the H-3_x proton signal to collapse to what appears to be a doublet (J = 10 Hz) and the H-4 signal becomes a poorly resolved quartet (J = 8-9 Hz) with a further doublet splitting (J = 3 Hz) of the quartet lines. Irradiation at H-6_x caused the H-7_n signal to collapse to a doublet (J = 3.5 Hz). The small coupling of H-7_n with H-8 (J = 1-2 Hz) is in reasonable agreement with that found in other [3,3,0] azabicyclic compounds (162).

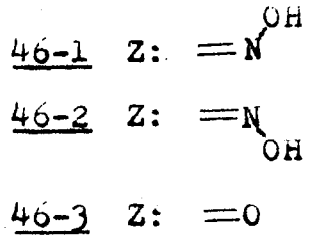
Confirmation of structure 42-1 came from LAH reduction to the cis-fused [3,3,0] bicyclic amine 45, which showed an M ion peak at m/e = 125. The picrate of 45 decomposed at 204-207° (literature 207° dec.) (160).

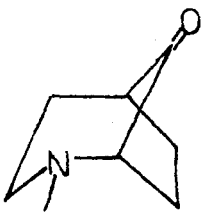
2-5 Photolysis of Alkenyl Nitrosamines

2-5-1 N-Nitroso-N-methyl-2-(2-cyclopentene)ethylamine (15-2)

Photolysis of 15-2 followed by chromatography of the crude residue on alumina gave anti-oxime 46-1 (48%), syn-oxime 46-2 (34%) and aminoketone 46-3 (9%). The isolated yields were lower when silicic acid chromatography was used, giving 46-1 (38%), 46-2 (27%), and 46-3 (3%).







47

The ir spectrum of anti-oxime 46-1 contained peaks at 3350, 1050 and 950 cm^{-1}. The nmr spectrum exhibited a doublet at τ 6.9 ($J = 8$ Hz) for H-8 and an N-methyl singlet at τ 7.59. The cis-fusion of the rings was assigned based on the same vicinal coupling constant($J_{4,8} = 8$ Hz) in 46-1 as that found in 42-1 and is also found in other cis-fused 5-membered rings (163). The mass spectrum of 46-1 contained the M^+ ion peak at 154.

Complete separation of syn-oxime 46-2 from the anti-isomer was not achieved, but a 75% pure sample showed a lower-field doublet at τ 6.12 ($J = 8$ Hz) for H-8 and the N-methyl singlet at τ 7.32. The syn-isomer was found to isomerize to anti-oxime 46-1 after storage in $CDCl_3$ as judged from the ratio of the H-8 doublets and the N-methyl singlets.

Aminoketone 46-3 could be obtained in 45% yield by bisulfite hydrolysis of the crude oxime mixture. Ketone

46-3 had an ir absorption at 1745 cm^{-1} with a shoulder at 1737 cm^{-1}. The absorptions are typical of cyclopentanone compounds (164); the presence of twin carbonyl absorptions in other amino-ketones has been attributed to Fermi interactions (165). The mass spectrum contained the M^+ ion peak (35%) and an unusually intense M+1 ion peak at 140 (12%). The nmr spectrum showed multiplets for two protons between τ 6.7 and τ 7.1, a broad doublet (J = 7 Hz), and the N-methyl singlet at τ 7.53.

Deuterium exchange of aminoketone in pyridine-D_2O at 50° was monitored by nmr spectroscopy. After one hour, the total proton integration for 46-3 had decreased by 1.7 protons and the DHO signal at τ 5.4 showed a corresponding integration increase. Although the amount of deuterium exchange does not differentiate between structure 46-3 and 47, the facile exchange under the mild conditions* indicate structure 47 is less likely. Exchange of the bridgehead protons of 37-2 occurs (147), but was not observed in 37-3 (149) in sodium methoxide -D_2O. The M^+ ion peaks of the exchanged sample of 46-3 were examined by gc-mass spectra to give the results shown in Table 2.7. There is a good correlation between the nmr and mass spectra values for the average amount of deuterium incorporated. The fact that 12 ± 3% of the molecules contain three deuterium atoms confirms the structure 46-3.

* The pyridine-D_2O exchange procedure has been used with base-sensitive carbohydrates (166).

Table 2.7 Deuterium Exchange of 46-3

m/e	Ion Peak Intensity (%)[1] Average	Corr'd Average[2]	Relative Percentage[3]	Fraction of Deuterium Content[4]
139	6	6	10	0
140	22	20	32	.32
141	38	31	47	.94
142	17	7	12	.36
				1.62 Total

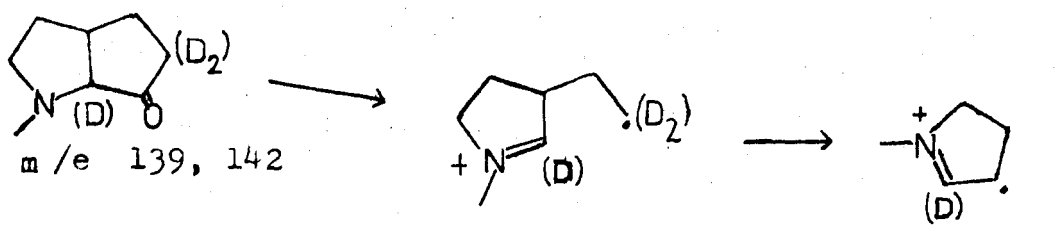
1) Values have maximum error of ± 25%.

2) Peak Intensity - ⅓ of corrected M^+ ion intensity for previous peak, assuming M+1 ion is the same intensity for each deuterated species.

3) Intensity of each peak as a percentage of total of all corrected M^+ ion intensities.

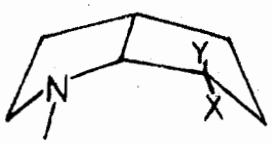
4) Fraction of the total number of molecules times the number of deuterium incorporated in each species.

The m/e = 111 peak showed the same deuterium incorporation ratio as the M^+ ion peak. The m/e = 84 peak showed an 11% increase. If the H-8 proton is assumed to be the least exchanged, the fragmentation pattern of 46-3 can be explained as shown in Scheme 2.5.



Scheme 2.5

Ketone 46-3 was reduced in acidic conditions over PtO_2 to the aminoalcohols 48-1 and 48-2 (3300 and 1020 cm^{-1}), although this same procedure had successfully reduced other aminoketones to amines (167). The nmr spectrum of a mixture of 48-1 and 48-2 showed

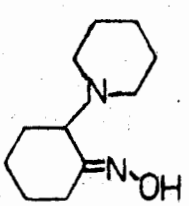


48-1 X = H, Y = OH

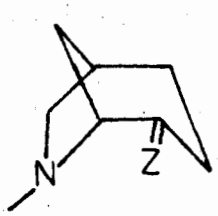
48-2 X = OH, Y = H

—CH—OH absorptions from τ 5.9 to τ 6.2 and two equal intensity singlets at τ 7.63 and τ 7.69.

A mixture of oximes 46-1 and 46-2 could also be hydrolyzed to aminoketone 46-3 using dilute HCl. Several other literature methods (See 5-12-1) were less efficient for hydrolysis of either this mixture, or 2-piperidinocyclohexanone oxime (49-1), to the corresponding ketone. Model compounds, oximes 28-1 and 28-2, were used in the alkaline hydrolysis — $NaBH_4$ reduction method of Bell (168), but gave a poor yield of alcohols 26-1 and 27-1 (See Experimental 5-12-1).



49-1

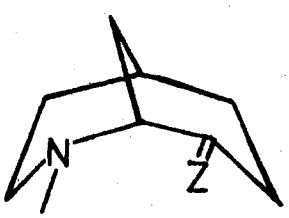


28-1 Z: $=N-OH$

28-2 Z: $=N-OH$

2-5-2 N-Nitroso-N-methyl-2-(3-cyclohexene)ethylamine (16-2)

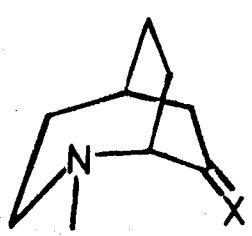
The photolysis of 16-2 in an acidic methanol solution gave products tentatively assigned as anti-oxime 50-1 (16%), syn-oxime 50-2 (9%), and aminoketone 50-3 (6%); the yields were calculated on the amount of reacted 16-2 (> 82%). The [3,3,1]bicyclic skeleton was assigned in analogy to the fact that other radical cyclizations at low temperatures give six-membered rings in preference to seven-membered ones (See Introduction 1-2, Table 1.3), but the alternate structures 51-1, 51-2 and 51-3 could not be excluded.



50-1 Z: $=N-OH$

50-2 Z: $=N-OH$

50-3 Z: $=O$



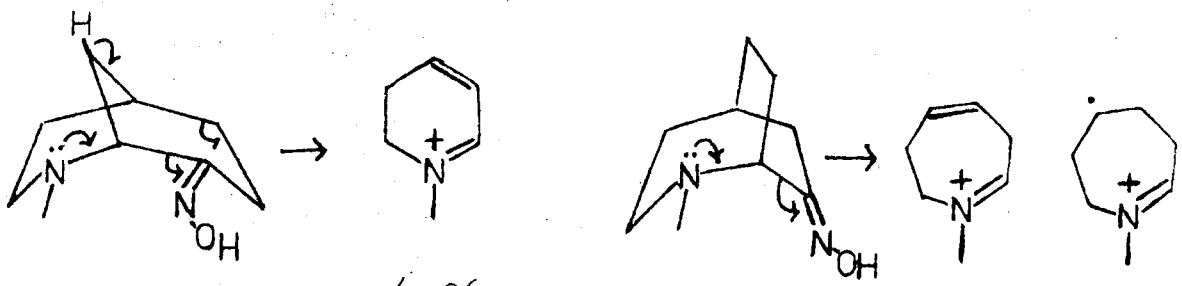
51-1 X: $=N-OH$

51-2 X: $=N-OH$

51-3 X: $=O$

The amino-oxime assigned as 50-1 showed ir absorptions at 3300, 2800, 1145 and 930 cm^{-1}; the nmr spectrum showed one proton multiplets at τ 6.75, τ 7.2 and τ 7.67, and the N-methyl singlet at τ 7.75. The mass spectrum gave acceptable exact mass for $C_8H_{16}N_2O$ and contained a major peak at m/e = 96. The latter peak would be expected from

the normal oxime fragmentation of 50-1, while an m/e = 111 or 110 ion peak might be expected from 51-1 (Scheme 2.6).



m/e 96 m/e 110,111

Scheme 2.6

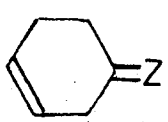
The product suggested to be syn-oxime 50-2 had similar ir absorptions to 50-1 and an M^+ ion peak of 108. The nmr spectrum exhibited a multiplet for H-1 at τ 6.4 and the N-methyl singlet at τ 7.40, both of which resonated at lower fields than those of the anti-isomer. When 50-2 was stored, the $N-CH_3$ signal decreased and the τ 7.75 singlet was seen. The amino-ketone assigned as 50-3 showed a carbonyl absorption at 1710 cm^{-1} and the nmr spectrum contained the N-methyl singlet at τ 7.73. Bisulfite hydrolysis of the crude photolysate residue gave only a low yield of 50-3, which decomposed on distillation.

2-5-3 N-Nitroso-N-methyl-(3-cyclohexen-1-yl)amine (17-2)

The photolysis of nitrosamine 17-2 could not be carried to completion due to an increasing product absorption band below 300nm which tailed into the nitrosamine $n \rightarrow \pi^*$ absorption. Of the material recovered from the photolysis in methanol, the acidic fraction comprised 57%

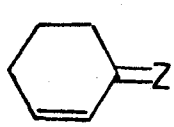
and was largely unreacted nitrosamine 17-2. The major component of the basic fraction was parent amine 17-1 (60% yield based on reacted nitrosamine).

The acid fraction contained a minor product with an ir absorption at 1720 cm^{-1} and gave a precipitate with dinitrophenylhydrazine (DNPH). The distilled solvent from the acidic acid photolysis was treated with DNPH to give the 2, 4-dinitrophenylhydrazone of an unsaturated ketone. The mass spectrum of the derivative contained an M^+ ion peak at 276 and the major mass peaks were two mass units less than the published spectrum of cyclohexanone DNPH (169). Because a sharp melting point could not be obtained and the uv spectrum of the DNPH showed λ_{max} at 372nm, a position between the absorption maxima of saturated and α,β-unsaturated DNPH derivatives (360-365 and 375-385 nm) (122), it is believed 52-2 is initially formed and isomerized to 52-4. This is supported by



52-1 Z: =O

52-2 Z: =N-NH-$C_6H_3N_2O_4$



52-3 Z: =O

52-4 Z: =N-NH-$C_6H_3N_2O_4$

the ir absorption at 1720 cm^{-1}, assignable to 52-1, in the crude acidic fraction.

Chromatography of the basic fraction from the photolysis in methanol gave the hydrochloride salt of 17-1, in addition to a minor amount of free amine 17-1 as indicated by the N-methyl singlet at τ 7.53. Hydrochloride 17-4 had ir absorptions at 2720 and 2450 cm^{-1}, and nmr signals at τ 4.30 (-CH = CH-), τ 7.0 (-$\dot{C}$H -N) and τ 7.36 (-N-CH_3). The remainder of the material was a mixture of compounds less polar than amine 17-1. The mixture showed ir absorptions at 3300, 3030 and 1660 cm^{-1}, and the continued presence of the τ 4.34 signal for the olefinic protons indicated no cyclization. They appeared to be products derived from α-hydrogen elimination, since there was no N-methyl singlet observable in the nmr spectra; they were not further investigated.

The basic fraction obtained from a separate photolysis of 17-2 in acetic acid contained at least six products, one of which had identical tlc retention time as nitrosamine 17-2. The major product appeared to be amine 17-1 from the N-methyl singlet at τ 7.55 and olefinic protons at τ 4.34. The low yield of this reaction deterred further examination of the products.

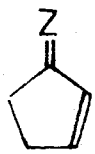
2-5-4 N-Nitroso-N-methyl-2-cyclopentene-1-methylamine (18-2)

The uv spectra of the photolysate of nitrosamine 18-2 showed no C-nitroso dimer absorption. Normal work-up

gave an acidic fraction which appeared to contain 2-cyclopentenone oxime, 53-1. The basic fraction showed a mixture of at least fifteen products when examined by gas chromatography. Of the three major peaks, one had an identical retention time as that of parent amine 18-1 (18% of the basic fraction), and the two others had longer retention times at 7.8 minutes (Compound A, 16%) and 10.4 minutes (Compound B, 18%).

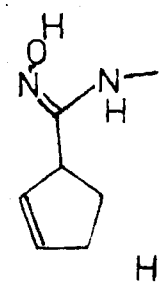
The possibility of 53-1 as a product in the acidic fraction was suggested by the nmr signals at τ 3.85 and τ 4.2 (-CH = CH-), and τ 7.2 - 8.2, but the product could not be crystallized. The two unknown compounds, A and B (1:2 ratio), were the major components of a fraction obtained by continuous extraction of the aqueous phase. The ir spectrum of this mixture contained absorptions at 3200, 3060, 1690 (m), 1115 and 915 cm^{-1}. The nmr spectrum showed only a broad absorption at τ 7.37 (2H, $W_{\frac{1}{2}}$ = 7 H_Z), and two singlets at τ 6.75 (2H) and τ 7.09 (3H). The gc-mass spectrum of compound A had a low intensity peak at m/e = 102, a 100% intensity peak at m/e = 59, and other major peaks at m/e = 89, 58 and 45. The gc-mass spectrum of B showed the highest peak at m/e = 154, a 100% peak at m/e = 96, and major peaks at m/e = 97, 80 and 53. Both the nmr and mass spectra rule out the products expected from the usual nitrosamine decomposition pathways, e.g., 53-1 (M^+ = 97), 53-2 (M^+ = 82), and 54-1 to 54-3

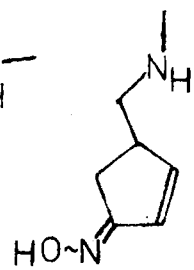
(M^+ = 140). The major portion of the basic fraction was volatile, and only polymer remained after an attempted distillation.

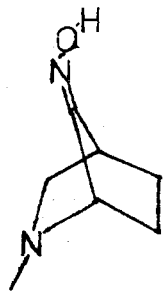


53-1 Z: N-OH

53-2 Z: =O



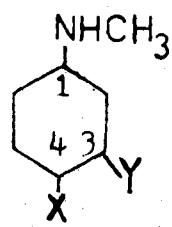




54-1 54-2 54-3

2-6 N-Chloro-N-methyl-(3-cyclohexen-1-yl)amine (17-3)

The iron-salt catalyzed decomposition of 17-3 in an acetic acid-water solution gave parent amine 17-1 (30%), and the compounds assigned as the $ClOAc$ adducts, 55-1 (10%) and 55-2 (15%), and the Cl_2 adduct, 55-3 (20%). The yields were calculated based on the amount of 17-1 used.



55-1 X = Cl, Y = OAc

55-2 X = OAc, Y = Cl

55-3 X,Y = Cl

Chromatography of the mixture did not give complete separation of the addition products and the data for these compounds was obtained from fractions containing primarily one component. All the -CH-Cl proton signals showed a large coupling indicative of the C-H bond orientation being trans-diaxial. Dichloramine 55-3 showed ir absorptions at 2800 and 730 cm^{-1}, and the nmr spectrum contained a multi-

plet at τ 5.71 (2 H) and the N-methyl singlet at τ 7.57. The gc-mass spectrum had a two chlorine pattern for M^+ ion at 181 and 183.

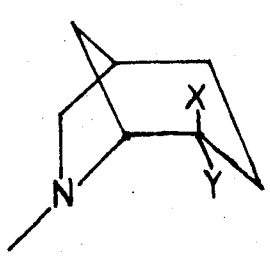
The ir spectrum of a mixture of chloroacetates 55-1 and 55-2 showed an absorption at 1740 cm^{-1}. They both showed the same fragmentation pattern in the gc-mass spectrum and had M^+ ion peak at 205 and 207 in a one chlorine pattern. The nmr spectrum exhibited two sets of signals, one tentatively assigned as 55-1 with multiplets at τ 5.1 (CH-OAc) and τ 5.9 (CH-Cl), and the acetate singlet at τ 7.92; the corresponding signals for 55-2 were found at τ 4.9, 5.95 and 7.84. The respective assignments are based on the assumption that the proton on the substituted carbon closest to the amine, i.e., C - 3, would resonate at lower field than the proton of the compound with the same substitution on C - 4.

The gc of the crude mixture also showed a peak (5%) with a mass spectrum containing peaks at m/e = 164 ± 1, 125, 83 and 82, but this compound was not identified. The minor quantities of the other compounds set the upper limit of cyclization as 3%.

2-7 Trapping of Nitrosamine Cyclization Intermediates

2-7-1 N-Nitroso-N-methyl-3-cyclohexene-1-methylamine (19-2) Under O_2

The oxidative photolysis of nitrosamine 19-2 in a methanol solution containing HCl gave endo-nitrate amine 26-3 (15%), aminoketone 28-3 (31%), and exo-alcohol 27-1 (20%). A similar photolysis using 70% perchloric acid as a proton source did not give a crystalline perchlorate salt, as found in other photo-oxidation reactions (142). The products from chromatography of this crude residue were endo-nitrate 26-3 (15%), aminoketone 28-3 (11%), exo-alcohol 27-1 (29%) and a 9% yield of a product assigned as the HCl salt of endo-alcohol 26-1, 26-4.



26-1	X = H, Y = OH
26-3	X = H, Y = ONO_2
26-5	X = H, Y = Br
27-1	X = OH, Y = H
27-3	X = ONO_2, Y = H

The nitrate ir absorptions of 26-3 were seen at 1620, 1275 and 860 cm^{-1}. The nmr spectrum showed the pattern of an axial proton for $-\overset{|}{C}H-ONO_2$ at τ 5.25 (J = 10, 6, and 2 H_Z) and the N-methyl singlet at τ 7.53. The mass spectrum contained the highest mass peak at m/e = 140 (M - NO_2) with

the 100% peak at m/e = 82, but no M^+ ion peak. In basic solution, endo-nitrate 26-3 was relatively stable, but nitration of exo-alcohol 27-1 gave an unisolated nitrate product which decomposed rapidly to ketone 28-3 as was witnessed by the equally intense peaks at 1720 and 1620 cm^{-1} when left at room temperature for 24 hours. Formation of exo-nitrate from 27-1 is most probable, since the same nitration procedure involving a nitronium ion was used by Shriner (170) to prepare nitrates with optical rotation in the same direction as the starting alcohols.

The [3,2,1]azabicyclic structure of endo-nitrate 26-3 was indicated by the 100% peak at m/e = 82 in the mass spectrum, and the doublet for H-5 (J = 7 H_z) at τ 6.80 in the nmr spectrum. Immediate reduction of the crude basic product, followed by oxidation, in a sequence similar to Eq 2.6 (2-2-1), gave ketone 28-3 (vide supra) in 55% overall yield. In view of the volatility of alconols 26-1 and 27-1, and the fact that the last step, CrO_3 oxidation gives no more than a 60% yield, it is necessary that nitrate 26-3 was one of the major sources of ketone 28-3.

The ir spectrum of exo-alcohol 27-1 showed absorptions at 3350, 2790 and 1005 cm^{-1}. The mass spectrum had the M^+ ion peak at 141 with the 100% peak at m/e = 82. The nmr spectrum contained a broad triplet at τ 6.1 (J = 5 H_z) and the N-methyl signal at τ 7.50 (Figure 2.7). Jones' oxidation to the known ketone 28-3 in 53% yield

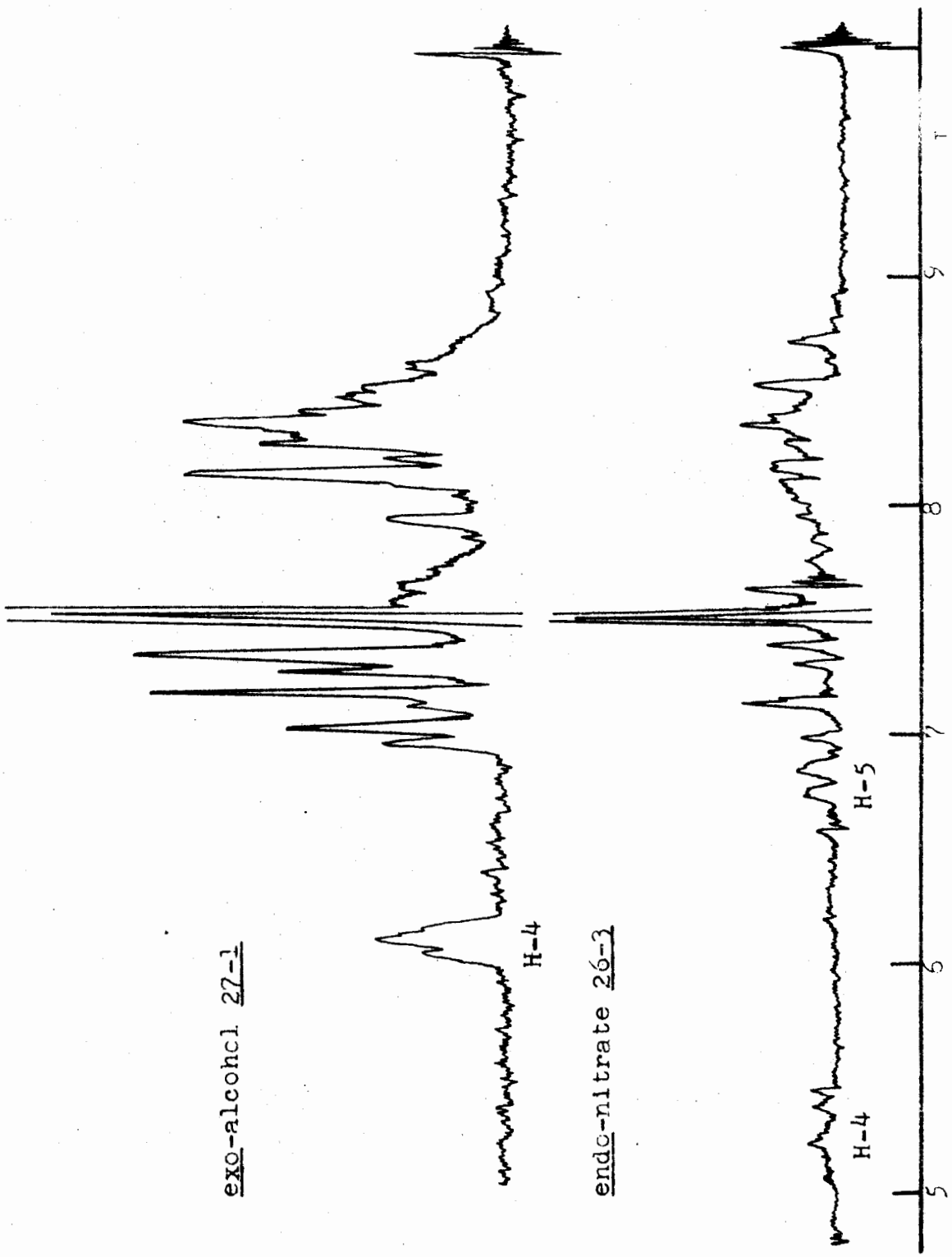


FIGURE 2.7 The NMR Spectra of exo-Alcohol 27-1 and endo-nitrate 26-3.

confirmed the [3,2,1]azabicyclic system.

The endo-alcohol HCl salt 26-4 was obtained by continuous extraction of the basic aqueous solution of the perchloric acid photolysate residue*. The ir spectrum of 26-4 showed absorptions at 2605 (HCl salt) and 1100 cm^{-1}. The nmr spectrum in D_2O contained a multiplet at τ 6.3 (-CH - O) and the N-methyl singlet at τ 6.66. The mass spectrum exhibited an M^+ ion for 26-1 at 141 and the intense m/e = 82 peak. Ketone 28-3 was obtained upon a Jones' oxidation.

A control photolysis of 19-2 under nitrogen in neutral methanol conditions caused no decrease in the nitrosamine $n \rightarrow \pi^*$ uv absorption. Addition of 0.2 equivalents of HCl, and continued irradiation, caused a 10% decrease in the uv absorption. Nitrosamine 19-2 (65%) was recovered from the photolysate.

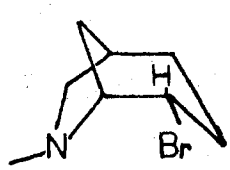
* The highly water soluble nature of azabicyclic amino alcohols has been noted by others (38).

2-7-2 Photolysis of Nitrosamine 19-2 in $BrCCl_3$

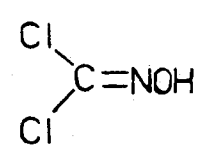
The distilled solvent from the photolysis of 19-2 in 25% $BrCCl_3$- methanol solution showed the blue color indicative of the presence of Cl_3C-NO (115). The basic fraction contained virtually pure (>90%) endo-bromoamine 26-5 (55% yield).

The ir spectrum of 26-5 showed Bohlmann bands at 2840 and 2780 cm^{-1}. The nmr spectrum contained the characteristic pattern of an axial H-4 of a [3,2,1] azabicyclic system at τ 5.98 (J = 9, 7.5 and 1.5 Hz), and the N-methyl singlet at τ 7.45 (Figure 2.4). The exact mass determination gave figures in agreement with $C_8H_{14}NBr^{79}$ (M^+ ion) and with C_5H_8N (m/e = 82 ion).

The acid fraction contained a major product in 64% yield by gc analysis. The gc-mass spectrum of this peak showed M^+ ion peaks at 113 and 115 in a two chlorine pattern, and showed the 100% peak at m/e = 78 containing one chlorine. The ir spectrum of the acid fraction showed absorptions at 3200 and 985. This compound was tentatively assigned as dichloroformyl oxime (56), which could arise from the decomposition of trichloronitrosomethane.



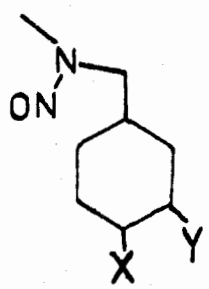
26-5



56

2-7-3 Photolysis of Nitrosamine 19-2 in the Presence of I_2

The iodine concentration used in this experiment (0.047M.) was similar to the nitrite photolysis trapping experiments (99, 171). In acidic methanol the iodine absorption in the 350 nm region was approximately 100 times greater than that of the nitrosamine $n \rightarrow \pi^*$ absorption. After twelve hours photolysis and removal of the iodine by thiosulfate, a strong nitrosamine uv absorption was observed, indicating a high percentage of unchanged nitrosamine. The usual workup procedure gave a basic fraction containing less than a 5% yield of parent amine 19-1 (vide infra), in addition to sulfur from the thiosulfate. The neutral products were nitrosamine 19-2 (23%), a chloroiodo adduct, which was either 57-1 or 57-2 (10%), and an unidentified compound C (ca. 12%).



57-1 X = I , Y = Cl

57-2 X = Cl, Y = I

The chloroiodo nitrosamine 57-1 or 57-2 showed ir absorptions at 1450, 1430, 1330 and 1160 cm^{-1}. The nmr spectrum exhibited a broad multiplet at τ 5.4 (2 H), doublets (J = 6.5 Hz) at τ 6.05 and 6.57, and singlets at τ 6.38 and 7.07 for the Z- and E - nitrosamine isomers

in a 1:4 ratio. The mass spectrum contained an M^+ ion peak at 316, 318 and the first fragmentation was the loss of CH_4N_2O to m/e = 256,258 in a one chlorine ratio (3:1).

The later fractions from chromatography of the photolysate residue contained both 19-2 and another product. Compound C appears to be a nitrosamine showing ir absorptions at 1450, 1430, 1330, 1180 and 1140 cm^{-1}. The nmr spectrum contained multiplets at τ 5.4 and 6.36, a doublet at τ 5.59 (J = 7 H_z), and singlets at τ 6.2 and 6.95. The mass spectrum had low-intensity peaks at m/e = 295 and 252, while the chlorine isotope pattern was not seen in any of the fragments.

In a dark control reaction under comparable conditions, the nmr spectrum of the crude product, isolated after three hours reaction time, showed the presence of 20% of the addition products, as judged by the intensity of the τ 5.4 multiplet.

2-8 N-Nitroso-N-methylphenethylamine (20-2)

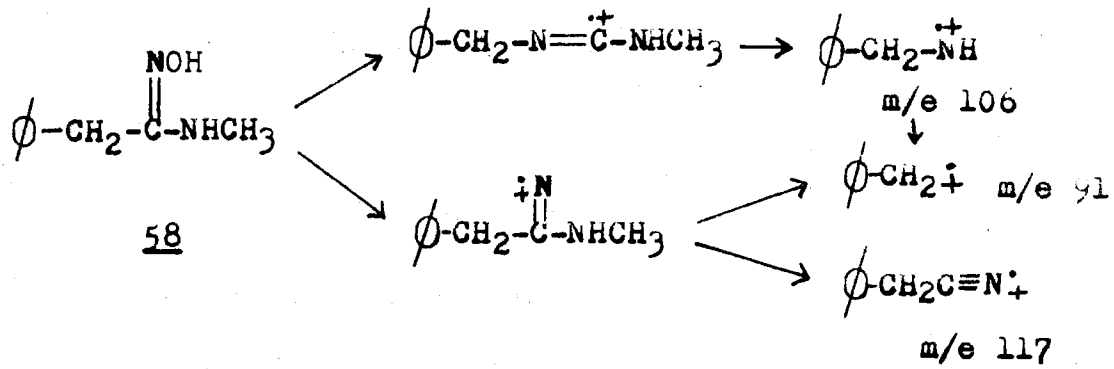
2-8-1 Photolysis of 20-2 in Acidic Methanol

Photolysis of nitrosamine 20-2 in the usual manner gave 20-2 (1%), benzaldehyde (BA, 4%), benzaldehyde oxime (BAO, 13%), amidoxime 58 (22%), parent amine 20-1 (10%), and a product tentatively assigned as phenethylamine (59-1, 3%).

Nitrosamine 20-2 and amine 20-1 were proven by identical gc retention times and spectra as those of authentic samples. The product assigned as amine 59-1 was not isolated but gc analysis of the crude residue showed a peak with the same retention time as that of 59-1. The gc retention times and spectral data of both benzaldehyde and its oxime were identical to those of the authentic compounds.

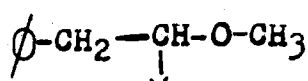
The ir spectrum of amidoxime 58 showed absorptions at 3400, 3200, 3060, 3025, 1650(b), 1630(b), and 715 cm^{-1}. The nmr spectrum exhibited a low-field exchangeable proton at τ 0.5, the aromatic protons at τ 2.85, the methylene singlet at τ 6.49, and the N-methyl singlet at τ 7.40. Only one oxime isomer was found, and was assigned the syn-form based on the arguments presented by Chow (172). The mass spectrum of 60-1 showed the intense M^+ ion peak with acceptable exact mass for $C_9H_{12}N_2O$. The peak at m/e = 106 (14% intensity) gave exact mass determination for C_7H_8N. This

peak could arise from a Beckmann rearrangement in the mass spectrometer (Scheme 2.7a), although Djerassi et.al.(173) have proven that such a rearrangement does not occur in benzophenone oxime.



Scheme 2.7

Chromatography also gave an unstable compound, designated D, which absorbed at 3350, 3060, 3025, 1120, 1060, 745 and 695 cm^{-1} in the ir spectrum. The nmr signals consisted of a multiplet at τ 2.9 (5 H), a triplet at τ 5.46 (1H, J = 5 Hz), a doublet at τ 7.08 (2H, J = 5 Hz), and a singlet at τ 6.70 (ca. 5 H). A possible structure for D might be the acetal 60-1 containing magnetically equivalent methyl groups, and could decompose to hemiacetal 60-2 or phenylacetaldehyde (PA).



60-1 X = OCH_3
60-2 X = OH

2-8-2 Photolysis of 20-2 in Acetic Acid

The photodecomposition of 20-2 in 1 molar H_2SO_4 in acetic acid could not be carried to completion because of an intense emerging absorption of a product overlapping with the nitrosamine $n \rightarrow \pi^*$ absorption in the 340 nm region. The products by gc analysis were identified as nitrosamine 20-2 (37%), amine 20-1 (2%), BA (18%), BAO (9%), and two other compounds whose retention times corresponded to amine 59-1 (3%) and phenylacetaldehyde (2%). BA was identified as the 2, 4-dinitrophenylhydrazone (m.p. 235-237°).

In the gc of the crude mixture, no peak was observed for the cyclization product N-methylindoline, 61. Amine 61, prepared by the methylation of indoline, showed in the nmr spectrum a distinct pattern of multiplets at τ 2.8 and 3.8 for the aromatic protons and between τ 6.7 and τ 7.4 for the aliphatic protons, and the N-methyl singlet at τ 7.42.

The products obtained from the photolysis in acetic acid containing HCl (0.11M) were nitrosamine 20-2 (6%), parent amine 20-1 (30%), BAO (12%), and N-formylphenethylamine (59-2, 19%). Formamide 59-2 was identical to an authentic sample, prepared by reacting formic acid with 59-1 (174). The ir absorptions were seen at 3300, 3060, 3030, 1660, 1530 (m), 745 and 700 cm^{-1}. The nmr spectrum showed a doublet at τ 2.04 ($J = 2$ Hz), a signal at τ 2.85 for the aromatic protons, a triplet at τ 7.25 ($J = 7$ Hz), and

a quintet at τ 6.61 (J = 7 H_z , $-CH_2-NH-$) which collapsed on D_2O exchange to a triplet. The expected M^+ ion peak at 149 was seen in the mass spectrum; the 100% peak was at m/e = 104 for the $C_6H_5-\overset{+}{C}H-CH_2\cdot$ fragment.

The nmr spectra of the other chromatographic fractions of the HCl-acetic acid photolysis residue showed a broad singlet for the aromatic protons in the τ 2.75 region. None of the mixtures showed the multiplet pattern at τ 2.9 and 3.8 of 61, and were not further investigated. A solution of benzaldehyde in methanol when evaporated under vacuum on the rotary evaporator gave less than a 50% recovery of benzaldehyde (See 5-18f). It is suspected that evaporation of acetic acid at a higher temperature caused extensive loss of BA. The actual yields of BA in both 2-8-1 and 2-8-2 therefore could be higher than reported.

2-9 Interconversion of Benzaldehyde and Benzaldehyde Oxime

Benzaldehyde, found as a product in the photo-decomposition of nitrosamine 20-2, could arise either by hydrolysis of the corresponding oxime or be produced by secondary photoreactions of 20-2. A photo-Beckmann rearrangement of BAO to benzamide does not occur when > 300 nm light was used (175).

A set of control reactions, using gc analysis, showed that acid hydrolysis of BAO at room temperature, or photolysis of BAO (Rayonet 350 nm lamps), or stirring BAO with

N-nitrosodimethylamine (NDM) in the dark gave 3 ± 1% BA and 1% yield of a product with identical retention time as benzonitrile. BA when stirred with NDM in acid gave 6% BAO, but photolysis (Rayonet) of this solution to 10-15% NDM decomposition gave only BA. When an acidic solution of equal amounts BAO and NDM was photolyzed (Rayonet 350 nm lamps) to 10% NDM decomposition, the yield of benzaldehyde increased to 9%. When an HCl-methanol solution of BAO and NDM (1:2 ratio) was photolyzed using a Nonex filter and 200 Watt lamp until 80% NDM decomposition, approximately 50% of the BAO had disappeared and BA increased to 25%. The dark control reaction under similar conditions showed only a 5% increase in BA.

2-10 Decomposition of N-Chloro-N-methylphenethylamine (20-3)

2-10-1 Reaction of 20-3 with Ferrous Sulfate

The reaction of chloramine 20-3 with ferrous ion in 1 Molar H_2SO_4 - acetic acid gave benzyl chloride (BC, 40%), parent amine 20-1 (42%) and a product with the gc retention time of 59-1 (2%). There was no peak in the gas chromatogram corresponding to amine 61. BC was identified by comparison of its ir and nmr spectra with an authentic sample. The yield of BC may be higher since a part was lost when the solvent was removed using the rotary evaporator.

2-10-2 Reaction of 20-3 with Silver Nitrate

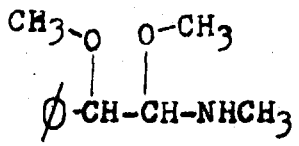
A nitrenium ion cyclization (33, 67) was attempted by reacting silver nitrate with chloramine 20-3 in refluxing methanol. The major product was parent amine (32%) ; no methyl indoline 61 could be detected by gc analysis.

The gc of the crude mixture contained a peak corresponding to that of benzylmethylether (BME, 2%) and none for benzaldehyde. However, both BA and BME were obtained from chromatography of the mixture. Impure BME had absorptions at τ 2.9, 5.5 and τ 6.67 in the nmr spectrum. BA is believed to be a product of secondary reactions on the chromatography column, possibly by Ag_2O oxidation of the minor product benzyl alcohol.

Three unidentified compounds were found in the chromatographic fractions. The first two, compounds E and F, each accounted for less than 3% of starting amine 20-1. Compound E showed ir absorptions at 3060, 1695, 1675, 1600, 1070 and 700 cm^{-1}. There were low-intensity peaks in the higher mass region at m/e = 160, 151, 121 and 105, and the peak at m/e = 75 was the most intense in the mass spectrum. The nmr spectrum showed multiplets at τ 1.85 (2H), between τ 2.4 - 2.8 (3H), and contained singlets at τ 4.8 (1H) and τ 6.52 (ca. 5H). At room temperature, compound E decomposed to benzoic acid as shown by the carbonyl absorption at 1700 cm^{-1} and the M^+ ion peak at 122, with m/e = 105

as the 100% peak. Impure compound F gave absorptions in the ir spectrum at 3300, 3060, 3025, 1670, 1070, 750 and 700 cm^{-1}. The nmr peaks were at τ 2.8 (m, 5H), τ 6.61 (s,1H), τ 6.76 (s, 1H), τ 7.2 (m, 4H), and τ 7.68 (s, 1H). The mass spectrum of F showed the M^+ ion peak at 268, and the intense peaks at m/e = 104 and 91 expected from a phenethyl fragment.

The third unknown, compound G (ca. 7% yield), absorbed at 3340, 3060, 3025, 2780, 1080, 1055 and 700 cm^{-1} in the ir spectrum. The nmr spectrum of G contained a multiplet at τ 2.8 (5H), doublets at τ 5.74 (1H) and τ 6.43 (1H) with couplings of 7 H_z, singlets at τ 6.04 (3H), τ 6.87 (3H) and τ 7.80 (3H), and one D_2O exchangeable proton at τ 8.03. The mass spectrum showed two low-intensity peaks at m/e = 196 and 195, and the 100% peak at m/e = 120. A product such as 62 would be consistent with all of the available data for G, but no plausible mechanism for the formation of this product can be advanced.



62

2-11 Alternative Methods of Generating Aminium Radicals

2-11-1 Radical Initiation of N-Chloramine Addition Reactions

Initiation with isobutyronitrite radicals, thermally generated from α,α -azo-bis-isobutyronitrile (AIBN), of the addition of N-chlorodiethylamine (CDE) to 1-butene in 4 Molar H_2SO_4-acetic acid gave the ionic addition product, 1-chloro-2-acetoxybutane (63-1, 24%), diethylamine (DE, 3%). The major product from the reaction was assigned as 2-acetoxybutane, 63-2. Chloramine radical addition products, if formed, were less than 0.5% yield judging from the amount of basic product.

Impure 63-1 was characterized by the nmr absorptions at τ 5.06 (CH-OAc), τ 6.41 (d, J = 5.5 Hz, Cl-CH_2-), τ 7.97 (-OAc), τ 8.35 (-CH_2-), and τ 9.08 (t, J = 7 Hz, -CH_3). The ir absorption of the acetate was at 1740 cm^{-1}, and the mass spectrum showed no M^+ ion peak but peaks at m/e = 121 and 123 (3:1 ratio). The nmr spectrum of 63-2, contaminated with 63-1, exhibited the acetate singlet at τ 8.0 and a multiplet for CH-OAc at τ 5.28. The ir spectrum showed 1735 and 1030 cm^{-1} absorptions.

$$X\text{-}CH_2\text{-}\underset{\displaystyle Y}{\underset{|}{CH}}\text{-}C_2H_5$$

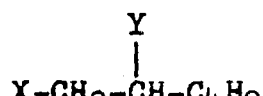
63-1 X = Cl, Y = OAc

63-2 X = H, Y = OAc

Since chloramines can decompose to N, N-dichloramines or Cl_2, either of which could initiate chain reactions (50, 132), the following reactions employed the more stable sulfuric acid salt of N-chlorodimethylamine (HCDM) (132). The reactions were run in 4 Molar H_2SO_4 in acetic acid. The percentage yields were calculated based on the starting dimethylamine hydrochloride and the reaction followed by Cl^+ disappearance monitored by thiosulfate titration.

The reaction of HCDM with 1-hexene gave the same products either from the dark control reaction in the absence of initiator, or from the photolysis (350 nm) of a solution containing α,α -azo-bis-cyclohexylnitrile (ACHN). The neutral fraction contained products assigned as chloro-acetoxyhexane 64-1 (ca. 14%) and 2-acetoxyhexane (64-2), based on the nmr singlets at τ 7.97 and τ 8.05, and the slightly longer gc retention times as compared to the butane analogues, 63-1 and 63-2. The basic fractions from both the control and photolysis reactions were in very small quantities. The nmr spectra of both basic fractions exhibited multiplets at τ 5.9, 6.4 and 7.3 and singlets at τ 7.51 and 7.98. The gc-mass spectrum suggested that one component(40% and 10% of the control and photolysis basic fractions respectively) may be 1-chloro-2-dimethyl-aminohexane, 64-3, which displayed the 100% peak at m/e = 114 for M - CH_2Cl but no M^+ ion peak. The photolysis basic fraction (90% one component by gc),when analyzed by direct

insertion ms, suggested the presence of a terminal dimethylamino group by the 100% intensity peak at m/e = 58 for $Me_2\overset{+}{N}{=}{=}CH_2$. Either 64-4 or 64-5, or a mixture, could explain the other peaks at m/e = 163 and 165 (3:1 ratio), and at m/e = 129 corresponding to M - 58 from 64-5. If all the basic photolysis product was chloramine adduct, the yield was ca. 2%.



64-1	X = Cl,	Y = OAc
64-2	X = H,	Y = OAc
64-3	X = Cl,	Y = $N(CH_3)_2$
64-4	X = $N(CH_3)_2$	Y = Cl
64-5	X = $N(CH_3)_2$	Y = OAc

In a photochemically-initiated AIBN radical reaction of HCDM with diallylether, the basic fractions of both the control and photolysis reactions contained the same mixture of products as shown by gc. The major portion of the basic material appeared to be amine-acetoxy adducts because of the nmr singlets at τ 7.63 (NCH_3) and τ 7.91 (OAc) and the ir absorption at 1740 cm^{-1}; these adducts may be formed by an S_n-2 reaction of amine with 65-1. The low yield (< 1%) made further investigation of limited value. The neutral fractions contained, as a major component, a product tentatively assigned as 1-chloro-2-acetoxy adduct 65-1 (25% yield). The ir absorptions of 65-1 were at 1740, 1050 and 740 cm^{-1}. In the nmr spectrum, multiplets were seen centred

at τ 4.1 (1H), 4.9 (3H), 5.95 (2H), 6.35 (4H), and the acetate singlet seen at τ 7.96.

$$Cl\text{-}CH_2\text{-}\underset{\displaystyle OAc}{\underset{|}{CH}}\text{-}CH_2\text{-}O\text{-}C_3H_5 \qquad \underline{05\text{-}1}$$

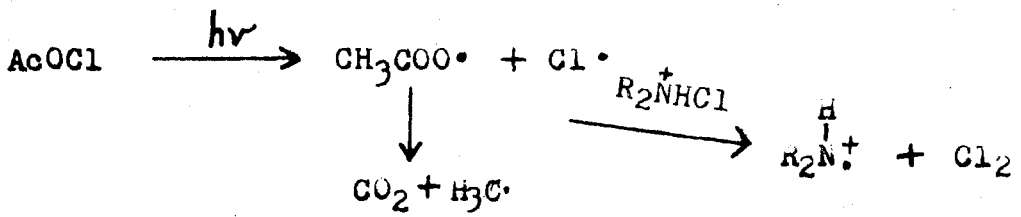
$$(CH_3)_2N\text{-}CH_2\text{-}CCl_2\text{-}CH_2Cl \qquad \underline{06\text{-}1}$$

The reaction of HCDM with 2, 3-dichloropropene, initiated by the photolysis of AIBN, gave the dimethylamino chloro adduct 66-1 (33%). Compound 66-1 showed ir absorptions at 2795 and 700 cm^{-1}. The nmr spectrum consisted of three singlets at τ 5.89, 6.97 and 7.58. The M^+ ion peak at 189 and 191 showed the expected pattern for three chlorine atoms, and the spectrum had the 100% m/e = 58 peak for $Me_2\overset{+}{N}{=}CH_2$.

2-11-2 Attempted Generation of Aminium Radicals from Protonated Amines

The facile formation of chloro-acetoxy adducts in the reaction of chloramines with simple olefins suggested the possibility of an equilibrium existing, as outlined in Scheme 2.8. Acetylhypochlorite might also be acting as a photoinitiator (Scheme 2.9), if its uv absorptions were similar to those of t-butylhypochlorite (305 nm, ε = 10) (176). The acetoxy radical,

Scheme 2.8



Scheme 2.9

or the methyl radical, from the decomposition of $Pb(OAc)_4$ in benzene preferentially abstracts an α-hydrogen rather than the N-H of an amine (177). A side reaction with $Pb(OAc)_4$ salt is formation of the acetamide derivative (177). The same α-hydrogen abstraction reaction is seen with hydroxy radicals and amines (178).

In a thermal reaction of $Pb(OAc)_4$ with dipentylamine (DP) in acetic acid, the products were DP (24%) and N, N-dipentylacetamide (67, 13%). Amide 67 showed an ir absorption at 1640 cm^{-1}, and nmr signals at τ 6.70 (CH_2-N) and τ 7.98 (OAc). The M^+ ion peak was visible at 199. Only parent amine DP was recovered from either a thermally or

a photochemically initiated decomposition of $Pb(OAc)_4$ in 4 Molar H_2SO_4 in acetic acid in the presence of DP.

When DP and calcium hypochlorite were stirred for one week in 4 Molar H_2SO_4-acetic acid, only DP was recovered and there was no indication of N-chlorodipentylamine (CDP) or N-pentyl-2-methylpyrollidine, the latter expected to show the 2-methyl doublet in the region of τ 9.0. When CDP was stirred in the same solvent for ten minutes in the dark, only CDP was recovered.

2-12 Attempted Initiation of N-Nitrosopiperidine Radical Reactions

Carbon radicals, iron ions, and amido radicals all proved to be unable to initiate the decomposition of N-nitrosopiperidine (NP) to the piperidinium radical in acidic media.

In the presence of cyclohexene, NP (0.1M) showed, by the decrease in the 345 nm peak intensity, approximately 15% decomposition after 46 hours refluxing in an HCl-methanol solution containing AIBN (0.005M). From the amount of basic material recovered, the maximum yield of addition product 49-1 was less than 1%. The nitroso peak intensity at 345 nm of an HCl-methanol solution containing NP (0.17M) and AIBN (0.015M) showed a 20% decrease after 41 hours refluxing. NP (67%) was recovered, and piperidine hydrochloride (HP, 8%) was the basic product. These yields are comparable to the results of acid hydrolysis in the

absence of radical initiator (172).

Initiation attempts with AIBN or benzoyl peroxide in a refluxing trifluoroacetic acid-benzene solution containing NP and cyclohexene proved unsuccessful, as shown by an increase in the absorption in the 330-370 nm region caused by evaporation of benzene. The basic fraction from the AIBN reaction in benzene appeared to be a decomposition product of AIBN, since no nmr signals were observed below τ 8.28 except for a D_2O exchangeable proton.

The use of Fe^{2+} ions as a redox catalyst, analogous to chloramine reactions (5), did not produce aminium radicals from NP, which was recovered from the reaction.

Photolysis of N-nitroso-N-methylacetamide (NMA) causes abstraction of allylic hydrogens rather than addition to the double bond (74), and photolysis of nitrosamides in acidic media give primarily the hydrogen abstraction product (179). Amido radicals might abstract the NO group from nitrosamines, since the N-N bond is of lower energy (53 kcal./mole) (19) than an allylic C-H bond (77 kcal./mole) (180); if such a nitroso group transfer occurs, in the presence of acid, aminium radicals may be generated. A trifluoroacetic acid-benzene solution containing NMA (0.13M), NP (0.04M), and cyclohexene (0.08M) was photolyzed with the filter solution which cut-off the energy below 400 nm. The photolysis was stopped when 38% of the nitrosamide absorption had disappeared. The basic fraction contained

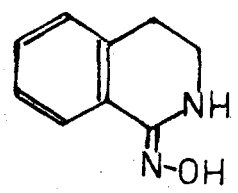
only NMA (vide infra) with no evidence for aminium radical products.

2-13 N-Nitrosamine Photo-elimination Reactions

2-13-1 N-Nitrosotetrahydroisoquinoline (21-2)

Previously it has been shown that nitrosamine 21-2 does not add photochemically to olefins in acidic media (128). Photodecomposition of 21-2 was carefully re-examined to determine the reactions of the aminium radical. In HCl -methanol, 21-2 gave amidoxime 68-1 (89%) and amine 21-1 (3%), based on > 98% of 21-2 reacting.

Examination of the ether extract of the photolysis residue by tlc showed only a spot for amidoxime 68-1. The spectral data of 68-1 was identical with those published previously (128).

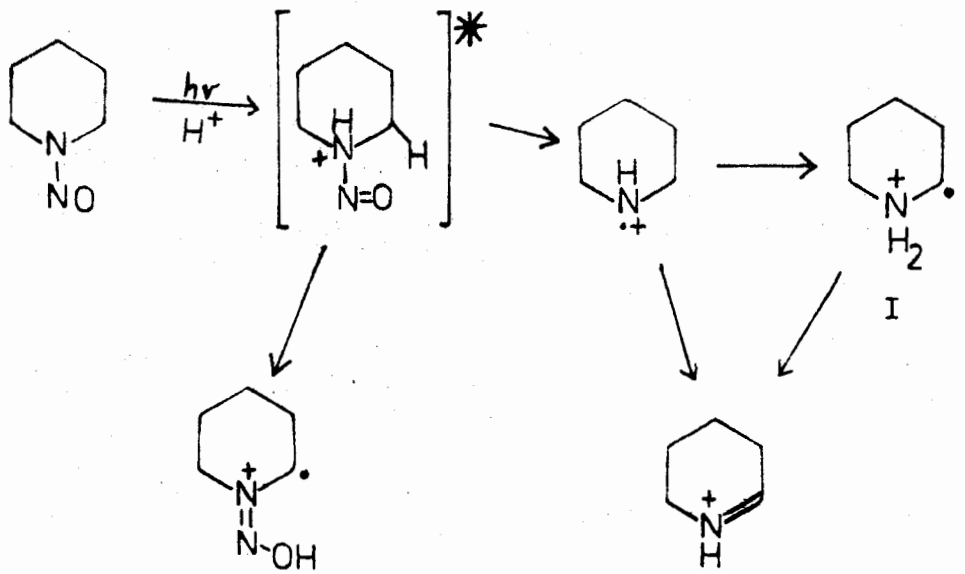


68-1

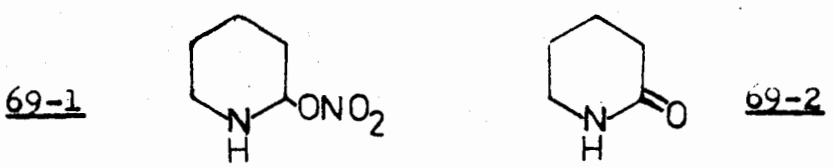
2-13-2 Photolysis of N-Nitrosopiperidine under O_2

Oxygen has been shown to be incapable of quenching the photolyses of nitrosamines (181) and, in the photoaddition of nitrosamines, effectively diverts the NO radical combination reaction to cleanly produce nitrate adducts (142). Although there are no examples of 1, 2 hydrogen

migrations in free radical chemistry (182), there existed a remote possibility that a nitrosamine photo-elimination reaction might involve a carbon radical, either I or II in Scheme 2.10, which could be trapped by an NO_3 radical or oxygen to give products such as 69-1 or 69-2. No such products were found in the photolysis of nitrosopiperidine (NP) under oxygen.



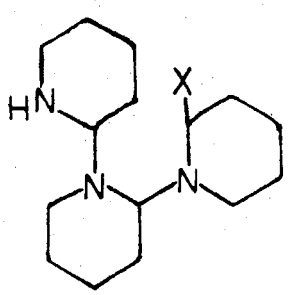
Scheme 2.10



The products from the oxidative photolysis of NP in

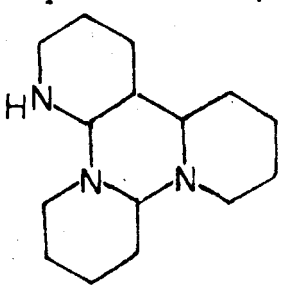
HCl-methanol were dipiperidinomethane (70, 21%), piperidine hydrochloride (HP, 29%), and N-formylpiperidine (71, ca. 10%). Compound 70 was identical with a sample prepared by reacting piperidine with CH_2Cl_2 in the presence of a base (183). Formamide 71 had identical ir (1670 cm^{-1}) and mass spectrum as those of an authentic sample (174).

When NP was photolyzed in aqueous HCl under oxygen, the reaction was slower than in acidic methanol, and NP (24%) was recovered. Piperidine hydrochloride (17%) was formed, but the major product was assigned as the unstable trimer nitrate 72-1 (43%). The expected strong ir absorptions for the nitrate were seen at 1630, 1280 and 880 cm^{-1}, and the nmr spectrum contained a multiplet at τ 5.0. The highest peak in the mass spectrum was at m/e = 249, which would correspond to M - HNO_3, and the 100% peak was at m/e = 83 for C_5H_9N . Attempted sublimation gave a semi-solid, which appeared to be alcohol 72-2 showing ir absorptions at 3300 and 1050 cm^{-1} and only a weak 1630 cm^{-1} absorption. These products are suggested to form from the same trimer intermediate as isotripiperidein, 72-3, found from the photolysis of NP under nitrogen in aqueous HCl (41).



72-1 X = ONO_2

72-2 X = OH



72-3

2-14 Quantum Yield of N-Nitrosodimethylamine Disappearance

The quantum yield of disappearance (Φ dis) of nitrosodimethylamine (NDM) in aqueous HCl under nitrogen was measured in a merry-go-round apparatus using a ferric oxalate actinometer. (See Experimental 5-21-1). The glass filter, CS 7-60, had maximum transmission at 350 nm, so only the $n \rightarrow \pi^*$ nitrosamine absorption was irradiated. The values obtained were corrected for the proportion of light absorbed by the sample compared to the actinometer, for example, 30% of the uv light was absorbed by a 0.01 Molar solution of NDM (Figure 5.7). The corrected Φ dis values were 0.26 and 0.29 for 0.1 and 0.01 Molar aqueous solutions respectively.

The quantum yield of nitrosamine disappearance does not appear to be significantly concentration dependent, considering that the total errors in Φ dis is ± 25%. The Φ dis values for nitrosamines in methanol have been found to be 2.5 (2) and 2.7 to 3.8 (2, 184), the latter in the presence of olefin. The Φ dis values in aqueous HCl are closer to that of N-nitrosodibenzylamine in trifluoroacetic acid-benzene Φ dis = 0.75 (44), or Φ dis of NMA in benzene (0.5) (185).

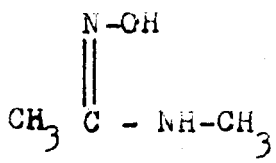
2-15 Analysis of Nitrosamine Photodecomposition Products

It was desirable to determine the quantum yield of product formation in the nitrosamine photodecomposition reactions, rather than the overall quantum yield of nitrosamine disappearance. In the concentration range used (0.1 to 0.01 M) in the quantum yield determinations, it was necessary to detect small quantities (ca. 10^{-4} moles) of decomposition products, i.e. primary and secondary amines, and amidoximes (1).

Gas chromatographic analysis of amine mixtures were examined. Of the variety of gc columns tested (See Table 5.2), the best separation of amines occurred on 20% Dowfax 9N9 (186), coated on a solid support containing a 20% loading of KOH, or on a Chromosorb 103 column (187). The Dowfax 9N9 column did not completely resolve methylamine (M) and dimethylamine (DM). The Chromosorb 103 column displayed 'ghost' peaks, i.e., when an aqueous basic solution containing no amine was injected into the column directly after an analysis of an amine solution, it produced peaks corresponding to those of the previously injected amines. This phenomena is common with gc of polar amines (188). Obviously quantitative work would be difficult under these conditions.

Attempts to utilize the complexation ability of amidoxime 73 with metal ions as an analytical method were

equally unsuccessful (See Table 5.3). Spectrophotometric changes occurred upon the addition of several ions, most notably Cu^{2+}, but the spectral shifts were judged to be not distinct enough for analysis of small quantities of amidoxime product.



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2-15 Summary

Together with comparable results of other workers, the results of the thesis experiments are summarized below in Tables 2.8 to 2.12.

Table 2.8 Amido Radical Cyclizations[a]

Amide Derivative	Olefin[b] Position	Isolated Products	Total Cyclic Product(%)[c]	Ring Size
8-2	5,6	22-1(37%), 22-2(19%) 22-3(18%), 23-1(6%)[d] 23-2(4%)[d], 25-1(6%)[d]	74	5
9-2	5,6	29-1(35%), 29-2(9%) 29-3(14%), 9-1(8%) 29-4(5%)[d]	56	5
10-2	4,5	31-2(44%)[d], 31-3(7%)[d]	44	4
11-2	4,5	11-1(37%), 33(9%) 34-2,2(8%)[d], 34-3(1%)[d]	0	-
12-2	6,7	35-1(25%)[d]	25	6[d]
13-2	4,5	13-2(98%) 6(20%)[e], 13-1(15%)[f]	0	-
8-3	5,6	23-4(33%), 24-4(39%) 8-1(7%)	72	5

Table 2.8 Amido Radical Cyclizations (cont'd)

Amide Derivative	Olefin Position	Isolated Products	Total Cyclic Product (%)	Ring Size
11-3	4,5	11-1(5%), 34-1,2(20%) 34-3(12%)	0	-
8-2[g]	5,6	23-2(35%), 24-2(17%) 8-1(8%)	52	5
14-2[h]	5,6	42-1(47%)[i]	47	5

a. Photolysis were run in benzene under N_2, and yields based on the amount of starting amide, except wnere noted.

b. Position of the olefinic carbons relative to the amido radical.

c. Includes only those confirmed as cyclic products.

d. Compounds tentatively assigned.

e. Yields based on 13-2, photolyzed in acetic acid.

f. Yields based on 13-2, photolyzed in tetranydrofuran.

g. Under oxygen atmosphere.

h. Bromotrichloromethane as solvent.

i. Yield based on 14-2 was 89%.

Table 2.9 Cyclization of Aminium Radicals

Amine Derivative	Olefin[b] Position	Isolated Products	Total[c] Cyclic	Ring Size
15-2	5,6	46-1(48%), 46-2(34%) 46-3(9%)	91%	5
16-2	6,7	50-1(16%)[d], 50-2(9%)[d] 50-3(6%)[d]	31%	6[d]
17-2	4,5	17-1(60%)	0	-
17-3[e]	4,5	17-1(30%), 55-1(16%)[d] 55-2(15%)[d], 55-3(20%)[d]	0-3%	-
18-2	4,5	18-1(18%)	0-3%	-
19-2 (189)	5,6	28-1(37%), 28-2(13%), 28-3(11%)	61%	5
19-2[f]	5,6	26-3(15%), 27-1(20%), 28-3(31%)	66%	5
19-2[g]	5,6	26-5(55%)	55%	5
19-2[h]	5,6	19-1(5%), 19-2(23%) 57-1,2 (18%)	0	-
74-2 (190)	5,6	75-1(18%), 75-2(13%) 76-1(9%), 76-2(4%)	31%	5

a. Photolysis were run in HCl-methanol under N_2 and yields based on the amount of reacted amine derivative (usually > 85%), except where noted.

b. Position of the olefinic carbons relative to the amido radical.

c. Includes only those confirmed as cyclic products.

d. Compounds tentatively assigned.

e. N-Chloramine 17-3 reaction catalyzed by iron ions.

f. Under oxygen atmosphere.

g. 25% Bromotrichloromethane-methanol as solvent.

h. I_2 present.

Table 2.10 Decomposition of N-Methylphenethylamine Derivatives

Amine Derivative	Conditions	Products[a]	β - scission
20-2	hν, HCl-MeOH	20-2(1%), 20-1(10%), 58 (22%), BA[b](4%), BAO(13%), 59-1(3%)[c]	17%
20-2	hν, H_2SO_4-HOAc	20-2(37%), 20-1(2%) BA(18%), BAO(9%), 59-1(3%)[c], PA(2%)[c]	27%
20-2	hν, HCl-HOAc	20-2(6%), 20-1(30%), BAO(12%), 59-2(19%)	12%
20-3	$Fe^{2+/3+}$, H_2SO_4-HOAc	20-1(42%), BC(40%), 59-1(2%)[c]	40%
20-3	$AgNO_3$, MeOH	20-1(32%), BME(2%)[c]	2%[b]

a. Yields based on the amount of amine derivative, except for the $AgNO_3$ reaction where they are based on amine 20-1.

b. BA = benzaldehyde , BAO = benzaldehyde oxime, BC = benzyl chloride , PA = phenylacetaldehyde, BME = benzylmethyl ether.

c. Tentative assignments.

Table 2.11 N-Chloramine Intermolecular Additions[a]

Chloramine	Initiator	Olefin	Products	Chloramine Adduct
CDE	AIBN, Δ	1-butene	63-1(24%), 63-2,DE[b](3%)	0-0.5%
CDE (191)	Fe^{2+}	1-butene	63-3(33%), 63-1(11%)	33%
HCDM	ACHN, hν	1-hexene	64-1(14%)[c], 64-2	0-2%
HCDM	AIBN, hν	diallyl-ether	65-1(25%)	0-1%
CDE (191)	hν	diallyl-ether	65-2(40%)	40%
HCDM	AIBN, hν	dichloro-propene	66-1(33%)	33%
CP (192)	hν	dichloro-propene	66-2(85%)	85%

a. Solvent is $4M H_2SO_4$ in acetic acid.

b. DE = diethyl amine, CDE = chlorodiethylamine, CP = chloropiperidine, HCDM = H_2SO_4 · chlorodimethylamine

c. Tentative assignment.

Table 2.12 Decomposition of Nitrosamine

Nitrosamine	Conditions	Products[a]	Elimination
21-2	N_2, HCl-MeOH	75-1(89%), 21-1(3%)	89%
NP (41)	N_2, HCl-MeOH	HP[b](57%), 72-3(3%)	3%
NP	O_2, HCl-MeOH	HP(29%), 70(21%) 71(10%)	0
NP (41)	N_2, HCl-H_2O	69-3(31%), 72-3(39%)	70%
NP[c]	O_2, HCl-H_2O	HP(17%), NP(24%),, 72-1(43%)[d]	43%[d]

a. Photolysis of $n \rightarrow \pi^*$ transition band yields based on reacted nitrosamine, except where noted.

b. NP = nitrosopiperidine , HP = HCl • piperidine

c. Yield based on NP

d. Tentative assignment.

CHAPTER 3

DISCUSSION

3-1 General

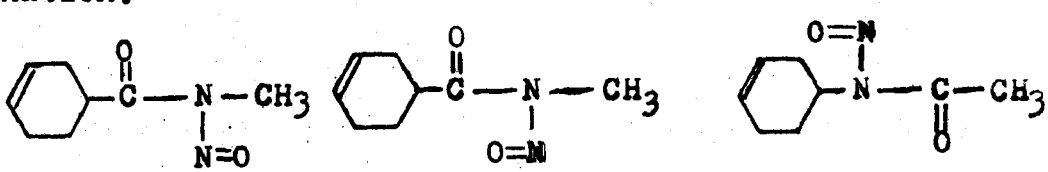
Throughout this work the primary emphasis has been placed on the synthetic aspects of aminium and amido radical reactions. Thus, for the cyclization reactions, the major effort was directed towards providing an overview of the conditions conducive to the intramolecular addition of a radical, rather than a detailed examination of the by-products to determine the reaction pathways.

The yields obtained in the majority of the cyclization reactions were not optimized and could be improved, particularly in the isolations of oximes in which the choice of column chromatography conditions was critical. This claim is self-evident by an examination of the results of the most extensively investigated photolyses of nitrosamide 8-2 and nitrosamine 15-2, which show the highest yields. Since in the photolyses of nitrosamides and chloramides, the yields reported were calculated on the amount of starting amide, the cyclizations were more efficient than those given in Table 2.8. Nitrosamides are known to be thermally unstable and also decompose in basic solution (130, 150); therefore, during the isolation of the crude nitrosamide, some decomposition was expected even though maximum precautions were taken. Also the olefinic bond may

react with the nitrosating or chlorinating agent (See Tables 2.2 and 2.4) which reduces the amount of cyclization product.

The spectral characteristics of the prepared compounds are comparable to those of other nitrosamides (150), chloramides (78), nitrosamines (19, 20), and chloramines (7). The nearly identical ir and nmr characteristics exhibited by saturated nitrosamide 7-2 and unsaturated nitrosamide 8-2 provides no indication that the nitroso group and the olefinic bond are intramolecularly interacting, although aromatic molecules form "collision complexes" with nitrosamines (193). The nmr olefinic proton signals of nitrosamines are shifted downfield slightly (0.1 to 0.2 ppm) compared to the parent amines, probably caused by a long range anisotropic effect of the nitrosamino group (194-196).

In contrast to nitrosamines, nitrosamides generally exhibit one set of proton signals in the nmr spectrum, and have been interpreted as having the anti-configuration(Figure 3.1)(179); a freely rotating NO group would be an alternate explanation.



anti-8-2 syn-8-2 anti-11-2

Figure 3-1

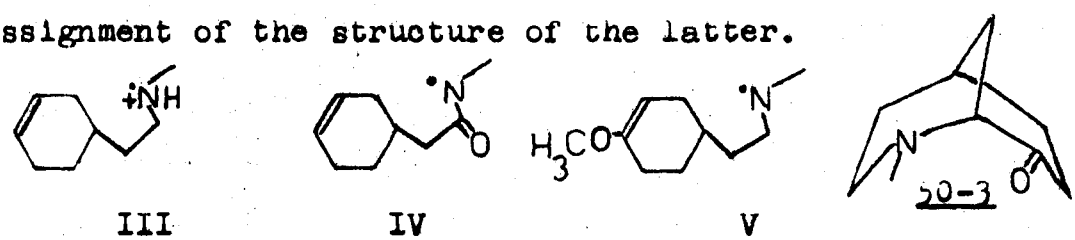
The cis-protons of nitrosamines, i.e., on the same side as the nitroso group, have been shown to generally resonate at higher field than the trans-protons (197). The assignment of the anti-configuration to the nitrosamides prepared in this work would be consistent with the observation that the olefinic protons of nitrosamides 9-2 and 11-2 (Figure 3-1) are shifted slightly upfield with respect to the parent amides (0.11 and 0.13 ppm respectively), in contrast to the small downfield shift (0.03 to 0.04 ppm) of the olefinic protons of the other nitrosamines, such as 8-2.

3-2 Intramolecular Cyclization

As can be seen by comparing Tables 1.1 to 1.3 with Tables 2.8 and 2.9 (Results, 2-16), the results of the nitrogen radical cyclizations in this work agree with, and extend further, the published observations on other radicals. The general rule, that whenever a choice exists between cyclization to either a five- or a six-membered ring the five-membered ring exclusively forms, is also true for both aminium and amido radicals. The results of nitrosamides 8-2 and 9-2 show that an amido radical will cyclize to either the acyl or the alkyl side chain. The differences in the cyclization yields are not sufficiently quantitative at this time to make definite comparisons concerning ease of cyclization.

The aminium radical from 16-2 (III) and the amido

radical from 12-2 (IV) have a choice of forming either a six- or a seven-membered ring (Figure 3.2), and cyclize in comparable yields (31% and 25%). The products are believed to be six-membered rings, largely based on the preference for this mode of cyclization in other radicals (See Table 1.3). Waegell et. al. (198) have recently shown that the metal-coordinated amine radical V cyclizes to a six-membered ring, and yields amino-ketone 50-3. The fact that the reported 100% intensity peak for 50-3 and a major peak of oxime assigned as 50-1 is the same at m/e = 96 (198) support the assignment of the structure of the latter.



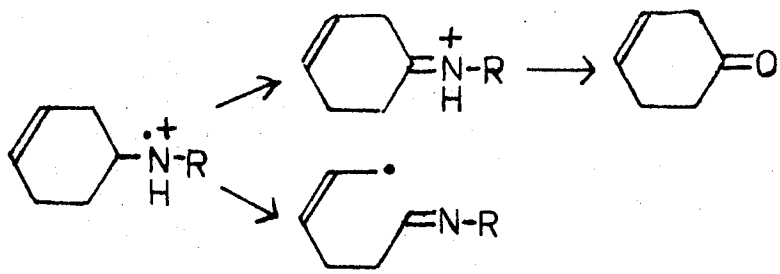
III IV V

Figure 3.2

The Hofmann - Loffler reaction of N-methylcyclohexylaminium radical, which involves hydrogen transfer in a boat form of a six-membered transition state, occurs in 11% yield (8), but only under drastic conditions. It is expected that the radicals from nitrosamide 11-2, nitrosamine 17-2, and chloramine 17-3 would be difficult to cyclize through a boat form of a five-membered transition state and prefer other pathways.* Indeed, both the amido and

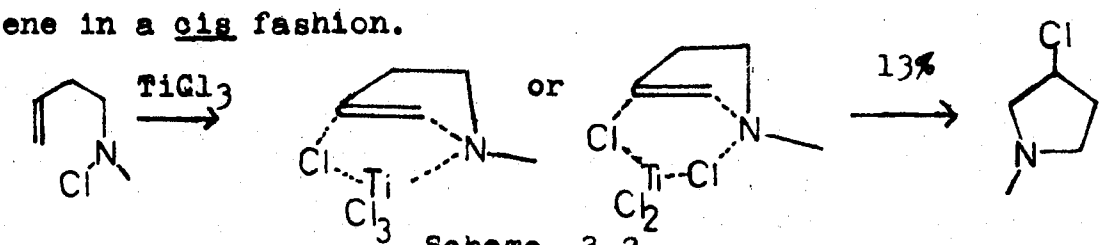
* The author has found that cyclohexen-3-ylnitrene, generated by Nagata's method from the primary amine (89), also fails to cyclize.

aminium radicals mentioned above and the radical from 18-2 decompose by α-elimination or β-scission (Scheme 3.1); the latter pathway leads to a resonance stabilized allylic radical as shown.



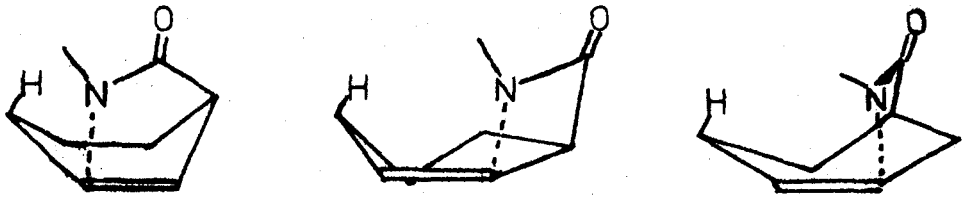
Scheme 3.1

Stella (112) found similar decomposition in the photolysis of the chloramine shown in Scheme 3.2, obtaining parent amine and polymeric products. Only the titanium-initiated reaction of the chloramine gave a 13% yield of a pyrrolidone derivative (112). Since a chloramine containing a $\Delta^{6,7}$ olefin also did not cyclize when photolyzed, but did in the presence of Ti^{3+}, there are strong indications that the metal ion complexes with the amine radical as well as the π-bond to bring the reactive centres in close proximity (Scheme 3.2). A similar intermediate was suggested by Minisci et. al. (10) to explain the metal ion initiated intermolecular addition of N-chloropiperidine to cyclohexene in a cis fashion.



Scheme 3.2

Examination of a Dreiding model of the amido radical from nitrosamide 10-2 reveals that the formation of a five-membered ring involves a transition state of boat conformation (VIa) which shows severe interactions between the amido function and the 'flag-staff' hydrogen, while the β-lactam formation (VIb) involves less non-bonded interactions (Figure 3.3). Also shown is the transition state for five-membered ring cyclization of the amido radical derived from 8-2 or 8-3 (VII). The formation of the β-lactam has no analogy in other radical cyclizations.



VIa VIb VII

Figure 3.3

Another example of steric restraints forcing a different cyclization pathway, other than a five-membered ring, can be found in the azatwistane synthesis by Heusler (102) in which the six-membered ring closure is favored.

The models of both VI and VII also indicate that an sp^3 - hybridized nitrogen of the amido radical can orient itself with the π-lobe of the double bond in a colinear arrangement. In contrast, an sp^2-hybridized nitrogen radical has an almost orthogonal arrangement of the p-orbital of the amido radical and the π-orbital if the radical has a π-configuration, but a good overlap can be achieved if

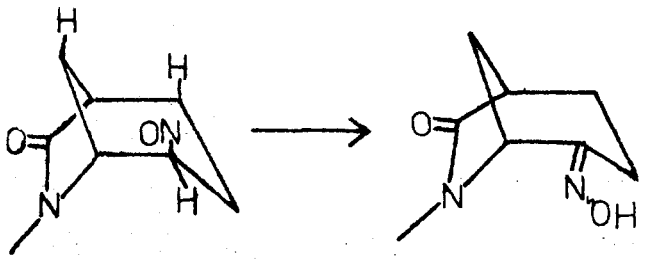
the radical has a Σ-configuration (70).

3-3 Product Formation

3-3-1 C-Nitroso Compounds

The intramolecular photo-additions of N-nitroso compounds in this work did not give entirely the same products as had been found in the photoreactions of earlier workers. When intramolecular addition occurred, the formation of a C-nitroso dimer was indicated by the increasing peak in the 295 nm region, except in the trapping experiments. Although the C-nitroso dimers have been isolated as products from the intermolecular addition of nitrosamines or the hydrogen abstraction of nitrosamides (72, 142), there were only three cases among the nitrosamide cyclizations in which C-nitroso dimers were possibly isolated in this work, i.e., 23-1, 24-1, and 29-4. In the case of nitrosamine cyclizations, the facile tautomerization to the oxime would be expected under the acidic methanol and basic extraction conditions (199, 200). The facile tautomerization of nitrosamide cyclization products is certainly not caused by light (142), since the filter solution absorbed all the light below 400 nm. A reasonable explanation is that the 1, 3 -diaxial interactions found in the azabicyclic amides are sufficiently large to promote the formation of oximes (Scheme 3.4). The exo-nitroso adduct would result from trans addition to the olefin, a process which predominates

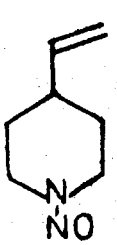
in the intermolecular photoadditions of nitrosamines (201).



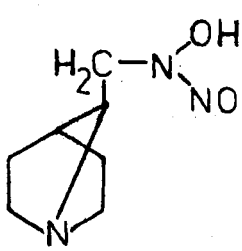
Scheme 3.4

3-3-2 N-Nitroso-N-Hydroxylamines

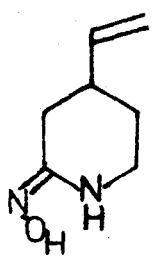
Water-soluble N-nitroso-N-hydroxylamino compounds (201), such as 75-2, may be formed but continuous extraction of the aqueous phase of a number of nitrosamine photolysates revealed no evidence for the formation of such products (ir absorption around 2500 cm^{-1}) (41). Nitrosohydroxylamines are formed by the addition of HNO to a C-nitroso compound; HNO being formed *in situ* by the photoelimination reaction of a nitrosamine. The absence of the elimination reaction in the intramolecular photoaddition proves that the aminium radical usually cyclizes very efficiently, as shown by the lack of amidoxime products, except in the photolysis of nitrosamine 74-2 (43).



74-2

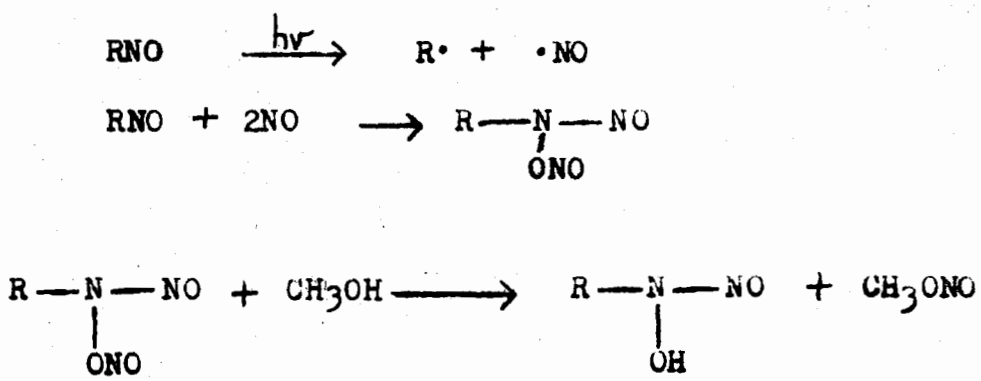


75-2



76-2

The mechanism requiring that HNO, rather than NO itself, is essential for the formation of nitrosohydroxylamines would explain the absence of these products in nitrosamide photolyses (72, 73), in which HNO elimination is less important. An alternate mechanism, similar to one proposed by Gwenlock et. al. (202), requires the intervention of hydrogen donating solvents as shown in Scheme 3.5. This mechanism is not consistent with the result that no nitrosohydroxylamines have been isolated when C-nitroso dimers were irradiated in methanol (199).

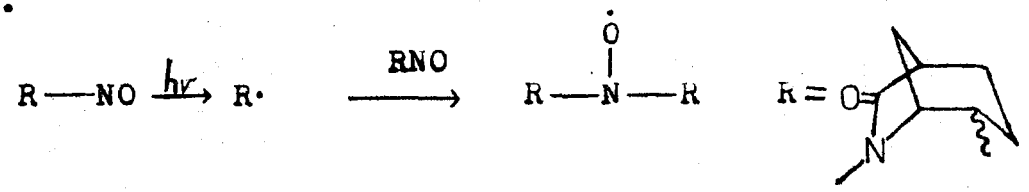


Scheme 3.5

3-3-3 Nitroxides

Using esr spectroscopy, Surzur's group (104) has shown the presence of nitroxide 23-6 in the photolysis of nitrosamide 8-2. In our reactions, this nitroxide may be formed in small amounts but has not been isolated. The quartz apparatus used in Surzur's work (no filter) could allow photochemical cleavage of the initially formed C-nitroso compound to produce nitroxides by the mechanism shown

in Scheme 3.6 (203), while our selective irradiation conditions (> 400 nm) would not cleave C-nitroso compounds (199).



23-6

Scheme 3.6

3-3-4 Nitrates and Nitro Compounds

Nitro compounds and nitrates have been found in nitrosamide photolyses with > 290 nm light energy (72, 73), and their formation is attributed to disproportionation of NO in the presence of a catalytic amount of NO_2, which could form with a trace amount of oxygen (Scheme 3.7) (205). In the cyclization reactions, the > 400 nm irradiation and the rapid combination of NO with a carbon radical would explain the lack of nitro and nitrate products under nitrogen. The minor amount of nitrate 23-2 from the photolysis of 8-2 under nitrogen is suspected to result from incomplete purging of oxygen from the apparatus, since nitrates were not obtained in the other nitrate photolyses.

$$2NO + O_2 \longrightarrow 2NO_2$$

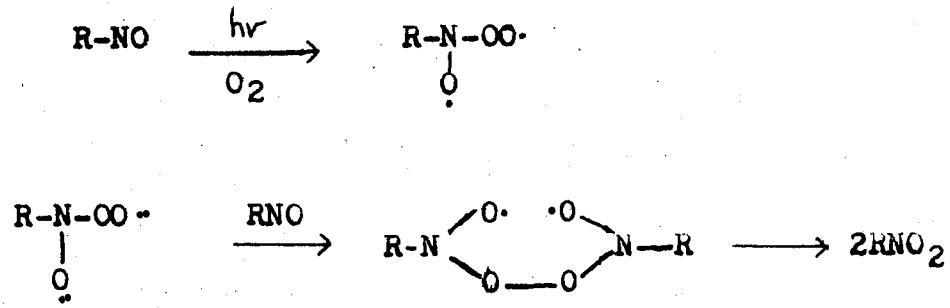
$$NO + O_2 \longrightarrow NO_3 \xrightarrow{NO} 2NO_2$$

$$NO + NO_2 \rightleftharpoons N_2O_3$$

$$NO_2 + NO_3 \rightleftharpoons N_2O_5$$

Scheme 3.7

In agreement with oxidative photoaddition (142), the photolysis of nitrosamide 8-2 under oxygen gave as major products nitratolactams 23-2 and 24-2. A minor product, tentatively assigned as either nitro-lactam 23-5 or 24-5, could result from the trapping of the carbon radical by the NO_2 radical, formed as shown in Scheme 3.7. Since no oximes are found in the photooxidative cyclizations, the initial formation of the C-nitroso compound, followed by the steps of Scheme 3.8 to produce nitro compounds (204), is a less probable mechanism for nitro compound formation.

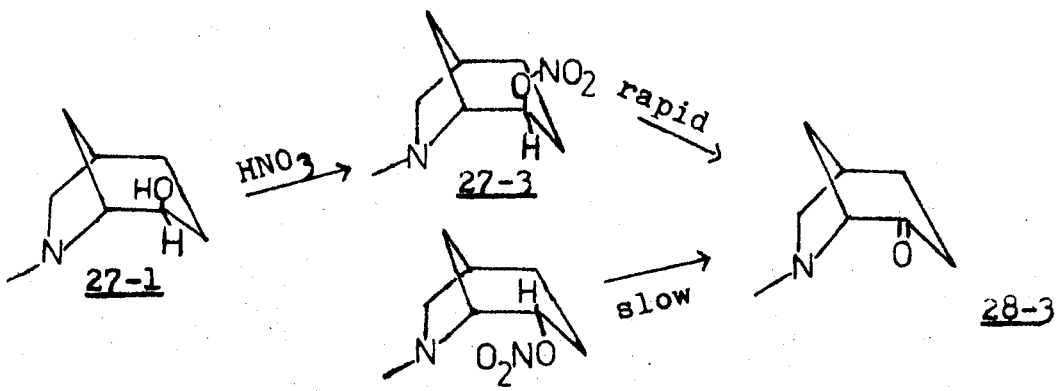


Scheme 3.8

3-3-5 Ketones

In the nitrosamine cyclizations under nitrogen, the ketone formed may arise from the usual base catalyzed decomposition of nitrate esters (143), formed by a trace amount of oxygen present, since in the oxidative photocyclization of nitrosamine 19-2 the major product was ketone 28-3. In the oxidative photocyclization, the indications that exo-nitrate 27-3 decomposes to ketone 28-3 faster than endo-

nitrate 26-3 can be interpreted as resulting from steric acceleration due to greater non-bonded interactions of the axial orientation in 27-3 (Scheme 3.9). An attempt to isolate 27-3, prepared from alcohol 27-1, failed because of the rapid decomposition to 28-3.

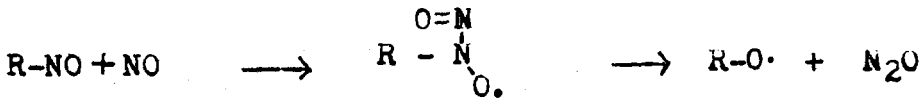


26-3

Scheme 3.9

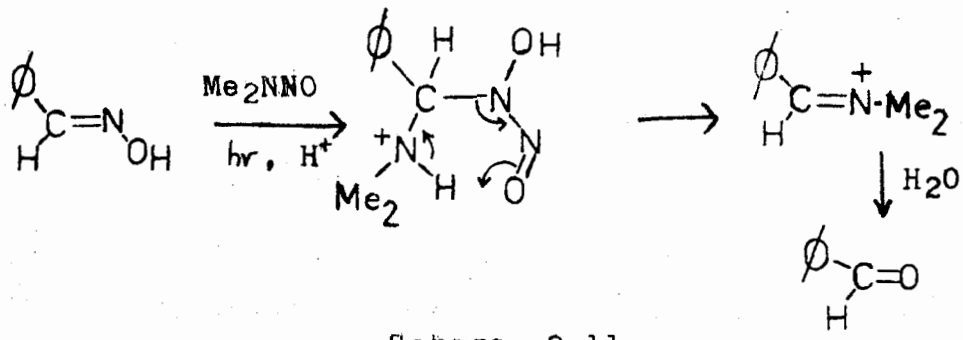
Since nitratolactams were the major products when nitrosamide 8-2 was photolyzed under oxygen, but no ketone 22-3 was formed, the nitratolactams do not form ketones under the cyclization conditions. Thus, the explanation involving nitrate decomposition is not applicable to the formation of ketones in the nitrosamide cyclization reactions under nitrogen. The mechanism given by Heicklen (205, 206) for the reaction of NO with a C-nitroso monomer would explain alkoxy radicals, as shown in Scheme 3.10, but the decomposition to ketones by hydrogen elimination is unlikely (207). Similarly, since amino-ketones products are

absent, or formed in small yield, in the intermolecular photoaddition of nitrosamines (1, 42) the nitrate decomposition mechanism does not appear to be sufficient explanation for even the nitrosamine cyclizations.



Scheme 3.10

The formation of carbonyl compounds from oximes using NO and radical reactions has been recently reviewed (208). Acetaldehyde was formed by radical reactions when acetaldehyde oxime was pyrolyzed in the presence of NO gas (209). Besides the mechanisms given in the above references, the photoconversion of benzaldehyde oxime to benzaldehyde may involve the addition of dimethylnitrosamine to the oxime double bond, followed by hydrolysis (Scheme 3.11). Because the cyclization of nitrosamine 19-2 has been shown to be preferred to intermolecular addition (210) and because amido radicals do not easily add to olefins, the mechanism in Scheme 3.11 would not account for ketone formation in the intramolecular cyclization reactions. Since aminoketones are not important products when the intermolecular photoaddition reaction is conducted in a three to four fold excess of nitrosamine to olefin (201), the photoreaction of nitrosamines with oximes may be restricted to BAO.



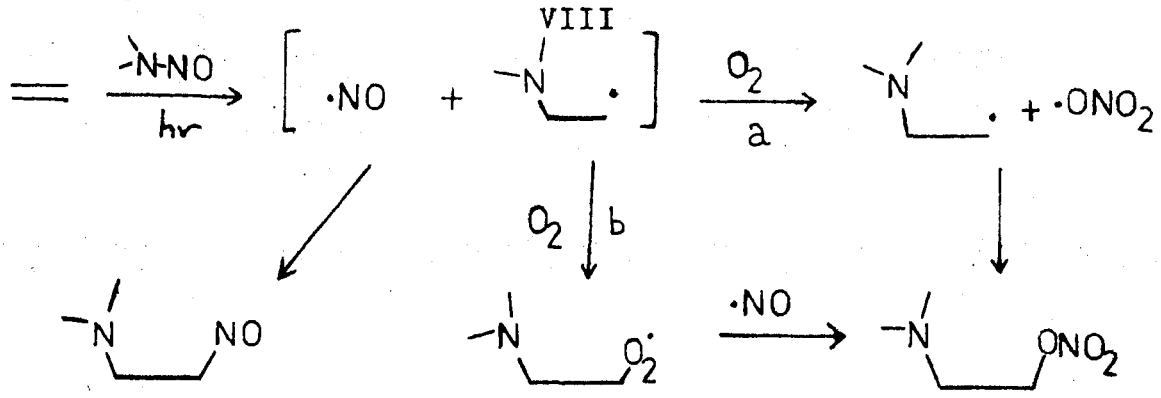
Scheme 3.11

Thus, with the evidence available, no plausible mechanism can be offered to explain the amount of ketone formed in the cyclization reactions.

3-3-6 Trapping Reactions

In the competitive reaction of nitrosamine 19-2 photolyzed in the presence of styrene (210), no significant decrease in the amount of styrene was noticed. Obviously, intramolecular addition of an aminium radical is very facile. The intermediate carbon radical (VIII, Scheme 3.12) reacts selectively with NO without causing addition reactions. The results of the trapping experiments indicate that the combination step does not occur within a solvent cage because oximes are not formed, but possibly involves a "loose radical pair" since intermolecular addition by the carbon radical does not occur (Scheme 3.12) (142). Since no oximes are found in the photooxidative cyclizations,

the reaction with oxygen must be faster than the combination with NO.



Scheme 3.12

The two possible mechanisms by which a nitrate may form are shown in Scheme 3.12a and 3.12b, but the present results do not differentiate between the two possibilities.

The iodine trapping experiment (2-7-3) was not successful in HCl-methanol, since the strong iodine absorption at 360 nm completely masks the nitrosamine $n \rightarrow \pi^*$ absorption. The iodine trapping experiments with nitrites in benzene have been successful (99, 115, 171) because a charge-transfer complex of iodine and benzene shifts the lower absorption to 500 nm (211). It is worthwhile noting that iodine in benzene has an absorption tail at 360 nm ($\epsilon \approx 300$) (211), while the nitrite extinction coefficient is ca.100 at this wavelength. Since the iodine concentration in the nitrite trapping experiments varies from one third to five times the nitrite concentrations, direct excitation of the nitrite

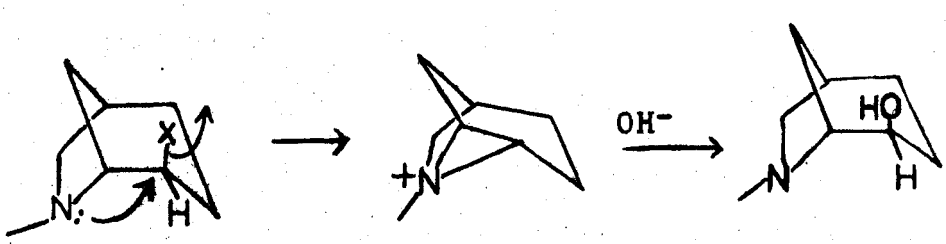
would be difficult. Although the photolysis times are longer with iodine present, at least certain photolyses (171) do not take as long as would be expected on the basis of relative extinction coefficients. Possibly a photo-excited iodine is participating in the reaction, either by photosensitization of nitrite decomposition or by an iodine radical initiating the formation of alkoxy radicals. Because the absorption of iodine-benzene complex has $\epsilon \approx 50$ at 400 nm, the iodine trapping method might be applicable in nitrosamide photolyses.

3-3-7 Stereochemistry

When other than a ketone or oxime azabicyclic product is formed, the stereochemistry of the cyclization product is determined by the termination step. The observation that both endo- and exo-derivatives of nitrate or chloro lactams are formed in the photolysis of 8-2 under oxygen or 8-3 alone, shows that the stereochemical control over the combination of the intermediate carbon radical with $\cdot NO_3$ or Cl· is minimal. The isolation of only exo-bromolactam 42-1 in a high yield from nitrosamide 14-2 may be a consequence of steric control of the bulkier $BrCCl_3$, which restricts the alternative endo approach.

The formation of only endo-bromoamine 26-5, and the absence of the exo-bromolactam 27-5, would not be predicted on the basis of steric control of the approach of $BrCCl_3$

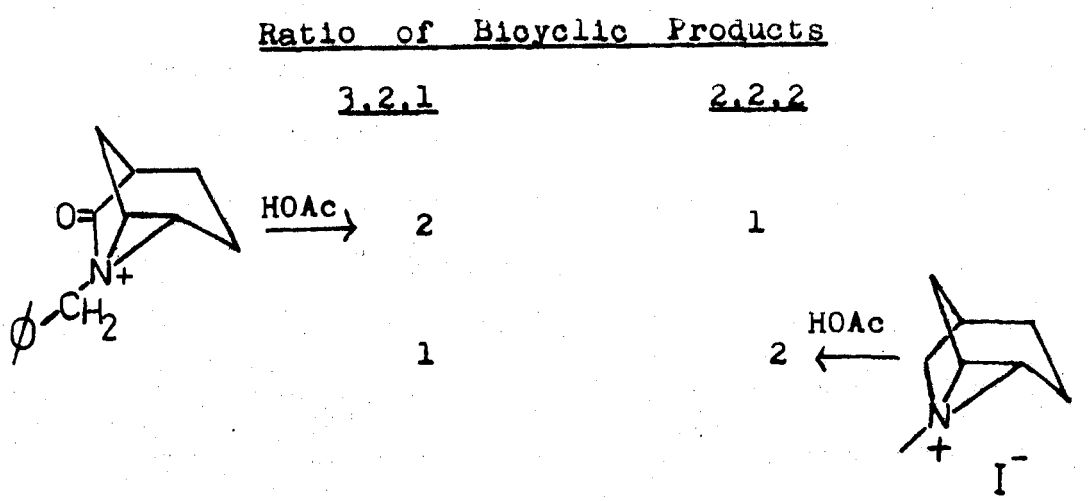
in the trapping photolysis of 19-2, since exo- approach seems as favored as endo-approach from examination of the Dreiding model. The yield of the endo-bromoamine 26-5 is also unusually low (55%) for a trapping reaction. Since more exo-chorolactam 24-3 than endo-chlorolactam 23-3 was found in the cyclization of chloramide 8-3, the formation of only endo-chloride 26-2 from the photolysis of chloramine 19-3 in methanol (54) requires an explanation. The absence of exo-chloroamine 27-2 in the LAH reduction products of a mixture of 23-3 and 24-3, and the apparent instability of 27-2 as shown by a similar reduction of exo-chlorolactam 24-3, indicate that the exo-chloramine is undergoing a secondary reaction. The absence of exo-nitrate 27-3 in the oxidative photoaddition of 19-2 is believed to be caused by a similar situation. It is suggested that aziridinium ions are being formed by the facile intramolecular dislacement of the exo-substituted compounds, as shown in Scheme 3.13, as a result of the favorable geometry of the molecule. Numerous examples of the formation of aziridinium ions in basic solution may be found in the literature (38, 212-214).



27-1

Scheme 3.13

The formation of aziridinium ions would account for exo-alcohol 27-1 being a major product from the photolysis of nitrosamine 19-2 under oxygen. The highly-water soluble nature of amino alcohols, coupled with their volatility, could be the reason for the alcohols not being detected in the $BrCCl_3$ trapping of 19-2 or chloramine cyclization reactions. A preference for the formation of [3,2,1] azabicyclic system, rather than the [2,2,2] bicyclic, has been found for the nucleophilic substitution of an acylaziridinium ion (135), but the [2,2,2] bicyclic system is the major product from a similar substitution of an N-methylaziridinium ion (89) (Scheme 3.14). As no [2,2,2] azabicyclic products have been isolated in this work, the intermediary of aziridinium ions must still be regarded as speculative.

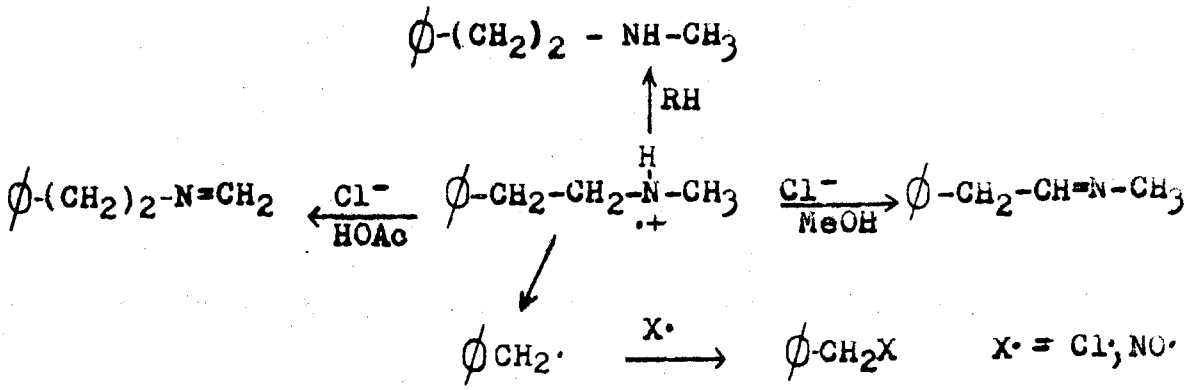


Scheme 3.14

3-4 Aminium Radical Reaction Pathways

Some effects of external variables, such as the acid concentration and the rate of initiation, upon the fate of an aminium radical are demonstrated in the latter part of the thesis. The unsuccessful N-methylindoline (61) formation from aminium radicals, generated in a low acidic condition from either N-nitrosomethylphenethylamine (20-2) or the corresponding N-chloramine 20-3), is comparable to the Ti^{3+} initiated reaction of 20-3 in aqueous acetic acid, in which Stella obtained 45% parent amine 20-1 and 22% benzyl chloride (112). Neale and Marcus (192) found that 20-3 in 4 molar H_2SO_4-acetic acid adds to 2-chloropropene in good yield, rather than undergoing intramolecular aromatic substitution. It appears that only in concentrated H_2SO_4 can 61 be formed in 27% yield (5).

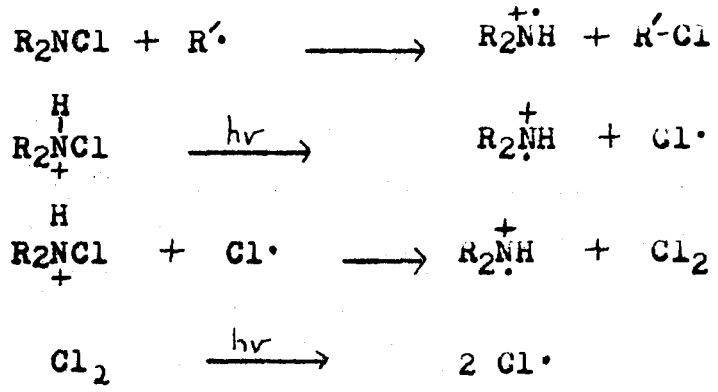
Because of the volatility of benzaldehyde and benzyl chloride, the isolations of the products derived from β-scission are not quantitative, and no accurate relationship between β-scission versus other pathways of the N-methylphenethylaminium radical has been obtained. It is not certain why only when HCl is used as a proton source the elimination products 58 and 59-2 are formed, nor why the direction of hydrogen elimination (methyl or methylene) varies with the solvent, i.e., amidoxime 58 is formed in methanol and formamide 59-2 in acetic acid (Scheme 3.15).



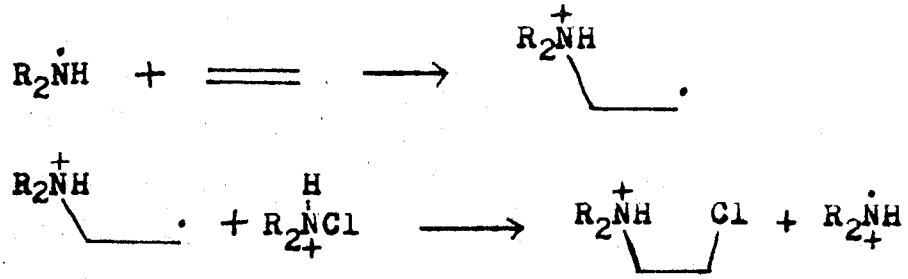
Scheme 3.15

Comparisons with the results of Neale (191, 192) (Table 2.11) indicate that the rate of the carbon radical initiated addition of N-chloramines to olefins appears to be significantly slower than those initiated by metal ions or light. The differences in the results are not a function of acidity, as all the reactions were run in 4 Molar H_2SO_4 in acetic acid. The yield of chloramine 2,3-dichloropropene adduct, 66-1, from the AIBN-initiated reaction (33%) is less than the yield of the corresponding compound, 66-2, from a direct photolysis (85%). The suggestion has been made that both the chlorine radical and aminium radical chain reactions participate during the photolysis of N-chloramines (132), and could explain the higher yields in Neale's work (Scheme 3.16).

Initiation



Propagation



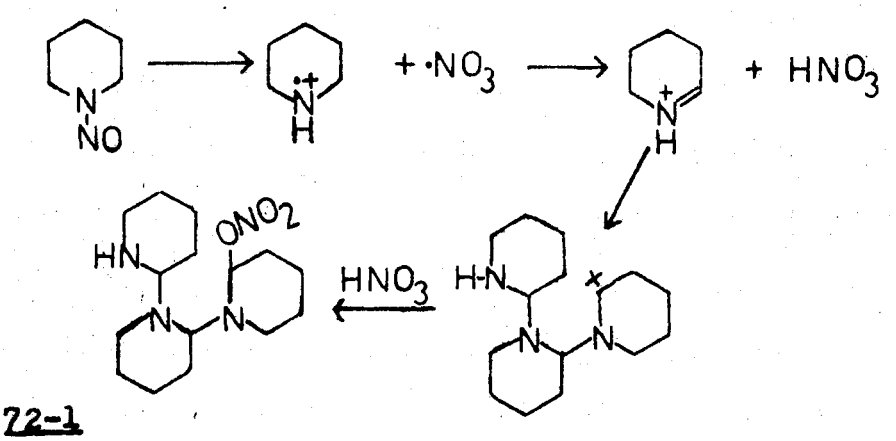
Scheme 3.16

The acetylhypochlorite - chloramine equilibrium, suggested in Scheme 2.8, appears to have no justification. An N-chloramine does not form from an ammonium ion and Cl·, nor does the chloramine rapidly equilibrate with the ammonium ion.

The preferential elimination of a benzylic hydrogen of the tetrahydroisoquinoline aminium radical, rather than intermolecular addition to olefins, has been attributed to

steric inhibition and the fact that the hydrogen being eliminated is benzylic (128). These same reasons could cause the low yield of parent amine 21-1, the methanol photoreduction product.

The photodecomposition of nitrosopiperidine (NP) in acidic methanol under oxygen follows the same major pathway as that under nitrogen (Table 2.12), namely hydrogen abstraction from methanol. The product assigned as trimer nitrate 72-1, obtained from the oxidative photodecomposition in aqueous HCl, was certainly formed by α-elimination to form 1, 2-dehydropiperidine (Scheme 3.17). The absence of amidoxime 69-3 indicates that there is a rapid trapping of NO, or possibly HNO, by oxygen. There is no evidence for the carbon radical intermediates on the 2-piperidino position, as shown in Scheme 2.10, being formed in the photodecomposition in either methanol or water, nor in the carbon-radical initiated reactions.



72-1

Scheme 3.17

The longer photolysis time required for the decomposition of NP in water, than that required in methanol, is consistent with the lower quantum yield of disappearance of nitrosodimethylamine in water (Φ_{dis} 0.3), compared to (Φ_{dis} 2.5) in methanol. The facile methanolic photoreduction of aminium radicals suggests the formation of the $\cdot CH_2OH$ ketyl radical, and is supported by the formation of formaldehyde in this reaction (41). The absence of carbon radical initiation, and consideration of the thermochemistry of the abstraction of NO from a nitrosamine (N-NO bond strength = 53 kcal./mole) (19) to form a C-nitroso compound (C-NO bond strength ≈ 40 kcal./mole) (202) as in the sequence given in Scheme 3.18, would indicate that NO abstraction by a carbon radical is not the important chain propagation step. Since no quantitative analytical methods could be developed to measure the quantum yields of appearance of the photodecomposition products (Results 2.15), the chain radical scheme involved in nitrosamine photolyses in methanol is not yet precisely known, although a possible sequence has been advanced for the photodecomposition reaction (41).

$$R_2\overset{+}{\underset{\cdot}{N}}H + CH_3OH \longrightarrow R_2\overset{+}{N}H_2 + \cdot CH_2OH \qquad \frac{\Delta H}{\approx 0}\ *$$

$$R_2N\text{-}NO + \cdot CH_2OH \xrightarrow[H^+]{} R_2\overset{+\cdot}{N}H + ON\text{-}CH_2OH \qquad +13$$

Scheme 3.18

* Energy given in kcal./mole; positive sign signifies an endothermic reaction. The N-H bond energy is 85-90 kcal./mole and methanol H-CH_2OH bond energy is 90 kcal./mole (215).

3-5 Scope and Limitations of Aminium and Amido Radical Reactions

There are different situations in which one method of generating a nitrogen radical will have particular advantages over another method. A comparison of the synthetic usefulness of the procedures used in this work with the radical and ionic methods of others is discussed in this section.

For both the intermolecular additions of aminium radicals and the intramolecular cyclization to a $\Delta^{5,6}$ olefinic bond, the nitrosamine precursor would appear to be the most suitable choice of reactant since no competitive ionic addition reaction occurs, as with chloramines (4,11), and relatively low acidic conditions are required. The rate of generation of aminium radicals can be specifically controlled with nitrosamines and the irradition wavelengths are at longer wavelength than chloramine photolyses (4, 57). The oxygen trapping reaction with nitrosamine adducts is more efficient and cleaner than the chloramine reactions (11, 39).

Three exceptions where a chloramine reactant would be required are given below. Obviously, if a chlorine substituent is specifically required, the chloramine reaction would be used, although the corresponding bromine derivative can be prepared easily in a $BrCCl_3$ trapping reaction with a nitrosamine adduct. If the reactant molecule is sensitive to acid, the metal initiated reaction of a chloramine

(10, 11) could be used, but it is worth noting that the low range of acidity required to cause nitrosamine photoadditions is not even sufficient to catalyze the polymerization of styrenes (41). If an aromatic amination is desired, the use of chloramines is essential, but the conditions of extreme acidity required for these reactions (5, 6) restrict the number of cases it can be applied without causing decomposition.

The nitrosamine aminium radical cyclization yields compare favorably with those of chloramine photolyses (11, 112) and metal-coordinated amino radicals (53, 54, 112). Aminium radical cyclizations to $\Delta^{5,6}$ olefinic bonds to form five-membered azacyclic compounds usually give better yields than other synthetic methods (139, 216). The aminium radical reactions are not prone to give a mixture of five- and six-membered rings as are formed in the Lewis acid catalyzed (35) or in silver-catalyzed (33, 38, 87) reactions of chloramines, or in nitrene intramolecular additions (88, 89). The intramolecular addition of an aminium radical to a $\Delta^{4,5}$ olefinic bond has only been accomplished using the titanium initiated chloramine reaction (Scheme 3.2), and the formation of a 7-azabicyclo [2,2,1] heptane appears to be presently best accomplished using a Hofmann-Loffler reaction (8) or an ionic reaction (217).

Although the formation of pyrollidone compounds can be accomplished in one step with the Hofmann-Loffler reaction,

the yields are generally no better than could be obtained by a sequence involving cyclization of chloramides or chloramines to $\Delta^{5,6}$ olefinic bonds, followed by LAH reduction. The Hofmann-Loffler reaction may also produce six-membered rings (6, 8), particularly if sterically restricted (218). A slightly higher yield of pyrollidone compounds without chlorine substituents is obtained when the one step ionic amino mercuration cyclization is used and seems to be a better method to obtain these compounds (85, 86). The nitrosamine- generated aminium radicals are not highly efficient at attacking a $\Delta^{6,7}$ olefinic bond (ca. 30% yield), and six-membered azabicyclic products can be formed in higher yields using metal-coordinated amino radicals (50-70%) (112, 198), or using ionic cyclization methods (85, 87, 198, 219, 220).

The photochemically initiated intramolecular cyclizations of nitrosamides (103, 104) and chloramide 8-3 (103) are the only reported cases of amido radical formation of γ-lactams by reaction with an olefinic bond. The photolyses of nitrosamides have the additional advantage of relatively long wavelength irradiation, which would be important if other chromophores are present in the molecule. The γ-lactams, such as 22-1 or 24-3, may be prepared in moderately high yields. On the other hand, δ-lactam 35-1 is only found in fair yield, but milder conditions are required than generally used in the ionic cyclization re-

actions (135, 136, 160, 221). The yield of β-lactam 31-1 is somewhat less than other preparations of β-lactams (145, 222). The nitrosamide photolysis method suffers from the disadvantage of requiring a β,γ-unsaturated amide, such as 10-1, but, since an intramolecular reaction is involved, it allows more control over the position of nitrogen addition.

The important synthetic advantage of the cyclizations described in this thesis is the simple maneuverability of the starting materials to create strained azabicylic systems containing a potentially useful substituent group. This substituent may be an oxime which can be reduced to a primary amine or hydrolyzed to a ketone, a nitrate which can be reduced to the alcohol, or a halogen.

CHAPTER 4

RESEARCH PROPOSALS

Although a substantial amount of work has been accomplished with aminium and amido radicals, there are still directions which have yet to be fully explored. Aspects of the experiments in this thesis require further investigation. Some of the 'clean-up' work that is required includes the following:

1. Optimization of the cyclization yields.
2. Definitive proof of the azabicyclic products assigned as six-membered nitrogen rings (Results 2-2-5, 2-5-2).
3. Experimentation to determine the generality of formation of β-lactams from β,γ—unsaturated amido radicals (2-2-3).
4. Photolysis of other N-chloramides to determine the ease of cyclization, particularly those containing a $\Delta^{6,7}$ olefinic bond in analogy to nitrosamide 12-2 (Results 2-2-5).
5. Proof of the existence of aziridinium ion intermediary from the reactions of halo and nitrato azabicyclic amines (Discussion 3-3-7).
6. Elucidation of the mechanism of ketone formation in the azabicyclic compounds (Discussion 3-3-5),

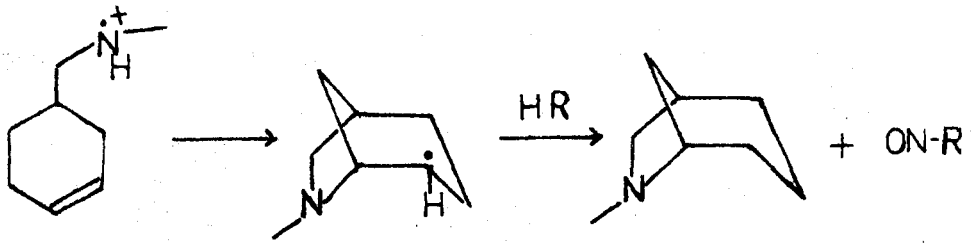
i.e., any dependency on reaction conditions.

7. Determination of the reaction occurring during the photolysis of nitrosamines in the presence of benzaldehyde oxime (Results 2-9, Discussion 3-3-5).

The following additional trapping experiments should be examined:

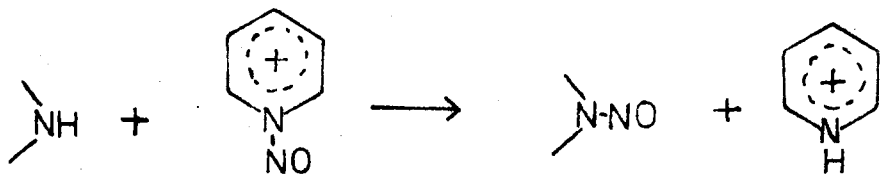
1. Vary the concentration of trapping reagent, e.g., $BrCCl_3$ in MeOH, to determine the minimal amount required for efficient trapping of the cyclization intermediates.
2. In view of the nitrite trapping experiments in benzene with iodine present, the same conditions for a photolysis of an alkenyl nitrosamide could give iodolactams (Discussion 3-3-6).
3. Use of other halogen donors as trapping reagents, such as CH_3I (223) to prepare iodo compounds.
4. Attempt the trapping of the chloramide cyclization intermediate to determine the relative rate of combination of the chlorine and carbon radicals versus that of oxygen combination or bromine abstraction.
5. Trapping with hydrogen donating reagents, such as $HSnBu_3$ (110) can be attempted. The purpose would be to produce unsubstituted aza-

bicyclic amines (Scheme 4.1). Hydrogen abstraction by the nitrogen radical might be expected to be minimal in view of the apparent efficiency of cyclization.



Scheme 4.1

A major difficulty in preparing alkenyl N-nitroso compounds is the tendency of the nitrosating agent to react with the π-bond. Preliminary experiments done in the course of this work have shown that the length of reaction time and the amount of nitrosating agent commonly used (17, 129) are greater than necessary to form the nitroso compound. The success of the N_2O_4 nitrosation of amide 11-1 in the presence of pyridine is similar to the improved yields of nitrosamines obtained with $NOBF_4$ in the presence of pyridine (18). The nitrosating agent in these systems may be the N-nitrosopyridinium cation; this could be tested by reacting the nitrosopyridinium ion, prepared by the method of Olah et. al. (224), with amides or amines (Scheme 4.2).



Scheme 4.2

Alternately, a number of other nitrosating agents could be utilized, e.g., the exchange reactions of amines with other nitroso compounds, such as N-nitroso carbamates (225). Nitrosamines have been prepared in a basic media using nitroprusside [$Fe(CN)_5NO^{2-}$] (226), which may be of advantage in preparing nitrosamines containing a double bond reactive to other nitrosating agents.

A recent report (227) outlines the effect of temperature, pH, and other anions upon the rate of nitrosation of morpholine; however the rate of addition of the nitrosating agent to the double bond is also enhanced by similar factors (228). Since chloride ion accelerates the rate of amine nitrosation (227) while having a less dramatic effect upon the rate of olefin addition (228), the addition of chloride ion may increase the yield of N-nitroso product without increased addition to the olefin.

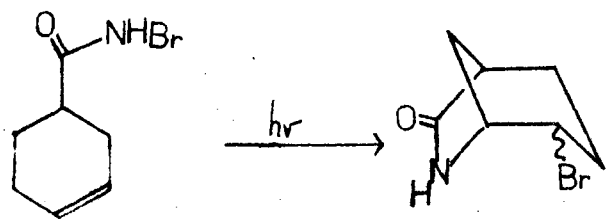
The factors controlling intramolecular radical addition reactions and the mechanisms involved could be stud-

ied in great detail. Determination of the quantum yields of nitrosamine, nitrosamide, and chloramide cyclizations could decide if a chain radical process is involved in these reactions. Esr techniques have not yet been successfully applied to nitrosamine radical reactions and, in the presence of spin trapping agents such as C-nitroso compounds (203) or nitrones (229), stable nitroxides could be obtained. The use of isotopically labelled alkenyl nitrosamines or nitrosamides would determine if NO is completely scrambled during intramolecular cyclizations, in a similar fashion as in the labelled N-nitrosodibenzylamine photodecomposition (3).

The photodecomposition products of nitrosamines have been shown to be dependent on the wavelength and solvent (41) and a solvent dependency for chloramine cyclizations was seen (53, 54). The effect of changing the temperature, the irradiation wavelength, and the photolysis solvent upon the yield and ring size in the aminium and amido radical cyclizations has not been fully determined. For example, at higher temperatures carbon radical intramolecular additions to a π-bond give higher yields of the thermodynamically more stable six-membered ring compound (90). Another variable in the nitrosamine intramolecular additions is the acid concentration, as can be suggested by the dependency of chloramine cyclizations upon acid concentration (11). For nitrosamines, the concentration range available

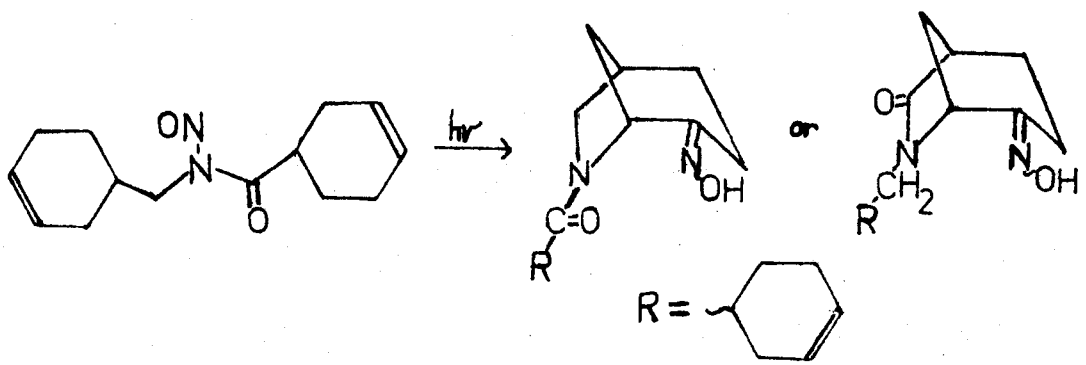
is limited by the decreased intensity of the nitrosamine uv absorptions at higher acid concentrations (230). The amount of cyclization may also depend upon the particular acid used as a proton source, such as trifluoroacetic acid or sulfuric acid compared to HCl. Because certain metal-initiated aminium radical cyclizations give a better yield of azabicyclic compound (Discussion 3-2), the effect of metal ions present during the photolysis of a nitroso compound could be investigated.

If quantum yield studies of chloramides indicate a radical chain process is occurring in the cyclization reaction as in chloramide intramolecular abstractions (79), then carbon radical initiated chloramide cyclization should be possible, analogous to the radical initiated chloramine intermolecular abstraction reactions (132). It is also probable that metal initiated halamido radical cyclizations would occur in a similar manner as the copper ion initiated intermolecular additions of halamides (81). The use of radical initiators in chloramide cyclizations would eliminate the high energy irradiation required. Primary alkenyl halamides, as shown in Scheme 4.3, and secondary alkenyl bromamides, prepared using t-butylhypobromite (4), could also undergo radical cyclizations to give bromolactam products.



Scheme 4.3

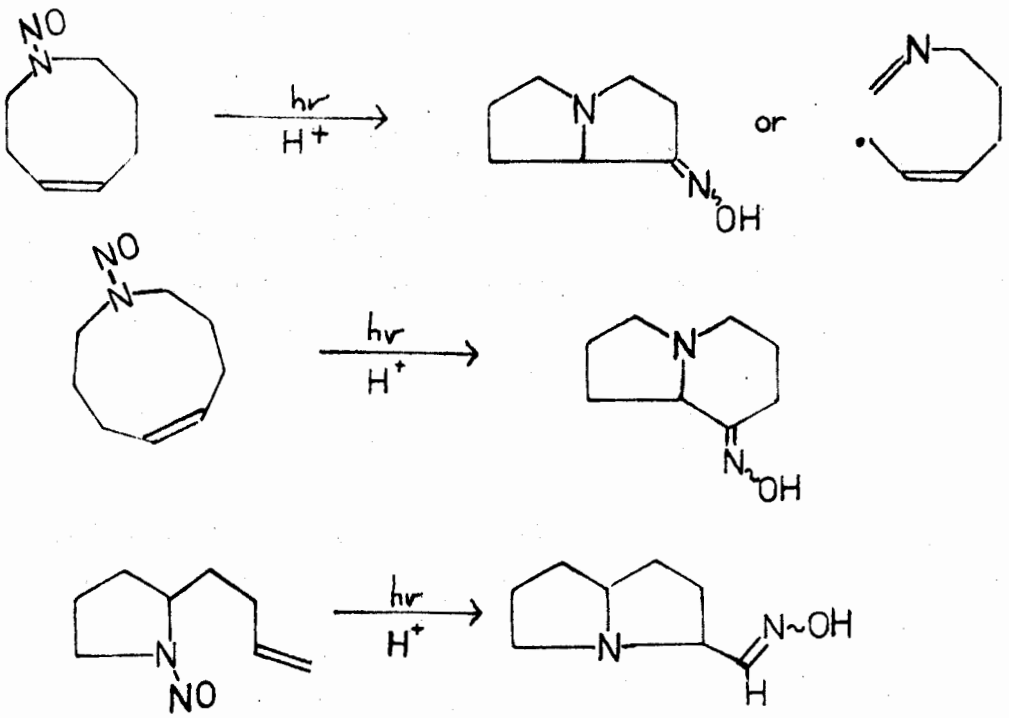
Since amido radicals are known to prefentially abstract a hydrogen from the alkyl, rather than the acyl, side chain (79), a competitive intramolecular cyclization may show similar type of preference for the direction of addition (Scheme 4.4).



Scheme 4.4

In this work simple cycloalkenyls have been investigated but several alternate starting materials can be proposed. Examples are shown in Scheme 4.5 of cyclizations involving a nitrogen already in a ring, an extension of the

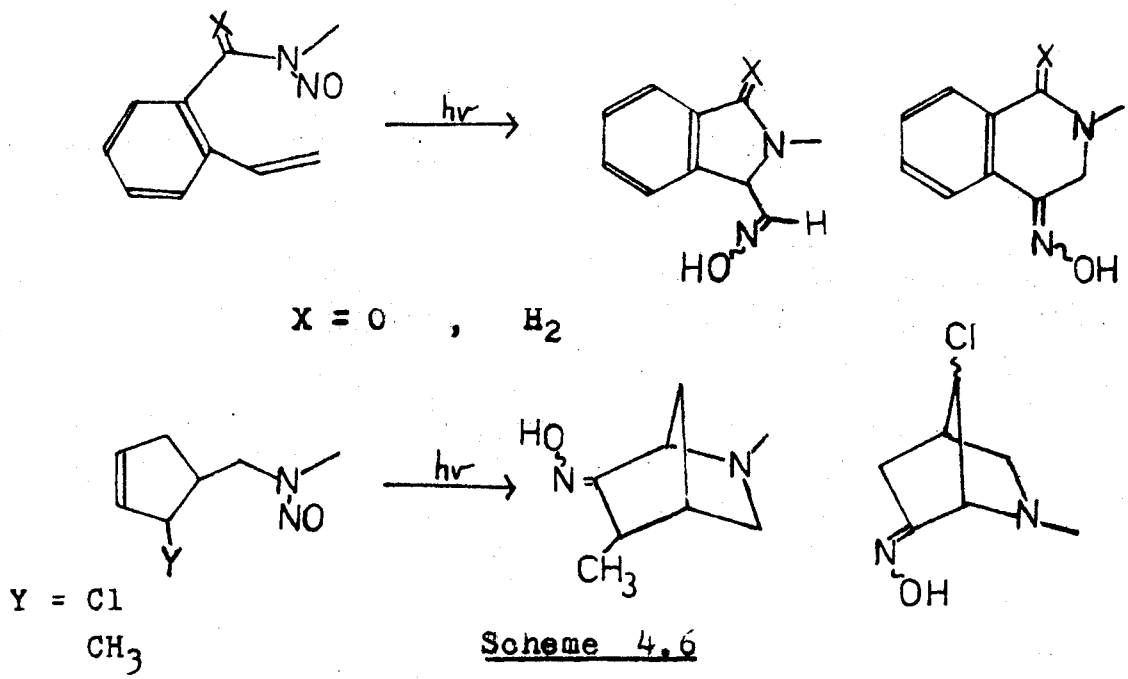
initial work by Chen with 74-2.



Scheme 4.5

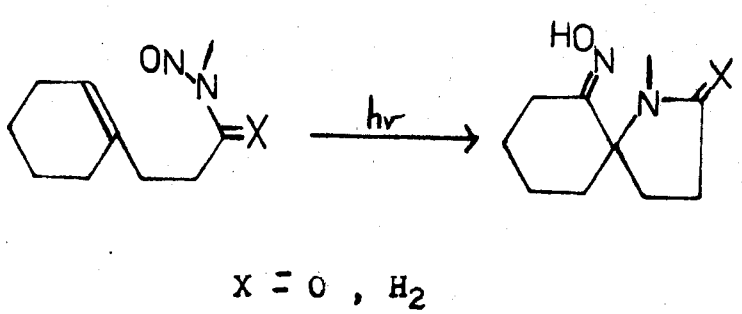
Substituent effects may be important in the formation of cyclic compounds, and could modify the ring size of the azacyclic compound or the direction of cyclization. The first two examples of Scheme 4.6 involve the possible intermediary of a more stable benzylic radical, provided the benzyl nitrosamine does not undergo facile benzylic hydrogen elimination; the compounds could be prepared from ortho-substituted styrenes (88). The last two examples involve nitrosamines in which cyclization to either end of the double bond would form a five-membered ring. The cyclizations may be controlled by the electron density at the π-orbitals and show substituent inductive effects,

which could be correlated with the Taft σ^*-constants as to the direction of cyclization.



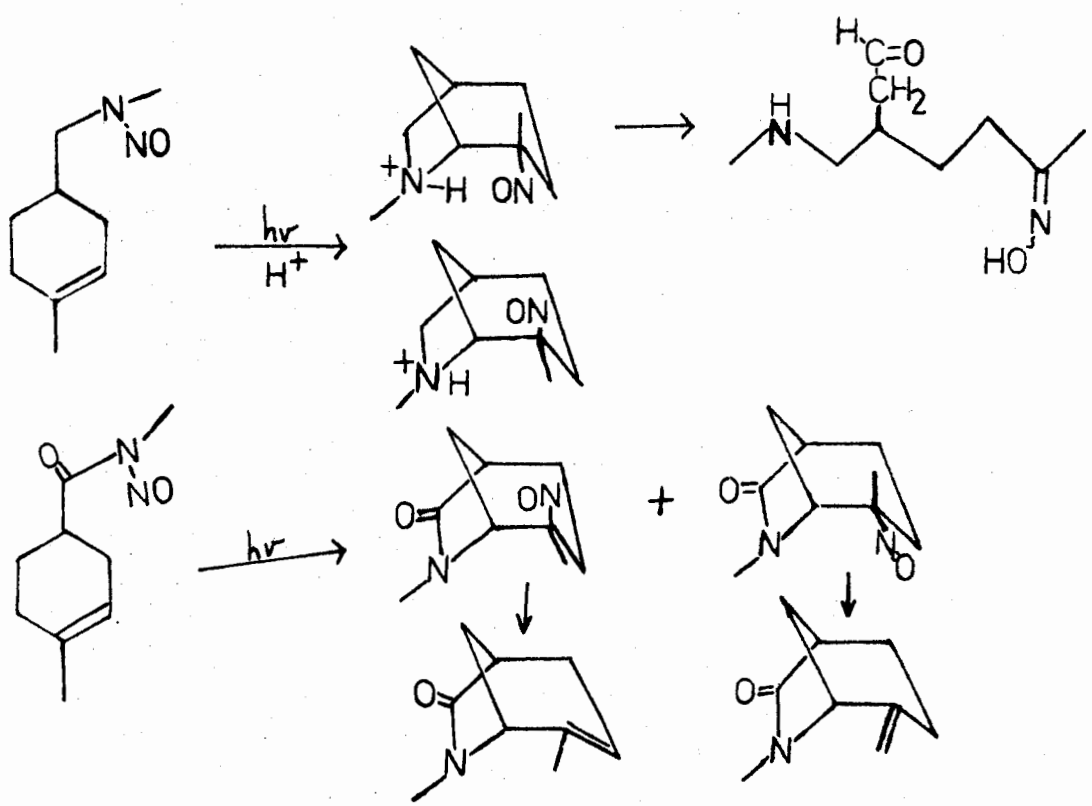
Scheme 4.6

The ability to form spiro azacycles using either aminium or amido radical cyclizations (Scheme 4.7) would be worthwhile investigating.



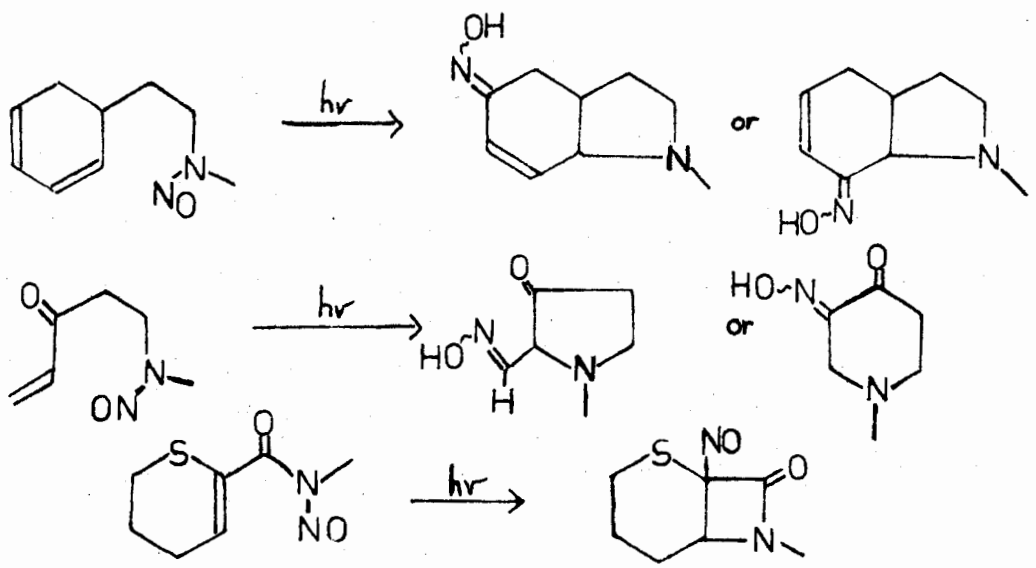
Scheme 4.7

Following the intermolecular addition of a nitrosamine to a 1, 1-dialkyl olefin, a cleavage reaction usually occurs (Eq 1.8) (1, 42). A similar reaction may also occur in the cyclization reactions (Scheme 4.8). Since the cleavage involes a cyclic transition state with the participation of the protonated amine, one isomer of the nitroso compound, i.e., endo-nitroso amine, may be decomposed specifically, if both are formed. Alternately, the C-nitroso adducts may eliminate HNO, in analogy to the corresponding nitrite cyclization products (97), to give the unsaturated azabicyclic compounds as illustrated with the amido cyclization products in Scheme 4.8.



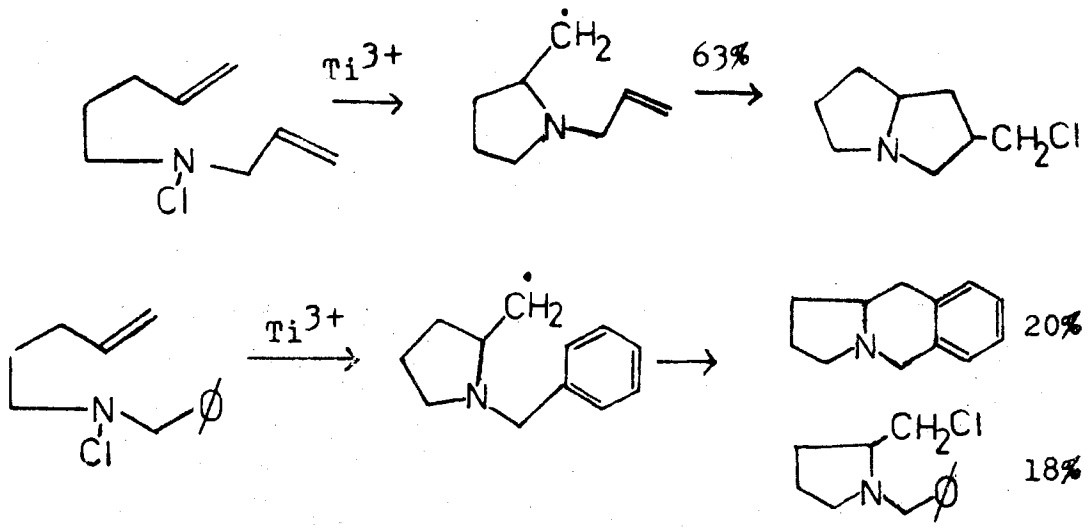
Scheme 4.8

As an extension of the work done in this laboratory (2), the cyclization reactions could be attempted with conjugated dienes, and α,β -unsaturated ketones, as shown in Scheme 4.9. The last reaction shown would form a carbon radical stabilized by both a carbonyl and a sulfur group, but, since the orbital overlap between the amido radical and the π-bond system is poor, the cyclization may be difficult.



Scheme 4.9

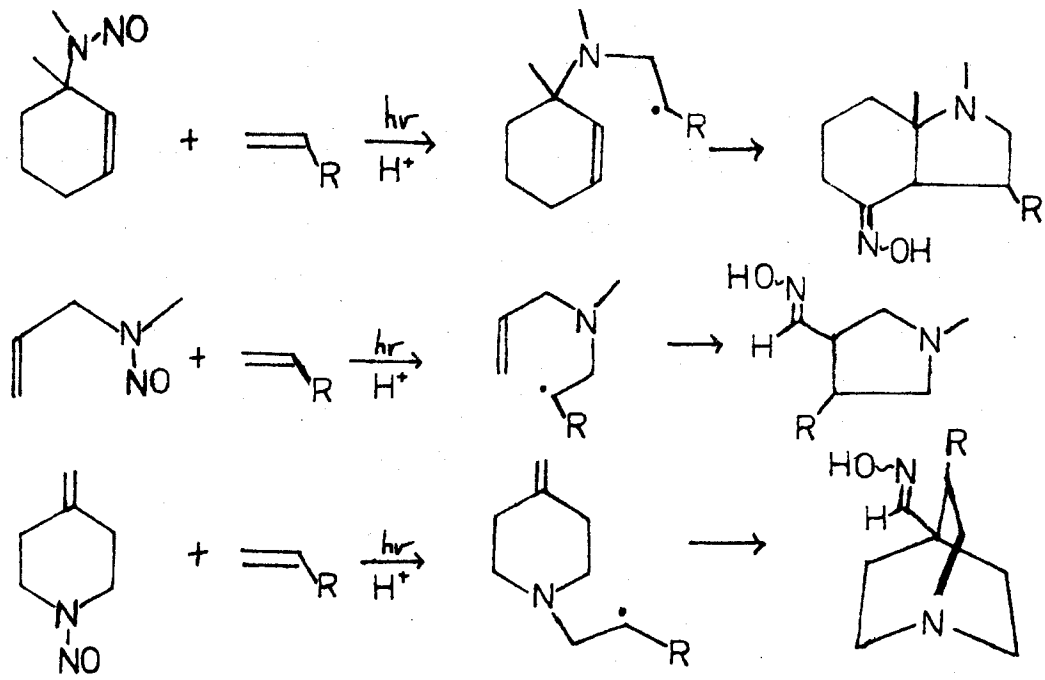
The extension of radical additions to double radical cyclizations was demonstrated by Stella (112), shown in Scheme 4.10, and may be tried with the corresponding nitroso compounds, as well as nitrosamides and chloramides.



Scheme 4.10

Although work in this laboratory (210) has shown that exclusive benzylic hydrogen elimination occurs in the photolysis of N-nitrosobenzylmethylamine rather than addition to styrene, the results of the photolysis of N-nitrosomethylphenethylamine show that β-scission and photo-elimination reactions are competitive. Since it is also known that photo-addition is ca. 10^3 times faster than α-elimination (1), the intermolecular addition of an alkenyl nitrosamine to an olefin, followed by intramolecular radical cyclization, could be a reasonable reaction sequence, particularly if α-elimination is not possible as shown in the first example of Scheme 4.11. Further justification for this proposal is found in the current research in this laboratory by K.S. Pillay and R.W. Lockhart, which demonstrated that intermolecular

addition of a nitrosamine to one π -bond of a non-conjugated diolefin was followed by a certain amount of intramolecular cyclization by the intermediate carbon radical.



Scheme 4.11

The last set of proposals involve modification of the environment of the nitrogen radical, and alternate methods of generating the radicals. The nitroso derivatives of alkenyl cyanamides (231), ureas (231), imides, N-t-butoxyamides (69), urethans, sulfonamides (232), ketimines (233, 234), hydroxyl amines (235), and their corresponding N-chloro derivatives (4), as shown in Figure 4.1, all could be tested for radical cyclizations to olefinic bonds. Other variations possible include the introduction of substituents further way from the nitrogen radical to determine their long range effect.

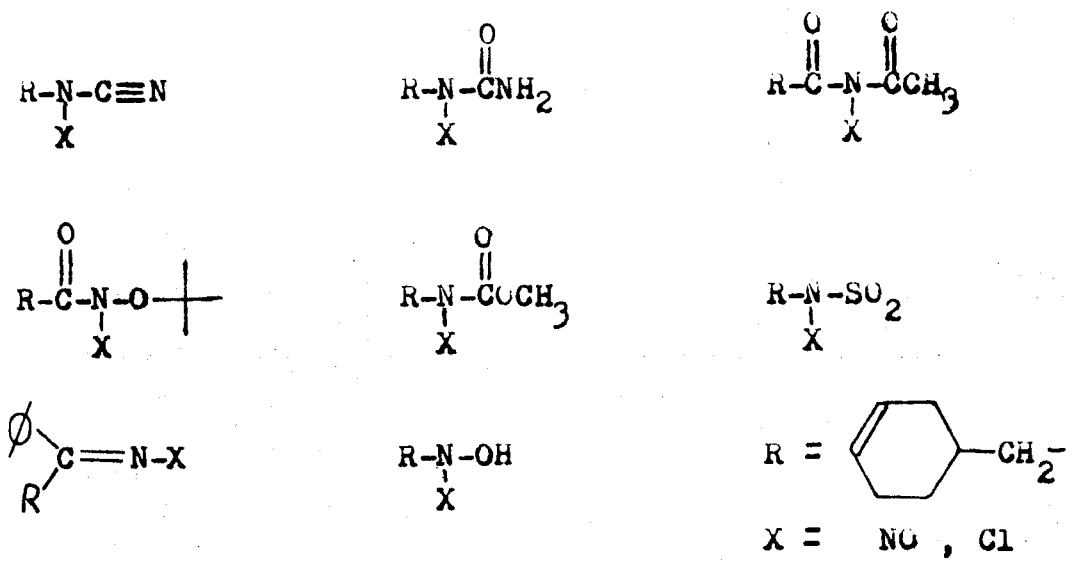


Figure 4.1

In a series of para-substituted benzamide derivatives, shown in Figure 4.2, changing the Y-group from electron-donating to electron-withdrawing substituents may affect the ability of the amido radical to cyclize to an olefin.

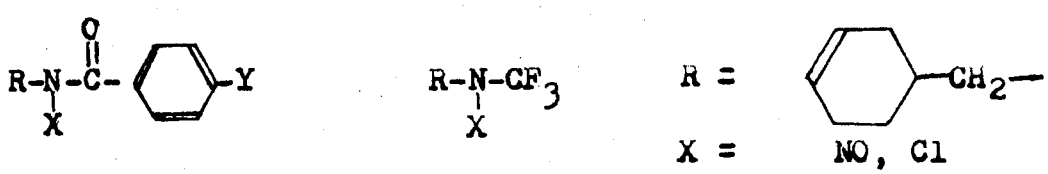


Figure 4.2

Similar to those methods mentioned in the Introduction, alternate procedures for generating nitrogen radicals are listed below and could be investigated with regard to radical intramolecular addition to olefins:

Aminium radicals: metal ion catalyzed decompositions of hydroxylamines (13) or hydroxylamine-O-sulfonic acids ($RNHOSO_3H$) (5,236).

Amino radicals: tetrazenes (48, 59, 60, 62), direct photolysis of amines (63) or amides (64), reacting amines with peroxides (48), decomposition of peroxycarbamates (R_2N-CO-OOR) (237).

Amido radicals: decomposition of N-O-diacylhydroxylamines (RCO-NH-OCOR) (71) or tetrazenes (67).

CHAPTER 5

EXPERIMENTAL

5-1 General Techniques

Unless otherwise stated the following procedures were standard:

Infrared (ir) spectra were measured either on a Perkin-Elmer model 457 or a Unicam SP200 grating spectrophotometer as a liquid film. Ultraviolet (uv) spectra were recorded on a Unicam SP800 or a Cary 14 spectrophotometer, and the absorptions (cm^{-1}) are strong, unless designated as b (broad), m (medium), w (weak) or sh (shoulder). Nuclear magnetic resonance (nmr) spectra were obtained on a Varian A56/60 or a Varian XL-100 spectrophotometer using deuterochloroform with TMS as an internal standard. The decoupling experiments were performed on the XL-100. Chemical shifts are reported in τ units, coupling constants (J) in hertz (H_z); the splitting patterns as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and b (broad); the half-height width of a resonance signal is given in hertz as $W\frac{1}{2}$, and a D_2O exchangeable proton is indicated by D_2O exch. Gas chromatography (gc) was performed on a Varian 1200 flame ionization chromatograph using a 20% SE-30 10' x $\frac{1}{8}$" stainless steel column, and the recorder was equipped with a Disc Chart Integrator (model 244). Mass spectra (ms) and high resolution mass spectra (Hrms) were

taken with a Hitachi-Perkin-Elmer RMU-GE instrument with an ion voltage of 80 ev and the intensity of the peaks is given as a percentage of the most intense peak. The gc-mass spectra (gc-ms) were performed using a Varian 1400 gas chromatograph using a 20% SE-30 column coupled to the mass spectra instrument.

Thin layer chromatography (tlc) was performed on alumina or silica gel plates (0.2 -0.3 mm thickness) impregnated with uv indicator, and examined by uv light and iodine vapor developer. The 'wet column' technique was utilized for chromatographic separations with Brockmann alumina (neutral or basic, activity 1, 80 - 200 mesh) or Mallinckrodt silicic acid (100 mesh). Melting points were determined on a Fisher-Johns hot stage or a Gallenkamp heating block apparatus, and the melting or boiling points were reported uncorrected. Elemental analyses were performed on a Perkin-Elmer 240 Microanalyzer.

The reported percentage yields of the products were generally estimated from column chromatography. Where gc integration was used, the product yields were uncorrected for individual response factors.

In general, the combined organic extracts were dried with anhydrous magnesium sulfate and filtered. Organic solvents were removed by evaporation under reduced pressure using a rotary evaporator.

5-2 Chemicals

Unless specified otherwise, the anhydrous solvents used were reagent grade, distilled and stored over sodium ribbon or molecular sieves (Type 3A). Reagent grade pyridine was stored over potassium hydroxide pellets. Used without further purification were 3-cyclopentenylacetic acid (Aldrich C11, 285-2), 3-cyclohexenylcarboxylic acid (Aldrich C10, 235), n-amyl alcohol (BA 1199), 3a,4,7,7a-tetrahydro-4,7 -methanoindene (dicyclopentadiene, MC and B TX315), 2-methyl-2-butene (Aldrich M3270-4), bis-(2-methoxyethyl) ether (diglyme, MC and B BX770), boron fluoride ethyl ether (Eastman 4272) 4-vinylcyclohexene (Aldrich V220-8), N-methyl-N-nitroso-p-toluenesulfonamide (Diazald, Aldrich D2800-0), 2-pyridone (Baker U660), bromotrichloromethane (Aldrich B8225-1), N-methylphenethylamine (Aldrich M6842), indoline (Aldrich I560-5), tetrahydroisoquinoline (Eastman 7065), and cyclohexene (MC and B CX2355). N-nitrosodimethylamine (Eastman 7370) and N-nitrosopiperidine (Eastman 2277) were distilled before use.

The gases used were obtained from Matheson Gas Company. Metal hydrides used were lithium aluminium hydride (LAH, Wilshire Chemical Co., 97%), sodium boronydride ($NaBH_4$, Fisher S-678, 98%), and sodium bis-(2-methoxyethoxy) aluminium hydride (Red-Al, 70% solution in C_6H_6, Aldrich 15,109-2). N-chloramines were prepared with

sodium hypochlorite solution (BA 2257, $Cl^+ > 5\%$) or Perfex bleach (Bristol-Meyers Co., $Cl^+ > 6\%$). Concentrated hydrochloric acid, sulfuric acid, glacial acetic acid, trifluoroacetic acid (Eastman 6287), and 70% perchloric acid (Mallinckrodt 2766) were used as supplied.

5-3 Preparation of Alkenyl Carboxylic Acids

5-3-1 3-Cyclopentenylacetic Acid (1)

The acid was prepared by the method of Noller and Adams (116). The intermediate diethylcyclopenten-3-ylmalonate distilled at 140-145° / 28 mm (Reported at 120° / 6 mm) (116). N-methylamide 14-1 is identical with that prepared from the commercial available acid (5-11-2).

5-3-2 4-Cyclohexenylacetic Acid (2)

(a) In the hydroboration procedure (117, 118), fresh boron trifluoride etherate (32 ml, 35g, 0.25 moles) was added to a mixture of $NaBH_4$ (7.5g, 0.195 moles) and 2-methyl-2-butene (30g, 0.43 moles) in diglyme (80 ml) kept at 0°, and the mixture was stirred under nitrogen for 1 hour. The suspension was forced under nitrogen pressure into another flask containing 4-vinylcyclohexene (35g, 0.325 moles) dissolved in diglyme (30 ml). An additional 20 ml of diglyme was used to transfer the remaining boron compounds. The reaction mixture was stirred for 2 hours at 0°. The excess hydride was decomposed by water (10 ml) and

the product oxidized by the addition of aqueous NaOH (3N, 50 ml), followed by a 30% hydrogen peroxide solution 50 ml), with the reaction temperature always kept below 50°. The mixture was extracted with ether twice and the ether dried and evaporated. The diglyme and unreacted 4-vinylcyclohexene were removed on a spinning band distillation apparatus (70-80°/25 mm) to leave, as the residue, crude 2-(4-cyclohexenyl)ethanol (19.7g, 0.156 moles, 63%).

The crude alcohol (5g, 0.04 moles) in acetone (100 ml) at 0° was oxidized with Jones' reagent (15 ml, CrO_3 = 2.65M, 0.04 moles) (238) by stirring for 0.5 hours. The reaction was filtered, and the acetone dried and evaporated. The crude residue was made basic with NaOH solution and stirred for 1 hour, then extracted with CH_2Cl_2. The aqueous layer was made acidic with dilute HCl and extracted with CH_2Cl_2. The CH_2Cl_2 acid extracts were dried and evaporated to give 2 (2.82g, 0.2 moles, 51%). The overall yield of 2 was ca. 30%.

Oxidations of the alcohol attempted with chromium trioxide in acetic acid (239) or silver oxide in dilute NaOH (240) gave low yields of acid 2.

(b) An Arndt-Eistert type syntnesis (120) was carried out by adding the acyl chloride prepared from acid 4 (20g, 0.16 moles) (5-4-1) to a distilled ethereal diazomethane solution, previously prepared by the decomposition

of Diazald (100g, 0.47 moles) (241). After reacting for 2 hours at 0°, the ether was removed under reduced pressure to give the diazo compound (ir 2100). This was taken up in a mixture of dioxane (150 ml) and concentrated NH_4OH (60 ml) and the solution heated to 60°. Silver oxide (1g) and a 10% methanolic solution of silver nitrate (10 ml) were added. The mixture was heated for 3 hours at 60°, then filtered. The solvent was evaporated and the crude product dissolved in CH_2Cl_2. After an aqueous NaOH wash, the CH_2Cl_2 was dried and evaporated. The amide product was refluxed for 8 hours in an aqueous solution (300 ml) of KOH (25g, 0.45 moles), then washed with CH_2Cl_2. The basic solution was acidified with dilute HCl, followed by CH_2Cl_2 extraction. The acidic CH_2Cl_2 extracts were dried and evaporated to give acid 2 (3.2g, 0.023 moles, 14.5%).

The spectra of 2 obtained from either method were identical: ir 3200(b, m), 3025(m), 2920, 2860(sh), 2200(b,m), 1705, 1650(sh), 655(m); nmr τ 0.28, (1H, s, D_2O exch), 4.82 (2H, s, $W_{\frac{1}{2}} = 4.5$), 7.5 - 8.8 (9H, m); ms (50°) m/e 140 (M^+, 9), 122 (13), 80 (100), 41 (25), 39 (33).

5-3-3 2-Cyclohexenylcarboxylic Acid (3)

(a) Modified Grignard method: Distilled 3-bromocyclohexene (28-30°/5 mm, 16g, 0.99 moles) dissolved in anhydrous ether (100 ml) was added to magnesium turnings (2.4g, 0.99 moles) in anhydrous ether (250 ml). The mixture was refluxed for 3 hours while a slow stream of carbon dioxide gas was bubbled through the solution. Dilute Na_2CO_3 was added to the solution, stirred, and the organic layer separated. The basic aqueous phase was acidified with dilute HCl, extracted with ether. The ether extracts were dried and evaporated to give acid 3 : 0.53g, 0.042 moles, 4.2%; ir 3100 (b,m), 3040 (m), 2940, 2840, 2150 (b,m), 1705, 1650 (sh), 1230, 675 (m) nmr τ 1.5 (1H, s, D_2O excn), 4.15 (2H, s, $W\frac{1}{2}$ = 4), 6.87 (1H, m), 7.8 - 816 (6H, m).

A similar procedure using lithium metal instead of magnesium, or following a normal Grignard procedure, involving addition of carbon dioxide after the alkyl magnesium was prepared, produced only the coupling product, 2-(2-cyclohexen-1-yl) cyclohexene.

(b) 2 - Cyclohexenyl anion (121): Sodium sand was prepared by heating sodium metal (11g, 0.48 moles) in refluxing xylene (100 ml), then vigorously shaking as the suspension cooled. The xylene was decanted and low boiling petroleum ether (800 ml) added. To this mixture was added 2-propanol(2 ml, 2.2g, 0.037 moles), cyclohexene (20g, 0.24

moles), and 1-amyl chloride (17.8g, 0.17 moles), previously prepared from the reaction of thionyl chloride with n-amyl alcohol. The reaction mixture was flushed with nitrogen, and left in a closed bottle for 48 days with occasional shaking. At the end of this time, carbon dioxide gas was bubbled through the solution for 3 hours, the solution was filtered and poured over solid CO_2. After 12 hours, the solution was made slightly acidic. The solvent was separated, dried, and evaporated to yield crude acid 3 (3.29g, ca. 0.026 moles, ca. 18%), contaminated with a small amount of amyl chloride.

5-3-4 Cyclohexanecarboxylic Acid (5)

Acid 5 was prepared in 37% yield by the $KMnO_4$ oxidation of cyclohexanecarboxaldehyde in H_2SO_4 (242), and converted directly into amide 7-1 (5-6-1).

5-4 Preparation of Alkenyl Amides and Amines

General procedures for the preparation of the required unsaturated nitrogen starting materials are given below. The data on specific compounds is found immediately preceeding the description of the decomposition reaction of their N-nitroso or N-chloro derivative.

5-4-1 Carboxamide Preparation

Through a benzene solution of the acyl chloride, obtained by either method a or b below, was bubbled methylamine gas (ammonia gas for a primary amide) until the solution was basic (ca. 2-3 hours), The solids were filtered off and washed with benzene. The combined benzene solutions were washed with water, dried, and evaporated to give the crude amide which was purified by crystallization or chromatography.

(a) To a stirred benzene solution (400 ml) at 0° containing the carboxylic acid (ca. 0.2 moles) and pyridine (20g, 0.25 moles), thionyl chloride (25g, 0.22 moles) was added dropwise. The solution was stirred for 1 hour, then the amine gas bubbled through as above.

(b) To the carboxylic acid (ca. 0.2 moles) and pyridine (1-20 ml) at 0°, thionyl chloride (25g) was slowly added, and the mixture left overnight at room temperature in a flask fitted with a drying tube. The excess thionyl chloride was removed by vacuum distillation. Benzene (150 ml) added to the residue, and either the amine was bubbled through as above, or the benzene solution used for the Curtius rearrangement (5-4-3).

5-4-2 Hydride Reduction of Amide (123)

An anhydrous ether solution of the amide (ca. 0.08 moles) was added to a suspension of LAH (5g, 0.13 moles) in ether (150 ml). The mixture was refluxed for 24 hours with an efficient condenser or stirred at room temperature for 48 hours. A 3N sodium hydroxide solution was slowly added to decompose the mixture, the ether was decanted, and the solids washed several times with ether. The combined ether solutions were dried, and the ether removed through a Vigreaux column to give the amine. An alternate procedure to obtain an HCl solution of the amine directly for further reactions, involved extraction of the ether solution with several washes of dilute HCl.

5-4-3 Curtius Rearrangement

A similar procedure (126) used acetone as the solvent but was found to be less satisfactory due to the formation of urea and primary amide products. The acyl chloride (5-4-1b) in a benzene solution was slowly added to a stirred aqueous solution (40 ml) of sodium azide (16g, 0.25 moles) while the temperature was kept below 5°. After 2-4 hours reaction at 0°, the layers were separated and the aqueous phase washed with benzene. The combined benzene solutions were dried (0°), and refluxed for 3 hours using two condensers in series. Decomposition of 3-cyclohexenylacyl azide required

40 hours reflux to complete the rearrangement.

5-4-4 Reduction of the Isocyanate

The benzene solvent could be evaporated to give the isocyanate, and an LAH reduction procedure (125) similar to 5-4-2 used to prepare the methylamine, but better yields were obtained in the procedure outlined below. A 70% solution of Red-Al (15 ml, 15g, 0.052 moles for theoretical 0.036 moles of isocyanate) (124), dissolved in benzene (15 ml), was added to the isocyanate benzene solution. After refluxing for 12 hours, the mixture was decomposed with water. The benzene solution was washed with dilute HCl several times, and the aqueous acid solution extracted with ether. The ether extracts were dried and evaporated using a Vigreaux column to give the methylamine.

5-4-5 Hydrolysis of the Isocyanate

The primary amine was prepared by stirring the isocyanate (ca. 0.12 moles) in benzene with concentrated HCl (30 ml) for 2 hours at room temperature, followed by 20 minutes refluxing. The benzene layer was separated and washed with dilute HCl. The combined acid solutions were basified with Na_2CO_3 and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and evaporated to give the amine.

5-4-6 Acetylation of the Primary Amine

The acetamide was prepared in the normal manner (122) using the following procedure. The amine (ca. 0.01 mole) in dilute HCl (75 ml, pH = 6) at 0° was stirred with acetic anhydride (10 ml). Then an aqueous solution (50 ml) of sodium acetate trihydrate (10g) was added, and the solution left overnight in the refrigerator. The solution was extracted with CH_2Cl_2, and the CH_2Cl_2 extracts dried and evaporated to yield the acetamide. The acetamide was purified by crystallization or chromatography.

5-5 Preparation of N-Nitroso and N-Chloro Compounds

The prepared N-nitrosamines were purified by chromatography through neutral alumina (ca. 20g, benzene or CH_2Cl_2 as elutants) or by distillation. Due to their thermal and photochemical instability, N-chloramines, N-chloramides (4), and N-nitrosamides (130) were used without further purification. The data for the radical precursors is summarized in Tables 2.2 to 2.6.

5-5-1 Sodium Nitrite Nitrosation

(a) Nitrosamines: The compounds were prepared by the standard method (128). The procedure for amines with reactive double bonds involved dissolving the amine (0.02 moles) in water (100 ml) containing concentrated HCl (2 ml, 0.06 moles) and etner (100 ml) was added. $NaNO_2$ (1.5g, 0.022

moles) was added in portions to the stirred solution at 0° and the mixture was allowed to react for 6 hours. The ether layer was separated and the aqueous layer washed with ether. After drying, the ether extracts were evaporated to give the nitrosamine.

(b) Nitrosamides: The procedure of White (129), using acetic acid and acetic anhydride as solvent, was followed in the majority of the preparations but a modified procedure, involving less $NaNO_2$, is outlined below. To an acetic acid (10 ml) and acetic anhydride (50 ml) solution at 0° containing the amide (0.007 moles) was added solid $NaNO_2$ (3.0g, 0.04 moles) over a period of 1 hour. The mixture was stirred for an additional 2.5 hours. Water (150 ml) was added and the solution was extracted with ether. The ether extracts were washed with water, then dilute Na_2CO_3 solution until basic, followed by another water wash. After drying, the ether was evaporated to give the nitrosamide.

5-5-2 Dinitrogen Tetroxide Nitrosation

(a) Nitrosamines: The method of White (129) was modified as shown. The amine (0.03 moles) was dissolved in CH_2Cl_2 (70 ml), anhydrous sodium acetate (9g, 1.1 moles) was added and the mixture cooled to -10° (acetone-ice bath). To the stirred mixture was added dropwise over a 2 hour period a cold solution (-10 to 0°) of N_2O_4 (3g, 0.032 moles) in

CH_2Cl_2 (30 ml). The mixture was stirred at -10° for 0.5 hours further. Water (50 ml) was added, and the CH_2Cl_2 layer separated. The solvent was washed with water, dilute HCl solution, dilute $NaCO_3$ solution until basic, then water again. The CH_2Cl_2 layer was dried and evaporated to give the nitrosamine.

(b) Nitrosamides: A similar procedure as above was used without the dilute HCl wash after nitrosation. In another preparation CCl_4 was used as the solvent and the N_2O_4 gas was condensed in a separate measuring cylinder, then allowed to evaporate into the stirred mixture of amide and sodium acetate in CCl_4 at -10°.

In the N_2O_4 nitrosation of 3-cyclohexen-1-ylacetamide, a fifty fold excess of pyridine, compared to acetamide II-1, present in the CCl_4 solution during nitrosation increased the yield of nitrosamide from 60% to 75%.

5-5-3 Preparation of N-Chloro Compounds

A standard procedure (32, 78) was used to prepare both chloramines and chloramides as outlined in this example. The secondary nitrogen compound (0.09 moles), dissolved in CH_2Cl_2 or ether (50 ml), was stirred at 0° and sodium hypochlorite solution (or Perfex bleach) (50 ml) was added. After 1 hour, the layers were separated and the aqueous portion extracted several times. The solvent was dried and evaporated to yield the crude N-chloro compound which was reacted immediately.

5-6 Preparation of Comparison Compounds

5-6-1 N-Nitroso-N-Methylcyclohexanecarboxamide (7-2)

Carboxylic acid 5 (1.27g) was converted in 60% yield using method 5-4-1b to N-methylcarboxamide 7-1 : m.p. 107-109° (C_6H_6 - C_6H_{12}); ir 3300(b), 2940, 2860, 1800, 1640, 1550; nmr τ 2.1 (1H, b, D_2O excn), 7.22 (3H, d, J = 4.5, collapses to singlet on D_2O exchange), 7.5 - 9.0 (11H, m); ms (100°) 142 ($M+1$, 15), 141 (M^+, 25), 112 (15), 100 (10), 86 (100), 83 (50), 73 (65), 58 (65), 55 (100).

$NaNO_2$ nitrosation (5-5-1b) gave an 87% yield of nitrosamide 7-3 : ir 2940, 2860, 1725, 1500, 1205, 905: nmr τ 6.3 (1H, b), 6.92 (3H, s), 7.8 - 8.9 (10H, m); uv (ε in C_6H_6) 429 (115), 410 (110), 393 (65), 375 (40).

5-6-2 N-Methylindoline (61)

Following a standard procedure (243), indoline (1.10g, 0.01 moles), methyl iodide (0.7 ml, 0.01 moles) and anhydrous Na_2CO_3 (2g) were stirred for 15 hours at 25° in anhydrous MeOH (50 ml). The solution was filtered, evaporated, and the residue taken up in ether. Evaporation of the ether gave an oil (0.85g) which was chromatographed on silicic acid (15g). Eluted with CH_2Cl_2, before the unreacted indoline, was N-methylindoline : 0.42g, gc (140°) 4.8 min; ir 3040 (m), 3020 (m), 2940, 2915, 2845, 2800, 1605, 1480,

1460, 1270, 1110, 740, 710; nmr τ 2.9 - 3.8 (4H, m), 6.7 - 7.4 (4H, m), 7.42 (3H, s).

5-7 Photolysis Apparatus and Filters

If not expressed in the text, the Apparatus is pyrex and the description of the conditions of the photolysis will be arranged as follows:

Apparatus (I, II or III), atmosphere (N_2 or O_2), lamp (Watts abbreviated as W) , filter .

5-7-1 Apparatus

For preparative scale photolyses, three types of apparatus were used.

(a) Apparatus I : Apparatus I (Figure 5.1) has been described previously (185, 190). The medium pressure lamp (200 W, Hanovia 654A36 ; 450W, Hanovia 679A36 ; 100W, Hanovia 8A36) was placed in the lamp well, within a cylindrical glass filter if required. Either tap cooling water or an externally cooled filter solution (circulated with a peristaltic pump) was passed through the cooling jacket. Nitrogen (scrubbed with Fieser's solution, then lead acetate solution, followed by concentrated H_2SO_4) or oxygen from a cylinder was bubbled through the gas inlet. The condenser was fitted with either a gas trap or a drying tube. A magnetic bar stirred the photolysate (ca. 225 ml). The apparatus was further cooled by immersion in a container of ice or cold water.

(b) Apparatus II : Apparatus II (Figure 5.2) was used for a smaller volume of photolysate (ca. 150 ml). The procedure was the same as for Apparatus I except that a stream of nitrogen served to agitate the solution.

(c) Apparatus III : Apparatus III (Figure 5.3) was photolyzed in a Rayonet photochemical reactor (Southern New England Ultraviolet Co.) with fifteen low pressure lamps (RPR 3500 A°). Nitrogen, passed through the gas inlet tube, provided agitation of the solution. In addition to the cooling fan, an externally cooled solution was circulated through the cooling shield.

5-7-2 Filters

The transmittance curves of the glass filters and the filter solution used in the photolyses are shown in Figure 5.4, and described below.

(a) Vycor

(b) Corex

(c) Pyrex

(d) New Nonex* (244)

(e) Old Nonex **

(f) Nonex and Pyrex (2 layers)

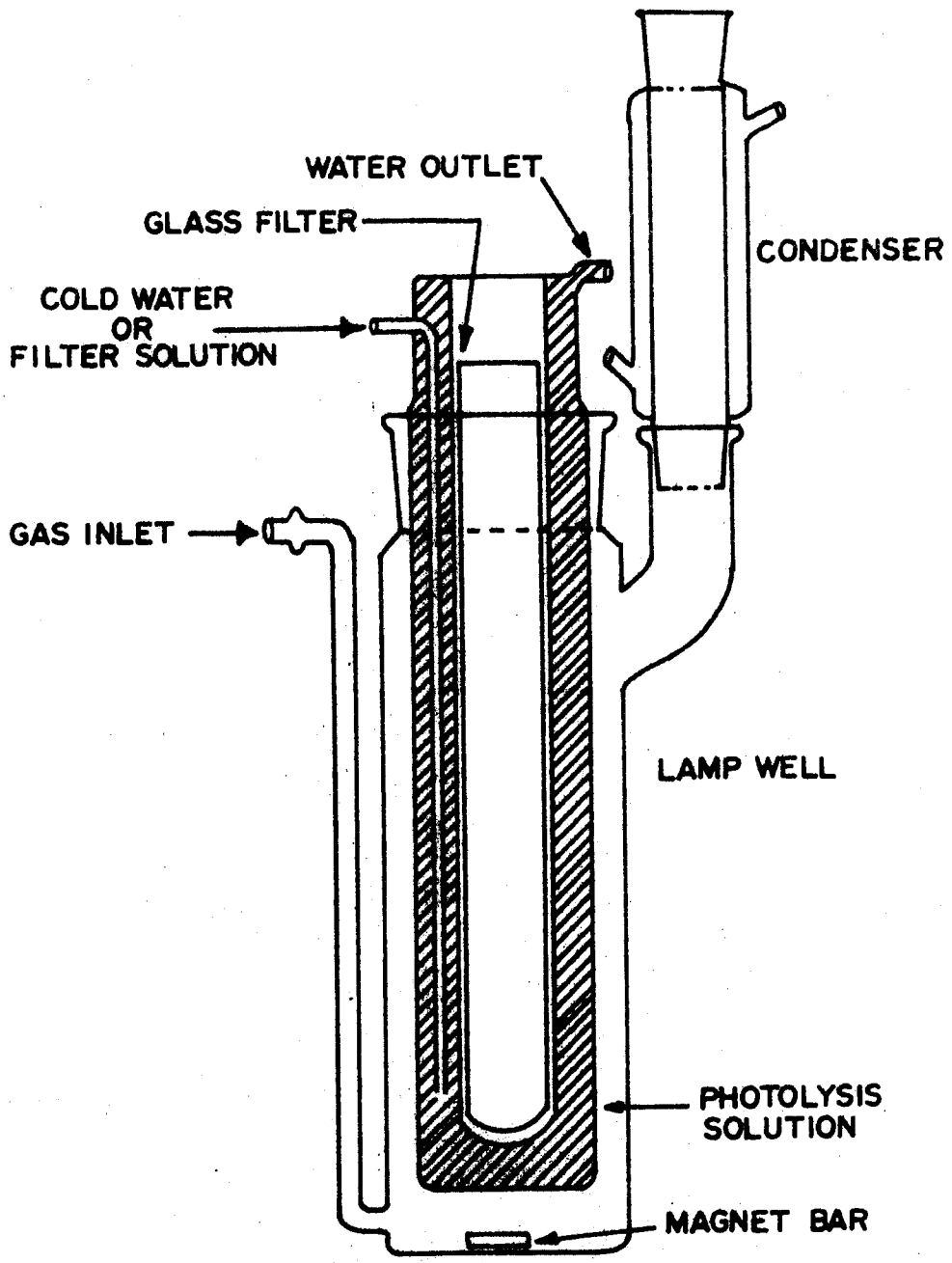
(g) GWV***

(h) Sodium nitrite sodium phthalate filter solution (245)

(i) Corning CS 7-60

* Courtesy of Corning Glass
** Courtesy of N.J. Turro
*** Courtesy of Janeger Glass

Figure 5.1 Apparatus 1



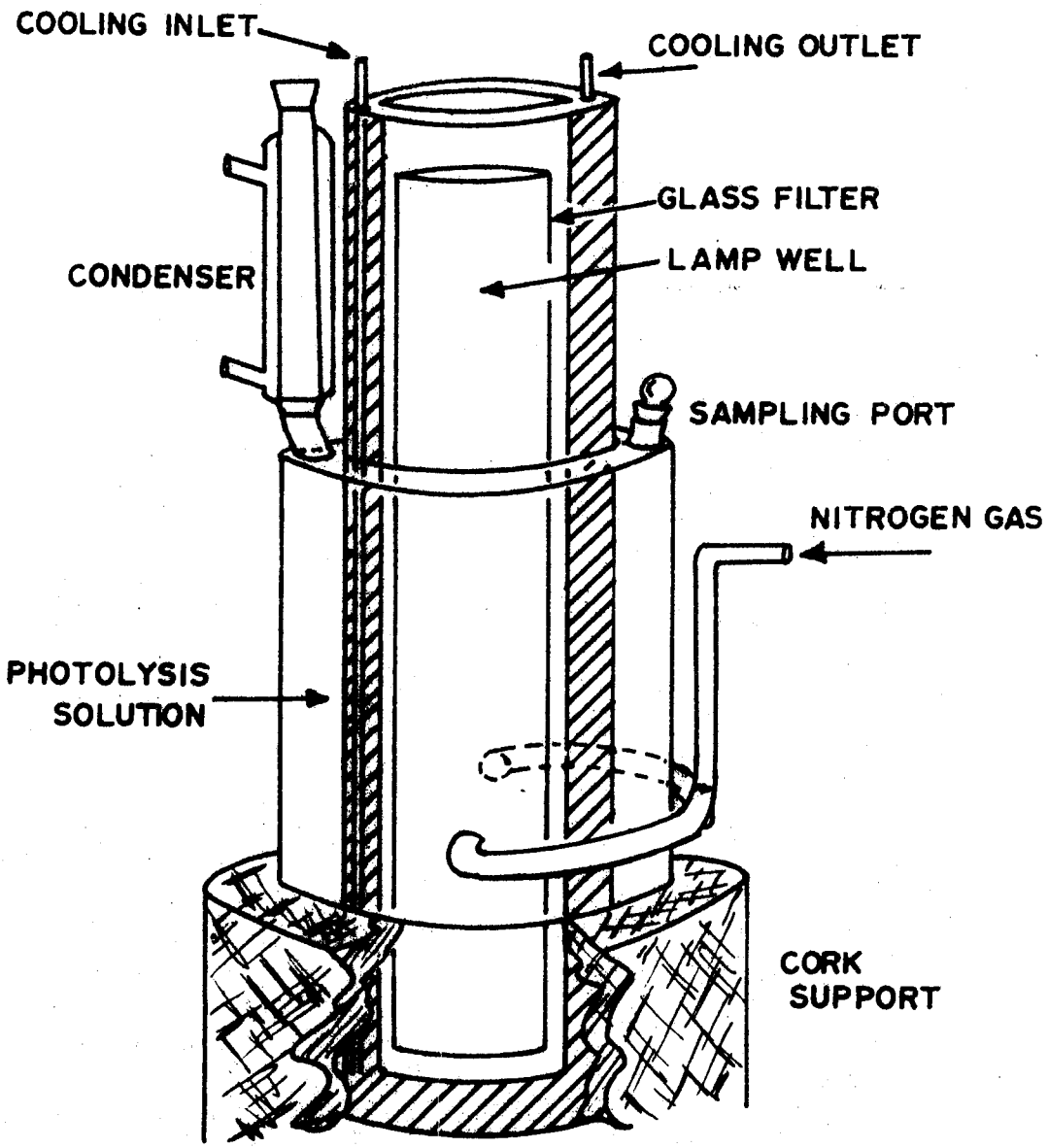


Figure 5.2 Apparatus II

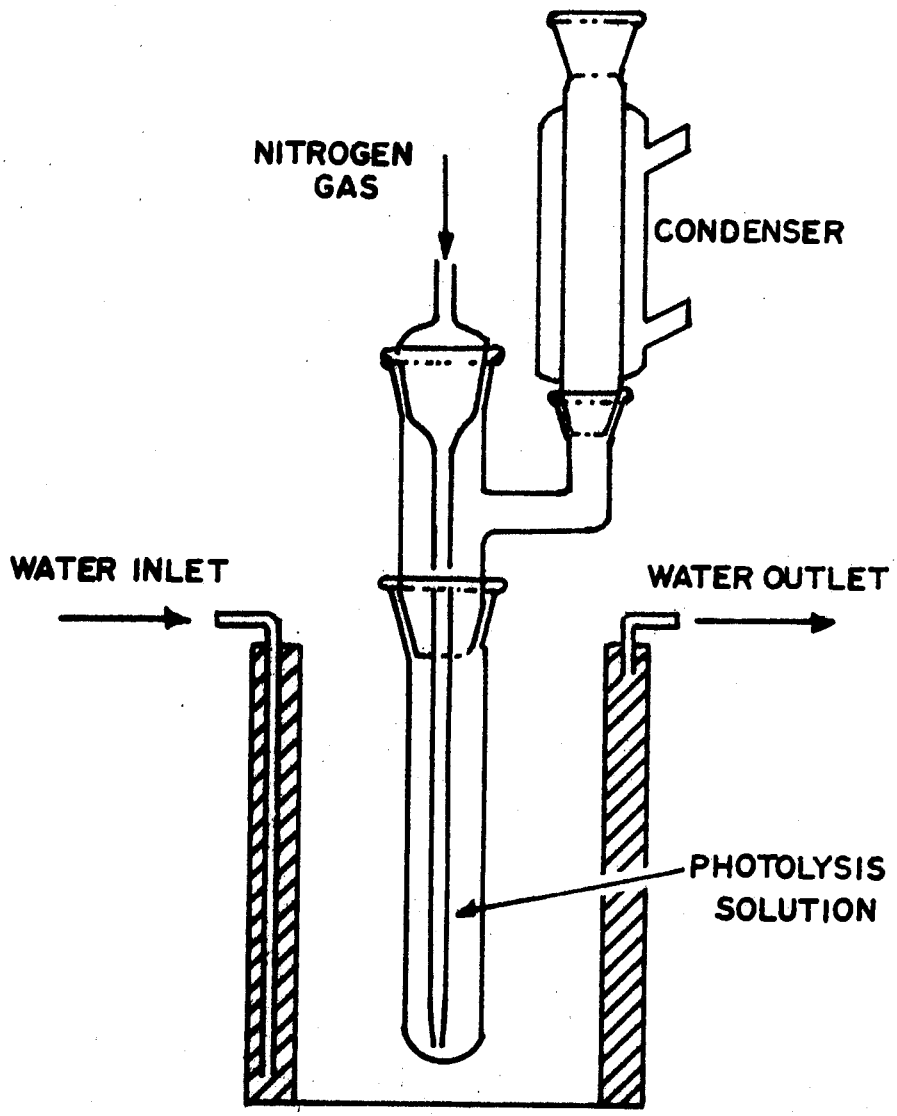
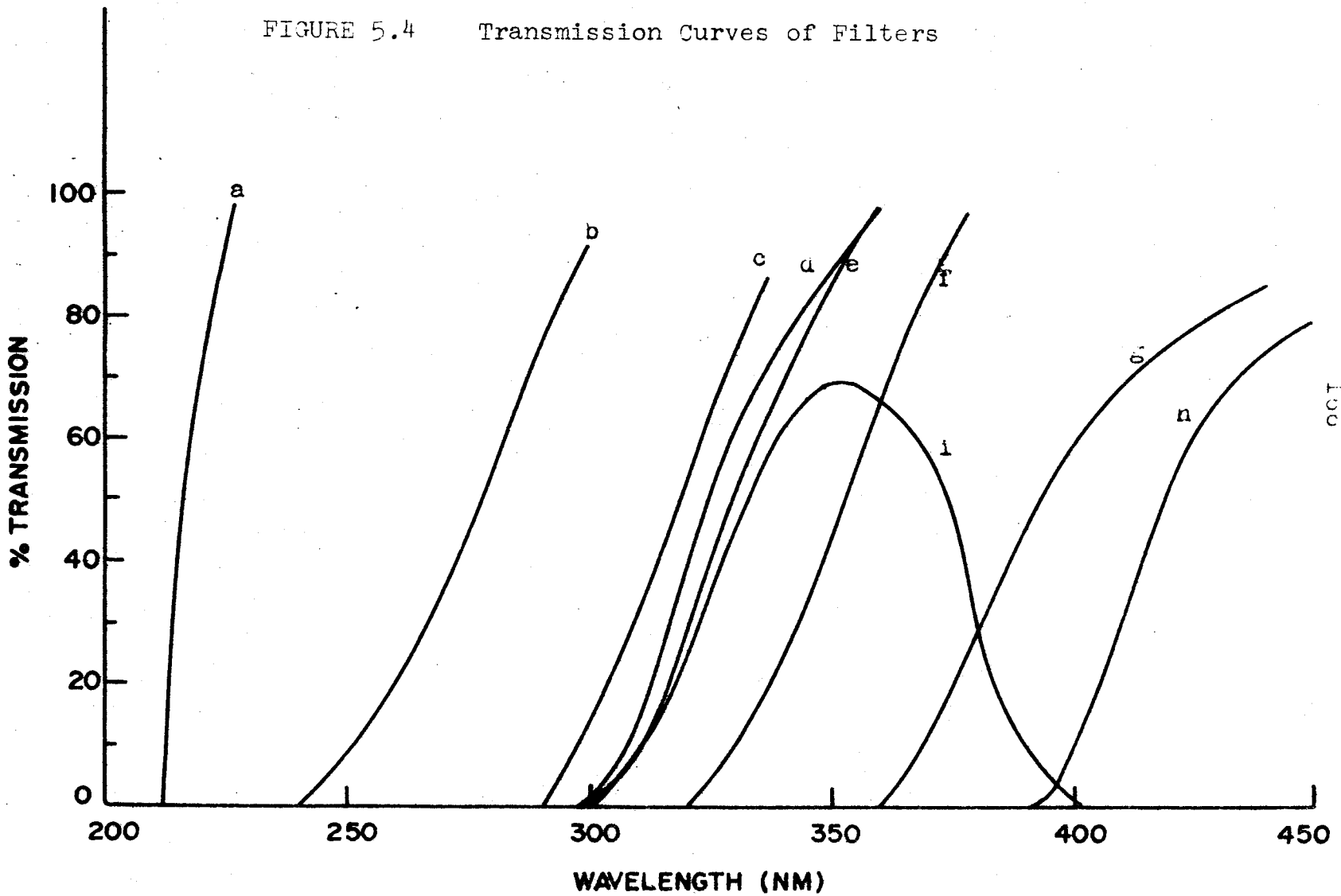


Figure 5.3 Apparatus III

FIGURE 5.4 Transmission Curves of Filters



5-8 Radical Generation Procedures

5-8-1 N-Nitrosamine Photolysis (42)

A methanol solution of the nitrosamine (ca. 0.03 M) containing concentrated HCl (ca. 1 ml, 0.012 moles) was placed in the apparatus, usually with a Nonex filter, and gas bubbled through for 15 - 20 minutes. The mixture was photolyzed until the $n \rightarrow \pi^*$ absorption (ca. 350 nm) had disappeared, normally within 4 hours. The reaction was monitored by uv, with aliquots of the photolysate removed at intervals and diluted to the desired volume. A zero hour sample was retained in the dark and the uv spectrum examined at the completion of the photolysis. There was no noticable decrease in the uv absorption, indicating the absence of thermal reactions.

The photolysate was evaporated about room temperature and the residue diluted with water (ca. 50 ml). After extraction of the neutral/acidic material with ether or a chlorinated solvent, the solution was basified to the pH 9-11 region with Na_2CO_3. The basic fraction was extracted. In some cases, continuous heavier-than-water liquid-liquid extraction was employed to recover additional material. The solvent extracts were dried and evaporated to yield the respective mixtures which were separated into components by column chromatography.

5-8-2 N-Nitrosamide Photolysis (73)

A procedure similar to the nitrosamine photolysis was followed, using benzene solution without acid. The sodium nitrite sodium phthalate filter solution (Figure 5.4) was used to cut off the light below 400 nm. The disappearance of the nitrosamide peaks about 405 nm were monitored to follow the reaction. After removal of the photolysate solvent, the mixture was chromatographed directly.

5-8-3 Photolysis of N-Chloro Compounds

The same procedures as above were used, 5-8-1 for chloramines and 5-8-2 for chloramides. The N-chloro compounds were dissolved in benzene, acetic acid or CCl_4 and photolyzed in a quartz apparatus using a Vycor filter. The disappearance of the N-chloro compound was monitored by iodometric titration of the positive chlorine (36) using a modified procedure. The photolysate (2 ml) was added to a solution of acetone (10 ml) containing ca. 1 ml of a 10% acetic acid solution saturated with KI. The liberated iodine was titrated with a 0.1 N sodium thiosulfate solution.

5-8-4 N-Chloramine Reactions with Metal Salts

(a) Iron Salts Catalyzed Reaction (10, 11) : The chloramine (ca. 6 mmoles) was stirred at 0° in an acetic acid solution (50 ml, glacial or 50% water) with varying

concentrations of H_2SO_4 or HCl. To this mixture was added from 0.3 to 1 equivalents of hydrated ferrous sulfate (ca. 1.5 g), and in one case a ferric chloride solution (ca. 0.5 equivalents of the chloramine). After more than 1 hour stirring, the mixture was extracted with an organic solvent and washed with dilute Na_2CO_3. After drying, the solvent was evaporated to give the crude residue. The residue was either separated into acidic and basic fractions as in 5-8-1, or chromatographed directly.

(b) Silver Nitrate Catalyzed Reaction (33, 34, 36) : To the chloramine (ca. 0.035 moles) in methanol (350 ml) was added silver nitrate (ca. 8g, 0.045 moles), and the mixture was refluxed for 2.5 hours in the dark. Saturated NaCl solution was added until no more precipitate formed and the solution was filtered. The solvent was evaporated and the products separated into acidic and basic fractions as in 5-8-1. The components were isolated by chromatography.

5-9 Photolysis of Alkenyl Nitrosamides under N_2

5-9-1 N-Nitroso-N-methyl-3-cyclohexene-1-carboxamide (8-2)

Reaction of acid 4 using method 5-4-1b, followed by recrystallization from EtOH -hexane gave an 81% yield of carboxamide 8-1 : m.p. 87-89° (literature 88-90°) (246); ir 3300(b), 3100(m), 3030(m), 2930, 2900, 2840, 1635, 1500, 640(m); nmr τ 4.0 (1 H, b, D_2O excn), 4.33 (2 H, s, $W_{\frac{1}{2}}$ = 4), 7.19 (3 H, d, J = 4.5, collapses to s on D_2O exchange),

7.5-8.3 (7 H, m); ms (85°) 139 (M^+, 100), 124 (13), 110 (40), 82 (73), 81 (83), 79 (49), 73 (32), 67 (60), 58 (79).

Nitrosamide 8-2 was prepared by either method 5-5-1b or 5-5-2b to give nearly quantitative yields. Weak peaks at 1645 and 1550 cm^{-1} were observed in the ir spectrum, caused by nitrate and nitro addition products. The nmr spectrum showed no amide resonance peaks at τ 7.19 and that > 90% olefinic bond remained. A sample containing > 95% 8-2 had the following characteristics : ir 3050 (m), 2940, 2840, 1725, 1500, 1210, 650 (m); nmr τ 4.30 (2 H, s, $W_{\frac{1}{2}}$ = 5), 6.2 (1 H, m), 6.9 (3 H, s), 7.5-8.2 (6 H, m); uv (ε in C_6D_6), 428 (90), 408 (85), 392 (60), 375 (50).

(a) A benzene solution (250 ml) of 8-2, prepared from 8-1 (2.2g, 0.0158 moles) was photolyzed for 2.5 hours (Apparatus I, N_2, 200 W, > 400 nm filter solution). The formation of C-nitroso dimer was indicated by an increasing peak at ca. 295 nm. Evaporation of the solvent gave a residue which showed dimer peaks at 1220 cm^{-1} and a singlet at τ 7.09. The dimer peaks disappeared when the sample kept or chromatographed. A solid (0.11g) precipitated from the photolysate and an additional 0.62g were obtained by crystallization of the residue (EtOH - H_2O). The combined solids were recrystallized from hexane - EtOH, then EtOH, to yield anti-oximinolactam 22-1 : m.p. 203-205°, ir (KBr) 3300 (b), 3100 (m), 2980, 2800, 1670, 1230, 950, 920; nmr (100 mc, pyridine - d_5) τ 5.92 (1 H, dd, J = 5.5 and 1),

6.4-6.7 (1 H, m), 7.26 (3 H, s), 7.48 (1 H, m), 7.7-8.4 (5 H, m); ms (130°) 168 (M^+, 14), 152 (14), 151 (100), 123 (14), 110 (37), 98 (26), 94 (14), 42 (40).

Hrms at M^+ : Calcd, 168.0898 ; Found, 168.0882.

Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.14; H, 7.14; N, 16.67.
Found : C, 57.27 ; H, 7.17; N, 16.60.

Decoupling experiments showed the τ 5.92 and τ 7.48 signals were not coupled to the τ 6.5 signal of the equatorial C - 3 proton (2). Selective reduction of the lactam carbonyl with trimethoxylithium aluminium hydride (247) or diborane (248) failed, since the recovered residue showed a strong lactam peak at 1670 cm^{-1}.

(b) Nitrosamide 8-2, prepared from 8-1 (2g, 0.014 moles), in benzene (230 ml) was photolyzed for 6 hours with the above conditions. After evaporation of the solvent, the residue was dissolved in a 50% EtOH solution (60 ml) containing sodium bisulfite (35g) (138), and was heated for 6 hours on a steam bath. The ethanol was distilled off and the solution basified to pH 9. CH_2Cl_2 extraction and evaporation of the extracts gave aminoketone 22-3 (1.23g 8 mmoles, 56%). A similar bisulfite hydrolysis of a mixture of anti- and syn- oximes 22-1 and 22-2 (2:3 ratio), isolated by chromatography as described in 5-8-1 c, gave a 70% yield of ketone 22-3 : Distilled at 84-88°/ 5 mm; ir (CCl_4) 2950, 2870 (sh), 1735 (sh), 1715, 1645, 1400; nmr τ 6.3 (1 H, dd, J = 5 and 2), 7.14 (3 H, s), 7.2-8.15

(7 H, m); ms (30°) 154 (M+1, 11), 153 (M^+, 64), 137 (11), 125 (44), 110 (22), 109 (17), 97 (100), 96 (44), 80 (20), 79 (22), 69 (67), 68 (42), 42 (92).

Hrms at M^+: Calcd for $C_8H_{11}NO_2$, 153.0789.
Found, 153.0744.

Other methods were attempted to prepare the ketone from the oxime mixture. Stirring the mixture with either cerium (249), or titanium (250) salts gave less than a 15% recovery of a mixture of compounds, as judged by tlc. Stirring the mixture in CH_2Cl_2 (15 ml) with 2 N HCl (12 ml) gave ca. 60% recovery of a mixture of oximes and ketone, as judged by the N - CH_3 singlets.

The attempted selective reduction of the amide carbonyl of 22-3 with $LiAl(OCH_3)_3$ (247) was unsuccessful since the product still showed the 1690 cm^{-1} peak. Heating ketone 22-3 with ethylene glycol in the presence of p-toluene sulfonic acid (251) gave a 38% yield of lactam ketal 22-4 : ir 2950, 2880 (m), 1690, 1450, 1390, 1115; nmr τ 6.4 (4 H, m), 6.7 (1 H, dd, J = 5 and 1), 7.15 (3 H, s). Treatment of the ketal 22-4 with diborane (248) gave a residue still showing the 1690 cm^{-1} absorption.

Ketolactam 22-3 (1.07g, 7 mmoles) was refluxed with LAH (2g, 0.05 moles) for 48 hours in ether (150 ml). The reaction mixture was treated with 3N NaOH solution and worked up in the usual fashion (5-4-2). The ether was removed through a Vigreaux column to give a mixture of endo- and exo- alcohols 26-1 and 27-1 (ca. 3:1 ratio) : 1.0g, 0.0065 moles, 92%; ir 3400(b), 2940, 2860, 2790(m), 1455,

1080, 1010; ir (hexane) 3534, 3622 (w) (literature 3539, 3628) (87); nmr τ 6.1 (0.25 H, b, $W_{\frac{1}{2}}$ = 8), 6.55 (0.75 H, b, $W_{\frac{1}{2}}$ = 11), 7.0 (1 H, s, D_2O exch), 7.52 (3 H, s).

The mixture of alcohols (0.15g, 0.001 moles) in acetone (1 ml) were shaken at 0° with Jones' reagent (1 ml, 2.65 M) for 20 minutes. Water (4 ml) was added and the acetone evaporated. Aqueous KOH was added until the solution was basic (pH 9), and the solution was extracted with CH_2Cl_2. After drying, the CH_2Cl_2 was evaporated to give aminoketone 28-3 : 0.09 g,0.7 mmole, 60%; ir 2940, 2870, 2780 (m), 1710, 1450, 1200; nmr τ 6.69 (1 H, dd, J = 9.5 and 6), 6.76 (1 H, bd, J = 5.5 and 1), 7.4 (1 H, m), 7.55 (3 H, s), 7.6-8.6 (7 H, m); ms (150°) 139 (M^+ , 25), 111 (23), 83 (23), 82 (100), 67 (7), 55 (7), 42 (39). The spectra were identical to 26-3 prepared Esposito et. al. (139).

Attempted oxidation of the alcohol mixture (0.11 g) with CrO_3 in acetic acid (252) for 5.5 hours gave a residue (0.07 g) which exhibited no N-CH_3 singlet in nmr spectrum. A mixture of the alcohol isomer of 2-piperidinocyclonexanol* were treated with $AgCO_3$ on celite in a benzene solution (253), or with DMSO in acetic anhydride (254), but the products from either reaction showed a strong 3300 cm^{-1} ir absorption for the alcohols and only a weak 1715 cm^{-1} peak for the ketone.

* Courtesy R.S. Pillay, this laboratory.

(c) Photolysis of 8-2, prepared from 8-1 (2.5 g, 0.018 moles), in benzene (350 ml) for 0.75 hours as above, followed by evaporation of the solvent, gave a residue (3 g) which showed four N - CH_3 singlets in the nmr spectrum (τ 7.09 major). A portion of the residue (2.4 g) was chromatographed on basic alumina (120 g). The first fraction (0.26 g) eluted with CH_2Cl_2 contained a 1:1 ratio of keto-lactam 22-3 and nitrate lactam 23-2 : ir 1630, 1280, 860; nmr τ 7.07 (s) (See 5-10-1). Ketolactam 22-3 (0.25 g) was eluted next with 1% MeOH - CH_2Cl_2. The third fraction gave a crude compound tentatively assigned as amide 25-1 : 0.08 g; ir 3400 (b), 2900 (b), 1670, 1550 (m), 1400, 1070 (m), 1050 (m); nmr τ 3.7 (1 H, m), 4.25 (1 H, m), 6.2-6.7 (2 H, m), 7.21 (3 H, s); ms (30°) 168 (M^+ , 67), 137 (90), 109 (27), 96 (67), 80 (87), 79 (100), 55(53), 42 (47). The next fraction (0.43 g) eluted with 2% MeOH - CH_2Cl_2 was estimated as a 4 : 2 : 3 : 2 mixture of the tentatively assigned C-nitroso dimer 23-1 or 24-1, amide 25-1, syn-oxime 22-2, and anti-oxime 22-1, based on the ratios of the N-CH_3 singlets in the nmr spectrum. 2-3% MeOH - CH_2Cl_2 as the elutant gave anti-oxime 22-1 : 0.31 g; nmr τ 6.1 (1 H, bd, J = 5), 7.18 (3 H, s). Later fractions (0.81 g), eluted with 4 - 100% MeOH, were shown to contain, in addition to anti-oxime 22-1, various percentages of syn-oxime 22-2 : nmr τ 5.35 (bd, J = 6 and 1), 7.11 (s).

The approximate yields based on starting amide 8-1

were 4% nitratolactam 23-2, 18% ketone 22-3, 6% amide 25-1, 6% C-nitroso dimer 23-1 or 24-1, 37% anti-oxime 22-1, and 19% syn-oxime 22-2.

5-9-2 N-Nitroso-N-(3-cyclohexen-1-ylmethyl) acetamide (9-2)

From carboxylic acid 4 (20 g), the acyl chloride was prepared and reacted in benzene with ammonia (5-4-1b). The primary carboxamide was reduced with LAH (5-4-2) to primary amine 19-4 : ir 3300 (b), 3030 (m), 2980, 2920, 2800, 1440, 650 (m); nmr τ 4.33 (2 H, s, $W_{\frac{1}{2}}$ = 4), 7.38 (2 H, d, J = 5.5), 7.6 (2 H, s, D_2O excn). The amine was acetylated (5-4-5) to give a 34% overall yield of acetamide 9-1 : 8.15 g; ir 3300 (b), 3080 (b), 3020 (m), 2915, 2840, 1645, 1545, 1435, 1370, 1295, 655 (m); nmr τ 3.0 (1 H, b, D_2O excn), 4.34 (2 H, s, $W_{\frac{1}{2}}$ = 4.5), 6.84 (2 H, bt, J = 6, collapses to d on D_2O exchange), 7.7-8.9 (10 H, m; s at 8.03); ms (50°) 154 (M+ 1, 22), 153 (M^+, 28), 94 (61), 79 (100), 74 (50), 73 (83), 60 (33), 43 (61); ms (30°) 154 (12), 153 (70), 125 (20).

Hrms at M^+ : Calcd for $C_9H_{15}NO$, 153.1154.
Found , 153.1124.

(a) Acetamide 9-1 (1 g, 6.5 mmoles) in CH_2Cl_2 with N_2O_4 (1.5 g, 0.016 moles) as described in method 5-5-2b to give nitrosamide 9-2 : 1.26 g; ir 3020 (m), 2920, 2840, 1725, 1640 (m), 1550 (m), 1500, 1380, 1120, 645 (m); nmr τ 4.43 (1.75 H, s, $W_{\frac{1}{2}}$ = 45), 5.77 (0.2 H, d, J = 6),

6.28 (1.8 H, bd, J = 6), 7.21 (3 H, s), 7.65-9.1 (8 H, m); uv (ε in C_6H_6)426 (90), 407 (85), 391 (50), 376 (30).

Nitrosamide 9-2 was photolyzed in benzene for 1.75 hours (Apparatus I, N_2, 200 W, GWV filter). The crude residue, after evaporation of the solvent, was chromatographed on basic alumina (70 g). The first fraction (0.07 g) eluted with CH_2Cl_2 was a phthalic ester, the plasticizer from the Tygon tubing used to transfer N_2O_4. The next four fractions (0.34 g), eluted with 0.5-1% MeOH - CH_2Cl_2 , were a mixture of the parent amide 9-1 8%; nmr τ 4.34 (s, $W_{\frac{1}{2}}$ = 4.5), 6.85 (bt) and two other compounds which showed acetate singlets at τ 8.0 and whose data was obtained from the fraction rich in the respective compound. The first compound formed anti-oxime 29-1, m.p. 180-185° (dec.), when allowed to stand in CH_2Cl_2 and was assigned as C-nitroso dimer 29-4 : 5%; ir 1220; nmr τ 4.93 (m, $W_{\frac{1}{2}}$ = 13), 6.38 (t, J = 3.5); ms (70°) 182 (21), 167 (32), 139 (26), 123 (53), 110 (47), 79 (37), 68 (100), 43 (53); uv (CH_2Cl_2) ca. 300 nm. The second compound was ketoamide 29-3 : 14%, sublimed 120°/ 1 mm; ir 2940, 2880, 1725, 1630; nmr τ 5.86 (bd, J = 6), 6.35 (d, J = 3), 657 (s, $W_{\frac{1}{2}}$ = 5); ms (100°) 167 (M^+, 28), 139 (25), 126 (50), 110 (50), 68 (100), 43 (56).

The remaining fractions (0.51 g) were a mixture of anti and syn-oximes 29-1 and 29-2 (44%, ca. 4:1 ratio).

The fractions containing largely syn-oxime 29-2 showed a broad doublet at τ 4.60 (J = 5.5). Anti-oxime was crystal-

lized from acetone : m.p. 160-163° (dec.); ir (KBr) 3300(b), 2940, 2880, 1615, 1460, 1420, 955, 940; nmr τ 0.5 (1 H, b, D_2O exch), 5.61 (1 H, bd, J = 5.5), 6.49 (2 H, m), 7.45 (1 H, bm), 7.93 (3 H, s), 7.6-8.6 (6 H, m); ms (90°) 182 (M^+ , 25), 165 (8), 123 (100), 85 (40), 83 (52), 80 (17), 68 (17), 59 (33), 43 (54).

Hrms at M^+ : Calcd for $C_9H_{14}N_2O_2$, 182.1055.
Found, 182.1009.

Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32: H, 7.74; N, 15.37.

Found: C, 59.18; H, 7.80; N, 15.40.

Treatment of a mixture of the oximes (0.11 g) in 6N HCl (20 ml) for 5 hours on a steam bath gave a mixture (0.08 g) of ketone and starting oximes, identified by tlc and the ir absorptions at 1725 and 950 cm^{-1}.

(b) Nitrosation of 9-1 (2 g, 0.013 moles) with $NaNO_2$ (30 g, 0.029 moles) by method 5-5-1b gave a mixture of compounds showing no olefinic protons in the nmr spectrum. These compounds were suggested to be N_2O_4-adducts of nitrosamides 30-1 and 30-2 : ir 1725, 1640, 1545, 1500; nmr τ 4.1 (m), 4.28 (m), 7.25 (s). Photolysis of this mixture in benzene (225 ml) for 6 hours (Apparatus I, N_2 , 200W, >400 nm filter solution) showed no C-nitroso dimer peak appearing in the uv spectra. Evaporation of the solvent and chromatography of the residue on neutral alumina (70 g) gave only 0.47 g of recovered material, none of which was an oxime product (vide infra). Each fraction decomposed

rapidly; those fractions eluted with 0.5-3% MeOH - CH_2Cl_2 showed ir and nmr spectra similar to ketone 29-3 but contained two spots on tlc with larger R_f values than 29-3.

5-9-3 N-Nitroso-N-methyl-2-cyclohexene-1-carboxamide (10-2)

Starting acid 3 (3.8 g, 0.03 moles) was converted to amide 10-1 (3.1 g, 80%) by method 5-4-1a. An attempt to purify 10-1 using alumina chromatography was unsuccessful. The crude amide was distilled at 130-150°/ 20 mm to give a mixture containing ca. 20% (.125 g) of what appears to be a derivative of the amyl chloride using in preparation of acid 3 (nmr shows broad signals at τ 8.9), and impure amide 10-1 : ca. 0.45 g; ir 3300 (b), 3080 (b), 3020 (m), 2930, 2860, 1635, 1530; nmr τ 3.5 (1 H, b, D_2O exch), 4.15 (2 H, m, $W_{\frac{1}{2}}$ = 30), 7.0 (1 H, m), 7.16 (3 H, d, J = 6, collapses to s on D_2O exchange); ms (30°) 139 (M^+, 70), 83 (74), 81 (74), 67 (70), 58 (100).

The mixture was treated with N_2O_4 (5-5-2b) to give crude 10-2 : ir 3030 (m), 2930, 2860, 1725, 1630 (m), 1500; nmr τ 4.18 (2 H, m, $W_{\frac{1}{2}}$ = 30), 5.6 (1 H, m), 6.90 (3 H, s); uv (ca. ε in C_6H_6) 422 (50), 403 (55), 387 (40), 372 (25). Photolysis of 10-2 in benzene (230 ml) for 2.75 hours (Apparatus I, N_2, 200 W, > 400 nm filter solution), followed by solvent evaporation, gave a crude residue (0.45 g). Crystallization from benzene-petroleum ether and

benzene gave a total of 0.15 g of a solid assigned as syn-oxime 31-2 : m.p. 145-150° (dec.), ir (KBr) 3200 (b), 3080 (m), 2920, 2870, 1725, 1650 (b, m), 1440, 935; nmr (100 mc) τ 1.3 (1 H, b, D_2O exch), 5.98 (1 H, d, J = 5), 6.45 (1 H, t, J = 5), 7.18 (3 H, s), 7.2-8.7 (6 H, m); ms (110°) 169 (M+1, 7), 168 (M^+, 4), 151 (5), 140 (5), 112 (36), 111 (100), 110 (27), 94 (48), 67 (39), 66 (63), 42 (36); ms (30°) 169 (M+1, 2), 168 (M^+, 9).

Hrms at M^+ (30°) : Calcd for $C_8H_{12}N_2O_2$, 168.0899.
Found, 168.0856.

Nmr decoupling experiments showed the signals at τ 5.98 and τ 6.45 were coupled to each other (J = 5) (See Results 2-2-3).

The combined mother liquors were chromatographed on neutral alumina (35 g), and the first fraction (0.08 g) eluted with CH_2Cl_2 was the suggested amyl derivative : ms (90°) 246, 176, 105; pattern showing repetitive loss of 14 mass units. The next two fractions (0.03 g) eluted with 0-0.5% MeOH - CH_2Cl_2 were a complex mixture when examined by tlc. The following fractions (0.1 g) eluted with 0.5-1% MeOH - CH_2Cl_2 were a 2:1 mixture of starting amide 10-1 [ca. 15%: ir 1635, 1535; nmr τ 4.3 (m) 7.1 (d); tlc identical] and a compound tentatively assigned as ketolactam 31-3 : ca. 7%; ir 1745 (b); nmr τ 6.4 (m), 7.10 (s). Preparative tlc (alumina) was unsuccessful in separation of this mixture. The remainder of the material (0.09 g) eluted from

the column with 0.5-20% MeOH - CH_2Cl_2 was oxime 31-1 : ir ($CHCl_3$) 3300 (b), 2940, 2870, 1730, 1660 (m), 1430, 935; ms and nmr vide supra. The total yield of oxime 31-1, based on 0.45 g of amide 10-1, was 44%.

5-9-4 N-Nitroso-N-(3-cyclohexen-1-yl) acetamide (11-2)

Carboxylic acid 4 (12.5 g) was converted to the acyl azide (ir 2140 cm^{-1}) and decomposed to isocyanate (ir 2260 cm^{-1}) by method 5-4-3. The benzene solution containing isocyanate was heated with HCl as in method 5-4-5 to obtain primary amine 17-5 : 4.8 g, 50%, ir 3350 (b), 3250 (b), 3020 (m), 2920, 2820, 1650 (w), 1440, 655 (m); nmr τ 4.48 (2 H, s, $W_{\frac{1}{2}}$ = 4), 7.1 (1 H, m), 7.7-8.9 (8 H, m with D_2O exch singlet at 8.2). Formed as a by-product was the symmetrical urea 77 : m.p. 185-187° (CH_2Cl_2 -ether); ir (Nujol) 3300 (b), 3020 (m), 1625, 1580, 650 (m); ms (150°) 220 (M^+ , 32), 141 (64), 97 (17), 87 (15), 81 (36), 80 (29), 79 (27), 61 (36), 43 (100).

Amine 17-5 was acetylated (5-4-5) and chromatographed on neutral alumina (50 g) to give an 83% yield of acetamide 11-1 : m.p. 61-62° (Hexane-benzene); ir 3300 (b), 3080 (b), 3030 (m), 2910, 2840, 1625, 1560, 650 (m); nmr τ 2.0 (1 H, b, D_2O exch), 4.37 (2 H, s, $W_{\frac{1}{2}}$ = 4), 6.0 (1 H, m, $W_{\frac{1}{2}}$ = 20), 7.4-8.8 (9 H, m, s at 8.02); ms (75°) 140 (M^+ 1, 3), 139 (M^+ , 3), 97 (5), 85 (30), 80 (50), 79 (35), 60 (100), 43 (100).

Hrms at M^+ : Calcd for $C_8H_{13}NO$, 139.0997.
Found, 139.0993.

Acetamide 11-1 (1.05 g, 7.6 mmoles) was nitrosated twice with N_2O_4 (0.7 ml), the second time in the presence of pyridine as described in 5-5-2b, to give impure nitrosamide 11-2 : 1.22 g, ir 3300 (b,w), 3030 (m), 2940, 2850 (m), 1730, 1640 (m), 1515, 650 (m); nmr τ 4.29 (0.4 H, s), 4.48 (1.6 H, t, J = 2), 5.7 (1 H, m), 7.34 (2.4 H, s), 7.6-8.0 (9 H, m, s at 7.98); uv (ca. ε in C_6H_6) 423 (60), 405 (55), 390 (40), 366 (25). The nitrosamide was photolyzed in benzene (220 ml) for 4.5 hours (Apparatus 1, N_2, 200 w, > 400 nm filter solution). The photolysate showed no increasing peak at ca. 295 nm in the uv spectra. The control reaction showed ca. 25% decrease in the absorptions of the nitrosamide about 400 nm.

The crude photolysis product (1.14 g) was chromatographed on neutral alumina (60 g). The first fraction (0.09 g), eluted with CH_2Cl_2 was the thermal decomposition product, ester 33 : ir 3030 (m), 2950, 2870, 1730, 1240, 1035, 655 (m); nmr τ 4.37 (2 H, s, $W_{\frac{1}{2}}$ = 4), 5.8 (1 H, bm), 7.5-9.1 (9 H, m with s at 7.97). The material (0.51 g) eluted with 0-3% MeOH - CH_2Cl_2 was acetamide 11-1 gc (170°) 77%, retention time of 4.2 min. , contaminated with two minor products (20%, gc retention time 8.4 min.; 3%, gc retention time 14 min.). The amounts of the minor products increased when the mixture was kept in CH_2Cl_2 solution. Gc-ms suggested the first product to be chloro acetamide 34-1 or 34-2 :

ms 177 (Cl^{37}, 14), 175 (M^+ with Cl^{35}, 38), 140 (81), 98

(92), 81 (51), 80 (57), 79 (27), 60 (100), 50 (100), 43 (85); and the second as dichloroacetamide 34-3 : ms 211 ($Cl^{35}Cl^{37}$, 2), 209 (Cl_2^{35}, 3), 176 (19), 174 (52), 134 (23), 132 (65), 96 (42), 79 (39), 60 (87), 43 (100) . The remaining material (0.04 g) from the column had small R_f values on tlc and appeared to be N_2O_4 adducts such as 31-4 : ir 3300 (b), 2940, 1650 (b), 1550; ms (120°) 185 (5), 95 (65), 59 (85), 45 (53), 44 (83), 43 (100).

5-9-5 N-Nitroso-N-methyl-3-cyclohexene-1-acetamide (12-2)

Crude amide 12-1 was prepared using method 5-4-1a from acid 2 (15.07 g) and chromatographed through neutral alumina (30 g) to give 12-1 : 7.75 g, 47%; m.p. 46-50°, ir 3300 (b), 3080 (b), 3020 (m), 2920, 2850, 1640, 1550, 650 (m); nmr τ 2.8 (1 H, b, D_2O exch), 4.37 (2 H, s, $W_{\frac{1}{2}}$ = 4.5), 7.25 (3 H, d, J = 5, collapses to s on D_2O exchange), 7.6-9.1 (9 H, m); ms (75°) 153 (M^+, 9), 74 (14), 73 (100), 58 (21), 45 (9). Amide 12-1 (1 g, 6.5 mmoles) was nitrosated by method 5-5-2b to give nitrosamide 12-2 : 1.39 g; ir 3020 (m), 2920, 2850, 1720, 1640 (m), 1550 (m), 1500, 1205, 655 (m); nmr τ 4.33 (1.8 H, s, $W_{\frac{1}{2}}$ = 5), 6.85 (2 H, d, J = 6), 6.88 (3 H, s), 7.4-9.3 (ca. 7 H, m); uv (ca. ε in C_6H_6) 421 (80), 402 (80), 386 (60).

The crude nitrosamide was photolyzed in benzene (230 ml) for 3.5 hours (Apparatus I, N_2, 200 W, > 400 nm filter solution). Several attempts to crystallize product from the

residue using EtOH - H_2O or acetone failed. Chromatography of the residue (0.95 g) on neutral alumina (50 g) gave first with CH_2Cl_2 the Tygon tubing plasticizer (0.02 g). The next fraction (0.29 g), eluted with 0.5-1% MeOH - CH_2Cl_2 contained as a major component an unidentified secondary amide : ir 3300 (b), 3080 (m), 2920, 2850, 1640, 1550; nmr signal at τ 7.2 (d, J = 4.5, collapses to s on D_2O exchange); ms (180°) 182 (1), 168 (3), 165 (3), 153 (6), 150 (6), 123 (9), 110 (11), 73 (100), 58 (49), 55 (37), 41 (49). Eluted with 1% MeOH - CH_2Cl_2 was an oxime (0.25 g, 25%), which was the only product eluted when the crude photolysate residue was chromatographed on silicic acid. The assigned structure for this product was anti-oxime 35-1 : crystallized from acetone, m.p. 165-167° (dec.); ir (KBr, CCl_4) 3200 (b), 3100 (b), 2920, 2860, 1605, 930; ir (nujol) 1608; nmr τ 0.0 (1 H, b, D_2O excn), 6.15 (1 H, t, J = 3), 6.75 (1 H, m), 7.12 (3 H, s), 7.15-8.8 (ca. 9, m); ms (110°) 182 (M^+, 10), 165 (60), 150 (40), 123 (35), 110 (35), 108 (50), 95 (10), 73 (100), 58 (35).

Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37

Found: C, 59.50; H, 7.80; N, 15.27

The remaining material (0.3 g) eluted with 3-100% MeOH - CH_2Cl_2 was largely one component. This compound was not purified but appeared to be a substituted secondary amide, such as would result from decomposition of amide 39 : ir 3300 (b), 2920, 2860, 1635, 1550; nmr τ

3.2 (b, D_2O exch), 4.8 (m), 6.3 (m), 7.20 (d, J = 4.5, singlet on D_2O exchange); ms (180°) 210 (4), 181 (7), 165 (32), 151 (21), 134 (21), 124 (32), 106 (100), 91 (36), 79 (36), 77 (36), 73 (79), 58 (68), 45 (36).

Lactam oxime 35-1 (0.08 g) was treated with bisulfite (138) to give a 25% yield of a product assigned as ketone 35-3 : ir 2920, 2860, 1720, 1625, 1395; ms (65°) 167 (M^+, 34), 139 (20), 123 (51), 110 (100), 82 (24), 73 (17), 68 (20), 59 (37), 57 (29), 42 (37).

5-9-6 N, N′ - Dinitroso-anti, trans- 3,6-pyrid-2-one Dimer (13-2)

As in the procedure of Taylor and Kan (127), 2-pyridone (6, 50 g, 0.53 moles) in MeOH (250 ml) was photolyzed with 450 W lamp in pyrex Apparatus I for 71 hours, with occasional removal of the insoluble material, to give dimer 13-1 : 15.5 g, 0.082 moles, 31%; crystallized from acetic acid, m.p. 220-223° (literature 225-227°) (127); ir (KBr) 3175 (b), 3080 (b), 2980, 2930, 2870, 1655, 1105, 760; nmr (CF_3COOH) τ 1.5 (2 H, b), 3.05 (2 H, t, J = 7), 3.6 (2 H, t, J = 7), 5.4 (2 H, bm), 6.0 (2 H, dd, J = 10, 7); ms (220°) 190 (M^+, 0), 95 (110), 67 (92), 39 (9). LAH reduction of a suspension of the dimer in ether was not successful.

$NaNO_2$ nitrosation of 13-1 (2.4 g, 0.013 moles) by method 5-5-1b gave a 94% yield of nitrosodimer 13-2 : 2.94 g,

0.012 moles; m.p. 208-210° (dec.), ir (KBr) 3065 (w), 3004 (w), 1720, 1510, 1350, 1120, 1020, 870 (m); ms (180°) polymer peaks, 124 (100), 95 (86), 67 (49); uv (HOAc) 442, 420, 400.

Anal. Calcd for $C_{10}H_8N_4O_4$: C, 48.39; H, 3.22; N, 22.58.

Found: C, 48.74; H, 3.23; N, 22.90.

(a) Photolysis of a suspension of 13-2 (1 g) in acetic acid (250 ml) for 17 hours (Apparatus 1, N_2, 200 W, > 400 nm filter solution) showed the appearance of a new peak at 297 nm. Ether extraction of the mixture, followed by base wash of the extracts, gave 2-pyridone : ca. 20%; ir 3400 (b), 3250 (b), 3100 (b), 3000, 2960, 2880, 1650, 1600; nmr τ 1.0 (1 H, b, D_2O exch), 2.6 (2 H, m), 3.6 (2H, m). A similar photolysis in benzene for 25 hours with a 450 W lamp gave complete recovery of nitrosodimer 13-2.

(b) Nitrosodimer 13-2 (2 g) in reagent grade tetrahydrofuran (550 ml) was photolyzed for 25 hours with a 450 W lamp as above. The precipitate was filtered and identified as amide dimer 13-1 : 0.23 g, 15%, vide supra. Evaporation of the solvent gave polymeric material (0.05 g) and an ether soluble mixture (1.5 g) which was chromatographed on silicic acid (50 g). The initial fractions (0.4 g) eluted with CH_2Cl_2 contained the solvent stabilizer, 4-methyl-2,6-t-butylphenol. The compound (0.3 g) eluted with 1% MeOH - CH_2Cl_2 was assigned as 2-hydroxytetrahydrofuran (40-1): ir 3300 (b), 2960, 2885, 1065, 940 (b); nmr τ 4.4 (1 H, m),

6.1 (2 H, m), 7.1 (4 H, m); ms (100°) 88 (M^+, 11), 86 (26), 75 (74), 57 (53), 56 (42), 44 (100). Eluted with 1-3% MeOH - CH_2Cl_2 was a compound (0.2 g) which was suggested to be γ-hydroxbutyraldehyde (40-2) : ir 1720; nmr τ 1.95 (bs). The remaining material (0.5 g) eluted with 3-5% MeOH - CH_2Cl_2 was pyridone 6 (vide supra).

(c) Nitrosodimer 13-2 was unchanged after refluxing in benzene for 48 hours or after heating for 1 hour at 150°. When heated to ca. 170° without solvent or in diphenyl ether, 13-2 decomposed to polymeric material and 2-pyridone (ca. 20%).

5-10 Photolysis of Alkenyl N-Chloramides

5-10-1 N-Chloro-N-methyl-3-cyclohexene-1-carboxamide (8-3)

Using method 5-5-3, amide 8-1 (1.125 g, 8 mmoles, described in 5-9-1) was converted to N-chloramide 8-3 : ca. 1.2 g, 85%, 6.9 mmoles; ir 3020 (m), 2910, 2840, 1660, 1440 (m), 650 (m); nmr τ 4.23 (2 H, s, $W_{\frac{1}{2}}$ = 4.5), 6.60 (3 H, s), 6.9 (1 H, m), 7.55-8.5 (6 H, m). This product contained 7% of unreacted amide 8-1 as shown by the τ 7.19 doublet. Chloramide 8-3 was photolyzed in benzene (250 ml) as described in 5-8-3, using quartz Apparatus 1 for 4 hours (N_2, 100W, Vycor filter). After evaporation of the solvent, the crude residue (1.2g) showed singlets at τ 0.95 and 7.12 and the amide doublet at τ 7.19 in the ratio of 41 : 53 : 6.

The gc (170°) showed peaks at 5.7, 5.0 and 3.5 minutes, the last corresponding to that of amide 8-1, in a ratio of 44 : 49 : 7. Another photolysis residue showed a singlet ratio of 1 : 1.15.

The residue (1.4g from 1.46g amide 8-1) was chromatographed on silicic acid (50 g). Elution with 0-3% MeOH - CH_2Cl_2 gave exo-chlorolactam 24-3 : 0.7 g, 39%; ir 2960, 2870, 1690, 1450, 815; nmr τ 5.68 (1 H, dd, J = 6, 3), 6.30 (1 H, bt, J = 4), 7.12 (3 H, s), 7.5 (1 H, b, $W_{\frac{1}{2}}$ = 7), 7.55-8.5 (6 H, m); ms 175° ($M + Cl^{37}$, 23), 173 ($M + Cl^{35}$, 67), 138 (68), 110 (100), 96 (64), 83 (22), 68 (30), 53 (29), 42 (42).

Hrms at M^+Cl^{35} : Calcd for $C_8H_{12}NOCl^{35}$, 173.0607

Found, 173.0602.

Next eluted with 3% MeOH-CH_2Cl_2 was a mixture (0.7 g). The yields estimated by gc and by nmr, from the τ 6.95 singlet and τ 7.19 doublet, were 33% endo-chlorolactam 23-3 (0.6 g) and 7% amide 8-1 (0.1 g). The fractions containing 23-3 were distilled at 95-97°/20 mm and were further chromatographed on acidic alumina, followed by silica gel preparative tlc to give a sample containing some exo-chlorolactam 24-3 and amide 8-1 as impurities, but was > 80% endo-chlorolactam 23-3 : ir 2960, 2870, 1690, 1450, 765, 750; nmr τ 5.75 (1 H, ddd, J = 9, 7 and 1), 6.14 (1 H, dd, J = 5.5 and 1), 6.95 (3 H, s), 7.5-8.5 (7 H, m); gc-ms was the same as 24-3 (vide supra).

Treatment of a mixture of 23-3 and 24-3 with sodium-t-butoxide in t-butanol (255) caused hydrolysis of the lactam ring giving a low yield of products showing no peak at 1690 cm^{-1}. LAH (0.8 g) reduction of the crude photolysate (0.1 g) in ether for 120 hours, followed by a reaction with picric acid gave picrate 41-3 : Crystallized from EtOH, m.p. 255° (dec.) (literature 250°) (152); ms (200°) 229 (22), 125 (33), 96 (86), 82 (100), 68 (22), 62 (22), 44 (22).

Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.46, H, 5.08; N, 15.82.

Found: C, 47.69, H, 5.12; N, 15.59.

A crude photolysate (1.2 g), consisting of 48% 24-3, 42% 23-3 and 10% 8-1 by gc analysis, was stirred with LAH (3 g) for 37 hours gave a mixture (1 g), which exhibited by gc (150°) three peaks with retention times of 1.7 (41-1), 1.8 (19-1) and 3.5 (26-2) minutes.

The LAH reduction over a longer period (120 hours) increased the peak at 1.7 minutes at the expense of the one at 3.5 minutes. The reduction mixture was chromatographed on neutral alumina, and eluted with 0-1% MeOH-CH_2Cl_2 was endo-chloroamine 26-1 : 0.36 g, ir 2940, 2860, 2840, 1450, 780 (m); nmr τ 6.8 (1 H, ddd, J = 9, 7 and 1.5) 7.04 (2 H, m), 7.48 (3 H, s), 7.65 (1 H, b, $W_{\frac{1}{2}}$ = 5), 7.35-8.8 (7 H, m); ms (100°) 161 (M^+Cl^{37}, 12), 159 (M^+Cl^{35}, 32), 124 (22), 96 (32), 82 (100), 67 (16), 55 (18), 42 (50). Decoupling experiments showed that the τ 6.2 signal was coupled to the

τ 7.0 region with J = 1.5 coupling, and was also coupled to the protons in the τ 7.4-7.7 region. This compound had identical ir and nmr spectra with 20-2 synthesized by Gassman (87) and Stella (112).

Further elution with 2-5% MeOH - CH_2Cl_2 gave amine 41-1 : 0.35 g; ir 2930, 2850, 2790 (m), 1450; nmr τ 7.60 (s). This amine readily formed the hydroscopic hydrochloride in CH_2Cl_2 or $CHCl_3$ to yield HCl salt 41-2 : nmr (D_2O) τ 6.2-6.85 (2 H, m), 7.0 (1 H, m), 7.10 (3 H, s), 7.6-8.6 (9 H, m); ms (150°) 125 (36), 96 (100), 82 (48), 68 (19), 44 (31), 42 (34), 36 (38). The final compound (0.1 g) eluted from the column was amine 19-1 (vide infra).

When exo-chlorolactam (0.18 g) was stirred with LAH (1 g) for 5.4 hours, it gave 25% 41-1 and another compound suspected to be exo-chloroamine 27-2 : 75%, ir 2930, 2860, 2790 (m), 1450, 760 (m); nmr τ 6.6 (2 H, m, $W_{\frac{1}{2}}$ = 7) 7.2 (1 H, m), 7.57 (3 H, s), 7.5-8.9 (8 H, m). The latter product decomposed on keeping, or on preparative gc purification.

5-10-1 N-Chloro-N-(3-cyclohexen-1-yl)acetamide (11-3)

Using method 5-5-3, from acetamide 11-1 (1 g) was prepared crude N-chloramide 11-3 : ir 3030 (m), 2940, 2860, 1670, 670 (m); nmr τ 4.39 (1.5 H, s, $W_{\frac{1}{2}}$ = 5), 5.45 (1 H, m), 7.76 (3 H, s), 7.5-8.8 (9 H, m). This product contained ca. 20% of olefin HCl adduct, as shown by the decreased integ-

ration for the olefinic protons. The unpurified chloramide was photolyzed for 5.5 hours in CCl_4 (220 ml) in quartz Apparatus I (N_2, 200 W, Corex filter) until > 75% of the positive chlorine had disappeared. The insoluble material formed during photolysis was dissolved by the addition of MeOH and the combined solution was evaporated to give a crude residue (1.47 g).

Gc analysis (170°) of the residue showed a minimum of fourteen peaks, with peaks corresponding to that of the parent amide 11-1 (ca. 5%), the H - Cl adducts 34-1 or 34-2 (30%) and the dichloro adduct 34-3 (12%). The last two were confirmed by gc - ms spectra identical to those obtained in 5-9-4 (vide supra).

The only other relatively major product ca. 7% was suspected to be C_2Cl_6 based on the gc - ms : 207, 205, 203, 201, 199 (5 Cl pattern, $C_2Cl_5^{35}$), 133, 131, 129 (3 Cl pattern), 121, 119, 117 (3 Cl pattern, 100%), 98, 96, 94 (2 Cl pattern), 84, 83, 82. The remainder of the products were each in 5% yield and isolation was not attempted.

5-11 Nitrosamide Photolyses in the Presence of Trapping Agents

5-11-1 Photolysis of 8-2 Under Oxygen

Crude nitrosamide 8-2 (5-9-1), prepared according to method 5-5-1b from amide 8-1 (1.2 g) was shown to contain > 90% of the olefinic bond as estimated by nmr. The benzene

solution (225 ml) of this nitrosamide was photolyzed for 2.75 hours while oxygen gas was bubbled through the solution (Apparatus I, 200 W, > 400 nm filter solution). The uv spectra showed a new peak appearing at 340 nm which decreased slightly on continued photolysis but no peak appeared at 295 nm. The crude residue (1.68 g) showed six spots on tlc. A similar photolysis in MeOH of >90% pure nitrosamide 8-2 showed the same spots, in addition to two other faint ones, on tlc.

Chromatography of the benzene photolysis residue on neutral alumina (65 g) eluted first, with 0-0.5% MeOH - CH_2Cl_2, a mixture (0.97 g) of endo and exo-nitratolactam 23-2 and 24-2 in the ratio of 2:1. The later fractions were contaminated with amide 8-1 (ca. 0.1 g). The estimates obtained from the nmr singlets at τ 7.05 and 7.08, and the doublet at τ 7.19 gave the yields at 35% 23-2, 17% 24-2 and 8% 8-1. The following fractions (0.2 g) eluted with 0.5-1% MeOH - CH_2Cl_2 were a mixture of two compounds by tlc, possibly the endo and exo-alcohol lactams 23-4 and 24-4 : ir 3400 (b), 2920, 1670, 1070; nmr τ 5.7 (m), 6.1 (m), 7.14 (s), weak 7.17 (s), 6.9-8.5 (m). The crude oil was heated with p-nitrobenzoyl chloride to give a product which showed a peak at 1715 cm^{-1} and a decreased 1070 cm^{-1} peak. Solid could not be obtained from this product upon crystallization from EtOH.

The mixture (0.5 g) obtained in the tail chromatographic fractions decomposed on attempted distillation. The

oil did not show the oxime band at 950 cm^{-1} and, upon treatment with bisulfite, did not yield ketolactam 22-5 (vide supra). The presence of nitrolactams, such as 23-5 and 24-5, was suggested by the spectral data : ir 1680, 1550; nmr τ 5.3 (m), ms 184 (M^+, 5%).

The fractions containing the nitrates were re-chromatographed on silicic acid (25 g) to elute first with CH_2Cl_2 exo-nitrate 24-2 : ir 2960, 1690, 1630, 1280, 860; nmr τ 4.74 (1 H, m, $W_{\frac{1}{2}}$ = 9), 6.18 (1 H, m), 7.06 (3 H, s), 7.0-8.5 (8 H, m); ms (80°) 200 (M^+, 0), 168 (4), 154 (52), 138 (19), 126 (17), 110 (89), 98 (81), 81 (22), 69 (33), 55 (33), 42 (100). Continued elution gave a fraction of endo-nitrate 23-2 : ir same as that of 24-2, nmr τ 4.90 (1 H, dd, J = 9 and 7), 6.15 (1 H, bd, J = 6), 7.05 (3 H, s), 7.2-8.6 (8 H, m); ms (75°) 154 (58), 138 (17), 126 (17), 110 (100), 98 (89), 83 (17), 81 (17), 69 (33), 55 (28), 42 (100); ms (70°) 200 (1), 154 (63); ms (70°, 15 ev) 200 (2.5), 154 (100). This fraction was contaminated by a trace of parent amide 8-1, and decomposed extensively on attempted distillation at 90-95°/ 1 mm.

Reduction of a portion of the crude photolysate (0.5 g) in ether (100 ml) with LAH (2 g), followed by oxidation with Jones' reagent (10 ml) in acetone, gave aminoketone 28-3 (0.15 g) with identical ir and nmr spectra as obtained previously (vide supra, 5-9-1).

5-11-2 N-Nitroso-N-methyl-2-cyclopentene-1-acetamide (14-2) in $BrCCl_3$

Acid 1 (10 g, 0.079 moles) was converted by method 5-4-1b to crude amide 14-2, which was distilled at 125-126° / 0.8 mm to yield amide 14-2 : 6 g, 0.043 moles, 54%; ir 3300 (b) 3050 (m), 2940, 2850, 1640, 1555, 720 (m); nmr τ 3.3 (1 H, b, D_2O exch), 4.31 (2 H, s, $W_{\frac{1}{2}}$ = 3), 6.9 (1 H, m), 7.22 (3 H, s, $W_{\frac{1}{2}}$ = 4, sharpens on D_2O exchange), 7.45 - 8.9 (6 H, m); ms (80°) 139 (M^+, 24), 138 (11), 107 (11), 81 (35), 79 (20), 73 (100), 67 (54), 58 (49), 41 (22).

Nitrosation of 14-1 (1 g, 7.2 mmoles) using method 5-5-2b in CCl_4 gave nitrosamide 14-2 : 0.64 g, 3.8 mmoles, 53%; ir 3050 (m), 2940, 2860, 1725, 1645 (w), 1500, 1400, 1200, 940; nmr (CCl_4) τ 4.25 (1.8 H, s, $W_{\frac{1}{2}}$ = 2.5), 6.77 (2 H, s, $W_{\frac{1}{2}}$ = 4), 6.92 (3 H, s), 7.35-9.0 (5 H, m); ms (50°) 168 (M^+, 0), 138 (13), 109 (30), 81 (40), 79 (24), 67 (100), 50 (23), 41 (25); uv (ε in CCl_4) 423 (95), 404 (90), 389 (55), 374 (40). The nitrosamide in $BrCCl_3$ (230 ml) was photolyzed for 3 hours (Apparatus I, N_2, 200 W, > 400 nm filter solution). The distilled solvent was collected and showed a weak uv absorption at 580 nm.

The crude residue (1.7 g) showed four peaks by gc analysis (150°) at 4.6 (2%), 5.7 (38%), 11.1 (20%) and 16.6 (40% minutes. Chromatography of the residue on neutral

alumina (65 g) gave first the Tygon tubing plasticizer (0.2 g), eluted with benzene, and its retention time was 4.6 min. in the gc. CH_2Cl_2 eluted an aromatic compound H, corresponding to the second gc peak : 0.11 g, ir 3400 (w), 3060, 2930, 1600, 1580, 1500, 1240, 1040, 755, 690; nmr τ 2.4-3.2 (5 H, m), 5.88 (2 H, m), 6.65 (1 H, m), 7.1 (2H, m); gc-ms 150 (58), 110 (16), 107 (23), 94 (100), 77 (61), 57 (39). With 0-0.5% MeOH - CH_2Cl_2 was eluted impure exo-bromolactam 42-1 (0.73 g, 89% based on 14-2, 47% based on 14-1; gc retention time 16.6 min.,), contaminated with trace amount of compound K. Finally eluted with 0.5-50% methanol was aromatic compound K : 0.65 g, gc retention time 11.1 min.; ir 3400 (b), 3060 (m), 3040 (m), 2930, 2880, 1600, 1585, 1495, 1245, 1045, 755, 690; nmr (100mc) τ 2.72 (2 H, m), 3.05 (3H, m), 5.86 (1 H, m), 5.97 (2 H, d, J = 5), 6.29 (2 H, d, J = 5), 6.8 (1 H, b, D_2O exch); gc-ms 188 (17), 186 (52), 144 (9), 142 (26), 107 (46), 95 (43), 94 (100), 77 (59), 51 (22). The spectra of Compound H were identical to those of the residue left after a commercial sample of $BrCCl_3$ was evaporated, and compound K appears to be the product resulting from HCl addition to compound H. Neither compound was investigated further.

Bromolactam 42-1 was not pure after distillation at 72-76°/ 0.5 mm and was rechromatographed on silicic acid (30 g). The impurity Compound K was eluted first with CH_2Cl_2, then eluted with 1-5% MeOH - CH_2Cl_2 was the exo-

bromolactam 42-1 : ir 2960, 1685, 1400, 1255, 600 (m); nmr (100 Mc) τ5.8 (2 H, m), 7.08 (3 H, s), 6.95-8.2 (6 H, m), 8.5 (1 H, m); gc-ms 219 ($M^+ Br^{81}$, 37), 217 ($M^+ Br^{79}$, 37), 138 (10), 110 (100), 96 (25), 82 (16), 68 (23), 42 (29).

Hrms for M^+Br^{79} ; Calcd for $C_8H_{12}NOBr^{79}$, 217.0103

Found, 217.0054.

The effect of $Eu(fod)_3$ on the nmr spectrum may be seen in Figure 2.6b(2-4-2).

Gc analysis of the crude bromolactam fractions on four types of columns at different temperatures at various temperature showed only one peak for 42-1. LAH reduction of 42-1 gave the cis-amine 45 : ir 2940, 2850, 2770, 1450, 1350; nmr τ 7.74 (s); ms (25°) 125 (M^+, 39), 124 (18) 110 (12), 97 (25), 96 (100), 82 (44), 42 (18). The picrate of 45 was recrystallized from EtOH : m.p. 204-207° (dec.) (literature 207°) (160). The respective values for trans-42-1 and 2-azabicyclo-[3,2,1]octane are 196-197° (256) and 273° (257).

5-12 Photolysis of Alkenyl Nitrosamines Under N_2

5-12-1 N-Nitroso-N-methyl-2-(2-cyclopentene) ethylamine (15-2)

Starting from cyclopentadiene as in Eq 2.1, followed by the amide preparation given in method 5-4-1a, gave a 10% overall yield of amide 14-1 (10.65 g, 0.077 moles, vide supra 5-11-2). Amide 14-1 was reduced with LAH (4.8 g) for 28 hours as in method 5-4-2. The ether extracts were stirred with 2N HCl solution and nitrosated with $NaNO_2$ (12 g) as described in 5-5-1 to yield nitrosamine 15-2. Nitrosamine 15-2 did not distill at 100°/ 6 mm and was chromatographed through silicic acid (200 g) with CH_2Cl_2 elutant to give 15-2 : 4.52 g, 0.029 moles, 38%; ir 3040 (m), 2920, 2840, 1620 (w), 1430, 1330, 1280, 1030, 720 (m); nmr τ 4.40 (2H, s, $W_{\frac{1}{2}}$ = 3.5), 5.90 (1.56 H, t, J = 7), 6.34 (0.66 H, s), 6.45 (0.44 H, t, J = 7), 7.08 (2.44 H, s), 7.2-8.8 (7 H, m); uv (ϵ in HCl - MeOH) 347 (95). The integration of the N - CH_3 singlets indicated that the E-isomer was 75%.

Nitrosamine 15-2 (2.31 g, 0.015 moles) in MeOH (200 ml) containing concentrated HCl (1.5 ml, 0.018 moles) was irradiated for 3.5 hours (Apparatus I, N_2, 200 W, Nonex filter). As the 347 nm peak decreased in the uv spectra, another peak at 290 nm appeared and showed a slight decrease with con-

tinued photolysis. Following the isolation procedure given in 5-8-1, the reaction mixture gave basic material (1.90 g) and acidic material; the latter was identified as unreacted 15-2 (vide supra).

The basic crude (1.6 g) was chromatographed on silicic acid (60 g) and gave, with 0-10% MeOH - CH_2Cl_2, a mixture (0.07 g) of three spots on tlc; the major component was aminoketone 46-3 (vide infra). Elution with 20% MeOH - CH_2Cl_2 gave anti-oxime 46-1 : 0.46 g; ir 3350 (b), 3100 (b,m), 2940, 2870, 2830, 2780, 1660 (w), 1450, 1050, 950, 875; nmr τ 1.5 (1 H, b, D_2O exch), 6.9 (2 H, bd, J = 8), 7.59 (3 H, s), 7.2-8.6 (8 H, m); ms (30°) 154 (M^+, 7), 137 (100), 96 (91), 94 (20), 83 (48), 82 (38), 67 (11), 42 (45), 41 (22). This was followed by fractions of 1:1 mixtures (0.12 g) of oximes 46-1 and 46-2. 20-50% MeOH - CH_2Cl_2 eluted syn-oxime 46-2 : 0.26 g, ir 3350 (b), 3100 (b,m), 2940, 2870, 2830, 2780, 1650 (w), 1450, 1050, 945, 930; nmr τ 1.7 (1 H, b, D_2O exch), 6.12 (1 H, bd, J = 8), 7.0 (2 H, m), 7.32 (3 H, s), 7.2-8.7 (7 H, m). When kept at room temperature or sublimation at 95°/ 1 mm, the τ 7.32 singlet of syn-oxime 46-2 disappeared and the τ 7.59 singlet of anti-oxime 46-1 was seen. An additional 0.2 g of oxime mixture (ca. 1:1) was eluted from the column with 100% MeOH and by continuous extraction of the basic aqueous solution with $CHCl_3$. The total yield of the oximes was 66%, based on reacted nitrosamine 15-2, in the anti : syn

ratio of 1.4 : 1. A similar chromatography of crude basic material (0.28 g) on neutral alumina (60 g) gave ketone 46-3 (0.025 g, 9%) and a mixture of oximes 46-1 and 46-2 (0.23 g, 82%, 1.4 : 1 ratio).

A mixture of oximes 46-1 and 46-2 (0.12 g) was treated with bisulfite (139) to give ketone 46-3 : 0.05 g, 45%; ir 2930, 2840, 2780, 1745, 1737 (sh), 1450; nmr τ 6.7-7.1 (2 H, m), 7.45 (1 H, d, J = 7), 7.53 (3 H, s), 7.5-8.7 (7 H, m); gc- ms (140°) 140 (M+1, 12), 139 (M^+, 35), 111 (35), 83 (100), 82 (75), 42 (45).

Refluxing the crude basic residue (0.87 g) for 2 hours in 1.5N HCl, followed by basification and extraction, gave aminoketone 46-3 (0.39 g, 50%). The picrate of 46-3 (m.p. 132-135°, dec.) was unstable in hot ethanol.

The nmr spectrum of aminketone 46-3 (0.06 g) dissolved in 20% D_2O in pyridine (ca. 1 ml) (100) was run immediately, then the sample heated for 1 hour at 50°. The decrease in the total integration of the protons of 46-3 was equivalent to 1.7 protons with a corresponding increase shown in the integration of the DHO peak. This sample was examined by gc-ms and the M^+ peaks compared to that of 46-3 which had not been deuterated. The results obtained are shown in Table 2.7 (2-5-1).

Other methods of converting an oxime mixture to the corresponding ketone were attempted but gave low yields of ketone or a mixture of ketone and oximes, as judged by ir

(CO absorption at 1745 for 46-3 or 1715 cm^{-1} for 49-2 versus oxime absorptions at 3300 and 950 cm^{-1}). and tlc examination. The reactions attempted with either a mixture of oximes 46-1 and 46-2 or the oxime isomers of 49-1* are given below. Oximes 46-1,2 (0.17 g), when treated with ceric ammonium sulfate (249), gave a mixture (0.55 g, 35%). Oximes 46-1,2 (0.15 g), when heated with $NaNO_2$ in HOAc (258), gave a mixture (0.5 g, 33%). A portion of the crude basic extract (0.9 g) in acetic acid was heated with zinc dust (2 g) (259) to give back oxime (0.9 g) with only a trace of ketone. Oxime 49-1 mixture (0.34 g), when stirred with levulinic acid (9 g) in 2N HCl (1 ml) for 3 hours (260), gave a mixture (0.28 g). Oxime 49-1 (0.4 g) in 2 N HCl (5 ml), when heated with formaldehyde (15 ml) for 1 hour at 100° (261), gave a mixture (0.26 g). Oxime 49-1 (0.49 g) in glacial acetic acid, when heated with $Pb(OAc)_4$ for 2 hours (262), gave a product (0.26 g) showing no 1715 cm^{-1} peak. A peak at 1750 cm^{-1} in the ir spectrum of this product may be caused by an oxime—O-acetate. When a 0.1 M $CuSO_4$ solution (10 mls) was added to a mixture of oximes 46-1,2 (0.12 g) a green color resulted. After evaporation of the solvent and addition of NH_4OH, CH_2Cl_2 extraction gave a 65% recovery of the mixture (0.08 g). A similar green color was observed when lactam oximes 22-1 and 22-2 were mixed with $CuSO_4$ solution.

* Courtesy K.S. Pillay, this laboratory

An attempt to hydrogenate ketone 46-3 (0.21 g) in 5N HCl in the presence of PtO_2 (167) gave a mixture of epimeric alcohols 48-1 and 48-2 : 0.13 g; ir 3300 (b), 2945, 2860, 2780, 1450, 1020; nmr τ 5.9-6.2 (1 H, m), 6.8-7.5 (3 H, m), 7.63 and 7.69 (3 H, two s, equal intensity), 7.7-8.7 (7 H, m). Alcohols 48-1 and 48-2 could be oxidized with Jones' reagent to ketone 46-3. The oximes 28-1 and 28-2* (0.14 g) were refluxed in 2N NaOH (10 ml) with $NaBH_4$ (0.4 g) for 3 hours (168) to give a low yield of a mixture of alcohols 26-1 and 26-2 (0.02 g, vide supra, 5-9-1).

5-12-2 N-Nitroso-N-methyl-2-(3-cyclohexene)ethylamine (16-2)

LAH (4 g, 0.1 mole) reduction of amide 12-1 (5.3 g, 0.022 moles) for 40 hours, as described in method 5-4-2, gave amine 16-1 : 2.5 g, 0.018 moles, 83%; ir 3300 (b), 3020 (m), 2920, 2850, 2790 (m), 1650 (w), 1450, 655 (m); nmr τ 4.37 (2 H, s, $W_{\frac{1}{2}}$ = 4), 7.4 (2 H, dt, J = 7,2), 7.58 (3 H, s), 7.94 (1 H, s, D_2O exch), 7.7-9.2 (9 H, m). Nitrosation according to method 5-5-1a gave crude nitrosamine (2.3 g), which was filtered in benzene through neutral alumina (15 g) to yield nitrosamine 16-2 : 1.3 g, 8 mmoles, 43%; ir 3025 (m), 2930, 2855, 1430, 1335, 1040, 655 (m); nmr τ 4.31 (1.5 H, s, $W_{\frac{1}{2}}$ = 4), 5.80 (1.54 H, dt, J = 7,2), 6.25 (0.65 H, s), 6.35 (0.46 H, m), 6.95 (2.35 H, s), 7.8-9.2 (10, m); ms (30°) 168 (M^+, 0), 153 (25), 151 (41), 137 (44),

* Courtesy B.C. Menon, this laboratory.

109 (19), 97 (22), 74 (50), 55 (62), 44 (100); uv (ε in HCl - MeOH) 343 (97). As estimated by the nmr integration, there was 78% E-isomer and ca. 75% of the olefin unreacted.

Nitrosamine 16-2 (0.7 g, 4 mmoles) was photolyzed for 2.5 hours in MeOH (220 ml) containing concentrated HCl (0.6 ml) (Apparatus 1, N_2, 200 W, Nonex filter). The usual work-up (5-8-1) gave the basic residue (0.48 g) and the acidic/neutral material (0.125 g); the latter composed of unreacted 16-2 and two minor impurities which were present in the starting material.

The basic compounds were chromatographed on basic alumina (50 g). The first fractions (0.08 g) eluted with 0-0.5% MeOH - CH_2Cl_2 were a mixture (3 spots on tlc) with no N-CH_3 or olefinic signals in the nmr spectrum. Eluted with 1% MeOH - CH_2Cl_2 was aminoketone (0.03 g, 6%, vide infra). Elution with 3-5% MeOH - CH_2Cl_2 gave the compound assigned as anti-oxime 50-1 : 0.09 g, 16%, sublimed 65-70°/ 0.5 mm; ir 3300 (b), 2920, 2850, 2800, 1650, (b,m), 1450, 1270, 1145, 930; nmr τ 0.8 (1 H, b, D_2O excn), 6.75 (1 H, m), 7.2 (1 H, m), 7.67 (2 H, m), 7.75 (3 H, s), 7.8-9.1 (ca. 9 H, m); ms (150°) 168 (M^+, 11), 151 (100), 110 (6), 96 (56), 82 (11), 70 (39), 60 (22), 59 (25), 55 (22), 42 (31).

Hrms at M^+ : Calcd for $C_9H_{16}N_2O$, 168.1263.
Found, 168.1325.

The remaining material (0.05 g), eluted with up to 100% EtOH, was assigned as syn-oxime 50-2 : 9%; ir 3300 (b), 2920, 2850, 2800, 1650 (b), 1450, 1270, 1145, 930; nmr τ 2.2 (1 H, b, D_2O exch), 6.4 (1 H, m), 6.9-7.3 (2 H, m), 7.40 (3 H, s), 7.4-9.3 (ca. 10 H, m); ms (100°) 168 (M^+, 4), 151 (20), 141 (20), 96 (11), 82 (7), 57 (26), 44 (100).

Photolysis of nitrosamine 16-2 (0.43 g) in MeOH (125 ml) containing concentrated HCl (0.5 ml) for 2.75 hours (Apparatus II, N_2, 200 W, Nonex filter), followed by usual work-up (5-8-1) gave a basic residue (0.27 g). This material was heated in 50% aqueous MeOH (10 ml) for 4 hours at 100° with sodium bisulfite (1 g). HCl (1 ml) was added, the MeOH evaporated, and the solution was basified. CH_2Cl_2 extraction and evaporation gave impure ketone 50-3: 0.06g, decomposed at 70-80°/0.5 mm; ir 2920, 2855, 2790, 1710, 1450; nmr τ 7.0-7.7 (m), 7.73 (s), 7.8-9.1 (m). This product was contaminated by a small amount of oxime [ir 3300 (b,w); nmr 7.75 (s). $CHCl_3$ continuous extraction of the aqueous phase from the bisulfite reaction gave unreacted oxime (0.09 g).

5-12-3 N-Nitroso-N-methyl-(3-cyclohexen-1-yl)amine (17-2)

Acid 4 was converted by the methods outlined in 5-4-3 and 5-4-4 to give methylamine 17-1 (55% overall; ir 3300(b), 3030 (m), 2920, 2840, 2790, 1650 (w), 1440, 655 (m); nmr τ 4.34 (2 H, s, $W_{\frac{1}{2}}$ = 5), 7.1-7.4 (1 H, m), 7.3 (1 H, s, D_2O exch), 7.53 (3 H, s), 7.55-8.9 (6 H, m); ms (130°)

111 (M^+, 23), 85 (25), 83 (35), 70 (20), 57 (100). Amine 17-1 (7 g, 0.063 moles) was treated with $NaNO_2$ (15 g, 0.22 moles) as described in method 5-5-1a in a mixture of ether and dilute HCl. The evaporated ether extracts gave nitrosamine 17-2 : 3.8 g, 43%; ir 3030(m), 2940, 2850, 1650 (m), 1440, 1365, 1330; nmr τ 4.25 (1.5 H, s, $W_{\frac{1}{2}}$ = 4), 5.5 (1 H, bm), 6.29 (0.3 H, s), 6.91 (2.7 H, s), 7.4-8.5 (ca. 7 H, m); uv (ϵ in HCl - MeOH) 340 (95). The ratio of the nmr singlets showed 91% E-isomer and olefinic proton signal showed 75% olefin.

(a) Unpurified nitrosamine 17-2 (1.5 g) in MeOH (320 ml) containing concentrated HCl (1.7 ml) was photolyzed for 1.5 hours (Apparatus I, N_2, 200 W, Nonex filter). The uv spectra showed a peak appearing below 308 nm which tailed into the nitrosamine absorption. The standard work-up (5-8-1) gave basic material (0.5 g) which was shown to be largely parent amine by the nmr spectrum, and acidic/neutral material (0.65 g) which was largely unreacted 17-2 as shown by tlc and nmr. The latter fraction showed a medium peak at 1720 cm^{-1} in the ir spectrum, and gave a precipitate with 2, 4-dinitrophenylhydrazine.

The combined basic fractions (0.91 g), obtained from several photolyses, were chromatographed on neutral alumina (50 g). The first material (0.2 g) eluted with 1% MeOH - CH_2Cl_2 was a mixture [nmr τ 4.34 (s, $W_{\frac{1}{2}}$ = 4.5), no N - CH_3 singlets] which distilled at 85-95°/ 2 mm : ir 3300 (b),

3030 (m), 2930, 2860, 1660, 1440, 655 (m); ms (100°) polymer like pattern, major peaks at 109 (40), 100 (79), 81 (92), 80 (77), 79 (65), 71 (54), 57 (44), 55 (100), 42 (50). The remaining material (0.45 g) eluted with 5-50% MeOH - CH_2Cl_2 contained a small amount of amine 17-1 (τ 7.5 singlet) with the major portion being the hydrochloride salt of amine 17-1 : ir 3350 (b), 3030 (m), 2930, 2840, 2720, 2450 (m), 1440, 660 (m); nmr τ 2.85 (2 H, s, D_2O exch), 4.30 (2 H, s, $W_{\frac{1}{2}}$ = 5), 7.0 (1 H, bm), 7.50 (3 H, s), 7.4-8.4 (6 H, m).

(b) Nitrosamine 17-2 (1.1 g) in glacial acetic acid (600 ml) containing concentrated HCl (1 ml) was photolyzed for 5.5 hours (Apparatus 1, N_2, 200 W, Nonex filter). The uv spectra showed only a shoulder at 350 nm for the nitrosamine $n \rightarrow \pi^*$ transition. During the photolysis, a strong absorption appeared which tailed below 300 nm. Water (500 ml) was added to the photolysate, the acid was neutralized with KOH, and the solution extracted with CH_2Cl_2. The extracts were washed several times with dilute acid, dried, and evaporated to give a liquid (0.34 g), which contained largely unreacted nitrosamine. The distilled solvent was treated with DNPH and the precipitate was recrystallized from 95% EtOH to give a solid, suggested to be a mixture of cyclohexene hydrazones 52-2 and 52-4 : 0.02 g, m.p. 128-132°; ms (180°) 276 (M^+, 100), 241 (7), 183 (4), 153 (4), 122 (7), 97 (79), 79 (71), 77 (64), 67 (82), 41 (40);

uv 372 nm.

The aqueous acid washes from above were basified and extracted to give mixture (0.2 g), showing 6 spots by tlc. The nmr spectrum of this fraction exhibited signals at τ 3.3 (b, D_2O exch), 4.35 (s, $W_{\frac{1}{2}}$ = 5), 7.55 (s), 6.7-8.6 (m). The mixture was not further investigated.

5-12-4 N-Nitroso-N-methyl-2-cyclopentene-1-methylamine (18-2)

Acid 1 (5 g, 0.04 moles) was converted using methods 5-4-3 and 5-4-4 to methylamine 18-1 : 3 g, 65%; ir 3300 (b), 3050 (m), 2930, 2850, 1640 (w), 720 (m); nmr τ 4.32 (2 H, s, $W_{\frac{1}{2}}$ = 4), 6.7 (1 H, s, D_2O exch), 7.77 (3 H, s), 7.4-8.7 (7 H, m). Nitrosation by procedure 5-5-2a, and filtration of a benzene solution through neutral alumina, yielded nitrosamine 18-1 : 1.56 g, 0.011 moles, 28% overall from 1; ir 3050 (m), 2930, 2855, 1450, 1430, 1330, 680 (m); nmr τ 4.3 (2 H, m, $W_{\frac{1}{2}}$ = 18), 5.96 (1.6 H, d, J = 7), 6.25 (0.6 H, s), 6.48 (0.4 H, d, J = 7), 6.99 (2.4 H, s), 7.4-8.8 (5 H, m); ms (50°) 140 (M^+, 5), 80 (66), 73 (41), 67 (100), 44 (98); uv (ε in HCl - MeOH) 345 (89). The ratio of the N - CH_3 singlets indicated 80% E-isomer of the nitrosamine.

A methanol solution (220 ml) of nitrosamine 18-2 (0.74 g , 5 mmoles) and concentrated HCl (0.6 ml) was photolyzed for 3.5 hours (Apparatus 1, N_2, 200 W, Nonex filter), followed by work-up procedure 5-8-1. No C-nitroso dimer

peak was seen in the uv spectra during the photolysis. The acidic/neutral extract (0.6 g) was primarily the Tygon tubing plasticizer, with a minor component which did not crystallize from EtOH, suggested to be cyclopentenone oxime 53-1 : ir 3300 (b), 1030, 950; nmr τ 3.85 (m), 4.2 (m), 7.2-8.2 (m).

The basic material (0.4 g) contained approximately 15 peaks in the gas chromatogram. The major peaks (80°) were at 2.2 minutes for parent amine 18-1 (18%), 7.8 (16%) and 10.4 (18%) minutes. The major portion of the basic fraction was lost during a distillation attempt at 30°/20 mm. Continuous extraction of the aqueous solution (pH = 8) with CH_2Cl_2 gave a mixture : 0.09 g, major gc peaks at 7.8 (Compound A) and 10.4 (Compound B) minutes, ca. 1 : 2 ratio; ir 3200 (b), 3060 (b), 2940, 2850, 2795, 1720 (w), 1690 (m), 1640 (w), 1445, 1260, 1235, 1115, 915; nmr (major peaks) τ 6.75 (2 H, s), 7.37 (2 H, m, $W_{\frac{1}{2}}$ = 7), 7.69 (3 H, s), 7.4-7.7 (1 H, m). Examination of the major products by gc-ms gave : Compound A 102 (2), 89 (45), 87 (9), 50 (100), 58 (72), 45 (59), 43 (28); Compound B 154 (4), 97 (93), 96 (100), 80 (56), 75 (26), 54 (37), 53 (81), 52 (37), 39 (41). Due to the low yields and volatility of the products, no further identification was attempted.

5-13 Metal Catalyzed Decomposition of N-Chloramine 17-3

Amine 17-1 (1 g, 9 mmoles), prepared as described in 5-12-3, was chlorinated according to procedure 5-5-3 in CH_2Cl_2 to give N-chloro-N-methyl-(3-cyclohexen-1-yl) amine (17-3) : 0.88 g, 6 mmoles, 67%; ir 3025 (m), 2920, 2845, 1640 (w), 1440, 1365, 660 (m); nmr τ 4.34 (2 H, s, $W_{\frac{1}{2}}$ = 4.5), 7.07 (3 H, s), 6.9-7.3 (1 H, m), 7.5-8.5 (6 H, m). The unpurified chloramine and ferric chloride (0.75 g) were stirred under nitrogen in 50% aqueous acetic acid (20 ml). Hydrated ferrous sulfate (0.5 g), dissolved in the same solvent (15 ml), was added at 0°, as described in method 5-8-4a. The mixture was allowed to warm to room temperature over 11 hours, then filtered. The solution was extracted with CH_2Cl_2 and the extracts washed with dilute Na_2CO_3. The solvent was dried and evaporated to yield a residue (ca. 1 g).

The major products were examined by gc-ms (150°) : 2.75 minutes (20%, parent amine 17-1); 4.8 minutes (5.5%) m/e 164 (6), 125 (11), 83 (100), 82 (67), 42 (50); 13.3 minutes (23%) m/e 183 (6), 181 (M^+ Cl_2^{35}, 11), 148 (37), 140 (100), 118 (12), 110 (29), 104 (26), 70 (35), 57 (44); 24.2 minutes (39%), separated into two peaks (20% and 19%) with identical ms when temperature programmed, m/e 207 (2), 205 (Cl^{35}, 5), 170 (40), 148 (8), 146 (25), 128 (30), 110 (50), 80 (65), 70 (80), 57 (100), 43 (70). The products with gc retention

times 13.3 and 24.2 minutes were assigned as dichloroamine 55-3, and chloroacetoxyamines 55-1 and 55-2, respectively. The other ten products were less than 3% yield each.

Chromatography of the residue (0.5 g) on basic alumina (35 g) gave incomplete separation and only 0.22 g total recovery. From the fractions containing primarily one compound the following characteristics were obtained: Dichloroadduct 55-3 : nmr τ 5.71 (bm), 7.57 (s). Chloroacetoxy adduct assigned as 55-1 : ir 1740; nmr τ 4.9 (bm), 5.95 (bm), 7.92 (s). Chloroacetoxy adduct assigned as 55-2 : ir 1740; nmr τ 5.1 (bm), 5.9 (bm), 7.84 (s). The low field multiplets all had large coupling constants (J ≈ 10 hz) and patterns of trans diaxial protons.

5-14 Nitrosamine Photolyses in the Presence of Trapping Agents

5-14-1 N-Nitroso-N-methyl-3-cyclohexene-1-methylamine (19-2) Under O_2

Methylamide 7-1 (5-9-1, 4.5 g, 0.032) was reduced with LAH (5 g) for 40 hours, as described in method 5-4-2, to give amine 19-1 : 2 g, 0.016 moles, 50%; ir 3300 (b), 3025 (m), 2920, 2840, 2795, 1650 (w), 1440, 1135, 655 (m); nmr τ 4.34 (2 H, s, $W_{\frac{1}{2}}$ = 4), 7.5 (2 H, d, J = 6), 7.57 (3 H, s), 7.6-8.7 (7 H, m), 8.66 (1 H, s, D_2O exch). After LAH reduction of 7-1 (5 g, 0.036 moles), the ether extracts were directly mixed with dilute HCl, and nitrosated with $NaNO_2$ (15 g) as described in method 5-5-1a to give the crude

nitrosamine. The product was chromatographed on neutral alumina (50 g) to give nitrosamine 19-2 : 4.9 g, 0.032 moles, 88%; ir 3025 (m), 2920, 2840, 1630 (w), 1430, 1345, 1325, 1155, 1030, 650 (m); nmr τ 4.25 (2 H, s, $W_{\frac{1}{2}}$ = 4.5), 5.89 (1.30 H, d, J = 8), 6.16 (0.66 H, s), 6.40 (0.44 H, d, J = 8), 6.91 (2.34 H, s), 7.7-8.9 (7 H, m); ms 154 (M^+, 1), 137 (51), 94 (28), 81 (81), 79 (72), 74 (64), 53 (34), 44 (100), 42 (57); uv (ε in HCl - MeOH) 345 (105). There was 78% E-isomer as estimated by nmr.

(a) Nitrosamine 19-2 (1 g, 6 mmoles) in MeOH (225 ml) containing concentrated HCl (0.6 ml) was photolyzed for 3.5 hours while oxygen gas was bubbled through the solution (Apparatus I, 100 W, Nonex filter). The uv spectra showed no C-nitroso peak at ca. 290 nm. The normal working-up procedure (5-8-1) gave unreacted nitrosamine (0.18 g) in the acidic fraction and the basic material (0.64 g).

A portion of the basic material (0.42 g) was chromatographed on basic alumina (50 g), eluting first with CH_2Cl_2 an impurity (0.03 g) from the $CHCl_3$ used in washing out nmr samples : ir 2960, 2860, 1740. Eluted with 1% MeOH - CH_2Cl_2 was endo-nitrate 26-3 : 0.07 g; ir 2940, 2860, 2790, 1620, 1450, 1275, 860: nmr τ 5.25 (1 H, ddd, J = 10, 6 and 2), 6.80 (1 H, bd, J = 6.5), 7.0-7.6 (2 H, m), 7.53 (3 H, s), 7.6-8.8 (7 H, m); ms (75°) 186 (M^+, 0), 140 (14), 138 (14), 124 (7), 96 (21), 82 (100), 58 (43), 55 (29), 42 (57), 41 (59). The next three fractions (0.18 g), eluted with 1-3% MeOH - CH_2Cl_2 contained aminoketone 28-3 (vide supra, 5-9-1), with

a minor amount of nitrate. Eluted with 10-50% MeOH - CH_2Cl_2 was <u>exo</u>-alcohol <u>27-1</u> : 0.1 g; ir 3350 (b), 2940, 2860, 2790, 1450, 1005; nmr τ 6.10 (1 H, bt, J = 5), 6.5 (1 H, s, D_2O exch), 6.9-7.4 (3 H, m), 7.50 (3 H, s), 7.51-8.7 (7 H, m); ms 141 (M^+, 18), 96 (15), 82 (100), 42 (15). Jones' oxidation of <u>exo</u>-alcohol <u>27-1</u> gave ketone <u>28-3</u> (53%), which compared with the previously prepared sample (5-9-1). The yields after chromatography, based on reacted nitrosamine (0.82 g), were 15% <u>endo</u>-nitrate <u>26-3</u>, 31% ketone <u>28-3</u> and 20% exo-alcohol <u>27-1</u>. The yields, estimated from the nmr spectrum of the crude basic fraction, were 15%, 35% and 45% respectively.

The ir absorption (1620 cm^{-1}) of <u>endo</u>-nitrate <u>26-3</u> was not significantly decreased relative to that of ketone <u>28-3</u> when a mixture (1 : 1.6 ratio) was examined either after storage for 2 months (25°), or after being stirred with 0.5N HCl for 21 hours at 25°. Reaction with 0.7N NaOH solution for 21 hours caused a decrease in nitrate peak relative to the ketone peak (ir ratio 1:2.2). <u>Endo</u>-nitrate <u>26-3</u> was relatively stable in pyridine, but decomposed more when treated with 5N NaOH for 1.5 hours to give a 1:3 ratio of nitrate to ketone ir absorption intensities. Reaction of <u>exo</u>-alcohol <u>27-1</u> for 0.75 hours with concentrated HNO_3 (0.25 ml) in concentrated H_2SO_4 (0.6 ml) (170), followed by basification and extraction, gave an impure nitrate : ir 1720 (w), 1620, 1275, 860. This product showed a ketone

to nitrate ratio of the ir peaks of 1:1.2 after 20 hours at 25°, and after 2 months the ratio was 3:1.

LAH (0.8 g) reduction for 28 hours of the basic residue (0.21 g) in ether at 25°, followed by removal of the solvent through a Vigreaux column gave a mixture of endo and exo-alcohols 26-1 and 27-1 (vide supra) in the ratio of 1:1.25. A Jones' oxidation of this mixture (0.059 g) produced ketone 28-3 (0.032 g, 55%).

A control photolysis of nitrosamine 19-2 (0.75 g), without acid, in MeOH (220 ml) (Apparatus 1, N_2, 200 W, Nonex filter) showed no decrease in the 340 nm absorption after 3.5 hours. The addition of 0.2 equivalents of concentrated HCl, and irradiation for 2 hours more, caused < 10% decrease in the uv absorption. 89% of nitrosamine 19-2 (vide supra) was recovered.

(b) Nitrosamine 19-2 (3 g, 0.019 moles) in MeOH (220 ml) containing 70% $HClO_4$ (3 ml, 0.02 moles) was photolyzed for 4.5 hours (Apparatus 1, O_2, 200 W, Nonex filter, then the solvent was evaporated. All attempts to crystallize perchlorate salts from a variety of solvents failed.

The photolysate residue was dissolved in benzene, washed several times with dilute acid, and the benzene evaporated. The residue obtained was separated into acidic/neutral material (0.18 g) and a basic fraction (0.19 g). The former was largely nitrosamine 19-2, with plasticizer and two minor components also present. The basic fraction was com-

prised of exo-alcohol 27-1 (vide supra).

The acid washes from above were basified and extracted with benzene to give a residue (1.53 g). Further extraction of the aqueous phase with CH_2Cl_2 and evaporation gave a mixture, which was separated into ether soluble and CH_2Cl_2 soluble compounds. The ether soluble material (0.11 g) was found by gc (125°) to contain 50% endo-alcohol 26-1 (12.4 min.), 40% exo-alcohol 27-1 (13.5 min.) and 10% of an unknown compound. The CH_2Cl_2 soluble fraction was shown to contain the HCl salt of endo-alcohol 26-1 : ir 3500 (b) 3050 (b,m), 2950, 2880, 2005 (w), 1450, 1100 (b); nmr (D_2O) τ 6.3 (1 H, m), 6.5-6.8 (2 H, m), 6.88 (3 H, s), 7.4-7.9 (5 H, m), 8.05-8.6 (3H, m); ms (170°) 141 (M^+, 26), 97 (26), 96 (37), 82 (100), 55 (11), 42 (26). Jones' oxidation of this salt gave ketone 28-3 (50%, vide supra).

The major basic fraction, obtained above, was chromatographed on neutral alumina (70 g). CH_2Cl_2 elution gave first a mixture (0.07 g) which showed no nitrate (1620 cm^{-1}) or ketone (1720 cm^{-1}) peaks. Next eluted with 1% MeOH - CH_2Cl_2 was a fraction (0.49 g) with endo-nitrate 26-3 (vide supra) as the major component. Continuing with the same elutant gave a mixture (0.3 g) of nitrate 26-3 and ketone 28-3. Using 2% MeOH - CH_2Cl_2, a mixture (0.16 g) of nitrate, ketone and alcohol 27-1 were obtained. The remaining fractions (0.5 g), eluted with 5-50% MeOH - CH_2Cl_2, contained exo-alcohol 27-1 (vide supra). Rechromatography of the fractions

rich in nitrate (0.79 g) on silicic acid (20 g) gave a fraction (0.08 g) of endo-nitrate 26-3, eluted with 5% MeOH - CH_2Cl_2. The fractions before and after this product contained mixtures of nitrate, ketone, alcohol and what appeared to be decomposition products, as shown by the olefinic proton signals in the nmr spectra.

The total yields of the various products were 0.5 g of neutral or decomposition products, endo-nitrate 26-3 (0.55 g, 15%), ketone 28-3 (0.3 g, 11%), exo-alcohol 27-1 (0.8 g, 29%), and the hydrochloride salt of endo-alcohol 26-1 (0.3 g, 9%).

5-14-2 Photolysis of 19-2 in the Presence of $BrCCl_3$

Nitrosamine 19-2 (0.95 g, 6 mmoles) and concentrated HCl (1.7 ml) in a mixture of $BrCCl_3$ (42 ml, 100 g) and MeOH (170 ml) were photolyzed for 3 hours (Apparatus 1, N_2, 200 W, Nonex filter. After removal of the solvent through a Vigreaux column, the residue was separated into acidic/neutral material (0.12 g) and basic material (0.69 g) in the usual fashion (5-8-1). The distilled solvent had a light blue color which disappeared after 2 weeks of refrigerated storage.

The basic residue contained one major compound (> 98%, retention time 12.9 min.) and a minor component (retention time 8.7 min.) when examined by gc (135°). The major product also showed one peak in programmed temperature

gc and was identified as endo-bromoamine 26-5: 55% yield; ir 2940, 2860, 2840, 2780, 1450, 765 (m); nmr τ 5.98 (1 H, ddd, J = 9, 7.5 and 1.5), 6.75-7.2 (2 H, m), 7.47 (3 H, s), 7.4-8.7 (8 H, m); ms 205 (Br^{81}, 22), 203 (M^+ Br^{79}, 22), 124 (56), 82 (100), 42 (27).

Hrms at M^+Br^{79} : Calcd for $C_8H_{14}NBr^{79}$, 203.0310.

Found, 203.0304.

Hrms at m/e = 82 : Calcd for C_5H_8N, 82.0657

Found , 82.0648.

The acidic/neutral fraction was composed of 5 principal compounds by gc analysis (120°), with one major component (64%, 2.3 min.). A minor peak with the same retention time was seen in the gc of the distilled solvent. This compound was tentatively assigned as the trichloronitrosomethyl monomer which forms dichloroformyl oxime (30) : ir 3200 (b), 985; gc-ms 115 ($Cl^{35,37}$, 65), 113 (Cl_2^{35}, 87), 98 (11), 96 (15), 80 (46), 79 (35), 78 (100), 77 (74), 63 (11), 61 (30), 47 (13), 43 (22). The next largest peak (19%) in the gc of the acidic fraction appeared to be of a compound containing two chlorines and a bromine from the gc-ms pattern: 189 (5), 187 (10), 185 (6), 159 (22), 157 (100), 155 (83), 121 (6), 119 (6), 107 (6), 105 (6), 95 (11), 93 (11), 77 (22), 75 (61).

5-14-3 Photolysis of 19-2 in the Presence of I_2

Nitrosamine 19-2 (1.6 g, 0.01 moles), concentrated HCl (2.6 ml), and iodine (2.6 g, 0.010 moles) were dissolved in MeOH (220 ml) and irradiated for 12 hours (Apparatus 1, N_2, 200 W, Nonex filter). The iodine absorption was ca. 100 time greater than that of the nitrosamine at 345 nm. During the photolysis, aliquots were removed and sodium thiosulfate added to cancel the iodine. The uv spectra showed no decrease in the nitrosamine peak. After photolysis, the iodine was reacted with sodium thiosulfate and the solvent evaporated. The residue was separated into the acidic/neutral material (1.69 g) and the basic material (0.096 g).

The basic fraction was found to be primarily sulfur (M^+ = 256) with a small amount of parent amine 19-1 (ca. 0.02 g). The neutral fraction was chromatographed on neutral alumina (30 g). The first fraction (0.73 g) eluted with benzene contained sulfur (yellow solid, M^+ = 256) and a compound assigned as chloroiodonitrosamine, either 57-1 or 57-2 : ir 2930, 2860 (m), 1450, 1430, 1330, 1160, 1030, 580; nmr τ 5.4 (2 H, m, $W_{\frac{1}{2}}$ = 12), 6.05 (1.6 H, d, J = 6.5), 6.38 (0.6 H, s), 6.57 (0.4, bd, J = 6.5), 7.07 (2.4 H, s), 7.4-9.0 (ca. 8H, m); ms (100°) 317 (M+1, 2), 316 (M^+, 2), 258 (14), 256 (46), 191 (7), 189 (23), 153 (17), 137 (42), 131 (15), 129 (46), 124 (54), 93 (100), 81 (71), 79 (94),

74 (58), 73 (75), 44 (79), 42 (92). This fraction contained ca. 20% nitrosamine 19-2, as judged by the nmr signal at τ 4.25. The next fraction (0.15 g) contained a mixture of nitrosamine 19-2 and nitrosamines 57-1 or 57-2. The fraction (0.07 g), eluted with 10% CH_2Cl_2 - C_6H_6, contained 19-2 (vide supra). The remaining material (0.52 g), eluted with 0-5% MeOH - CH_2Cl_2, consisted of a mixture (ca. 1:3 ratio) of 19-4 and an unidentified Compound C : ir 3400 (b,w), 3020 (w), 2930, 2830 (sh), 1450, 1430, 1330, 1180, 1140, 820 (m); nmr τ 5.4 (m, $W_{\frac{1}{2}}$ = 8), 5.95 (d, J = 7), 6.2 (s), 6.38 (m), 6.95 (s), 7.5-8.9 (m); ms (90°) 295 (3), 252 (4), 153 (25), 125 (33), 124 (25), 111 (13), 93 (58), 85 (71), 83 (100), 79 (75), 44 (71).

Nitrosamine 19-2 was stirred in MeOH for 3 hours in the dark with similar concentrations of HCl and iodine, and worked up in the same manner as above. The nmr of the crude residue showed ca. 20% yield of the products giving rise to the τ 5.4 signal.

5-15 Photolysis of N-Nitroso-N-methylphenethylamine (20-2)

Amine 20-1 (27 g, 0.2 moles) was nitrosated with $NaNO_2$ (18 g, 0.26 moles) according to method 5-5-1a, and the product distilled at 147-148°/ 12 mm to give nitrosamine 20-2 : 11.3 g, 0.07 moles, 34%; ir 3085 (m), 3060, 3025, 2935, 2860, 1605, 1585 (m), 1450, 1430, 1340, 1200, 1140,

1040, 750, 700; nmr τ 2.95 (5 H, s, W½ = 3), 5.82 (1.66 H, t, J = 7.5), 6.40 (0.34 H, dt, J = 7.5 and 2), 6.62 (0.51 H, s), 7.13 (1.66 H, t, J = 7.5), 7.21 (2.49 H, s), 7.38 (0.34 H, dt, J = 7.5 and 2); uv (ε in HCl - MeOH) 345 (110). From the ratio of the singlets at τ 6.62 and 7.21, 83% was E-isomer.

5-15-1 Photolysis in Methanol

A MeOH solution (250 ml) of nitrosamine 20-2 (4.1 g, 0.025 moles) and concentrated HCl (4.5 ml, 0.054 moles) was photolyzed for 5 hours (Apparatus III, N_2, 350 nm lamps, pyrex). Solid Na_2CO_3 (2.7 g, 0.025 moles) was added and the mixture was stirred. After evaporation of the solvent, the bulk of the residue was taken up in ether. Evaporation of the ether gave a mixture (2.75 g); a portion of this mixture (0.49 g) was separated into acidic/neutral compounds (0.14 g) and basic compounds (0.32 g).

The ether soluble compounds (2 g) were chromatographed on silicic acid (40 g). The first fractions (0.07 g), eluted with CH_2Cl_2, contained benzaldehyde (BA) : gc (140°) 1.7 min.; ir 3040, 3020, 2920, 2840, 1695, 1590, 1200, 740; nmr τ 0.05 (1 H, s), 2.1-2.8 (5 H, m). Further elution with CH_2Cl_2 gave a fraction (0.1 g) which contained nitrosamine 20-2 (gc 13 min., ca. 20%), and an unstable compound D : gc 4.8 min.; ir 3350 (b), 3060, 3025, 2930, 2830, 1450, 1120, 1000, 745, 695; nmr τ 2.9 (5 H, m), 5.46 (1 H, t, J = 5), 6.70 (ca. 5 H, s), 7.08 (2 H, d, J = 5). Attempts to isolate this

compound by preparative tlc or preparative gc failed.

An equal mixture (0.15 g) of compound D (gc 4.8 min.) and benzaldehyde oxime (BAO, gc 4.2 min.) was eluted next with CH_2Cl_2, followed by fractions (0.1 g) eluted with 0-0.5% EtOH - CH_2Cl_2 containing BAO : ir 3300 (b), 3090, 3050, 2980, 2880, 1670 (b,w), 1600, 1450, 1190, 940, 750, 690; nmr τ -0.98 (1 H, s, D_2O excn), 1.84 (1 H, s), 2.35-2.9 (5 H, m). The fractions (0.08 g) eluted with 2% EtOH - CH_2Cl_2 contained a mixture of BAO (nmr τ 1.84) and amidoxime 58 nmr τ 6.5 (s), 7.4 (s) . Elution with 2-10% EtOH - CH_2Cl_2 gave crude 58 (0.62 g), which was purified by rechromatography on silicic acid (10 g) and crystallization from ethyl acetate to give amidoxime 58 : m.p. 82-84°; ir 3400 (b), 3200 (b), 3060, 3025, 2940, 2850, 1650 (b), 1630, 1600 (m), 1490, 1375, 965, 715; nmr τ 0.5 (1 H, b, D_2O excn), 2.82 (5 H, s), 6.49 (2 H, s), 7.40 (3 H, s); ms (90°) 164 (M^+, 86), 147 (45), 132 (18), 117 (18), 106 (14), 91 (100), 73 (20), 65 (25), 56 (41), 39 (14).

Hrms at M^+: Calcd for $C_9H_{12}N_2O$, 164.0950

Found, 164.0952.

Hrsm at m/e = 106 : Calcd for C_7H_8N , 106.0656

Found, 106.0648.

Eluted with 20-50% EtOH - CH_2Cl_2 was a mixture (0.26 g) which showed gc peaks corresponding to phenethylamine (59-1, 3.2 min., 20%) and parent amine 20-1 (3.9 min., 80%). Next eluted with 100% EtOH was amine 20-1 : 0.12 g, ir 3300 (b),

3090 (m), 3065, 3030, 2940, 2890, 2850, 2795, 1605, 1585 (m), 1495, 1470, 1455, 1125, 1115, 750, 700; nmr τ 2.86 (5 H, s, $W_{\frac{1}{2}}$ = 2), 7.26 (4 H, s), 7.78 (3 H, s), 9.1 (1 H, s, D_2O exch).

The ether insoluble portion of the photolysate residue was dissolved in dilute acid (50 ml) and extracted to give a fraction (0.1 g) containing primarily BAO (gc 4.8 min.). Basification and extraction gave a mixture (0.08 g) of parent amine 20-1 [gc 3.9 min., 85%; nmr τ 7.25 (s), 7.78 (s)] and a compound with a peak corresponding to amine 59-1 (gc 3.2 min., 15%).

The total yields of the products, based on the amount of starting nitrosamine, were nitrosamine 20-2 (1%), BA (4%), BAO (13%), amidoxime 58 (22%), parent amine 20-1 (10%), and tentatively assigned amine 59-1 (3%).

5-15-2 Photolysis in Acetic Acid

(a) Nitrosamine 20-2 (4.1 g, 0.025 moles) dissolved in a 1 M H_2SO_4 - HOAc solution was photolyzed for 6 hours (Apparatus III, N_2 , 350 nm lamps, pyrex). The uv spectrum showed a 330 nm peak ($\epsilon \approx 60$), which became obscurred by a product absorbing below 300 nm. Water (400 ml) was added, and the solution brought to pH8 with Na_2CO_3. Ether extraction gave a mixture (2.5 g) which, by comparison with standard compounds in the gc (135°), contained BA (1.7 min., 18%), parent amine 20-1 (3.8 min., 1%), BAO (4.2 min., 10%),

and nitrosamine 20-2 (13 min., 60%). Extraction of the aqueous solution at pH 11 gave a mixture (0.15 g) of amine 59-1 (66%), amine 20-1 (24%) and nitrosamine 20-1 (6%), as analyzed by gc.

The aqueous layer was evaporated and the residue taken up in CH_2Cl_2 to give a fraction [0.12 g; ir 3300 (b), 3050 (m), 2920, 2850, 1720, 1680 (b), 1450 (b), 695] which gc indicated consisted of BA (20%), BAO (10%), nitrosamine 20-2 (15%), and a major product (50%) with a retention time corresponding to phenylacetaldehyde (PA, 1.8 min.).

Treatment of a portion (0.66 g) of the major basic extract with 2, 4 - DNPH gave the benzaldehyde 2, 4-dinitrophenylhydrazone : 0.21 g; crystallized from 95% EtOH, m.p. 235-237° (literature 237°) (215).

Repetitive silicic acid chromatography of the major basic fraction, followed by preparative tlc failed to isolate the minor products (< 2% yields), but there was no gc peak corresponding to N-methylindoline (61, 4.8 min.) in any of the fractions. The overall product yields, obtained from the gc of the fractions, were BA (18%), BAO (9%), parent amine 20-1 (2%), nitrosamine 20-2 (37%) and the products assigned as amine 59-1 (3%) and phenylacetaldehyde (2%).

(b) Nitrosamine 20-2 (2 g, 0.012 moles) in acetic acid (230 ml) containing concentrated HCl (2.2 ml, 0.026 moles) was photolyzed for 4.5 hours (Apparatus I, N_2, 200 W, pyrex). The acetic acid was evaporated and dilute acid (50 ml) was

added to the residue. Extraction with CH_2Cl_2 gave a mixture (0.8 g). Na_2CO_3 was added until the pH = 9, and CH_2Cl_2 extraction gave a residue (1.02 g). The tlc, ir and nmr spectra of both fractions were similar, except for nitrosamine 20-2 present in the acidic extract [ca. 15% as judged by nmr, τ 5.82 (t)].

The basic fraction was chromatographed on neutral alumina (65 g). The first four fractions (0.3 g), eluted with 0-0.3% MeOH - CH_2Cl_2, were a mixture of four compounds by tlc : ir 3060, 3030, 2930, 2860, 1665, 1630 (sh), 1595, 750 (sh), 740, 700; nmr τ 2.75 (m, $W_{\frac{1}{2}}$ = 9), 6.1 (m), 6.5 (m), 7.0-7.15 (m). The next compound (0.21 g) eluted with 0.5-1.5% MeOH - CH_2Cl_2 was identified as N-formylphenethylamine (59-2) : 3300 (b), 3060, 3030, 2930, 2870, 1660, 1530 (m), 1385, 745, 700; nmr τ 2.04 (1 H, d, J = 2), 2.85 (5 H, s, $W_{\frac{1}{2}}$ = 4), 6.61 (2 H, quintet, J = 7, collapses on D_2O exchange), 7.25 (2 H, t, J = 7); ms (80°) 149 (M^+, 21), 122 (6), 105 (36), 104 (100), 91 (46), 77 (27), 72 (17), 58 (30), 44 (17). The spectra were identical with formamide 59-2 (0.8 g) prepared by refluxing phenethylamine (0.7 g) with formic acid (5 ml) for 36 hours (174).

Next eluted with 1.5% MeOH - CH_2Cl_2 was a mixture (0.07 g) of 59-2 and BAO, followed by a fraction (0.1 g) containing BAO (vide supra). With 3-5% MeOH - CH_2Cl_2 as the elutant, another mixture (0.09 g) was obtained, and it exhibited a strong singlet at τ 2.75 in the nmr spectrum.

Finally eluted with 5-100% MeOH was parent amine 20-1 (0.5 g, vide supra). None of the mixtures exhibited a complex nmr pattern in the region of τ 2.9-3.8.

Assuming the acidic extract only differed from the basic extract by containing nitrosamine 20-2, the estimated product yields were nitrosamine 20-2 (6%), BAO (12 %), formamide 59-2 (19%) and parent amine (30%).

5-16 Interconversion of Benzaldehyde and Benzaldehyde Oxime

5-16-1 H_2SO_4 in Acetic Acid

The reactants were dissolved in a solution of 1 M H_2SO_4 in acetic acid. Following the reaction period, the solution was treated with 2N NaOH and extracted with ether. Analysis by gc (110°) for BA and BAO gave the results shown.

(a) BAO (1.2 g) was stirred in the acid solution (25 ml) for 12 hours in the dark. After extraction at pH 8, the gc showed BA (3%), BAO (96%) and a peak corresponding to the retention time of benzonitrile (1%). Benzonitrile was shown in a separate experiment to be unchanged under these conditions, although benzamide did not give a gc peak under the analysis conditions.

Similar yields (± 1%) were obtained when BAO was extracted at pH 11, or photolyzed for 2 hours in pyrex Apparatus III (N_2 , 350 nm lamps), or stirred in the dark with 0.8 equivalents of N-nitrosodimethylamine (NDM).

(b) BAO (0.6 g) and NDM (0.3 g) in the acid solution (9 ml) were photolyzed for 2 hours (ca. 10% NDM decomposition) in pyrex Apparatus III (N_2, 350 nm lamps). The gc analysis showed BA (9%) and BAO (91%).

(c) BA (0.4 g) and NDM (0.28 g) were stirred in the solution (10 ml) for 12 hours in the dark. Extraction at pH 6, and gc analysis showed BA (94%) and BAO (0%). BA and $NaNO_2$ under the same conditions gave only BA.

(d) BA (0.38 g) and NDM (0.25 g) were stirred for 12 hours in the dark, then photolyzed in pyrex Apparatus III for 2.5 hours (ca. 10-15% decrease in NDM peak at 330 nm, N_2, 350 nm lamps). Extraction at pH6 and gc analysis showed only BA.

(e) When the solvent of a MeOH solution (50 ml) of BA (0.1 g) was removed on the rotary evaporator 48% yield of BA was obtained. The yield of BA was ≈85% when ether was used as a solvent.

5-16-2 Photolysis in Methanol

Crude BAO (1.2 g, 0.01 mole), containing 5% BA, and NDM (1.5 g, 0.02 moles) were photolyzed in MeOH (220 ml) containing concentrated H Cl (3 ml, 0.036 moles) for 7 hours (Apparatus I, N_2, 200 W, Nonex filter) until the uv absorption at 345 nm had decreased 80%. Evaporation of the solvent, basification and CH_2Cl_2 extraction, gave a residue (1.8 g) in which gc analysis indicated that the BA peak had increased

25% while the BAO peak had decreased 50%, relative to an internal standard.

A control reaction, stirred in the dark at 0°, showed a 5% increase in the BA peak after a similar work up.

5-17 Decomposition of N-Chloro-N-methylphenethylamine (20-3)

To a mixture of 5% sodium hypochlorite solution (40 ml), water (80 ml), and ether (100 ml) at 0° was added a solution of amine 20-1 (17 g, 0.125 moles) in dilute HCl (40 ml). The mixture was stirred for 15 minutes, the ether layer separated, and the aqueous layer extracted with ether. The combined extracts were evaporated to give chloramine 20-3 : 3 g, 0.02 moles, 14%; ir 3085 (m), 3060, 3030, 2950, 2860, 1600 (m), 1450, 1435, 745, 695; nmr τ 2.95 (5 H, s), 7.10 (4 H, m), 7.24 (3 H, s).

5-17-1 Reaction with Ferrous Sulfate

Chloramine 20-3 (0.7 g, 4 mmoles) was stirred in a solution of 1 M H_2SO_4 in acetic acid (50 ml) at 25°, and hydrated ferrous sulfate ($FeSO_4 \cdot 7\ H_2O$, 1.4 g, 5 mmoles) was added. After 10 minutes, the solution was extracted with petroleum ether (60-110°). Evaporation gave a fraction (0.26 g) which contained ca. 20% non-volatile material from the petroleum ether [nmr τ 3.0 (m), 7.75 (m), 8.78 (s), 9.15 (m)], identical with the residue obtained from evaporation of petroleum ether. The aqueous solution was basified to pH 8,

and extracted with petroleum ether to give a mixture (0.19 g), containing the petroleum ether involatiles (ca. 20%).

The neutral fraction was chromatographed on silicic acid (10 g). First eluted with CH_2Cl_2 was benzyl chloride (BC) : 0.08 g, gc (130°) 2.4 min.; ir 3090 (m), 3065, 3040, 2965, 1600, 1450, 1270, 700, 680; nmr τ 2.74 (5 H, s), 4.52 (2 H, s); identical with an authentic sample. A mixture of BC and aqueous acetic acid when evaporated on the rotary evaporator gave ≈10% recovery of BC. The remaining material (0.4 g), eluted from the column with 0-50% MeOH - CH_2Cl_2, had gc peaks corresponding to the petroleum ether residue (1.8 min. major, ir 1740).

Gc analysis of the basic extract showed the major component to be amine 20-1 : 80%, 5 min.; nmr τ 2.96 (s), 7.26 (s), 7.78 (s). The aqueous phase was further extracted with ether at pH 11 to give a mixture (0.1 g), which gc analysis showed to contain parent amine 20-1 (90%) and the peak corresponding to amine 59-1 (10%, 4.2 min.). Chromatography of the combined basic extracts on silicic acid (7 g) gave the petroleum ether residue (0.02 g, gc 1.8 min. major) with 0-1% EtOH - CH_2Cl_2. The remaining fractions (0.08 g), eluted with 2-100% EtOH contained parent amine 20-1 (vide supra, 5-15-1). None of the fractions showed the gc peak of N-methylindoline (6 min.).

The overall yields of the products, calculated from gc and nmr, were BC (40%), amine 20-1 (42%) and assigned

amine 59-1 (2%).

5-17-2 Reaction with Silver Nitrate

Amine 20-1 (6.8 g, 0.05 moles) was converted to chloramine 20-3 as described above, using pentane instead of etner as a solvent. The pentane extracts containing 20-3 were evaporated until ca. 50 ml remained, then MeOH (200 ml) was added, and the solution again concentrated to a 50 ml volume. MeOH (ca. 250 ml) and $AgNO_3$ (12.8 g, 0.075 moles) were added and the mixture refluxed for 2.5 hours in the dark. The precipitate was filtered, and the solution concentrated to ca. 25 ml. Saturated NaCl solution (50 ml) was added, and the mixture left overnight. The precipitate was filtered, and the solution extracted with etner. Evaporation of the extracts gave a mixture (3.33 g), which showed gc peaks at 2.3 min. (4%, benzylmethylether), 3.9 min. (4%, compound F), 4.2 min. (2%, 59-1), 4.8 min. (66%, 20-1), 11 min. (4%, compound E), and 11.7 min. (20%, compound G).

The mixture (2.7 g) was chromatographed on silicic acid (50 g). Eluted with CH_2Cl_2 was a mixture (0.42 g), indicated by gc to be composed of benzaldehyde (2.0 min.; ir 1695; nmr τ 0.05 singlet) and benzylmethyletner (BME), [2.3 min., nmr τ 2.9 (s), 5.5 (s) 6.67 (s)]. Eluted with 1% EtOH - CH_2Cl_2 was a fraction (0.16 g) which distilled at 65°/1 mm to give impure compound E : gc 11 min (> 85%); ir 3060, 2930, 2830, 1695, 1675, 1600, 1450, 1070, 700;

nmr τ 1.85 (2 H, m), 2.4-2.8 (3 H, m), 4.8 (1 H, s), 6.52 (ca. 5 H, s); ms (175°) 160 (2), 151 (3), 121 (4), 105 (10), 97 (7), 77 (21), 75 (100), 51 (7), 47 (14). This compound appears to decompose on storage to benzoic acid : ir 1700; ms 122 (80), 105 (100), 77 (75), 51 (60).

The next fraction (0.41 g), eluted with 1% EtOH - CH_2Cl_2, was rechromatographed on silicic acid and one fraction (0.22 g) was distilled at 80°/ 1 mm to give impure compound F : gc 3.9 min. (75%); ir 3300 (b,m), 3060, 3025, 2930, 2850, 2820, 1670, 1600 (m), 1450, 1070, 750, 700; nmr τ 2.8 (6 H, m), 6.61 (1 H, s), 6.76 (1 H, s), 7.2 (4 H, m), 7.68 (1 H, s); ms (175°) 268 (5), 224 (55), 163 (38), 134 (30), 105 (63), 104 (88), 91 (60), 77 (25), 75 (30), 72 (100), 44 (75).

Eluted with 2-5% EtOH - CH_2Cl_2 was a fraction (0.59 g) which was distilled at 90°/ 3 mm to give compound G : gc 11.8 min.; ir 3340 (b), 3060, 3025, 2960, 2830, 2780, 1450, 1120, 1080, 1055, 755 (m), 700; nmr τ 2.8 (5 H, m), 5.74 (1 H, d, J = 7), 6.43 (1 H, d, J = 7), 6.64 (3 H, s), 6.87 (3 H, s), 7.80 (3 H, s), 8.03 (1 H, s, D_2O exch); ms (175°) 196 (1), 195 (1), 164 (3), 148 (5), 134 (8), 132 (10), 120 (100), 91 (15), 77 (10), 75 (20), 42 (20). The remaining product (0.3 g), eluted with 10-100% EtOH was parent amine 20-1.

None of the fractions contained a gc peak which corresponded to 61 (6 min.). The yields of the major products

of gc analysis were amine 20-1 (32%) and the unidentified compound G (ca. 7%).

5-18 Alternate Methods of Generating Aminium Radicals

5-18-1 Radical Initiated Chloramine Intermolecular Additions

The reactions given below were followed by iodometric titration (5-8-3).

(a) The hydrochloride salt of diethylamine (DE, 11 g, 0.1 moles) was converted by the method described in 5-5-3 to N-chlorodiethylamine (CDE). The ether extracts were concentrated by evaporation, acetic acid (100 ml) was added, and the remainder of the ether evaporated. The solution was made up to 4 M H_2SO_4 in acetic acid (200 ml) and α,α- azo-bis-isobutyronitrile (AIBN, 0.66 g, 0.004 moles) was added. The mixture was heated to 33-35° in the dark, and 1-butene gas was passed through the solution for 4 hours. The solution was extracted with ether, the extracts washed with dilute base, and evaporated to give a residue. The residue was separated into acidic/neutral material (9.31 g) and basic material (0.32 g) by the usual extraction procedure.

The major component of the basic fraction was DE : gc 80%; ir 3400 (b), 2970, 2930, 2870, 2820 (m), 1460; nmr τ 5.40 (1 H, s, D_2O exch), 7.45 (4 H, q, J = 7), 9.0 (6 H, t, J = 7). The gc (105°) of the neutral fraction showed peaks at 1.8 min. (52%), 4.0 min. (40%) and 4.3 min

(8%). Distillation of the neutral fraction at 40°/ 3 mm gave impure chloroacetoxybutane 63-1 : 1.33 g; gc 4 min. (85%), 4.3 min. (15%); ir 2970, 2940, 2880 (m), 1740, 1235, 1030, 735 (m); nmr τ 5.06 (1 H, m), 6.41 (2 H, d, J = 5.5), 7.97 (3 H, s), 8.35 (2 H, m), 9.08 (3 H, t, J = 7) ; ms (175°) 150 (M^+, 0), 123 (2), 121 (7), 101 (51), 85 (44), 83 (67), 73 (11), 72 (9), 61 (18), 55 (20), 49 (6), 47 (17), 43 (100); ms (30°, 20 ev) 121 (8), 101 (100). From the liquid nitrogen trap was obtained the more volatile material (1.8 g). The major component was assigned as 2-acetoxybutane (61-2) : gc 1.8 min. (65%), 4.0 min. (25%); ir 2970, 2920, 2880 (m), 1735, 1245, 1030; nmr τ 5.28 (m), 8.10 (s), 8.3-9.4 (m).

(b) Dimethylamine hydrochloride (8.1 g, 0.1 moles) was treated with NaOCl solution as described in method 5-5-3. The ether extracts were dried, and concentrated H_2SO_4 (5 ml) was added at 0° (132). The precipitated sulfuric acid salt of N-chlorodimethylamine (HCDM) was filtered, washed with ether, and dried under vacuum in the dark. The salt was dissolved in a 4 M H_2SO_4 - HOAc solution (200 ml) containing 1-hexene (8.3 g, 0.1 mole). Half the solution was kept at room temperature in the dark. To the other half was added α,α - azo-bis-cyclohexylnitrile (ACHN, 0.37 g, 1.5 mmoles) and the mixture was photolyzed for 7.75 hours (apparatus III, N_2, 350 nm lamps, pyrex). The photolysate was separated into neutral (2.67 g) and basic (0.16 g) fractions. The same procedure with the control solution gave neutral (3.27 g)

and basic (0.18 g) fractions.

Both neutral fractions showed gc peaks (130°) at 1.8 min. (45%), 4.4 min. (45%), and 4.7 min. (10%), and have the same ir absorptions (2960, 2940, 1740, 1240). From the comparable gc retention times and the similar nmr signals as the neutral fraction from 5-18-1a above, the major compounds were tentatively assigned as 2-acetoxynexane (64-2) and 1-chloro-2-acetoxynexane (64-1) : nmr τ 5.08 (m), 8.43 (d, J = 5), 7.97 (s), 8.05 (s), 8.3-9.3 (m). The nmr spectra of both basic fractions were similar : τ 5.9 (m), 8.4 (m), 7.3 (m), 7.51 (s), 7.98 (s). The gc (115°) showed peaks at 6.3 min. [40% of the control and 10% of the photolysis fraction; gc-ms 114 (100), 84 (7), 72 (10), 71 (10), 58 (26), 42 (14)] and 4.8 min. [ms (90% pure) 165 (2), 163 (5), 129 (11), 114 (10), 87 (8), 54 (14), 69 (10), 58 (100), 43 (71), 42 (24)].

(c) HCDM, prepared from the hydrochloride salt of DM (8.1 g) as described above, was dissolved in a 4 M H_2SO_4 - HOAc solution (200 ml) containing diallyletner (9.8 g, 0.1 moles). Half the solution was kept in the dark as a control. AIBN (0.33 g, 2 mmoles) was added to the other half and the mixture irradiated for 1.25 hours (Apparatus III, N_2, 350 nm lamps, pyrex). The usual extraction procedure gave neutral material (3.85 g from both solutions) and basic fractions (0.15 g from photolysis, 0.18 g from control solution).

Both neutral fractions have major peaks in the gc (150°) at 8.7 min. (ca. 65%) and 9.5 min. (ca. 20%). The major product was tentatively assigned as the 1-chloro-2-acetoxypropylallylether (65-1) : ir 3080 (m), 3020 (m), 2950, 2865, 1740, 1235, 1050, 740 (m); nmr τ 3[redacted] (1 H, m), 4.65-5.1 (ca. 3H, m), 5.7-6.1 (2 H, m), 6.2-6.5 (4 H, m), 7.96 (3 H, s). The basic fractions were not further investigated but had a major peak (ca. 60%) in the gc at 8.7 min.: ir 2940, 2860, 2820, 2770, 1740, 1235; nmr τ 4.2-5.05 (m), 5.7-6.7 (m), 7.2-7.5 (m), 7.63 (s), 7.91 (s).

(d) A similar procedure as given in 5-18-1c with HCDM was followed, using as the olefin 2, 3-dichloropropene (11.1 g, 0.1 moles), and the irradiation period was 1 hour. The neutral fraction (0.32 g) from the control contained greater than 10 peaks in the gc (105°), while the neutral fraction (0.3 g) from the photolysis showed one peak : 5.5 min; ir 3350 (b), 2990, 2840, 2240 (m), 1660 (b), 1450, 1220, 750; nmr τ 8.40 (s), 8.58 (s).

The base-extracted material (0.02 g) from the control was primarily 2, 3-dichloropropene[nmr τ 4.5 (m), 4.68 (m), 5.9 (s)] . The basic fraction (3.55 g) from the photolysis was 1-amino-2-chloro adduct 66-1 : gc 9 min. ; ir 2955, 2830, 2785, 1455, 1280, 1050,1005,950,700;nmr τ 5.89 (2 H,s) 6.97 (2 H, s), 7.58 (6 H, s); ms (100°) 191 (5), 189 ($M^{+}Cl_3^{35}$, 4), 156 (2), 154 (Cl_3^{35}, 3), 142 (6), 140 (Cl_2^{35}, 9), 120 (4), 118 (Cl^{35}, 9), 107 (6), 105 (Cl^{35}, 19), 85 (66), 84 (13),

83 (78), 58 (100), 44 (11), 42 (23).

5-18-2 Attempted Generation of Aminium Radical from Protonated Amine

(a) Dipentylamine (DP, 1 g, 6 mmoles) and calcium hypochlorite (1 g, 8 mmoles) were dissolved in 4 M H_2SO_4 - HOAc (120 ml) and left in room light for 1 week at 25°. Neutralization and extraction gave DP : 0.31 g; ir 2920, 2860, 2810 (m), 1470, 1330, 730; nmr 7.42 (4 H, m), 8.4-9.3 (ca. 19 H, m).

DP (1 g) was reacted with NaOCl solution (100 ml) as outlined in method 5-5-3 to give N-chlorodipentylamine (CDP): 0.84 g, 69%; ir 2930, 2860, 1460, 1375, 1070, 720; nmr 7.09 (4 H, m), 8.2-9.3 (18 H, m). CDP was dissolved in 4 M H_2SO_4 - HOAc (60 ml). After 10 minutes in the dark, the solution was neutralized and extracted to give CDP (0.35 g, vide supra).

(b) DP (2.15 g, 0.014 moles) and lead tetra-acetate (9.2 g, 0.021 moles) were dissolved in 4 M H_2SO_4 - HOAc (700 ml). A third of the solution was left in the dark, a third was heated on the steam bath for 2.5 hours, and a third was photolyzed for 1.5 hours (Apparatus III, N_2, 350 nm lamps, pyrex). Neutralization and extraction gave DP (vide supra) from the control (0.58 g), the thermal (0.59 g) and the photochemical (0.58 g) reactions.

DP (1 g, 6 mmoles) in HOAc (120 ml) was heated on a steam bath with $Pb(OAc)_4$ (4 g) for 3.5 hours. Neutralization

and extraction gave a mixture (ca. 0.4 g) of NP (ca. 60% from τ 7.45 multiplet) and a compound assigned as N, N-dipentylacetamide (67): ir 1640; nmr τ 8.70 (m), 7.98 (s), 8.3-9.3 (m); gc-ms 199 (M^+, 6), 184 (11), 156 (12), 142 (46), 128 (51), 114 (15), 109 (76), 87 (22), 86 (20), 75 (100), 44 (50).

5-19 Attempted Initiation of Nitrosopiperidine Radical Reactions

5-19-1 Carbon Radical Initiators

(a) N-Nitrosopiperidine (NP, 2.28 g, 0.02 moles) and cyclohexene (1.64 g, 0.02 moles) were refluxed for 40 hours in the dark in a MeOH solution (200 ml) which contained concentrated HCl (2 ml, 0.024 moles) and AIBN (0.16 g, 1 mmole). The uv spectrum showed ca. 15% increase in the 350 nm absorption. MeOH was evaporated, and the residue separated into neutral and basic fractions. The neutral material (1.9 g) was NP : ir 2940, 2840, 1425, 1360, 1285, 1260, 1370, 1090, 980; nmr τ 5.81 (2 H, m), 6.24 (2 H, m), 8.0-9.1 (6 H, m). The basic fraction (0.15 g) was largely NP (similar ir) with possibly some piperidine (P) present [ir 3350 (b,m), 1320 (w)].

(b) NP (3.9 g, 0.034 moles), concentrated HCl (3 ml, 0.036 moles) and AIBN (0.5 g, 3 mmoles) in MeOH (200 ml) were refluxed in a covered vessel for 41 hours, then left for 4 days at room temperature. The uv spectrum showed

ca. 20% decrease in the 350 nm peak. Evaporation and extraction gave the neutral NP (2.61 g, vide supra). Basification and CH_2Cl_2 extraction gave the hydrochloride salt of piperidine (HP): 0.34 g; ir (KBr) 2940, 2800, 2740, 2510, 1460, 560; nmr τ 0.07 (2H, b, D_2O exch), 6.83 (4 H, m), 7.8-8.7 (6 H, m).

(c) NP (2 g, 0.018 moles), cyclohexene (1.64 g, 0.02 moles), trifluoroacetic acid (2.3 g, 0.02 moles), and AIBN (0.16 g, 1 mmole) were refluxed in the dark for 20 hours in benzene (200 ml). The uv spectrum showed ca. 10% increase in the broad peak from 330 to 370 nm. Evaporation of the solvent and extraction gave NP (1.75 g, vide supra). The extracted basic material (0.06 g) was not identified: ir 3300 (b), 2930, 2850, 1670 (b), 1450, 1200, 1170, 1130; nmr τ 6.85 (b, D_2O exch), 8.1 (b, D_2O exch), 8.25 (s), 8.43 (s), 8.5-9.0 (m).

(d) NP (1.2 g, 0.01 moles), cyclohexene (2 g, 0.024 moles) and trifluoroacetic acid (1.5 ml, 0.02 moles) in benzene (120 ml) were refluxed in the dark while benzoyl peroxide (1 g, 4 mmoles) was added in portions. The solution was refluxed for an additional 5 hours, then left at 25° for 15 hours. The uv spectrum showed ca. 30% increase in the 325 to 380 nm region and was not further examined.

5-19-2 Reaction with Ferrous Sulfate

NP (1 g, 9 mmoles), concentrated HCl (1 ml, 0.012 moles) and cyclohexene (1 g, 0.012 moles) were dissolved in MeOH (20 ml). Hydrated ferrous sulfate ($FeSO_4 \cdot 7\ H_2O$, 2.5 g, 9 mmoles) was added to the solution at 0° and the mixture stirred for 2.25 hours in the dark. The solution was filtered and evaporated. Aqueous Na_2CO_3 was added and the solution extracted to give NP (0.79 g, vide supra).

5-19-3 Photoinitiation with N-Nitroso-N-methylacetamide

NP (1 g, 9 mmoles), trifluoracetic acid (1.5 ml, 0.02 moles), cyclohexene (1.5 g, 0.018 moles) and N-nitroso-N-methylacetamide (NMA, 3 g, 0.029 moles) in benzene (220 ml) were photolyzed for 5.5 hours (Apparatus 1, N_2, 200 w, > 400 nm filter solution). The uv spectrum showed a 58% decrease in the 420 nm peak of NMA. The solvent was evaporated and water (100 ml) was added. After extraction of the neutral material, the solution was basified to pH 8. Ether extraction of the basic solution and evaporation gave N-methylacetamide : 0.12 g, ir 3300 (b), 3100 (b), 2930, 1640 (b), 1560, 1410, 1370; nmr τ 7.22 (3 H, d, J = 5, collapses on addition of D_2O), 8.03 (3 H, s).

5-20 Nitrosamine Photoelimination Reactions

5-20-1 N-Nitrosotetrahydroisoquinoline (21-2)

Tetrahydroisoquinoline 21-1, 13.3 g, 0.1 (mole) was nitrosated with $NaNO_2$ (9 g, 0.13 moles), according to method 5-5-1, to give a neutral fraction (15.6 g) which was crystallized from EtOH -H_2O to give pale yellow nitrosamine 21-2 : 11.66 g, 0.072 moles, 72%; m.p. 42-44°; ir 3025 (m), 2985 (m), 2930, 1500 (m), 1425, 1350, 1340, 1325, 1290, 1050; nmr (CCl_4) τ 2.90 (4 H, m), 4.66 (0.93 H, s), 5.32 (2.07 H, s), 5.50 (1.38 H, t, J = 6), 6.21 (0.62 H, t, J = 6.5), 7.0 (2 H, m); uv (ε in HCl - MeOH) 347 (100). The nmr spectrum indicated 69% E-isomer (syn to benzylic protons).

Nitrosamine 21-2 (8.1 g, 0.05 moles) and concentrated HCl (4.2 ml, 0.05 moles) in MeOH (400 ml) were photolyzed for 10 hours (Apparatus III, N_2, 350 nm lamps, pyrex). The MeOH was evaporated and dilute acid (200 ml) added. Ether extraction gave nitrosamine 21-2 (0.15 g, tlc and ir identical). Na_2CO_3 was added until the solution was basic and ether extraction gave amidoxime 68-1 (7.06 g, 89%, one spot tlc) which was crystallized from benzene-hexane to give green-yellow 68-1 : m.p. 103-104°: (literature 105-106°) (128); ir 3200 (b), 3070 (m), 2940, 2860, 1650, 1600 (m), 1570 (m), 1335, 965, 905, 780, 760; nmr τ 1.68 (1 H, b, D_2O exch), 2.2 (1 H, m), 2.85 (3 H, m), 6.67 (2 H, t, J = 6). 7.18 (2 H, t, J = 6).

The aqueous phase was basified to pH 12 and extracted

with CH_2Cl_2 to give a mixture (0.15 g) of amidoxime 68-1 and parent amine 21-1 by tlc and nmr. The water was evaporated and the residue extracted to give amine 21-1 : 0.15 g, tlc identical ; ir 3360 (b, m), 3030 (m), 2930, 2840, 2815, 2745 (m), 1585 (w), 1500, 1455, 1325, 750; nmr τ 5.05 (4 H, s, $W_{\frac{1}{2}}$ = 4), 6.20 (2 H, s), 7.05 (2 H, m), 7.35 (2 H, m), 8.4 (1 H, s, D_2O exch).

5-20-2 N-Nitrosopiperidine under Oxygen

(a) NP (2.3 g, 0.02 moles) and concentrated HCl (2 ml, 0.024 moles) were photolyzed in MeOH (230 ml) in an oxygen atmosphere for 3 hours (Apparatus I, 200 W, Nonex filter) until the uv spectrum showed the disappearance of the 350 nm peak. The usual work up (method 5-8-1) gave the acidic/neutral material [0.03g; ir 3300 (b), 2930, 2855, 1630 (b), 1525, 1280] and the basic fractions (1.46 g) extracted with CH_2Cl_2.

Chromatography of the basic fraction on neutral alumina (60 g) eluted first, with 0-1% MeOH - CH_2Cl_2, dipiperidinomethane (70) : 0.38 g, 21%; ir 2935, 2855, 2780, 1440, 1130; nmr τ 7.24 (2 H, s), 7.6 (8 H, m), 8.3-8.7 (12 H, m); ms (100°) 182 (M^+ + 1, 1), 181 (M^+, 2), 98 (100), 85 (25), 84 (45), 70 (11), 57 (21), 56 (25). The fractions eluted with 1% MeOH - CH_2Cl_2 [0.23 g; ir 1660 (b); nmr τ 7.4 (4 H, m), 8.4 (6 H, m)] were purified to give the product assigned as N-piperidinoformamide (71): ir 2935,

2860, 1670, 1440, 1105; ms (100°) 113 (100), 98 (50), 84 (44), 73 (44), 56 (50). Eluted with 1-50% MeOH - CH_2Cl_2 was piperidine hydrochloride (HP) : 0.68 g, 29%; ir vide supra, 5-19-16; nmr (D_2O) τ 6.79 (4 H, m), 8.2 (6 H, m).

(b) NP (2.3 g) and concentrated HCl (2 ml) in water (230 ml) were photolyzed for 11 hours under oxygen using the same conditions as above. The uv spectrum showed ca. 20% of the 340 nm absorption remained. The solution was extracted to give a neutral fraction (0.44 g) containing NP (vide supra, 15-19-1a).

The photolysate was basified and extracted to give the basic material (2 g) which was chromatographed on neutral alumina (60 g). Eluted first with CH_2Cl_2 was NP (0.11 g, vide supra). The next CH_2Cl_2 eluted fraction (0.23 g) was ca. 50% NP, as indicated by nmr. Eluted with 1-3% MeOH - CH_2Cl_2 was an unstable product, suggested to be tripiperidinonitrate 72-1: 0.91 g; ir 3350 (w), 2970, 2830, 2800, 1630, 1280, 880; nmr τ 5.0 (1 H, m), 6.2-7.8 (ca. 16 H, m), 7.8-9.0 (ca. 20H, m); ms (75°) 249 (5), 192 (27), 165 (5), 100 (9), 84 (91), 83 (100), 55 (95). Attempted sublimation at 40°/ 1 mm gave a semi-solid, suggested to be impure tripiperidinoalcohol 72-2 : ir 3300 (b,m), 2930, 2855, 2800, 1630 (m), 1445, 1050.

Anal. Calcd for $C_{15}H_8N_3O$: C, 67.37: H, 10.93; N, 15.71

Found : C, 67.82; H, 10.32; N, 14.96

The remaining material eluted with 5-50% MeOH - CH_2Cl_2 was HP (0.42 g, vide supra).

5-21 Quantum Yield of N-Nitrosodimethylamine Disappearance

5-21-1 Apparatus and Procedure

The quantum yield measurements were done on a merry go round apparatus (263). A 450 Watt lamp, inside a water cooled sleeve, was placed in the centre well of the apparatus and the light filtered through a Corning CS 7-60 (# 5840) glass filter(See Figure 5.4). The path length to the 0.5 by 2 cm photolysis slits was ca. 10 cm. Scrubbed nitrogen gas was bubbled through the aqueous solution (5 ml) containing N-nitrosodimethylamine (NDM) and HCl (same molarity as that of NDM), then the pyrex tube was stoppered. The samples were irradiated in a constant temperature bath at 25° and removed at specific time intervals.

A ferric oxalate actinometer (264) was used and the amount of ferrous ion formed was determined the absorption of the complex at 510 nm. The calibration plot for the ferrous complex is given in Figure 5.5. A quantum yield of 1.21 was assumed in the calculations for the formation of ferrous ions. The lamp intensity, after a warm up period (ca. 10 minutes), was found to be relatively constant (± 10%) and the average light intensity entering the sample tubes was 6×10^{17} quanta/minute.

In a separate experiment the amount of light absorbed related to the molarity of NDM was determined in the apparatus shown in Figure 5.6. The average values for the percentage of incident light absorbed were plotted against molarity of NDM in Figure 5.7. The actinometer solutions absorb > 98% of the light at the 0.006 M concentrations used.

5-21-2 Experimental Data

The percentage decrease of the 340 nm NDM absorption during the photolysis was plotted against time. The points gave linear slopes with deviations of ± 10%. The quantum yields of disappearance (Φ_{dis}) of NDM were calculated from the slopes and the value for the average light intensity. These Φ_{dis} values are given in Table 5.1 with the correction for the amount of light absorbed by the sample at that molarity.

5-22 Analysis of Nitrosamine Photodecomposition Products

5-22-1 Gas Chromatography of Amines

A number of gc columns were tested for their ability to separate low molecular weight amines. The columns and the major difficulties found with an injection of an aqueous basic amine mixture were listed in Table 5.2. The amines tested were methylamine (M), etnylamine (E) and dimethylamine (DM). All the gc columns were found to be unsuitable for

Figure 5.5 Calibration Curve for Fe^{2+}

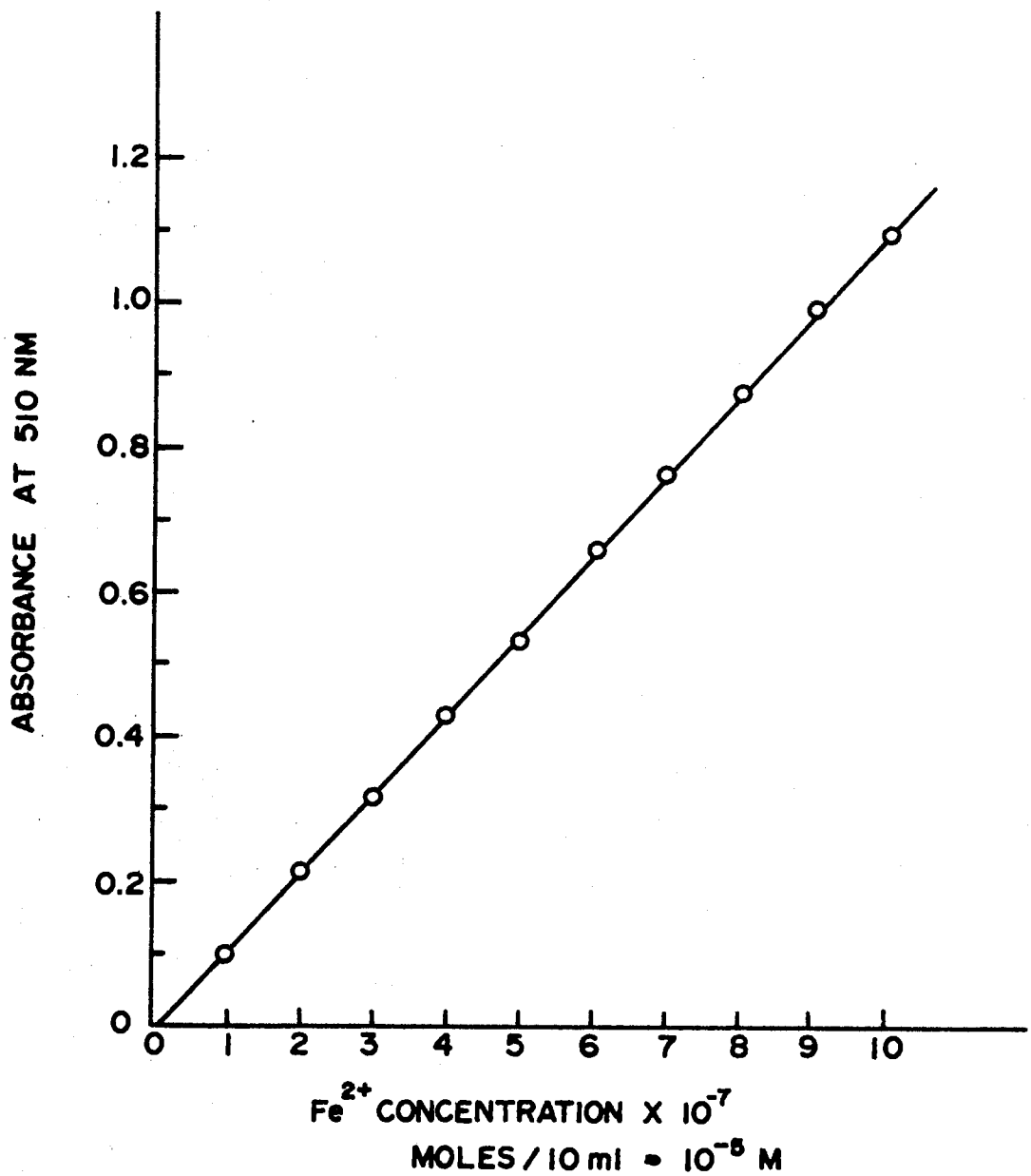


Figure 5.6 Apparatus for Determination of the % Absorbed Light

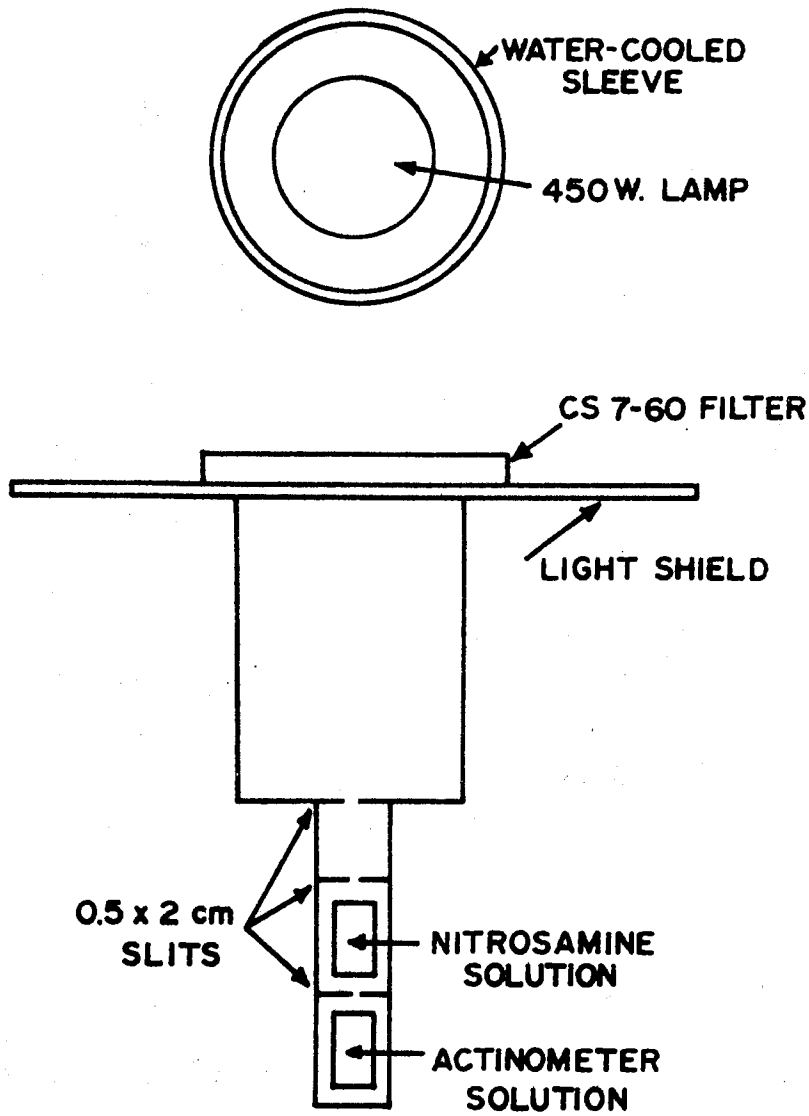


Figure 5.7 Percentage of Incident Light Absorbed as a Function of NDM Concentration

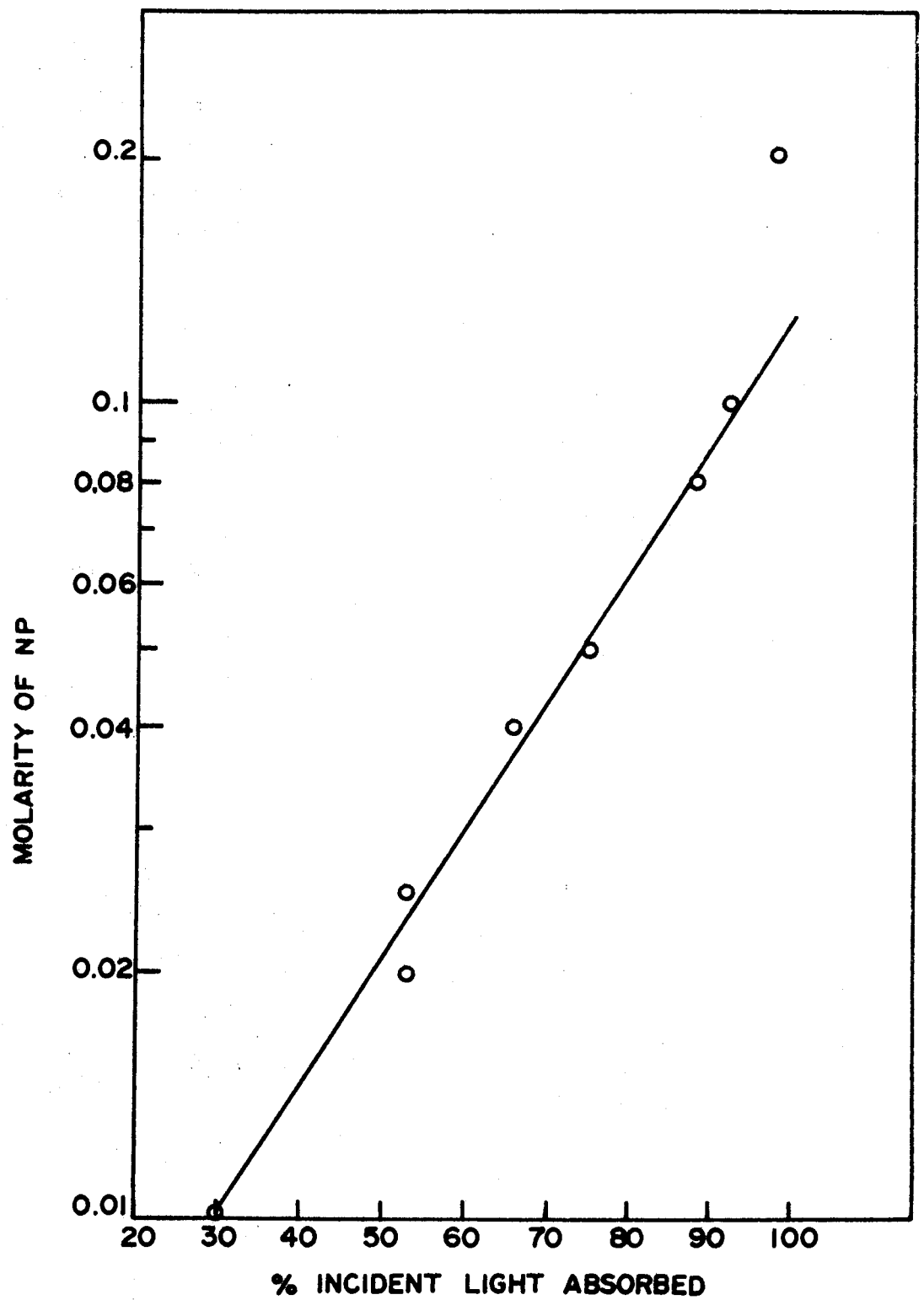


Table 5.1 Quantum Yield of NDM Disappearance*

NDM Molarity	% Disappearance/Minutes	Average % Disappearance/Min	Molecules Reactec/ Minute X10^{17}	Φ dis	Fraction of ** Light Aosorbed	Φ corr dis
0.1M	0.08	0.08	1.44	0.24	.92	0.26
0.01M	0.32					
		0.29	0.52	0.087	.30	0.29
0.01M	0.26					

* Based on the average lamp output/tube of 6x10^{17} quanta/minute

** From Figure 5.7

one, or more, of the following reasons:

(a) Incomplete separation of amines.

(b) No separation of amines.

(c) Amines did not come through the column.

(d) Asymmetric peaks, which made integration difficult.

(e) 'Ghost' peaks (188), i.e., subsequent injections of only dilute NaOH produced peaks corresponding to the previously injected amines.

The phenylthiocyanate derivative of dimethylamine was also tested in ten gc columns but gave either asymmetric or broad peaks. Amidoxime 73 gave similar results when tested on Chromosorb 103 or Dowfax 9N9 (20% KOH).

5-22-2 Amidoxime Metal Complexes

The uv and visible spectra of a dilute acidic solution of N-methylacetamido oxime (73)* in the presence of a series of metal ions were examined. The observed peak shifts of the metal ions were not well separated from the original absorptions. The values listed in Table 5.3 were observed when equimolar quantities of the metal ion and 73 were mixed together.

* Obtained by Dr. N. Chiu in this laboratory from the photodecomposition of N-nitrosomethylethylamine.

Table 5.2 Separation of Amines by Gas Chromatography

Literature Reference	Liquid Phase	Support	Unsuitability* Reasons
	20% Cetyl Alcohol	Celite 545	(a), DM and E
265	8% THEED	Chrom W	(a), DM and E
265	3% THEED, 5% TEP	Chrom W	(b), DM and E
186	20% Dowfax 9N9, 2% NaOH	Chrom W	(a), (e)
**	20% Dowfax 9N9, 20% KOH	Chrom W	(a), DM and M
**	20% Dowfax 9N9, 10% TEP	Chrom W	(a), DM and M
266	10% Versamid 900	Tide (40/60 mesh)	(b), (c)
267	10% Apiezon L	Tide	(b)
	10% TEP	Tide	(a), DM and E
	10% Dowfax 9N9	Tide	(c)
	10% Amine 220	Chrom W	(c)
	20% Hyprose SP-80	Chrom P	(c)
268	10% Ucon 50	Chrom T	(c)
	5% Ucon 50	Poropak Q	(c)
	20% XF-1150	Chrom W	(a), DM and E
	20% XF-1150, 2% NaOH	Chrom W	(a), (iv)
	10% Versamid 900, 5% KOH	Chrom W	(a), DM and M
	10% FFAP	Chrom W	(b)
	3% QF-1	Aeropak 30	(b)

Table 5.2 (cont'd)

Reference		Liquid	Support	Reason
		20% SE-30	Chrom W	(c)
		5% DC 550	Chrom W	(a), DM and M
		--	Chrom T	(c)
		--	Poropak R	(c)
187	**	--	Chromosorb 103	(e)

* Reasons are explained in text.

** Best overall columns for separation and symmetrical peaks.

Table 5.3 Metal Ions Complexed with Amidoxime 23

Metal Ion	Spectral Change upon Addition of 23
Mg^{2+}	Colorless in visible spectrum to 700nm
Zn^{2+}	Colorless in visible spectrum
Co^{2+}	No change in visible spectrum
Cr^{2+}	Green color, 410nm peak shifts to 425 nm
Ni^{2+}	Green Color; 390 nm peak appears, shifting from 400 nm
Fe^{3+}	Green color; 440 shoulder appears. Solution slowly decays to yellow color
Cu^{2+}	Dark green precipitate forms in neutral or acidic conditions. 770 nm peak broadens to peak centered at 700 nm. 410 nm peak shifts to 425 nm.

REFERENCES

1. Y.L. Chow, Accts. Chem. Res., 6, 000 (1973) Sept.
2. Y.L. Chow, C.J. Colón, H.H. Quon, and T. Nojelsky, Can. J. Chem., 50, 1065 (1972); and preceding paper.
3. T. Axenrod and G.W.A. Milne, Tet., 24, 5775 (1968).
4. R.S. Neale, Syntn., 1 (1971).
5. F. Minisci, Synth., 1 (1973).
6. N.C. Deno, "Methods in Free Radical Chemistry", Vol. 3, M. Dekker, New York, 1972. Chap. 3.
7. P. Kovacic, M.K. Lowery, and K.W. Field, Chem. Rev., 70, 639 (1970).
8. M.E. Wolff, Chem. Rev., 61, 55 (1961).
9. G. Sosnovsky and D.J. Rawlinson, "Advances in Free Radical Chemistry", Vol. 4, Academic Press, New York, 1971. Chap. 4.
10. F. Minisci, R. Galli, and M. Cecere, Chim. Ind. (Milan), 48, 132, 347 (1966); Tetrahedron Lett., 3103 (1966).
11. J.M. Surzur, L. Stella, and P. Tordo; Bull. Soc. Chim. Fr., 115 (1970).
12. C.J. Albesetti, D.D. Coffman, F.W. Hoover, E.L. Jenner, and W.E. Mochel, J. Am. Chem. Soc., 81, 1489 (1959).

13. M. Simic and E. Hayon, J. Am. Chem. Soc., 93, 5982 (1971).

14. F. Minisci, R. Galli, and M. Cecere, Tetranedron Lett., 4663 (1965).

15. J.P. Ferris, F.D. Gerwe, and G.R. Gapski, J. Org. Chem., 33, 3493 (1968).

16. M.C.R. Symons, J. Chem. Soc., Perkin II, 797 (1973).

17. S.R. Sandler and W. Karo, "Organic Functional Group Preparations", Vol. 12-II, Organic Chemistry Monographs, Academic Press, New York, 1971. Chap. 17.

18. H.T. Hagasawa, P.S. Fraser, and D.L. Yuzon, J. Med. Chem., 16, 583 (1973).

19. A.L. Fridman, F.M. Makhametshin, and S.S. Novikov, Russ. Chem. Rev., 40, 34 (1971).

20. P.A.S. Smith, "Open Chain Nitrogen Compounds", Vol.2, W.A. Benjamin, New York, 1966, Chap. 15.

21. C.G. Overberger, J. Anselme, and J. Lombardino, "Organic Compounds with Nitrogen- Nitrogen Bonds", Ronald Publishing, New York, 1966. Chap. 7.

22. S. Billets, H.H. Jaffé, and F. Kaplan, Org. Mass Spect., 7, 431 (1973).

23. P.R. Farina, Tetranedron Lett., 4971 (1970).

24. R.R. Fraser, G. Boussard, I.D. Mostescu, J.J. Whiting, and Y.Y. Wigfield, Can. J. Chem., 51, 1109 (1973).

25. D. Seebach and D. Enders, Ang. Chem. Int., 11, 1101, 1102 (1972).

26. P.S. Portoghse and D.L. Larsen, J. Med. Chem., 16, 420 (1973).

27. C.J. Michejda and R.W. Schluenz, J. Org. Chem., 38, 2412 (1973).

28. H. Alper, Organomet. Chem. Syntn., 1, 69 (1970/71).

29. A. Tanaka and J.P. Anselme, Tetrahedron Lett., 3507 (1971).

30. T.B. Morgan and D.L. Williams, J. Chem. Soc., Perkin II, 74 (1972).

31. T.G. Lunt, D.G. Fueggle, and C.L. Walters, Anal. Lett., 6, 369 (1973).

32. J.M. Surzur, P. Tordo, and L. Stella, Bull. Soc. Chim. Fr., 111 (1970).

33. P.G. Gassman, Accts. Chem. Res., 3, 26 (1970).

34. P.G. Gassman and G.D. Hartman, J. Am. Chem. Soc., 95, 449 (1973).

35. A. Heumann, R. Furstoss, and B. Waegell, Tetrahedron Lett., 993 (1972).

36. O.E. Edwards, D. Vocelle,and J.W. ApSimon, Can. J. Chem., 50, 1167 (1972).

37. O.E. Edwards, D.H. Paskovich, and A.H. Readoch, Can. J. Chem., 51 978 (1973).

38. J.W. Bastable, J.D. Hobson, and W.D. Riddell, J. Chem. Soc., Perkin I, 2205 (1972).

39. F. Minisci and R. Galli, Tetrahedron Lett., 3197 (1964).

40. F. Minisci, R. Galli, and R. Bernardi, Tetrahedron Lett., 699 (1966).

41. Y.L. Chow, M.F. Lau, R.A. Perry, and J.N.S. Tam, Can. J. Chem., 50, 1044 (1972).

42. Y.L. Chow, C. Colon, and S.C. Chen, J. Org. Chem., 32, 2109 (1967).

43. Y.L. Chow, R.A. Perry, B.C. Menon, and S.C. Chen, Tetrahedron Lett., 1545, 1549 (1971).

44. E.M. Burgess and J.M. Lavanish, Tetrahedron Lett., 1227 (1965).

45. R.S. Neale and N.R. Walsh, J. Am. Chem. Soc., 87, 1225 (1965).

46. W.C. Danen and R.C. Rickard, J. Am. Chem. Soc., 94, 3254 (1972).

47. K.F. Purcell and W.C. Danen, J. Am. Chem. Soc., 94, 7613 (1972).

48. W.C. Danen and T.T. Kensler, Tetrahedron Lett., 2247 (1971); J. Am.Chem.Soc., 92, 5235 (1970).

49. A.L. Poznyak, S.I. Arznankov, and G.A. Smagisultanova, Russ. J. Phys. Chem., 46, 445 (1972).

50. T. Toda, E. Mori, H. Horiuchi, and K. Murayama, Bull. Chem. Soc. Jap., 45, 1802 (1972).

51. A. Good and J.C.J. Thynne, J. Chem. Soc. B, 884 (1967).

52. B.A. Crowley and W.A. Waters, J. Chem. Soc., 1228 (1971).

53. J.M. Surzur, L. Stella, and P. Tordo, Tetrahedron Lett., 3107 (1970).

54. J.M. Surzur, L. Stella, and R. Nouguier, Tetrahedron Lett., 903 (1971).

55. R.E. Jacobson, K.M. Johnston, and G.H. Williams, Chem. and Ind., 157 (1967).

56. R.S. Neale, N.L. Marcus, and R.G. Schepers, J. Am. Chem. Soc., 88, 3051 (1966).

57. S. Shin, R.J. Buenker, S.D. Peyerimhoff, and C.J. Michejda, J. Am. Chem. Soc., 94, 7020 (1972).

58. S. Wawzonek and J.D. Nordstrom, J. Org. Chem., 27, 3726 (1962).

59. K.M. Johnston, G.H. Williams, and M.J. Williams, J. Chem. Soc. B, 1114 (1966).

60. C.J. Michejda and W.P. Hoss, J. Am. Chem. Soc., 92, 6298 (1970).

61. H. Prakash and H.H. Sisler, J. Org. Chem., 35, 3111 (1970).

62. J.R. Roberts and K.U. Ingold, J. Am. Chem. Soc., 95, 3228 (1973).

63. M.A. Ratcliff, Jr. and J.K. Kochi, Tetrahedron, 28, 4467 (1972).

64. P.W. Jones and H.D. Gesser, J. Chem. Soc. B, 1873 (1971).

65. D. Mackay and W.A. Waters, J. Chem. Soc. C, 813 (1966).

66. C.H. Bamford, J. Chem. Soc., 12 (1939).

67. P. Tordo, E. Flesia, and J.M. Surzur, Tetrahedron Lett., 183 (1972).

68. P. Tordo, E. Flesia, G. Labrot, and J.M. Surzur, Tetrahedron Lett., 1413 (1972).

69. T. Koenig, J.A. Hoobler, and W.R. Mabey, J. Am. Chem. Soc., 94, 2514 (1972).

70. W.C. Danen and R.W. Gellert, J. Am. Chem. Soc., 94, 6853 (1972).

71. F.R. Stermitz and D.W. Neiswander, J. Am. Chem. Soc., 95, 2630 (1973).

72. Y.L. Chow, J.N.S. Tam, and A.C.H. Lee, Can. J. Chem., 47, 2441 (1969).

73. Y.L. Chow and J.N.S. Tam, J. Chem. Soc. C, 1138 (1970).

74. L.P. Kuhn, G.G. Klenspehn, and A.C. Duckworth, J. Am. Chem. Soc., 89, 3858 (1967).

75. O.E. Edwards and R.S. Rosien, Can. J. Chem., 45, 1287 (1967).

76. D.H.R. Barton, A.L.J. Beckwith, and A. Goosen, J. Chem. Soc., 181 (1965).

77. A.L.J. Beckwith and J.E. Goodrich, Aust. J. Chem., 18, 747 (1965).

78. O.E. Edwards, J.M. Paton, M.H. Benn, R.E. Mitchell, C. Watanatada, and R.N. Vohra, Can. J. Chem., 49, 1648 (1971).

79. Y.L. Chow and T.C. Joseph, Chem. Commun., 490 (1969).

80. B. Danieli, P. Manitto, and G. Russo, Chem. and Industry, 203 (1971).

81. D. Touchard and J. Lessard, Tetrahedron Lett., 4425 (1971).

82. J.N.S. Tam and L.K. Magdzinski, unpublished results from this laboratory.

83. S. Wolfe and D.V.C. Awang, Can. J. Chem., 49, 1504 (1971).

84. V.I. Staninets and E.A. Shilov, Russ. Chem. Rev., 40, 272 (1971).

85. J.J. Périé, J.P. Laval, J. Roussel, and A. Lattes, Tetrahedron, 28, 675, 701 (1972).

86. H. Hodjat, A. Lattes, J.P. Laval, J. Roulines, and J.J. Périé, J. Hetero. Chem. 9, 1081 (1972).

87. P.G. Gassman and J.H. Dygos, Tetrahedron Lett., 4745, 4749 (1970).

88. I. Brown, O.E. Edwards, J.M. McIntosh, and D. Vocelle, Can. J. Chem., 47, 2751 (1969).

89. W. Nagata, S. Hirai, T. Okumura, and K. Kawata, J. Am. Chem. Soc., 90, 1650 (1969); ibid, 89, 5046 (1967).

90. M. Julia, Accts. Chem. Res., 4, 386 (1971); Pure Appl. Chem., 15, 167 (1967).

91. A.L.J. Beckwith, "Essays on Free-Radical Chemistry", Chem. Soc. Special Publication #24, London, 1970. Chap. 9.

92. C. Walling and A. Cioffari, J. Am. Chem. Soc., 94, 6059 (1972).

93. H.G. Richey, Jr. and A.M. Rothman, Tetrahedron Lett., 1457 (1968).

94. J.K. Crandall and D.J. Keyton, Tetrahedron Lett., 1653 (1969).

95. Z. Cekovic, Tetrahedron Lett., 749 (1972).

96. E. Van Bruggen, Rec. Trav. Chim. 87, 1154 (1968).

97. J.M. Surzur, P. Cozzone, and M.P. Bertrand, C.R. Acad. Sci., Paris, C 267, 908 (1968).

98. J.M. Surzur, M.P. Bertrand, and R. Nouguier, Tetrahedron Lett., 4197 (1969).

99. R.D. Rieke and N.A. Moore, J. Org. Chem., 37, 415 (1972).

100. J.M. Surzur, C. Dupuy, M.P. Bertrand, and R. Nouguier, J. Org. Chem. 37, 2782 (1972).

101. M.L. Michailovic and Z. Cekovic, Synth., 209 (1970).

102. K. Heusler, Tetrahedron Lett., 97 (1970).

103. Y.L. Chow and R.A. Perry, Tetrahedron Lett., 531 (1972).

104. E. Flesia, A. Croatto, P. Tordo, and J.M. Surzur, Tetrahedron Lett., 535 (1972).

105. J.M. Surzur, R. Nouguier, M.P. Crozet, and C. Dupuy, Tetrahedron Lett., 2035 (1971).

106. J.M. Surzur, C. Dupuy, M.P. Crozet, and M. Aimar, C.R. Acad. Sci., Paris, C 269, 849 (1969).

107. J.H. Davis, J.D. Downer, and P. Kirby, J. Chem. Soc., 245 (1966).

108. B. Capon and C.W. Rees, Ann. Rep. Chem. Soc., 61, 221 (1964).

109. P. Tordo, Thesis, University de Provence, May 1971.

110. A.L.J. Beckwith, G.E. Gream, and D.L. Stubble, Aust. J. Chem., 25, 1081 (1972).

111. R.F. Gardwood, C.J. Scott, and B.C.L. Weedon, Chem. Commun., 14 (1965).

112. L. Stella, Thesis, University de Provence, March 1972.

113. J.M. Surzur, M.P. Crozet, and C. Dupuy, C.R. Acad., Sci., Paris, C 264, 610 (1967).

114. J.M. Surzur, M.P. Crozet, and C. Dupuy, Tetrahedron Lett., 2025 (1971).

115. M. Akhtar, D.H.R. Barton, and P.G. Sammes, J. Am. Chem. Soc., 87, 4601 (1965).

116. C.R. Noller and R. Adams, J. Am. Chem. Soc., 48, 2444 (1926).

117. H.C. Brown and G. Zweifel, J. Am. Chem. Soc., 82, 3223 (1960).

118. R. Monson, "Advanced Organic Synthesis", Academic Press, New York, 1971.

119. G.P. Kugatova-Shemyakina and R.A. Poskiene, Zh, Org. Khim., 2, 844 (1966).

120. W.R. Boehme, J. Org. Chem., 26, 2107 (1961).

121. A.A. Morton and R.A. Finnegan, J. Polymer Sci., 38, 19 (1959).

122. D. Pasto and C. Johnston, "Organic Structure Determination", Prentice-Hall, Toronto, 1969.

123. H.C. Brown, P.M. Weissman, and N.M. Yoon, J. Am. Chem. Soc., 88, 1458 (1966).

124. M. Cerny, J. Malek, M. Capka, and V. Chvalovsky, Coll. Czech. Chem. Commun., 34, 1033 (1969).

125. W. Reid and F. Muller, Chem. Ber., 85, 470 (1952).

126. A.C. Murdock and R.B. Angier, J. Org. Chem., 27, 2395 (1960).

127. E.C. Taylor and R.O. Kan, J. Am. Chem. Soc., 85, 776 (1963).

128. Y.L. Chow and C.J. Colon, Can. J. Chem., 45, 2559, (1967).

129. E.H. White, J. Am. Chem. Soc., 77, 6008 (1955).

130. E.H. White and C.A. Aufdermarsen, Jr., J. Am. Chem. Soc., 83, 1174, 1179 (1961).

131. F.W. Stacey and J.F. Harris, 'Org. Reactions', 13, 225 (1963).

132. J. Spanswick and K.U. Ingold, Can. J. Chem., 46, 546 (1970).

133. P. Brun, R. Furstoss, P. Teissier, W. Tuoiana, and B. Waegell, C.R. Acad. Sci. (Paris) C269., 427 (1969).

134. W.J. Gensler, C.D. Gatsonis, and G.A. Ahmed, J. Org. Chem., 33, 2968 (1968).

135. J.W. Huffman, T. Kamiya, and C.B.S. Rao, J. Org. Chem., 32, 700 (1967).

136. H. Pracejus, M. Kehlen, H. Kehlen, and H. Matschiner, Tetrahedron 21, 2257 (1965).

137. W.P. Giering, S. Raghu, M. Rosenblum, A. Cutler, D. Ehntholt, and R.W. Fish, J. Am. Chem. Soc., 94, 8231 (1972).

138. S.H. Pines, J.M. Chemerda, and M.A. Kozlowski, J. Org. Chem., 31, 3446 (1966).

139. G. Esposito, R. Furstoss, and B. Waegell, Tetrahedron Lett., 899 (1971).

140. H.P. Fisher and C.A. Grob, Helv. Chim. Acta., 45, 2528 (1962).

141. A.Mackor and Th.J. Deboer, Rec. Trav. Chim., 89, 151 (1970).

142. Y.L. Chow, J.N.S. Tam, C.J. Colon, and K.S. Pillay, Can. J. Chem., 51, 2409 (1973).

143. R. Boschan, R.T. Merrow, and R.W. VanDolah, Chem. Rev., 55, 485 (1955).

144. Y. Becker, A. Eisenstadt, and Y. Shuo, Tetrahedron Lett., 3183 (1973).

145. A.K. Bose, H.P.S. Chawla, B. Dayal, and M.S. Manhas, Tetrahedron Lett., 2503 (1973).

146. J.P. Ferris and N.C. Miller, J. Am. Chem. Soc., 85, 1325 (1963).

147. R.A. Johnson, M.E. Herr, H.C. Murray, L.M. Reineke and G.S. Fonken, J. Org. Chem., 33, 3195 (1968).

148. L.A. Paquette and L.D. Wise, J. Am. Chem. Soc., 87, 1561 (1965).

149. W.L. Nelson and K.F. Nelson, J. Org. Chem., 36, 607 (1971).

150. T.J. Lobl, J. Chem. Educ., 49, 730 (1972).

151. F. Bohlmann, Chem. Ber., 91, 2157 (1958).

152. R. Furstoss, P. Teissier, and B. Waegell, Chem. Commun., 384 (1970).

153. J. Deutsch and B. Sklarz, Is. J. Chem., 10, 51 (1972).

154. R. Furstoss, A. Heumann, and B. Waegell, Org. Mass Spect., 6, 1207 (1972).

155. J.E. Dewhurst, J.J. Kaminski, and J.H. Supple, J. Hetero. Chem., 9, 507 (1972).

156. C.R. Johnson and F.L. Billman, J. Org. Chem., 36, 855 (1971).

157. J.O. Pavlik, P.I. Flooard, A.C. Somersall, and J.E. Guillet, Can. J. Chem., 51, 1435 (1973).

158. H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San. Fransisco, 1967.

159. W. Prandtl and K. Sennewald, Chem. Ber., 62, 1754 (1929).

160. A. Bertho and G. Rodl, Chem. Ber., 92, 2218 (1959).

161. H.L. Ammon, P.H. Mazzocchi, W.J. Kopecky, Jr., H.J. Tamburin, and P.H. Watts, Jr., J. Am. Chem. Soc., 95, 1968 (1973).

162. K. Fujita, K. Hata, R. Oda, and I. Tabushi, J. Org. Chem., 38, 2640 (1973).

163. W.E. Noland, R.B. Hart, W.A. Joern, and R.G. Simon, J. Org. Chem., 34, 2058 (1969).

164. C.L. Angell, P.J. Kruger, R. Lauzon, L.C. Leiton, K. Noack, R.J.D. Smith, and R.N. Jones, Spect. Acta., 11, 920 (1959).

165. H.O. House and H.C. Miller, J. Org. Chem., 27, 4455 (1962).

166. G.M. Cree and A.S. Perlin, Can. J. Biochem., 46, 705 (1968).

167. H.S. Aaron and L.P. Rieff, J. Hetero. Chem. 5, 423 (1968).

168. K.H. Bell, Aust. J. Chem., 24, 1089 (1971).

169. J. Seibl, Org. Mass Spect., 3, 417 (1970).

170. R.L. Shriner and E.A. Parker, J. Am. Chem. Soc., 55, 766 (1933).

171. D.H.R. Barton, D. Kumari, P. Welzel, L.J. Danks, and J.F. McGhie, J. Chem. Soc. C, 332 (1969).

172. Y.L. Chow, Can. J. Chem. 45, 53 (1967).

173. D. Goldsmith, D. Becher, S. Sample, and C. Djerassi, Tetrahedron Supplement No. 7, Pergamon Press, 1966.

174. M.P. Lau, Ph.D. Thesis, Simon Fraser University, 1970.

175. H. Izawa, P. deMayo, and T. Tabata, Can. J. Chem. 47, 51 (1969).

176. D.J. Carlsson and K.U. Ingold, J. Am. Chem. Soc., 89, 4885 (1967).

177. A. Stojiljkovic, V. Andrejevic, and M.L. Minailovi, Tetrahedron, 23, 721 (1967).

178. M. Anbar, D. Meyerstein, and P. Neta, J. Chem. Soc. B, 742 (1966).

179. Y.L. Chow and A.C.H. Lee, Can. J. Chem., 45, 311 (1967).

180. R.T. Morrison and R.N. Boyd, "Organic Chemistry", Allyn and Bacon, Boston, 1959.

181. M.P. Lau, A.J. Cessna, Y.L. Chow, and R.W. Yip, J. Am. Chem. Soc., 93, 3808 (1971).

182. E.S. Huyser, "Free Radical Chain Reactions", Wiley-Interscience, New, York, 1970. Chap. 9.

183. H.H. Quon, work done in this laboratory.

184. C.J. Colon, Ph.D. Thesis, Simon Fraser University, 1970.

185. J.N.S. Tam, PhD. Thesis, Simon Fraser University, 1970.

186. J.F. O'Donnell and C.K. Mann, Anal. Chem., 36, 2097 (1964).

187. S.B. Dave, J. Chrom. Sci., 7, 389 (1969).

188. R.A. Simonaitis and G.C. Guvernator III, J. Gas Chrom., 49 (1969).

189. B.C. Menon, work done in this laboratory.

190. S.C. Chen, Ph.D. Thesis, Simon Fraser University, 1970.

191. R.S. Neale, J. Org. Chem., 32, 3263 (1967).

192. R.S. Neale, and N.L. Marcus, J. Org. Chem., 32, 3273 (1967).

193. Y.L. Chow and M.M. Feser , Chem. Commun., 259 (1967).

194. Y.L. Chow and C.J. Colon, Can. J. Chem., 46, 2827 (1968).

195. R.K. Harris and R.A. Spragg, J. Mol. Spect., 23, 158 (1967).

196. J.W. ApSimon and J.D. Cooney, Can. J. Chem., 49, 2377 (1971).

197. G.J. Karabatsos and R.A. Taller, J. Am. Chem. Soc., 86, 4373 (1964).

198. R. Tadayoni, A. Heumann, R. Furstoss, and B. Waegell, Tetrahedron Lett., 2879 (1973).

199. Y.L. Chow, J.N.S. Tam, and K.S. Pillay, Can. J. Chem., 51, 2477 (1973).

200. A. DiGiacomo, J. Org. Chem., 30, 2014 (1965).

201. Y.L. Chow, S.C. Chen, and D.W.L. Chang, Can. J. Chem., 49, 3069 (1971).

202. B.G. Gwenlock, G. Kresze, and J. Pfab, Tetrahedron Lett., 593 (1972).

203. J.A. Maason and Th.J. deBoer, Rec. Trav. Chim., 92, 185 (1973).

204. J.A. Maason and Th.J. deBoer, Rec. Trav. Chim., 91, 1329 (1972).

205. J. Heicklen and N. Conn, "Advances in Photochemistry", Interscience, New York, 1968. Chap. 8.

206. T. Johnston and J. Heicklen, J. Phys. Chem., 70, 3088 (1966).

207. K. Maruyama and K. Murakami, Bull. Chem. Soc. Jap., 41, 1401, (1968).

208. J.P. Freeman, Chem. Rev., 73, 283 (1973).

209. G.B.M. Eastmond and G.L. Pratt, J. Chem. Soc., A, 2337 (1970).

210. T. Mojelsky, work done in this laboratory.

211. H.A. Benesi and J.H. Hildebrand, J. Am. Chem. Soc., 71, 2703 (1949).

212. C.F. Hammer, M. McCarthy Ali, and J.D. Weber, Tetrahedron, 29, 1767 (1972).

213. G.F. Hennion and A.C. Hazy, J. Org. Chem., 30, 2650 (1965).

214. V. Rautenstrauch, Chem. Commun., 1122 (1969).

215. Handbook of Chemistry and Physics, Chemical Rubber Co., Edition 50.

216. G.R. Krow, R. Rodebaugh, C. Hyndman, R. Carmosin, and G. DeVicaris, Tetrahedron Lett., 2175 (1973).

217. R.R. Fraser and R.B. Swingle, Can. J. Chem. 48, 2065 (1970).

218. R.M. Dupeyre and A. Rassat, Tetrahedron Lett., 2699 (1973).

219. A. Rassat and P. Rey, Tetrahedron, 28, 741 (1972).

220. R. Furstoss, G. Esposito, and B. Waegell, C.R. Acad. Sci. (Paris), C273, 478 (1971).

221. R.F. Borne, C.R. Clark, and J.M. Holbrook, J. Med, Chem., 16, 853 (1973).

222. E. Nativ and P. Rona, Is. J. Chem., 10, 58 (1972).

223. R.H. Hesse, "Advances in Free Radical Chemistry," Vol.3, Academic Press, New York, 1969. Chap. 2.

224. G.A. Olah, J.A. Olah, and N.A. Overchuk, J. Org. Chem., 30, 3373 (1965).

225. C.L. Bumgardner, K.S. McCallum, and J.P. Freeman, J. Am. Chem. Soc., 83, 4417 (1961).

226. H. Maltz, M.A. Grant, and M.C. Navoroli, J. Org. Chem., 36, 363 (1971).

227. T.Y. Fan and S.R. Tannenbaum, J. Agric. Food Chem., 21, 237 (1973).

228. J.R. Park and D.L.H. Williams, J. Chem. Soc. Perkin II, 2158 (1972).

229. E.G. Rosantzer and V.D. Sholle, Russ. Chem. Rev., 40, 223 (1971).

230. W.S. Layne, H.H. Jaffe, and H. Zimmer, J. Am. Chem. Soc., 85, 435, 1816 (1963).

231. S.S. Mirvish, D.L. Nagel, and J. Sams, J. Org. Chem. 38, 1325 (1973).

232. E.E.J. Dekker, J.N.F. Engberts, T.J. deBoer, Tetrahedron Lett., 2651 (1969).

233. J. Jappy and F.N. Preston, Tetrahedron Lett., 1157 (1970).

234. K. Akiba, I. Fukawa, N. Nomura, and N. Inamoto, Bull. Chem. Soc. Jap., 45, 1867 (1972).

235. C.J. Thoman and I.M. Hunsberger, J. Org. Chem., 33, 2852, (1968).

236. M. Maeda and Y. Kawazoe, Tetrahedron Lett., 2751 (1973).

237. E.L. O'Brien, F.M. Beringer, and R.B. Mesrobian, J. Am. Chem. Soc., 81, 1506 (1959).

238. C. Djerassi, R.R. Engle, and A. Bowers, J. Org. Chem., 21, 1547 (1956).

239. K. Nakanishi and L.F. Fieser, J. Am. Chem. Soc., 74, 3910 (1952).

240. E. Campaigne and W.M. LeSauer, Organic Syntheses, Vol. 4, 919 (1963).

241. Th.J. deBoer and H.J. Backer, Rec. Trav. Chim. 73, 229 (1954).

242. A.I. Vogel, "Practical Organic Chemistry", Longmans, Green and Co., London, 1956. P. 356.

243. D.A. Shirley and P.A. Russel, J. Am. Chem. Soc., 75, 375 (1953).

244. N.J. Turro and R. Engel, J. Am. Chem. Soc., 91, 7113 (1969).

245. C.M. Orlando, Jr., H. Mark, A.K. Bose, and M.S. Manke, J. Org. Chem., 33, 2512 (1968).

246. J.H. Dygos, Ph.D. Thesis, Ohio State, 1971.

247. H.C. Brown and P.M. Weissman, J. Am. Chem. Soc., 87, 5614 (1965).

248. G. Zweifel and H.C. Brown, Organic Reactions, Vol. 13, 1 (1963).

249. J.W. Bird and D.G.M. Diaper, Can. J. Chem. 47, 145 (1969).

250. G.H. Timms and E. Wildsmith, Tetrahedron Lett., 195 (1971).

251. W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, J. Am. Chem. Soc., 89, 1499 (1967).

252. S.J. Angyal and K. James, Chem. Commun., 617 (1969).

253. M. Fetizon, M. Golfer, and J.M. Louis, Chem. Commun., 1102 (1969).

254. J.D. Albright and L. Goldman, J. Am. Chem. Soc., 89, 2416 (1969).

255. P.G. Gassman and P.G. Pape, J. Org. Chem., 29, 160 (1961).

256. M.A. Volodina, G.V. Kiryushkina, and A.P. Terent'ev, Dokl. Akad. Nauk. SSSR, 102, 90 (1955).

257. P. Kovacic, M.A. Lowery, and P.D. Roskos, Tetrahedron, 26, 529 (1970).

258. M.L. Wolfrom, L.W. Georges, and S. Soltzberg, J. Am. Chem. Soc., 56, 1794 (1934).

259. M.S. Ahmad and A.H. Siddiqui, J. Ind. Chem. Soc., 46, 44 (1969).

260. C.H. DePuy and B.W. Ponder, J. Am. Chem. Soc., 81, 4629 (1959).

261. J.A. Barltrop, A.J. Johnson, and G.D. Meakins, J. Chem. Soc., 181 (1951).

262. Y. Yukawa, M. Sakai, and S. Suzuki, Bull. Chem. Soc. Jap., 32, 2266 (1969).

263. A.A. Lamola and G.S. Hammond, J. Chem. Phys. 43, 2129 (1965)..

264. C.G. Hatchard and C.A. Parker, Proc. Roy. Soc. A235, 518 (1956).

265. Y.L. Sze, M.L. Borke, and D.M. Ottenstein, Anal. Chem. 35, 240 (1963).

266. A.W. Decora and G.U. Dinneen, Anal. Chem., 32, 104 (1960).

267. R.V. Golovnya, G.A. Mironov, and I.L. Zhurableva, J. Anal. Chem. USSR, 22, 529 (1967).

268. C. Landault and G. Guiochon, J. Chrom. 9, 193 (1962).